Accident and Emergency presentations for Adverse Events Following Immunisation in the post 4CMenB era: increases in attendance in infancy but not at 12 months

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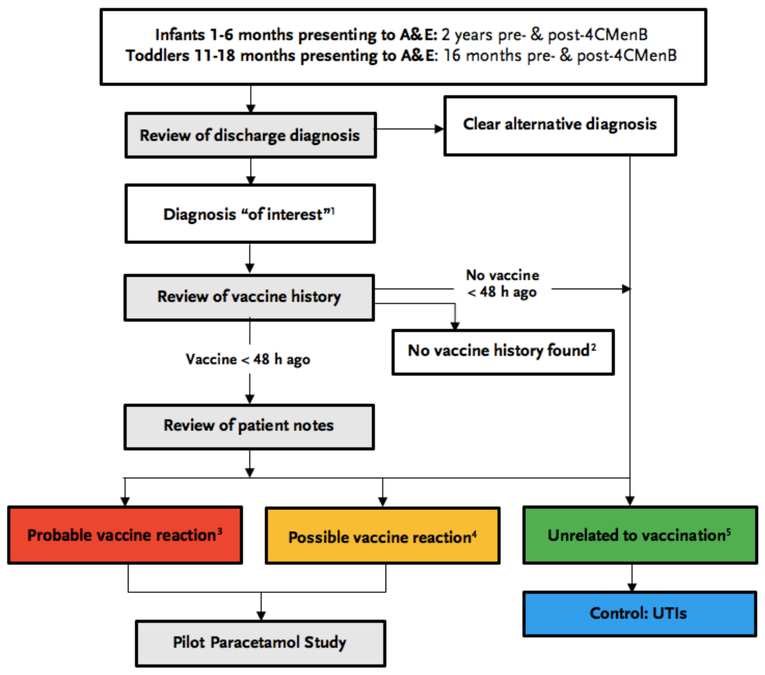
BACKGROUND

- The 4CMenB vaccine was introduced into the UK national immunisation schedule at 2, 4 and 12 month immunisation episodes in September 2015 for prevention of capsular group B meningococcal disease. Routine 12 month doses began in May 2016.
- Due to high vaccine reactogenicity, Public Health England advises a three-dose course of prophylactic paracetamol following the infant doses.
- However, an increase in presentations to Oxfordshire Accident and Emergency (A&E) departments for acute Adverse Events Following Immunisation (AEFIs) was observed in the first year post-4CMenB. This increase (from an annual average of 12 infants with probable/possible vaccine reactions in 2013/2015, to 38 infants in 2015/2016) was observed at 2 months (increase from 1.03 to 3.4 per 1000 immunisations) and 4 months (0.14 to 1.13 per 1000 immunisations) but not at 3 months.[1]
- A study from Belfast also showed higher rates of admission (8 per 1000 vaccine-eligible infants) despite 94% receiving prophylactic paracetamol, and high proportions of unnecessary admissions, venepunctures and cultures.[2] A Scottish study also showed an increased risk of hospitalisation for AEFI in the post-introduction model following immunisation at 2 and 4 months, but not at 3 months. This extrapolated to an additional 1430 hospitalisations across the UK.[3]
- **Aim**: To ascertain whether this increase in infant A&E presentations would continue into the second year post-4CMenB introduction, and and be apparent in the first cohort receiving a 12-month booster dose (an age at risk of febrile convulsions). To also determine rates of prophylactic paracetamol use in children who present.

METHODOLOGY

- Retrospective study evaluating presentations of infants 1 to 6 months old at the Oxford University Hospital NHS Trust (Paediatric Emergency Departments at John Radcliffe, Oxford and Horton Hospital, Banbury) from 1 September 2016 – 31 August 2017 (2nd post-4CMenB year). This was compared to 1st year post-4CMenB (2015-16), and 2 years pre-4CMenB (2013-14, 2014-15).
- Also evaluating presentations of all children aged 11 to 16 months between 1 January 2015 and 31 August 2017 (16 months before and after introduction of 4CMenB immunisation for 12-month-olds).
- Control groups of children presenting with confirmed urinary tract infections (UTIs) were used for all groups, and A&E discharge diagnoses, immunisation history and patient discharge summaries were analysed.
- Participants were separated into groups depending on whether their symptoms were probably related to immunisation, possibly related to immunisation or unrelated to immunisation

***Figure 1**. Study protocol for infants and toddlers presenting to A&E in pre- and post-4CMenB eras.*



[1] Crying, irritability, sepsis, floppiness, unwell, fever, or 'conditions of interest' (meningitis, seizure, rash)
[2] Vaccination history neither found in Oxfordshire Care Summary nor in Child Health Record Dept. Database.
[3] Discharge summaries and/or clinical notes report vaccine reaction as clinical diagnosis
[4] Records show no clear alternative diagnosis obtained and immunisation occurred within previous 48 hours
[5] Clear alternative diagnosis/conditions that are unlikely to be related to immunisation or no immunisation within previous 48 hours

RESULTS - Summary

- Of 1737 infants aged 1 to 6 months old presenting to Oxfordshire A&Es from September 2016 to August 2017, 708 with diagnoses of interest were reviewed. Of 5918 toddlers aged 11 to 16 month olds from January 2015 to August 2017, 2158 with diagnoses of interest were reviewed as per Fig 1.
- Figures 2–4 show the number of presentations for infants, toddlers and the rates of presentation per 1000 doses of vaccine. Figures 5–7 show numbers and rates of admissions. Figures 8 & 9 show rates of clinical interventions for infants and toddlers, and figure 10 shows WBC and CRP counts for 2 & 4 month olds.
- A sustained increase in presentations for AEFI was observed in the 1-6 month infant population in the second year post-4CMenB.
  - Overall rates of AEFIs presenting per 1000 doses of vaccine increased in 2 & 4 month olds from 0.57 to 2.80 (p<0.001, OR 4.89)
  - Rates were not significantly raised at 3 months (0.47 to 0.72, p=0.621, OR 1.36). UTI control group was unchanged.
- For 12-month olds, there were 9 presentations including 1 case of febrile convulsion pre-4CMenB, and 14 presentations including 3 febrile convulsions post-4CMenB.
- Among 'probable' and 'possible' reactions, 54.1% of infants and 30.4% of toddlers were admitted for further management, with subsequent increases in invasive investigations and IV antibiotic use.
- Figure 11 depicts infant and toddler attendances across each hour of the day. 88% infants and 74% of infants presented "after hours"

RESULTS - Infant and Toddler Study

PRESENTATIONS TO A&E

***Figure 2**. No. of AEFIs presenting to A&E in infants, 2 years pre- & post-4CMenB*

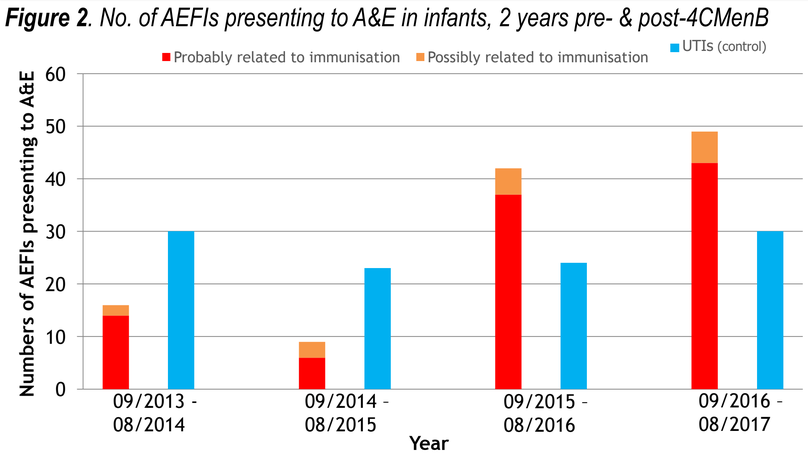


***Figure 3**. No. of AEFIs presenting to A&E in toddlers, 16 months pre- & post-4CMenB*

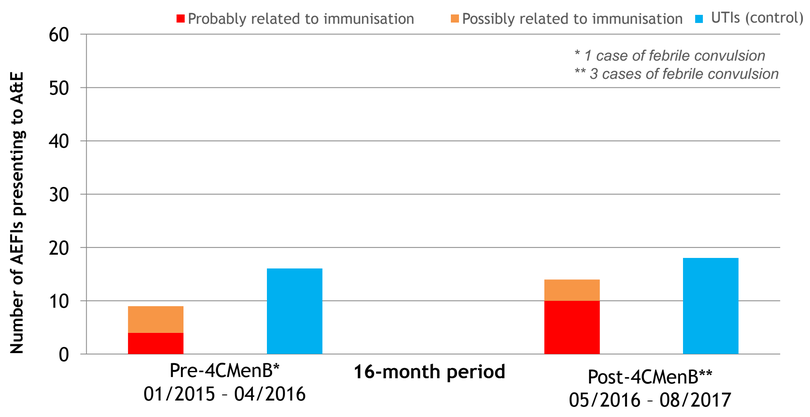
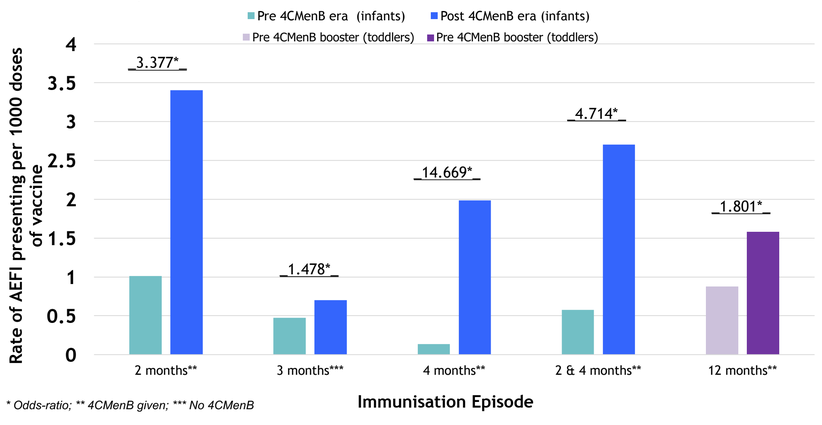


***Figure 4**. Rates of AEFIs presenting to A&E per 1000 doses of vaccine, by immunisation episode – infants and toddlers*



* Odds-ratio; ** 4CMenB given; *** No 4CMenB

ADMISSIONS TO HOSPITAL

***Figure 5**. No. of admissions to hospital (ward or CDU) probably or possibly related to immunisation – infants*

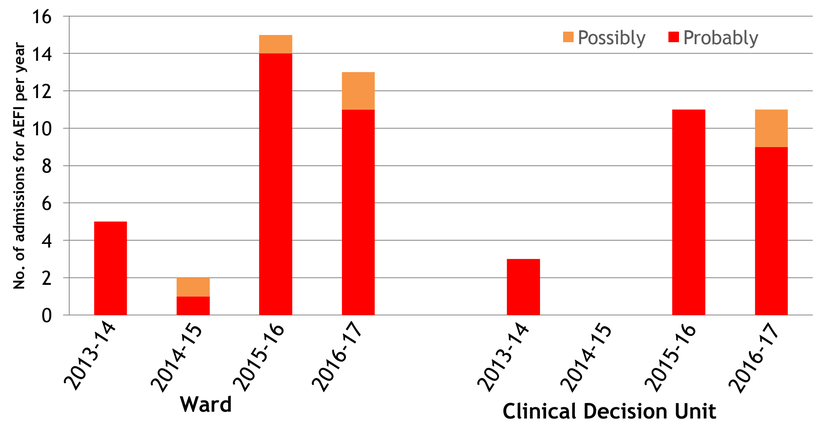


***Figure 6**. No. of admissions to hospital (ward or CDU) probably or possibly related to immunisation – toddlers*

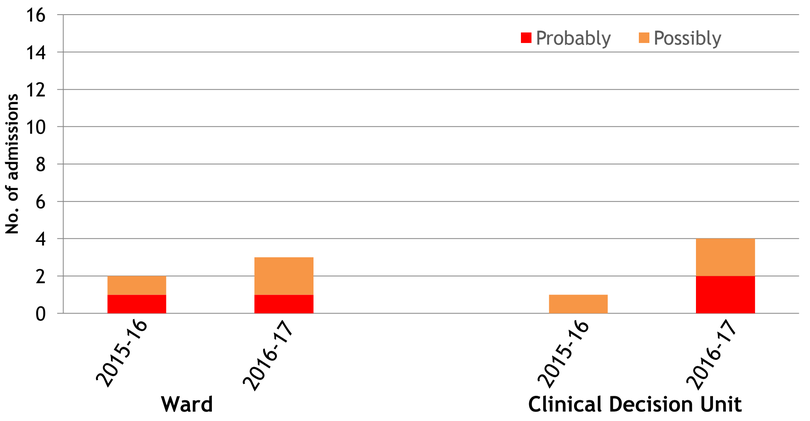
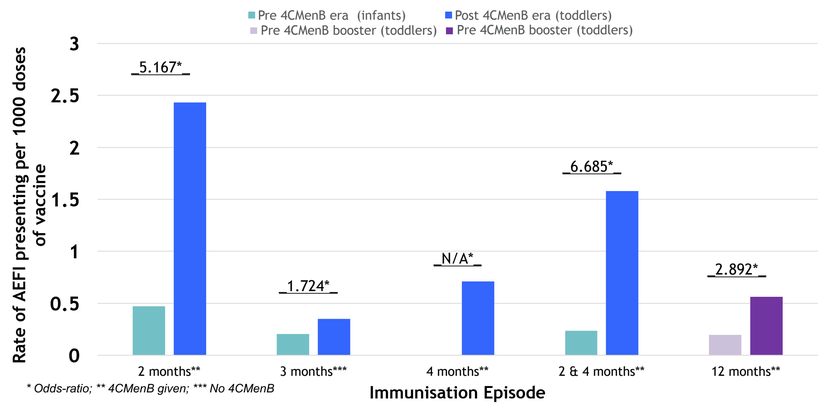


***Figure 7**. Rates of admissions to hospital for AEFIs per 1000 doses of vaccine, by immunisation episode – infants and toddlers*



* Odds-ratio; ** 4CMenB given; *** No 4CMenB

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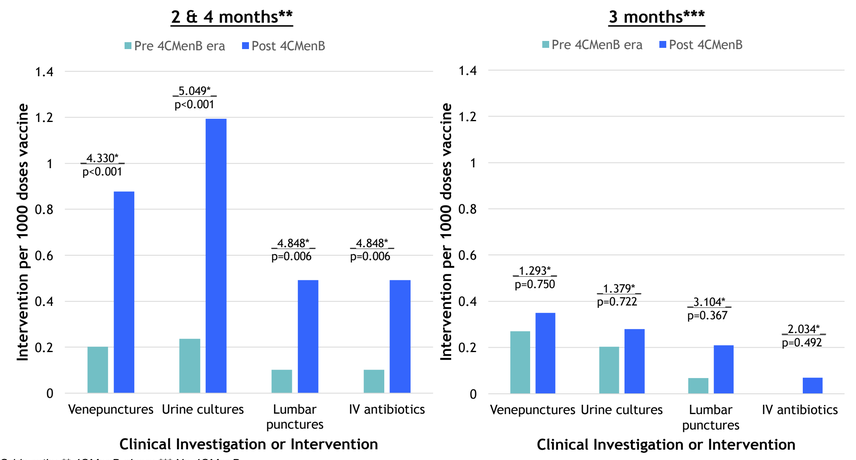
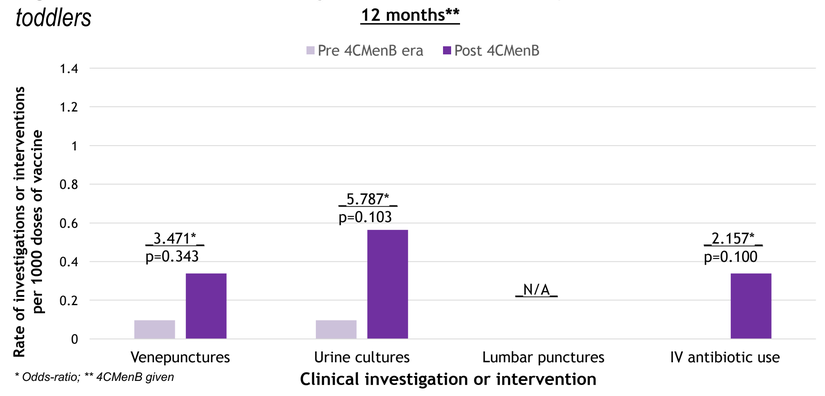
***Figure 8**. Rate of clinical investigations and interventions per 1000 doses of vaccine – 2 & 4 month olds compared with 3 month olds*



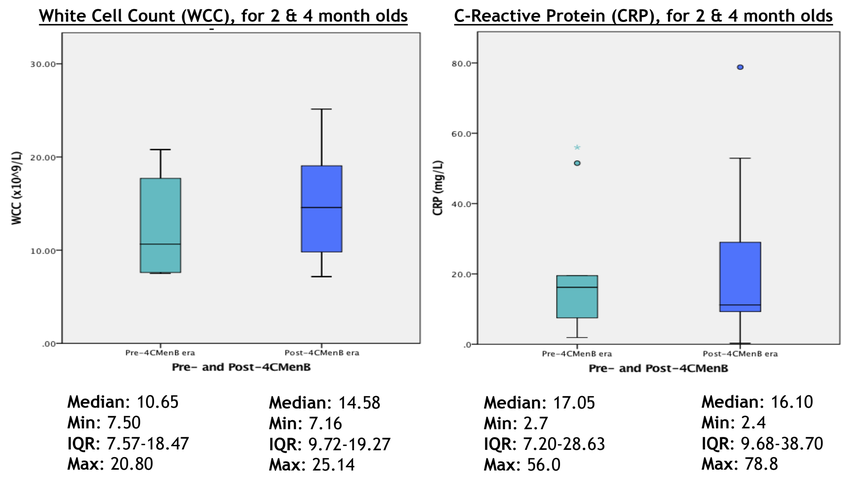
* Odds-ratio; ** 4CMenB given; *** No 4CMenB

***Figure 9**. Rate of clinical investigations and interventions per 1000 doses of vaccine – toddlers*



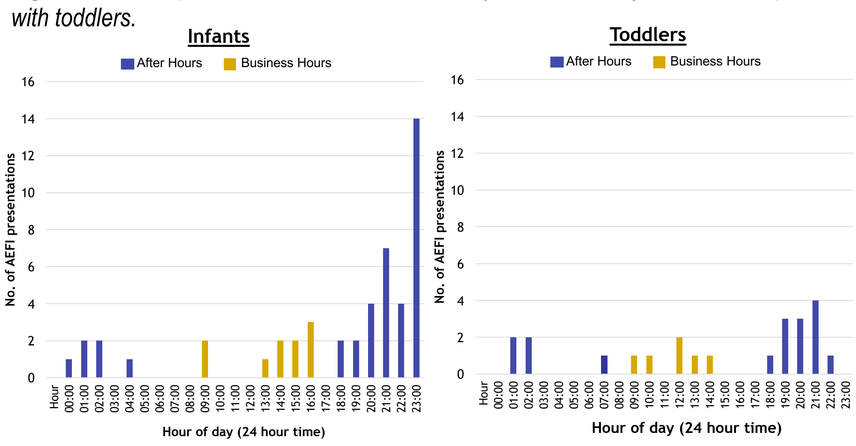
* Odds-ratio; ** 4CMenB given

***Figure 10**. White blood cell and C-reactive protein results, for 2&4 month olds with AEFIs*



WCC		CRP	
Median: 10.65	**Median:** 14.58	**Median:** 17.05	**Median:** 16.10
Min: 7.50	**Min:** 7.16	**Min:** 2.7	**Min:** 2.4
IQR: 7.57-18.47	**IQR:** 9.72-19.27	**IQR:** 7.20-28.63	**IQR:** 9.68-38.70
Max: 20.80	**Max:** 25.14	**Max:** 56.0	**Max:** 78.8

***Figure 11**. No. of presentations to A&E for AEFI, by hour of the day – infants compared with toddlers.*



RESULTS - Pilot Paracetamol Study

- From July 2017, infants presenting to A&E within 48 hours of having received a vaccine were followed up with a phone call to gather more information about prophylactic paracetamol use.
- Of the 11 patients thus far, all had received their 1st dose <1hr post-immunisation.
- The majority received their 2nd prophylactic dose before reacting.
- 9 of 10 were given at least 3 doses of paracetamol, prophylactically and reactively.
- This data collection is ongoing.

***Figure 12**. Pilot paracetamol study*

CONCLUSIONS

- There is a sustained increase in infants presenting to A&E with AEFIs in the 2nd year post-4CMenB introduction. The increase in presentations has led to increases in admissions, invasive investigations and empirical IV antibiotics.
- There is no significant in toddlers presenting to A&E with AEFIs in 16 months after first cohort received booster doses, despite this cohort not receiving prophylactic paracetamol. No septic workup is recommended at this age, which is reflected in lower numbers of admissions, investigations and IV antibiotic use.
- The pilot study shows that patients are presenting despite using prophylactic paracetamol as recommended.
- While these data do not detract from the success of the 4CMenB campaign, they do highlight the need for guidelines to specifically manage fever post-4CMenB.

Reference: **1.** 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 Aug 09.
2. Kapur S, Bourke T, Maney JA, Moriarty P. Emergency department attendance following 4-component meningococcal B vaccination in infants. Arch Dis Child. 2017 Jun 21.
3. Murdoch H, McFadden M, Smith-Palmer A, von Wissmann B, Cameron C. Active monitoring of potential adverse immunisation events with hospital admission data and linked analysis in Scotland. Lancet. 2014 Nov 19;384:10-10.