

OPEN

Is Systemic Lupus Erythematosus Associated With a Declined Immunogenicity and Poor Safety of Influenza Vaccination?

A Systematic Review and Meta-Analysis

Yafang Huang, MD, PhD, Huili Wang, MD, PhD, Ling Wan, Msc, Xiaoqin Lu, MD, PhD, and Wilson W.S. Tam, PhD

(*Medicine* 95(19):e3637)

Abstract: There are conflicts on whether influenza vaccinated systemic lupus erythematosus (SLE) patients are associated with a decreased immunogenicity and safety, compared with healthy controls. We conducted meta-analyses to compare SLE patients with healthy controls for flu-vaccine immunogenicity, as well as for adverse events.

PubMed, MEDLINE, and Cochrane Library were searched by October 15, 2015. Studies were included when they met the inclusion criteria. Two reviewers independently extracted data on study characteristics, methodological quality, and outcomes. The primary outcome was seroprotection (SP) rate after immunization.

A total of 15 studies were included. There were significant differences in SP rates between the SLE patients and healthy controls, respectively, for H1N1 (RR 0.79, 95% CI 0.73–0.87) and B strain (RR 0.75, 95% CI 0.65–0.87), but not for H3N2 (RR 0.84, 95% CI 0.68–1.03). Subgroup analyses demonstrated SLE patients with immunosuppressants, corticosteroids, azathioprine and prednisone had significantly lower SP rates, compared with healthy controls. SLE patients with nonadjuvanted H1N1 vaccine had significantly lower SP rate, compared with healthy controls. SLE patients were not associated with increased adverse events (RR 1.88, 95% CI 0.94–3.77).

SLE generates immunogenicity differently, compared with healthy controls in pandemic H1N1 and B strains, but same in seasonal H3N2 strain. Nonadjuvant and special kind of immunosuppressive biologics can play an important role in SLE immunogenicity to flu vaccine. There is no significant difference in adverse event rates between SLE patients and healthy controls.

Editor: Mario Cardiel.

Received: January 25, 2016; revised: April 13, 2016; accepted: April 15, 2016.

From the School of General Practice and Continuing Education, Capital Medical University (YH, HW, XL); School of Health Management and Education, Capital Medical University (LW), Beijing, China; and Alice Lee Centre for Nursing Studies, Yong Loo Lin School of Medicine, National University of Singapore (WWST), Singapore.

Correspondence: Yafang Huang and Huili Wang, School of General Practice and Continuing Education, Capital Medical University, Beijing, China (e-mail: huangyafang85@163.com; wanghuilicmu@163.com).

YH and HW contribute equally to this work.

HW and YH contributed to the conception and design of the study. YH and WT carried out the literature search. YH, HW, and WT contributed to study selection, data extraction, and quality assessment. YH and WT performed the analyses and drafted the manuscript. LW and XL revised the manuscript critically for important intellectual content. All the authors contributed to the final approval of the version to be submitted.

Supplemental digital content is available for this article.

The authors have no conflicts of interest to disclose.

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

This is an open access article distributed under the Creative Commons Attribution-NoDerivatives License 4.0, which allows for redistribution, commercial and non-commercial, as long as it is passed along unchanged and in whole, with credit to the author.

ISSN: 0025-7974

DOI: 10.1097/MD.0000000000003637

Abbreviations: AZA = azathioprine, CIs = confidence intervals, HCQ = hydroxychloroquine, NOS = Newcastle–Ottawa scale, PRED = prednisone, RR = relative risk, SC = seroconversion, SLE = systemic lupus erythematosus, SLEDAI = systemic lupus erythematosus disease activity index, SP = seroprotection.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease with widespread inflammation and tissue damage caused by autoantibodies attacking self-cells.¹ The immune dysfunction triggered by self-antigen in SLE patients leads to weakened immunity against pathogens and presents much higher risk of infection, compared with healthy people.^{1,2} Flu virus infection and its complications is a major reason for morbidity and mortality of SLE patients.

Nevertheless, rheumatologists are reluctant to vaccinate patients with SLE and the coverage of flu vaccination for SLE is surprisingly as low as 25%.² On one hand, the safety of flu vaccination in SLE should be taken into consideration. Although early in the United States, the safety of flu vaccine in SLE patients has been approved in several studies,^{3–5} there are still more accumulated adverse events afterward.^{6–9} The rheumatologists indicated the theory. Because virus infection can cause the exacerbation of SLE or aggravate the activity of SLE, it is reasonable that the dead virus in vaccine may lead to harmful immune responses by the same mechanism as the pathogenic virus doing for SLE.^{6–9} On the other hand, different studies showed conflicting results in immunogenicity of SLE patients with flu vaccination. Five studies^{4,5,10–12} reported significantly decreased immunogenicity of flu-vaccinated SLE patients compared with the healthy control, whereas 4 other studies^{3,13–15} did not prove so. Therefore, comprehensive systematic review and meta-analyses for immunogenicity and safety in SLE patients with flu vaccination are needed.

The objective of this study is to determine whether influenza vaccine works effectively and safely in SLE patients, compared with healthy people. In subgroup analyses, we also evaluate the effect of different classes of immunosuppressive drugs and “with or without adjuvant” effect on immunogenicity of flu vaccine in SLE patients, compared with healthy controls.

MATERIAL AND METHODS

Data Sources and Searches

We followed the MOOSE (Meta-analysis of Observation Studies in Epidemiology) guidelines¹⁶ to conduct a meta-analysis of observational studies that reported SP rate and/or

seroconversion (SC) rate between SLE patients and healthy controls after receiving inactivated anti-influenza vaccine. A systematic literature search was conducted on October 15, 2015 using the following electronic databases: PubMed (1809 to present), MEDLINE (1946 to present), Cochrane Library (1996 to present), and Web of Science (1965 to present). Supplemental file S1, <http://links.lww.com/MD/A956> showed the detailed search terms. No language restriction was used. Reference lists of the included articles were searched manually to find additional studies.

Study Selection

Studies that met the following criteria were included in this meta-analysis: (a) Participants: both male and female participants of any age who were received anti-influenza vaccine. (b) SLE group: patients diagnosed as having SLE according to the American College of Rheumatology classification criteria for SLE.¹⁷ (c) Healthy control group: healthy subjects should be used as controls. (d) The original article that reported the SP rate or SC rate was selected.

Studies that did not meet the above criteria were excluded. We also excluded reviews, commentary, case reports, and duplicated publications. Two authors independently evaluated the articles for inclusion. Any discrepancies were resolved by further discussion and consultation of a third author. The selection process by means of a flow chart was presented in Figure 1.

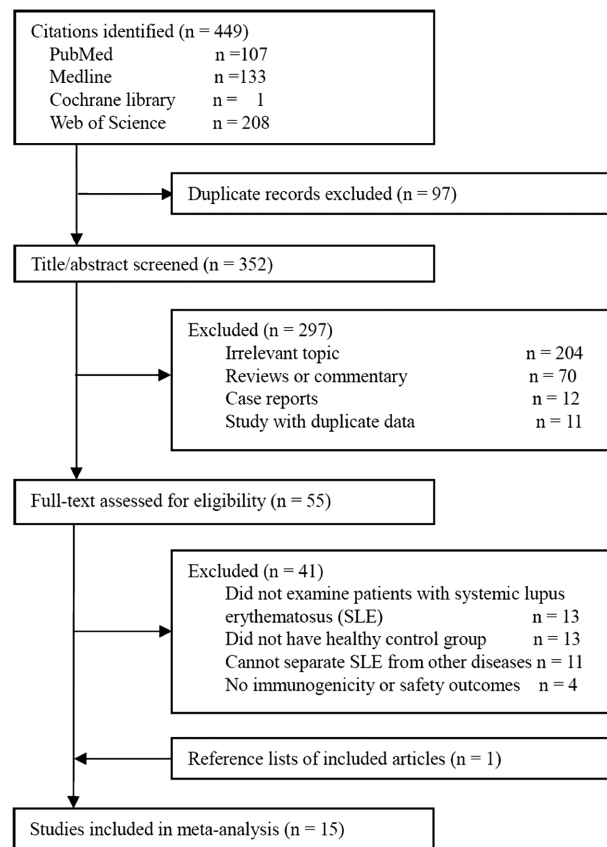


FIGURE 1. Flowchart of study selection.

Outcome Measures

Primary outcome, SP rate (defined as the percentage of participants with antibody titers $\geq 1:40$ on the hemagglutination inhibition assay after vaccination); secondary outcome, SC rate (defined as the percentage of participants with a ≥ 4 -fold antibody titer rise after vaccination); adverse events including occurrence of local reactions (pain, redness, swelling, itching) and systematic reactions (arthralgia, fever, headache, myalgia, sore throat, cough, diarrhea, rhinorrhea, nasal congestion). SLE disease activity was assessed by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).¹⁸

Data Extraction and Quality Assessment

A standardized data extraction form was used. The following information was extracted: first author; publication year; age; number of women; disease duration; number of participants in the SLE and healthy control group; medication; evaluating time after vaccination; region; vaccine company; vaccine valence; type of influenza strains (H1N1, H3N2, B); adjuvant using; SP and SC rate. The quality of studies was assessed using *Newcastle–Ottawa scale* (NOS).¹⁹ Two authors independently extracted the data and assessed the methodological quality of studies. Any discrepancies were resolved by a third author.

Data Synthesis and Analysis

Baseline characteristics were summarized. Results were expressed as the relative risk (RR) with 95% confidence intervals (CIs). We used random effects model via generic inverse variance weighting to combine the effects. Forest plots graphically displayed the effect size in each study and in the pooled estimate. Results were considered statistically significant when P value was less than 0.05. Heterogeneity was quantified by means of I^2 (an I^2 value of 75% or greater was considered representative of considerable heterogeneity).²⁰

Subgroup analyses were conducted for the primary and secondary outcome with medication using, vaccine adjuvant using, type of SLE (Juvenile or adult SLE). Chi-square tests for interaction were applied to these subgroup analyses. Revman software (version 5.2) was used. This software was available through the Cochrane Collaboration (www.cochrane.org).²¹

Publication bias was evaluated by using the Egger regression test.²² This test was done in Stata/IC, version 12 (Stata Corp, College Station, Texas). No protocol of the present review has been published or registered.

RESULTS

Literature Search

We identified 449 citations. After excluding 97 duplicate records, 2 authors screened 352 titles and abstracts to identify the potentially relevant studies. Totally 55 full-text articles were assessed for eligibility. A total of 15 studies met the final eligibility criteria for meta-analysis.^{3–5,11–14,23–30} The detailed selection process was described in Figure 1.

Characteristics of Included Studies

Overall, the 15 studies comprised 1651 participants (1057 SLE patients and 594 healthy controls). Mean age was 35.1 years. Around 1317 (85.5%) participants were women. Mean disease duration for SLE patients was 8.9 years. Table 1 summarized the study characteristics. Additional study characteristics were shown in supplemental Table S1, <http://links.lww.com/MD/A956>.

TABLE 1. Studies Included in the Meta-Analysis

Source	Year	Age (mean)	Women (%)	Disease Duration (mean)	No. of Patients in SLE Group	No. of Healthy Control Group	Immunosuppressive Medication Used	Evaluating Time After Vaccination	Region
Borba et al ²³	2012	37.2 y	668 (92.1)	13 y	555	170	CQ, PRED, AZA, MMF	3 wk	Brazil
Brodman et al ²⁴	1978	37.1 y	75 (72.1)	Not clear	46	58	CS, AZA, HCQ	1 mo	USA
Campos et al ²⁵	2013	16.0 y	142 (64.5)	Not clear	118	102	AM, PRED, AZA, MMF, MTX, CTX, CYA	3 wk	Brazil
Del Porto et al ¹³	2006	43.4 y	Not clear	Not clear	14	10	Not clear	1 mo	Italy
Elkayam et al ²⁶	2011	44.3 y	33 (71.9)	11 y	21	25	MTX, PRED, TNF blockers (IFA, ECP, ADA), HCQ	4–6 wk	Israel
Herron et al ¹⁴	1979	37.5 y	Not clear	8.2 y	20	30	CS	1 wk, 3 wk, 4 mo	US
Holvast et al ¹¹	2006	45 y	64 (87.7)	8.5 y	56	17	HCQ, AZA, PRED	1 mo	Netherlands
Long et al ²⁷	2012	10.3 y	26 (65.0)	Not clear	20	20	MMF, PRED	4–6 wk	USA
Louie et al ³	1978	33.2 y	15 (78.9)	Not clear	11	8	No medication	4 wk	USA
Lu et al ²⁸	2011	36.4 y	30 (83.3)	Not clear	21	15	PRED, AZA, HCQ, NSAID	3 wk, 6 mo	Taiwan
Mercado et al ¹²	2004	32.9 y	36 (100)	8.4 y	18	18	PRED	1 mo	Mexico
Ristow et al ⁵	1978	43 y	56 (96.6)	Not clear	29	29	PRED, AZA, CTX, CLB	1 mo, 2 mo	USA
Wallin et al ²⁹	2009	38.4 y	69 (93.2)	8.6 y	47	27	CS, MTX, AZA	6 wk	Brazil
Wiesik-Szewczyk et al ³⁰	2010	38.5 y	103 (94.5)	4.8 y	62	47	Not clear	4 wk, 12 wk	Poland
Williams et al ⁴	1978	32.6 y	Not clear	Not clear	19	18	NSAID, PRED	1–20 wk	USA

ADA = adalimumab, AM = antimalarial drugs, AZA = azathioprine, CLB = chlorambucil, CQ = chloroquine, CS = corticosteroids, CTX = cyclophosphamide, CYA = cyclosporine, ECP = etanercept, HCQ = hydroxychloroquine, IFA = infliximab, IS = immunosuppressors, MMF = mycophenolate mofetil, MTX = methotrexate, NSAID = nonsteroidal anti-inflammatory drugs, PRED = prednisone, SLE = systemic lupus erythematosus, TNF = tumor necrosis factors.

Assessment of Study Quality

Complete study quality assessment was performed for all studies. One study got 8 stars²³, 10 studies got 7 stars,^{3-5,11,12,14,24,25,27,28,30} and 3 studies got 6 stars.^{13,26,29} The study quality and potential risk of bias were reported in supplemental Table S2, <http://links.lww.com/MD/A956>.

Immunogenicity of Influenza Vaccination in SLE Patients versus Healthy Population

Around 12 studies (1545 participants) provided information on SP rate for the H1N1 strain^{5,11-13,23-30} whereas 10 studies reported decreased SC rates among SLE patients comparing with healthy controls.^{5,11-13,23-26,29,30} Four of them were statistically significant.^{11,23,25,30} Pooling of the mean proportion showed that 65.7% participants in the SLE patients group achieved SP, compared with 84.0% in the healthy control group (RR 0.79, 95% CI 0.73-0.87, $P < 0.001$; heterogeneity $P = 0.04$, $I^2 = 46\%$). This result indicated that SLE was associated with a significant decrease in SP rate for the H1N1 strain (Figure 2).

A total of 6 studies (395 participants) provided information on SP rate for the H3N2.^{11-13,24,29,30} Pooling of the mean proportion showed that 63.7% participants in the SLE patients group achieved SP, compared with 73.3% in the healthy control group. There was no significant difference between the SLE and healthy control groups (RR 0.84, 95% CI 0.68-1.03, $P = 0.09$; heterogeneity $P = 0.009$, $I^2 = 68\%$) (Figure 2).

In this study, 5 studies (316 participants) provided information on SP rate for influenza B strain.^{11-13,29,30} Pooling of the mean proportion showed that 60.4% participants in the SLE patients group achieved SP, compared with 79.8% in the healthy control group. There was significant difference between SLE patients and healthy controls (RR 0.75, 95% CI 0.65-0.87, $P < 0.001$; heterogeneity $P = 0.44$; $I^2 = 0\%$) (Figure 2).

Around 13 studies (1511 participants) provided information on SC rate for H1N1 strain.^{3-5,11,13,14,23,25-30} Twelve

studies reported decreased SC rates among SLE patients comparing with healthy controls.^{3-5,11,13,14,23,25,26,28-30} Six of them were statistically significant.^{4,11,23,25,29,30} Pooling of the mean proportion of the 13 studies showed that 57.6% participants in the SLE patients group achieved SC, comparing with 79.9% in the healthy control group. The meta-analysis showed that SLE was associated with a significant decrease in SC rate (RR 0.71, 95% CI 0.62-0.81, $P < 0.001$; heterogeneity $P = 0.007$, $I^2 = 56\%$) (Figure 2).

Seven studies (386 participants) provided information on SC rate for the H3N2 strain.^{3,4,11,13,14,29,30} Pooling of the mean proportion showed that 50.2% participants in the SLE patients group achieved SC, comparing with 73.2% in the healthy control group. There was no significant difference in SC rate between SLE patients and healthy controls (RR 0.73, 95% CI 0.53-1.01, $P = 0.06$; heterogeneity $P = 0.001$, $I^2 = 72\%$) (Figure 2).

Four studies (280 participants) provided information on SC rate for influenza B strain.^{11,13,29,30} Pooling of the mean proportion showed that 41.9% participants in the SLE patients group achieved SC, compared with 63.4% in the healthy control group. There was significant difference between SLE patients and healthy controls (RR 0.66, 95% CI 0.52-0.82, $P < 0.001$; heterogeneity $P = 0.62$; $I^2 = 0\%$) (Figure 2).

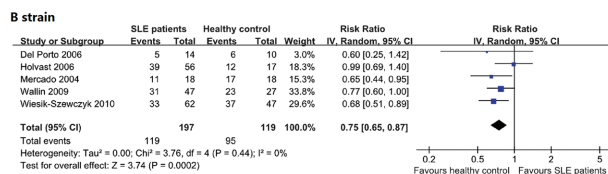
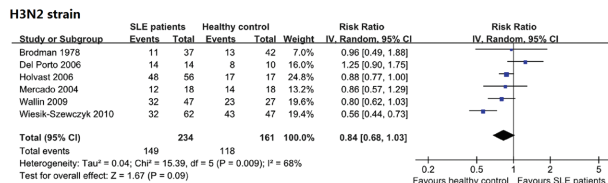
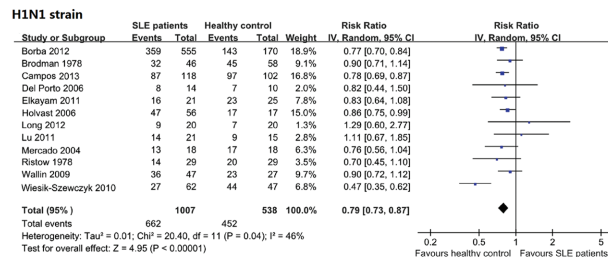
Publication bias was examined by the Egger's test. No potential publication bias was detected (supplemental Table S3, <http://links.lww.com/MD/A956>).

Subgroup Analysis

The Effect of Immunosuppressive Medication on Immunogenicity of Influenza Vaccination.

Subgroup analyses show SP rates in SLE patients receiving immunosuppressants, corticosteroids, azathioprine (AZA), prednisone (PRED) were significantly lower than the healthy controls whereas in SLE patients receiving no medication, antimalarial drugs, hydroxychloroquine (HCQ) it was not

Seroprotection



Seroconversion

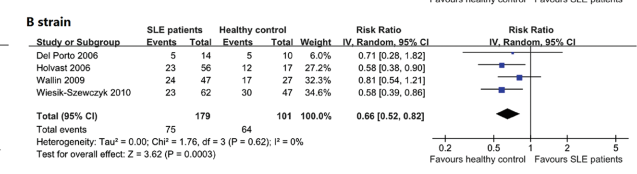
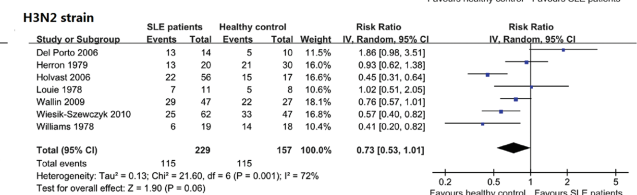
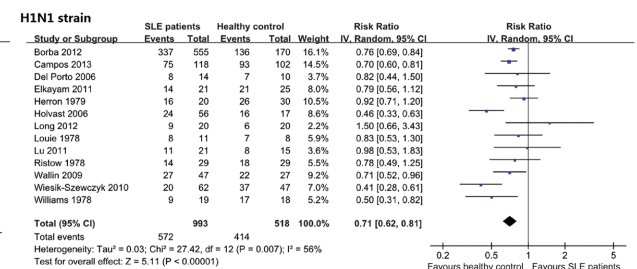


FIGURE 2. Relative risk of achieving seroprotection and seroconversion after vaccination (comparing SLE patients versus healthy controls).

(Table 2). The interaction test showed that these subgroups did not differ significantly ($\chi^2 = 11.96, P = 0.10$).

Immunogenicity of Nonadjuvanted or Adjuvanted Influenza Vaccine

SLE patients who received nonadjuvanted vaccine had significantly lower SP rate, compared with healthy controls, whereas SLE patients who received adjuvanted vaccine did not (Table 2). The interaction test between adjuvanted and nonadjuvanted for this difference was insignificant ($\chi^2 = 0.21; P = 0.65$).

Immunogenicity Between Juvenile and Adult SLE Patients versus Healthy Control

Adult SLE patients had significantly lower SP rate, compared with healthy controls, whereas Juvenile SLE patients did not (Table 2). The interaction test did not show significant result ($\chi^2 = 0.16; P = 0.69$).

Safety of Influenza Vaccine

Eight studies reported local responses in SLE and healthy control group.^{3,11–13,23,25,26,28} Meta-analysis showed that SLE patients were not associated with significant increase in local responses comparing with healthy control (RR 2.01, 95% CI 0.48–8.39, $P = 0.34$; heterogeneity $P < 0.001, I^2 = 81\%$). Eleven studies reported systematic reactions.^{3,5,11–14,23–26,28} Meta-analysis showed no significant difference in systematic reaction rates between SLE patients and healthy control group (RR 2.00, 95% CI 0.73–5.53, $P = 0.18$; heterogeneity $P < 0.001, I^2 = 81\%$) (supplemental Figure S1, <http://links.lww.com/MD/A956>).

SLEDAI was examined in 9 studies.^{11–13,23,25,26,28–30} Only one study showed significant decrease of SLEDAI value after influenza vaccine administration in SLE patients.¹²

DISCUSSION

Vaccination is the best way for healthy people to prevent influenza and its complications, which produce optimal immunogenicity and low side-effects.¹ Based on the 15 clinical studies included above which all compared SLE patients with healthy controls for the responses to influenza vaccine, we gave the first meta-analyses which assess the humoral immunogenicity and safety of influenza vaccination in total 1057 SLE patients against those in 594 healthy controls. We concluded the humoral response and side-effects in SLE patients with influenza vaccination, compared with healthy controls. This study may be helpful to previous controversial and conflicting studies on this topic.

There is no significant difference in SP rates between SLE patients without medications and healthy controls for H1N1, H3N2, and B strains. Thus, these three strains have the same good ability to stimulate the humoral response in both SLE patients and healthy controls. Nevertheless, for the patients treated with corticosteroids or immunosuppressive agents, their SP rates were associates with a significant decrease compared with healthy people. In contrast to immunosuppressants, anti-malarial drugs that target antimetabolic mechanisms did not decrease significantly the 3 strain SP rates in SLE patients with flu vaccination. These results outline the SLE patients under different medical conditions with different degrees of humoral responses assessed by SP rates. Immunosuppressive therapies dramatically attenuated the immunogenicity to the vaccine.

TABLE 2. Subgroup Analysis: Relative Risk of Achieving Seroprotection and Serconversion (Comparing SLE Patients Versus Healthy Population)

Variable	H1N1 Strain		H3N2 Strain		B Strain	
	RR (95% CI) for SP	RR (95% CI) for SC	RR (95% CI) for SP	RR (95% CI) for SC	RR (95% CI) for SP	RR (95% CI) for SC
No medication	0.89 (0.79–1.01)	0.86 (0.74–1.00)	1.00 (0.87–1.14)	0.77 (0.51–1.16)	1.30 (0.91–1.84)	0.83 (0.47–1.46)
With medication	0.80 (0.75–0.84)	0.72 (0.63–0.83)	0.84 (0.74–0.95)	0.61 (0.40–0.91)	0.78 (0.65–0.94)	0.66 (0.43–1.03)
Immunosuppressants	0.69 (0.54–0.87)	0.61 (0.37–1.00)	0.62 (0.41–0.96)	0.09 (0.01–0.58)	0.87 (0.51–1.48)	0.33 (0.12–0.92)
Corticosteroids	0.84 (0.74–0.95)	0.66 (0.53–0.82)	0.87 (0.71–1.07)	0.49 (0.26–0.91)	0.72 (0.53–0.98)	0.51 (0.24–1.09)
Antimalarial drugs	0.92 (0.83–1.02)	0.79 (0.50–1.26)	0.94 (0.80–1.11)	0.53 (0.31–0.91)	1.00 (0.65–1.54)	0.67 (0.37–1.20)
AZA	0.71 (0.58–0.88)	0.63 (0.38–1.05)	0.62 (0.41–0.96)	0.09 (0.01–0.58)	0.87 (0.51–1.48)	0.33 (0.12–0.92)
PRED	0.84 (0.74–0.95)	0.66 (0.53–0.82)	0.87 (0.71–1.07)	0.49 (0.26–0.91)	0.72 (0.53–0.98)	0.51 (0.24–1.09)
HCQ	0.94 (0.66–1.34)	0.74 (0.26–2.07)	0.94 (0.80–1.11)	0.53 (0.31–0.91)	1.00 (0.65–1.54)	0.67 (0.37–1.20)
Adjuvant using						
Adjuvanted	0.83 (0.64–1.08)	0.79 (0.56–1.12)	NA	NA	NA	NA
Nonadjuvanted	0.78 (0.72–0.83)	0.74 (0.69–0.81)	1.25 (0.90–1.75)	1.86 (0.98–3.51)	0.60 (0.25–1.42)	0.71 (0.28–1.82)
Type of SLE						
Juvenile SLE	0.86 (0.58–1.28)	0.91 (0.45–1.87)	NA	NA	NA	NA
Adult SLE	0.79 (0.71–0.88)	0.69 (0.59–0.81)	0.84 (0.68–1.03)	0.79 (0.56–1.10)	0.75 (0.65–0.87)	0.66 (0.52–0.82)

AZA = azathioprine, CI = confidence interval, HCQ = hydroxychloroquine, NA = not applicable, PRED = prednisone, RR = relative risk, SC = seroconversion, SLE = systemic lupus erythematosus, SP = seroprotection, TNF = tumor necrosis factor.

Therefore, we strongly support the flu vaccination recommended for SLE that the time point for vaccination should be set several weeks before receiving immunosuppressive therapy. It is very important to choose the flu shot time point, avoiding the period of these immunosuppressive drug therapy.

Nonadjuvanted vaccine becomes more acceptable in clinics for the patients with abnormal immunity such as allergy and kidney transplant.^{31,32} The reason is normally thought that adjuvants are “dirty” things.³³ Adjuvant may cause inflammatory “Autoimmune Syndrome Induced by Adjuvants (ASIA).”³⁴ However, flu vaccination with or without adjuvants in SLE patients is still a dilemma. Flu vaccine with adjuvant can boost a more effective humoral response in immunocompromised patients.³⁵ In this systematic review, SLE patients who received nonadjuvanted vaccine had significantly lower SP and SC rates of H1N1 than healthy controls, whereas SLE patients who received adjuvanted vaccine did not. The roles of adjuvant in a vaccine are much clearly illustrated because adjuvant receptors such as toll-like receptors have been identified and adjuvant pharmacology has been revolutionized.^{36,37} Clinical trials showed new adjuvants like squalene-based AS03 and MF59 with much better boosting effect and safety than traditional adjuvants.³¹ In this study, we noticed adjuvant effects in SLE patients with flu vaccination for pandemic H1N1 strain. By our results, we suggest further that in further study of adjuvants adjuvant role in immunocompromised patients with flu vaccination should not be neglected.

Our meta-analysis showed that SLE is not associated with significantly increased adverse events by flu vaccine. Adverse effects on SLE patients were mild and occurred at lower frequencies and there was no significant difference compared with healthy controls. The safety of vaccination in SLE has been debated for many years.^{38,39} The sporadic severe adverse events such as glomerulonephritis and even death are continuously reported.^{6,40} This may lead to the physicians’ reluctance to prescribe vaccination due to concerns about its safety. SLE patients have lower flu shot coverage than their counterparts with other systemic inflammatory diseases, for example, systemic sclerosis, rheumatoid arthritis, or vasculitis. Theoretically, flu virus vaccine is a foreign substance which may be a trigger for flare-up of potential SLE patients. Etiological studies show virus infection, polluted environment, ultraviolet, vaccination, and even see foods could cause SLE symptom among those susceptible individuals.^{6,41} It is very hard to elucidate some rare cases of serious adverse events and flare-up among SLE patient with flu vaccination. Normally, the serious adverse event is a case report, thus it has no statistical significance. Although the rare adverse effect case reports cannot be neglected by physicians, US CDC and the European League Against Rheumatism^{42,43} and the 2010 Recommendations of the Advisory Committee on Immunization Practices⁴⁴ suggest that SLE patients should get a flu shot. Of 15 studies in this systematic review, totally 14 studies reported slight and transient adverse symptoms in SLE patients with flu vaccination, and moreover the incidence of exacerbations was close to the incidence expected in a comparable population of SLE patients except Brodman 1978 study²⁴ that 11 of 46 patients occurring flare-up of SLE after a monovalent H1N1 influenza vaccination. Nevertheless, Brodman explained that they observed the aggravation of abnormalities noted before enrolment, and this tended to remit spontaneously. Brodman study is the earliest one among all 15 studies and in contrast to this study, no latter studies reported the same high adverse event rate. It is very likely that at that time, the techniques for flu vaccine production

may not be so advanced and Freund’s complete adjuvant was commonly used. Similarly, at that time in 1979, Herron et al’s study¹⁴ which reported 6 of 17 patients occurring flare-up of rheumatoid arthritis after a bivalent influenza vaccination. The adjuvants might play an important role in exacerbations of flu vaccinated autoimmune patients.³⁴ Reasonably, some studies even adopted two dose injection of nonadjuvanted flu vaccine for SLE patient against immunosuppressive therapy and no more adverse events was found in these studies.⁴⁵ Nowadays, the oil-in-water emulsified and squalene-based adjuvant AS03 and MF59, respectively, from GlaxoSmithKline and Novartis proved to have more immunogenicity boosting ability and less side effect. Fewer and fewer adverse events were reported today. For another score of adverse effect after flu vaccine in SLE, we indicate that SLEDAI was examined in 9 studies. Only one of them showed significant difference between the values of SLEDAI before and after influenza vaccine administration in SLE patients.¹²

Some limitations should be mentioned. First, studies included in our meta-analyses did not show yearly long time following up side effect results. Second, we cannot synthesize parameter of side effect from the lab detection such as anti-nuclear autoantibodies, since many studies just described adverse events by verbal expression due to slight adverse effects. We keep on observing this for more information of these two aspects on SLE with flu vaccine immunization.

CONCLUSIONS

This study gives a first systematic review on humoral immunogenicity and adverse events of influenza vaccine in SLE patients and illustrates whether the flu vaccine works effectively and safely in SLE patients as it does in healthy controls. Adverse event rate has no significant difference between SLE and the health controls. Subgroup analysis demonstrates that immunosuppressive therapies and the non-adjuvanted lead to less immunogenicity in humoral response in flu-vaccinated SLE patients.

REFERENCES

- Centers for Disease Control and Prevention (US). Systemic Lupus Erythematosus: Public Health and Genomic Insights. <http://www.cdc.gov/genomics/public/features/SLE.htm>. Accessed on March 26, 2016.
- Lanternier F, Henegar C, Mouthon L, et al. Low influenza-vaccination rate among adults receiving immunosuppressive therapy for systemic inflammatory disease. *Ann Rheum Dis*. 2008;67:1047.
- Louie JS, Nies KM, Shoji KT, et al. Clinical and antibody responses after influenza immunization in systemic lupus erythematosus. *Ann Intern Med*. 1978;88:790–792.
- Williams GW, Steinberg AD, Reinertsen JL, et al. Influenza immunization in systemic lupus erythematosus. A double-blind trial. *Ann Intern Med*. 1978;88:729–734.
- Ristow SC, Douglas RG Jr, Condemi JJ. Influenza vaccination of patients with systemic lupus erythematosus. *Ann Intern Med*. 1978;88:786–789.
- Morihara K, Arakawa Y, Takenaka H, et al. Systemic lupus erythematosus following vaccination against 2009 influenza A (h1n1). *Lupus*. 2011;20:775–776.
- Older SA, Battafarano DF, Enzenauer RJ, et al. Can immunization precipitate connective tissue disease? Report of five cases of systemic lupus erythematosus and review of the literature. *Semin Arthritis Rheum*. 1999;29:131–139.

8. Stratta P, Cremona R, Lazzarich E, et al. Letter to the editor: life-threatening systemic flare-up of systemic lupus erythematosus following influenza vaccination. *Lupus*. 2008;17:67–68.
9. Tarjan P, Sipka S, Lakos G, et al. Influenza vaccination and the production of anti-hospholipid antibodies in patients with systemic lupus erythematosus. *Scand J Rheum*. 2006;35:241–243.
10. Abu-Shakra M, Press J, Varsano N, et al. Specific antibody response after influenza immunization in systemic lupus erythematosus. *J Rheumatol*. 2002;29:2555–2557.
11. Holvast A, Huckriede A, Wilschut J, et al. Safety and efficacy of influenza vaccination in systemic lupus erythematosus patients with quiescent disease. *Ann Rheum Dis*. 2006;65:913–918.
12. Mercado U, Acosta H, Avendano L. Influenza vaccination of patients with systemic lupus erythematosus. *Rev Invest Clin*. 2004;56:16–20.
13. Del Porto F, Lagana B, Biselli R, et al. Influenza vaccine administration in patients with systemic lupus erythematosus and rheumatoid arthritis—safety and immunogenicity. *Vaccine*. 2006;24:3217–3223.
14. Herron A, Dettliff G, Hixon B, et al. Influenza vaccination in patients with rheumatic diseases. Safety and efficacy. *JAMA*. 1979;242:53–56.
15. Kanakoudi-Tsakalidou F, Trachana M, Pratsidou-Gertsi P, et al. Influenza vaccination in children with chronic rheumatic diseases and long-term immunosuppressive therapy. *Clin Exp Rheumatol*. 2001;19:589–594.
16. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (moose) group. *JAMA*. 2000;283:2008–2012.
17. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*. 1997;40:1725–1725.
18. Bombardier C, Gladman DD, Urowitz MB, et al. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. *Arthritis Rheum*. 1992;35:630–640.
19. Stang A. Critical evaluation of the Newcastle–Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25:603–605.
20. Deeks JJ, Higgins JPT, Altman DG. Chapter 9: Analysing data and under taking meta-analyses. In: Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. The Cochrane Collaboration; 2011. <http://www.Cochrane-handbook.org>. Accessed on February 18, 2014.
21. Cochrane Informatics & Knowledge Management Department. Rev Man. <http://tech.cochrane.org/revman>. Accessed on October 18, 2015.
22. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med*. 2006;25:3443–3457.
23. Borba EF, Saad CG, Pasoto SG, et al. Influenza A/H1N1 vaccination of patients with SLE: can antimalarial drugs restore diminished response under immunosuppressive therapy? *Rheumatology*. 2012;51:1061–1069.
24. Brodman R, Gilfillan R, Glass D, et al. Influenza vaccine response in systemic lupus erythematosus. *Ann Intern Med*. 1978;88:735–740.
25. Campos LMA, Silva CA, Aikawa NE, et al. High disease activity: an independent factor for reduced immunogenicity of the pandemic influenza A vaccine in patients with juvenile systemic lupus erythematosus. *Arthritis Care Res*. 2013;65:1121–1127.
26. Elkayam O, Amir S, Mendelson E, et al. Efficacy and safety of vaccination against pandemic 2009 influenza A (H1N1) virus among patients with rheumatic diseases. *Arthritis Care Res*. 2011;63:1062–1067.
27. Long CB, Ramos I, Rastogi D, et al. Humoral and cell-mediated immune responses to monovalent 2009 influenza A/H1N1 and seasonal trivalent influenza vaccines in high-risk children. *J Pediatr*. 2012;160:74–81.
28. Lu CC, Wang YC, Lai JH, et al. A/h1n1 influenza vaccination in patients with systemic lupus erythematosus: safety and immunity. *Vaccine*. 2011;29:444–450.
29. Wallin L, Quintilio W, Locatelli F, et al. Safety and efficiency of influenza vaccination in systemic lupus erythematosus patients. *Acta Reumatol Port*. 2009;34:498–502.
30. Wiesik-Szewczyk E, Romanowska M, Mielnik P, et al. Anti-influenza vaccination in systemic lupus erythematosus patients: an analysis of specific humoral response and vaccination safety. *Clin Rheumatol*. 2010;29:605–613.
31. McElhaney JE, Beran J, Devaster J-M, et al. As03-adjuvanted versus non-adjuvanted inactivated trivalent influenza vaccine against seasonal influenza in elderly people: a phase 3 randomised trial. *Lancet Infect Dis*. 2013;13:485–496.
32. Dormitzer P, Tsai T, Del Giudice G. New technologies for influenza vaccines. *Hum Vaccin Immunother*. 2011;8:45–58.
33. Woodland DL, Blackman MA. Vaccine development: baring the 'dirty little secret'. *Nat Med*. 2005;11:715–716.
34. Shoenfeld Y, Agmon-Levin N. 'Asia'—autoimmune/inflammatory syndrome induced by adjuvants. *J Autoimmun*. 2011;36:4–8.
35. Vogel FR. Improving vaccine performance with adjuvants. *Clin Infect Dis*. 2000;30(suppl 3):S266–S270.
36. Hennessy EJ, Parker AE, O'Neill LA. Targeting toll-like receptors: emerging therapeutics? *Nat Rev Drug Discov*. 2010;9:293–307.
37. Kaisho T, Akira S. Toll-like receptors as adjuvant receptors. *Biochim Biophys Acta*. 2002;1589:1–13.
38. Aron-Maor A, Shoenfeld Y. Vaccination and systemic lupus erythematosus: the bidirectional dilemmas. *Lupus*. 2001;10:237–240.
39. O'Neill SG, Isenberg DA. Immunizing patients with systemic lupus erythematosus: a review of effectiveness and safety. *Lupus*. 2006;15:778–783.
40. Stratta P, Cremona R, Lazzarich E, et al. Life-threatening systemic flare-up of systemic lupus erythematosus following influenza vaccination. *Lupus*. 2008;17:67–68.
41. James JA, Harley JB, Scofield RH. Epstein-Barr virus and systemic lupus erythematosus. *Curr Opin Rheumatol*. 2006;18:462–467.
42. van Assen S, Agmon-Levin N, Elkayam O, et al. Eular recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis*. 2011;70:414–422.
43. Mosca M, Tani C, Aringer M, et al. European league against rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. *Ann Rheum Dis*. 2010;69:1269–1274.
44. Fiore AE, Uyeki TM, Broder K, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Morb Mortal Wkly Rep*. 2010;59:1–62.
45. Mathian A, Devilliers H, Krivine A, et al. Factors influencing the efficacy of two injections of a pandemic 2009 influenza A (H1N1) nonadjuvanted vaccine in systemic lupus erythematosus. *Arthritis Rheum*. 2011;63:3502–3511.