



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



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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.

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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].

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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.

gender (50.2% male). The majority (55.6%) were vaccinated during the summer (June–August). The demographic profile of the matched comparison population (N = 31,065) was similar to that of MenACWY-D recipients.

4.1. Safety

There was a total of 1660 outcomes assessed after vaccination in pre-specified observation intervals. Of these, 21 (1.3%) were significantly elevated (6 in the short-term analysis and 15 in the long-term analysis), and 44 (2.7%) were significantly decreased (all in the long-term analysis) (Tables 2 and 3). Significantly elevated findings in the short-term risk interval and long-term matched cohort analyses were investigated further (Table 4).

4.2. Short-term risk-interval cohort analysis results

In the ED setting among all ages combined, abdominal pain, febrile illness, and suicidal ideation/attempt were significantly elevated during the 30 days after MenACWY-D when compared with the comparison interval. These results were mostly elevated due to their rate of occurrence in the 11–16 year old group age group. Abdominal pain events were distributed throughout the 30-day period and did not appear to cluster after vaccination. Abdominal pain was more common in females, with gynecologic pain being more common than other syndromes. Although there was an elevated risk of febrile illness in the 30 days after MenACWY-D, the overall risk was low at 0.38 cases per 1000 person months. There were 12 cases of febrile illness within the 30-day window; 4 on day 1, 1 on day 5, 1 on day 7, and the remaining 6 cases occurred on day 9 or later. Review of all suicide ideation/attempt events for which records were available (5/6) revealed the cases occurred in subjects who already had risk factors (e.g., prior attempts, depression, stressors, alcohol abuse) prior to vaccination.

No hospital events or pre-specified clinic events were significantly elevated in the 30 days following MenACWY-D vaccination when compared with the 30-day comparison interval.

4.3. Long-term matched cohort analysis results

In the ED setting among all ages combined, when compared with matched controls, febrile illness, genital pain, hyperglycemia, mononucleosis, and vomiting were significantly elevated within 180 days after MenACWY-D. Febrile illness and vomiting were also significantly elevated in the 11–16 year age group, and mononucleosis was also significantly elevated in the 17–18 year age group. Type 1 diabetes with prior onset, difficulty breathing/shortness of breath, and otitis externa, were elevated in 11–16 year olds, but not in the all ages combined group.

In the hospital setting, elective procedure and tympanic perforation events were significantly elevated within 180 days after MenACWY-D among all ages combined. Having an elective procedure was also significantly elevated after MenACWY-D among 11–16 year olds.

Among all ages combined, none of the pre-specified clinic events were significantly elevated during the 180 days following MenACWY-D compared with matched controls. Among 11–16 year olds, hives/urticaria was significantly elevated within 180 days after MenACWY-D vaccination when compared with matched controls; of note, all hives/urticaria events occurred ≥ 2 days after vaccination.

4.4. Active telephone surveillance

Analysis of data collected from the active telephone surveillance cohort (N = 2745) did not detect any significantly elevated post-vaccination events in the ED or hospital setting. Similarly, no pre-specified outpatient events were increased within 30 days after MenACWY-D vaccination compared with the 30-day comparison interval. The most common post-vaccination events were ED visits for trauma, with a rate of 3.67 cases per 1000 person months

Table 2
Summary of Significantly Elevated Findings.

| Clinical setting | Analysis | Age category | Diagnosis | Risk window | | Control window | | IRR | 95% CI LB, UB | P-value |
|------------------|--------------------------|-------------------|--|-------------|-------------------|----------------|-------------------|-------|---------------|---------|
| | | | | N | Rate ^a | N | Rate ^a | | | |
| ED | Short-term risk interval | All ages combined | Abdominal pain | 31 | 0.98 | 16 | 0.52 | 1.91 | 1.05, 3.56 | 0.03 |
| ED | Short-term risk interval | 11–16 years old | Abdominal pain | 23 | 1.07 | 8 | 0.38 | 2.83 | 1.29, 6.72 | <0.01 |
| ED | Long-term matched | 11–16 years old | Diabetes, type 1 (prior onset) | 5 | 0.04 | 0 | 0.00 | NE | 1.22, NE | 0.03 |
| ED | Long-term matched | 11–16 years old | Difficulty breathing/shortness of breath | 9 | 0.07 | 2 | 0.02 | 4.50 | 1.07, 30.57 | 0.04 |
| Hospital | Long-term matched | All ages combined | Elective procedure | 35 | 0.19 | 16 | 0.09 | 2.15 | 1.20, 3.98 | <0.01 |
| Hospital | Long-term matched | 11–16 years old | Elective procedure | 25 | 0.20 | 8 | 0.06 | 3.13 | 1.45, 7.38 | <0.01 |
| ED | Short-term risk interval | All ages combined | Febrile illness | 12 | 0.38 | 1 | 0.03 | 11.80 | 2.04, 254.6 | <0.01 |
| ED | Short-term risk interval | 11–16 years old | Febrile illness | 7 | 0.33 | 1 | 0.05 | 6.88 | 1.06, 156.3 | 0.04 |
| ED | Long-term matched | All ages combined | Febrile illness | 47 | 0.25 | 24 | 0.13 | 1.93 | 1.18, 3.20 | <0.01 |
| ED | Long-term matched | 11–16 years old | Febrile illness | 29 | 0.23 | 15 | 0.12 | 1.93 | 1.04, 3.70 | 0.04 |
| ED | Long-term matched | All ages combined | Genital pain | 5 | 0.03 | 0 | 0.00 | NE | 1.20, NE | 0.03 |
| Clinic | Long-term matched | 11–16 years old | Hives/urticaria | 51 | 0.40 | 30 | 0.24 | 1.70 | 1.09, 2.70 | 0.02 |
| ED | Long-term matched | All ages combined | Hyperglycemia | 6 | 0.03 | 0 | 0.00 | NE | 1.52, NE | 0.02 |
| ED | Long-term matched | All ages combined | Mononucleosis | 5 | 0.03 | 0 | 0.00 | NE | 1.20, NE | 0.03 |
| ED | Long-term matched | 17–18 years old | Mononucleosis | 5 | 0.10 | 0 | 0.00 | NE | 1.13, NE | 0.04 |
| ED | Long-term matched | 11–16 years old | Otitis externa | 5 | 0.04 | 0 | 0.00 | NE | 1.22, NE | 0.03 |
| ED | Short-term risk interval | All ages combined | Suicidal ideation/attempt | 6 | 0.19 | 0 | 0.00 | NE | 1.52, NE | 0.02 |
| ED | Short-term risk interval | 11–16 years old | Suicidal ideation/attempt | 5 | 0.23 | 0 | 0.00 | NE | 1.20, NE | 0.03 |
| Hospital | Long-term matched | All ages combined | Tympanic perforation | 5 | 0.03 | 0 | 0.00 | NE | 1.20, NE | 0.03 |
| ED | Long-term matched | All ages combined | Vomiting | 39 | 0.21 | 21 | 0.11 | 1.83 | 1.08, 3.16 | 0.02 |
| ED | Long-term matched | 11–16 years old | Vomiting | 23 | 0.18 | 11 | 0.09 | 2.09 | 1.03, 4.46 | 0.04 |

Abbreviations used: ED = Emergency department; N = Number of cases; IRR = Incidence rate ratio; CI = Confidence interval; LB = Lower bound; UB = Upper bound; NE = Not evaluable.

^a Incidence rate per 1000 person months.

Table 3
Summary of significantly decreased findings.

| Clinical setting | Analysis | Age category | Diagnosis | Risk window | | Control window | | IRR | 95% CI LB, UB | P-value |
|------------------|-------------------|-------------------|----------------------------|-------------|-------------------|----------------|-------------------|------|---------------|---------|
| | | | | N | Rate ^a | N | Rate ^a | | | |
| ED | Long-term matched | 30–55 years old | Abdominal pain | 1 | 0.21 | 9 | 1.89 | 0.11 | 0.00, 0.67 | 0.01 |
| ED | Long-term matched | All ages combined | Abscess/cellulitis | 22 | 0.12 | 46 | 0.25 | 0.47 | 0.28, 0.78 | <0.01 |
| ED | Long-term matched | 11–16 years old | Abscess/cellulitis | 7 | 0.06 | 17 | 0.13 | 0.41 | 0.16, 0.97 | 0.04 |
| ED | Long-term matched | All ages combined | Allergic reaction | 2 | 0.01 | 11 | 0.06 | 0.18 | 0.03, 0.72 | 0.01 |
| ED | Long-term matched | 11–16 years old | Allergic reaction | 0 | 0.00 | 5 | 0.04 | 0.00 | 0.00, 0.82 | 0.03 |
| ED | Long-term matched | All ages combined | Allergy, drug | 0 | 0.00 | 5 | 0.03 | 0.00 | 0.00, 0.81 | 0.03 |
| Hospital | Long-term matched | All ages combined | Benign lesion | 23 | 0.12 | 44 | 0.24 | 0.51 | 0.31, 0.85 | <0.01 |
| Hospital | Long-term matched | 11–16 years old | Benign lesion | 12 | 0.09 | 28 | 0.22 | 0.43 | 0.21, 0.83 | 0.01 |
| Hospital | Long-term matched | All ages combined | Congenital anomaly | 19 | 0.10 | 33 | 0.18 | 0.57 | 0.32, 0.99 | 0.05 |
| Hospital | Long-term matched | 11–16 years old | Congenital anomaly | 11 | 0.09 | 27 | 0.21 | 0.41 | 0.19, 0.81 | <0.01 |
| Hospital | Long-term matched | All ages combined | Cyst | 8 | 0.04 | 19 | 0.10 | 0.41 | 0.17, 0.93 | 0.03 |
| Hospital | Long-term matched | 11–16 years old | Cyst | 4 | 0.03 | 12 | 0.09 | 0.33 | 0.09, 1.00 | 0.05 |
| ED | Long-term matched | All ages combined | Fatigue | 1 | 0.01 | 7 | 0.04 | 0.14 | 0.01, 0.91 | 0.04 |
| ED | Long-term matched | All ages combined | Insect bite | 2 | 0.01 | 9 | 0.05 | 0.22 | 0.03, 0.92 | 0.04 |
| ED | Long-term matched | All ages combined | Musculoskeletal pain | 50 | 0.27 | 71 | 0.39 | 0.69 | 0.48, 0.99 | 0.05 |
| ED | Long-term matched | All ages combined | Pelvic pain | 2 | 0.01 | 15 | 0.08 | 0.13 | 0.02, 0.50 | <0.01 |
| ED | Long-term matched | 17–18 years old | Pelvic pain | 0 | 0.00 | 8 | 0.17 | 0.00 | 0.00, 0.42 | <0.01 |
| Hospital | Long-term matched | All ages combined | Poisoning/ingestion | 3 | 0.02 | 13 | 0.07 | 0.23 | 0.05, 0.74 | 0.01 |
| ED | Long-term matched | All ages combined | Postoperative complication | 1 | 0.01 | 12 | 0.07 | 0.08 | 0.00, 0.47 | <0.01 |
| Hospital | Long-term matched | All ages combined | Postoperative complication | 1 | 0.01 | 8 | 0.04 | 0.12 | 0.01, 0.77 | 0.02 |
| ED | Long-term matched | 17–18 years old | Postoperative complication | 1 | 0.02 | 7 | 0.15 | 0.13 | 0.01, 0.85 | 0.03 |
| Hospital | Long-term matched | All ages combined | Pregnancy - delivery | 0 | 0.00 | 6 | 0.03 | 0.00 | 0.00, 0.64 | 0.01 |
| ED | Long-term matched | All ages combined | Psychiatric | 83 | 0.44 | 129 | 0.70 | 0.63 | 0.48, 0.83 | <0.01 |
| Hospital | Long-term matched | All ages combined | Psychiatric | 62 | 0.33 | 107 | 0.58 | 0.57 | 0.41, 0.78 | <0.01 |
| Hospital | Long-term matched | 11–16 years old | Psychiatric | 41 | 0.32 | 66 | 0.52 | 0.62 | 0.42, 0.91 | 0.02 |
| ED | Long-term matched | 17–18 years old | Psychiatric | 21 | 0.43 | 61 | 1.34 | 0.32 | 0.19, 0.52 | <0.01 |
| Hospital | Long-term matched | 17–18 years old | Psychiatric | 19 | 0.38 | 35 | 0.77 | 0.50 | 0.28, 0.87 | 0.01 |
| ED | Long-term matched | All ages combined | Testicular pain | 1 | 0.01 | 10 | 0.05 | 0.10 | 0.00, 0.59 | <0.01 |
| ED | Long-term matched | 11–16 years old | Testicular pain | 1 | 0.01 | 8 | 0.06 | 0.12 | 0.01, 0.78 | 0.02 |
| Hospital | Long-term matched | All ages combined | Tonsillitis | 16 | 0.09 | 52 | 0.28 | 0.30 | 0.17, 0.52 | <0.01 |
| Hospital | Long-term matched | 11–16 years old | Tonsillitis | 11 | 0.09 | 33 | 0.26 | 0.33 | 0.16, 0.65 | <0.01 |
| ED | Long-term matched | 17–18 years old | Tonsillitis | 2 | 0.04 | 10 | 0.22 | 0.18 | 0.03, 0.76 | 0.02 |
| Hospital | Long-term matched | 17–18 years old | Tonsillitis | 5 | 0.10 | 18 | 0.39 | 0.26 | 0.09, 0.66 | <0.01 |
| ED | Long-term matched | All ages combined | Trauma | 695 | 3.77 | 923 | 5.13 | 0.73 | 0.67, 0.81 | <0.01 |
| ED | Long-term matched | 11–16 years old | Trauma | 485 | 3.88 | 581 | 4.66 | 0.83 | 0.74, 0.94 | <0.01 |
| ED | Long-term matched | 17–18 years old | Trauma | 177 | 3.62 | 236 | 5.27 | 0.69 | 0.56, 0.83 | <0.01 |
| ED | Long-term matched | 19–29 years old | Trauma | 17 | 3.53 | 57 | 10.9 | 0.32 | 0.18, 0.55 | <0.01 |
| Hospital | Long-term matched | 19–29 years old | Trauma | 0 | 0.00 | 7 | 1.28 | 0.00 | 0.00, 0.60 | 0.01 |
| ED | Long-term matched | 30–55 years old | Trauma | 12 | 2.52 | 43 | 9.41 | 0.27 | 0.14, 0.50 | <0.01 |
| Hospital | Long-term matched | 30–55 years old | Trauma | 0 | 0.00 | 5 | 1.05 | 0.00 | 0.00, 0.82 | 0.03 |
| Hospital | Long-term matched | All ages combined | Vision disorder | 2 | 0.01 | 9 | 0.05 | 0.22 | 0.03, 0.92 | 0.04 |
| ED | Long-term matched | All ages combined | Well care/reassurance/FU | 13 | 0.07 | 44 | 0.24 | 0.29 | 0.15, 0.53 | <0.01 |
| ED | Long-term matched | 11–16 years old | Well care/reassurance/FU | 6 | 0.05 | 21 | 0.17 | 0.29 | 0.11, 0.68 | <0.01 |
| ED | Long-term matched | 17–18 years old | Well care/reassurance/FU | 5 | 0.10 | 17 | 0.37 | 0.27 | 0.09, 0.71 | <0.01 |

Abbreviations used: ED = Emergency department; FU = Follow-up; N = Number of cases; IRR = Incidence rate ratio; CI = Confidence interval; LB = Lower bound; UB = Upper bound; NE = Not evaluable.

^a Incidence rate per 1000 person months.

compared with 7.45 cases per 1000 person months during the comparison interval.

4.5. Pregnancy outcomes

There was a total of 25 KPNC patients who were exposed to MenACWY-D during pregnancy; of these, 18 had data available for review: 12 had a live birth (including birth of an infant with a dermoid cyst), 5 had elective abortions, and there was 1 fetal death at 23 weeks' gestation.

4.6. Deaths

There were three deaths in the study population (pancreatic cancer with onset preceding vaccination, metastatic melanoma with onset preceding vaccination, myocardial fibrosis with probable cardiac arrhythmia 177 days after vaccination). None of the deaths were considered related to vaccination by the study investigator.

4.7. Serious adverse events

There were two serious adverse events that were considered possibly related to vaccination by the study investigator. The first was an instance of new-onset diabetes mellitus approximately 4 weeks after vaccination in a patient with a family history of diabetes mellitus. The second was a case of new-onset juvenile rheumatoid arthritis with onset approximately 3 weeks after vaccination, in a subject with a significant family history for the condition and prodromal symptoms at the time of vaccination. Based on clinical review, it was felt that vaccination was not a likely cause for the conditions; however, vaccination as a cause or contributor could not be ruled out.

5. Discussion

In this study, we evaluated the safety of routine use of MenACWY-D in adolescents. After investigating all events that

Table 4
Investigation of significantly elevated events.

| Event category | Findings |
|--|--|
| Diabetes, type 1 | 5 cases, all with onset prior to vaccination: Events occurring on days 38 through 165. |
| Difficulty breathing/ shortness of breath | 9 events were distributed between days 6 and 154, with a mean latency of 82 days and median latency of 61 days. There was no obvious pattern to the distribution. |
| Elective procedure | Not researched further. |
| Febrile illness | 47 events: 4 events on day 1; 1 event on day 5; 3 events on day 125; 2 events each on days 121, 137 and 180; occasional other days with 1 case. Fever is a known common adverse event following vaccination. |
| Genital pain | 5 events: Dysmenorrhea on days 16 and 135; ovarian cyst on day 90; unspecified male genital disorder on day 129; menometrorrhagia on day 171. There was no obvious pattern to the distribution of events in time. On review, they were disparate in type, so we did not investigate further. |
| Hives/urticaria | 51 events in the 11–16 year age group were distributed between days 2 and 180, with an average latency of 93 days and a median latency of 95 days. |
| Hyperglycemia | 6 events: Days 4, 16, 126, 130, 150 and 168. There was no obvious pattern to the distribution and we did not investigate further. |
| Mononucleosis | There were 5 events, all in the 17–18 year old age group, where such an incidence can be expected. |
| Otitis externa | 5 events: Days 20, 22, 66, 82, and 119. |
| Suicidal ideation/ attempt | All events of suicide ideation/attempt for which records were available (5/6) revealed risk factors prior to vaccination (e.g., prior attempts, depression, stressors, alcohol abuse). |
| Tympanic perforation | All events represented planned tympanoplasty surgeries. |
| Vomiting | The range of days for 39 events was between day 1 and 178, with an average latency of 96 days and a median latency of 97 days. There was no obvious pattern associated with these vomiting cases; they appear to be evenly distributed within the interval, with >1 event of vomiting occurring on only six days (days 76, 113, 124, 127, 171, and 177). One case of vomiting occurred the day after vaccination which was considered to be related to receipt of MenACWY-D. |

were significantly elevated after vaccination, the events either represented known common side effects of vaccination (e.g., fever) or were not associated with MenACWY-D for the following reasons: the events were not temporally clustered after vaccination, latency associated with the elevated events varied widely, and/or a biological mechanism for the vaccine causing the events was lacking. We investigated an elevated finding for suicidal ideation/attempt with 6 cases in the short-term risk-interval analysis, and although statistically significant the observed rate and case review findings are consistent with other reports that the prevalence for suicidal ideation/attempt is high in youth, where approximately 1 in 8 have seriously considered attempting suicide and approximately 1 in 14 have attempted suicide (2007 data) [3]. Overall, we did not identify any new short- or long-term safety concerns following MenACWY-D vaccination.

There were 44 events which were significantly decreased after MenACWY-D when compared with events in the matched comparison population. Although we did not conduct detailed chart reviews on these outcomes, we do not believe that these decreased findings were due to a protective vaccine effect. Rather, as many of the outcomes were biologically implausible (e.g., congenital anomaly, unrelated postoperative complications, well care visits), we think it more likely that these findings were related to chance, due to the large number of comparisons conducted, or unobserved

confounding effects, such as a healthy vaccinee bias. As stated above, we did not statistically adjust for multiple comparisons. However, we note that by chance alone we might have expected approximately 40 each of significantly elevated and decreased outcomes. The number of observed decreased findings is approximately the number we might have expected by chance alone while the number of increased findings observed ($N = 21$) is approximately half of what we might have expected based on chance alone.

Available data for pregnancy did not suggest an increased risk of pregnancy complications or an unusual pattern of adverse events among their infants; however, this study included very few pregnancies. Other reviews of exposure with MenACWY-D in pregnancy have also not identified safety concerns [4,5].

A 2017 study by Tseng of 48,899 recipients of MenACWY-CRM using a self-controlled case-series analysis [6] found a temporal association between receipt of MenACWY-CRM and Bell's palsy that appeared to be focused in subjects receiving other vaccines concomitantly. Bell's palsy was a pre-specified neurologic outcome in our study and we did not detect a significantly increased risk after MenACWY-D. By way of comparison, approximately 57.9% of our study subjects also received MenACWY-D concomitantly with other vaccines (data not shown). Although the reason for this differing result is not clear, it may be related to differences between the vaccines (including between protein conjugates), differing study populations, methodological differences between the studies, or Bell's palsy after MenACWY-CRM being a chance finding in the Tseng study.

This study had limitations. Although we calculated IRRs for all protocol-specified safety events that arose in this study, detailed investigation of all events was not feasible for a safety surveillance study of this scale. We therefore focused our efforts on investigating outcomes that were significantly elevated and for which there was some biological plausibility for MenACWY-D vaccination causing the event. We did not further investigate a finding for mononucleosis in 17–18 year olds because the observed rate was consistent with rates in literature [7]. We were also not able to always differentiate outcomes that occurred acutely post-vaccination from those that occurred prior to vaccination (i.e., "history of" diagnoses) without medical record review, which could have led to misclassification bias. However, we believe that through our use of different analytic approaches with differing comparison periods and control vaccines, we potentially minimized biases that could be associated with such misclassification. Similarly, since this design compares only those who are vaccinated (i.e., comparing a near ["at risk"] interval in recipients of MenACWY-D to a more remote interval, or comparing MenACWY-D recipients to recipients of other vaccines) there is less risk of either indication bias or healthy vaccinee bias, which can be introduced in comparisons that use non-vaccinated controls. We did not use scan statistics to formally analyze temporality. Of note, we did not compare identical vaccines so residual indication bias may occur to the extent that recipients of MenACWY-D are different from recipients of Td, hepatitis A, hepatitis B, and/or hepatitis A/hepatitis B combination vaccines. Similarly, KPNC members receiving these comparison vaccines did so in the year preceding MenACWY-D surveillance, prior to the introduction of the adolescent vaccination schedule. Thus, the comparison population may have been more likely to have had medical visits for reasons other than vaccinations or well care. Also, considering that 55.6% of subjects were vaccinated in the summer, the short-term risk-interval analyses may have been biased toward showing more seasonal infections in the later comparison period; however, the long-term cohort analyses should not have been as susceptible to this bias as the comparison cohort was matched on month of vaccination in the prior year. Another limitation is that a six-month win-

dow of observation may not be sufficient to capture conditions that can develop over longer periods of time, such as certain chronic conditions. Finally, although more than 30,000 MenACWY-D recipients were under surveillance, this study was still not large enough to detect extremely rare outcomes such as Guillain-Barré syndrome. Larger studies of Guillain-Barré syndrome after MenACWY-D have been conducted using administrative and claims data and have not found a link between MenACWY-D and Guillain-Barré syndrome [8–10].

In summary, there were no unanticipated or new safety findings of concern identified with MenACWY-D administration. This large surveillance study reaffirms the safety of MenACWY-D that was demonstrated throughout the vaccine's clinical development. Post-licensure surveillance, such as this study, can further advance the knowledge of the safety of MenACWY-D vaccination as it is used in larger populations despite the limitations of such surveillance.

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