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Post-licensure safety surveillance study of routine use of quadrivalent meningococcal diphtheria toxoid conjugate vaccine (MenACWY-D) in infants and children

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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, in 2007 for children 2–10 years of age, and in 2011 for infants/toddlers 9–23 months of age. We conducted two studies at Kaiser Permanente Northern California (KPNC), an integrated health care organization, to assess the safety of MenACWY-D in 2–10-year-olds and 9–23-month-olds receiving the vaccine during routine clinical care.

Methods: We conducted observational, retrospective studies of MenACWY-D in 2–10-year-olds (October 2007–October 2010) and in 9–23-month-olds (June 2011–June 2014). We monitored all subjects for non-elective hospitalizations, emergency department visits, and selected outpatient outcomes (specified neurological conditions, hypersensitivity reactions and new-onset autoimmune diseases) up to 6 months after vaccination, depending on the study. Using a self-control risk-interval design, we calculated incidence rate ratios (IRRs) comparing outcomes during the post-vaccination risk interval (0–30 days) with those during more remote post-vaccination comparison intervals (31–60 and 31–180 days [children] or 31–75 days [infants/toddlers]).

Results: There were 1421 children aged 2–10 years and 116 infants/toddlers aged 9–23 months who received MenACWY-D. Approximately 30% of the 2–10-year-olds and 67% of the 9–23-month-olds were considered at increased risk of meningococcal disease. Among 2–10-year-olds, there was 1 hospitalization on post-vaccination day 5 for fever, which was considered possibly related to vaccination. The only significantly elevated outcome among 2–10-year-olds was cellulitis/abscess (2 cases occurred during the risk interval versus 0 during comparison interval; IRR not evaluable [NE], 95% CI: 1.42, NE). After medical record review, the 2 cases were considered unrelated to vaccination. Among 9–23-month-olds, no outcomes were significantly elevated after vaccination and there were no hospitalizations. There were no deaths observed during the three-year accrual and subsequent six-month surveillance period for either study.

Conclusions: Immunization of infants and young children with MenACWY-D vaccine was not associated with any new safety concerns; however, these small studies had limited power to detect rare or uncommon safety events.

ClinicalTrials.gov Identifiers are NCT00728260 and NCT01689155.

1. Introduction

Neisseria meningitidis, a gram-negative diplococcus bacterium, can cause life-threatening sepsis and meningitis. Although there are at least 12 known capsular-type serogroups, five—A, B, C, W, and Y—are responsible for most invasive meningococcal disease

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(IMD) worldwide [1]. In the United States (US), there are currently two licensed meningococcal conjugate vaccines designed to protect against IMD caused by serogroups A, C, W, and Y (Menactra®, Sanofi Pasteur [MenACWY-D] and Menveo®, GlaxoSmithKline [MenACWY-CRM]). MenACWY-D was first licensed in 2005 for individuals aged 11–55 years. In October 2007, the age indication was expanded to include 2–10-year-olds, and then expanded further in 2011 to include infants and toddlers aged 9–23 months. In the latter age group, MenACWY-D is administered as a two-dose series, with doses given three months apart.

The US Advisory Committee on Immunization Practices (ACIP) currently recommends routine use of quadrivalent meningococcal conjugate vaccine (MenACWY) in all adolescents aged 11–18 years, and in children 2 months–10 years of age considered at increased risk for meningococcal disease: those with persistent complement component deficiencies, functional or anatomic asplenia, living with human immunodeficiency virus (HIV), living in communities experiencing a meningococcal disease outbreak, or traveling to or residing in areas where meningococcal disease is hyperendemic or epidemic [2–4].

While several studies have investigated the safety of MenACWY-D administered routinely to adolescents and adults [5–8], there are limited data on the safety of MenACWY-D administered to those children younger than 11 years of age who are currently recommended to receive the vaccine.

We monitored the safety of MenACWY-D routinely administered to children 9 months–10 years of age in two separate post-licensure safety surveillance studies. The first study investigated the safety of MenACWY-D safety in children aged 2–10 years and the second evaluated the vaccine's safety in 9–23-month-olds.

2. Methods

2.1. Study population

The two studies were Phase 4, retrospective, observational studies performed as post-licensure commitments to the US Food and Drug Administration (FDA). Both studies were conducted at Kaiser Permanente Northern California (KPNC), an integrated healthcare organization that provides comprehensive medical care to nearly 4 million members. Approximately 450,000 KPNC members are ≤10 years of age. KPNC maintains databases that capture all medical care, including, but not limited to, inpatient, emergency department (ED), and outpatient clinic visits; immunizations; and pharmacy and radiology data. We identified deaths through state death reports and KPNC medical records.

2.2. Study design

Each study was initiated at the time the MenACWY-D license was expanded by the FDA to include the respective age group. Each study included all appropriately aged MenACWY-D vaccinees. Both studies were planned to be conducted in two phases using a similar design. In the first phase, we accrued all age-appropriate MenACWY-D recipients during a maximum three-year period after each licensed age expansion. A second phase was to occur if the ACIP recommended routine MenACWY-D vaccination of all individuals in the respective age group (i.e., 2–10-year-olds or 9–23-month-olds). Had the ACIP made these recommendations, a minimum of 20,000 MenACWY-D-vaccinated 2–10-year-olds and 20,000 MenACWY-D-vaccinated 9–23-month-olds would have been monitored. Since the ACIP did not recommend universal use of MenACWY in either age group, both studies only included the first phase (i.e., the three-year accrual period after each expansion of the MenACWY-D age indication). The accrual period for the 2–10-year-old population was October 2007 through the end of October 2010; the accrual period for the 9–23-month-old population was June 2011 through the end of June 2014.

2.3. Outcomes

Both studies included all post-vaccination ED visits and hospitalizations. We limited monitoring of outpatient outcomes to the following pre-specified conditions: neurological conditions (Bell's palsy, seizure, neuritis [including optic neuritis], Guillain-Barré syndrome [GBS], encephalopathy, encephalitis, epilepsy, transverse myelitis, acute disseminated encephalomyelitis, multiple sclerosis, and meningitis); 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 using International Classification of Diseases, 9th Revision (ICD-9), diagnostic codes. During the accrual period and during the six months following the end of the accrual period, we monitored for all deaths using state and KPNC records and reviewed available records of all identified deaths. For example, a subject vaccinated on the first day of the study was monitored for 3.5 years, whereas a subject vaccinated on the last day in the accrual period was monitored for six months. Formal analyses on deaths were not planned nor conducted.

2.4. Statistical analyses

2.4.1. Risk-interval cohort analyses

For both studies, we conducted risk-interval analyses comparing rates of outcomes during post-vaccination risk intervals with rates of outcomes in the same subjects during more remote post-vaccination comparison intervals. We used a 0–30 day post-vaccination risk interval for both studies. We used a 31–60 day comparison interval for the study of 2–10-year-olds, and a 31–75 day comparison interval after each dose in the study of 9–23-month-olds to account for the two doses recommended for the latter population. We calculated incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for all outcomes, along with unadjusted 2-sided P-values estimated using the exact conditional method with mid-probability adjustment.

2.4.2. Cox regression analyses

We also performed Cox regression analyses to adjust for covariates such as age, sex, and seasonality [9–11]. For the study in 2–10-year-olds, we compared outcome rates during the 0–30 day post-vaccination risk interval with rates during a 31–180 day comparison interval. We used this larger comparison interval to generate more stable background rates.

For the study in 9–23-month-olds, we compared rates during the 0–30 day risk interval with rates during a 31–75 day comparison interval after each dose. We used the 31–75 day comparison interval to generate more stable background event rates, consistent with the risk-interval analyses described above. However, this comparison interval was shorter than that for 2–10-year-olds because there is only a 3-month interval between the two recommended doses of MenACWY-D for 9–23-month-olds.

For both studies, we did not perform Cox regression analyses where strata were too sparsely populated. We did not adjust for multiple comparisons in any of the analyses. We used SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) for all analyses.

The KPNC Institutional Review Board approved both studies. The ClinicalTrials.gov Identifiers for these two studies are NCT00728260 (2–10-year-olds) and NCT01689155 (9–23-month-olds).