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Post-licensure observational safety study after meningococcal B vaccine 4CMenB (*Bexsero*) vaccination within the routine UK immunisation program

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ABSTRACT

The study investigated the safety of 4-component meningococcal serogroup B vaccination (4CMenB) in routine care. 4CMenB exposure and seizures, febrile seizures and Kawasaki disease were identified from The Health Improvement Network (THIN) database of UK electronic primary healthcare records, 2015–2018. A self-controlled case series analysis was completed. Anaphylaxis, Guillain-Barré syndrome and acute disseminated encephalomyelitis were secondary outcomes.

A total of 107,231 children aged 1–18 months received ≥1 doses of 4CMenB vaccination. Most 4CMenB exposure (93%) was on the same day as other vaccines within a complete national immunisation program stage. With day 0 as day of vaccination, 43 seizures occurred in days 0–6 after 239,505 doses, and 23 febrile seizures occurred in days 0–6, and 4 Kawasaki disease cases in days 1–28 after 194,929 4CMenB doses. Adjusted incidence rate ratios including all 4CMenB exposures were 1.43 (95%CI: 1.02–2.02) for seizures and 1.72 (95%CI: 1.08–2.75) for febrile seizures. There were insufficient cases to model Kawasaki disease, and no cases of the secondary outcomes in risk periods when they may be associated with the vaccination.

This study shows few cases of the outcomes after vaccination including 4CMenB with an increased risk of seizures and febrile seizures. It is not possible to attribute the finding to one specific vaccination as the majority of 4CMenB was given with other vaccinations.

Trial registration: NA.

1. Introduction

Meningococcal disease is caused by the bacterium *Neisseria meningitidis* and is associated with considerable mortality and morbidity [1] with young children and teenagers at highest risk of the disease [2]. The 4-component meningococcal serogroup B vaccine (4CMenB; *Bexsero*, GSK) was the first multicomponent meningococcal serogroup B vaccine and was included in the UK National Immunisation Programme (NIP) from September 2015 (Table 1) for infants born after July 2015 with a catch-up programme for children born from 1st May 2015 [2].

Increased rates of fever [3] and cases of febrile seizures [4] after 4CMenB have been reported in some individual clinical trials or meta-analyses when compared to other vaccinations. Cases of possible or confirmed Kawasaki disease were reported in the 4CMenB clinical studies however a relationship with the vaccination could not be established [5].

The purpose of this study was to assess the safety of 4CMenB vaccination within UK routine care with regards to three primary

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Table 1
Age-sex distribution of the descriptive cohort at 4CMenB vaccination, in total and by NIP stage (at September 2015), data to 31st December 2018.

	N	Age (months) Median (IQR); range	% male[†]
Children with:			
≥1 4CMenB vaccination[*]	107,231	2.20 (1.84, 2.99); 1.05–18.05	51.3
NIP stage 1: 5-in-1, PCV, rotavirus, 4CMenB (1st dose)	79,038	2.04 (1.78, 2.30); 1.05–14.10	51.1
NIP stage 3: 5-in-1, PCV, 4CMenB (2nd dose)	83,486	4.14 (3.81, 4.64); 2.04–18.05	51.1
NIP stage booster: Hib, Men C, PCV, MMR, 4CMenB (3rd dose)	59,294	12.75 (12.33, 13.35); 2.43–18.08	51.0
Outside a standard NIP stage	17,687	4.44 (3.25, 12.49); 1.05–18.05	51.9

4CMenB, 4-component meningococcal serogroup B vaccine; 5-in-1, diphtheria-tetanus-pertussis/polio/Haemophilus influenzae type b (and hepatitis B added in autumn 2017); Hib, Haemophilus influenzae type b; IQR, interquartile range; MenC, meningitis C; MMR, measles-mumps-rubella; NIP, National Immunisation Programme; PCV, 13-valent pneumococcal vaccine.

[*] Population for the descriptive analysis, age at first 4CMenB vaccination in observation period. Recommended ages in NIP: Stage 1, 2 months; Stage 3, 4 months; Booster 12–13 months.

[†] Unique children.

(seizures, febrile seizures and Kawasaki disease) and three secondary (acute disseminated encephalomyelitis [ADEM], Guillain-Barré syndrome [GBS], and anaphylaxis) outcomes.

2. Methods

2.1. Data source

The database population comprised 460 practices which contributed data to The Health Improvement Network (THIN) database of primary care electronic healthcare records for all or part of the study period (1st May 2015 to 31st December 2018 inclusive) (Supplementary table 1). THIN includes demographics, clinical events, prescriptions, and preventive medicine routinely recorded against date within individual patient records. Secondary care diagnoses and deaths are captured because of the structure of the UK National Health Service. Medical events, automatically coded using the Read coding system [6], can be supplemented with unstructured text. Vaccination details are recorded in specific fields. THIN covers approximately 5% of the UK population (2015 figures) and has been shown to be generalizable to the UK population although with slightly fewer people aged under 20 years [7]. The study used THIN version IMRD 1809, and IMRD 1801 for the May 2018 data cut.

THIN has a multicentre ethics approval for observational studies (Southeast MREC, ref: 03/01/073). This study was approved by the THIN Scientific Review Board (reference 11THIN028).

2.2. Setting and participants

The study population included children permanently registered at a practice in the database population when aged between 1 and 18 months on or after 1st May 2015, and who received one or more vaccination with 4CMenB during an observation period.

An observation period was set to allow appropriate evaluation of exposure (vaccine administration) and outcome. Observation for each child started at the most recent of four dates: 1st May 2015, (to include pre-exposure data on children in the catch-up), date of birth plus one month (as part of the first month of life is usually spent in secondary care), transfer-in from another practice plus three months (prevalent events can be recorded at post-registration), or data quality assurance dates (based on use of Vision software and Acceptable Mortality Reporting Dates [8] and further review). Observation ended at the earliest of four dates: the month of birth plus 18 months, deregistration (including death and moving practice), last data collection from the practice, or the end of the study period for that outcome.

Seizure analyses included the overall study period to 31st December 2018. All other outcomes used unstructured text in case identification. This became unavailable under the European General Data Protection Regulation [9] in May 2018. The study period for outcomes other than seizure was therefore truncated at the last data cut which included the unstructured text used in case identification (May 2018). More than one observation period was possible if a child left and then re-joined the same practice (0.01% of the study population). When more than one transfer-out date was recorded for an observation the earliest was used to calculate the observation period (0.8% of the study population). The self-controlled case series (SCCS) population for each outcome comprised a sub-group of the study population who had that outcome during their observation.

2.3. Variables

All variables were identified from THIN. 4CMenB vaccination was defined as a coded entry in the Additional Health Data (AHD), medical or therapy files. A second 4CMenB vaccination of the same NIP stage within 28 days was not included (0.1% of exposures).

Seizures, febrile seizures and Kawasaki disease were primary outcomes, ADEM, GBS, and anaphylaxis were secondary outcomes. A seizure was defined as a Read code for seizure or convulsion in Medical or AHD files during observation (see Supplementary table 2 for all case definitions and Supplementary table 3 for codes). Febrile seizures were a sub-set of seizures defined as a specific code or evidence of a concomitant fever, without previous diagnosis or treatment for epilepsy or other relevant concurrent central nervous system disease [10]. Date of onset was the date of the seizure code. Seizure records within 30 days of a previous record were treated as the same episode as these were assumed to be follow-up visits rather than incident events.

Possible Kawasaki disease was identified by specific code in Medical or AHD files or 'kawasa' in unstructured text [11] during observation plus two months to capture late diagnoses. These episodes were adjudicated against a case definition and assigned a date of onset by authors (PP, PH, GH) (Supplementary table 2 for case definition and date of onset rules) when blinded to exposure dates. Adjudication was based on the electronic health record including unstructured text. Additional information was requested from the practice via a third party and the record re-reviewed if required. When the initial reviews differed, the case was discussed until agreement was reached. Episodes of ADEM, GBS, and anaphylaxis were identified by code or text and adjudicated using similar procedures as those for Kawasaki disease. Deaths were reviewed for a cause that was a study outcome. Date of birth was assumed to be 16th of the month of birth as THIN includes only the month for children. Other NIP vaccinations were identified from the AHD file.

Two validation steps were completed. A questionnaire was sent to the practices of a random sample of 100 children with a seizure dated in the first study year and registered at practices which had agreed to respond to questionnaires. Information was requested on the date of any seizures and if these were febrile. Positive predictive value (PPV) was computed using the questionnaire as the 'gold standard'. The second validation was completed when unstructured text became unavailable, to understand the effect of losing

unstructured text. The original adjudication of outcomes with unstructured text to the May 2018 data cut was treated as the gold standard. The adjudication of the outcomes was repeated without the unstructured text and the two sets of results compared with validation indices estimated.

2.4. Study size

THIN comprises patient records from a set number of practices. Consequently, the study size can only be varied by increasing its duration. The number of cases and so the number of required study years required to detect an incidence rate ratio (IRR) of 3 and 10 with 80% power and a 0.05 alpha was estimated from published background incidence rates and assuming three exposures to 4CMenB per 35,000 newborns per annum (from previous years in the data source) [12]. The study size for seizures and febrile seizures was estimated as 88 (IRR 3) and 12 (IRR 10) cases which would be expected to occur within 1 year observation for both outcomes. For Kawasaki disease sample size and duration was estimated as 32 cases and 6 years (IRR 3) and 7 cases and 1 year (IRR 10). For secondary outcomes, an SCCS was planned if at least one episode was identified in the risk period, and the number of outcomes was that required to detect an IRR of 10 with 80% power.

2.5. Statistical methods

The risk period for each outcome was defined as the number of days following vaccination during which an outcome would be expected to occur if causally associated with the vaccine (Fig. 1). The risk window were assigned based on a review of the literature during development of the protocol (http://www.encepp.eu/encepp/viewResource.htm?id=33532). A pre-exposure period was also defined for each outcome as that period of time after an outcome when a vaccination may be delayed and so a period when the incidence of outcomes will be low. Baseline time was outside these two periods and was when the vaccination was assumed to have no effect on the incidence of the outcome. The incidence rate of each study outcome was estimated including all episodes of an outcome in the specific risk period. The incidence pre- and post-vaccination was plotted. Post-vaccination incidence was plotted against time intervals between the start of the risk period and the earliest of the next exposure, 112 days post-exposure or observation end. Pre-vaccination plots start on the most recent of the previous exposure, 112 days pre-exposure or observation start, and end on the day before the risk period. One outcome can therefore be depicted in both plots if it is after one exposure but before subsequent exposures.

In an SCCS analysis IRRs compared the rate of events during exposed periods of time (risk period) with the rate during other observed time periods (baseline or control time) [13]. The SCCS method is derived from the cohort method and relies on intra-person comparisons in a population of individuals who have both the outcome and exposure of interest. This method removes the potential confounding effect of characteristics that vary between individuals, such as risk factors for disease. Timelines and risk periods for the SCCS are given in Fig. 1. Day 0 was the day of exposure. All exposures to 4CMenB were treated as equivalent risk periods.

Conditional Poisson regression was used to calculate IRRs and 95% confidence intervals (95%CIs) comparing the incidence rate of the outcome in the outcome specific risk period with that during in the baseline period. Time-varying covariates age (by month), year of vaccination and respiratory illness season (by quarter) were included in the model. The pre-exposure period was treated separately in the model, as vaccination may be delayed after an outcome, and so in order to satisfy the SCCS method assumption that outcomes do not influence the chance of future exposure (Fig. 1). The primary analysis included the first episode and primary risk period. If a risk period from one exposure overlapped with the next pre-exposure period, this time only included the risk period. If two risk periods overlapped, (for example, if vaccinations were given within 28 days of each other), the overlapping time was included in the first risk period only. Time and outcomes for an exposure before observation were excluded (for example if a child registered at a practice shortly after vaccination). The SCCS for seizures was repeated by NIP stage. NIP stage was defined as a record of receiving all vaccinations in the NIP (as of September 2015) [2] on the same day (Table 1), regardless of age, vaccination history, or additional vaccinations. Adjustment of the individual NIP stage model was not stable for febrile seizures (due to low numbers of outcomes after some NIP stages) so NIP booster, and a combination of all other exposures in one group was modelled.

Several sensitivity analyses were completed. As per the protocol, SCCS models with a longer risk period (seizures), including observation to 31st December 2018 (febrile seizures and Kawasaki disease) and including all new episodes rather than first episodes (febrile seizures) were analysed. A 'new episode' was defined as a gap of 30 or more days since a previous seizure code. Post-hoc sensitivity analyses (further defined after review of results) added NIP stage 2 to the NIP stage SCCS for seizures and, separately, excluded exposures with concomitant Hepatitis B vaccine (HepB). HepB was added to NIP stages 1, 2 and 3 during the study period. The analysis was completed using SAS Enterprise Guide Version: 7.13 HF3 for Windows [14].

3. Results

The overall study included 239,505 doses of 4CMenB with 194,929 in the observation period to May 2018 (Fig. 2). The majority of exposures (93%) were on the same day as other vaccinations, as part of a complete NIP stage (Table 1). There were 816 episodes of seizures in 695 children, and 399 episodes of febrile seizures in 370 children. Fourteen episodes of anaphylaxis and 9 of Kawasaki disease of 605 adjudicated events (366 anaphylaxis, 105 Kawasaki disease, 3 GBS, and 38 ADEM and 93 deaths, 29 agreed after initial difference) both fulfilled the case definition and were dated within observation. No second episode of an outcome was identified for any child. The incidence rate in the primary risk period was 9.4 per 1000 person-years (95%CI 6.8–12.6) for seizures, 6.2 per 1000

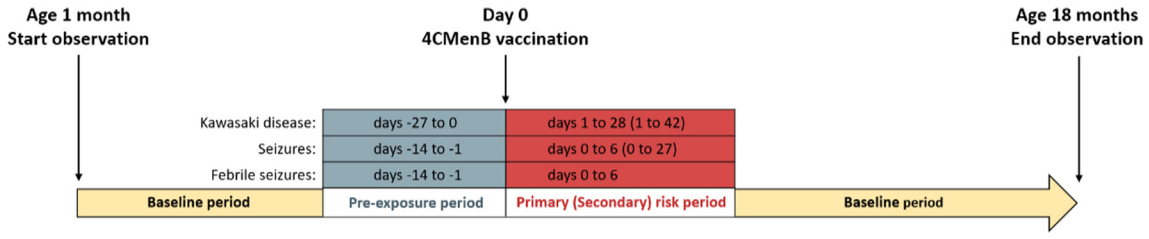

Fig. 1. Illustrative self-controlled case series observation period.

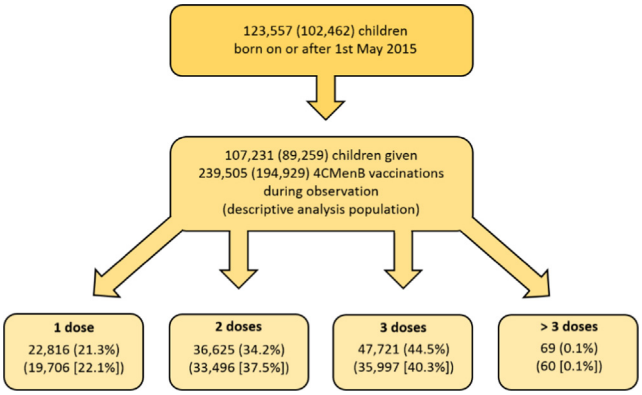

Fig. 2. Identification of the study populations and the number of 4CMenB doses recorded per child: to 31st December 2018 (May 2018 data cut) *Children may have had additional 4CMenB vaccinations outside their study observation period. 4CMenB, 4-component meningococcal serogroup B vaccine.

person-years (95%CI 3.9–9.3) for febrile seizures and 27.3 (95%CI 7.4–69.8) per 100,000 person-years for Kawasaki disease. In secondary risk periods the incidence rate was 7.3 (95%CI 6.1–8.7) per 1000 person-years for seizures and 23.0 (95%CI 7.5–53.6) per 100,000 person-years for Kawasaki disease. No GBS or ADEM was identified during the observation period and no anaphylaxis in the risk period. The temporal relationship between 4CMenB exposure and first outcomes is shown in Fig. 3.

In the primary SCCS analyses (Table 2) the adjusted IRR and 95% CI in the risk period for seizures and febrile seizures were above 1 (Table 3). The NIP stage analysis showed similar IRRs for seizures across stages with 95%CI above 1 only after exposure to the booster dose of 4CMenB. An increased risk of febrile seizures (95%CI above 1) was observed after the combination of stages except for the booster stage. Less than 5 episodes of Kawasaki disease in the primary risk period of 1.6 person-years and five in the baseline period of 8.0 person years were too few for an adjusted analysis.

In sensitivity analyses, although the second risk period for seizures resulted in a lower IRR the 95% CI remained above 1 and otherwise the interpretation remained unchanged (Table 4). All additional cases (<5) of Kawasaki disease in follow-up to the end of 2018 were in the baseline period. The post-hoc seizure analysis including NIP stage 2 reported similar IRRs across vaccination stages although only booster stage confidence intervals were above 1.

The PPV for identification by THIN compared to the practice questionnaire (91% return) was 80.2% (95%CI 70.2–87.6) for seizures and 84.3% (95%CI 70.9–92.5) for febrile seizures overall. This indicates that the majority of outcomes identified as seizures were in fact a seizure. The PPV for five seizures in the risk period was 60.0% (95%CI 17.0% to 92.7%) and 78.3%, (95%CI 67.6% to 86.3%) for 83 events in the baseline period. As pre-defined, no adjustment was made for outcome misclassification as there was no significant difference between groups given the small numbers. Validation indices for identification of episodes without unstructured text are given in Supplementary table 4. Episodes of Kawasaki disease and febrile seizures identified without unstructured text were identified without false positives (all PPV 100%) in both risk and baseline periods, however, sensitivity was lower. Anaphylaxis outcomes were missed when only coded entries were included (sensitivity 35.3%).

4. Discussion

This study identified few cases of seizure, febrile seizure, and Kawasaki disease, and no cases of anaphylaxis, GBS, or ADEM, directly after routine vaccination which included 4CMenB. None of the cases was fatal. The majority of 4CMenB exposure was concomitant with other NIP vaccinations. Consequently, it was not possible to differentiate whether the approximately 1.5 times increased risk of seizures and febrile seizures was due to one or other (or the combination) of routine vaccinations.

The strengths of the study are its size (239,505 4CMenB vaccinations), comparative design, and observation of events in routine care. Differential outcome misclassification cannot be ruled out for seizure outcomes as the confidence intervals surrounding the validation indices against the practice questionnaire were wide. Broad search criteria followed by adjudication for other outcomes will have minimised outcome misclassification although a bias may persist if diagnosis is more likely after exposure to a vaccination. Most seizures in the study age group are febrile [10]. However, UK clinicians don't always classify a seizure as febrile until a child is a certain age depending on local practice - one, three or six months. Febrile seizures not classified as such will have been included in the seizure category. In addition, two risk periods have been selected for the analysis of seizures; one week to reflect febrile seizures and four weeks to include other seizures. Vaccination outside the practice will not have impacted the results as the design does not include unexposed comparators. Despite the study size, no SCCS analysis was possible for Kawasaki disease and comparison between NIP stages for seizure outcomes is limited due to a lack of statistical power to estimate the IRR with precision. Differentiating between the effects of individual vaccinations in routine practice with any methodology is difficult given the recommended schedule.

This is the first investigation of seizures post-vaccination within current UK routine practice, although an increased risk of febrile seizures post-vaccination has been reported in other populations. A much higher risk of febrile seizures (IRR 23, 95%CI 5.13–100.8) following a median of four concomitant vaccinations (not including 4CMenB) was reported in US infants. UK NIP stages in the current analysis include up to nine vaccinations, and at least one at every stage has been associated with a risk of seizures individually [15–17]. Danish infants had an increased risk of febrile seizures on the day of the first and second, but not the third diphtheria/tetanus/pertussis-polio-*Haemophilus influenzae* type b (DTaP-IPV-Hib) vaccination, but found no increased risk 0–7 days after any vaccination stage [15]. The incidence of seizures doubled in days 0–59 after dose 1 of the rotavirus vaccine used in the UK [16]. An increased risk of seizures is also consistent with the effects of the measles component of measles-mumps-rubella (MMR) vaccination 7–10 days or 6–11 days [18] after exposure which is later than, or slightly overlapping, the primary risk period in our study. Our post-hoc analysis including NIP stage 2 (no 4CMenB) may indicate an increased risk of seizures across all NIP vaccination stages, however there were too few outcomes to estimate the effect with good precision. A UK population study reported similar incidences of seizures of 8.3 (95%CI 8.1–8.6) per 1000 person-years aged 2–12 months (1999–2011) [10]. The slightly higher risk of seizures when pre-exposure time and outcomes were reassigned into baseline time would be expected if the events cause a delay in vaccination (shown by the lower risk in pre-exposure periods), as this would render a small portion of the baseline time to be immortal with respect to the outcome and increase the incidence at other times.

While there were more cases of Kawasaki disease in the shorter risk period than in the baseline period, a small number of additional cases identified in the sensitivity analysis to the end of 2018 were in the baseline period demonstrating the risk of interpreting results based on small numbers. Kawasaki disease incidences in the current study are aligned (within the wide confidence intervals) from a study based on the same database

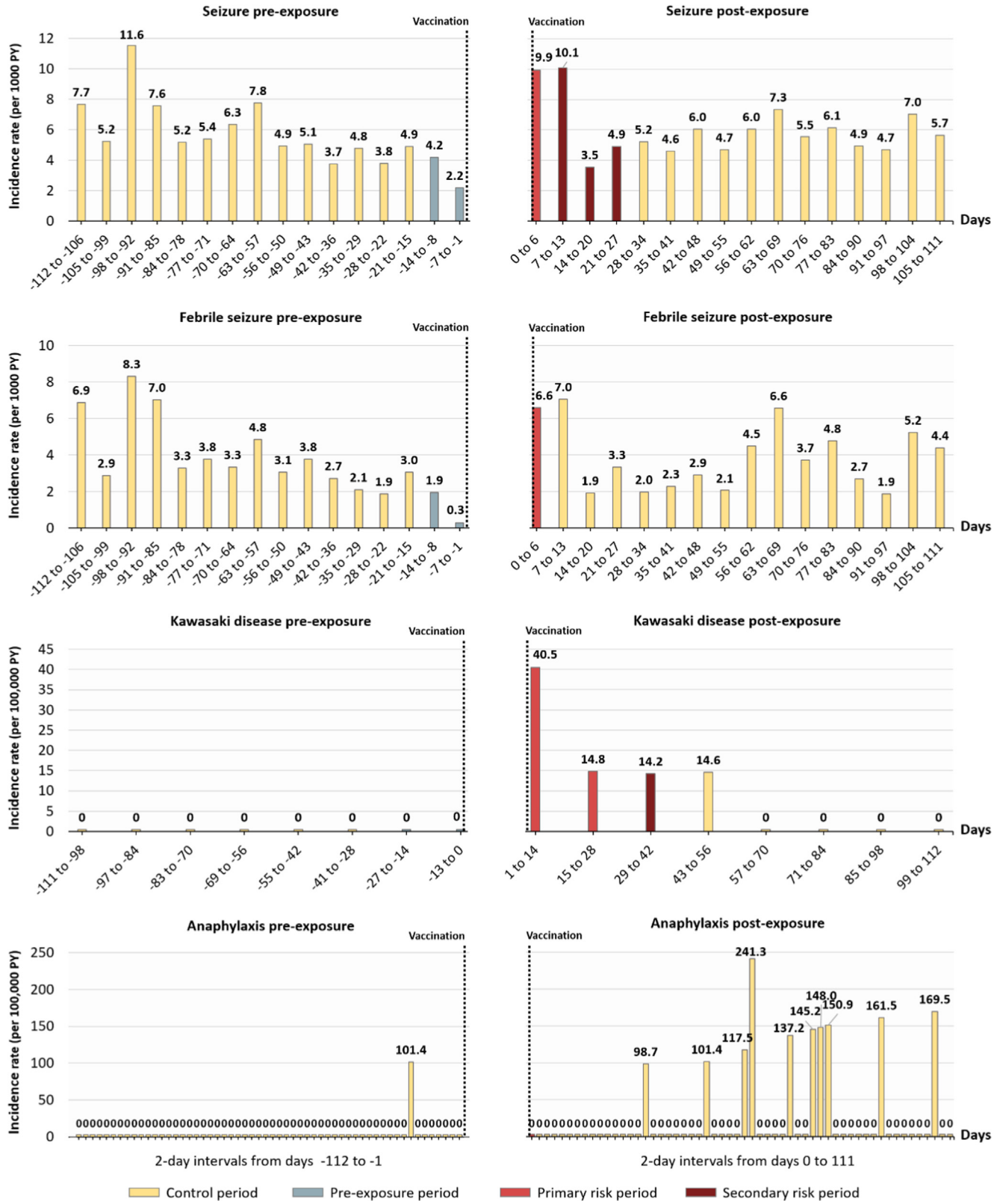

Fig. 3. Incidence of 1st outcomes in relation to 4CMenB exposure * Outcomes can be in both the pre- and post-exposure plot in relation to different exposures. Includes outcomes 4 months pre- & post-exposure only. Episodes outside this time were not plotted including 3 Kawasaki disease episodes. Seizure and febrile seizures in children with multiple study periods were excluded. Anaphylaxis horizontal axis is in 2-day intervals with post-exposure starting at day 0. 4CMenB, 4-component meningococcal serogroup B vaccine; PY, person years.

Table 2
Description of self-controlled case series primary analysis outcomes* (1st outcome).

	Seizures	Febrile seizures	Kawasaki disease
Patients (n)	695	370	9
Male (%)	51.2	54.6	33.3
Mean age at first outcome, months (SD)	11.2 (4.4)	12.4 (3.3)	6.5 (4.9)
Year of episode n (%)			
2015	16 (2.3)	NR	0 (0.0)
2016	195 (28.1)	118 (31.9)	5 (55.6)
2017	270 (38.8)	179 (48.4)	NR
2018	214 (30.8)	71 (19.2)	0 (0.0)
Season of episode n (%)			
Spring	179 (25.8)	98 (26.5)	NR
Summer	153 (22.0)	66 (17.8)	5 (55.6)
Autumn	169 (24.3)	79 (21.4)	0 (0.0)
Winter	194 (27.9)	127 (34.3)	NR

*Seizures includes data to 31st December 2018, other outcomes to a data cut in May 2018.
SD, standard deviation; NR, not reported as cell contained <5 events.

prior to 4CMenB, rotavirus and HepB vaccination introduction [19]. Moreover, a recent UK secondary care based study which assessed the effects of 4CMenB on KD separately to other vaccination exposures reported no increased risk for 4CMenB exposure (relative incidence 1.03 [95% CI 0.51–2.05] after doses 1 or 2 and 0.64 [95% CI 0.08–5.26] after dose 3) [20].

The clustering of anaphylaxis episodes from approximately 30 days after exposure is consistent with events at the age of first exposure to solid foods. Previous studies of anaphylaxis have reported no cases related to 'routine' infant and preschool vaccination in a UK and Ireland study (2008–2009) [21] and post-vaccine doses [22] in those aged under 18 years. ADEM and GBS are rare events and the finding of no episodes within the observation period is consistent with 54 cases of GBS reported in the US in 2004, [23] and an incidence of ADEM of 0.1–0.2 per 100,000 vaccinated individuals [24].

Overall, the study demonstrates the safety of 4CMenB after its inclusion in the UK routine vaccination schedule, with regard to the study outcomes. This information can be used in conjunction with effectiveness data to demonstrate the risk-benefit relationship of infant vaccination.

5. Role of the funding source

GlaxoSmithKline Biologicals SA funded this study (GSK study identifier: 205512). Bexsero is a trademark owned by or licensed to the GSK group of companies.

Author Contibutions

GCH and VA affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. GCH proposed the study design and led the study conduct with IQVIA. VA was the accountable person for the conduct of the study from the sponsor's perspective. ID and JK were responsible for the statistical analysis and DR was the accountable person from the sponsor's perspective. PTH and PP contributed to the design and, with GCH, were part of the Adjudication Committee. GCH wrote the initial manuscript draft. All authors participated in the design or implementation or analysis, and interpretation of the study and the development of this manuscript. Authors had full access to the data. All authors gave final approval before submission. GH and VA are guarantors for the study. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: GCH received payment from IQVIA for the conduct of

Table 3
Self-controlled case series primary analysis of all exposures and by complete NIP stage at which 4CMenB is given (1st outcome and primary risk period - day 0–6).

	Number of events rate ratio (95% CI)	Person years rate ratio (95%CI) †	Crude incidence	Adjusted incidence
Primary analysis-all exposures				
Seizures*				
Baseline period	627	723.5	Reference	Reference
Risk periods	39	31.6	1.37 (0.99, 1.89)	1.43 (1.02, 2.02)
Pre-exposure periods	29	57.8	0.55 (0.38, 0.81)	0.59 (0.40, 0.86)
Febrile seizures*				
Baseline period	341	380.5	Reference	Reference
Risk periods	21	16.8	1.35 (0.87, 2.10)	1.72 (1.08, 2.75)
Pre-exposure periods	8	30.8	0.28 (0.14, 0.56)	0.36 (0.17, 0.73)
SCCS by NIP stage				
Seizures*				
Baseline period	627	723.5	Reference	Reference
NIP stage 1	8	9.2	0.94 (0.47, 1.90)	1.50 (0.67, 3.36)
NIP stage 3	8	10.3	0.87 (0.43, 1.75)	1.57 (0.74, 3.33)
NIP booster	22	9.3	2.69 (1.75, 4.14)	1.57 (1.01, 2.46)
4CMenB outside NIP stages	NR	NR	0.37 (0.05, 2.65)	0.36 (0.05, 2.62)
Pre-exposure period	29	57.8	0.55 (0.38, 0.80)	0.59 (0.40, 0.87)
Febrile seizures*				
Baseline period	341	380.5	Reference	Reference
NIP stage 1, 3 and outside the NIP stages combined	6	11.9	0.55 (0.25, 1.24)	2.62 (1.09, 6.27)
NIP booster	15	4.9	3.24 (1.91, 5.50)	1.51 (0.88, 2.61)
Pre-exposure period	8	30.8	0.28 (0.14, 0.56)	0.36 (0.17, 0.73)

4CMenB, 4-component meningococcal serogroup B vaccine; CI, confidence interval; NIP, National Immunisation Programme; SCCS, self-controlled case series, NR, not reported as cell contained <5 events.
* Seizures includes data to 31st December 2018, febrile seizures to a data cut in May 2018. †Adjusted for age, season and year.

Table 4
Self-controlled case series sensitivity analyses.

	Number of events	Person years	Crude incidence rate ratio (95%CI)	Adjusted incidence rate ratio (95%CI)
All episodes of an outcome rather than 1st episodes				
Febrile seizures (day 0–6)				
Baseline period	368	378.6	Reference	Reference
Risk period	23	16.8	1.36 (0.89, 2.08)	1.83 (1.16, 2.87)
Pre-exposure period	8	0.8	0.25 (0.13, 0.51)	0.34 (0.16, 0.70)
Using risk period 2				
Seizures (day 0–27)				
Baseline period	543	630.8	Reference	Reference
Risk period	123	124.3	1.11 (0.91, 1.36)	1.29 (1.02, 1.64)
Pre-exposure period	29	57.3	0.56 (0.38, 0.81)	0.62 (0.42, 0.93)
Reassigning pre-exposure period and outcomes as baseline				
Seizures (day 0–6)				
Baseline period	656	781.3	Reference	Reference
Risk period	39	31.6	1.42 (1.03, 1.97)	1.55 (1.11, 2.18)
Febrile seizures (day 0–6)				
Baseline period	349	411.3	Reference	Reference
Risk period	21	16.8	1.44 (0.93, 2.24)	1.91 (1.20, 3.04)
Including data to 31st December 2018				
Febrile seizures (day 0–6)				
Baseline period	415	486.7	Reference	Reference
Risk period	27	21.2	1.47 (1.00, 2.18)	1.82 (1.20, 2.75)
Pre-exposure period	13	38.8	0.39 (0.22, 0.67)	0.48 (0.27, 0.85)
Excluding exposures with concomitant HepB				
Seizures (day 0–6)				
Baseline period	627	723.5	Reference	Reference
Risk period	32	26.4	1.42 (0.99, 2.03)	1.48 (1.02, 2.15)
Pre-exposure period	29	57.8	0.56 (0.38, 0.81)	0.59 (0.40, 0.87)
Febrile seizures (day 0–6)				
Baseline period	341	380.5	Reference	Reference
Risk period	18	14.9	1.32 (0.82, 2.12)	1.68 (1.02, 2.77)
Pre-exposure period	8	30.8	0.28 (0.14, 0.57)	0.36 (0.17, 0.74)
Including NIP vaccination stage 2				
Seizures (day 0–6)				
Baseline period	617	697.5	Reference	Reference
NIP stage 1 (with 4CMenB)	8	9.2	0.91 (0.45, 1.84)	1.55 (0.68, 3.51)
NIP stage 2 (no 4CMenB)	6	9.8	0.66 (0.29, 1.47)	1.40 (0.58, 3.35)
NIP stage 3 (with 4CMenB)	8	10.3	0.84 (0.42, 1.70)	1.54 (0.73, 3.26)
NIP booster (with 4CMenB)	22	9.3	2.63 (1.71, 4.05)	1.57 (1.01, 2.46)
4CMenB outside NIP stages	NR	NR	0.36 (0.05, 2.64)	0.36 (0.05, 2.62)
Pre-exposure period	33	74.0	0.48 (0.34, 0.68)	0.58 (0.40, 0.85)

4CMenB, 4-component meningococcal serogroup B vaccine; 95%CI, 95% confidence interval; HepB, hepatitis B vaccination; NIP, National Immunisation Programme, NR, not reported as cell contained <5 events.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.02.065.

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