Characteristics of children with invasive pneumococcal disease eligible for the 1+1 compared with the 2+1 PCV13 infant immunisation schedule in England: a prospective national observational surveillance study

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Summary

Background On Jan 1, 2020, the UK transitioned from a 2+1 to a 1+1 national infant immunisation schedule with the 13-valent pneumococcal conjugate vaccine (PCV13). We assessed whether the 1+1 PCV13 schedule had any impact on incidence, disease characteristics, or outcomes after invasive pneumococcal disease (IPD) in eligible children aged 0–3 years.

Methods The UK Health Security Agency conducts IPD surveillance and serotyping of invasive pneumococcal isolates via whole-genome sequencing in England. IPD was defined as identification of *Streptococcus pneumoniae* in a sterile site. We compared IPD incidence, demographics, clinical presentation, comorbidity prevalence, serotype distribution, and case-fatality rates (CFRs) in children from a single birth cohort eligible for the 1+1 schedule (born between Jan 1, 2020, and Dec 31, 2022) who developed IPD in the 2022–23 financial year (April to March) with children from three equivalent historical birth cohorts (born between Jan 1, 2015, and Dec 31, 2019) eligible for the 2+1 schedule who developed IPD during three respective pre-pandemic financial years: 2017–18, 2018–19, and 2019–20.

Findings There were a total of 702 IPD episodes in 697 children, including 158 (incidence 8·99 per 100 000 person-years) in the single 1+1 birth cohort and 544 (incidence 9·39 per 100 000 person-years) in the 2+1 birth cohorts, with no significant difference in the incidence of overall IPD (incidence rate ratio 0·96, 95% CI 0·80–1·14, p=0·63), PCV13-type IPD (1·21, 0·71–2·00, p=0·45), or pneumococcal meningitis (0·97, 0·66–1·40, p=0·88). Comorbidity prevalence, clinical presentation, and CFRs were also similar between the two cohorts, as was the percentage of cases in infants too young to be vaccinated (<2 months old) and infants aged 5–11 months who received one or two PCV13 priming doses, in the 1+1 and 2+1 cohorts respectively.

Interpretation After 3 years, the 1+1 schedule continues to provide direct and indirect protection against PCV13-type IPD in children, with no significant change in overall IPD incidence, serotype distribution, clinical presentation, or CFRs in children eligible for the 1+1 compared with the 2+1 schedule. Ongoing surveillance will be important to assess longer-term direct and indirect population protection.

Funding None.

Introduction

Streptococcus pneumoniae is a major cause of infectious morbidity and mortality worldwide, with infections ranging from non-invasive respiratory tract infections such as otitis media and sinusitis to more severe invasive pneumococcal disease (IPD), including septicaemia and meningitis.[1] Over 100 immunologically distinct pneumococcal serotypes have been identified.[2] Pneumococcal conjugate vaccines (PCVs) are highly effective in preventing IPD caused by the respective vaccine serotypes.[3] In September, 2006, the UK implemented a seven-valent PCV (PCV7) into the national infant immunisation programme with a 2+1 schedule (at 8 weeks, 16 weeks, and 1 year of age), which was replaced with a 13-valent PCV (PCV13) in April, 2010.[4] Both programmes were associated with large declines in vaccine-type IPD across all age groups through a combination of direct protection in vaccinated children and indirect (herd) protection due to PCVs preventing carriage acquisition of vaccine serotypes in vaccinated children and interrupting onward transmission to unvaccinated individuals.[5–7] Following both programmes, however, there was an increase in IPD due to non-vaccine serotypes, known as serotype replacement, although overall IPD incidence has remained lower than in the pre-PCV era.[8]

By the 2014–15 epidemiological year, 4 years after PCV13 implementation, there were no further reductions in PCV13-type IPD as maximum benefit had been achieved.[7] Consequently, in 2018, the UK Joint Committee on Vaccination and Immunisation recommended

Research in context

Evidence before this study

We searched PubMed on March 6, 2024, using the terms ("invasive pneumococcal disease" OR "IPD" OR "pneumococcal") AND ("pneumococcal conjugate vaccine" OR "PCV" OR "conjugate vaccine") AND ("schedule" or "reduced schedule" or "1+1") in the title, for articles in English and without date restrictions. In 2020, the UK became the first country to reduce the 13-valent pneumococcal conjugate vaccine (PCV13) infant immunisation schedule from a 2+1 schedule (at 8 weeks, 16 weeks, and 1 year of age) to a 1+1 schedule (at 12 weeks and 1 year of age), after PCV13-type invasive pneumococcal disease (IPD) cases plateaued across all age groups. No other country uses a 1+1 PCV immunisation schedule for comparison, but several clinical trials have recently investigated the immunogenicity and impact on carriage of 1+1 PCV infant immunisation schedules. A South African immunogenicity trial found a 1+1 schedule to be non-inferior for ten of the 13 serotypes when PCV13 was administered at 6 weeks and 40 weeks of age, and non-inferior to 11 serotypes when administered at 14 weeks and 40 weeks of age, with lower colonisation rates with PCV13 serotypes at age 15 months compared with the 2+1 group. In India, similar immune responses were observed in the second year of life in infants receiving a 1+1 or a 2+1 PCV13 schedule, with a 45% decrease (odds ratio 0·55 [95% CI 0·31–0·97]) in carriage of PCV13 serotypes compared with unvaccinated controls.

Added value of this study

In March, 2020, the COVID-19 pandemic coincided with the first children receiving the reduced PCV13 immunisation schedule. Restrictions implemented to reduce the spread of SARS-CoV-2 led to large reductions in respiratory infections, including pneumococcal disease, which hampered the evaluation of the 1+1 PCV13 programme. After 3 years, using national surveillance data and complete clinical follow-up of all eligible children with confirmed IPD, this is the first evaluation of the demographics, vaccination status, underlying comorbidities, serotypes responsible, clinical presentation, and outcomes of IPD in a cohort of children eligible for the 1+1 PCV13 immunisation schedule compared with three cohorts eligible for the 2+1 schedule. We found overall IPD and pneumococcal meningitis rates were not significantly different between the two groups. Of the IPD cases with serotyped isolates, serotypes 3, 19A, and 19F were responsible for 98% of PCV13-type IPD, with similar serotype distributions between the two cohorts. Clinical presentations were also similar between the two groups, with bacteraemic pneumonia predominating. Case fatality rates remained very low across both groups and, notably, there were no deaths due to PCV13-type IPD in the 1+1 cohort.

Implications of all the available evidence

Our findings provide further evidence to support the transition from a 2+1 to a 1+1 PCV13 infant immunisation schedule in the context of a mature PCV vaccination programme. 3 years into the programme in England, the 1+1 PCV13 programme continues to maintain direct and indirect protection against PCV13-type IPD in children, with no evidence of any change in disease incidence, severity, or outcomes in the eligible population. Our findings are relevant for policy makers in high-income countries with established national childhood PCV programmes. As we continue to emerge out of the COVID-19 pandemic, national surveillance will be important for monitoring the ongoing and longer-term impact of the 1+1 immunisation schedule.

a reduced 1+1 PCV13 infant immunisation schedule, based on evidence from surveillance data showing sustained low PCV13-type IPD incidence across all age groups,[7,8] a randomised controlled trial showing acceptable pneumococcal serotype-specific antibody concentrations after the 12-month booster,[9] and modelling studies predicting little change in IPD cases or outcomes with the 1+1 schedule.[10]

On Jan 1, 2020, the UK became the first country to implement a 1+1 PCV13 infant immunisation schedule at 12 weeks and 1 year of age.[11] The first infants received the first of their two PCV13 doses in April, 2020, which coincided with the start of the COVID-19 pandemic. Non-pharmaceutical interventions, including national lockdowns, implemented in March, 2020 to reduce the spread of SARS-CoV-2 resulted in large declines in respiratory viral and bacterial infections, including IPD.[12] With the removal of all pandemic restrictions in July, 2022, IPD cases in England increased, especially in young children, although overall IPD incidence in 2022–23 remained 14% below pre-pandemic rates.[13] Notably, the percentage of IPD due to PCV13 serotypes increased from 19·4% in 2019–20 to 29·7% in 2022–23.[13] This increase was mainly due to serotypes 3, 19F, and 19A, which have continued to circulate in carriage and disease, alongside a decrease in IPD due to some non-PCV13 serotypes, especially 8, 9N, and 12F.[13]

In children, however, the risk of breakthrough infections (PCV13-type IPD after primary immunisation) and vaccine failure cases (PCV13-type IPD after booster) in a single birth cohort of children eligible for the 1+1 PCV13 schedule who developed IPD during 2022–23 (19 cases in the single birth cohort) was similar to three equivalent historical birth cohorts eligible for the 2+1 schedule who developed IPD between 2017–18 and 2019–20 (44 cases over three cohorts), and the combined incidence of breakthrough infections and vaccine failures was not significantly different between the two groups (1·08 per 100 000 person-years *vs* 0·76 per 100 000 person-years, respectively; p=0·20).[13] While these data provide reassurance for the continuation of the childhood 1+1 PCV13 programme, little is known about the risks,

characteristics, severity, or outcomes of IPD in children eligible for the 1+1 PCV13 schedule compared with the 2+1 schedule. There were concerns that a single priming dose might be associated with increased risk of IPD in the first year of life, when meningitis (the most severe clinical manifestation of IPD, with the highest case fatality rates [CFRs] and serious neurodevelopmental sequelae)[14] is most prevalent. It was also possible that a higher proportion of previously healthy infants might develop IPD because of lower protection offered by the single PCV13 priming dose or, alternatively, that the prevalence of specific comorbidities associated with increased IPD risk in children with IPD might have changed.[15]

By extending our previous study[13] we followed up all children with confirmed IPD in England and investigated the incidence of overall IPD and PCV13-type IPD, as well as demographics, age distribution, responsible serotypes, clinical presentation, comorbidities, and CFR in the same single birth cohort of children eligible for the 1+1 PCV13 schedule compared with the three equivalent historical birth cohorts eligible for the 2+1 schedule.

Methods

Enhanced surveillance

The UK Health Security Agency (UKHSA) conducts enhanced IPD surveillance in England.[16] National Health Service (NHS) hospitals across England routinely report laboratory-confirmed invasive pneumococcal infections to UKHSA electronically via the Second-Generation Surveillance System and submit invasive pneumococcal isolates to the UKHSA reference laboratory for confirmation and serotyping via whole-genome sequencing.[7] Reported invasive infections without submitted isolates are actively followed up to maintain high isolate submission rates; subsequently, over 90% of all invasive pneumococcal isolates are routinely sequenced. For confirmed IPD cases, surveillance questionnaires are sent to general practitioners to collect information on vaccination history, demographics, comorbidities, and outcomes. IPD cases were also linked to Hospital Episode Statistics Admitted Patient Care[17] records to improve information on ethnicity, comorbidities, and gestational age at birth using relevant fields and International Classification of Diseases (10th Revision) codes from inpatient episodes before and during the IPD episode. The Personal Demographics Service, a national electronic database of patients registered with the NHS, was used to confirm deaths within 30 days of diagnosis.

UKHSA has legal permission to process confidential information for the purpose of national surveillance of communicable diseases without individual patient consent (Regulation 3 of Health Service Regulations 2002) and so ethics committee approval is not required.

Definitions

IPD was defined as isolation of *S pneumoniae* from a normally sterile site, or detection of pneumococcal DNA by PCR in cerebrospinal fluid or pleural fluid. Multiple samples within 28 days from the same individual were considered a single IPD episode. We analysed cases by financial year (April 1 to March 30). Eligibility for the 1+1 schedule was determined by date of birth and included children born from Jan 1, 2020, to Dec 31, 2022 who developed IPD in the 2022–23 financial year (1+1 cohort; figure 1). This cohort was compared against three equivalent birth cohorts eligible for the 2+1 schedule (2+1 cohort) who were born (1) between Jan 1, 2015, and Dec 31, 2017 and developed IPD during 2017–18, (2) between Jan 1, 2016, and Dec 31, 2018 and developed IPD during 2018–19, and (3) between Jan 1, 2017, and Dec 31, 2019 and developed IPD during 2019–20 (figure 1).

Comorbidities are defined according to the Green Book, Immunisation against Infectious Disease.[15] Comorbidity status was categorised into none or one or more

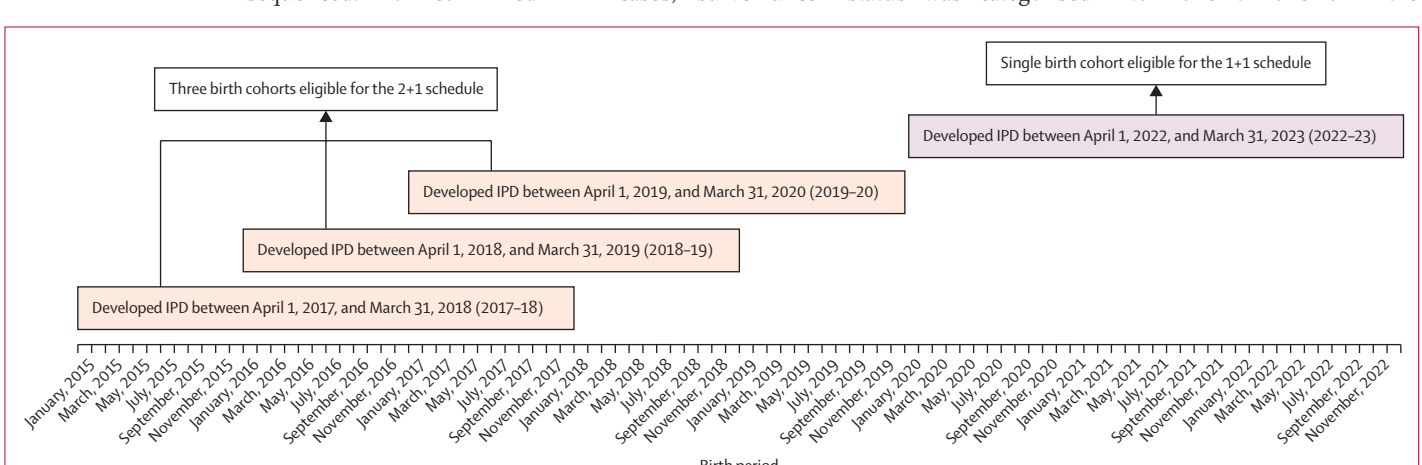

Figure 1: **Birth cohort criteria and inclusion criteria**
The birth periods for each cohort (three birth cohorts eligible for the 2+1 schedule and one birth cohort eligible for the 1+1 schedule) are shown in the timeline. The inclusion in the analysis depends on cases occurring the specified financial year and birth period. IPD=invasive pneumococcal disease.

comorbidities.[15] Cases were categorised as being born preterm if reported to have been born before 37 weeks gestation. Ethnicity was categorised broadly as White or White British, Black or Black British, Asian or Asian British, and Mixed or Other due to small numbers. Clinical presentation was defined hierarchically as meningitis, bacteraemic pneumonia, other presentations, and septicaemia (appendix p 3).

Only vaccination doses received at least 14 days before IPD diagnosis were included in the analyses. We defined breakthrough infections as PCV13-type IPD at least 14 days after one or more PCV13 doses received before the first birthday and vaccine failures as PCV13-type IPD at least 7 days after one or more PCV13 doses administered after the first birthday. CFRs were defined as death within 30 days of IPD diagnosis.

Statistical analysis

Data were analysed using Stata 17 and R 4.3.2. Percentages of categorical variables were compared using the χ^2 or Fisher's exact test where expected cell counts were less than 5. Using logistic regression models, each categorical variable found to be non-significant ($p>0\cdot05$) following comparisons by χ^2 or Fisher's exact tests was adjusted for any variables found to be significant ($p<0\cdot05$), in order to check for any significant differences in those variables between cohorts following adjustment. Age is presented as median with IQR and compared using the Mann–Whitney *U* test. Age groups were categorised as younger than 2 months, 2–4 months, 5–11 months, and 1–3 years (a child aged, eg, 4·9 months, 11·9 months, or 3 years and 11 months would be included in the 2–4 month, 5–11 month, and 1–3 year categories, respectively). The cohorts were compared and analysed by PCV13-type IPD (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) and non-PCV13 IPD. Serotypes in higher-valent vaccines were further categorised, including additional PCV15 serotypes (22F and 33F), additional PCV20 serotypes (8, 10A, 11A, 12F, and 15B or C), and additional 23-valent pneumococcal polysaccharide vaccine (PPV23) serotypes (2, 9N, 17F, and 20). Isolates classified as "15B or C" have not been resolved as either 15B or 15C by typing methods and so have been included among PCV20.[13] Crude incidence rates were calculated using the Office for National Statistics livebirths data for England. Incidence rate ratios (IRRs) and 95% CIs were determined using Poisson regression with the 2+1 cohort used as the reference group.

Role of the funding source

There was no funding source for this study.

Results

There were a total of 702 IPD episodes in 697 children, including 158 episodes in 157 children in the single 1+1 birth cohort (IPD incidence, 8·99 per 100 000 person-years) and 544 episodes in 540 children in the three equivalent historical birth cohorts (9·39 per 100 000 person-years (table 1, appendix p 4). The IRRs did not show a significant difference between the two cohorts for overall IPD (IRR 0·96, 95% CI 0·80–1·14, p=0·63), PCV13-type IPD (1·21, 0·71–2·00, p=0·45), or non-PCV13 IPD (0·92, 0·75–1·13, p=0·43; appendix p 4).

The median age of children with IPD was 12 months (IQR 6–20); 388 (55·3%) of 702 cases were in males and 314 (44·7%) in females (table 1). The median age at IPD in the 1+1 cohort was 15 months (IQR 9–22) compared with 12 months (6–19) in the 2+1 cohort. 98 (62·0%) of

See Online for appendix

	2+1 cohort	1+1 cohort	Total	p value
Total IPD episodes	544	158	702	..
IPD episodes with serotype information	496 (91·2%)	144 (91·1%)	640 (91·2%)	..
Median age, months (IQR)	12 (6–19)	15 (9–22)	12 (6–20)	0·0024
Age group	..	..	..	0·065
<2 months	39 (7·2%)	10 (6·3%)	49 (7·0%)	..
2–4 months	71 (13·1%)	13 (8·2%)	84 (12·0%)	..
5–11 months	160 (29·4%)	37 (23·4%)	197 (28·1%)	..
1–3 years	274 (50·4%)	98 (62·0%)	372 (53·0%)	..
Sex*	..	..	..	0·90
Female	244 (44·9%)	70 (44·3%)	314 (44·7%)	..
Male	300 (55·1%)	88 (55·7%)	388 (55·3%)	..
Ethnicity*	..	..	..	0·039
White or White British	423 (77·8%)	125 (79·1%)	548 (78·1%)	..
Black or Black British	31 (5·7%)	4 (2·5%)	35 (5·0%)	..
Asian or Asian British	59 (10·8%)	12 (7·6%)	71 (10·1%)	..
Mixed or other	31 (5·7%)	17 (10·8%)	48 (6·8%)	..
Vaccine serotype†	..	..	..	0·32
PCV13	60 (12·1%)	22 (15·3%)	82 (12·8%)	..
Non-PCV13	436 (87·9%)	122 (84·7%)	558 (87·2%)	..
Vaccine serotype—additional†	..	..	..	0·23
PCV13	60 (12·1%)	22 (15·3%)	82 (12·8%)	..
Additional PCV15 serotypes	71 (14·3%)	22 (15·3%)	93 (14·5%)	..
Additional PCV20 serotypes	188 (37·9%)	49 (34·0%)	237 (37·0%)	..
Additional PPV23 serotypes	25 (5·0%)	2 (1·4%)	27 (4·2%)	..
Non-vaccine serotypes	152 (30·6%)	49 (34·0%)	201 (31·4%)	..
Breakthrough infections and vaccine failures†‡	..	..	..	0·31
Breakthrough infection	28 (5·6%)	9 (6·3%)	37 (5·8%)	..
Vaccine failure	16 (3·2%)	10 (6·9%)	26 (4·1%)	..
Non-vaccine serotype IPD episode	410 (82·7%)	112 (77·8%)	522 (81·6%)	..
Breakthrough infection <14 weeks of age§	2 (0·4%)	0	2 (0·3%)	..
Not age eligible for vaccination	40 (8·1%)	13 (9·0%)	53 (8·3%)	..
Clinical presentation	..	..	..	0·87
Meningitis	129 (23·7%)	38 (24·1%)	167 (23·8%)	..
Bacteraemic pneumonia	194 (35·7%)	52 (32·9%)	246 (35·0%)	..
Other presentation	62 (11·4%)	17 (10·8%)	79 (11·3%)	..
Septicaemia	159 (29·2%)	51 (32·3%)	210 (29·9%)	..
Comorbidities group	..	..	..	0·27
None recorded	400 (73·5%)	123 (77·8%)	523 (74·5%)	..
≥1 comorbidities	144 (26·5%)	35 (22·2%)	179 (25·5%)	..

(Table 1 continues on next page)

	2+1 cohort	1+1 cohort	Total	p value
(Continued from previous page)				
Gestational age	..	..	..	0·019
Term	455 (83·6%)	144 (91·1%)	599 (85·3%)	..
Preterm	89 (16·4%)	14 (8·9%)	103 (14·7%)	..
Death within 30 days	20 (3·7%)	9 (5·7%)	29 (4·1%)	0·26

Data are n (%) unless otherwise stated; n refers to the number of IPD episodes, and denominators for percentages are the total number of IPD episodes unless otherwise stated. IPD=invasive pneumococcal disease. PCV=pneumococcal conjugate vaccine. PPV=pneumococcal polysaccharide vaccine. *Sex was determined from the Personal Demographics Service and surveillance questionnaires; ethnicity was determined from surveillance questionnaires and Hospital Episode Statistics Admitted Patient Care records. †Stated percentages use IPD episodes with serotype information as denominators. ‡Cases without serotype information have been omitted. §Children eligible for the 2+1 PCV13 schedule receive priming doses at 8 weeks and 16 weeks of age, compared with 12 weeks for children eligible for the 1+1 PCV13 schedule. To fit within the definition of a breakthrough infection and ensure comparability, breakthrough infections before age 14 weeks are categorised separately for the 2+1 schedule.

Table 1: **Age, demographics, vaccine serotype group, and clinical and disease characteristics of children eligible for the 1+1 PCV13 schedule with confirmed IPD in 2022–23 and children eligible for the 2+1 schedule with confirmed IPD in 2017–18 to 2019–20**

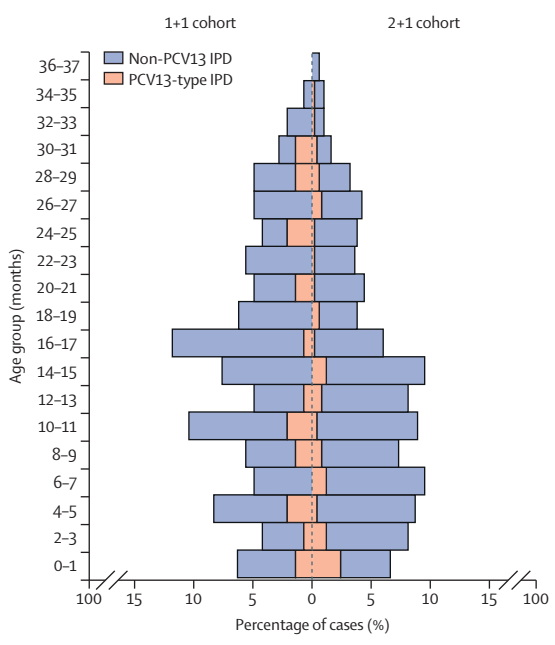

Figure 2: **Percentage of PCV13-type and non-PCV13 IPD by age in the 1+1 and 2+1 cohorts**

Distribution of PCV13-type IPD and non-PCV13 IPD by age group (2-months intervals) as a percentage of cases of IPD (with known serotype) in the 1+1 cohort (left) and the 2+1 cohort (right). In the 1+1 cohort, there were 122 cases of non-PCV13 IPD and 22 cases of PCV13-type IPD. In the 2+1 cohort, there were 436 cases of non-PCV13 IPD and 66 cases of PCV13-type IPD. IPD=invasive pneumococcal disease. PCV=pneumococcal conjugate vaccine.

158 cases in the 1+1 cohort and 274 (50·4%) of 544 in the 2+1 cohort were diagnosed in children aged 1 year or older (table 1). Nearly all children eligible for vaccination had received at least one PCV13 dose at least 14 days before developing IPD, including 143 (97·3%) of 147 eligible children aged 12 weeks or older in the 1+1 cohort and 496 (97·4%) of 509 eligible children aged 8 weeks or older in the 2+1 cohort.

Overall, 640 (91·2%) of 702 isolates were serotyped, including 144 (91·1%) of 158 in the 1+1 cohort and 496 (91·2%) of 544 in the 2+1 cohort (table 1). Of IPD cases with serotyped isolates, the vaccine serotype distribution was similar between the two cohorts (table 1). PCV13 serotypes were responsible for 82 (12·8%) of 640 cases with available serotype, including 22 (15·3%) of 144 in the 1+1 cohort and 60 (12·1%) of 496 in the 2+1 cohort (table 1). The distribution of PCV13-type and non-PCV13 IPD by age at IPD was similar in the two cohorts (figure 2; appendix p 5). In the 1+1 cohort, 11 (50·0%) of 22 PCV13-type IPD cases were diagnosed in children aged 1 year or older, similar to 28 (46·7%) of 60 in the 2+1 cohort (table 2). The PCV13 serotypes responsible for IPD were similar across the two cohorts (p=0·46), with serotypes 3 (41 [50·0%] of 82), 19A (26 [31·7%] of 82), and 19F (13 [15·9%] of 82) comprising 98% of all PCV13-type IPD (figure 3).

Non-PCV13 serotypes caused 558 (87·2%) of 640 IPD cases, including 122 (84·7%) of 144 in the 1+1 cohort and 436 (87·9%) of 496 in the 2+1 cohort (table 2). Serotype 10A was the most common serotype in both cohorts, representing 24 (19·7%) of 122 non-PCV13 IPD cases in the 1+1 cohort and 56 (12·8%) of 436 in the 2+1 cohort (figure 3). Serotype 12F, which was the second most common non-PCV13 serotype overall, was responsible for 53 (12·2%) of 436 non-PCV13 IPD cases in the 2+1 cohort but only one (0·8%) of 122 in the 1+1 cohort.

Overall, 179 (25·5%) of 702 episodes were in children with one or more comorbidities, with similar prevalence between the 1+1 and 2+1 cohorts (22·2% [35 of 158] *vs* 26·5% [144 of 544]; table 1). Congenital abnormalities were the most prevalent underlying comorbidity in both cohorts, with a prevalence of 8·9% (14 of 158) in the 1+1 and 10·8% (59 of 544) in the 2+1 cohort. In the 1+1 cohort, children aged 1–3 years were more frequently immunosuppressed (12 [12·2%] of 98) compared with the same age group in the 2+1 cohort (17 [6·2%] of 274), where congenital anomalies were the most common comorbidity (29 [10·6%] of 274 in the 2+1 cohort *vs* nine [9·2%] of 98 in the 1+1 cohort).

Among PCV13-type IPD, only one (4·5%) of 22 episodes in the 1+1 cohort, compared with 15 (25·0%) of 60 in the 2+1 cohort, occurred in children with at least one comorbidity (table 2). The prevalence of comorbidities in the 1+1 and 2+1 cohorts was similar in children with PCV13-type and non-PCV13 IPD (table 2). Overall, 103 (14·7%) of 702 cases occurred in children who were known to have been born preterm, with a significantly lower prevalence in the 1+1 compared with the 2+1 cohort (8·9% [14 of 158] *vs* 16·4% [89 of 544]; table 1).

Bacteraemic pneumonia was the most common clinical presentation overall (246 [35·0%] of 702), followed by septicaemia (210 [29·9%] of 702), meningitis (167 [23·8%] of 702), and other clinical presentations (79 [11·3%] of 702; table 1), with a similar distribution between the 1+1 and

	Non-PCV13 IPD			PCV13-type IPD		
	2+1 cohort	1+1 cohort	p value	2+1 cohort	1+1 cohort	p value
Total IPD episodes	436	122	..	60	22	..
Median age, months (IQR)	12 (6–19)	15 (9–21)	0·022	9 (2–19)	12 (4–25)	0·27
Age group	..	..	0·12	..	..	0·69
<2 months	21 (4·8%)	7 (5·7%)	..	12 (20·0%)	2 (9·1%)	..
2–4 months	56 (12·8%)	9 (7·4%)	..	8 (13·3%)	4 (18·2%)	..
5–11 months	134 (30·7%)	30 (24·6%)	..	12 (20·0%)	5 (22·7%)	..
1–3 years	225 (51·6%)	76 (62·3%)	..	28 (46·7%)	11 (50·0%)	..
Clinical presentation	..	..	0·70	..	..	0·64
Meningitis	115 (26·4%)	32 (26·2%)	..	5 (8·3%)	2 (9·1%)	..
Bacteraemic pneumonia	151 (34·6%)	36 (29·5%)	..	28 (46·7%)	12 (54·5%)	..
Other presentation	44 (10·1%)	14 (11·5%)	..	9 (15·0%)	1 (4·5%)	..
Septicaemia	126 (28·9%)	40 (32·8%)	..	18 (30·0%)	7 (31·8%)	..
Comorbidities group	..	..	0·49	..	..	0·057
None	315 (72·2%)	92 (75·4%)	..	45 (75·0%)	21 (95·5%)	..
≥1 comorbidities	121 (27·8%)	30 (24·6%)	..	15 (25·0%)	1 (4·5%)	..
Comorbidities	..	..	0·47	..	..	1·00
Sickle-cell disease	3 (0·7%)	1 (0·8%)	..	2 (3·3%)	0	..
Asplenia or splenic dysfunction	6 (1·4%)	0	..	1 (1·7%)	0	..
Immunosuppression or malignancy	24 (5·5%)	9 (7·4%)	..	2 (3·3%)	0	..
Congenital abnormality	50 (11·5%)	12 (9·8%)	..	5 (8·3%)	1 (4·5%)	..
Central nervous system disease	3 (0·7%)	1 (0·8%)	..	0	0	..
Chronic lung disease	26 (6·0%)	4 (3·3%)	..	3 (5·0%)	0	..
Chronic heart disease	25 (5·7%)	4 (3·3%)	..	5 (8·3%)	0	..
Chronic renal disease	7 (1·6%)	1 (0·8%)	..	0	0	..
Chronic liver disease	12 (2·8%)	1 (0·8%)	..	0	0	..
Diabetes	0	1 (0·8%)	..	0	0	..
Cochlear implant	3 (0·7%)	1 (0·8%)	..	1 (1·7%)	0	..
Coeliac disease	0	0	..	0	0	..
Gestational age	..	..	0·065	..	..	0·42
Term	368 (84·4%)	111 (91·0%)	..	47 (78·3%)	19 (86·4%)	..
Preterm	68 (15·6%)	11 (9·0%)	..	13 (21·7%)	3 (13·6%)	..
Death within 30 days	17 (3·9%)	9 (7·4%)	0·11	2 (3·3%)	0	0·39

Data are n (%) unless otherwise stated; n refers to the number of IPD episodes, and denominators for percentages are the total number of IPD episodes. IPD=invasive pneumococcal disease. PCV=pneumococcal conjugate vaccine.

Table 2: **Age, clinical, and disease characteristics of IPD grouped by PCV13-type and non-PCV13 IPD in children eligible for the 1+1 PCV13 schedule with confirmed IPD in 2022–23 and children eligible for the 2+1 schedule with confirmed IPD in 2017–18 to 2019–20**

2+1 cohorts (table 1, figure 4A, appendix p 6). In the 1+1 cohort, 38 (24·1%) of 158 cases presented with meningitis (2·16 per 100 000 person-years) compared with 129 (23·7%) of 544 in the 2+1 cohort (2·23 per 100 000 person-years; table 1, appendix p 4). The IRRs were not significant for overall meningitis (IRR 0·97, 95% CI 0·66–1·40, p=0·88), PCV13-type meningitis (1·32, 0·13–8·05, p=0·72), or non-PCV13 meningitis (0·92, 0·60–1·37, p=0·68) between the two cohorts (appendix p 4).

In the 1+1 cohort, of the 22 episodes of PCV13-type IPD, two (9·1%) presented as meningitis compared with the 2+1 cohort in which five (8·3%) presented as meningitis out of the 60 PCV13-type IPD cases (table 2). Among PCV13-type IPD cases in the 1+1 cohort, none of the six children younger than 5 months, one of five aged 5–11 months, and one of 11 aged 1–3 years developed meningitis (p=0·48; figure 4B; appendix p 6). This compares with five (25·0%) of 20 children younger than 5 months and none of 40 aged 5 months and older with PCV13-type IPD in the 2+1 cohort (figure 4B; appendix p 6). The distribution of PCV13 serotypes causing meningitis was similar between the two cohorts (none of five in the 2+1 cohort *vs* one [50·0%] of two in the 1+1 cohort with serotype 19A; one [20·0%] of five in the 2+1 cohort *vs* none of two in the 1+1 cohort with serotype 19F; and four [80·0%] of five in the 2+1 cohort *vs* one [50·0%] of two in the 1+1 cohort with serotype 3; p=0·52).

A similar proportion developed meningitis due to non-PCV13 serotypes in the 1+1 (32 [26·2%] of 122) and

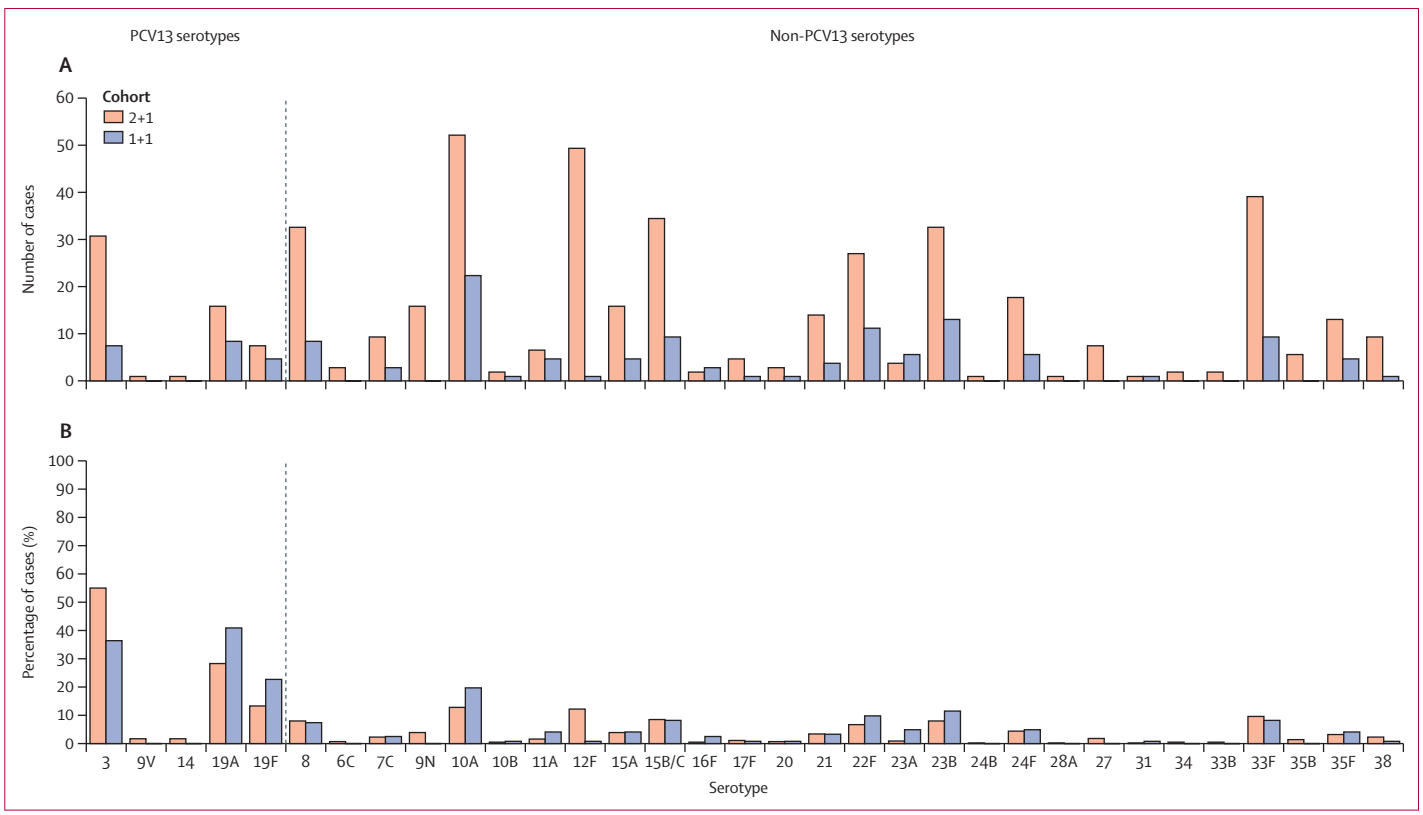

Figure 3: **Serotype distribution among PCV13-type IPD and non-PCV13 IPD cases in the 1+1 and 2+1 cohorts**
(A) Cases of PCV13-type and non-PCV13 IPD by serotype in the single 1+1 birth cohort compared with the three 2+1 birth cohorts. (B) Percentage of cases by PCV13 and non-PCV13 serotypes the 1+1 and 2+1 cohorts. The denominators for the percentage in panel B are total PCV13-type IPD cases for PCV13 serotypes and total non-PCV13 IPD cases for non-PCV13 serotypes. IPD=invasive pneumococcal disease. PCV=pneumococcal conjugate vaccine.

2+1 (115 [26·4%] of 436) cohorts (figure 4C; appendix p 4). Among non-PCV13 serotype IPD cases, meningitis was the most common presentation in children aged 2–4 months, where four (44·4%) of nine in the 1+1 cohort and 28 (50·0%) of 56 in the 2+1 cohort developed meningitis. The most common non-PCV13 serotypes causing meningitis in the 1+1 cohort were 10A (seven [21·9%] of 32) and 15B or C (five [15·6%] of 32), compared with 10A (24 [20·9%] of 115) and 8 (15 [13·0%] of 115) in the 2+1 cohort.

The 30-day CFR was 4·1% overall (29 of 702; 95% CI 2·8–5·9). There were nine deaths in the 1+1 cohort (CFR 5·7%; 2·6–10·8; table 1), including three in children with comorbidities. Septicaemia was the most common presentation leading to death (four of nine cases) followed by meningitis (three of nine) and bacteraemic pneumonia (two of nine). None of the deaths in the 1+1 cohort were associated with PCV13-type IPD (table 2), while the non-PCV13 serotypes 15B or C and 22F were responsible for two fatalities each. In the 2+1 cohort, there were 20 deaths (CFR 3·7%; 2·2–5·7) and, of the 19 with serotype information, two deaths were due to the PCV13 serotypes 3 and 19A, while serotype 23B, a non-PCV13 serotype, was responsible for four fatalities.

Logistic regression showed no further characteristics were significantly different between the cohorts when adjusted for by age, ethnicity, or gestational age.

Discussion

We compared children who developed IPD in England after the introduction of a 1+1 PCV13 national infant immunisation schedule with three historical birth cohorts of children eligible for a 2+1 PCV13 schedule to evaluate any changes in IPD risk, severity, or outcome. Most importantly, we found no evidence of an increase in overall IPD incidence in the 1+1 compared with the 2+1 cohort. A small, non-significant increase in PCV13-type IPD incidence was countered by a small, non-significant decrease in non-PCV13 IPD in the 1+1 compared with the 2+1 cohort. Additionally, both the incidence and percentage of meningitis presentations were similar between the two cohorts. The percentage of children with underlying comorbidities was also similar. Reassuringly, CFR has remained low, with no predominating serotype, and no deaths associated with PCV13-type IPD in the 1+1 cohort.

The unique decision by the UK to adopt the 1+1 schedule hinged on the reduced schedule being able to generate similar population (indirect) protection as the

2+1 schedule.[7,18] This indirect protection would continue to protect unvaccinated older children and adults against PCV13-type IPD, as well as infants younger than 1 year who would only be partially protected by a single priming dose at 12 weeks. Several clinical trials in other countries have examined the immunogenicity of a 1+1 PCV infant immunisation schedule and reported findings consistent with the trial used to inform the UK's decision.[9] A South African trial found serotype-specific post-booster antibody responses to be non-inferior and with lower colonisation with PCV13 serotypes at age 15 months in children receiving the 1+1 compared with a 2+1 schedule.[19,20] In India, a 1+1 PCV13 schedule yielded similar immune responses in the second year of life as a 2+1 schedule, alongside a 45% reduction in PCV13 serotype carriage compared with unvaccinated controls.[21]

Our findings add to our previous report of very low rates of breakthrough infections and vaccine failures in the same cohorts of children receiving the 1+1 schedule (19 cases) and the three historical cohorts that received the 2+1 schedule (13, 19, and 12 cases).[13] Overall, PCV13 serotypes were responsible for 15·3% and 12·1% of cases in the two cohorts, respectively, with most cases driven by non-PCV13 serotypes. Importantly, the percentage of IPD cases in infants too young to be vaccinated (<2 months old) was similar between the cohorts, providing additional support of excellent indirect protection. A particular concern with the 1+1 schedule was a potential increase in infants presenting with meningitis, which has the highest incidence in the first year of life,[14] and is associated with high CFR and severe long-term neurodevelopmental complications.[22] Reassuringly, the percentages and rates of both overall and PCV13-type pneumococcal meningitis were similar.

The 1+1 cohort includes children born during the COVID-19 pandemic, when IPD was rare, which might explain the higher median age of IPD cases. Importantly, concerns about children with underlying conditions being less protected by the 1+1 schedule remain unfounded since the prevalence of comorbidities was similar in the two cohorts. The lower percentage of IPD cases who had been born preterm in the 1+1 cohort is not easily explained and merits further investigation in future studies.

Among PCV13-type IPD cases, serotype 3 is particularly concerning as it is associated with more severe disease than other serotypes.[23] In England, serotype 3 IPD

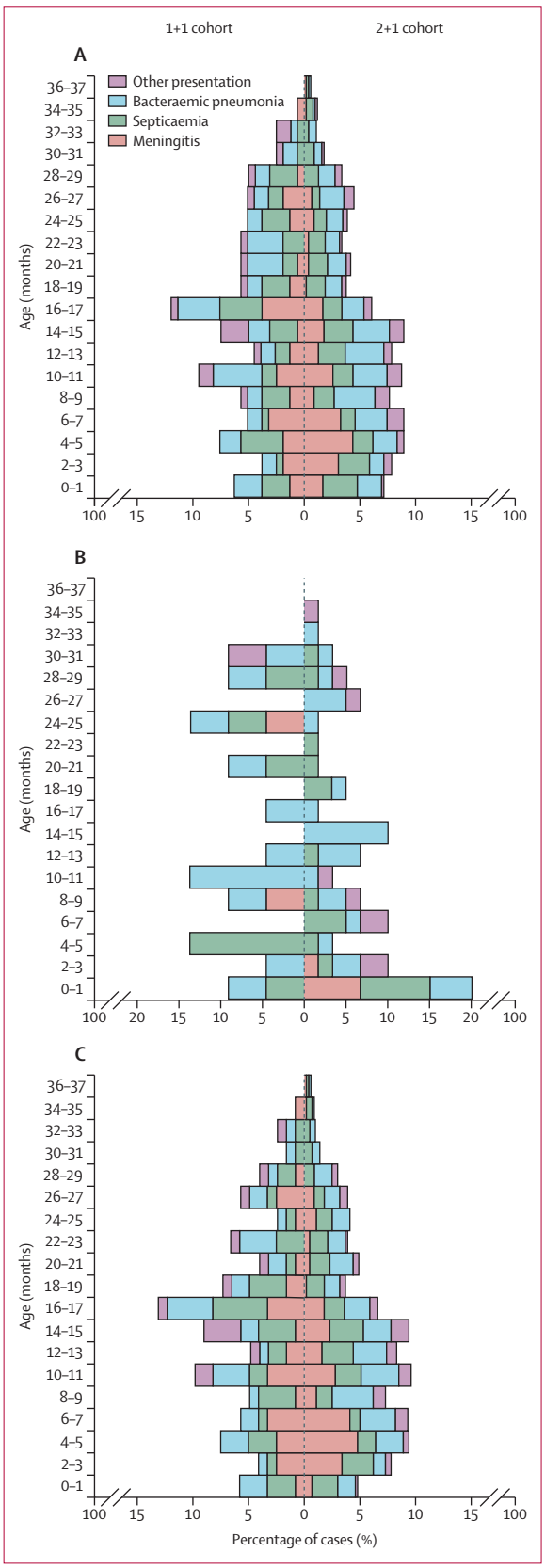

Figure 4: **Clinical presentations of IPD of all IPD cases, PCV13-type IPD, and non-PCV13 IPD by age group (2-month intervals)**

(A) Clinical presentations in children in the 1+1 cohort compared to the 2+1 cohort as a percentage of all IPD cases per cohort. (B) Clinical presentations of PCV13-type IPD, in children in the 1+1 cohort compared with the 2+1 cohort, as a percentage of PCV13-type IPD cases per cohort. (C) Clinical presentations of non-PCV13 IPD, in children in the 1+1 cohort compared with the 2+1 cohort, as a percentage of non-PCV13 IPD cases per cohort. Note: the scales on the axes differ. IPD=invasive pneumococcal disease. PCV=pneumococcal conjugate vaccine.

increased after pandemic restrictions were lifted and is currently responsible for one in six IPD cases.[13] PCV13 effectiveness against serotype 3 IPD is estimated to be very low,[24] and the recent increase observed in England likely reflects secular trends since other countries with 2+1 and 3+1 PCV13 schedules have also observed similar post-pandemic increases in serotype 3 IPD incidence.[25,26] Reassuringly, in children younger than 1 year in the 1+1 cohort, those least protected by vaccination because they were either too young for vaccination or had received only one PCV13 dose, there was only one serotype 3 IPD case. The remaining PCV13-type IPD cases were mainly due to serotypes 19A and 19F, which have continued to circulate in carriage and, consequently, in disease even within a mature childhood PCV13 immunisation programme with a 2+1 schedule before the pandemic, highlighting the lower protection afforded by PCV13 against these serotypes.[8,27] The failure of other PCV13 serotypes to re-emerge following the reduced 1+1 schedule supports the protection provided by the reduced programme. However, PCV13-type IPD will require continued close monitoring since any loss of protection against carriage of vaccine serotypes could take several years to manifest in national surveillance, which focuses primarily on invasive disease. We also observed changes in non-PCV13 serotypes causing IPD in the 1+1 cohort—notably, a decline in serotype 12F, again most likely due to secular trends[13]—but, reassuringly, these changes did not affect the clinical presentation, disease severity, or outcomes.

The 1+1 PCV13 schedule is pertinent to both high-income countries with established PCV programmes, as well as lower-income and middle-income countries considering PCV implementation, because of its dose-sparing and cost-saving potential. While surveillance has been complicated by the pandemic, our analysis identified no adverse consequences 3 years after shifting to a reduced national infant immunisation schedule. However, the change in schedule in the UK relied on the very low PCV13-type IPD rates achieved by the 2+1 programme, as well as the high and timely vaccine uptake in infants to maintain very low PCV13 carriage rates in young children, alongside near real-time national surveillance to monitor changes in disease activity. As such, the UK experience might not be applicable to other countries with different disease epidemiology, carriage rates, and in particular, different vaccine schedules and uptake, which is critical for maintaining indirect protection. While higher-valent PCVs, such as PCV20, will offer added protection against additional serotypes, countries will need to consider the schedules for these vaccines in their own right given the decreased serotype-specific immunogenicity that might accompany higher-valent PCVs and, consequently, the potential impact on carriage and indirect (herd) protection.[28–30]

We used data from a well established national surveillance programme with high ascertainment and standardised serotyping in a single national reference laboratory. Linkage with multiple national datasets also improved data completeness. Although we compared cohorts with equivalent follow-up time, the 1+1 cohort will have experienced a different infectious disease landscape compared with the 2+1 cohorts who developed IPD during the pre-pandemic years, including different contact patterns, exposures to seasonal viruses, and secular trends in individual serotypes. Furthermore, we were only able to include a single 1+1 cohort and so ongoing surveillance will be required, given the small case numbers in the 1+1 cohort. Our findings, however, provide a comprehensive analysis of the initial 3 years of a world-first 1+1 PCV13 national infant immunisation programme.

In conclusion, while acknowledging the impact of the pandemic and associated restrictions, the transition from a 2+1 to a 1+1 PCV13 infant immunisation schedule was not associated with any change in IPD incidence, disease characteristics, severity, or outcomes in the eligible cohorts during the first 3 years of the programme. Ongoing surveillance will be critical in the post-pandemic years.

Contributors

SNL, MER, and NJA were responsible for the conceptualisation of the study. FA and MB were involved in data curation. FA conducted the epidemiological analysis. FA and MB accessed and verified the data. FA 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 the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

The UKHSA Immunisation and Vaccine Preventable Diseases Division (affiliated with FA, MB, Y-WC, NJA, DJL, MER, and SNL) has provided vaccine manufacturers with post-marketing surveillance reports on pneumococcal and meningococcal infections which the companies are required to submit to the UK Licensing authority in compliance with their 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 (affiliated with JCD, SE, and DJL) at UKHSA has received grant funding from vaccine manufacturers for investigator-led research projects on pneumococcal surveillance.

Data sharing

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

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