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Anthrax Vaccine and the Risk of Rheumatoid Arthritis and Systemic Lupus Erythematosus in the U.S. Military: A Case–Control Study

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Abstract

U.S. military personnel assigned to areas deemed to be at high risk for anthrax attack receive Anthrax Vaccine Adsorbed (AVA). Few cases of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) have been reported in persons who received AVA. Using a matched case–control study design, we assessed the relationship of RA and SLE with AVA vaccination using the Defense Medical Surveillance System. We identified potential cases using International Classification of Diseases, 9th Revision, Clinical Modification codes and confirmed cases with medical record review and rheumatologist adjudication. Using conditional logistic regression, we estimated odds ratios (OR) for AVA exposure during time intervals ranging from 90 to 1,095 days before disease onset. Among 77 RA cases, 13 (17%) had ever received AVA. RA cases were no more likely than controls to have received AVA when looking back 1,095 days (OR: 1.03; 95% confidence interval [CI]: 0.48–2.19) but had greater odds of exposure in the prior 90 days (OR: 3.93; 95% CI: 1.08–14.27). Among the 39 SLE cases, 5 (13%) had ever received AvA; no

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This study was approved by institutional review boards at the Centers for Disease Control and Prevention and the Department of Defense (Department of the Navy [National Naval Medical Center], Department of the Army [Walter Reed Army Medical Center], Department of the Air Force [Wilford Hall Ambulatory Surgical Center], and the Uniformed Services University of Health Sciences).

significant difference in receipt of AVA was found when compared with controls (OR: 0.91; 95% CI: 0.26–3.25). AVA was associated with recent onset RA, but did not increase the risk of developing RA in the long term.

INTRODUCTION

Anthrax is an infectious disease caused by the bacterium *Bacillus anthracis*, which can be used as a bioweapon. Anthrax Vaccine Adsorbed (AVA) was licensed in the United States in 1970 for the prevention of anthrax. The first large-scale use of AVA was in 1991 for U.S. military personnel deployed during the Persian Gulf War. In 1998, the U.S. military started the Anthrax Vaccine Immunization Program to protect U.S. military active duty and reserve members as well as emergency-essential civilians assigned to areas deemed to be at high risk for anthrax attack.[1] From March 1998 through September 2005, nearly 5.6 million doses of AVA were administered to 1.5 million U.S. military personnel.[2] Service member and public concerns about the safety of AVA led to epidemiologic studies of the association of AVA with various medical conditions, yet no increased risks have been identified.[2] One concern was about arthralgia following vaccination, and in particular, 1 case of rheumatoid arthritis (RA) and 2 cases of systemic lupus erythematosus (SLE) were reported in U.S. military personnel.[3,4]

RA and SLE are chronic inflammatory autoimmune diseases that share some clinical and laboratory features along with the other connective tissue diseases. The exact etiology of these diseases is unknown, though they are believed to result from a complex interplay of genetic, environmental, and hormonal factors. Various infectious and noninfectious environmental exposures have been proposed as possible triggers of the disease process, including vaccines. Case reports of new-onset RA and SLE following receipt of various types of vaccines date back to the 1940s.[3–9] Reports have involved hepatitis B (hep B),[8,9] influenza,[7] rubella,[6] tetanus,[10] rabies,[10] and anthrax vaccines,[4] though no association has been confirmed in population-based epidemiologic studies to date.[11]

In response to the case reports of RA and SLE following AVA in military personnel, the objective of our study was to assess the relationship between those two diseases following vaccination with AVA. RA and SLE are both diffuse connective tissue diseases that share some similar features but are distinct and occur with different epidemiology, and therefore are examined separately.

METHODS

Study Population and Design

The study population was drawn from the Defense Medical Surveillance System (DMSS) database. The DMSS is a longitudinal surveillance database with current and historical data for military personnel since 1990.[12] DMSS continuously captures a range of information including immunizations, inpatient and outpatient medical conditions coded using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), demographic characteristics, military personnel data, and deployment-related information.

Medical encounter data are most comprehensive for active duty personnel. We performed a case–control study, and selected subjects from military personnel who were on active duty at any time during the period from January 1, 1998 through December 31, 2005.

Case Identification, Validation, and Classification

Case identification involved the following steps: (1) identification of all personnel with a first time ICD-9-CM code for RA or SLE in any inpatient or outpatient setting in the electronic database (including codes for RA and RA variants: 714.0, 714.1, 714.2, 714.81, and the code for SLE: 710.0); (2) review of the preselected individual's chart, if available at either the National Personnel Records Center, St. Louis, Missouri, or the respective Military Treatment Facility (MTF); (3) medical record abstraction to obtain clinical, laboratory, and radiology information; and (4) medical record review and case adjudication by rheumatologist clinical reviewers (JBH, MPK, PJP, and WRG). Medical records were abstracted up to 3 years before the date of diagnosis or back to the enlistment date for those enlisted <3 years, and up to 1 year following the date of diagnosis.

The de-identified disease-specific abstracted information was provided to the rheumatologist clinical reviewers to validate and classify the cases according to the 1987 revised American Rheumatology Association (ARA) criteria for the classification of RA and the modification to the 1982 revised criteria for the classification of SLE.[13–15] Cases were classified as "probable—fulfills criteria," "probable—does not fulfill criteria," or "unconfirmable" according to the case definitions in Table I. Cases were classified as "probable—does not fulfill criteria" when the patient had an established diagnosis of the disease in the medical record, but the documentation available for abstraction was either not complete or did not include a statement of all the specific criteria present. If the two primary reviewers disagreed on the diagnosis, the case was reviewed by a third reviewer. The clinical reviewers were blinded to the vaccination status of the subjects. Only the cases classified as "probable—fulfills criteria" or "probable—does not fulfill criteria" were included in our analyses.

The clinical reviewers identified the cases' disease onset date based on the medical record abstraction information. This date was used as the index date for the study. Controls were randomly selected from among active duty military personnel who never had any of the ICD-9-CM codes recorded in the DMSS for RA, SLE, other diffuse connective tissue diseases, or other conditions or symptoms that could represent early undiagnosed forms of these diseases (ICD9 codes in Tables AI and AII of the Appendix). Each case was individually matched to three controls on sex, age, service branch, and calendar time of beginning under medical surveillance. For one case, only one matched control could be identified.

Vaccine Exposure

History of vaccination with AVA and other vaccines during military service was retrieved from the DMSS. During our study period, the originally licensed AVA administration schedule was followed, consisting of a 6-dose priming series of 0.5-mL subcutaneous injections given at 0, 2, and 4 weeks, and 6, 12, and 18 months followed by annual boosters thereafter. A biologically plausible time interval from a putative environmental exposure

(i.e., vaccine) to the onset of RA or SLE is not known, so we examined exposure to AVA during exposure intervals previously used to assess RA following vaccinations.[16] Because AVA is given as a multidose series and risk could potentially be related to the number of doses received, we also assessed the number of doses received in each exposure interval as well as the total number of doses received before the index date. In addition, we compared those who had received at least 3 doses of the priming series with those who had not.

Statistical Analysis

We used conditional logistic regression models to estimate the matched odds ratio (mOR) comparing the odds of the cases having been vaccinated to the odds of vaccination in the controls. RA and SLE were analyzed separately. Confounding variables were identified using directed acyclic graphs. In addition to sex, age, and service branch, which were controlled for via matching, deployment status was also a confounder and was included in the multivariable models. We attempted to assess effect measure modification between AVA and the other types of vaccines previously speculated to be associated with RA (inactivated influenza vaccine, measles–mumps–rubella combination vaccine [MMR], hep B vaccine, tetanus–diphtheria vaccine [Td], or tetanus–toxoid [TT] vaccine), but the number of individuals exposed to the various combinations of these vaccines during the same exposure intervals as AVA was low and did not provide adequate statistical power (data not shown). We performed the analysis using SAS software version 9.3 (SAS Institute Inc., Cary, North Carolina).

RESULTS

In the DMSS database, we identified 5,049 individuals with one of the RA ICD 9-CM codes and 1,646 with the SLE code, including 23 with codes for both diseases. Medical record abstraction was completed for 211 patients whose adjudicated case classification was: RA (n = 133), SLE (n = 81), both RA and SLE (n = 3). Among these, 77 were determined to be “probable” RA cases (92.2% fulfilled criteria) and were matched to 229 controls, and 39 were determined to be “probable” SLE cases (71.8% fulfilled criteria) and were matched to 117 controls (Table II). One individual was determined to be a “probable” case of both RA and SLE. The final study population size was dependent on the resources available for case medical record abstraction, which resulted in a number of cases below the goal size of 260 “probable” cases for each disease that had been calculated a priori to be needed to achieve a statistical power ≥80% to detect an OR of ≥1.6. Our sample was sufficiently powered (80%) to detect an OR > 2.2 for RA and an OR > 3.1 for SLE.

The majority of RA cases were men (67.5%), whereas the majority of SLE cases were women (71.8%). RA cases were somewhat evenly distributed by age at onset, with the largest portion in the 25- to 34-year-old range (38.9%), whereas the age at onset for SLE cases tended to be younger, with most in the 18- to 24- year-old range (53.8%). RA cases were most frequently non-Hispanic white (68.8%), whereas SLE cases were most frequently non-Hispanic black (43.6%).

RA Analysis

Compared with controls, fewer individuals with RA ever received a dose of AVA during their military service before the index date (16.9% vs. 22.3%; Table II). The number of days between receipt of the most recent dose of AVA and the index date was shorter for the RA cases (median 55 [interquartile range: 21–258; range: 5–1,753]) than for controls (median 380 [interquartile range: 141–908; range: 7–2,030]). When examining the odds of having received AVA during each specified exposure interval, we found cases were more often exposed to AVA within the 90 days before the index date than were controls (mOR: 3.93; 95% confidence interval [CI]: 1.08–14.27; Table III). As the length of the exposure interval increased, the OR for AVA exposure consistently decreased from 2.21 (95% CI: 0.75–6.52) for the 180-day interval to 1.03 (95% CI: 0.48–2.19) for the 1,095-day interval. Only the result for the 90-day interval was statistically significant, and the power to detect the OR of 3.93 was determined post hoc to be 99%. Among the 7 cases vaccinated during the 90-day exposure interval, 6 only received 1 dose during that interval but it was after the first 3 doses of the priming series for 5 of them (fourth dose, n =1; fifth dose, n = 2; sixth dose, n =1; seventh dose, n = 1). One case received the first 3 doses of the AVA priming series during the 90-day interval, compared with 3 of the 8 controls. Half of the 8 controls received only 1 AVA dose during the 90-day exposure interval (first dose, n = 1; second dose, n =1; fourth dose, n = 2). One control received the second and third AVA priming doses during the 90-day exposure interval.

When assessing the number of AVA doses received during each of the five exposure intervals, we found no significant difference between cases and controls (Table III and Fig. 1). When comparing the total number of AVA doses ever received vs. receiving no doses of AVA, we found no significant differences between cases and controls for any number of doses from 1 through 7 (Table III). Cases were less likely than controls to have received 3 or more doses compared to less than 3 doses (OR: 0.56; 95% CI: 0.25–1.25) though this was not statistically significant. In addition, among those who had received at least 3 AVA doses, the difference was not significant between cases and controls in the median number of days from receiving the first dose of AVA and the index date (cases: 787 days vs. controls: 817 days, p = 0.83).

SLE Analysis

Among the 39 SLE cases, 5 (12.8%) had ever received a dose of AVA compared with 19 (16.2%) of the 117 controls. Because of the small sample size for the SLE analysis, we were unable to assess the OR for each exposure interval. However, we did look at the odds of ever having received AVA, adjusting for deployment status, and found no association (mOR: 0.91; 95% CI: 0.26–3.25). The mean number of total AVA doses ever received before the index date was slightly lower among cases, but not significantly different from the controls (Table II). The number of days between receipt of the most recent dose of AVA and the index date was longer for SLE cases (median 1,001 [interquartile range: 593–1,968; range: 577–2,115]) than for controls (median: 243 [interquartile range: 113– 604; range: 14–2,074]).

DISCUSSION

In this case–control study, we found no association between RA and SLE and having ever received AVA, or with the number of doses of AVA received. Moreover, those diagnosed with RA or SLE were less frequently exposed to AVA than their matched controls and received fewer total doses of AVA before the onset of their disease. Yet, we identified an increased risk of new-onset RA associated with having received AVA within 90 days before disease onset. The majority of cases (71%) who received AVA within the 90 days before disease onset received more than the first 3 doses of priming series (i.e., fourth to seventh dose), whereas only 2 (25%) of the controls received a fourth dose of the priming series. As the vaccine exposure interval increased from 90 days up to the longest exposure interval we examined of 1,095 days, the OR consistently trended down toward 1, indicating no difference in risk over the longer term for those persons who received AVA. This pattern suggests that exposure to AVA might hasten the onset of RA in some individuals, but eventually, those individuals would have developed RA as a result of exposure to other factors, regardless of receipt of AVA.

In the general population, the incidence of RA has been estimated to be 300 to 500 per 1 million persons per year, whereas for SLE, it is 25 to 100 per 1 million person-years.[17] In the military population represented in the DMSS database, we found a larger number of persons with an RA diagnosis code than with an SLE diagnosis code as expected. We also observed a difference in age distribution of disease onset between RA and SLE cases in our adjudicated study population, which was expected because the incidence of RA increases with age, peaking at 75 to 84 years old, whereas SLE incidence peaks in middle age.[18,19] In the general population, RA has a slight female predominance (2:1), whereas SLE has a strong female predominance (9:1).[19,20] In our study population, which was derived from the U.S. military population which is majority male, most of the RA cases occurred in males and most SLE cases occurred in females, which is consistent with what would be expected based on the differences in the sex-specific incidence rates between the two diseases in the general population. Although the military population does not resemble the age and sex distribution of the general population, our study population is representative of persons who are most likely to receive the AVA vaccine, as the vast majority of AVA administered in the United States is given to military personnel.

As with other autoimmune diseases, certain genes in the HLA complex have been associated with increased or decreased risk of developing the diffuse connective tissue diseases, disease severity, response to pharmacological therapy, and prognosis. The specific haplotypes and subhaplo-types conferring risk or protection appear to vary by disease; however, no single gene completely accounts for increased genetic risk as multiple genes are likely involved.[21,22] Among persons genetically susceptible to developing RA, it is believed an external factor is needed to trigger disease onset. It is unlikely that all cases can be attributed to a single type of trigger; rather it is probable that a number of agents are capable of triggering the autoimmune process.[22] In a person genetically predisposed to developing RA, avoidance of one trigger would not preclude exposure to a different trigger initiating the disease process at a later date. Therefore, evaluating the risk of disease over longer follow-up periods would tend to obscure the effects of an individual exposure with shortterm risk, such

as a vaccine exposure, but provide a better estimate of the overall contribution of that exposure to the cumulative risk of developing the disease. It may be that a possible short-term risk of RA being triggered within the 90 days following exposure to AVA is balanced over the longer time period by the risk of RA due to other triggers. Confirmed triggers for RA are still unknown, so whether there are any triggers that could be avoided or mitigated to prevent RA onset is also unknown. There would appear to be no long-term benefit to avoid exposure to AVA vaccine in regard to the development of RA because the short-term risk associated with AVA is balanced out by other sources of risk within 2 to 3 years.

In our SLE analysis, we found no risk associated with having ever been exposed to AVA, but due to the small number of cases and controls exposed to AVA vaccine, we were unable to examine multiple exposure intervals. Therefore, we could not determine if there was a pattern of short-term risk similar to that seen with RA, but the lack of long-term risk is reassuring and argues against AVA as an influential cause of SLE at the population level.

Two broad screening studies have been conducted to assess potential adverse events following AVA in U.S. military personnel, one conducted using the DMSS and one using DoD's Ambulatory Data System, neither of which identified any significant safety concerns.[23,24] Our study is the first specifically designed to examine the risk of RA or SLE associated with AVA, though other studies have previously examined the risk of these diseases in relation to other types of vaccines. A Swedish case–control study of incident cases of RA found no increased risk of RA within 5 years following immunization with influenza, tetanus, diphtheria, hep A or B, polio, or pneumococcal vaccines.[11] A population-based case–control study in the United Kingdom found no increase in risk of RA within 3 months or greater than 3 months after hep B vaccine.[25] In addition, a cohort study of Northern California Kaiser Permanente health plan members found nonstatistically significant elevated relative risks for RA for exposure intervals (90, 180, 365, and 730 days) following hep B and tetanus vaccines; receipt of influenza vaccine within an interval of 6 or 12 months was associated with a statistically significantly increased risk of RA in a cohort analysis but not a case–control design.[16] A separate retrospective cohort study from the same health plan found no statistically significant risk of developing RA within 1 year of receipt of rubella vaccination in immunized women 15 to 59 years old.[26] A population-based study of SLE in the United Kingdom found no statistically significant association between risk of SLE within 12 months of receipt of hep B vaccine in the full sample, but did observe an elevated risk among a subset of persons older than 40 years (relative risk = 2.6, 95% CI: 1.1–6.0).[27] Though most studies have not found a risk of new-onset RA associated with other vaccines, some analyses indicate a potential low-level risk with other types of vaccines similar to the magnitude of short-term risk we observed with AVA. Our study was focused on examining the risk with AVA, and while not designed to examine the risk with other vaccines, we did not observe an increased risk of RA or SLE with ever having received hep B vaccine, Td/TT vaccine, inactivated influenza vaccine, or MMR vaccine (data not shown), which have previously been suggested as having a possible association with RA or SLE.

The main limitation of our study was a relatively small sample size. Though the OR for the association of RA with AVA during the 90-day interval of 3.93 (95% CI: 1.08–14.27) was statistically significant, the wide CI indicates uncertainty in the magnitude of the risk.

Unfortunately, we were unable to review charts for all potential cases in the DMSS population during the study period due to limited resources, which constrained our sample size and thus lowered statistical power. The sample size for the SLE analysis was smaller than the RA analysis due to the fact that SLE is a less common disease.

We used the 1987 ARA classification criteria, which were current during the entire study period, including the study's initiation.[13] Since then, the 2010 American College of Rheumatologists/European League Against Rheumatism Collaborative Initiative RA criteria were released, which were meant to improve on the sensitivity of the 1987 ARA criteria for detecting early forms of the disease (i.e., classification rules that applied to newly presenting patients with undifferentiated synovitis would (1) identify the subset at high risk of chronicity and erosive damage, (2) be used as a basis for initiating disease-modifying therapy, and (3) not exclude the capture of patients later in the disease course).[28] With the emphasis being the identification of early vs. established RA, no difference in the risk profile of cases would be expected and this would not affect our study since we used the case–control design, which does not depend on detection of all possible cases in a population. In addition, our study erred on the side of sensitivity by including the cases classified as "probable—does not fulfill criteria." Medical record review and adjudication by a team of rheumatologists was an important strength of this study, which helped to avoid potential bias from misdiagnosis of cases or misclassification of vaccine exposure as it relates to time of disease onset.

We studied a time period during which the original AVA dosing and administration recommendations were in effect. In 2008, the Food and Drug Administration approved reducing the number of doses for the pre-exposure series from 6 doses to 5 doses and changing the route of administration from subcutaneous to intramuscular; the Advisory Committee on Immunization Practices published updated recommendations including these changes in 2010.[29] Whether this new schedule would have the same pattern of association with RA or SLE that we have observed in this study is unknown. Differences would not be anticipated, however, because in a randomized clinical trial, the new schedule was shown to induce a noninferior protective immune response and had similar rates of systemic adverse events and lower rates of injection site adverse events in comparison to the original schedule at both 7 and 43 months of follow-up.[30,31]

In conclusion, in this study, we observed an increased risk of new-onset RA associated with receipt of AVA when looking back 90 days, but no long-term risk for either RA or SLE when looking back up to 3 years. Although our observations suggest that AVA might be a potential trigger for RA disease onset, additional studies would be needed, including assessing possible biological mechanisms, such as a specific autoimmune pathway that can be triggered by epitopes present in the vaccine, before this hypothesis could be confirmed.

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APPENDIX

TABLE AI.

ICD-9-CM Codes Used to Identify Potential Cases of RA or SLE

710.0	Systemic Lupus Erythematosus
714.0	Rheumatoid Arthritis
714.1	Felty's Syndrome
714.2	Rheumatoid Arthritis With Visceral or Systemic Involvement
714.81	Rheumatoid Lung

TABLE AII.

ICD-9-CM Codes Used to Exclude Patients From the Pool of Potential Control Subjects

17	Tuberculosis of other organs
135	Sarcoidosis
283.0	Autoimmune hemolytic anemia
283.9	Acquired hemolytic anemia, unspecified
286.5	Coagulation disorder due to circulating anticoagulants
286.5	Hemorrhagic disorder due to circulating anticoagulants
287.3	Primary thrombocytopenia
287.4	Secondary thrombocytopenia
287.5	Thrombocytopenia, unspecified
288.0	Agranulocytosis
293	Transient organic psychotic conditions
325	Phlebitis and thrombophlebitis of intracranial venous sinuses
345	Epilepsy
357.1	Polyneuropathy in collagen vascular disease
359.6	Symptomatic inflammatory myopathy in diseases classified elsewhere
359.9	Myopathy, unspecified
370.33	Keratoconjunctivitis sicca
373.34	Discoid lupus erythematosus of the eyelid
375.15	Tear film insufficiency
403	Hypertensive renal disease
420	Acute pericarditis
422	Acute myocarditis
423	Other diseases of the pericardium
424.9	Endocarditis, valve unspecified
429.0	Myocarditis, unspecified
443.0	Raynaud's syndrome/phenomenon
444	Arterial embolism and thrombosis
451	Phlebitis and thrombophlebitis
453	Other venous embolism and thrombosis
511	Pleurisy
515	Postinflammatory pulmonary fibrosis

516.3	Idiopathic fibrosing alveolitis
517	Lung involvement in conditions classified elsewhere
517.2	Lung involvement in systemic sclerosis
517.8	Pulmonary involvement in others
527.1	Hypertrophy of salivary glands
527.2	Sialoadenitis
527.7	Disturbance of salivary secretion
528	Diseases of the oral soft tissue
529	Diseases and other conditions of the tongue
530.0	Achalasia and cardiospasm
580	Acute glomerulonephritis
581	Nephrotic syndrome
582	Chronic glomerulonephritis
583	Nephritis and nephropathy not specified as acute or chronic
584	Acute renal failure
585	Chronic renal failure
586	Renal failure and unspecified
587	Pulmonary congestion and hypostasis
587	Renal sclerosis and unspecified
588	Disorders resulting from impaired renal function
599.7	Hematuria
646.2	Unspecified renal disease in pregnancy without mention of hypertension
692.79	Other dermatitis due to solar radiation
695.4	Lupus erythematosus
701.0	Circumscribed scleroderma
704.0	Alopecia
710.0	Systemic lupus erythematosus
710.1	Systemic sclerosis
710.2	Sicca syndrome (Sjogren’s)
710.3	Dermatomyositis
710.4	Polymyositis
710.8	Other specified diseases of connective tissue
710.9	Unspecified diffuse connective tissue disease
714.0	Rheumatoid arthritis
714.1	Felty’s syndrome
714.2	Rheumatoid arthritis with visceral or systemic involvement
714.81	Rheumatoid lung
714.89	Other specified inflammatory arthropathies
714.3	Juvenile chronic polyarthritis
716.5	Unspecified polyarthropathy or polyarthritis
716.8	Other specified arthropathy
716.9	Arthropathy, unspecified
719.0	Effusion of joint-specific sites (includes “joint swelling”)

719.4	Pain in joint (arthralgia)
719.5	Stiffness of joint, not elsewhere classified
729.0	Rheumatism, unspecified and fibrositis
729.1	Myalgia and myositis, unspecified
780.3	Convulsions
782.8	Changes in skin texture
786.52	Painful respiration
791.0	Proteinuria
794.17	Abnormal electromyography
795.6	False positive serology test for syphilis
V42.0	Kidney transplant
V45.1	Postsurgical states, renal dialysis status
V56	Encounter for dialysis and dialysis catheter care
V82.1	Special screening for rheumatoid arthritis
V82.2	Special screening for other rheumatic disorders

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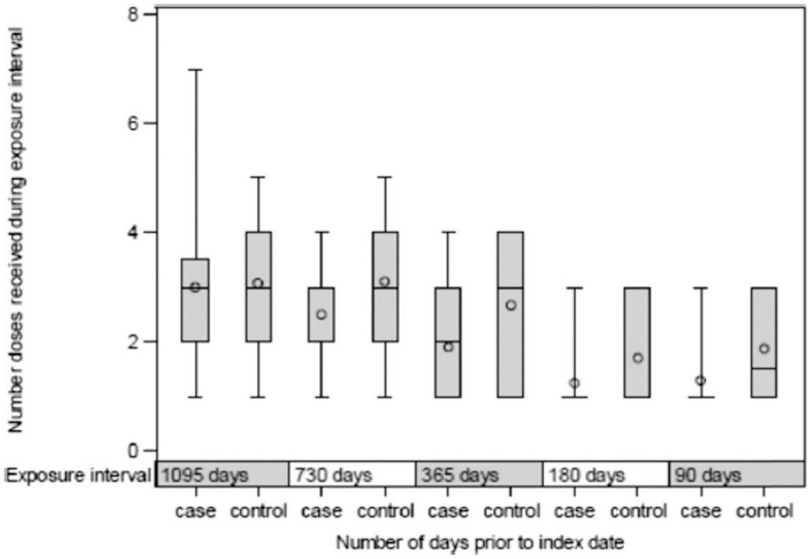

FIGURE 1.

RA analysis: box plot of the number of AVA doses received during each exposure interval (median, interquartile range, and range) for cases and controls. The horizontal line in the middle of the box plot is the median. The circle is the mean. The length of the box represents the interquartile range (distance between the 25th and 75th percentiles). The vertical lines (called whiskers) issuing from the box extend to the group minimum and maximum values.

TABLE I.

Clinical Reviewer Classification Categories for RA and SLE

Probable—fulfills criteria	• Meets disease-specific classification criteria.[a] • Evidence from the medical chart (including clinical and laboratory findings, study results, treatment regimen, and specialist seen) highly supports the diagnosis of the specific DCTD.[b] • The diagnosis has not been later retracted by a rheumatologist. • No evidence suspicious for DCTD or DCTD-like symptoms resulting from other factors (e.g., drugs, infection)
Probable—does not fulfill criteria	• Not enough information to confirm that patient meets disease-specific classification criteria. • Evidence from the medical chart (including clinical and laboratory findings, study results, treatment regimen, specialist seen) highly supports the diagnosis of the specific DCTD. • The diagnosis has not been later retracted by a rheumatologist. • No evidence suspicious for DCTD or DCTD-like symptoms resulting from other factors (e.g., drugs, infection).
Unconfirmable	• Inadequate information in the medical record to confirm or disconfirm the specified diagnosis. • Evidence to suggest a possible inflammatory disease/DCTD is present, though it may be nonspecific. • Patient may or may not meet disease-specific classification criteria. (Occasionally, classification criteria are fulfilled by patients with conditions other than DCTD, such as malignancy or other chronic illness.) • From the medical record, history may or may not be suspicious for an alternative, nonrheumatologic diagnosis (e.g., HIV, malignancy) or DCTD resulting from other factors (e.g., drugs, infection).

[a]For RA, the patient must satisfy at least 4 of the 7 criteria: morning stiffness, arthritis of three or more joint areas, arthritis of hand joints, symmetric arthritis, rheumatoid nodules, serum rheumatoid factor, radiographic changes.[13] For SLE, a patient must satisfy at least 4 of the 11 criteria: malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorder, neurologic disorder, hematologic disorder, immunologic disorder, antinuclear antibody.[14,15]

[b]DCTD, diffuse connective tissue disease.

TABLE II.

Case–Control Study Patient Characteristics

	RA			SLE		
	Cases, *n* = 77	Controls, *n* = 229		Cases, *n* = 39	Controls, *n* = 117	
	n (%)	*n* (%)	*p* Value	*n* (%)	*n* (%)	*p* Value
Case Status						
Probable, Fulfills Criteria	71 (92.2)	n/a		28 (71.8)	n/a	
Probable, Does Not Fulfill Criteria	6 (7.8)	n/a		11 (28.2)	n/a	
Sex						
Male	52 (67.5)	156 (68.1)	0.9236	11 (28.2)	33 (28.2)	1.0000
Female	25 (32.5)	73 (31.9)		28 (71.8)	84 (71.8)	
Age at Disease Onset or Index Date						
18–24 Years	22 (28.6)	66 (28.8)	0.9670	21 (53.8)	63 (53.9)	0.9904
25–34 Years	30 (38.9)	95 (41.5)		11 (28.2)	32 (27.3)	
35–44 Years	21 (27.3)	58 (25.3)		7 (18.0)	22 (18.8)	
45+ Years	4 (5.2)	10 (4.4)		0	0	
Race/Ethnicity						
Non-Hispanic White	53 (68.8)	154 (67.3)	0.8495	13 (33.3)	79 (67.5)	<0.0001
Non-Hispanic Black	13 (16.9)	46 (20.1)		17 (43.6)	16 (13.7)	
Other (Includes Hispanic)	9 (11.7)	26 (11.3)		6 (15.4)	17 (14.5)	
Unknown	2 (2.6)	3 (1.3)		3 (7.7)	5 (4.3)	
Deployed During the Study Period						
Yes	13 (16.9)	40 (17.5)	0.9067	3 (7.7)	17 (14.5)	0.2687
No	64 (83.1)	189 (82.5)		36 (92.3)	100 (85.5)	
Ever Received Vaccine in the Military						
AVA	13 (16.9)	51 (22.3)	0.3146	5 (12.8)	19 (16.2)	0.7987
Hep B	13 (16.9)	44 (19.2)	0.6495	9 (23.1)	25 (21.4)	0.8252
Td/TT	37 (48.1)	132 (57.6)	0.1432	21 (53.9)	74 (63.3)	0.2974
Influenza (Inactivated)	35 (45.5)	119 (52.0)	0.3229	12 (30.8)	62 (53.0)	0.0172
MMR	33 (42.9)	96 (41.9)	0.8856	19 (48.7)	62 (53.0)	0.6437
Among Those Vaccinated, Mean Number of Total AVA Doses Ever Received Before Index Date	4.07 (Range: 1–7)	4.16 (Range: 1–6)	0.3182	3.40 (Range: 2–4)	3.63 (Range: 1–9)	0.7952

If cell size < 5, Fisher's exact test was used; otherwise chi-squared test was used. For comparisons of medians, the Wilcoxon rank-sum test was used.

TABLE III.

RA Case–Control Analysis: Association Between RA and Exposure to AVA by Timing and Number of Doses Received

	Cases	Controls			
Received AVA (Yes/No) During Each Exposure Interval					
Exposure Interval[a]	***n* (%)**	***n* (%)**	**mOR**[b]	**95% CI**	***p* Value**
90 Days	7 (9.1)	8 (3.5)	3.93	1.08, 14.27	0.0374
180 Days	8 (10.4)	14 (6.1)	2.21	0.75, 6.52	0.1496
365 Days	11 (14.3)	24 (10.5)	1.58	0.67, 3.70	0.2973
730 Days	12 (15.6)	31 (13.5)	1.26	0.56, 2.87	0.5763
1,095 Days	12 (15.6)	45 (19.7)	1.03	0.48, 2.19	0.4041
Number of AVA Doses Received During Each Exposure Interval					
Exposure Interval	**Doses Received, Median (Range)**	**Doses Received, Median (Range)**	**mOR**	**95% CI**	***p* Value**
90 Days	1 (1, 3)	1.5 (1, 3)	1.38	0.75, 2.56	0.3003
180 Days	1 (1, 3)	1 (1, 3)	1.15	0.65, 2.05	0.6265
365 Days	2 (1. 4)	3 (1, 4)	1.00	0.71, 1.40	0.9864
730 Days	3 (1, 4)	3 (1, 5)	0.98	0.75, 1.27	0.8556
1,095 Days	3 (1, 7)	3 (1, 5)	0.91	0.72, 1.14	0.4162
Total Number of AVA Doses Received Before the Index Date					
Doses	***n* (%)**	***n* (%)**	**mOR**	**95% CI**	***p* Value**
0	64 (83.1)	178 (77.7)	Ref	—	—
1	2 (2.6)	1 (0.4)	5.76	0.52, 63.9	0.1540
2	0	2 (0.9)	—	—	—
3	4 (5.2)	13 (5.7)	0.77	0.24, 2.53	0.6692
4	1 (1.3)	17 (7.4)	0.15	0.02, 1.16	0.0692
5	3 (3.9)	8 (3.5)	0.84	0.19, 3.63	0.8141
6	1 (1.3)	10 (4.4)	0.26	0.03, 2.31	0.2285
7	2 (2.6)	0	—	—	—
≥3 vs. <3 doses	11 (14.3)	48 (21.0)	0.56	0.25, 1.25	0.1562

[a]The exposure interval is the number of days before the index date.

[b]mOR, matched odds ratio, controlling for deployment status.