MenB vaccine in preterm infants

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To The Editor,

The 4CMenB vaccine was introduced into the routine immunization schedule in the UK in September 2015 to protect against group B *Neisseria meningitidis* meningitis and septicemia. The vaccine is reactogenic in young infants, causing fever in 51-65% when co-administered with other vaccines [1, 2]. This led to the unprecedented recommendation that all infants receive prophylactic paracetcmol (acetaminophen) with the vaccine. Preterm infants are immunized at the same chronological age and same schedule as term infants but have higher rates of post-immunization adverse events (AEs), particularly those infants born at <28 weeks gestation who are hospitalized in the neonatal unit when immunized [3]. Preterm babies were excluded from 4CMenB trials pre-licensure and no such trials have been registered (clinicaltrials.gov, 14th October 2016). Administration of a reactogenic vaccine in this population has led to heightened concern about AEs. This may impact on use of the vaccine in very preterm infants until they are discharged home, thus delaying protection of this vulnerable group against meningococcal disease.

During a study of rotavirus vaccine in hospitalized preterm infants (RotaNeo), we recruited babies before and after introduction of 4CMenB in the UK (clinicaltrials.gov, NCT02252029), providing a unique opportunity to compare preterm babies who did or did not receive 4CMenB. The primary study objective was to establish the duration of fecal rotavirus vaccine excretion post-immunization. Solicited and unsolicited AEs were collected contemporaneously up to 7 days post-immunization from parents, nursing staff and medical records. Sixty-four post-immunization data points were collected for each participant, with no missing data. Of 17 babies who completed the study, 8 received 4CMenB and 9 did not; all received other routine

immunizations. The overall mean gestational age at birth was 27.1 weeks (range 24.0-29.6 weeks) and mean age at immunization was 9.5 weeks, with no difference between those who did and did not receive 4CMenB (Table). Only 3 babies who were given 4CMenB received paracetamol. Of the 5 who did not, 1 had a post-immunization fever and 3 had a low temperature in the 2 days post-immunization. None of the babies who did not receive 4CMenB had temperature instability. Overall 4CMenB recipients were significantly more likely to have any temperature instability (50% vs 0%, p=0.029). Decreased feeding and reduced activity were more common in the 4CMenB group, whereas irritability and crying occurred more frequently in the babies not receiving 4CMenB (Table), which may be in part due to the use of acetaminophen in some of the 4CMenB recipients.

This study provides the first data on AEs following 4CMenB in preterm hospitalized infants, suggesting an increase in some AEs with 4CMenB, most notably temperature instability. Larger studies are needed (~70 babies per group for 90% power with 5% alpha based on these data) to inform guidance for monitoring post-immunization in these infants and use of prophylactic acetaminophen, since low temperature was more common than fever.

Table. Demographics and rates of post-immunization adverse events in babies who did or did not receive 4CMenB up to 2 days and 7 days post-immunization

	No 4CMenB (n=9)	4CMenB (n=8)	*p*-value[1]
Demographics			
Birth GA (wks), mean (SD)	26.4 (0.9)	27.9 (2.2)	0.106
Age (wks), mean (SD)	9.4 (1.4)	9.5 (1.4)	0.882
Paracetamol (acetaminophen) given, n (%)	0	3 (38)	na
Adverse events on day of and up to 2 days post-immunization			
Any adverse event, n (%)	6 (67)	6 (75)	1.000
Fever ≥38.0°C, n (%)	0	1 (13)	0.471
Low temperature, n (%)	0	3 (38)	0.082
Any temperature instability, n (%)	**0**	**4 (50)**	**0.029**
Decreased feeding, n (%)	1 (11)	4 (50)[2]	0.131
Less active, n (%)	2 (22)[3]	6 (75)[4]	0.057
More irritable, n (%)	3 (33)	0	0.206
Cried persistently, n (%)	2 (22)	0	0.471
Vomiting, n (%)	3 (33)	2 (25)	1.000
Diarrhea, n (%)	2 (22)	1 (13)	1.000
Respiratory compromise, n (%)	1[5]	4[6]	0.131
Adverse events on day of and up to 7 days post-immunization			
Any adverse event, n (%)	6 (67)	7 (88)	0.577
Fever ≥38.0 °C, n (%)	0	2 (25)	0.206
Low temperature, n (%)	0	3 (38)	0.082
Any temperature instability, n (%)	**0**	**5 (63)**	**0.009**
Decreased feeding, n (%)	1 (11)	4 (50)[2]	0.131
Less active, n (%)	2 (22)[3]	6 (75)[4]	0.057
More irritable, n (%)	3 (33)	1 (13)	0.576
Cried persistently, n (%)	2 (22)	0	0.471
Vomiting, n (%)	3 (33)	4 (50)	0.637
Diarrhea, n (%)	3 (33)	1 (13)	0.576
Respiratory compromise, n (%)	2[5,7]	4[6]	0.3348

[1]Comparison of 4CMenB vs non-4CMenB groups done using Fisher's exact test; [2]1 classified as severe (day 1 post-immunization); [3]1 classified as severe (day of immunization); [4]3 classified as severe (all day 1 post-immunization); [5]Apnoea, bradycardia and desaturation; [6]Apnoea and desaturation in 1 baby and desaturation only in 3 babies; [7]Event on day 7 post-immunization required re-intubation

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Conflict of Interest

MS has been an investigator on investigator-initiated research studies funded by Pfizer. AJP is a Jenner Investigator and James Martin Senior Fellow and has previously conducted research on behalf of Oxford University funded by vaccine manufacturers. MS and AJP have not received any personal remuneration from vaccine manufacturers. AJP is chair of the UK Department of Health's (DH) Joint Committee on Vaccination and Immunization (JCVI); the views presented in this manuscript do not necessarily represent the views of DH or JCVI. Other authors have no conflict of interest.

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