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Risk for Shoulder Conditions After Vaccination: A Population-Based Study Using Real-World Data

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Abstract

Background: Although shoulder conditions have been reported as an adverse event after intramuscular vaccination in the deltoid muscle, epidemiologic data on shoulder conditions after vaccination are limited.

Objective: To estimate the risk for shoulder conditions after vaccination and assess possible risk factors.

Design: Retrospective cohort study.

Setting: Kaiser Permanente Southern California, a large integrated health care organization.

Participants: Kaiser Permanente Southern California members aged 3 years or older who had an intramuscular vaccination administered in the deltoid muscle between 1 April 2016 and 31 December 2017.

Measurements: A natural language processing (NLP) algorithm was used to identify potential shoulder conditions among vaccinated persons with shoulder disorder diagnosis codes. All NLP-identified cases were manually chart confirmed on the basis of our case definition. The characteristics of vaccinated persons with and without shoulder conditions were compared.

Results: Among 3 758 764 administered vaccinations, 371 cases of shoulder condition were identified, with an estimated incidence of 0.99 (95% CI, 0.89 to 1.09) per 10 000 vaccinations. The incidence was 1.22 (CI, 1.10 to 1.35) for the adult (aged ≥18 years) and 0.05 (CI, 0.02 to 0.14) for the pediatric (aged 3 to 17 years) vaccinated populations. In the adult vaccinated population, advanced age, female sex, an increased number of outpatient visits in the 6 months before vaccination, lower Charlson Comorbidity Index, and pneumococcal conjugate vaccine were associated with a higher risk for shoulder conditions. Among influenza vaccines, quadrivalent vaccines were associated with an increased risk for shoulder conditions. Simultaneous administration of vaccines was associated with a higher risk for shoulder conditions among elderly persons.

Limitation: Generalizability to other health care settings, use of administrative data, and residual confounding.

Conclusion: These population-based data suggest a small absolute risk for shoulder conditions after vaccination. Given the high burden of shoulder conditions, clinicians should pay attention to any factors that may further increase risks.

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Vaccination prevents disease by stimulating the immune system (1). Health problems can occur after vaccination but may or may not be related to vaccination. The National Vaccine Injury Compensation Program (VICP) provides financial compensation to those who had serious adverse effects listed in its vaccine injury table (2). In 2017, the VICP added shoulder injury related to vaccine administration (SIRVA) to the vaccine injury table (3). The addition of SIRVA to the VICP was based on published case series and a report from the Institute of Medicine (4, 5). The report concluded that "the evidence convincingly supports a causal relationship between the injection of a vaccine and deltoid bursitis" (4). Besides bursitis, other shoulder conditions have been linked to vaccination with imaging and surgical pathologic evidence (5–18). The proposed mechanism is that the shoulder conditions are caused by immune responses when vaccines are injected into the shoulder joint, instead of the deltoid muscle (5, 12, 13, 18–22).

Most publications about SIRVA have been case reports and case series (5, 11, 12, 18, 23–25). The only population-based study examined the risk for subdeltoid bursitis after influenza vaccination but did not examine other shoulder conditions (19). Population-based studies require costly manual medical record reviews. We used a validated natural language processing (NLP) algorithm along with chart review to identify shoulder conditions after vaccination from electronic health records (26–28). Our objectives were to estimate the risk for shoulder conditions after intramuscular vaccination and examine possible risk factors.

Methods

Setting

This retrospective cohort study was done at Kaiser Permanente Southern California (KPSC), an integrated health care system that provides comprehensive health care to more than 4.7 million racially, ethnically, and socioeconomically diverse members at its 15 hospitals and 234 medical offices (29). The prepaid health plan incentivizes members to use services at KPSC facilities. The electronic health record system at KPSC stores all aspects of member care, such as sociodemographic characteristics, medical encounters, diagnoses, laboratory tests, pharmacy use, vaccination records, membership history, and billing and claims. For case identification, the NLP method used both structured and free-text data. Chart abstractors reviewed medical records for case confirmation.

Population

We included KPSC members aged 3 years or older who received at least 1 intramuscular vaccine injected in an arm at a KPSC facility between 1 April 2016 and 31 December 2017. The unit of analysis, vaccination, was specified by the member's medical record number, vaccination date, and vaccination laterality. The index date was the date of vaccination. Eligible vaccinations did not have another intramuscular vaccine injected in the same

arm within postvaccination days 1 and 180. We also excluded members who were not continuously enrolled in the KPSC health plan in the 180 days before and after the index date, allowing us to assess their shoulder conditions.

Case Definition

The VICP developed the only standard definition of SIRVA (Appendix Method 1, available at Annals.org), which was a legal definition used for compensation, not a medical definition used for diagnosis. On the basis of the VICP definition, we created a case definition to identify shoulder conditions after vaccination, although this may not necessarily reflect injury due to vaccination. We defined a case as a shoulder condition that occurred in the same arm in which a vaccine was injected, with onset within the first 7 days of vaccination and lasting for more than 30 days. Vaccination was also identified as a possible cause of the shoulder condition, with no other known causes. Our definition had some differences from the VICP definition. On the basis of previous publications (5, 12, 19, 30), instead of 2 days, a 7-day onset window to permit later occurrence was used. To exclude injection-site reactions and cases with transient and self-resolving symptoms (31), we required symptoms to last for more than 30 days, which is not required by the VICP.

Nomenclature

The word “injury” implies causation. The VICP criteria show that proving causality is difficult: “To receive the compensation, the petitioners do not need to prove that the vaccine caused the injury and/or condition”; “Settled compensations also do not admit that the vaccine caused the alleged injuries” (2). Our approach was able to establish association but not causality. Therefore, we refer to our outcome as “shoulder conditions” after vaccination rather than SIRVA.

Outcomes

We used a previously developed and validated NLP algorithm (26–28) to identify persons in the vaccinated population who had at least 1 shoulder-related International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) diagnosis code (Supplement, available at Annals.org) within 180 days after the index date but not within the 180 days before the index date, from all clinical notes documented within 180 days after the index date. All NLP-identified cases were manually chart confirmed on the basis of our case definition. The abstraction form is shown in the Supplement. During manual chart confirmation, we excluded cases where previous shoulder symptoms were documented in the medical records. We also excluded medical conditions that were unlikely to be caused by vaccination, such as arthritis, brachial neuritis, and radiculopathy (26).

Statistical Analysis

Incidence was calculated as the number of cases per 10 000 vaccinations. For all vaccines combined, we estimated the overall and age-specific incidences. Among vaccinated adults, we evaluated crude and age- and sex-adjusted incidence by vaccine type. For vaccine-specific incidence estimation, when multiple vaccinations were intramuscularly administered on the same day in the same arm, they were counted as “simultaneous administration

of vaccines" (32) (hereafter called simultaneous vaccination) rather than as individual vaccine types. Various influenza vaccines have different properties affecting immune responses, such as the number of strains (33), doses (34), adjuvants (35), or vaccine technologies (32) (Appendix Table 1, available at Annals.org). We also evaluated incidence by influenza vaccine type; for this analysis, we included influenza vaccinations regardless of simultaneous administration with other vaccines. The 95% CIs for the incidence estimates were calculated using the Wilson score interval because of its accuracy and robustness when the proportion is close to 0 or 1 (36).

We compared the characteristics of the adult vaccinated population with and without shoulder conditions after vaccination. For categorical variables, we used the χ^2 test or Fisher exact test to calculate *P* values. We also calculated standardized difference, which quantifies the extent of difference between groups regardless of sample size. An absolute value of standardized difference larger than 0.10 was defined as a difference (37).

To assess potential risk factors for shoulder conditions in vaccinated adults, we used multivariable logistic regression. Covariates of clinical importance were selected for the adjusted analyses (Appendix Method 2, available at Annals.org). We used the least absolute shrinkage and selection operator (LASSO) (38) method in the GLMSELECT (SAS Institute) procedure to select the interaction terms among the covariates. Because some persons had multiple vaccination records, we used a generalized estimating equations logistic regression model to account for correlated data. For rare events like shoulder conditions after vaccination, logistic regression with penalized likelihood (Firth method) can reduce bias as compared with the conventional maximum likelihood logistic model (39). Thus, we used the Firth method to estimate odds ratios (ORs) and 95% CIs. The OR could be used to approximate the relative risk because the outcome was extremely rare. As a confirmation step, we also fitted a standard logistic regression model and a Poisson model to estimate the rate ratio using the same selected variables. To reduce bias caused by missing data, we performed the generalized estimating equations logistic regression using complete case analysis. In addition, we did sensitivity analyses on all study participants, where missing data were imputed and analyzed using the multiple imputation technique with 5 imputed data sets. SAS, version 9.4 (SAS Institute), was used for all statistical analyses. The institutional review board at KPSC approved this study.

Role of the Funding Source

This study was funded by the Centers for Disease Control and Prevention (CDC). The authors had complete control over the design, analysis, and decision to submit the manuscript for publication.

Results

Study Population and Case Identification

There were 2269 359 unique members who received 3758 764 eligible intramuscular vaccinations between 1 April 2016 and 31 December 2017 (Figure 1). Among them, we identified 53 585 cases with a shoulder-related ICD-10-CM code. During follow-up

(1 to 180 days from the index date), the NLP search of clinical notes identified 467 potential cases. Manual chart confirmation of these 467 cases yielded 371 cases of shoulder conditions after vaccination (26). These 371 cases came from 371 distinct persons. Among these 371 cases, 358 had explicit documentation that symptoms began after vaccination. There were 147 cases where explicit statements about vaccination-related causality were made. Of those, 40 cases had mention of incorrect vaccine administration; the term *SIRVA* was used specifically in 7 of them.

Incidence of Shoulder Conditions After Vaccination

The estimated incidence of shoulder conditions per 10000 vaccinations was 0.99 (95% CI, 0.89 to 1.09) (Table 1). The incidence was 1.22 (CI, 1.10 to 1.35) for the adult (aged ≥18 years) and 0.05 (CI, 0.02 to 0.14) for the pediatric (aged 3 to 17 years) vaccinated populations. For ages 18 to 49, 50 to 64, and ≥65 years, the incidences were 0.62, 1.60, and 1.67, respectively.

The most commonly administered vaccine among adults was the influenza vaccine, which had an age- and sex-adjusted incidence of 1.13 per 10000 vaccinations (Table 2). Adjusted incidence after various vaccine types ranged from 0.76 (hepatitis A vaccine) to 2.83 (pneumococcal conjugate vaccine [PCV13]) per 10000 vaccinations. Persons who received simultaneous vaccination had an incidence of 2.06 per 10000 vaccinations. Among the influenza vaccines, the standard-dose inactivated influenza vaccine trivalent (SD-IIV3) had the lowest incidence of 0.88 per 10000 vaccinations. Incidence increased to 1.36 per 10000 vaccinations for standard-dose inactivated influenza vaccine quadrivalent (SD-IIV4), 1.39 per 10000 vaccinations for high-dose inactivated influenza vaccine trivalent (HD-IIV3), 1.52 per 10000 vaccinations for adjuvanted inactivated influenza vaccine trivalent (aIIV3), and 2.21 per 10000 vaccinations for cell culture–based inactivated influenza vaccine quadrivalent (ccIIV4).

Shoulder Conditions Among Pediatric Vaccinees

In more than 750000 pediatric vaccine recipients, there were only 4 cases of shoulder conditions that were attributed to vaccination (ages 10, 12, 14, and 15 years). Vaccines were administered to the nondominant arm in all 4 cases. Two cases had simultaneous vaccination of 2 vaccines. All 4 cases were initially diagnosed with shoulder or arm pain, with symptoms appearing within 4 days of vaccination. The shoulder problem was resolved within 6 months in all cases.

Shoulder Conditions Among Vaccinated Adults

Given the rarity of shoulder conditions among pediatric vaccine recipients, the following analyses were restricted to the adult vaccinated population (n = 3006733). Table 3 and Appendix Table 2 (available at Annals.org) show the characteristics of these vaccinated adults. The median age of adults with shoulder conditions after vaccination was 62.4 years at the time of vaccination, and 65.1% were female. The 3006366 vaccinations without shoulder conditions after were linked to 1 821 748 persons, with 1022886 (56.1%) of them receiving 2 or more vaccinations spaced more than 6 months apart. The 367 cases of shoulder conditions represented 367 persons, with 273 (74.4%) of them having had 2 or

more vaccinations separated by at least 6 months. Most of these shoulder conditions (n = 344 [93.7%]) began within 2 days of vaccination.

Among the presumptive cases with shoulder-related diagnosis codes (n = 53 585), 50 492 (94.2%) were among adults. Appendix Table 3 (available at Annals.org) lists the shoulder-related ICD-10-CM codes that were associated with these presumptive cases. Almost all of the shoulder condition cases (n = 363 [98.9%]) had at least 1 of the shoulder disorder or symptom codes, and only 4 cases were solely coded by the shoulder injury codes from chapter 19 of ICD-10-CM. Shoulder bursitis was coded for only 17 (4.6%) cases, of which 12 (70.6%) occurred after influenza vaccination. The proportion of confirmed shoulder conditions among the various ICD-10-CM codes ranged from 0.24% to 2.48%.

Risk Factors for Shoulder Conditions Among Vaccinated Adults

The adjusted ORs for risk factors for shoulder conditions after vaccination are shown in Figure 2. The risk for shoulder conditions was higher in females, persons who had more outpatient visits in the 6 months before vaccination, and persons with a lower Charlson Comorbidity Index (CCI). The PCV13 was associated with a higher risk for shoulder conditions than other types of vaccines (adjusted OR, 1.63 [CI, 1.01 to 2.62]). Among influenza vaccines, compared with SD-IIV3, the adjusted ORs for HD-IIV3, aIIV3, SD-IIV4, and ccIIV4 were 1.27 (CI, 0.40 to 4.08), 1.40 (CI, 0.56 to 3.50), 1.51 (CI, 1.16 to 1.97), and 2.55 (CI, 1.28 to 5.09), respectively. Among nonsimultaneous vaccinations, compared with persons aged 18 to 49 years, those aged 50 to 64 years and 65 years or older had similarly increased risks. Among simultaneous vaccinations, compared with those aged 18 to 49 years, persons aged 65 years or older had a much higher increased risk than those aged 50 to 64 years. The adjusted rate ratios estimated from the standard logistic regression model and Poisson model were almost the same as the adjusted ORs from the generalized estimating equations logistic regression model. Sensitivity analyses using multiple imputation to address missing data yielded similar results.

Discussion

Our study provides real-world data on the incidence of shoulder conditions after vaccination and associated risk factors. In contrast to another epidemiologic study that restricted cases to those with codes for shoulder bursitis after influenza vaccination (19), we investigated a broader variety of shoulder disorder diagnoses and included all vaccines intramuscularly administered into the deltoid muscle of the arm. In our study, only 4.6% of shoulder conditions after vaccination were coded as shoulder bursitis, and 70.6% occurred after influenza vaccinations. Symptom-related codes, such as shoulder pain, were the most frequently used. Overall, the incidence of shoulder conditions after vaccination was low, with less than 1 case per 10000 vaccinations. The incidence was rare in the pediatric population, with 5 cases per 1 million vaccinations, which is consistent with previous studies (5, 12, 19, 30). Adults had a nearly 23-fold higher incidence than the pediatric population. Females were more likely to develop shoulder problems after vaccination, which is consistent with earlier studies (5, 12, 19, 30).

The mechanism for shoulder conditions after vaccination is hypothesized to be needle overpenetration into the shoulder joint, which results in immune-mediated inflammation (5, 12, 13, 18–22). Injection too high and/or too deep could lead to overpenetration. Immunization guidelines recommend a 1-inch length needle for most adults (40), but this may cause overpenetration in 50% of adults (41). Older adults and females generally have lower muscle mass (42–46) and may be more vulnerable to needle overpenetration. Simultaneous vaccination may also result in overpenetration. To differentiate local reactions from each vaccination, best practices for multiple injections to the same limb include spacing injection sites by at least 1 inch (40). The recommended injection site for the deltoid muscle is about 2 inches long (47). The spacing between multiple injections in this small area can increase the probability of overpenetration by injecting too high. The needle overpenetration hypothesis is supported by our findings of increased incidence of shoulder conditions after vaccination by age and female sex and simultaneous vaccination among elderly persons.

Besides overpenetration, the immune-mediated inflammation theory suggests that shoulder conditions are caused by immune responses when vaccines are injected into the shoulder joint (5, 20, 21). In this theory, vaccines believed to induce stronger immune responses may be associated with a higher risk for shoulder conditions. We examined influenza vaccines that had published comparative immunogenicity data. Compared with SD-IIV3, other types of influenza vaccines induced stronger immune responses because of the increased number of virus strains (SD-IIV4) (33), higher virus dose (HD-IIV3) (34), additional adjuvant (aIIV3) (48), or the vaccine technology (ccIIV4) (49). For instance, both trivalent (IIV3) and quadrivalent (IIV4) influenza vaccines have the same 3 virus strains; however, IIV4 has 1 more virus strain that can induce a stronger immune response. On the basis of the point estimates, compared with SD-IIV3, we saw an increased risk for shoulder conditions for these more immunogenic influenza vaccines. This finding is consistent with the subdeltoid bursitis study: Cases in the risk interval were more likely to be vaccinated with SD-IIV4 and HD-IIV3 than cases in the control interval (19). The OR for shoulder conditions among quadrivalent influenza vaccines also increased from egg-based to cell-based vaccine, which is more immunogenic (49). Our findings that persons with simultaneous vaccinations were more likely to have shoulder conditions after vaccination could also add support for the immune-mediated inflammation theory.

Lower body mass index may also be associated with lower deltoid muscle mass, which increases the chance of overpenetration (11). However, our study did not find a statistically significant association between body mass index and the risk for shoulder conditions after vaccination in the adjusted model. Improper injection technique can also cause overpenetration. Previous studies examined the association between SIRVA and the credentials of the vaccinator (19, 30). We did not find any association between shoulder conditions and vaccinator credentials. Although credentials may reflect training, a clinical credential itself may not necessarily reflect the skill of an individual vaccinator.

We also found that shoulder conditions were associated with prior outpatient visits but not emergency department or inpatient visits. This could be related to residual confounding, in which persons who have more outpatient visits are more likely to seek medical care for

shoulder problems. Although no association with any of the individual comorbidities was found, higher CCI was associated with a lower risk for shoulder conditions. This association may be explained by the weakened immune response associated with comorbidities and lowered functional status (50). Furthermore, persons with a lower CCI may engage in more physical activities, which could increase the risk for overuse injury while enhancing the immune response to the vaccine (50, 51).

Our findings offer some potential insights about mechanisms for shoulder conditions associated with vaccination. However, such findings should be interpreted with caution. The exact cause or causal pathway of each shoulder condition is difficult, if not impossible, to determine. Shoulder problems are often multifactorial. The associations between risk factors and shoulder conditions could be explained in various ways. For example, the increased incidence of shoulder conditions in the older population may also be related to a decrease in rotator cuff vascularity, which impairs vaccine clearance if accidentally injected (52). The higher risk for shoulder conditions in females could also be because of their greater pain sensitivity (53).

This study has some limitations. Our study could underestimate the incidence of shoulder conditions after vaccination. In our base population, we included vaccinations given to persons who had a shoulder-related diagnosis before or during the vaccination as well as persons who only had a shoulder-related diagnosis with unspecified laterality during follow-up. Given the difficulty in determining the underlying causes of their postvaccination shoulder problems, we excluded them from the presumed cases; nonetheless, they may still be at risk for new or worsening shoulder conditions. The risk for underestimating the incidence was small because these subsets of vaccinations accounted for just 2% and 1% of all eligible vaccinations, respectively. In addition, rather than searching the entire population, the NLP algorithm identified possible cases among those with a shoulder-related diagnosis code. However, underascertainment seemed unlikely because we used a broad set of diagnosis codes. Furthermore, even though our analysis included many clinical variables, residual confounding and unmeasured factors could be unaccounted for in our model. Moreover, shoulder conditions may not be related to vaccination. For instance, shoulder conditions may develop insidiously, as a result of cumulative damage from various factors. Although the clinical notes may contain statements linking the shoulder condition to vaccination, such statements do not prove causation. Patients and clinicians may attribute the vaccine as the likely cause of the shoulder condition using “after this, therefore because of this” logic. Temporality based on patient recollection is likewise prone to error. Finally, our onset period (7 days) overlapped with the VICP-defined onset interval for brachial neuritis (2 to 28 days) (3–5, 12, 30). Nevertheless, brachial neuritis was unlikely to be included in our cases because we specifically excluded neuritis conditions (26).

In conclusion, we developed an approach to evaluate the incidence of shoulder conditions after vaccination that may be used in clinical research with electronic health record data. Our study identified a small absolute risk for shoulder conditions among those who received intramuscular vaccinations. These risk estimates offer a new population-based perspective on this rare event. Needle overpenetration may be a part of the causal pathway. Although shoulder conditions may be preventable if caused by inappropriate vaccine administration,

this study was not able to determine their true cause. More research is needed to better understand the risk factors and causal pathways for shoulder conditions after vaccination.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix: Case Definition and Variable Selection Process Used in the Adjusted Multivariable Logistic Regression

Appendix Method 1. Our Case Definition of Shoulder Condition After Vaccination Versus the VICP Case Definition of SIRVA

The VICP (3) defines SIRVA as shoulder pain and limited range of motion occurring after the administration of a vaccine intended for intramuscular administration in the upper arm. "A vaccine recipient shall be considered to have suffered SIRVA if such recipient manifests all of the following:

- **i.** No history of pain, inflammation or dysfunction of the affected shoulder prior to intramuscular vaccine administration that would explain the alleged signs, symptoms, examination findings, and/or diagnostic studies occurring after vaccine injection;
- **ii.** Pain occurs within the specified time-frame*;
- **iii.** Pain and reduced range of motion are limited to the shoulder in which the intramuscular vaccine was administered; and
- **iv.** No other condition or abnormality is present that would explain the patient's symptoms (e.g. NCS/EMG or clinical evidence of radiculopathy, brachial neuritis, mononeuropathies, or any other neuropathy)."

* Forty-eight hours or less.

In this study, a valid shoulder condition after vaccination case needed to meet 5 criteria:

1. Damage to the shoulder region occurred and was confirmed by signs and symptoms (that is, pain, limited range of motion, weakness, and stiffness) and clinical diagnosis.
2. The shoulder condition occurred in the same arm in which a vaccine was injected.
3. The shoulder condition started within 7 days after vaccination.

4. Vaccination was a possible cause of the shoulder condition, and no other known causes were associated with the shoulder condition.

5. The shoulder condition lasted more than 30 days after vaccination.

Appendix Method 2. Variable Selection Process

We first preselected 14 variables on the basis of the literature review and clinical importance. We tested for possible 2-way interactions of these 14 variables using logistic regression one at a time. Twenty-four interaction terms with $P < 0.20$ were entered in the pool together with the 14 preselected variables. Because of the large number of interaction terms, we used the SAS GLMSELECT procedure to select the interaction terms. The LASSO regression models can select the most important features and minimize over-fitting (38). Therefore, in the GLMSELECT procedure, we used the LASSO with the CV PRESS score option. The model yielding the smallest value of the CV PRESS statistic was selected (54).

The LASSO method resulted in the selection of an interaction between age and simultaneous vaccine. We then added this interaction term together with the 14 variables to the logistic regression. All variables with a $P < 0.05$ were selected for our final logistic model.

The 14 variables were age, sex, race/ethnicity, body mass index, CCI, prior health care use (number of outpatient visits, number of emergency department visits, and vaccination history within the 6 months before the index vaccination), simultaneous vaccine, vaccinated arm, vaccinator credentials, PCV13, influenza vaccine, and type of influenza vaccine received.

Appendix Table 1.

Comparisons of the Properties of Influenza Vaccines

Influenza Vaccines	Strains, *n*	Dose	Adjuvant	Vaccine Design
SD-IIV3	3	Standard dose	None	Egg-based
HD-IIV3	3	High dose*	None	Egg-based
aIIV3	3	Standard dose	Adjuvant*	Egg-based
SD-IIV4	4*	Standard dose	None	Egg-based
ccIIV4	4*	Standard dose	None	Cell culture-based*

aIIV3 = adjuvanted inactivated influenza vaccine trivalent; ccIIV4 = cell culture–based inactivated influenza vaccine quadrivalent; HD-IIV3 = high-dose inactivated influenza vaccine trivalent; SD-IIV3 = standard-dose inactivated influenza vaccine trivalent; SD-IIV4 = standard-dose inactivated influenza vaccine quadrivalent.

*Properties associated with enhanced immune responses.

Appendix Table 2.

Additional Characteristics of Adults at the Time of Vaccination for Adults With Versus Without Shoulder Conditions After Vaccination ($n = 3\,006\,733$ Vaccinations)

Characteristic	No Shoulder Condition ($n = 3\,006\,366$)	Shoulder Condition ($n = 367$)	*P* Value	Standardized Difference*
Charlson Comorbidity Index, *n* (%)			0.37	−0.004

Characteristic	No Shoulder Condition (*n* = 3 006 366)	Shoulder Condition (*n* = 367)	*P* Value	Standardized Difference*
0	1 794 197(99.988)	209 (0.012)		
1–2	779 982(99.986)	107 (0.014)		
≥3	432 187(99.988)	51 (0.012)		
Comorbidities, *n* (%)				
Chronicpulmonary disease	379 082(99.988)	44(0.012)	0.72	−0.019
Peripheral vascular disease	367 011 (99.986)	51 (0.014)	0.32	0.050
Diabetes without complications	331 894(99.986)	46(0.014)	0.36	0.046
Diabetes with complications	242 022(99.988)	28(0.012)	0.77	−0.016
Renal disease	243 905(99.988)	30(0.012)	0.97	0.002
Moderate or severe liver disease	98 510(99.990)	10(0.010)	0.55	−0.032
Cancer	77 813(99.990)	8(0.010)	0.62	−0.027
Congestive heartfailure	75 272 (99.988)	9(0.012)	0.95	−0.003
Myocardial infarction	70 948(99.983)	12(0.017)	0.25	0.055
Cerebrovascular disease	66 434 (99.985)	10(0.015)	0.50	0.033
Connective tissue disease–rheumatic disease	45 086(99.984)	7(0.016)	0.52	0.032
Dementia	34 723 (99.997)	1 (0.003)	0.114	−0.105
Metastatic carcinoma	20 976(99.995)	1 (0.005)	0.33	−0.061
Paraplegia and hemiplegia	10 787(100)	0 (0)	0.25	−0.085
Peptic ulcer disease	10 374(99.990)	1 (0.010)	0.81	−0.013
AIDS/HIV	7551 (99.987)	1 (0.013)	0.94	0.004
Mean number of clinical visits (6 mo before the index vaccination) (SD), *n*				
Outpatient	4.1 (5.9)	4.6 (5.8)	0.100	0.087
Emergency department	0.2 (0.6)	0.1 (0.4)	0.120	−0.095
Inpatient	0.0 (0.3)	0.0 (0.3)	0.84	−0.011
Season of vaccination, *n* (%)			0.91	0.022
1 April to 31 July 2016	120 463(98.672)	16(0.013)	0.73	0.018
1 August 2016 to 31 July 2017	1 510 215(98.769)	186(0.012)	0.86	0.009
1Augustto31 December 2017	1 375 688(98.801)	165(0.012)	0.76	−0.016
Vaccinated arm, *n* (%)			0.93	0.004
Left	2 255 148(99.988)	276 (0.012)		
Right	751 218(99.988)	91 (0.012)		

* Difference in means or proportions divided by SD; absolute standardized difference <0.10 is considered a negligible difference.

Appendix Table 3.

Shoulder-Related ICD-10-CM Codes Appearing in Presumptive Shoulder Condition Cases of the Adult Vaccinated Population Within 180 Days After Vaccination (*n* = 50 492)

ICD-10-CM Code and Description	Chart-Confirmed Shoulder Condition Cases	
	No (*n* = 50 125)	Yes (*n* = 367)
Shoulder disorder or symptom codes, *n* (%)	41 088 (99.124)	363 (0.876)

ICD-10-CM Code and Description	Chart-Confirmed Shoulder Condition Cases	
	No (*n* = 50 125)	Yes (*n* = 367)
Shoulder disorder codes	16 571 (99.026)	163(0.974)
Reported in the SIRVA literature	10 731 (99.022)	106 (0.978)
M75.0* Adhesive capsulitis/frozen shoulder	1319(97.776)	30 (2.224)
M75.1* Rotator cufftear or rupture	7199(99.132)	63 (0.868)
M75.2* Bicipital tendinitis	877 (99.320)	6 (0.680)
M75.3* Calcific tendinitis of shoulder	701 (98.872)	8(1.128)
M75.5* Bursitis ofshoulder	1248(98.656)	17 (1.344)
Not previously reported in the literature	7395 (98.903)	82 (1.097)
M75.4* Impingement syndrome ofshoulder	3945 (98.699)	52(1.301)
M75.8* Other shoulder lesions	2643 (99.026)	26 (0.974)
M24.81* Other shoulder joint derangements	505 (99.020)	5 (0.980)
Shoulder symptom codes	31 210 (98.982)	321 (1.018)
M25.51* Pain in shoulder	25 833 (99.133)	226 (0.867)
M25.61* Stiffness of shoulder	1133(98.607)	16(1.393)
M79.60* Pain in arm	5849(97.516)	149 (2.484)
M79.62* Pain in upper arm	302 (98.693)	4(1.307)
Shoulder injuries from chapter 19 of ICD-10-CM: injury, poisoning, and other external causes, *n* (%)	12 009 (99.759)	29 (0.241)

ICD-10-CM = International Classification of Diseases, 10th Revision, Clinical Modification; SIRVA = shoulder injury related to vaccine administration.

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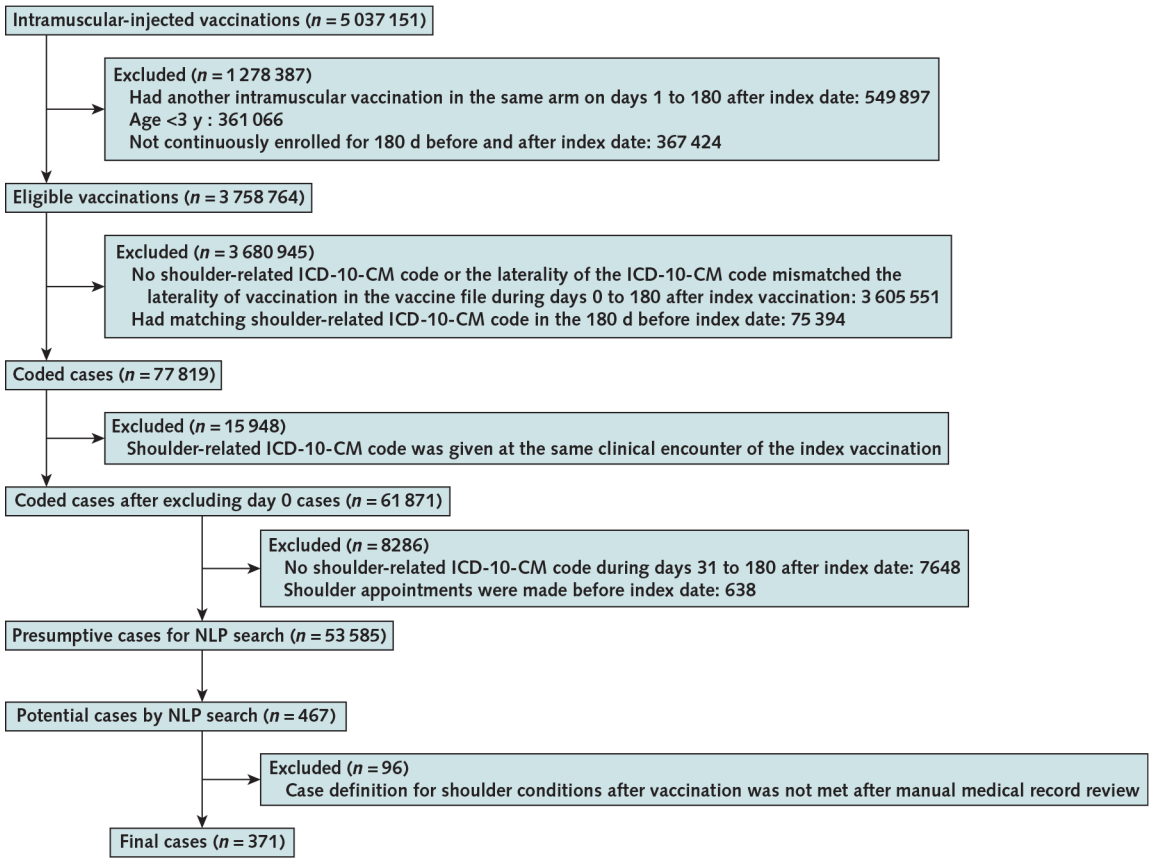

Figure 1.

Flow diagram showing cohort eligibility, case finding by the NLP algorithm, and case confirmation.

The index date is the vaccination date. ICD-10-CM= International Classification of Diseases, 10th Revision, Clinical Modification; NLP= natural language processing.

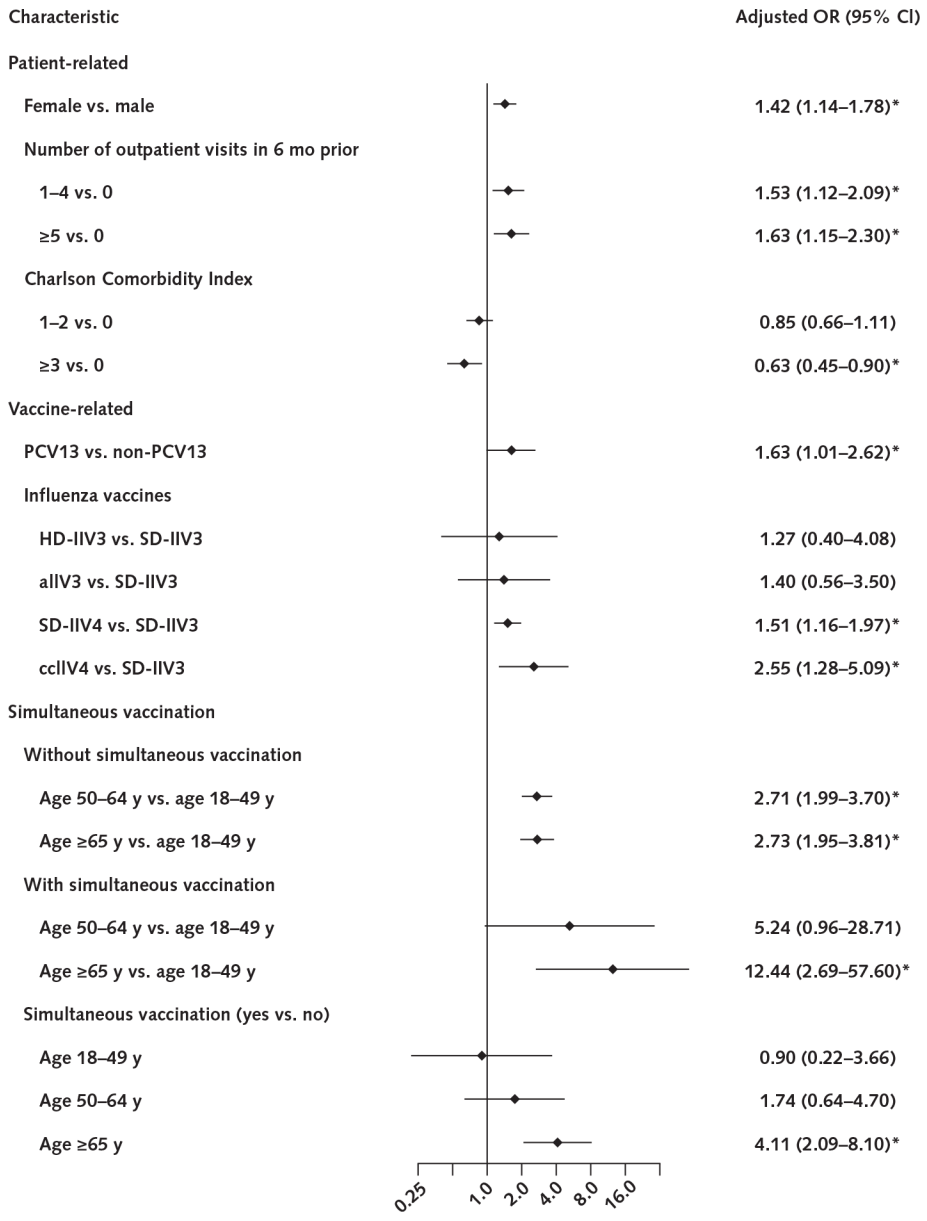

Figure 2.

Adjusted ORs for shoulder conditions and associated risk factors among adults at the time of vaccination (n = 3006733).

The final model included age, sex, Charlson Comorbidity Index, number of outpatient visits within the 6 mo before the index vaccination, PCV13, type of influenza vaccine, simultaneous vaccination, and the interaction between age and simultaneous vaccination. aIIV3= adjuvanted inactivated influenza vaccine trivalent; ccIIV4 = cell culture–based inactivated influenza vaccine quadrivalent; HD-IIV3= high-dose inactivated influenza vaccine trivalent; OR = odds ratio; PCV13= pneumococcal conjugate vaccine; SD-IIV3= standard-dose inactivated influenza vaccine trivalent; SD-IIV4= standard-dose inactivated influenza vaccine quadrivalent.

* Values are statistically significant ($P < 0.05$).

Table 1.

Incidence of Shoulder Conditions per 10 000 Vaccinations by Age Group (n = 3 758 764 Vaccinations)

Age Group	Vaccinations, *n*	Shoulder Condition Cases, *n*	Incidence per 10 000 Vaccinations (95% CI)
3–17 y	752 031	4	0.05(0.02–0.14)
≥18 y	3 006 733	367	1.22(1.10–1.35)
18–49 y	1 233 716	76	0.62 (0.49–0.77)
50–64 y	822 586	132	1.60(1.35–1.90)
≥65 y	950 431	159	1.67(1.43–1.95)
All (≥3 y)	3 758 764	371	0.99(0.89–1.09)

Table 2.

Incidence of Shoulder Conditions per 10 000 Vaccinations by Type of Vaccine in the Adult Vaccinated Population (n = 3 006 733 Vaccinations)

Vaccine*	Vaccinations, *n*	Cases, *n*	Incidence per 10 000 Vaccinations (95% CI)	
			Crude Incidence	Age- and Sex-Adjusted Incidence†
Influenza	2 284 229	260	1.14(1.01–1.29)	1.13(0.96–1.32)
Hepatitis A	40 194	3	0.75 (0.25–2.19)	0.76 (0.23–2.49)
Hepatitis B	97 777	15	1.53 (0.93–2.53)	1.52(0.80–2.91)
Human papillomavirus	48 942	4	0.82 (0.32–2.10)	0.72(0.18–2.90)
Meningococcal	22 663	2	0.88 (0.24–3.22)	0.93(0.19–4.63)
Pneumococcal conjugate	101 899	29	2.85 (1.98–4.09)	2.83(1.63–4.89)
Pneumococcal polysaccharide	105 918	15	1.42 (0.86–2.34)	1.54 (0.82–2.86)
Tetanus, diphtheria, pertussis	211 114	22	1.04 (0.69–1.58)	1.07(0.62–1.83)
Simultaneous vaccination	76 613	16	2.09 (1.29–3.39)	2.06 (1.11 –3.83)
Influenza vaccine‡				
SD-IIV3	1 056 851	93	0.88 (0.72–1.08)	0.88(0.67–1.17)
HD-IIV3	22 146	3	1.35 (0.46–3.98)	1.39(0.30–6.41)
aIIV3	33 350	5	1.50 (0.64–3.51)	1.52(0.65–3.55)
SD-IIV4	1 182 543	162	1.37 (1.17–1.60)	1.36(1.12–1.65)
ccIIV4	40 969	9	2.20 (1.16–4.17)	2.21 (1.15–4.24)

aIIV3 = adjuvanted inactivated influenza vaccine trivalent; ccIIV4 = cell culture–based inactivated influenza vaccine quadrivalent; HD-IIV3 = high-dose inactivated influenza vaccine trivalent; SD-IIV3 = standard-dose inactivated influenza vaccine trivalent; SD-IIV4 = standard-dose inactivated influenza vaccine quadrivalent.

*Vaccines coadministered with other vaccines in the same arm on the same day were not counted individually but counted only once in the “simultaneous vaccination” group.

†The standard population included year 2017 Kaiser Permanente Southern California vaccinated members who were aged ≥18 y with known sex. For vaccines with specific age recommendations, we adjusted by the recommended ages: human papillomavirus vaccine was adjusted by age ≤26 y and aIIV3 and SD-IIV4 were adjusted by age ≥65 y.

‡Influenza vaccines coadministered with other vaccines in the same arm on the same day were counted.

Table 3.

Characteristics of Adults at the Time of Vaccination for Adults With Versus Without Shoulder Conditions After Vaccination (*n* = 3 006 733 Vaccinations)

Characteristic	No Shoulder Condition (*n* = 3 006 366)	Shoulder Condition (*n* = 367)	*P* Value	Standardized Difference*
Median age (IQR), *y*	55.3(38.7–67.7)	62.4(52.6–69.7)	<0.001	0.46
Age, *n* (%)			<0.001	0.45
18–49 y	1 233 640(99.994)	76 (0.006)		
50–64 y	822 454 (99.984)	135(0.016)		
≥ 65 y	950 272 (99.983)	159(0.017)		
Sex, *n* (%)			0.002	0.19
Female	1 687 872 (99.986)	239 (0.014)		
Male	1 318 481 (99.990)	128(0.010)		
Unknown	13(100)	0(0)		
Race/ethnicity, *n* (%)			0.004	0.22
Hispanic	996 940 (99.990)	103 (0.010)		
Non-Hispanic White	1 184 775(99.986)	167(0.014)		
Non-Hispanic Black	225 713 (99.983)	39(0.017)		
Non-Hispanic Asian	357 211 (99.992)	28 (0.008)		
Multiple/other	139 882 (99.989)	15(0.011)		
Unknown	101 845 (99.985)	15(0.015)		
Median body mass index (IQR), *kg/m*^{2}	28.1 (24.6–32.6)	27.5(24.4–31.6)	0.049	−0.11
Number of outpatient visits (6 mo before the index vaccination), *n* (%)			0.002	0.19
0	708 240 (99.992)	59 (0.008)		
1–4	1 412 804(99.987)	182 (0.013)		
≥5	885 322 (99.986)	126(0.014)		
History of vaccine refusal (6 mo before the index vaccination), *n* (%)	273 171 (99.984)	44 (0.016)	0.053	0.095
Vaccinator credential, *n* (%)			0.001	0.13
Medical assistant	525 454 (99.987)	68(0.013)		
Licensed vocational nurse	1 971 042 (99.988)	242(0.012)		
Registered nurse	470 717 (99.989)	50(0.011)		
Other credentials†	7750 (100)	0(0)		
More than 1 credential‡	1526 (86.911)	2(0.131)		

Characteristic	No Shoulder Condition (*n* = 3 006 366)	Shoulder Condition (*n* = 367)	*P* Value	Standardized Difference*
Missing	29 877 (99.327)	5(0.017)		
Vaccine received, *n* (%) §				
Influenza	2 283 969 (99.989)	260 (0.011)	0.022	−0.12
Hepatitis A	40 191 (99.993)	3 (0.007)	0.39	−0.050
Hepatitis B	97 762 (99.985)	15(0.015)	0.37	0.044
Human papillomavirus	48 938 (99.992)	4(0.008)	0.42	−0.047
Meningococcal	22 661 (99.991)	2 (0.009)	0.64	−0.026
Pneumococcal conjugate	101 870 (99.972)	29(0.028)	<0.001	0.20
Pneumococcal polysaccharide	105 903 (99.986)	15(0.014)	0.56	0.030
Tetanus, diphtheria, pertussis	211 092 (99.99)	22(0.010)	0.44	−0.046
Simultaneous vaccination	76 597 (99.979)	16(0.021)	0.028	0.099
Other vaccines	17 383(99.994)	1 (0.006)	0.44	−0.047
Influenza vaccine received, *n* (%) //				
Not specified	1165 (100)	0 (0)	0.71	−0.028
SD-IIV3	1 090 256(99.991)	98(0.009)	<0.001	−0.21
RIV3	181 (100)	0 (0)	0.88	−0.011
HD-IIV3	22 143(99.986)	3(0.014)	0.86	0.009
aIIV3	33 345 (99.985)	5(0.015)	0.64	0.023
SD-IIV4	1 182 381 (99.986)	162(0.014)	0.059	0.098
ccIIV4	40 960 (99.978)	9 (0.022)	0.072	0.080

aIIV3 = adjuvanted inactivated influenza vaccine trivalent; ccIIV4 = cell culture–based inactivated influenza vaccine quadrivalent; HD-IIV3 = high-dose inactivated influenza vaccine trivalent; IQR = interquartile range; RIV3 = recombinant influenza vaccine trivalent; SD-IIV3 = standard-dose inactivated influenza vaccine trivalent; SD-IIV4 = standard-dose inactivated influenza vaccine quadrivalent.

* Difference in means or proportions divided by SD; absolute standardized difference <0.10 is considered a negligible difference.

† Includes medical doctor, physician assistant, and nurse practitioner.

‡ Multiple vaccinations were given on the same arm on the same day by different vaccinators who had different types of credentials.

§ Vaccines coadministered with other vaccines in the same arm on the same day were not counted individually but counted only once in the “simultaneous vaccination” group.

// Influenza vaccine coadministered with other vaccines were included.