Title	Post-licensure observational safety study after meningococcal B vaccine 4CMenB (Bexsero®) vaccination in routine UK care.
Protocol version identifier	2
Date of last version of protocol	24 AUG 15
EU PAS registry number	TBC
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)	Novartis Vaccines and Diagnostics srl; Via Fiorentina, 1; 53100 Siena (Italy)
Joint PASS study	No
Research question and objectives	The objective of this post-marketing observational study is 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 outcomes.
Country(ies) of study	United Kingdom
Author	Gillian Hall, Independent Consultant in Pharmacoepidemiology, Grimsdyke House, London, EN5 4ND, UK Reviewed by: Mirna Robert-Du Ry van Beest Holle, Global Epidemiology, Vaccines, GSK, The Netherlands.

	Marianne Cunnington, Head, Global Epidemiology, Vaccines, GSK, UK.

Marketing authorisation holder(s)

Marketing authorisation holder(s)	Novartis Vaccines and Diagnostics srl; Via Fiorentina, 1; 53100 Siena (Italy)
MAH contact person	Mirna Robert-Du Ry van Beest Holle, MD MPH; Global Epidemiology, GSK, Hullenbergweg 81-89, 1101 CL Amsterdam, The Netherlands

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2. LIST OF ABBREVIATIONS

ADEM	Acute Disseminated Encephalomyelitis
AHD	Additional health data
ATC	Anatomical Therapeutic Chemical
CI	Confidence Intervals
EMA	European Medicines Authority
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
KD	Kawasaki disease
MAHs	Market authorisation holder
MMR	Measles, mumps, rubella
MMRV Vaccine	Measles, mumps, rubella, and varicella
NIP	National immunisation programme
NVx	Novartis Vaccines and Diagnostics
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

THIN	The Health Information Network

3. RESPONSIBLE PARTIES

3.1 Main Author(s) of the Protocol

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

3.2 Principal Investigator

Gillian Hall who has regular contracted access to THIN through IMS (Information Solutions Medical Research Limited, 1 Canal Side Studios, 8-14 St. Pancras, London NW1 0QG).

3.3 Coordinating Investigator(s)

The study will be performed at one center.

3.4 Advisory Committee

There will be no Advisory Committee for this study but an Adjudication Committee will be developed. See Section 9.4.4 for details and responsibilities.

4. ABSTRACT

Name of MAH: Novartis Vaccines and Diagnostics srl – Via Fiorentina, 1 – 53100 Siena (Italy)	**Protocol number:** V72_36OB	**Date of Protocol Abstract:** 24 AUG 15
Title of Study: Post-licensure observational safety study after meningococcal B vaccine 4CMenB (Bexsero®) vaccination in routine UK care.		
Study Period: The study will start on 31st December 2015 (first data cut) and will include data from 1st May 2015 for three years.	**Study Type:** Required observational post-authorization safety study.	
Rationale and Background: 4CMenB vaccine (Bexsero®) is a multicomponent meningococcal serogroup B vaccine [redacted] European approval was given in 2013 and 4CmenB is to be added to the UK National Immunisation program (NIP) in September 2015. For infants born after July 2015 the vaccination is to be given at 2, 4 and 12-13 months. A catch-up program includes children born from 1st May 2015 who will also be given three doses unless the first dose is at four months when they will receive two doses of 4CMenB. [redacted] [redacted] The purpose of this study is to investigate the safety of 4CMenB vaccination in routine post-marketing use in the UK as a post-authorisation safety study.		
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 for primary outcomes based on a database of UK primary care records.		

Name of MAH: Novartis Vaccines and Diagnostics srl – Via Fiorentina, 1 – 53100 Siena (Italy)	**Protocol number:** V72_36OB	**Date of Protocol Abstract:** 24 AUG 15

Population: The baseline population will be those children permanently registered at a UK primary care practice which contributes data to The Health Information Network (THIN) database between a start date and an end date (observation period). The start date for each child will be the most recent of 1st May 2015 (data collection start), date of birth plus one month, or transfer from another practice plus three months. The first month of life is not included as part of this time is usually spent in secondary care. The three months after transfer into the practice is not included so that prevalent events recorded at a registration visit during this period are not mistaken for incident episodes. The end date will be the earliest of date of birth plus 18 months, transfer out of the practice, last data collection or the study end. There are no exclusion criteria.

Descriptive analysis – The study population will be all children in the baseline population who receive one or more vaccinations with 4CMenB during their observation period.

Self-Controlled case series (SCCS) – For each outcome the study population will be children selected in the baseline population and who had a diagnosis of that outcome and had received at least one dose of 4CMenB vaccine in their observation period.

Variables:

Exposure(s) of interest

The exposure of interest is 4CMenB vaccine administered in routine clinical practice. 4CMenB vaccination will be identified from the 'Additional Health Data' file of THIN database of primary care records which includes records of preventive medicine. This section of the practice software has specific screens for entering vaccination details as they are given. The file will be searched for records of any 4CMenB vaccination during the child's observation period. In the UK, all preschool vaccinations are routinely given in primary care and recorded in the child's primary care record.

Outcome(s)

The primary outcomes are seizures (all and febrile seizures), and Kawasaki disease. ADEM, GBS, and anaphylaxis are also included in this study.Cases will be identified by searching the Medical and Additional Health Data files of THIN database.

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The definition of a seizure will be a record of an appropriate Read code for seizure or convulsion dated in the child's observation period. Febrile seizures will be a sub-set of all seizures and will have a specific code or evidence of a concomitant fever, occur after one month of age, but no previous diagnosis or treatment for epilepsy or concurrent central nervous system infection.

The Kawasaki disease cases will be identified by code and text searches. The case definition will be a secondary care diagnosis of Kawasaki disease or a record of a diagnosis in the primary care record if this is supported by evidence of secondary care involvement (Hall et al, in press). A sensitivity analysis will include possible cases. All records with a code or text term for Kawasaki disease will be reviewed and classified as a case or not against the case definition by an independent Adjudication Committee.

Cases of ADEM, GBS, and anaphylaxis will be identified using the same procedure as Kawasaki disease. Case definitions and search terms will be confirmed by the Adjudication Committee before the first data cut and will be documented in the Statistical Analysis Plan.

Other Variables

Age and sex will be 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 will be assumed to be 16th of their month of birth.

Other NIP vaccinations will be identified in the same manner as 4CMenB from the THIN Additional Health Data file.

Data Sources: THIN is an observational database of primary care electronic medical records from practices throughout the UK and covers approximately 6% of the UK population. 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. Medical events are automatically coded at entry using the Read coding system (NHS Centre for Coding and

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Classification 1996) and can be supplemented with unstructured text including 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 immunization 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 (Blak 2011).

Study Size: THIN comprises patient records from a number of practices. Consequently the study size can only be varied by increasing its duration. There are approximately 35,000 new born babies registered on THIN each year who are eligible for the NIP and the majority of whom will receive three exposures to 4CMenB.

For the SCCS analysis – It is estimated based on a birth cohort of 35,000 infants a year and an observation period of 68 weeks (from 1 to 18 months of age) based on 80% power, an alpha of 0.05, one year of 4CmenB exposures will be required to provide a relative incidence (RI) of 3 for seizures. Two years of data will be required to provide a relative incidence of 10 for the for Kawasaki disease (see Section 9.5 and Table 9.5.3.1-1).

No episodes of GBS, ADEM or Anaphylaxis are expected in the risk period because of a combination of the incidence and the length of the risk period. Only the descriptive analysis, including plots, will be reported for these outcomes, no SCCS is planned. However, if at least one of the secondary outcomes is identified in the risk period (see SCCS analysis below) and the total number of outcomes is sufficient to detect a relative incidence of 10 then a SCCS will be completed (see Section 9.5 and Table 9.5.3.1-1).

Data Analysis:

Descriptive analysis: The incidence of each outcome will be estimated as the number of episodes observed per 100,000 patient years. The incidence during each risk period, in total and after each immunisation dose (2, 4 and 12-13 months) will be estimated. A plot will be produced to show the temporal distribution of cases of outcomes around the date

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of the exposure. See section 9.7.3 Figure 1 for an example.

SCCS - Relative incidence and 95% confidence intervals will be estimated using the self-controlled case series (SCCS) method. Within the SCCS design outcome specific post-exposure risk periods will be defined. These risk periods are the time frame when an outcome might be expected to occur if it was caused by the exposure based on known mechanisms, published studies or case reports. Person time and outcomes for each individual will be assigned to the risk period or a control period outside this risk period. A relative incidence will then be calculated.

A pre-risk period (pre-exposure) will also be defined for each outcome. This is the period of time after an outcome when vaccination may be postponed. The incidence of an outcome may therefore be lower than the normal background rate during this period so the person time and outcomes during this period will excluded from the analysis.

Informed Consent and Ethical Approval: The study was submitted to, and approved by, the THIN research ethics committee.

Milestones:

Study start (first data cut): 31st December 2015

Initial report on study numbers: 31st May 2016

Interim report: to NVx 30th November 2017, to EMA 31st December 2017

Final report: to NVx 30th November 2019, to EMA 31st December 2019

5. AMENDMENTS AND UPDATES

Amended on 24rth August 2015 (version 2.0)

Version 1 of the protocol was completed in 2011 before the UK NIP schedule for 4CMenB was known. This version reflects changes to the protocol based on details of the NIP. All sections of the protocol have been amended.

6. MILESTONES

Table 6-1 Overview of study milestones

Milestone	Planned date [DD MMM YY]
Submission to Ethics Committee/Institutional Review Board	12th June 2015
Registration in the EU PAS register	1st December 2015
Start of data collection (receipt of 1st data extraction)	31st December 2015
Study progress report 1	Provided to NVx, 1st May 2016 Provided to EMA 31st May 2016
Study progress report 2	Provided to NVx, 1st November 2016 Provided to EMA 30th November 2016
Data collection cut off for interim analysis	31st December 2016
Study progress report 3	Provided to NVx, 1st May 2017 Provided to EMA 31st May 2017
Study progress report 4	Provided to NVx, 1st November 2017 Provided to EMA 30th November 2017
Interim report	Data cut off, 31st December 2016 Provided to NVx, 30th November 2017 Provided to EMA 31st December 2017
Study progress report 5	Provided to NVx, 1st May 2018 Provided to EMA 31st May 2018
Study progress report 6	Provided to NVx, 1st November 2018 Provided to EMA 30th November 2018
Final report of study results	Data cut off, 31st December 2018 Provided to NVx, 30th November 2019 Provided to EMA 31st December 2019

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 (Viner 2012). Young children and teenagers are at highest risk of the disease, with the peak incidence in those under one year of age (JVCI March 2014).

There are thirteen different types of the bacterium distinguished by the composition of the capsular polysaccharide. Six of these capsular types A, B, C, W, X and Y - cause almost all of the disease cases worldwide (Chang 2012). The most common types in the UK are B, C, W and Y. Since the Meningococcal C vaccine was introduced in the UK in 1999, there has been a sharp fall in cases of this form of the disease (Campbell 2009). In 2012, meningococcal group B was responsible for 85% of the 716 laboratory confirmed cases of meningococcal disease in England and Wales although the numbers have been falling (Health Protection Agency 2012). Conversely, cases of Meningococcal W disease have been on the increase in the UK since 2009.

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 strain [redacted] European approval was given in 2013 and it is to be added to the UK National Immunisation program (NIP) from September 2015. For infants born after July 2015 the vaccination is to be given at 2, 4 and 12-13 months (NIP Dose 1, 3 and booster). A catch-up program includes children born from 1st May 2015 who will also be given three doses unless the first dose is at four months when they will receive two doses.

[redacted] The purpose of this study is to investigate the safety of 4CMenB vaccination in routine post-marketing use in the UK as a post-authorisation safety study (PASS).

8. 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.

9. RESEARCH METHODS

9.1 Study Design

Two observational analyses will be completed based on a database electronic primary care records. The first analysis will describe the incidence of each study outcome after vaccination and provide a temporal plot of each outcome in relation to 4CMenB exposure (9.7.3 Statistical Methods). Stage two will be a self-controlled case series (SCCS) of the primary outcomes.

The SCCS method was developed to estimate the relative incidence of an acute event in a pre-defined post-vaccination risk period, compared to other time, which constitutes the control period (Farrington 1996). It is a conditional, retrospective, risk-interval cohort method. SCCS analyses assume that the incidence of the adverse event of interest is increased only during the pre-specified time period after an exposure, known as the risk period. Outside this risk period, the exposure is assumed to have no effect on the incidence of the adverse event, so the incidence during this control period is the background rate. The risk period is defined based on the evidence of when any study outcome due to the exposure is likely to occur. For example, if febrile seizure due to exposure might be expected to occur on days seven to ten after vaccination, then the risk period for febrile seizure would comprise these four days. An overall study time-window is chosen to maximize the chance that individuals experience both risk and control periods. This is usually defined by age and calendar time boundaries. The method can be used for repeat exposures as with multiple dose vaccines (Whitaker 2007). More detail of the method is given in Section 9.7.3 and Figure 1.

Alternative methods were considered for this study. Cohort and case-control designs were reviewed but the removal of bias due to fixed variables in the SCCS is an important advantage as there is the possibility of confounding due to unmeasured variables such as race and genetic susceptibility. Time varying confounders such as age and calendar time are not automatically accounted for in a SCCS so will be addressed in the study design. SCCS also has the advantage of increased power compared to a case-control study. Each study outcome was reviewed to confirm that it fulfilled the Poisson requirement that events could reoccur or are rare and that repeated events are independent.

The additional major benefit of observational studies is that they reflect the true clinical situation, taking into account the actual environment including patient profile, concomitant treatment or vaccination, etc. One limitation of an observational database study is that the researcher can use only that information which is routinely available in general practice. In the present study, the only information available on the study outcomes is that in the general practice record including correspondence from secondary care. It is therefore likely that, for many episodes, there will be insufficient clinical detail available to researchers to classify diagnoses using detailed published case definitions.

Consequently, any case identified through Read codes will be compared to a study case definition. The exception is seizures as febrile seizures may not be referred to secondary care depending on severity (Andrews 2010). For this study outcome, all cases identified through Read codes will be included and a validation exercise completed.

9.2 Setting

9.2.1 Study Period

The study will start in 31st December 2015 (first data cut) and will include data from 1st May 2015 for three years.

9.2.2 Study Subjects

The baseline population will be those children permanently registered at a UK primary care practice which contributes data to The Health Information Network (THIN) database between a start date and an end date (observation period). The start date for each child will be the most recent of 1st May 2015 (earliest data included), date of birth plus one month, or transfer from another practice plus three months. The first month of life is not included as part of this time is usually spent in secondary care. The three months after transfer in is not included so that prevalent events recorded at a registration visit during this period are not mistaken for incident episodes. The end date will be the earliest of date of birth plus 18 months, transfer out of the practice, last data collection or the study end. There are no exclusion criteria.

9.2.3 Study Population Selection

Descriptive analysis – The study population will be all children in the baseline population who receive one or more vaccination with 4CMenB in their observation period.

SCCS – For both primary outcomes the study population will be children in the baseline population who had a diagnosis of that outcome and had received at least one dose of 4CMenB vaccine.

9.3 Variables

9.3.1 Exposure of Interest

The exposure of interest is 4CMenB vaccine administered in routine clinical practice. This will include infants immunised within the UK NIP shown in Table 1 and those in the catch-up scheme.

Table 9.3.1-1 Vaccinations included in the UK National Immunisation Program for children under two years from September 2015

Dose (recommended age)	Vaccinations
Dose 1 (2 months)	5-in-1 (DTaP/IPV/Hib); PCV, rotavirus; 4CMenB
Dose 2 (3 months)	5-in-1 (DTaP/IPV/Hib); meningitis C, rotavirus
Dose 3 (4 months)	5-in-1 (DTaP/IPV/Hib); PCV; 4CMenB
Booster (12-13 months)	Hib; Meningitis C; PCV; MMR; 4CMenB

DTaP = diphtheria, tetanus, pertussis;
IPV = polio;
Hib = haemophilus influenzae type b;
PCV = pneumococcal vaccine;
MMR = measles, mumps and rubella.
From: http://www.patient.co.uk/doctor/immunisation-schedule-uk

9.3.2 Outcome(s)

The primary outcomes are seizures (all and febrile seizures), and Kawasaki disease [redacted]

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 immunization are mostly triggered by fever induced by the vaccine (febrile seizures) or are not vaccine related (Bonhoeffer 2004).

A recent UK primary care study reported that age specific rates of generalized convulsive seizure increased sharply from 3.5 per 1000 patient years at 2 months of age, peaking at 19.2 per 1,000 person years at 16 months and decreasing until approximately 6 years of age. Febrile seizures rates also followed this age trend peaking at 16.1 per 1000 person years at 16 months of age while afebrile seizure rates remained relatively stable across these age groups, 2-4 seizures per 1,000 patient years (Sammon In press). 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: 10.1-13.1) within 14 days and 42 days of vaccination respectively (Ferreira and Carrigan 2009).

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 (Eleftheriou 2014). 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 (Newburger

2004; Moore 2014). Disease definitions require a fever for five days plus four of the five remaining criteria in North American guidelines (Newburger 2004), or five of the six symptoms in Japan (Ayusawa 2005). Incomplete cases have fewer characteristics, whereas atypical Kawasaki disease generally includes only 2 or 3 of the criteria plus coronary artery aneurysms.

A recent of Kawasaki disease study based on THIN reported an incidence per 100,000 of 15.0 (95% CI 5.6, 39.9) in the 28 days post immunisation with stages 1, 3 or booster of the NIP active during 2008 to 2012 (before rota virus was added to dose 1) (Hall et al, pre-publication report available on request). Other Northern European countries have reported annual incidences for the under-fives of between 4.5 and 11.4 per 100,000 (Fischer 2007; Olafsdottir 2012; Salo 2012; Tacke 2014).

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 so will be included in the study definition.

A recent German study, reported a crude incident rate for GBS of 0.4 per 100,000 population for those under 3 years (estimated from chart) with a slightly higher rate in those aged 4 to 9 years (Hense 2014). The VAESCO study in eight European countries reported a background rate per 100,000 person-years of 0.6 to 1.3 in children under10 years. The UK rate was 0.8 per 100,000 person-years (VAESCO 2011).

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 immunization (Sejvar 2007). 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.

This is a rare condition, with an annual US incidence of 0.4 per 100,000 population under 20 years and 0.6 per 100,000 population under 5 years (Leake 2004).

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 immunizations (Ruggeberg 2007).

UK studies have reported an annual incidence per 100,000 of anaphylaxis as 5.0 to known triggers and 1.7 with no identified trigger in those under 10 years (VAESCO

2011) and 7.9 per 100,000 (95% confidence intervals (CI) 7.0, 9.0) across all ages (Sheikh 2008). Annual incidences per 100,000 of any anaphylactic reaction in children from other countries vary greatly, 10 or 70 (Bohlke 2004; Decker 2008).

9.3.3 Other Variables

Age and sex, and date and type of all other pre-school vaccinations listed in Table 1 will be identified from THIN.

9.4 Data Sources

THIN is an observational database of primary care electronic medical records from practices throughout the UK and covers approximately 6% of the UK population. 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 (NHS Centre for Coding and Classification 1996) and can be supplemented with unstructured text including electronic discharge summaries. Details of preventive medicine 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 immunization 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 (Blak 2011).

UK electronic primary care records have previously been used for the study of the safety of vaccines (Kaye 2001; Tata 2003; Stowe 2011) and in SCCS designs (Smeeth 2004; Hubbard 2005). Recent studies have estimated the incidence of Kawasaki disease (Hall In press) and seizures (Sammon In press) and have developed methods of case identification as well as case definitions.

9.4.1 Operational Exposure Definition

4CMenB vaccination will be identified from the AHD file of THIN. The file will be searched for records of any meningitis B vaccination during the child's observation period (9.2.3 Study Population Selection). The vaccination, dose (first or third dose of the

NIP or booster) and date will be identified. Those labelled as 'given' rather than 'refused' or 'advised' will be considered to be delivered.

At present 4CMenB is the only vaccination against meningitis B available in the UK NIP. If other vaccinations become available then 4CMenB will be identified by batch number. Vaccination batch numbers have been shown to be routinely recorded on THIN (Hall and Hill 2014).

9.4.2 Operational Outcome Definition and Identification Process

Each of the six outcomes is considered below. Cases will be identified from the Medical and AHD files of THIN database. As the Read code dictionary is updated biannually final code lists and search terms will be developed and agreed with the Adjudication Committee shortly before the first data cut and at updates. The code lists and agreed case definitions will be included in an Identification and Review Plan which will be included in an Appendix to the Statistical Analysis Plan (SAP) and attached to the interim and final reports.

Primary outcomes

All seizures and febrile seizures: As seizures can be diagnosed in primary care without referral, the definition of a seizure will be a record of an appropriate Read code for seizure or convulsion in the patient's file during their observation period. Cases will not be reviewed by the Adjudication Committee. Instead a validation exercise will be completed by questionnaire. A case of febrile seizure will be defined as:

- a code specifically indicating febrile seizure OR
- a general seizure code linked to unstructured text indicating the presence of 'fever' OR
- a general seizure code and either a Read code for fever or a temperature of >38^{o}C on that day or in the previous 5 days

But NO

- Read code for epilepsy or an anticonvulsant prescription on the date of, or prior to, the seizure code OR
- Read code for a central nervous system infection in the 14 days before to 42 days after the date of seizure OR
- Age of onset less than one month

(Sammon In press)

The date of onset will be the date of the seizure code. Second cases within 30 days will be excluded as these will be assumed to be follow-up visits rather than incident episodes.

Kawasaki disease – The searches will identify records with a Read code for Kawasaki disease or 'kawasaki' in the unstructured text. The search strategy was developed in a study on THIN which used a range of search criteria and reported positive and negative predictive values (Hall In press).The search period will be 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 will be reviewed independently by at least two members of the Adjudication Committee who will classify the event as an incident episode or not against a case definition and assign a date of onset. The review will be blinded to the date of vaccination. The accuracy of the diagnosis will not be judged as the full secondary care notes will not be available. If there is insufficient information to form a decision based on the electronic record then the practice will be contacted and asked for further information. If there is any discordance in the initial review the outcome will be discussed with the Committee as a whole and a consensus taken.

The recent study on THIN looked at the incidence of Kawasaki disease and trends across seasons and years. An Adjudication Committee developed a case definition of a documented final secondary care diagnosis of Kawasaki disease 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 (Hall In press). Onset was the date that the fever started or, if this was not recorded, the date of the first clinical characteristic of Kawasaki disease. If these details were not available, then onset was assumed to be the date of diagnosis. The recent analysis identified records with a final secondary care discharge diagnosis of possible Kawasaki disease (Hall In press). A sensitivity analysis will include a possible category defined as a final secondary care diagnosis such as '?' or 'suspected' Kawasaki disease (or similar), or, for cases not included in the full Kawasaki disease category, 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.

Secondary outcomes

Episodes of ADEM, GBS, and anaphylaxis will be identified and reviewed using the same procedure as Kawasaki disease. Case definitions and search terms will be agreed by the Adjudication Committee before the first data cut and will be documented in the Identification and Review Plan. The case definitions will be based on published definitions such as the Brighton Collaboration (Ruggeberg 2007; Sejvar 2007; Sejvar 2011) but may be modified to work with primary care records.

9.4.3 Operational Variable(s) Definition

Age and sex will be 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 will be assumed to be 16th of their month of birth.

Other NIP vaccinations will be identified in the same manner as 4CMenB (9.4.1 Operational Exposure Definition).

9.4.4 Advisory Committee(s)

There will be no Advisory Committee for this study. An Adjudication Committee will be set-up prior to the start of the study. The role of the Adjudication Committee will be to:

- agree case definitions for GBS, ADEM and anaphylaxis,
- advise on code lists and search terms for all outcomes,
- adjudicate cases of Kawasaki disease, GBS, ADEM and anaphylaxis against the case definition,
- review and agree risk windows for all outcomes,
- comment on interim and final reports.

The Adjudication Committee will include clinical expertise in neurology and immunology and will be external to NVx.

9.5 Study Size

THIN comprises patient records from a number of practices. Consequently the study size can only be varied by increasing its duration. There are approximately 35,000 new born babies registered on THIN each year who are eligible for the NIP (personal communication IMS Health) and who will 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 9.5.3.1-1 for each outcome. The post-exposure risk periods were based on data in Appendix 3 other than anaphylaxis which was accepted to occur on the day of exposure to a trigger or the next day.

It is likely that no cases of GBS, ADEM and Anaphylaxis will be identified in the risk period because of a combination of the incidence of these outcomes and the length of their risk period. If at least one outcome is 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 9.5.3.1-1), then a SCCS will be completed.

Table 9.5-1 The number of years required based on 80% power, an alpha of 0.05 and 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
All seizures	900[1]	315	12	32	<1	7	<1
All 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 (Sammon In press)
[2] Hall et al report available
[3] (Hense 2014)
[4] (Leake 2004)
[5] (VAESCO 2011)
[6] based on 35,000 infants
[7] based on data in Appendix 3 and assuming 3 exposures so =risk period*3
[8] (Musonda 2006)

9.6 Data Management

9.6.1 Data Processing

The THIN database will be searched for the study variables, Read codes and text terms at regular intervals of approximately two months following a programming specification agreed with the Principal Investigator. The programing and cuts of data for this study will be completed by staff at IMS Health who have direct access to the database. These cuts are subject to routine quality assurance following standard operative procedures.

The output from these searches will be provided to the Principal Investigator. All potential cases of Kawasaki disease, GBS, ADEM and anaphylaxis will be reviewed by the Adjudication Committee and judged as a case or not and a date of onset assigned. In addition, all deaths will be reviewed for a cause of death that is a study outcome. When additional data or a validation request are required a request will be sent to the practice via a third party following an establish process to maintain confidentiality. The review will include the electronic record and any additional information received from the practice.

9.6.2 Software and Hardware

Further details on software will be reported in the SAP.

9.7 Data Analysis

9.7.1 Statistical Hypotheses

Descriptive analysis – the descriptive analysis does not involve hypothesis testing.

SCCS – The hypothesis for the SCCS is that there is no increased risk of the study events in the risk periods immediately after exposure when compared to the control period. The study is designed to detect a signal rather than refute that there is no signal.

9.7.2 Analysis of Demographics and Baseline Characteristics

The number of exposed children, the mean age at exposure (and interquartile range) and percentage male will be reported by 4CMenB dose.

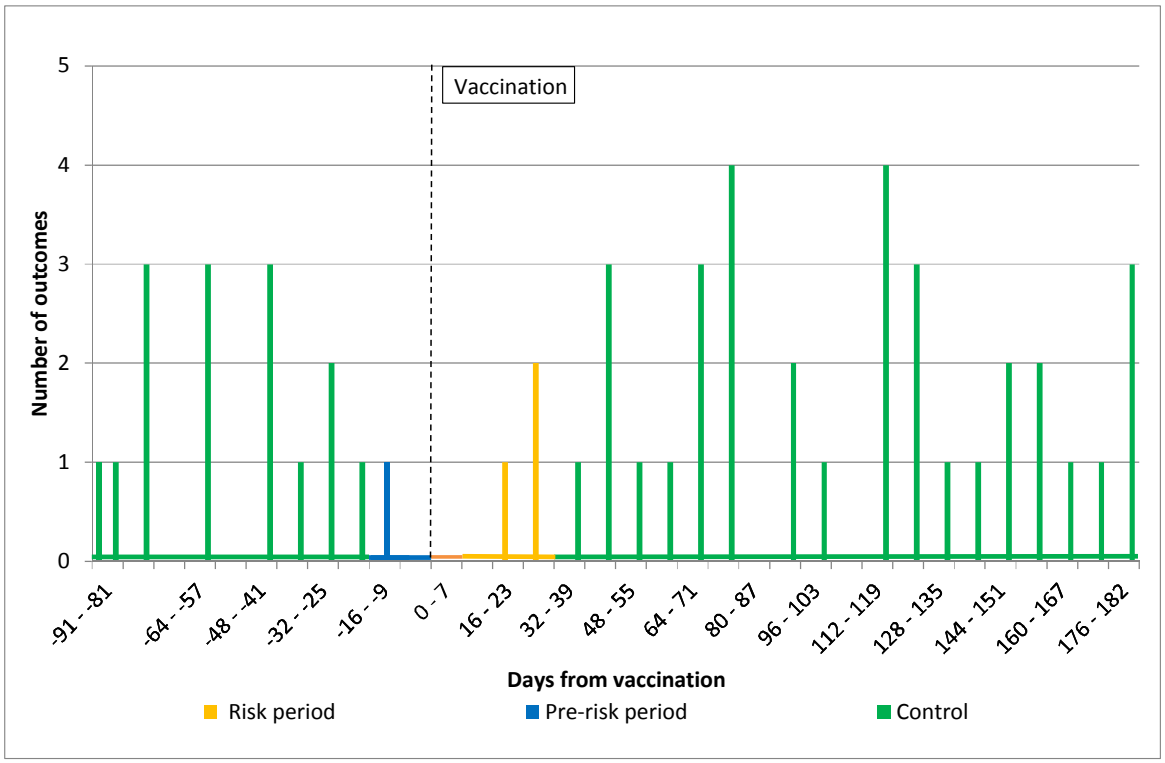
9.7.3 Statistical Methods

A SAP will be completed before the study is started which will include quality control procedures.

Descriptive analysis: The incidence of each outcome will be estimated as the number of episodes per 100,000 person years with 95% confidence intervals. The incidence during each risk period in total and after each immunisation dose will be estimated.

A plot will be produced for each outcome to show the temporal distribution of outcomes around the date of the vaccination (Stowe 2009). See Figure 1 for an example.

Figure 9.7.3-1 Example plot of temporal distribution of outcomes around vaccination date



SCCS - Relative incidence and 95% confidence intervals will be estimated using the SCCS method (Whitaker 2006) for each primary outcome. Person time and outcomes for each individual will be assigned to either a post-exposure risk period or a control period outside this risk period. A relative incidence will then be calculated. The risk period for each outcome is given in Table 1 based on published studies and case reports given in Appendix 3. These, and the pre-risk periods, will be agreed with the Adjudication Committee. Multiple risk windows can be used. Multiple exposures will be included in the analysis. Time and outcomes during the pre-risk period will be excluded. If the distribution of cases in the temporal plots indicates a clustering or lack of outcomes which does not fit the pre-defined risk periods, then the Adjudication Committee will decide if additional sensitivity analyses with new risk periods are required for both the incidence estimation and any SCCS.

Full details of the SCCS analysis will be included in the SAP. The analysis will be adjusted for time-varying exposures such as age, respiratory virus seasons and calendar year. If concurrent vaccinations are time-varying exposures (for example a new vaccination is introduced) these will be accounted for in a sensitivity analysis. Tests for interactions will be completed, if necessary. If appropriate, the analysis can be repeated

treating each vaccination stage separately as the risk may be different due to different levels of immune response. The primary analysis will include the first episode of an outcome with a sensitivity analysis including all episodes (Section 9.7.4).

9.7.4 Statistical Considerations

In general the self-controlled case series method is suitable for independent recurrent events (Whitaker 2007). It may also be applied to rare non-recurrent events. If recurrent events are not independent yet the occurrence of a first event is rare, then the method can be applied using just the first event. This approach also accounts for the difficulties in distinguishing new episodes of an outcome on electronic healthcare records. Although the Adjudication Committee review for Kawasaki disease episodes and other secondary outcomes will identify new episodes.

While there is a possibility of reduced vaccine use in cases who had already had a study outcome (for example GBS) (Andrews 2011), this should be accounted for with pre-vaccination control time as further vaccination is recommended in these cases. Reduced vaccine use for a short period after illness or treatment will be addressed by using the pre-risk period.

9.8 Quality Control

9.8.1 Validation

A sample of those patients with a record of a seizure identified in the first study year will be validated against a practice questionnaire. The questionnaire will ask if the patient experienced any seizure during that child's observation period and whether or not this was febrile. A positive predictive value (PPV) will be estimated for the presence of seizure and of febrile seizure. While the questionnaire will be treated as the 'gold standard' this is not always the case. From Table 9.5.3.1-1 , 310 infants would be expected to have a seizure during the first year, the majority febrile seizures. The questionnaire will be sent to random sample of 100 of these children selected from practices that have agreed to respond to questionnaires.

For the other less common outcomes each potential case will be reviewed by the Adjudication Committee against the case definition and additional data will be requested from the practice if required.

9.8.2 Record Retention

Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced will be retained for a period of 5 years in accordance with Good Pharmacoepidemiological Practice guidelines. This will include study records

or documents may include the analyses files, syntaxes (usually stored at the site of the database), but also questionnaires.

9.9 Limitations of the Research Methods

Co-administration of other vaccines will occur within the NIP. Within the UK NIP, PCV is given at the same stages as 4CMenB. It may not be possible to differentiate between the effects of individual vaccinations with any methodology based on data from routine care. For example, an increased risk of febrile seizures has been reported after MMR immunisation (Miller and Andrews 2007; Klein 2010). MMR will be given at the same time as 4CMenB in children aged 12-13 months. It may not be possible to differentiate the effects of the two vaccinations.

It is possible that differential misclassification will occur if it is known that a study outcome has been associated with vaccinations in the past, for example in GBS. The misclassification should be minimized by use of study definitions. However, in some cases only the primary care record will be available, particularly for seizures. It may be difficult to classify seizures as febrile or not based on the primary care record. As most seizures in the study age range are febrile two risk windows have been selected for the analysis of all seizures; one week to reflect febrile seizures and four weeks for other seizures. These will be discussed with the Adjudication Committee for approval.

The study is powered to study all seizures and febrile seizures. The SCCS analysis, although being appropriate for rare events, may still not be feasible for Kawasaki disease, either because there are no cases in the risk periods or there are too few cases for analysis. In this case the plots of outcomes against time from vaccination will provide information on the distribution of outcomes against exposure and may generate the need for further study.

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.

9.10 Other Aspects

The Read dictionary will no longer be updated after spring 2016 and it is expected that UK primary care systems will move to the Systematized Nomenclature of Medicine (SNOMED) dictionary at some later time. If this happens during the study period additional code lists will be developed.

10. PROTECTION OF HUMAN SUBJECTS

10.1 Regulatory and Ethical Compliance

This study was designed and shall be implemented and reported in accordance with Good Pharmacoepidemiological Practice, with applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed Consent

Not required.

10.3 Responsibilities of the Investigator

Practice and patient confidentiality will be maintained throughout the study. Patient records on the database are anonymous. Both the practice and patient identifying details are replaced by codes which cannot be broken by the researchers. The study will require validation of information recorded on the database. Retrieval of unstructured text and practice documents will use an established system via a third party which requires removal of all potentially identifying details before any information is passed to researchers. This third party will contact the practice where the patient can be identified. Any reply will be vetted by the third party to ensure that no information has been included which could reveal the identity of the patient, practice or healthcare provider, before forwarding any documents to the researchers. When access to the computerized comments field is required, the third party will vet the free text in the same manner to ensure that no identifying details are included.

10.4 Protocol Adherence

The investigator will apply due diligence to avoid protocol deviations.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

[redacted] Data will be reported as per study design and timelines.

12. PLANS FOR DISSEMINATING AND COMMUNICATING RESULTS

12.1 Registration in Public Database(s)

The protocol will be posted on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) register of studies before the study is started.

12.2 Publications

The results of this study will be submitted for publication as scientific papers in peer-reviewed journals. The manuscripts will be prepared independently by the investigators and in accordance with the current guidelines including STrengthening the Reporting of OBservational studies in Epidemiology (Elm 2007). NVx will be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication. NVx will also have the opportunity to comment on all reports before they are submitted to the EMA.

13. REFERENCES

Andrews, N., J. Stowe, et al. (2011). "Guillain Barré syndrome and H1N1 (2009) pandemic influenza vaccination using an AS03 adjuvanted vaccine in the United Kingdom: Self-controlled case series." Vaccine **29**(45): 7878-7882.

Andrews, N., J. Stowe, et al. (2010). "Post-licensure comparison of the safety profile of diphtheria/tetanus/whole cell pertussis/haemophilus influenza type b vaccine and a 5-in-1 diphtheria/tetanus/acellular pertussis/haemophilus influenza type b/polio vaccine in the United Kingdom." Vaccine **28**(44): 7215-7220.

Ayusawa, M., T. Sonobe, et al. (2005). "Revision of diagnostic guidelines for Kawasaki disease (the 5th revised edition)." Pediatrics International **47**(2): 232-234.

Blak, B. T., M. Thompson, et al. (2011). "Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates." Inform Prim Care **19**(4): 251-255.

Bohlke, K., R. L. Davis, et al. (2004). "Epidemiology of anaphylaxis among children and adolescents enrolled in a health maintenance organization." The Journal of allergy and clinical immunology **113**(3): 536-542.

Bonhoeffer, J., J. Menkes, et al. (2004). "Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation." Vaccine **22**(5-6): 557-562.

Campbell, H., R. Borrow, et al. (2009). "Meningococcal C conjugate vaccine: the experience in England and Wales." Vaccine **27 Suppl 2**: B20-29.

Chang, Q., Y.-L. Tzeng, et al. (2012). "Meningococcal disease: changes in epidemiology and prevention." Clinical Epidemiology **4**: 237-245.

Decker, W. W., R. L. Campbell, et al. (2008). "The etiology and incidence of anaphylaxis in Rochester, Minnesota: a report from the Rochester Epidemiology Project." The Journal of allergy and clinical immunology **122**(6): 1161-1165.

Eleftheriou, D., M. Levin, et al. (2014). "Management of Kawasaki disease." Arch Dis Child **99**(1): 74-83.

Elm, E. v., D. G. Altman, et al. (2007). "Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies " BMJ **335**(7624): 806-808.

Farrington, C. P., J. Nash, et al. (1996). "Case series analysis of adverse reactions to vaccines: a comparative evaluation." Am J Epidemiol **143**(11): 1165-1173.

Ferreira, G. and Carrigan (2009). "Incidence Rate of Febrile Convulsions in Toddlers-A Database Study in the United Kingdom." Pharmacoepidemiology and Drug Safety **18**(s1): S1-S273.

Fischer, T. K., R. C. Holman, et al. (2007). "Kawasaki syndrome in Denmark." Pediatr Infect Dis J **26**(5): 411-415.

Hall, G. C. and F. Hill (2014). "Descriptive investigation of the recording of influenza vaccination details on The Health Information Network database." Pharmacoepidemiology and Drug Safety **23**(6): 595-600.

Hall , G. C., L. E. Tulloh, et al. (In press). "An observational study of Kawasaki disease incidence in children and adolescents " BJGP.

Health Protection Agency (2012) "Invasive meningococcal infections laboratory reports, England and Wales by capsular group and calendar year, 1998-2012.".http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317136087786; Sept 14, 2012.

Hense, S., T. Schink, et al. (2014). "Estimation of background incidence rates of Guillain-Barre syndrome in Germany - a retrospective cohort study with electronic healthcare data." Neuroepidemiology **43**(3-4): 244-252.

Hubbard, R., S. Lewis, et al. (2005). "Bupropion and the risk of sudden death: a self-controlled case-series analysis using The Health Improvement Network." Thorax **60**(10): 848-850.

JVCI (March 2014) "JCVI position statement on use of Bexsero® meningococcal B vaccine in the UK." https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/294245/JCVI_Statement_on_MenB.pdf.

Kaye, J. A., M. del Mar Melero-Montes, et al. (2001). "Mumps, measles, and rubella vaccine and the incidence of autism recorded by general practitioners: a time trend analysis." BMJ **322**(7284): 460-463.

Klein, N. P., B. Fireman, et al. (2010). "Measles-Mumps-Rubella-Varicella Combination Vaccine and the Risk of Febrile Seizures." Pediatrics **126**(1): e1-e8.

Leake, J. A., S. Albani, et al. (2004). "Acute disseminated encephalomyelitis in childhood: epidemiologic, clinical and laboratory features." Pediatr Infect Dis J **23**(8): 756-764.

Miller, E. and Andrews (2007). "Risks of convulsion and aseptic meningitis following measles-mumps-rubella vaccination in the United Kingdom." American Journal of Epidemiology **165**(6): 704.

Moore, A., A. Harnden, et al. (2014). Recognising Kawasaki disease in UK primary care: a descriptive study using the Clinical Practice Research Datalink. British Journal of general practice. **64:** e477-e483.

Musonda, P., C. P. Farrington, et al. (2006). "Sample sizes for self-controlled case series studies." Stat Med **25**(15): 2618-2631.

Newburger, J. W., M. Takahashi, et al. (2004). "Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Statement for Health Professionals From the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association." Pediatrics **114**(6): 1708-1733.

NHS Centre for Coding and Classification (1996). The READ Codes Version 3. London, Stationary Office.

Olafsdottir, H., G. Oskarsson, et al. (2012). "Kawasaki disease in Iceland 1996-2005, epidemiology and complications." Laeknabladid **98**(2): 91-95.

Ruggeberg, J. U., M. S. Gold, et al. (2007). "Anaphylaxis: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data." Vaccine **25**(31): 5675-5684.

Salo, E., E. P. Griffiths, et al. (2012). "Incidence of Kawasaki disease in northern European countries." Pediatrics International **54**(6): 770-772.

Sammon, C. J., R. A. Charlton, et al. (In press). "The incidence of childhood and adolescent seizures in the UK from 1999 to 2011; a retrospective cohort study using the Clinical Practice Research Datalink." Vaccine.

Sejvar, J. J., K. S. Kohl, et al. (2007). "Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data." Vaccine **25**(31): 5771-5792.

Sejvar, J. J., K. S. Kohl, et al. (2011). "Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data." Vaccine **29**(3): 599-612.

Sheikh, A., J. Hippisley-Cox, et al. (2008). "Trends in national incidence, lifetime prevalence and adrenaline prescribing for anaphylaxis in England." J R Soc Med **101**(3): 139-143.

Smeeth, L., C. Cook, et al. (2004). "MMR vaccination and pervasive developmental disorders: a case-control study." Lancet **364**(9438): 963-969.

Stowe, J., N. Andrews, et al. (2011). "Risk of convulsions in children after monovalent H1N1 (2009) and trivalent influenza vaccines: a database study." Vaccine **29**(51): 9467-9472.

Stowe, J., N. Andrews, et al. (2009). "Investigation of the Temporal Association of Guillain-Barré Syndrome With Influenza Vaccine and Influenzalike Illness Using the United Kingdom General Practice Research Database." American Journal of Epidemiology **169**(3): 382-388.

Tacke, C. E., W. B. Breunis, et al. (2014). "Five Years of Kawasaki Disease in the Netherlands: A National Surveillance Study." Pediatr Infect Dis J **33**(8): 793-797.

Tata, L. J., J. West, et al. (2003). "Does influenza vaccination increase consultations, corticosteroid prescriptions, or exacerbations in subjects with asthma or chronic obstructive pulmonary disease?" Thorax **58**(10): 835-839.

VAESCO. (2011). "Background Rates." Retrieved 30th April, 2012, from http://vaesco.net/vaesco/results/BGR-2010.html.

Viner, R. M., R. Booy, et al. (2012). "Outcomes of invasive meningococcal serogroup B disease in children and adolescents (MOSAIC): a case-control study." The Lancet Neurology **11**(9): 774-783.

Whitaker, H. J., M. N. Hocine, et al. (2007) "The methodology of self-controlled case series studies." **18**, 7-26 DOI: 10.1177/0962280208092342.http://statistics.open.ac.uk/802576CB00593013/(httpInfoFiles)/BB09CA18A45620D880257789004FBF8B/$file/SMMR10.pdf.

Whitaker, H. J., C. Paddy Farrington, et al. (2006). "Tutorial in biostatistics: the self-controlled case series method." Statistics in Medicine **25**(10): 1768-1797.

APPENDIX 1: LIST OF STAND-ALONE DOCUMENTS

None.

APPENDIX 2: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

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

Study reference number:
V72_36OB

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	10,14,16
1.1.2 End of data collection[2]	☒	☐	☐	16
1.1.3 Study progress report(s)	☒	☐	☐	16
1.1.4 Interim progress report(s)	☒	☐	☐	16
1.1.5 Registration in the EU PAS register	☒	☐	☐	16
1.1.6 Final report of study results.	☒	☐	☐	16

Comments:

All milestones are in table 6-1 on page 16

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	10,17

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1.2 The objective(s) of the study?	☒	☐	☐	10,18
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	11,20
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	28
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	10,19
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	11,21,22
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	13,28

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	11,20
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	11,20
4.2.2 Age and sex?	☒	☐	☐	12,21,26
4.2.3 Country of origin?	☒	☐	☐	20
4.2.4 Disease/indication?	☐	☐	☒	
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?	☒	☐	☐	29
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	24

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	11,20,21
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	19,31
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	21-23

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	11,21,22
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	21-25,31

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	26

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	26

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	12,23
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	12,23
8.1.3 Covariates?	☒	☐	☐	26
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	23,24
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	24,25
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	26

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.3 Is a coding system described for:	☒	☐	☐	25
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)				
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	25
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	24
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	23, 27

Comments:

Outcomes will be found through READ codes and/or text fields

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	26,27

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☒	☐	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	28,29

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.3 Are descriptive analyses included?	☒	☐	☐	28
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	19
10.6 Does the plan describe methods addressing effect modification?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☐	☒	☐	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	27,28,30
11.3 Are methods of quality assurance described?	☒	☐	☐	30
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	30,31
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	12,24-26

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	31
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	31
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	26,27
12.3 Does the protocol address other limitations?	☒	☐	☐	31

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	32
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	30,32

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	15

Comments:

No future amendments foreseen at this point in time

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	16,34
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	16,34

Comments:

Name of the main author of the protocol: _____

Date: 24/08/2015

Signature: _____

APPENDIX 3: PULISHED INFORMATION ON RISK PERIODS POST-VACCINATION AND OTHER POTENTIAL TRIGGERS

Table 1 Seizures

Study type **Type of seizure / Exposure**	**Time between exposure and seizures or pre-defined study risk periods**
Case reports	
Febrile / flu vaccine (Rowhani-Rahbar 2012)	1-2 days live attenuated vaccine, 0-1 days inactivated vaccine
Clinical trial cases	
Febrile / review influenza and PCV vaccine trials (Rowhani-Rahbar 2012)	Within 48 hours
Other studies reporting days post-trigger with increased risk	
Febrile / MMRV vaccine versus MMR _ varicella vaccines (Klein 2010)	Clustered at 7 – 10 days Pre-defined risk periods (days 0–4, 5– 6, 11–12, 13–30, and 31– 42).
Febrile / diphtheria, tetanus, pertussis and MMR vaccines (Farrington 1995)	↑risk: 0-3 days after 3rd dose DTP, 6-11 days after MMR, 15-35 days after MMR with Urabe mumps strain.
Febrile / MMR vaccination (Vestergaard 2004)	↑risk 0-3 days
Any / DTaP5/Hib/IPV (Andrews 2010)	DTwP/Hib ↑ risk day 0, non-significant ↑day 1-3 DTaP5/Hib/IPV non-significant ↑ day 0, 4-7 days no ↑ risk.
Both / DTP and MMR vaccination (Barlow 2001)	DTP febrile seizures ↑ risk day 0 MMR febrile seizures ↑ risk day 8-14 Pre-define risk periods were 0 to 7, 8 to 14, and 15 to 30 days.
Any / monovalent H1N1 – trivalent influenza (Stowe 2011)	H1N1, 1-3 days post 2nd dose Pre-defined risk periods: 0, 1–3, 4–7 days
Febrile convulsion or fit not otherwise specified / MMR vaccination (Miller and Andrews 2007)	6–11 days post vaccination 15–35 days also used but no ↑ risk.
Other studies chosen risk windows	
Any / meningococcal group C conjugate (Andrews 2007)	No ↑ risk in 2 week window

Table 2 Kawasaki disease

Study type Exposure	Time between exposure and Kawasaki disease or pre-defined study risk periods
Case reports	
DPT vaccination (Oka 2012)	4 days X2 in one patient
Hepatitis B vaccination (Miron 2003)	1 day
Yellow fever vaccination (Schmöeller 2009)	20 days
Clinical trial cases	
Pneumococcal conjugate vaccine (Gutiérrez Brito 2013)	5 days
Rotavirus vaccine; DPT control (Merck & Co., 2011).	23 days post-dose 3; 22 days post-dose 2 of the control
4CMenB vaccination 2 randomised trials (Vesikari 2013)	3, 7, and 14 weeks and 23 weeks in a control.
4CMenB vaccination randomised trial (Gossger 2012)	2 cases, 1 considered possibly related to the study vaccine by an independent expert panel. No time post-vaccine given.
4CMenB vaccination; review of trials including the previous 2 studies (O'Ryan 2014)	1 day to 5.5 months: 3 within and 3 after 1 month, (7 suspected cases were reported across 4CMenB studies, 6 after receiving a 4CMenB-containing vaccine regimen).
MeNZB* Trial (McNicholas 2007)	6–258 days post vaccination, with a mean of 108 days, 8 cases
Other studies chosen risk windows	
PCV13 versus PCV7cohort study (Tseng 2013)	1-28 days, expanded to 56 days to capture late diagnosis
Case-control study of vaccination, carpet cleaning, respiratory illness, humidifier, animal, sick relative (Treadwell 2002)	30 days
Any vaccine (Abrams 2015)	1–14 days , 1–28 days 8–14 days 8–28 days 8–42 days 15–42 days after vaccination
Any vaccine; Vaccine Adverse Event Reporting System (Hua 2009)	35% of reports Kawasaki disease occurred 0 – 1 days after any vaccine, 89% within 21 days, none in days 22-28 and 91% within 30 days

Study type **Exposure**	**Time between exposure and Kawasaki disease or pre-defined study risk periods**
Wind direction change (Rodo 2014)	Results suggest a very short incubation period (<24 h): 'an immediate response in the form of an idiosyncratic immune reaction in genetically susceptible children that takes place within 24 h after inhalation of the etiologic trigger is further reinforced by our results.'

Table 3 ADEM

Study Type **Exposure**	**Days between exposure and ADEM onset, or pre-defined risk periods**
Case reports	
Japanese encephalitis, rubella, hepatitis B, and live poliovirus vaccines (Torisu 2010)	Mean 17 days (range: 9–30 days).
VAERS (Rowhani-Rahbar 2012)	No clustering (n = 56); mode of the distribution days 11 and 12.
Clinical trial cases	
Febrile / 7 influenza and 3 PCV vaccine trials (Rowhani-Rahbar 2012)	Within 48 hours
Other studies reporting days post-trigger with increased risk	
Natural infection / review (Rowhani-Rahbar 2012)	Between 6.2 and 17.8 days

Table 4 Guillain-Barré syndrome

Data source / Exposure	**Time between exposure and Guillain-Barré syndrome onset or pre-defined risk periods**
Case reports	
*C jejuni e*nteritis (Hughes and Rees 1997)	Mean 10.5 days (SD 4.6; range 5–21)
Swine flu vaccination (Parkin 1978)	1 – 102 days; 80% within 5 weeks
H1N1 flu (Salmon 2013)	1-42 days
Clinical trial cases	
meningococcal conjugate vaccine (A, C, Y, and W135) (CDC 2005)	17-18 years had symptom onset 14-31 days

Data source / Exposure	Time between exposure and Guillain-Barré syndrome onset or pre-defined risk periods
Other studies reporting days post-trigger with increased risk	
Any vaccine (Haber 2004)	The median onset interval (13 days)
Influenza vaccine and influenza type illness (Stowe 2009)	Greatest RI within 30 days (16.64, 95% confidence interval: 9.37, 29.54).Also used 90 days but no ↑ risk
Swine flu (Langmuir 1984)	18 consecutive 7 day windows. Highest numbers days 8-21. Rates appeared to be higher than the background days 1 – 63.
Other studies with chosen risk windows	
Any vaccination (Hughes Ra 2006)	42 days
During influenza vaccination season (Lasky 1998)	60 days
Pandemic influenza vaccination (Dieleman 2011)	1 day to 6 weeks
Swine influenza (Andrews 2011)	6 weeks
Influenza (Juurlink 2006)	Primary: weeks 2-7
Swine flu (Breman and HAYNER 1984)	6 weeks
Campylobacter infection (Tam 2007)	2 months
Seasonal flu (Stowe 2009)	3 risk periods of 0–30, 31–60, 61–90 and 0-90 days
Meningococcal conjugate vaccine MCV4 (Velentgas 2012)	6 weeks

Appendix 3 References

Abrams, J. Y., E. S. Weintraub, et al. (2015). "Childhood vaccines and Kawasaki disease, Vaccine Safety Datalink, 1996-2006." Vaccine **33**(2): 382-387.

Andrews, N., J. Stowe, et al. (2011). "Guillain Barré syndrome and H1N1 (2009) pandemic influenza vaccination using an AS03 adjuvanted vaccine in the United Kingdom: Self-controlled case series." Vaccine **29**(45): 7878-7882.

Andrews, N., J. Stowe, et al. (2007). "Post-Licensure Safety of the Meningococcal Group C Conjugate Vaccine." Human Vaccines **3**(2): 59-63.

Andrews, N., J. Stowe, et al. (2010). "Post-licensure comparison of the safety profile of diphtheria/tetanus/whole cell pertussis/haemophilus influenza type b vaccine and a 5-in-1 diphtheria/tetanus/acellular pertussis/haemophilus influenza type b/polio vaccine in the United Kingdom." Vaccine **28**(44): 7215-7220.

Barlow, W. E., R. L. Davis, et al. (2001). "The Risk of Seizures after Receipt of Whole-Cell Pertussis or Measles, Mumps, and Rubella Vaccine." New England Journal of Medicine **345**(9): 656-661.

Breman, J. G. and N. S. Hayner (1984). "Guillain-Barre syndrome and its relationship to swine influenza in Michigan, 1976–1977." American Journal of Epidemiology **119**(6): 880-889.

CDC (2005). "Guillain-Barré Syndrome Among Recipients of Menactra® Meningococcal Conjugate Vaccine --- United States, June--July 2005." Morb Mortal Wkly Rep **54**(40): 1023-1025.

Dieleman, J., S. Romio, et al. (2011). "Guillain-Barré syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: multinational case-control study in Europe." BMJ **343**(d3908).

Farrington, P., M. Rush, et al. (1995). "A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines." The Lancet **345**(8949): 567-569.

Gossger, N., M. D. Snape, et al. (2012). "Immunogenicity and tolerability of recombinant serogroup b meningococcal vaccine administered with or without routine infant vaccinations according to different immunization schedules: A randomized controlled trial." JAMA **307**(6): 573-582.

Gutiérrez Brito, M., A. Thompson, et al. (2013). "Immunogenicity and safety of 13-valent pneumococcal conjugate vaccine in Mexico." Revista Panamericana de Salud Pública **33**: 414-421.

Haber, P., F. DeStefano, et al. (2004). "Guillain-Barré Syndrome Following Influenza Vaccination." JAMA: The Journal of the American Medical Association **292**(20): 2478-2481.

Hua, W., H. S. Izurieta, et al. (2009). "Kawasaki Disease After Vaccination: Reports to the Vaccine Adverse Event Reporting System 1990-2007." The Pediatric Infectious Disease Journal **28**(11): 943-947 910.1097/INF.1090b1013e3181a66471.

Hughes Ra, C. J. L. R. G. M. C. (2006). "NO association between immunization and guillain-barré syndrome in the united kingdom, 1992 to 2000." Archives of internal medicine **166**(12): 1301-1304.

Hughes, R. A. C. and J. H. Rees (1997). "Clinical and Epidemiologic Features of Guillain-Barré Syndrome." Journal of Infectious Diseases **176**(Supplement 2): S92-S98.

Juurlink, D. N., T. A. Stukel, et al. (2006). "Guillain-Barre syndrome after influenza vaccination in adults: a population-based study." Arch Intern Med **166**(20): 2217-2221.

Klein, N. P., B. Fireman, et al. (2010). "Measles-Mumps-Rubella-Varicella Combination Vaccine and the Risk of Febrile Seizures." Pediatrics **126**(1): e1-e8.

Langmuir, A. D., D. J. Bregman, et al. (1984). "An epidemiologic and clinical evaluation of guillain-barré syndrome reported in association with the administration of swine influenza vaccines." American Journal of Epidemiology **119**(6): 841-879.

Lasky, T., G. J. Terracciano, et al. (1998). "The Guillain–Barré Syndrome and the 1992–1993 and 1993–1994 Influenza Vaccines." New England Journal of Medicine **339**(25): 1797-1802.

McNicholas, A., Y. Galloway, et al. (2007). "Post-marketing safety monitoring of a new group B meningococcal vaccine in New Zealand, 2004-2006." Hum Vaccin **3**(5): 196-204.

Miller, E. and Andrews (2007). "Risks of convulsion and aseptic meningitis following measles-mumps-rubella vaccination in the United Kingdom." American Journal of Epidemiology **165**(6): 704.

Miron, D., D. Fink, et al. (2003). "Kawasaki disease in an infant following immunisation with hepatitis B vaccine." Clinical Rheumatology **22**(6): 461-463.

Oka, K., W. Shimamura, et al. (2012). "Kawasaki disease after diphtheria-pertussis-tetanus (DPT) vaccination: A case report." Pediatrics International **54**: 119.

Parkin, W., H. Beecham, et al. (1978). "Relationship studied in Pennsylvania. Guillain-Barré syndrome and influenza immunization." Pa Med **81**(4): 47-48.

Rodo, X., R. Curcoll, et al. (2014). "Tropospheric winds from northeastern China carry the etiologic agent of Kawasaki disease from its source to Japan." Proc Natl Acad Sci U S A **111**(22): 7952-7957.

Rowhani-Rahbar, A., N. P. Klein, et al. (2012). "Biologically plausible and evidence-based risk intervals in immunization safety research." Vaccine **31**(1): 271-277.

Salmon, D. A., M. Proschan, et al. (2013). "Association between Guillain-Barré syndrome and influenza A (H1N1) 2009 monovalent inactivated vaccines in the USA: a meta-analysis." The Lancet **381**(9876): 1461-1468.

Schmöeller, D., M. W. Keiserman, et al. (2009). "Yellow Fever Vaccination and Kawasaki Disease." The Pediatric Infectious Disease Journal **28**(11): 1037-1038.

Stowe, J., N. Andrews, et al. (2011). "Risk of convulsions in children after monovalent H1N1 (2009) and trivalent influenza vaccines: a database study." Vaccine **29**(51): 9467-9472.

Stowe, J., N. Andrews, et al. (2009). "Investigation of the Temporal Association of Guillain-Barré Syndrome With Influenza Vaccine and Influenzalike Illness Using the United Kingdom General Practice Research Database." American Journal of Epidemiology **169**(3): 382-388.

Tam, C. C., S. J. O'Brien, et al. (2007). "Guillain-Barré syndrome and preceding infection with campylobacter, influenza and Epstein-Barr virus in the general practice research database." PLoS ONE **2**(4): e344.

Torisu, H., R. Kira, et al. (2010). "Clinical study of childhood acute disseminated encephalomyelitis, multiple sclerosis, and acute transverse myelitis in Fukuoka Prefecture, Japan." Brain Dev **32**(6): 454-462.

Treadwell, T. A., R. A. Maddox, et al. (2002). "Investigation of kawasaki syndrome risk factors in colorado." The Pediatric Infectious Disease Journal **21**(10): 976-978.

Tseng, H. F., L. S. Sy, et al. (2013). "Postlicensure surveillance for pre-specified adverse events following the 13-valent pneumococcal conjugate vaccine in children." Vaccine **31**(22): 2578-2583.

Velentgas, P., A. A. Amato, et al. (2012). "Risk of Guillain–Barré syndrome after meningococcal conjugate vaccination." Pharmacoepidemiology and Drug Safety **21**(12): 1350-1358.

Vesikari, T., S. Esposito, et al. (2013). "Immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccinations: results of two randomised trials." The Lancet **381**(9869): 825-835.

Vestergaard, M., A. Hviid, et al. (2004). "MMR vaccination and febrile seizures: evaluation of susceptible subgroups and long-term prognosis." JAMA **292**(3): 351-357.

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