Title	Post-licensure observational safety surveillance study of quadrivalent meningococcal ACWY conjugate vaccine MenACWY-CRM (MENVEO®) in children 2 months through 23 months of age.
Protocol version identifier	V. 2
Date of last version protocol	11 AUG 16
EU PAS registry number	Not applicable.
Active substance	Not applicable.
Medicinal product	Not applicable.
Product reference	Not applicable.
Procedure number	Not applicable.
Marketing authorisation holder(s)	GlaxoSmithKline Biologicals S.A.
Joint PASS study	NO

Research question and objectives	To describe medical events that require emergency room visit or hospitalization in 6 months following MenACWY-CRM vaccination in children 2-23 months of age in a health maintenance organization (HMO) in the United States.
Country(ies) of study	United States
Author	Dr. PPD, GSK
Marketing authorisation holder(s) details	GlaxoSmithKline Biologicals S.A Rue de I'Institut, 89 BE-1330 Rixensart. Belgium
MAH contact person	Dr. PPD Clinical and Epidemiology R&D GSK Amsterdam, The Netherlands Email: PPD

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2.0 LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
EMR	Electronic medical record
FDA	Food and Drug Administration
GSK	GlaxoSmithKline Biologicals S.A.
HCP	Health Care Providers
HIPAA	Health Insurance Portability and Accountability Act
HMO	Health maintenance organization
ICD-9	International Classification of Diseases, Ninth Revision
ICD-10	International Classification of Diseases, Tenth Revision
IRB	Institutional Review Board
MAH	Market authorisation holder
MenACWY-CRM	Meningococcal ACWY vaccine conjugated to a carrier protein Cross reacting Material 197 (CRM 197)
PMC	Post-marketing commitment
PMS	Post-marketing study
KPSC	Kaiser Permanente Southern California
RIPC	Regional Immunization Practice Committee
RDW	Research Data Warehouse
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
US	United States

3.1 RESPONSIBLE PARTIES

3.2 Main Author(s) of the Protocol

PPD

GSK

Amsterdam, the Netherlands

PPD 3.2

3.3 Principal Investigator

PPD

Department of Research and Evaluation

Kaiser Permanente, Southern California

Pasadena, US

PPD

3.4 Coordinating Investigator(s)

Not applicable.

3.5 CRO or Other Service Provider

Not Applicable.

3.6 Advisory Committee

Not Applicable

4.0 ABSTRACT

Name of Sponsor GlaxoSmithKline Biologicals S.A.	**Protocol number:** V59_74OB	**Health authority study registration number(s):**	**Date of Protocol Abstract:** 11AUG16

Title of Study:

Post-licensure observational safety surveillance study of quadrivalent meningococcal ACWY conjugate vaccine MenACWY-CRM (MENVEO) among children 2 months through 23 months of age.

Study Period:	**Study Type:** This study is an observational post-marketing safety study required by the United States Food and Drug Administration (FDA).
The study will start by December 2014 and data collection period will continue for 3 years.	

Rationale and Background:

Meningococcal disease is caused by *Neisseria meningitidis*. Multiple serogroups are responsible for invasive meningococcal disease (groups A, B, C, X, Y, and W-135). The relative importance of each serogroup depends on geographic location [1-5], as well as other factors, such as age. The overall incidence of meningococcal disease in the US during 2005-2011 has been approximately 0.3 cases per 100,000 population. [6]

MenACWY-CRM (MENVEO) is a Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine. The safety of Men ACWY-CRM has been evaluated in clinical trials in infants and toddlers 2 to 23 months of age. No safety concerns were raised.[7]

In February 2010, MenACWY-CRM was approved for use in persons 11-55 years of age in the United States. As of August 2013 MenACWY-CRM was approved for use in persons 2 months through 55 years of age in the United States. In infants initiating vaccination at 2 months of age, MenACWY-CRM is to be administered as a four-dose series at 2, 4, 6, and 12 months of age. Among children 7-23 months of age who have not previously received a dose of MenACWY-CRM, MenACWY-CRM is to be administered as a two-dose series with the second dose administered in the second year of life and at least three months after the first dose. The Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) recommends the meningococcal conjugate vaccine MenACWY-CRM for use in infants

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and toddlers 2-23 months of age who are at increased risk for meningococcal disease.

This study will provide additional information to the current safety knowledge of MenACWY-CRM in the population 2-23 months of age.

Research Question and Objectives:

To describe medical events that require emergency room visit or hospitalization in 6 months following MenACWY-CRM vaccination in children 2-23 months of age in a health maintenance organization (HMO) in the United States.

Study Design:

The study is a descriptive observational safety surveillance study.

Medical events in emergency rooms and inpatient care units in children 2-23 months of age who were vaccinated with any dose of MenACWY-CRM vaccine will be described. Only medical events that occur within 6 months after a MenACWY-CRM vaccination will be captured. Events will be identified from electronic medical records of emergency care and inpatient care encounters. Medical records of these events will be reviewed and described.

Population:

Children 2-23 months of age who receive at least one dose of MenACWY-CRM vaccine at a Kaiser Permanente Southern California (KPSC) facility while enrolled as a KPSC health plan member.

Variables:

Exposure(s) of interest

All administered doses of MenACWY-CRM at a KPSC facility are considered as exposures of interest in children 2-23 months of age who are KPSC members. The exposure of interest is MenACWY-CRM vaccine given as part of routine clinical care in all medical centers in KPSC. This study is strictly observational. MenACWY-CRM will be the only meningococcal vaccine used in children 2-23 months of age to prevent *N. meningitidis* serogroup A, C, W135 and Y caused meningococcal disease in KPSC.

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While health care providers (HCP) are advised to follow the ACIP Recommended Childhood Vaccine schedule, vaccination decisions will be determined by the treating HCP and the caregivers. MenACWY-CRM vaccine as a *N. meningitidis* A, C, W135 and Y vaccine will be used in infants and toddlers 2-23 months of age with high risk indications for the vaccine in KPSC. No special labeling will be required for the MenACWY-CRM vaccine used in this study. Co-administration of other vaccines may occur as consistent with clinical practice.

- Date (s) of MenACWY-CRM vaccination (s): exposure to MenACWY-CRM vaccination is defined as a registration of a MenACWY-CRM vaccination in the medical records. The date of vaccine administration in the medical records is considered as the vaccination date. Age at vaccination will be expressed in number of months after birth.
- Observation period: For each individual, the observation period is defined as the time from the first dose of MenACWY-CRM vaccination up to 6 months after the last dose of MenACWY-CRM vaccination received between 2-23 months of age, disenrollment, death, or the end of data collection, whichever occurs sooner.

Outcome(s)

Outcomes include medical events that require emergency room visits or hospitalizations in children 2-23 months of age following any dose of MenACWY-CRM vaccination. Events with a history of the same diagnosis prior to the first dose of MenACWY-CRM vaccination will be excluded as a pre-existing condition. The medical records prior to the first dose of MenACWY-CRM will be searched for the same diagnosis code.

For each identified emergency department or inpatient visit the following information will be collected:

- Diagnosis of medical events
- Date of diagnosis: the date of the documented code after any dose of MenACWY-CRM vaccination is considered the date of diagnosis. The date of diagnosis is expressed as the number of days following the 1st, 2nd, 3rd, or 4th dose of MenACWY-CRM vaccination.
- Health care setting: hospitalization or emergency room

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Other Variables

- Baseline characteristics: these data will be extracted from patients' medical records.
  - Date of birth, expressed as age at vaccination
  - Gender
- Underlying condition of the MenACWY-CRM vaccine indication (i.e., persistent complement component deficiencies, asplenia or other), if available.
- Vaccination history
  - Concomitant vaccinations (specify)
  - History of other vaccinations (specify)
  - Vaccinations occurring during the observation period (specify)

Data Sources:

Medical events occurring within 6 months following a MenACWY-CRM vaccination will be searched in electronic medical records from emergency care and inpatient care units. Vaccination information will be searched from vaccination records. Diagnoses occurring in any care setting (inpatient, outpatient, or emergency room) prior to the first dose of MenACWY-CRM vaccination will be searched in electronic medical records for evidence of pre-existing medical events.

Study Size:

There is no planned number of vaccinees. The study will include medically attended events that require an emergency room visit or hospitalization in the study population.

Data Analysis:

This study is descriptive in nature and there will be no hypothesis testing.

Informed Consent and Ethical Approval:

Subjects included in this study will be identified among KPSC health plan members. Informed consent for receipt of MenACWY-CRM vaccine is not required as it is given to eligible KPSC members as part of routine care. KPSC will obtain IRB approval and

Name of Sponsor GlaxoSmithKline Biologicals S.A.	**Protocol number:** V59_74OB	**Health authority study registration number(s):**	**Date of Protocol Abstract:** 11AUG16
will request waivers for both informed consent and written HIPAA authorization prior to initiating data collection.			
Milestones: Start of data collection: December 1, 2014 End of data collection: November 30, 2017 Final report of study results: November 30, 2018			

5.0 AMENDMENTS AND UPDATES

Number	Date	Section of the study protocol	Amendment or update	Reason
1	11AUG16	Throughout the text of this protocol.	Amendment	Main reason: To reflect the change of Sponsor from Novartis Vaccines and Diagnostics Inc. to GlaxoSmithKline Biologicals S.A.
1	11AUG16	Throughout the text of this protocol.	Amendment	Minor change: Name of the vaccine (MENVEO) has been capitalized.

6.0 MILESTONES

Milestone	Planned date
Start of data collection	December 1, 2014
End of data collection	November 30, 2017
Final report of study results	November 30, 2018

7.0 RATIONALE AND BACKGROUND

Meningococcal disease is caused by *Neisseria meningitidis*. Multiple serogroups are responsible for invasive meningococcal disease (groups A, B, C, X, Y, and W-135). The relative importance of each serogroup depends on geographic location, as well as other factors, such as age. Serogroup B and C strains are most prevalent in Europe, and serogroups B, C and Y strains are most prevalent in North America. Serogroup A strains are rarely isolated in Europe and North America. [1-5]The overall incidence of meningococcal disease in the US during 2005-2011has been approximately 0.3 cases per 100,000 population. [6] Children younger than 1 year of age have the highest incidence of meningococcal disease in the United States.

MenACWY-CRM (MENVEO) is a Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine. Safety of Men ACWY-CRM with 2-dose and 4-dose schedules has been primarily evaluated in multiple clinical studies in infants and toddlers 2 to 23 months of age. Serious adverse events (SAEs) were similar between the MenACWY-CRM and routine paediatric vaccination groups. Rates of severe unsolicited adverse events (AEs) reported in subjects who received MenACWY-CRM in co-administration with routine childhood vaccination and those who received routine childhood vaccination alone are similar. No vaccine related death was reported.[7]

In February 2010, MenACWY-CRM was approved for use in persons 11-55 years of age in the United States. As of August 2013 MenACWY-CRM was approved for use in persons 2 months through 55 years of age in the United States. In infants initiating vaccination at 2 months of age, MenACWY-CRM is to be administered as a four-dose series at 2, 4, 6, and 12 months of age. Among children 7-23 months of age who have not previously received a dose of MenACWY-CRM, MenACWY-CRM is to be administered as a two-dose series, with the second dose administered in the second year of life and at least three months after the first dose. The Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) recommends the meningococcal conjugate vaccine MenACWY-CRM for use in infants and toddlers 2-23 months of age who are at increased risk for meningococcal disease. Children at increased risk include those who have persistent complement deficiencies, have functional or anatomic asplenia, are at risk during a community outbreak attributable to a vaccine serogroup, or travel to or are residents of countries where meningococcal disease is hyperendemic or epidemic.[6]

The study is to be conducted in collaboration with Kaiser Permanente Southern California (KPSC) in the United States.

This study will add to the current knowledge about the safety of MenACWY-CRM in children 2-23 months of age in the setting of routine medical care.

8.0 RESEARCH QUESTION AND OBJECTIVES

To describe medical events that require an emergency room visit or hospitalization in 6 months following MenACWY-CRM vaccination in children 2-23 months of age in a health maintenance organization (HMO) in the United States.

9.1 RESEARCH METHODS

9.2 Study Design

This is a post marketing commitment (PMC) agreed upon with FDA Center for Biologics Evaluation and Research (CBER) to establish an open label, descriptive, epidemiological safety surveillance study of MENVEO in children 2 through 23 months of age who receive medical care at the site where the study is being conducted. Part I will continue for 3 years, or until commencement of Part II, whichever occurs first. Part II of the study will be initiated if there is a recommendation by the Advisory Committee on Immunization Practices (ACIP) for routine use of meningococcal conjugate vaccine in at least one birth cohort within the 2 through 23 months of age range.

Part II will commence with the effective date of the ACIP recommendation, and will continue until 20,000 children are enrolled, or until 1 year has elapsed, whichever occurs last. If initiated, a final study report for Part II will be submitted 1 year after the last subject has completed study Part II. In the event there is no recommendation for routine use of meningococcal conjugate vaccine in this age group, Part II will be considered fulfilled when Part I is completed.

This study protocol and timelines pertain only to Part I since there is currently no ACIP recommendation for routine use of meningococcal conjugate vaccine among children 2 through 23 months of age.

In Part I, medical events in emergency rooms and inpatient care units in children 2-23 months of age who were vaccinated with any dose of MenACWY-CRM vaccine will be described. Only medical events that occur within 6 months after a MenACWY-CRM vaccination will be captured. Events will be identified from electronic medical records of emergency care and inpatient care encounters. Medical records of these events will be reviewed and described.

9.3 Setting

The study will be conducted at Kaiser Permanente Southern California (KPSC), the largest managed care organization in Southern California, serving over 3.7 million members that are broadly representative of the diverse racial, ethnic and socioeconomic background of the source population in Southern California.[8] The racial/ethnic breakdown of the KPSC population is 41% Hispanic, 36% Non-Hispanic White, 11% Asian/Pacific Islander, 9% Black, and 3% other.

Prepaid, comprehensive health care is provided to KPSC members at 14 medical centers and over 200 satellite clinics. All health care encounters are tracked through electronic data systems, with detailed information on diagnoses applied, procedures performed, and

immunizations administered, regardless of setting. KPSC members may seek emergency medical care from outside health care providers. For outside providers to be reimbursed by the health plan for covered emergency care, claims have to be submitted with documentation of the episode of care, and that information is entered into the administrative data systems. Thus, the capture of care delivered to KPSC members by electronic data is very comprehensive.

KPSC health plan members can enroll through their employer or the employer of a family member, through individual and family plans, or through state or federal programs such as California Public Employees' Retirement System, MediCal, and Medicare.

The KPSC Regional Immunization Practice Committee (RIPC) makes recommendations to ensure appropriate use of vaccination and implementation of new ACIP immunization recommendations within KPSC. KPSC has a proactive immunization program that includes: 1) alerts in the electronic medical record that indicate which age-appropriate routine vaccines are due based on vaccines that the member has already received, 2) a policy of vaccinating at all visits, not just well child or physical exam appointments, and 3) giving immunizations on a walk-in basis without appointment and at no-cost nurse visits. Since there is no charge for immunizations for KPSC members, there is an incentive to receive immunizations within the KPSC system.

9.2.1 Study Period

The total study period will be up to 3.5 years, which includes vaccination period and observation period.

- Vaccination period will start at earliest in May 2014, and at latest in December 2014 to implement ACIP recommendation on preventing meningococcal serogroups A, C, W_{135} and Y caused meningitis in persons aged 2 through 23 months.
- Observation period: For each individual, the observation period is defined as the time from the first dose of MenACWY-CRM vaccination up to 6 months after the last dose of MenACWY-CRM vaccination received between 2-23 months of age, disenrollment, death, or the end of data collection, whichever occurs sooner.

Pre-existing medical events will be assessed prior to the first dose of MenACWY-CRM vaccination.

9.2.2 Study Subjects

According to the ACIP recommended immunization schedule for persons aged 0 through 18 years, MenACWY-CRM is recommended for children 2-23 months of age with high-risk conditions and other persons at increased risk of disease. This population includes:

- children with anatomic or functional asplenia (including sickle cell disease)
- children with persistent complement component deficiency
- children who travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic
- children at risk during a community outbreak attributable to a vaccine serogroup.

There are approximately 500,000 births per year in California,[9] equivalent to nearly 1 million infants and toddlers age 2-23 months. There were approximately 38,000 babies delivered at KPSC facilities and contracting hospitals in 2012.

There were approximately 122,000 infants and toddlers age 2-23 months enrolled in the KPSC health plan in 2013. Among this population, there were approximately 30 individuals diagnosed with sickle cell, asplenia, or persistent complement deficiency.

9.2.3 Study Population Selection

Children 2-23 months of age who receive at least one dose of MenACWY-CRM vaccine at a KPSC facility while enrolled as a KPSC health plan member are considered as the study population.

Inclusion criteria:

- children 2-23 months of age at the time of MenACWY-CRM vaccination
- hold KPSC membership at the time of MenACWY-CRM vaccination
- vaccinated with MenACWY-CRM during the study period in KPSC

There are no exclusion criteria for selection of the study population.

9.3 Variables

The sections below describe the theoretical aspects of relevant variables. Data sources and operational definitions are discussed in 9.4.

9.3.1 Exposure of Interest

Doses of MenACWY-CRM administered at a KPSC facility are considered as exposures of interest in children 2-23 months of age who are KPSC members. The exposure of interest is MenACWY-CRM vaccine given as part of routine clinical care in all medical centers in KPSC. This study is strictly observational. MenACWY-CRM will be the only meningococcal vaccine used in children 2-23 months of age to prevent *N. meningitidis* serogroup A, C, W135 and Y caused meningococcal disease in KPSC. While HCPs are

advised to follow ACIP immunization recommendations, decisions regarding vaccinations and vaccination schedule will be determined by the HCP and caregivers. The MenACWY-CRM vaccination recommendation will be implemented at all KPSC medical centers.

No special labeling will be required for the MenACWY-CRM vaccine used in this study. Other vaccines may be co-administered as consistent with clinical practice.

According to the ACIP recommendation, MenACWY-CRM is recommended for infants and toddlers 2-23 months of age with high risk of meningococcal disease. The recommended meningococcal vaccination schedules for these high risk populations are as follows: [10]

- Children with anatomic or functional asplenia (including sickle cell disease):

1. For children younger than 19 months of age, administer a 4-dose infant series of MenHibrix or MENVEO at 2, 4, 6, and 12 through 15 months of age.
2. For children aged 19 through 23 months who have not completed a series of MenHibrix or MENVEO, administer 2 primary doses of MENVEO at least 3 months apart.

- Children with persistent complement component deficiency:

1. For children younger than 19 months of age, administer a 4-dose infant series of either MenHibrix or MENVEO at 2, 4, 6, and 12 through 15 months of age.
2. For children 7 through 23 months who have not initiated vaccination, two options exist depending on age and vaccine brand:
    a. For children who initiate vaccination with MENVEO at 7 months through 23 months of age, a 2-dose series should be administered with the second dose after 12 months of age and at least 3 months after the first dose.
    b. For children who initiate vaccination with Menactra at 9 months through 23 months of age, a 2-dose series of Menactra should be administered at least 3 months apart.

- For children who travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic, including countries in the African meningitis belt or the Hajj, administer an age appropriate formulation and series of Menactra or MENVEO for protection against serogroups A and W meningococcal disease. Prior receipt of MenHibrix is not sufficient for children traveling to the meningitis belt or the Hajj because it does not contain serogroups A or W.

- For children at risk during a community outbreak attributable to a vaccine serogroup, administer or complete an age- and formulation-appropriate series of MenHibrix, Menactra, or MENVEO.

Catch-up recommendation of MenACWY-CRM for persons with high-risk conditions is as follows:

For children who initiate vaccination with MENVEO at 7 months through 9 months of age, a 2-dose series should be administered with the second dose after 12 months of age and at least 3 months after the first dose.

9.3.2 Outcome(s)

Outcomes include medical events that require an emergency room visit or hospitalization in children 2-23 months of age within 6 months following any dose of MenACWY-CRM vaccination.

9.3.3 Other Variables

- Baseline characteristics: these data will be extracted from patients' medical records.
  - Date of birth, expressed as age at vaccination
  - Gender
- Underlying condition of the MenACWY-CRM vaccine indication (i.e., persistent complement component deficiencies, asplenia or other), if available.
- Vaccination history
  - Concomitant vaccinations (specify)
  - History of other vaccinations (specify)
  - Vaccinations occurring during the observation period (specify)

9.4 Data Sources

The study will be conducted using the KPSC Oracle Research Data Warehouse (RDW) which supports external and internal research projects conducted in the Department of Research & Evaluation, KPSC as well as patient care management programs. The data warehouse is an integrated and comprehensive resource. It contains information as far back as 1980, including records related to membership, benefits, utilization, pharmacy, vital signs, laboratory, vaccines, geocoding, mortality, and procedures.

Medical events will be searched in the electronic medical record (EMR). All care provided at KPSC is recorded using the EMR. All details of a patient encounter, including diagnoses, procedures, and physician's notes, are entered into the EMR at the point of care. All vaccinations are entered into the EMR when they are given, with vaccine, dose, manufacturer, and lot number entered at the time of vaccination.

9.4.1 Operational Exposure Definition

Vaccination information will be searched from vaccination records. Documented MenACWY-CRM vaccination record is considered as evidence of exposure.

The date of vaccine administration in the medical records is considered as the vaccination date. Age at vaccination will be extracted from date of vaccination and date of birth. Age at vaccination will be expressed in number of months after birth.

The first dose of MenACWY-CRM vaccination administered at a KPSC facility to a KPSC member 2-23 months of age is the starting point of observation period for each study individual.

For each individual, the observation period is defined as the time from the first dose of MenACWY-CRM vaccination up to 6 months after the last dose of MenACWY-CRM vaccination received between 2-23 months of age, disenrollment, death, or the end of data collection, whichever occurs sooner.

9.4.2 Operational Outcome Definition and Identification Process

Medical events occurring in emergency and inpatient settings within 6 months following a MenACWY-CRM vaccination will be searched in electronic medical records. Diagnoses occurring in any care setting (inpatient, outpatient, or emergency room) prior to the first dose of MenACWY-CRM vaccination will be searched in electronic medical records for evidence of pre-existing medical events.

Events with a history of the same diagnosis prior to the first dose of MenACWY-CRM vaccination will be excluded as a pre-existing condition. The medical records prior to the first dose of MenACWY-CRM will be searched for the same diagnosis code. As there will be a transition from International Classification of Diseases, Ninth Revision (ICD-9) to Tenth Revision (ICD-10) coding, in the event that the diagnosis following a MenACWY-CRM vaccination is coded using ICD-10, both the same ICD-10 code and an equivalent ICD-9 diagnosis code will be searched in the period prior to the first dose.

If a study subject is first seen in the emergency department and subsequently transferred to the hospital, this will be treated as a single episode of care. Multiple records of a single medical event will be consolidated and treated as 1 report.

Medical events are considered as eligible if they occur in eligible study subjects during the observation period and are not pre-existing conditions.

For each identified emergency department or inpatient visit the following information will be collected:

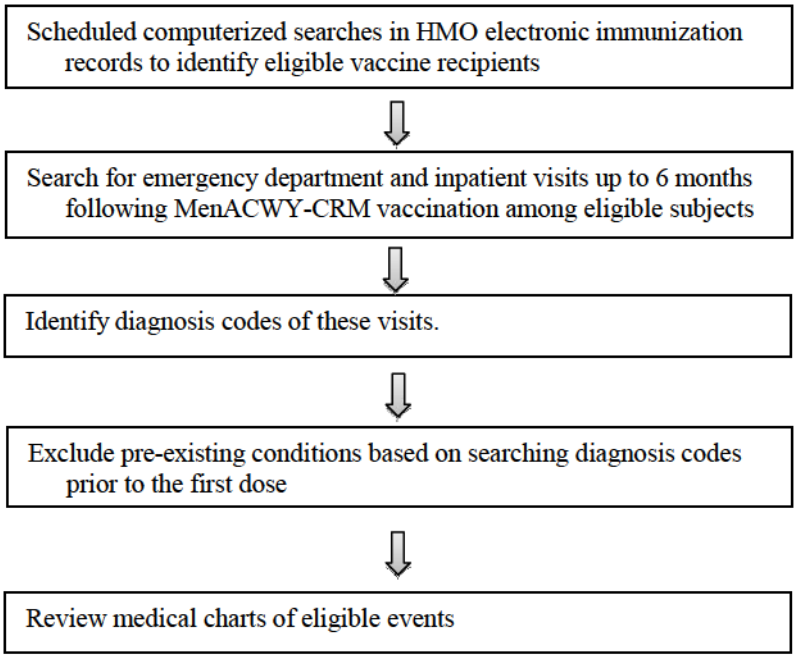
- Diagnosis of medical events
- Date of diagnosis: the date of the documented code after any dose of MenACWY-CRM vaccination is considered the date of diagnosis. The date of diagnosis is expressed as the number of days following the 1st, 2nd, 3rd, or 4th dose of MenACWY-CRM vaccination.
- Health care setting: hospitalization or emergency room visit

Process of medical events identification

Eligible medical events identification process is illustrated in Figure 1:

1. Children 2-23 months of age vaccinated with MenACWY-CRM will be identified by immunization records in electronic medical records.
2. Medical events will be searched up to 6 months following MenACWY-CRM vaccination in the electronic records of emergency department and inpatient care units in all medical centers of KPSC.
3. Diagnosis codes of medical events from these visits will be identified.
4. Pre-existing conditions will be excluded by automated search.
5. Medical charts of identified eligible events will be reviewed and described.

Figure 9.4.2-1: Process of eligible medical events identification



9.4.3 Operational Variable(s) Definition

To describe medical events, baseline characteristics, including date of birth, gender, date of diagnosis, and underlying condition will be extracted from medical records. Vaccination history will be extracted from immunization records.

9.4.4 Advisory Committee(s)

There is no Advisory Committee for this study.

9.5 Study Size

There is no planned number of vaccinees. The study will describe all eligible medically attended events that require emergency room visit or hospitalization in the study population.

Approximately 245,000 infants and toddlers aged 2-23 months were enrolled in the KPSC health plan in the period from 2011 to 2013. Among this population, there were around 60 children aged 2-23 months old with high risk conditions. It is estimated that the number of infants with high risk conditions would likely fall between 60-100 in the study

period.

9.6 Data Management

9.6.1 Data Processing

Data collection and retrieval will be performed using the HMO's standard procedures in agreement with GSK. Quality assurance measures as implemented at the HMO will be used.

Blinding

This study is an open-label study conducted in a routine medical care setting. Reviewers are not blinded to the patient identity or vaccination status. All study staff with access to protected health information are trained in procedures to protect the confidentiality of subject data.

Data linkage

An important aspect of the KPSC managed care environment is its integrated approach to the delivery of medical care. This approach depends on, and therefore facilitates, the development and maintenance of a large number of databases, linkable through a unique medical record number. These databases include those that track membership, encounters, claims, pharmaceuticals dispensed and appointments. They also include test results as well as text excerpts of their interpretation. There are also a number of derivative files that have been developed for research purposes, including those for disease identification, geocoding files and mortality follow-up files.

9.6.2 Software and Hardware

The data analysis in this study will be performed by Research & Evaluation programmers and analysts in KPSC. SAS (Enterprise Guide 4.3 or higher) will be used to perform data programming and data analysis in the study. Data management will be done in both PC and Unix environments.

9.7 Data Analysis

9.7.1 Statistical Hypotheses

This study is descriptive in nature and there will be no hypothesis testing.

9.7.2 Analysis of Demographics and Baseline Characteristics

Age at vaccination (extracted from date of birth and date of vaccination) will be presented by mean, median, standard deviation, minimum and maximum. Gender will be described by absolute numbers and percentages. Vaccination history (including vaccine name and age or relative timing of vaccination) will be summarized descriptively.

9.7.3 Statistical Methods

This descriptive study will analyze collected data to report frequencies of MenACWY-CRM exposure and analysis of medical events. The frequencies will be presented as absolute numbers and percentages of relevant total.

Frequency of exposure to MenACWY-CRM vaccination

This descriptive study will report the frequency of exposure among infants and toddlers 2-23 months of age vaccinated at least one dose of MenACWY-CRM during the study period. Frequency of exposure will be summarized as follows:

- Overall
- 1 dose
- 2 doses
- 3 doses
- 4 doses

Analysis of medical events

Eligible medical events in the study will be described as follows:

- Frequency of individual medical events

  The frequency of medical events is defined as the total number of each individual event. The frequency will be described by absolute number of each individual medical event and percentage of each individual medical event of total number of captured medical events during the observation period.

  If the number of medical events allows, captured medical events will be stratified by dose.

- Rate of medical events

  The rate of medical events is defined as the number of all captured events divided by the total person-time following MenACWY-CRM doses administered during the study period. 95% confidence interval of the rate of medical events will be calculated. Person-time for each dose will begin at the vaccination and end at 6 months following vaccination, disenrollment, death, the end of data collection, or receipt of an additional dose of MenACWY-CRM, whichever comes first. If data permit, rate will be further stratified by dose.

- Description of medical events

  Medical events following MenACWY-CRM exposure in children 2-23 months of age will be described. Medical events will be reviewed and described, at least including age at vaccination, gender, vaccination history, diagnoses, and if available, underlying condition. Recurrence of the same medical event after repeated MenACWY-CRM vaccination of the same person will be included in the description as well.

9.7.4 Statistical Considerations

Misclassification of diagnosis

As this study focuses on medical events requiring hospitalization and emergency care among children 2-23 months of age enrolled as KPSC health plan members, it is unlikely that serious and acute outcomes would be missed or misclassified. Also, due to the ICD-9 to ICD-10 transition, both ICD-9 and ICD-10 codes may need to be searched to exclude pre-existing conditions. Some pre-existing conditions may be missed from the automated search due to imperfect mapping between ICD-9 and ICD-10.

Misclassification of exposure

Depending on the available data in the medical record database on the recording of a vaccination, it may be that not all vaccinations are given through the HMO, resulting in not all vaccination data being present in the medical record. However, loss of these data should not affect results because analyses are confined to those individuals with a recorded vaccine administration.

Missing Data

No imputation will be performed. We expect there to be a very low rate of missing data regarding population characteristics, such as age and gender, and diagnoses. The study uses electronic medical records as the source of information for diagnoses, so events that do not result in a medical visit may be missed. Subjects missing the stratification factors will be excluded from subgroup analysis where the stratification factor is unknown. We expect that most vaccines will be captured by the electronic medical record, with very little missing information. It is possible that some study subjects will have received meningococcal vaccine prior to joining the health plan, and these prior doses may not be captured. This number is expected to be small and not to have a material impact on the results.

Handling of Loss to Follow-up

We expect there to be minimal loss to follow-up due to the high retention of KPSC health plan members in this age group. Any loss will be addressed in the data analysis by the truncation of person-time in the event rate calculation.

9.8 Quality Control

9.8.1 Validation

Vaccination and medical event data will be extracted directly from the electronic medical record, which is the legal record of all medical care received within the KPSC system. Records of vaccinations and medical events can only be entered by medical staff, and are assumed to be an accurate representation of care received. No validation will be performed regarding vaccination. Medical events will be individually reviewed in order to determine the primary reason for the encounter as well as whether the condition pre-dated the first receipt of MenACWY-CRM.

All data in the study is extracted and maintained in the electronic database at KPSC. The database is maintained on a daily basis, and undergoes quality validations regularly. Only authorized study personnel with passwords can access to databases. Validations of data in the study database will include range and consistency checks.

9.8.2 Record Retention

The participating HMO's standard procedures for medical record and data file retention will be used for this study.

9.9 Limitations of the Research Methods

This is a descriptive, observational study conducted in a routine medical care setting. The decisions to use MenACWY-CRM and other vaccinations are independently made by HCPs and caregivers.

The validity of the study may be limited by several aspects. First, the generalizability will be limited by the characteristics of the population covered by KPSC. KPSC has a larger proportion of Hispanics compared to the US population, but it is broadly representative of the California population. Second, the study may not be able to capture all medical events following Men ACWY-CRM vaccination, due to children moving out of the KPSC region. Given that the population is relatively stable, it is less likely that the study will be affected. Finally, medical events described in the study will be severe due to the nature of diseases requiring inpatient and emergency room visits.

9.10 Other Aspects

There are no other aspects of the research method not covered by the previous sections.

10.1 PROTECTION OF HUMAN SUBJECTS

KPSC electronic medical records will be used to conduct the study. Personal information is maintained at KPSC with firewall protection. Identifiable data can be only accessed by authorized study staff through password protected accounts. Data transmission is through encrypted software to assure confidentiality.

GSK respects the subjects' rights to privacy and will ensure the confidentiality of their medical information in accordance with applicable laws and regulations.

10.2 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.

10.3 Informed Consent

Subjects included in this study will be identified among KPSC health plan members. Informed consent for receipt of MenACWY-CRM vaccine is not required as it is given to eligible KPSC members as part of routine care. KPSC will obtain IRB approval and will request waivers for both informed consent and written HIPAA authorization prior to initiating data collection.

10.4 Responsibilities of the Investigator and IRB/IEC/REB

The protocol and waiver of informed consent must be reviewed and approved by a properly constituted IRB/IEC/REB before study start. A signed and dated statement that the protocol has been approved by the IRB/IEC/REB and waiver of informed consent must be given to GSK before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol. If an inspection of the site is requested by a regulatory authority, the investigator must inform GSK immediately that this request has been made.

10.5 Protocol Adherence

Investigators will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact GSK or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a change to the protocol would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment

is agreed upon by GSK and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

11.0 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

Adverse reactions reporting is not required, as this is a non-interventional study based on secondary use of KPSC electronic records. Vaccination information, medical events and pre-existing conditions will be searched in the computer database. SAEs cannot be identified spontaneously under the current methodology, so there will not be a general tabulation of SAEs that occurred and were reported spontaneously in this study.

12.1 PLANS FOR DISSEMINATING AND COMMUNICATING RESULTS

12.2 Registration in Public Database(s)

GSK assures that the key design elements of this protocol will be posted in a publicly accessible database where applicable and in compliance with current regulations.

GSK also assures that key results of this study will be posted in a publicly accessible database within the required time-frame from completion of the data collection where applicable and in compliance with current regulations (for study registration numbers see title page).

12.3 Publications

Decisions of publication will be under the agreement of GSK and the study site.

13.0 REFERENCES

1. Schwartz, B., P.S. Moore, and C.V. Broome, *Global epidemiology of meningococcal disease.* Clin Microbiol Rev, 1989. **2 Suppl**: p. S118-24.
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4. Berron, S., et al., *Increasing incidence of meningococcal disease in Spain associated with a new variant of serogroup C.* Eur J Clin Microbiol Infect Dis, 1998. **17**(2): p. 85-9.
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6. Cohn, A.C., et al., *Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP).* MMWR Recomm Rep, 2013. **62**(RR-2): p. 1-28.
7. Novartis Vaccines and Diagnostics, I., *MenACWY Investigator's Brochure.* 2013.
8. Koebnick, C., et al., *Sociodemographic characteristics of members of a large, integrated health care system: comparison with US Census Bureau data.* Perm J, 2012. **16**(3): p. 37-41.
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10. Akinsanya-Beysolow, I., et al., *Advisory Committee on Immunization Practices recommended immunization schedules for persons aged 0 through 18 years - United States, 2014.* MMWR Morb Mortal Wkly Rep, 2014. **63**(5): p. 108-9.

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The individuals listed have approved this document for implementation using an electronic signature in the Atlas EDMS. / PPD
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UserName: PPD
Title: Cluster Physician
Date: Monday, 15 August 2016, 05:35 GMT
Meaning: As an approver, I agree with the content and format of this document.
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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, including appendices

STUDY TITLE: Post-licensure observational safety surveillance study of quadrivalent meningococcal ACWY conjugate vaccine MenACWY-CRM (MENVEO®) in children 2 months through 23 months of age

Study: 205534 (MENACWY CONJ-035 EPI VS US DB (V59_74OB))

Development Phase: Post-licensure observational safety surveillance 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: Michele Pellegrini

Title of Sponsor Signatory: Clinical & Epidemiology Research and Development Project Lead

Signature: PPD

Date: 16/NOV/2018

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