GlaxoSmithKline

STATISTICAL ANALYSIS PLAN

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.
Protocol Number:	V59_74OB
Phase of Development:	Phase IV
IND number:	11278
Sponsor:	GlaxoSmithKline 350 Massachusetts Avenue Cambridge, MA 02139
Coordinating/Principal Investigator(s):	PPD Department of Research and Evaluation Kaiser Permanente Southern California 100 S. Los Robles Ave, 2nd Floor Pasadena, CA 91101, USA
Epidemiologist:	Dr. PPD Global Epidemiology GlaxoSmithKline Amsterdam, The Netherlands Email: PPD
Plan Prepared by:	PPD, MS Research Manager, Biostatistics Kaiser Permanente Southern California
Version and Date:	Version 1.2: 30 October 2015

Approvals

Approvers, Organization & Role	Approval Status	Date
PPD , MS KPSC Research and Evaluation Research Manager, Biostatistics		
PPD KPSC Research and Evaluation Principal Investigator		
PPD Department of Epidemiology GlaxoSmithKline Epidemiologist		

Publication Record

Version	Date	Primary Author	Description
1.0	September 18, 2015	PPD	1st Draft for GSK Review
1.1	October 16, 2015	PPD	2nd Draft for GSK Review
1.2	October 30, 2015	PPD	Final draft for GSK Review
2.0			Approvals obtained, SAP finalized

Definitions

Concomitant vaccination(s) – any other vaccination(s) administered to a subject on the same date as a MenACWY-CRM vaccination.

Day 0 - For the calculation of study day, Day 0 is the date when the index vaccination is received.

Event – Events are classified on an encounter level and a diagnosis level. For encounters, an inpatient admission, emergency department (ED) visit, or an ED visit resulting in an inpatient admission will each be treated as a single event. For diagnoses, all medical diagnoses made during ED and inpatient visits are considered events, which will be further classified as pre-existing, new, recurrent, or part of an ongoing episode.

Episode – Diagnosis-type medical events that result in multiple encounters during the observation period are considered episodes. Episodes comprise the course of a disease or condition, from initial presentation through resolution, as determined through chart review. An episode will be consolidated as a single event for analysis. For each episode, the first diagnosis date in any care setting will be used for analyses.

First-dose - no prior dose of a quadrivalent meningococcal conjugate vaccine recorded in the full medical history

Index vaccination – The first receipt of MenACWY-CRM at a KPSC facility between July 1, 2014 and June 30, 2017 in a study subject of which the date of administration defines the start of the observation period.

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 (November 30, 2017), whichever occurs sooner. For each dose, the observation period is defined as the time from the dose of MenACWY-CRM vaccination up to six months following that dose, receipt of a subsequent MenACWY-CRM vaccination, disenrollment, death, or the end of data collection, whichever occurs sooner.

Pre-existing conditions – Diagnoses occurring in any care setting (inpatient, outpatient, or emergency department) 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.

ABBREVIATIONS
ACIP: Advisory Committee on Immunization Practices
CBER: Center for Biologics Evaluation and Research

CDC: Centers for Disease Control and Prevention
ED: Emergency Department
EMR: Electronic Medical Record
FDA: Food and Drug Administration
GSK: GlaxoSmithKline
HCP: Health Care Providers
HMO: Health Maintenance Organization
ICD-9: International Classification of Diseases, Ninth Revision
ICD-10: International Classification of Diseases, Tenth Revision
KPSC: Kaiser Permanente Southern California
MenACWY- CRM – Meningococcal Quadrivalent CRM-197 Conjugate Vaccine, Menveo
PHI: Protected Health Information
SAP: Statistical Analysis Plan
SAS: Statistical Analysis System, an integrated system of software published by SAS Institute Inc. for accessing, managing, analyzing, and reporting data

Contents

1. INTRODUCTION

Meningococcal disease remains a significant public health burden, particularly in toddlers and infants. GlaxoSmithKline (GSK)'s quadrivalent meningococcal CRM-197 conjugate vaccine (MenACWY-CRM, or Menveo) is expected to fill this unmet need, and as a first step in the process of licensure across all age groups, MenACWY-CRM was submitted for review by the Center for Biologics Evaluation and Research (CBER) in late 2008, and granted approval for use in individuals aged 11-55 years by the Food and Drug Administration (FDA) on February 19, 2010. 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. This study will provide additional information to the current safety knowledge of MenACWY-CRM in the population 2-23 months of age.

This Statistical Analysis Plan (SAP) document provides a detailed description of the data considerations, statistical methods, data analysis and results presentation as previously proposed in its related protocol and amendments, where applicable.

2. STUDY OBJECTIVES

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

3. STUDY DESIGN

3.1 Overview of study design

This study is a descriptive observational study expected to span multiple years. This study will include members of Kaiser Permanente Southern California (KPSC) HMO vaccinated with MenACWY-CRM as part of their routine clinical care. Patients will be between the ages of 2 and 23 months.

The vaccination period spans three years, with the number of study subjects determined by the number of KPSC members aged 2-23 months who receive their index MenACWY-CRM vaccination between July 1, 2014 and June 30, 2017. The observation period for each recipient 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 (November 30, 2017), whichever occurs sooner. Vaccination status is obtained from the information in the vaccination records of the electronic medical record (EMR).

Medical events in ED and inpatient care units in children 2-23 months of age who were vaccinated with any dose of MenACWY-CRM vaccine will be described. Medical events that occur up to six months following a dose of MenACWY-CRM, receipt of a subsequent MenACWY-CRM vaccination, disenrollment, death, or the end of data collection, whichever occurs sooner will be captured. Events will be identified from EMRs of ED and inpatient care encounters. 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. Medical records of these events will be reviewed and described.

All events occurring during the observation period are assessed retrospectively. One subject can experience multiple different events. All identified events will be reviewed by a general physician (study co-investigator) to determine the final diagnosis/diagnoses for the encounter.

3.2 Sample Size and Power Considerations

As the study is descriptive in nature, there is no hypothesis testing and therefore no requirement for a given sample size or power. The sample size will be determined by the total number of children aged 2-23 months vaccinated in KPSC during a three-year period.

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 medical conditions. It is estimated that the number of infants with high risk conditions would likely fall between 60-100 in the study period.

The following table provides the width of the confidence intervals for the incidence rate estimates for different sample sizes and observed event rates. It assumes that each individual recipient will provide, on average, one person-year of follow-up among all doses.

Table: Expected confidence intervals by event rate and study sample size.

Event rate per 100 person-years	Number of vaccinated subjects		
	N=50	N=100	N=150
0.1	0.0-7.6	0.0-3.9	0.0-2.7
1.0	0.0-9.4	0.0-5.6	0.1-4.3
10	3.3-23.3	4.8-18.4	5.6-16.5
100	74.2-131.8	81.4-121.6	84.6-117.3

3.3 Study population, exposures and outcomes

3.3.1 Study population

This study will include members of KPSC vaccinated with MenACWY-CRM as part of their routine clinical care, between the ages of 2 and 23 months. Baseline medical history and vaccination status is obtained from the medical records.

3.3.2 Exposure

MenACWY-CRM vaccination will be received as part of routine clinical care. All vaccinations are documented in the EMR at time of administration. 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 other meningococcal vaccines are available for vaccination of KPSC members over 23 months of age, each vaccine has a unique identifier in the KPSC electronic databases and is therefore distinguishable.

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. 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.

3.3.3 Outcomes

Outcomes include medical events that require ED visits or hospitalizations in children 2-23 months of age following any dose of MenACWY-CRM vaccination. Medical events occurring in ED and inpatient settings within 6 months following a MenACWY-CRM vaccination will be searched in the EMR. Evidence of the same pre-existing medical event (based on ICD diagnosis code) will be searched for in all care settings (inpatient, outpatient, or ED) prior to the first 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. 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 ED and subsequently transferred to the hospital, this will be treated as a single event.

For each identified ED 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 ED or both
- First occurrence vs. recurrence of the diagnosis

One subject can experience multiple different events. In the specific situation where an eligible child received multiple doses during the observation period and the event occurred after the administration of a later dose, the timing of the event is calculated from the date of administration of the most recent dose. In the case of a recurrence of the same condition, the initial diagnosis and the recurrent diagnosis will each be separately described relative to the most recent dose.

4. ANALYSIS OF STUDY POPULATION AND CHARACTERISTICS

All analyses will be performed using SAS Enterprise Guide (version 5.1 or higher).

4.1 Description of study population selection

The selection of the study population will be summarized, including the total number of enrolled members aged 2-23 months and the number of members aged 2-23 months vaccinated with MenACWY-CRM. See Appendix A, Table Shell 1, for details.

4.2 Characteristics of MenACWY-CRM recipients

Characteristics of the study population of infant recipients of the MenACWY-CRM vaccine will be described. The description includes demographics (age, gender), underlying condition of the vaccine indication, if available (see Appendix B), and concomitant and prior vaccinations (any and by type).

Separately, duration of follow-up and number and timing of subsequent MenACWY-CRM vaccinations will be described. Other vaccines received during follow-up will be described by name and whether they were given concomitantly with a subsequent MenACWY-CRM dose.

Descriptive statistics (mean, standard deviation, median, Q1, Q3, minimum and maximum) are presented for continuous variables and frequency distributions (n, %) for categorical variables. See Appendix A, Table Shells 2 and 3, for details. For these tables, information on any cell with count >0 but less than 3 will be suppressed in the final report.

These data will be provided for the entire population and for the following strata if sufficient numbers are available (each reported stratum will have $n \geq 5$ recipients):

- Number of MenACWY-CRM doses received during the study period.

In addition, the frequency of vaccinations will be presented graphically in calendar time intervals, overall and by number of doses as stacked bars to distinguish first, second, third and fourth doses received during the period.

5. ANALYSES OF OBJECTIVE

The outcome data will be provided for the entire population and for the following stratum if sufficient numbers are available ($n \geq 5$ in each stratum):

- Number of MenACWY-CRM doses received during the study period.

5.1 Identification and review of events

Medical events occurring in ED and inpatient settings within 6 months following a MenACWY-CRM vaccination will be searched in the EMR.

Medical events will be characterized two ways: by encounter (hospitalization only, ED only, or both ED and hospitalization) and by diagnosis (see Appendix A, Table Shell 4 for details). The analysis allows for any recurrent events (i.e. different episodes of the same diagnosis) to be counted independently.

For characterization by encounter (Table 4a), all dates used for analysis will be the date of the ED encounter or hospital admission. Encounters will be considered pre-existing if all diagnoses made during the encounter are present in the medical record prior to the first dose of vaccine. Upon chart review by the study physician co-investigator, an encounter will be refuted if it is found to not be a true ED or hospital encounter. Each encounter will be reported as a single event, regardless of the number of diagnoses made during the encounter.

For characterization by diagnosis (Table 4b), all dates used for analysis will be the first date that the diagnosis is recorded in the EMR in any medical setting. A diagnosis will be excluded as pre-existing if the same ICD diagnosis code appears in any medical setting prior to the first dose of MenACWY-CRM vaccination. A diagnosis will be considered refuted if, upon chart review by the study physician co-investigator, there is no evidence of the diagnosis in the medical record. Multiple diagnoses associated with the same episode will be identified, but only the first diagnosis date (in any setting) will be counted in the analysis of each episode. Subsequent diagnoses for the same episode will be marked in Table 4b as "Diagnosis is continuation of an ongoing episode." An episode will be considered as ended when there is symptom resolution as determined by chart review (e.g., symptoms stated to have resolved or the diagnosis/symptoms have been absent from the medical record before they are mentioned again). In the case of recurrent events, the date used will be the date of the first diagnosis in the medical record following resolution of the prior episode. Recurrent events will be marked in Table 4b as "Diagnosis is a recurrence". Each diagnosis will be described independently. It is possible that different diagnoses from the same inpatient or ED encounter could have different diagnosis

dates, and that some could be pre-existing while others are in the post-vaccine observation period.

5.2 Frequency and rate of 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.

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. The rate and Poisson 95% confidence interval of the rate of medical events will be calculated and presented as number per 1000 person-years.

If the number of medical events allows, captured medical events will be stratified by dose and by the status of the diagnosis as first occurrence or recurrence. 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.

Frequency and rate of events will be characterized two ways: by encounter (hospitalization only, ED only, or both ED and hospitalization) and by diagnosis (see Appendix A, Table Shell 5 for details). For the analysis by encounter, the encounter date will be used to determine the timing of the encounter relative to the timing of vaccine dose. For the analysis by diagnosis, the first diagnosis date for each diagnosis in any care setting will be used to determine the timing of the diagnosis relative to the timing of vaccine dose. The analysis by diagnosis will be stratified by setting of diagnosis and recurrence when the number of events in each stratum is ≥ 5. The setting of diagnosis reflects whether the diagnosis was captured by automated search in the inpatient setting, ED setting, or both. If possible, diagnoses will be grouped by category, and the frequency and rate of diagnoses will be presented by category.

5.3 Description of events

Diagnosis-type medical events following MenACWY-CRM exposure in children 2-23 months of age will be described if five or more of a diagnosis or diagnosis grouping are observed. Medical events will be reviewed and summarized, at least including age at vaccination, gender, age at diagnosis, MenACWY-CRM vaccination history, setting of diagnosis, and if available, underlying condition of vaccination. Recurrence of the same medical event after repeated MenACWY-CRM vaccination of the same person will be included in the description as well. See Appendix A, Table Shell 6 for details.

5.4 Sensitivity analysis

No sensitivity analyses are planned.

6. STATISTICAL CONSIDERATIONS AND LIMITATIONS

6.1 Statistical considerations

Due to the expected small sample size, no formal hypothesis testing or statistical analysis is planned.

6.2 Internal Validity

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. As vaccinations are available at no cost to members of the HMO, we expect that very few vaccinations will be received outside of the HMO. 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 EMRs 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 EMR, 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.

7. STUDY REPORT

The final report will include all data generated from this study as specified in this SAP.

8. LIST OF REPORT TABLES, LISTINGS AND FIGURES

	Population* (all or per event)	Description	Strata**
Table 1	All	Study population selection	
Table 2	All	Baseline Characteristics of MenACWY-CRM recipients 2-23 months of age	Number of vaccinations received
Table 3	All	Follow-up characteristics of MenACWY-CRM recipients 2-23 months of age	Number of vaccinations received
Table 4	Per event	Summary of event identification and review	
Table 5	Per event	Frequency and rate of events among infant MenACWY-CRM recipients	Number of vaccinations received, care setting (5b only), recurrence (5b only)
Table 6	Per event	Description of diagnoses among infant MenACWY-CRM recipients	
Figure 1	All	Vaccinations by Month	Number of vaccinations received

*All = all MenACWY-CRM recipients,
Per event will include all recipients with no history of that event prior to the first MenACWY-CRM dose
** Data are only presented in stratum if sufficient numbers are available in each stratum ($n \geq 5$).

9. QUALITY CONTROL

9.1 Data Management

Data for this study will include vaccination, demographics, membership, utilization, death, and data from the identification and validation of serious medically-attended events that may occur in the six months following vaccination. The contents of the various datasets are specified separately in a data dictionary, which will be provided with the relevant SAS programming.

9.2 Data Quality Checks

Range checks and general frequency tables will be produced such that missing values, outliers, and inappropriate or abnormal values will be identified. Comparisons between date of birth, date of death, event dates and vaccination dates will be made. All data will be checked for duplicate records.

A record of data quality problems and resolutions will be kept in the form of an Excel spreadsheet or other method appropriate to the circumstances (e.g. commented code, detailed correspondence). All inconsistencies and/or data quality issues will be documented. Revisions will be noted in order to capture the change made, the change date, identification of the individual making the change, as well as noting any further actions to be taken to identify and/or resolve additional data quality problems of this type.

All programming will be reviewed by a second programmer. Additionally, prior to reviewing the original programming, the second programmer will independently extract vaccination data. The results of the original and validation programming will be compared and any discrepancies will be investigated. A report will be created, listing discrepancies, their causes, and any action taken to resolve them. It is expected that there may be a small number of discrepancies due to a difference in the date on which the original and validation programs are run, as they are pulling from live databases which are updated regularly. If this cause is suspected, both programs may be run again on the same date as a means to eliminate this potential cause of discrepancies.

9.3 Confidentiality of Data

Any research data containing subject protected health information (PHI) is confidential. KPSC staff will not discuss the protocol or research data with anyone other than KPSC project personnel, or representatives of GSK. All sharing of confidential information shall be in accordance with the confidentiality agreement detailed in the study contract.

Appendix A: Table shells

Table shells are provided in a separate Excel file.

Appendix B: Underlying condition of vaccine indication

Vaccine recipients will be determined to have the following underlying conditions for vaccination if the associated diagnosis codes are present in the medical record six months prior to index vaccination, including the date of index vaccination.

1. Asplenia

Functional - Hemoglobinopathies (primarily sickle cell [SS or SC] disease)

ICD-9 Codes:

Diagnosis	**ICD-9 Diagnostic Code**
Sickle cell disease unspecified	282.60
HB-SS disease with crisis	282.62
Sickle cell thalassemia without crisis	282.41
Sickle cell/HB-C disease without crisis	282.63
Sickle cell/HB-C disease with crisis	282.64
Other sickle cell disease without crisis	282.68
Other sickle cell disease with crisis	282.69
Sickle cell thalassemia with crisis	282.42

ICD-10 Codes:

Diagnosis	**ICD-10 Diagnostic Code**
Sickle cell disease without crisis	D57.1
HB-SS disease with crisis, unspecified	D57.00
Sickle cell thalassemia without crisis	D57.40
Sickle cell/HB-C disease without crisis	D57.20
Sickle cell/HB-C disease with crisis, unspecified	D57.219
Other sickle cell disorders without crisis	D57.80

Other sickle cell disease with crisis, unspecified	D57.819
Sickle cell thalassemia with crisis, unspecified	D57.419
Hyposplenism	D73.0

Anatomic Asplenia

ICD-9 Codes:

Diagnosis	**ICD-9 Diagnostic Code**
Anomalies of spleen congenital	759.0

ICD-10 Codes:

Diagnosis	**ICD-10 Diagnostic Code**
Asplenia (congenital)	Q89.01
Congenital malformations of spleen	Q89.09
Acquired asplenia	Z90.81

2. Persistent Complement Component Deficiencies

ICD-9 Codes:

Diagnosis	**ICD-9 Diagnostic Code**
Other specified disorders involving the immune mechanism	279.8

ICD-10 Codes:

Diagnosis	**ICD-10 Diagnostic Code**

Defects in the complement system	D84.1

GlaxoSmithKline

STATISTICAL ANALYSIS PLAN

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.
Protocol Number:	V59_74OB
Phase of Development:	Phase IV
IND number:	11278
Sponsor:	GlaxoSmithKline 350 Massachusetts Avenue Cambridge, MA 02139
Coordinating/Principal Investigator(s):	PPD Department of Research and Evaluation Kaiser Permanente Southern California 100 S. Los Robles Ave, 2nd Floor Pasadena, CA 91101, USA
Epidemiologist:	Dr. PPD Global Epidemiology GlaxoSmithKline Amsterdam, The Netherlands Email: PPD
Plan Prepared by:	PPD, MS Research Manager, Biostatistics Kaiser Permanente Southern California
Version and Date:	Version 2.0: 17 November 2015

Approvals

Approvers, Organization & Role	Approval Status	Date
PPD , MS KPSC Research and Evaluation Research Manager, Biostatistics	Approved	11/17/2015
PPD KPSC Research and Evaluation Principal Investigator	Approved	11/17/2015
PPD Department of Epidemiology GlaxoSmithKline Epidemiologist	Approved	11/17/2015

Publication Record

Version	Date	Primary Author	Description
1.0	September 18, 2015	PPD	1st Draft for GSK Review
1.1	October 16, 2015	PPD	2nd Draft for GSK Review
1.2	October 30, 2015	PPD	Final draft for GSK Review
1.3	November 6, 2015	PPD	Comments on Draft 1.2
1.4	November 11, 2015	PPD	Final draft for GSK Review
2.0	November 17, 2015	PPD	Approvals obtained, SAP finalized

Definitions

Concomitant vaccination(s) – any other vaccination(s) administered to a subject on the same date as a MenACWY-CRM vaccination.

Day 0 - For the calculation of study day, Day 0 is the date when the index vaccination is received.

Event – Events are classified on an encounter level and a diagnosis level. For encounters, an inpatient admission, emergency department (ED) visit, or an ED visit resulting in an inpatient admission will each be treated as a single event. For diagnoses, all medical diagnoses made during ED and inpatient visits are considered events, which will be further classified as pre-existing, new, recurrent, or part of an ongoing episode.

Episode – Diagnosis-type medical events that result in multiple encounters during the observation period are considered episodes. Episodes comprise the course of a disease or condition, from initial presentation through resolution, as determined through chart review. An episode will be consolidated as a single event for analysis. For each episode, the first diagnosis date in any care setting will be used for analyses.

First-dose - no prior dose of a quadrivalent meningococcal conjugate vaccine recorded in the full medical history

Index vaccination – The first receipt of MenACWY-CRM at a KPSC facility between July 1, 2014 and June 30, 2017 in a study subject of which the date of administration defines the start of the observation period.

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 (November 30, 2017), whichever occurs sooner. For each dose, the observation period is defined as the time from the dose of MenACWY-CRM vaccination up to six months following that dose, receipt of a subsequent MenACWY-CRM vaccination, disenrollment, death, or the end of data collection, whichever occurs sooner.

Pre-existing conditions – Diagnoses occurring in any care setting (inpatient, outpatient, or emergency department) 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.

ABBREVIATIONS
ACIP: Advisory Committee on Immunization Practices
CBER: Center for Biologics Evaluation and Research

CDC: Centers for Disease Control and Prevention
ED: Emergency Department
EMR: Electronic Medical Record
FDA: Food and Drug Administration
GSK: GlaxoSmithKline
HCP: Health Care Providers
HMO: Health Maintenance Organization
ICD-9: International Classification of Diseases, Ninth Revision
ICD-10: International Classification of Diseases, Tenth Revision
KPSC: Kaiser Permanente Southern California
MenACWY- CRM – Meningococcal Quadrivalent CRM-197 Conjugate Vaccine, Menveo
PHI: Protected Health Information
SAP: Statistical Analysis Plan
SAS: Statistical Analysis System, an integrated system of software published by SAS Institute Inc. for accessing, managing, analyzing, and reporting data

Contents

1. INTRODUCTION

Meningococcal disease remains a significant public health burden, particularly in toddlers and infants. GlaxoSmithKline (GSK)'s quadrivalent meningococcal CRM-197 conjugate vaccine (MenACWY-CRM, or Menveo) is expected to fill this unmet need, and as a first step in the process of licensure across all age groups, MenACWY-CRM was submitted for review by the Center for Biologics Evaluation and Research (CBER) in late 2008, and granted approval for use in individuals aged 11-55 years by the Food and Drug Administration (FDA) on February 19, 2010. 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. This study will provide additional information to the current safety knowledge of MenACWY-CRM in the population 2-23 months of age.

This Statistical Analysis Plan (SAP) document provides a detailed description of the data considerations, statistical methods, data analysis and results presentation as previously proposed in its related protocol and amendments, where applicable.

2. STUDY OBJECTIVES

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

3. STUDY DESIGN

3.1 Overview of study design

This study is a descriptive observational study expected to span multiple years. This study will include members of Kaiser Permanente Southern California (KPSC) HMO vaccinated with MenACWY-CRM as part of their routine clinical care. Patients will be between the ages of 2 and 23 months.

The vaccination period spans three years, with the number of study subjects determined by the number of KPSC members aged 2-23 months who receive their index MenACWY-CRM vaccination between July 1, 2014 and June 30, 2017. The observation period for each recipient 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 (November 30, 2017), whichever occurs sooner. Vaccination status is obtained from the information in the vaccination records of the electronic medical record (EMR).

Medical events in ED and inpatient care units in children 2-23 months of age who were vaccinated with any dose of MenACWY-CRM vaccine will be described. Medical events that occur up to six months following a dose of MenACWY-CRM, receipt of a subsequent MenACWY-CRM vaccination, disenrollment, death, or the end of data collection, whichever occurs sooner will be captured. Events will be identified from EMRs of ED and inpatient care encounters. 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. Medical records of these events will be reviewed and described.

All events occurring during the observation period are assessed retrospectively. One subject can experience multiple different events. All identified events will be reviewed by a general physician (study co-investigator) to determine the final diagnosis/diagnoses for the encounter.

3.2 Sample Size and Power Considerations

As the study is descriptive in nature, there is no hypothesis testing and therefore no requirement for a given sample size or power. The sample size will be determined by the total number of children aged 2-23 months vaccinated in KPSC during a three-year period.

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 medical conditions. It is estimated that the number of infants with high risk conditions would likely fall between 60-100 in the study period.

The following table provides the width of the confidence intervals for the incidence rate estimates for different sample sizes and observed event rates. It assumes that each individual recipient will provide, on average, one person-year of follow-up among all doses.

Table: Expected confidence intervals by event rate and study sample size.

Event rate per 100 person-years	Number of vaccinated subjects		
	N=50	N=100	N=150
0.1	0.0-7.6	0.0-3.9	0.0-2.7
1.0	0.0-9.4	0.0-5.6	0.1-4.3
10	3.3-23.3	4.8-18.4	5.6-16.5
100	74.2-131.8	81.4-121.6	84.6-117.3

3.3 Study population, exposures and outcomes

3.3.1 Study population

This study will include members of KPSC vaccinated with MenACWY-CRM as part of their routine clinical care, between the ages of 2 and 23 months. Baseline medical history and vaccination status is obtained from the medical records.

3.3.2 Exposure

MenACWY-CRM vaccination will be received as part of routine clinical care. All vaccinations are documented in the EMR at time of administration. 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 other meningococcal vaccines are available for vaccination of KPSC members over 23 months of age, each vaccine has a unique identifier in the KPSC electronic databases and is therefore distinguishable.

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. 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.

3.3.3 Outcomes

Outcomes include medical events that require ED visits or hospitalizations in children 2-23 months of age following any dose of MenACWY-CRM vaccination. Medical events occurring in ED and inpatient settings within 6 months following a MenACWY-CRM vaccination will be searched in the EMR. Evidence of the same pre-existing medical event (based on ICD diagnosis code) will be searched for in all care settings (inpatient, outpatient, or ED) prior to the first 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. 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 ED and subsequently transferred to the hospital, this will be treated as a single event.

For each identified ED 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 ED or both
- First occurrence vs. recurrence of the diagnosis

One subject can experience multiple different events. In the specific situation where an eligible child received multiple doses during the observation period and the event occurred after the administration of a later dose, the timing of the event is calculated from the date of administration of the most recent dose. In the case of a recurrence of the same condition, the initial diagnosis and the recurrent diagnosis will each be separately described relative to the most recent dose.

4. ANALYSIS OF STUDY POPULATION AND CHARACTERISTICS

All analyses will be performed using SAS Enterprise Guide (version 5.1 or higher).

4.1 Description of study population selection

The selection of the study population will be summarized, including the total number of enrolled members aged 2-23 months and the number of members aged 2-23 months vaccinated with MenACWY-CRM. See Appendix A, Table Shell 1, for details.

4.2 Characteristics of MenACWY-CRM recipients

Characteristics of the study population of infant recipients of the MenACWY-CRM vaccine will be described. The description includes demographics (age, gender), underlying condition of the vaccine indication, if available (see Appendix B), and concomitant and prior vaccinations (any and by type).

Separately, duration of follow-up and number and timing of subsequent MenACWY-CRM vaccinations will be described. Other vaccines received during follow-up will be described by name and whether they were given concomitantly with a subsequent MenACWY-CRM dose.

Descriptive statistics (mean, standard deviation, median, Q1, Q3, minimum and maximum) are presented for continuous variables and frequency distributions (n, %) for categorical variables. See Appendix A, Table Shells 2 and 3, for details. For these tables, information on any cell with count >0 but less than 3 will be suppressed in the final report.

These data will be provided for the entire population and for the following strata if sufficient numbers are available (each reported stratum will have $n \geq 5$ recipients):

- Number of MenACWY-CRM doses received during the study period.

In addition, the frequency of vaccinations will be presented graphically in calendar time intervals, overall and by number of doses as stacked bars to distinguish first, second, third and fourth doses received during the period.

5. ANALYSES OF OBJECTIVE

The outcome data will be provided for the entire population and for the following stratum if sufficient numbers are available ($n \geq 5$ in each stratum):

- Number of MenACWY-CRM doses received during the study period.

5.1 Identification and review of events

Medical events occurring in ED and inpatient settings within 6 months following a MenACWY-CRM vaccination will be searched in the EMR.

Medical events will be characterized two ways: by encounter (hospitalization only, ED only, or both ED and hospitalization) and by diagnosis (see Appendix A, Table Shell 4 for details). The analysis allows for any recurrent events (i.e. different episodes of the same diagnosis) to be counted independently.

For characterization by encounter (Table 4a), all dates used for analysis will be the date of the ED encounter or hospital admission. Encounters will be considered pre-existing if all diagnoses made during the encounter are present in the medical record prior to the first dose of vaccine. Upon chart review by the study physician co-investigator, an encounter will be refuted if it is found to not be a true ED or hospital encounter. Each encounter will be reported as a single event, regardless of the number of diagnoses made during the encounter.

For characterization by diagnosis (Table 4b), all dates used for analysis will be the first date that the diagnosis is recorded in the EMR in any medical setting. A diagnosis will be excluded as pre-existing if the same ICD diagnosis code appears in any medical setting prior to the first dose of MenACWY-CRM vaccination. A diagnosis will be considered refuted if, upon chart review by the study physician co-investigator, there is no evidence of the diagnosis in the medical record. Multiple diagnoses associated with the same episode will be identified, but only the first diagnosis date (in any setting) will be counted in the analysis of each episode. Subsequent diagnoses for the same episode will be marked in Table 4b as "Diagnosis is continuation of an ongoing episode." An episode will be considered as ended when there is symptom resolution as determined by chart review (e.g., symptoms stated to have resolved or the diagnosis/symptoms have been absent from the medical record before they are mentioned again). In the case of recurrent events, the date used will be the date of the first diagnosis in the medical record following resolution of the prior episode. Recurrent events will be marked in Table 4b as "Diagnosis is a recurrence". Each diagnosis will be described independently. It is possible that different diagnoses from the same inpatient or ED encounter could have different diagnosis

dates, and that some could be pre-existing while others are in the post-vaccine observation period.

5.2 Frequency and rate of 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 out of the total number of captured medical events during the observation period and included for analysis (as per Tables 4a or 4b).

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. The rate and Poisson 95% confidence interval of the rate of medical events will be calculated and presented as number per 1000 person-years using SAS PROC GENMOD.
If the number of medical events allows, captured medical events will be stratified by dose and by the status of the diagnosis as first occurrence or recurrence. Person-time for each dose will begin at the date of 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.

Frequency and rate of events will be characterized two ways: by encounter (hospitalization only, ED only, or both ED and hospitalization) and by diagnosis (see Appendix A, Table Shell 5 for details). For the analysis by encounter, the encounter date will be used to determine the timing of the encounter relative to the timing of vaccine dose. For the analysis by diagnosis, the first diagnosis date for each diagnosis in any care setting will be used to determine the timing of the diagnosis relative to the timing of vaccine dose. The analysis by diagnosis will be stratified by setting of diagnosis and recurrence when the number of events in each stratum is ≥ 5. The setting of diagnosis reflects whether the diagnosis was captured by automated search in the inpatient setting, ED setting, or both. If possible, diagnoses will be grouped by category, and the frequency and rate of diagnoses will be presented by category.

5.3 Description of events

Diagnosis-type medical events following MenACWY-CRM exposure in children 2-23 months of age will be described if five or more of a diagnosis or diagnosis grouping are observed. Medical events will be reviewed and summarized, at least including age at vaccination, gender, age at diagnosis, MenACWY-CRM vaccination history, setting of diagnosis, and if available, underlying condition of vaccination. Whether this is a first occurrence or recurrence of the same medical event after repeated MenACWY-CRM vaccination of the same person will be included in the description as well. See Appendix A, Table Shell 6 for details.

5.4 Sensitivity analysis

No sensitivity analyses are planned.

6. STATISTICAL CONSIDERATIONS AND LIMITATIONS

6.1 Statistical considerations

Due to the expected small sample size, no formal hypothesis testing or statistical analysis is planned.

6.2 Internal Validity

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. As vaccinations are available at no cost to members of the HMO, we expect that very few vaccinations will be received outside of the HMO. 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 EMRs 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 EMR, 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.

7. STUDY REPORT

The final report will include all data generated from this study as specified in this SAP.

8. LIST OF REPORT TABLES, LISTINGS AND FIGURES

	Population* (all or per event)	Description	Strata**
Table 1	All	Study population selection	
Table 2	All	Baseline Characteristics of MenACWY-CRM recipients 2-23 months of age	Number of vaccinations received
Table 3	All	Follow-up characteristics of MenACWY-CRM recipients 2-23 months of age	Number of vaccinations received
Table 4	Per event	Summary of event identification and review	
Table 5	Per event	Frequency and rate of events among infant MenACWY-CRM recipients	Number of vaccinations received, care setting (5b only), recurrence (5b only)
Table 6	Per event	Description of diagnoses among infant MenACWY-CRM recipients	
Figure 1	All	Vaccinations by Month	Number of vaccinations received

*All = all MenACWY-CRM recipients,
Per event will include all recipients with no history of that event prior to the first MenACWY-CRM dose
** Data are only presented in stratum if sufficient numbers are available in each stratum ($n \geq 5$).

9. QUALITY CONTROL

9.1 Data Management

Data for this study will include vaccination, demographics, membership, utilization, death, and data from the identification and validation of serious medically-attended events that may occur in the six months following vaccination. The contents of the various datasets are specified separately in a data dictionary, which will be provided with the relevant SAS programming.

9.2 Data Quality Checks

Range checks and general frequency tables will be produced such that missing values, outliers, and inappropriate or abnormal values will be identified. Comparisons between date of birth, date of death, event dates and vaccination dates will be made. All data will be checked for duplicate records.

A record of data quality problems and resolutions will be kept in the form of an Excel spreadsheet or other method appropriate to the circumstances (e.g. commented code, detailed correspondence). All inconsistencies and/or data quality issues will be documented. Revisions will be noted in order to capture the change made, the change date, identification of the individual making the change, as well as noting any further actions to be taken to identify and/or resolve additional data quality problems of this type.

All programming will be reviewed by a second programmer. Additionally, prior to reviewing the original programming, the second programmer will independently extract vaccination data. The results of the original and validation programming will be compared and any discrepancies will be investigated. A report will be created, listing discrepancies, their causes, and any action taken to resolve them. It is expected that there may be a small number of discrepancies due to a difference in the date on which the original and validation programs are run, as they are pulling from live databases which are updated regularly. If this cause is suspected, both programs may be run again on the same date as a means to eliminate this potential cause of discrepancies.

9.3 Confidentiality of Data

Any research data containing subject protected health information (PHI) is confidential. KPSC staff will not discuss the protocol or research data with anyone other than KPSC project personnel, or representatives of GSK. All sharing of confidential information shall be in accordance with the confidentiality agreement detailed in the study contract.

Appendix A: Table shells

Table shells are provided in a separate Excel file.

Appendix B: Underlying condition of vaccine indication

Vaccine recipients will be determined to have the following underlying conditions for vaccination if the associated diagnosis codes are present in the medical record six months prior to index vaccination, including the date of index vaccination.

1. Asplenia

Functional - Hemoglobinopathies (primarily sickle cell [SS or SC] disease)

ICD-9 Codes:

Diagnosis	**ICD-9 Diagnostic Code**
Sickle cell disease unspecified	282.60
HB-SS disease with crisis	282.62
Sickle cell thalassemia without crisis	282.41
Sickle cell/HB-C disease without crisis	282.63
Sickle cell/HB-C disease with crisis	282.64
Other sickle cell disease without crisis	282.68
Other sickle cell disease with crisis	282.69
Sickle cell thalassemia with crisis	282.42

ICD-10 Codes:

Diagnosis	**ICD-10 Diagnostic Code**
Sickle cell disease without crisis	D57.1
HB-SS disease with crisis, unspecified	D57.00
Sickle cell thalassemia without crisis	D57.40
Sickle cell/HB-C disease without crisis	D57.20
Sickle cell/HB-C disease with crisis, unspecified	D57.219
Other sickle cell disorders without crisis	D57.80

Other sickle cell disease with crisis, unspecified	D57.819
Sickle cell thalassemia with crisis, unspecified	D57.419
Hyposplenism	D73.0

Anatomic Asplenia

ICD-9 Codes:

Diagnosis	**ICD-9 Diagnostic Code**
Anomalies of spleen congenital	759.0

ICD-10 Codes:

Diagnosis	**ICD-10 Diagnostic Code**
Asplenia (congenital)	Q89.01
Congenital malformations of spleen	Q89.09
Acquired asplenia	Z90.81

2. Persistent Complement Component Deficiencies

ICD-9 Codes:

Diagnosis	**ICD-9 Diagnostic Code**
Other specified disorders involving the immune mechanism	279.8

ICD-10 Codes:

Diagnosis	**ICD-10 Diagnostic Code**

Defects in the complement system	D84.1

Table 1: Study population selection

Population	Total (n)
Total number of persons within the KPSC cohort	
Total number of children 2-23 months old in the KPSC cohort	
Total MenACWY-CRM vaccine recipients among age 2-23 months	

Date tables created:
Period captured in the tables:
Report integrates the tables:

Table 2: Baseline Characteristics of MenACWY-CRM Recipients 2 to 23 Months of Age

Characteristic	Total	Number of doses received			
		One	Two	Three	Four
Age at first vaccination (months)					
	mean (sd)				
	median				
	Q1, Q3				
	(min - max)				
Age 2-6 months at first vaccination	n (%)				
Age 7-23 months at first vaccination	n (%)				
Gender					
Male	n (%)				
Female	n (%)				
Underlying condition of index vaccine indication					
Persistent complement component deficiencies	n (%)				
Asplenia (functional, anatomic)	n (%)				
Unknown	n (%)				
Concomitant vaccinations	n (%)				
1 concomitant vaccination	n (%)				
≥ 2 concomitant vaccinations	n (%)				
vaccine 1	n (%)				
vaccine 2	n (%)				
Other*	n (%)				
Vaccinations <6 months prior to index	n (%)				
Any vaccination prior to index	n (%)				
vaccine 1	n (%)				
vaccine 2	n (%)				
Other*	n (%)				

* Includes all vaccines with less than 10 recipients

N/A = Not Applicable

† Any cell with count >0 but less than 3 is presented as "<<"

Table 3: Characteristics of MenACWY-CRM Recipients 2-23 Months of Age during the Observation Period

Characteristic		Total	Number of doses received			
			One	Two	Three	Four
MenACWY-CRM vaccination during observation period						
1 dose	n (%)					
2 doses	n (%)					
3 doses	n (%)					
Days from index vaccination to second dose						
	mean (sd)					
	median					
	Q1, Q3					
Days from second vaccination to third dose						
	mean (sd)					
	median					
	Q1, Q3					
Days from third vaccination to fourth dose						
	mean (sd)					
	median					
	Q1, Q3					
Other vaccines received during observation period	n (%)					
Any vaccination during observation period	n (%)					
vaccine 1	n (%)					
vaccine 2	n (%)					
Other*	n (%)					
Other vaccines received concomitantly with subsequent MenACWY-CRM dose	n (%)					
Any vaccination received concomitantly	n (%)					
vaccine 1	n (%)					
vaccine 2	n (%)					
Other*	n (%)					
Completed 6-month observation period following last dose	n (%)					
Duration of observation period (months) with censoring						
	mean (sd)					
	median					
	Q1, Q3					
	(min - max)					

* Includes all vaccines with less than 10 recipients during observation period

† Any cell with count >0 but less than 3 is presented as "<<"

N/A = Not Applicable

Table 4a: Summary of Hospitalization and Emergency Room Visit Event Identification and Review

Event	Automated Algorithm			Physician Review			
	Potential events identified (a)	Excluded events based on pre-existing condition (b)	Events remaining from automated identification (c=a-b)	Events confirmed (d)	Events refuted (e)	Confirmed events with diagnosis determined to be prior to index vaccination (f)	Total Events for Analysis (g=a-b-e-f)
Hospitalization only							
Emergency department only							
Emergency department and hospitalization							

Number of recipients experiencing a single hospitalization or emergency encounter	
Number of recipients experiencing multiple different hospitalization or emergency encounters	

N/A = Not Applicable

Table 4b: Summary of Diagnosis Identification and Review

Event	Automated Algorithm			Physician Review					
	Potential diagnoses identified (a)	Excluded diagnoses based on pre-existing condition (b)	Diagnoses remaining from automated algorithm identification (c=a-b)	Diagnoses confirmed (d)	Diagnoses refuted (e)	Confirmed events with diagnosis determined to be prior to index vaccination (f)	Diagnosis is continuation of an ongoing episode (g)	Diagnosis is a recurrence (h)	Total Diagnoses for Analysis (i=a-b-e-f-g)
Specific diagnoses									
diagnosis 1									
diagnosis 2									
Diagnosis groupings									
grouping 1									
grouping 2									
Number of recipients experiencing a single diagnosis									
Number of recipients experiencing multiple different diagnoses									

N/A = Not Applicable

Table 5a: Frequency and rate of hospitalization and emergency events observed following vaccination with MenACWY-CRM

Event	Overall		Number of vaccines received prior to event							
			One		Two		Three		Four	
	Frequency n (%)	Rate (95% CI)*	Frequency n (%)	Rate (95% CI)*	Frequency n (%)	Rate (95% CI)*	Frequency n (%)	Rate (95% CI)*	Frequency n (%)	Rate (95% CI)*
Hospitalization only										
Emergency department only										
Emergency department and hospitalization										

*Events per 1000 person years

Table 5b: Frequency and rate of diagnoses observed following vaccination with MenACWY-CRM

Event	Overall		Number of vaccines received prior to event								Setting of initial presentation with the diagnosis[+]						First occurrence or recurrence			
			One		Two		Three		Four		Inpatient		Emergency		Both settings		First occurrence		Recurrence	
	Frequency n (%)	Rate (95% CI)*	Frequency n (%)	Rate (95% CI)*	Frequency n (%)	Rate (95% CI)*	Frequency n (%)	Rate (95% CI)*	Frequency n (%)	Rate (95% CI)*	Frequency n (%)	Rate (95% CI)*	Frequency n (%)	Rate (95% CI)*	Frequency n (%)	Rate (95% CI)*	Frequency n (%)	Rate (95% CI)*	Frequency n (%)	Rate (95% CI)*
Specific diagnoses																				
diagnosis 1																				
diagnosis 2																				
Diagnosis groupings																				
grouping 1																				
grouping 2																				
etc.																				

*Events per 1000 person years

[+]The setting where the diagnosis is initially captured from our automated search, which may differ from the setting of first diagnosis found on chart review

Table 6: Description of diagnoses observed following vaccination with MenACWY-CRM

Diagnosis or diagnosis group	Age at most recent vaccination (months)	Age at first diagnosis (months)*	Gender		Setting[+]			Number of MenACWY-CRM vaccinations received prior to diagnosis				Underlying condition of vaccine indication			First occurrence or recurrence	
	mean (SD)	mean (SD)	Male, %	Female, %	Inpatient, %	ED, %	Both, %	One dose, %	Two doses, %	Three doses, %	Four doses, %	Persistent complement component deficiencies, %	Asplenia, %	Other or Unknown, %	First occurrence, %	recurrence, %

Table includes any diagnosis or diagnosis grouping with at least five episodes confirmed by chart review

*The age of the first diagnosis in any setting for this episode, found on chart review

[+]The setting where the diagnosis is initially captured from our automated search, which may differ from the setting of first diagnosis for this episode found on chart review

SD = standard deviation

Figure 1. Number of MenACWY-CRM vaccine recipients age 2-23 months by calendar month