Invasive pneumococcal disease 3 years after introduction of a reduced 1+1 infant 13-valent pneumococcal conjugate vaccine immunisation schedule in England: a prospective national observational surveillance study

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Summary

Background The UK transition from a 2+1 to a 1+1 infant immunisation schedule with the 13-valent pneumococcal conjugate vaccine (PCV13) on Jan 1, 2020, coincided with the start of the COVID-19 pandemic. We describe the epidemiology of invasive pneumococcal disease (IPD) in England over 6 financial years (April 1 to March 31) between 2017–18 and 2022–23.

Methods We used prospective national surveillance data, including serotyping and whole-genome sequencing of invasive isolates, to analyse IPD trends in England by age and financial year. We compared breakthrough infections and vaccine failure rates in 2022–23 among children eligible for the 1+1 schedule with rates in cohorts of children eligible for the 2+1 schedule between 2017–18 and 2019–20. We assessed genomic changes over time by comparing Global Pneumococcal Sequencing Clusters and multilocus sequence types among PCV13 serotypes causing IPD.

Findings There were 4598 laboratory-confirmed IPD cases in 2022–23, 3025 in 2021–22, 1240 in 2020–21, and 5316 in 2019–20. IPD incidence in 2022–23 was 14% lower than in 2019–20 (incidence rate ratio [IRR] 0·86, 95% CI 0·81–0·91; p<0·001). IPD incidence in 2022–23 compared with 2019–20 was 34% higher in children (aged <15 years) (378 cases *vs* 292 cases; IRR 1·34, 95% CI 1·08–1·68; p=0·009) and 17% lower in adults (aged 15 years and older; 4220 *vs* 5024; 0·83, 0·78–0·88; p<0·001). The proportion of PCV13-type IPD increased from 19·4% (95% CI 18·2–20·4; 957 of 4947) in 2019–20 to 29·7% (28·3–31·0; 1283 of 4326) in 2022–23, mainly due to serotype 3, but also serotypes 19F, 19A, and 4, alongside a decrease in non-PCV13 serotypes 8, 12F, and 9N. The increase in IPD incidence due to serotypes 3, 19A, and 19F was driven by clonal expansion of previously circulating strains, whereas serotype 4 expansion was driven by newer strains (ie, sequence types 801 and 15603). Breakthrough infections and vaccine failure rates were similar in children eligible for the 1+1 (1·08 per 100 000 person-years) and 2+1 (0·76 per 100 000 person-years; IRR 1·42, 95% CI 0·78–2·49; p=0·20) PCV13 schedules.

Interpretation Overall, IPD incidence in England was lower in 2022–23, 2 years after removal of pandemic restrictions, than in 2019–20. Breakthrough and vaccine failure rates were not significantly different between children who received the 1+1 compared with the 2+1 PCV13 immunisation schedule. The post-pandemic increase in childhood IPD incidence and especially PCV13-type IPD will require close monitoring.

Funding None.

Introduction

Streptococcus pneumoniae is a major cause of infectious morbidity and mortality worldwide. More than 100 different pneumococcal serotypes have been identified. Pneumococcal conjugate vaccines (PCVs) targeting the most prevalent serotypes have been highly effective in preventing invasive pneumococcal disease (IPD) caused by vaccine serotypes.[1] By vaccinating young children, who are the main nasopharyngeal carriers of pneumococci, PCVs can prevent carriage acquisition and interrupt onward transmission, thereby protecting unvaccinated individuals and providing indirect (ie, herd) protection across the population.[2]

A seven-valent PCV (PCV7) was licensed as a three-dose infant priming schedule at 2 months, 4 months, and 6 months of age followed by a booster at 1 year of age (3+1 schedule) in the USA in 2000 and in Europe in 2001. In 2006, the UK implemented PCV7 as a reduced 2+1 schedule (at age 2 months, 4 months, and 12 months) after showing similar serotype-specific immunogenicity between the 2+1 and 3+1 schedules.[3] In 2010, the UK replaced PCV7 with a 13-valent PCV (PCV13), which targeted six additional serotypes.[4] Within 4 years of both programmes, the maximum benefit of reducing IPD due to the relevant PCV serotypes was reached, with a plateauing of cases across all age groups.[4] With both

Research in context

Evidence before this study

We searched PubMed using the terms ("invasive pneumococcal disease" [Title/Abstract]) OR ("IPD") OR (("pneumococcal" [Title/Abstract]) AND ("epidemiology" [Title/Abstract])) on July 31, 2023, with no date restrictions, and we used the snowball process to identify additional relevant publications through searching of the reference lists within relevant articles. Only publications in English were included. We excluded publications unrelated to invasive pneumococcal disease (IPD) or pneumococcal conjugate vaccines (PCVs). The UK was the first country worldwide to implement a reduced 1+1 PCV immunisation schedule nationally (at age 12 weeks and 1 year), replacing a 2+1 schedule (at age 8 weeks and 12 weeks, followed by a booster at 1 year) on Jan 1, 2020. This decision was based on a randomised controlled trial that found that infants receiving a 1+1 schedule of the 13-valent PCV (PCV13) had higher post-booster antibody responses to four serotypes (1, 4, 14, and 19F), lower responses to four other serotypes (6A, 6B, 18C, and 23F), and similar responses to the remaining five serotypes (3, 19A, 7F, 9V, and 5) than infants receiving the 2+1 schedule. These data, alongside the very low disease incidence for PCV13-type IPD, very low carriage of most PCV13 serotypes (except for 3 and 19A) in vaccinated children, and modelling studies showing little effect on overall IPD rates with the reduced 1+1 schedule, all contributed to the decision to implement a reduced 1+1 PCV13 infant immunisation schedule. No other country recommends a reduced 1+1 PCV infant immunisation schedule for comparison. Implementation of the reduced schedule, however, coincided with the start of the COVID-19 pandemic and, similar to many other countries, the UK also had large declines in respiratory infections, including pneumococcal disease, during pandemic restrictions, followed by a resurgence in infections when the restrictions were lifted.

Added value of this study

We present the first real-world evidence for a reduced 1+1 PCV13 infant immunisation schedule, which we obtained following a thorough analysis of IPD trends in England over 6 financial years (April 1 to March 31) between 2017–18 and 2022–23, including the first 3 years since the COVID-19 pandemic started. In 2022–23, overall IPD incidence was 14% below 2019–20 incidence (incidence rate ratio 0·86, 95% CI 0·81–0·91; p<0·001), although incidence was higher in children younger than 15 years (1·34, 1·08–1·68; p=0·009). In 2022–23, the proportion of cases with serotyped isolates that were due to PCV13 serotypes was higher (1283 [29·7%] of 4326) than in 2019–20 (957 [19·4%] of 4947), mainly driven by increases in serotype 3 for all ages, 19A and 19F in children, and serotype 4 in adults, alongside a decrease in some of the most common non-PCV13 serotypes (8, 12F, and 9N). Genomic analyses revealed that the increases were mostly due to an expansion of previously circulating strains, except for serotype 4. In children, we found that breakthrough PCV13 infection and vaccine failure rates were not significantly different in children who received the 1+1 schedule compared with those who received the 2+1 schedule, and were driven by the same PCV13 serotypes, with no signs of waning protection against PCV13-type IPD up to 3 years of age.

Implications of all the available evidence

In England, overall IPD incidence was lower in 2022–23 than in 2019–20 and rates of breakthrough infections and vaccine failure among children who received a reduced 1+1 schedule were not significantly different to rates in children who received a 2+1 schedule. An increase in IPD due to some PCV13 serotypes, especially serotype 3, which is now responsible for 18% of IPD cases in England, as well as the increase in overall IPD incidence in children after pandemic restrictions were lifted will require careful monitoring.

vaccines, a rise in IPD caused by non-vaccine serotypes (ie, replacement disease) was observed, mainly in adults aged 65 years and older,[5] although overall IPD incidence in 2016–17 remained below pre-PCV rates.[5] In the UK, adults aged 65 years and individuals aged 2 years and older who are identified as high risk for pneumococcal disease are also offered a one-off dose of the 23-valent pneumococcal polysaccharide vaccine (known as PPV23).

Given the excellent indirect protection (also known as herd protection or population protection) offered by the childhood PCV13 programme resulting in a very low incidence of PCV13-type IPD caused across all age groups, and evidence from clinical trials and modelling studies,[1] the UK implemented a reduced 1+1 PCV13 immunisation schedule at 12 weeks and 1 year of age for infants born on or after Jan 1, 2020.[6] With the emergence of SARS-CoV-2 in December, 2019, the UK, like many other countries, implemented national lockdowns and other mitigations in March, 2020,[7] which not only reduced the spread of SARS-CoV-2 but also led to large declines in other respiratory diseases.[8] On July 19, 2021, all restrictions were lifted in England, which resulted in out-of-season resurgences of viral[9] and bacterial[10] infections. An initial decline in IPD incidence early in the COVID-19 pandemic[11] was followed by an increase in infections during the winter of 2021, as was reported in other countries.[12,13] Although overall IPD incidence remained 30% below the 3-year (2017–19) mean winter rate,[14] infections in children younger than 15 years exceeded pre-pandemic levels, raising concerns about the effectiveness of the 1+1 PCV13 immunisation schedule in maintaining direct and indirect protection.[14] Here, we describe the epidemiology, serotype distribution, and clinical characteristics of IPD cases during six financial years (April 1 to March 31) between 2017–18 and 2022–23 in England, covering the first 3 years (2020–21 to 2022–23) since the contemporaneous start of the COVID-19 pandemic and implementation of the 1+1 PCV13 infant immunisation schedule.

Methods

Surveillance data

In this prospective national observational surveillance study, we used data from the UK Health Security Agency (UKHSA) for each of the six financial years between 2017–18 and 2022–23. The UKHSA conducts enhanced national surveillance of IPD in England, as described previously.[4] Briefly, National Health Service (NHS) hospitals electronically report laboratory-confirmed infections to the UKHSA using the Second-Generation Surveillance System and submit invasive pneumococcal isolates to the UKHSA national reference laboratory for confirmation and serotyping. General practitioners of patients with confirmed IPD routinely complete a surveillance questionnaire on demographics, comorbidities, vaccination history, clinical features, and outcomes of the disease. Unreturned questionnaires and missing information were followed up with general practitioners, hospital clinicians, pathologists, and coroners by telephone, email, or letter, as needed. Death status was confirmed through the Personal Demographics Service, an electronic national database of NHS-registered patients. Data for all cases in individuals residing in England were included in the analyses.

UKHSA has legal permission to process confidential information for national surveillance of communicable diseases without individual patient consent (Regulation 3 of Health Service Regulations 2002) and, as such, ethics committee approval was not required for this study.

Laboratory methods

S pneumoniae was identified by colony morphology, optochin sensitivity, and bile solubility at the national reference laboratory and, since Oct 1, 2017, by whole-genome sequencing at the UKHSA's Central Sequencing laboratory.[15] *S pneumoniae* serotype and multilocus sequence type were inferred from reads, as previously described.[16] Reads were also assembled with quality control (appendix p 2). The Global Pneumococcal Sequencing Cluster (GPSC) of isolates was assigned using the Global Pneumococcal Sequencing Project's database (version 6)[17] and PopPUNK (version 2.6.0).[18] Whole-genome sequencing results were used to assess genomic changes in PCV13 serotypes causing IPD (appendix p 2).

See Online for appendix

Definitions

IPD was defined as isolation of *S pneumoniae* from a normally sterile site, or detection of pneumococcal DNA by PCR in cerebrospinal fluid (CSF) or pleural fluid. Clinical presentation was classified as meningitis (*S pneumoniae* detected in the CSF or pneumococcal isolation from the blood with clinical or radiological features of meningitis or a CNS focus) or non-meningitis.

We analysed data by financial year (from April 1 to March 31) over 6 years (2017–18 to 2022–23) to align with the start of pandemic-associated restrictions from March 23, 2020.[7] The 2017–18 to 2019–20 financial years were considered pre-pandemic years, 2020–21 as the pandemic year, and subsequent years as post-pandemic. To assess pre-pandemic and post-pandemic differences, we compared the latest year (2022–23) with the last pre-pandemic year (2019–20).

Serotypes were grouped as covered by PCV7 (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F); PCV13 (serotypes in PCV7 and serotypes 1, 3, 5, 6A, 7F and 19A); and non-PCV13 serotypes, which include the additional 15-valent PCV (PCV15) serotypes (22F and 33F), additional 20-valent PCV (PCV20) serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F), additional 23-valent PCV (PCV23) serotypes (2, 9N, 17F, and 20), and non-vaccine types. Isolates classified as 15B/C (not resolved as 15B or 15C by typing methods) were included among PCV20 serotypes due to evidence that serotype 15B induces cross-functional antibodies against serotype 15C.[19] In a sensitivity analysis, serotype 3 was classified as a non-PCV13 type given the low PCV13 effectiveness against this serotype.[1]

We assessed incidence and epidemiology of IPD overall and in age subgroups of younger than 1 year, 1–4 years, 5–14 years, 15–44 years, 45–64 years, 65–79 years, and 80 years and older. Adults were defined as those aged 15 years and older, and children were defined as those younger than 15 years. In addition, we assessed childhood cases in smaller age groups, including younger than 4 months (too young to be vaccinated or received one dose only at <1 month with the 1+1 schedule), 4–6 months (with maximal protection from one PCV13 dose given at the recommended 12 weeks of age), and 7–12 months (to assess potential evidence of waning immunity after a single PCV13 dose). We also assessed cases in children aged 13–23 months and 24–59 months for potential evidence of waning immunity after the 1-year booster with the 1+1 schedule.

Statistical comparisons were made for 2022–23 against 2019–20, aside from those for breakthrough infections and vaccine failures. We assessed cases of IPD that were breakthrough infections or vaccine failures in individuals eligible for the 1+1 schedule (born between Jan 1, 2020, and Dec 31, 2022) who developed IPD in 2022–23 compared with three birth cohorts of the same age range who had been eligible for the 2+1 schedule and developed disease during 2017–18 (born between Jan 1, 2015, and Dec 31, 2017), 2018–19 (born between Jan 1, 2016, and Dec 31, 2018), or 2019–20 (born between Jan 1, 2017, and Dec 31, 2019; appendix p 3). Breakthrough infections were defined as PCV13-type IPD diagnosed at least 14 days after one or more PCV13 doses received before 1 year of age and vaccine failure was defined as PCV13-type IPD diagnosed at least 7 days after one or more PCV13 dose received from 1 year of age.

Statistical analysis

Data were analysed using Stata version 17. Proportions of categorical variables witihin different test groups were

compared using the χ^2 test. IPD incidence was calculated using mid-year Office of National Statistics population estimates as denominators, with counts assumed to come from a Poisson distribution to obtain exact 95% CIs. CIs for proportions were calculated using the Normal approximation for a binomial distribution. We calculated corrected incidence since 2000–01 using a Poisson regression model and accounting for missing serotype and age data. Changes in surveillance sensitivity up to 2009–10 were adjusted for by correcting disease incidence according to the upward trend in age-specific total disease rates in the pre-PCV7 years, as previously described.[5] During the period of 2017–18 to 2022–23, trends were adjusted for missing serotypes, where the same serotype distribution as for individuals with serotyped isolates was assumed. Age was known for all individuals with IPD in this time period. Incidence rate ratios (IRRs) and 95% CIs were calculated using an over-dispersed Poisson model, whereby the over-dispersion parameter of 2·1 came from the variability seen in the corrected counts before vaccine introduction (2000–06), as previously described.[5] We also compared the proportion of meningitis cases and the 30-day case-fatality rate between 2019–20 and 2022–23. Crude rates of vaccine failures and breakthrough infections were calculated using the Office of National Statistics livebirths data for England. The IRR was calculated comparing this rate for the 1+1 eligible cohort with the combined 2+1 eligible cohorts. GPSC diversity among isolates expressing the same serotype was assessed using the Simpson diversity index (SDI), calculated in R (version 4.3.1; vegan version 2.6.4 package).

Role of the funding source

There was no funding source for this study.

Results

In 2022–23, there were 4598 laboratory-confirmed cases of IPD in England, compared with 3025 in 2021–22, 1240 in 2020–21, and 5316 in 2019–20. Seasonality in 2022–23 was similar to pre-pandemic years, with a large peak in December, compared with smaller peaks during 2020–21 and 2021–22 (figure 1). Despite an overall 52·0% (IRR 1·52, 95% CI 1·42–1·62; p<0·0001) increase in 2022–23 compared with 2021–22, IPD incidence remained 14% lower than in 2019–20 (IRR 0·86, 95% CI 0·81–0·91; p<0·001), mainly due to fewer cases in adults (4220 in 2022–23 *vs* 5024 in 2019–20; figure 2). 2402 (52·2%) of 4598 individuals with IPD in 2022–23 were male compared with 2701 (50·8%) of 5316 in 2019–20. Regional distributions of cases and serotypes causing disease did not change throughout the surveillance period (appendix p 4).

In infants younger than 1 year, IPD cases declined during 2020–21 and then returned to pre-pandemic levels in subsequent years, with no evidence of an increase in any age subgroup (figure 2A). In children aged 1–4 years, IPD cases were slightly higher in 2022–23 compared with 2019–20 in those aged 13–23 months (72 in 2022–23 *vs* 58 in 2019–20) and 24–59 months (126 in 2022–23 *vs* 74 in 2019–20). This increase was due to an increase in some non-PCV13 serotypes (ie, 10A, 22F, 23B, and 23A; figure 2A; appendix p 7) and PCV13 serotypes (mainly serotypes 3, 19A, and 19F), including PCV13 serotypes that had rarely caused disease (0–1 cases) in pre-pandemic years (2017–18 and 2019–20; eg, serotypes 23F and 9V; figure 2C).

In children younger than 15 years, IPD incidence declined from 2019–20 (2·9 cases per 100 000, 95% CI 2·6–3·2; n=292) to 2020–21 (1·1 per 100 000, 0·9–1·3; n=109), before increasing in 2021–22 (3·5 per 100 000, 3·2–3·9; n=346) and 2022–23 (3·9 per 100 000, 3·5–4·3; n=378), to higher than was seen in 2019–20 (IRR 1·34, 95% CI 1·08–1·68; p=0·009). The difference was significant only in children aged 1–4 years (table 1, figure 3).

In individuals aged 15 years and older, IPD incidence in 2022–23 was lower compared with 2019–20 (9·0 *vs* 10·9 cases per 100 000; IRR 0·83, 95% CI 0·78–0·88; p<0·001), which was observed to a similar extent across all adult age subgroups (table 1, figure 3). IPD incidence in 2022–23 was highest in adults aged 80 years and older (37·5 per 100 000, 35·3–39·9) and declined with decreasing age (2·8 per 100 000, 2·5–3·0 in those aged 15–44 years; table 1).

The proportion of IPD isolates serotyped was 93·7% (24 195 of 25 829; range 91·4% [1133 of 1240] in 2020–21 to 94·1% [4326 of 4598] in 2022–23). Serotype group distribution was similar before, during, and immediately after pandemic restrictions (appendix p 5). Across all ages, PCV13 serotypes were responsible for 19·4% (95% CI 18·2–20·4, 957 of 4947) of serotyped isolates in 2019–20 and 20·0% (17·6–22·3, 226 of 1133) in 2020–21, but increased to 29·7% (28·3–31·0, 1283 of 4326) in 2022–23 (p<0·001). This increase was observed both in those aged 15 years and older (19·7%, 95% CI 18·6–20·8

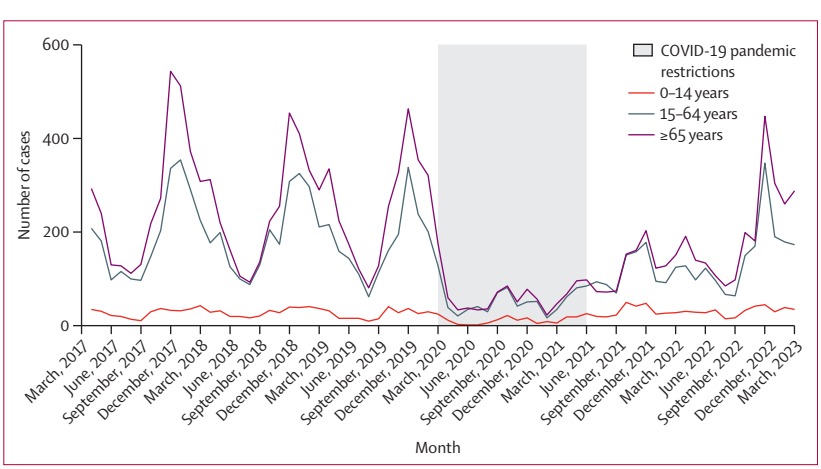

Figure 1: **Invasive pneumococcal disease cases by month and age group, 2017–18 to 2022–23**
The shaded area indicates the period with pandemic-associated restrictions of varying severity.

[922 of 4681], in 2019–20 *vs* 30·4%, 29·0–31·9 [1213 of 3985], in 2022–23; p<0·001) and children younger than 15 years (13·2%, 9·6–17·2 [35 of 266] in 2019–20 *vs* 20·5%, 16·2–24·8 [70 of 341], in 2022–23; p=0·02; appendix p 5). The increase was driven primarily by an increase in serotype 3 disease alongside a

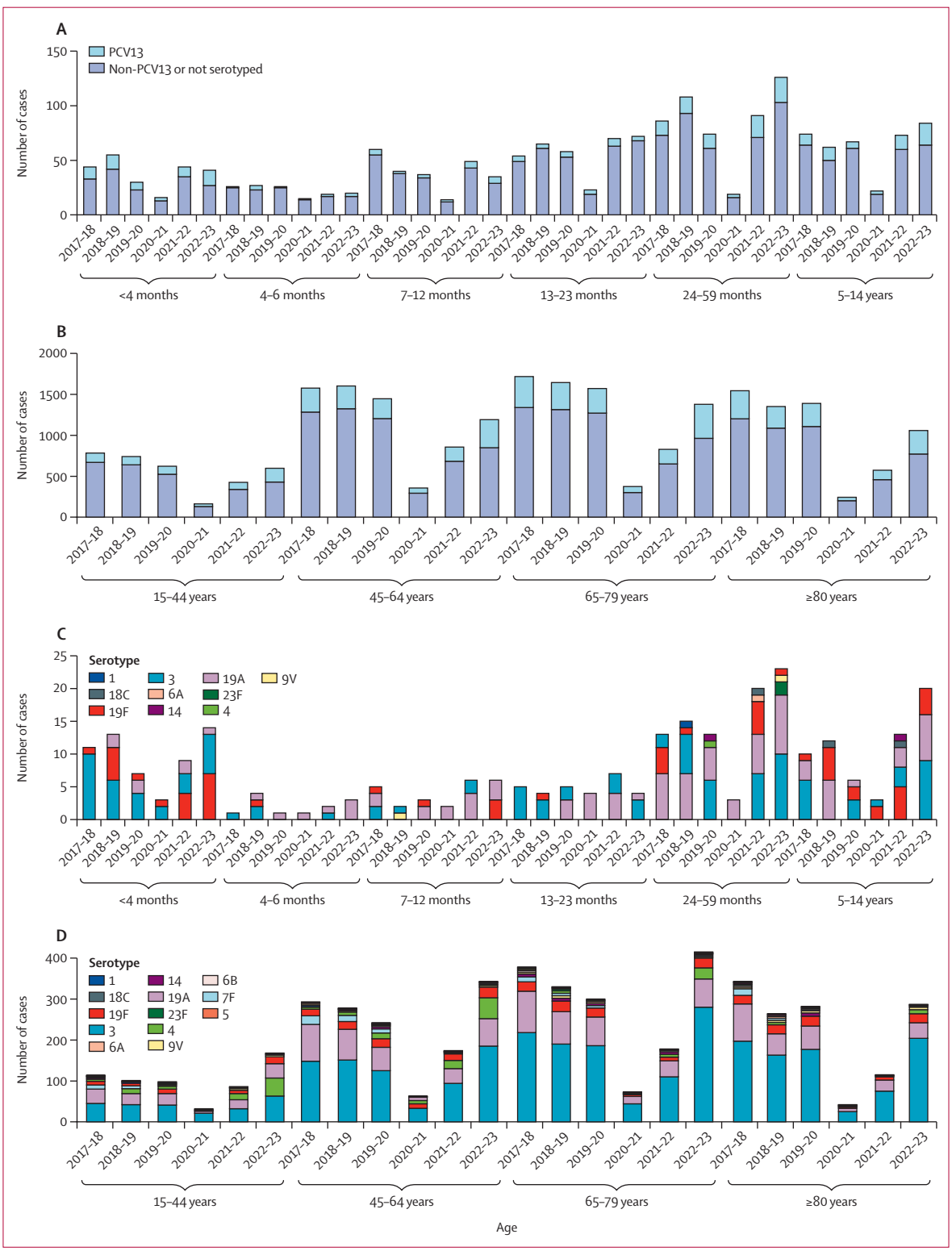

Figure 2: **Invasive pneumococcal disease cases by financial year, serotype, and age group**
(A) Cases by year in subgroups of individuals younger than 15 years; cases are grouped according to serotype group (PCV13 serotypes *vs* non-PCV13 serotypes or not typed). (B) Cases by year in subgroups of individuals aged 15 years and older; cases are grouped according to serotype group (PCV13 serotypes *vs* non-PCV13 serotypes or not typed). (C) PCV13-type invasive pneumococcal disease cases by year in subgroups of individuals younger than 15 years; cases are grouped according to serotype. (D) PCV13-type invasive pneumococcal disease cases by year in subgroups of individuals aged 15 years and older; cases are grouped according to serotype. PCV13=13-valent pneumococcal conjugate vaccine.

contemporaneous decrease in some of the common non-PCV13 serotypes (8, 9N, and 12F; appendix pp 6–7). IPD due to some of the other PCV13 serotypes also increased, including serotypes 19A and 19F in children and serotype 4 in adults.

Overall, PCV13 IPD rates remained low and below pre-PCV13 rates (figure 3), but incidence was significantly higher in 2022–23 than in 2019–20 (IRR 1·33, 95% CI 1·18–1·50; p<0·001; table 1). By contrast, non-PCV13 IPD incidence was significantly lower (0·76, 0·71–0·81; p<0·001) in 2022–23 compared with 2019–20 across all ages, except in children aged 1–4-years, for whom it was higher (table 1). In the sensitivity analysis considering serotype 3 as a non-PCV13 serotype, PCV13 IPD incidence remained significantly higher overall in 2022–23 than in 2019–20 (1·26, 1·05–1·52; p=0·02), although PCV13 incidence was only significant for those aged 15–44 years in a subgroup analysis (appendix p 8). Non-PCV-13 disease incidence remained significantly lower overall and in all age groups older than 45 years in 2022–23 than in 2019–20 (appendix p 8).

In 2022–23, serotype 3 replaced serotype 8 as the most prevalent serotype causing IPD (760 [17·6%] serotype 3 and 720 [16·6%] serotype 8 of all 4326 serotyped cases; appendix pp 6–7). In total, whole-genome sequencing results were available for 22 185 (91·7%) of 24 195 serotyped cases (range 69·0% [3899 of 5649] in 2017–18 to 99·1% [1123 of 1133] in 2020–21). This whole-genome sequencing data identified very similar circulating strains within serotype 3 isolates throughout the whole studied period (2017–18 to 2022–23), with most cases belonging to GPSC12 (2528 [92·1%] of 2746; appendix p 10). Within GPSC12, multilocus sequence type (ST) 180 strains accounted for 2469 (97·7%) of the 2528 isolates overall and 674 (98·1%) of 687 in 2022–23. SDI for GPSCs expressing serotype 3 remained low throughout the surveillance period (0·17 in 2017–18 and 0·15 in 2022–23; appendix p 9). Notably, 28 (96·6%) of 29 serotype 3 breakthrough cases and vaccine failures were GPSC12, all of which were ST180. Following Kwun and colleagues' methods,[20] GPSC12 was subdivided into discrete clades (appendix p 2), which showed that clade I was the most frequent clade in 2017–18 (208 [50·6%] of 411 isolates), but clade IV increased and was predominant in 2022–23 (464 [67·5%] of 687; figure 4A; appendix p 11).

As with serotype 3, the greatest number of cases of IPD caused by serotype 19F was in 2022–23 (n=104). Strains expressing serotype 19F were more diverse than those expressing serotype 3 (SDI range 0·81 in 2017–18 to 0·65 in 2022–23; appendix p 9) and, overall, GPSC44 was most prevalent (139 [34·9%] of 398), followed by GPSC119 (127 [31·9%] of 398) and GPSC6 (68 [17·1%] of 398). In 2022–23, following an increasing trend, GPSC119 became the most common strain (47 [45·6%] of 103) and main driver of the increase in IPD caused by serotype 19F, followed by GPSC44 (38 [36·5%] of 104) and GPSC6 isolates (nine [8·7%] of 104; appendix p 12). Within GPSC119, most isolates were ST654 (108 [85·0%] of 127 overall and 39 [83·0%] of 47 in 2022–23), followed by ST3423 (15 [11·8%] of 127 overall and seven [14·9%] of 47 in 2022–23).

Cases due to serotype 19A had the highest frequency in children in 2022–23 (n=24), although similar to previous years overall (appendix p 7). Serotype 19A strain diversity was similar to serotype 19F (SDI range 0·77–0·81; appendix p 9), with four predominant strains overall: GPSC4 (408 [36·1%] of 1130 serotyped 19A isolates), GPSC17 (225 [19·9%]), GPSC27 (166 [14·7%]), and GPSC146 (126 [11·2%]). In 2022–23, the proportion of GPSC17 strains (66 [28·8%] of 229 serotype 19A isolates) was similar to the proportion of GPSC4 (71 [31·0%] of 229), which was predominate in the previous years (appendix p 13). The proportion of GPSC27 strains also declined from 18·0% (43 of

	2019–20		2022–23		Incidence rate ratio for 2022–23 *vs* 2019–20 (95% CI)	p value
	n (adjusted n*)	Incidence per 100 000	n (adjusted n*)	Incidence per 100 000		
Overall invasive pneumococcal disease by age						
<1 year	87 (93)	14·06	92 (105)	15·88	1·13 (0·74–1·73)	0·57
1–4 years	138 (131)	5·15	202 (208)	8·15	1·58 (1·16–2·17)	0·004
5–14 years	67 (59)	0·97	84 (75)	1·24	1·28 (0·80–2·04)	0·30
15–44 years	621 (624)	2·91	596 (590)	2·75	0·94 (0·80–1·11)	0·49
45–64 years	1445 (1314)	10·03	1190 (1069)	8·16	0·81 (0·73–0·91)	<0·001
65–79 years	1570 (1262)	20·89	1377 (1087)	18·00	0·86 (0·78–0·96)	0·005
≥80 years	1388 (1154)	48·93	1057 (885)	37·53	0·77 (0·68–0·86)	<0·001
All ages	5316 (4930)	9·44	4598 (4245)	8·13	0·86 (0·81–0·91)	<0·001
PCV13 invasive pneumococcal disease by age						
<1 year	10 (12)	1·78	23 (29)	4·40	2·46 (0·84–7·21)	0·10
1–4 years	19 (19)	0·76	27 (30)	1·18	1·54 (0·66–3·60)	0·32
5–14 years	6 (6)	0·10	20 (21)	0·35	3·23 (0·85–12·21)	0·070
15–44 years	98 (106)	0·49	168 (176)	0·82	1·69 (1·18–2·42)	0·004
45–64 years	242 (236)	1·80	343 (323)	2·47	1·40 (1·10–1·77)	0·006
65–79 years	300 (260)	4·30	415 (350)	5·79	1·36 (1·09–1·68)	0·005
≥80 years	282 (251)	10·63	287 (254)	10·77	1·02 (0·81–1·30)	0·84
All ages	957 (954)	1·83	1283 (1259)	2·40	1·33 (1·18–1·51)	<0·001
Non-PCV13 invasive pneumococcal disease by age						
<1 year	69 (81)	12·28	60 (76)	11·48	0·93 (0·56–1·53)	0·77
1–4 years	110 (112)	4·39	159 (178)	6·97	1·56 (1·10–2·22)	0·013
5–14 years	52 (53)	0·87	52 (54)	0·90	1·02 (0·58–1·78)	0·95
15–44 years	480 (518)	2·42	394 (413)	1·93	0·81 (0·67–0·98)	0·031
45–64 years	1106 (1078)	8·23	791 (746)	5·69	0·71 (0·62–0·81)	<0·001
65–79 years	1157 (1002)	16·59	874 (737)	12·20	0·74 (0·65–0·84)	<0·001
≥80 years	1016 (903)	38·30	713 (631)	26·76	0·71 (0·61–0·81)	<0·001
All ages	3990 (3976)	7·62	3043 (2986)	5·72	0·76 (0·71–0·81)	<0·001

PCV13=13-valent pneumococcal conjugate vaccine. *Numbers of invasive pneumococcal disease cases were adjusted as if they had the same population size as in 2009–10 in both years, for comparison purposes. There were no individuals with missing age between 2019–20 and 2022–23, and the adjustment accounting for non-serotyped cases did not have an effect on overall numbers.

Table 1: **Comparison of invasive pneumococcal disease cases between 2019–20 and 2022–23**

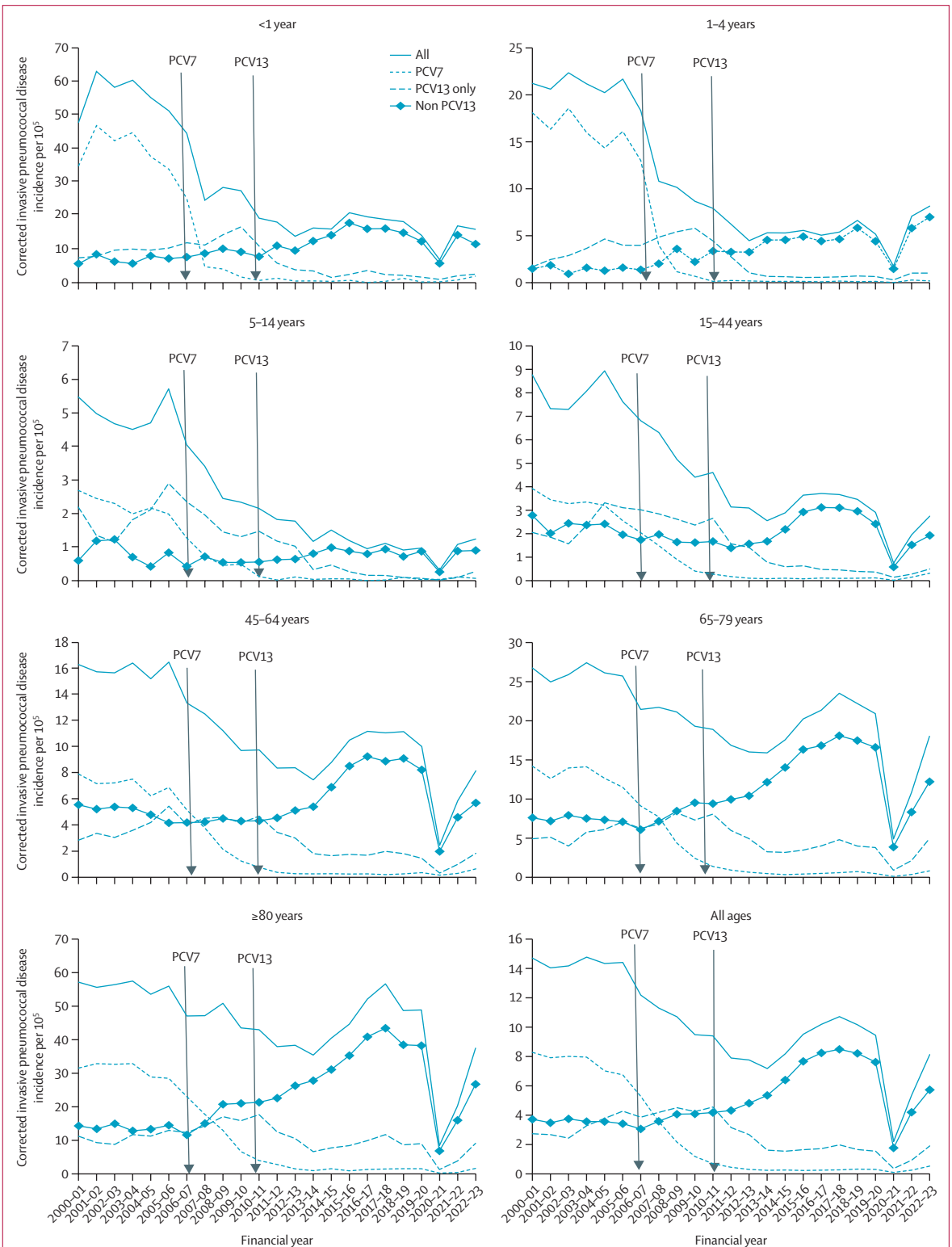

Figure 3: **Corrected disease incidence by age group, serotype group, and financial year, 2000–01 to 2022–23**
The scales of the y-axes vary. PCV7=seven-valent pneumococcal conjugate vaccine. PCV13=13-valent pneumococcal conjugate vaccine.

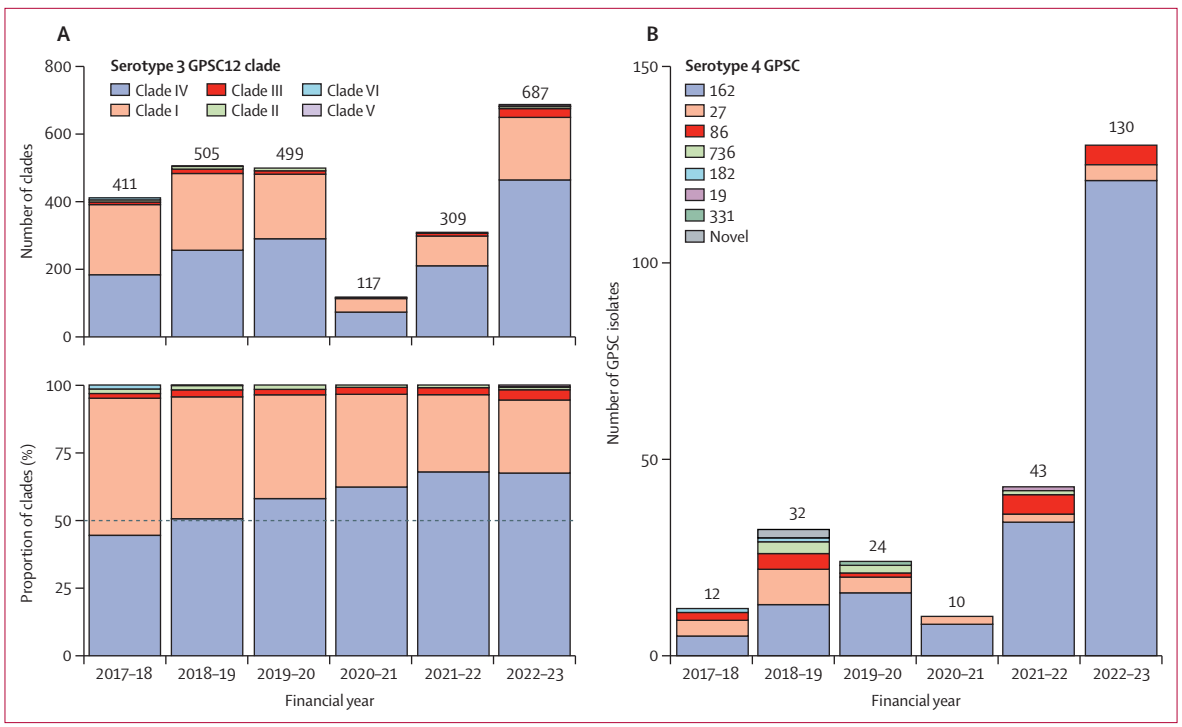

Figure 4: **Serotype 3 GPSC12 clade distribution (A) and serotype 4 GPSC distribution (B), by financial year**
Clades are as described by Kwun and colleagues.[20] GPSC=Global Pneumococcal Sequencing Cluster.

239 serotype 19A isolates) in 2017–18 to 10·9% (25 of 229) in 2022–23 (appendix p 13).

IPD caused by serotype 4, which was rare in previous years, increased from 24 cases in 2019–20 to 132 in 2022–23, mostly among those aged 15–64 years (95 [72·0%] of 132) and 65–79 years (27 [20·5%] of 132), compared with only one infection in those younger than 15 years overall, which occurred in 2019–20. Serotype 4 strain diversity was high in 2017–18 (SDI 0·65), with most isolates in 2017–18 belonging to GPSC162 (five [41·7%] of 12) and GSPC27 (four [33·3%] of 12). However, strain diversity has followed a decreasing trend since 2018–19, reaching 0·13 in 2022–23 (appendix p 9), driven by rapid expansion of GPSC162 (figure 4B), which accounted for 93·1% (121 of 130) of serotype 4 isolates in 2022–23. Within GPSC162, the increase was mainly driven by two STs (ST801 and ST15063), which are single locus variants of each other and were first identified in our dataset in 2018–19 (ST801) and 2020–21 (ST15063). A GPSC162 phylogeny revealed that the ST801 and ST15063 isolates were in two separate but closely related clades (appendix p 14).[21] Within the predominant ST801 clade, the ST13753 isolates, which were prevalent in the pre-pandemic period (2017–18 to 2019–20) and are single locus variants of ST801, are also spread polyphyletically. Both ST801 and ST15063 isolates are more distantly related to the less frequent ST1022 and ST7776 lineages.

There were ten vaccine failures and nine breakthrough infections in 2022–23 in children eligible for the 1+1 schedule, compared with three to eight failures and eight to 11 breakthrough infections annually in the three comparable birth cohorts of children eligible for the 2+1 schedule in the pre-pandemic years (2017–18 to 2019–20). Most cases were due to serotypes 3, 19A, and 19F (table 2). The combined rate of vaccine failure and breakthrough infections in 1+1 eligible children in 2022–23 (1·08 per 100 000 person-years [19 of 1 758 189 livebirths]) was not significantly different to the rate in 2+1 eligible children between 2017–18 and 2019–20 (0·76 per 100 000 person-years [44 of 5 792 902 livebirths]; IRR 1·42, 95% CI 0·78–2·49; p=0·20).

In 2022–23, 300 (6·5%) of 4598 IPD cases presented as meningitis compared with 274 (5·2%) of 5316 in 2019–20 (p=0·003). Overall, meningitis presentations decreased with increasing age, from 400 (21·9%) of 1826 cases in those younger than 15 years to 399 (2·9%) of 13 659 cases in those older than 65 years.

The 30-day case-fatality rate (CFR) was 18·3% (843 of 4598) in 2022–23, which was similar to the 30-day CFR in 2019–20 (17·3%, 918 of 5316; p=0·16). There was also no significant difference within age groups. For children younger than 15 years, the 30-day CFR was 7·4% (28 of 378) in 2022–23 and 4·1% (12 of 292) in 2019–20 (p=0·074). For those aged 15–64 years, the 30-day CFR was 10·4% (185 of 1786) in 2022–23 and 9·6% (198 of 2066) in 2019–20 (p=0·42). For adults aged 65 years and older, the 30-day CFR was 25·9% (630 of 2434) in 2022–23 and 23·9% (708 of 2958) in

	2+1 schedule, 2017–18 (n=1 974 350)*	2+1 schedule, 2018–19 (n=1 935 602)†	2+1 schedule, 2019–20 (n=1 882 950)‡	1+1 schedule, 2022–23 (n=1 758 189)§
Breakthrough infection				
Total	8 (0·41)	11 (0·57)	9 (0·48)	9 (0·51)
Serotype				
19A	2 (0·10)	1 (0·05)	5 (0·27)	7 (0·40)
19F	1 (0·05)	2 (0·1)	1 (0·05)	2 (0·11)
3	5 (0·25)	7 (0·36)	2 (0·11)	0
9V	0	1 (0·05)	0	0
14	0	0	1 (0·05)	0
Vaccine failure				
Total	5 (0·25)	8 (0·41)	3 (0·16)	10 (0·57)
Serotype				
19A	1 (0·05)	5 (0·26)	1 (0·05)	2 (0·11)
19F	0	0	0	1 (0·06)
3	4 (0·20)	3 (0·15)	2 (0·11)	7 (0·40)

Data are n (rate per 100 000). Breakthrough infection was defined as PCV13-type invasive pneumococcal disease at least 14 days after ≥1 PCV13 dose received before 1 year of age. Vaccine failure was defined as PCV13-type invasive pneumococcal disease ≥7 days after ≥1 PCV13 dose received on or after 1 year of age. Further details for cohort selection are available in the appendix (p 3). PCV13=13-valent pneumococcal conjugate vaccine. *Children born between Jan 1, 2015, and Dec 31, 2017. †Children born between Jan 1, 2016, and Dec 31, 2018. ‡Children born between Jan 1, 2017, and Dec 1, 2019. §Children born between Jan 1, 2020, and Dec 31, 2022.

Table 2: **Vaccine failures and breakthrough infections by vaccine schedule eligibility**

2019–20 (p=0·10). There have been no deaths within 30 days of IPD diagnosis in vaccinated children younger than 5 years since 2019–20.

Discussion

In England, there were large declines in IPD during 2020–21, which coincided with COVID-19 pandemic lockdowns and restrictions; cases started to rise again in 2021–22 when all restrictions were removed on July 19, 2021, with cases in children rapidly reaching pre-pandemic levels, whereas adult cases increased more gradually and remained below pre-pandemic rates in 2022–23. PCV13 serotypes contributed to a higher proportion of IPD cases in 2022–23 than in 2019–20, driven particularly by an increase in serotype 3, which is poorly protected by PCV13,[1] alongside a contemporaneous decline in infections caused by some of the more common non-PCV13 serotypes. Whole-genome sequencing revealed that the post-pandemic increases in serotypes 3, 19A, and 19F were driven mainly by the same pre-pandemic strains, although serotype 3 GPSC12 clade IV strains now predominate, consistent with previous analyses.[16] The 1+1 infant immunisation schedule implemented on Jan 1, 2020, has not yet been associated with an increase in breakthrough and vaccine failure rates in children. Additionally, the same PCV13 serotypes remained responsible for breakthrough infections and vaccine failures before and after the change in immunisation schedule. Reassuringly, CFRs remained unchanged between 2019–20 and 2022–23, meaning that the large decline in IPD cases during the pandemic led to fewer pneumococcal deaths. However, the proportion of individuals presenting with meningitis increased, probably because of changes in the age distribution of cases and the responsible serotypes.

The increase in IPD cases after pandemic restrictions were removed was first observed in children younger than 5 years in several countries, including the UK,[12,13,22] with cases exceeding pre-pandemic rates and raising concerns about a potential loss of herd protection.[14] The increasing IPD trend in young children and adults continued in 2022–23 for both PCV13 and non-PCV13 serotypes but overall incidence in 2022–23 was 14% below incidence in 2019–20.[23]

The number and proportion of IPD cases that were due to PCV13 serotypes increased significantly in 2022–23 compared with 2019–20, driven mainly by serotype 3, but also serotypes 19A and 19F in children. This increase is, however, unlikely to be due to changes in the infant immunisation schedule, since breakthrough infections and vaccine failures have remained low and stable, similar to pre-pandemic. Additionally, non-PCV13 disease incidence also increased in children aged 1–4 years. Early in the pandemic, restrictions in mixing, including national lockdowns, school closures, and working from home, were associated with large reductions in respiratory infections, resulting in less exposure to pathogens and rendering large cohorts of young children susceptible to these infections. This so-called immunity debt or population-susceptibility gap is considered to explain a compensatory increase in respiratory infections in the immediate post-pandemic years after all restrictions were removed.[24] The large and out-of-season surges in respiratory viruses might have contributed to increases in secondary IPD,[13,22,25] potentially affecting case numbers and shaping serotype distributions of circulating pneumococci, depending on specific viral–serotype interactions.[26] Despite the negative effect of the pandemic on childhood immunisation rates,[27] PCV13 uptake has remained high in England, at 93·2% for infant doses by age 12 months and 90·4% for the complete schedule by age 24 months in 2019–20 compared with 93·8% and 89·3%, respectively, in 2021–22. This coverage should help sustain the high population (ie, herd) protection offered by the current PCV13 immunisation programme. Other countries using 2+1 and 3+1 PCV13 schedules have also reported post-pandemic increases in overall IPD[12,13] and IPD caused by PCV13 serotypes,[28] which suggest that the observed IPD increase in children is more likely due to a changing pattern of social mixing over the pandemic and changing viral circulation than to the change in the immunisation schedule.

The recent increase in PCV13-type IPD will require careful monitoring. PCV13 effectiveness is lower for the PCV13 serotypes that increased in incidence (3, 19A, and 19F), especially serotype 3.[1] These serotypes are the most common among breakthrough infections and vaccine failures,[1] and also among the most frequently carried

vaccine serotypes in vaccinated children,[29,30] indicating that they will probably continue to circulate and cause occasional disease, irrespective of the infant PCV13 schedule. As such, vaccines with better protection against serotype 3 are urgently needed, given that this serotype now accounts for one in six IPD cases in England and is associated with severe disease and death.[31]

The increase in serotype 4 IPD in adults is new and unexpected. For serotype 4, antibody levels after the booster were higher in children receiving the 1+1 than the 2+1 schedule, which is not consistent with a reduction in herd immunity related to the schedule change.[32] Serotype 4 has previously been reported to cause outbreaks, particularly among individuals who are homeless and people who inject drugs,[33] and it was recently also reported to have increased adults in Canada.[23] Whole-genome sequencing of serotype 4 isolates in Canada (2010–18) identified that most (187 of 190) were ST244, ST205, and ST695.[33] These STs are associated with GPSC27, which has now largely been replaced by GPSC162 in England. The expanding ST801 lineage within GPSC162 has previously been linked to shipyard outbreaks in northern Europe.[34]

The strength of this study is the use of a well established national surveillance system, with very high rates of serotyping and whole-genome sequencing of invasive isolates, which allowed us to report rates and trends in near-real time. As such, we were quickly able to report the post-pandemic changes in IPD 3 years after the first lockdown in England. Assessment of the PCV13 1+1 schedule has been challenging because its implementation coincided with the start of pandemic restrictions. However, this surveillance only captures invasive disease; therefore, we are unable to comment on trends in non-IPD, especially pneumonia, but we anticipate trends to be similar to those observed with IPD.[35] Additionally, our experience with the 1+1 PCV13 immunisation schedule in England might not be generalisable to other countries for many reasons, including pre-vaccine IPD epidemiology, viral co-circulation, pneumococcal serotype distribution, and vaccine uptake. Finally, given the difficulties in directly assessing the effect of the 1+1 PCV13 programme, especially on a background of large and out-of-season resurgence in respiratory viral infections,[13,22,24] ongoing surveillance with additional birth cohorts will remain crucial, especially given the small serotype-specific disease case numbers in children eligible for the 1+1 PCV13 immunisation schedule.

In conclusion, the change from a 2+1 to a 1+1 PCV13 infant immunisation schedule in England coincided with the start of the COVID-19 pandemic, hindering formal assessment of the reduced schedule. 2 years after the removal of all pandemic-associated restrictions, overall IPD incidence was 14% lower than pre-pandemic rates but 34% higher in children, mainly due to an increase in IPD due to non-PCV13 serotypes and an increase in some PCV13 serotypes causing IPD, especially serotype 3. During the first 3 years of the 1+1 PCV13 programme, the rate of breakthrough infections and vaccine failures was not significantly different to rates in a comparable cohort of children receiving the 2+1 schedule. Because of small case numbers, ongoing surveillance with additional birth cohorts is warranted. The increase in IPD due to some PCV13 serotypes, particularly serotype 3, will also require careful monitoring.

Contributors

SNL, MER, DJL, and NJA were responsible for the conceptualisation of the study. MB, JCD'A, and FA curated the data. MB conducted the epidemiological analysis and JCD'A, SE, and DJL did the genomic analysis and interpreted the results. MB and JCD'A accessed and verified the data. MB wrote the first draft of the manuscript, which was edited and reviewed by all authors. All authors have seen and approved the final manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

The Immunisation and Vaccine Preventable Diseases Division (UKHSA) provides vaccine manufacturers with post-marketing surveillance reports on pneumococcal and meningococcal infections, which the companies are required to submit to the Medicines and Healthcare products Regulatory Agency in compliance with the companies' Risk Management Strategy. A cost recovery charge is made for these reports. SNL performs contract research on behalf of St George's University of London and the UKHSA for pharmaceutical companies but receives no personal remuneration. The Respiratory and Vaccine Preventable Bacteria Reference Unit (UKHSA) has received grant funding from vaccine manufacturers for investigator-led research projects on pneumococcal surveillance. All other authors declare no competing interests.

Data sharing

Applications for relevant anonymised data should be submitted to the UKHSA Office for Data Release via https://www.gov.uk/government/publications/accessing-ukhsa-protected-data.

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