Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: an observational cohort study

Pauline A Waight, Nicholas J Andrews, Shamez N Ladhani, Carmen L Sheppard, Mary P E Slack, Elizabeth Miller

Summary

Background The 13-valent pneumococcal conjugate vaccine (PCV13) protects against key serotypes that increased after routine immunisation with the seven-valent vaccine (PCV7), but its potential for herd protection and serotype replacement is uncertain. The aim of this study was to analyse the effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction.

Methods We used a national dataset of electronically reported and serotyped invasive pneumococcal disease cases in England and Wales to estimate incidence rate ratios (IRRs) for vaccine and non-vaccine type invasive pneumococcal disease between July, 2013, and June, 2014, versus the pre-PCV13 and pre-PCV7 baseline. Incidence rates were corrected for missing serotype data and changes in surveillance sensitivity over time. An over-dispersed Poisson model was used to estimate IRRs and confidence intervals.

Findings Incidence of invasive pneumococcal disease in the epidemiological year 2013/14 decreased by 32% compared with the pre-PCV13 baseline (incidence 10·14 per 100 000 in 2008–10 *vs* 6·85 per 100 000 in 2013/14; IRR 0·68, 95% CI 0·64–0·72). This was due to an 86% reduction of the serotypes covered by PCV7 (1·46 *vs* 0·20 per 100 000; IRR 0·14, 0·10–0·18) and a 69% reduction of the additional six serotypes covered by PCV13 (4·48 *vs* 1·40 per 100 000; IRR 0·31, 0·28–0·35). When compared with the pre-PCV7 baseline, there was a 56% overall reduction in invasive pneumococcal disease (15·63 *vs* 6·85 per 100 000; IRR 0·44, 95% CI 0·43–0·47). Compared with the pre-PCV13 baseline, the incidence of non-PCV13 serotypes increased (incidence all ages 4·19 *vs* 5·25 per 100 000; IRR 1·25, 95% CI 1·17–1·35) due to increases across a broad range of serotypes in children younger than 5 years and in people aged 45 years or more. In children younger than 5 years, incidence of non-PCV13 serotypes in 2013/14 was higher than in 2012/13 (age <2 years: 12·03 *vs* 10·83 per 100 000; age 2–4 years: 4·08 *vs* 3·63 per 100 000).

Interpretation 8 years of PCV use in England and Wales has reduced the overall incidence of invasive pneumococcal disease by more than 50%. The herd protection induced by PCV7 is continuing, and similar indirect protection is occurring from the additional serotypes covered by PCV13. There is, however, evidence of increasing invasive pneumococcal disease due to non-PCV13 serotypes, particularly in children younger than 5 years in 2014. If this increase continues, the maximum benefit of the PCV13 programme in children might already have been achieved.

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Introduction

Pneumococcal disease is a major cause of morbidity and mortality in young children, both in developed and developing country settings.[1] Use of the seven-valent pneumococcal conjugate vaccine (PCV7) in developed country settings has substantially decreased the incidence of PCV7-type invasive pneumococcal disease, both in vaccinated children and older unvaccinated individuals,[2] because of a reduction in carriage of vaccine serotypes. However, reduction in vaccine-type invasive pneumococcal disease has generally been accompanied by an increase in invasive pneumococcal disease from non-vaccine serotypes, such as 19A and 7F, thus diminishing the effect of PCV7 on overall invasive pneumococcal disease incidence.[2–4] Before PCV7 introduction, invasive pneumococcal disease caused by these and other emerging serotypes was relatively uncommon and hence they were not included in PCV7, the composition of which matched the main serotypes causing invasive pneumococcal disease in North American children in the pre-PCV era.[5] Higher valency PCV containing ten (PCV10) or 13 (PCV13) serotypes were developed to provide protection against the key additional serotypes and others that, although not common causes of invasive pneumococcal disease in North America and Europe, were prevalent in Africa and other high-incidence settings.[6] Efficacy of these additional serotypes was assumed by extrapolation of an aggregate immunological correlate of protection established for PCV7 serotypes, rather than direct evidence of efficacy.[7] Whereas the correspondence between immunogenicity and protection varies between serotypes, data[7] from England and Wales confirms the efficacy of four of the additional six serotypes in PCV13; for serotype 3, significant protection

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was not shown, and for serotype 5, there were insufficient cases for analysis.

In the UK, PCV7 was introduced in September, 2006, with a catch-up for all children younger than 2 years, and rapidly achieved a routine coverage greater than 90%.[8] Within 4 years, vaccine-type invasive pneumococcal disease had decreased by 86% across all ages, but there was a significant increase in non-PCV7 disease that was largest in children younger than 5 years and adults aged 65 years or more.[4] The 23-valent plain polysaccharide vaccine given to more than 70% of the latter group had no effect on non-PCV7 disease.[9] PCV13 replaced PCV7 in April, 2010, and a high coverage for the routine 2, 4, 12 month schedule (two plus one) was achieved, similar to PCV7, but with no catch-up.[8] On the basis of experience with PCV7 and carriage studies,[10] we expected that the overall pneumococcal carriage rate in the nasopharynx would change little, but that the colonising serotypes would have less potential to cause invasive pneumococcal disease.

Public Health England manages the largest national invasive pneumococcal disease dataset in the world, with around 5000 annual reports of invasive pneumococcal disease from England and Wales, of which more than 90% are serotyped.[2] Using this national dataset, we assessed the effect of the PCV13 programme on the serotype-specific incidence of invasive pneumococcal disease in vaccinated cohorts and older unvaccinated age groups during the first 4 years of the programme. We also assessed the combined effect of the PCV7 and PCV13 programmes on the incidence of invasive pneumococcal disease, compared with the pre-PCV7 baseline.

Methods

Study design

Since 2010, invasive pneumococcal disease has been one of the infections that diagnostic microbiology laboratories in England and Wales are required to notify under Health Protection Legislation to Public Health England[11] or Public Health Wales.[12] Before 2010, reporting was voluntary. Reporting is done electronically, and cases from both England and Wales are collated in a central database by the Public Health England Centre for Infectious Disease Surveillance and Control. Isolates are also sent to the Public Health England Respiratory and Vaccine Preventable Bacteria Reference Unit for serotyping. Laboratories sending an electronic report for which no isolate has been received by the Respiratory and Vaccine Preventable Bacteria Reference Unit are contacted to request isolate referral.

A single dataset of laboratory-confirmed invasive pneumococcal disease cases in England and Wales has been created from electronic reports linked with data for the isolates sent for serotyping, using personal identifiers common to both datasets. The two datasets are reconciled annually by epidemiological year (July 1, to June 30). Multiple samples collected within 30 days of each other from the same individual are regarded as from the same episode. Cases of invasive pneumococcal disease are defined as *Streptococcus pneumoniae* cultured from a normally sterile site. Diagnosis by DNA detection is done by a minority of laboratories and contributed between 0·2% and 3·8% of the total; because this proportion varied between years, these cases were excluded from the analysis. Antimicrobial susceptibility data for penicillin and erythromycin were obtained from the electronic reports and categorised as susceptible, intermediate, or resistant. Data for isolates referred for serotyping are analysed every 2 weeks and presented as cumulative numbers by age group and week throughout the epidemiological year.[13]

Public Health England has approval under PIAG Section 60 of the Health and Social Act 2001 (which has been subsumed into the National Information Governance Board for Health and Social Care with Section 60—now Section 251 of the NHS Act 2006) to process confidential information from patients for the purposes of monitoring the effect, efficacy, and safety of vaccination programmes.

Procedure

We calculated incidence rate ratio (IRR) for invasive pneumococcal disease by comparing incidence in the epidemiological year 2013/14 with the average incidence in the 2 years preceding PCV13 introduction (July, 2008, to June, 2010) and the average of the pre-PCV7 baseline years (July, 2000, to June, 2006) using Poisson regression. As previously described,[4] we corrected for missing age and serotype by assuming that reports with missing information had the same age and serotype distribution as reports for which these parameters were known. The proportion with missing serotype decreased from 50% of reports in 2001/02 to less than 10% of reports since PCV13 introduction; less than 1% of reports were missing age. We corrected for changes in surveillance sensitivity over time by increasing the incidence of invasive pneumococcal disease before 2009/10, according to the upward trend seen in age-specific total rates of invasive pneumococcal disease for the pre-PCV7 period (2000/01–2005/06).[4] We assumed that pre-PCV7 trends would continue to 2009/10 and that surveillance sensitivity was stable thereafter. For example, in children younger than 2 years, the reported cases of invasive pneumococcal disease increased by 3·3% annually, so for 2005/06 (4 years before 2009/10), an inflation factor ($1·033^4$=1·14) was applied to the raw numbers for that year. Annual population data for incidence calculations were obtained from the Office for National Statistics.[14]

To assess the effect of PCV13 and PCV7, overall incidence of invasive pneumococcal disease was calculated, then stratified by vaccine type and non-vaccine type invasive pneumococcal disease. Vaccine-type invasive pneumococcal disease was further stratified by the serotypes covered by PCV7 (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) and by the additional six serotypes in PCV13 (serotypes 1, 3, 5, 6A, 7F, and 19A). Age-specific incidence rates in 2013/14 were then compared with the

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average annual rates in 2008/09 and 2009/10 (pre-PCV13 baseline) and 2000/01 to 2005/06 (pre-PCV7 baseline) with a Poisson model on unadjusted counts with an offset in the model for denominators (person-years), proportion of reports missing age or serotype each year, and the underlying trend. To account for extra-Poisson variability between years, the confidence intervals were inflated on the basis of the extra-Poisson variability seen in the 2000–06 corrected data (a period without interventions).

For the main incidence analysis, six age groups were used (<2, 2–4, 5–14, 15–44, 45–64, and ≥65 years). The serotype-specific IRR analyses used broader age groups (<5, 5–64, and ≥65 years). To examine the effect of PCV13 on the incidence of invasive pneumococcal disease from serotypes 6A and 6C, we split the data on the basis of results of retyping a random subset of one in four isolates before 2009 (when these serotypes were routinely distinguished) and applying the proportions that were 6A and 6C to isolates not re-typed. We calculated IRRs with 6A included in the PCV7 group because of assumed cross-protection from the 6B component of PCV7. Significance (for testing the null hypothesis of IRR=1) was set at 5% for serotype-grouped analyses and at 1% for serotype-specific analyses.

We used Stata version 13 for all statistical analyses.

Role of the funding source

The funder of the surveillance (Public Health England) had no role in study design, data analysis, data interpretation, or writing of the report. Information on the electronically reported cases of invasive pneumococcal disease is part of the national laboratory-based surveillance dataset managed by Public Health England. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 and table 1 show the adjusted annual incidence rates by age and serotype grouping. The overall incidence

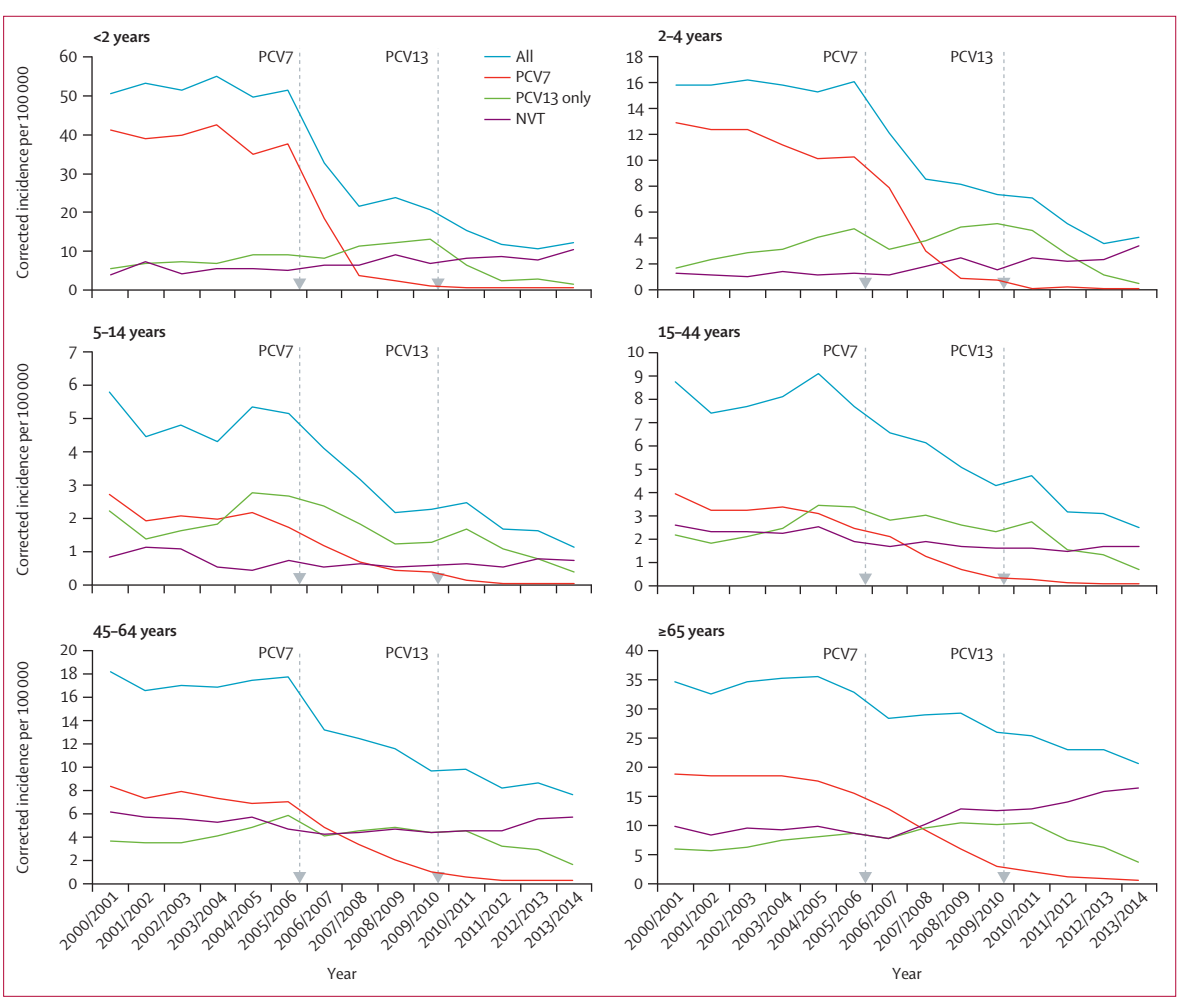

Figure 1: **Corrected* invasive pneumococcal disease incidence from epidemiological year 2000/01 to 2013/14, by serotype grouping and age**
PCV7=seven-valent pneumococcal conjugate vaccine. PCV13=13-valent pneumococcal conjugate vaccine. NVT=non-vaccine type. *Corrected for proportion of samples serotyped, missing age, and for the trend in total invasive pneumococcal disease up to 2009/10 (after which no trend correction was applied).

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	2008–10 corrected* (raw) cases	2008–10 incidence per 100 000	2013/14 corrected* (raw) cases	2013/14 incidence per 100 000	IRR 2013/14 relative to 2008–10 (95% CI†)
Age <2 years					
All	304 (297)	22·22	165 (172)	12·03	0·54 (0·42–0·69)
PCV7	22 (20)	1·58	5 (5)	0·38	0·24 (0·06–0·93)
PCV13 only	174 (158)	12·67	20 (19)	1·43	0·11 (0·06–0·22)
Non-vaccine type	109 (99)	7·97	140 (136)	10·23	1·28 (0·94–1·77)
Age 2–4 years					
All	157 (149)	7·77	82 (88)	4·08	0·52 (0·37–0·74)
PCV7	16 (14)	0·78	3 (3)	0·15	0·20 (0·04–1·12)
PCV13 only	100 (90)	4·98	9 (9)	0·46	0·09 (0·04–0·25)
Non-vaccine type	41 (36)	2·02	70 (67)	3·46	1·71 (1·07–2·81)
Age 5–14 years					
All	143 (134)	2·23	73 (74)	1·14	0·51 (0·35–0·74)
PCV7	26 (22)	0·40	2 (2)	0·03	0·09 (0·01–0·67)
PCV13 only	81 (70)	1·27	24 (22)	0·38	0·30 (0·16–0·57)
Non-vaccine type	36 (31)	0·56	46 (42)	0·72	1·29 (0·73–2·27)
Age 15–44 years					
All	1056 (994)	4·67	566 (563)	2·50	0·54 (0·47–0·62)
PCV7	120 (97)	0·53	21 (19)	0·09	0·17 (0·09–0·35)
PCV13 only	562 (463)	2·49	156 (142)	0·69	0·28 (0·22–0·36)
Non-vaccine type	373 (308)	1·65	389 (354)	1·72	1·04 (0·86–1·26)
Age 45–64 years					
All	1473 (1380)	10·59	1057 (1094)	7·60	0·72 (0·65–0·80)
PCV7	216 (176)	1·55	33 (31)	0·24	0·15 (0·09–0·27)
PCV13 only	633 (527)	4·55	230 (216)	1·65	0·36 (0·29–0·45)
Non-vaccine type	624 (520)	4·49	794 (747)	5·71	1·27 (1·11–1·46)
Age ≥65 years					
All	2468 (2425)	27·58	1841 (2036)	20·58	0·75 (0·69–0·81)
PCV7	410 (356)	4·58	47 (48)	0·53	0·11 (0·08–0·18)
PCV13 only	924 (808)	10·33	333 (340)	3·72	0·36 (0·30–0·43)
Non-vaccine type	1134 (992)	12·67	1461 (1491)	16·33	1·29 (1·17–1·42)
All age groups					
All	5599 (5386)	10·14	3784 (4032)	6·85	0·68 (0·64–0·72)
PCV7	809 (685)	1·46	111 (108)	0·20	0·14 (0·10–0·18)
PCV13 only	2474 (2120)	4·48	772 (750)	1·40	0·31 (0·28–0·35)
Non-vaccine type	2316 (1989)	4·19	2900 (2839)	5·25	1·25 (1·17–1·35)

IRR=incidence rate ratio. PCV=pneumococcal conjugate vaccine. PCV7=serotypes in the pneumococcal conjugate vaccine 7. PCV13 only=serotypes in the PCV13 vaccines but not the PCV7 vaccine. *Corrected for proportion of samples serotyped, missing age, denominator compared with 2009/10, and for the trend in total invasive pneumococcal disease up to 2009/10 (after which no trend correction was applied). †95% CI inflated from a Poisson interval based on over-dispersion of 2·1 seen from modelling 2000–06 pre-PCV7 all invasive pneumococcal disease data.

Table 1: **Number of cases and incidence of invasive pneumococcal disease in epidemiological year 2013/14, compared with the baseline average of 2008/09 and 2009/10 (2008–10), by age and serotype grouping**

See Online for appendix

of invasive pneumococcal disease across all age groups decreased by 32% (IRR 0·68, 95% CI 0·64–0·72) in 2013/14 compared with the pre-PCV13 baseline of 2008–10. Incidence of PCV7-type invasive pneumococcal disease continued to decline in all age groups after PCV13 introduction (0·14, 0·10–0·18). Incidence for the additional six serotypes in PCV13 also showed a significant overall decrease of 69% (0·31, 0·28–0·35), with the largest reduction in children younger than 5 years (age group <2 years: 0·11, 0·06–0·22; age group 2–4 years: 0·09, 0·04–0·25). In 2013/14, 858 (21%) of 4032 cases of invasive pneumococcal disease were attributed to serotypes included in PCV13 (table 1), with the lowest prevalence of 36 (14%) of 260 cases in children younger than 5 years.

In 2013/14, non-PCV13 serotypes increased significantly in children younger than 5 years and in adults 45 years or older, compared with the pre-PCV13 baseline (for all ages IRR 1·25, 95% CI 1·17–1·35) across all age groups (table 1). For children younger than 5 years, the increase in non-PCV13 invasive pneumococcal disease compared with the pre-PCV13 baseline was most marked in 2013/14 (2012/13: 1·01, 0·76–1·36; 2013/14: 1·41, 1·08–1·83). The increase in non-PCV13 invasive pneumococcal disease in children younger than 5 years in 2013/14 resulted in a higher overall incidence of invasive pneumococcal disease, compared with 2012/13 (12·03 per 100 000 in 2013/14 *vs* 10·83 per 100 000 in 2012/13 for children younger than 2 years; 4·08 per 100 000 in 2013/14 *vs* 3·63 in 2012/13 for children aged 2–4 years). Despite the increase in non-PCV13 invasive pneumococcal disease in people aged 45–64 and 65 years or more, there was a continuing downward trend in overall invasive pneumococcal disease incidence in both groups (figure 1).

When serotype 6A was included as a PCV7 serotype, IRRs in 2013/14 were similar to those in table 1, although with generally smaller reductions for the additional PCV13 serotypes, especially in older age groups (appendix).

Compared with the pre-PCV7 baseline years July, 2000, to June, 2006, the overall incidence of invasive pneumococcal disease in 2013/14 was reduced by 56% (IRR 0·44, 95% CI 0·43–0·47) and the incidence of PCV7-type invasive pneumococcal disease decreased by 97% (0·03, 0·02–0·04; appendix). The incidence of non-PCV13 type invasive pneumococcal disease, compared with the pre-PCV baseline, increased by 28% (1·28, 1·20–1·35) and was attributable to increases in incidence in children less than 5 years and adults 65 years or older (appendix).

Figure 2 and table 2 show adjusted annual serotype-specific incidence rates and IRR for five of the six additional serotypes in PCV13 in 2013/14 compared with the pre-PCV13 baseline; there were insufficient cases of serotype 5 to merit analysis. Serotypes 1, 6A, 7F, and 19A decreased significantly in all age groups. For serotype 3, there were year-on-year fluctuations in incidence for all age-groups (figure 2), although significant reductions in 2013/14 compared with the baseline years were observed for the 5–64 year and 65 years and older age groups. No significant changes in serotype 6C incidence were observed in any age group.

Non-PCV13 serotypes 8, 10A, 12F, 15A, and 24F increased significantly in 2013/14, compared with the pre-PCV13 baseline, in people aged 5 years or more (table 2). There was a similarly diverse range of serotypes

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Figure 2: **Corrected* invasive pneumococcal disease incidence for individual serotypes grouping from epidemiological year 2000/01 to 2013/14, by age**
PCV7=seven-valent pneumococcal conjugate vaccine. PCV13=13-valent pneumococcal conjugate vaccine. *Corrected for proportion of samples serotyped, missing age, and for the trend in total invasive pneumococcal disease up to 2009/10 (after which no trend correction was applied).

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	Age <5 years			Age 5–64 years			Age ≥65 years		
	2008–10 corrected* (raw) cases	2013/14 corrected* (raw) cases	IRR (95% CI†) 2013/14 relative to 2008–10	2008–10 corrected* (raw) cases	2013/14 corrected* (raw) cases	IRR (95% CI†) 2013/14 relative to 2008–10	2008–10 corrected* (raw) cases	2013/14 corrected* (raw) cases	IRR (95% CI†) 2013/14 relative to 2008–10
Additional serotypes covered by PCV13‡									
1	59 (54)	5 (5)	0·09 (0·02–0·32); p<0·0001	458 (382)	77 (71)	0·17 (0·12–0·26); p<0·0001	102 (89)	13 (13)	0·13 (0·06–0·28); p<0·0001
3	26 (24)	8 (8)	0·32 (0·11–0·94)	178 (148)	73 (68)	0·41 (0·28–0·62); p<0·0001	256 (224)	143 (146)	0·56 (0·43–0·73); p<0·0001
6A	10 (9)	0 (0)	0·00 (0·00–0·38); p=0·002	53 (44)	5 (5)	0·10 (0·03–0·44); p=0·001	94 (82)	5 (5)	0·05 (0·01–0·19); p<0·0001
7F	90 (82)	8 (8)	0·09 (0·03–0·26); p<0·0001	430 (361)	160 (148)	0·37 (0·29–0·50); p<0·0001	173 (152)	75 (77)	0·44 (0·30–0·63); p<0·0001
19A	85 (77)	7 (7)	0·09 (0·03–0·25); p<0·0001	225 (191)	104 (97)	0·46 (0·35–0·68); p<0·0001	279 (246)	97 (99)	0·35 (0·25–0·47); p<0·0001
Non-PCV13 serotypes									
6C	6 (5)	2 (2)	0·37 (0·04–3·38)	46 (39)	33 (31)	0·72 (0·36–1·32)	88 (78)	62 (63)	0·70 (0·45–1·06)
8	13 (12)	15 (15)	1·22 (0·48–3·13)	267 (221)	354 (329)	1·33 (1·07–1·63); p=0·009	153 (134)	220 (224)	1·43 (1·11–1·86); p=0·006
9N	3 (3)	1 (1)	0·37 (0·02–8·41)	55 (46)	63 (59)	1·15 (0·72–1·88)	60 (52)	71 (72)	1·18 (0·77–1·83)
10A	6 (5)	7 (7)	1·29 (0·32–5·31)	25 (21)	43 (40)	1·73 (0·95–3·54)	17 (15)	44 (45)	2·58 (1·31–5·02); p=0·006
11A	7 (6)	4 (4)	0·62 (0·12–3·21)	49 (41)	30 (28)	0·62 (0·30–1·12)	67 (59)	56 (57)	0·83 (0·53–1·32)
12F	7 (7)	15 (15)	2·13 (0·74–6·33)	106 (88)	157 (146)	1·48 (1·04–1·99)	49 (43)	105 (107)	2·12 (1·41–3·22); p<0·0001
15A	3 (3)	18 (17)	6·49 (1·50–26·94)	14 (12)	66 (62)	4·69 (1·92–8·26); p<0·0001	29 (26)	129 (132)	4·50 (2·78–7·09); p<0·0001
16F	2 (2)	1 (1)	0·47 (0·02–11·19)	18 (16)	21 (20)	1·17 (0·48–2·83)	39 (35)	53 (54)	1·34 (0·80–2·25)
22F	25 (23)	23 (22)	0·91 (0·44–1·91)	204 (169)	132 (123)	0·65 (0·47–0·87); p=0·005	239 (209)	186 (190)	0·78 (0·61–1·00)
24F	3 (3)	28 (27)	10·15 (2·53–40·21); p=0·001	7 (6)	71 (67)	10·77 (4·12–35·41); p<0·0001	14 (12)	84 (86)	6·15 (3·19–11·83); p<0·0001
31	0 (0)	0 (0)	..	16 (13)	14 (13)	0·88 (0·33–2·44)	23 (20)	35 (36)	1·54 (0·80–2·96)
33F	17 (15)	20 (19)	1·17 (0·52–2·73)	63 (53)	64 (60)	1·03 (0·66–1·72)	76 (67)	74 (76)	0·98 (0·65–1·47)
35B	2 (2)	2 (2)	0·94 (0·08–10·94)	8 (7)	20 (19)	2·48 (0·98–9·41)	13 (12)	25 (26)	1·96 (0·86–4·37)

Where p values are not shown, comparisons were not significant. IRR=incidence rate ratio. PCV=pneumococcal conjugate vaccine. *Corrected for proportion of samples serotyped, missing age, denominator compared with 2009/10, and for the trend in total invasive pneumococcal disease up to 2009/10 (after which no trend correction was applied). †95% CI inflated from a Poisson interval based on over-dispersion of 2·1 seen from modelling of 2000–06 pre-PCV7 all invasive pneumococcal disease data. ‡Excluded serotype 5, which is an outbreak strain, with corrected numbers for each of the 14 years from 2000/01–2013/14 of 49, 5, 7, 23, 5, 0, 16, 62, 43, 10, 4, 1, 4, 0.

Table 2: **Serotype-specific number of cases and incidence rate ratio of invasive pneumococcal disease in epidemiological year 2013/14, compared with the average of 2008/09 and 2009/10 (2008–10), by age**

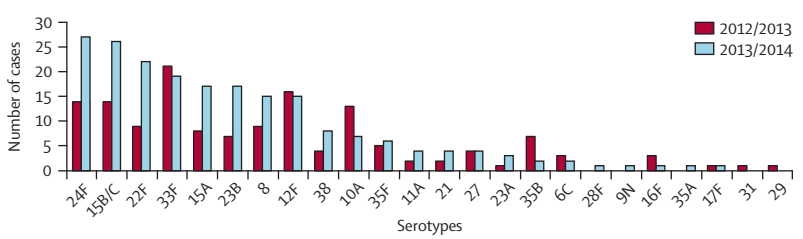

Figure 3: **Number of invasive pneumococcal disease cases due to non-PCV13 serotypes in children younger than 5 years from July, 2012, to June, 2013, and from July, 2013, to June, 2014**
Serotypes 15B and 15C were combined because they are considered to be one rapidly interconverting serotype.

showing an increase in 2013/14 in children under 5 years compared with 2012/13, including serotypes 8, 15A, 15B/C, 22F, 23B, and 24F (figure 3). No increase in antimicrobial resistance for these serotypes was observed in 2013/14, compared with previous years; in children younger than 5 years, only four (3%) of 139 non-PCV13 serotypes with information on penicillin susceptibility showed intermediate or full resistance in 2013/14, compared with one (1%) of 88 in 2012/13 and three (3%) of 115 in 2011/12. The equivalent rates for erythromycin were seven (6%) of 115 in 2013/14, four (6%) of 72 in 2012/13, and six (8%) of 76 in 2011/12.

Discussion

PCVs have profound effects on nasopharyngeal carriage of *S pneumoniae*. Whereas experience in both developed and developing countries shows that carriage of vaccine-type serotypes is consistently reduced by vaccination with PCV,[15–19] the effect of PCV on non-vaccine type carriage, and therefore on non-vaccine type invasive pneumococcal disease, is more difficult to predict. Our large national database of serotyped invasive pneumococcal disease cases in England and Wales provides a unique opportunity to document the direct and indirect effects of PCV across all age groups in a developed country with high vaccine coverage (panel).[8] Furthermore, the use of a reduced two plus one vaccination schedule in the UK provides a demanding test of the programme's ability to generate herd protection.

The reductions in vaccine-type invasive pneumococcal disease are consistent with the estimates of serotype-specific vaccine-effectiveness derived for PCV13-immunised children in England and Wales.[7] In children, protection from four of the additional PCV13 serotypes (serotypes 1, 6A, 7F, and 19A) was direct and significant,[7] with evidence of herd protection for these same serotypes in older age groups. Despite the absence of a catch-up

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programme for PCV13, a reduction in invasive pneumococcal disease from the additional serotypes in PCV13 in older age groups was already evident in the second year after PCV13 introduction (figure 2). For serotype 6A, for which there was some direct cross-protection from the 6B component of PCV7, effectiveness was substantially higher with PCV13.[7] Accordingly, the indirect protection against serotype 6A invasive pneumococcal disease in older age groups was substantially greater with PCV13. Data[21] from the USA suggest that herd protection for 6A from PCV7 was substantial, which might reflect the more immunogenic three-dose priming schedule at 2, 4, and 6 months. In view of the higher antibody concentrations needed to protect against carriage compared with invasive pneumococcal disease,[22] a greater effect of PCV7 on serotype 6A carriage might be expected in the USA than the UK.

Despite the high effectiveness of the 6A component of PCV13[7] and a reduction of more than 80% in serotype 6A invasive pneumococcal disease in older unvaccinated age groups (table 2), no significant changes in serotype 6C incidence have been reported. Some cross-protection might have been expected, with reports of reduction in 6C carriage,[16] as well as induction of functional opsonophagocytic killing responses against serotype 6C by PCV13.[23] The IRRs of serotype 3 show reductions in all age groups and are less than 1 in people aged 5 years or more, although the fluctuations in the pre-PCV13 baseline complicate interpretation. Significant protection from this serotype was not shown in the recent Public Health England effectiveness study,[7] for which the estimate was 25·8% (–69·4% to 67·5%). Although significant protection against serotype 3 was found in a US case-control study,[24,25] the confidence intervals around the point estimate were wide, with no evidence of a reduction in serotype 3 disease at the population level.

The decline in invasive pneumococcal disease from PCV7 serotypes has continued post-PCV13, with a further 86% decrease in incidence across all ages in 2013/14, compared with 2008–10, consistent with the findings from countries with more than 4 years PCV7 use.[2] By 2013/14, the overall incidence of PCV7-type invasive pneumococcal disease had decreased by 97% compared with the pre-PCV7 baseline (appendix). This near-extinction of PCV7-associated invasive pneumococcal disease within 8 years of introduction of conjugate vaccination is in accordance with UK model predictions[26] and shows the profound effect of PCV7 on carriage.[10] Although the effect of PCV7 on non-bacteraemic pneumococcal pneumonia is difficult to measure directly, its incidence has probably decreased similarly, in line with the reduction in PCV7 serotype carriage. Since the effect on carriage[17] and herd immunity of the additional effective serotypes in PCV13 appears similar to that of the PCV7 serotypes, it is reasonable to assume that, in the coming years, there will be a similar near-extinction of PCV13-attributable disease, including non-bacteraemic pneumonia. As carriage of vaccine-type pneumococci and the disease they cause become progressively less common, the direct benefit of vaccinating older at-risk people will therefore diminish. In the UK, PCV13 vaccination of high-risk groups was shown to be not cost-effective,[27] despite their greatly elevated risk of disease, because of the progressive decline in vaccine-type disease in future cohorts.[28]

In England and Wales, early post-PCV13 carriage data[17] showed complete serotype replacement in the nasopharynx within 2 years of its introduction, predominantly with less invasive serotypes that have a lower propensity to cause invasive pneumococcal disease.

Panel: **Research in context**

Systematic review

We searched PubMed using the terms "pneumococcal conjugate vaccine", "impact after introduction", "herd immunity", "trends", "serotype replacement", "effects after introduction", and "reductions in invasive disease". We searched for population-based surveillance studies that had data for all age groups and provided incidence rates for vaccine-type and non-vaccine-type invasive pneumococcal disease for at least 3 years after the introduction of 13-valent pneumococcal conjugate vaccine (PCV13). Most papers had less than 3 years of post-PCV13 incidence data, but among these papers there was consistent evidence of a reduction in invasive pneumococcal disease from the additional serotypes covered by PCV13 in the paediatric cohorts targeted for immunisation, with an overall reduction in invasive pneumococcal disease in children. Most studies also showed early evidence of reduction in PCV13-type invasive pneumococcal disease in older age groups. The effect of PCV13 on non-PCV13 invasive pneumococcal disease was less consistent, but the duration of follow-up and power of the dataset to detect changes were generally restricted. No papers reported data after the third year of PCV13 use.

Interpretation

Our analysis of a large national surveillance dataset shows that the introduction of PCV13 has resulted in an overall reduction in invasive pneumococcal disease in a developed country setting compared with the period before PCV use and compared with the reduction achieved by PCV7. However, as with PCV7,[2] our study shows that the overall effect is now being attenuated by the increase in non-PCV13 invasive pneumococcal disease, both in adults aged 65 years and older and in children younger than 5 years—the two groups with the highest incidence of pneumococcal-attributable disease. The increase in non-PCV13 invasive pneumococcal disease involved a broad range of serotypes suggesting that the next generation of higher valency vaccines with a narrow additional serotype coverage might have limited public health benefit. Confirmation of our experience in other settings with mature PCV13 programmes and in countries that use PCV10 will add impetus to the development of universal pneumococcal vaccines, such as those based on identification of conserved protective protein antigens. Few data for herd immunity and non-vaccine-type disease exist in countries using PCV10, where the potential for serotype replacement might be less because of the very low carriage prevalence of serotypes 1 and 7F (two of the additional three serotypes covered by PCV10 compared with PCV7).[10] The effect of PCV10 and PCV13 vaccines in resource-poor settings, where the burden of disease, serotype distribution, and force of infection differ from those in Europe and North America,[20] is as yet unclear. Comparative population-based, serotype-specific surveillance data of invasive pneumococcal disease in different epidemiological settings for countries using PCV13 and PCV10 are needed to properly understand the effect of PCV with restricted serotype coverage.

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The increase in non-vaccine-type invasive pneumococcal disease from a wide range of serotypes in the fourth year after PCV13 introduction in children younger than 5 years was not associated with a change in antibiotic resistance, and some of the replacing serotypes (figure 3) were thought to have a low invasive potential.[17] Sudden annual increases in non-PCV13 invasive pneumococcal disease have occurred in children younger than 5 years in the past, but has returned to baseline in the subsequent year (figure 1). However, provisional data[13] for 2014/15 show that the increase in non-PCV13 type invasive pneumococcal disease has continued. These non-vaccine-type isolates are now being sequenced to investigate whether the 2014/15 increase is associated with the emergence of new clones, and a further carriage study is planned to understand current transmission dynamics of non-vaccine-type serotypes in young children who, as shown by the rapidity of the herd protection effects in older age groups, are key transmitters of infection in the population. The steady serotype replacement in invasive pneumococcal disease in older age groups is less surprising because both increasing age and the presence of comorbidities increase the risk of invasive pneumococcal disease by serotypes with low case to carrier ratios.[29]

Our study has a number of strengths. The dataset is based on national reporting, not sentinel reporting, and since blood cultures are rarely done outside a hospital setting in the UK, the clinical criteria for diagnostic investigation of suspected cases of invasive pneumococcal disease should be relatively stable with time. Furthermore, our incidence rates are not based solely on reference laboratory data, which might be affected by the propensity of primary diagnostic laboratories to refer isolates for serotyping and vagaries of isolate viability. Since our surveillance spans several decades, we can adjust for trends in surveillance sensitivity over time and take into account natural secular changes in individual serotypes. For baseline incidence of invasive pneumococcal disease, we averaged data for 2008/09 and 2009/10 because there was a relatively large increase in non-PCV13 invasive pneumococcal disease in children younger than 5 years in 2008/9 (figure 1), which returned to the 2007/08 rate in 2009/10. For the additional serotypes in PCV13, because the replacement induced by PCV7 continued in unvaccinated age groups for a further year after PCV13 introduction, this upward trend should arguably be projected to infer what the incidence might have been in post-PCV13 years, had the vaccine not been introduced. Whereas this counterfactual approach has been used for the analysis of post PCV-13 effect data from the sentinel Active Bacterial Core surveillance system in the USA,[24] we chose not to make this assumption. Our herd protection estimates for the additional PCV13 serotypes are, therefore, likely to be conservative. Although we do not audit completeness of reports by laboratories, there is a statutory requirement for all diagnostic laboratories to report laboratory-confirmed, clinically significant infections to Public Health England,[11,12] and laboratories now have automated procedures to extract and report such cases to meet statutory requirements. Since statutory reporting has been in place since 2010, we decided not to extrapolate the upward trends[30] in reporting of all invasive pneumococcal disease on the assumption that surveillance sensitivity plateaued in 2010.

In conclusion, our study provides robust evidence of herd protection from the additional serotypes in PCV13. Although there is evidence of replacement disease, overall invasive pneumococcal disease has been reduced by 56%, compared with the pre-PCV7 baseline. However, the increase in non-PCV13 serotypes in children younger than 5 years in 2013/14 caused a higher incidence of invasive pneumococcal disease than in 2012/13, suggesting that, if this increase continues, the maximum population benefit in this age group (in which only 14% of remaining invasive pneumococcal disease in 2013/14 was potentially preventable by PCV13) might already have been achieved. The increase in non-PCV13 invasive pneumococcal disease in children and older adults involved a broad range of serotypes, suggesting that the 15-valent vaccine containing two additional serotypes, 22F and 33F,[31] which in 2013/14 included only 17% of the total non-PCV13 serotypes, might be insufficient to cover the emerging non-vaccine type invasive pneumococcal disease.

Contributors

PAW and EM were responsible for data collection and data management. MPES was the microbiological lead for pneumococcal surveillance activities. CLS was the scientific lead for the pneumococcal laboratory surveillance activities. SNL was the clinical lead for pneumococcal surveillance. NJA was responsible for the statistical analysis. PAW, EM, and NJA wrote the report. All authors read, commented on, and approved the final version of the report.

Declaration of interests

MPES has served on ad-hoc advisory boards for Pfizer and GlaxoSmithKline. CLS is and MPES has been an employee of the Public Health England Respiratory and Vaccine Preventable Bacteria Reference Unit (Colindale, London, UK), which has received research funding from Pfizer and GlaxoSmithKline. SNL has worked on clinical trials for vaccine manufacturers including GlaxoSmithKline and Pfizer on behalf of St George's University of London (London, UK), but has received no personal remuneration. EM, PAW, and NJA declare no competing interests.

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