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Original article

Invasive pneumococcal infections in France: Changes from 2009 to 2021 in antibiotic resistance and serotype distribution of *Streptococcus pneumoniae* based on data from the French Regional Pneumococcal Observatories network



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ABSTRACT

Objective: The 23 French Regional Pneumococcal Observatories (ORPs) analyzed antibiotic resistance and serotypes of *Streptococcus pneumoniae* strains isolated from invasive infections in France over a 12-year period.

Methods: Between 2009 and 2021, the ORPs analyzed 19,319 strains, including 1,965 in children and 17,354 in adults. Strains were assessed for their resistance to penicillin G, amoxicillin and cefotaxime. Serotypes were identified in collaboration with the National Reference Centre.

Results: During this period, the number of strains collected yearly decreased significantly. The decrease was particularly pronounced up until 2013, especially in children (-61.0%). However, penicillin non-susceptible strains (PNSPs) increased in children (24.7% in 2009 vs 45.0% in 2021, $p < 0.0001$) and in adults (27.1% in 2009 vs 31.3% in 2021, $p < 0.05$), as well as resistance (I + R) to amoxicillin (children: 12.5% in 2009 vs 19.4% in 2021, $p < 0.05$; adults: 13.4% in 2009 vs 14.5% in 2021, NS) and resistance (I + R) to cefotaxime (children: 8.0% in 2009 vs 13.1% in 2021, $p < 0.05$; adults: 7.1% in 2009 vs 11.9% in 2021, $p < 0.0001$). All in all, the proportion of strains belonging to serotypes present in the PCV13 vaccine has fallen sharply, from 64.8% in 2009 to 23.6% in 2021. At the same time, serotypes such as 8, 10A, 11A, 15B/C and 9N, not included in PCV13, were increasing.

Conclusion: During the study period, data collected by the network highlighted an increase of invasive PNSPs in children and non-vaccine serotypes. Surveillance of resistance and serotypes remains instrumental, particularly to monitor the evolution of vaccine efficacy.

1. Introduction

Streptococcus pneumoniae is a commensal bacterium of the oropharyngeal microbiota colonizing the upper respiratory tract of children and adults. *S. pneumoniae* infections are frequent and mostly community-acquired. In France, invasive pneumococcal diseases (IPD) represent the leading cause of community-

acquired bacterial pneumonia and meningitis in adults, and estimated mortality ranges between 10 and 30% [1]. Although both children and adults might be affected, the incidence is higher in infants and people over 65 years of age [2,3].

In 2001, the percentage of pneumococci with decreased susceptibility to penicillin G (PDSP) isolated from IPD reached its highest rate in France, with an overall proportion of 47.3%, reaching 50.7% in children [4]. At the end of that year, the French national plan went into effect, aiming to rationalize the use of antibiotics and to preserve their effectiveness, associating them with vaccination of young children with the 7-valent pneumococcal conjugate vaccine (PCV7, containing serotypes 4, 6B, 9V, 14, 18C, 19F, 23F) which

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was initiated in 2003. It enabled decreased incidence of *S. pneumoniae* isolates resistant to antibiotics and of invasive infections due to vaccine serotypes [5]. However, starting in 2005 increased incidence of IPD due to serotypes not contained in PCV7, particularly serotypes 7F and 19A, was observed [6–8]. It led to the introduction in 2010 of the 13-valent pneumococcal conjugate vaccine (PCV13, containing PCV7 serotypes + additional serotypes 1, 3, 5, 6A, 7F, 19A) for all children under 2 years of age. From 2011, primary vaccination coverage of PCV13 exceeded 90% in 9-month-old children [9]. Since January 1st, 2018, this vaccine is mandatory for children, and administered from the age of 2 months. Coverage at 8 months of age with at least one dose of vaccine for children born in the first trimester of 2021 was estimated at 99.7% [10]. In addition, a 23-valent pneumococcal polysaccharide vaccine (PPV-23, containing serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F) is available in France. This vaccine is indicated for immunocompromised patients and for those with an underlying disease associated with specific risks of IPD (aspleny, congenital heart disease, chronic obstructive pulmonary disease, severe asthma, renal failure, chronic liver disease, unbalanced diabetes, osteo-meningeal breach...).

The need to assess the impact of pneumococcal vaccination on serotype distribution and the evolution of pneumococcal resistance to antibiotics warranted increased epidemiological surveillance at the national level [11–14]. To carry it out, the French Regional Pneumococcal Observatories (Observatoires Régionaux du Pneumocoque, ORP), created in 1995, and working in collaboration with the National Reference Center for Pneumococci and Public Health France, set up a network of 323 biological laboratories (78% public laboratories and 22% private laboratories) which serve 418 health facilities throughout mainland France [11].

In this paper we present the results of resistance and serotype surveillance of pneumococci isolated in IPD between 2009 and 2019 in France.

2. Material and methods

2.1. Collection of strains

Every odd year from January 1, 2009 to December 31, 2021, all pneumococcal strains isolated from cerebrospinal fluid (CSF) or blood culture were included in the study. For patients with several isolates, only the one isolate from the CSF was retained. Patients aged at least 16 years were defined as adults, and those aged under 16 years were defined as children.

2.2. Susceptibility to antibiotics

The minimum inhibitory concentrations (MIC) of penicillin G (PEN), amoxicillin (AMX) and cefotaxime (CTX) were determined by the coordinating centers (composed of 253 public and 70 private laboratories) of the Regional Pneumococcal Observatories according to the reference method (dilution in agar medium until 2015, and then microdilution in a liquid medium (Sensititre – ThermoFisher) from 2017). Strains were categorized as susceptible or resistant according to breakpoints of 0.06 and 2 mg/L for PEN, and 0.5 and 2 mg/L for AMX and CTX. A penicillin MIC > 0.064 mg/L defined the pneumococci with decreased susceptibility to PEN (PDSP) [15]. Susceptibility to erythromycin (ERY), cotrimoxazole (SXT) and norfloxacin (NOR) was evaluated in each participating laboratory by the methods used routinely, according to CA-SFM – EUCAST (Comité de l'Antibiogramme de la Société Française de Microbiologie - European Committee on Antimicrobial Susceptibility Testing) guidelines [15]. Susceptibility to pristinamycin was

assessed from 2017. Three reference strains, R6WT (wild phenotype), ATCC49619 (PDSP) and 32475 (PDSP), provided by the National Reference Center for Pneumococci, served as quality controls.

2.3. Serotyping of strains

Every odd year, all strains isolated from CSF in adults and children, from blood in children and a random sample of strains isolated from blood in adults (1 strain out of 5 on average over the 10 years of study) were sent to the National Reference Center for Pneumococci for serotyping using antisera (Statens Serum Institut, Copenhagen, Denmark).

2.4. Statistical analysis

Statistical analysis was performed using SAS version 9.1.3., issued by SAS (version 9.1.3., SAS Institute, Cary, USA). Statistical analysis was performed using the χ^2 -test for trends; a *p* value < 0.05 was considered significant.

3. Results

Between 2009 and 2021, the 23 ORPs studied 19,319 pneumococcal strains isolated from invasive infections (meningitis and/or bacteremia), including 1965 strains (10.2%) in children and 17,354 (89.8%) in adults. The distribution of the strains analyzed by the ORP during the study period is presented in Fig. 1. The median number of strains collected by each ORP over this period was 748, with extremes ranging from 202 to 1786. For each year of study, the recruitment of strains by each ORP remained stable.

Between 2009 and 2015, the total number of strains collected decreased significantly, by 49.2% (from 4272 strains to 2167, *p* < 0.05). This drop was particularly significant in children, with a 67.8% decrease (from 575 strains to 185 – Fig. 2-A). In adults, the number of strains isolated from IPD during that period decreased by 46.4%, from 3,697 to 1,982 (*p* < 0.05) (Fig. 2-B). Between 2015 and 2019, the number of strains analyzed remained stable, declining in 2021 at the time of the COVID pandemic (–22.3% between 2019 and 2021 in children; –46.0% between 2019 and 2021 in adults).

3.1. Susceptibility to antibiotics

The susceptibility of pneumococcal strains to antibiotics is displayed in Table 1 and Table 2. During the full study period (2009–2021), the proportion of PDSPs isolated in a context of meningitis increased by 22.2% in children (from 29.2% to 51.4%, *p* < 0.05) and by 20% in adults (from 26.1% to 46.1%, *p* < 0.0001) (*p* < 0.05). With regard to strains isolated in blood cultures, the PDSP rate in children increased from 23.7% to 43.1% (+19.4%, *p* < 0.0001), and less pronouncedly in adults from 27.2% to 29.8% (+2.6%, *p* < 0.0001).

Regarding strains resistant to AMX isolated from CSF (MIC > 0.5 mg/L), the changes were similar during the full study period, with an increase from 13.2% to 29.7% (+16.5%, *p* < 0.05) in children, and a slight increase from 14.2% to 20.0% (+5.8%, NS) in adults. Between 2009 and 2021, the frequency of strains not susceptible to AMX (MIC > 0.5 mg/L) isolated from blood cultures increased from 12.4% to 16.3% (+3.9%, NS) in children and from 13.3% to 13.9% (+0.6%, NS) in adults.

Regarding CTX, the frequency of resistant strains (MIC > 0.5 mg/L) isolated from CSF in children increased slightly, from 7.5% to 16.2% (+8.7%, NS), with only 1 strain in 2019 exhibiting a MIC of 4 mg/L. Regarding strains isolated from blood cultures in children,

the proportion of non-susceptible strains (MIC > 0.5 mg/L) increased from 8.1% to 12.2% (+4.1%, NS), with 2 resistant strains with a MIC of 8 mg/L. The proportion of strains isolated from CSF in adults and not susceptible to CTX (MIC > 0.5 mg /L) increased from 6.1% to 16.5% (+10.4%, $p < 0.001$), with 9 CTX-resistant strains with a MIC ≥ 4 mg/L, 2 being isolated in 2021. The frequency of strains isolated from blood cultures and not susceptible to CTX (MIC > 0.5 mg/L) likewise increased, from 7.2% to 11.4% (+4.2%, $p < 0.0001$), with 28 resistant strains (MIC ≥ 4 mg/L).

With regard to the other antibiotics assessed, between 2009 and 2021 the percentage of strains resistant (I + R) to ERY increased slightly in children (from 23.8% to 28.8%, NS), and fell in adults (from 29.3% to 22.7%, $p < 0.0001$). Similar results were observed for resistance (I + R) to SXT between 2009 and 2021, as the rate in children increased from 15.0% to 17.6% (NS) and decreased in adults from 15.3% to 9.2% ($p < 0.0001$). Finally, concerning resistance to NOR between 2009 and 2021, the rate in children fell from 28.7% to 1.9% ($p < 0.0001$) and in adults from 29.7% to 1.8% ($p < 0.0001$). Only 4 unrelated pristinamycin-resistant strains were isolated, all of them in 2017.

3.2. Serotype distribution

A total of 7875 *S. pneumoniae* strains isolated from invasive infections in adults ($n = 6054$) and children ($n = 1821$) were serotyped during the study period (Figs. 3 and 4). Between 2009 and 2021, the rate of serotypes present in PCV13 decreased significantly, from 64.8% to 23.6%, ($p < 0.05$).

In children, this decrease was more pronounced, with a disappearance of serotypes 1 and 7F (23.6% and 21.4% in 2009, respectively, vs 0% in 2021 for both), and a significant decrease of serotype 19A (19.6% in 2009 vs 2.6% in 2021) (Fig. 3). Although included in PCV13, the serotype 3 kept circulating, with 5.2% in 2009 and 3.9% in 2021. During this period, an increase of serotypes 8, 10A, 11A, 15B/C, 33F, particularly 24F, none of them included in the PCV13 vaccine, was observed. The highest increase was observed for 24F serotype, ranging from 3.7% in 2009 to 15.6% in

2021. This growth was particularly pronounced in the 0–23-month age group (5.2% vs 18.1%) and 2–5 years (4.3% vs 14.9%). In 0–23 months, serotypes 8 and 11A, absent in 2009, both represented 6.4% of the strains in 2021. Finally, other serotypes emerged in the 0–23-month age group: 10A (1.2% vs 10.6%), 15B/C (2.8% vs 8.5%), 23B (0.4% vs 3.2%) and 33F (2.4% vs 6.4%).

Among the 2–5-year age group, no vaccine serotype was clearly dominant. Regarding non-vaccine serotypes, 24F increased by 10.6% (4.3% vs 14.9%). The 15B/C serotype emerged (from 0.7% to 8.5%). The other serotype that increased significantly in this age group was 10A (0.7% vs 12.8%; $p < 0.005$) but in 2021, only 47 strains were serotyped in this age group.

Finally, among the 6–15-year age group, among the non-vaccine serotypes, 8 showed the greatest increase, from 0% to 16.7% between 2009 and 2021, followed by 9N (1.9% vs 8.3%) and 33F (0.6% vs 8.3%). In 2021, only 12 strains in this age group were isolated and serotyped.

In adults, a decrease in the PCV13-included serotypes was likewise observed, in particular serotypes 7F (15.4% vs 0.0%) and 1 (7.5% vs 0.0%), which disappeared, and 19A (10.8% vs 4.9%) (Fig. 4). Of note, serotype 3 remained predominant among the vaccine serotypes (9.4% vs 12.5%), with the majority of strains isolated from patients over 65 years of age. Serotypes, 8, 9N, 10A and 11A, not included in PCV13 but included in PPV23, increased during the study period.

3.3. Serotype and resistance

Among the strains whose serotype is included in PCV13, among those isolated from CSF ($n = 576$), the rate of strains I + R at CTX was 14.4% (vs 6.9% overall) and mainly involved strains of serotypes 19A and 19F ($n = 231$), of which 29.0% of the isolates had a MIC > 0.5 mg/L (Fig. 5). For those isolated from blood culture and whose serotype is included in PCV13 ($n = 2,386$), the frequency of strains I + R to AMX was 19.3% (vs 11.4% overall), and involved mainly serotypes 14, 19A and 19F (Fig. 6).

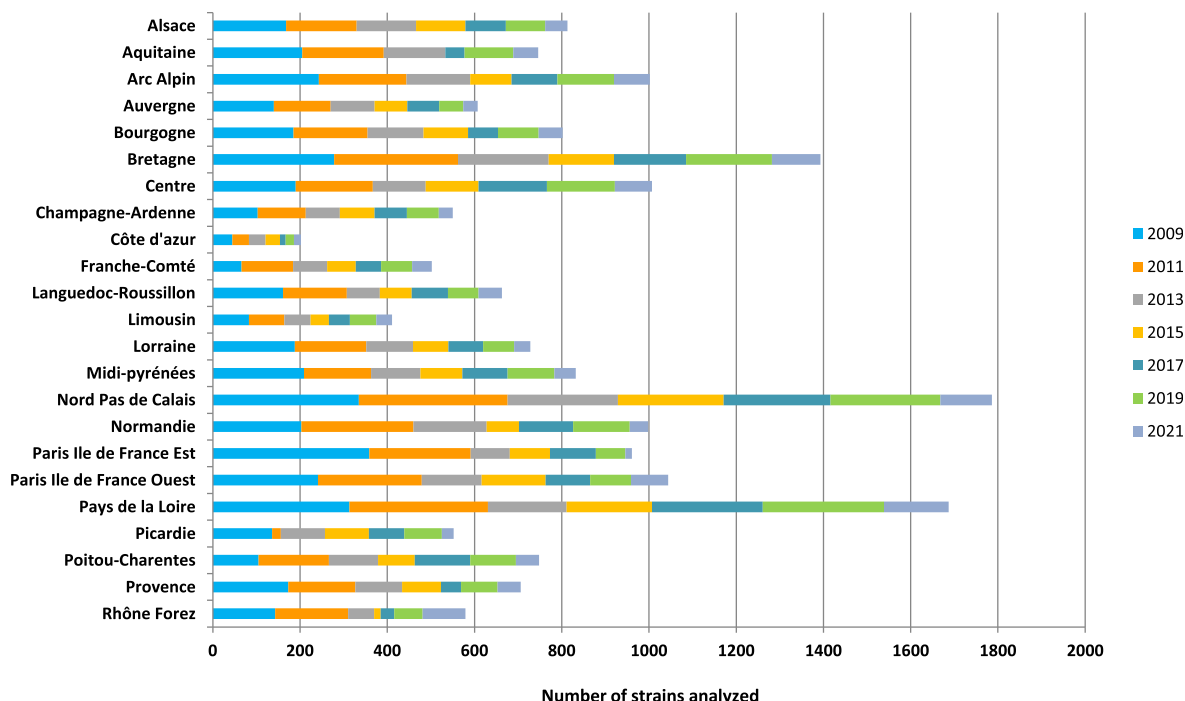


Fig. 1. Distribution between 2009 and 2021 of pneumococcal strains analyzed by the 23 Regional Pneumococcal Observatories, France.

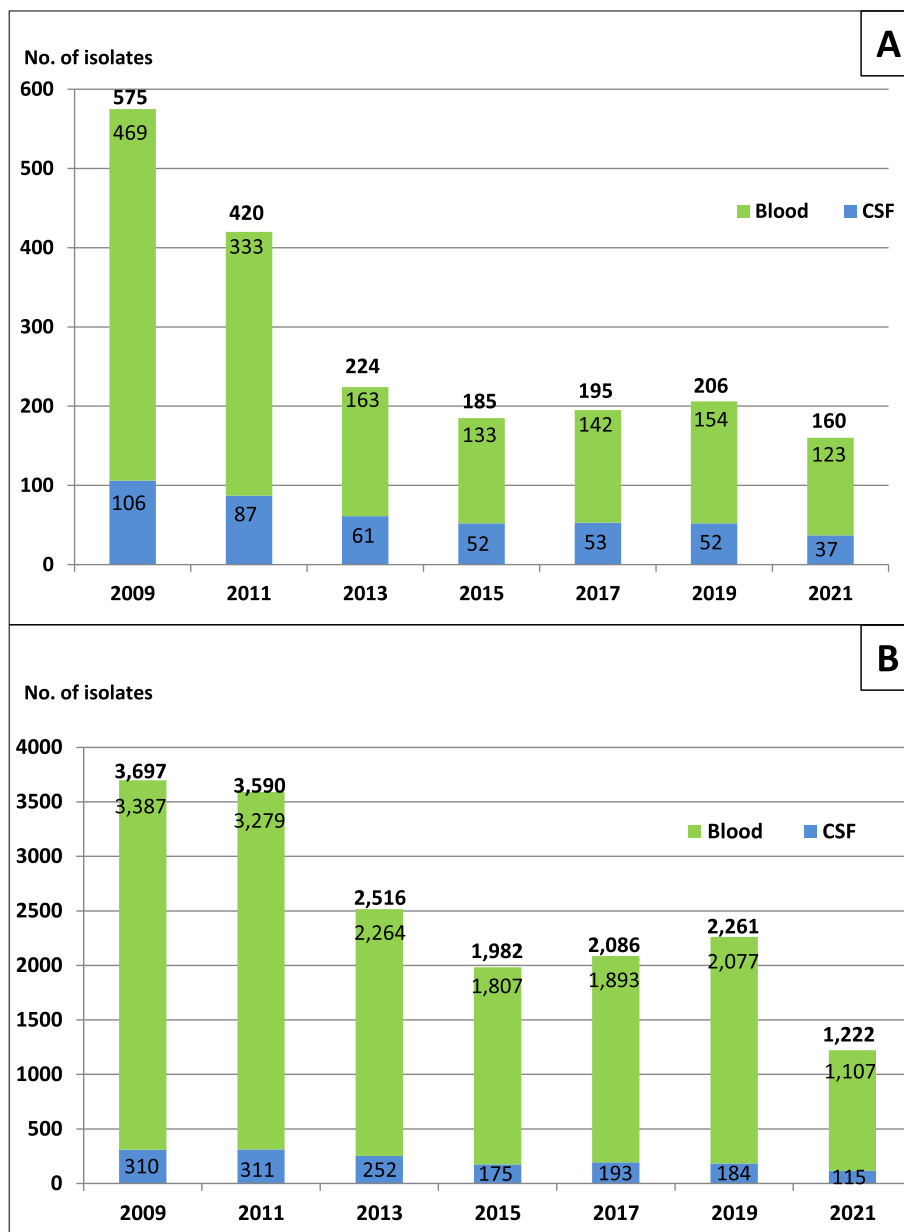


Fig. 2. Evolution between 2009 and 2021 of the number of pneumococcal strains isolated from cerebrospinal fluids (in blue) and blood cultures (in green), A: in children; B: in adults. Data from the Regional Pneumococcal Observatories network, France.

Concerning serotypes 8, 9N, 10A, 11A, 15A, 15B/C 23B, 24F and 33F, known as “emerging” in children and/or in adults during the study period, the frequency of decreased susceptibility to AMX or CTX was low, with the exception of serotype 11A.

4. Discussion

The surveillance of strains involved in IPD is essential to assess the impact of pneumococcal vaccination, adapt the vaccine formula according to emerging serotypes and, if necessary, change the recommendations for the management of these infections according to the evolution of resistance. In conjunction with the National Reference Center for Pneumococci and the French agency of Public Health, the ORPs constitute an essential nationwide network, monitoring the evolution of resistance and the distribution of pneumococcal serotypes. The stability of the collection of strains observed within each ORP illustrates the constant participation of

the laboratories associated with the various coordinating centers of the surveillance network and is a guarantee of its quality.

Our study included 12 years of data, with constant participation of laboratories linked with the coordinating centers of the surveillance network, and with trained and stable data collectors. The stability of the strain collection procedures renders our data comparable over the years. However, we collected the data only every two years (odd years), instead of annually. Nevertheless, this is unlikely to have affected the long-term trends monitored in this study.

Between 2015 and 2021, a significant increase in the frequency of PDSPs was observed among pneumococcal strains isolated from CSF and blood culture, both in adults and in children. Moreover, a significant increase of pneumococcal strains not susceptible to CTX (MIC ≥ 0.5 mg/L) was also observed in CSF and blood culture from adults. The change of technique for determining MICs (from dilution in agar medium until 2015 to microdilution in a liquid med-

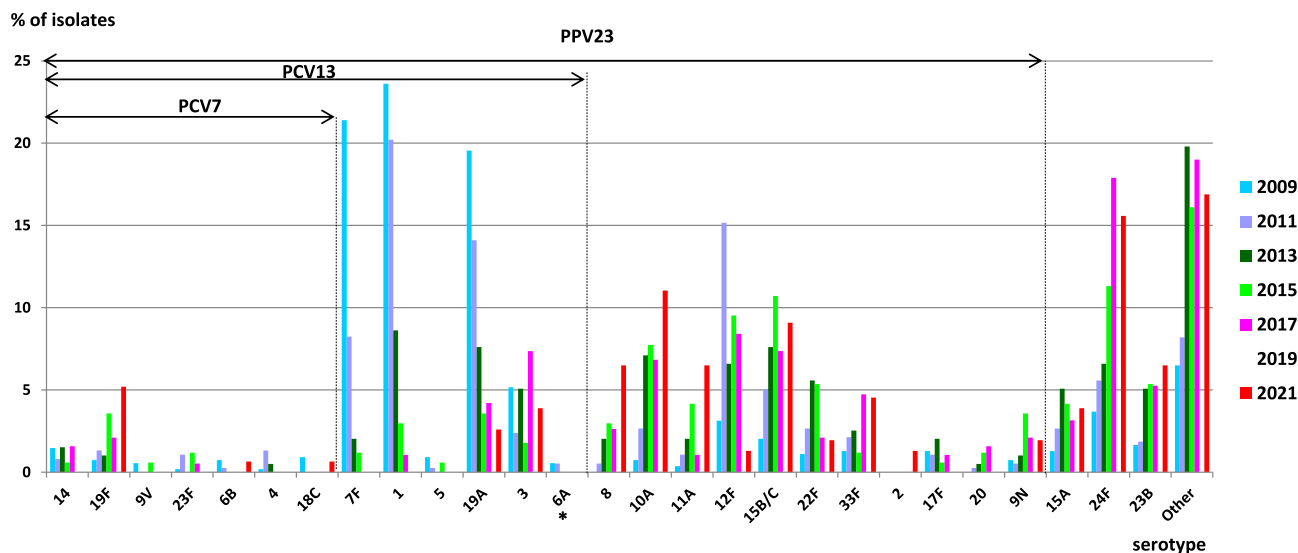


Fig. 3. Distribution of serotypes of pneumococcal strains isolated from invasive infections (CerebroSpinal Fluid + Blood) in children in 2009 ($n = 542$), 2011 ($n = 376$), 2013 ($n = 197$), 2015 ($n = 168$), 2017 ($n = 190$), 2019 ($n = 194$) and 2021 ($n = 154$). *: serotype not included in the PPV23 vaccine.

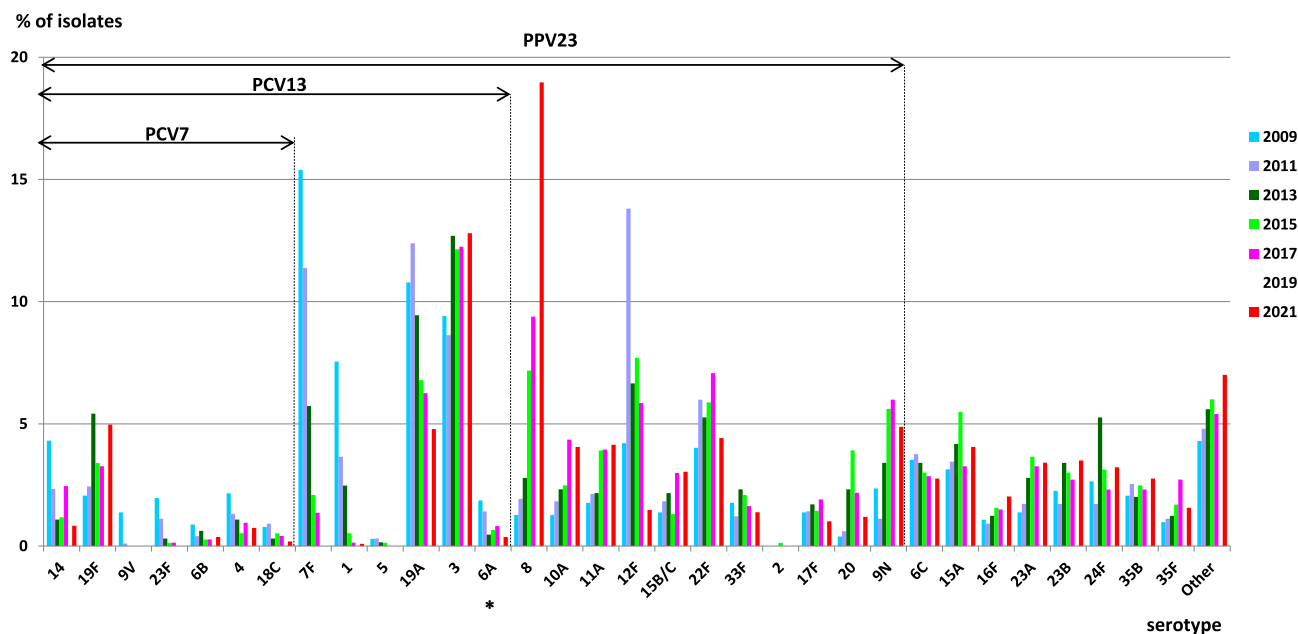


Fig. 4. Distribution of serotypes of pneumococcal strains isolated from invasive infections (CerebroSpinal Fluid + Blood) in adults in 2009 ($n = 1,020$), 2011 ($n = 985$), 2013 ($n = 646$), 2015 ($n = 766$), 2017 ($n = 735$), 2019 ($n = 768$) and 2021 ($n = 1,134$). *: serotype not included in the PPV23.

ium) does not seem to be involved, as the increase was only observed for benzylpenicillin. This trend will be worth monitoring in the coming years. AMX and CTX (or ceftriaxone) therefore remain the reference molecules in France for the treatment of pneumonia and meningitis, respectively. Regarding the alternative to β -lactams, e.g., in case of confirmed allergy, if the proportion of strains resistant to macrolides remained high (around 25%), resistance to fluoroquinolones remained very low, and resistance to pristinamycin, evaluated only from 2017, was likewise very low.

Between 2009 and 2021, regular monitoring by the ORP network revealed a significant decrease in the number of pneumococcal strains isolated from invasive infections, whether for children or adults. However, this decrease was observed mainly between 2009 and 2013 and can be largely explained by the introduction of the PCV13 vaccine in June 2010 [12,16]. This decrease is in agreement with the observations of Ouldali *et al.* who showed a

decreased incidence rate of invasive pneumococcal infections in France from 0.78 cases per 100,000 inhabitants in 2010 to 0.52 at the end of 2014 [3]. These observations were in line with those reported in other European countries that have introduced the PCV13 vaccine, such as Denmark, which observed a 21% drop in the incidence in its population of invasive pneumococcal infections [17], England or Germany [18,19].

The decrease in the number of pneumococcal strains isolated was also associated with a significant change in the distribution of serotypes over the study period, resulting in the near-disappearance of PCV13 vaccine serotypes, with the notable exception of serotype 3. The reason for the lower effectiveness of PCV13 against serotype 3 remains unclear.

To conclude, in 2021, only 23.6% of the strains responsible for invasive infections had a serotype included in PCV13, compared to 64.8% in 2009. In children, the percentage of PCV13 vaccine

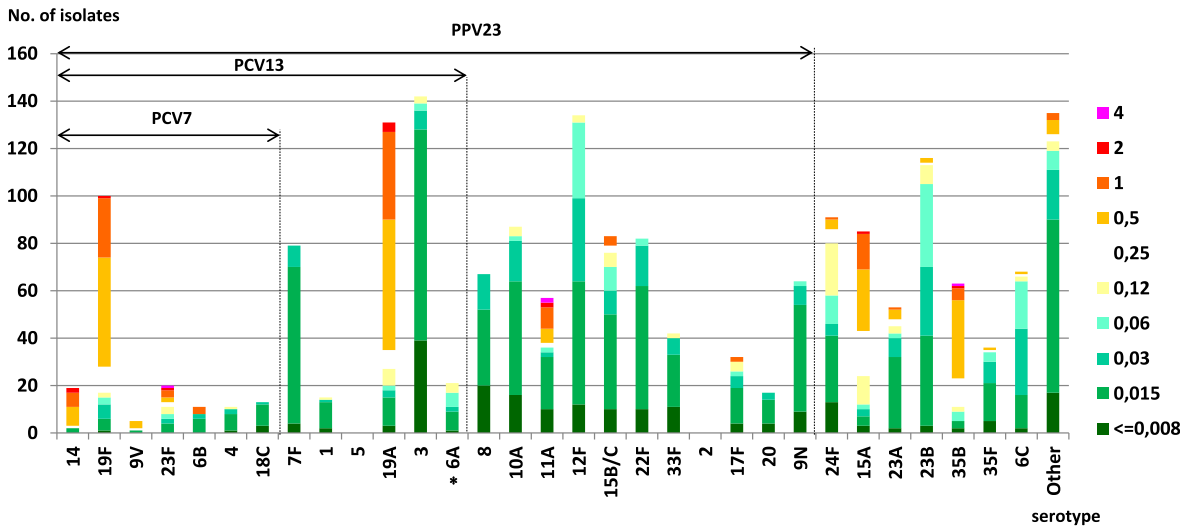


Fig. 5. Distribution of serotypes of pneumococcal strains isolated from cerebrospinal fluid between 2009 and 2021 (n = 1889), according to minimal inhibitory concentration (mg/L) of cefotaxime. *: serotype not included in the PPV23.

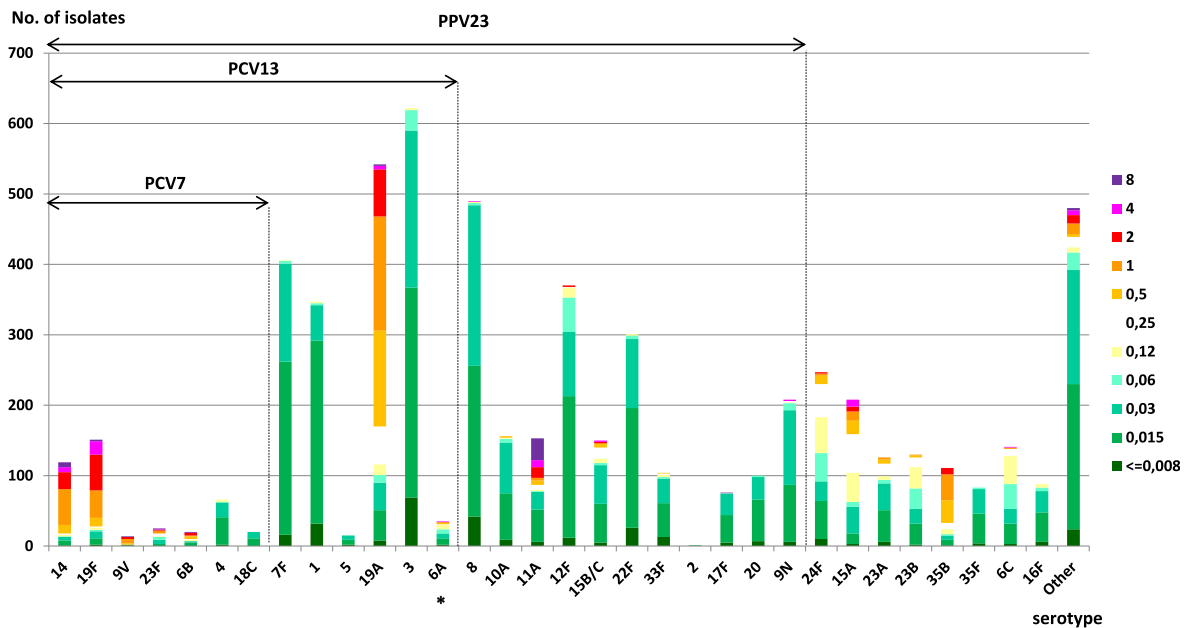


Fig. 6. Distribution of serotypes of pneumococcal strains isolated from blood cultures between 2009 and 2021 (n = 6113), according to the minimal inhibitory concentration of amoxicillin. *: serotype not included in the PPV23.

strains fell very sharply, from 76.0% in 2009 to 13.0% in 2021. These observations were corroborated by data from the SpIDnet study (*Streptococcus pneumoniae* Invasive Disease network) on the evolution of the circulation of pneumococcal serotypes in children in 8 European countries [20]. In adults, Hanquet *et al.* observed a decrease in the incidence rate of IPD due to PCV13-vaccine strains in 10 European countries, while non-vaccine strains emerged [21]. The same observation applied to the serotype coverage of PVV23, recommended in patients at risk; in 2021, 66.1% of IPDs in adults were due to a serotype included in this vaccine, as opposed to 79.4% in 2009. However, vaccination program in children less than 2 years led to the emergence of non-vaccine serotypes, such as serotypes 8, 10A, 15B/C and especially 24F, in children, as well as serotypes 8, 9N, and 10A, in adults. This was also observed in other countries providing PCV13 vaccination [22]. Therefore, epidemiological monitoring of pneumococcal serotypes responsible for IPD

remains critical. The upcoming availability of two conjugate vaccines, one with 15 serotypes (adding the 22F and 33F serotypes to the PCV13 serotypes), the other with 20 serotypes (adding the 8, 10A, 11A, 12F, 15B, 22F and 33F to the PCV13 serotypes) will be very interesting from an epidemiological point of view [23]. According to our data, in 2021, 56.9% of IPDs in France were linked to a strain of serotype included in the future PCV20 and 27.4%, to a strain of serotype included in the future PCV15.

5. Conclusion

The ORP, in conjunction with the National Reference Center for Pneumococci and Public Health France, constitute an essential national network for the surveillance of invasive pneumococcal infections. Indeed, the success of this surveillance is based on a

structured and stable network over the long term, whose geographical representativeness is almost nationwide, with trained and dedicated participants monitoring trends in antibiotic resistance, the evolution of the distribution of serotypes and the emergence of serotypes. The data provided by the ORP assess the epidemiological impact of vaccination in France. The data are useful not only insofar as they contribute to the composition of future vaccines but also insofar as they help to change, if necessary, IPD management recommendations according to the evolution of resistance. All in all, widespread surveillance remains critical, as *S. pneumoniae* infections remain, by their frequency and severity, a major public health issue.

Authors' contributions

All authors affiliated to the Regional Pneumococcal Observatories collected the *Streptococcus pneumoniae* strains from the laboratories participating in their observatory and performed antibiograms. JB, CC, AEM and EV performed serotyping. CG, AL and SL managed data. CP, MCP, EV and MK drafted the article. All authors performed article review and edited the final manuscript.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MK reports grants from Pfizer and MSD to present the results in the congress 23rd *Journées Nationales d'Infectiologie* congress held in Bordeaux from 15 June to 17 June 2022. EV reports grants from Santé Publique France, Pfizer, and MSD, outside of the submitted work. The other authors declare that they have no competing interest concerning this article.

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