

Immunogenicity of the UK group B meningococcal vaccine (4CMenB) schedule against groups B and C meningococcal strains (Sched3): outcomes of a multicentre, open-label, randomised controlled trial

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Summary

Background The use of the multicomponent meningococcal vaccine 4CMenB in the UK schedule at 2, 4, and 12 months of age has been shown to be 59·1% effective at preventing invasive group B meningococcal disease. Here, we report the first data on the immunogenicity of this reduced-dose schedule to help to interpret this effectiveness estimate.

Methods In this multicentre, parallel-group, open-label, randomised clinical trial, infants aged up to 13 weeks due to receive their primary immunisations were recruited via child health database mailouts in Oxfordshire and via general practice surgeries in Gloucestershire and Hertfordshire. Infants were randomly assigned (1:1) with permuted block randomisation to receive a 2+1 (2, 4, and 12 months; group 1) or 1+1 (3 and 12 months; group 2) schedule of the 13-valent pneumococcal conjugate vaccine (PCV13). All infants also received 4CMenB at 2, 4, and 12 months of age, and had blood samples taken at 5 and 13 months. Participants and clinical trial staff were not masked to treatment allocation. Proportions of participants with human complement serum bactericidal antibody (hSBA) titres of at least 4 were determined for group B meningococcus (MenB) reference strains 5/99 (Neisserial Adhesin A [NadA]), NZ98/254 (porin A), and 44/76-SL (factor H binding protein [fHbp]). Geometric mean titres (GMTs) with 95% CIs were also calculated, and concomitant vaccine responses (group C meningococcus [MenC], *Haemophilus influenzae* b [Hib], tetanus, diphtheria, and pertussis) were compared between groups. The primary outcome was PCV13 immunogenicity, with 4CMenB immunogenicity and reactogenicity as secondary outcomes. All individuals by randomised group with a laboratory result were included in the analysis. The study is registered on the EudraCT clinical trials database, 2015-000817-32, and ClinicalTrials.gov, NCT02482636, and is complete.

Findings Between Sept 22, 2015, and Nov 1, 2017, of 376 infants screened, 213 were enrolled (106 in group 1 and 107 in group 2). 204 samples post-primary immunisation and 180 post-boost were available for analysis. The proportion of participants with hSBA of at least 4 was similar in the two study groups. For strain 5/99, all participants developed hSBA titres above 4 in both groups and at both timepoints. For strain 44/76-SL, these proportions were 95·3% (95% CI 88·5–98·7) or above post-priming (82 of 86 participants in group 1), and 92·4% (84·2–97·2) or above post-boost (73 of 79 participants in group 1). For strain NZ98/254, these proportions were 86·5% (78·0–92·6) or above post-priming (83 of 96 participants in group 2) and 88·6% (79·5–94·7) or above post-boost (70 of 79 participants in group 1). The MenC rabbit complement serum bactericidal antibody (rSBA) titre in group 1 was significantly higher than in group 2 (888·3 vs 540·4; $p=0\cdot025$). There was no significant difference in geometric mean concentrations between groups 1 and 2 for diphtheria, tetanus, Hib, and pertussis post-boost. A very small number of children did not have a protective response against 44/76-SL and NZ98/254. Local and systemic reactions were similar between the two groups, apart from the 3 month timepoint when one group received an extra dose of PCV13 and recorded more systemic reactions.

Interpretation These data support the recent change to the licensed European schedule for 4CMenB to add an infant 2+1 schedule, as used in the routine UK vaccine programme with an effectiveness of 59·1%. When compared with historical data, our data do not suggest that effectiveness would be higher with a 3+1 schedule, however a suboptimal boost response for bactericidal antibodies against vaccine antigen fHbp suggests a need for ongoing surveillance for vaccine breakthroughs due to fHbp-matched strains. Changing from a 2+1 to a 1+1 schedule for PCV13 for the UK is unlikely to affect protection against diphtheria, tetanus, and Hib, however an unexpected reduction in bactericidal antibodies against MenC seen with the new schedule suggests that ongoing surveillance for re-emergent MenC disease is important.

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Research in context

Evidence before this study

The 4CMenB meningococcal vaccine is administered in a 2 + 1 schedule in the UK (2, 4, and 12 months of age), with one fewer dose than the initially licensed 3 + 1 schedule for infants between 2 and 5 months of age. The immunogenicity of the 3 + 1 schedule has been well described during vaccine development, but that of the reduced-dose schedule in the context of UK infant vaccination has not. 1 + 1 schedules for either 4cMenB or PCV13 have not, to our knowledge, been described before this trial. To review the immunogenicity of the two 4CMenB schedules, we searched PubMed, Embase, and Cochrane Library for articles published in English from Jan 1, 2010, to June 27, 2019. Search terms included "4CMenB", "meningococcus B vaccine", AND "Bexsero". This search returned 154 articles, of which six were randomised controlled trials describing the immunogenicity of 4CMenB in either a licensed or reduced-dose schedule and were included in the discussion. Overall, 4CMenB is immunogenic and a 3 + 1 schedule has been more extensively described than a 2 + 1 schedule. The immunogenicity of 4CMenB does not appear to be affected by co-administration with other routine vaccines, but this may result in increased reactogenicity.

Added value of this study

Our study, which was part of the Sched3 trial, found that there was no difference in immunogenicity of 4CMenB in the

2 + 1 schedule when given with varying doses of 13-valent pneumococcal conjugate vaccine (PCV13). Both post-priming and post-boost, at least 86% of participants had human complement serum bactericidal antibody titres above the correlate of protection (≥ 4) for the three MenB strains tested 44/76-SL, 5/99, and NZ98/254. However, for 44/76-SL, geometric mean titres were no higher post-boost than post-prime. Our study also showed no cross-protection from 4CMenB against the meningococcal group C strain tested, but the strain tested does not correlate with the current pathogenic circulating strains. Reduction in PCV13 doses also did not lead to clinically significant differences in the immunogenicity of other concomitant vaccines in the schedule.

Implications of all the available evidence

This study provides reassurance that the changes to the PCV13 schedule in the UK national immunisation programme, with a reduction from 2 + 1 (given at 2, 4, and 12 months of age) to 1 + 1 (given at 3 and 12 months of age) doses, will not alter the immunogenicity of 4CMenB or other concomitant routine vaccines. It adds to the body of knowledge surrounding 4CMenB immunogenicity and will allow interpretation of the effectiveness data in light of known vaccine immunogenicity.

Introduction

Neisseria meningitidis is a major cause of bacterial meningitis and septicaemia worldwide in children and adolescents. It presents with rapid disease onset and progression, with high mortality rates and serious long-term sequelae in around 19% of individuals.^{1,2} From the 12 known capsular groups of *N meningitidis*, six (A, B, C, W, X, Y) are responsible for the majority of disease.³ Capsular group B meningococcus (MenB) is one of the leading causes of meningococcal disease in high-income countries.⁴ In the epidemiological year 2018–19 in England, MenB disease accounted for 58% of all laboratory-confirmed cases (80% of meningococcal disease in children younger than 5 years).⁵

To decrease disease burden, from September, 2015, the UK became the first country in the world to routinely use the multicomponent vaccine 4CMenB (Bexsero; GlaxoSmithKline, Rixensart, Belgium). The vaccine was deployed using a schedule with vaccinations at 2, 4, and 12 months of age, with a reported effectiveness against all strains of MenB of 24.1% after one dose, 52.7% after two doses, and 59.1% after three doses.⁶ The administration of three doses of 4CMenB was 71.2% effective against vaccine-preventable invasive MenB disease⁶ (ie, those strains sufficiently well matched to the vaccine antigens on the Meningococcal Antigen Typing System.⁷ Of note, the implemented schedule

comprises one fewer primary dose than the licensed schedule, which recommends three priming doses between 2 and 5 months of age.⁸ The reduced schedule in the UK was intended to optimise the cost-effectiveness of the 4CMenB immunisation campaign and was informed by data showing little difference in vaccine-induced immune responses between the second and third infant doses of 4CMenB.⁹

To date, the immunogenicity of the reduced priming schedule of 4CMenB in the UK has not been described. Immunogenicity data from the specific schedule used in the UK are crucial to providing the context for understanding the reported 4CMenB effectiveness. Analysis of 4CMenB immunogenicity was done as a prespecified secondary objective in the Sched3 trial, for which Goldblatt and colleagues have already reported the primary outcome of the immunogenicity of a reduced-dose schedule of 13-valent pneumococcal conjugate vaccine (PCV13).¹⁰ In this study, in which around half of the participants received the routine immunisation schedule in the UK at the time of the trial and half received the subsequently adopted reduced-dose PCV13 schedule,¹¹ we aimed to evaluate the immunogenicity and reactogenicity of 4CMenB when administered separately from PCV13, as well as the immunogenicity of concomitant routine vaccines (meningococcal group C [MenC], *Haemophilus influenzae* type b [Hib], and tetanus–diphtheria–pertussis).

Methods

Study design and participants

The full study methods of this multicentre, parallel-group, open-label, randomised clinical trial have been previously reported.¹⁰ In brief, healthy infants aged up to 13 weeks, due to receive their primary vaccinations as per the UK immunisation schedule with the exception of PCV13, were recruited via child health database mailouts in Oxfordshire and via general practice surgeries in Gloucestershire and Hertfordshire. Infants with bleeding disorders, at risk of invasive pneumococcal disease, or with a history of allergic reactions to any of the vaccine components were excluded.

Written informed consent was obtained from the parent or guardian before enrolment. Ethical approval was granted by the Oxfordshire Research Ethics Committee (reference number 15/SC/0387).

Randomisation and masking

Participants were randomly assigned to receive the PCV13 vaccine in either a 2+1 schedule (vaccination at 2, 4, and 12 months of age; group 1) or a 1+1 schedule (vaccination at 3 and 12 months of age; group 2). Randomisation of participants (1:1) was done by computer-generated permuted block randomisation, with a block size of six. Study numbers were allocated sequentially. Participants and clinical trial staff were not masked to treatment allocation.

Procedures

4CMenB (Bexsero) was administered intramuscularly to all infants at 2, 4, and 12 months of age.⁸ Infant doses of paracetamol were recommended to parents post-4CMenB vaccine administration at 2 and 4 months of age, as per Public Health England (PHE) recommendations to reduce reactogenicity. Other vaccines administered (appendix p 2) were the combined diphtheria toxoid, tetanus toxoid, acellular pertussis, Hib, and inactivated polio vaccine (Infanrix-IPV-Hib, GlaxoSmithKline, Rixensart, Belgium); PCV13 (Prevenar 13, Pfizer, New York, NY, USA); oral rotavirus vaccine (Rotarix, GlaxoSmithKline, Rixensart, Belgium); MenC-Hib (Menitorix, GlaxoSmithKline, Rixensart, Belgium); and the measles, mumps, and rubella vaccine (Priorix, GlaxoSmithKline, Rixensart, Belgium).

At 5 months (1 month after completion of primary vaccine doses) and 13 months of age (1 month after booster vaccine doses) up to 5 mL of blood was collected for analysis of human complement serum bactericidal antibody (hSBA). hSBA assays were done by use of reference strains for three key 4CMenB vaccine antigens:¹² factor H binding protein 1 (fHbp) by 44/76-SL, NadA by 5/99, and OMV (porin A [PorA]) by NZ98/254. These assays, along with an assay for rabbit complement SBA (rSBA) titres for the recommended MenC reference strain C11 (C:16:P1.7-1,1), were done at the Vaccine Evaluation Unit, PHE, Manchester, UK, by means of a previously published methodology.^{13,14}

Antigen-specific IgG concentrations were measured by ELISA at the ImmunoAssay Group PHE Porton Down laboratory (Salisbury, UK; assay methods published previously)¹⁵ by use of serum samples collected at 5 and 13 months of age for Hib polysaccharide (polyribosylribitol phosphate [PRP]), pertussis antigens (pertussis toxin, pertactin, filamentous haemagglutinin), and tetanus and diphtheria toxoids.

Local reactions and systemic symptoms were recorded by means of a paper-based health diary completed by parents during a period of 7 days after each immunisation (at 2, 3, 4, and 12 months of age). Temperatures were recorded by means of an axillary thermometer in the first 24 h after immunisation and once a day on the following days. Local reactions (redness, swelling, and tenderness) were solicited, as were systemic reactions (decreased feeding, less activity, more irritability, crying persistently, vomiting, and diarrhoea). Further, non-solicited adverse events, including medically attended adverse events, observed in the 7 days after immunisation were also recorded. Serious adverse events were reported for the duration of the study.

Outcomes

The primary outcome of the Sched3 trial was an evaluation of geometric mean concentrations (GMCs) of blood serotype-specific pneumococcal antibody responses measured after the final infant vaccinations (around 13 months of age) in group 1 compared with group 2. Secondary outcomes, which are reported here, were the proportion of study participants who achieved an hSBA titre of at least 4, the established correlate of response,¹⁴ for each of the three vaccine 4CMenB antigens at both study timepoints. MenB hSBA geometric mean titres (GMTs) with 95% CIs were also calculated. The proportion of participants achieving an rSBA titre of at least 8, the correlate of protection against MenC,¹³ was calculated. GMCs were determined for: anti-PRP IgG and the proportion of infants with concentrations of at least 0.15 g/mL and at least 1.0 g/mL; IgG to pertussis toxin, pertactin, and filamentous haemagglutinin in IU/mL; anti-tetanus toxoid IgG and proportions of at least 0.1 IU/mL and at least 1.0 IU/mL; and anti-diphtheria toxoid IgG and proportions of at least 0.1 IU/mL and at least 1.0 IU/mL. Additionally, GMCs of pertussis antigens and fimbriae 2 and 3 (not components of Infanrix-IPV Hib) in U/mL were measured. Reactogenicity was measured by local and systemic reactions.

Statistical analysis

As previously reported by Goldblatt and colleagues,¹⁰ the sample size of 220 infants was calculated on the basis of the primary objective of the Sched3 trial (immunogenicity of PCV13). Analysis was by modified intention to treat, with all individuals included by randomised group if they had a laboratory result. All analyses were prespecified, with the exception of a post-hoc analysis of the numbers of individual participants whose hSBA titres did not

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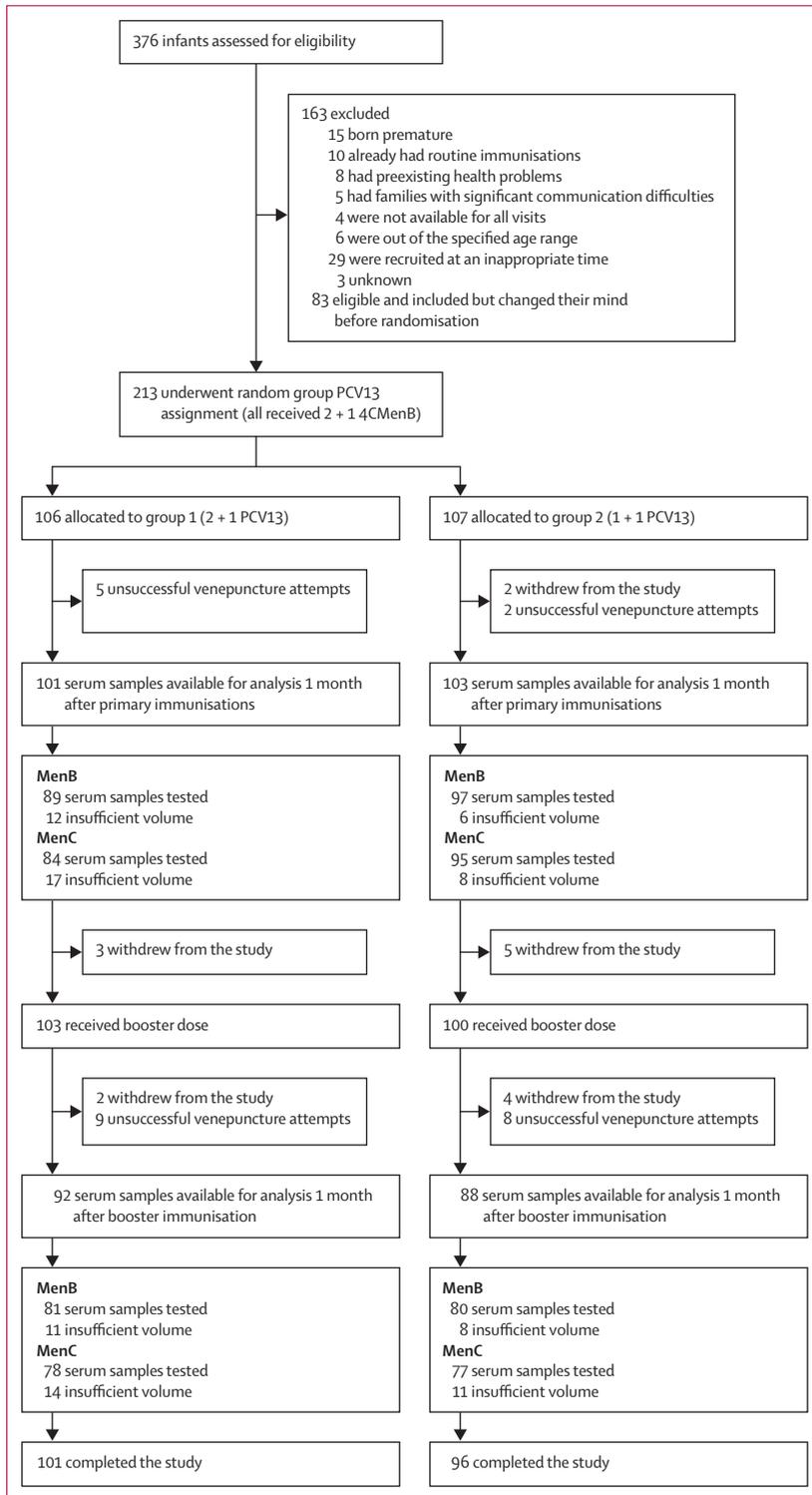


Figure 1: Trial profile
 4CMenB= group B meningococcal vaccine. MenB=capsular group B meningococcus. MenC=capsular group C meningococcus. PCV13=13-valent pneumococcal conjugate vaccine.

reach above 4 for any of the 4CMenB reference strains post-priming or post-boost.

For the secondary trial outcome measures reported in this paper, the measures of immunogenicity for each antigen and their 95% CIs were calculated for each PCV13 group, and between-group comparisons were made by means of log transformation and normal errors regression (equivalent to an unpaired *t* test for two groups). This analysis was also used to obtain geometric mean fold ratios (with 95% CIs) between the groups. If the log-transformed data were not normally distributed, then the Kruskal-Wallis test was used to compare groups. Proportions above titre thresholds were compared by means of Fisher's exact test and proportions calculated within groups with 95% CIs. Differences are shown at a 5% significance level.

A comparative analysis of reactogenicity data between different PCV13 groups was also done. The analysis was based on the maximum severity level reported over the 7 days and on proportions with any ($\geq 38^{\circ}\text{C}$ for temperature and >0 mm for local reactions) or severe ($\geq 39^{\circ}\text{C}$ and ≥ 50 mm) reactions. Groups were compared by Fisher's exact test. The grading of local and systemic reactions is described in the appendix (p 1). The University of Oxford Trials Safety Group did the data monitoring. The study is registered on the EudraCT clinical trials database (2015-000817-32) and ClinicalTrials.gov (NCT02482636). All data were analysed using STATA-IC 13.

Role of the funding source

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

Results

Between Sept 22, 2015, and Nov 1, 2017, 376 infants were assessed for eligibility (figure 1). 163 infants were excluded before randomisation. 213 eligible infants were therefore enrolled, and 106 were randomly allocated to group 1 (2+1 PCV13 schedule) and 107 to group 2 (1+1 PCV13 schedule). The results are presented according to the different PCV13 schedules that the participants received. A total of 204 samples were available for analysis after primary immunisations and 180 samples after booster immunisations. Overall, 197 participants completed the study. Baseline characteristics of the study participants have been reported previously.¹⁰

At both 1 month post-primary vaccination and 1 month post-booster vaccination, there was no significant difference in the proportion of infants with hSBA titres of at least 4 between the two different PCV13 schedules, for each MenB target strain (table 1, figure 2). The numbers of participants with hSBA titres of at least 4 against the strain 44/76-SL were 82 (95%) of 86 and 95 (98%) of 97 in

	Post-primary		p value*	Post-boost		p value*
	Group 1 (N _{max} =89)	Group 2 (N _{max} =97)		Group 1 (N _{max} =81)	Group 2 (N _{max} =80)	
MenB strain 5/99 (NadA)	100% (95.8–100); 87/87	100% (96.2–100); 96/96	NA	100% (95.4–100); 79/79	100% (95.4–100); 78/78	NA
MenB strain 44/76-SL (fHbp)	95.3% (88.5–98.7); 82/86	97.9% (92.7–99.7); 95/97	0.42	92.4% (84.2–97.2); 73/79	93.8% (86.0–97.9); 75/80	0.77
MenB strain NZ98/254 (PorA)	88.5% (79.9–94.3); 77/87	86.5% (78.0–92.6); 83/96	0.82	88.6% (79.5–94.7); 70/79	92.1% (83.6–97.0); 70/76	0.59
MenC	2.4% (0.3–8.3); 2/84	2.1% (0.3–7.4); 2/95	0.64	98.7% (93–100); 76/77	97.4% (91–99.7); 76/78	0.51

Data are % (95% CI); n/N. Group 1 received 2 + 1 PCV13 and 4CMenB at 2, 4, and 12 months of age. Group 2 received 1 + 1 PCV13 at 3 and 12 months of age and 4CMenB at 2, 4, and 12 months of age. hSBA=human complement serum bactericidal antibodies. rSBA=rabbit complement serum bactericidal antibodies. N_{max}=maximum number of serum samples tested. MenB=meningococcal serogroup B. MenC=meningococcal serogroup C. fHbp=factor H binding protein. NA=not applicable. NadA=Neisserial Adhesin A. PCV13=13-valent pneumococcal conjugate vaccine. PorA=porin A. *Fisher's exact test.

Table 1: Proportion of participants with *Neisseria meningitidis* reference strain MenB hSBA titres of at least 4 and MenC rSBA titres of at least 8

the two PCV13 groups' post-primary immunisations, and post-boost these were 73 (92%) of 79 and 75 (94%) of 80, with a similar lack of increase from post-prime to post-boost for the NZ98/254 strain (table 1). The minimal increase for strain 44/76-SL is shown in this strain's GMTs (eg, 39.5 [95% CI 29.8–52.3] post-primary and 34.0 [24.4–47.4] post-boost in group 1), and to a lesser extent for NZ98/254 (14.1 [10.4–19.1] post-primary and 26.6 [18.3–38.7] post-boost; table 2).

To investigate the extent to which variations in response to 4CMenB immunisation left individual children potentially vulnerable to MenB disease, we analysed the data across both groups to identify any children who persistently responded suboptimally to immunisation. Given that all children responded with bactericidal antibody titres of at least 4 against strain 5/99, attention was focused on strains 44/76-SL and NZ98/254. Looking at both strains together, of 182 children with hSBA titre results available for both 44/76-SL and NZ98/254 post-priming, two (1%) did not have protective hSBA titres of at least 4 against either strain. Of 153 children with hSBA titre results available for both strains 44/76-SL and NZ98/254 post-boost, three (2%) did not have protective hSBA titres of at least 4 for both strains. Of 133 children with paired samples post-prime and post-boost for both strains 44/76-SL and NZ98/254, one infant (1%) did not respond to both strains at either timepoint (appendix p 4).

Looking at each strain separately, eight (6%) of 135 children tested for NZ98/254 at both timepoints did not develop hSBA titres above the correlate of protection at either post-primary or post-boost vaccination, and one (1%) of 139 children tested for 44/76-SL at both timepoints did not develop hSBA titres above the correlate of protection against 44/76-SL (table 3). A lack of bactericidal antibody post-priming did predict hSBA titres lower than 4 post-boost for strain NZ98/254 ($p=0.0055$ for group 1, $p=0.0017$ for group 2), but not for 44/76-SL. Nine (6%) of 139 children tested for 44/76-SL who had hSBA titres of at least 4 against 44/76-SL post-priming did reach this

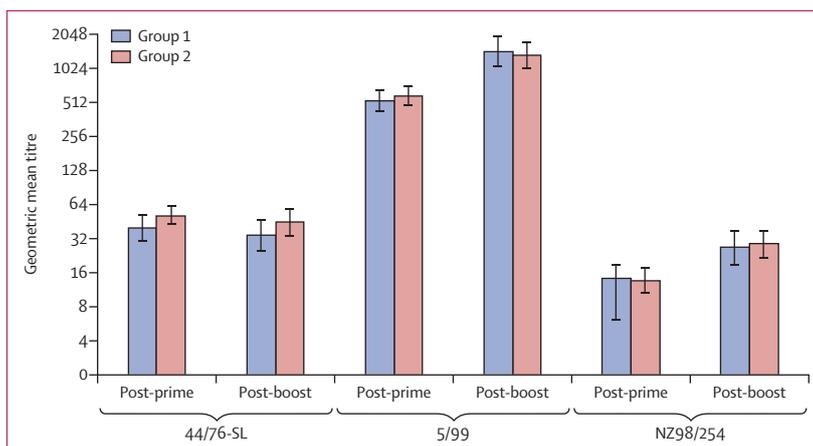


Figure 2: *Neisseria meningitidis* capsular group B reference strain hSBA geometric mean titres
Group 1 post-prime refers to post primary series of 4CMenB given at 2 and 4 months of age. Post-boost refers to post booster dose of 4CMenB given at 12 months of age. 44/76-SL, 5/99, and NZ98/254 are the *Neisseria meningitidis* group B reference strains. Error bars show 95% CI. See Table 2 for exact values. hSBA=human serum bactericidal antibody.

threshold post-boost, which also happened for five (4%) of 135 children tested for for strain NZ98/254.

Only 2.1–2.4% of participants had MenC rSBA titres of at least 8 post-primary immunisation (two [2%] of 84 infants in group 1, two [2%] of 95 in group 2), but almost all participants reached this threshold post-boost (table 1), after they had received MenC–Hib (appendix p 2). The MenC rSBA GMT of group 1 at 13 months (888.3 [95% CI 640.0–1232.8]) was significantly higher than the GMT of group 2 (540.4 [404.1–722.8], $p=0.025$; table 2, appendix pp 3, 4).

In terms of diphtheria, tetanus, Hib, and pertussis, there was no significant difference between the two PCV13 groups with the exception of anti-diphtheria IgG GMC in group 1 being higher than that of group 2 post-primary immunisation (appendix p 5). Antibodies against the pertussis antigens fimbriae 2 and 3 were also higher in group 2 post-primary immunisation.

	Post-primary				Post-boost			
	Group 1 GMTs (N _{max} =89)	Group 2 GMTs (N _{max} =97)	GMFR	p value*	Group 1 GMTs (N _{max} =81)	Group 2 GMTs (N _{max} =80)	GMFR	p value
MenB strain 5/99 (NadA)	528.6 (420.1–665.0)	587.3 (476.8–723.4)	1.11 (0.82–1.51)	0.50	1454.5 (1054.0–2007.3)	1336.8 (1001.8–1784.0)	0.92 (0.60–1.41)	0.70
MenB strain 44/76-SL (fHbp)	39.5 (29.8–52.3)	51.3 (41.9–62.8)	1.30 (0.93–1.82)	0.13	34.0 (24.4–47.4)	44.5 (33.1–59.8)	1.31 (0.84–2.02)	0.23
MenB strain NZ98/254 (PorA)	14.1 (10.4–19.1)	13.7 (10.4–18.1)	0.98 (0.65–1.46)	0.91	26.6 (18.3–38.7)	28.7 (21.2–38.8)	1.08 (0.67–0.94)	0.76
MenC	2.2 (1.9–2.4)	2.2 (2.0–2.5)	1.03 (0.88–1.20)	0.33	888.3 (640.0–1232.8)	540.4 (404.1–722.8)	0.61 (0.40–0.94)	0.025

Data are titres or ratios (95% CIs). Group 1 received 2 + 1 PCV13 and 4CMenB at 2, 4, and 12 months of age. Group 2 received 1 + 1 PCV13 at 3 and 12 months of age and 4CMenB at 2, 4, and 12 months of age. GMFR=geometric mean fold ratio. GMT=geometric mean titre. N_{max}=maximum number of serum samples tested. MenB=meningococcal serogroup B. MenC=meningococcal serogroup C. fHbp=factor H binding protein. NadA=Neisserial Adhesin A. PCV13=13-valent pneumococcal conjugate vaccine. PorA=porin A. *t test on log-transformed data except for MenC post-primary where Kruskal-Wallis test was used.

Table 2: *Neisseria meningitidis* reference strain GMTs and GMFRs

	44/76-SL (fHbp)	5/99 (NadA)	NZ98/254 (PorA)
hSBA titres ≥4 not seen	1	0	8
hSBA titres ≥4 seen post-prime only	9	0	5
hSBA titres ≥4 seen post-boost only	5	0	11
hSBA titres ≥4 seen both post-prime and post-boost	124	136	111
Total	139	136	135

fHbp=factor H binding protein. hSBA=human serum bactericidal assay. MenB=meningococcal serogroup B. NadA=Neisserial Adhesin A. PorA=porin A.

Table 3: Post-primary and post-boost vaccine titres ≥4 in paired samples by MenB hSBA target strain in both groups combined

Severe adverse reactions have been described elsewhere.¹⁰ The only significant between-group difference in local or systemic reactogenicity was at the 3-month immunisations when group 2 received a dose of PCV13 and group 1 did not, at which time there were generally more reactions recorded in group 2 (with fever being significantly higher; figure 3).

Discussion

Here, we present the first immunogenicity data from the reduced infant priming schedule of 4CMenB used in the UK, with doses administered at 2, 4, and 12 months of age. These data provide essential context for the reported effectiveness of the vaccine,⁶ and support the recent change to the European schedule to incorporate a 2 + 1 schedule of 4CMenB.¹² This trial also shows that the newly introduced reduction in PCV13 doses in the UK schedule¹¹ does not affect the immunogenicity of 4CMenB, but is unlikely to result in reduced reactogenicity.

It was reassuring that most study participants had hSBA titres of at least 4 against each of the three MenB vaccine strains after primary immunisations. However, it was striking that for the 44/76-SL strain, there was no change in the proportion with hSBA titres of at least 4 post-boost compared with post-priming. Furthermore, GMTs were lower post-boost than post-primary immunisations. We

also did not expect that there would be no increase in the proportion of participants with hSBA titres of at least 4, and only a minimal increase in GMT against the NZ98/254 strain, post-boost immunisations compared with post-primary immunisations.

The hSBA GMTs for 44/76-SL tended to be lower both post-priming (39.5 and 51.3) and post-boost (34.0 and 44.5) for both PCV13 groups than in previous studies of 4CMenB in infants that used three-dose priming schedules with the same hSBA target strain (hSBA GMTs ranging from 73 to 103 post-prime, and 92 to 178 post-boost).^{12,16–18} This difference could reflect either reduced immunogenicity of the 2 + 1 immunisation schedule or interlaboratory variation. The latter issue can be partially addressed by evaluating the post-boost to post-prime ratio within studies, and it is notable that in the above three-dose priming studies, this ratio was between 1.02 and 1.68, compared with a ratio of 0.86 for both PCV13 groups reported here. In another three-dose priming study by Findlow and colleagues,⁹ for which hSBAs were done within the same laboratory as the hSBAs reported here, post-boost hSBA GMTs were 106.0, and post-boost to post-prime ratios were 3.53. Although these findings might suggest that three infant doses prime the immune response to the fHbp antigen better than two, in another study, which was the only one we found in which a two-dose (3, 5, and 11 months of age) and a three-dose (2, 3, 5, and 11 months of age) priming schedule were directly compared, similar post-booster dose GMTs following both schedules were observed.¹⁹

Different patterns of response were observed for strain 5/99, where hSBA GMTs appeared higher in the Sched3 study than those in Findlow and colleagues' study both post-prime (528.6 [95% CI 420.1–665] vs 126 [77.0–205.0]) and post-boost (1454.5 [1054.0–2007.3] vs 629 [324.0–1219.0]). These findings could suggest that a 2 + 1 schedule is more immunogenic for the NadA antigen than a 3 + 1 schedule (eg, if an extra priming dose of 4CMenB were to impair the booster response to the

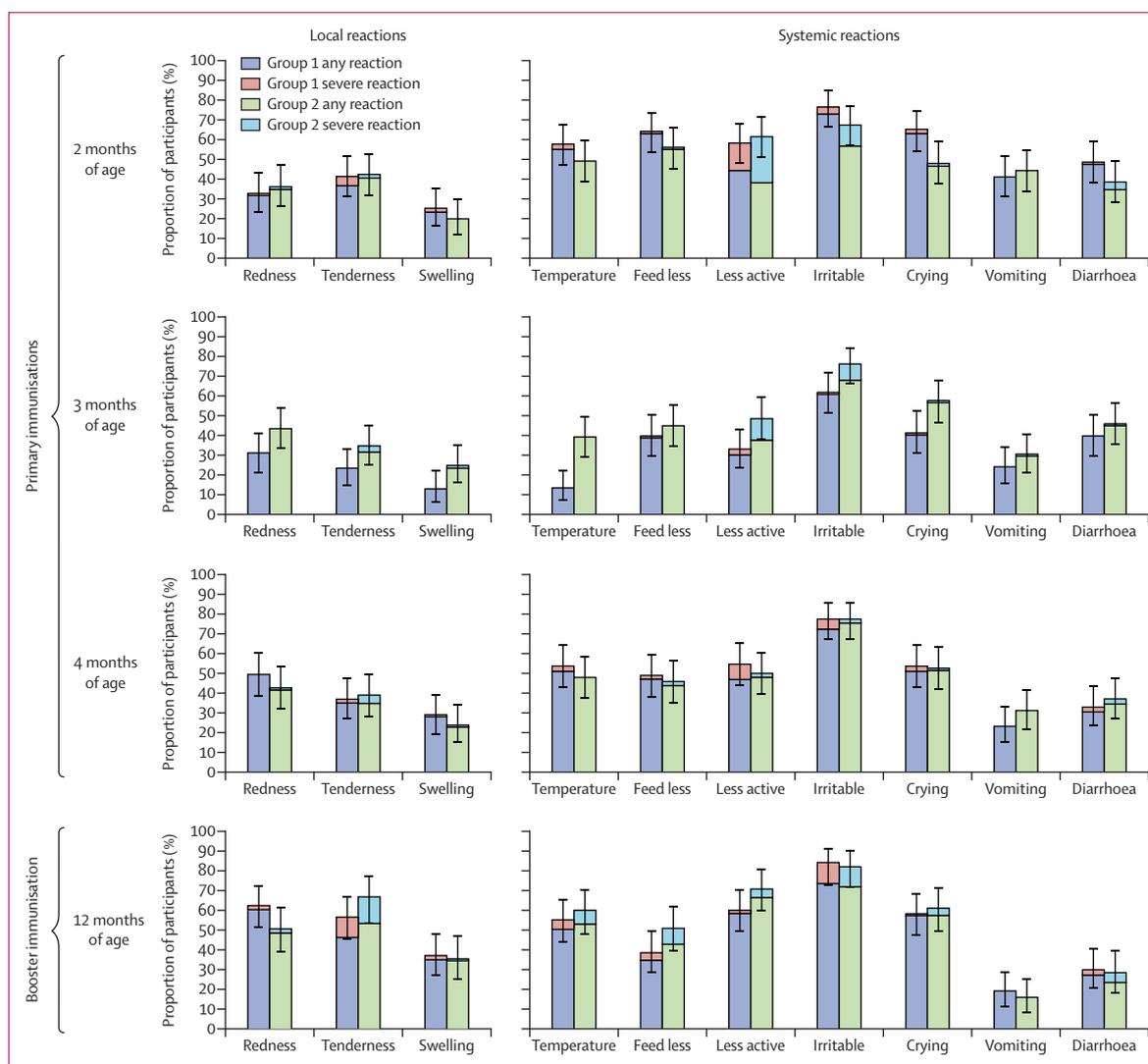


Figure 3: Local reactions at any vaccine site and systemic reactions after each vaccine visit

Local reaction refers to a reaction at any of the vaccine sites at each timepoint. Error bars represent 95% CI for any reaction.

5/99 strain). By contrast, Gossger and colleagues¹² showed GMTs against 5/99 post-three-dose priming similar to those seen in this study (520 [475–570]), as did Vesikari and colleagues¹⁶ (post-prime GMT of 634 [606–664]; post-boost GMT of 1403 [1255–1568]), albeit within the limitations of interlaboratory variations.

For strain NZ98/254, the post-boost hSBA GMT of 26.6 (group 1) was similar to Findlow and colleagues' study (29.0) and slightly below the range (36.0–47.0) of hSBA GMTs reported in studies done in the manufacturer's laboratory.^{16,20}

It would therefore appear that, compared with the licensed schedule, the reduced-dose schedule might be slightly less immunogenic for the fHbp antigen (as measured by 44/76-SL), more immunogenic for the NadA antigen (5/99), and of similar immunogenicity for the PorA antigen (NZ98/254). These comparisons will be

further informed by data on the persistence of antibodies following immunisation, and these are being collected in a follow-up study. Nevertheless, the response rates of 92.4% or higher for even the 44/76-SL strain emphasise that most children are mounting an immune response to the UK 4CMenB immunisation schedule.

Our data do not give any strong indication that effectiveness of the UK 4CMenB campaign (reported at 59.1%) could be improved if the licensed 3+1 schedule were to be used, albeit with the caveat that we have not analysed the response to the vaccine neisserial heparin binding antigen.

In our study, hSBA titres of at least 4 for 4CMenB were primarily used as a means of showing a response to vaccine antigens for licensing and were not intended to correlate with all-cause effectiveness. Our data reinforce the point that a measured serum response to three strains

designed to show proof of principle might not directly translate to vaccine effectiveness. Of relevance to this is that only 66% of invasive MenB isolates in the UK were predicted by Meningococcal Antigen Typing System to be covered by 4CMenB in the epidemiological year 2014–15,⁷ and most of this coverage was a result of the presence of fHbp (59% of strains bearing matched antigens) and neisserial heparin binding antigen (33%), with minimal contribution from NadA (2%). Ultimately, interpreting these data in light of the emerging information on 4CMenB vaccine effectiveness in England and Wales will inform the correlation between 4CMenB reference strain-specific bactericidal antibodies and antigen-specific effect on disease. For example, if strains causing disease in children yet to receive a booster dose of 4CMenB were disproportionately bearing NadA, and relatively few strains bearing NadA caused disease in those receiving a completed schedule, this might suggest that the higher 5/99 titres observed post-boost (compared with post-prime) are required for a sufficient immune response to this antigen, and could in turn lead to a recalibration of the protective threshold for this strain. Conversely, any difference in effectiveness for strains bearing matched fHbp from post-prime to post-boost (despite the very similar post-prime to post-boost hSBA for 44/76-SL) could highlight inherent limitations in the ability of hSBAs to predict vaccine effectiveness. It will also be important to consider PorA-matched vaccine breakthroughs considering the knowledge that 6% of children in our study had no response to either primary or booster immunisation for strain NZ98/254.

It is also important to bear in mind this variability in individuals' response when considering data derived from pooled sera. An example from Biolchi and colleagues²¹ showed that pooled sera from infants receiving two-dose or three-dose priming schedules generated hSBA titres of at least 4 for 40% of strains from the UK in 2007–08 post-priming, increasing to 87.5% post-boost. These proportions were not influenced by the number of priming doses. Although these data provide some reassurance regarding the use of the reduced-dose schedule in the UK, it is worth considering that these data would not identify any subset of infants for whom three priming doses were required.

We could not assess whether 4CMenB provided any cross-protection against the MenC strains causing disease in the UK because the WHO-recommended MenC strain, which forms the basis of rSBA testing, is different from circulating pathogenic MenC strains. Nevertheless, of potential relevance is the significantly higher MenC rSBA GMTs at 13 months in group 1 compared with group 2, despite all participants receiving MenC–Hib at 12 months of age. Although more than 97% of participants in both groups had rSBA titres of at least 8, it is possible that waning to below this protective threshold will occur more quickly in group 2, and this will be tested in the follow-up study. It is not readily apparent why differing exposure to

PCV13 (containing a cross-reactive material 197 [CRM197] carrier protein) should alter the response to MenC–Hib (containing a tetanus-toxoid carrier protein), given that the vaccines do not have either polysaccharide or protein antigens in common. Previous studies suggest that increasing the CRM197 content of the primary immunisation schedule might reduce the response to MenC–Hib, although in these historical studies the CRM197 in the primary schedule was conjugated to MenC polysaccharide, so any variation might be explained by differing exposure to the polysaccharide antigen.^{22,23} With regard to the other concomitant vaccines against diphtheria, pertussis, and Hib, the only significant difference between the two groups related to GMT against diphtheria (unsurprising given the additional dose of CRM197-containing PCV13 in group 1), and between fimbriae 2 and 3 (antigens that were not included in any vaccines administered to the study population), for which the cause was unclear.

Giving 4CMenB concomitantly with routine infant vaccines increases reactogenicity, especially fever.^{16,24,25} This is an important consideration given that the addition of 4CMenB into the UK immunisation schedule has resulted in increases in emergency-room attendances for infants with a fever,^{24,26} with a subsequent increase in admissions, investigations, and antibiotic use for adverse events following immunisation.^{25,26} Unfortunately, separating infant PCV13 and 4CMenB administration (as in group 2 in this study) did not reduce reactogenicity at 2 and 4 months of age; in fact, there was an increase in overall reactogenicity in group 2, owing to significantly increased incidence of fever at 3 months. However, these results should be interpreted in the context that parents were instructed to administer three doses of prophylactic paracetamol to their child when 4CMenB was given at 2 and 4 months of age, but not at 3 months.

Following on from these findings, the opportunity exists to establish whether the antibody titres to MenB strains, PCV13 serotypes, and other vaccines remain similar between the two study groups at 24–30 months of age. It will also be important to assess whether or not waning MenB hSBA titres are associated with a decline in effectiveness and whether this can assist in disease modelling, as has been possible with MenC disease.²⁷ This ongoing study will further inform the growing body of knowledge regarding optimal PCV13 and MenB vaccination programmes, both in the UK and globally.

Contributors

KD wrote the first draft of the paper with input from MVP, and all authors contributed to subsequent drafts. MDS, EM, JS, NJA, and DG designed the trial. JS, JP, MVP, EP, and MDS oversaw the clinical trial, clinical data collection, and clinical data management. NJA did the statistical analysis. RB oversees the meningococcal laboratory. HF, SP, and AH worked on meningococcal assays. BH, MM, and AE worked on other routine vaccine assays. All authors read and approved the final version of the report.

Declaration of interests

MDS acts on behalf of the University of Oxford and Oxford Vaccine Group (OVG) as Principal Investigator on clinical trials sponsored or funded by

vaccine manufacturers including Pfizer, GlaxoSmithKline, Novavax, Medimmune, MCM Vaccine, and Janssen. MDS has participated in advisory boards for vaccine manufacturers and at industry-sponsored symposia; payment for these activities was made to the University of Oxford and MDS received no personal financial benefit. MVP is a member of the Portuguese National Immunisation Technical Advisory Group (Comissão Técnica de Vacinação da Direção Geral de Saúde). DG has served on ad-hoc advisory boards for Merck. RB and AH do contract research on behalf of Public Health England (PHE) for GlaxoSmithKline, Pfizer, and Sanofi Pasteur. KD, NJA, HF, JS, JP, EP, SP, MM, AE, BH, and EM declare no competing interests. JS and EM's salaries were funded by a National Institute for Health Research (NIHR) grant.

Data sharing

Data collected for the study, including de-identified participant data and data dictionaries defining each field in the set, the study protocol, statistical analysis plan, and informed consent form will be made available on reasonable written request to the corresponding author. These data will be available with publication and will be shared by the OVG with NIHR approval.

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References

- Leca M, Bornet C, Montana M, Curti C, Vanelle P. Meningococcal vaccines: current state and future outlook. *Pathol Biol (Paris)* 2015; **63**: 144–51.
- Andrews SM, Pollard AJ. A vaccine against serogroup B *Neisseria meningitidis*: dealing with uncertainty. *Lancet Infect Dis* 2014; **14**: 426–34.
- Sadarangani M, Pollard AJ. Serogroup B meningococcal vaccines—an unfinished story. *Lancet Infect Dis* 2010; **10**: 112–24.
- Sridhar S, Greenwood B, Head C, et al. Global incidence of serogroup B invasive meningococcal disease: a systematic review. *Lancet Infect Dis* 2015; **15**: 1334–46.
- PHE. Invasive meningococcal disease in England: annual laboratory confirmed reports for the epidemiological year 2018 to 2019. London: Public Health England, 2019. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/842368/hpr3819_IMD-ann.pdf (accessed April 6, 2019).
- Ladhani SN, Andrews N, Parikh SR, et al. Vaccination of infants with meningococcal group B vaccine (4CMenB) in England. *N Engl J Med* 2020; **382**: 309–17.
- Parikh SR, Newbold L, Slater S, et al. Meningococcal serogroup B strain coverage of the multicomponent 4CMenB vaccine with corresponding regional distribution and clinical characteristics in England, Wales, and Northern Ireland, 2007–08 and 2014–15: a qualitative and quantitative assessment. *Lancet Infect Dis* 2017; **17**: 754–62.
- Bexsero Meningococcal Group B vaccine for injection in pre-filled syringe—(eMC) 2017 <https://www.medicines.org.uk/emc/medicine/28407/SPC/Bexsero+Meningococcal+Group+B+vaccine+for+injection+in+pre-filled+syringe/> (accessed Feb 23, 2019).
- Findlow J, Borrow R, Snape MD, et al. Multicenter, open-label, randomized phase II controlled trial of an investigational recombinant meningococcal serogroup B vaccine with and without outer membrane vesicles, administered in infancy. *Clin Infect Dis* 2010; **51**: 1127–37.
- Goldblatt D, Southern J, Andrews NJ, et al. Pneumococcal conjugate vaccine 13 delivered as one primary and one booster dose (1+1) compared with two primary doses and a booster (2+1) in UK infants: a multicentre, parallel group randomised controlled trial. *Lancet Infect Dis* 2018; **18**: 171–79.
- PHE. Christmas special vaccine update PCV. London: PHE Publications, Public Health England, 2019. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/852623/PHE_1103_vaccine_update_303_PCV_special_edition_December_2019.pdf (accessed June 2, 2020).
- Gosger N, Snape MD, Yu LM, et al. Immunogenicity and tolerability of recombinant serogroup B meningococcal vaccine administered with or without routine infant vaccinations according to different immunization schedules: a randomized controlled trial. *JAMA* 2012; **307**: 573–82.
- Maslanka SE, Gheesling LL, Libutti DE, et al. Standardization and a multilaboratory comparison of *Neisseria meningitidis* serogroup A and C serum bactericidal assays. *Clin Diagn Lab Immunol* 1997; **4**: 156–67.
- Borrow R, Aaberge IS, Santos GF, et al. Interlaboratory standardization of the measurement of serum bactericidal activity by using human complement against meningococcal serogroup b, strain 44/76-SL, before and after vaccination with the Norwegian MenBvac outer membrane vesicle vaccine. *Clin Diagn Lab Immunol* 2005; **12**: 970–76.
- Ladhani SN, Andrews NJ, Southern J, et al. Antibody responses after primary immunization in infants born to women receiving a pertussis-containing vaccine during pregnancy: single arm observational study with a historical comparator. *Clin Infect Dis* 2015; **61**: 1637–44.
- Vesikari T, Esposito S, Prymula R, et al. Immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccinations: results of two randomised trials. *Lancet* 2013; **381**: 825–35.
- Esposito S, Prymula R, Zuccotti GV, et al. A phase 2 randomized controlled trial of a multicomponent meningococcal serogroup B vaccine, 4CMenB, in infants (II). *Hum Vaccin Immunother* 2014; **10**: 2005–14.
- Snape MD, Voysey M, Finn A, et al. Persistence of bactericidal antibodies after infant serogroup B meningococcal immunization and booster dose response at 12, 18 or 24 months of age. *Pediatr Infect Dis J* 2016; **35**: e113–23.
- Martinón-Torres F, Safadi MAP, Martínez AC, et al. Reduced schedules of 4CMenB vaccine in infants and catch-up series in children: immunogenicity and safety results from a randomised open-label phase 3b trial. *Vaccine* 2017; **35**: 3548–57.
- Snape MD, Dawson T, Oster P, et al. Immunogenicity of two investigational serogroup B meningococcal vaccines in the first year of life: a randomized comparative trial. *Pediatr Infect Dis J* 2010; **29**: e71–79.
- Biolchi A, Tomei S, Santini L, et al. Evaluation of strain coverage of the multicomponent meningococcal serogroup B vaccine (4CMenB) administered in infants according to different immunisation schedules. *Hum Vaccin Immunother* 2019; **15**: 725–31.
- Findlow H, Borrow R, Andrews N, et al. Immunogenicity of a single dose of meningococcal group C conjugate vaccine given at 3 months of age to healthy infants in the United Kingdom. *Pediatr Infect Dis J* 2012; **31**: 616–22.
- Pace D, Khatami A, McKenna J, et al. Immunogenicity of reduced dose priming schedules of serogroup C meningococcal conjugate vaccine followed by booster at 12 months in infants: open label randomised controlled trial. *BMJ* 2015; **350**: h1554.
- Kapur S, Bourke T, Maney JA, Moriarty P. Emergency department attendance following 4-component meningococcal B vaccination in infants. *Arch Dis Child* 2017; **102**: 899–902.
- Esposito S, Tagliabue C, Bosis S. Meningococcal B vaccination (4CMenB) in infants and toddlers. *J Immunol Res* 2015; **2015**: 402381.
- Nainani V, Galal U, Buttery J, Snape MD. An increase in accident and emergency presentations for adverse events following immunisation after introduction of the group B meningococcal vaccine: an observational study. *Arch Dis Child* 2017; **102**: 958–62.
- Campbell H, Andrews N, Borrow R, Trotter C, Miller E. Updated postlicensure surveillance of the meningococcal C conjugate vaccine in England and Wales: effectiveness, validation of serological correlates of protection, and modeling predictions of the duration of herd immunity. *Clin Vaccine Immunol* 2010; **17**: 840–47.