

# BMJ Open Adverse events following immunisation with four-component meningococcal serogroup B vaccine (4CMenB): interaction with co-administration of routine infant vaccines and risk of recurrence in European randomised controlled trials

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## ABSTRACT

**Objectives** (1) To assess if co-administration of four-component meningococcal serogroup B vaccine (4CMenB) and other routine vaccines caused an interaction increasing the risk and/or severity of adverse events following immunisation (AEFI) compared with administration at separate visits and (2) to estimate the risk of AEFI recurrence.

**Design** Risk-interval design

**Setting** Three randomised controlled trials conducted in Europe.

**Participants** A total of 5026 healthy 2-month-old to 15-month-old infants.

**Interventions** 4CMenB and routine vaccines (hexavalent combined diphtheria-tetanus-acellular pertussis-inactivated polio-Haemophilus influenzae type b-hepatitis B vaccine+seven-valent pneumococcal conjugate vaccine or measles-mumps-rubella-varicella vaccine) administered concomitantly or separately 1 month apart, in regular (2, 4, 6 and 12 months), accelerated (2, 3, 4 and 12 months) or delayed (two doses of 4CMenB at ≥12 months of age) schedules.

**Outcome measures** Primary: Fever (≥38°C) during the first 48 hours post immunisation. Secondary: crying, change in eating habits, diarrhoea, irritability and tenderness at the 4CMenB injection site.

**Results** Compared with separate administration, concomitant administration decreased the overall incidence of fever (≥38°C), 86% versus 75%, and other systemic AEFIs but increased the incidence of 4CMenB injection site tenderness, 55% versus 66%, moderate/severe fevers (≥39°C), 13% versus 18%, and long-lasting (>1 day) fevers, 23% versus 33%. Co-administration reduced AEFI risk by 4%–49% with the greatest impact among infants with prior AEFI(s). Fever recurrence risk was proportional to the number of prior fever events: 79% at dose 2 with one prior episode; 44% and 74% at dose 3 with one and two prior episodes, respectively; and 29%, 45% and 60% at dose 4 with one, two and three prior episodes, respectively. Severity was not

## Strengths and limitations of this study

- Adverse events following immunisation (AEFI) recurrence risk was assessed by vaccination group (concomitant or separate—1 month staggered—administration of four-component meningococcal serogroup B vaccine and routine infant vaccines); and prior AEFI history, including the number and chronological rank of prior episodes.
- The interaction contrast approach was used to compare the AEFI risk following vaccine co-administration versus the sum of AEFIs following vaccine administration at separate visits among study participants who were randomly assigned to the various vaccination groups.
- The analysis did not include rare AEFIs and was limited to infants aged 2–15 months.
- In infants, aged 12–15 months, the at-risk period for measles-mumps-rubella-varicella vaccine was monitored for fever but not for other systemic AEFIs.

increased at recurrence and a similar pattern of recurrence risk proportional to the number of prior events was observed for other AEFIs.

**Conclusions** The cumulative risk of AEFI is reduced with concomitant versus separate administration of 4CMenB and routine infant vaccines. Infants with a prior AEFI are at higher risk of the same AEFI at subsequent immunisations, but severity with recurrence is usually not increased.

**Trials registration number** NCT00657709, NCT00847145, NCT00721396 and NCT02712177; Pre-results.

## INTRODUCTION

Bexsero (GlaxoSmithKline [GSK]) is a four-component meningococcal serogroup

B vaccine (4CMenB) first licensed in 2013 and currently approved for use in more than 35 countries including Canada, the UK, the USA, France and Australia.<sup>1–6</sup> In young infants, the 4CMenB vaccination schedule usually includes two or three doses administered before 1 year of age followed by a booster dose at 12 months of age.<sup>1 7</sup> Since September 2015 infants in the UK are immunised with three doses of 4CMenB given at 8 weeks, 16 weeks and 1 year of age. The effectiveness of two doses of 4CMenB was 82.9% against all invasive meningococcal serogroup B infections. Compared with the prevaccine period, this vaccination programme reduced by 50% the incidence rate of meningococcal B infections in the vaccine-eligible cohort irrespective of the infant's vaccination status or predicted meningococcal B strain coverage.<sup>8</sup>

The postmarketing safety of 4CMenB assessed with the UK Yellow Card Scheme found no significant safety concerns with most reports being related to local reactions (41%) or fever (40%).<sup>9</sup> Nevertheless, the incidence of vaccine-related acute serious adverse events in individuals receiving 4CMenB is significantly higher than that of routine vaccines.<sup>10–12</sup> For practical and financial reasons, 4CMenB doses would ideally be administered concomitantly with other routine infant vaccines. However, prelicensure randomised controlled trials (RCTs) and postmarketing surveillance data suggested that 4CMenB is more reactogenic when co-administered with routine vaccines.<sup>10 11 12</sup> Pain at the 4CMenB injection site occurred in 55% of infants receiving 4CMenB and in 66% of those receiving 4CMenB concomitantly with routine vaccines.<sup>7 10 11</sup> Fever ( $\geq 38^{\circ}\text{C}$ ) occurred in 71% of infants receiving 4CMenB and in 76%–80% of those receiving 4CMenB concomitantly with routine vaccines.<sup>10 11</sup> While this suggests that co-administration results in a greater risk of adverse events following immunisation (AEFI), only the adverse events following 4CMenB and not those occurring following other routine infant vaccines were reported, thus underestimating the total cumulative AEFI risk potentially associated with alternating visits.<sup>10 11</sup> When co-administering 4CMenB and routine vaccines, it should not be surprising to observe more AEFIs since this would include AEFIs associated with 4CMenB *and* those associated with other routine vaccines given at the same visit.<sup>13</sup> In fact, co-administration should only be interpreted to cause an interaction increasing reactogenicity if the AEFI risk following co-administration is significantly higher than the *sum* of AEFI risks following each 4CMenB and routine vaccines given at separate visits and/or if AEFIs following co-administration are associated with greater severity.<sup>13</sup>

For infants who suffer an AEFI with a 4CMenB dose, parents and providers might be concerned about the recurrence risk and potential for increased severity of the AEFI with administration of the next vaccine dose(s).<sup>14–16</sup> Such concern could lead to immunisation delay or hesitancy that could leave the child with suboptimal protection. While prior 4CMenB RCTs have reported AEFI frequencies, they have not reported their recurrence risk with subsequent doses.<sup>10 11</sup>

The aim of this study was to assess if the co-administration of 4CMenB and other routine vaccines caused an interaction increasing the risk and/or severity of AEFI compared with administration at separate visits and to estimate the risk of AEFI recurrence at subsequent 4CMenB immunisations.

## METHODS

### Study population

This study used data from three RCTs that compared the immunogenicity and reactogenicity of 4CMenB when co-administered or not with routine vaccines in infants aged 2–15 months.<sup>10 11</sup> Table 1 presents the RCT designs and details. The eligibility criteria and further details for each RCT have been previously published.<sup>10 11</sup> Each of the participating centres obtained institutional review board approval for the RCT prior to initiation.

Among the 5516 infants included in the RCTs, our analysis was limited to the 5026 who received 4CMenB vaccine and/or routine vaccines (ie, excluding the 490 who received routine vaccines and meningococcal serogroup C vaccine). During stage 1, infants <12-month old were randomised to receive three doses of routine vaccines only or 4CMenB administered concomitantly with or separately from (1 month before) routine vaccines in regular (2, 4 and 6 months) or accelerated (2, 3 and 4 months) 4CMenB schedules (table 1).<sup>10 11</sup> Routine vaccines were commercial preparations of seven-valent pneumococcal conjugate vaccine (PCV7, Prevenar, Pfizer) and the hexavalent combined diphtheria-tetanus-acellular pertussis-inactivated polio-Haemophilus influenzae type b-hepatitis B vaccine (DTaP-IPV-Hib-HepB, Infanrix Hexa, GSK). All vaccines were administered by intramuscular injection in the anterolateral thigh; 4CMenB and routine vaccines given concomitantly were administered in opposite limbs.<sup>10 11</sup>

Stage 2 was done in infants aged 12–15 months and included 39% (n=1957) of stage 1 participants. Infants were divided into two subgroups: those given 4CMenB and routine vaccines during stage 1 received their fourth dose of 4CMenB and those given only routine vaccines during stage 1 received their first two doses of 4CMenB.<sup>11</sup> In both subgroups, infants were randomised to receive 4CMenB concomitantly with or separately from measles-mumps-rubella-varicella vaccine (MMRV, Priorix-Tetra, GSK) (table 1).<sup>11</sup> MMRV was administered subcutaneously in the opposite limb to 4CMenB, in the deltoid muscle or anterior thigh when deltoid mass was insufficient.<sup>11</sup> At both stages, 4CMenB and routine vaccines were given 1 month apart when administered separately. However, 4CMenB preceded routine vaccines in stage 1 and among those receiving their fourth dose in stage 2, but a reverse order (routine vaccines preceding 4CMenB) was used among those receiving their first doses of 4CMenB in stage 2 (table 1). For the purpose of this study, infants were divided into three groups according to the vaccine(s) received: 4CMenB alone, routine vaccines

**Table 1** Main features of the randomised control trials and vaccination groups

| Stage                            | Study (identifier)                     | Study design   | N    | Vaccine schedule   | Vaccination group in the present study                     |
|----------------------------------|--|--|------|--|--|
| Stage 1<br>(<12 months of age)   | Gossger <i>et al</i><br>(NCT00721396)  | Multicentre, open-label, randomised controlled trial (1885 children)                                   | 627  | 4CMenB and routine vaccines at age 2, 4 and 6 months   | Co-administration  |
|                                  |  |  | 628  | 4CMenB at age 2, 4 and 6 months and routine vaccines at age 3, 5 and 7 months                        | 4CMenB (2, 4 and 6 months)<br>Routine* (3, 5 and 7 months) |
|                                  |  |  | 318  | 4CMenB and routine vaccines at age 2, 3 and 4 months   | Co-administration  |
|                                  |  |  | 312  | Routine vaccines at age 2, 3 and 4 months  | Routine*   |
|                                  | Vesikari <i>et al</i><br>(NCT00657709) | Multicentre, open-label (2627 children) and observer-blind (1003 children) randomised controlled trial | 2481 | 4CMenB (one of three lots) and routine vaccines at age 2, 4 and 6 months                             | Co-administration  |
|                                  |  |  | 660  | Routine vaccine at age 2, 4 and 6 months   | Routine*   |
| Stage 2<br>(12–15 months of age) | Vesikari <i>et al</i><br>(NCT00847145) | Multicentre, open-label randomised controlled trial  | 490  | MenC-C and routine vaccines at age 2, 4 and 6 months   | Excluded   |
|                                  |  |  | 765  | 4CMenB (fourth dose) and routine vaccine at age 12 months  | Co-administration  |
|                                  |  |  | 790  | 4CMenB (fourth dose) at 12 months and routine vaccine at age 13 months                               | 4CMenB (12 months)<br>Routine* (13 months)                 |
|                                  |  |  | 116  | 4CMenB (first dose) and routine vaccine at 12 months, 4CMenB (second dose) at 14 months              | Co-administration (12 months)<br>4CMenB (14 months)        |
|                                  |  |  | 286  | Routine vaccine at 12 months, 4CMenB (first dose) at 13 months and 4CMenB (second dose) at 15 months | 4CMenB (13 and 15 months)<br>Routine* (12 months)          |

\*At stage 1, the routine vaccines are DTaP-IPV-Hib-HepB (Infanrix Hexa, GSK)+PCV7 (Prevnar, Wyeth Pharmaceuticals or Prevenar, Pfizer) and at stage 2, the routine vaccine is MMRV (Priorix-Tetra, GSK). 4CMenB, four-component meningococcal serogroup B vaccine; DTaP-IPV-Hib-HepB, hexavalent combined diphtheria-tetanus-acellular pertussis-inactivated polio-Haemophilus influenzae type b-hepatitis B vaccine; GSK, GlaxoSmithKline; MenC-C, meningococcal conjugate serogroup C vaccine (Menjugate, GSK); MMRV, measles-mumps-rubella-varicella vaccine; PCV7, seven-valent pneumococcal conjugate vaccine.

(DTaP-IPV-Hib-HepB+PCV7 or MMRV) alone and co-administration (table 1).

### Surveillance and outcomes

Administration of antipyretics/analgesics, and solicited local and systemic AEFIs were recorded daily for 7 days (days 1–7) following vaccination, except fever, which was monitored for 28 days (days 1–28) after MMRV vaccination.<sup>10 11</sup> The primary outcome was fever (temperature  $\geq 38^\circ\text{C}$ ) and the secondary outcomes were systemic AEFIs other than fever: crying, change in eating habits, diarrhoea and tenderness at the 4CMenB injection site (*hereafter called 4CMenB-tenderness*). Severity of systemic AEFIs was based on parental report and classified as: mild or  $38^\circ\text{C}$ – $38.9^\circ\text{C}$ , moderate or  $39^\circ\text{C}$ – $39.9^\circ\text{C}$  and severe or  $\geq 40^\circ\text{C}$ , for non-fever and fever reactions, respectively. 4CMenB-tenderness' severity was classified as: mild (discomfort when touching the vaccinated limb), moderate (obvious discomfort when touching the vaccinated limb) or severe (pain on movement of the vaccinated limb). For each outcome, severity was also analysed

in terms of duration ( $\leq$  or  $>1$  day). AEFI recurrence was defined as the occurrence of the *same* AEFI with subsequent vaccine doses.

### Statistical analysis

Two main analyses were conducted using SAS V.9.4: we assessed interaction by comparing reactivity of co-administration of 4CMenB and routine vaccines versus separate administration and we estimated the risk of AEFI recurrence and impact of prior AEFI(s) on reactivity of subsequent vaccine doses. The at-risk period for 4CMenB-tenderness was defined as days 1 and 2, and the control period as days 6–7 regardless of the vaccine(s) administered or stage. For systemic AEFIs, the at-risk period for 4CMenB and inactivated routine vaccines (DTaP-IPV-Hib-HepB, PCV7) was defined as days 1 and 2, and the control period as days 6–7. At stage 2, we only considered AEFIs occurring during days 1 and 2, MMRV was not considered because of a distinct systemic AEFI at-risk period (=days 5–12). Also, recurrence post-MMRV

could not be evaluated as only one dose of MMRV was administered.

### Analysis of the interaction between 4CMenB and routine vaccines

The interaction between 4CMenB and routine vaccines was analysed using a risk interval analysis and was restricted to doses 1, 2 and 3 owing to the different at-risk period for systemic AEFIs following MMRV. Interaction was assessed on the additive scale using the interaction contrast (IC) calculated as follows:  $IC = (R_{11} - R_{00}) - ([R_{01} - R_{00}] + [R_{10} - R_{00}])$  where  $R_{01}$  represents the risk of a given AEFI following 4CMenB administration alone,  $R_{10}$  the risk following routine vaccines alone,  $R_{11}$  the risk following co-administration of 4CMenB and routine vaccines and  $R_{00}$  the baseline risk (no vaccine administered).<sup>13</sup> The AEFI risks in each vaccination group ( $R_{10}$ ,  $R_{01}$  and  $R_{11}$ ) were estimated as the cumulative incidence during their respective at-risk periods. The baseline risk ( $R_{00}$ ) was calculated as the cumulative incidence during control periods. The IC was estimated by adding an interaction term for 4CMenB×routine vaccines to a repeated measures binomial model with an identity link.<sup>17</sup> If  $IC < 0$  then co-administration reduces AEFI incidence (negative interaction), if  $IC > 0$  then co-administration increases AEFI incidence (positive interaction) and if  $IC = 0$  then there is no difference between co-administration and separate visits (no interaction).<sup>13</sup>

### Analysis of AEFI recurrence

We compared the cumulative incidence of AEFI outcomes during their at-risk periods in infants who did (recurrence) and did not (occurrence) have these outcomes at previous doses. The risk ratios (RRs) comparing AEFI cumulative incidences in infants with or without a prior AEFI were estimated using log-binomial models adjusted for sex, age, RCT, antipyretic/analgesic prophylaxis and vaccination group. To account for the repeated measure nature of the study design, we used the SAS PROC Genmod with the repeated statement with an autoregressive correlation matrix. When building the adjusted models, each potential confounder was tested alone. Backward elimination was then used and only adjustment variables changing the fully adjusted RR by more than 10% were kept in the final model. Following the backward elimination, each of the retained confounders was added and removed while keeping all others in the model to confirm their impact on confounding.

Sensitivity analyses were conducted by varying the at-risk (days 1–3) and the control periods (days 5–7). Statistical testing was bilateral with statistical significance at  $p < 0.05$ .

### Patients and public involvement

Patients and/or the public were not involved in the design of this study.

## RESULTS

### Demographics

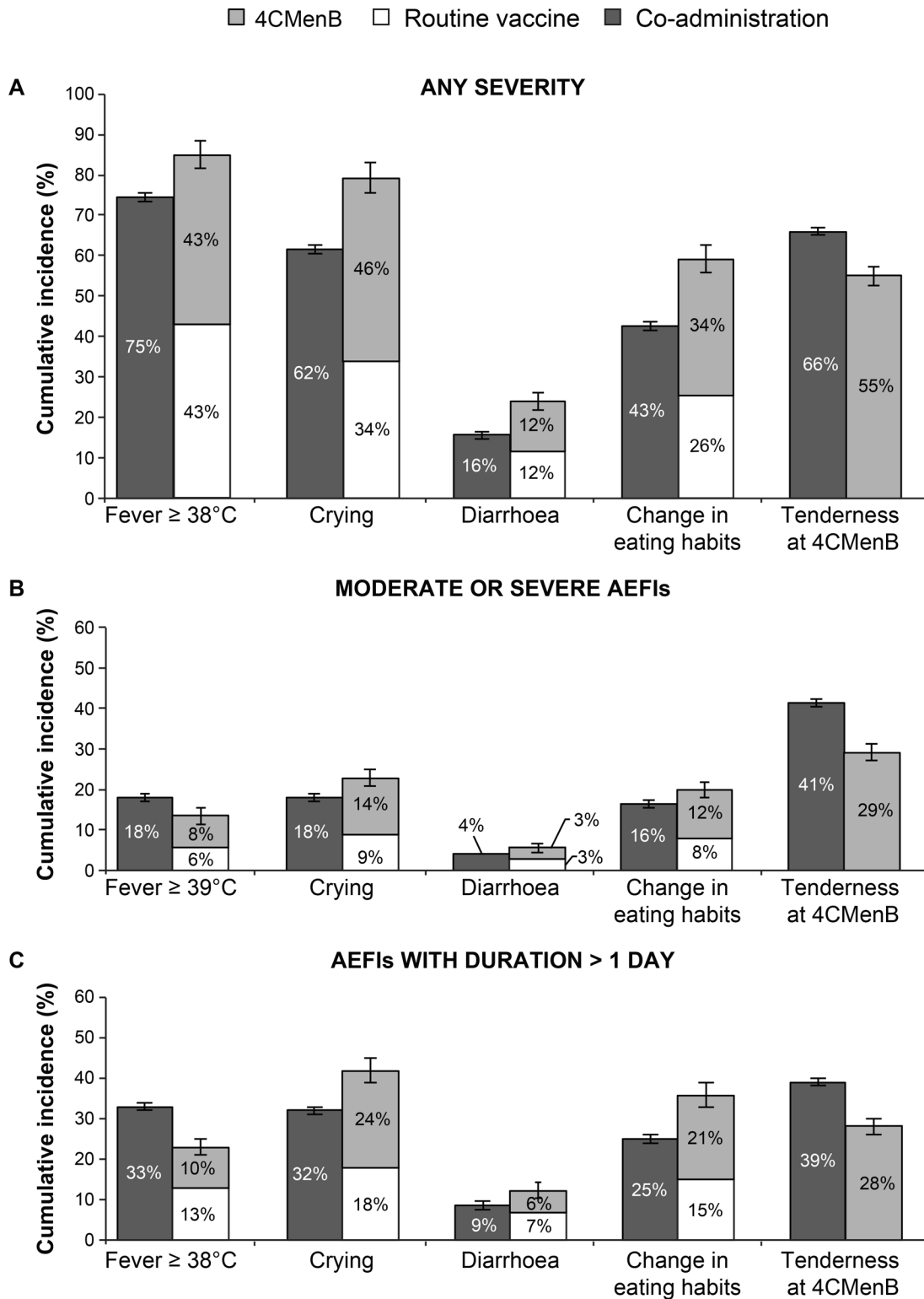
A total of 5026 and 1957 infants were vaccinated at stage 1 and stage 2, respectively; 97%–99% of infants were vaccinated according to the protocol. Demographic characteristics (ethnicity, race and gender) were similar across groups. Overall, 51% of infants were male and ≥97% were Caucasian (online supplementary table S1).

### Vaccine reactogenicity

Regardless of the stage, the vaccine dose number or the vaccination group, >90% of reported AEFIs began during the defined at-risk period, except for diarrhoea (75% of diarrhoeas began during the at-risk period). About 0% (4CMenB-tenderness) to 4% (diarrhoea) of AEFIs began during the control period (online supplementary figure S1). The median duration was 1 day for 4CMenB-tenderness and 2 days for all systemic AEFIs. Overall for doses 1–3, 4CMenB-tenderness was reported in 55% (9% severe) and 66% (16% severe) of infants in the 4CMenB and co-administration groups, respectively ( $p < 0.001$ ) (figure 1). Among systemic AEFIs, the AEFI incidences in the 4CMenB, routine and co-administration groups were as follow: fever (43%, 43% and 75%), crying (46%, 34% and 62%), change in eating habits (34%, 26% and 43%) and diarrhoea (12%, 12% and 16%) (figure 1A). The reactogenicity of 4CMenB was comparable to that of routine vaccines. The sum of AEFIs when 4CMenB and routine vaccines were given separately was higher than reactogenicity following co-administration. This sum of AEFI may be viewed as inflating the reactogenicity level given that 7%–28% of children had the same AEFI at both visits (lowest for diarrhoea and greatest for crying, online supplementary table S2), but has the advantage of taking the perspective of children and parents for whom each AEFI episode counts. In all vaccination groups, <1% of infants had fever ≥40°C. For all systemic AEFIs, the proportion of severe events was comparable between vaccination groups (online supplementary table S3). The proportion of severe 4CMenB-tenderness was higher when 4CMenB was co-administered with routine vaccines (24%) than when administered alone (17%,  $p < 0.001$ ) (online supplementary table S3). At dose 4 (stage 2), likely because of the delayed reactogenicity of MMRV (=days 5–12), the incidences of systemic AEFIs during days 1 and 2 in the co-administration group were smaller than or equal to that observed at doses 1, 2 and 3 (online supplementary table S4).

### Interaction between 4CMenB and routine vaccines

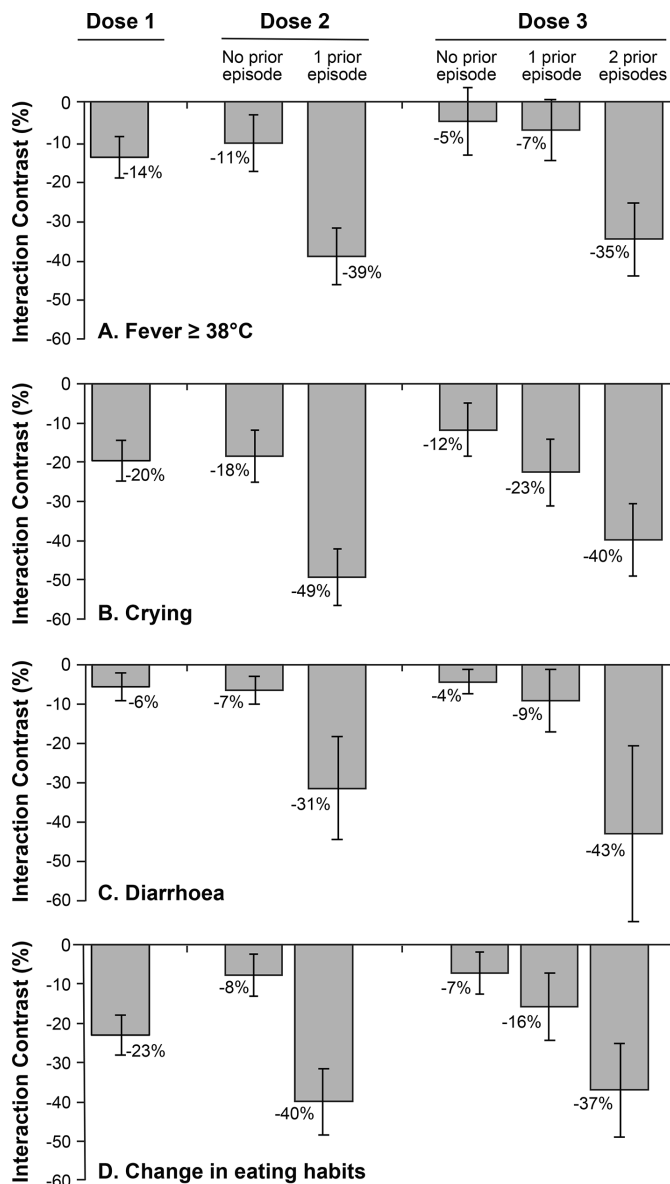
Compared with separate visits, co-administration of 4CMenB and routine vaccines resulted in an overall reduction in episodes of fever ≥38°C (75% [95% CI 74% to 76%] vs 86% [95% CI 82% to 89%], figure 1A) but an increased incidence of fever ≥39°C (18% [95% CI 17% to 19%] vs 14% [95% CI 12% to 15%], figure 1B) and of fever ≥38°C lasting >1 day (33% [95% CI 32% to 34%] vs 23% [95% CI 21% to 25%], figure 1C). For



**Figure 1** Cumulative incidence of adverse events following immunisation (dose 1–3 administered before 12 months of age). 4CMenB, four-component meningococcal serogroup B vaccine; AEFIs, adverse events following immunisations.

systemic AEFIs other than fever and 4CMenB-tenderness, co-administration always reduced AEFI cumulative incidence (including moderate/severe AEFIs and AEFI with duration >1 day, [figure 1A–C](#)). The AEFI reduction resulting from co-administration was greater in infants with a prior AEFI compared with those without

([figure 2](#)). Following doses 2 and 3, the estimated ICs in infants with prior AEFIs varied from  $-7\%$  (95% CI  $-15\%$  to  $1\%$ ) to  $-39\%$  (95% CI  $-47\%$  to  $-32\%$ ) for fever,  $-23\%$  (95% CI  $-31\%$  to  $-14\%$ ) to  $-49\%$  (95% CI  $-57\%$  to  $-42\%$ ) for crying,  $-16\%$  (95% CI  $-24\%$  to  $-7\%$ ) to  $-40\%$  (95% CI  $-48\%$  to  $-31\%$ ) for change in eating



**Figure 2** Interaction contrast for dose 1–3 administered before 12 months of age evaluating the impact of co-administration in children who previously had the same AEFI or not. AEFI, adverse events following immunisation.

habits and  $-9\%$  (95% CI  $-17\%$  to  $-1\%$ ) to  $-43\%$  (95% CI  $-65\%$  to  $-21\%$ ) for diarrhoea (figure 2).

### Risk of AEFI recurrence

For co-administration or separate visits, the overall risk of AEFI increased with the number of prior episodes. As an example, following dose 2, the overall risk of fever on days 1 and 2 was of 48% in those who had no fever at dose 1 and 79% in those with fever at dose 1 (table 2). Following dose 3, this risk was 23% in those without fever at the previous two doses but 44% and 74% in infants with one and two prior episodes of fever, respectively. At dose 4, it was 25%, 29%, 45% and 60% in infants with zero, one, two and three prior episodes of fever, respectively. A similar pattern of increasing recurrence with the number of prior episodes was observed for all other AEFIs and across all vaccination

groups (table 2). The adjusted comparison of cumulative incidence of AEFIs also showed the risk to increase with the number of prior episodes (table 3). The likelihood and severity of recurrent AEFIs also corresponded to the severity of the prior AEFI, but did not worsen with recurrence (online supplementary table S5). Most recurrences were less or equally severe to the preceding event (online supplementary table S5) and duration was comparable (data not shown). At doses 3 and 4, a trend analysis of the rank of the prior AEFI showed that recurrence was more likely when the previous AEFI episode occurred with the most recent prior dose in the series (online supplementary figure S2). At stage 2, the pattern of AEFI recurrence was similar between infants who received their first dose of 4CmenB at 2 months and those receiving their first two doses of 4CmenB at 12 months of age or more (online supplementary table S6).

### DISCUSSION

This study indicates that co-administration of 4CmenB and routine vaccines reduced the AEFI risk compared with the cumulative AEFI risk across separately administered vaccines. This reduction in AEFI risk among children co-administered versus those given the vaccines separately was greater in infants with than without prior AEFI(s) and increased with the number of prior AEFIs. Infants with a prior AEFI history are at significantly higher risk of presenting the same AEFI with subsequent vaccinations, but recurrent episodes are not usually accompanied by increased severity. The rate of AEFI recurrence is proportional to the number of prior events and is greater when the previous event occurred with the most recent prior dose in the series.

When the reactogenicity reported with co-administration of two vaccines exceeds that of the individual reactogenicity of each vaccine at separate visits, it is often interpreted as evidence of synergistic interaction between products causing more AEFIs. In fact, interaction can only be properly assessed using the IC, which showed that the sum of AEFIs in separate visits was greater than with co-administration. While co-administration increased the peak temperature and duration of fever, it was reassuring to note that less than 1% of infants experienced fever  $\geq 40^{\circ}\text{C}$  and fever had an average duration of 2 days. The higher temperature was not accompanied by increase in other systemic AEFIs and the clinical significance of an increase of  $\sim 5\%$  for fever  $\geq 39^{\circ}\text{C}$  and  $\sim 10\%$  for fever lasting  $>1$  day with co-administration is uncertain. As co-administration slightly increased the incidence ( $+11\%$ ) and severity ( $+7\%$ ) of 4CmenB-tenderness, prophylactic analgesics/antipyretics might be considered to reduce AEFI occurrence or recurrence; however, caution is required as they may also impair immunogenicity.<sup>18–21</sup> The reason explaining why co-administration was associated with a greater reduction (IC) of AEFIs in individuals who had previous episode(s) of the same AEFI is unclear. The higher risk of AEFI in children with previous episodes

**Table 2** Cumulative incidence of adverse events following immunisation (AEFI) in days 1 and 2 in children who did or did not previously have the same AEFI at prior doses

|  | Doses 1–3     |           | Dose 1*             |                            | Dose 2*             |                                     | Dose 2*                               |                     | Dose 3               |                       | Dose 3              |                      | Dose 4                |                     | Dose 4               |                       |                         |
|--|---------------|-----------|---------------------|----------------------------|---------------------|-------------------------------------|---------------------------------------|---------------------|----------------------|-----------------------|---------------------|----------------------|-----------------------|---------------------|----------------------|-----------------------|-------------------------|
|  | Overall n (%) | n (%)     | No prior AEFI n (%) | Prior AEFI at dose 1 n (%) | No prior AEFI n (%) | One prior AEFI at dose 1 or 2 n (%) | Two prior AEFIs at dose 1 and 2 n (%) | No prior AEFI n (%) | One prior AEFI n (%) | Two prior AEFIs n (%) | No prior AEFI n (%) | One prior AEFI n (%) | Two prior AEFIs n (%) | No prior AEFI n (%) | One prior AEFI n (%) | Two prior AEFIs n (%) | Three prior AEFIs n (%) |
| <b>Fever ≥ 38°C</b>                          |               |           |                     |                            |                     |                                     |                                       |                     |                      |                       |                     |                      |                       |                     |                      |                       |                         |
| Overall                                      | 10366 (62)    | 3576 (63) | 975 (48)            | 2790 (79)                  | 238 (23)            | 740 (44)                            | 2047 (74)                             | 17 (25)             | 55 (29)              | 202 (45)              | 511 (60)            |                      |                       |                     |                      |                       |                         |
| 4CMenB                                       | 794 (43)      | 312 (49)  | 111 (36)            | 174 (58)                   | 63 (27)             | 96 (56)                             | 101 (46)                              | 267 (59)            |                      |                       |                     |                      |                       |                     |                      |                       |                         |
| Routine¶                                     | 2004 (43)     | 657 (41)  | 359 (39)            | 434 (67)                   | 201 (35)            | 245 (57)                            | NA                                    | NA                  | NA                   | NA                    |                     |                      |                       |                     |                      |                       |                         |
| Co-administration                            | 7568 (75)     | 2607 (76) | 505 (64)            | 2182 (85)                  | 92 (33)             | 476 (54)                            | 1706 (79)                             | 7 (22)              | 35 (32)              | 101 (44)              | 244 (62)            |                      |                       |                     |                      |                       |                         |
| <b>Crying</b>                                |               |           |                     |                            |                     |                                     |                                       |                     |                      |                       |                     |                      |                       |                     |                      |                       |                         |
| Overall                                      | 8679 (52)     | 3201 (57) | 797 (33)            | 2238 (71)                  | 248 (16)            | 672 (40)                            | 1523 (69)                             | 31 (11)             | 83 (25)              | 154 (37)              | 290 (56)            |                      |                       |                     |                      |                       |                         |
| 4CMenB                                       | 848 (46)      | 313 (50)  | 101 (33)            | 205 (68)                   | 38 (19)             | 75 (38)                             | 116 (58)                              | 13 (9)              | 40 (23)              | 75 (35)               | 145 (56)            |                      |                       |                     |                      |                       |                         |
| Routine¶                                     | 1598 (34)     | 595 (37)  | 256 (26)            | 330 (57)                   | 88 (12)             | 150 (30)                            | 179 (55)                              | NA                  | NA                   | NA                    | NA                  |                      |                       |                     |                      |                       |                         |
| Co-administration                            | 6233 (62)     | 2293 (67) | 440 (40)            | 1703 (75)                  | 122 (19)            | 447 (45)                            | 1228 (72)                             | 18 (13)             | 43 (26)              | 79 (39)               | 145 (56)            |                      |                       |                     |                      |                       |                         |
| <b>Diarrhoea</b>                             |               |           |                     |                            |                     |                                     |                                       |                     |                      |                       |                     |                      |                       |                     |                      |                       |                         |
| Overall                                      | 2460 (15)     | 910 (16)  | 578 (12)            | 313 (35)                   | 337 (8)             | 203 (17)                            | 119 (39)                              | 98 (10)             | 73 (19)              | 38 (28)               | 14 (45)             |                      |                       |                     |                      |                       |                         |
| 4CMenB                                       | 220 (12)      | 82 (13)   | 55 (10)             | 26 (33)                    | 34 (7)              | 12 (11)                             | 11 (42)                               | 44 (9)              | 37 (18)              | 18 (29)               | 4 (29)              |                      |                       |                     |                      |                       |                         |
| Routine¶                                     | 569 (12)      | 196 (12)  | 143 (10)            | 69 (35)                    | 88 (7)              | 46 (17)                             | 27 (40)                               | NA                  | NA                   | NA                    | NA                  |                      |                       |                     |                      |                       |                         |
| Co-administration                            | 1671 (16)     | 632 (18)  | 380 (14)            | 218 (35)                   | 215 (9)             | 145 (19)                            | 81 (38)                               | 54 (11)             | 36 (20)              | 20 (28)               | 10 (59)             |                      |                       |                     |                      |                       |                         |
| <b>Change in eating habits</b>               |               |           |                     |                            |                     |                                     |                                       |                     |                      |                       |                     |                      |                       |                     |                      |                       |                         |
| Overall                                      | 6188 (37)     | 2375 (42) | 742 (23)            | 1241 (53)                  | 451 (19)            | 663 (37)                            | 717 (58)                              | 116 (22)            | 155 (34)             | 170 (48)              | 120 (56)            |                      |                       |                     |                      |                       |                         |
| 4CMenB                                       | 625 (34)      | 269 (43)  | 66 (19)             | 126 (48)                   | 43 (15)             | 57 (29)                             | 64 (52)                               | 62 (23)             | 73 (32)              | 97 (52)               | 56 (53)             |                      |                       |                     |                      |                       |                         |
| Routine¶                                     | 1217 (26)     | 458 (29)  | 192 (17)            | 215 (47)                   | 132 (14)            | 121 (28)                            | 100 (47)                              | NA                  | NA                   | NA                    | NA                  |                      |                       |                     |                      |                       |                         |
| Co-administration                            | 4346 (43)     | 1648 (48) | 484 (28)            | 900 (55)                   | 276 (22)            | 485 (41)                            | 553 (62)                              | 54 (21)             | 82 (36)              | 73 (44)               | 64 (59)             |                      |                       |                     |                      |                       |                         |
| <b>Tenderness (at 4CMenB injection site)</b> |               |           |                     |                            |                     |                                     |                                       |                     |                      |                       |                     |                      |                       |                     |                      |                       |                         |
| Overall                                      | 7620 (64)     | 2641 (65) | 572 (42)            | 1963 (76)                  | 215 (27)            | 648 (54)                            | 1581 (81)                             | 94 (39)             | 153 (57)             | 294 (74)              | 567 (88)            |                      |                       |                     |                      |                       |                         |
| 4CMenB                                       | 1013 (55)     | 376 (59)  | 85 (35)             | 244 (66)                   | 34 (22)             | 94 (46)                             | 180 (75)                              | 46 (37)             | 82 (59)              | 152 (78)              | 284 (86)            |                      |                       |                     |                      |                       |                         |
| Co-administration                            | 6607 (66)     | 2265 (66) | 487 (43)            | 1719 (77)                  | 181 (29)            | 554 (56)                            | 1401 (82)                             | 48 (42)             | 71 (55)              | 142 (70)              | 283 (89)            |                      |                       |                     |                      |                       |                         |

\*Excludes children who have received their first two doses of 4CMenB at ≥ 12 months of age.

†One prior AEFI at dose 1, 2 or 3.

‡Two prior AEFIs at doses 1 and 2, 1 and 3 or 2 and 3.

§Three prior AEFIs at doses 1, 2 and 3.

¶At dose 1, 2 and 3, the routine vaccines are DTaP-IPV-Hib-HepB and PCV7, and at dose 4, the routine vaccine is MMRV.

‡‡4CMenB, four-component meningococcal serogroup B vaccine; DTaP-IPV-Hib-HepB, hexavalent combined diphtheria-tetanus-acellular pertussis-inactivated polio-Haemophilus influenzae type b-hepatitis B vaccine; MMRV, measles-mumps-rubella-varicella vaccine; NA, not applicable (at dose 4, the routine vaccine was MMRV, which was administered once); PCV7, seven-valent pneumococcal conjugate vaccine.

**Table 3** Adjusted risk ratios comparing the cumulative incidence of adverse events following immunisation (AEFI) in days 1 and 2 in children who did or did not previously have the same AEFI\*

|                     | Risk ratio (95% CI) |                     |                     |                         |                                       |
|---------------------|---------------------|---------------------|---------------------|-------------------------|---------------------------------------|
|                     | Fever $\geq$ 38°C   | Crying              | Diarrhoea           | Change in eating habits | Tenderness at 4CMenB's injection site |
| <b>Dose 2</b>       |                     |                     |                     |                         |                                       |
| No prior AEFI       | Reference           | Reference           | Reference           | Reference               | Reference                             |
| AEFI at dose 1      | 1.34 (1.27 to 1.41) | 1.56 (1.48 to 1.66) | 2.51 (2.16 to 2.69) | 1.74 (1.63 to 1.87)     | 1.79 (1.67 to 1.91)                   |
| <b>Dose 3</b>       |                     |                     |                     |                         |                                       |
| No prior AEFI       | Reference           | Reference           | Reference           | Reference               | Reference                             |
| One prior AEFI†     | 1.72 (1.52 to 1.95) | 2.30 (2.04 to 2.60) | 2.14 (1.83 to 2.51) | 1.80 (1.63 to 1.98)     | 1.96 (1.73 to 2.22)                   |
| Two prior AEFIs‡    | 2.48 (2.21 to 2.79) | 3.06 (2.73 to 3.45) | 4.15 (3.52 to 4.89) | 2.45 (2.23 to 2.68)     | 2.85 (2.54 to 3.21)                   |
| <b>Dose 4</b>       |                     |                     |                     |                         |                                       |
| No prior AEFI       | Reference           | Reference           | Reference           | Reference               | Reference                             |
| One prior AEFI§     | 1.16 (0.74 to 1.81) | 2.18 (1.52 to 3.13) | 1.87 (1.43 to 2.44) | 1.52 (1.26 to 1.83)     | 1.41 (1.20 to 1.66)                   |
| Two prior AEFIs¶    | 1.81 (1.20 to 2.71) | 3.03 (2.17 to 4.25) | 2.75 (2.03 to 3.72) | 1.97 (1.66 to 2.35)     | 1.58 (1.37 to 1.83)                   |
| Three prior AEFIs** | 2.28 (1.53 to 3.40) | 3.99 (2.89 to 5.52) | 4.02 (2.88 to 5.60) | 2.29 (1.92 to 2.72)     | 1.74 (1.51 to 2.01)                   |

\*The risk ratios were adjusted for administration of prophylactic analgesics/antipyretics and vaccination group.

†One prior AEFI at dose 1 or 2.

‡Two prior AEFIs at doses 1 and 2.

§One prior AEFI at dose 1, 2 or 3.

¶Two prior AEFIs at doses 1 and 2, 1 and 3 or 2 and 3.

\*\*Three prior AEFIs at doses 1, 2 and 3.

4CMenB, four-component meningococcal serogroup B vaccine.

provides more room for reduction but this is unlikely to fully explain this observation.

The greater AEFI risk in infants with a prior history that we observed applied to all AEFIs and vaccination groups that we assessed and has also been reported in other studies on influenza, DTaP-containing and DTwP-containing vaccines.<sup>22–27</sup> The exact mechanistic pathway triggered by the vaccine component and causing an AEFI likely varies with each specific AEFI and is often not well known. In individuals with underlying biological or immunological characteristics that gave rise to a first AEFI episode, it should not be a surprise to see recurrences on re-immunisation with the same trigger. Despite their increased risk of AEFI, it is reassuring that infants with prior events do not generally experience AEFI of greater severity at recurrence.

This is the first study to evaluate AEFI recurrence following administration of 4CMenB with or without routine vaccines. Studies involving the same vaccine combinations are not otherwise available in the published literature. In previous studies with other vaccines, the estimated risks of AEFI recurrence were variable, likely due in part to differences in vaccine(s) and populations analysed (eg, general population, patients referred to special immunisation clinics, infants or adults).<sup>22–25</sup> However, similar to this analysis, all previous studies suggest that re-immunisation is safe in most patients with a prior AEFI. The risk of AEFI recurrence is of substantial interest to parents and providers struggling with the decision whether

or not to re-immunise. The context that the current study provides in quantifying and comparing the risk of recurrence by vaccine regimen, taking into account cumulative risks across separate administrations, as well as the number and chronological rank of prior events might be relevant for other investigators to consider in presenting findings from future RCTs.

This study has some limitations. The analysis included common but not rare AEFIs (eg, allergic-like events), which may have different risk of recurrence or severity. The analysis was limited to infants and may not apply to adolescents and young adults who receive 4CMenB.<sup>2 6 28 29</sup> While it is possible that parents of a child with an AEFI may be more likely to report the same AEFI at subsequent immunisations, such observer bias is unlikely given that the effect was also present on measurable AEFIs, such as fever. When analysing moderate/severe AEFIs, our results mostly apply to moderate AEFIs as few were actually severe. While the risk interval design analyses only vaccinated subjects, thus minimising bias due to differences between vaccinated and unvaccinated individuals, its validity relies on the accurate choice of the at-risk and control periods. In this study, the at-risk and control periods were defined a priori based on the three RCTs' published results and were further confirmed during descriptive analyses. Also, we inserted a washout period between the at-risk and control periods to minimise carry-over effects. The sensitivity analyses gave similar results to the main analysis (not shown) suggesting an appropriate choice of at-risk and



control periods. Finally, infants were randomly assigned to the various vaccination groups, thus ensuring an even distribution of unmeasured confounders given the large sample size.

The successful implementation of vaccine programmes depends on many factors including patient/parent acceptability of the reactogenicity profile. The comparative reactogenicity of vaccine co-administration should be in relation to that of the cumulative reactogenicity that would otherwise accrue across separate visits to properly present, interpret and understand the complete reactogenicity profile. However, we do not know if parents prefer co-administration resulting in high fever rate during fewer visits over more separate visits with lower rate of fever. AEFIs may also have different implications at different ages. For example, a 2-month-old with irritability and high fever is more likely to be brought to the emergency room and to have a septic screen than an older child. Finally, the stretching out of the immunisation schedule by opting for separate immunisations leaves children unprotected for a longer time.

## CONCLUSION

Overall, 4CMenB and routine infant vaccine(s) do not interact to increase reactogenicity when co-administered. Infants with a prior AEFI history are at higher risk of presenting the same AEFI at subsequent vaccinations, especially if the last episode was associated with the most recent prior dose. However, recurrent AEFIs are not generally associated with increased severity. Finally, it should be the standard of practice to assess the risk of AEFI recurrence when evaluating the reactogenicity of vaccines requiring several doses.

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