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An open-label, phase IV randomised controlled trial of two schedules of a four-component meningococcal B vaccine in UK preterm infants

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ABSTRACT

Objective To compare immunological responses of preterm infants to a four-component meningococcal B vaccine (4CMenB; Bexsero) following a 2+1 vs a 3+1 schedule, and to describe reactogenicity of routine vaccines.

Design An open-label, phase IV randomised study conducted across six UK sites.

Setting Neonatal units, postnatal wards, community recruitment following discharge.

Participants 129 preterm infants born at a gestation of <35 weeks (64 in group 1 (2+1), 65 in group 2 (3+1)) were included in the analysis. Analysis was completed for postprimary samples from 125 participants (59 in group 1, 66 in group 2) and for postbooster samples from 118 participants (59 in both groups).

Interventions Infants randomised to 4CMenB according to a 2+1 or a 3+1 schedule, alongside routine vaccines.

Main outcome measures Serum bactericidal antibody (SBA) assays performed at 5, 12 and 13 months of age: geometric mean titres (GMTs) and proportions of infants achieving titres ≥4 compared between groups.

Results There were no significant differences in SBA GMTs between infants receiving a 2+1 compared with a 3+1 schedule following primary or booster vaccination, but a significantly higher proportion of infants had an SBA titre ≥4 against strain NZ98/254 (porin A) at 1 month after primary vaccination using a 3+1 compared with a 2+1 schedule (3+1: 87% (95% CI 76 to 94%), 2+1: 70% (95% CI 56 to 81%), p=0.03).

At 12 weeks of age those in the 3+1 group, who received a dose of 4CMenB, had significantly more episodes of fever >38.0°C than those in the 2+1 group who did not (group 2+1: 2% (n=1); 3+1: 14% (n=9); p=0.02).

Conclusions Both schedules were immunogenic in preterm infants, although a lower response against strain NZ98/254 was seen in the 2+1 schedule; ongoing disease surveillance is important in understanding the clinical significance of this difference.

Trial registration number NCT03125616.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Routine vaccination against *Neisseria meningitidis* serogroup B (MenB) was introduced in the UK in 2015 using a 2+1 schedule at 8 and 16 weeks, followed by a booster at 12 months of age.

⇒ This schedule has been shown to be immunogenic and effective in term infants, but there is no evidence about the use of this schedule in preterm infants who are known to have reduced responses to some vaccines.

WHAT THIS STUDY ADDS

⇒ This study is the first to investigate the immunogenicity of a recombinant protein-based, four-component outer membrane protein meningococcal B (Bexsero) vaccination in preterm infants, comparing two vaccination schedules: one administered at 8 and 16 weeks followed with a booster at 12 months of age (2+1 schedule), and the other administered at 8, 12 and 16 weeks with a booster at 12 months of age (3+1 schedule).

⇒ The 2+1 schedule was immunogenic in preterm infants, although following the primary series, the proportion of infants with titres ≥4 against strain NZ98/254 (porin A (PorA)) was lower compared with those receiving the 3+1 schedule.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ It is important that surveillance continues to monitor cases of invasive meningococcal disease so that any increase in cases caused by PorA expressing strains, particularly in preterm infants, can be identified.

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INTRODUCTION

Invasive meningococcal disease (IMD) is most common in infants <1 year, with *Neisseria meningitidis* serogroup B (MenB) predominating.[1] A four-component MenB vaccine (4CMenB; Bexsero, GlaxoSmithKline, Belgium), was licensed for protection against MenB by the European Medicines Agency in 2013 to be given according to a three-dose priming schedule in infants followed by a booster in the second year of life.[2] Routine MenB vaccination was introduced in the UK in 2015, using a two-dose priming schedule at 8 and 16 weeks

with a booster at 1 year. Two studies have since demonstrated acceptable immunogenicity of this schedule in term infants.[3 4]

Preterm infants may mount suboptimal immune responses to vaccines compared with term infants,[5] although most infants achieve responses above putative protective thresholds.[6–11] There are, however, no data on 4CMenB immunogenicity in preterm infants when used at the reduced 2+1 schedule. We conducted a randomised controlled trial to assess the immunogenicity of 4CMenB 1 month after a two-dose or three-dose priming schedule in preterm infants followed by a booster at 1 year, and compared 4CMenB antigen-specific antibody responses at 5, 12 and 13 months. We also assessed the reactogenicity of routine immunisation schedules including 4CMenB in preterm infants.

METHODS

Study design

This was an open-label, phase IV randomised trial conducted across six UK sites. The study was prospectively registered on clinicaltrials.gov in April 2017 (NCT03125616). Recruitment was between September 2017 and September 2018.

Participants

Preterm infants born at <35 weeks (50% <30 weeks), with no contraindications to vaccination according to the UK guidance,[12] no life-limiting congenital abnormality or prior diagnosis of an immunodeficiency syndrome.

Interventions

Infants were randomised to receive 4CMenB using a 2+1 (8 weeks, 16 weeks and 1 year) or 3+1 (8 weeks, 12 weeks, 16 weeks and 1 year) schedule alongside routine vaccinations (online supplemental table 1). Randomisation was performed by the study statistician and used two computerised block randomisation lists, one for participants born at <30 weeks of gestation and one for those born at 30–34+6 weeks of gestation. Participants were enrolled by a member of the research team. Allocation was according to a 1:1 ratio, was not blinded and vaccines were given by a member of the research team. As per national guidelines, prophylactic paracetamol was recommended following 4CMenB vaccination at 8, 12 and 16 weeks of age. Blood sampling was performed at 5, 12 and 13 months of age.

Main outcome measures

Immunogenicity was assessed using serum bactericidal antibody (SBA) assays. These were performed at UK Health Security Agency Vaccine Evaluation Unit Manchester.[13] Both geometric mean titre (GMT) and proportions achieving a titre ≥4 against the tested strains (44/76-SL (factor H binding protein (fHbp)), 5/99 (Neisseria adhesin A (NadA)) and NZ98/254 (porin A (PorA))) were calculated for each sampling time point. Reactogenicity was assessed by the caregiver completing a 7-day diary after each vaccine; infants vaccinated as inpatients had their cardiorespiratory status recorded for 24 hours before and 72 hours after vaccination by nursing staff.

Statistical analysis

The primary outcome was antigen-specific responses as measured by SBA assays at 5 months (postprimary vaccines) in preterm infants receiving two or three priming doses. Secondary outcomes included antigen-specific responses prior to and 1 month following the booster dose, and reactogenicity assessment following each vaccine.

The SD of the GMT responses to the three antigens was expected to be around 1.0 log units. A sample size of 60 per group was predicted to allow a 1.7-fold difference between groups to be detectable at 80% power at the 5% significance level. A drop-out rate of around 10% was expected so the minimum sample size was 132.

For each schedule, GMTs of the SBA titres against three strains (44/76-SL (fHbp), 5/99 (NadA) and NZ98/254 (PorA)) were calculated with 95% CI 1 month after primary vaccination. Titres were compared using a Kruskall-Wallis test because of non-normal distribution of the log-titres. Proportions with titres ≥4 were also calculated with exact binomial 95% CI and compared using Fisher's exact test. The analysis was conducted using a modified intention-to-treat approach, including all participants for whom at least one antibody result was available. To investigate protection against individual strains at different time points, analysis was performed using paired postprimary and postbooster samples to assess protective thresholds (SBA ≥4) in individual infants and the percentage of infants with SBA >4 at neither time point, one time point and both time points were calculated. Reactogenicity rates between groups were compared using Fisher's exact test. Statistical analysis was performed using STATA V.17 (StataCorp, College Station, Texas, USA).

RESULTS

136 infants were recruited: 3 died, 2 were lost to follow-up and 7 withdrew from the study, leaving 124 infants who completed all visits (figure 1). For seven babies who did not complete the study there was no confirmation of consent that data could be used, and analysis therefore included 129 infants. Table 1 summarises the baseline characteristics of these infants.

Immunogenicity

Following both primary immunisation and booster, there were no significant differences between schedules in SBA GMTs against strains 44/76-SL (fHbp), 5/99 (NadA) or NZ98/254 (PorA) (figure 2; online supplemental table 2). Prior to boosting, however, the SBA GMT against strain NZ98/254 (PorA) was lower for infants receiving the 2+1 compared with the 3+1 schedule (p=0.002).

There were no significant differences in the percentage of infants with an SBA titre ≥4 against strain 44/76-SL (fHbp) or 5/99 (NadA) at any time point. A higher percentage of infants receiving the 3+1 schedule had SBA titres ≥4 against strain NZ98/254 (PorA) after primary immunisation and before the booster, but not after the booster (table 2).

All infants achieved a protective titre against strain 5/99 (NadA) at both time points. Fewer infants receiving a 2+1 schedule reached a protective threshold against strain NZ98/254 (PorA) compared with those receiving a 3+1 schedule (*2+1*: both time points=67.3% (n=35), postbooster only 19.2% (n=10), neither time point=13.4% (n=7); *3+1*: both time points=87.0% (n=47), postbooster only=7.4% (n=4), neither time point=5.8% (n=3)). The results were similar between schedules for strain 44/76-SL (fHbp) (online supplemental table 3).

Comparison of fold-changes between postprimary and postbooster doses identified modest responses against strain 44/76-SL (fHbp) in both groups, lower than for the other vaccine antigens (figure 2, online supplemental table 4).

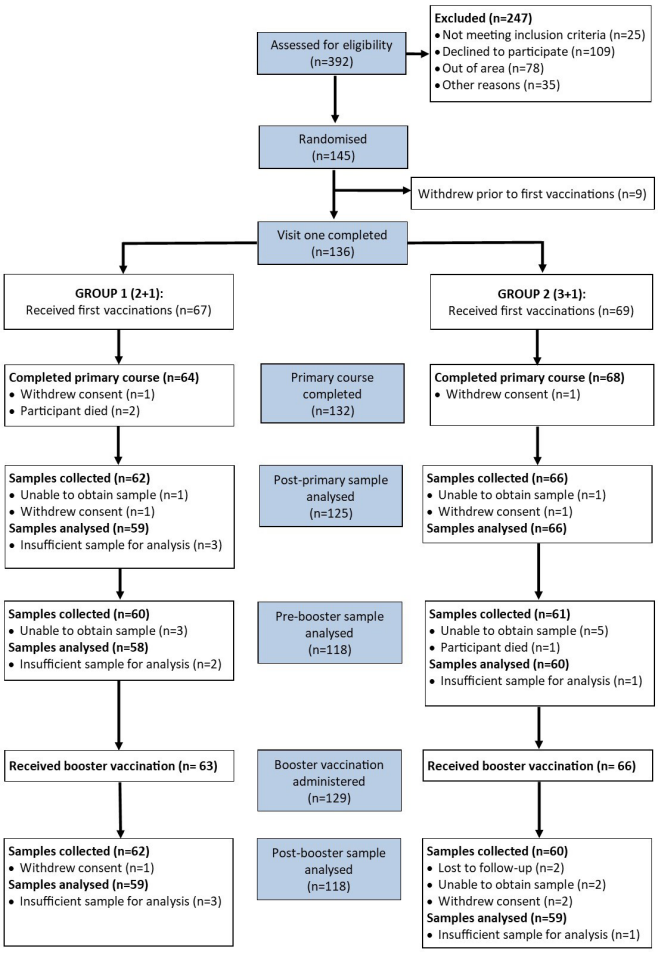

Figure 1 Consolidated Standards of Reporting Trials flow diagram of participants.

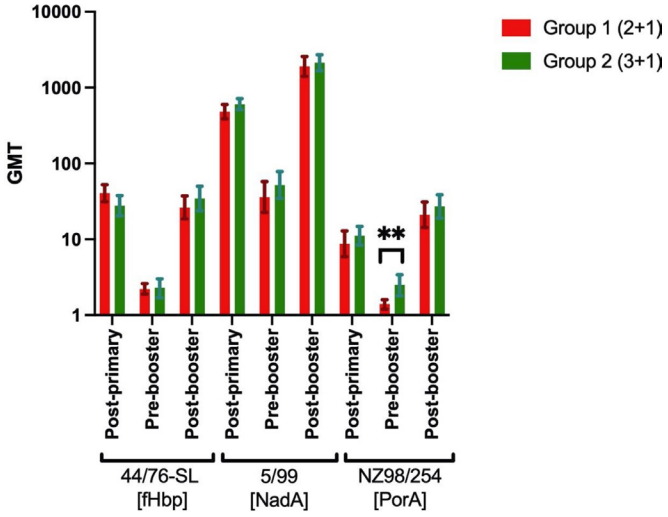

Figure 2 GMTs and 95% CIs for serum bactericidal antibody against three strains postprimary, prebooster and postbooster vaccination. Blood sampling was performed at 5 months (postprimary), 12 months (prebooster) and 13 months (postbooster). fHbp, factor H binding protein; GMT, geometric mean titre; NadA, Neisseria adhesin A; PorA, Porin A. **P=0.002.

Reactogenicity

Overall, 84 vaccinations in 56 participants took place in a neonatal unit (online supplemental table 5). In the 72 hours following first and second vaccinations, there was no significant difference in rates of apnoea, bradycardia or desaturation compared with the 24-hour periods preceding (online supplemental figures 1 and 2). There were no episodes of apnoea or bradycardia reported before or after the third vaccines, and one infant experienced a single desaturation following these. Local reactions (online supplemental figures 3-7) and non-febrile systemic reactions (figure 3) after routine vaccines were common in both groups at every time point.

A larger proportion of infants experienced fever within 7 days of each subsequent vaccination (first vaccines: 6%, second vaccine 2+1: 2%, second vaccines 3+1: 14%, third vaccines: 2+1: 20%, second vaccines 3+1: 14%, fourth vaccines 26%) (online supplemental table 6). Infants receiving the 3+1 schedule had significantly more fever episodes at the time of the second

Table 1 Baseline characteristics of infants included in phase IV randomised controlled trial of two schedules of a four-component meningococcal B vaccine in UK preterm infants

Characteristic	N	Group 1 (2+1 schedule)	N	Group 2 (3+1 schedule)
Gestational age Median (range)	64	30^{+2} (23^{+0}–34^{+3})	65	30^{+2} (24^{+2}–34^{+3})
Ethnicity (white) N (%)	64	52 (81.3)	65	57 (87.7)
Sex (female) N (%)	64	32 (50)	65	41 (63.1)
Birth weight (g) Median (range)	64	1262.5 (575–2790)	65	1350 (490–2610)
CLD N (%)	64	17 (26.6)	65	15 (23.1)
SGA N (%)	64	5 (7.8)	65	10 (15.4)
Blood transfusion N (%)	64	25 (39.1)	65	27 (41.5)
Antenatal steroids N (%)	64	59 (92.2)	65	63 (96.9)
Postnatal steroids N (%)	64	5 (7.8)	65	2 (3.1)

CLD, chronic lung disease (supplementary oxygen±mechanical ventilation at >28 days of life and at a corrected gestational age of >36 weeks of gestation); SGA, small for gestational age (<10th percentile for gestational age at birth).

Table 2 Percentages of participants with SBA titres ≥4 for each of the tested antigens postprimary series and prebooster and postbooster vaccination

	Infants with SBA titre ≥4 % (95% CI)								
	Postprimary (5 months)			Prebooster (12 months)			Postbooster (13 months)		
	Group 1 (2+1)	Group 2 (3+1)	P value*	Group 1 (2+1)	Group 2 (3+1)	P value*	Group 1 (2+1)	Group 2 (3+1)	P value*
44/76-SL (fHbp)	98 (n=55/56) (90 to 100)	94 (n=59/63) (85 to 98)	0.37	30 (n=17/56) (19 to 44)	33 (n=20/60) (22 to 47)	0.84	98 (n=56/57) (91 to 100)	95 (n=52/55) (85 to 99)	0.36
(5/99) NadA	100 (n=56/56) (94 to 100)	100 (n=63/63) (94 to 100)	–	86 (n=49/57) (74 to 94)	88 (n=53/60) (77 to 95)	0.79	100 (n=58/58) (94 to 100)	100 (n=57/57) (94 to 100)	–
(NZ98/254) PorA	70 (n=39/56) (56 to 81)	87 (n=53/61) (76 to 94)	**0.03**	11 (n=6/57) (4 to 22)	33 (n=20/60) (22 to 47)	**0.004**	88 (n=51/58) (77 to 95)	95 (n=52/55) (85 to 99)	0.32

Blood sampling performed at 5 months (postprimary), 12 months (prebooster), 13 months (postbooster).
Results with a p value of <0.05 are highlighted in bold.
*Fisher's exact test.
fHbp, factor hour binding protein; GMT, geometric mean titre; NadA, Neisseria adhesin A; PorA, porin A; SBA, serum bactericidal activity.

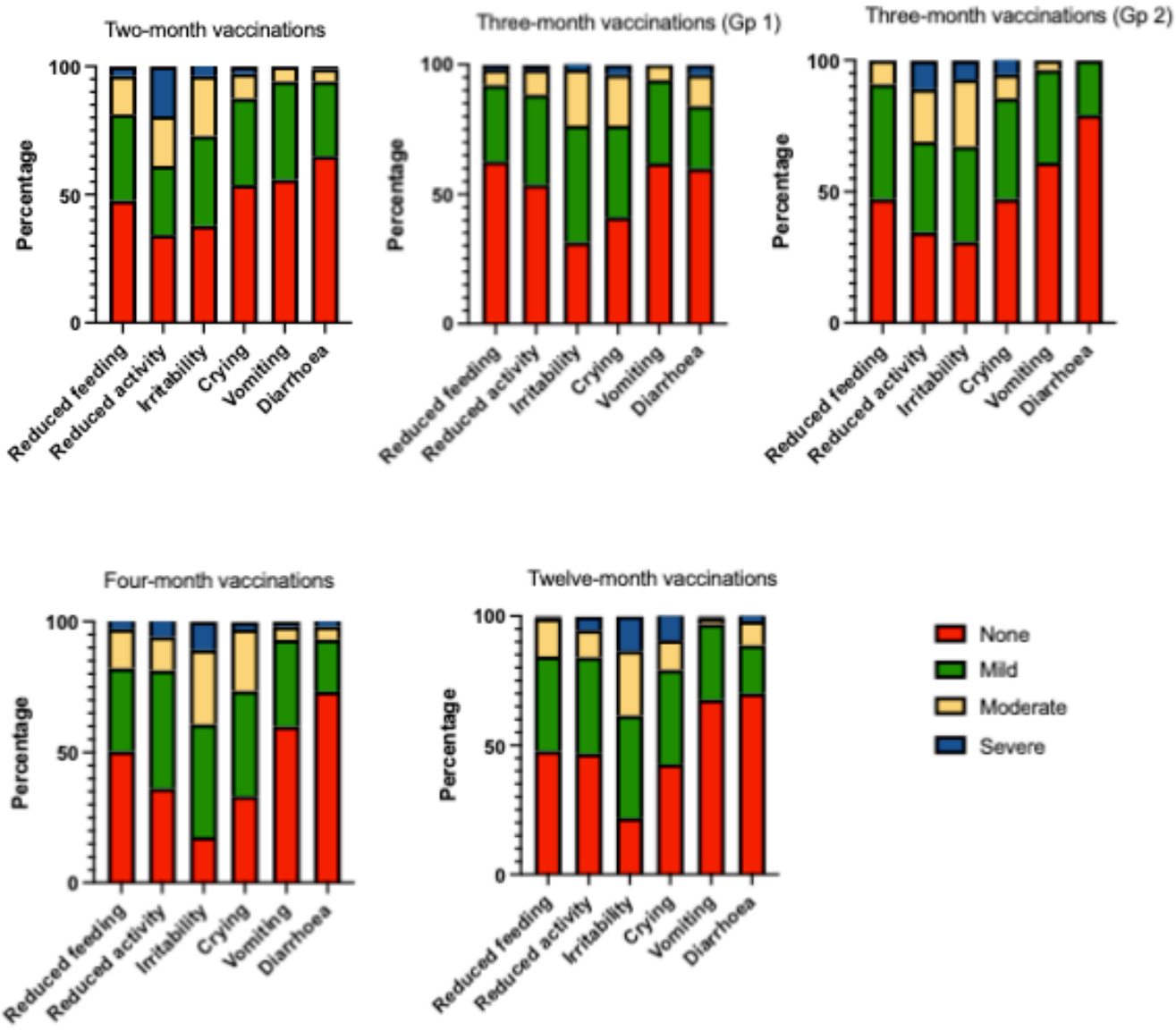

Figure 3 Systemic reactions following four-component meningococcal B vaccination alongside routine immunisations at 8, 12 and 16 weeks followed by a booster at 1 year of age.

vaccines than those receiving the 2+1 schedule (2+1: 1/58 (2%) vs 3+1: 9/64 (14%); p=0.02), although the proportion of infants experiencing a grade 3 fever (≥39.0°C) was similar (2+1: 0/58 (0%) vs 3+1: 1/64 (2%); p=1.0), as was the proportion of infants investigated for sepsis after the second vaccines (2+1: 2/63 (3.2%) vs 3+1: 2/65 (3.1%); p=1.0) (online supplemental table 7). Most infants (V1: 104/114, 91.2%, V2 3+1: 56/59, 94.9%, V3: 95/99, 96%, V4: 86/91, 94.5%) received at least one paracetamol dose on the day of 4CMenB vaccination (online supplemental table 8). The proportion of babies receiving paracetamol remained high following the booster vaccines at 12 months; indications included prophylaxis in 76.7% (n=46), fever in 18.3% (n=11), both in 3.3% (n=2) and an unrelated symptom in 1.7% (n=1).

Safety

There were 100 serious adverse events (SAEs) reported (online supplemental table 9), mainly in infants born at <30 weeks of gestation (73/100, 73%). Six SAEs were related to vaccination: 4 probably related (3 apnoea, 1 fever), all following vaccines including 4CMenB, and 2 definitely related (elective hospitalisation for monitoring because of apnoea following previous vaccination). Three infants died during the study (two in the 3+1 group and one in the 2+1 group); none was assessed to be vaccine-related (RSV bronchiolitis, rhinovirus bronchiolitis, sudden unexpected collapse in hospital).

DISCUSSION

We found that both 2+1and 3+1 schedules for 4CMenB were immunogenic in preterm infants, although the GMT against strain NZ98/254 (PorA) at 12 months, and the proportions of infants with postprimary and prebooster SBA titres ≥4 were significantly higher with the 3+1 than 2+1 schedule. The vaccine antigen PorA is the immunodominant component of outer membrane vesicle (OMV) vaccines. The immunogenicity of these vaccines is known to be greater when a 3+1 compared with a 2+1 schedule is used.[14 15] The clinical significance of a lower proportion of infants with protective titres against one strain is not clear and, importantly, there was no statistically significant difference after the booster dose meaning that protection after the booster is likely to be similar in the two cohorts. A higher proportion of infants receiving an additional dose of 4CMenB at 3 months experienced fever, although this is unlikely to be of clinical significance since rates of high fever and number of infants investigated for sepsis following vaccination were similar in the two groups.

The GMTs for preterm infants receiving a 2+1 schedule in this trial are similar to those found in term infants following the primary series when a 2+1 schedule was used and when analysis was performed in the same laboratory.[4 16] After the booster dose, the reported GMTs in this preterm cohort were similar to those reported by Davis *et al*,[4] but the fHbp GMTs were slightly lower compared with those found by Valente Pinto *et al*.[16] These two studies in term infants also investigated proportions of preterm infants with putative protective titres after the primary vaccine series and the booster dose, and reported similar results to those found in our preterm population.[4 16] Another study using a 2+1 schedule in term infants found slightly higher proportions protected after the booster dose compared with our preterm population, but this study was performed in a different country, using a different assay.[17] Overall, our results indicate that preterm infants receiving the 2+1 schedule had similar immune responses to term infants receiving the same schedule.

In line with the findings of Davis *et al* and Valente Pinto *et al* in term infants,[4 16] we found a relatively low response following booster vaccination for fHbp in preterm infants who received a 2+1 schedule. While this might suggest the superiority of a 3+1 schedule in priming, this is not supported by the findings of Martinon-Torres *et al*.[17] Although it is noteworthy that in that study both of the reduced schedules were administered slightly later (3.5 and 5 months or 6 and 8 months) compared with our study, or with the schedules used in the studies by Davis *et al* and Valente Pinto *et al* (all at 2 and 4 months), which may explain this difference. The similarity of fHbp responses after the booster irrespective of the priming schedule in preterm infants is reassuring and suggests that both groups would likely be similarly protected in the medium-to-long term.

The protection offered by 4CMenB involves immune responses against four major meningococcal surface protein antigens and many minor antigens in the OMV, which is also part of the vaccine.[18] How the observed immunogenicity is translated into clinical protection against IMD is complex because the vaccine antigens are not present on the surface of all meningococci and, when present, their expression on the meningococcal surface varies considerably between strains. Consequently, clinical protection depends on the characteristics of circulating strains causing IMD in different populations.

Estimation of likely vaccine strain coverage in a population is possible using the Meningococcal Antigen Typing System (MATS), which assesses whether a particular meningococcal strain expresses antigens which cross-react with those in 4CMenB.[19] In the light of the most recent UK MATS data, it is reassuring that a high proportion of the preterm infants in this study had titres ≥4 against strain 44/76-SL (fHbp) after both primary and booster vaccinations as MATS coverage is often due to fHbp (59% of isolates with matched antigens). Also, as MATS coverage was less dependent on PorA (16% of isolates with matched antigens, and PorA as the single matched antigen in <1% of isolates), it is perhaps less concerning that 13.4% of infants vaccinated according to a 2+1 schedule did not reach a protective threshold for this antigen either after primary or booster vaccination.[18] Similar results have been observed in a Canadian study.[20]

Overall, routine vaccination including 4CMenB was well tolerated. The number of reported SAEs reflects the vulnerability of the preterm population, especially concerning increased hospital admissions related to infections unrelated to vaccination, for example, respiratory tract infections.[21 22] Fever after 4CMenB administration, especially when given with other routine infant immunisations, is a particular concern. Reassuringly, preterm infants in the current study experienced fewer fever episodes than previously reported in term infants, irrespective of whether or not they had received prophylactic paracetamol.[23–27] Additionally, we observed no differences between study groups in proportions with fever ≥39.0°C or number of infants investigated for sepsis. Systemic and local reaction rates were similar to those previously reported in term infants, apart from local tenderness and vomiting, which were reported more frequently in preterm infants than term infants in some previous studies.[23–27]

Strengths and limitations

A major strength of this study was the ability to recruit a large and broad sample of preterm infants. One potential limitation of the study is that we did not collect baseline prevaccination antibody titres, but most infants are likely to have very low antibody titres,[26] which should be similar between the two study groups. We also did not include a term comparator group and, therefore, our

comparisons with vaccine responses in term infants should be interpreted with caution, although two of the UK trials in term infants were conducted in the same reference laboratory using the same methodology and testing protocols.[4 16] The study was not blinded, which is particularly relevant for reactogenicity assessment at 12 weeks when infants in group 2 received an additional dose of 4CMenB. It is possible that this increased reporting of reactogenicity in these infants. Finally, we did not follow-up the participants beyond 13 months and, therefore, we cannot comment on long-term immune responses.

CONCLUSION

The 2+1 schedule was immunogenic in preterm infants, although proportions of infants with putative protective titres against strain NZ98/254 (PorA) were lower postprimary and prebooster in infants after a 2+1 compared with a 3+1 schedule, similar to previous studies in term infants and consistent with previous studies of OMV vaccines.[14 15] Postbooster responses against strain NZ98/254 (PorA), however, were similar after the two schedules. Our findings support the current 2+1 4CMenB schedule for both preterm and term infants.

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Contributors AC, PTH and SNL devised the study. AC, SB, CB, BB, JC, PC, ACC, KF, NH, CEJ, GP, MP, TS and MS were responsible for study set up in individual sites, participant recruitment, study procedures and follow up, data collection and safety monitoring. RB and JL coordinated the laboratory analysis. AC and NA performed the statistical analysis. AC wrote the first draft of the paper. PTH, SL, CEJ, KLD and NA provided significant input into the first draft of the paper and all authors reviewed the manuscript, made improvements and approved the final version. AC, PTH and NA had full access to the data. AC and PTH are guarantors.

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Competing interests JL and RB perform contract research on behalf of UKHSA for GlaxoSmithKline (GSK), Pfizer and Sanofi. JC works for an institution which conducts meningococcal vaccine research on behalf of GSK; he receives no personal payment or inducement of any kind. MS was an employee of the University of Oxford and Oxford University Hospitals Foundation NHS trust up until September 2022, and in this role acted as an investigator for clinical research studies funded or otherwise supported by the vaccine manufacturers GSK, Janssen, AstraZeneca, Pfizer, Novavax and MCM vaccines. He received no personal financial benefit for this work. As of September 2022, MS has been an employee of Moderna UK and holds equity in this company; however, all study activities and data analysis were completed before this date.

Patient consent for publication Not applicable.

Ethics approval Ethical approval was received from York and Humber Research Ethics Committee (17/YH/0150) and the Health Research Authority. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

Author note Both Meningitis Now and GlaxoSmithKline were provided with the opportunity to review the final version of the manuscript and the supplementary materials for factual accuracy but the authors are solely responsible for the content, interpretation and conclusions from the work.

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REFERENCES

1 UK Health Security Agency. Laboratory confirmed cases of invasive meningococcal infection in England: April to June 2022, Available: https://www.gov.uk/government/publications/meningococcal-disease-laboratory-confirmed-cases-in-england-in-2021-to-2022/laboratory-confirmed-cases-of-invasive-meningococcal-infection-in-england-april-to-june-2022
2 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.
3 Martinón-Torres F, Safadi MAP, Martinez 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.
4 Davis K, Valente Pinto M, Andrews NJ, *et al*. 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. *Lancet Infect Dis* 2021;21:688–96.
5 Chiappini E, Petrolini C, Sandini E, *et al*. Update on vaccination of Preterm infants: a systematic review about safety and efficacy/effectiveness. proposal for a position statement by Italian society of pediatric allergology and immunology jointly with the Italian society of neonatology. *Expert Rev Vaccines* 2019;18:523–45.
6 Kent A, Ladhani SN, Andrews NJ, *et al*. Schedules for pneumococcal vaccination of preterm infants: an RCT. *Pediatrics* 2016;138:e20153945.
7 Heath PT, Booy R, McVernon J, *et al*. Hib vaccination in infants born prematurely. *Arch Dis Child* 2003;88:206–10.
8 Rouers EDM, Bruijning-Verhagen PCJ, van Gageldonk PGM, *et al*. Association of routine infant vaccinations with antibody levels among preterm infants. *JAMA* 2020;324:1068.
9 Clarke P, Robinson MJ, Ahmad I, *et al*. Response of steroid-treated former preterm infants to a single dose of meningococcal C conjugate vaccine. *Vaccine* 2006;24:3273–8.
10 Moss SJ, Fenton AC, Toomey JA, *et al*. Responses to a conjugate pneumococcal vaccine in preterm infants immunized at 2, 3, and 4 months of age. *Clin Vaccine Immunol* 2010;17:1810–6.
11 Ruggeberg JU, Collins C, Clarke P, *et al*. Immunogenicity and induction of immunological memory of the heptavalent pneumococcal conjugate vaccine in preterm UK infants. *Vaccine* 2007;25:264–71.
12 UK Health Security Agency. Contraindications and special considerations. In: Ramsay M, ed. *Immunisation against infectious disease*. 2017.
13 Lucidarme J, Louth J, Townsend-Payne K, *et al*. Meningococcal serogroup A, B, C, W, X and Y serum bactericidal anibody assays. In: Seib KL, Peak IR, eds. *Methods Mol Biol*. 2019.
14 Holst J, Feiring B, Fuglesang JE, *et al*. Serum bactericidal activity correlates with the vaccine efficacy of outer membrane vesicle vaccines against neisseria meningitidis serogroup B disease. *Vaccine* 2003;21:734–7.

15 Tappero JW, Lagos R, Ballesteros AM, *et al*. Immunogenicity of 2 serogroup B outer-membrane protein meningococcal vaccines - A randomized controlled trial in Chile. *J Am Med Assoc* 1999;281:1520–7.
16 Valente Pinto M, O'Connor D, Galal U, *et al*. Immunogenicity and reactogenicity of a reduced schedule of a 4-component capsular group B meningococcal vaccine: a randomized controlled trial in infants. *Open Forum Infect Dis* 2020;7:faa143.
17 Martinon-Torres F, Gimenez-Sanchez F, Bernaola-Iturbe E, *et al*. A randomized, phase 1/2 trial of the safety, tolerability, and immunogenicity of bivalent Rlp2086 meningococcal B vaccine in healthy infants. *Vaccine* 2014;32:5206–11.
18 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.
19 Donnelly J, Medini D, Boccadifuoco G, *et al*. Qualitative and quantitative assessment of meningococcal antigens to evaluate the potential strain coverage of protein-based vaccines. *Proc Natl Acad Sci U S A* 2010;107:19490–5.
20 Bettinger JA, Scheifele DW, Halperin SA, *et al*. Diversity of Canadian meningococcal serogroup B isolates and estimated coverage by an investigational meningococcal serogroup B vaccine (4Cmenb). *Vaccine (Auckl)* 2013;32:124–30.
21 Elder D, Hagan R, Evans S, *et al*. Hospital admissions in the first year of life in very preterm infants. *J Paediatrics Child Health* 1999;35:145–50.
22 Coathup V, Boyle E, Carson C, *et al*. Gestational age and hospital admissions during childhood: population based, record linkage study in England (TIGAR study). *BMJ* 2020;371:m4075.
23 Prymula R, Esposito S, Zuccotti GV, *et al*. A phase 2 randomized controlled trial of a multicomponent meningococcal serogroup B vaccine (I). *Hum Vaccin Immunother* 2014;10:1993–2004.
24 Findlow J, Borrow R, Snape MD, *et al*. 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.
25 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:e71–9.
26 Gossger N, Snape MD, Yu L-M, *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.
27 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.