Published in final edited form as:

Ann Intern Med. 2020 August 18; 173(4): 253–261. doi:10.7326/M19-3176.

Risk for Subdeltoid Bursitis After Influenza Vaccination:

A Population-Based Cohort Study

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M19-3176.

Reproducible Research Statement: *Study protocol and statistical code:* Not available. *Data set:* The Vaccine Safety Datalink has a data sharing program administered by the National Center for Health Statistics Research Data Center. Information about how to access data from Vaccine Safety Datalink studies is available on the CDC website: www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/accessing-data.html.

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Abstract

Background: Subdeltoid bursitis has been reported as an adverse event after intramuscular vaccination in the deltoid muscle. Most published case reports involved influenza vaccine.

Objective: To estimate the risk for subdeltoid bursitis after influenza vaccination.

Design: Retrospective cohort study.

Setting: The Vaccine Safety Datalink, which contains health encounter data for 10.2 million members of 7 U.S. health care organizations.

Patients: Persons who received an inactivated influenza vaccine during the 2016–2017 influenza season.

Measurements: Potential incident cases were identified by searching administrative data for persons with a shoulder bursitis diagnostic code within 180 days after receiving an injectable influenza vaccine in the same arm. The date of reported bursitis symptom onset was abstracted from the medical record. A self-controlled risk interval analysis was used to calculate the incidence rate ratio of bursitis in a risk interval of 0 to 2 days after vaccination versus a control interval of 30 to 60 days, which represents the background rate. The attributable risk was also estimated.

Results: The cohort included 2 943 493 vaccinated persons. Sixteen cases of symptom onset in the risk interval and 51 cases of symptom onset in the control interval were identified. The median age of persons in the risk interval was 57.5 years (range, 24 to 98 years), and 69% were women. The incidence rate ratio was 3.24 (95% CI, 1.85 to 5.68). The attributable risk was 7.78 (CI, 2.19 to 13.38) additional cases of bursitis per 1 million persons vaccinated.

Limitation: The results may not be generalizable to vaccinations done in other types of health care settings.

Conclusion: Although an increased risk for bursitis after vaccination was present, the absolute risk was small.

Primary Funding Source: Centers for Disease Control and Prevention.

Subdeltoid bursitis, characterized by pain and loss of motion in the shoulder, has been reported as an adverse event after intramuscular vaccination in the deltoid muscle (1). Subdeltoid or subacromial bursitis, which we will refer to as “subdeltoid bursitis” or “bursitis,” is common, with a prevalence around 1% in the general U.S. population (2), and often develops as a result of injury or overuse. For many patients, rest and anti-inflammatory

medications can lead to symptom resolution within a few weeks, although physical therapy, steroid injections, or surgery may be used in refractory cases.

In 2012, the Institute of Medicine published a report on adverse effects of vaccines. Among other findings, the report concluded that "the evidence convincingly supports a causal relationship between the injection of a vaccine and deltoid bursitis" (1). Although it noted the lack of epidemiologic evidence for this relationship, it based this conclusion on published case reports of 16 patients with bursitis after intramuscular vaccine injection (1). The proposed mechanism by which vaccination could cause bursitis is injection of the vaccine into the bursa, either by injecting too close to the acromion process or by injecting through the deltoid muscle (3, 4). Since 2012, additional case reports have been published describing the relationship between intramuscular vaccination and subdeltoid bursitis (4–7). From 2012 to 2016, the number of claims for shoulder adverse events submitted to the National Vaccine Injury Compensation Program increased by 20-fold (8), suggesting an increased awareness, but population-based evidence is needed to understand how common these adverse events are or what risk factors may be involved. Most published case reports involved influenza vaccine (4, 5, 7–10), which is recommended each year for persons aged 6 months or older in the United States (11), where more than 160 million doses are distributed annually (12). Our objective was to enhance the rigor of epidemiologic evidence by estimating the risk for subdeltoid bursitis after influenza vaccination.

Methods

Study Overview

This was a retrospective cohort study using data from the Vaccine Safety Datalink, a collaborative project involving the Centers for Disease Control and Prevention (CDC) and several integrated health care delivery systems (sites) (13). This study used data from 7 sites, with a combined population of approximately 10.2 million members. We studied influenza vaccinations received from 1 September 2016 through 1 June 2017. We first used administrative health care data to identify the study population and then did manual medical record abstraction to collect additional information on presumptive bursitis cases. The study was approved by institutional review boards at the CDC and each participating site.

Study Sample

Eligibility criteria included receipt of an inactivated influenza vaccine (IIV) in the arm during the 2016–2017 influenza season, age 3 years or older on the date of vaccination, and continuous enrollment in the site's health care organization from at least 180 days before the IIV dose through 180 days after. For patients with multiple IIV vaccinations during the 2016–2017 influenza season, we included only the vaccination with the earliest date. We excluded children younger than 3 years because they are typically vaccinated in the lateral thigh (14). The enrollment requirement was to allow adequate time before the vaccination to detect preexisting shoulder conditions and after the vaccination for presentation and new bursitis diagnoses to be made. We excluded patients if laterality of vaccination or bursitis diagnosis could not be determined from administrative health care data; if they had International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM),

diagnostic codes for bursitis or related shoulder conditions in that arm before vaccination; or if they received any other vaccinations in the same arm in the 180 days after the IIV vaccination. Persons who received other vaccines on the same day were not excluded.

Outcome

Three ICD-10-CM diagnostic codes are used to indicate shoulder bursitis or a related shoulder bursa diagnosis (M75.5* [bursitis of shoulder], M71.31* [other bursal cyst, shoulder], and M71.81* [other specified bursopathies, shoulder]). These codes are side specific, indicating to which shoulder the diagnosis applies. Patients with any of these codes recorded during the 180 days after receipt of IIV for the arm that was vaccinated were presumptive cases.

We manually abstracted medical records for all presumptive cases at 5 sites, which each had fewer than 100 cases. We selected a random sample of 150 presumptive cases for medical record abstraction at the remaining 2 sites, which had a larger number than was feasible to review manually. We determined a priori that at least 225 charts would have to be abstracted to detect an incidence rate ratio (IRR) of 2.0 or greater with a power of 0.8 and α of 0.05. Our final number of charts abstracted allowed us to detect an IRR of 1.7 or greater (15, 16). We excluded presumptive cases if abstraction identified a miscode for the outcome or a rule-out diagnosis, there was evidence of a preexisting shoulder condition before vaccination in the medical records, or adequate medical records were not available.

On the basis of chart abstraction, we defined cases with 3 levels of diagnostic certainty: definite (bursitis diagnosis confirmed by ultrasonography, magnetic resonance imaging, or surgical findings, or the patient reported a positive response to a corticosteroid injection associated with a bursitis diagnosis), probable (bursitis diagnosis made or confirmed by a musculoskeletal specialty provider, including orthopedic surgeon, rheumatologist, physiatrist, or physical or occupational therapy provider), or possible (bursitis diagnosis made by any other provider).

Chart abstractors collected variables of interest not available in administrative data, including the credentials of the vaccinator; vaccination setting; patient height and weight; and patient statements about date of symptom onset, to what causes the patient attributed their symptoms, and when symptoms resolved. Chart abstractors collected information about symptom onset from up to 4 different medical encounters: the visit on the date of vaccination, the first visit in which the patient mentioned the shoulder symptoms, the first visit in which a bursitis diagnosis was assigned, and the first visit to a specialty provider. We reviewed the symptom onset statements for precision and consistency among visits. We classified symptom onset statements into 3 categories of precision: exact (a specific day was indicated), approximate (symptom duration was stated in definite units of time but did not specify an exact date [for example, “3 weeks”]), or vague (duration was stated using indefinite units of time, such as “a few weeks”). For records with approximate or vague statements, adjudicators assigned an estimated onset date by back calculating from the medical visit date at which the statement was documented.

Medical record abstraction data were collected and managed using REDCap electronic data capture tools (17, 18). The abstraction form is shown in the Supplement (available at Annals.org).

Statistical Analysis

We did a self-controlled risk interval analysis, which compared incidence of subdeltoid bursitis with symptom onset during a postvaccination risk interval versus incidence during a control interval (16, 19). We prespecified the risk interval as the first 3 days after IIV vaccination (days 0 to 2, where day 0 is the day of vaccination), which we selected on the basis of a prior case series of shoulder adverse events related to vaccine administration (8). We defined the control interval as days 30 to 60 after vaccination, which we selected to represent the background rate (that is, a time during which the outcome is not influenced by vaccination). The case ascertainment period of 180 days after vaccination ensured that persons with symptom onset during both the risk and control intervals would have adequate time to present for care and receive a bursitis diagnosis. We calculated the IRR and the Wald 95% CI using Poisson regression (GENMOD procedure) in SAS, version 9.4 (SAS Institute). The model independent variable was the number of cases occurring during the interval. The dependent variable was an indicator of risk or control interval. The offset term was the log of the number of person-days in each interval, which accounts for different interval lengths. Each person contributed person time to both intervals, thereby implicitly acting as their own control, and could only be counted as a case once during the follow-up.

To estimate the attributable risk, we first calculated the incidence rate in each interval as the number of cases divided by the number of vaccinated person-days in the interval. We used the Byar method to calculate the CIs of the difference between risk and control interval incidence rates and multiplied the results by the length of the risk interval. To account for random sampling of chart reviews done at 2 sites, we adjusted the vaccinated person-days by the chart-sampling fraction at each site.

We did sensitivity analyses to see how the strength of association would change with changes in risk or control intervals, levels of diagnostic certainty, or precision of symptom onset date information. We also performed an exploratory, non–self-controlled analysis of potential risk factors for vaccine-associated bursitis by comparing characteristics of cases with symptom onset during the risk interval with cases with symptom onset during the control interval using the Fisher exact and Kruskal–Wallis tests.

Role of the Funding Source

This study was funded by internal funds of the CDC. The authors had complete control over design, analysis, and the decision to submit the manuscript for publication.

Results

Cohort and Case Identification

Our cohort included 2 943 493 persons who received IIV during the 2016–2017 influenza season and met study eligibility criteria (Table 1). Among these, we identified 1098

presumptive cases of bursitis. We used random sampling to select 526 presumptive cases for medical record abstraction, of which 421 met the case definition for an incident diagnosis of subdeltoid bursitis (Figure). Bursitis symptom onset began after vaccination for 257 cases: 16 (6.2%) had symptom onset in the risk interval, 51 (19.8%) had symptom onset in the control interval, and 190 (74.0%) had symptom onset in neither prespecified interval (Appendix Figure, available at Annals.org). The distribution of cases by study site is shown in Table 2.

Case Description

The 421 cases of subdeltoid bursitis were classified as definite (n = 135 [32%]), probable (n = 44 [10.5%]), or possible (242 [57.5%]). All cases occurred in adults except for 6, which occurred in adolescents aged 14 to 17 years. The median number of days between reported symptom onset and the first medical visit for bursitis symptoms was 20 (range, 0 to 3653 days).

Characteristics of cases with symptom onset during the prespecified risk or control intervals are shown in Table 3. The median age of patients in the risk interval was 57.5 years (range, 24 to 98 years), and 68.8% were women. We did not observe any differences between cases in the risk interval and those in the control interval by sex, age, body mass index, race/ethnicity, vaccination setting, or laterality of the vaccinated arm. Almost half of the vaccinators for cases in the risk interval were medical assistants. Compared with cases in the control interval, those in the risk interval were more likely to be vaccinated by medical assistants than nurses (including registered nurses, licensed practical nurses, and licensed vocational nurses) (P = 0.052).

Risk Estimation

The self-controlled risk interval analysis found an increased risk for subdeltoid bursitis with symptom onset in the 3 days after vaccination compared with the 30 to 60 days after vaccination (IRR, 3.24 [95% CI, 1.85 to 5.68]). This corresponds to an attributable risk of 7.78 (CI, 2.19 to 13.38) excess cases of subdeltoid bursitis during the 3 days after vaccination per 1 million persons vaccinated. The association between influenza vaccination and subdeltoid bursitis remained elevated in all sensitivity analyses (Table 4).

Clinical Course

The median follow-up after vaccination for cases was 576 days (range, 189 to 781 days). Among definite cases in the risk interval, 4 had surgical procedures for bursitis or mentioned bursitis on surgical reports. The intervals from vaccination to surgery were 90, 115, 210, and 266 days. Four definite cases had findings of bursitis on magnetic resonance imaging at 11, 101, 167, and 217 days after vaccination. One definite case reported a positive effect of a corticosteroid injection in the affected shoulder. The 1 probable case was diagnosed with bursitis by an orthopedic surgeon. Resolution of symptoms was documented in the medical record for 2 of the 16 (12.5%) risk interval cases (by 62 and 207 days after symptom onset). A similar proportion of control interval cases (5 of 51 [9.8%]) had symptom resolution documented (by days 81, 106, 136, 190, and 322 after symptom onset). The 14 risk interval cases without documented resolution of symptoms had a median time to the last visit with

persistent shoulder symptoms of 386 days (range, 21 to 781 days), whereas the median for control interval cases was 95 days (range, 4 to 690 days).

Patient's Attribution of the Cause of Bursitis Symptoms

Documentation in medical records showed that 12 case patients specifically mentioned the influenza vaccine as being the cause of their symptoms (Appendix Table, available at Annals.org). Nine of the 16 case patients (56%) in the risk interval attributed their injuries to vaccination; 2 of the 9 voiced specific concerns about the technique by which the vaccine was administered. One patient expressed that the vaccination was given too high, and the other that it was too deep. Three case patients outside of the risk interval also attributed their shoulder symptoms to vaccination: 2 identified their symptom onset outside of the risk interval (at days 3 and 5), and 1 did not have specific statements about symptom onset in the medical record. The median time from reported symptom onset to the first medical visit among patients attributing their symptoms to vaccination was 21 days (range, 3 to 144 days), which was similar to that for control interval cases (median, 22 days; range, 0 to 123 days) ($P = 0.90$).

Discussion

We are unaware of any other epidemiologic studies estimating the risk for subdeltoid bursitis associated with IIV. Using data from the Vaccine Safety Datalink, we estimated that an additional 7.78 cases of bursitis occurred during the 3 days after vaccination for every 1 million persons vaccinated with IIV.

Almost all cases of bursitis after vaccination in our study occurred in adults. The youngest case patient with symptom onset during the risk interval was 24 years old. This is consistent with previous case reports of shoulder dysfunction after vaccination (7–9). In general, soft tissue shoulder conditions, such as bursitis, are uncommon in pediatric populations (20). Previously proposed explanations for the lack of shoulder adverse events after vaccination among children include less extensively developed bursae (21); differences in vaccination technique, such as "bunching" of subcutaneous and deltoid tissue to increase the distance between skin and subdeltoid bursa (21, 22); a lower likelihood of preexisting asymptomatic shoulder conditions that can be aggravated by an inflammatory reaction related to vaccination; and increased vascularity of musculoskeletal structures at younger ages (23). Three published reviews of case reports of shoulder adverse events related to vaccination showed a female predominance (7–9). In our study, women represented most cases in the risk interval. We did not observe a statistically significant difference in risk for women compared with men, but this comparison had low statistical power.

Previous case reports have frequently identified in-appropriate site of vaccine injection (that is, too high) as a suspected cause of vaccine-related subdeltoid bursitis and other shoulder adverse events (5, 6, 8, 10, 24, 25). Two case patients in our study reported potential errors in proper vaccination technique. However, in our study, we could not assess vaccination technique or the vaccinators' prior vaccination training or experience, and we cannot conclude from our data that improper technique was a factor in the development of bursitis. Our finding that case patients with symptom onset during the risk interval were more likely

to have been vaccinated by medical assistants versus registered nurses and licensed practical or vocational nurses deserves further assessment, although this should be interpreted with caution because of the relatively small number of cases involved in this comparison. The Commission on Accreditation of Allied Health Education Programs, an accreditation system for medical assistant training programs, lists selection of proper anatomical sites and administration of parenteral medication as skills that must be demonstrated, but it does not specify the number of hours of instruction in these skills that programs must provide (26). State laws vary with regard to credentials and number of training hours required for vaccinators. Regardless of their credential or state, a person administering a vaccine should use proper technique. Education programs and trainings that focus on proper vaccine handling and administration, such as those offered by the CDC, are available (27, 28).

The National Vaccine Injury Compensation Program added shoulder injury related to vaccine administration to the list of compensable conditions in 2017. To be eligible for compensation for this injury, symptoms must begin within 48 hours of vaccination (29). In our study, 12 patients with bursitis attributed it to vaccination; 3 reported onset outside this specified risk interval, including 2 who reported symptom onset at 3 and 5 days. Although most shoulder vaccine adverse event cases in the literature reported symptom onset within this 48-hour interval (4–9, 24, 29, 30), there are previous reports of events considered to be vaccine-associated with more prolonged symptom onset intervals (7, 9, 24).

A strength of the self-controlled risk interval design is that by including only vaccinated cases, which act as their own control, many potential sources of bias are implicitly controlled for. However, bias could be introduced if either the patient or the provider's knowledge of the vaccination history led to a differential rate of bursitis diagnosis or statement of symptom onset between risk and control intervals. We did not observe any indications in our data that providers approached cases differently by date of reported onset. Cases in the 2 intervals had a similar distribution of case classification levels, which indicates similar utilization of diagnostic imaging and specialty care. We also found no statements in medical records to indicate that any providers believed vaccination was the cause of a patient's bursitis. The variation in days from reported symptom onset to presentation was also similar for cases in both intervals; however, we relied on the patient's self-reported date of symptom onset. The degree to which the patient's perception of vaccination (or another discrete event) as the cause of symptoms could lead to misclassification of the onset date is unknown, making it a potential source of residual bias.

A negative control outcome analysis (for example, bursitis risk in the unvaccinated arm) could have helped to detect potential residual bias, but we were unable to do this analysis because it would have required many additional chart reviews (1398 patients had a bursitis diagnosis code after vaccination for the unvaccinated arm compared with 1098 for the vaccinated arm). A negative control analysis requires comparability between factors associated with the primary and control outcomes. In this study, case ascertainment factors related to health care use or diagnosis would probably be similar for the unvaccinated arm, but comparability is less certain for patient-related factors, such as influence of preexisting conditions on the choice of arm in which to receive the vaccine and influence of vaccination on patient-reported symptom onset date.

This study has other potential limitations. Our case-finding approach used bursitis diagnostic codes, followed by confirmation through chart review, which was aimed at high specificity for subdeltoid bursitis but may have had low sensitivity if other patients with bursitis were only given generic codes, such as shoulder pain. If our case-finding approach did not detect all true bursitis cases in our study population, then the attributable risk could be underestimated. Given that we examined bursitis only after IIV, generalizability to other intramuscular vaccinations should be done with caution and represents a direction for future research. We examined influenza vaccinations given within integrated health care networks; this excluded vaccinations done in pharmacies, which previous reviews of shoulder adverse events after vaccination identified as a frequent location of implicated vaccination (8, 31) and it may not be possible to generalize our findings to other vaccination settings in relation to staff training or quality control measures used. Our analysis of potential risk factors was exploratory and limited by the relatively small number of cases, which precluded doing a multivariate analysis; potential risk factors that have been suggested in the literature should be examined more thoroughly in future studies.

In public health and individual patient decision making, the risks for adverse events, such as subdeltoid bursitis, must be weighed against the benefits of vaccination to prevent influenza infection and its complications. Influenza infection causes an estimated 9 to 45 million illnesses in the United States annually, with 12 000 to 61 000 deaths. During the 2016–2017 influenza season, the period of this study, the CDC estimated that influenza vaccination prevented more than 5.2 million illnesses, 2.6 million medical encounters, 72 000 hospitalizations, and 5000 deaths (32).

We identified a small risk for subdeltoid bursitis with new symptom onset after injection of an influenza vaccine. This study provides epidemiologic evidence of an association that was previously supported by clinical evidence from case reports. Strategies to prevent this adverse event, which may include improved education and training about proper vaccination technique, need to be identified and implemented.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment:

The authors thank Beth Hibbs for her insights and expertise about shoulder adverse events after vaccination and the following persons for their contributions to data collection and medical record abstraction: Radha Bathala, Kate Burniece, Jennifer Covey, Bernie Dizon, Joy Gel-fond, Kayla Hanson, Stacy Harsh, Linda Heeren, Claire Jang, Sunhea Kim, Anna Lawless, Kerresa Morrissette, Denison Ryan, Karen Schenk, and Erica Scotty. The authors also thank the following Vaccine Safety Datalink sites for participation in this study: HealthPartners, Kaiser Permanente Colorado, Kaiser Permanente Northern California, Kaiser Permanente Northwest, Kaiser Permanente Southern California, Kaiser Permanente Washington, and the Marshfield Clinic.

Financial Support:

By internal funds of the CDC. The Vaccine Safety Datalink sites are funded through a contract from the CDC.

Appendix

Appendix Table.

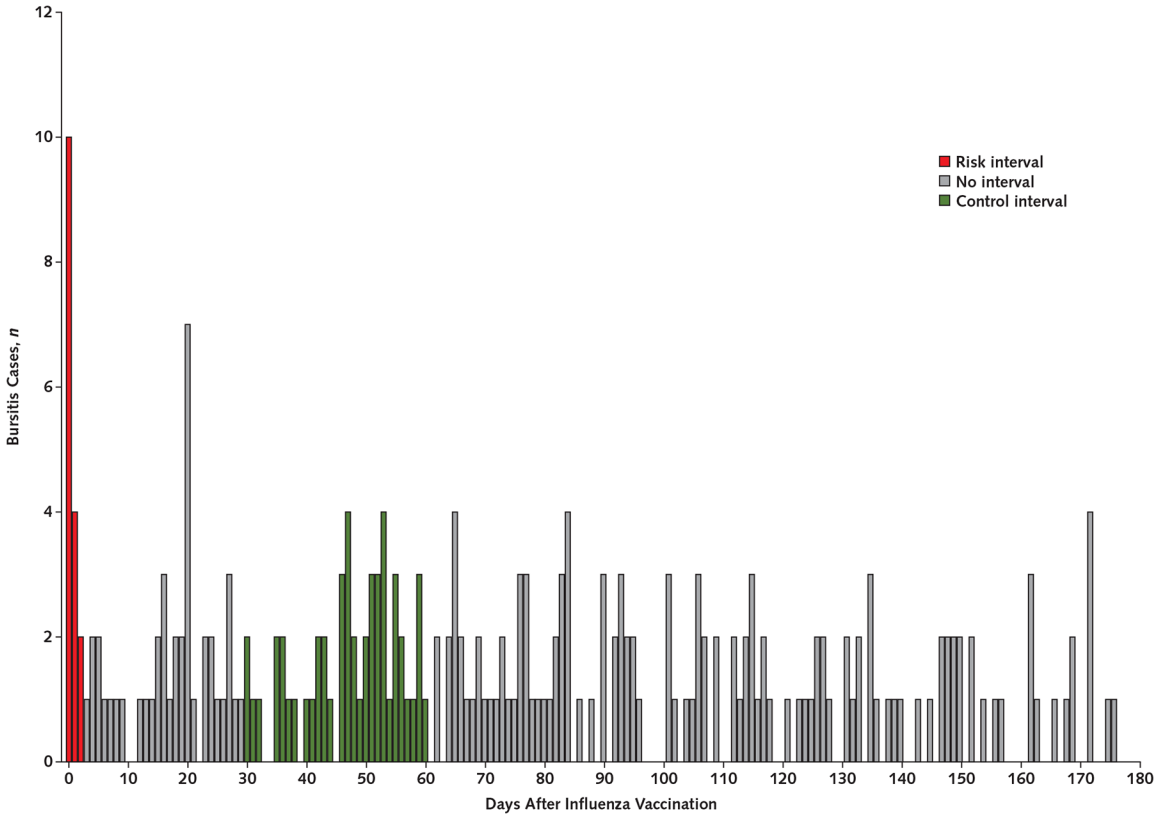
Narrative Details of Cases in Which the Patient Attributed Bursitis Symptom Onset to the Influenza Vaccination

Case Number	Age, *y*	Race	Sex	Vaccinated Arm	Location of Vaccination	Vaccinator's Credentials	Onset	Initial Symptoms	Treatments	Case Classificatio
Cases with symptom onset during the risk interval										
1	24	White	Male	Left	Physician's office	Medical assistant	Day 0: "since flu shot"	Pain	PT, home exercises, topical analgesics, and steroid injection	Definite
2	62	Unknown	Female	Left	Flu vaccine drive	Registered nurse	Day 0: "pain started after flu shot"	Pain	Warm/cool compresses, steroid injection, PT, home exercises, and surgery	Definite
3	34	White	Female	Left	Physician's office	Licensed practical nurse	Day 0: "after flu shot"	Pain, radiating pain, and reduced range of motion	Analgesics, PT, and home exercises	Possible
4	44	White	Female	Left	Work	Registered nurse	Day 0: "about 2 hours after flu shot, pain got progressively worse"	Pain	Narcotics, PT, and steroid injection	Definite
5	87	White	Female	Right	Physician's office	Medical assistant	Day 0: "since she had a flu shot"	Pain, radiating pain, and reduced range of motion	Ice and PT	Possible
6	72	White	Male	Right	Physician's office	Licensed practical nurse	Day 0: "since he got the flu shot"	Pain and reduced range of motion	Ice, home exercises, steroid injection, and surgery	Definite
7	56	White	Female	Right	Flu vaccine drive	Medical assistant	Day 1: "the next day she had pain in her shoulder"	Pain	NSAIDs, steroid injection, topical analgesics, PT, and surgery	Definite
8	48	Black	Female	Left	Unknown	Licensed practical nurse	Day 0: "had swelling, still sore"	Pain and swelling	Home exercises	Possible
9	70	White	Female	Left	Flu vaccine drive	Medical assistant	Day 0: "it was very	Pain	Home exercises	Possible

Case Number	Age, *y*	Race	Sex	Vaccinated Arm	Location of Vaccination	Vaccinator's Credentials	Onset	Initial Symptoms	Treatments	Case Classificatio
							painful that night"			
Cases with symptom onset outside the risk interval										
10	41	White	Female	Left	Physician's office	Licensed practical nurse	Unknown	Pain and reduced range of motion	NSAIDs	Possible
11	51	White	Female	Right	Physician's office	Licensed practical nurse	Day 5	Pain, tingling, and numbness	NSAIDs, steroid injection, and surgery	Definite
12	65	White	Female	Right	Physician's office	Licensed practical nurse	Day 3: "significant stiffness 3 days after flu vaccine"	Pain, radiating pain, reduced range of motion, numbness, and tingling	NSAIDs, steroid injection, and PT	Definite

NSAID = nonsteroidal anti-inflammatory drug; PT = physical therapy.

*As determined by the study case definition. See text for complete definition.



Appendix Figure.
Day of subdeltoid bursitis symptom onset after vaccination.

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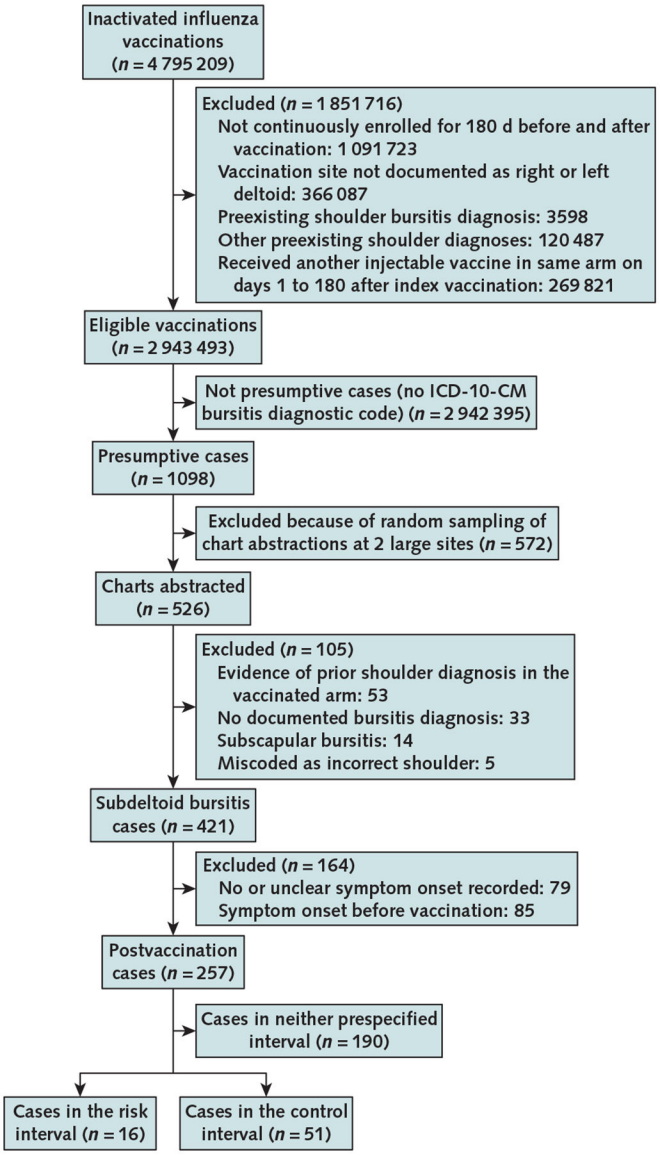

Figure.

Flow diagram showing cohort eligibility, case finding, and case confirmation.

The prespecified primary analysis used a risk interval of 0 to 2 days after vaccination and a control interval of 30 to 60 days after vaccination. ICD-10-CM = International Classification of Diseases, 10th Revision, Clinical Modification.

Table 1.

Characteristics of the Vaccinated Study Population (n = 2 943 493)*

Characteristic	Value, *n* (%)
Vaccine Safety Datalink site	
1	1 315 178 (44.7)
2	1 108 120 (37.7)
3	157 714 (5.4)
4	136 560 (4.6)
5	119 504 (4.1)
6	60 176 (2.0)
7	46 241 (1.6)
Sex	
Female	1 646 393 (55.9)
Male	1 297 045 (44.1)
Unknown	55 (0)
Age	
3–8 y	192 099 (6.5)
9–17 y	313 798 (10.7)
18–49 y	882 750 (30)
50–64 y	696 675 (23.7)
≥65 y	858 171 (29.1)
Influenza vaccine received	
SD-IIV3	1 766 195 (60)
SD-IIV4	724 522 (24.6)
HD-IIV3	340 493 (11.6)
ccIIV4	106 166 (3.6)
RIV3	508 (0)
aIIV3	75 (0)
Not specified	5634 (0.2)
Vaccinated arm	
Left	2 323 790 (78.9)
Right	619 703 (21.1)
Number of vaccines received in the vaccinated arm on day 0	
1 (i.e., influenza vaccine only)	2 802 251 (95.2)
≥2	141 242 (4.8)

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

*The cohort included 2 943 493 vaccinated persons.

Table 2.

Number of Presumptive Cases and Chart Abstraction–Confirmed Cases, by Study Site

Vaccine Safety Datalink Site	Vaccinated Cohort, *n*	Presumptive Cases, *n* [*]	Charts Abstracted, *n* [†]	Chart-Confirmed Cases, *n*	Cases With Symptom Onset During the Risk Interval, *n* [‡]	Cases With Symptom Onset During the Control Interval, *n* [‡]
1	1 315 178	574	150	125	4	14
2	1 108 120	298	150	128	4	17
3	157 714	57	57	52	1	7
4	136 560	72	72	51	0	5
5	119 504	44	44	37	3	5
6	60 176	46	46	27	4	3
7	46 241	7	7	1	0	0
Total	2 943 493	1098	526	421	16	51

[*] These patients had an International Classification of Diseases, 10th Revision, Clinical Modification code for shoulder bursitis in the vaccinated arm.

[†] Random sampling of presumptive cases was done at the 2 large sites.

[‡] The prespecified primary risk interval was postvaccination days 0 through 2, and the control interval was postvaccination days 30 through 60.

Table 3.

Characteristics of Cases With Symptom Onset During the Risk and Control Intervals

Characteristic	Risk Interval Cases (*n* = 16)	Control Interval Cases (*n* = 51)	*P* Value
Case classification, *n* (%)			
Definite	6 (37.5)	21 (41.2)	0.79
Probable	1 (6.3)	5 (9.8)	>0.99
Possible	9 (57.2)	25 (49.0)	0.61
Sex, *n* (%)			0.167
Female	11 (68.8)	25 (49.0)	
Male	5 (31.2)	26 (51.0)	
Median age (range), *y*	57.5 (24–98)	60 (31–87)	0.51
Median body mass index (range), *kg/m*^{2}	28.1 (17.0–51.7)	30.2 (22.2–56.4)	0.23
Race/ethnicity, *n* (%) *			
Asian	2 (12.5)	2 (3.9)	0.48
Black	1 (6.3)	1 (2.0)	0.85
Hawaiian/Pacific Islander	—	1 (2.0)	>0.99
Hispanic	—	12 (23.5)	0.053
White	12 (75.0)	35 (68.6)	0.88
Other	1 (6.3)	3 (5.9)	>0.99
Influenza vaccine received, *n* (%)			
SD-IIV3	4 (25.0)	27 (52.9)	0.051
HD-IIV3	5 (31.3)	14 (27.5)	0.99
SD-IIV4	7 (43.7)	9 (17.6)	0.079
ccIIV4	—	1 (2.0)	>0.99
Number of vaccines received on day 0, *n* (%)			
1 (i.e., influenza vaccine only)	16 (100)	47 (92.0)	0.65
2	—	3 (6.0)	0.87
3	—	1 (2.0)	>0.99
Number of vaccines received in the influenza-vaccinated arm on day 0, *n* (%)			>0.99
1 (i.e., influenza vaccine alone)	16 (100)	50 (98.0)	
2	—	1 (2.0)	

Characteristic	Risk Interval Cases (*n* = 16)	Control Interval Cases (*n* = 51)	*P* Value
Vaccinator credentials, *n* (%)			
Medical assistant	7 (43.8)	8 (15.7)	0.052
Licensed practical nurse/licensed vocational nurse	6 (37.5)	27 (52.9)	0.56
Registered nurse	3 (18.7)	14 (27.5)	0.73
Nurse practitioner	—	1 (2.0)	>0.99
Unknown	—	1 (2.0)	>0.99
Vaccinated arm, *n* (%)			>0.99
Left	11 (68.8)	35 (68.6)	
Right	5 (31.2)	16 (31.4)	
Vaccination setting, *n* (%)			
Clinic/physician's office	9 (56.3)	25 (49.0)	0.61
Flu vaccine clinic/booth	5 (31.2)	16 (31.4)	0.99
Urgent care	—	1 (2.0)	>0.99
Work	1 (6.3)	—	0.48
Unknown	1 (6.3)	9 (15.5)	0.50
Patient's statement about cause of bursitis, *n* (%)			
Attributed to vaccination	9 (56)	0 (0)	<0.001
Attributed to something otherthan vaccination	4 (25)	20 (39)	0.38
No attribution documented	3 (19)	31 (61)	0.003

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.

*Three persons in the control interval reported more than 1 race/ethnicity.

Table 4.

Self-controlled Risk Interval Primary and Sensitivity Analyses With Corresponding Attributable Risk Estimates

Case Classification Categories*	Symptom Onset Precision Categories†	Risk Interval			Control Interval			Incidence Rate Ratio (95% CI)	Attributable Risk (95% CI)‖
		Postvaccination Period, *d*‡	Cases, *n*	Incidence Rate§	Postvaccination Period, *d*	Cases, *n*	Incidence Rate§		
Prespecified primary analysis									
All	All	0 to 2	16	3.75	30 to 60	51	1.16	3.24 (1.85 to 5.68)	7.78 (2.19 to 13.38)
Sensitivity analyses for interval lengths									
All	All	0 to 5	21	2.46	30 to 60	51	1.16	2.13 (1.28 to 3.54)	7.83 (1.23 to 14.43)
All	All	0 to 7	23	2.02	30 to 60	51	1.16	1.75 (1.07 to 2.86)	6.92 (−0.16 to 14.00)
All	All	0 to 2	16	3.75	30 to 180	181	0.84	4.45 (2.67 to 7.42)	8.73 (3.20 to 14.25)
All	All	0 to 5	21	2.46	30 to 180	181	0.84	2.92 (1.86 to 4.59)	9.71 (3.35 to 16.07)
All	All	0 to 7	23	2.02	30 to 180	181	0.84	2.40 (1.55 to 3.70)	9.43 (2.75 to 16.12)
Sensitivity analyses for case classification levels of diagnostic certainty									
Definite	All	0 to 2	6	1.41	30 to 60	21	0.48	2.95 (1.19 to 7.31)	2.79 (−0.64 to 6.22)
Definite and probable	All	0 to 2	7	1.64	30 to 60	26	0.59	2.78 (1.21 to 6.41)	3.15 (−0.56 to 6.86)
Sensitivity analyses for symptom onset statement precision									
All	Exact	0 to 2	7	1.64	30 to 60	12	0.27	6.03 (2.37 to 15.31)	4.11 (0.43 to 7.78)
All	Exact and approximate	0 to 2	14	3.28	30 to 60	44	1.00	3.29 (1.80 to 6.00)	6.85 (1.62 to 12.09)
Sensitivity analysis for influenza vaccine given without other vaccines in the same arm									
All	All	0 to 2	16	3.94	30 to 60	50	1.19	3.31 (1.88 to 5.81)	8.25 (2.37 to 14.12)

*Cases were classified into 3 levels of diagnostic certainty: definite, probable, and possible.

†Statements about symptom onset in the medical record were classified into 3 categories of precision: exact, approximate, and vague.

‡Day 0 is the day of vaccination.

[§] The incidence rate is per 1 million person-days, calculated using the number of people vaccinated, adjusted for the chart sampling rate.

[‖] The attributable risk is the number of excess cases during the corresponding risk interval per 1 million persons vaccinated.