Short communication

Pneumococcal carriage following PCV13 delivered as one primary and one booster dose (1 + 1) compared to two primary doses and a booster (2 + 1) in UK infants

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ABSTRACT

In January 2020 the UK changed from a 2 + 1 schedule for 13-valent pneumococcal conjugate vaccine (PCV13) to a 1 + 1 schedule (doses at 3 and 12 months) based on a randomized immunogenicity trial comparing the two schedules. Carriage prevalence measured at the time of booster and 6 months later in 191 of the 213 study infants was 57 % (109/191) and 60 % (114/190) respectively. There were eight episodes of vaccine-type (VT) or vaccine-related 6C carriage in the 2 + 1 and six in the 1 + 1 group; $\geq$4-fold rises in serotype-specific IgG in 71 children with paired post-booster and follow up blood samples at 21–33 months of age were found in 20 % (7/35) of the 2 + 1 and 15 % (6/41) of the 1 + 1 group. VTs identified in carriage and inferred from serology were similar comprising 3, 19A and 19F. Dropping a priming dose from the 2 + 1 PCV 13 schedule did not increase VT carriage in the study cohort. Ongoing population level carriage studies will be important to confirm this.

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1. Introduction

Pneumococcal conjugate vaccines (PCVs) provide direct protection against vaccine-type (VT) invasive pneumococcal disease (IPD) in children and generate indirect immunity in the population by reducing VT carriage [1,2]. In the UK the seven-valent PCV (PCV7) was introduced in 2006 and in 2010 was replaced by the thirteen-valent PCV (PCV13), both vaccines being administered using a 2 + 1 schedule (priming doses at 2 and 4 months and a booster at 12 months). With the high PCV coverage achieved in the UK the incidence of IPD due to the serotypes in PCV7 and PCV13 in under 2 year olds has been reduced to low levels (0.07 and 1.54 per 100,000 in 2016/17 [3] respectively) with a reducing incidence of VT IPD in older age groups. The substantial reduction in VT transmission in the population prompted the suggestion that

in countries with a mature PCV programme two priming doses would no longer be required to sustain indirect immunity [4].

The key assumption behind the proposed move to a single priming dose was that maintenance of indirect immunity was reliant on the impact of the booster dose in the second year of life and that protection against pneumococcal carriage afforded by the booster dose would not be compromised by removal of one of the two priming doses. In 2018 we published a trial comparing booster responses to PCV13 when administered as a single dose priming at 3 months of age with a booster dose at 12 months (1 + 1) compared to the standard UK 2 + 1 [5]. This study showed that booster responses to the reduced dose priming were superior for 4 serotypes, inferior for 4 serotypes and equivalent for the remainder. Based on these results and those from a modelling study [6] the UK Joint Committee of Vaccination and Immunisation recommended a change to a 1 + 1 PCV13 schedule for UK infants born from January 1st 2020 (https://www.gov.uk/government/publications/routine-childhood-immunisation-schedule).

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Given the importance of not compromising protection against VT carriage, as a secondary objective in the 1 + 1 trial we incorporated nasopharyngeal (NP) swabbing at the time of the booster and six months later. Evidence of VT carriage was also sought by the detection of fourfold rises in serotype-specific IgG between the immediate post-booster sample and a follow up sample in a subset of participants taken around a year later to assess antibody persistence.

2. Methods

2.1. Participants and recruitment

The original trial was an multicentre, open-label, randomised controlled clinical trial conducted by the Oxford Vaccine Group (University of Oxford) and Public Health England (now UK Health Security Agency), which recruited infants aged between 7 and 12 weeks of age. Ethics approval was granted by the Berkshire Research Ethics Committee (reference number 15/SC/0355). The study is registered on the EudraCT clinical trials database (2015–000817-32) and ClinicalTrials.gov (NCT02482636). Study methods are fully described elsewhere [5]. Briefly, participants were randomised to receive all vaccines as per the UK national immunisation schedule except PCV13, which was given in either the routine 2 + 1 schedule or a 1 + 1 schedule. NP swabs were collected prior to the booster vaccinations at 12 months of age and six months later. Following a substantial amendment parents/-guardians were asked if they would consent their child to a further blood test about a year after the booster dose.

2.2. Swabbing methods

The NP swabs were collected by study staff, placed directly in skim milk, tryptone, glucose, and glycerin (STGG) broth and then in a cool storage box with icepacks. Samples were either frozen locally before being transferred to the central testing laboratory or transferred on the day to the Respiratory and Vaccine Preventable Bacteria Reference Unit, Public Health England, Colindale where they were frozen and stored at -80 °C. *S.pneumoniae* colonies were identified from cultures grown on Columbia blood agar or Streptococcus-selective Blood agar (COBA) and serotyped by a mixture of genomic and phenotypic methods as previously described [7].

2.3. Blood sampling and serological methods

Serological analysis was performed at the World Health Organisation (WHO) reference laboratory for pneumococcal serology, Great Ormond Street Institute of Child Health, University College London. Blood samples were received in the laboratory coded with no access to individual sample identities. Sera were stored at -70 °C prior to assay for serotype-specific immunoglobulin G (IgG) and in a subset with sufficient sera for functional antibodies by a multiplexed opsonophagocytic assay (OPA) to 13 vaccine-type capsular polysaccharides (1, 3, 4, 5, 6A, 6B, 7F, 9 V, 14, 18C, 19A, 19F and 23F) as previously described [5].

2.4. Power and statistical analysis

The target sample size for the original study was 110 per group with an anticipated 10 % loss to achieve 100 evaluable participants per group for IgG post-booster. The study was not powered for pneumococcal carriage. Overall carriage prevalence and by VT and non-vaccine type (NVT) at the two time points was compared between groups by Fisher's exact test.

For the subset who provided a follow up blood sample, geometric mean IgG antibody concentrations (GMCs) and OPA titres (GMTs) were calculated with 95 % confidence intervals (CIs). Normal errors regression on logged IgG titres was used to adjust for sex and time since boosting for comparing the two vaccine groups, whereas for OPA comparison was by the Kruskal-Wallis due to the non-normal distribution. Geometric mean declines post booster to follow up were also calculated and compared between the vaccine groups using normal errors regression with adjustment for sex and time since boosting. The number of participants with $\geq$ 4-fold rises in serum serotype-specific IgG concentrations between the immediate post-booster and later follow up blood sample were determined and considered evidence of carriage of that serotype.

2.5. Role of the funding source

The funders had no role in study design or the collection, analysis, interpretation, write up of the data or decision to submit the data for publication. The corresponding author had full access to all the study data and final responsibility for submission.

3. Results

Of the 213 original study recruits, pneumococcal carriage results at the time of the 12 month booster were obtained for 191 (90 %) of participants; 98 in the 2 + 1 and 93 in the 1 + 1 group, with carriage results obtained for 190 (89 %) six months later. Follow up blood samples at 21 to 33 months of age were obtained for 76 children, 35 of whom were from the 2 + 1 and 41 from the 1 + 1 group, representing 33 % and 38 % of those originally recruited to the two study groups respectively.
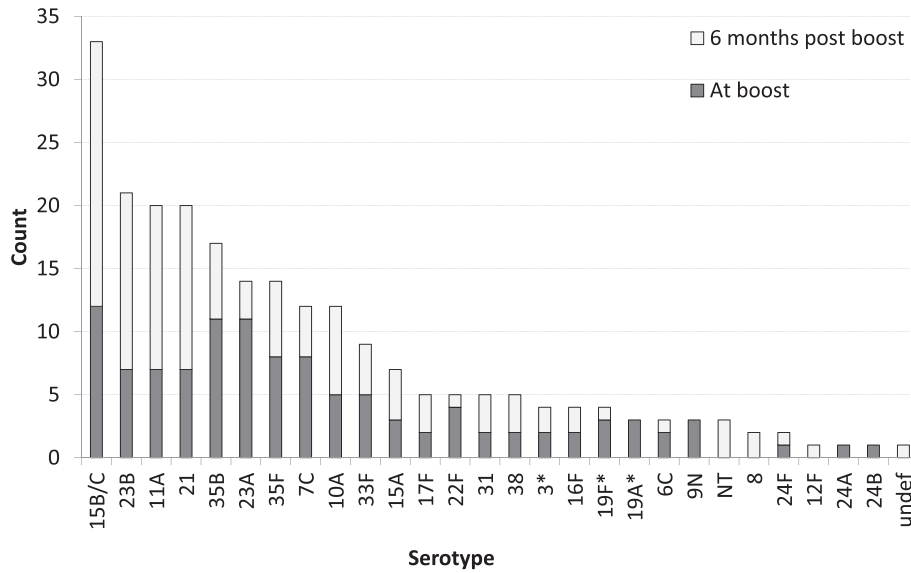
3.1. Carriage

Pneumococcal carriage was detected in 109/191 (57 %) children at the time of the booster dose and in 114/190 (60 %) six months later. Overall, 139/191 (72.8 %) carried a pneumococcus at either time point. The majority of pneumococci identified were NVTs (Fig. 1). There were eleven VT carriage episodes of which serotypes 3 and 19F comprised four each and 19A comprising three; these eleven VT carriage episodes occurred in nine individuals. A further three individuals carried the vaccine-related serotype 6C. There were no significant differences between the two vaccine groups in overall carriage prevalence at the two time points (Table 1). The eleven VT carriage episodes and the three with a vaccine-related serotype 6C were evenly distributed between groups with eight in the 2 + 1 and six in the 1 + 1 group.

The available post-primary and post-booster IgG responses in the individuals carrying a VT or 6C at one of the two swabbing time points are shown in Table 2. When analysing the response to primary vaccination in carriers compared with the GMCs after primary immunisation in the trial [5] six of the nine individuals carrying at the time of the booster had post primary IgG concentration in the lower quartile (p = 0.01) for that serotype and schedule.

Among the subset of 71 paired post-booster and follow up blood samples, 13 (18 %) $\geq$ 4-fold rises in titre to a VT were identified, 7 in the 2 + 1 group (20 %) and 6 in the 1 + 1 group (15 %). Eight rises were to serotype 3, two each to 19A and 19F and one to 23F.

3.2. Antibody persistence

Serotype-specific post-booster IgG GMCs for the subset who provided a follow up blood sample reflected those in the original trial cohort. GMCs at follow up were significantly lower for six ser-

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Fig. 1. Serotype distribution of pneumococcal carriage isolates sampled at the time of booster (dark bars) and 6 months later (light bars). The undefined serotypes (undef) and non-typeable isolates (NT) are counted as non-vaccine types for the purpose of the analysis. PCV13 serotypes are indicated by *.

Table 1
Comparison of pneumococcal carriage prevalence prior to the PCV13 booster and 6 months later by vaccine group and serotype (ST) grouping.

Carriage prevalence	At time of boost			6 months later		
	2 + 1 group	1 + 1 group	Exact P-value	2 + 1 group	1 + 1 group	Exact P-value
Any serotype	62/98 (63.3 %)	47/93 (50.5 %)	0.08	65/100 (65.0 %)	49/90 (54.4 %)	0.14
PCV13 serotype	5/98* (5.1 %)	3/93** (3.2 %)	0.72	2/100 *** (2.0 %)	1/90 **** (1.1 %)	1.00
PCV13 related serotype (6C)	0/98 (0 %)	2/93 (2.2 %)	0.24	1/100 (1 %)	0/90	1.00
Non PCV13 serotype	59/98 (60.2 %)	42/93 (45.2 %)	0.04	62/100 (62.0 %)	49/90 (54.4 %)	0.31

* One ST3, two ST19A, two ST19F; ** one ST3, one ST19A, one ST19F; *** one ST3, one ST 19F; **** one ST3.

Table 2
Antibody responses in eight carriers of a PCV13 serotype and the three carrying the vaccine related serotype 6C at the time of boosting or six months later. For 6C, IgG levels shown are for those to 6A. No antibody results available for one serotype (ST) 3 carrier in 2 + 1 group at time of booster.

Schedule	Swab at time of booster	Swab 6 months post-booster	Post primary IgG concentration to carried serotype(s)	Post booster IgG concentration to carried serotype(s)
2 + 1	19A		1.23	12.21
	19A	19F	2.25 (19A)	12.99 (19A)
			5.88 (19F)	50.34 (19F)
	19F	3	2.60* (19F)	11.80 (19F)
			0.31 (3)	0.28 (3)
	19F		0.82*	76.80
		6C	NA	0.46
1 + 1	3		0.075*	NA
	19A		0.17*	3.04 (OPA = 2451)
	19F		1.19*	20.13
		3	NA	0.28
	6C		0.075*	2.86
	6C		0.075*	0.473[b]

*denotes response in lower quartile for that schedule and serotype in the study by Goldblatt et al [5].
NA: no IgG result available.

otypes (5, 6A, 6B, 7F, 18C and 23F) in the 1 + 1 group of which four (6A, 6B, 18C and 23F) were also significantly lower by OPA (Table 3). Titres to serotype 1 by both ELISA and OPA, and to serotype 5 by OPA, were significantly higher in the 1 + 1 group. The percentage reduction in serotype-specific IgG titres between the post-booster and follow up was around 80–90 % for most serotypes (data not shown). The decline was significantly greater (P < 0.05)

for the 1 + 1 than the 2 + 1 schedule for four serotypes (1, 4, 5 and 14).

4. Discussion

The results reported here form part of the global first trial comparing a 1 + 1 PCV13 schedule to the standard 2 + 1 schedule

Table 3

Serotype-specific geometric means concentrations (95% confidence intervals) measured by ELISA and geometric mean titres (95% confidence intervals) measured by opsonophagocytosis assay (OPA) at follow-up by PCV13 schedule.

Sero-type	GMCs by ELISA			GMTs by OPA		
	2 + 1 group N = 32 to 34	1 + 1 group N = 35 to 41	P value*	2 + 1 group N = 24 to 29	1 + 1 group (95 % CI) N = 31 to 37	P-value**
1	0.19 (0.15–0.24)	0.30 (0.23–0.38)	0.022	4.0 (4.0–4.0)***	9.4 (6.3–13.9)	0.0002
3	0.32 (0.19–0.54)	0.28 (0.17–0.46)	0.997	16.7 (7.4–37.4)	12.7 (7.0–23)	0.63
4	0.21 (0.15–0.30)	0.18 (0.14–0.22)	0.194	35.2 (18–68.7)	45.4 (26.6–77.4)	0.45
5	0.60 (0.46–0.78)	0.41 (0.35–0.50)	0.024	15.0 (9.6–23.3)	24.6 (16.7–36.2)	0.049
6A	0.97 (0.73–1.29)	0.56 (0.45–0.69)	0.002	148.3 (88.6–248.2)	47.3 (24.0–93.2)	0.028
6B	0.61 (0.47–0.80)	0.36 (0.28–0.45)	0.004	60.0 (27.7–129.8)	21.4 (11.8–38.8)	0.035
7F	0.41 (0.34–0.51)	0.29 (0.24–0.34)	<0.001	942.1 (627.4–1414.5)	656.1 (483.6–890.1)	0.17
9 V	0.49 (0.38–0.62)	0.37 (0.30–0.47)	0.156	150.5 (62.5–362.2)	98.5 (49.2–197.1)	0.45
14	0.99 (0.66–1.49)	1.24 (0.87–1.78)	0.620	354.2 (195.3–642.5)	338.1 (203.8–560.9)	0.78
18C	0.22 (0.16–0.30)	0.14 (0.11–0.18)	0.034	96.5 (47.5–196.3)	33.4 (19.7–56.5)	0.012
19A	1.20 (0.84–1.72)	0.96 (0.73–1.25)	0.336	43.7 (21.1–90.8)	61.6 (34.2–110.8)	0.35
19F	1.26 (0.93–1.72)	1.02 (0.73–1.41)	0.364	58.4 (29.6–115.2)	64.2 (33.6–122.5)	0.74
23F	0.83 (0.53–1.31)	0.37 (0.27–0.51)	0.002	541.9 (257–1142.7)	143.4 (64–321.5)	0.006

* From normal errors regression model adjusting for sex and time since booster.
** Kruskal Wallis test.
***All results were < 8.

although the study was not powered for carriage [5]. Overall carriage rates were around 60 %, similar to those seen in children under 5 years of age in other contemporaneous UK carriage surveys, (49–52 %) [7,8]. The majority of carriage episodes were of NVTs with VT carriage identified in only 2.9 % of children, similar to the VT prevalence observed in the other contemporaneous surveys. Carriage episodes of VT and vaccine-related serotypes were evenly distributed between the two study groups as were episodes inferred from documenting ≥ fourfold rises in titre in the subset who provided a follow up blood sample. The serotype distribution in those with serological evidence of carriage reflected the VTs isolated from swabs and is consistent with continuing low level carriage of PCV13 serotypes (mainly 3, 19A and 19F) as observed elsewhere even in settings using a 3 + 1 schedule [9]. The higher proportion of children with a serologically inferred carriage episode (18 %) than identified through swabbing is expected as serology provides a cumulative incidence estimate whereas swabbing provides a point prevalence estimate.

Our findings are supported by preliminary results from a cluster randomised study in Vietnam that showed similar VT carriage prevalence pre-booster in infants who received a 1 + 1 or a 2 + 1 PCV13 schedule, 2.0 % (7/353) vs 1.5 % (5/343) respectively [10]. This study was conducted following a catch-up PCV13 vaccination campaign for under 3 year olds to accelerate the induction of indirect immunity. In South Africa, carriage was studied in a 1 + 1 vs 2 + 1 schedule using PCV13 and PCV10 [11] and no difference was found in carriage prevalence between the two schedules [15].

The serotype-specific post-primary IgG responses in 6 of the 9 children carrying a VT or 6C at the time of the booster were in the lower quartile range for their group. However, with the substantially higher post-primary GMCs for all serotypes (apart from serotype 3) in the 2 + 1 than 1 + 1 group [5], the post-primary IgG levels in the carriers in the 2 + 1 group were still greater than the comparable post-primary GMC in the 1 + 1 group. This suggests that being a poor responder to priming doses of PCV13 is indicative of an increased risk of subsequent carriage of a VT serotype but that the actual IgG antibody concentration is not predictive, at least not at the levels induced by primary vaccination. The lack of association between maternally-derived serotype-specific IgG and risk of carriage in early infancy supports this interpretation [12].

Correlates of protection used for licensure of PCVs were derived from associations between post-primary IgG concentrations and pre-booster efficacy and their utility as a predictor of protection post-booster is unknown. In the subset tested 15–21 months post-booster antibodies had declined by 80–90 % irrespective of schedule. However, PCV13 effectiveness data show continuing high levels of protection for at least seven years under the 2 + 1 schedule [13], suggesting mechanisms other than IgG levels, such as immune memory, may mediate longer-term protection post-booster.

Shortly after changing to the 1 + 1 schedule in the UK, pneumococcal transmission was substantially reduced by the social distancing measures implemented to limit spread of SARS-CoV-2 [14]. While this has prevented early evaluation of the schedule change, the comprehensive laboratory-based IPD surveillance in place in England will allow the longer term impact of the 1 + 1 schedule on indirect immunity and direct vaccine effectiveness to be assessed.

5. Authors' contributions

EM, JS, NA, MDS and DG designed the trial. MDS, JS, PKA, HR and EPl oversaw the clinical trial, clinical data collection and clinical data management. DG and EPe generated the ELISA data, DG, LR and MJ generated the OPA data. CLS, SR, DJL and NKF were responsible for the carriage data, PW was responsible for data management and NA conducted the statistical analysis. DG and EM wrote the first draft of the paper and all authors contributed to subsequent drafts. All read and approved the final version of the paper.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Matthew Snape reports financial support was provided by National Institute for Health and Care Research. David Goldblatt reports financial support was provided by Bill & Melinda Gates Foundation. NA, CLS, SR and DJL have no conflicts of interest. The UKHSA Immunisation and Vaccine Preventable Diseases (previously Public Health England) has provided vaccine manufactures with post-marketing surveillance reports, which the Marketing Autho-

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