GSK Vaccines Controlled Document

Documentum Name : EPI-MENB REC 2ND GEN (V72)-007 EPI VS GB DB (205512) V72_36OB (205512) Redacted Report (20-Feb-2020)

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In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.

The following guiding principles have been applied to the disclosure:

- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
- *Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*
- *Aggregate data will be included; with any direct reference to individual patients excluded*

**Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

PASS information

Title	Post-licensure observational safety study after meningococcal B vaccine 4CMenB (Bexsero) vaccination in routine UK care
Version identifier of the final study report	205512 [MENB REC 2ND GEN-007 EPI VS GB DB (V72_36OB)]
Date of last version of the final study report	Final: 20 February 2020
EU PAS Register Number	ENCEPP/SDPP/11728
Active substance	ATC code J07AH09, substance INNs: *Neisseria meningitidis* serogroup B recombinant proteins NHBA fusion; fHbp fusion; and NadA; and outer membrane vesicles from serogroup B strain NZ98/254.
Medicinal product	4CMenB (Bexsero)
Product reference	NA
Procedure number	NA
Marketing Authorisation Holder(s)	GSK Vaccines S.r.l.; Via Fiorentina, 1; 53100 Siena (Italy)
Joint PASS	No
Research question and objectives	The objective of this post-marketing observational study is to assess the safety of 4CMenB vaccination within the UK National Immunisation Program (NIP) with regards to three primary (all seizures, febrile seizures and Kawasaki disease) and three secondary outcomes.
Country of study	United Kingdom
Author	PPD, Independent Consultant in Pharmacoepidemiology, Grimsdyke House, London, EN5 4ND, UK

Marketing authorisation holder(s)

Marketing authorisation holder(s)	GSK Vaccines S.r.l.; Via Fiorentina, 1; 53100 Siena (Italy)
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GlaxoSmithKline Biologicals (GSK) PASS Study Report INS-BIO-PASS-1010 version 02

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1. ABSTRACT

Title

Post-licensure observational safety study after meningococcal B vaccine 4CMenB (Bexsero) vaccination in routine United Kingdom (UK) care.

Keywords

Meningitis B, vaccination, safety, seizures, Kawasaki disease

Rationale and background

4CMenB vaccine (Bexsero) is a multicomponent meningococcal serogroup B vaccine. 4CMenB was filed for registration with European Medicines Agency (EMA) in December 2010. European approval was given in January 2013 through a Centralised Procedure and 4CMenB was added to the UK National Immunisation Program (NIP) in September 2015. For infants born on or after July 2015, the vaccination is given at 2, 4 and 12-13 months of age. A catch-up program included children born from 1st May 2015 who were given three doses of 4CMenB unless the first dose was at four months when it was recommended that they received two doses. Kawasaki disease, febrile seizures and seizures were identified by EMA as potential safety concerns based on clinical trial data. Acute disseminated encephalomyelitis (ADEM), Guillain-Barré syndrome (GBS), and anaphylaxis are also included in line with events identified through clinical studies and post authorization experience as described in the Risk Management Plan. The purpose of this study is to investigate the safety of 4CMenB vaccination in routine post-marketing use in the UK (in children 1 to 18 months) as a post-authorisation safety study.

This Final Report comprises descriptive and comparative analyses of exposures and final outcomes to 31st December 2018 inclusive for seizures, and to a May 2018 data cut for other outcomes (see Section 10.2 for details of the observation periods). Six, six monthly progress reports and an Interim Report have been completed. The Interim Report was provided to the EMA on the 30 January 2018.

Research question and objectives

To assess the safety of 4CMenB vaccination within the UK NIP with regards to three primary (all seizures, febrile seizures and Kawasaki disease) and three secondary (ADEM, GBS, and anaphylaxis) outcomes.

Study design

An observational descriptive study, followed by a comparative self-controlled case series (SCCS) for primary outcomes, based on a database of UK primary care records.

Setting

The source population is patients registered with UK primary care practices. The database population is The Health Information Network (THIN) database of electronic primary healthcare records.

Subjects and study size

Descriptive analysis – The population for the descriptive analysis includes children permanently registered at a listed THIN practice when aged between one and eighteen months on or after 1st May 2015, and who received one or more vaccinations with 4CMenB during this observation period.

SCCS – The population for each outcome comprises a sub-group of the descriptive analysis population who also had a diagnosis of that outcome during their observation period for that outcome.

See Section 10.7 for study size estimations.

Variables and data sources

Data Source: THIN is an observational database of primary care electronic medical records from practices throughout the UK and covers approximately 5% of the UK population (2015 data). Details of demographics and administrative data, clinic events, prescriptions and preventive medicine are routinely recorded against date in separate files within individual patient records. Secondary care diagnoses and deaths are also captured because of the structure of the National Health Service. Medical events are automatically coded at entry using the Read coding system during the study period (1) and could be supplemented with unstructured text (to May 2018) and with electronic discharge summaries. Details of preventive medicine including vaccines, and laboratory results are included in the Additional Health Data (AHD) file. The date, type (tetanus, polio, etc.) and dose (1st, booster, etc.) of routine vaccinations are recorded in specific immunisation fields as they are administered. THIN has been shown to be generalizable to the UK population although with slightly fewer people aged under 20 years compared to the general UK population (2).

Exposure: The exposure of interest is 4CMenB vaccine administered in routine clinical practice. 4CMenB vaccination was predominantly identified from the AHD file of THIN which includes records of preventive medicine (see Section 10.4.1). This section of the practice software has specific screens for entering vaccination details as they are given. The file was searched for records of any 4CMenB vaccination. In the UK, all pre-school vaccinations are routinely given in primary care and recorded in the child's primary care record.

Outcomes: The primary outcomes were seizures, febrile seizures and Kawasaki disease. ADEM, GBS, and anaphylaxis were also included in this study. Cases were identified by searching the Medical and AHD files of THIN database.

The definition of a seizure was a record of an appropriate Read code for seizure or convulsion dated in the child's observation period. Febrile seizures were a sub-set of seizures defined as a specific code for febrile seizure or evidence of a concomitant fever, but no previous diagnosis or treatment for epilepsy or other relevant concurrent central nervous system disease (3).

The Kawasaki disease cases were identified by code and text searches. All records with a code or text term for Kawasaki disease were reviewed and classified as a case or not against a case definition by an Adjudication Committee. The case definition required a secondary care diagnosis of Kawasaki disease, or a record of a diagnosis in the primary care record if this was supported by evidence of secondary care involvement (4). A sensitivity analysis included possible cases. Cases of ADEM, GBS, and anaphylaxis were identified using the same procedure as Kawasaki disease. Case definitions and search terms have been developed with an Adjudication Committee. Details are given in the Appendix Table 1.

Other Variables: Age and sex were identified from THIN. For confidentiality reasons THIN includes the month of birth for children up to the age of 15 and the year of birth for older people. As this study only includes young children, the date of birth was assumed to be 16th of their month of birth. Other NIP vaccinations were identified from the THIN AHD file in the same manner as 4CMenB.

Results

This final report provides descriptive and SCCS analyses of exposures and study outcomes from the launch of 4CMenB in September 2015 to an end date. The analysis of seizures was right censored at 31st December 2018, and analyses of other outcomes were right censored at a data cut in May 2018 (see Section 10.2 for more detail). Overall, the analysis included 239,505 doses of 4CMenB given to 107,231 children during their observation period. The age – sex distribution of the populations and sub-groups who received 4CMenB within each NIP stage is given in Table 1-1. Most children received 4CMenB with other vaccinations as part of the NIP.

Table 1-1 Age - sex distribution of the descriptive cohort at 4CMenB vaccination, in total and by NIP stage and data cut

	N	Age (months) Median (IQR); range	% male
Data to 31st December 2018 -analysis of seizures			
Any 4CMenB vaccination	239,505	4.01 (2.27, 12.00) 1.05-18.08	51.3‡
Children with:			
≥ 1 4CMenB vaccination*	107,231	2.20 (1.84, 2.99) 1.05-18.05	51.3
NIP stage 1†	79,038	2.04 (1.78, 2.30) 1.05-14.10	51.1
NIP stage 3 (2nd 4CMenB)†	83,486	4.14 (3.81, 4.64) 2.04-18.05	51.1
NIP stage booster (3rd 4CMenB)†	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
Data to May 2018 data collection – analysis of other outcomes			
Any 4CMenB vaccination	194,929	3.98 (2.27, 11.90) 1.05-18.08	51.1
Children with:			
≥ 1 4CMenB vaccination*	89,259	2.20 (1.84, 3.06) 1.05-18.01	51.1
NIP stage 1†	65,206	2.04 (1.78, 2.30) 1.05-14.10	50.9
NIP stage 3 (2nd 4CMenB)†	68,976	4.14 (3.81, 4.64) 2.04-18.05	51.0
NIP stage booster (3rd 4CMenB)†	45,592	12.75 (12.33, 13.35) 2.43-18.08	50.9
Outside a standard NIP stage	15,155	4.34 (3.25, 12.39) 1.05-18.01	51.8

IQR, interquartile range.
*Population for the descriptive analysis, age at first 4CMenB vaccination in observation period.
†Received a complete NIP stage as described in 'Table 10.4-1' on the same day, regardless of age, vaccination history, or additional vaccinations.
‡Unique children.

There were cases of Kawasaki disease, seizures and febrile seizures with a date of onset during the outcome specific risk period. The risk period is the number of days following vaccination during which an outcome caused by the vaccination would be expected to occur. Kawasaki disease and seizures had two predefined risk periods while febrile seizures had one. The incidence of the outcomes during the outcome specific risk period is given in Table 1-2. No cases of anaphylaxis, GBS or ADEM occurred in the risk period for that outcome.

Table 1-2 Incidence of outcomes in the outcome specific risk period after first 4CMenB vaccination*

Outcome, risk period*	Number of outcomes	PY	Incidence (95 % CI)
Incidence per 1000 PY			
Seizures			
Risk period 1 day 0 – 6	43	4582	9.4 (6.8, 12.6)
Risk period 2 day 0 – 27	133	18,126	7.3 (6.1, 8.7)
Febrile seizures, day 0-6	23	3726	6.2 (3.9, 9.3)
Incidence per 100,000 PY			
Kawasaki disease			
Risk period 1 day 1 – 28	4	14,665	27.3 (7.4, 69.8)
Risk period 2 day 1 – 42	5	21,752	23.0 (7.5, 53.6)

PY, person years
* Seizures includes events to 31st December 2018, other outcomes to data cut in May 2018. No anaphylaxis, GBS or ADEM occurred in the outcome specific risk period. Day 0 = day of exposure.

Conditional Poisson regression was used to calculate incidence rate ratios (IRR) comparing the risk of the primary outcomes after exposure to 4CMenB with periods of non-exposure, adjusting for age, year of vaccination and season. The adjusted IRR and confidence intervals were above 1 for both seizures and febrile seizures in the primary SCCS analysis of first event and first risk period (Table 1-3). There were 9 cases of Kawasaki disease in total (risk and other periods), so the numbers were insufficient to complete the SCCS analysis. Four cases of Kawasaki disease were in the primary risk period of 1-28 days and five were in the larger control period.

Table 1-3 Self-controlled case series primary analysis (first event and risk period for any 4CMenB vaccination)*

	Number of events	Person years	Crude incidence rate ratio (95% CI	Adjusted incidence rate ratio (95% CI)**
Seizures† (risk period day 0 – 6)				
Control period	627	723.5	Ref	Ref
Risk period	39	31.6	1.37 (0.99, 1.89)	1.43 (1.02, 2.02)
Pre-exposure period (day -14 – -1)	29	57.8	0.55 (0.38, 0.81)	0.59 (0.40, 0.86)
Febrile Seizure† (risk period day 0 – 6)				
Control period	341	380.5	Ref	Ref
Risk period	21	16.8	1.35 (0.87, 2.10)	1.72 (1.08, 2.75)
Pre-exposure period (day -14 – -1))	8	30.8	0.28 (0.14, 0.56)	0.36 (0.17, 0.73)
Kawasaki disease (risk period day 1 – 28)				
Control period	5	8.0	-	-
Risk period	4	1.6	-	-
Pre-exposure period (day -27 – 0)	0	1.5	-	-

Ref, reference category
* Seizures includes events to 31st December 2018, other outcomes to data cut in May 2018.
**Adjusted for age, season and year.
†Febrile seizures are a sub-set of seizures.

Discussion

This large study of children aged 1 - 18 months, identified few cases of seizure, febrile seizure and Kawasaki disease directly after 4CMenB-containing vaccination, and no cases of anaphylaxis, GBS or ADEM. The majority of 4CMenB is given on the same day as other vaccinations within the NIP. 4CMenB-containing vaccination is associated with an increased risk of seizures and febrile seizures but it is not possible to attribute the finding specifically to one vaccination type. Increased risks of seizures and febrile seizures have been reported by some previous studies of infant vaccination.

The study demonstrates that Kawasaki disease is rare after 4CMenB-containing vaccination. The small number of cases did not allow us to draw any conclusion concerning the association between 4CMenB-containing vaccination and Kawasaki disease. The incidence is within the wide confidence intervals of published post-vaccination rates before 4CMenB (and rotavirus and Hepatitis B vaccines) were added to the NIP (4).

Marketing Authorisation Holder(s)

GSK Vaccines S.r.l – Via Fiorentina, 1 – 53100 Siena (Italy)

Names and affiliations of principal investigators

Gillian Hall, Grimsdyke House, Ravenscroft Park, London, EN5 4ND, UK

2. LIST OF ABBREVIATIONS

ADEM	Acute disseminated encephalomyelitis
AHD	Additional health data
ATC	Anatomical Therapeutic Chemical
CI	Confidence intervals
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
GDPR	General Data Protection Regulation
GSK	GlaxoSmithKline Vaccines S.r.l.
GVIF	Generalised variance inflation factor
HepB	Hepatitis B vaccination
IRR	Incident rate ratio
KD	Kawasaki disease
MAH	Marketing authorisation holder
MenC	Meningitis C
MMR	Measles, mumps, rubella
MMRV	Measles, mumps, rubella, and varicella
NIP	National immunisation program
NPV	Negative predictive value
PASS	Post authorization safety study
PCV	Pneumococcal vaccine
PPV	Positive predictive value
RI	Relative incidence
SAP	Statistical analysis plan
SCCS	Self-controlled case series
SNOMED	Systematized Nomenclature of Medicine
SRC	Scientific Review Board
THIN	The Health Information Network
UK	United Kingdom

3. ETHICS

3.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The Health Improvement Network has a single multicentre ethics approval for all observational studies using THIN data (Southeast MREC, ref: 03/01/073). The study protocol was approved by the Scientific Review Board (SRC) of THIN (reference number 11THIN028). The SRC approved updated letters to practices on the 8th March 2016 and acknowledged (as a minor amendment on 9th April 2019) the change of study period when unstructured text became unavailable due to the introduction of new European privacy laws (see Section 10.2.1).

3.2. Ethical conduct of the study

The study was conducted in accordance with the International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices (5) and in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Guide on Methodological Standards in Pharmacoepidemiology (6).

This is a non-interventional study using secondary data collection. All data collected in the study was pseudonymised with no breach of confidentiality with regard to personal identifiers or health information. This post-authorisation safety study (PASS) complies with the definition of the non-interventional (observational) study provided in the 2016 Revision 2 of the Guideline on Good Pharmacovigilance Practice (GVP): Module VIII – Post-Authorisation Safety Studies (7).

3.3. Subject information and consent

This is a retrospective observational study using secondary pseudonymised electronic healthcare records so informed consent was not required.

4. INVESTIGATORS

Principle Investigator: Dr Gillian Hall, Grimsdyke House, Ravenscroft Park, London, EN5 4ND, UK.

5. OTHER RESPONSIBLE PARTIES

Responsibility for the provision and quality control of data cuts as specified by the Principal Investigator, statistical analysis of the data and data management: IQVIA, 210 Pentonville Road, London, N1 9JY, UK (formerly IMS Health Ltd).

Review of statistical analysis (Interim and Final Reports): Professor PPD
Professor of Pharmacoepidemiology, Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London.

The Adjudication Committee comprised the Principal Investigator and the clinicians noted below. See Sections 10.4.2, 10.8, 10.9.4 and 10.10 for details of responsibiliti

Professor PPD, Professor of Paediatric Infectious Diseases, St George's, University of London.

Dr PPD, Consultant and Honorary Associate Professor in Paediatric Neurology, Great Ormond Street Hospital for Children NHS Foundation Trust, London.

6. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	31 DEC 2015	08 DEC 15	
End of data collection	MAR 2019 data cut	MAR 2019 data cut	
Study progress report 1	Provided to GSK, 01 MAY 16 Provided to EMA 31 MAY 16	Final 11 MAY 16 27 MAY 2016	
Study progress report 2	Provided to GSK, 01 NOV 16 Provided to EMA 30 NOV 16	Final 14 NOV 16 28 NOV 2016	
Study progress report 3	Provided to GSK, 01 MAY 17 Provided to EMA 31 MAY 17	Final 15 MAY 17 25 MAY 2017	
Study progress report 4	Provided to GSK, 01 NOV 17 Provided to EMA 30 NOV 17	Final 15 NOV 17 28 NOV 2017	
Interim report 1	Data cut off, 31 DEC 16 Provided to GSK, 30 NOV 17 Provided to EMA 31 DEC 17*	31 DEC 2016 Initial 30 NOV 17 Final 18 JAN 18 30 JAN 18	* Updated to 31JAN 2018, in agreement with EMA.
Study progress report 5	Provided to GSK, 01 MAY 18 Provided to EMA 31 MAY 18	Initial 30 APR 18 Final 15 MAY 18 30 MAY 2018	
Study progress report 6	Provided to GSK, 01 NOV 18 Provided to EMA 30 NOV 18	Initial 31 OCT2018 Final 26 NOV 2018 Not submitted	As per EMA agreement with GSK, Progress Report 6 won't be provided to EMA according to this planned date.
Registration in the EU PAS register	30 NOV 15	Initial 30 NOV 15 Amendment 13 MAR 16	
Approval from Ethics Committee/Institutional Review Board	NA	Initial 19 JUN 15 Amendments 08 MAR 16 and 09 APR 2019	
Final report of study results	Provided to GSK, 30 NOV 19	Initial 03 DEC 19 Amendment 20 FEB 20	

7. RATIONALE AND BACKGROUND

Meningococcal disease is caused by the bacterium *Neisseria meningitidis*. It causes a range of serious diseases including septicaemia and meningitis, and is associated with considerable mortality and morbidity (8). Young children and teenagers are at highest risk of the disease, with the peak incidence in those under one year of age (9). There are

thirteen different types of the meningitis bacterium distinguished by the composition of the capsular polysaccharide. The most common types in the UK are B, C, W and Y (10). Since the introduction of routine immunisation against meningococcal C (1999) and B (2015) there has been a fall in the number of cases of both forms of the disease (10, 11).

4CMenB vaccine (Bexsero) is a multicomponent meningococcal serogroup B vaccine containing four main immunogenic components; three recombinant proteins and outer membranes vesicles derived from meningococcal NZ98/254 outbreak strain. 4CMenB was filed for registration with EMA in December 2010. European approval was given in January 2013 and it was added to the UK National Immunisation program (NIP) from September 2015. The vaccination is given at 2, 4 and 12-13 months (NIP stage 1, 3 and booster) for infants born after July 2015. A catch-up program included children born from 1st May 2015 who were given three doses unless the first dose was at four months, when the recommendation was to receive two doses.

During development, approximately 12,350 subjects were exposed to any formulation of meningococcal group B vaccine, including 11,094 who were exposed to the final formulation (rMenB+OMV NZ), in GSK (formerly Novartis) sponsored investigational clinical trials since the Development International Birth Date. Kawasaki disease, febrile seizures and seizures were identified by EMA as potential safety concerns based on clinical trial data from infants. Acute disseminated encephalomyelitis (ADEM), Guillain-Barré Syndrome (GBS), and anaphylaxis were also included in this study in line with events identified through clinical studies and post authorization experience as described in the Risk Management Plan. The purpose of this study is to investigate the safety of 4CMenB vaccination in routine post-marketing use in the UK as a PASS.

8. RESEARCH QUESTION AND OBJECTIVES

To assess the safety of 4CMenB vaccination within the UK NIP with regards to three primary (seizures, febrile seizures and Kawasaki disease) and three secondary (ADEM, GBS, and anaphylaxis) outcomes.

9. AMENDMENTS AND UPDATES

Version 1 of the protocol was completed in 2011 before the UK NIP schedule for 4CMenB was known. Version 2 of the protocol (dated 24th August 2015) reflected changes to the protocol based on details of the NIP. All sections of the protocol were amended. Version 3 of the protocol (dated 13th November 2015) reflects change in Sponsorship: Novartis Vaccines and Diagnostics S.r.l. changed its name into GlaxoSmithKline Vaccines S.r.l., in short GSK Vaccines S.r.l., on 1st September 2015. Therefore, the Sponsor name for this study protocol has been changed to GSK Vaccines S.r.l.

The Statistical Analysis Plan (SAP) was updated with changes to study periods (see Section 10.1) and validation analyses before the final analysis (dated 2nd September 2019).

10. RESEARCH METHODS

10.1. Study design

Two observational analyses were completed during the study based on a database of electronic primary care records (Section 10.9 Statistical Methods). The first analysis describes the incidence of each study outcome after vaccination and provides a temporal plot of the incidence of each outcome in relation to 4CMenB exposure. Stage two is a self-controlled case series (SCCS) of the primary outcomes.

10.2. Setting

10.2.1. Study Period

The study period for seizure analyses includes data from 1st May 2015 to 31st December 2018 inclusive as described in the protocol. The study periods for febrile seizures, Kawasaki disease, anaphylaxis, ADEM and GBS were truncated at a data cut in May 2018 rather than at a specific date. The unstructured text used in the case identification of these outcomes was no longer provided with THIN after the introduction of the General Data Protection Regulation (GDPR) in May 2018. The data cut in May 2018 was used rather than a specific date as it maximised the number of potential outcomes with unstructured text. The SAP was updated with this amendment before the final analysis (dated 2nd September 2019).

The study started on the 8th December 2015, the date of the first data cut from THIN.

10.3. Subjects

10.3.1. Source population

The source population is the UK population. The database population comprises electronic healthcare records from 460 primary care practices which have contributed data for some, or all, of the study period and were a subset of the overall THIN database based on dates and quality of data provision.

10.3.2. Inclusion and exclusion criteria for the study population

Descriptive analysis – The population for the descriptive analysis includes children permanently registered at a practice in the database population and who received one or more vaccination with 4CMenB during their observation period. The observation period for each child started at the most recent of 1st May 2015, date of birth plus one month, transfer-in from another practice plus three months, or quality assurance dates (based on use of Vision software and Acceptable Mortality Reporting Dates (12) and further review). The first month of life is not included as part of this time is usually spent in secondary care. The three months after transfer is not included so that prevalent events recorded at a registration visit during this period were not mistaken for incident episodes.

The end of observation is the earliest of date of birth plus 18 months, transfer-out of the practice, last data collection from the practice or the end of the study period for that outcome. Analyses of seizures included the full study period to 31st December 2018. The study period for febrile seizures, Kawasaki disease, anaphylaxis, ADEM and GBS was truncated at a data cut in May 2018 because provision of unstructured text used in case adjudication was halted after the introduction of the General Data Protection Regulation (GDPR).

A small number of children had more than one transfer-out date 827 (0.8%) because of changes to their record at the practice. When this occurred the earliest transfer out date was used to calculate observation period. Children could have more than one observation period if they left and then re-joined a practice 15 (0.01%).

SCCS – The population for the SCCS analyses comprises a sub-group of the descriptive analysis population who also had a diagnosis of the outcome during their observation period.

10.4. Variables

10.4.1. Exposure of Interest

The exposure of interest is 4CMenB vaccine administered in routine clinical practice. This exposure includes immunisations within the NIP (Table 10.4-1) and those in the catch-up scheme.

Table 10.4-1 Vaccinations included in the UK National immunisation program for children under two years from September 2015

Stage (recommended age)	Vaccinations
Stage 1 (2 months)	5-in-1 (DTaP/IPV/Hib)†, PCV, rotavirus, 4CMenB
Stage 2 (3 months)	5-in-1 (DTaP/IPV/Hib)†, MenC*, rotavirus
Stage 3 (4 months)	5-in-1 (DTaP/IPV/Hib)†, PCV, 4CMenB (2nd dose)
Booster (12-13 months)	Hib, meningitis C, PCV, MMR, 4CMenB (3rd dose)

DTaP, diphtheria, tetanus, pertussis; IPV, polio; Hib, Haemophilus influenzae type b; PCV, 13 valent pneumococcal vaccine; MenC, Meningitis C; MMR, measles, mumps and rubella (13). †Hepatitis B added September / October 2017. *MenC was removed in 2016.

4CMenB vaccination was identified from the AHD file of THIN which was searched for records of any meningitis B vaccination during the child's observation period (see Appendix Table 2). Those labelled as 'given' rather than 'refused' or 'advised' were considered to have been delivered. In the first weeks of inclusion in the NIP, some practices did not record any 4CMenB vaccinations in the AHD file. It was assumed that the practice software had not been updated and so 4CMenB exposure was also identified from the Medical and Therapy files in addition to the AHD file. 4CMenB was the only vaccination against meningitis B available in the UK NIP during the study period. More than one 4CMenB vaccination less than 28 days apart and labelled as the same NIP stage were treated as the same vaccination using the earliest date.

10.4.2. Outcomes

The primary outcomes were seizures (all and febrile seizures) and Kawasaki disease, which were identified by EMA as potential safety concerns based on clinical trial data. ADEM, GBS, and anaphylaxis are also included in this study as secondary outcomes.

Each of the six outcomes is considered below. Cases were identified from the Medical and AHD files of THIN database. Code lists and search terms were developed with the Adjudication Committee before the first data cut and are appended to this report (see Appendix Table 3). These were updated as the study progressed in line with updates provided to the practices. The case definitions and SCCS risk periods agreed with the Adjudication Committee are reported in Appendix Table 1.

Primary outcomes

Seizures are episodes of neuronal hyperactivity most commonly resulting in sudden, involuntary muscular contractions. They may also manifest as sensory disturbances, autonomic dysfunction and behavioural abnormalities, and impairment or loss of consciousness. Seizures occurring soon after immunisation are mostly triggered by fever induced by the vaccine (febrile seizures) or are not vaccine related (14).

As seizures can be diagnosed in primary care without referral, the definition of a seizure is a record of an appropriate Read code for seizure or convulsion in the patient's file during their observation period. Cases were not reviewed by the Adjudication Committee. Instead a validation exercise was conducted by practice questionnaire (Section 10.10).

Febrile seizures are a sub-set of seizures and were defined as a specific code for febrile seizure or evidence of a concomitant fever, but no previous diagnosis or treatment for epilepsy or other relevant concurrent central nervous system disease.

For both seizures and febrile seizures, the date of onset is the date of the seizure code. Seizure records within 30 days were treated as the same episode throughout the study as these were assumed to be follow-up visits rather than incident events.

Kawasaki disease is an acute systemic vasculitis of unknown cause. The epidemic nature and high rates in siblings support an infectious agent inducing the disease in genetically susceptible individuals (15). Kawasaki disease is characterized by a persistent fever, bilateral non-exudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash and cervical lymphadenopathy (16, 17). Diseas e definitions require a fever for five days plus four of the five remaining criteria in North American guidelines (16), or five of the six symptoms in Japan (18). Incomplete case s have fewer characteristics, whereas atypical Kawasaki disease generally includes only 2 or 3 of the criteria plus a coronary artery aneurysm.

Possible episodes of Kawasaki disease were identified by a specific code or 'kawasa' in the unstructured text. The search strategy was previously reported in a THIN study (19) and is detailed in Appendix Table 2. The search period was the observation period of that child plus two months after the study end to capture cases with onset during the observation period but a later diagnosis. Identified records were reviewed independently by all members of the Adjudication Committee who classified the event as an incident

episode or not against a case definition and assigned a date of onset when blinded to the date of vaccination (see Appendix Table 1 for case and date of onset definition). The accuracy of the diagnosis was not judged as the full secondary care notes were not available. If there was insufficient information to form a decision based on the electronic record, then the practice was contacted and asked for further information and the record reviewed again.

Secondary outcomes

Guillain-Barré syndrome (GBS) is an acute polyneuropathy consisting of different subtypes. Acute inflammatory demyelinating polyradiculoneuropathy, the classic demyelinating form of GBS, accounts for 90% of all GBS cases in the Western world. It is characterized by an acute or subacute onset of varying degrees of weakness in limbs or cranial nerve-innervated muscles and associated decreased or absent deep tendon reflexes. Miller Fisher is a variant of GBS and is included in the study definition.

Acute Disseminated Encephalomyelitis (ADEM) is a monophasic syndrome of brain inflammation and demyelination, occurring in temporal association with an antecedent immunologic challenge, such as infection or an immunisation (20). ADEM is generally a monophasic illness lasting weeks to months but approximately 10% of children have recurrent demyelinating episodes and in some this is ultimately diagnosed as multiple sclerosis.

Anaphylaxis is an acute hypersensitivity reaction with multi-organ system involvement that can present as, or rapidly progress to, a severe life-threatening reaction. It may occur following exposure to allergens from a variety of sources including food, aeroallergens, insect venom, drugs, as well as immunisations (21).

Episodes of ADEM, GBS, and anaphylaxis were identified by Read code and text terms and reviewed by the Adjudication Committee using similar procedures to those described for Kawasaki disease. Outcome specific case definitions and search terms were agreed by the Adjudication Committee and are documented in Appendix Table 1 and

Appendix Table 3. The case definitions are modified versions of published definitions such as those the Brighton Collaboration (20, 21, 22) developed to work with primary care records.

10.4.3. Other Variables

Age and sex, and date and type of all other pre-school vaccinations listed in Table 10.4-1 were identified from THIN. THIN includes only the month of birth for children for confidentiality reasons. The date of birth was assumed to be 16th of their month of birth. Other NIP vaccinations were identified from the AHD file in the same manner as 4CMenB (see Section 10.4.1, Exposure of Interest definition).

10.5. Data sources and measurement

THIN is an observational database of primary care electronic medical records from practices throughout the UK and covers approximately 5% of the UK population (2015 figures). Details of demographics and administrative data, clinic events, prescriptions and

preventive medicine are routinely recorded against date in separate files within individual patient records. Secondary care diagnoses and deaths are also captured because of the structure of the National Health Service where primary care physicians act as "gatekeepers" to secondary care and are informed of diagnoses and procedures. Major events from before computerization are added retrospectively. Data on preventive medicine can be recorded including details of any vaccinations. Medical events are automatically coded at entry using the Read coding system (1) and can be supplemented with unstructured text including electronic discharge summaries. Details of preventive medicine and laboratory results are included in the AHD file. The date, type (tetanus, polio, etc.) and stage (1st, booster, etc.) of routine vaccinations are recorded in specific immunisation fields as they are administered. It should be noted that for many practices the electronic record is the primary record and there is no paper version for comparison. THIN has been shown to be generalizable to the UK population for demographics, major condition prevalence and death rates, and similar in terms of deprivation although with slightly fewer people aged under 20 years compared to the general UK population (2).

10.6. Bias

It is possible that a physician might be more likely to diagnose or record a condition after 4CMenB if there was a recognised association between that condition and vaccination for example in GBS (23). This outcome misclassification should be minimized by use of study definitions. However, in some cases only the primary care record is used or is available, particularly for seizures.

It may be difficult to classify seizures as febrile or not simply based on the primary care record as a clinician may preferentially report as a febrile seizure (or not) based on their own perceptions of age at which febrile seizures may or may not occur. Additionally, a clinician may be hesitant to diagnose a seizure as febrile until a child is aged one, three or six months depending on local practice. Bias may occur if more cases of febrile seizure are classified as such after one of these age points. The analysis of seizures should minimise this bias as most seizures in the study age range are febrile anyway (3). 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.

Outcome dates may be misclassified, for example if medical attention is not sought immediately or diagnosis or recording is delayed. If the delay is short, this should not bias results, but longer delays could place an event that belongs during the risk period in a baseline period and would bias results towards the null. This bias is minimised by the Adjudication Committee review of those events which may be diagnosed after a delay such as Kawasaki disease and GBS. The Adjudication Committee assigns a date of onset based on the date of the first symptom where possible. The exception is seizures when the date of onset is assumed to be the date of the first record.

10.7. Study size

THIN comprises patient records from a set number of practices. Consequently, the study size can only be varied by increasing its duration. There were approximately 35,000 newborn babies registered on THIN each year who were eligible for the NIP (personal

communication IQVIA 2015) and who would usually receive three exposures to 4CMenB. The number of years required to detect a relative incidence (RI) of 3 and 10 with 80% power and a 0.05 alpha using this figure and an observation period of 68 weeks (from 1 to 18 months of age) is given in Table 10.7-1 for each outcome. The post-exposure risk periods were based on data in the Study Protocol Appendix 1 (V72_36OB-04 Revised Protocol-v3-2015-11-13-77293343 pdf) other than anaphylaxis which was accepted to occur on the day of exposure to a trigger or the next day.

It was stated a priori that if at least one episode of GBS, ADEM and anaphylaxis was identified in the risk period, and the total number of outcomes is at least that required to detect a relative incidence of 10 with 80% power (Table 10.7-1), then a SCCS would be completed. The combination of the incidence of these outcomes and the length of their risk period meant that it was unlikely that cases would be identified in the risk period.

Table 10.7-1 The number of years required based on 80% power, an alpha of 0.05 and a relative incidence of 3 or 10

Outcome	Incidence per 100,000	Expected in THIN per year[6]	Total risk period (weeks)[7]	Cases required RI=3[8]	Years observation required	Cases required RI=10[8]	Years observation required
Seizures	900[1]	315	12	32	<1	7	<1
Seizures	900[1]	315	3	88	<1	12	<1
Febrile seizures	800[1]	280	3	88	<1	12	<1
KD	15[2]	5	12	32	6	7	1
KD	15[2]	5	18	28	6	7	1
GBS	0.4[3]	0	12	28	-	7	-
ADEM	0.6[4]	0	12	32	-	7	-
Anaphylaxis	6.7[5]	2	0.9	265	>100	30	15

KD, Kawasaki disease. [1]estimated from (3), [2](19) ,[3](24), [4](25), [5](26), [6]based on 35,000 infants, [7]and assuming 3 exposures so =risk period*3, [8] (27).

10.8. Data transformation

The THIN database was searched for the study variables at intervals of approximately two months following a programming specification from December 2015 to March 2019. The programming and cuts of data for this study and quality control were completed by staff at IQVIA who have direct access to the database. These cuts were subject to routine quality assurance following standard operative procedures.

All potential cases of Kawasaki disease, GBS, ADEM and anaphylaxis were reviewed by the Adjudication Committee and judged to be a case or not and a date of onset assigned for cases. In addition, all deaths were reviewed for a cause of death that was a study outcome. When additional data or a questionnaire request were required, a request was sent to the practice via a third party following an establish process to maintain confidentiality. The Adjudication Committee review included the electronic record and any additional information received from the practice.

10.9. Statistical methods

10.9.1. Main summary measures

Descriptive analysis – age and sex at 4CMenB, each NIP stage that includes 4CMenB and immunisations outside the NIP schedule; incidence of outcomes in outcome specific risk periods and descriptive plots of time from exposure. The risk period is the number of days following vaccination during which an outcome caused by the vaccination would be expected to occur.

SCCS – incident rate ratios (IRR) for the primary outcomes. The primary analysis incudes first event and risk period.

10.9.2. Main statistical methods

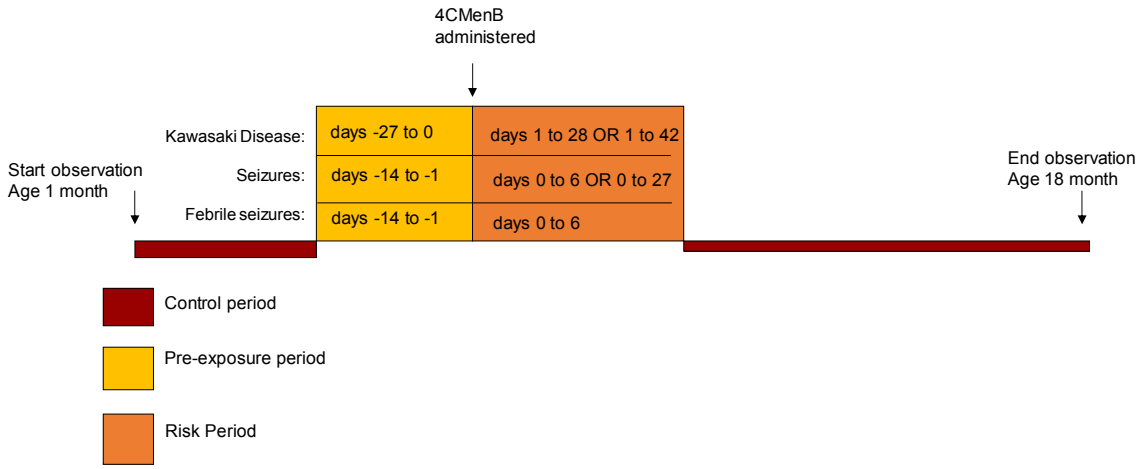
Descriptive analysis: The incidence of each outcome in the risk period was estimated as the number of episodes per 1000 or 100,000 person years with 95% confidence intervals. Appendix Table 1 sets out the risk periods. The incidence calculations were completed for all episodes (not limited to first events) if there was at least one episode in the relevant risk period.

Plots were produced for each outcome with at least one episode in the time period covered by the plot. These show the temporal distribution of incidence of first outcomes around the date of the vaccination. In each case, pre- and post- exposure periods were plotted separately. The post-exposure plots start on the date of the 4CMenB vaccination (anaphylaxis, seizures) or the next day (Kawasaki disease) in-line with the SCCS risk period start, and end at the earliest of the end of observation, the next 4CMenB vaccination or 112 days post-vaccination. The pre-exposure plots start on the most recent of start of observation, the previous 4CMenB vaccination, or 112 days pre-vaccination and end on the day before observation (anaphylaxis and seizures) or the next day (Kawasaki disease, GBS, ADEM). In both plots, time was divided into intervals and the incidence of the outcome is estimated from the number of first outcomes and person years in that interval. One outcome can therefore be depicted in both the pre- and post-exposure plots.

SCCS - Conditional Poisson regression was used to calculate IRRs and 95% confidence intervals comparing the risk of the primary outcomes after exposure to 4CMenB with periods of non-exposure, adjusting for age (by month), year of vaccination and respiratory illness season (by quarter). The primary analysis included only the first episode of an outcome and risk period 1 (but see Section 10.9.4 for sensitivity analyses).

SCCS timelines are given in Figure 10.9-1. For each outcome, exposure is defined as the risk period for each outcome, i.e. the period following vaccination during which an outcome would be expected to occur if it were caused by the vaccination. Non-exposure for each outcome was defined as time periods outside of the risk period when the exposure was assumed to have no effect on the incidence of the outcome. All exposures to 4CMenB were treated as equivalent risk periods.

Figure 10.9-1 Illustrative SCCS observation period for a child showing one administered 4CMenB dose. Further administered doses would trigger identical pre-exposure and risk periods



A pre-exposure period for each outcome was also defined as that period of time after an outcome when a vaccination may be delayed (See Figure 10.9-1 for pre-exposure periods). Outcomes and person-times during this period were treated separately from control time to avoid underestimating event rate during control time and analysed as a separate risk period. These outcomes and time were included as control time in a sensitivity analysis. If a risk period from one exposure overlapped with the pre-exposure period from the next exposure, then the overlapping time of the pre-exposure period was counted only as risk period. If two risk periods overlapped the overlapping time was included in the first risk period only. This strategy was used because overlapping risk periods are only likely to occur with the second, longer risk periods which were included to investigate delayed events. When a child had a record of an 4CMenB exposure shortly before the start of observation, then any period of time and outcomes that would be in the risk period for that exposure were excluded from the observation period.

Subgroup and effect modification: An SCCS treating risk periods defined by vaccination stage separately is reported for seizures. For febrile seizures, adjustment of the individual vaccination stage model was not feasible due to insufficient outcomes in the stratified analysis; there was only 1 episode of febrile seizures in the control period at a younger age than the 1 episode in vaccination stage 1. Consequently, two vaccination sub-groups were included in the SCCS model rather than individual NIP stages. The two febrile seizure sub-groups were NIP booster, and a combination of NIP stages 1 and 2 and 4CMenB given outside the NIP.

Age and immunisation stage were highly correlated in the interim analysis by vaccination stage in both seizure SCCS models which did not run because of collinearity. An alternative strategy was included in the SAP to be completed in the event that collinearity persisted in the final report. The alternative strategy involved completing the analysis on two age groups only or, if collinearity persisted, a self-controlled risk interval analysis with a short control period. Collinearity was defined as generalised variance inflation factor (GVIF) $> 10^{\frac{1}{(2*df)}}$ within a linear model (28) and (29).

Adjustment for confounders: The time-varying covariates age (by month), respiratory virus season (December- February, March – May etc.) and calendar year were included as factors in the Poisson model.

10.9.3. Missing values

Only those children with a record of 4CMenB vaccination were included in the analysis. The analyses used the maximal available information. No imputation was applied.

10.9.4. Sensitivity analyses

The following sensitivity analyses to the SCCS were outlined in the SAP to be completed when appropriate:

1. Analysis of all episodes rather than first episodes. For seizures (febrile and all), a 'new episode' was defined as seizure code with a gap of 30 or more days since a previous seizure code. Sensitivity analyses including all episodes were not completed if >10% of first seizures had a repeat seizure record within 30 days, as it was uncertain which events were truly incident, and there was not a validated methodological work around available to account for this.
2. Analysis of first episodes using risk period 2 for seizures and Kawasaki disease.
3. Pre-exposure outcomes and person times reassigned as control time in the SCCS model.
4. Analysis of first episodes when possible cases were included, both for the incidence estimates and the SCCS.
5. Exclusion of deaths when an outcome is a cause of death.
6. Inclusion of data to 31st December 2018 for the outcomes where the primary analysis used observation truncated at the May 2018 data cut (febrile seizures and Kawasaki disease).
7. Exploration of the relationship with 4CMenB and other vaccination combinations following a significant effect estimate. An additional vaccination stage analysis was completed for seizures and is treated as a post hoc analysis. This SCCS included NIP stage 2 in the same manner as other stages. NIP stage 2 does not include 4CMenB but includes other vaccinations given with 4CMenB at some NIP stages (see Table 10.4-1 for details of vaccinations included in NIP stages).
8. Investigation of the effect of NIP vaccinations as time-varying exposures (for example if a new vaccination is introduced). Hepatitis B was added to the UK NIP in autumn 2017 changing the current 5 in 1 to a 6 in 1 vaccination at NIP stages 1, 2 and 3. A sensitivity analysis of the SCCS of first event and the primary risk period included only exposures with no hepatitis B on the same day.
9. Review of the calendar quarters included to adjust for respiratory virus season quarter if, for example, a flu epidemic during the study doesn't fit with the categorization.

10. Extension of the pre-exposure period by a further two week pre-exposure period if the relative incidence for the primary pre-exposure period is different from 1 (indicating a difference and therefore a substantial short term reduction in likelihood of vaccination following the outcome).
11. Adjustment of the risk periods if the Adjudication Committee feel that these do not reflect the distribution demonstrated in the plots.
12. Correction of the seizure or febrile seizure IRR for outcome misclassification should the validation step report a positive predictive value (PPV) which is differs by exposure status (risk period versus outside risk period).

A validation study of data to May 2018 (the last data cut when unstructured text was available) was completed to indicate the scale of misclassification of outcomes that would be introduced by using THIN without unstructured text compared to classification of outcomes based on full THIN data (see Section 10.2.1 for details on unstructured text provision). Febrile seizures, Kawasaki disease and anaphylaxis were included in the validation as no ADEM or GBS outcomes were identified up to and including the May 2018 data cut, and seizures were identified by code only. Potential outcomes identified up to the May 2018 data cut were reclassified without unstructured text but otherwise in the same manner as within the main study. The date of onset assignment for Kawasaki disease and anaphylaxis could use unstructured text so date was included in the reclassification of these outcomes. Febrile seizures date of onset did not use unstructured text. True positives were an outcome in both classifications, true negatives were not an outcome in either classification, false negatives were an outcome in the initial classification with unstructured text but not in the second classification without unstructured text and false positives were not an outcome in the first classification but were an outcome in the second classification. The PPV, negative predictive value (NPV) sensitivity and specificity were estimated. The risk and other periods were treated separately for Kawasaki disease and febrile seizures. There were no events in the risk period for anaphylaxis. To understand the potential effect of no unstructured text on anaphylaxis episodes in the risk period events were categorized as a true positive if they both matched the ‘gold standard’ as an outcome and had a date of onset within one day either side of the ‘gold standard’ to match the anaphylaxis risk period of 2 days.

10.9.5. Amendments to the statistical analysis plan

The SCCS analysis by vaccination stage was amended for febrile seizures. See Subgroup and effect modification for details. A two-tailed Fisher exact test was used to investigate the hypothesis of no difference between the PPV in the risk period when compared to other time during observation in the seizure validation. There were no other amendments to the final statistical analysis plan version 5.2.

10.10. Quality control

Outcome classification

The Adjudication Committee classified each potential episode of Kawasaki disease, anaphylaxis, GBS and ADEM as an outcome or not against the case definition and assigned a date of onset. The practice was asked for additional information if required.

This adjudication should have minimized false positive outcomes. A wide search strategy was used in the initial identification of potential cases from THIN to reduce the number of false negatives (see Appendix Table 3 for details).

Validation of outcomes

A random sample of 100 children with a record of a seizure identified in the first study year and registered at practices that had agreed to respond to questionnaires were validated against a practice questionnaire. The sample was selected from196 children (276 seizures) identified in the year, 133 (48.2%) of the seizures were febrile. The questionnaire asked if the patient experienced any seizure, the date and whether this was febrile.

Identification of seizures from THIN was compared to the questionnaire which was treated as the 'gold standard' after review and agreement by two members of the Adjudication Committee (PH and PP). A PPV was estimated for the presence of a definite seizure, and febrile seizure, overall, and a definite seizure in a risk period or other time.

Ninety-one completed questionnaires (91%) were returned and included in the analysis; 59% female, mean age 9 months and 51 (56%) where a febrile seizure was identified from THIN. The PPV for identification by THIN compared to the practice questionnaire was 80.2% (95%CI 70.2, 87.6) for seizures and 84.3% (95%CI 70.9, 92.5) for febrile seizures. Three of 5 seizures identified from THIN in the risk period were confirmed in the questionnaire (PPV 60.0%, 95%CI 17.0%, 92.7%) and 65 of 83 in the control period (PPV 78.3%, 95%CI 67.6%, 86.3%). A two-tailed Fisher exact test indicated that there was not enough evidence to reject the null hypothesis of no difference between the PPV in the risk period when compared to other time (p-value 0.32). Consequently, no adjustment for outcome misclassification was made.

Statistical analysis

IQVIA is responsible for providing the Statistical Analysis as set out in the Statistical Analysis Plan (SAPMenB_11THIN028 V72_36OB-04 v5.2). This work was conducted within the work-frame of the IQVIA Quality Management System (QMS) and in accordance with the IQVIA Real World Evidence policies and procedures.

11. RESULTS

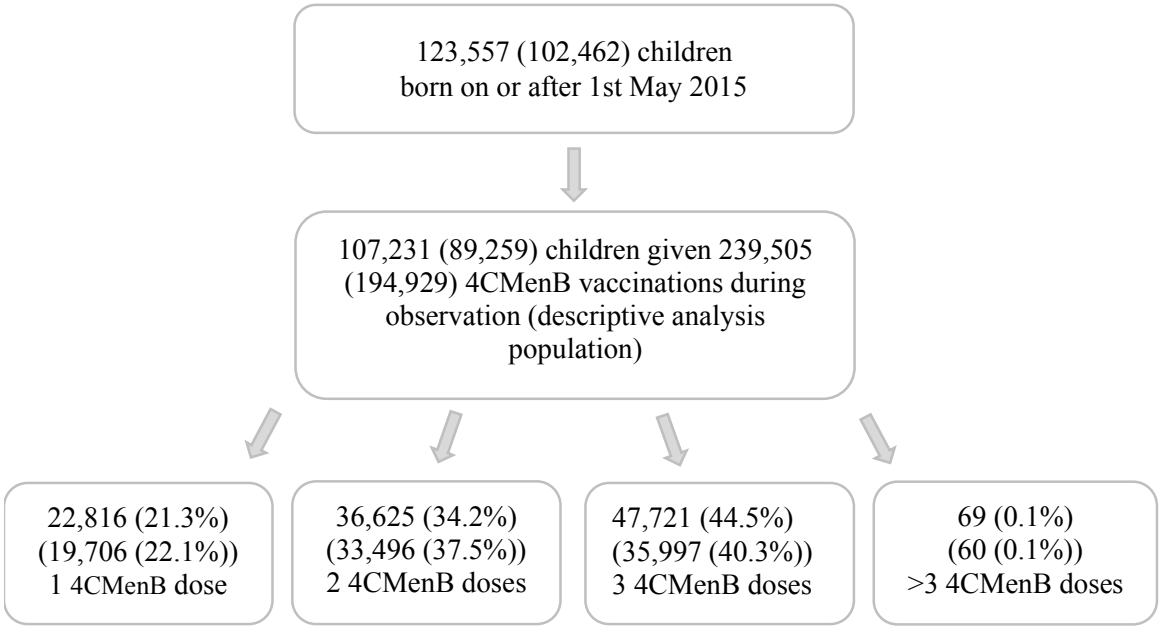
These are the results of the final analysis which comprise descriptive analyses of exposures and plots of outcomes in relation to exposure and SCCS analysis of the primary outcomes.

11.1. Participants

The data were cut on 25th March 2019 from the IMRD 1809 version of THIN for the observation period ending 31st December 2018 and on 11th May 2018 from the IMRD 1801version of THIN for the May 2018 data cut. There were 239,505 4CMenB vaccinations given to 107,231 children during their observation period (descriptive

analysis population) to 31st December 2018. The May data cut included 194,929 4CMenB vaccinations in 89,259 children. The identification of the study population and number of 4CMenB vaccinations per child is reported in Figure 11.1-1. Overall, 276 vaccination doses (0.1%) were excluded because a dose labelled as the same NIP stage had been given less than 28 days earlier. The 69 (0.06%) children with more than three doses of MenB recorded remained in the cohort.

Figure 11.1-1 The identification of the study populations from THIN database 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

11.2. Descriptive data

For the majority of children 4CMenB was administered on the same day as other vaccinations as part of the NIP. The age-sex distribution of the descriptive analysis population by NIP stage is given in Table 11.2-1.

Table 11.2-1 Age-sex distribution of the descriptive cohort at 4CMenB vaccination, in total and by NIP stage

	N	Age (months) Median (IQR); range	% male‡
Data to 31st December 2018			
Any 4CMenB vaccination	239,505	4.01 (2.27, 12.00) 1.05- 8.08	51.3‡
Children with:			
≥ 1 4CMenB vaccination*	107,231	2.20 (1.84, 2.99) 1.05-18.05	51.3
NIP stage 1†	79,038	2.04 (1.78, 2.30) 1.05-14.10	51.1
NIP stage 3 (2nd 4CMenB)†	83,486	4.14 (3.81, 4.64) 2.04-18.05	51.1
NIP stage booster (3rd 4CMenB)†	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
Data to May 2018 data collection			
Any 4CMenB vaccination	194,929	3.98 (2.27, 11.90) 1.05-18.08	51.1
Children with:			
≥ 1 4CMenB vaccination*	89,259	2.20 (1.84, 3.06) 1.05-18.01	51.1
NIP stage 1†	65,206	2.04 (1.78, 2.30) 1.05-14.10	50.9
NIP stage 3 (2nd 4CMenB)†	68,976	4.14 (3.81, 4.64) 2.04-18.05	51.0
NIP stage booster (3rd 4CMenB)†	45,592	12.75 (12.33, 13.35) 2.43-18.08	50.9
Outside a standard NIP stage	15,155	4.34 (3.25, 12.39) 1.05-18.01	51.8

*Population for the descriptive analysis, age at first 4CMenB vaccination in observation period.
†Received a complete NIP stage as described in Table 10.4-1 on the same day, regardless of age, vaccination history, or additional vaccinations.
‡Unique children.

11.3. Outcome data

The Adjudication Committee reviewed a total of 605 potential outcomes from the data cut in March 2019 in a child with at least one 4CMenB vaccine (366 anaphylaxis, 105 Kawasaki disease, 3 GBS, 38 ADEM), and 93 deaths. The Adjudication Committee concluded that 19 episodes of anaphylaxis, 14 of Kawasaki disease, 1 of possible Kawasaki disease and 1 of GBS were consistent with the case definitions and that 1 cause of death was a febrile seizure. Fourteen of the anaphylaxis episodes and 9 episodes of Kawasaki disease had a date of onset within a child's observation period and so were included in the analysis. There were no second episodes of Kawasaki disease or anaphylaxis. The febrile seizure death, GBS and possible Kawasaki disease were outside the observation period for the particular child. A total of 816 episodes of seizures in 695 children, and 399 episodes of febrile seizures in 370 children, during observation were identified directly from THIN (seizures less than 30 days from a previous record were counted as one episode).

Episodes of Kawasaki disease, seizures and febrile seizures had a date of onset during an outcome specific risk period. None of the cases of anaphylaxis were dated in the risk period. The number and incidence of the outcomes during each risk period are given in Table 11.3-1.

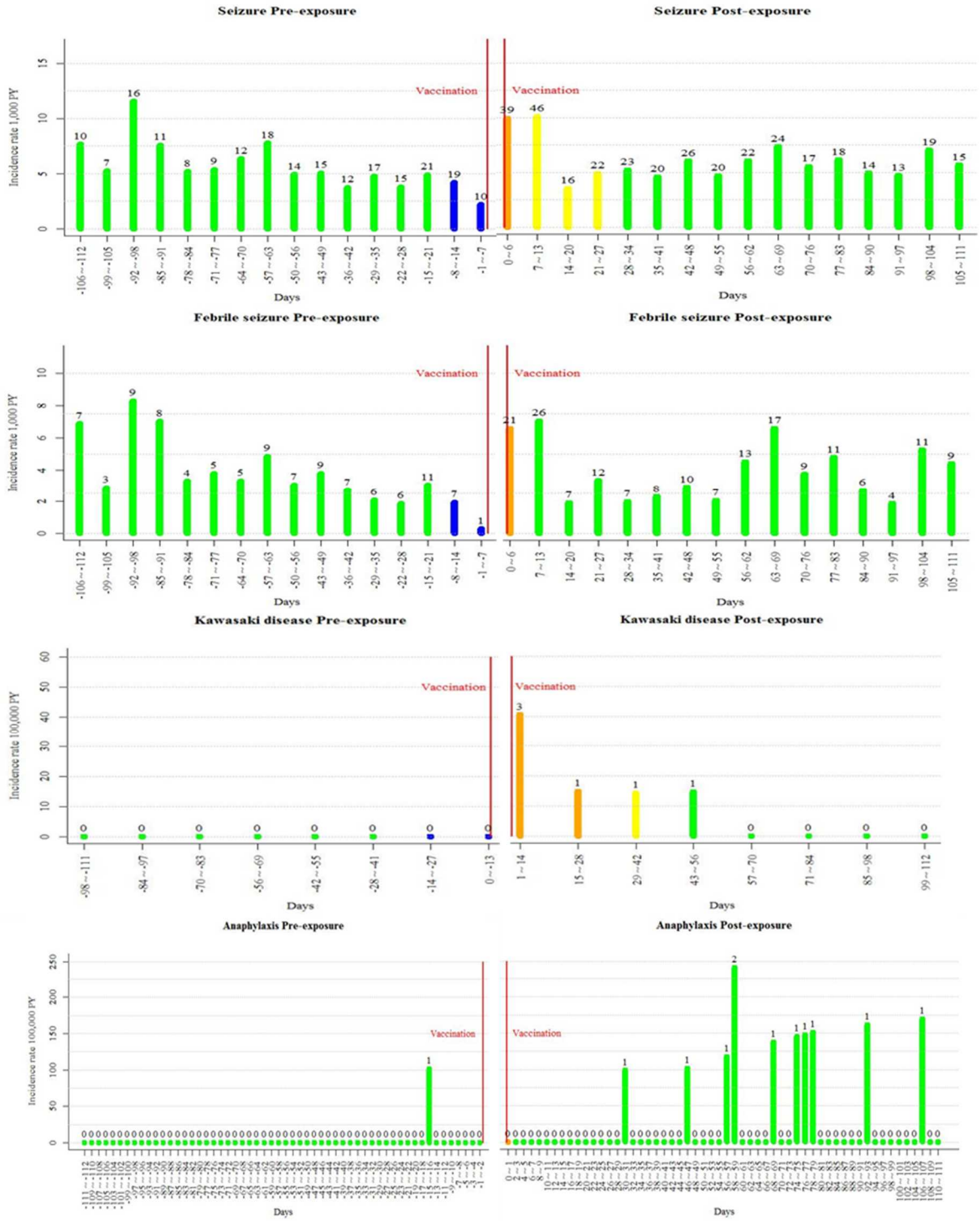
Table 11.3-1 Incidence of all outcomes in outcome specific risk periods after vaccination including 4CMenB*

Outcome, risk period days** (Day 0 = day of exposure)	Number of outcomes	PY	Incidence (95 % CI)
Seizure†			
Risk period 1 day 0 – 6	43	4582	9.4 (6.8, 12.6)
Risk period 2 day 0 – 27	133	18,126	7.3 (6.1, 8.7)
Febrile seizure†			
Day 0 - 6 risk period	23	3726	6.2 (3.9, 9.3)
Kawasaki disease‡			
Risk period 1 day 1 – 28	4	14,665	27.3 (7.4, 69.8)
Risk period 2 day 1 – 42	5	21,752	23.0 (7.5, 53.6)
Anaphylaxis			
Day 0 – 1 risk period	0	1067	-
ADEM and GBS			
Risk period 1 day 1 – 28	0	14,665	-
Risk period 2 day 1 – 42	0	21,752	-

PY, person years.
*Seizures includes data to 31st December 2018, other outcomes to a data cut in May 2018
**the period when an outcome might be expected to occur if associated with the exposure, some outcomes have two risk periods assigned.
†Per 1000 PY, those within 30 days treated as the same episode and associated PY excluded, febrile seizures are a subset of seizures.
‡Per 100,000 PY

The temporal relationship between 4CMenB exposure and outcomes is shown in Figure 11.3-1. It should be noted that the plots include episodes with a date of onset in the 4 months pre- and post-exposure only. Episodes within observation, but outside this time frame, were not plotted.

Figure 11.3-1 Incidence of outcomes in relation to 4CMenB exposure*



*The number at the top of each bar is the number of outcomes identified in that time interval. Denominator time varied between time intervals so the number may not be in relation to the height of the bar. Includes outcomes 4 months pre- & post-exposure only. Episodes outside this time were not plotted including 3 Kawasaki disease episodes. 1 seizure and 2 febrile seizures in children with multiple study periods were excluded. Anaphylaxis horizontal axis in 2 day intervals with post-exposure starting at day 0.

11.4. Main results

The primary SCCS analysis included first episodes of outcomes and the primary definition of risk period. Table 11.4-1 describes the SCCS primary analysis cohorts.

Table 11.4-1 Description of SCCS primary analysis outcomes (1st episode, risk period 1)*

	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)	2 (0.5)	0 (0.0)
2016	195 (28.1)	118 (31.9)	5 (55.6)
2017	270 (38.8)	179 (48.4)	4 (44.4)
2018	214 (30.8)	71 (19.2)	0 (0.0)
Season of episode n (%)			
Spring	179(25.8)	98 (26.5)	1 (11.1)
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)	3 (33.3)

*Seizures includes data to 31st December 2018, other outcomes to a data cut in May 2018

The results of the SCCS primary analysis are shown in Table 11.4-2. The adjusted IRR and 95% confidence interval (CI) for both seizures and febrile seizures are above 1. There were 9 cases of Kawasaki disease, which was insufficient to complete the SCCS analysis, and no cases of GBS, ADEM and anaphylaxis in the relevant risk period.

Table 11.4-2 Self-controlled case series primary analysis (first event and risk period for any 4CMenB vaccination)*

	Number of events	Person years	Crude incidence rate ratio (95% CI)	Adjusted incidence rate ratio (95% CI)**
Seizures† (day 0 – 6)				
Control period	627	723.5	Ref	Ref
Risk period	39	31.6	1.37 (0.99, 1.89)	1.43 (1.02, 2.02)
Pre-exposure period	29	57.8	0.55 (0.38, 0.81)	0.59 (0.40, 0.86)
Febrile Seizure† (day 0 – 6)				
Control period	341	380.5	Ref	Ref
Risk period	21	16.8	1.35 (0.87, 2.10)	1.72 (1.08, 2.75)
Pre-exposure period	8	30.8	0.28 (0.14, 0.56)	0.36 (0.17, 0.73)
Kawasaki disease (day 1 – 28)				
Control period	5	8.0	NR	NR
Risk period	4	1.6	NR	NR
Pre-exposure period	0	1.5	NR	NR

NR, not reported, Ref, reference category.
* Seizures includes events to 31st December 2018, other outcomes to data cut in May 2018.
**Adjusted for age, season and year.
†Febrile seizures are a sub-set of seizures.

A sub-group analysis by vaccination stage for the primary outcome and risk period is given for febrile seizures and seizures in Table 11.4-3. The IRR for seizures are similar across NIP vaccination stages with confidence intervals above 1 only after the booster stage which included a larger number of episodes. The febrile seizure SCCS reports two groups rather than individual vaccination stages, booster stage and a combined group of all other 4CMenB-containing vaccinations. The combined group of 4CMenB-containing vaccine exposures outside the booster were associated with an increased risk of febrile seizures. However, as noted earlier, stratification by vaccine stage led to inadequate numbers of outcomes during the control period, and it is possible that this problem also affected these results. Four of the 6 episodes of febrile seizures in the combined group were dated after vaccination stage 3 and one each after stage 1 and 4CMenB outside any NIP stage. No collinearity with vaccination stage and age was identified in either seizure model (seizures: GVIF 1.07, cut-off for collinearity 1.26; febrile seizures: GVIP 1.11, cut-off 1.25). Four of the 9 episodes of Kawasaki disease had a date of onset in the primary risk period of days 1 to 28, 3 after the first NIP vaccination stage and 1 after vaccination stage 3. The remaining 5 cases were in the control period.

Table 11.4-3 Primary analysis sub-grouped by NIP stage* at which 4CMenB is given (first event and risk period)**

	Number of events	Person years	Crude incidence rate ratio (95% CI)	Adjusted incidence rate ratio (95% CI)†
Seizure				
Control period	627	723.5	Ref	Ref
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	1	2.8	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 Seizure‡				
Control period	341	380.5	Ref	Ref
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)

Ref, reference category
*Received a complete NIP stage as described in Table 11.4-1 on the same day, regardless of age, vaccination history, or additional vaccinations.
** Seizures includes events to 31st December 2018, other outcomes to a data cut in May 2018.
†Adjusted for age, season and year.
‡Febrile seizures are a sub-set of seizures; NIP stage 1 and 3, and events not in a complete stage (other) were combined as adjustment of the model was not valid by individual stage.

11.5. Other analyses

The results of pre-defined sensitivity analyses are shown in Table 11.5-1. No sensitivity SCCS analyses were completed for Kawasaki disease as there were insufficient episodes.

- **Analysis of all episodes –** An analysis of all episodes of febrile seizures was completed as, at 6.8%, it met the criteria of <10% with a second record within 30 days of the primary event. The IRR for all episodes was similar to that in the primary analysis when only first episodes were included. The sensitivity analysis was not completed for seizures as 10.2% of first seizures had a second record of seizure within 30 days (see Section 10.9.4 Sensitivity Analyses).

- **Using the second risk period –**The inclusion of day 0 to day 27 in the SCCS for seizures resulted in a change in the IRR to 1.29 (95%CI 1.02, 1.64) from 1.43 (95%CI 1.02, 2.02).
- **Pre-exposure outcomes and person times reassigned –** When pre-exposure time was reassigned as control time the adjusted IRRs for both seizures and febrile seizures were slightly higher, as would be expected, but the interpretation was unchanged.
- **Analysis of febrile seizures and Kawasaki disease using data to 31st December 2018:** In febrile seizures the IRR and CI remained above 1, although slightly higher than in the primary analysis. An additional 3 cases of Kawasaki disease were all in the control period.

Table 11.5-1 Pre-defined SCCS 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 first episodes				
Febrile Seizure (day 0-6)†				
Control period	368	378.6	Ref	Ref
Risk period	23	16.8	1.36 (0.89, 2.08)	1.83 (1.16, 2.87)
Pre-exposure period	8	30.8	0.25 (0.13, 0.51)	0.34 (0.16, 0.70)
Using risk period 2:				
Seizures (day 0 - 27)				
Control period	543	630.8	Ref	Ref
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)
Kawasaki disease (day 1–42)				
Control period	4	7.4	NR	NR
Risk period	5	2.3	NR	NR
Pre-exposure period	0	1.5	NR	NR
Reassigning pre-exposure period and outcomes as control				
Seizures (day 0 - 6)				
Control period	656	781.3	Ref	Ref
Risk period	39	31.6	1.42 (1.03, 1.97)	1.55 (1.11, 2.18)
Febrile seizures (day 0 - 6)†				
Control period	349	411.3	Ref	Ref
Risk period	21	16.8	1.44 (0.93, 2.24)	1.91 (1.20, 3.04)
Including data to 31st December 2018				
Febrile Seizure (day 0-6)†				
Control period	415	486.7	Ref	Ref
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)
Kawasaki disease (day 1–28)				
Control period	8	10.6	NR	NR
Risk period	4	2.2	NR	NR
Pre-exposure period	0	2.0	NR	NR

Ref, reference category; NR, not reported.
* Seizures includes events to 31st December 2018, other outcomes to a data cut in May 2018 unless specified. Analyses are primary analyses except for the specified sensitivity change.
**Adjusted for age, season and year.
†Febrile seizures are a sub-set of seizures

Additional sensitivity analyses were included in the SAP to be specified provided that certain conditions were met. These are reported in Table 11.5-2 and should be treated as post hoc analyses as the details of the analysis were specified after the preliminary results were available.

- Concurrent vaccinations as time-varying exposures: removal of exposures with concomitant hepatitis B made little difference to the IRR, 1.48 (95%CI 1.02, 2.15) for seizures compared to 1.43 (1.02, 2.02) when all 4CMenB exposures were included and 1.68 (1.02, 2.77) and 1.72 (1.08, 2.75) respectively for febrile seizures.
- Exploration of the relationship with 4CMenB-containing vaccination and other vaccination combinations following a significant effect estimate. The primary analysis IRR and 95% confidence intervals were above 1 for both seizures and febrile seizures and the IRR was similar across NIP vaccination stages for seizures (see Table 11.4-3 for the vaccination stage analyses). An additional vaccine stage SCCS for seizures was completed including NIP stage 2. The UK NIP stage 2 does not include 4CMenB. The IRR was similar across vaccination stages although only booster stage confidence intervals were above 1. A vaccine stage analysis could not be completed for febrile seizures as discussed in Section 11.4.

Table 11.5-2 SCCS sensitivity analyses included in the SAP but detailed after final results*

	Number of events	Person years	Crude rate ratio (95% CI)	Adjusted rate ratio (95% CI)**
Including only exposures with no concomitant HepB				
Seizures (day 0-6)				
Control period	627	723.5	Ref	Ref
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) †				
Control period	341	380.5	Ref	Ref
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)				
Control period	617	697.5	Ref	Ref
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	1	2.8	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)

HepB, hepatitis B vaccination. Ref, reference category.
* Seizures includes events to 31st December 2018, other outcomes to data cut in May 2018. Analyses are primary analyses except for the specified sensitivity change.
**Adjusted for age, season and year.
†Febrile seizures are a sub-set of seizures
‡Received a complete NIP stage as described in Table 11.4-1 on the same day, regardless of age, vaccination history, or additional vaccinations.

No other sensitivity analyses were completed as the pre-defined assumptions were not met. There were no suspected cases Kawasaki disease, or deaths which might be due to an outcome, during a child's observation period. No additional time varying exposures or factors which could affect the respiratory season were identified. No ADEM or GBS outcomes were identified between the May 2018 data cut and 31st December 2018. The plots for seizures and febrile seizures demonstrated that the pre-exposure risk periods were appropriate. Consequently, the SCCS were not repeated with a longer pre-exposure period despite the relative incidence for the pre-exposure period compared with baseline being different to 1. The validation of seizures showed a lower PPV in the risk period versus other time periods which did not reach significance as numbers in the risk period were small.

The results of the validation of outcomes identified without unstructured text (see Section 10.9.4) against those identified with the unstructured text as the gold standard are reported in Table 11.5-3. All episodes of Kawasaki disease and febrile seizures identified without unstructured text were also outcomes in the gold standard (PPV 100%), but sensitivity was lower outside the risk period (96.7% and 83.3% respectively) as some episodes were missed when text was not used. Febrile seizures not identified without text would have been included in the seizure analysis as only the 'febrile' classification required unstructured text, consequently there was no seizure validation. Anaphylaxis outcomes were frequently missed when text was unavailable resulting in a sensitivity of 35.3%.

Table 11.5-3 Validation of outcome classification without unstructured text compared to that with unstructured text as gold standard

	Febrile Seizures†		Kawasaki disease		Anaphylaxis
	Primary risk period	Outside risk period	Primary risk period	Outside risk period	Both all-time and +/- 1 day‡
Potential episodes of outcomes identified with text	383		74		327
True +ve (False +ve)	20 (0)	351 (0)	5 (0)	5 (0)	6 (1)
False -ve (True -ve)	0 (0)	12 (0)	0 (69)	1 (68)	11 (309)
PPV % (95%CI)	100 (79.9, 100)	100 (98.6, 100)	100 (46.3, 100)	100 (46.3, 100)	85.7 (42.0, 99.2)
NPV % (95%CI)	NR	NR	100 (93.4, 100)	98.6 (91.1, 99.9)	96.6 (93.8, 98.2)
Sensitivity % (95%CI)	100 (79.9,100)	96.7 (94.1, 98.2)	100 (46.3, 100)	83.3 (36.5, 99.1)	35.3 (15.3, 61.4)
Specificity % (95%CI)	NR	NR	100 (93.4,100)	100 (93.3, 100)	99.7 (97.9, 100)

NPV, Negative predictive value; PPV, positive predictive value; +ve, positive; -ve, negative.
*Unstructured text was used to assign the date of onset for both Kawasaki disease and anaphylaxis so validation indices were calculated in each time period for all potential events. The date of onset for febrile seizures did not use unstructured text so validation indices were estimated based on the date of the outcome.
†All febrile seizure identified from THIN as the gold standard were outcomes so false +ves and true -ves were not possible.
‡Results are the same for both time periods, there were no episodes of anaphylaxis identified in the risk period so a period of +/- 1 day was used to represent the 2 day risk period.

When risk period 2 was used for Kawasaki disease all validation indices remained the same as in Table 11.5-3 except for the control period specificity which was 80.0% (95%CI 29.9, 98.9).

11.6. Adverse events/adverse reactions

Individual cases of safety outcomes possibly associated with 4CmenB vaccination during this study were not to be reported as it is a retrospective database study. Data is reported as per study design and timelines.

12. DISCUSSION

12.1. Key results

This final report includes 239,505 exposures to 4CMenB in 107,231 children in analyses of seizures between 1st May 2015 and 31st December 2018, and 194,929 exposures to 4CMenB in 89,259 children in analyses of other outcomes between 1st May 2015 and a May 2018 data cut. There were few episodes if any outcomes in the risk intervals when an event associated with exposure might be expected to occur. In the primary analyses, 39 seizures, 21 febrile seizures, 4 Kawasaki disease and no episodes of GBS, anaphylaxis and ADEM were identified in the risk interval. None of these episodes was fatal.

The adjusted IRR and 95% confidence intervals for both seizures and febrile seizures were above 1 in the primary analysis (IRR 1.43 (95%CI 1.02, 2.02) and 1.72 (1.08, 2.75), respectively). In the sub-group analysis by vaccination stage for seizure, the adjusted IRR was above 1 and consistent across all NIP vaccination stages which include 4CMenB, but confidence intervals above 1 only after the booster stage. The seizure IRR for NIP stage 2 (which does not include 4CMenB) was similar to that in other vaccination stages when it was added to the model in a post hoc analyses. However, whilst the IRR point estimates were similar across all vaccination stages, confidence in any comparison between them is limited due to a lack of statistical power to estimate the IRR with accurate precision.

An SCCS was not possible for Kawasaki Disease because of low numbers of cases. There were 9 episodes in the primary analysis, 4 in the 28-day primary risk period of 1.6 person years and 5 in the larger control period of 8.0 person years. One episode moved from control to risk with a 42 day risk period. Three additional Kawasaki disease cases identified without unstructured text in the follow-up to the end of 2018 were in the control period. Classification of Kawasaki disease was similar with and without unstructured text in this control period (PPV 100%, sensitivity 83%).

Limitations

There were too few cases of Kawasaki disease to complete the adjusted SCCS. The number of primary care practices contributing to THIN decreased over the study period. The incidence of Kawasaki disease in the risk period and plots of outcomes against time from vaccination are provided to allow the rate to be compared to published information and to demonstrate the temporal distribution of outcomes against exposure.

4CMenB is always co-administered with other vaccines within the NIP. It may not be possible to differentiate between the effects of individual vaccinations with any methodology based on data from routine care. For example, PCV is routinely given at the same time as each 4CMenB vaccination within the NIP. However, a sensitivity analysis including the UK NIP stage 2 without 4CMenB is reported for seizures to aid interpretation although the statistical power is low.

No SCCS by individual 4CMenB-containing vaccination stages is reported for febrile seizures as the model could not be adjusted, probably because there was only one febrile seizure at a younger age than the first in the risk period. The model was run including two groups, booster stage and all other 4CMenB vaccinations combined. While this is reported, it should be noted that the adjustment may still be affected. The possibility of collinearity between age and NIP stage was investigated but none was identified.

It is possible that a physician would differentially diagnose an outcome after a vaccination if it is known that the condition has been associated with vaccinations in the past, for example in a case of Guillain Barre syndrome. The misclassification should be minimized by use of outcome adjudication against study definitions. This adjudication also allowed a more accurate estimate of date of onset. Adjudication was not completed for seizures which were identified and had a date of onset from the electronic health record. In addition, seizures may be misclassified as non-febrile in younger children (see Section 10.6). These outcomes will be captured in the overall seizure category and most seizures in the study age range are febrile. Misclassification may also occur if the date of onset is incorrect resulting in an outcome being classified in a risk rather than background period or vice versa. This could occur if an outcome was reported to a healthcare professional on the date of vaccination. The validation study of seizures reported a difference in misclassification between risk and other periods which was not statistically significant, however, the number of children with seizures in the risk period was small and confidence intervals were wide. Misclassification that was differential between time periods may have impacted point estimates.

Details of vaccination outside the primary care practice will not be captured using this method. However, as the study design does not involve comparison between exposed and non-exposed individuals this should not affect the results.

12.2. Interpretation

An increased risk of seizures and febrile seizures was identified post-vaccination when all 4CMenB-containing vaccination stages were considered together. The vast majority of 4CMenB was given in combination with multiple other vaccinations. There were up to nine vaccinations included in the UK NIP stages (see Table 11.4-1 for NIP schedule). A US study determined an IRR of 23 (95%CI 5.13, 100.8) in days 0 - 1 versus days 14 - 20 for probable febrile seizures following a median of 4 vaccines simultaneously (excluding 4CMenB) in children aged 1 - 5 months, although the vaccine combinations and age at vaccination differed from the UK NIP (30).

Vaccinations in each of the NIP stages have been associated with seizures in some previous analyses making it difficult to identify the role of any one component. A large Danish SCCS analysis (2003 – 2008) of DTaP-IPV-Hib vaccine including acellular pertussis (as in the current study) in children aged 3, 5 and 12 months reported no increased risk of febrile seizures 0 - 7 days after the first, second or third vaccination (IRR 1.65 95%CI 0.94, 2.90; IRR 1.32 95%CI 0.90, 1.92 and IRR 0.99 95%CI 0.86, 1.15 respectively) (31). An increased risk of febrile seizure was found on the day of the first and second vaccinations, but not the third vaccination (IRR 6.49, 95%CI 3.10, 13.61; IRR 3.97, 95%CI 2.20, 7.16 and IRR 1.07, 95%CI 0.73, 1.57 respectively), nor in days 1

- 3, or days 4 - 7 after any vaccination. A doubling in the incidence of convulsions (days 0 - 59) was reported in a US study after dose 1 of the rotavirus vaccine used in the UK compared to cohorts using an alternative rotavirus vaccine or no rotavirus vaccine (IRR 2.07, 95% CI: 1.27, 3.38 and IRR 2.05, 95%CI 1.24, 3.38 respectively) but not after dose 2 (32). Only one of the two study data resources demonstrated an increased risk when analysed individually. A trans-European methodological feasibility SCCS study in children 1 month to <6 years (1990 – 2015) reported an elevated IRR for convulsions 0 - 72 hours after dose 1 of an acellular pertussis across European databases (1.53 95%CI1.02, 2.30) but not for other doses (33). Children could be exposed to other vaccinations.

An increased risk of febrile seizures is consistent with the known effects of the measles component of measles, mumps, rubella (MMR) vaccine (34, 35). As this is a liv e attenuated vaccine, the risk period is generally considered to be 7-10 days (35, 36) or 6 -11 days (34) after exposure which is later than, or slightly overlapping, the primary risk window in the current study, although increased risk of febrile seizures after MMR compared to non-vaccinated children has been reported in both the first and second week after vaccination (37). Some MMR associated events may be included in the current study risk windows after the booster, particularly in the longer risk period of 0 - 27 days post-vaccination.

The sensitivity analysis including NIP stage 2 (no 4CMenB) in the current study may indicate an increased risk of seizures across vaccination stages, not just those including 4CMenB, although only the NIP booster had confidence intervals above 1. This was a post-hoc analysis designed after the preliminary results were reviewed and was unable to estimate the effect of stage 2 NIP with good precision.

Clinical trials of 4CMenB reported an increased rate of fever (which may in turn be associated with seizures i.e. febrile seizures) in infants after 4CMenB given with routine vaccinations (77%) compared to routine vaccinations alone (45%) or with MenC (47%) (38). Fever rates are reported to be lower in observational studies (39). A UK ‘ecological ’ study reported that the rate of seizures did not increase post vaccination after the addition of 4CMenB to the routine UK NIP schedule (40). A systematic review and meta-analysis of clinical trials reported 7 febrile seizures after 4CMenB and 1 after other vaccinations (41).

The SCCS sensitivity analysis which reassigned pre-exposure time and outcomes as control time and outcomes reported higher IRR and 95% confidence intervals than the primary analysis for both seizures and febrile seizures. This would be expected if the events causing a delay in vaccination (shown by the lower IRR in pre-exposure periods) increased the incidence in the control period before pre-exposure time, thereby lowering the primary IRR.

The incidence of seizures or febrile seizures in the current study risk periods are consistent with published population rates, although higher than some estimates after vaccine exposure. A THIN database population study (1999 – 2011) reported the incidence of generalised convulsive seizures as 8.3 (95%CI 8.1, 8.6) per 1000 years at 2-12 months, but with a sharp increase from 2 to 16 months (from graph) (3). An earlier

UK study reported that the incidence of febrile seizures in toddlers was 9.5 per 1000 person years (95% CI 9.0, 9.9) in total and 13.4 (95% CI 10.9, 16.4) and 11.5 (95% CI 10.,13.1) within 14 days and 42 days of vaccination respectively (42). The trans -European methodological feasibility study reported incidences of 3.0 (95%CI 2.4, 3.7) per 1000 PY for all seizures from the THIN database, and 5.0 (95%CI 3.3, 7.1) from an alternative UK primary care resource, 0 – 72 hours after either whole cell or acellular pertussis vaccination in children aged 1 month to <6 years (33). In the large Danish study, the incidence rates 0 – 7 days after the first, second or third vaccination were reported as 0.8, 1.3 and 8.5 per 100,000 person-days respectively, which approximately equates to 2.9, 4.7 and 31.0 per 1,000 person years (31).

The nine cases of Kawasaki disease identified in 194,927 4CMenB vaccinations were insufficient for an SCCS analysis. While there were more cases in the shorter risk period than in the control period, an additional 3 cases identified in the sensitivity analysis to the end of 2018 were all in the control period which highlights the risk of interpreting results based on small numbers.

Small numbers of Kawasaki disease have been reported after 4CMenB and other vaccinations elsewhere. Six cases of Kawasaki disease were reported in approximately 4000 children aged less than 5 years of age who received at least one dose of 4CMenB in clinical trials (43) - a higher rate than in the current study although a case 14 weeks after exposure and one with no details were included. Spontaneous reporting after introduction of 4CMenB reported 3 cases with an unadjusted observed-to-expected ratio of 1·40 (95% CI 0·29–4·08) (40). The incidence of Kawasaki disease of 27.3 per 100,000 (95%CI 7.4, 69.8) 1 - 28 days after vaccination and 23.0 (7.5, 53.6) 1 - 42 days after vaccination are higher than - but within the confidence intervals - of published post-vaccination rates from the same data source before the introduction of 4CMenB, rotavirus and HepB vaccinations (see Table 12.2-1) (4). Five cases of Kawasaki disease occurred among 36,150 infants who received a rotavirus immunisation, compared with 1 case among 35,536 infants given placebo (44). Thirty cases of Kawasaki disease were reported after 599,229 doses in the 1–56 days following PCV13 vaccination, with a relative risk of 1.94 (95% CI 0.79, 4.86) compared to PCV7 in the 28 days after exposure (45). A US Vaccine Safety Datalink based cohort study concluded that neither MMR nor MMR-varicella were associated with an increased risk of Kawasaki disease, and estimated an incidence of 1 KD case per 11,824 doses of MMR- varicella (35).

Table 12.2-1 Published incidence of Kawasaki disease per 100,000 post-NIP vaccination prior to the inclusion of 4CMenB and rota virus vaccinations (4)

	Incidence (95 % CI) post-vaccination	
	28 days	**42 days**
1st NIP	27.4 (8.8, 84.8)	24.0 (9.0, 64.0)
3rd NIP	9.5 (1.3, 67.7)	6.3 (0.9, 44.9)
Booster	0.0 (0.0, 69.7)	12.6 (1.8, 89.3)
Stage 1, 3 or booster	15.0 (5.6, 39.9)	14.8 (6.7, 33.0)

No episodes of anaphylaxis were identified in the outcome specific risk period although there were 14 episodes in the control period. The clustering of episodes from 30 days after exposure is consistent with events at the age when children often have a first exposure to solid foods. Solids are introduced at about six months of age so within the four months plotted after the second 4CMenB (at four months of age) but before the time plotted prior to the booster vaccination. The finding of no episodes of anaphylaxis in the risk period after the vaccinations is consistent with other sources. A UK and Ireland study (2008 – 2009) of anaphylaxis after vaccination reported that none of 7 cases were related to 'routine' infant and preschool vaccination, although a rate of 12 per 100,000 doses was reported for the single component measles vaccine (46). An Australian reports-based system found an incidence of anaphylaxis of between 0.4 and 2.5 per 100,000 doses after vaccination given singly or in combination to those aged less than 18 years (47). A US study of electronic healthcare records reported 0.65 cases of anaphylaxis /million vaccine doses (95% CI 0.21, 1.53) (1991 - 1997, under 18 years) (48) and 1.31 (95% CI, 0.90, 1.84) per million doses (2009 - 2011) across age groups (49).

ADEM and GBS are rare events and the finding of no episodes within observation is consistent with published data (Table 10.7-1). The one episode of GBS adjudicated as a case was after the child was eighteen months old. There were 54 cases of GBS reported in the US in 2004 (23) while the incidence of ADEM after vaccination is reported to be between 0.1 to 0.2 per 100,000 vaccinated individuals (50).

12.3. Generalisability

The study results should be generalisable across the UK. However, although THIN practices are distributed across the UK, the distribution is not uniform. If there are differences in 4CMenB uptake across regions and differences in respiratory and other viral seasons, then this could affect generalizability.

13. OTHER INFORMATION

None.

14. CONCLUSION

There were few cases of seizure, febrile seizure and Kawasaki disease, and no cases of anaphylaxis, GBS or ADEM, directly after a 4CMenB-containing vaccination in this large study of children aged 1 to 18 months. The majority of 4CMenB is given on the same day as other vaccinations within the NIP. 4CMenB-containing vaccination is associated with an increased risk of seizures and febrile seizures but it is not possible to attribute the finding specifically to one vaccination type. Increased risks of seizures and febrile seizures have been reported by some previous analyses of infant vaccination.

Kawasaki disease is rare after 4CMenB-containing vaccination. The small number of cases identified in the study does not allow us to draw any conclusion concerning the association between 4CMenB-containing vaccination and Kawasaki disease. The incidence is within the wide confidence intervals of published post-vaccination rates before 4CMenB (and rotavirus and HepB) were added to the NIP (4).

15. REFERENCES

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APPENDIX: OUTCOME IDENTIFICATION AND REVIEW PLAN

Appendix Table 1 Outcome case definitions, risk periods and pre-exposure period

Outcome	Case definition (For codes and terms used in identification see Table A2)	Date of onset	Days from exposure (Day of exposure = 0)	
			Risk period (2nd risk period)	Pre-exposure period
Anaphylaxis (severe allergic reaction)	Evidence of secondary care diagnosis, confirmation or treatment of an episode of anaphylaxis, anaphylactoid reaction, or severe angioedema (with respiratory/ airways involvement) and no later alternative diagnosis for the event.	1st symptom	0 - 1	-1 - -14
Kawasaki disease	A documented final secondary care diagnosis of KD OR a record of a diagnosis in the primary care record (not a primary care diagnosis) if this is supported by evidence of a diagnosis of a coronary artery aneurysm, or concomitant initiation of aspirin therapy or monitoring that could identify a coronary artery aneurysm. Possible KD: a final secondary care diagnosis such as '?' or 'suspected' Kawasaki disease (or similar) OR a diagnosis of Kawasaki disease in the primary care record with a record of fever for at least five days and three principle characteristics of the condition but not fulfilling the primary Kawasaki disease definition. Possible KD cases should have evidence of a diagnosis of a coronary artery aneurysm, or concomitant initiation of aspirin therapy or monitoring that could identify a coronary artery aneurysm.	1st symptom	1 - 28 (1 - 42)	0 - -28
ADEM	An incident event with evidence that a diagnosis of ADEM or CIS, or transverse myelitis was made or confirmed in secondary care and no later alternative diagnosis. A sensitivity analysis will include cases of suspected ADEM, CIS or TM made or confirmed in secondary care with no later alternative diagnosis if any are identified by the AC.	1st symptom	1 - 28 (1 - 42)	0 - -28

Appendix Table 1 Cont. Case definitions, risk periods and pre-exposure period

Outcome	Case definition (For codes and terms used in identification see Table A2)	Date of onset	Days from exposure (Day of exposure =0)	
			Risk period (2nd risk period)	Pre-exposure period
GBS	An incident event with evidence that this was made or confirmed in secondary care and no later alternative diagnosis. A sensitivity analysis will include cases of suspected GBS made or confirmed in secondary care with no later alternative diagnosis, if any are identified.	1st symptom	1 - 28 (1 - 42)	0 - -28
Any seizure	A record of an appropriate Read code for seizure or convulsion in the patient's file during their observation period. Records within 30 days considered as the same event.	1st record	0 - 6 (0 - 27)	-1 - -14
Febrile seizure	A seizure with evidence of fever and without evidence of epilepsy (a Read code or a prescription), or other cause such as nervous system infection and nervous system condition. Evidence of fever is defined as: • a code for febrile seizure, • a code for fever or a temperature over 38^0C, on the same day or in the previous 5 days. • a term for fever linked to a seizure code (see Table A2). • A code for nervous system infections and conditions dated from 14 days before to 42 days after seizure code. Records within 30 days considered as the same event.	1st record	0 - 6	-1 - -14

Appendix Table 2 Codes and text terms used in the identification of possible outcomes

Read Code	Read Code Description
Other neurological disease included in identification of febrile seizures	
6571000	First meningitis B vaccination
6571100	Second meningitis B vaccination
6571200	Third meningitis B vaccination
6571300	Fourth meningitis B vaccination
6571400	Meningitis B vaccination given by other healthcare provider
6571500	1st meningitis B vaccinatn givn by other healthcare provider
6571600	2nd meningitis B vaccinatn givn by other healthcare provider
6571700	3rd meningitis B vaccinatn givn by other healthcare provider
6571800	4th meningitis B vaccinatn givn by other healthcare provider
6571900	Bstr men B vacc gvn by oth HCP
6571A00	Booster men B vaccination

Appendix Table 3 Codes and text terms used in the identification of possible outcomes

Read Code	Read Code Description	Unstructured text search
Kawasaki disease (code or text term identified)		
G751000	Kawasaki disease	Kawasa[a]
GBS		
F370000	Guillain-Barre syndrome	guillain[a]
F370.00	Acute infective polyneuritis	guillian[a]
F370100	Postinfectious polyneuritis	giullain[a]
F370z00	Acute infective polyneuritis NOS	fisher syndrome[d]
F364.00	Idiopathic progressive polyneuropathy	barre syndrome[d]
F366.00	Polyneuropathy	polyneuritis[a]
F370200	Miller-Fisher syndrome	demyelinat[a]
F374z00	Polyneuropathy in disease NOS	Barré[a]
F377.00	Other toxic agent polyneuropathy	miller syndrome[d]
F37X.00	Inflammatory polyneuropathy, unspecified	GBS[c]
F37z.11	Polyneuropathy unspecified	ascending paralysis[d]
Fyu7B00	[X]Inflammatory polyneuropathy, unspecified	miller fisher[d]
Fyu7C00	[X] Polyneuropathy, unspecified	
1B3..11	Paralysis symptoms	
1B33.00	Paralysis present	
F24z.00	Paralysis NOS	
ADEM		
F03..00	Encephalitis, myelitis and encephalomyelitis	ADEM[c]
F03..11	Encephalomyelitis	myelitis[a]
F03y.11	Encephalomyelitis NOS	encephalo[a]
F03z.11	Encephalomyelitis NOS	clinically isolated syndrome[d]
Fyu0600	[X]Other encephalitis, myelitis and encephalomyelitis	devic's[c]
Fyu0800	[X]Encephalitis,myelitis+encephalomyelitis/viral disease CE	devic[c]
Fyu0A00	[X]Encephalitis,myelitis+encephalomyelitis/other diseases CE	devics[c]
F283.00	Unspecified encephalopathy	
E2A3.11	Post-encephalitis syndrome	**b) Terms to be excluded**
F213.00	Clinically isolated syndrome	Myalgic Encephalomyelitis[b]
F210.00	Neuromyelitis optica	Myalgia Encephalomyelitis[b]
F210.11	Devic's disease	Myalgic encephalopathy[b]
F21X.00	Acute disseminated demyelination, unspecified	Myalgia encephalopathy[b]
F21y.00	Other specified central nervous system demyelinating disease	Osteomyelitis[c]
F21y300	Central demyelination of corpus callosum	Poliomyelitis[c]
F21yz00	Other specified central nervous system demyelination NOS	Encephalocele[c]
F21z.00	Central nervous system demyelination NOS	hypoxic encephalopathy[b]
F03..12	Myelitis	neonatal encephalopathy[d,f]

[a]Contains. [b]All words, [c]A complete word. [d]All words together (in any order) [e]All words in order.[f]From Run 2. N.B Code lists were updated during the study in-line with practice lists.

Appendix Table 3 cont. Codes and text terms used in the identification of possible outcomes

Read Code	Read Code Description
ADEM	**cont.**
F03..13	Transverse myelitis
F037.00	Transverse myelitis
Fyu0900	[X]Encephl,myelitis+encphmylitis/oth infct+parasit diseas CE
F037000	Varicella transverse myelitis
Fyu4.00	[X]Demyelinating diseases of the central nervous system
Fyu4000	[X]Other specified acute disseminated demyelination
Fyu4100	[X]Other specified demyelinating diseases/the CNS
Seizure	
2822.00	O/E - grand mal fit
2823.00	O/E - petit mal fit
2824.00	O/E - focal (Jacksonian) fit
2824.11	O/E - Jacksonian fit
2824.12	O/E - focal fit
2828.00	Absence seizure
13ZD.00	Eye witness to epileptic seizure
1B27.00	Seizures in response to acute event
1B63.00	Had a fit
1B63.11	Fit - had one, symptom
1B64.00	Had a convulsion
1B64.11	Convulsion - symptom
1B6B.00	Febrile convulsion
282..00	O/E - fit/convulsion
282..11	O/E - a convulsion
282..12	O/E - a fit
282..13	O/E - a seizure
282Z.00	O/E - fit/convulsion NOS
F132z12	Myoclonic seizure
F25..00	Epilepsy
F250000	Petit mal (minor) epilepsy
F251.00	Generalised convulsive epilepsy
F251000	Grand mal (major) epilepsy
F251011	Tonic-clonic epilepsy
F251200	Epileptic seizures - clonic
F251300	Epileptic seizures - myoclonic
F251400	Epileptic seizures - tonic
F251500	Tonic-clonic epilepsy

[a]Contains. [b]All words, [c]A complete word. [d]All words together (in any order) [e]All words in order.[f]From Run 2. N.B Code lists were updated during the study in-line with practice lists.

Appendix Table 3 cont. Codes and text terms used in the identification of possible outcomes

Read Code	Read Code Description	
Seizure cont.		
F251600	Grand mal seizure	
F251y00	Other specified generalised convulsive epilepsy	
F251z00	Generalised convulsive epilepsy NOS	
F252.00	Petit mal status	
F253.00	Grand mal status	
F253.11	Status epilepticus	
F255011	Focal epilepsy	
F255012	Motor epilepsy	
F259.00	Early infant epileptic encephalopathy wth suppression bursts	
F25A.00	Juvenile myoclonic epilepsy	
F25G.00	Severe myoclonic epilepsy in infancy	
F25H.00	Generalised seizure	
F25X.00	Status epilepticus, unspecified	
F25y.00	Other forms of epilepsy	
F25y200	Locl-rlt(foc)(part)idiop epilep&epilptic syn seiz locl onset	
F25y300	Complex partial status epilepticus	
R003211	[D]Fit (in non epileptic) NOS	
F25z.00	Epilepsy NOS	
F25z.11	Fit (in known epileptic) NOS	
Q480.00	Convulsions in newborn	
Q480.11	Fits in newborn	
Q480.12	Seizures in newborn	
R003.00	[D]Convulsions	
R003000	[D]Convulsions, febrile	
R003011	[D]Pyrexial convulsion	
R003100	[D]Convulsions, infantile	
R003z00	[D]Convulsion NOS	
R003z11	[D]Seizure NOS	
Ryu7100	[X]Other and unspecified convulsions	

[a]Contains. [b]All words, [c]A complete word. [d]All words together (in any order) [e]All words in order.[f]From Run 2. N.B Code lists were updated during the study in-line with practice lists.

Appendix Table 3 cont. Codes and text terms used in the identification of possible outcomes

Read Code	Read Code Description
Febrile seizures	
Febrile seizures were identified as a specific code (below), or a code for seizure (list above) plus, a code for fever (list below) or a temperature $\leq 38^0$C within 5 days, or text linked to the seizure code indicating a fever but no history of epilepsy (Read or drug code), or other neurological disease in the 7 days before to 42 days after the seizure code (lists below): Acceptable linked text: 'febrile' or 'pyrexial' with fit(s), seizure(s), convulsion(s)[e] and not preceeded by a negative such as not, non, possible, or the 1st term in text is: febrile[c,] fever[c], pyrexial[c] or pyrexia[c]	
Febrile seizure codes	
2827.00	O/E – febrile convulsion
1B6B.00	Febrile convulsion
R003000	[D]Convulsions, febrile
R003011	[D]Pyrexial convulsion
Fever codes	**in the identification of febrile seizure**
14k..00	H/O: fever
14k..11	H/O: pyrexia
14OS.00	Green traff light - low risk serious illn (Fever illn child)
14OT.00	Amber traff light - intermed risk serious illn (Fever child)
14OV.00	Red traffic light - hi risk of serious illn (Feverish child)
1653.00	Fever with sweating
1656.00	Feverish cold
171F.00	Cough with fever
2E...00	Examination of fever
2E...11	O/E - fever
2E1..00	O/E - fever - general
2E12.00	O/E - fever examination - NAD
2E13.00	O/E -pyrexia of unknown origin
2E13.11	O/E - pyrexia - ? cause
2E1Z.00	O/E - fever - general NOS
2E2..00	O/E - method fever registered
2E2Z.00	O/E - method fever taken NOS
2E3..00	O/E - level of fever
2E34.00	O/E - temperature elevated
2E35.00	O/E - hyperpyrexia-> 40.5 oCEL
2E4..00	O/E - character of fever
2E4..11	O/E - temperature character
2E41.00	O/E - fever - acute rise
2E42.00	O/E - fever - gradual rise
2E43.00	O/E - fever - continuous
2E44.00	O/E - fever - remittent
2E45.00	O/E - fever - intermittent
2E46.00	O/E - staircase fever
2E47.00	O/E - fever - irregular
2E48.00	O/E - fever - fast fall-crisis
2E49.00	O/E - fever-gradual fall-lysis

[a]Contains. [b]All words, [c]A complete word. [d]All words together (in any order) [e]All words in order.[f]From Run 2. N.B Code lists were updated during the study in-line with practice lists.

Appendix Table 3 cont. Codes and text terms used in the identification of possible outcomes

Read Code	Read Code Description
Fever codes cont.	
2E4Z.00	O/E - fever character NOS
2EZ..00	O/E - fever NOS
H00..13	Febrile cold
H00..15	Pyrexial cold
R006.00	[D]Pyrexia of unknown origin
R006.11	[D]Fever of unknown origin
R006000	[D]Chills with fever
R006100	[D]Hyperpyrexia NOS
R006200	[D]Fever NOS
R006300	[D]Persistent fever
R006400	[D]Drug-induced fever
R006y00	[D]Other specified fever
R006z00	[D]Pyrexia of unknown origin NOS
Epilepsy codes - in the identification of febrile seizures	
1473.00	H/O: epilepsy
6674.00	Epilepsy associated problems
6677.00	Epilepsy drug side effects
6678.00	Epilepsy treatment changed
6679.00	Epilepsy treatment started
2126000	Epilepsy resolved
13ZD.00	Eye witness to epileptic seizure
1O30.00	Epilepsy confirmed
212J.00	Epilepsy resolved
667A.00	Epilepsy treatment stopped
667B.00	Nocturnal epilepsy
667C.00	Epilepsy control good
667D.00	Epilepsy control poor
667E.00	Epilepsy care arrangement
667F.00	Seizure free >12 months
667J.00	Epilepsy impairs education
667K.00	Epilepsy limits activities
667L.00	Epilepsy does not limit activities
667M.00	Epilepsy management plan given
667N.00	Epilepsy severity
667P.00	No seizures on treatment
667Q.00	1 to 12 seizures a year
667R.00	2 to 4 seizures a month
667S.00	1 to 7 seizures a week
667T.00	Daily seizures
667V.00	Many seizures a day

N.B Code lists were updated during the study in-line with practice lists.

Appendix Table 3 cont. Codes and text terms used in the identification of possible outcomes

Read Code	Read Code Description
Epilepsy cont.	
667W.00	Emergency epilepsy treatment since last appointment
667X.00	No epilepsy drug side effects
667Z.00	Epilepsy monitoring NOS
8BIF.00	Epilepsy medication review
Eu05212	[X]Schizophrenia-like psychosis in epilepsy
Eu06013	[X]Limbic epilepsy personality
Eu80300	[X]Acquired aphasia with epilepsy [Landau - Kleffner]
F132100	Progressive myoclonic epilepsy
F25..00	Epilepsy
F250.00	Generalised nonconvulsive epilepsy
F250000	Petit mal (minor) epilepsy
F250011	Epileptic absences
F250100	Pykno-epilepsy
F250200	Epileptic seizures - atonic
F250300	Epileptic seizures - akinetic
F250400	Juvenile absence epilepsy
F250500	Lennox-Gastaut syndrome
F250y00	Other specified generalised nonconvulsive epilepsy
F250z00	Generalised nonconvulsive epilepsy NOS
F251.00	Generalised convulsive epilepsy
F251000	Grand mal (major) epilepsy
F251011	Tonic-clonic epilepsy
F251100	Neonatal myoclonic epilepsy
F251111	Otohara syndrome
F251200	Epileptic seizures - clonic
F251300	Epileptic seizures - myoclonic
F251400	Epileptic seizures - tonic
F251500	Tonic-clonic epilepsy
F251600	Grand mal seizure
F251y00	Other specified generalised convulsive epilepsy
F251z00	Generalised convulsive epilepsy NOS
F252.00	Petit mal status
F253.00	Grand mal status
F254.00	Partial epilepsy with impairment of consciousness
F254000	Temporal lobe epilepsy
F254100	Psychomotor epilepsy
F254200	Psychosensory epilepsy
F254300	Limbic system epilepsy
F254400	Epileptic automatism
F255012	Motor epilepsy
F255100	Sensory induced epilepsy
F255200	Somatosensory epilepsy
F255300	Visceral reflex epilepsy
F255311	Partial epilepsy with autonomic symptoms
F254500	Complex partial epileptic seizure

N.B Code lists were updated during the study in-line with practice lists.

Appendix Table 3 cont. Codes and text terms used in the identification of possible outcomes

Read Code	Read Code Description
Epilepsy cont.	
F254z00	Partial epilepsy with impairment of consciousness NOS
F255.00	Partial epilepsy without impairment of consciousness
F255000	Jacksonian, focal or motor epilepsy
F255011	Focal epilepsy
F255400	Visual reflex epilepsy
F255500	Unilateral epilepsy
F255600	Simple partial epileptic seizure
F255y00	Partial epilepsy without impairment of consciousness OS
F255z00	Partial epilepsy without impairment of consciousness NOS
F256.12	West syndrome
F256000	Hypsarrhythmia
F257.00	Kojevnikov's epilepsy
F258.00	Post-ictal state
F259.00	Early infant epileptic encephalopathy wth suppression bursts
F259.11	Ohtahara syndrome
F25A.00	Juvenile myoclonic epilepsy
F25B.00	Alcohol-induced epilepsy
F25C.00	Drug-induced epilepsy
F25D.00	Menstrual epilepsy
F25E.00	Stress-induced epilepsy
F25F.00	Photosensitive epilepsy
F25G.00	Severe myoclonic epilepsy in infancy
F25G.11	Dravet syndrome
F25y.00	Other forms of epilepsy
F25y000	Cursive (running) epilepsy
F25y100	Gelastic epilepsy
F25y200	Locl-rlt(foc)(part)idiop epilep&epilptic syn seiz locl onset
F25y400	Benign Rolandic epilepsy
F25y500	Panayiotopoulos syndrome
F25yz00	Other forms of epilepsy NOS
F25z.00	Epilepsy NOS
F25z.11	Fit (in known epileptic) NOS
Fyu5000	[X]Other generalized epilepsy and epileptic syndromes
Fyu5100	[X]Other epilepsy
R003400	[D]Nocturnal seizure
SC20000	Traumatic epilepsy

Appendix Table 3 cont. Codes and text terms used in the identification of possible outcomes

Anticonvulsants - in the identification of febrile seizures
Beclamide
Brivaracetem
Carbamazepine
Clobazam
Clonazepam
Diazepam
Dronabinol / Cannabidiol
Eslicarbazepine
Ethosuximide
Fosphenytoin
Gabapentin
Lacosamide
Lamotrigine
Levetiracetam
Methylphenobarb
Oxcarbazepine
Perampanel
Phenobarbital Sodium
Phenobarbitone
Phenytoin Sodium
Pregabalin
Rufinamide
Sodium Valproate
Stiripentol
Tiagabine
Topiramate
Valproic Acid
Vigabatrin
Zonisamide

N.B Code lists were updated during the study in-line with practice lists.

Appendix Table 3 cont. Codes and text terms used in the identification of possible outcomes

Read Code	Read Code Description
Other neurological disease included in identification of febrile seizures	
65VC.00	Notification of acute meningit
67E6.00	Outbreak of meningitis - advice
683A.00	Bacterial meningitis screen
A022100	Salmonella meningitis
A13..00	Tuberculosis of meninges and central nervous system
A130.00	Tuberculous meningitis
A130200	Tuberculous leptomeningitis
A130300	Tuberculous meningoencephalitis
A130z00	Tuberculous meningitis NOS
A136.00	Tuberculous encephalitis or myelitis
A136000	Tuberculous encephalitis
A136z00	Tuberculous encephalitis or myelitis NOS
A13y.00	Other specified tuberculosis of central nervous system
A13z.00	Tuberculosis of central nervous system NOS
A206.00	Plague meningitis
A360.00	Meningococcal meningitis
A361.00	Meningococcal encephalitis
A365.00	Meningococcal meningitis with acute meningococcal septicaem
A366.00	Meningococcal meningitis with meningococcal septicaemia
A41..00	Slow viral central nervous system infection
A412.00	Subacute sclerosing panencephalitis
A412.11	Dawson's inclusion body encephalitis
A41y.00	Other slow virus central nervous system infections
A41z.00	Slow virus central nervous system infection NOS
A42..00	Meningitis due to enterovirus
A420.00	Coxsackie viral meningitis
A421.00	ECHO viral meningitis
A42y.00	Other specified viral meningitis
A42z.00	Viral meningitis NOS
A42z.11	Aseptic meningitis
A4y..00	Other enterovirus diseases of central nervous system
A4y0.00	Enteroviral encephalitis
A4z..00	Non-arthropod-borne viral dis.central nervous system OS/NOS
A4z0.00	Lymphocytic choriomeningitis
A4z1.00	Adenoviral meningitis
A4zy000	Acute inclusion body encephalitis
A4zy100	Acute necrotising encephalitis
A4zy200	Epidemic encephalitis
A4zy300	Encephalitis lethargica
A4zy400	Von Economo's encephalitis
A4zy500	Adenoviral encephalitis

Appendix Table 3 cont. Codes and text terms used in the identification of possible outcomes

Read Code	Read Code Description
Other neurological disease included in identification of febrile seizures cont.	
A4zz.11	Viral encephalitis NOS
A520.00	Postvaricella encephalitis
A530.00	Herpes zoster with meningitis
A531.00	Herpes zoster with other central nervous system complication
A531400	Zoster encephalitis
A543.00	Herpetic meningoencephalitis
A54x100	Herpes simplex meningitis
A550.00	Postmeasles encephalitis
A553.00	Measles complicated by meningitis
A62..00	Mosquito-borne viral encephalitis
A620.00	Japanese encephalitis
A621.00	Western equine encephalitis
A622.00	Eastern equine encephalitis
A623.00	St. Louis encephalitis
A624.00	Australian encephalitis
A624.11	Murray - Valley encephalitis
A625.00	California viral encephalitis
A62y.00	Other specified mosquito-borne virus encephalitis
A62y.11	Ilheus virus encephalitis
A62z.00	Mosquito-borne viral encephalitis NOS
A63..00	Tick-borne viral encephalitis
A630.00	Russian spring-summer (taiga) encephalitis
A631.00	Louping ill encephalitis
A632.00	Central European encephalitis
A63y.00	Other tick-borne viral encephalitis
A63y000	Langat encephalitis
A63y100	Powassan encephalitis
A63yz00	Other tick-borne viral encephalitis NOS
A63z.00	Tick-borne viral encephalitis NOS
A64..00	Viral encephalitis from other arthropods
A64..11	Negishi virus encephalitis
A721.00	Mumps meningitis
A722.00	Mumps encephalitis
A904100	Congenital syphilitic encephalitis
A904200	Congenital syphilitic meningitis
A918000	Acute secondary syphilitic meningitis
A942.00	Syphilitic meningitis
A94y000	Syphilitic encephalitis
A98y100	Gonococcal meningitis
AA0y000	Leptospiral meningitis
AB2y200	Candidal meningitis

Appendix Table 3 cont. Codes and text terms used in the identification of possible outcomes

Read Code	Read Code Description
Other neurological disease included in identification of febrile seizures cont.	
AB32.00	Coccidioidal meningitis
AB40100	Histoplasma capsulatum with meningitis
AB41100	Histoplasma duboisii with meningitis
AB4z100	Histoplasmosis with meningitis
AB65200	Cryptococcal meningitis
AC31000	Cysticercosis of central nervous system
AD00.00	Toxoplasma meningoencephalitis
AD62.11	Naegleria meningoencephalitis
AE01.00	Late effects of central nervous system tuberculosis
AE20.00	Late effects of viral encephalitis
Ayu8.00	[X]Viral infections of the central nervous system
Ayu8000	[X]Acute paralytic poliomyelitis, other and unspecified
Ayu8100	[X]Acute poliomyelitis, unspecified
Ayu8200	[X]Other slow virus infections of central nervous system
Ayu8300	[X]Slow virus infection/central nervous system, unspecified
Ayu8400	[X]Rabies, unspecified
Ayu8500	[X]Other mosquito-borne viral encephalitis
Ayu8600	[X]Mosquito-borne viral encephalitis, unspecified
Ayu8700	[X]Other tick-borne viral encephalitis
Ayu8800	[X]Tick-borne viral encephalitis, unspecified
Ayu8900	[X]Arthropod-borne viral encephalitis, unspecified
Ayu8A00	[X]Other specified viral encephalitis
Ayu8B00	[X]Unspecified viral encephalitis
Ayu8C00	[X]Other viral meningitis
Ayu8D00	[X]Viral meningitis, unspecified
Ayu8E00	[X]Other specified viral infections/central nervous system
Ayu8F00	[X]Unspecified viral infection/central nervous system
AyuJ000	[X]Sequelae of central nervous system tuberculosis
AyuJ800	[X]Sequelae of viral encephalitis
E2A3.11	Post-encephalitis syndrome
F00..00	Bacterial meningitis
F000.00	Haemophilus meningitis
F001.00	Pneumococcal meningitis
F002.00	Streptococcal meningitis
F003.00	Staphylococcal meningitis
F004.00	Meningitis - tuberculous
F005.00	Meningitis - meningococcal
F007.00	Meningitis in other bacterial disease classified elsewhere
F007000	Meningitis due to gonococcus
F007100	Meningitis due to listeriosis
F007200	Meningitis due to neurosyphilis

Appendix Table 3 cont. Codes and text terms used in the identification of possible outcomes

Read Code	Read Code Description
Other neurological disease included in identification of febrile seizures cont.	
F007300	Meningitis due to salmonella
F007400	Meningitis due to congenital syphilis
F007500	Meningitis due to secondary syphilis
F007600	Meningitis due to typhoid fever
F007700	Meningitis due to actinomycosis
F007800	Meningitis due to pertussis
F007z00	Unspecified meningitis in bacterial disease EC
F00y.00	Other specified bacterial meningitis
F00y000	Meningitis due to aerobacter aerogenes
F00y100	Meningitis due to bacillus pyocyaneus
F00y200	Meningitis due to escherichia coli
F00y211	Meningitis due to escherichia coli
F00y212	Escherichia coli meningitis
F00y300	Meningitis due to Friedlander bacillus
F00y311	Friedlander meningitis
F00y400	Meningitis due to klebsiella pneumoniae
F00y411	Klebsiella meningitis
F00y500	Meningitis due to proteus morganii
F00y511	Proteus morganii meningitis
F00y600	Meningitis due to pseudomonas
F00y611	Pseudomonas meningitis
F00yz00	Other specified bacterial meningitis NOS
F00z.00	Bacterial meningitis NOS
F01..00	Meningitis due to other organisms
F010.00	Meningitis due to fungal organisms
F010000	Meningitis due to cryptococcus
F010z00	Other fungal meningitis
F011.00	Meningitis due to viral organisms EC
F011000	Meningitis due to coxsackie virus
F011100	Meningitis due to ECHO virus
F011200	Meningitis due to herpes zoster virus
F011211	Herpes zoster meningitis
F011300	Meningitis due to herpes simplex virus
F011311	Herpes simplex meningitis
F011400	Meningitis due to mumps virus
F011411	Mumps meningitis
F011500	Meningitis due to lymphocytic choriomeningitis virus
F011511	Lymphocytic choriomeningitis
F011600	Meningitis due to adenovirus
F011611	Adenovirus meningitis
F011700	Varicella meningitis

Appendix Table 3 cont. Codes and text terms used in the identification of possible outcomes

Read Code	Read Code Description
Other neurological disease included in identification of febrile seizures	
F011y00	Other viral meningitis
F011z00	Meningitis - viral NOS
F011z11	Acute aseptic meningitis
F012.00	Meningitis due to trypanosomiasis
F013.00	Meningitis due to sarcoidosis
F01y.00	Other non-bacterial meningitis
F01y000	Meningitis due to leptospira
F01yz00	Other non-bacterial meningitis NOS
F01z.00	Meningitis due to organism NOS
F022.00	Chronic meningitis
F024.00	Benign recurrent meningitis
F02z.00	Unspecified meningitis
F03..00	Encephalitis, myelitis and encephalomyelitis
F030.00	Encephalitis in viral disease EC
F030000	Encephalitis due to kuru
F030011	Kuru encephalitis
F030100	Encephalitis due to subacute sclerosing panencephalitis
F030200	Encephalitis due to poliomyelitis
F030211	Poliomyelitis encephalitis
F030300	Encephalitis due to arthropod-borne virus
F030400	Encephalitis due to herpes simplex virus
F030411	Herpes simplex encephalitis
F030500	Encephalitis due to mumps virus
F030511	Mumps encephalitis
F030600	Encephalitis due to rubella virus
F030611	Rubella encephalitis
F030700	Encephalitis due to cytomegalovirus
F030711	Cytomegaloviral encephalitis
F030800	Encephalitis due to influenza-specific virus not identified
F030900	Encephalitis due to herpes zoster
F030911	Herpes zoster encephalitis
F030A00	Encephalitis due to influenza-virus identified
F030z00	Encephalitis in viral disease NOS
F031.00	Encephalitis due to rickettsia EC
F032.00	Encephalitis due to protozoa EC
F032000	Encephalitis due to malaria
F032011	Malarial encephalitis
F032100	Encephalitis due to trypanosomiasis
F032111	Trypanosomiasis encephalitis
F032z00	Encephalitis due to protozoa EC NOS
F033.00	Encephalitis due to other infection EC

Appendix Table 3 cont. Codes and text terms used in the identification of possible outcomes

Read Code	Read Code Description
Other neurological disease included in identification of febrile seizures cont.	
F033000	Encephalitis due to meningococcus
F033011	Meningococcal encephalitis
F033100	Encephalitis due to congenital syphilis
F033111	Syphilis encephalitis
F033200	Encephalitis due to syphilis unspecified
F033300	Encephalitis due to tuberculosis
F033311	Tuberculous encephalitis
F033400	Encephalitis due to toxoplasmosis
F033411	Toxoplasmosis encephalitis
F033z00	Unspecified encephalitis due to other infection EC
F034.00	Postimmunisation encephalitis
F034000	Post BCG vaccination encephalitis
F034100	Post typhoid vaccination encephalitis
F034200	Post paratyphoid vaccination encephalitis
F034300	Post cholera vaccination encephalitis
F034400	Post plague vaccination encephalitis
F034500	Post tetanus vaccination encephalitis
F034600	Post diphtheria vaccination encephalitis
F034700	Post pertussis vaccination encephalitis
F034800	Post smallpox vaccination encephalitis
F034900	Post rabies vaccination encephalitis
F034A00	Post typhus vaccination encephalitis
F034B00	Post yellow fever vaccination encephalitis
F034C00	Post measles vaccination encephalitis
F034D00	Post polio vaccination encephalitis
F034E00	Post mumps vaccination encephalitis
F034F00	Post rubella vaccination encephalitis
F034G00	Post influenza vaccination encephalitis
F034H00	Post hepatitis A vaccination encephalitis
F034J00	Post hepatitis B vaccination encephalitis
F034x00	Post mixed vaccination encephalitis
F034y00	Post other specified vaccination encephalitis
F034z00	Postimmunisation encephalitis NOS
F035.00	Postinfectious encephalitis
F035000	Encephalitis following chickenpox
F035011	Encephalitis due to varicella
F035100	Encephalitis following measles
F035z00	Postinfectious encephalitis NOS
F036.00	Toxic encephalitis
F036000	Toxic encephalitis due to lead
F036100	Toxic encephalitis due to mercury

Appendix Table 3 cont. Codes and text terms used in the identification of possible outcomes

Read Code	Read Code Description
Other neurological disease included in identification of febrile seizures cont.	
F036200	Toxic encephalitis due to thallium
F036z00	Toxic encephalitis NOS
F03X.00	Bacterial meningoencephalitis+meningomyelitis,NEC
F03y.00	Other causes of encephalitis
F03z.00	Encephalitis NOS
F212.00	Acute and subacute haemorrhagic leukoencephalitis [Hurst]
F292400	Chemical meningitis
Fyu0000	[X]Other bacterial meningitis
Fyu0100	[X]Meningitis in viral diseases classified elsewhere
Fyu0200	[X]Meningitis in mycoses classified elsewhere
Fyu0300	[X]Meningitis/other specifd infectious+parasitic diseases CE
Fyu0400	[X]Meningitis due to other specified causes
Fyu0500	[X]Bacterial meningoencephalitis+meningomyelitis,NEC
Fyu0600	[X]Other encephalitis, myelitis and encephalomyelitis
Fyu0700	[X]Encephalitis,myelitis+encephalomyelitis/bactrl disease CE
Fyu0800	[X]Encephalitis,myelitis+encephalomyelitis/viral disease CE
Fyu0A00	[X]Encephalitis,myelitis+encephalomyelitis/other diseases CE
N000611	Systemic lupus erythematosus encephalitis
A560100	Rubella encephalomyelitis
F023.00	Arachnoiditis
F03..11	Encephalomyelitis
F03..12	Myelitis
F03..13	Transverse myelitis
F03y.11	Encephalomyelitis NOS
F03y.12	Myalgic encephalomyelitis
F03z.11	Encephalomyelitis NOS
FyuK100	[X]Other and unspecified heterotropia
P240.00	Congenital cerebral cyst
P240.11	Congenital intracerebral cyst
P240000	Single congenital cerebral cyst
P240100	Multiple congenital cerebral cysts
P240z00	Congenital cerebral cyst NOS

Appendix Table 3 Cont. Codes and text terms used in the identification of possible outcomes

Anaphylaxis was identified in 3 ways:
1. A code for anaphylaxis alone, or a term for anaphylaxis with no preceding negative (List A).
2. A code for allergic reaction*.
3. A term indicating allergic reaction*.
*2 and 3 also require a term indicating this was severe (List B) but no preceding negative (including List A).

List A Exclusions across anaphylaxis searches if immediately before term or with an intervening 'an' (list specific exclusions are given below):
(if, rarely) [a]; (discussed, maternal, no, H/O, HO, hx, not)[c];
(any sx of, advice of, sx of, advice on features of, advice on signs of, advice on symptoms of , any signs of, if signs, if sx of, no evidence that (s)he has, no features of, no sx of, no symptoms of , have had, if any, if any evidence of , if evidence of, never had, no evidence of, no triggering, not as, not had, risk(s) of)[e].

List B inclusion criteria in searches 2 and 3: (Severe, serious, adrenaline, icu, life-threatening)[c]; (life threatening, intensive care)[e] BUT NOT (serious eczema, severe eczema)[e].

Read Code	Read Code Description	Unstructured text search
Anaphylaxis 1 (code or text term identified)		
D310011	Anaphylactoid purpura	Anaphyl[a]
K032300	Anaphylactoid glomerulonephritis	Angioedema[a]
SN50.00	Anaphylactic shock	Angioneurotic oedema[d]
SN50.11	Anaphylaxis	Angioneurotic edema[d]
SN50000	Anaphylactic shock due to adverse food reaction	Angiodema[a]
SN50100	Anaphy shock due/adv efect/correct drug or med proprly admin	**Exclusions:** List A or: Anywhere in the same text: (from standard practice consent text) consent[a]; discussed side effects[e]; warned[c] Immediately prior to term: previous[a]; hereditary[c]; (history of, SE inc. no evidence, if evidence, any evidence, no sx, any sx, no symptoms, any symptom, if symptoms, if signs (of), no signs of, any sign(s), any signs, no sign(s), no progression towards, been having)[e].
SN51.00	Angioneurotic oedema	
SN51.11	Angioedema	
SN59400	Anaphylactic shock due to wasp sting	
SN59300	Anaphylactic shock due to bee sting	
Anaphylaxis 2 A code for allergic reaction if linked to a text term in List B with no exclusion preceding the list B term)		
SN53000	Allergic reaction	**Exclusions:** List A or: (?, previous)[c] ; (a probable, been having, history of, if signs of, likely to have, not as)[e]
SN59000	Allergic reaction to bee sting	
SN59100	Allergic reaction to insect bite	
SN59200	Allergic reaction to wasp sting	
SN53.11	Hypersensitivity NOS	
SN52.12	Allergic drug reaction NOS	
Anaphylaxis 3 A term listed below and one from list B with no exclusion (from list A or below) preceding either term		
Terms: allergic reaction[b]. hypersensitivity[c]. **Exclusions:** List A or: (likely to have, a probable, been having, history of, not as, if signs of)[e], [c].		

[a]Contains. [b]All words, [c]A complete word. [d]All words together (in any order) [e]All words in order.[f]From Run 2. N.B Code lists were updated during the study in-line with practice lists

Signature of Principal or Coordinating Investigator

GlaxoSmithKline Biologicals
Vaccines R&D
Investigator Approval Page

STUDY TITLE: Post-licensure observational safety study after meningococcal B vaccine 4CMenB (Bexsero) vaccination in routine UK care

Study: 205512 [MENB REC 2ND GEN-007 EPI VS GB DB (V72_36OB)]

Development Phase: Observational Study

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Investigator:	Gillian Hall
Affiliation /investigational centre:	Independent Consultant in Pharmacoepidemiology
Signature of Investigator:	_____
Date:	_____

- ----------Checksum----------!Ver.!Created On - -
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GlaxoSmithKline Biologicals
Vaccines R&D
Sponsor Signatory Approval Page

Please note that by signing this page, you take responsibility for the content of the Study Report

STUDY TITLE: Post-licensure observational safety study after meningococcal B vaccine 4CMenB (Bexsero) vaccination in routine UK care

Study: 205512 [MENB REC 2ND GEN-007 EPI VS GB DB (V72_36OB)]

Development Phase: Observational Study

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory:	Daniela Toneatto
Title of Sponsor Signatory:	Clinical and Epidemiology Project Lead
Signature:	_____
Date:	_____

- ----------Checksum----------!Ver.!Created On - -
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