Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Post-licensure safety surveillance study of routine use of quadrivalent meningococcal diphtheria toxoid conjugate vaccine

J. Hansen [a,*], L. Zhang [a], N.P. Klein [a], C.A. Robertson [b], M.D. Decker [b,c], D.P. Greenberg [b,d], E. Bassily [b], R. Baxter [a]

[a] Kaiser Permanente Vaccine Study Center, 1 Kaiser Plaza 16B, Oakland, CA 94612, USA
[b] Sanofi Pasteur, 1 Discovery Drive, Swiftwater, PA 18370, USA
[c] Department of Health Policy, Vanderbilt University School of Medicine, Nashville, TN 37212, USA
[d] Department of Pediatrics, University of Pittsburgh School of Medicine, 3550 Terrace St., Pittsburgh, PA 15213, USA

ARTICLE INFO

Article history:
Received 20 June 2017
Received in revised form 1 September 2017
Accepted 10 September 2017
Available online xxxx

Keywords:
Meningitis
Meningococcal infections
Meningococcal vaccines

ABSTRACT

Background: Menactra® vaccine (MenACWY-D) was licensed in the United States in 2005 for persons 11–55 years of age. The aim of this study was to assess the safety of MenACWY-D administered as part of routine clinical care to patients at Kaiser Permanente Northern California (KPNC).
Methods: This was an observational, retrospective study that included all KPNC members who received MenACWY-D during the study period. We monitored all vaccine recipients for non-elective hospitalizations, emergency department visits, and selected outcomes captured in the clinic setting (Bell's palsy, seizures, neuritis, Guillain-Barré syndrome, encephalopathy, encephalitis, epilepsy, transverse myelitis, multiple sclerosis, hypersensitivity reactions, idiopathic thrombocytopenic purpura, diabetes, arthritis, hemolytic anemia, collagen-vascular disease) through 6 months after vaccination. Using vaccine recipients as their own controls, we calculated incidence rate ratios (IRRs) of outcomes during the post-vaccination risk interval and compared these with rates during a comparison interval more remote from vaccination. We also compared rates of outcomes in MenACWY-D recipients with those in matched controls who received selected vaccines in the prior year. We reviewed medical records for selected outcomes.
Results: From April 2005 through April 2006, 31,561 KPNC patients (>99% of whom were 11–55 years of age) received MenACWY-D. Overall, there were 21 outcomes with significantly elevated IRRs and 44 outcomes with significantly reduced IRRs. Medical record review of outcomes with significantly elevated IRRs did not suggest any relationship with MenACWY-D. Two serious adverse events were considered possibly related to vaccination by the study investigator.
Conclusions: This study did not detect any safety concerns following MenACWY-D and provides reassurance that MenACWY-D administered as part of routine care was not associated with unexpected safety risks.
ClinicalTrials.gov Identifier is NCT00254995.

1. Introduction

Neisseria meningitidis, a gram-negative diplococcus bacterium, can cause life-threatening sepsis and meningitis. Of the 13 known capsular-type serogroups, A, B, C, W, and Y are responsible for most invasive disease worldwide [1]. In the United States (US), there are currently three vaccines licensed for use in children and adults to protect against serogroups A, C, W, and Y: one plain polysaccharide vaccine (Menomune®, Sanofi Pasteur) and two conjugate vaccines (MenACWY-D, Menactra, Sanofi Pasteur; MenACWY-CRM, Menveo®, GlaxoSmithKline). Although MenACWY-D is licensed for persons 9 months through 55 years of age, the Advisory Committee for Immunization Practices (ACIP) currently recommends its routine use in adolescents ages 11–12 years with a booster at age 16, and in certain high-risk groups. Prior to licensure, MenACWY-D safety was evaluated in seven clinical studies with approximately 7600 subjects 11–55 years of age. Overall, in both adolescents 11–18 and adults 18–55 years of age, serious adverse events occurred at a rate of 1.0% [2].

* Corresponding author at: 1 Kaiser Plaza 16B, Oakland, CA 94612, USA.
E-mail address: john.hansen@kp.org (J. Hansen).

http://dx.doi.org/10.1016/j.vaccine.2017.09.032
0264-410X/

The aim of this study was to evaluate the safety of MenACWY-D in routine use in adolescents and adults within Kaiser Permanente Northern California (KPNC).

2. Methods

2.1. Study population

This Phase 4, retrospective, observational study was conducted at KPNC, an integrated healthcare organization that provides comprehensive medical care to its members (4 million as of 2017, 3.1 million in 2005). KPNC maintains databases that capture all medical care received by its members, including, but not limited to, all inpatient, emergency department (ED), and outpatient clinic visits, immunizations, pharmacy, and radiology data. We captured mortality data through state death reports and KPNC medical records.

In order to evaluate the safety of MenACWY-D, we included all 11–55-year-old patients who received the vaccine as part of routine clinical care in KPNC. This study began with the introduction of MenACWY-D within KPNC in April 2005 (four months following MenACWY-D licensure). The study planned to accrue new vaccinees through the end of the first year following MenACWY-D introduction at KPNC, and was to continue beyond that if necessary until a minimum of 20,000 subjects had received MenACWY-D. We followed each MenACWY-D recipient for six months after vaccination. We followed all vaccinees who received MenACWY-D while pregnant throughout their pregnancy.

To further investigate college-age individuals who may have received MenACWY-D at KPNC shortly before leaving home for college and who may have had post-vaccination events outside of KPNC, we created a second (“active surveillance”) cohort of 17–18-year-olds. We telephoned the parents of 17–18-year-old subjects approximately 2 months following vaccination to obtain current contact information for the vaccinee. We then contacted the vaccinee to obtain information regarding their medical care and whether there were health status changes during the 2 months following MenACWY-D vaccination. We made at least 3 attempts to contact the vaccinees. The study planned to complete a minimum of 2000 interviews in this cohort, unless fewer doses were given in this age group.

2.2. Outcomes

Study outcomes included all ED visits and hospitalizations. In the outpatient clinic setting, we limited surveillance to the following pre-specified outcomes of interest: neurological conditions (Bell’s palsy, seizure, neuritis, Guillain-Barré syndrome, encephalopathy, encephalitis, epilepsy, transverse myelitis, and multiple sclerosis), hypersensitivity reactions (including urticaria, angioedema, and anaphylaxis), and new-onset autoimmune disease (including idiopathic thrombocytopenic purpura, diabetes, arthritis, hemolytic anemia, and collagen-vascular disease). We identified all outcomes through use of ICD-9 diagnostic codes. Surveillance of women who received MenACWY-D during pregnancy included all visits for management of pregnancy, childbirth, therapeutic abortion, or complications thereof. We monitored for all deaths during the study period using state and KPNC records and reviewed the charts where available. Study investigators were responsible for assessing causality of adverse events through medical record review.

3. Statistical analyses

3.1. Short-term risk-interval cohort analysis

We conducted a risk-interval analysis in which we compared rates of events during days 0–30 post-vaccination (risk interval) with rates of events in the same subjects during days 31–60 post-vaccination (comparison interval).

3.2. Long-term matched cohort analysis

To analyze safety during a longer risk period, we matched each MenACWY-D recipient to one control on age (±1 year), sex, and receipt of a comparison vaccine during the same month as the matched MenACWY-D recipient but in the prior year. The comparison vaccines included tetanus and diphtheria toxoids (Td), hepatitis A, hepatitis B, or hepatitis A/hepatitis B combination vaccine. Rates of events occurring during the 6 months following vaccination with MenACWY-D were compared with rates of events occurring in the control cohort during the 6 months following vaccination with comparison vaccines.

For all analyses, we calculated incidence rate ratios (IRRs) for all outcomes, along with 95% confidence intervals (CIs) and unadjusted 2-sided P-values estimated using the exact conditional method with mid-probability adjustment. No adjustments were made for multiple comparisons. All analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

This study was approved by the KPNC Institutional Review Board. The ClinicalTrials.gov Identifier is NCT00254995.

4. Results

The study population included a total of 31,561 KPNC members who received MenACWY-D from April 2005 through April 2006 (Table 1). Most were vaccinated at 11–16 years and 17–18 years of age. The study population was well-balanced with respect to

Table 1
Study population attributes.

	MenACWY-D population	Control population
Passive surveillance	N (%)	N (%)
Younger than 11 years of age	108 (0.3)	108 (0.3)
11–16 years of age	21,407 (67.8)	21,418 (68.9)
17–18 years of age	8355 (26.5)	7742 (24.9)
19–29 years of age	823 (2.6)	929 (3.0)
30–55 years of age	807 (2.6)	807 (2.6)
Older than 55 years of age	61 (0.2)	61 (0.2)
All ages combined	31,561 (100.0)	31,065 (100.0)
Active surveillance (17–18 years of age)	2745 (32.9[a])	N/A
Sex (Passive surveillance population)	N (%)	N (%)
Male	15,836 (50.2)	15,696 (50.5)
Female	15,722 (49.8)	15,369 (49.5)
Not available	3 (<0.1)	0 (0.0)
Race/ethnicity (Passive surveillance population)	N (%)	N (%)
Caucasian	12,965 (41.1)	12,032 (38.7)
Hispanic	5432 (17.2)	5566 (17.9)
Asian	4124 (13.1)	3669 (11.8)
Black	2911 (9.2)	2997 (9.7)
Mixed	1030 (3.3)	680 (2.2)
Native American	115 (0.4)	132 (0.4)
Pacific Islander	110 (0.4)	151 (0.5)
Not available	4874 (15.4)	5838 (18.8)
Season of vaccination[b]	N (%)	N (%)
December – February	4689 (14.8)	4671 (15.0)
March – May	3605 (11.4)	3602 (11.6)
June – August	17,577 (55.6)	17,080 (55.0)
September – November	5739 (18.2)	5712 (18.4)

[a] This is the percentage of 17–18 year olds in the passive surveillance population that were in the active surveillance population.

[b] Subjects that received more than one dose of MenACWY-D are counted for each dose in the seasonality section and only once in race and sex sections. There are 49 such subjects in the MenACWY-D population.

Please cite this article in press as: Hansen J et al. Post-licensure safety surveillance study of routine use of quadrivalent meningococcal diphtheria toxoid conjugate vaccine. Vaccine (2017), http://dx.doi.org/10.1016/j.vaccine.2017.09.032