Safety of Quadrivalent Meningococcal Conjugate Vaccine in 11- to 21-Year-Olds

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abstract

BACKGROUND: Meningococcal conjugate vaccination is recommended in the United States. This study evaluates the safety of quadrivalent meningococcal conjugate vaccine in a cohort aged 11 to 21 years.

METHODS: This cohort study with self-controlled case-series analysis was conducted at Kaiser Permanente Southern California. Individuals receiving MenACWY-CRM, a quadrivalent meningococcal conjugate vaccine, during September 30, 2011 to June 30, 2013, were included. Twenty-six prespecified events of interest (EOIs), including neurologic, rheumatologic, hematologic, endocrine, renal, pediatric, and pediatric infectious disease EOIs, were identified through electronic health records 1 year after vaccination. Of these, 16 were reviewed by case review committees. Specific risk and comparison windows after vaccination were predefined for each EOI. The relative incidence (RI) and 95% confidence intervals (CIs) were estimated through conditional Poisson regression models, adjusted for seasonality.

RESULTS: This study included 48 899 vaccinated individuals. No cases were observed in the risk window for 14 of 26 EOIs. The RI for Bell's palsy, a case review committee-reviewed EOI, was statistically significant (adjusted RI: 2.9, 95% CI: 1.1–7.5). Stratified analyses demonstrated an increased risk for Bell's palsy in subjects receiving concomitant vaccines (RI = 5.0, 95% CI = 1.4–17.8), and no increased risk for those without concomitant vaccine (RI = 1.1, 95% CI = 0.2–5.5).

CONCLUSIONS: We observed a temporal association between occurrence of Bell's palsy and receipt of MenACWY-CRM concomitantly with other vaccines. The association needs further investigation as it could be due to chance, concomitant vaccination, or underlying medical history predisposing to Bell's palsy.

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Dr Tseng had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Tseng contributed to conception and design of the study, conduct of the study, and analysis and interpretation of data; Ms Sy contributed to conception and design of the study, conduct of the study, acquisition of data, and analysis and interpretation of data; Dr Ackerson and Mr Takhar contributed to conception and design of the study, conduct of the study, and acquisition of data; Drs Hechter and Haag contributed to conception and design of the study, conduct of the study, and analysis and interpretation of data; Drs Tartof and Miao contributed to the conduct of the study and analysis and interpretation of data; Mr Slezak and Ms Luo contributed to the conduct of the study, acquisition of data, analysis and interpretation of data, and statistical analysis; Ms Fischetti contributed to the conduct of the study, acquisition of data, and analysis and interpretation of data; Dr Cunnington contributed to analysis and interpretation of the data; Ms Solano contributed to the conduct of the study and

WHAT'S KNOWN ON THIS SUBJECT: There are growing concerns about the safety of vaccines targeting adolescents, including human papillomavirus, acellular pertussis, and meningococcal conjugate vaccines. Although the safety of meningococcal vaccines has been evaluated in clinical trials, postlicensure safety data are lacking.

WHAT THIS STUDY ADDS: We found only 1 significant increased risk of a prespecified adverse event after MenACWY-CRM vaccination. We observed a temporal association between occurrence of Bell's palsy and receipt of MenACWY-CRM concomitantly with other vaccines that needs further investigation.

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Meningococcal disease is caused by *Neisseria meningitidis*, an encapsulated bacterium whose pathogenic strains are divided into serogroups on the basis of components of the polysaccharide capsule. In the United States, the most common serogroups are B, C, and Y.[1–4] Incidence varies by age, with highest incidence observed in those younger than 5 years of age and a second peak observed in mid to late adolescence.[1,2,5] The case–fatality ratio has been reported to be between 10% and 14% among adolescents.[2] Morbidity from the disease is also high, with 11% to 27% of survivors experiencing significant sequelae, including neurologic disability, amputations, allergic complications, and hearing loss.[6–8]

Due to the serious nature of infections caused by *N meningiditis*, vaccines have been developed to protect against the infection. In the United States, there are currently 2 licensed quadrivalent meningococcal conjugate vaccines (MCV4) that protect against serogroups A, C, Y, and W—MenACWY-D (Menactra; Sanofi Pasteur, Swiftwater, PA) and MenACWY-CRM (Menveo; GlaxoSmithKline, Middlesex, United Kingdom). The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices recommends routine vaccination with meningococcal vaccines for persons 11 through 18 years of age, as well as for children and adults who are at an increased risk of invasive meningococcal infection.[1] Although the safety of both of these vaccines has been evaluated in clinical trials in mainly healthy populations, postlicensure safety data have been lacking. To understand the safety profile of MenACWY-CRM outside the clinical trial setting, we conducted a postlicensure safety study in a large cohort aged 11 to 21 years in the United States.

METHODS

Study Setting and Population

This cohort study was conducted in 3 medical centers of Kaiser Permanente Southern California (KPSC), an integrated health care organization that provides prepaid comprehensive health care to 4.2 million racially and socioeconomically diverse members.[9] Electronic health records (EHRs) store medical information about sociodemographics, utilization (outpatient, emergency department, and inpatient encounters), diagnoses, laboratory tests, procedures, pharmacy utilization, vaccination records, membership history, and death. There are several factors that help ensure the capture of relevant health information. The prepaid health plan provides strong motivation for members to use services at KPSC facilities. In addition, information on encounters occurring outside KPSC is captured via claims since documentation of outside care is required by KPSC for reimbursement. The study population included members aged 11 through 21 years (inclusive) who were vaccinated with MenACWY-CRM as part of routine clinical care at the participating KPSC medical centers between September 30, 2011, and June 30, 2013, and had at least 6 months membership with KPSC before receiving the vaccine.

Exposure

The first dose of MenACWY-CRM (Menveo, GlaxoSmithKline) received on or after September 30, 2011, was referred to as the "index vaccination," which served as the baseline and start of the observation period for this study (day 0). Ascertainment of the date, type, and brand of the vaccine administered was based on vaccination records captured in the EHR.

Outcomes

There were 26 prespecified events of interest (EOIs) under investigation, including neurologic, rheumatologic, hematologic, endocrine, renal, pediatric, and pediatric infectious disease EOIs (Supplemental Table 4). Occurrence of incident episodes of these EOIs was identified during a 1-year observation period after the index vaccination for each individual. Specific risk windows—time periods in which we hypothesized that the risk of events might be affected by vaccination—following index vaccination were predefined for each EOI, on the basis of the previous published literature. The comparison window was defined as the period from the end of the risk period up to 1 year after vaccination or to disenrollment, whichever came first. EOIs were classified as occurring within the risk window or the comparison window.

EOIs were first identified through automated case identification algorithms (Supplemental Information 1), which included *International Classification of Diseases, Ninth Revision* (ICD-9) diagnostic codes, prescription records, and laboratory results. To ensure that identified EOIs were incident events after vaccination, the EHRs were searched up to 3 years before the date of the EOI episode, as identified by the algorithm, for evidence of preexisting illness. For a prespecified subset of EOIs, medical records of subjects identified as potential cases using the algorithm were additionally reviewed by an independent case review committee (CRC), consisting of specialists from KPSC. In general, CRC-reviewed EOIs were chronic conditions, or those for which the onset might be insidious, or those for which the automated algorithm was expected to lead to false-positives. The CRC was masked to the date of vaccination and was requested to confirm the diagnosis and determine the symptom onset date. For non-CRC-reviewed EOIs, the date of first documentation of a relevant ICD-9 code in the medical records for the EOI

was considered to be the onset date. EOI cases found to have a preexisting diagnosis before vaccination, on the basis of automated algorithm, initial review, or CRC confirmation of date of symptom onset, were excluded from the analysis of that particular EOI. Each individual could experience 1 or more different types of EOI during the observation period and thus be included in the analysis for multiple EOIs.

Statistical Analysis and Further Case Review

The self-controlled case series (SCCS) method was used to determine the relative incidence (RI) of an EOI in the risk window compared with that in the comparison window. Conditional Poisson regression was used to estimate the RI and its associated 95% confidence interval (CI) for each EOI. The SCCS method implicitly controls for fixed covariate effects. However, there might still be relevant covariates that could change over time within a person. To address the concern of time-varying confounding, we adjusted for seasonality of EOI onset in the analysis. Additionally, the physician investigator (Dr Ackerson) reviewed records of non-CRC-reviewed EOIs if an elevated risk was found after the initial SCCS analysis, with the aim of confirming the diagnosis and determining the date of onset. Although the physician investigator was not masked to the patient's vaccination record (as it is available in the patient's medical record), he was only provided with a list of patient medical record numbers and dates of diagnosis and was instructed not to look for the date of vaccination when conducting the reviews. If the increased risk remained after analyzing reviewed results, we further reviewed the confirmed cases with onset date in the risk window to examine possible etiologies. The process of case review is shown in Supplemental Information 2.

TABLE 1 Baseline Characteristics of MenACWY-CRM Recipients 11 Through 21 Years of Age, KPSC, Including the Period From 2011 to 2013

Characteristics	Numbers
Total, *n*	48 899
Sex, *n* (%)	
Men	23 540 (48.1)
Women	25 359 (51.9)
Race/ethnicity, *n* (%)	
Hispanic	24 046 (49.2)
White	14 563 (29.8)
African American	4584 (9.4)
Asian	2750 (5.6)
Native American/Alaskan	75 (0.2)
Pacific Islander	344 (0.7)
Multiple	403 (0.8)
Other	517 (1.1)
Unknown	1617 (3.3)
Age at index vaccination, mean (SD), y	15.0 (3.4)
Median (Q1, Q3)	16 (11, 17)
11–17, *n* (%)	37 028 (75.7)
18–21, *n* (%)	11 871 (24.3)
Previous MCV4 vaccination, *n* (%)	
No	27 951 (57.2)
>6 mo before index vaccination	20 888 (42.7)
≤6 mo before index vaccination	60 (0.1)
Time since most recent MCV4 dose, mean (SD), y	4.1 (1.5)
Median (Q1, Q3)	4.2 (3.1, 5.0)
Minimum–maximum	0.0–12.6
Other vaccinations <6 mo before index vaccination, *n* (%)	
Yes	8656 (17.7)
No	40 243 (82.3)
Concomitant vaccination, *n* (%)	
Yes	35 184 (72.0)
No	13 715 (28.0)

Q1, first quartile; Q3, third quartile.

No formal adjustment for multiple comparisons was performed. Because this was a safety study, a conservative approach was taken without performing adjustments (eg, Bonferroni adjustment) to avoid missing a potential safety signal. No SCCS analysis was performed for meningococcal disease because only the risk window (15–365 days post index vaccination) but no comparison window was defined for that EOI.

All analyses were performed in SAS version 9.2 and 9.3 (SAS Institute, Inc, Cary, NC) and SAS Enterprise Guide version 4.3 and 5.1. This study was approved by the KPSC Institutional Review Board with a waiver of informed consent.

RESULTS

During the study period, there were 48 899 individuals 11 to 21 years of age with at least 6 months of KPSC membership who received MenACWY-CRM at a participating medical center. The demographic distribution is presented in Table 1. Approximately 57% of subjects received their MenACWY-CRM index vaccination as a first dose of MCV4 vaccination.

Approximately 72% of subjects received 1 or more other vaccines concomitantly with their MenACWY-CRM index vaccination. The most commonly received concomitant vaccines were human papillomavirus vaccine (HPV; 42%), tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, adsorbed (Tdap;

34%), and influenza vaccine (23%). Approximately 18% of subjects received 1 or more other (ie, non-MCV4) vaccines in the 6 months before their index vaccination date, with the most common being influenza vaccine (13%), followed by Tdap (4%) and HPV (3%).

A total of 4240 potential cases of EOIs were identified through the algorithms (Table 2). Of these, 3000 were excluded on the basis of evidence of preexisting conditions. Of the remaining cases, the most frequently occurring EOI at any time during the 1-year observation period was asthma (n = 841), followed by seizure (n = 81). Of the 158 EOI cases predesignated for CRC review, 33 cases were excluded as preexisting after initial review. Among the 125 cases sent to the CRC for review, 81 were refuted by the CRC members as noncases or were determined to have an onset date before the start of the risk window. After these exclusions, there were a total of 1127 incident EOI cases for analyses, including all the cases that were CRC reviewed and confirmed, and those that were identified by the automated algorithm but not CRC reviewed. There were only 14 subjects who experienced an episode of more than 1 EOI during the observation period.

Among the 1127 EOI cases, there were 260 incident cases that occurred in the risk window and 867 cases in the comparison window (Table 3). No cases of Guillain-Barre syndrome, acute disseminated encephalomyelitis, cerebellar ataxia, brachial neuritis, myasthenia gravis, systemic lupus erythematosus, or meningococcal disease were observed during the observation period. Multiple sclerosis, transverse myelitis, rheumatoid arthritis, Henoch-Schonlein purpura, nephrotic syndrome, autoimmune hemolytic anemia, and aseptic meningitis had at least 1 case occurring in the comparison window but none in the risk window.

The RI for acute glomerulonephritis could not be calculated because there were no cases in the comparison window. The single case in the risk window had a history of recurrent streptococcal infection, so poststreptococcal glomerulonephritis likely explains the condition. The patient may have had preexisting disease, but this cannot be confirmed because no urinalysis tests were available before vaccination.

The adjusted RIs for juvenile diabetes mellitus, Graves' disease, asthma, allergic urticaria, and suicide attempt were above 1, but were not statistically significant. For idiopathic thrombocytopenic purpura (ITP) the adjusted analysis could not converge because there was 1 case in the risk window and 1 case in the comparison window, each in different seasons.

For the non-CRC reviewed EOIs, the initial adjusted RIs for seizure (RI = 2.9, 95% CI: 1.5–5.9), iridocyclitis (RI = 3.1, 95% CI: 1.1–8.7), Hashimoto disease (RI = 5.5, 95% CI: 2.3–13.3), and anaphylaxis (RI = 5.5, 95% CI: 1.1–26.2) were statistically significant. These cases underwent further review by the physician investigator, which resulted in exclusion of cases as preexisting, refutation of diagnosis, or identification of causes other than vaccination.

For seizure, there were 9 cases in the risk window, of which 8 were diagnosed on day 0 (the date of vaccination). Subsequent chart review confirmed that all 9 seizures occurred before vaccination. There were 5 iridocyclitis cases identified in the risk window and 13 cases in the comparison window. Chart review of these cases confirmed that there were 4 incident cases in the risk window and 10 cases in the comparison window. Among the 4 confirmed cases in the risk window, 3 were found to be traumatic and 1 was found to be parasitic; hence although the point estimate of the RI remained elevated after chart review, all 4 cases in the risk window were highly unlikely to be related to vaccination. The automated case identification algorithm found 21 cases of Hashimoto's disease. Further chart review confirmed that there were 2 incident cases in the risk window and 3 in the comparison window. Overall, 13 cases were refuted with onset before vaccination on the basis of the date of diagnostic tests and/or date of symptom onset. For 3 other cases, the diagnosis was refuted. The analysis on the basis of the chart-confirmed Hashimoto disease cases revealed an adjusted RI of 5.1 with a wide CI, which included 1 (95% CI: 0.5–55.0). There were 2 anaphylaxis cases in the risk window, both with diagnosis on day 0. Subsequent chart review confirmed that both cases were historical with a diagnostic code appearing on the date of vaccination. Thus, there were no anaphylaxis cases in the risk window after physician investigator chart review.

Based on the Bell's palsy cases confirmed by the CRC, there was a statistically significant increased adjusted RI for Bell's palsy (RI = 2.9, 95% CI: 1.1–7.5; 8 cases in the 84-day risk window and 10 cases in the comparison window; Table 3). Among the 8 Bell's palsy cases in the risk window, 6 received 1 or more concomitant vaccines (HPV, HPV, influenza, Tdap, HPV + Tdap, HPV + Tdap + influenza) and 2 did not. Stratified analyses demonstrated an increased risk for Bell's palsy in subjects receiving concomitant vaccines (RI: 5.0, 95% CI: 1.4–17.8), and no increased risk for those without concomitant vaccine (RI = 1.1, 95% CI: 0.2–5.5). Additional factors, including comorbidities and infections, that may have influenced the likelihood of outcome of Bell's palsy were examined for these 8 Bell's palsy cases in the risk window. One patient had coldlike symptoms before the onset of Bell's palsy; this patient did not receive a concomitant vaccine. One patient had concurrent

TABLE 2 Summary of Case Identification and Review for EOIs

	Automated Algorithm			Initial Chart Review	CRC/ Physician Investigator Review			
EOI	Potential Cases Identified (a)	Excluded Cases Based on Preexisting Condition (b)	Cases Identified From Automated Algorithm (c = a–b)	Cases Excluded As Preexisting Condition (d)	Cases Confirmed (e)	Cases Refuted (f)	Cases With Onset Determined to Be Before Start of Risk Window (g)	Total Cases for Analysis (h = a–b–d–f–g)
CRC-reviewed EOIs								
Bell's palsy	24	3	21	1	18	2	0	18
Multiple sclerosis	9	3	6	1	2	3	0	2
Guillain-Barre syndrome	0	0	0	0	0	0	0	0
Acute disseminated encephalomyelitis	2	0	2	0	0	2	0	0
Cerebellar ataxia	2	1	1	1	0	0	0	0
Transverse myelitis	2	0	2	0	1	1	0	1
Brachial neuritis	34	4	30	2	0	28	0	0
Myasthenia gravis	23	7	16	2	0	14	0	0
Systemic lupus erythematosus	20	16	4	0	4[a]	1	4	0
Rheumatoid arthritis	36	26	10	2	7	1	4	3
Henoch-Schonlein purpura	6	1	5	1	2	2	1	1
Juvenile diabetes mellitus	236	202	34	20	12	2	1	11
Graves' disease	45	28	17	1	11	5	4	7
Acute glomerulonephritis	19	13	6	1	2	3	1	1
Nephrotic syndrome	8	6	2	1	1	0	0	1
Meningococcal disease	2	0	2	0	0	2	0	0
Non-CRC reviewed EOIs								
Seizure	111	30	81	N/A	N/A	N/A	N/A	81
Seizure (chart reviewed)[b]	N/A	N/A	N/A	N/A	39	42	14	25
Iridocyclitis (uveitis)	23	5	18	N/A	N/A	N/A	N/A	18
Iridocyclitis (uveitis) (chart reviewed)[b]	N/A	N/A	N/A	N/A	15	3	1	14
Hashimoto disease	73	52	21	N/A	N/A	N/A	N/A	21
Hashimoto disease (chart reviewed)[b]	N/A	N/A	N/A	N/A	18	3	13	5
Anaphylaxis	14	2	12	N/A	N/A	N/A	N/A	12
Anaphylaxis (chart reviewed)[b]	N/A	N/A	N/A	N/A	10	2[c]	6	4
ITP	8	6	2	N/A	N/A	N/A	N/A	2
Autoimmune hemolytic anemia	2	1	1	N/A	N/A	N/A	N/A	1
Aseptic meningitis	4	0	4	N/A	N/A	N/A	N/A	4
Asthma	3430	2589	841	N/A	N/A	N/A	N/A	841
Allergic urticaria	31	2	29	N/A	N/A	N/A	N/A	29
Suicide attempt	76	3	73	N/A	N/A	N/A	N/A	73
Total[d]	4240	3000	1240	33	56	66	15	1127
Number of subjects experiencing a single EOI								1099
Number of subjects experiencing multiple different EOIs								14

N/A, not applicable.

[a] One subject identified from the automated algorithm with acute glomerulonephritis was confirmed as systemic lupus erythematosus.

[b] For non-CRC reviewed EOIs for which elevated RIs were observed in the initial analysis, medical records underwent further review by a physician investigator.

[c] Non-KPSC records were not available with which to verify the medical encounter details for 1 anaphylaxis case in the comparison window. This case was included with refuted cases for the purpose of analyses.

[d] Totals do not include physician investigator chart review data.

TABLE 3 RI and 95% CI Estimated by SCCS Analysis

EOI	Cases in Risk Window, *n*	Cases in Comparison Window,[b] *n*	RI (95% CI)[a] Unadjusted	RI (95% CI)[a] Adjusted[c]
CRC-reviewed EOIs				
Bell's palsy	8	10	2.7 (1.1–6.8)	2.9 (1.1–7.5)
Multiple sclerosis	0	2	. (.)	. (.)
Guillain-Barre syndrome	0	0	. (.)	. (.)
Acute disseminated encephalomyelitis	0	0	. (.)	. (.)
Cerebellar ataxia	0	0	. (.)	. (.)
Transverse myelitis	0	1	. (.)	. (.)
Brachial neuritis	0	0	. (.)	. (.)
Myasthenia gravis	0	0	. (.)	. (.)
Systemic lupus erythematosus	0	0	. (.)	. (.)
Rheumatoid arthritis	0	3	. (.)	. (.)
Henoch-Schonlein purpura	0	1	. (.)	. (.)
Juvenile diabetes mellitus	3	8	1.3 (0.3–4.7)	1.2 (0.3–4.7)
Graves' disease	1	6	1.3 (0.2–10.6)	1.1 (0.1–10.0)
Acute glomerulonephritis	1	0	. (.)	. (.)
Nephrotic syndrome	0	1	. (.)	. (.)
Meningococcal disease	0	N/A	N/A	N/A
Non-CRC reviewed EOIs				
Seizure	9	72	2.9 (1.5–5.8)	2.9 (1.5–5.9)
Seizure (chart reviewed)	0	25	. (.)	. (.)
Iridocyclitis (uveitis)	5	13	3.0 (1.1–8.3)	3.1 (1.1–8.7)
Iridocyclitis (uveitis) (chart reviewed)	4	10	3.1 (0.96–9.8)	3.4 (1.02–11.2)
Hashimoto disease	13	8	5.4 (2.3–13.1)	5.5 (2.3–13.3)
Hashimoto disease (chart reviewed)	2	3	2.2 (0.4–13.3)	5.1 (0.5–55.0)
Anaphylaxis	2	10	4.7 (1.02–21.3)	5.5 (1.1–26.2)
Anaphylaxis (chart reviewed)	0	4	. (.)	. (.)
ITP	1	1	7.7 (0.5–123.0)	. (.)[d]
Autoimmune hemolytic anemia	0	1	. (.)	. (.)
Aseptic meningitis	0	4	. (.)	. (.)
Asthma	206	635	1.1 (0.9–1.3)	1.1 (0.9–1.3)
Allergic urticaria	2	27	1.7 (0.4–7.3)	1.8 (0.4–7.4)
Suicide attempt	9	64	1.1 (0.5–2.2)	1.1 (0.5–2.2)
Total[e]	260	867		

N/A, not applicable.

[a] The RIs of EOIs with 0 cases in either the risk or comparison window were not calculated.

[b] Comparison window starts from the end of the risk window until the end of the 1-year observation period.

[c] Adjusted for seasonal effect by separating observation period into winter (December 1st to March 31st) and nonwinter periods.

[d] The adjusted RI for ITP could not be calculated. The model could not converge due to there being 1 case in the risk window and 1 case in the comparison window, each in different seasons.

[e] Totals do not include physician investigator chart review data.

eczema with Bell's palsy; this patient did not receive a concomitant vaccine. Finally, 1 patient had an upper respiratory tract infection/cough before the Bell's palsy diagnosis; this patient received concomitant vaccine (influenza) with MenACWY-CRM. Cases in the risk window occurred primarily between 5 and 10 weeks after vaccination. All 8 Bell's palsy cases resolved completely.

DISCUSSION

We conducted a large-scale cohort study in a real-world setting to evaluate the safety of 1 of the currently available quadrivalent meningococcal conjugate vaccines in the United States, MenACWY-CRM. The population includes individuals receiving the vaccine, as a first dose or a booster dose, at the recommended age of 11 to 18 years old, as well as young adults through 21 years old who are at an increased risk of invasive meningococcal infection. We were able to confirm the diagnosis, determine the onset date, and identify alternative causes of the events using EHRs. The within-person comparison inherent to the SCCS design allowed for control of potential confounders. We observed a temporal association between occurrence of Bell's palsy and receipt of MenACWY-CRM concomitantly with other vaccines. Three of the 8 Bell's palsy patients in the risk window had comorbidities and infections that could be a prelude to the condition. All 8 cases resolved completely.

The etiology and pathogenesis of Bell's palsy remains unclear. The health records of all suspected cases of Bell's palsy during the observation period were reviewed by members of the neurology CRC.

We expect no systematic bias in assigning case status or symptom onset date inside or outside of the risk window because the CRC members were masked to date of vaccination. Although the diagnosis of Bell's palsy relies on the exclusion of known congenital, genetic, and acquired causes of peripheral facial nerve palsy, it is uncommon to perform exclusionary laboratory or radiographic studies in patients presenting with uncomplicated acute onset facial nerve palsy whose symptoms resolve within an expected time frame.[10,11] This was true for the cases in our study, and review of clinical history and physical examination notes by the CRC was intended to confirm the diagnosis instead of identifying potential etiology.

There is no clear biological plausibility for a causal relationship between vaccination and Bell's palsy. Some have suggested an immune response mechanism, although there is no current evidence to support this theory.[12] Bell's palsy has been considered as an adverse event after vaccination for several other vaccines. However, the evidence from observational studies has been inconsistent. Several reports have described Bell's palsy cases after vaccination with influenza and hepatitis B virus vaccines.[11] A study of the Vaccine Adverse Event Reporting System suggested a potential risk for Bell's palsy after vaccination with an intramuscular influenza vaccine.[13] However, there were only 5 cases younger than 18 years of age in that study. Another virosomal inactivated influenza intranasal vaccine has been associated with Bell's palsy among persons aged 18 years or older.[14] In this study, the relative risk of Bell's palsy was 19 times the risk in the controls even with conservative estimation. The period of highest risk was 31 to 60 days after vaccination.[14] In a recent study examining Bell's palsy and immunization with trivalent influenza vaccine, hepatitis B vaccine, or any vaccine, Rowhani-Rahbar et al[15] did not find an association between vaccination and Bell's palsy during risk intervals of 1 to 14 days, 1 to 28 days, and 29 to 56 days after immunization among children aged 18 years or younger.[15] In our study, Bell's palsy cases occurring in the risk window were mainly during the 35 to 70 days after vaccination and the increased risk was found among those who received other vaccines concomitantly (HPV, Tdap, and influenza vaccines). Facial palsy is reported as a potential adverse event in the labels of the Adacel (Tdap; Sanofi Pasteur, Swiftwater, PA), Fluzone (seasonal influenza; Sanofi Pasteur, Swiftwater, PA), and Fluarix (seasonal influenza; GlaxoSmithKline, Middlesex, United Kingdom) vaccines used within the KPSC settings. Thus, it is difficult to disentangle the effect of different vaccines given concomitantly in this study.

Our study had several additional potential limitations. First, given the observational nature of this study, it is not designed to confirm a causal link between vaccination and a specific event. Second, EOIs under investigation were prespecified at the time when the product was licensed. Certain events reported from postmarketing experiences were not included, such as syncope.[1] Third, the analysis approach requires a priori definition of a risk window; however, the true risk windows are usually unknown. The study used generally accepted risk windows in vaccine safety studies on the basis of biological plausibility so that the results could be compared with other studies.[16] Fourth, for non-CRC reviewed events, medical records were further reviewed only when there was a statistically significant increased risk. Thus, false-negative results might potentially be overlooked. Finally, we had limited power to assess very rare EOIs (ie, ≤1 case in the risk window). Nevertheless, based on Poisson CIs, the chance of the true incidence exceeding 1 case in the risk window per 10 000 doses of MenACWY-CRM is less than 2%.

CONCLUSIONS

This observational study was not intended to provide conclusive evidence of causality. Rather, it detected potential temporal associations between MenACWY-CRM vaccination and adverse events. With nearly 50 000 individuals vaccinated with MenACWY-CRM included in this study, we observed a temporal association between occurrence of Bell's palsy and receipt of MenACWY-CRM concomitantly with other vaccines. The association needs further investigation because it could be due to chance, concomitant vaccination, or underlying medical history predisposing to Bell's palsy.

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ABBREVIATIONS

CI: confidence interval
CRC: case review committee
EHR: electronic health record
EOI: event of interest
HPV: human papillomavirus vaccine
ICD-9: *International Classification of Diseases, Ninth Revision*
ITP: idiopathic thrombocytopenic purpura
KPSC: Kaiser Permanente Southern California
MCV4: quadrivalent meningococcal conjugate vaccine
RI: relative incidence
SCCS: self-controlled case series
Tdap: tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, adsorbed

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