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Safety of meningococcal group B vaccination in hospitalised premature infants

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Abstract

Objectives: To assess the risk of significant adverse events in premature infants receiving the novel group B meningococcal vaccine (4CMenB) with their routine immunisations at 2 months of age

Participants, design and setting: In December 2015, Public Health England requested neonatal units across England to voluntarily participate in a national audit; 19 units agreed to participate. Anonymised questionnaires were completed for infants receiving 4CMenB alongside their routine immunisations. For comparison, a historical cohort of premature infants receiving their primary immunisations without 4CMenB or paracetamol prophylaxis was used.

Main Outcome Measures: Paracetamol use; temperature, cardiovascular, respiratory and neurological status before and after vaccination; management and investigations post-vaccination, including serum C-reactive protein levels, infection screens and antibiotic use.

Results: Complete questionnaires were returned for 133 premature infants (<35 weeks gestation) who received their first dose of 4CMenB at 8 weeks of age, including 108 who received prophylactic paracetamol according to national recommendations. Overall, 7% (8/108) of infants receiving 4CMenB with paracetamol had fever (>38°C) after vaccination compared with 20% (5/25) of those receiving 4CMenB without paracetamol (p=0.06) and none of those in the historical cohort. There were no significant differences between cohorts in the proportion of infants with apnoea, bradycardia, desaturation and receiving respiratory support after vaccination.

Conclusions: 4CMenB does not increase the risk of serious adverse events in hospitalised premature infants. This audit supports the current national recommendations to offer 4CMenB with other routine vaccinations and prophylactic paracetamol to premature infants at their chronological age.

INTRODUCTION

In the UK, the novel, multi-component, protein-based vaccine against group B invasive meningococcus disease (4CMenB, Bexsero, GSK, Rixensart) was introduced into the national infant immunisation schedule in September 2015.[1] Infants are offered the vaccine at 2 and 4 months of age, with a booster dose at 12 months. The vaccine was quickly shown to be highly effective against meningococcal B (MenB) disease, with a nearly 50% reduction in cases among vaccine-eligible infants.[2]

Initial pre-licensure clinical trials of 4CMenB in term infants identified high rates of fever in up to 60% of cases, as well as irritability, sleepiness and poor appetite, when administered alongside routine infant immunisations.[3,4] Subsequently, a randomised controlled trial reported that prophylactic paracetamol with the first dose, administered around the time of vaccination, reduced the frequency of such adverse events to rates reported in infants receiving routine immunisations without 4CMenB.[5] Moreover, prophylactic paracetamol did not have any adverse impact on the immune response to any of the vaccine antigens. Consequently, prophylactic paracetamol at the time of vaccination with two further doses given 4-6 hours apart was recommended for all infants receiving 4CMenB along with their routine primary immunisations, including for preterm infants.[6] There has, however, been a small increase in hospitalisations for fever following vaccination, especially after the first dose.[7–10]

Premature infants are known to have a higher risk of serious bacterial infections compared to infants born at term.[11] It is therefore critical that they are protected through timely vaccination. In the UK, premature infants are recommended to receive their routine immunisations at their chronological age, without any correction for prematurity.[12] There are, however, concerns that premature infants – especially extremely premature infants and those with on-going health problems – may be at increased risk of adverse events following vaccination, particularly cardio-

respiratory instability and apnoea.[13] This had led some neonatal units (NNUs) to delay immunisation with 4CMenB. Since cases of MenB disease increase from birth and peak by 5 months of age, any delay in vaccination could leave the infant vulnerable to meningococcal disease, especially because at least two priming doses of 4CMenB are required for adequate protection.[2]

Data on the safety and immunogenicity of 4CMenB in premature infants are limited. Following a number of anecdotal reports of rapid deterioration following 4CMenB vaccination in some premature infants, Public Health England (PHE) initiated a prospective national audit to assess the outcomes of immunisation in premature infants receiving 4CMenB with their routine immunisations in NNUs across England.[14]

METHODS

Participants

In December 2015, the Immunisation Department at PHE, through the British Association for Perinatal Medicine (BAPM), invited NNUs across England to voluntarily participate in a national audit to monitor the rate of adverse events in premature infants receiving 4CMenB concomitantly with their routine immunisations, 19 units agreed to participate.

Vaccination

Participating units immunised premature infants (gestational age <37 weeks at birth) as part of routine clinical care. Immunisations took place between 04/10/2015 and 25/01/2017. The administered vaccines included 4CMenB, 5-in-1 DTaP-IPV-Hib (diphtheria, tetanus, pertussis, inactivated polio and *Haemophilus influenzae* type b [Hib]; Infanrix-IPV-Hib®, GSK or Pediacel®, Sanofi Pasteur), the 13-valent pneumococcal conjugate vaccine (PCV13; Prevenar13®; Pfizer) and the oral rotavirus vaccine (Rotarix®; GSK Biologicals, Rixensart).

Clinical Management of Infants

Any blood sampling, investigations or change in clinical management was conducted at the discretion of the clinical team as part of clinical care. All samples were analysed at the infants' local hospital laboratory.

Data collection

An anonymised questionnaire was completed by the clinical team for all infants and included gestational age, vaccination details and paracetamol use, temperature, cardiovascular, respiratory and neurological status prior to and for 48 hours after vaccination, changes in clinical management, results of any blood tests or microbiological investigations performed, and use of antibiotics after vaccination. This evaluation was conducted to audit a nationally recommended intervention and thus met NRES criteria for a service evaluation. Formal ethics review was, therefore, not required. All information collected was anonymised at source.

Comparator Group

For comparison, adverse reactions after vaccine administration were compared with data from a historical cohort of premature infants who had received their primary immunisations without 4CMenB in similar NNUs across England as part of a randomised controlled trial assessing different pneumococcal vaccination schedules (PUNS).[14] In the PUNS study, infants were vaccinated by the study team after obtaining written informed consent from parents. Infants received 5-in-1 DTaP-IPV-Hib (Pediacel®), meningococcal C conjugate vaccine (Menjugate®, Novartis, Siena) and PCV13. Prophylactic paracetamol was not recommended but paracetamol could be administered post-vaccination if required.

Data Management and Analysis

Completed questionnaires were faxed or emailed securely to PHE at regular intervals. Data were entered into a custom Microsoft Access Database and transferred to Stata version 13 (Stata Corp, College Station, Texas) for analysis. For comparison with the PUNS cohort, only infants born before 35 weeks gestation were included in the analysis. An infant was considered to have received prophylactic paracetamol if the first dose was administered within two hours of vaccination. Fever was defined as temperature greater than 38.0°C. Data that were not normally distributed are described as medians with interquartile ranges. Statistical comparisons were performed using the nonparametric Kruskal-Wallis one-way analysis of variance test, X^2 test or Fisher's exact test as appropriate. Statistical significance was defined as $P<0.05$.

RESULTS

Study population

Complete questionnaires were returned for 133 premature infants (<35 weeks gestation) receiving their first dose of 4CMenB (4CMenB cohort). Their median gestational age at birth was 26.9 (IQR, 25.0-28.6) weeks and they were immunised at a median postnatal age of 63 (IQR, 59-74) days; 122 (92%) received concomitant vaccinations (Table 1). The PUNS cohort (n=68) had a similar gestational age at birth (median 27.6 weeks, IQR 26.1-28.6) and postnatal age at vaccination (median 63 days, IQR 57-68). All PUNS infants received concomitant vaccinations (Table 1). In the 48 hours prior to vaccination, a similar proportion of infants in each cohort were receiving respiratory support (Table 1).

Most infants in the 4CMenB cohort received prophylactic paracetamol (n=108, 81%), with 91 infants receiving all 3 paracetamol doses. None of the infants in the PUNS cohort had received prophylactic paracetamol, and only five (9%) received paracetamol after vaccination for symptom management (e.g. pain, unsettled). At the time of vaccination, infants receiving 4CMenB without paracetamol were older (median, 75 vs. 62 days, p<0.001) and more likely to have episodes of desaturation (60% vs. 31%, p<0.001) compared with infants in the PUNS cohort.

Cardiorespiratory events and respiratory support after vaccination

There were no significant differences between the three cohorts in the proportion of infants with apnoea, bradycardia, desaturation and receiving respiratory support after vaccination. Infants who received 4CMenB without prophylactic paracetamol had a higher rate of desaturations before and after vaccination compared with the other two groups (p=0.024) (Table 2). Infants born at less than 28 weeks gestation were more likely to have an increase in desaturations (43% versus 14%, p=0.002) and bradycardias (35% versus 6%, p=0.001) compared with infants born after 28 weeks gestation. These increased rates of desaturations and bradycardias after vaccination are similar in the historical PUNS cohort.

In the prophylactic paracetamol group, 11 infants (11%) had an increase in their ventilatory support requirements, mainly infants who were spontaneously ventilating in air and required low-flow oxygen support after vaccination (Supplementary table 1); one infant in this group had Gram-negative sepsis and required intubation and ventilation. Among infants who did not receive prophylactic paracetamol, three of ten on high-flow oxygen required increased respiratory support, including one case each of continuous positive airway pressure ventilation (CPAP), biphasic positive airway pressure ventilation (BIPAP) and intubation with invasive ventilation. In the PUNS cohort, 4 infants (6%) required escalation of ventilatory support to either high flow oxygen or CPAP, and 9% self-ventilating infants had increased supplementary oxygen requirements after vaccination.

Fever after vaccination

Overall, 7% (8/108) of infants receiving 4CMenB with paracetamol had fever (38.0°C-39.0°C) after vaccination compared with 20% (5/25) of those receiving 4CMenB without paracetamol (38.0°C-38.7°C) (p=0.06) and none of those in the historical PUNS cohort (p=0.15 when comparing the 3 groups). In the group receiving 4CMenB without prophylactic paracetamol, 5 out of 205 (2.4%)

temperature measurements taken within 48 hours of vaccination were >38.0°C compared with 7 out of 906 measurements (0.8%) in those who received 4CMenB with paracetamol (p=0.037).

Sepsis assessment after vaccination

Assessment for sepsis was not routinely reported for infants in the PUNS cohort. In the 4CMenB cohort, 31 infants (25%) had screening bloods, 11 (9%) had a blood culture and 6 infants (5%) received empiric IV antibiotics during the first 48 hours after vaccination. A similar proportion of infants in the PUNS cohort (n=3, 4%) received IV antibiotics after vaccination. C-reactive protein (CRP) results following vaccination are shown in Figure 1. Of the 17 infants in the 4CMenB cohort who had a CRP level measured within 48 hours of vaccination, 13 (76%) had CRP levels >10 mg/dL, 4 (24%) >50 mg/dL and 1 (6%) >100 mg/dL. The median highest CRP following vaccination was 25.0 mg/dl (IQR 15.9-45.4). There was no difference in CRP levels between infants who received 4CMenB with and without prophylactic paracetamol.

The only infant with CRP levels greater than 200mg/dL had *Enterobacter cloacae* bacteraemia, while another infant with a peak CRP level of 73mg/dL had bacteraemia due to *Pantoea sp*.

DISCUSSION

4CMenB has the potential to significantly reduce the burden of invasive meningococcal disease in infants and young children. The disease peaks at 5 months of age and, therefore, delays in vaccination could potentially put the infants at increased risk. This is particularly the case for premature infants who are known to be more susceptible to infection. 4CMenB is reactogenic, especially when co-administered with the other routine infant immunisations, but clinical trials in support the use of prophylactic paracetamol to reduce the rate of adverse events. The national decision to offer prophylactic paracetamol to all premature infants was divisive among neonatologists, with a number of units offering paracetamol only for treatment of vaccine-related adverse events such as fever, either because they surmised that premature infants were less likely to

mount a high pro-inflammatory response to vaccination or because of safety concerns regarding unnecessary paracetamol use in this vulnerable age group. We found no evidence of any increase in significant adverse events when premature infants are administered 4CMenB with their routine vaccinations under prophylactic paracetamol cover. Our data also indicate that most premature infants tolerated immunisation well and remained clinically stable during the period after vaccination.

Although we used a historical cohort for comparison, all the infants were vaccinated under real-life conditions with their on-going health problems in NNUs across England. The demographics of the PUNS and 4CMenB cohorts prior to vaccination and their outcomes after immunisation were very similar, thus providing reassurance that the risk of adverse events has not increased following the introduction of 4CMenB into the routine immunisation schedule. We found that post-vaccination fever was infrequent in all groups, especially when compared with pre-licensure clinical trials in term infants with and without prophylactic paracetamol.[4,15,16] We also found some evidence of infants receiving 4CMenB without prophylactic paracetamol having a higher risk of fever after vaccination. This observation would support the current national recommendation for prophylactic paracetamol with 4CMenB for all infants.[6]

A significant concern among neonatologists was the potential for respiratory deterioration after vaccination that might require escalation of ventilatory support. This, however, was uncommon, with the majority of infants not requiring any additional support or only supplemental oxygen. In particular, escalation to invasive ventilation after vaccination was uncommon in all cohorts.

There were also concerns that the use of very reactogenic vaccine may lead to a higher number of infection screens being performed with increased consequent empiric antibiotic use. Whilst information on investigations performed was not systematically collected for the PUNS cohort, the

proportion of infants treated for suspected (culture-negative) sepsis was low in both groups. Of note, most infants who had a blood test during the first 48 hours after receiving 4CMenB had raised CRP levels, which is to be expected since the vaccine, in common with all vaccinations, aims to trigger a pro-inflammatory response to induce immune protection. [17] This [the raised CRP levels] needs to be taken into consideration when assessing infants who appear unwell after 4CMenB vaccination.

Our data confirm that a small proportion of preterm infants, especially those born under 28 weeks gestation, will deteriorate after vaccination, irrespective of whether they receive 4CMenB with or without paracetamol prophylaxis. It is, therefore, reassuring that the infants are being closely monitored in neonatal units and can, therefore, receive immediate care to manage any adverse reaction. The approach by some NNUs to delay 4CMenB vaccination until the day of hospital discharge or to request general practitioners to give the first vaccinations to the infant in the community is, therefore, questionable, especially given the number of infant MenB cases that might have been prevented through timely vaccination.[2]

Strengths and limitations

This multicentre audit exemplifies the willingness of NNUs across the country to work together to provide near-real time data to support national policy. The lack of safety data in preterm infants for such a novel vaccine had raised concerns among neonatologists, which was fuelled by anecdotal reports of severe adverse events, mainly relating to escalation of ventilatory support and increased screening for sepsis because of fever and associated symptoms after vaccination. This audit began within a few weeks of the 4CMenB programme and near real-time monitoring of the completed questionnaires provided on-going reassurance to support the current national recommendations to vaccinate premature infants according to their chronological age. One limitation of this analysis was the inevitable use of a historical cohort because it would be unethical to have a contemporaneous

comparator cohort without 4CMenB. As with any historical comparison, our analysis was limited to the available data. The routine vaccines offered with alongside 4CMenB, for example were similar to but not exactly the same as those used in the clinical trial. However, the overall risk of adverse events after immunisation is likely to be more important for clinicians, rather than risks associated with specific vaccines or vaccine combinations. Due to the nature of audits decisions relating to individual infants – such as fitness for vaccination, decisions to offer paracetamol prophylaxis, managing adverse events after vaccination, initiating sepsis screening and empiric antibiotics – were not standardised as in a clinical trial, for example, but were at the discretion of the attending clinician. The inclusion of so many NNUs in the audit should, however, provide a representative overview of the current status across the country.

CONCLUSION

When compared with previous vaccine schedules, the inclusion of 4CMenB is not associated with any significant increase in severe adverse events among hospitalised premature infants. This audit supports the current national recommendation to immunise premature infants at their chronological age and to offer a routine three-dose prophylactic paracetamol course when 4CMenB is given alongside the routine vaccinations. The Medicines and Healthcare products Regulatory Agency (MHRA) continues to monitor the safety of all vaccines in the national immunisation programme; any severe/unexpected adverse events should be reported to the MHRA.

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What is already known on this topic:

- Premature infants are at higher risk of many vaccine preventable diseases and timely vaccination is critical. However, there are concerns about adverse events following vaccination of premature infants.
- 4CMenB (Bexsero) protects against invasive meningococcal disease but is associated with high rates of post-vaccination fever and systemic side-effects. Paracetamol co-administration is recommended nationally.
- There are currently no published data on adverse events following 4CMenB vaccination in premature infants

What this study adds:

- Administration of 4CMenB did not increase desaturations, bradycardias and apnoeas in hospitalised preterm infants
- We found some evidence of increased fever after vaccination in infants immunised with 4CMenB without paracetamol prophylaxis
- CRP level >10mg/dL was common after vaccination

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Tables

Table 1. Baseline characteristics of premature infants at the time of first vaccination in the PUNS cohort and the 4CMenB (Bexsero) cohorts with and without paracetamol.

	PUNS	Bexsero	Bexsero with paracetamol	Bexsero without paracetamol
N	68	133	108	25
Gestation	27.6 (26.1-28.6)	26.9 (25.0-28.6)	26.9 (25.2-28.5)	26.9 (23.9-28.7)
Ventilated days	NA	7 (2-29)	5.5 (1-24)	30 (7-53)*
Postnatal age	63 (57-68)	63 (59-74)	62 (59-71)	75 (64-102)*
Concomitant vaccinations	68 (100)	122 (92)	101 (94)	21 (84)
Fever	NA	3 (2)	3 (3)	0 (0)
Apnoea	3 (4)	10 (8)	9 (8)	1 (4)
Desaturations	28 (41)	48 (36)	33 (31)	15 (60)*
Bradycardia	11 (16)	19 (14)	14 (13)	5 (20)
Reduced consciousness	NA	1 (1)	1 (1)	0 (0)
Analgesia	NA	9 (7)	9 (8)	0 (0)
Respiratory Support	40 (59)	98 (74)	78 (72)	20 (80)

Median (IQR) or n(%). Respiratory support at the time of vaccination includes supplementary oxygen. Ventilated days: days of invasive ventilation only. Fever: Temperature ≥38°C. NA indicates data not available. *p<0.05

Table 2: Adverse events in the 48 hours after immunisation among premature infants in the PUNS cohort and the 4CMenB (Bexsero) cohorts with and without paracetamol.

	PUNS	Bexsero (all)	Bexsero with paracetamol	Bexsero without paracetamol
N	68	122	108	25
Fever	0 (0)	13 (10)	8 (7)	5 (20)
Apnoea	11 (16)	19 (14)	18 (17)	1 (4)
Improved	3 (4)	3 (2)	2 (2)	1 (4)
Deteriorated	8 (12)	15 (11)	14 (13)	1 (4)
No change	57 (84)	102 (77)	80 (74)	22 (88)
Desaturations	26 (38)	72 (54)	53 (49)	19 (76)*
Improved	9 (13)	12 (9)	8 (7)	4 (16)
Deteriorated	18 (26)	43 (32)	33 (31)	10 (40)
No change	39 (57)	52 (39)	45 (42)	7 (28)
Bradycardia	15 (22)	44 (33)	36 (33)	8 (32)
Improved	4 (6)	5 (4)	4 (4)	1 (4)
Deteriorated	12 (18)	32 (24)	25 (23)	7 (28)
No change	50 (74)	76 (57)	60 (56)	16 (64)
Respiratory support	40 (59)	102 (77)	82 (76)	20 (80)
Improved	2 (3)	5 (4)	6 (6)	0 (0)
Deteriorated	4 (6)	14 (12)	11 (12)	3 (14)
No change	62 (91)	102 (84)	82 (82)	19 (86)
Reduced consciousness	N/A	3 (3)	3 (2)	0 (0)
Improved		0 (0)	0 (0)	0 (0)
Deteriorated		3 (2)	3 (3)	0 (0)
No change		110 (83)	88 (81)	22 (88)

Respiratory support includes supplemental oxygen. Fever was defined as temperature ≥38°C. Improved, deteriorated and no change are compared with pre-vaccination status i.e. no change means the infants either had no symptoms prior to and in the 48 hours following vaccination, or they had symptoms but these were stable before and after the vaccination period. Data on reduced consciousness were not collected for the PUNS cohort. Due to missing data, percentages may not total to 100%. Median (IQR) or n (%). NA indicates data not available. *p<0.05

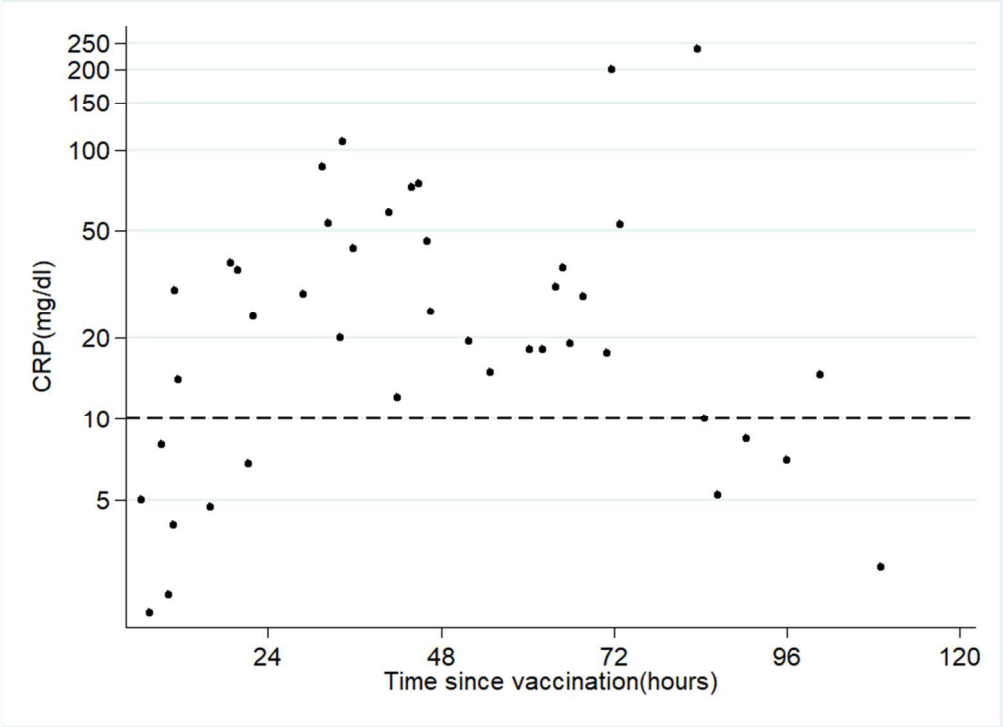

Figure 1. Distribution of CRP levels in preterm infants having a blood test after receiving 4CMenB with their routine immunisations in the neonatal unit. Dashed horizontal line marks the normal range upper limit (10mg/dL). Note the logarthmic Y axis. The two outlying results greater than 200 mg/dl dL are from an a single infant with Gram negative bacteraemia.

71x51mm (300 x 300 DPI)

Supplementary data

Supplementary table 1: Change in ventilatory support in the 48 hours after vaccination in infants receiving 4CMenB with prophylactic paracetamol

		After vaccination					
		SVIA	Low flow O_2	High flow O_2	CPAP	BiPAP	IPPV
Before vaccination	SVIA	22	6	0	0	0	0
	Low flow O_2	2	35	1	3	0	0
	High flow O_2	0	2	20	0	0	1
	CPAP	0	0	0	5	0	0
	BiPAP	0	0	0	1	0	0
	IPPV	0	0	0	0	0	1

SVIA: Self-ventilating in air, CPAP: continuous positive airway pressure, BiPAP: Biphasic positive airway pressure, IPPV: Intermittent positive pressure ventilation. Respiratory support is the maximum respiratory support given immediately prior to and within 48 hours after vaccination.

Supplementary table 2: Change in ventilatory support in the 48 hours after vaccination in infants receiving 4CMenB without prophylactic paracetamol

		After vaccination					
		SVIA	Low flow O_2	High flow O_2	CPAP	BiPAP	IPPV
Before vaccination	SVIA	5	0	0	0	0	0
	Low flow O_2	0	4	0	0	0	0
	High flow O_2	0	0	7	1	1	1
	CPAP	0	0	0	2	0	0
	BiPAP	0	0	0	0	1	0
	IPPV	0	0	0	0	0	0

SVIA: Self-ventilating in air, CPAP: continuous positive airway pressure, BiPAP: Biphasic positive airway pressure, IPPV: Intermittent positive pressure ventilation. Respiratory support is the maximum respiratory support given immediately prior to and within 48 hours after vaccination.