Biennial Report

Typing & Antimicrobial Susceptibilities of isolates causing Invasive Pneumococcal Disease (IPD) in Ireland – Results from 2022-2023

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Executive Summary

Streptococcus pneumoniae is a bacterial pathogen which can lead to severe invasive infections including invasive disease. Invasive pneumococcal disease (IPD) is a legally notifiable disease in Ireland. This report summarises the results from IPD isolates submitted to the Irish Meningitis and Sepsis Reference Laboratory (IMSRL) for typing from 2022 and 2023 and compares the serotype distribution and disease epidemiology to previous years.

The number of IPD isolates typed increased in 2022 and 2023 (*n*=305 and 379) in comparison to 2020 and 2021 but were similar to previous years (*n*=267-448 for 2008-2019). The highest incidence of IPD was observed in 2018 (*n*=448) which coincided with a high influenza season in 2017-18 [1]. This was followed by a decline in 2020 and 2021 (*n*=181 and 160, respectively) which was associated with the emergence of the SARSCoV-2 (COVID-19) pandemic and lockdown measures [2]. International surveillance suggested that changes in practice such as mask wearing and reduced social mixing, reduced the transmission of respiratory pathogens such as *S. pneumoniae*. However, during the past two years, there has been a resurgence in the number of IPD cases typed annually in Ireland and elsewhere.

In 2021-2022, two new pneumococcal conjugate vaccines (PCV15 and PCV20) were approved for use in adults by the European Medicines Agency (EMA). Both vaccines were approved for use in children more recently, PCV15 in November 2022 and PCV20 in March 2024. While these are not part of the current vaccine schedule in Ireland, the vaccine-serotype coverage (i.e. potential protection) offered by the current and future vaccines is examined in this report. Most PCV13 serotypes have declined following the introduction of the vaccine with the exception of serotypes 19A and 3, which have persisted in children and adults and serotype 4, which has re-emerged in adults and is covered in both PCV7 and PCV13.

Serotype replacement has also been observed. Some of the non-PCV13 serotypes that have emerged in recent years, such as serotypes 22F, 33F are covered in both vaccines PCV15 and PCV20, and serotypes 8, 10A and 15B/C, which are covered in PCV20. However, other serotypes such as 23B, which is not covered in the current or newly approved vaccines has become a predominant serotype in children and are also associated with antimicrobial resistance.

The recent changes in serotype epidemiology and the continual emergence of non-vaccine serotypes highlight the vital role of national surveillance of IPD to assess the effectiveness of the current vaccines and potential impact of additional vaccines that have recently been approved for use in Europe.

Background

The bacterium

Streptococcus pneumoniae is a major cause of life-threatening infections such as meningitis and bloodstream infection, i.e. invasive pneumococcal disease (IPD). Pneumonia remains a leading cause of death in children worldwide and accounts for up to 14% of deaths of children < 5 years of age [3]. *S. pneumoniae* is the leading bacterial pathogen associated with pneumonia in this cohort. The population groups at highest risk of pneumococcal infection are young children and the elderly [4]. The Centres for Disease Control and Prevention (CDC) in the USA estimate that the mortality rate due to IPD is much greater in adults ≥65 years of age (18/100,000 population) than in children <2 years (0.4/100,000) in the post vaccine-era [5].

S. pneumoniae is a successful pathogen in part due to the diversity of the circulating capsular serotypes. The continued identification of new serotypes based on the chemical composition of the polysaccharide capsule, indicates that over 90 immunologically distinct serotypes exist [6]. Immune responses elicited by current pneumococcal vaccines are also directed towards the polysaccharide capsule [7]. The conjugate vaccines were developed to reduce the burden of the predominant serotypes circulating in paediatric populations at the time of development. However, serotype prevalence data varies depending on patient demographics, vaccination schedules and the geographical area. Therefore, it is critical that IPD clinical notification, laboratory surveillance including serotype and antimicrobial resistance data, are continually monitored at a national and international level to inform vaccine and antimicrobial use and policies.

Laboratory surveillance

The National IPD surveillance programme is a collaborative project between the Royal College of Surgeons in Ireland (RCSI) Education and Research Centre, the Health Protection Surveillance Centre (HPSC) and The Irish Meningitis and Sepsis Reference Laboratory (IMSRL), based at Children's Health Ireland (CHI) at Temple Street. The programme was established in April 2007 to provide reference laboratory support for the investigation of IPD in advance of the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) in 2008. However, continual changes in serotype epidemiology and the potential introduction of new conjugate vaccines have meant that IPD surveillance remains an essential component of public health surveillance.

The vaccine schedule in Ireland

In September 2008, PCV7 was introduced to the Irish infant immunisation schedule at 2, 6 and 12 months of age. A catch-up programme was offered to children who were < 2 years of age at that time. The PCV7 vaccine offered protection against seven serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, which were commonly associated with invasive disease in children at that time. In December 2010, PCV7 was replaced by the 13-valent pneumococcal conjugate vaccine (PCV13), which offers protection against six additional serotypes; 1, 3, 5, 6A, 7F and 19A. In December 2016, the schedule for children born on or after October 1st, 2016 was changed to a dose of PCV13 at 2, 6 and 13 months. This was done to accommodate vaccination with the newly introduced *Neisseria meningitis* type B vaccine at 12 months.

The uptake of PCV and some other paediatric vaccines has declined in recent years. In quarter two of 2023, the uptake of three doses of PCV13 by 24 months was recorded at 82.2% in comparison to an uptake peak of 92.5% in quarter four of 2015 [8]. A 23-valent polysaccharide vaccine (PPV23) is recommended for adults ≥65 or for high-risk adults <65 years with immunosuppressive conditions or co-morbidities. However, PPV23 uptake in adults in Ireland is low (27-36%) in comparison to the paediatric schedule, based on data collected by the Health Protection Surveillance Centre HPSC in 2013 [8,9]. As a result, it is difficult to assess any impact PPV23 may have had on serotype epidemiology in Ireland. Since 2015, a single dose of PCV13 prior to PPV23 administration is recommended for those with immunosuppressive conditions or co-morbidities. All vaccine information is available on http://www.hse.ie/eng/health/immunisation/hcpinfo/guidelines/chapter3.pdf. **Table 1** summarises vaccines approved for use against IPD. Two new pneumococcal conjugate vaccines (PCV15 and PCV20) were recently approved for use by the European Medicine Agency (EMA). While these are not part of the current vaccine schedule in Ireland, the vaccine-serotype coverage (*i.e.* potential protection) offered by the current and future vaccines is examined in this report.

Table 1: Summary of Pneumococcal Vaccines currently approved for use

Type	Serotypes	Introduced	Schedule	Uptake
PCV7	4, 6B, 9V, 14, 18C, 19F and 23F	Sept 2008	2, 6 and & 12 months. Catch up for those < 2 years.	82-92% from 2015-2023 [8]
PCV13	PCV7 + 1, 3, 5, 6A 7F and 19A	Dec 2010	2, 6 and 13 months. No catch up.	
PPV23	PCV13* + 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F (**excluding 6A*)	Recommended since 1980s	Those ≥65 years of age. Additional 1 dose of PCV13 for high-risk adults i.e. immunosuppressive conditions, co-morbidities (Aug.2015)	27-36% from 2013 report [9]
PCV15	PCV13 and 22F + 33F		Not currently part of the Irish vaccination schedule. Approved for use in adults in December 2021 and children in November 2022.	
PCV20	PCV13 and 8, 10A, 11A, 12F, 15B, 22F + 33F		Not currently part of the Irish vaccination schedule. Approved for use in adults in February 2022 and children in March 2024.	

1. Methods

Invasive *S. pneumonia*e isolates (from blood, cerebrospinal fluid and other sterile sites) are referred by clinical microbiology laboratories throughout the Republic of Ireland to the IMSRL. Typing is performed using a combination of serological co-agglutination using antisera from the Statens Serum Institute and multiplex PCR, as previously described [10]. Susceptibility to antimicrobials is assessed using Broth Micro Dilution (BMD) using the Sensititre system (Thermo Fisher Scientific), and the results are interpreted using the European Union Criteria for Antimicrobial Susceptibility Testing (EUCAST) criteria [11]. The EUCAST breakpoints of MIC >0.06 µg/ml for penicillin, >0.5 µg/ml for cefotaxime and >0.25 µg/ml for erythromycin were considered as non-susceptible [11]. Typing based on whole genome sequencing (WGS) analysis is performed on isolates in batches periodically, however, serology is still considered the gold standard for definitively serotyping *S. pneumoniae.*

Due to the COVID-19-related fall in IPD (particularly 2020-2022), in some instances when comparing the serotype trends, the results are presented as a percentage of proportion of IPD cases typed within that period, in addition to absolute numbers or incidence rates. Incidence rates represent the incidence rates (IR) of typed isolates referred to the IMSRL using data from the 2022 census of the population (http://www.cso.ie/en/census/) and rates are expressed as the number of serotyped isolates from cases per 100,000 population (/100,000). This has resulted in minor differences in incidence rates calculated in comparison to previous annual reports which used 2016 census data, which have now been revised. The results presented in this report may differ from the number of notifiable cases reported through Computerised Infectious Disease Reporting (CIDR) to the HPSC, which may also include IPD cases that are confirmed by PCR only with no culture available. They may also include cases that were culture positive but isolates were not referred to the reference laboratory for typing.

2. Results

Overall number of isolates

More *S. pneumoniae* isolates were referred for typing in 2022 (*n*=340) and 2023 (*n*=416) in comparison to the COVID pandemic period of 2020-2021 during which the numbers had declined (*n*=180, *n*=202 respectively). Overall, the numbers in 2022-2023 have returned to what was observed in previous years (range of *n*=268-457 from the 2008-2020 surveillance period). Duplicate isolates from different sites from the same patient i.e. blood and cerebrospinal fluid (CSF), repeat isolates from the same patient, multiple isolates from one patient but referred from different hospitals, or multiple isolates from the same patient within the same week were typed, and reported to the referring laboratory, but are not included in the summary of this report. Once all duplicate isolates and non-invasive query isolates were removed, the total number of typed IPD isolates (based on sample taken/isolation date) was compared with other years using the same criteria. The number of IPD

isolates typed in 2022 and 2023 were *n*=305 and *n*=379 in comparison to *n*=374, *n*=181 and *n*=160 in 2019, 2020 and 2021, respectively.

The number of isolates per sample patent group, sample type, quarter and geographical region

Similar to previous years, in 2022 and 2023, 57-58% of the isolates typed were from male patients, with most samples being from blood (*n*=95-98%) followed by CSF samples (1-2%) and other sterile sites (1-4%). As indicated in **Figure 1**, the number of isolates typed in 2022 and 2023 (*n*=305, *n*=279, respectively) was much greater than the pandemic period of 2020 and 2021 (*n*=181, *n*=160 respectively) but was similar to what was observed in previous years, prior to the COVID-19 pandemic. The largest decline in samples was observed in quarter 1 (January to March) of 2021 (*n*=22) and quarter 2 (April to June) of 2020 and 2021. However, by quarter 2 of 2022 onwards, the number of IPD cases was back to pre-pandemic levels. Quarter 4 of 2022 was the busiest quarter for receipt of IPD samples (*n*=122), with a range of 70-119 samples received during this period in previous years from 2008-2019 and a notable drop during 2020 (*n*=32). The results indicate that the number of infections and seasonality of the disease have both returned to what was observed previously, with quarter 1 and 4 accounting for the greatest disease burden.

The number of isolates typed per Health Service Executive (HSE) Region[1] based on referring hospital location is displayed in **Figure 2**. The largest proportion of isolates were received from the three regions including Dublin, Dublin and Midlands region, Dublin and North East and Dublin and South East Regions which is reflective of population demographics. Overall there was limited change in the distribution of IPD isolates typed within the regions over the extent of this surveillance.

[1] HSE Region breakdown information is available on https://about.hse.ie/health-regions/

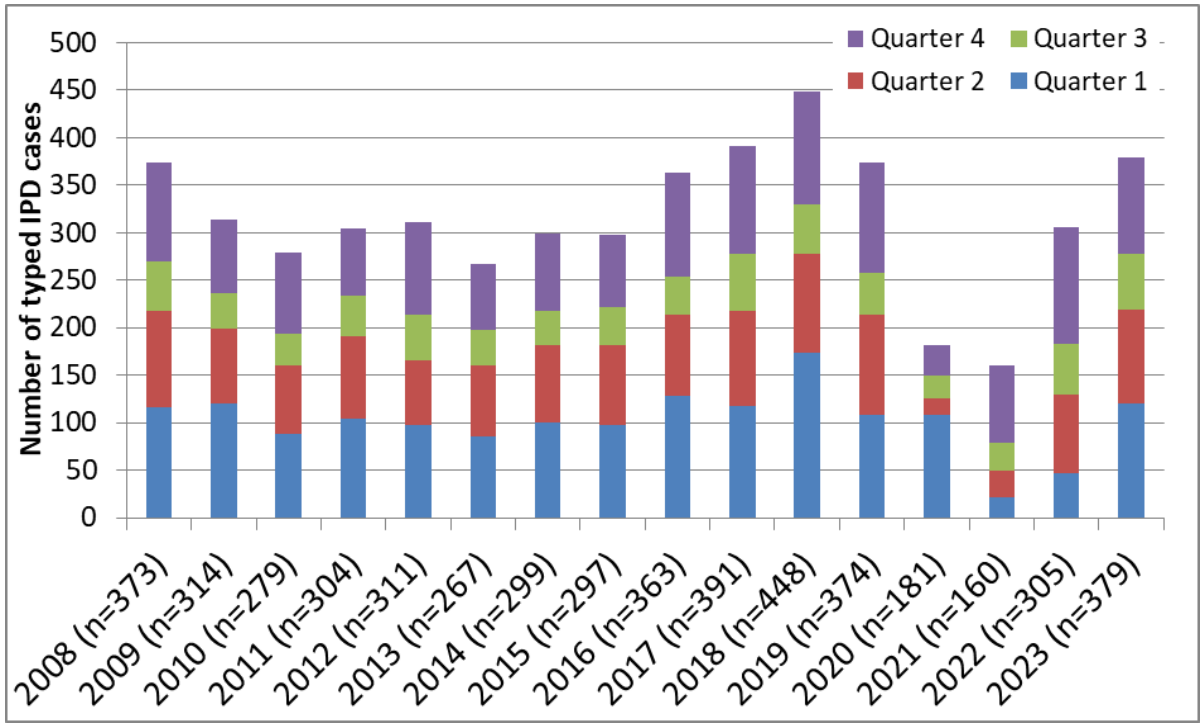


Figure 1. Number of IPD isolates in all patient age groups typed per quarter from 2008 to 2023

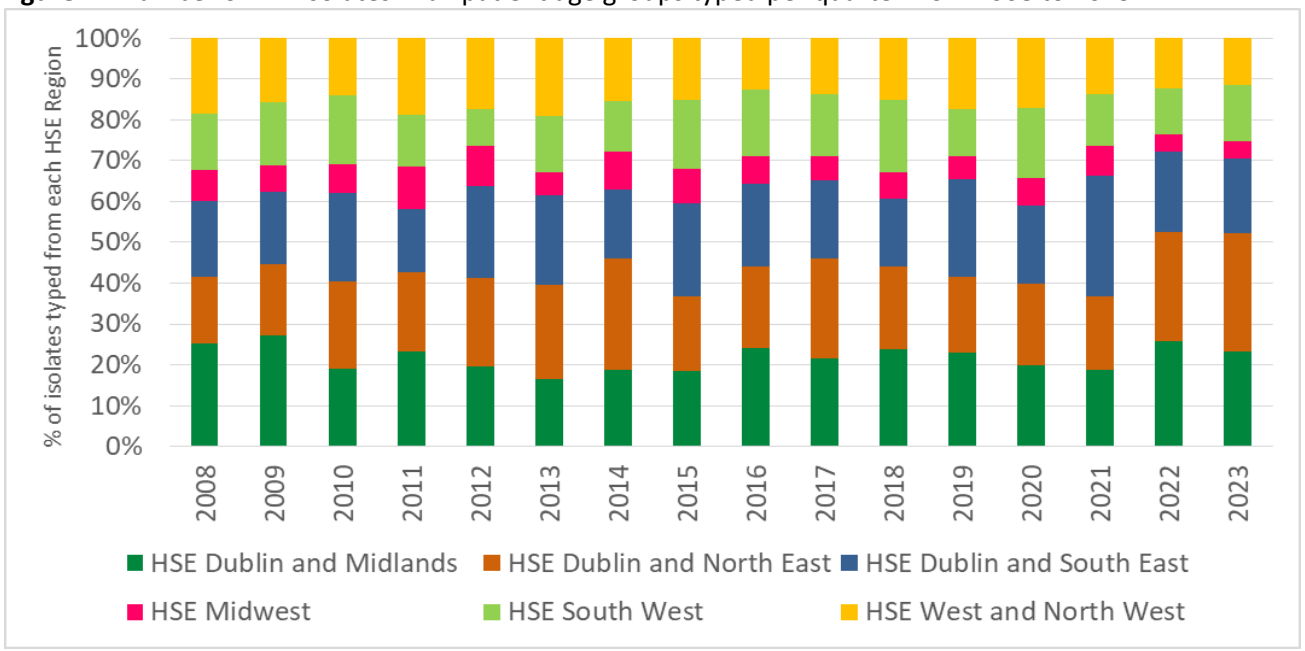


Figure 2. Percentage of typed IPD isolates from each HSE area and from 2008 to 2023.

The number of isolates in each age group

The number of IPD cases fell in Ireland during the pandemic, similar to what was observed elsewhere [2]. However, as clearly indicated in **Figure 3A** the number of typed IPD cases in 2022 and 2023 have returned to pre-pandemic levels. The long-term impact of COVID-19 and the resurgence of particular respiratory diseases remains under investigation as part of the global collaborative project with other reference laboratories (https://pubmlst.org/projects/iris).

Adults aged ≥65 years of age and children < 2 years of age, have the highest IPD disease burden in comparison to other age groups (**Figure 3B**). Interestingly, these two age groups had the largest drop in incidence rate during the pandemic and recovered in 2022 and 2023, whereas for the other age groups (2-4 years, 17-34 years and 35-64 years) the IPD incidence remained relatively unchanged. Based on incidence rates (IR per 100, 000), adults ≥65 years of age remain at highest risk of IPD with an incidence rate of 24.7/100,000 in 2023 (**Figure 3B**). While this represents a decline in comparison to previous years (IR=36.5/100,000 in 2018 when there was a high disease burden in all age groups), its likely to continue to increase in the coming years, particularly as this age group had the most notable decline during the pandemic and subsequent resurgence in incidence. The specific serotypes associated with this resurgence are discussed further in this report.

After older adults, the next highest incidence rate was observed in children < 2 years of age (IR=14.0/100,000 in 2022 and 2023). As observed in **Figure 3B**, the introducing PCV7 (2008) and PCV13 (2010) into the paediatric vaccination schedule had the greatest impact on this age group. The incidence rate in children < 2 years of age ranged from a peak in 2008, IR=34.7/100,000 (year PCV7 was introduced) to the lowest rate of IR=9.2/100,000 in 2015, prior to the pandemic decline (IR=7.9-8.5/100,000 in 2020 and 2021). The third highest disease incidence was in children aged between 2-4 years of age, which ranged from IR=10.1/100,000 in 2009 to IR=7.2/100,000 and IR=4.5/100,000 in 2022 and 2023, respectively.

Based on the incidence rate trends, IPD rates in children aged 2-4 years and those aged 5-16 were not impacted by the pandemic as much as older adults. This was also confirmed when the proportion of cases per age group (as percentage of total received) was examined. Based on **Figure 3C** those aged < 16 years of age represented 12-14% of all IPD cases in 2020-2021, in comparison to 11-12% in 2022 and 2023 and 11% of cases in the post-PCV13 vaccine era (2010-2019). However, there has been a recent increase in IPD in older children, in 2023 specifically. The number of cases doubled in those aged 5-16 years of age from 9 cases in 2022 (3% of total IPD) to 18 cases in 2023 (5% of IPD). IPD in this age group accounted for 2-3% of IPD cases in previous years, including during the pandemic. There was also an increase in antimicrobial resistance in children which is discussed further in this report.

The proportion of cases from those ≥65 years of age was lower in 2020 (47%) and 2021 (41%) but has increased to 48-53% in 2022 and 2023, which is similar to previous years when ≥50% of the IPD cases were from adults ≥65 years of age.

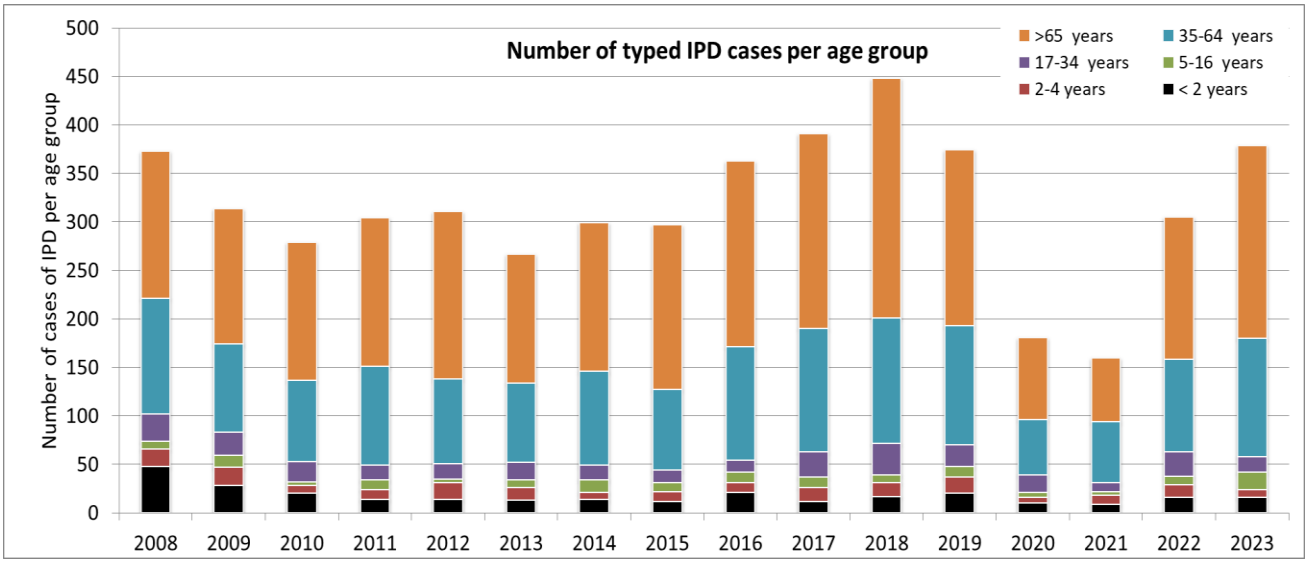


Figure 3A. Number of IPD isolates typed based on patient age from 2008-2023

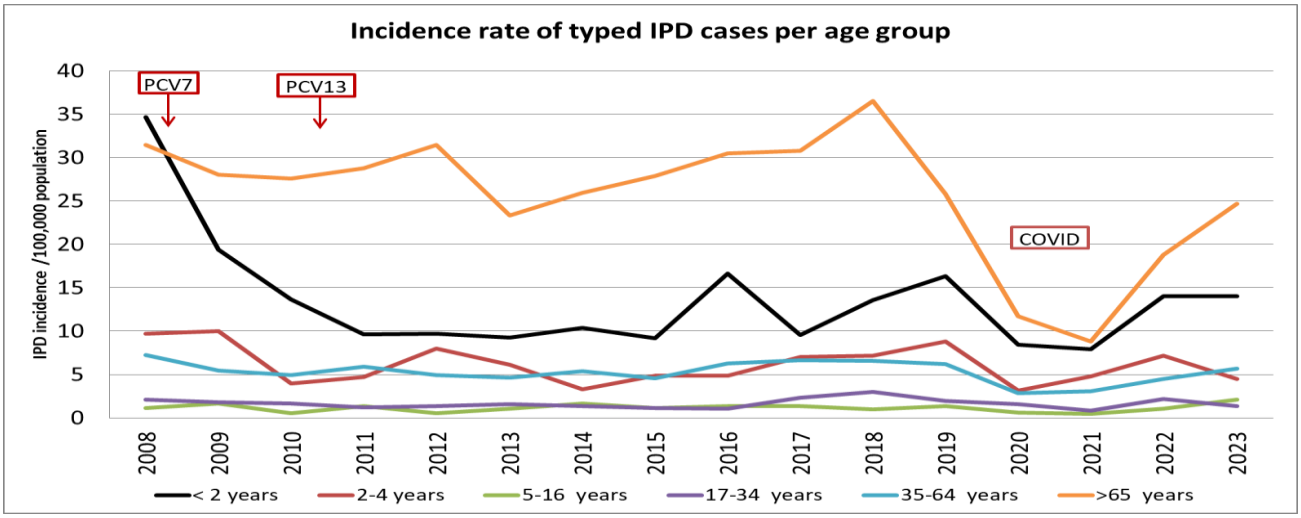


Figure 3B. Incidence Rate of typed IPD isolates based on patient age from 2008-2023

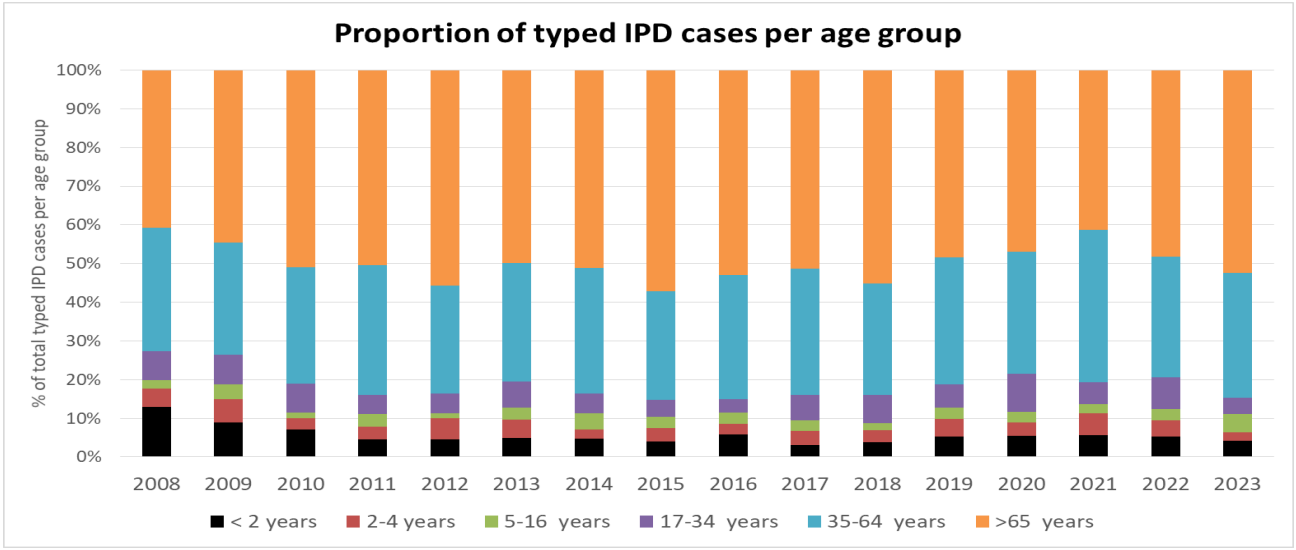


Figure 3C. Proportion of IPD isolates typed based on patient age from 2008-2023

The distribution of predominant serotypes associated with disease in all age groups

The leading serotypes in 2022 and 2023 included serotypes 8 (*n*=50, 64; 16% and 17% in 2022 and 2023 respectively), 3 (*n*=34, 41; 11% both years), 19A (*n*=35, 38; 10%, 11%), 9N (*n*=6, 30; 2%, 8%) and 4 (*n*=27, 27; 9%, 7%). **Figure 4A** displays the number of isolates typed in relation to PCV7 and PCV13-7 serotypes (i.e. the serotypes that are included in PCV13 but not PCV7). As displayed, PCV13-7 serotypes 3 and 19A are persistently associated with disease, despite a decline in the numbers in 2020 and 2021, when there was an overall decline in IPD. These two serotypes have been consistently responsible for 15-20% of typed IPD cases in Ireland annually. There were limited isolates associated with the other PCV13-7 serotypes, including serotype 1 (*n*=1 case 2016), serotype 5 (*n*=1 case 2019), serotypes 6A or 7F (*n*=2, 3 cases, respectively in 2019).

There has, however, been an increase in the number of PCV7 serotypes associated with disease, including serotype 19F (*n*=12, 11 in 2022 and 2023, respectively, representing 3% of cases in 2022 and 2023) and particularly serotype 4. Serotype 4 was a predominant serotype when PCV7 was introduction in 2008 (*n*=34) with a rapid decline observed in subsequent years with one to five cases annually from 2016-2019, but there was a sharp increase in 2022 (*n*=27, 9% of IPD cases) and 2023 (*n*=27, 7% of IPD cases). The age demographic is of interest, as aside from one case in a child in 2022, since 2010, all other serotype 4 cases have been in adults, with the highest proportion in adults aged 35-64 years. Of the 27 cases in 2022, 19 cases (70%) were in those aged 35-64 years of age and three cases (11%) in those ≥65 years of age. Similarly in 2023, 14 cases (52%) were in those aged between 35-64 years and 10 cases (37%) were in those ≥65 years of age. This represents a large increase in both age groups, which would have had one to four cases of serotype 4 annually post PCV7 introduction.

The resurgence of serotype 4 in adults is of concern as this PCV13 vaccine preventable serotype has not re-emerged in children, therefore suggesting another reservoir of disease resulting in this increase and limited herd immunity. Increased incidence of serotype 4 has been reported elsewhere in the United Kingdom [12], Northern Europe [13], the United States [14] and Canada [15]. Most Irish isolates with sequence data available to date (*n*=13/14, 93%) clustered into the Global Pneumococcal Sequencing Cluster (GPSC) 162 and Multi Locus Sequence Type (ST) ST801 and with one clustering into GPSC27 ST205. This is very similar to recent findings in the UK, which also found that GPSC162 was responsible for 93% of serotype 4 cases in 2022-2023 [12]. GPSC162 has also been linked with outbreaks in shipyards in Norway, Finland and Northern Ireland [13]. WGS data of the shipyard strains indicated that the diversity of GPSC162-ST801 strains within the outbreaks could not be explained by recent transmission alone, suggesting that harsh environmental and associated living conditions, such as those reported among shipyard workers, may facilitate invasion of this serotype [13]. The increase in

serotype 4 in the USA and Canada was significantly associated with those experiencing homelessness and in these countries the serotype 4 cases were associated with sequence types (ST) ST10172, ST244, and specifically ST695 in the USA [14], and ST244, ST205 and ST695 in Canada [15].

Some vaccine replacement serotypes have also emerged in recent years, these include serotype 22F and 33F (which are included in PCV15 and PCV20) and serotypes 8, 10A, 11A, 12F and 15B/C which are included in PCV20 only, which is displayed in **Figure 4B**. It is possible that changing to a higher valency vaccine could reduce the incidence of these serotypes, particularly serotype 8, which is covered in PCV20 and which accounted for 16-17% of IPD cases in 2022 and 2023 (*n*=50/305, 64/379) and up to 30% of IPD cases (n=55/181) in 2020.

The increase in serotypes not covered in the current or broader PCVs that have recently been licensed also requires close monitoring. **Figure 4C** displays the predominant non-PCV20 serotypes (*i.e.* serotypes not covered in PCV20, PCV15, PCV13 nor PCV7). In 2023, there were 22 different non-PCV20 serotypes associated with IPD including two non-typable (NT) strains. The two leading non-PCV20 serotypes were serotype 9N (*n*=30, 8% of IPD in 2023) and serotype 23B (*n*=18, 5% of IPD in 2023). In recent years, serotype 23B has become a prominent non-vaccine type in paediatrics, rather than adults where in contrast there are a number of different non-vaccine serotypes that fluctuate each year. Because of the continual change in predominant serotypes associated with IPD, particularly in adults, consistent reviewing of epidemiological data to further understand the protection offered by the current vaccines and the potential protection offered future vaccines is required.

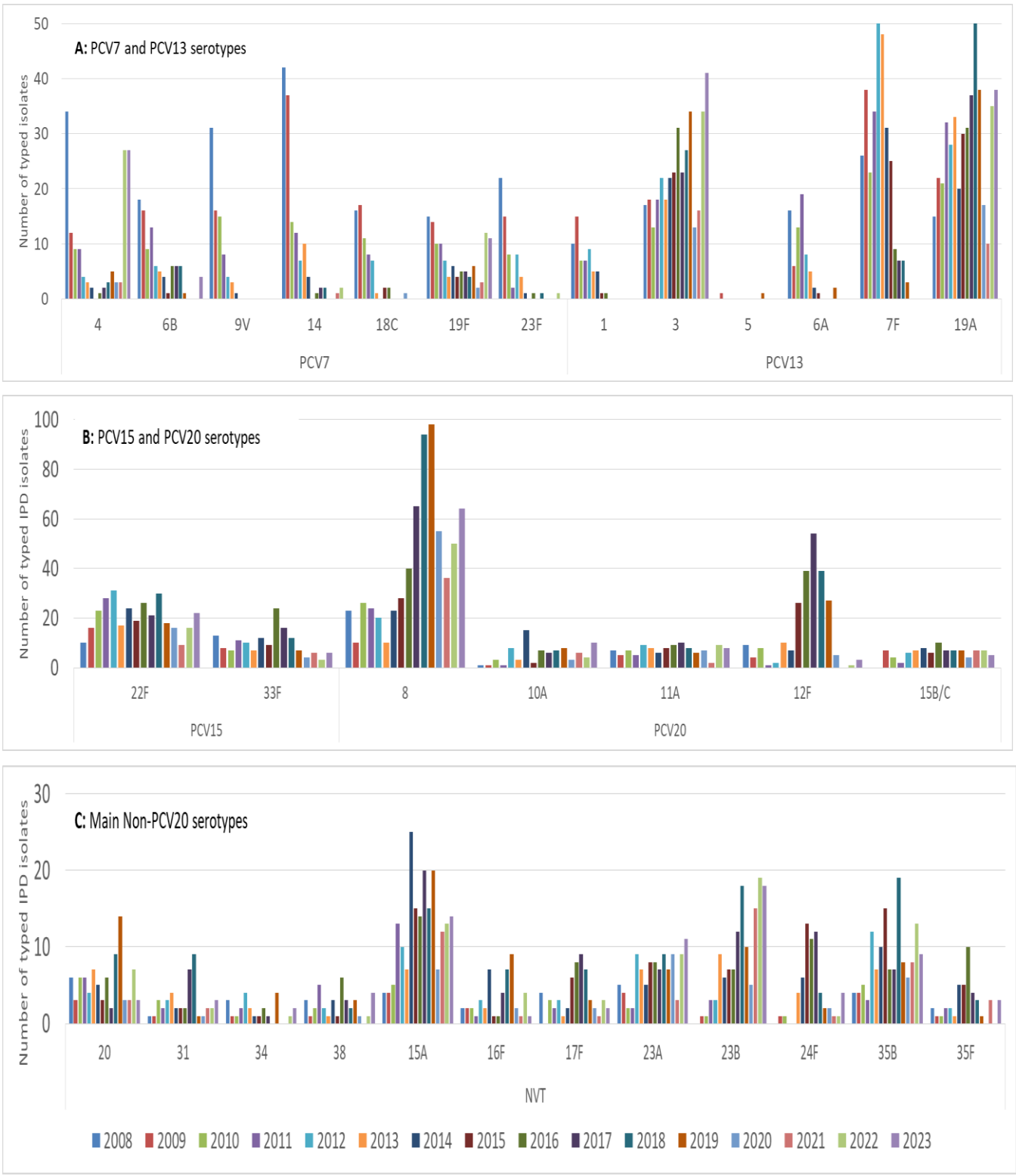


Figure 4A-C. Main serotypes associated with IPD in all age groups based on associated pneumococcal conjugate vaccines; **4A** displays the serotypes covered in PCV7 and PCV13; **4B** displays the additional serotypes covered in PCV15 and PCV20) and **4C** displays the serotypes not covered with any of the current conjugate vaccines (i.e. non-PCV20 serotypes) from 2008-2023

IPD and the distribution of serotypes amongst children

The number of typed IPD cases in children ≤ 16 years of age increased in 2022 (*n*=38) and 2023 (*n*=42) after a decline in 2020 and 2021 (*n*=21, 22 respectively). The number of PCV7 serotypes has remained low in this population (*n*=2, 1) and accounted for 2-5% of cases in children in 2022 and 2023 as displayed in **Figures 5A** and **5B**. These three isolates were serotypes 4 (*n*=1) and 19F (*n*=2), with two of the three cases were in children too young to be fully vaccinated based on age (< 13 months old), the third case (serotype 19F) was in a child aged 2-4 years.

However, there was also a large increase in the number of PCV13 serotype cases not covered in PCV7 (i.e. PCV13-7) in children in 2022 (*n*=10/38, 26% of paediatric IPD cases) and 2023 (*n*=14/42, 33% of paediatric IPD) in comparison to 2019 and 2020 when PCV13-7 serotypes only accounted for 5-14% of paediatric IPD cases. Aside from 7F (*n*=1 in 2019 and 2020), all other PCV13-7 cases in children in recent years have been associated with two persistent PCV13 vaccine preventable serotypes, namely serotype 3 and 19A. In 2022, there were three cases of serotype 3 and seven cases of serotype 19A in children ≤16 years of age and in 2023 there were four cases of serotype 3 and ten cases of serotype 19A. Overall these two PCV13-7 serotypes alone accounted for 26-33% of paediatric IPD cases in 2022 and 2023. Based on patient age, six of the children were < 13 months old and were not likely to be fully vaccinated, whereas the rest of the cases were in children aged 13-24 months (*n*=4), those aged 2-4 years (n=7) or those aged 5-16 years (*n*=7). Vaccine uptake and potential vaccine failures and breakthrough cases are monitored by the Department of Public Health and HPSC.

The persistence of serotype 19A in vaccine eligible children in Ireland was previously assessed using whole genome sequencing (WGS) and was found to be associated with a clade within the Global Pneumococcal Sequence Cluster (GPSC) 1 Clonal Complex (CC) 320 that was unique to Ireland and significantly linked to vaccine failures/breakthrough cases [16]. After serotype 19A, serotype 3 is the second leading vaccine-preventable serotype associated with disease in Ireland, however, this serotype is associated with paediatric IPD and potential vaccine failures and breakthrough cases to a much greater extent in other countries [12,17].

In relation to the two new broader spectrum vaccines, there were two cases of 22F typed in children in both 2022 and 2023. This serotype is covered in PCV15, along with serotype 33F which was previously associated with IPD in children, but has not been observed in more recent years (*n*=4, 2, 1 in 2016, 2018 and 2019, respectively). Serotypes covered in PCV15 but not covered in PCV13 (i.e. PCV15-13) accounted for 5% of paediatric IPD cases in 2022 and 2023. Overall PCV15 provides protection against 37-40% of paediatric cases in 2022-2023 in comparison to 32-36% with PCV13 over the same period. PCV20 provides protection against the two PCV15

serotypes (22F and 33F) and five additional serotypes: 8, 10A, 11A, 12F, and 15B. Additional PCV20-15 serotypes (i.e. serotypes only covered in this PCV20) accounted for 21-24% of paediatric IPD cases in 2022 and 2023. This was mainly due to serotype 10A which accounted for six isolates in 2023 (14% of paediatric cases) and a mix of serotype 8 (*n*=3), 11A (*n*=1), 12F (*n*=1) and 15B/C (*n*=4) in 2022. Overall, 61-62% of paediatric cases were serotypes covered in PCV20. However, it is difficult to assess the potential impact of PCV15 or PCV20 against serotype 3 and 19A given that PCV13 has had limited success at reducing these two particular serotypes in Ireland, whereas all other PCV13 serotypes fell amongst the paediatric population.

There has also been an increase in the number of IPD cases from serotypes not covered in any of the conjugate vaccines. In 2019 and 2020 there were 18 and 8 non-PCV20 serotype cases in children respectively (accounted for 38% of paediatric IPD cases both years), this increased to 64% in 2021 (*n*=14/22) and fell back again to 38-39% in 2022 and 2023 with 9 cases reported both years. In particular, a sharp increase in serotype 23B in these years was associated with this increase in non-PCV cases, as displayed in **figure 6**. In 2020 there were two cases of serotype 23B (10% of paediatric IPD cases) and this increased to nine cases in 2021 (41% of paediatric IPD cases). While the numbers/proportion of cases dropped back again in 2022 (*n*=5/38, 13%) and 2023 (*n*=6/42, 14%), this is still of concern given that none of the current PCV vaccines provide protection against this serotype, which is also associated with antimicrobial resistance. The emergence of this serotype in the post-PCV13 and post-pandemic era has also been reported elsewhere [18,19].

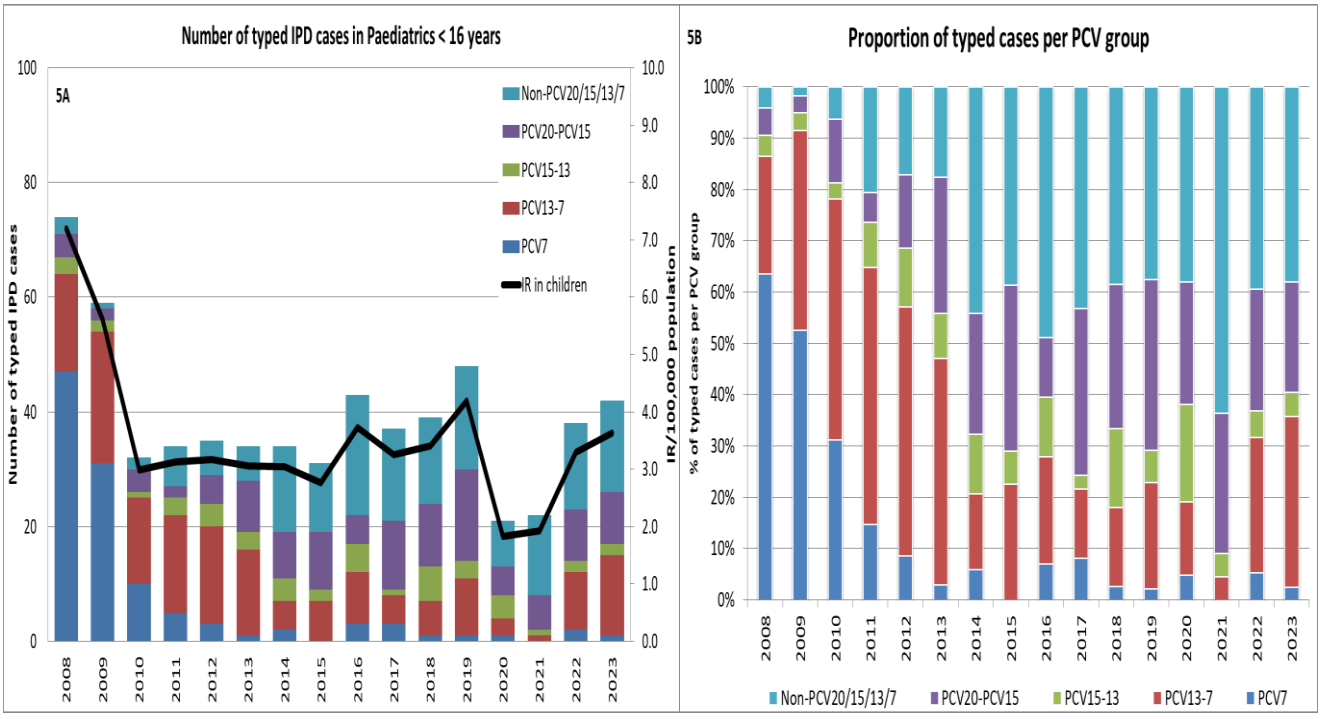


Figure 5A-5B. The proportion of IPD cases in children ≤16 years of age per vaccine group for all of the PCVs from 2008 to 2023

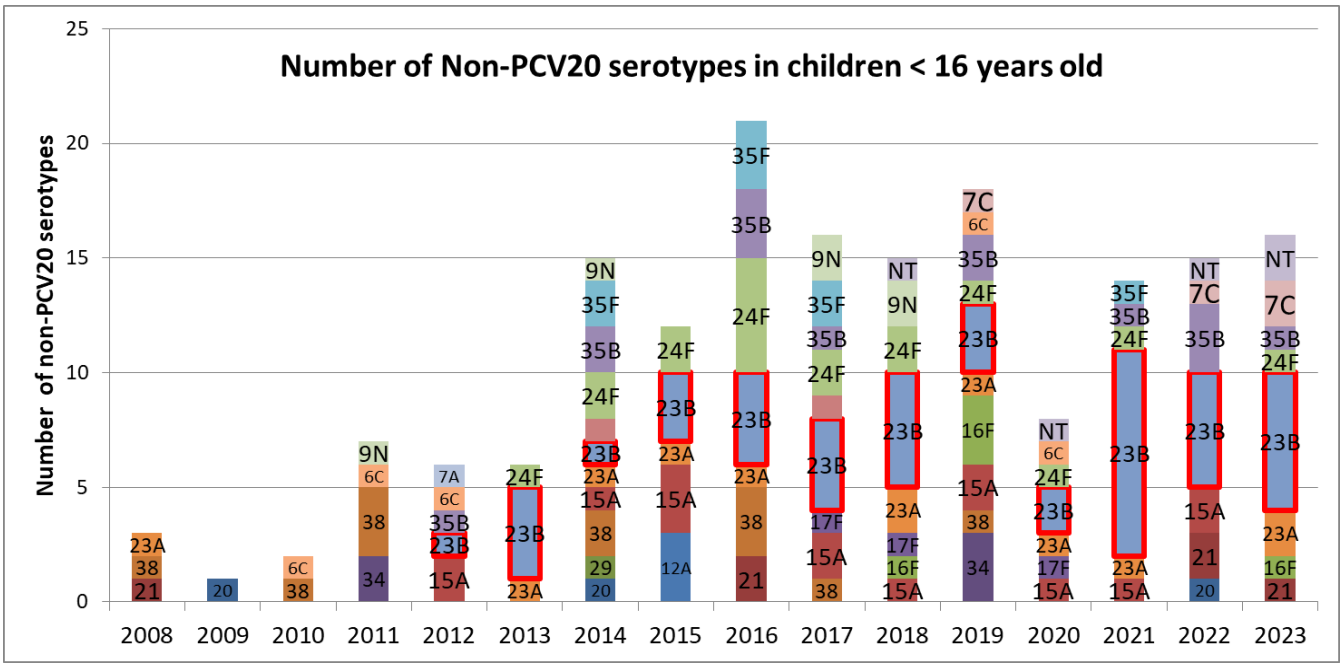


Figure 6. Predominant serotypes associated with IPD in children ≤16 years of age not associated with PCV20 i.e. also not covered in PCV7, PCV13, PCV15) from 2008 to 2023

IPD and the distribution of serotypes associated amongst adults, ≥65 years of age

The number of typed IPD cases in adults ≥65 years, which had declined in 2020 and 2021 (*n*=85, 66, respectively) has increased back to pre-pandemic levels in 2022 (*n*=147) and 2023 (*n*=199) (**Figure 7A**). As a result, the disease incidence rate has also returned to previous levels (IR=24.7/100,000 in 2023). Unlike the trends in children, there has been an increase in the proportion of PCV7 serotypes in adults in 2022 and 2023. Following the introduction of PCV7 into the paediatric schedule in 2008, there was a decline in these serotypes in adults, indicative of positive herd immunity. The number of cases fell from 65 cases in 2008 (43% of IPD cases in older adults) to 7-10 cases each year from 2016-2019 (4% of IPD cases in older adults). By 2023, PCV7 serotypes accounted for 10% of IPD cases in older adults (*n*=19). Of those 19 cases, ten were serotype 4, followed by six serotype 19F and three serotype 6B. As previously discussed, there was a large increase in serotype 4 in adults aged between 35-64 years of age and those ≥65 years in Ireland and elsewhere [12-15]. The sequence data from the serotype 4 cases is still under review.

In addition to the re-emergence of PCV7 serotype 4 in older adults, two predominant PCV13 serotypes have also persisted in adults in 2022 and 2023. Serotype 19A accounted for 9-13% of cases in older adults in 2022 (*n*=19/146) and 2023 (*n*=18/199), while serotype 3 represented 12% of cases in older adults in 2022 (*n*=18/146) and 2023 (*n*=23/199), respectively. Given the increase in serotype 4, coupled with the persistence of serotypes 3 and 19A, PCV13 serotypes still represent 30% of serotypes circulating in older adults in Ireland in 2023. This warrants attention when considering updates to vaccination policies in adults.

Figure 7B displays the proportion of isolates per vaccine group. Increased vaccination uptake of PPV23 or changes in the vaccine schedule to include PCV13 or new vaccines PCV15 or PCV20, could provide protection against IPD serotypes associated with older adults. **Figure 8** provides detail of the serotypes in adults ≥65 years. While the serotype epidemiology is continually evolving, a substantial proportion is still covered by either the polysaccharide or the conjugate vaccines. In 2023, 30%, 39%, 57% and 69% of IPD cases were serotypes covered in PCV13, PCV15, PCV20 and PPV23, respectively. While polysaccharide vaccines such as PPV23 do not provide as effective an immune response in older adults in comparison to conjugate vaccines in children, a single dose of PCV13 prior to PPV23 immunisation was initially recommended for older adults in the United States to improve the immune response. These recommendations have now changed to include recommendations for PCV15 or PCV20 for adults ≥65 years [20]. For adults ≥65 years with no other co-morbidities in the US, when PCV15 is provided, it should be followed by a dose of PPSV23 at least 1 year later. When PCV20 is used, it does not need to be followed by a dose of PPSV23.

In Ireland, a single dose of PCV13 prior to PPV23 administration is recommended for those with immunosuppressive conditions or co-morbidities. However, this is not routinely offered for all other adults ≥65 years of age (with no other conditions/co-morbidities) who are offered PPV23 alone. Based on the IPD data from 2023, 39% were PCV15 serotypes and 57% were PCV20 vaccine serotypes. Therefore, direct immunisation with a conjugate vaccine followed by PPV23, rather than herd protection from PCV13 in children could reduce the burden of disease in this population. While PPV23 serotype coverage was also high in this population (69% coverage in 2023), there is low uptake and waning immunity reported, hence, direct vaccination with a PCV alone or PCV followed by PPV23 may provide greater protection to older adults who now bear the highest disease burden.

Overall 68% and 70% of IPD cases in adult's ≥65 years of age in 2022 and 2023 were associated with serotypes that are not covered in PCV13. Leading non-PCV13 serotypes included serotype 22F which accounted for 7% of IPD cases in older adults both years (*n*=11, 14) and is covered in PCV15 and PCV20, and serotype 8 (*n*=16, 26, 11-13%) which is covered in PCV20. There has, however, been some changes in the epidemiology of these serotypes: serotype 8 alone accounted for 20-28% of IPD cases in older adults pre-pandemic (*n*=37, 24 in 2019 and 2020), but now only accounts for 11-13% of cases. Similarly, serotype 12F accounted for 5-8% of IPD cases in older adults in 2018-2019 but has fallen significantly in more recent years with only one isolate recovered from this patient age group in 2021-2023. Instead, a diverse collection of different serotypes that are not covered in any of the broader spectrum PCVs has begun to emerge. As displayed in **Figure 7** these non-PCV20 serotypes included 9N (*n*=5, 19), 7C (*n*=5, 9), 15A (*n*=8, 9), 6C (*n*=6, 8), 23B (*n*= 9, 9) and 23A (*n*=8, 6) in 2022 and 2023.

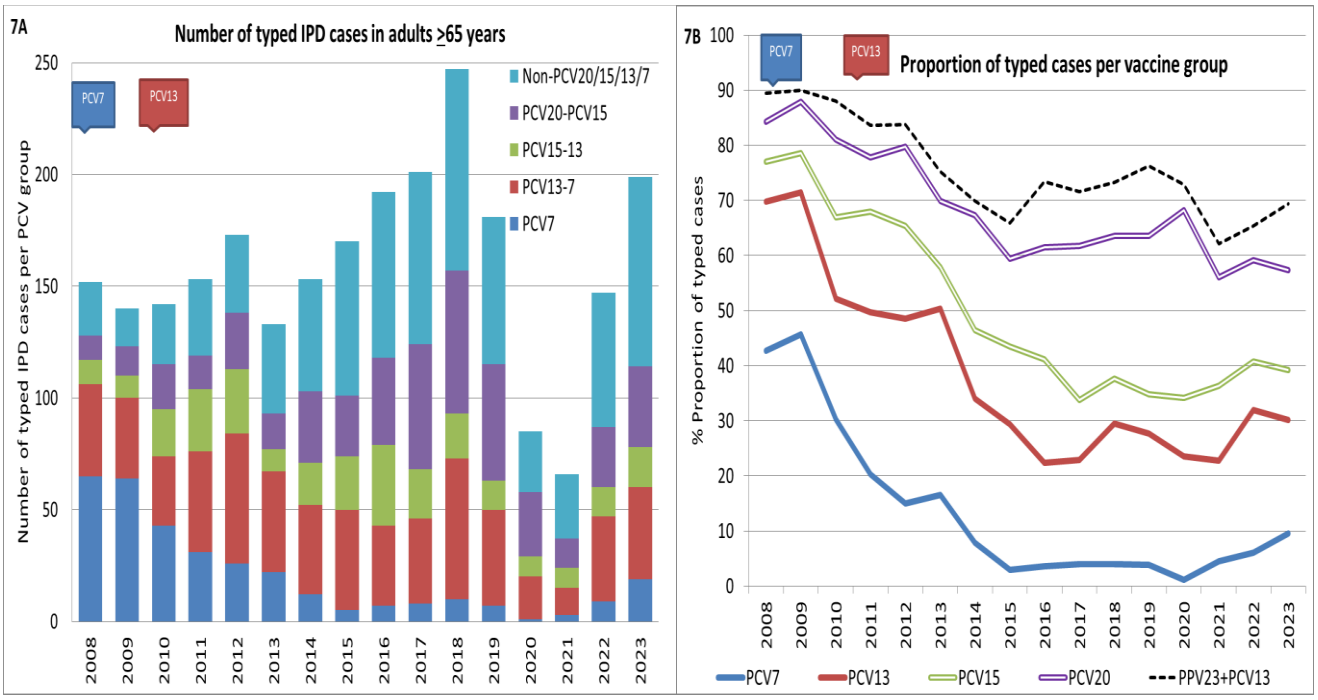


Figure 7A-B. Number of typed IPD cases in adults ≥65 years of age grouped by vaccine-preventable serotypes (PCV7, PCV13, PCV15, PCV20, PPV23) from 2008 to 2023.

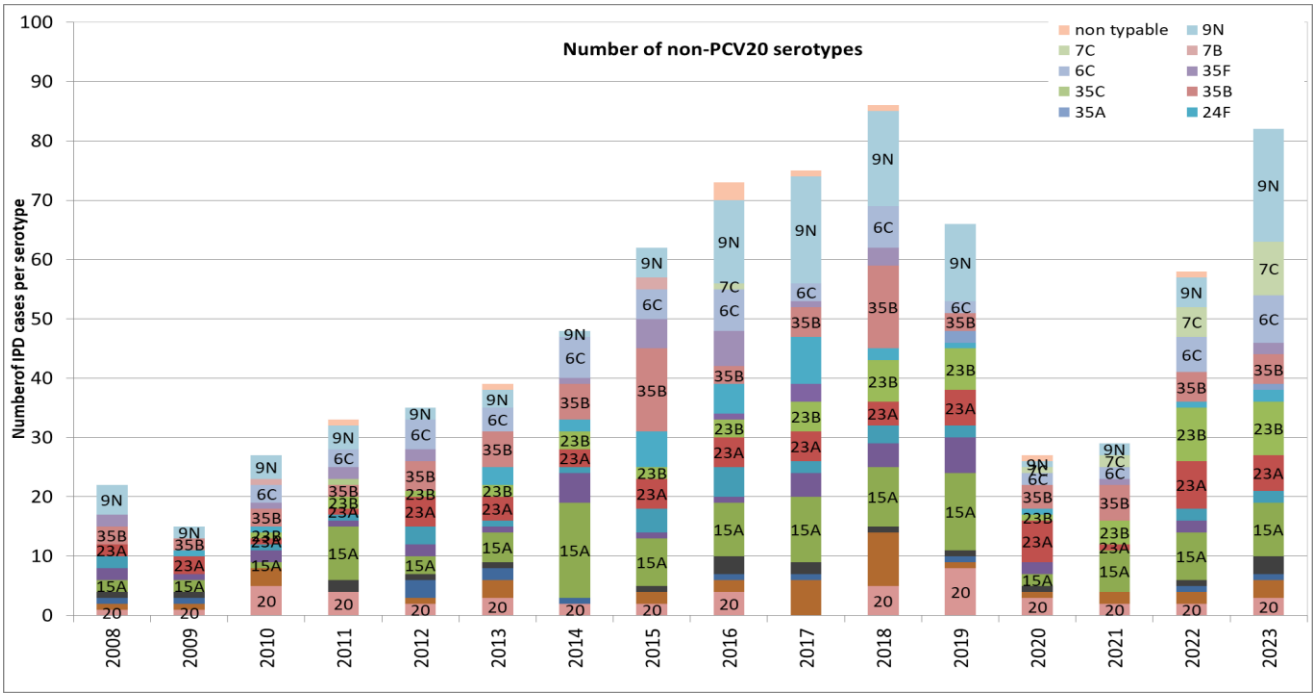
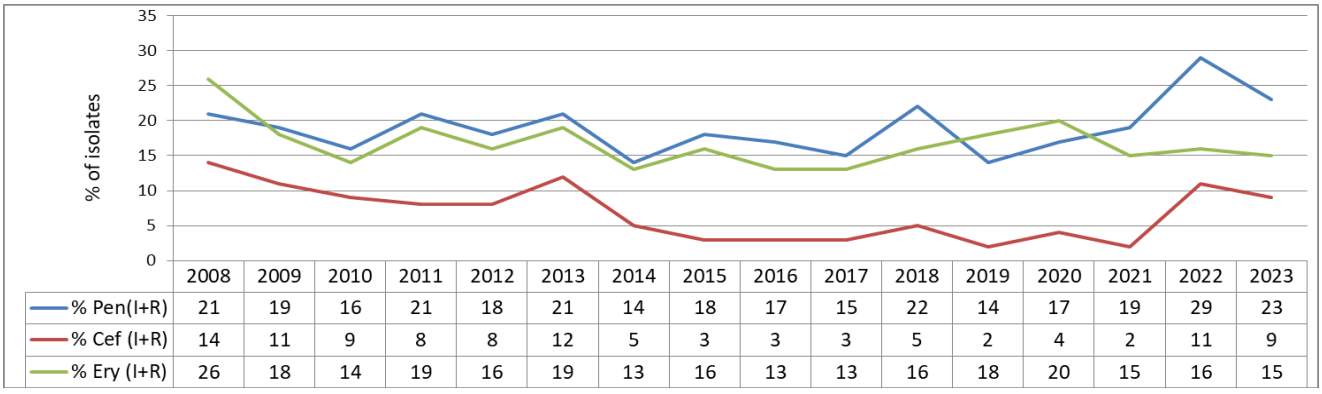


Figure 8. Number of typed IPD cases caused by serotypes not covered in any of the conjugate vaccines (PCV7, PCV13, PCV15, PCV20,) in adults ≥65 years of age from 2008 to 2023.

The distribution of serotypes associated with antimicrobial resistance

During 2022 and 2023, there was an increase in the number of isolates non-susceptible or with reduced susceptibility to most antimicrobials using the EUCAST breakpoints of MIC >0.06 µg/ml for penicillin, >0.5 µg/ml for cefotaxime and >0.25 µg/ml for erythromycin considered non-susceptible (**Figure 9**). Penicillin non-susceptibility pneumococci (PNSP) increased from 17-19% in 2020-2021 to 29% in 2022 and 23% in 2023. The percentage of isolates with reduced susceptibility to cefotaxime also increased in 2022 (11%) and 2023 (9%), in comparison to 2020 (4%) and 2021 (2%). The proportion of erythromycin resistance, however, remained relatively stable from 15-20% in 2020-2021 to 15-16% in 2022-2023. Similar to previous years, a small number of serotypes were responsible for most reduced susceptibility to antimicrobials. As displayed in **Figure 10** the increase in PNSP occurred with the increase in vaccine preventable serotypes 19A, 19F and an increase in serotypes 15A, 23A, 23B and 35B, 6C, that are not included in any of the current PCVs. In most instances, those strains with reduced susceptibility to penicillin were also more likely to also exhibit reduced susceptibility or resistance to cefotaxime and erythromycin.



	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
% Pen(I+R)	21	19	16	21	18	21	14	18	17	15	22	14	17	19	29	23
% Cef (I+R)	14	11	9	8	8	12	5	3	3	3	5	2	4	2	11	9
% Ery (I+R)	26	18	14	19	16	19	13	16	13	13	16	18	20	15	16	15

Figure 9. The percentage of IPD isolates with reduced susceptibility (intermediate (I) or resistant (R)) to penicillin (Pen), cefotaxime (Cef) and Erythromycin (Ery) from 2008-2023

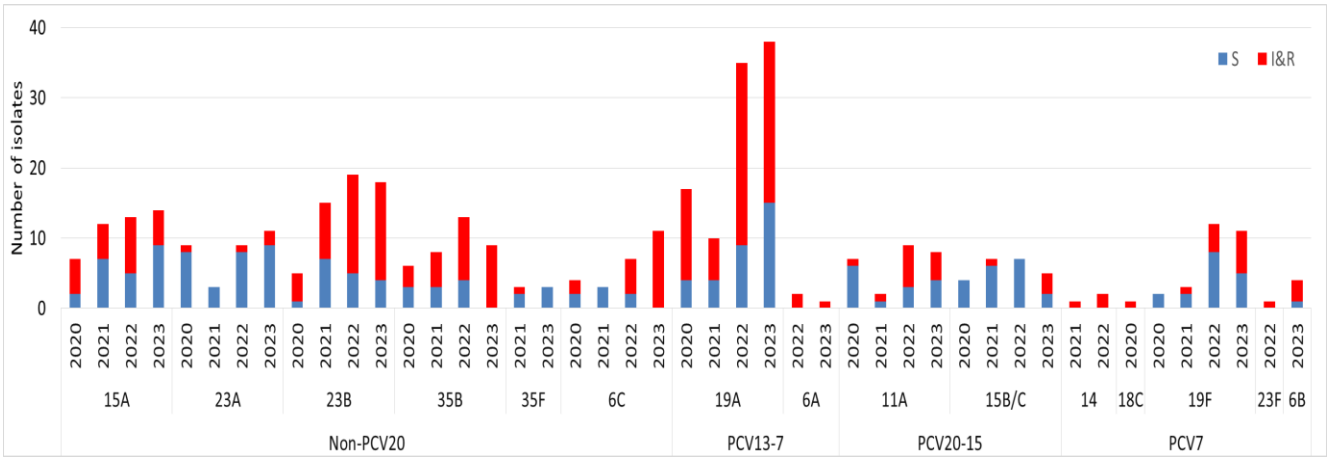


Figure 10. The predominant serotypes associated with reduced susceptibility to penicillin, including intermediate (I) and resistant (R) isolates.

As indicated in **Figure 11**, the penicillin non-susceptible pneumococci (PNSP) prevalence in children has increased significantly recently. It was much higher in children < 2 years of age, those aged 2-4 years of age and in those aged 5-16 years (44%, 50% and 44%, respectively) in 2023 than in 2019 (10%, 29%, 9%). While the number of cases is lower (*n*=19 isolates with reduced susceptibility to penicillin in 2023) this still represents 45% of all *S. pneumoniae* isolates associated with children in 2023. Most of these cases were serotype 19A (*n*=8), which is a PCV13 vaccine preventable serotype, and serotypes 23B (*n*=6), which is of concern as it is not covered in the new vaccines currently approved for use (PCV15/PCV20). The percentage of PNSP overall increased in all adult age groups. The percentage of PNSP isolates increased from 16% in 2019 to 32% and 24% respectively in 2022 and 2023 in older adults ≥65 years of age.

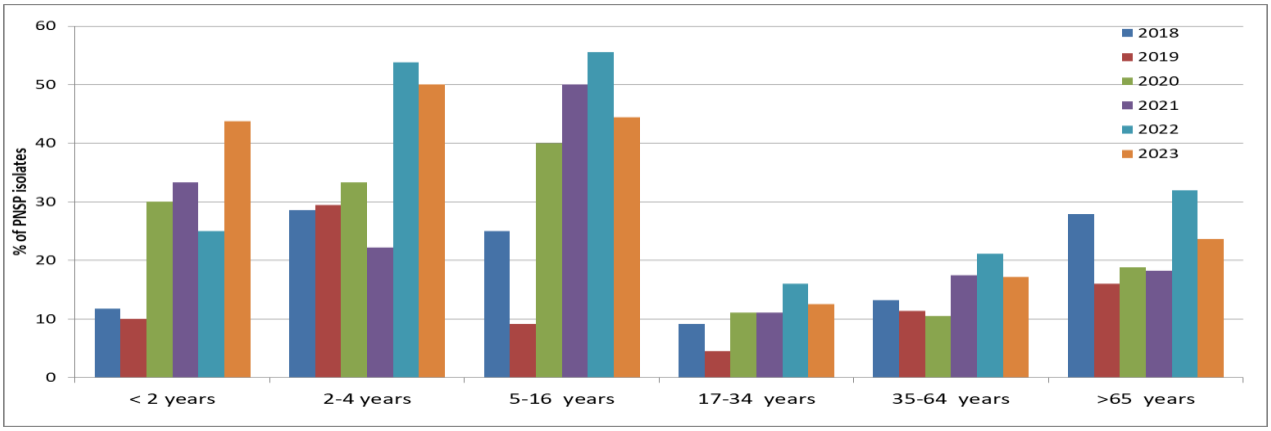


Figure 11. The percentage of PNSP per age group from 2018 to 2023

3. Implications and the future

Continued national surveillance of serotypes causing IPD is necessary to monitor the epidemiology of IPD in Ireland, assess the effectiveness of the national vaccination programme in Ireland, detect the presence of non-vaccine serotypes, and monitor the emergence of replacement serotypes and their association with antibiotic resistance. All of this also contributes to European and worldwide IPD surveillance networks and to wider public health management of IPD.

Ireland has a relatively high incidence of PNSP isolates in comparison to other EU countries, and we need to monitor these rates in conjunction with improvements in antimicrobial prescribing practices particularly when an increase in resistance has been observed after the pandemic. The introduction of the PCV7/13 resulted in a reduction in the number of IPD isolates and led to the reduction in the PNSP rate in subsequent years. The emergence of non-vaccine associated serotypes (such as 23B) and the persistence of some vaccine preventable serotypes (such as 19A) that are also associated with antimicrobial resistance is of concern.

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Recent Manuscripts with Irish IPD data

Humphreys H, Corcoran M, Mereckiene J, Cunney R, Cotter S. Invasive pneumococcal surveillance to assess the potential benefits of extended spectrum conjugate vaccines (PCV15/PCV20) in older adults. *Epidemiology and Infection* 2022;151:e27. doi: 10.1017/S0950268823000110. PMID: 36700424

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