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Effectiveness of the seven-valent and thirteen-valent pneumococcal conjugate vaccines in England: The indirect cohort design, 2006–2018

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ABSTRACT

Background: The 7-valent pneumococcal conjugate vaccine (PCV7) was introduced into the UK childhood immunisation programme in 2006 and replaced with a 13-valent vaccine (PCV13) in 2010. Both vaccines led to rapid declines in vaccine-serotype invasive pneumococcal disease (IPD). Here, we assessed the long-term vaccine-effectiveness (VE) of both vaccines in England.
Methods: Public Health England conducts enhanced national surveillance of IPD in England. VE against IPD was estimated using vaccine-serotype IPD cases and non-vaccine serotype IPD controls among vaccine-eligible children from September 2006 to June 2018 (the Broome method).
Results: Vaccine history was available for 3421 IPD cases, including 1299 due to the additional PCV13 serotypes and the PCV13-related serotype 6C, 274 PCV7 serotypes and 1848 non-PCV13 serotypes. For the complete 2 + 1 schedule, both PCV7 and PCV13 showed high effectiveness against PCV7 serotypes with a combined VE of 92.0% (95%CI, 81.7–96.7). For the 2 + 1 schedule, PCV13 VE against the additional PCV13 serotypes plus 6C was 73.7% (31.1–89.9) compared to 90.0% (75.3 - 96.0) for PCV7 against PCV7 serotypes, although PCV13 VE increased to 84.8% (58.7–94.4) if serotype 3 was excluded; all 36 eligible serotype 3 IPD cases were fully-vaccinated with PCV13. Case numbers were low in older ages but there was evidence of waning, which was significant for serotype 19A for which there were sufficient numbers of cases for analysis.
Conclusions: PCVs are highly effective in preventing vaccine-serotype IPD except for serotype 3 which has been increasing in incidence. Serotype 19A IPD has also persisted, likely due to a slightly lower VE and/or more rapid waning of protection.

1. Background

Streptococcus pneumoniae remains the leading cause of vaccine-preventable bacterial infections globally. The pneumococcus can cause sinusitis, otitis media and pneumonia as well as severe invasive infections such as meningitis and septicaemia. Almost 100 different pneumococcal serotypes have been identified based on their distinct antigenic polysaccharide capsule. A pneumococcal conjugate vaccine against the seven most prevalent serotypes causing invasive pneumococcal disease (IPD) in children (PCV7, Prevenar®, Pfizer) was introduced into the UK national immunisation schedule in 2006 and led to a rapid and sustained decline in IPD in children and adults through a combination of direct and indirect (population) protection [1]. Despite a reduced primary schedule of two priming doses at 8 and 16 weeks compared to the licensed 3-dose priming infant schedule, followed by a booster around the first birthday, PCV7 vaccine effectiveness (VE) against the vaccine serotypes was very high at 95% [2].

In 2010, PCV7 was replaced with a 13-valent PCV (PCV13) which aimed to protect against six additional serotypes, including serotypes 19A and 7F, which became the major replacing serotypes causing IPD after PCV7 introduction [3]. This vaccine, too, was associated with a rapid decline in IPD due to the additional PCV13 serotypes during the first four years of the programme, with a 69% reduction in overall IPD incidence from 4.48/100,000 prior to PCV13 introduction to 1.40/100,000 in 2013/14 [3]. Since then,

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however, IPD cases due to serotype 3 increased rapidly, while cases due to serotypes 19A and 19F plateaued, with small increases in IPD due to these latter serotypes observed in some of the age groups. These three serotypes have also been observed in recent carriage studies among PCV13-immunised children [4].

We have previously reported PCV13 VE in the first 15 months and 3.5 years after PCV13 replaced PCV7 in 2010 [5,6]. In this study, we aimed to estimate long-term VE and assess waning for both PCV7 and PCV13 against vaccine-serotype IPD since they were implemented into the national immunisation schedule in England using the same case-control design in which non-vaccine serotype cases serve as controls.

2. Methods

2.1. Enhanced IPD surveillance

Public Health England (PHE) conducts enhanced surveillance for IPD in England and provides a national reference laboratory service for confirmation, serotyping and characterisation of invasive pneumococcal isolates. PHE also routinely receives electronic reports of invasive pneumococcal isolates from National Health Service (NHS) hospital laboratories across England, and actively requests referral of invasive isolates to the reference laboratory if not already done. For confirmed cases in vaccine-eligible children, additional clinical details including vaccination history, comorbidities, clinical presentations and outcomes are obtained from the child's general practitioner using standard surveillance questionnaires sent by post with telephone follow-up if necessary. IPD was defined as culture of *Streptococcus pneumoniae* from a normally sterile site or DNA detection in pleural fluid or cerebrospinal fluid. Risk group was defined according to the Green Book on Immunisation (https://www.gov.uk/government/publications/immunisation-against-infectious-disease-the-green-book-front-cover-and-contents-page). Multiple samples collected in a 30-day time period from the same individual were regarded as the same episode of infection.

2.2. Case selection for VE analysis

IPD cases in England with complete serotype information for the infecting isolate and with specimen dates up to the end of June 2018 were extracted from the reconciled database held at PHE at the end of December 2018. For inclusion in the VE analysis, cases and controls had to be old enough to have received the doses assessed, born in a period where they would be eligible to receive the vaccine being assessed and have a specimen taken within the period when the vaccine was available. For assessment of PCV7, any individual receiving a dose of PCV13 was excluded and, for assessment of PCV13 against PCV7 serotypes, any individual receiving a PCV7 dose was excluded as were cases due to the additional serotypes in PCV13. When PCV13 was assessed against the additional serotypes in PCV13, cases with PCV7-type IPD were excluded and, as in previous analyses, serotype 6C was included as a vaccine-preventable serotype. The Appendix gives full details of the inclusion criteria for the various analyses.

2.3. Exposure

Doses of PCV were counted if given within at least 14 days prior to the specimen date. For the VE analyses, doses were considered as follows: (i) at least one dose for all cases aged ≥3 months, (ii) at least two doses given aged <12 months or one dose aged ≥12 months (defined as 2/1) for cases aged ≥4 months, (iii) one dose aged <12 months for cases aged <13 months, (iv) 2 doses aged <12 months for cases aged 4 to <13 months, (v) 2 doses aged <12 months and one dose aged ≥12 months (defined as 2 + 1) for cases aged ≥13 months, and (vi) 1 dose aged ≥12 months for cases aged ≥13 months.

2.4. Statistical methods

VE was calculated using a case-control design where cases had PCV-type IPD and controls had non-PCV serotype IPD (known as the Broome or indirect cohort method) [2]. Logistic regression was used to adjust for age (2.5–5, 6–12, 13–17, 18–23, 24–35, 36–47, and 48–56 months) and year of infection (2006–2018) and to examine any need to adjust for clinical risk group, such as underlying comorbidities or prematurity, which might affect VE. For adjustment by period when assessing PCV7 serotypes, all years from 2012 are combined due to small numbers of PCV7 serotypes after this date. Where sufficient numbers of cases were available, serotype-specific VE was calculated based on at least one dose, 2/1 doses, 2 doses given aged <12 months and 2 + 1 doses. VE of 2/1 doses was also assessed by risk group status.

Waning of effectiveness was assessed by using age as a continuous linear variable (on the log-odds scale) and testing for any interaction between age and vaccination for the analysis of 2/1 doses and 2 + 1 doses and restricting to age ≥13 months. As well as using a continuous variable, VE was calculated stratified by age-groups of 1, 2, and ≥3 years for PCV7, and 1, 2, 3–4, and ≥5 years for PCV13 as well as 1 and ≥2 years for serotypes 3 and 19A. The waning function was plotted along with the age-group estimates within the range of ages contributing to the estimate. Data were analysed using Stata 15 (StatCorp, Texas, USA).

2.5. Ethical approval

PHE has legal permission, provided by Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002, to process patient confidential information for national surveillance of communicable diseases (http://www.legislation.gov.uk/uksi/2002/1438/regulation/3/made). This includes PHE's responsibility to monitor the safety and effectiveness of vaccines.

3. Results

PCV immunisation history was available for 3421 of 3447 IPD cases that met the inclusion criteria, including 1299 due to the additional PCV13 serotypes, 274 due to PCV7 serotypes and 1848 due to non-PCV13 serotypes. Cases were confirmed by culture (3129/3421, 91.5%) or PCR (292/3421, 8.5%). The characteristics of children with IPD by serotype group are summarised in Table 1. Serotype distribution varied by age (**Supplement 2**) and vaccination status (**Supplement 3**). When assessing VE against individual and overall vaccine serotypes, adjustment by risk group or vaccination status made very little difference to the analysis; therefore, only age group and time period were adjusted for.

3.1. PCV7 and PCV13 VE against PCV7 serotypes

PCV7 VE was high overall and against individual serotypes with the possible exception of 6B where VE of 2/1 doses was 60% (95% CI, −2.7 to 84.5) (Table 2). After PCV13 replaced PCV7 in 2010, there were too few cases of PCV7-type IPD to assess PCV13 VE against individual PCV7 serotypes, but overall the 2 + 1 schedule had an adjusted VE of 81.2% (95% CI, −6.7 to 96.7), while receipt of 2/1 doses had a VE of 76.6% (95% CI, 30.8 to 92.1). Combining PCV7 and PCV13 vaccines gave similar results to those when PCV7 was assessed alone, with an overall VE of 92.0% (95% CI,

Table 1
Description of 3421 cases according to serotype grouping.

Factor	Level	NVT (N = 1848)	xPCV13 + 6C (N = 1299)	PCV7 (N = 274)	Total (N = 3421)
Age	<6 m	234 (59%)	127 (32%)	34 (9%)	395
	6–12 m	468 (58%)	260 (32%)	80 (10%)	808
	13–17 m	239 (56%)	128 (30%)	57 (13%)	424
	18–23 m	151 (52%)	103 (36%)	34 (12%)	288
	2 yrs	209 (50%)	176 (42%)	30 (7%)	415
	3–4 yrs	315 (48%)	307 (47%)	30 (5%)	652
	5+ yrs	232 (53%)	198 (45%)	9 (2%)	439
Period	2006	8 (6%)	27 (22%)	90 (72%)	125
	2007	55 (24%)	99 (43%)	77 (33%)	231
	2008	89 (32%)	156 (57%)	29 (11%)	274
	2009	103 (28%)	252 (68%)	18 (5%)	373
	2010	114 (30%)	258 (67%)	12 (3%)	384
	2011	137 (41%)	186 (56%)	9 (3%)	332
	2012	135 (55%)	99 (40%)	11 (4%)	245
	2013	157 (71%)	58 (26%)	7 (3%)	222
	2014	208 (79%)	51 (19%)	3 (1%)	262
	2015	247 (86%)	33 (11%)	8 (3%)	288
	2016	244 (85%)	39 (14%)	3 (1%)	286
	2017	218 (87%)	30 (12%)	2 (1%)	250
	2018	133 (89%)	11 (7%)	5 (3%)	149
Risk Group	No	1196 (50%)	972 (41%)	206 (9%)	2374
	Yes	539 (71%)	157 (21%)	61 (8%)	757
	Missing	113 (39%)	170 (59%)	7 (2%)	290
Born Premature	No	1300 (58%)	804 (36%)	132 (6%)	2236
	Yes	234 (62%)	116 (31%)	25 (7%)	375
	Missing	314 (39%)	379 (47%)	117 (14%)	810
Died	No	1663 (56%)	1058 (36%)	226 (8%)	2947
	Yes	99 (58%)	53 (31%)	19 (11%)	171
	Missing	86 (28%)	188 (62%)	29 (10%)	303

81.7 to 96.7) for the 2 + 1 schedule and 80.8% (95% CI, 69.8 to 87.8) for 2/1 doses.

3.2. PCV13 VE against additional PCV13 serotypes

PCV13 VE against the extra PCV13 serotypes was lower overall than PCV7 VE against PCV7 serotypes, with 2 + 1 VE at 73.7% (95% CI, 31.1-89.9%) and 2/1 VE at 67.3% (95% CI, 52.4–77.5) (Table 3). PCV13 VE was particularly low for serotype 3 with 2/1 VE at 0.0% (95% CI, −103 to 50.2%); for the 2 + 1 schedule; notably, all 36 eligible cases were fully vaccinated. Based on the 2/1 VE, the next lowest VE was for serotype 19A at 61.2% (95% CI, 33.2 to 77.4), although this appears to be driven by the lower VE for partial vaccination since the 2 + 1 VE is 84.2% (95% CI, 51.6–94.9). Exclusion of serotype 3 improved the VE against the remaining serotypes to values closer to that seen for PCV7 against PCV7 serotypes. VE against the vaccine-related serotype 6C was high.

3.3. VE in risk groups

VE was lower in at-risk children for both PCV7 (p = 0.05) and PCV13 (p = 0.01). For PCV7, the 2/1 VE for those in a risk group was 78.6% (95% CI, 43.0 to 92.0) compared to 90.8% (95% CI, 83.5 to 94.9) for those not is a risk group. For PCV13, 2/1 VE for those in a risk group was 42.0% (95% CI, −40.3 to 76.0) compared to 70.2% (95% CI, 52.8 to 81.2) for those not is a risk group.

3.4. VE waning over time

Waning over time was difficult to assess because of the large herd effects of the childhood PCV programme, leading to smaller numbers of cases over time as well as a changing serotype distribution. Overall, there was evidence of waning, reaching statistical significance for PCV13 2/1 and 0+1 doses as well as for PCV13 VE against 19A when assessing this serotype, which had the largest number of cases (Table 4). In addition, for PCV13 VE against serotype 3, there did appear to be some non-significant evidence of effectiveness in those aged 13–23 months when considering VE for 2/1 doses, which rapidly waned to a negative VE; this waning, however, was not significant (p = 0.25) likely due to small numbers of cases. The waning function depicted in Fig. 1 demonstrates high levels of protection during the first seven years after the complete PCV schedules but, after this period, there is much uncertainty about the shape of the waning function as indicated by the very wide confidence intervals because of small numbers of cases.

4. Discussion

We estimated longer-term vaccine effectiveness for PCV7 and PCV13 in children receiving a 2 + 1 immunisation schedule in England, from the time when the vaccines were implemented in 2006 and 2010, respectively, until 2018. We found that the initial childhood PCV7 programme continues to provide high levels of protection against the seven most prevalent serotypes causing IPD in children prior to routine PCV introduction. Overall PCV13 VE against the additional PCV13 serotypes was also high, apart from serotype 3, for which VE was low and non-significant, and to a lesser extent serotype 19A. We found some evidence of a decline in VE over time when assessed as a trend by age. We also estimated lower VE in children at-risk for IPD compared to healthy children. Finally, we demonstrated continued effectiveness against the vaccine-related serotype 6C.

Vaccine effectiveness and waning of protection are important when considering long-term impact and population protection following implementation of any vaccine into the national immunisation programme. We have previously reported short-term VE for both PCV7 [2] and PCV13 [5,6] in the UK. For the majority of PCV13 serotypes, a high VE has been observed, along with a large

Table 2
Vaccine effectiveness (VE) estimates for PCV7 with 95% confidence interval (CI) by serotype and schedule.

Serotype	VE measure	Age of cases	Cases vaccinated: unvaccinated	Controls vaccinated: unvaccinated	Adjusted VE* (95% CI)
4	≥1 dose	2.5 m to ≤12 y	2:6	1417:154	96.9 (81.6–99.5)
	≥2 dose <12 m or 1 dose >12 m	4 m to ≤12 y	2:6	1256:142	97.0 (82.1–99.5)
	2 doses (aged <12 m)	4 to <13 m	0:1	264:29	Too few
	2 + 1 doses	13 m to ≤12 y	2:1	567:61	Too few
6B	≥1 dose	2.5 m to ≤12 y	31:22	1417:154	54.9 (4.3–78.7)
	≥2 dose <12 m or 1 dose >12 m	4 m to ≤12 y	16:21	1256:142	60.0 (−2.7 to 84.5)
	2 doses (aged <12 m)	4 to <13 m	6:11	264:29	56.1 (−192 to 93.4)
	2 + 1 doses	13 m to ≤12 y	0:5	567:61	100 (not estimable)
9V	≥1 dose ≥2 dose <12 m or 1 dose >12 m	2.5 m to ≤12 y 4 m to ≤12 y	6:8 5:7	1417:154 1256:142	84.7 (64.5–95.6) 84.7 (41.0–96.0)
	2 doses (aged <12 m)	4 to <13 m	0:1	264:29	Too few
	2 + 1 doses	13 m to ≤12 y	1:3	567:61	Too few
14	≥1 dose	2.5 m to ≤12 y	9:59	1417:154	93.2 (83.9–97.1)
	≥2 dose <12 m or 1 dose >12 m	4 m to ≤12 y	3:59	1256:142	97.6 (91.0–99.4)
	2 doses (aged <12 m)	4 to <13 m	1:21	264:29	96.0 (60.2–99.6)
	2 + 1 doses	13 m to ≤12 y	0:14	567:61	100 (not estimable)
18C	≥1 dose	2.5 m to ≤12 y	8:12	1417:154	81.0 (43.4–93.6)
	≥2 dose <12 m or 1 dose >12 m	4 m to ≤12 y	6:12	1256:142	81.0 (35.8–94.4)
	2 doses (aged <12 m)	4 to <13 m	1:4	264:29	Too few
	2 + 1 doses	13 m to ≤12 y	4:4	567:61	54.9 (−186 to 92.8)
19F	≥1 dose	2.5 m to ≤12 y	20:20	1417:154	76.1 (47.9–89.1)
	≥2 dose <12 m or 1 dose >12 m	4 m to ≤12 y	15:20	1256:142	83.4 (60.2–93.1)
	2 doses (aged <12 m)	4 to <13 m	7:9	264:29	87.8 (46.2–97.3)
	2 + 1 doses	13 m to ≤12 y	3:3	567:61	89.0 (35.7–98.1)
23F	≥1 dose	2.5 m to ≤12 y	11:16	1417:154	86.5 (65.6–94.7)
	≥2 dose <12 m or 1 dose >12 m	4 m to ≤12 y	8:16	1256:142	88.4 (67.1–95.9)
	2 doses (aged <12 m)	4 to <13 m	2:7	264:29	98.7 (73.0–99.9)
	2 + 1 doses	13 m to ≤12 y	2:2	567:61	91.3 (31.3–98.9)
All PCV7 seroty pes	≥1 dose	2.5 m to ≤12 y	87:143	1417:154	81.6 (72.5–87.7)
	≥2 dose <12 m or 1 dose >12 m	4 m to ≤12 y	55:141	1256:142	86.6 (78.6–91.6)
	1 dose (aged <12 m)	2.5 m to <13 m	24:56	126:41	63.6 (23.4–82.7)
	2 doses (aged <12 m)	4 m to <13 m	17:54	264:29	90.4 (74.8–96.4)
	1 dose (aged ≥12 m)	13 m to ≤12 y	20:87	244:113	80.3 (62.0–89.8)
	2 + 1 doses	13 m to ≤12 y	12:31	567:61	90.0 (75.3–96.0)

* By age (2.5 m–5 m, 6–12 m, 13–17 m, 18–23 m, 2 yrs, 3–4 yrs, ≥5 yrs) and period (2006, 2007, 2008, 2009, 2010, 2011, 2012–2018 for all types and 2006, 2007, 2008, 2009–2018 for serotype specific).

herd impact, leading to near elimination of these serotypes in carriage [4] and disease [7]. At the population level, replacement of PCV7 with PCV13 in the UK childhood immunisation schedule led to an 89%, 64% and 69% reduction in IPD due to the additional PCV13 serotypes in children aged <5 years, adults aged ≥65 years and across all age-groups, respectively, between 2008-10 and 2013/14 [3]. These reductions were consistent with our high initial VE estimates of 90% (95% CI, 34–98%) and 73% (95% CI, 55–84%) for the PCV7 and the additional PCV13 serotypes, respectively [6]. The lower PCV13 VE against the additional PCV13 serotypes compared to the initial PCV7 VE against PCV7 serotypes has been observed in other countries, even after exclusion of serotype 3 from the PCV13 VE analysis. In a recent study case-control study from Barcelona, for example, VE for ≥1 dose of any PCV was 82% (95% CI: 67.8–89.9%) overall and 91.9% (95% CI: 76.5–97.2%) for PCV7 compared to 77.2% (48.6–89.9%) for PCV13 [8].

Compared to our previous VE estimates for both PCV7 [2] and PCV13 [5,6] in the UK, the current VE estimates are slightly lower. For example, PCV13 VE for 2/1 doses was 67% (95% CI 52–78) in the current study compared to 73% (95% CI, 55–84) in 2014. Because of the longer follow-up period in the current study, this would be consistent with some waning of immunity. Changes in the serotype distribution causing IPD over time may also have contributed to the lower VE. The decline in serotype 3 and serotype 19A IPD during the first four years after PCV13 implementation was similar to that observed with PCV7 serotypes after PCV7 introduction. However, unlike the other additional PCV13 serotypes causing IPD, such as 1 and 7F, which have continued to decline throughout the PCV13 period, the incidence of IPD due to serotype 19A plateaued since 2013/2014, while serotype 3 IPD incidence increased, especially in adults and older adults [7]. In contrast to an earlier study two to three years after PCV13 implementation in the same geographical regions in England [9], a more recent carriage study in a similar cohort and in the same geographical regions in England detected on-going carriage of serotypes 3 and 19A even in fully immunised children, albeit at a lower prevalence [4]. A possible hypothesis may be that the current programme continues to offer some direct protection against disease caused by these persisting serotypes in vaccinated children but not sufficient to prevent carriage or offer indirect (herd) protection to the population.

Other countries with PCV13 programmes have also failed to control serotype 3 IPD [10]. Unlike the other PCV13 serotypes, serotype 3 is able to release its capsular polysaccharide because it is not covalently linked to the bacterial cell wall. This unusual characteristic interferes with antibody-mediated killing and limits the protection offered by anti-serotype 3 antibodies [11], which likely explains the lower PCV13 VE against serotype 3. In contrast to the established pneumococcal correlate of protection of 0.35 μg/mL, it

Table 3
Vaccine effectiveness estimates for PCV13 with 95% confidence interval (CI) by serotype and schedule.

Serotype	VE measure	Age of cases	Cases vaccinated: unvaccinated	Controls vaccinated: unvaccinated	Adjusted VE* (95% CI)
1	≥1 dose	2.5 m to ≤9 y	19:24	1262:136	65.5 (21.2–84.9)
	≥2 dose <12 m or 1 dose >12 m	4 m to ≤9 y	16:24	1107:123	74.8 (37.8–89.8)
	2 doses (aged <12 m)	4 m to <13 m	2:0	376:19	Too few
	2 + 1 doses	13 m to ≤9 y	6:0	508:15	Too few
3	≥1 dose	2.5 m to ≤9 y	82:18	1262:136	4.4 (−83.3 to 50.1)
	≥2 dose <12 m or 1 dose >12 m	4 m to ≤9 y	72:17	1107:123	0.0 (−103 to 50.2)
	2 doses (aged <12 m)	4 m to <13 m	13:1	376:19	17.8 (<−200 to 91.8)
	2 + 1 doses	13 m to ≤9 y	36:0	508:15	−∞ (−∞ to 72.8)**
6A	≥1 dose	2.5 m to ≤9 y	5:6	1262:136	72.4 (−23.8 to 93.9)
	≥2 dose <12 m or 1 dose >12 m	4 m to ≤9 y	3:6	1107:123	77.4 (−49.6 to 96.6)
	2 doses (aged <12 m)	4 m to <13 m	1:1	376:19	Too few
	2 + 1 doses	13 m to ≤9 y	0:0	508:15	No cases
6C	≥1 dose	2.5 m to ≤9 y	15:5	1262:136	70.0 (2.0–91.8)
	≥2 dose <12 m or 1 dose >12 m	4 m to ≤9 y	13:5	1107:123	78.4 (23.6–93.9)
	2 doses (aged <12 m)	4 m to <13 m	5:1	376:19	81.8 (−103 to 98.4)
	2 + 1 doses	13 m to ≤9 y	4:2	508:15	94.3 (64.9–99.1)
7F	≥1 dose	2.5 m to ≤9 y	22:44	1262:136	87.5 (74.3–93.8)
	≥2 dose <12 m or 1 dose >12 m	4 m to ≤9 y	9:38	1107:123	90.0 (76.0–96.6)
	2 doses (aged <12 m)	4 m to <13 m	4:2	376:19	83.6 (−30.0 to 97.7)
	2 + 1 doses	13 m to ≤9 y	4:0	508:15	Too few
19A	≥1 dose	2.5 m to ≤9 y	74:54	1262:136	66.5 (44.6–79.8)
	≥2 dose <12 m or 1 dose >12 m	4 m to ≤9 y	67:51	1107:123	61.2 (33.2–77.4)
	2 doses (aged <12 m)	4 m to <13 m	21:2	376:19	52.2 (−138 to 90.4)
	2 + 1 doses	13 m to ≤9 y	26:5	508:15	84.2 (51.6–94.9)
xPCV13 + 6C	≥1 dose	2.5 m to ≤9 y	218:152	1262:136	65.9 (52.3–75.7)
	≥2 dose <12 m or 1 dose >12 m	4 m to ≤9 y	181:142	1107:123	67.3 (52.4–77.5)
	1 dose (aged <12 m)	2.5 m to <13 m	34:16	135:32	47.0 (−19.8 to 76.6)
	2 doses (aged <12 m)	4 m to <13 m	46:7	376:19	65.6 (7.2–87.4)
	1 dose (aged ≥12 m)	13 m to ≤9 y	36:109	101:93	67.2 (46.2–81.2)
	2 + 1 doses	13 m to ≤9 y	76:8	508:15	73.7 (31.1–89.9)
xPCV13 + 6C but not ST3	≥1 dose	2.5 m to ≤9 y	136:134	1262:136	74.2 (62.6–82.2)
	≥2 dose <12 m or 1 dose >12 m	4 m to ≤9 y	109:125	1107:123	76.1 (63.8–84.3)
	1 dose (aged <12 m)	2.5 m to <13 m	26:14	135:32	57.7 (−5.2 to 83.0)
	2 doses (aged <12 m)	4 m to <13 m	33:6	376:19	73.7 (23.6–91.0)
	1 dose (aged ≥12 m)	13 m to ≤9 y	25:94	101:93	76.2 (56.9–86.9)
	2 + 1 doses	13 m to ≤9 y	40:8	508:15	84.8 (58.7–94.4)
xPCV13 but not ST3 or 6C	≥2 dose <12 m or 1 dose >12 m	4 m to ≤9 y	96:120	1107:123	74.6 (60.8–83.5)
	2 doses (aged <12 m)	4 m to <13 m	28:5	376:19	71.1 (9.3–90.8)
	2 + 1 doses	13 m to ≤9 y	36:6	508:15	79.1 (37.0–93.1)
xPCV13 but not 6C	≥2 dose <12 m or 1 dose >12 m	4 m to ≤9 y	168:137	1107:123	65.3 (49.1–76.4)
	2 doses (aged <12 m)	4 m to <13 m	41:6	376:19	62.0 (−9.9 to 86.8)
	2 + 1 doses	13 m to ≤9 y	72:6	508:15	63.1 (−6.3 to 87.1)

* By age (2.5–5 m, 6–12 m, 13–17 m, 18–23 m, 2 yrs, 3–4 yrs, ≥5 yrs) and period (years, or for some serotypes 2008, 2009, 2010, 2011, 2012–18).
** Exact 95% CI unadjusted

is estimated that a serum IgG concentration of 2.33 μg/mL would be required for protection against serotype 3 IPD – a level rarely attained through vaccination [6]. Indeed, early studies with an experimental 11-valent PCV that contained serotype 3 showed no protection against acute otitis media due to serotype 3 and resulted in the removal of this serotype from the vaccine, which was eventually licensed as a 10-valent PCV [12]. Early carriage studies also failed to demonstrate any reduction in nasopharyngeal acquisition of serotype 3 between infants receiving PCV7 (which does not contain serotype 3) or PCV13 (which contains serotype 3) [13].

On the other hand, a recent systematic review and meta-analysis conducted in collaboration with the manufacturers of PCV13 estimated the pooled PCV13 VE against serotype 3 in children to be 63.5% (95% CI, 37.3–89.7%) [14]. The analysis included data from a European collaboration (including the UK) with more than 6 million children aged <5 years which reported PCV13 VE against serotype 3 IPD using indirect cohort analysis to be 70% (95% CI, 44–83%) for ≥1 PCV13 dose and 57% (95% CI, 5–81) for fully-immunised children. The authors of the meta-analysis also found some evidence of higher VE estimates following ≥1 dose of PCV13 in countries with a 3 + 1 compared to a 2 + 1 immunisation schedule. However, clinical trials have found no significant difference in serotype 3 post-booster immunogenicity between these two schedules in children [15]. Notably, too, post-booster responses were also nearly identical in infants receiving a 1 + 1 schedule compared to those receiving the 2 + 1 schedule [16].

In our analysis, PCV13 VE against serotype 19A was also somewhat lower when compared to the other PCV13 serotypes, especially during the period after the two-dose infant priming schedule and before the 12 month-booster (Table 3). Serotype 19A in PCV13 is very immunogenic after the current UK schedule of two-doses given two months apart in infancy followed by a booster at 12 months [16]. Whilst PCV13-serotype IPD is rare after

Table 4
Assessment of waning of vaccine effectiveness for PCV7 and PCV13.

Vaccine	Serotype	VE measure	Age of cases	Cases vaccinated: unvaccinated	Controls vaccinated: unvaccinated	Adjusted VE* (95% CI)	P-value for trend in VE by age
PCV7	All PCV7	≥2 doses <12 m or 1 dose >12 m	13–23 months	14:61	234:23	89.8 (74.9 to 95.8)	0.07
			2 years	6:15	178:10	94.4 (78.7 to 98.5)	
			3–12 years (median 4.7)	18:11	580:80	71.2 (30.8 to 88.0)	
PCV7	All PCV7	2 + 1 doses	13–23 months	1:28	119:17	98.4 (85.8 to 99.8)	0.10
			2 years	3:2	120:4	95.9 (65.5 to 99.5)	
			3–11 years (median 4.6)	8:2	328:40	18.4 (−580 to 90.2)	
PCV7	All PCV7	0 + 1 doses	13–23 months	9:61	13:23	64.4 (−16.2 to 89.1)	0.21
			2 years	3:15	30:10	91.5 (59.6 to 98.2)	
			3–12 years (median 4.9)	8:11	201:80	71.5 (20.0 to 89.9)	
PCV13	xPCV13 + 6C but not ST3	≥2 doses <12 m or 1 dose >12 m	13–23 months	22:19	285:21	90.4 (61.9 to 97.6)	0.004
			2 years	18:32	150:18	67.2 (4.2 to 89.4)	
			3–4 years	26:30	208:21	84.8 (56.2 to 94.7)	
			5–9 years (median 6.0)	10:13	85:33	2.8 (−277 to 75.0)	
PCV13	xPCV13 + 6C but not ST3	2 + 1 doses	13–23 months	10:2	202:5	92.7 (30.1 to 99.2)	0.69
			2 years	11:2	118:4	73.4 (−123 to 96.8)	
			3–4 years	14:3	145:3	93.8 (47.7 to 99.3)	
			5–8 years (median 5.6)	5:1	43:2	76.2 (<−286 to 98.5)	
PCV13	xPCV13 + 6C but not ST3	0 + 1 doses	13–23 months	8:19	29:21	86.6 (31.2 to 97.4)	0.03
			2 years	5:32	12:18	71.4 (−5.0 to 92.2)	
			3–4 years	7:30	37:21	85.3 (46.4 to 95.9)	
			5–9 years (median 6.4)	5:13	23:33	2.5 (−294 to 75.9)	
PCV13	3	≥2 doses <12 m or 1 dose >12 m	13–23 months	25:7	285:21	72.2 (−19.0 to 93.5)	0.25
			2–9 years (median 3.5)	34:8	443:72	−141 (−700 to 17.3)	
PCV13	19A	≥2 doses <12 m or 1 dose >12 m	13–23 m	12:8	285:21	84.3 (11.1 to 97.2)	0.02
			2–9 years (median 3.5)	34:27	443:72	62.7 (17.7 to 83.1)	

* By age (in years) and period (2006, 2007, 2008, 2009–2018 for PCV7 and all years for PCV13).

PCV13 immunisation in children, serotype 19A is the second most common cause of vaccine failure after serotype 3 [17]. Among UK children, we also found that serotype 19A vaccine failure cases clustered around the first birthday, which would support waning of immunity after the two infant priming doses; this was not observed for any other serotype [17]. These observations, together with the high correlate of protection predicted for serotype 19A (1.00 μg/L; 95% CI, 0.60 to 2.47) [6], and the plateauing of serotype 19A IPD incidence since 2013/14 [7], suggest that this serotype is also likely to continue to circulate and cause disease with the current childhood PCV13 programme.

4.1. Strengths and limitations

A major strength of this study is the enhanced national surveillance for IPD alongside a very active national reference laboratory which has been in place for more than two decades. Serotyping rates for invasive pneumococcal isolates as well as questionnaire follow-up of confirmed cases in the vaccine-eligible cohorts remains consistently high. The very high vaccine uptake rates in the UK and the high estimated vaccine effectiveness overall means that there are few PCV13 serotype-specific IPD cases – and, particularly, unvaccinated cases – available for VE analysis. The indirect cohort method for estimating VE has the advantage over other methods such as case-control, screening and cohort designs in that it only requires IPD data for cases with serotyped isolates because cases with non-vaccine serotypes can serve as well-matched controls in terms of risk factors and healthcare utilisation. On the other hand, this method may underestimate VE if there is cross-protecting against non-vaccine serotypes which is why we included serotype 6C as a vaccine serotype. The indirect cohort method may also overestimate VE when there are herd protection effects and replacement of vaccine serotypes with non-vaccine serotypes in disease. We investigated this bias previously and found that this effect is likely to be small (2–5%) when compared to the precision of the VE estimates and will reduce as carriage of vaccine serotypes continues to decline over time. Interpretation of waning of VE is complicated by the changing serotype distribution by time and age within the vaccine types which means that it is the serotypes for which the vaccine is less effective that remain. This is why we analysed serotype 3 separately for waning. Finally, the shape of the waning function suggests that vaccine effectiveness lasts at least 7 years after the booster dose, with rapid waning in later years. This assumption, however, is based on longer-term VE with very small numbers of cases and, therefore, should be interpreted with caution. The high level of short-term protection, however, is reassuring and confirms the high individual and population protection afforded by the current programme.

5. Conclusions

Long-term vaccine effectiveness after a 2 + 1 immunisation schedule remains very high for both PCV7 and PCV13, consistent with the rapid and sustained decline in IPD incidence due to the respective vaccine serotypes. Further studies are needed to better understand the continued circulation of serotypes 3 and 19A in carriage and disease in the face of a highly effective national immunisation programme.

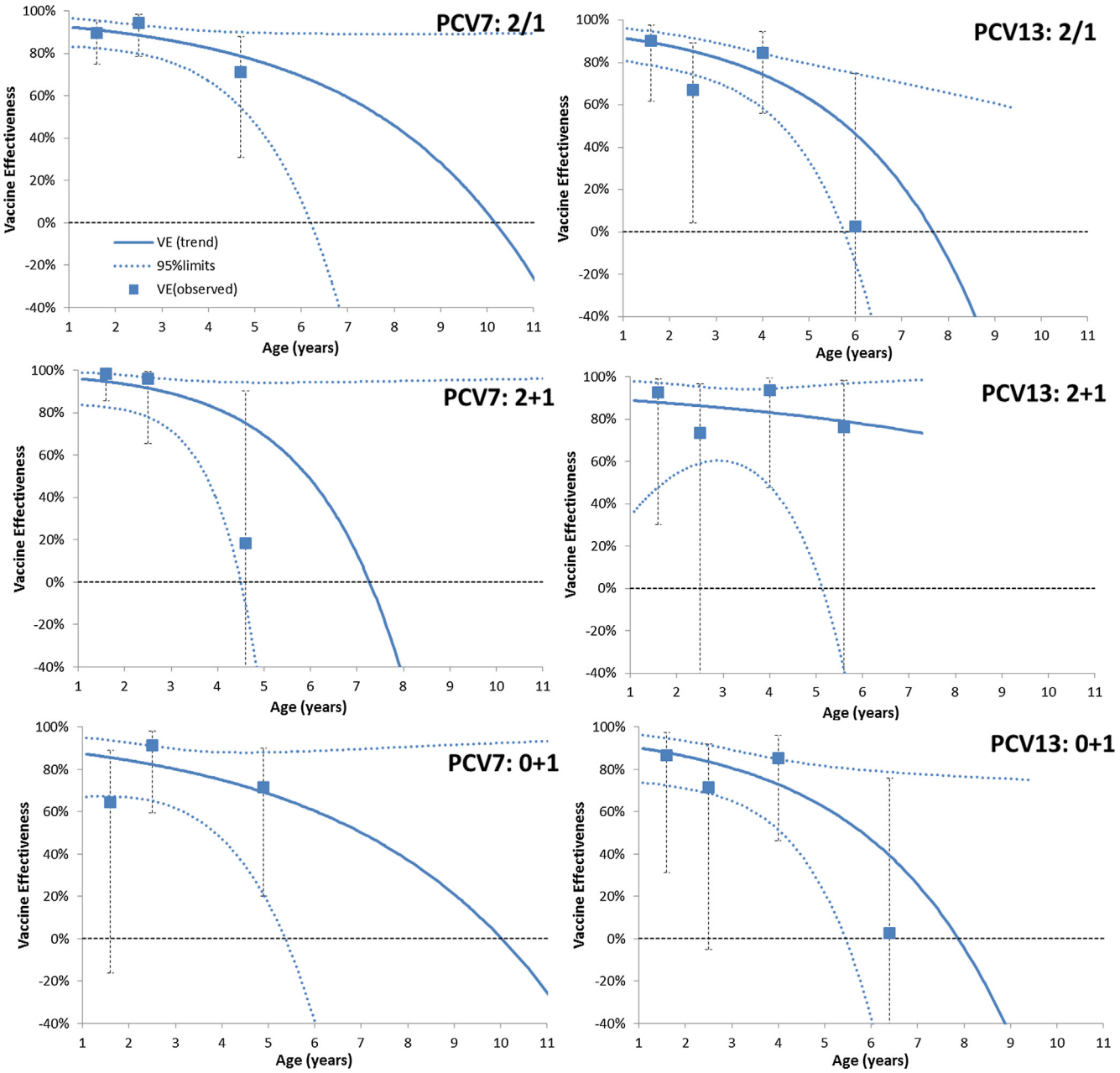

Fig. 1. Waning of vaccine effectiveness for PCV7 and PCV13 by schedule. The solid line gives the fitted decline, dotted lines the 95% confidence limits for the decline and the squares give the estimates at age intervals as given in Table 4. Serotype 3 IPD was not included the estimates.

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Declaration of Competing Interest

SNL, NF and CS conduct contract research for pharmaceutical industries on behalf of Public Health England; SNL also conducts contract research for pharmaceutical industries on behalf of St George's University of London. None of the authors receive personal remuneration. All other authors: no conflicts.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.06.071.

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