REVIEW

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Influenza Vaccination in Systemic Lupus Erythematosus: Efficacy, Effectiveness, Safety, Utilization, and Barriers

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ABSTRACT

Influenza increases morbidity and mortality in systemic lupus erythematosus (SLE) and lupus nephritis but is preventable through vaccination. This systematic review of PubMed, Embase, CENTRAL, WHO Clinical Trials, and ClinicalTrials.gov publications until August 2021 identified 45 reports (16,596 patients), including 8.5% with renal involvement or lupus nephritis: 9 studies (10,446 patients) on clinical effectiveness, 20 studies (1327 patients) on vaccine efficacy, 22 studies (1116 patients) on vaccine safety, 14 studies (4619 patients) on utilization rates, and 5 studies (3220 patients) on barriers. Pooled seroconversion rates ranged between 46% and 56%, while seroprotection rates ranged from 68% to 73% and were significantly associated with age and disease duration. Influenza infection was lower in vaccinated patients with systemic lupus erythematosus compared with unvaccinated patients. Disease activity scores did not change significantly after vaccination and reported flares were mild to moderate. Pooled current vaccination rate was 40.0% (95% confidence interval [CI]: 33.7%-46.5%) with significant heterogeneity and associated with the gross domestic product (P = .002) and disease duration (P = .001). Barriers to vaccination were the lack of doctor recommendation (57.4%) and concerns over the safety or efficacy of the vaccine (12.7%).

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KEYWORDS: Effectiveness; Influenza vaccine; Lupus nephritis; Meta-analysis; Safety; Systematic review; Systemic lupus erythematosus

INTRODUCTION

Infections are frequent in patients with systemic lupus erythematosus and lupus nephritis due to inherent immune dysregulation and use of potent immunosuppressants.[1] Indeed, lupus nephritis was one of the most frequent biopsy-proven glomerulonephritides to require potent immunosuppressive therapy.[2] Respiratory tract infections accounted for most infection-related hospitalizations in lupus nephritis.[3] Among these respiratory tract infections, influenza infection is associated with increased morbidity and mortality among immunocompromised individuals.[4,5] Yet, influenza infections are highly preventable because vaccination has been shown to reduce infections in the general population.[6] Although vaccinations are advocated in immunocompromised individuals,[7] there is concern about vaccine efficacy and safety in systemic lupus erythematosus, an immune-mediated condition characterized by defective immune tolerance mechanism with altered immune responses.[8,9] Additionally, renal involvement in lupus nephritis with impaired kidney function may potentially impair dendritic cell function and reduce T- and B-lymphocytic response to vaccination,[10] while treatment with immunosuppressants may further impair vaccine response. Yet there was postulation that immunization with a foreign protein may enhance B-lymphocyte hyperactivity with

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consequent production of potentially pathogenic autoantibodies.[11,12] Concerns about autoimmune disease flares may have contributed to the low influenza vaccination rates in some centers.[13,14]

Knowledge of influenza vaccination efficacy and safety have largely been limited to small, single-center studies that limit the power to detect significant associations with patient, disease, or treatment factors, while real-world data on vaccine effectiveness in preventing clinical events, utilization, and barriers to vaccination is sparse. In addition, a recent systematic review conducted to inform recommendations for vaccinations in autoimmune inflammatory rheumatic diseases that included publications until August 2018,[15] as well as older reviews,[16-18] had focused on immunogenicity and safety. Yet, information on utilization and barriers to influenza vaccination will be useful to address concerns and guide implementation strategies to improve influenza vaccination coverage and outcomes among at-risk individuals with lupus. We thus conducted a systematic review and meta-analyses to investigate the 1) efficacy and effectiveness, 2) safety, 3) utilization, and 4) barriers to influenza vaccination in systematic lupus erythematosus and lupus nephritis.

CLINICAL SIGNIFICANCE

- Influenza vaccination is effective and safe in patients with systemic lupus erythematosus (SLE) and lupus nephritis.
- Current influenza vaccination rates are low (40.0%).
- Common barriers to vaccination were the lack of doctor recommendation and concerns over the safety or efficacy of the vaccine.
- Targeted strategies should address the barriers identified by this study to increase the uptake of influenza vaccines among patients with SLE and lupus nephritis.

METHODS

Database

A systematic search was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[19] in PubMed (from 1979), Embase (from 1981), Cochrane Central Register of Controlled Trials (CENTRAL), the World Health Organization International Clinical Trials Registry Platform (https://trialsearch.who.int/Default.aspx), and ClinicalTrials.gov (www.ClinicalTrials.gov). The databases were searched up to August 16, 2021 without language, publication year, or publication status restrictions.

Search Strategy

The search strings included Boolean terms 'AND', 'OR', and 'NOT' with the following keywords and their respective variants or derivates in any relevant combination: systemic lupus erythematosus, lupus nephritis, vaccine, and influenza (Supplementary Table S1, available online). Two authors (CL and JS) independently selected full studies for evaluation by analyzing titles and abstracts from the databases searched. We retrieved the full text of potentially relevant reports selected for evaluation and linked multiple reports of the same study together. A hand search of all relevant studies and their citation list was performed to identify articles for inclusion following full-text evaluation. Disagreement about selection of a study was resolved by discussion. We contacted authors of included papers and abstracts to request additional information where required, such as for unpublished studies identified in the trial registries or when data was not presented specifically for systemic lupus erythematosus subgroup but aggregated with other autoimmune diseases.

Study Selection

Articles were selected for systematic review if they included individuals with lupus nephritis or systemic lupus erythematosus who received treatment with influenza vaccination, with or without comparison to placebo or no treatment and were assessed for the outcomes of interest. We included randomized controlled trials (RCTs) and quasi-RCTs, both prospective and retrospective cohort studies, as well as cross-sectional studies. We included both published and nonpublished studies. For multiple studies that included overlapping patients, only the largest study was included. We excluded case reports and case series with fewer than 5 patients per recommendations by the Cochrane Statistical Methods Group.[20] Abstracts with incomplete information regarding the patient population or outcomes and whose authors did not respond were also excluded because the study eligibility could not be ascertained.

Data Extraction and Outcome Measures

Relevant data, including type of study design and setting, participant characteristics, interventions, confounders such as factors related to patient and immunosuppression, and detailed nature of outcomes were independently extracted by 2 authors into a structured form specifically designed for this review.

The primary outcome of interest was the effectiveness of influenza vaccination. Effectiveness was evaluated according to occurrence of clinical events related to influenza infection, as defined by the studies. The other outcomes of interest were 1) efficacy, 2) safety, 3) utilization, and 4) barriers to vaccination. Vaccine efficacy was assessed using seroconversion and seroprotection rates after vaccination. Seroconversion was defined as a greater than 4-fold increase in serum hemagglutination inhibition titer after vaccination. Seroprotection was defined as a serum hemagglutination inhibition titer of at least 1:40 after vaccination.

Five aspects were evaluated in terms of safety: 1) change in disease activity score, 2) disease flares, 3) local or systemic clinical adverse events, 4) change in complement levels, and 5) change in autoantibody titers. We assessed utilization rates according to those currently vaccinated within the past year and those who have ever received the influenza vaccination.

Quality Assessment

We used the Cochrane risk of bias tool (RoB 2) to assess the risk of bias of eligible RCTs.[21] Each potential source of bias is assessed by providing a description of what happened in the study and providing a grade for high, low, or unclear risk of bias. We assessed risk of bias in nonrandomized studies using the ROBINS-I tool.[22]

Statistical Analysis

Statistical analyses were performed using R software (version 3.6.3) with the packages *meta* and *dmetar*.[23] Pooled proportions were calculated with the inverse variance method using the Freeman-Tukey double arcsine transformation.[24] Where means and standard deviations (SDs) of continuous variables were not available, they were estimated from the medians, minimum, and maximum ranges and interquartile ranges using the methods proposed by Hozo et al and Wan et al[25,26] or *P* values as advised by the Cochrane Handbook for Systematic Reviews of Interventions.[27] Meta-analysis for the effect of influenza vaccination on the outcomes of interest was performed if there were at least 3 studies with similar study design. Unadjusted estimates for dichotomous outcomes were analyzed using the Mantel Hanszel method with random effects analysis as the cohorts were from a wide geo-socioeconomic spectrum.[28] Univariable study-level meta-regression was conducted when at least 6 data points were collected to explore potential sources of heterogeneity or prognostically relevant study-level covariates.

We evaluated heterogeneity by visual inspection of the forest plots, the χ^2 test and the I^2 statistic. An I^2 value of 0% to 40% might not be important, whereas values of 30% to 60%, 50% to 90%, and 75% to 100% represents moderate, substantial, and considerable heterogeneity, respectively.[29] The importance of the observed value of I^2 depends on: 1) magnitude and direction of effects and 2) strength of evidence for heterogeneity (such as the *P* value from the χ^2 test, or a confidence interval for I^2). We considered a *P* value $< .10$ for χ^2 as significant for heterogeneity.

Funnel plots and Egger test were used to document the potential presence of publication bias, where asymmetrical distribution of studies will be suggestive of bias.[30]

RESULTS

Literature Review

Our search yielded 744 unique articles from 5 databases. After screening for title and abstract, we reviewed the full text of 105 publications and finally included 45 reports from 44 studies comprising 16,596 individuals.[11,13,31-73] Figure 1 shows the study flow as recommended by the PRSIMA 2020 updated guideline.[74] Abu Shakra et al reported different outcomes of the same study in separate reports, which were both included.[11,31] Four reports had the same ClinicalTrials.gov identifier number (NCT01151644) and assessed similar outcomes; thus, only the largest report (Saad 2011) was included.[61,75-77] A subset of patients included in Crowe et al[12] were also included in the 2012 study by Vista;[67] thus, only the larger study was included.

The cohort characteristics of all included reports are shown in Table 1: 9 studies (10,446 patients) evaluated clinical effectiveness, 20 studies (1327 patients) evaluated vaccine efficacy, 22 studies (1116 patients) evaluated vaccine safety, 14 studies (4619 patients) evaluated utilization rates, and 5 studies (3220 patients) evaluated barriers to influenza vaccination (Supplementary Table S2, available online). The majority were nonrandomized trials with moderate risk of bias (Supplementary Table S3, available online), while 2 were RCTs that warranted some concerns regarding their risk of bias (Supplementary Table S4, available online). The participants were predominantly female (90.2%). The pooled mean age was 41.2 years (95% confidence interval [CI]: 37.4-44.9 years), mean disease duration was 11.1 years (95% CI: 8.2-14.0 years), and mean systemic lupus erythematosus Disease Activity Index (SLEDAI) score was 4.0 (95% CI: 3.0-5.0). Renal involvement or lupus nephritis was present in 8.5%.

Clinical Effectiveness and Efficacy

The clinical effectiveness and efficacy outcomes of relevant studies are shown in Table 2. Among the studies that evaluated the clinical effectiveness of influenza vaccination in real-world settings, the clinical events studied included pneumonia (5 studies; 10,337 individuals), acute bronchitis (3 studies; 188 individuals), viral respiratory infections (2 studies; 99 individuals), and influenza infections (5 studies; 244 individuals). All-cause hospitalization, hospitalization for septicemia, bacteremia, and viremia; intensive care unit admission; and mortality were reported in only 1 study. The risk of influenza infection was significantly lower in vaccinated patients with systemic lupus erythematosus compared to nonvaccinated patients in the only 2 studies with comparators.[56,72] Influenza vaccination significantly reduced acute bronchitis in 2 nonrandomized trials performed in Serbia,[62,63] but the protective effect did not reach statistical significance in a retrospective cohort study with a smaller cohort of patients with lupus.[56] A large retrospective cohort study of national claims data in Taiwan showed a trend toward reduced risk of pneumonia after adjustment for age, sex, and comorbidities (adjusted hazard ratio 0.70, 95% CI: 0.49-1.00),[33] and the 3 studies with smaller samples had large effect sizes which were not statistically significant.[56,62,63] Meta-analysis was not performed for the outcomes of clinical effectiveness due to the heterogeneity

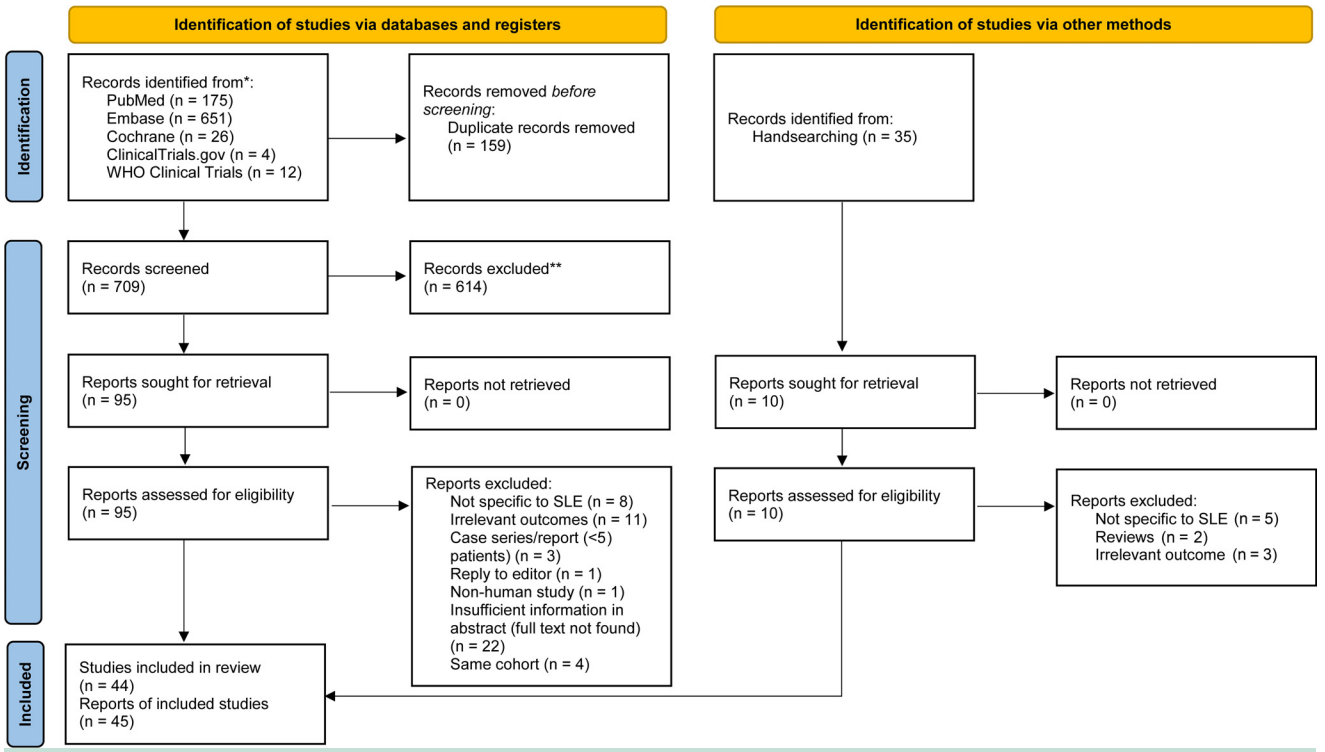

Figure 1 PRISMA study flow diagram. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

of study designs. This study did not identify any cost-effectiveness study for influenza vaccination in systemic lupus erythematosus or lupus nephritis.

Pooled seroconversion rates among patients with systemic lupus erythematosus who received the influenza vaccination were 56.6% (95% CI: 48.3%-64.7%) for swine flu (H1N1), 56.7% (95% CI: 44.5%-68.6%) for influenza variant A (H3N2), and 46.8% (95% CI: 33.0%-60.9%) for influenza variant B (B) strains. Pooled seroprotection rates were 68.2% (95% CI: 60.0%-76.0%) for H1N1, 73.7% (95% CI: 59.6%-85.8%) for H3N2, and 69.9% (95% CI: 59.6%-79.3%) for B influenza strains. Meta-regression for age, disease duration, disease activity score, and presence of renal involvement found that seroconversion for H3N2 influenza was inversely related to the presence of renal involvement ($P = .05$), whereas seroprotection for H3N2 influenza strain was significantly associated with age and disease duration (Supplementary Table S5, available online).

Safety

Supplementary Table S6, available online summarized the findings for the aspects of influenza vaccine safety in lupus: disease activity score, autoantibody levels, disease flares, and postvaccination adverse effects. Changes in lupus disease activity scores were evaluated in 12 studies with 538 patients, with the majority reporting no significant worsening. Compared to baseline, the pooled mean SLEDAI was changed by −0.28 (95% CI: −1.43-0.87, $P = .58$) at 3-4 weeks postvaccination, and −0.68 (95% CI: −3.01-1.64, $P = .48$) at 1.5-3.5 months postvaccination. Complement levels did not change significantly, as the pooled mean differences in C3 and C4 titers between baseline and 3-4 weeks postvaccination were 2.3 mg/dL (95% CI: −0.3-4.8, $P = .07$) and −0.8 mg/dL (95% CI: −5.8-4.2, $P = .63$), respectively. However, some studies reported increased autoantibody levels or increased seroconversion early postvaccination that appeared to be transient.[11,69] Results for autoantibodies were not pooled due to clinical heterogeneity in the assessment and reporting of autoantibodies.

Disease flares were described by 11 studies that included 617 patients (Supplementary Table S6, available online), ranging between 0% and 42.6% at any time during study follow up. Most of the flares were described as mild to moderate. Clinical adverse events after vaccination were reported in 10 studies with a total of 488 patients. Local adverse events such as itching, erythema, and induration at the injection site occurred in 100 patients (20.5%). Systemic adverse events occurred in 130 (26.6%) patients, most frequently arthralgia, myalgia, fever, headache, and chills.

Utilization

Twelve cross-sectional studies (2578 patients) reported current vaccination rates, defined as influenza vaccination within 1 year of the study. The pooled proportion was 40.0% (95% CI: 33.7%-46.5%), but there was significant

Table 1 Characteristics of All Included Studies

Study	Country	Design	Abstract only	Participants Total/ Vaccinated/ nonvaccinated	Age, years	Male N (%)	Disease			Immunosuppressants reported	Vaccine
							Activity score*	Duration, years	Renal N (%)		
Abu-Shakra 2002a Abu-Shakra 2002b	Israel	NRCT	N	24/24/0	46.1 ± 13.9	0 (0)	6.6 ± 9.3	NR	NR	GC, AZA, HCQ, MTX	H1N1, H3N2, B
Brodman 1978	United States	NRCT	N	46/46/0	36.0 (SD NR)	2 (4.3)	NR	NR	1 (2.2)	GC, AZA, HCQ	H1N1†
Chang 2016	Taiwan	RC	N	10,125/1765/8360	38.9 ± 14.5	1172 (11.6)	NR	NR	460 (4.5)	NR	SIV
Chehab 2018	Germany	CS	N	579/NA/NA	52.3 ± 13.4	35 (6.0)	SLAQ 13.5 ± 7.5	16.8 ± 9.1	NR	GC	SIV
Cherny 2018	United States	CS	Y	397/NA/NA	NR	NR	NR	NR	NR	NR	SIV
Chiganer 2021	Latin America, Europe	CS	N	1874/NA/NA	39.8 ± 11.4	67 (3.6)	NR	13.7 ± 6.3	306 (16.3)	GC, HCQ	SIV
Del Porto 2006	Italy	NRCT	N	28/14/14	42.6 ± 11.5	1 (3.6)	6.6 ± 3.8	NR	NR	NR	H1N1, H3N2, B
Elkayam 2011	Israel	NRCT	N	21/21/0	41.7 ± 14.5	4 (19.0)	0.9 ± 1.0	20.5 ± 14.3	NR	GC, HCQ, MTX	H1N1
Figueroa-Parra 2021	Mexico	CS	N	15/NA/NA	NR	NR	NR	NR	NR	NR	SIV
Harris 2017	United States	CS	N	75/NA/NA	13.7 ± 3.8	12 (16.0)	SDI 0.8	4.2 ± 3.3	36 (48.0)	HCQ, GC	SIV
Hernandez 2015	Philippines	PC	Y	24/24/0	NR	NR	NR	NR	NR	NR	SIV
Herron 1979	United States	NRCT	N	20/20/0	41.8 ± 3.1	2 (10.0)	NR	8.2 ± 1.3	NR	GC	H1N1, H3N2
Holvast 2006	Netherlands	NRCT	N	56/56/0	46.1 ± 12.9	6 (10.7)	NR	14.3 ± 10.6	NR	GC, AZA, HCQ	H1N1, H3N2, B
Holvast 2009a	Netherlands	RCT	N	78/54/24	45.0 ± 12.9	12 (15.4)	3.7 ± 2.5	NR	NR	GC, AZA, HCQ, MTX	H1N1, H3N2
Holvast 2009b	Netherlands	NRCT	N	52/52/0	45.2 ± 10.0	9 (17.3)	2.0 ± 0.9	NR	NR	GC, AZA, HCQ	(H1N1, H3N2, B)†
Huerta-Yáñez 2010	Mexico	CS	Y	71/NA/NA	45.0 ± 10.1	4 (5.6)	NR	NR	NR	GC, HCQ	SIV, H1N1
Kim 2013	Korea	NRCT	N	31/31/0	39.5 ± 10.0	0 (0)	2.3 ± 4.2	6.2 ± 3.9	NR	GC, MTX, TNFα blocker, HCQ, AZA	H1N1
Kostianovsky 2012	France	NRCT	N	32/32/0	NR	NR	NR	NR	NR	NR	H1N1,† SIV
Krasselt 2018	Germany	CS	N	68/NA/NA	51.3 ± 15.3	4 (5.8)	5.0 ± 6.0	11.3 ± 10.3	22 (32.4)	GC, AZA, HCQ, MMF, MPA, CYC, MTX, biologics	SIV
Launay 2013	France	NRCT	N	27/27/0	44.4 ± 10.6	1 (3.7)	3.9 ± 3.8	NR	NR	GC, HCQ, AZA, MPA, CYC, CsA, MTX	H1N1, H3N2, B
Lawson 2015	United States	CS	N	485/NA/NA	50.0 ± 12.0	34 (7.0)	SLAQ 17.5 ± 7.6	19.8 ± 7.8	152 (31.3)	GC, AZA, MMF, CsA, CYC, MTX, biologics	SIV
Long 2012	United States	NRCT	N	20/20/0	12.7 ± 3.4	4 (20.0)	NR	NR	NR	GC, MMF	H1N1
Louie 1978	United States	NRCT	N	11/11/0	35.5 ± 11.9	1 (9.1)	NR	NR	2 (18.2)	GC, AZA	H1N1, H3N2
Lu 2011	Taiwan	NRCT	N	21/21/0	34.3 ± 11.8	1 (4.8)	3.8 ± 1.9	NR	NR	GC, AZA, HCQ	H1N1
Malysheva 2012	Germany	CS	Y	65/49/0	NR	NR	NR	NR	NR	NR	SIV
Mathian 2011	France	PC	N	111/111/0	35.2 ± 10.6	9 (8.1)	9.0 ± 6.3	NR	NR	GC, AZA, HCQ, MMF, CYC, MTX	H1N1†
Milanovic 2013	Serbia	CS	N	30/19/11	52.3 ± 12.5	NR	NR	NR	NR	NR	H1N1, H3N2, B
Mitchell 1982	United Kingdom	NRCT	N	6/6/0	NR	NR	NR	NR	NR	GC, AZA, HCQ, CsA	H3N2, B
Qendro 2019	Canada	CS	N	69/69/0	44.6 ± 15.6	11 (15.9)	NR	11.4 ± 11.5	NR	DMARD, biologics	SIV
Ristow 1978	United States	NRCT	N	29/29/0	NR	1 (3.4)	NR	NR	1 (3.4)	GC, AZA, CYC, CLB	H1N1
Ritterhouse 2011	United States	NRCT	N	60/60/0	42.7 ± 11.9	0 (0)	4.4 ± 5.5	NR	19 (31.7)	GC, MTX, MMF, AZA, CYC, HCQ	SIV
Saad 2011	Brazil	NRCT	N	572/572/0	NR	NR	NR	NR	NR	NR	H1N1
Stojanovich 2006	Serbia	NRCT	N	69/23/46	44.7 ± 13.6	NR	NR	NR	NR	NR	SIV
Stojanovich 2009	Serbia	NRCT	Y	89/43/46	44.7 ± 13.6	NR	NR	NR	NR	NR	SIV
Tarjan 2006	Hungary	NRCT	N	18/18/0	41.2 ± 13.9	NR	NR	5.3 ± 4.6	NR	GC, AZA, HCQ	H1N1, H3N2, B
Urowitz 2011	Canada	RC	N	103/103/0	43.9 ± 15.2	9 (8.7)	4.4±4.3	14.2 ± 11.1	NR	GC, HCQ	H1N1
Vieira de Rezende 2019	Brazil	CS	N	173/79/94	NR	11 (6.4)	NR	11 ± 9	61 (35.1)	GC, HCQ	SIV
Vista 2012	United States	NRCT	N	101/101/0	43.9 ± 14	8 (7.9)	NR	NR	NR	NR	SIV
Wallin 2009	Brazil	NRCT	N	47/47/0	40.6 ± 9.9	1 (2.1)	1.2 ± 2.0	8.6 ± 5.5	0 (0)	CsA, MTX, AZA	H1N1, H3N2, B

Table 1 (*Continued*)

Study	Country	Design	Abstract only	Participants Total/ Vaccinated/ nonvaccinated	Age, years	Male N (%)	Disease			Immunosuppressants reported	Vaccine
							Activity score*	Duration, years	Renal N (%)		
Wiesik-Szewczyk 2010	Poland	NRCT	N	62/62/0	37.8 ± 10.7	3 (4.8)	4.8 ± 5.1	4.8 ± 5.1	26 (41.9)	GC, AZA, HCQ, MTX, CYC, CsA	H1N1, H3N2, B
Williams 1978	United States	RCT	N	40/19/21	32.5 (SD NR)	3 (7.5)	NR	NR	28 (70.0)	GC	H1N1, H3N2
Yazdany 2010	United States	CS	N	783/742/685	50.1 ± 12.0	0 (0)	SLAQ 13 ± 8	NR	NR	NR	SIV
Yu 2019	China	CS	Y	109/42/67	NR	NR	NR	NR	NR	NR	SIV
Ziade 2020	Lebanon	CS	N	63/63/0	42.8 ± 13.7	4 (6.3)	NR	7.8 (SD NR)	NR	GC, DMARD, biologics	SIV

AZA = Azathioprine; B = influenza variant B; CYC = Cyclophosphamide; CS = cross-sectional; CsA = Cyclosporin A; DMARD = disease-modifying antirheumatic drug; GC = glucocorticosteroid; H1N1 = swine flu; H3N2 = influenza variant A; HCQ = Hydroxychloroquine; MMF = Mycophenolate mofetil; MTX = Methotrexate; N = no; NA = not available; NR = not reported; NRCT = nonrandomized clinical trial; NSAID = nonsteroidal anti-inflammatory drug; PC = prospective cohort; RC = retrospective cohort; RCT = randomized controlled trial; SD = standard deviation; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index; SIV = seasonal influenza vaccine; SLAQ = Systemic Lupus Activity Questionnaire; TNFα = necrosis factor alpha; Y = Yes.

*Disease activity score refers to SLEDAI unless otherwise specified.

†Received 2 doses of the vaccine on separate occasions at a time interval apart.

heterogeneity in the current vaccination rates (Figure 2). Meta-regression found that current vaccination rates in systemic lupus erythematosus were significantly associated with higher gross domestic product of the country[78] (P = .002) and longer disease duration (P = .001) (Supplementary Figure S1, available online). It was not significantly associated with study year (P = .79) or age (P = .98). The pooled ever-vaccination rate was 60.2% (95% CI: 53.0%-67.2%) from 4 studies (899 patients), again with significant heterogeneity (Supplementary Figure S2, available online). The pooled current vaccinated rate was significantly lower than the pooled ever-vaccinated rate ($P < .001$).

Barriers to Influenza Vaccination

Five studies (2635 patients) from Germany, North America, Brazil, and China investigated barriers to influenza vaccination in lupus.[13,35,50,66,72] The most common reasons for influenza vaccine hesitancy were lack of doctor recommendation or medical prescription (57.4%), concerns over the efficacy or safety of the vaccine (12.7%), lack of interest or rejection of the vaccines (11.8%), unavailability or high cost of vaccines (8.2%), and having experienced side effects of other vaccines previously (4.7%). Other barriers to vaccination are shown in Supplementary Figure S3, available online.

Publication Bias

Funnel plots and an Egger regression test were done to assess for publication bias for influenza vaccine effectiveness (pneumonia and influenza infection), changes in SLEDAI, and vaccination rates (Supplementary Figure S4, available online). There was no statistically significant publication bias for all the outcomes of pneumonia (P_{egger} = 0.09), bronchitis (P_{egger} = .39), change in SLEDAI at 3-4 weeks (P_{egger} = .52) and 1.5-3.5 months (P_{egger} = .43) from baseline, current vaccination rates (P_{egger} = .099), and ever-vaccinated rates (P_{egger} = .77).

DISCUSSION

This systematic review summarized the available data on efficacy, effectiveness, safety, uptake, and barriers to influenza vaccination among individuals with systemic lupus erythematosus and lupus nephritis. Pooled seroconversion ranged 46%-56%, and pooled seroprotection rates ranged 68%-73% and were significantly associated with age and disease duration. These findings are similar to previously reported pooled seroprotection rates in patients with systemic lupus erythematosus of 66%-68%, 64%-76%, and 60%-66% against H1N1, H3N2, and B strains, respectively.[16,17] In addition to our findings that influenza vaccination was efficacious and generally safe in quiescent lupus, this study highlighted that the effectiveness of influenza vaccination in preventing clinically significant events were reported in only a handful of studies, while cost-

Table 2 Studies Evaluating Effectiveness and Efficacy of Influenza Vaccination in Systemic Lupus Erythematosus

Study	Follow-up, months	Effectiveness			Seroconversion,* %			Seroprotection,* %		
		Outcome	Clinical event among vaccinated, N (%)	Clinical event among nonvaccinated, N (%)	H1N1	H3N2	B	H1N1	H3N2	B
Abu-Shakra 2002b	3	NA	NA	NA	37.5	58.3	62.5	33.3	66.7	91.7
Brodman 1978	1	NA	NA	NA	NA	NA	NA	69.0	NA	NA
Chang 2016	12	Total hospitalization Pneumonia Septicemia, bacteremia, viremia Hospitalization for heart disease ICU admission In hospital dialysis Death	405 (22.9) 47 (2.7) 33 (1.9) 150 (8.5) 46 (2.6) 10 (0.6) 34 (1.9)	1894 (22.7) 174 (2.1) 161 (1.9) 480 (5.7) 202 (2.4) 73 (0.9) 137 (1.6)	NA	NA	NA	NA	NA	NA
Del Porto 2006	6	Influenza infection	1 (7.1)	NA	57.1	100.0	35.7	57.1	100.0	35.7
Elkayam 2011	1-1.5	NA	NA	NA	NA	NA	NA	76.2	NA	NA
Hernandez 2015	12	'Flu or flu-like' illnesses Pneumonia	5 (20.8) 2 (8.3)	NA	NA	NA	NA	NA	NA	NA
Herron 1979	4	NA	NA	NA	81.0	67	NA	NA	NA	NA
Holvast 2006	1	Influenza infection	0 (0)	NA	42.9	39.3	41.1	83.9	85.7	69.6
Holvast 2009a	3-4	NA	NA	NA	44.4	68.5	NA	81.5	75.9	NA
Holvast 2009b	2	NA	NA	NA	34.6	25.0	19.2	86.5	80.8	61.5
Kim 2013	1	NA	NA	NA	96.8	NA	NA	77.4	NA	NA
Kostianovsky 2012	0.75	NA	NA	NA	85.7	NA	NA	65.6	NA	NA
Long 2012	1-1.5	NA	NA	NA	40.0	NA	NA	45.0	NA	NA
Louie 1978	1	NA	NA	NA	72.7	63.6	NA	NA	NA	NA
Lu 2011	6	Influenza infection	0 (0)	NA	76.2	NA	NA	76.2	NA	NA
Mathian 2011	1.5	NA	NA	NA	71.8	NA	NA	80.0	NA	NA
Milanovic 2013	12-60	Total viral infections Bronchitis Pneumonia Influenza infection	5 (26.3) 1 (5.3) 1 (5.3) 1 (5.3)	10 (90.9) 3 (27.3) 2 (18.2) 6 (54.5)	NA	NA	NA	NA	NA	NA
Mitchell 1982	0.75	NA	NA	NA	NA	83.3	83.3	NA	83.3	83.3
Ristow 1978	1	NA	NA	NA	48.3	NA	NA	48.3	NA	NA
Saad 2011	0.75	NA	NA	NA	60.5	NA	NA	64.9	NA	NA
Stojanovich 2006	12	Acute bronchitis Pneumonia Viral respiratory infection	1 (4.3) 0 (0) 5 (21.7)	17 (36.9) 1 (8.7) 21 (45.6)	NA	NA	NA	NA	NA	NA
Stojanovich 2009	NR	Acute bronchitis Pneumonia	4 (9.3) 0 (0)	17 (37.0) 1 (2.2)	NA	NA	NA	NA	NA	NA
Wallin 2009	1.5 3	NA NA	NA NA	NA NA	57.4 53.0	51.7 55.0	51.1 56.0	76.6 62.0	68.0 67.0	63.9 73.0

Table 2 (*Continued*)

Study	Follow-up, months	Effectiveness			Seroconversion,* %			Seroprotection,* %		
		Outcome	Clinical event among vaccinated, N (%)	Clinical event among nonvaccinated, N (%)	H1N1	H3N2	B	H1N1	H3N2	B
Wiesik-Szewczyk 2010										
Williams 1978	0.25-5	NA	NA	NA	47.4	31.8	NA	NA	NA	NA
Yu 2019	NR	Influenza infection	3 (7.1)	16 (23.9)	NA	NA	NA	NA	NA	NA

B = influenza variant B; H1N1 = swine flu; H3N2 = influenza variant A; ICU = intensive care unit; NA = not applicable; NR = not reported.
*Seroconversion and seroprotection rates refer to the highest proportions of patients seroconverted or seroprotected during follow-up.

effectiveness studies were not available. Prior studies had largely focused on the immunogenicity of influenza vaccines in lupus,[15-18] possibly because the objective and easily standardized outcomes of seroconversion and seroprotection can be assessed at relatively short and well-defined time intervals, whereas effectiveness trials to assess clinical outcomes such as influenza infection or pneumonia require much larger sample sizes, significantly longer recruitment and follow up, and therefore, greater resources. Yet, such effectiveness data on the ability of influenza vaccination to prevent clinically significant infections would be given considerably greater weight when physicians discuss vaccinations with patients during shared decision-making. More information regarding the influence of the different types and intensity of immunosuppressive therapy on the clinical effectiveness of influenza vaccination is eagerly anticipated, but real-world studies will need to account for confounders such as baseline risk and the highly variable immunosuppressive regimens used in routine clinical practice.

As influenza infection risk, morbidity, and mortality are significantly amplified in autoimmune disease and immunosuppression,[4,79] influenza vaccination in systemic lupus erythematosus is advocated by international guidelines.[80] The European League Against Rheumatism (EULAR) recommended annual administration of nonlive influenza vaccines to patients with lupus during quiescent disease.[80] This study identified that the pooled currently vaccinated rate was significantly lower than the pooled ever-vaccinated rates, suggesting possible low adherence to annual influenza vaccination. Moreover, current vaccination rates were not associated with study year, suggesting that vaccination rates have not improved over time. Because many of the included studies were from developed countries, the actual vaccination rates worldwide may be lower than those reported. As such, targeted strategies should address the common themes of inadequate physician advocation and patient education regarding vaccine effectiveness or safety identified by the study to be the dominant barriers to increase the uptake of influenza vaccines.

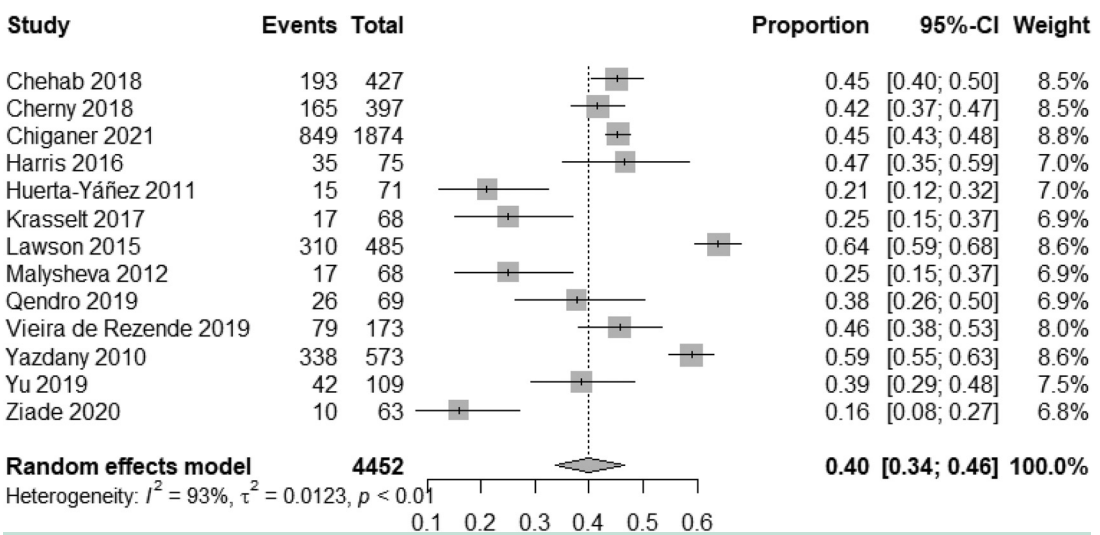

Figure 2 Proportion of patients with systemic lupus erythematosus currently vaccinated (within 1 year) against influenza.

There are limitations to this study. None of the studies reported data on patients with lupus nephritis separately; thus, we were unable to specifically ascertain the outcomes of influenza vaccination in these individuals with proteinuria or impaired kidney function who may have altered immunogenicity to vaccinations,[10] increased susceptibility to infections, and greater infection-related morbidity.[3] Patients with active lupus were frequently excluded from the included studies on vaccine efficacy; hence, the results are restricted to those with quiescent disease. As most of the studies were from Europe and North America with few studies from Central or South America, Middle East, and Asia, the generalizability of the results to cohorts from different geo-socioeconomic settings may also be limited.

CONCLUSION

Influenza vaccination is efficacious and safe in systemic lupus erythematosus and lupus nephritis, but further clinical effectiveness and cost-effectiveness studies may be required to augment support for policy changes or large-scale implementation of targeted strategies to overcome barriers.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2021.08.038.

Supplementary Table S1 Search Strategies and Terms

PubMed

No	Search	Results
1	Lupus OR (systemic lupus erythematosus) OR SLE OR (lupus nephritis)	98,323
2	Vaccin* OR inoculat* OR immunis* OR immuniz*	644,558
3	Influenza	142,593
4	1 AND 2 AND 3	175

Embase

No	Search	Results
1	'lupus'/exp OR lupus OR (systemic AND ('lupus'/exp OR lupus) AND erythematosus) OR 'sle'/exp OR sle OR (('lupus'/exp OR lupus) AND ('nephritis'/exp OR nephritis))	164,288
2	Vaccin* OR inoculat* OR immunis* OR immuniz*	811,292
3	'influenza'/exp OR influenza	172,354
4	1 AND 2 AND 3	651

Cochrane

No	Search	Results
1	Lupus OR (systemic lupus erythematosus) OR SLE OR (lupus nephritis)	4001
2	Vaccin* OR inoculat* OR immunis* OR immuniz*	30780
3	Influenza	8741
4	1 AND 2 AND 3	26

ClinicalTrials.gov

No	Search	Results
1	MeSH descriptor: [Systemic lupus erythematosus] explode all trees	698
2	MeSH descriptor: [Vaccine OR inoculate OR immunize] explode all trees	8374
3	MeSH descriptor: [Influenza, Human] explode all trees	2453
4	1 AND 2 AND 3	4

WHO Clinical Trials

ID	Search	Results
1	Lupus OR (systemic lupus erythematosus) OR SLE OR (lupus nephritis)	2019
2	Vaccin* OR inoculat* OR immunis* OR immuniz*	15145
3	Influenza	3764
4	1 AND 2 AND 3	12

Supplementary Table S2 Outcomes Evaluated in the Included Studies of Influenza Vaccination in Systemic Lupus Erythematosus Are Marked with "Yes"

Study name	Outcome of interest				
	Effectiveness	Efficacy	Safety	Utilization	Barriers
Abu-Shakra 2002a			Yes		
Abu-Shakra 2002b		Yes			
Brodman 1978		Yes	Yes		
Chang 2016	Yes				
Chehab 2018				Yes	Yes
Cherny 2018				Yes	
Chiganer 2021				Yes	Yes
Del Porto 2006	Yes	Yes	Yes		
Elkayam 2011		Yes	Yes		
Figueroa-Parra 2021				Yes	
Harris 2017				Yes	
Hernandez 2015	Yes				
Herron 1979		Yes	Yes		
Holvast 2006	Yes	Yes	Yes		
Holvast 2009a		Yes	Yes		
Holvast 2009b		Yes	Yes		
Huerta-Yáñez 2011				Yes	
Kim 2013		Yes			
Kostianovsky 2012		Yes	Yes		
Krasselt 2018				Yes	
Launay 2013			Yes		
Lawson 2015				Yes	Yes
Long 2012		Yes			
Louie 1978		Yes	Yes		
Lu 2011	Yes	Yes	Yes		
Malysheva 2012				Yes	
Mathian 2011		Yes	Yes		
Milanovic 2013	Yes				
Mitchell 1982		Yes			
Qendro 2019				Yes	
Ristow 1978		Yes	Yes		
Ritterhouse 2011			Yes		
Saad 2011		Yes			
Stojanovich 2006	Yes				
Stojanovich 2009	Yes				
Tarjan 2006			Yes		
Urowitz 2011			Yes		
Vieira de Rezende 2019				Yes	Yes
Vista 2012			Yes		
Wallin 2009		Yes	Yes		
Wiesik-Szewczyk 2010		Yes	Yes		
Williams 1978		Yes	Yes		
Yazdany 2010				Yes	
Yu 2019	Yes		Yes	Yes	Yes
Ziade 2020				Yes	

Supplementary Table S3 Risk of Bias for Nonrandomized Studies (NRS) Using ROBINS-I Tool

Study	Baseline confounding	Selection of participants	Classification of intervention	Deviation from intended intervention	Missing data	Measurement of outcomes	Selection of reported results	Overall risk of bias
Abu-Shakra 2002a	Moderate	NI	Low	Low	Low	Low	Low	NI
Abu-Shakra 2002b	Moderate	NI	Low	Low	Low	Low	Low	NI
Brodman 1978	Low	Low	Low	Low	Low	Low	Low	Low
Chang 2016	Moderate	Moderate	Moderate	Low	Low	Low	Low	Moderate
Chehab 2018	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate
Cherny 2018	Low	Low	Low	Low	Moderate	Moderate	Low	Moderate
Chiganer 2021	Low	Moderate	Low	Low	NI	Low	Low	Moderate
Crowe 2011	Moderate	NI	Low	Low	Low	Low	Low	NI
Del Porto 2006	Moderate	Moderate	Low	Low	Low	Low	Moderate	Moderate
Elkayam 2011	Low	Low	Low	Low	Low	Low	Low	Low
Figueroa-Parra 2021	Moderate	Serious	Moderate	Low	Moderate	Low	Low	Serious
Harris 2017	Low	Moderate	Low	Moderate	Moderate	Moderate	Low	Moderate
Hernandez 2015	Serious	NI	Low	Low	Moderate	Serious	Low	Serious
Herron 1979	Low	Moderate	Low	Low	Serious	Low	Low	Serious
Holvast 2006	Low	NI	Low	Low	Low	Low	Moderate	NI
Holvast 2009b	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Huerta-Yanez 2010	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Kim 2013	NI	Moderate	Low	Low	Low	Low	Low	NI
Kostianovsky 2012	Low	Low	Low	Low	Moderate	Moderate	Low	Moderate
Krasselt 2018	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Launay 2013	Low	Low	Low	Low	Low	Low	Low	Low
Lawson 2015	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate
Long 2012	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Louie 1978	NI	NI	Low	Low	Moderate	Low	Low	NI
Lu 2011	Moderate	NI	Low	Low	Low	Low	Low	NI
Malysheva 2012	NI	NI	Low	Low	Moderate	Low	Low	NI
Mathian 2011	Low	Low	Low	Low	Moderate	Low	Low	Moderate
Milanovic 2013	Low	Low	Low	Low	Low	Moderate	Low	Moderate
Mitchell 1982	Moderate	NI	Low	Low	Serious	Low	Moderate	Serious
Qendro 2019	Low	Low	Low	Low	Moderate	Low	Low	Moderate
Ristow 1978	NI	NI	Low	Low	Moderate	Low	Low	NI
Ritterhouse 2011	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Saad 2011	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Stojanovich 2006	NI	NI	Low	Low	Moderate	NI	Low	NI
Stojanovich 2009	NI	NI	Low	Low	Low	Moderate	Moderate	NI
Tarjan 2009	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Urowitz 2011	Moderate	Low	Low	Low	Low	Low	Low	Moderate

Supplementary Table S3 (*Continued*)

Study	Baseline confounding	Selection of participants	Classification of intervention	Deviation from intended intervention	Missing data	Measurement of outcomes	Selection of reported results	Overall risk of bias
Vieira de Rezende 2019	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Vista 2012	Low	Low	Low	Low	Moderate	Low	Moderate	Moderate
Wallin 2009	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Wiesik-Szewczyk 2010	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Yazdany 2010	Low	Low	Low	Low	Low	Low	Low	Low
Yu 2019	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Ziade 2020	Moderate	Low	Low	Low	Low	Low	Low	Moderate

NI = No information.

Supplementary Table S4 Risk of Bias for Randomized Trials Using RoB 2 Tool

Study	Risk of bias arising from the randomization process	Deviations from the intended interventions	Missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result	Overall
Holvast 2009a	Some concerns	Some concerns:	Low	Some concerns	Low	Some concerns
Williams 1978	Low	Low	Low	Some concerns	Low	Some concerns

RoB = Risk of bias

Supplementary Table S5 Analysis of Factors Associated with Influenza Vaccine Efficacy in Systemic Lupus Erythematosus

	Seroconversion for H1N1 strain	Seroconversion for H3N2 strain	Seroconversion for B strain	Seroprotection for H1N1 strain	Seroprotection for H3N2 strain	Seroprotection for B strain
Age	−0.0017 [−0.0145, 0.0110] (*P* = .79)	0.0025 [−0.0271, 0.0322] (*P* = .87)	−0.0183 [−0.0601, 0.0235] (*P* = .39)	0.0080 [−0.0025, 0.0186] (*P* = .14)	0.0383 [0.0083, 0.0682] (*P* = .01)	0.0087 [−0.0308, 0.0483] (*P* = .67)
Disease duration	−0.0102 [−0.0496, 0.0291] (*P* = .61)	−0.0179 [−0.0474, 0.0116] (*P* = .23)	−0.0163 [−0.0353, 0.0027] (*P* = .09)	0.0105 [−0.0049, 0.0260] (*P* = .18)	0.0241 [0.0051, 0.0432] (*P* = .01)	−0.0036 [−0.0227, 0.0154] (*P* =.71)
SLEDAI	−0.0051 [−0.0595, 0.0494] (*P* = .85)	0.0543 [−0.0267, 0.1352] (*P* = .19)	0.0301 [−0.0482, 0.1084] (*P* = .45)	−0.0263 [−0.0692, 0.0166] (*P* = .23)	0.0202 [−0.0386, 0.0789] (*P* = .50)	0.0115 [−0.0571− 0.0801] (*P* = .74)
Renal involvement	−0.150 [−0.488, 0.188] (*P* = .38)	−0.337 [−0.675, 0.0011] (*P* = .05)	NIL	−0.299 [−0.694, 0.0956] (*P* = .14)	0.416 [−1.28, 2.11] (*P* = .63)	NIL

B = influenza variant B; H1N1 = swine flu; H3N2 = influenza variant A; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index.

Supplementary Table S6 Safety of Influenza Vaccination in Systemic Lupus Erythematosus and Lupus Nephritis

	FU (mo)	Disease activity*	Complements		Autoantibodies†										Flares‡		Adverse Events‡	
			C3	C4	Anti-dsDNA	ANA	Anti-Sm	Anti-RNP	Anti-Ro	Anti-La	Anti-CL IgM	Anti-CL IgG	LAC	Others	Any (%)	Severe (%)	Systemic (%)	Local (%)
Abu-Shakra 2002b	0	6.6 ± 9.2	NR	NR	45.8%	NR	4.0%	16.7%	25.0%	0	12.5%	37.5%	NR	NR	NR	NR	—	—
	1.5	4.9 ± 7.2	NR	NR	45.8%	NR	16.7%	33.3%	37.5%	12.5%	20.8%	58.3%	NR	NR	NR	NR	NR	NR
	3	5.1 ± 6.2	NR	NR	50.0%	NR	0	12.5%	20.8%	8.3%	16.7%	50.0%	NR	NR	NR	NR	NR	NR
Brodman 1978	0	NR	138.7 ± 56.9	34.2 ± 31.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	—	—
	1*	NR	141.6 ± 63.8	32.3 ± 31.3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	23.9	0	19.6	NR
	2	NR	138.8 ± 58.4	34.0 ± 31.0	NR	NSI	NR	NR	NR	NR	NR	NR	NR	NR	35.1	0	35.1	NR
Del Porto 2006	0	6.2 ± 2.5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	—	—
	1	6.6 ± 4.4	NR	NR	NSI	NSI	NR	NR	NR	NR	NSI	NSI	NR	NR	14.3	0	0	12.5
	3	7.8 ± 3.9	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR				
	6	6.5 ± 4.5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR				
Elkayam 2011	0	0.9 ± 1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	1-1.5	0.3 ± 0.7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Herron 1979	4	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	20.0	5.0	NR	NR
Holvast 2006	1	NR§	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	33.9	5.3
Holvast 2009a	0	4 ± 2.6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	—	—
	1	4.3 ± 2.9	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	16.0	30.0
	3-4	3.5 ± 2.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR		
Holvast 2009b	0	2 ± 0.9	91.5 ± 22.1	20.5 ± 11.1	108 ± 87.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	—	—
	1§	3.3 ± 1.8	90.5 ± 24.4	21 ± 11.1	78.8 ± 60.	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	2	3 ± 1.8	90.5 ± 25.2	21 ± 10.6	75.3 ± 57.1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	19.6
Kostianovsky 2012	0.75	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	10.3	3.4	NR	NR
Launay 2013	0	3.9 ± 3.8	90 ± 20	20 ± 10	109 ± 172	NR	NR	NR	NR	NR	NR	NR	NR	RF	NR	NR	—	—
	1	3.3 ± 3.7	90 ± 20	20 ± 10	120 ± 211	NSI	NR	NR	NR	NR	NR	NR	NR	Anti-histone IFNα	NR	NR	55.5	51.8
Louie 1978	0	NR	82.4 ± 33.2	NR	NR	NSI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	—	—
	1	NR	87.7 ± 48.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lu 2011	0	4.1 ± 1.9	76.1 ± 8.3	13.2	70.1	NR	2.265	24.5	125.0	9.2	2.0	6.0	1.1	aGPI	NR	NR		
	0.75	4.5	81.1 ± 8.3	13.8	50.1	NR	3.59	25.5	121.2	11.0	1.7	7.9	1.1		4.8	4.8	0	0
	6	4.3	79 ± 10.5	24.7	38.6	NR	3.66	21.9	106.1	6.9	3.2	5.4	1.1					
Mathian 2011	0	9 ± 6.3 SELENA	100 ± 26	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	9.9	7.2	—	—
	0.75§	6 ± 3.9	100 ± 25	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	9.0	0.9	41.3	36.9
	1.5	4.5 ± 2.8	98 ± 23	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	2.7	0.0	42.3	30.2
Ristow 1978	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	3.4	24.1
Ritterhouse 2011	0	NR	NR	NR	33.3%	NR	18.3%	36.7%	41.7%	20.0%	NR	NR	NR	NR	NR	NR	—	—
	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	41.7	5.0	NR	NR
Tarjan 2006	0	NR	NR	NR	15.5	NR	NR	NR	NR	NR	15.4	48.3	NR	aGPI	NR	NR	-	-
	1	NSI	NR	NR	57.7	NR	NR	NR	NR	NR	10.1	36.0	NR		NR	NR	NR	NR
	2		NR	NR	69.6	NR	NR	NR	NR	NR	9.9	31.0	NR		NR	NR	NR	NR
Urowitz 2011	0	4.2 ± 4.4	NR	NR	34.1%	79.4%	10.8%	25.8%	48.4%	16.1%	NR	NR	NR	RF	NR	NR	—	—
	1	NR	NR	NR	33.8%	81.7%	9.5%	27.0%	39.2%	12.2%	NR	NR	NR	Scl-70	NR	NR	NR	NR
	3.5	3.9 ± 4.1	NR	NR	34.0%	73.7%	13.0%	26.1%	35.9%	14.1%	NR	NR	NR		11.5	NR	NR	NR
Vista 2012	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	10.9	NR	NR	NR	NR	—	—
	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	22.8	NR	NR	42.6	NR	4.0	NR
Wallin 2009	0	1.2 ± 2.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	1.5	1.6 ± 2.6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	NR	NR	NR

Supplementary Table S6 (*Continued*)

	FU (mo)	Disease activity*	Complements		Autoantibodies†										Flares‡		Adverse Events‡	
			C3	C4	Anti-dsDNA	ANA	Anti-Sm	Anti-RNP	Anti-Ro	Anti-La	Anti-CL IgM	Anti-CL IgG	LAC	Others	Any (%)	Severe (%)	Systemic (%)	Local (%)
Wiesik-Szewczyk 2010	0	4.8 ± 5.1	94 ± 86.7	36.0 ± 33.4	35.5%	61.3%	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	1	NR	93.7 ± 80.6	25.3 ± 31.2	51.6%	80.6%	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	3	NR	93 ± 82.1	24.3 ± 27.4	35.5%	79.0%	NR	NR	NR	NR	NR	NR	NR	NR	11.3	1.6	NR	NR
Williams 1978	0.25-5	NR	NSI	NR	NSI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Yu 2019	NR	NSI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	NR

aGPI = anti-beta-2 glycoprotein I; ANA = antinuclear antibodies; Anti-CL = anticardiolipin; Anti-dsDNA = anti-double-stranded deoxyribonucleic acid; Anti-La = anti—Sjögren's-syndrome-related antigen B; Anti-RNP = anti-ribonucleoprotein; Anti-Ro = anti—Sjögren's-syndrome-related antigen A; Anti-Sm = anti-Smith; C3 = complement component 3; C4 = complement component 4; FU = follow up; IFNα = interferon alpha; Ig = immunoglobulin; LAC = lupus anticoagulant; mo = months; N = no significant increase; NR = not reported; RF = rheumatoid factor; SD = standard deviation; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index.

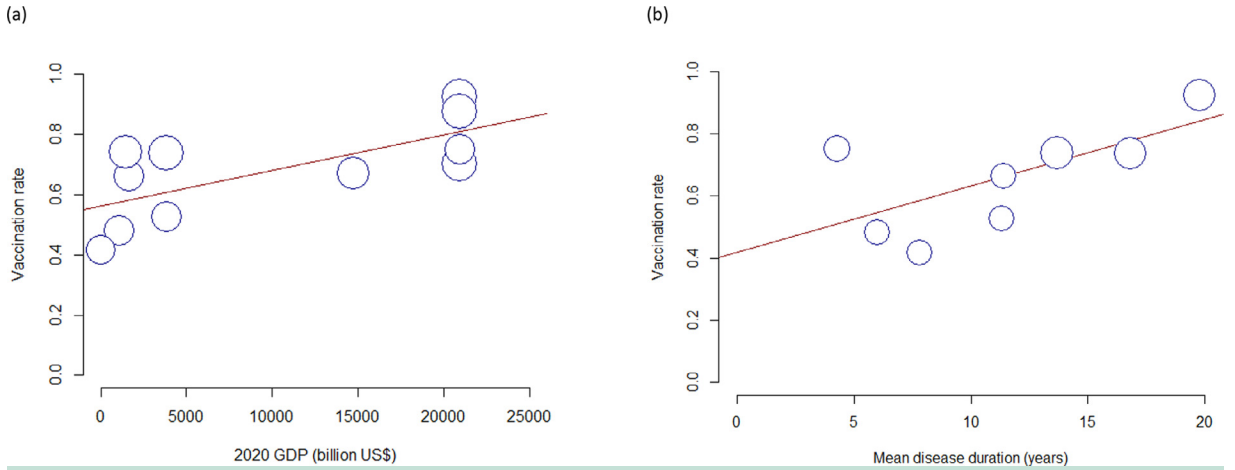
Categorical data are generally reported as percentages and continuous data are reported as mean ± SD. Study data reported as medians, minimum, and maximum ranges, and interquartile ranges were converted according to recommended statistical methods.

*Disease activity evaluated by the SLEDAI unless otherwise stated.

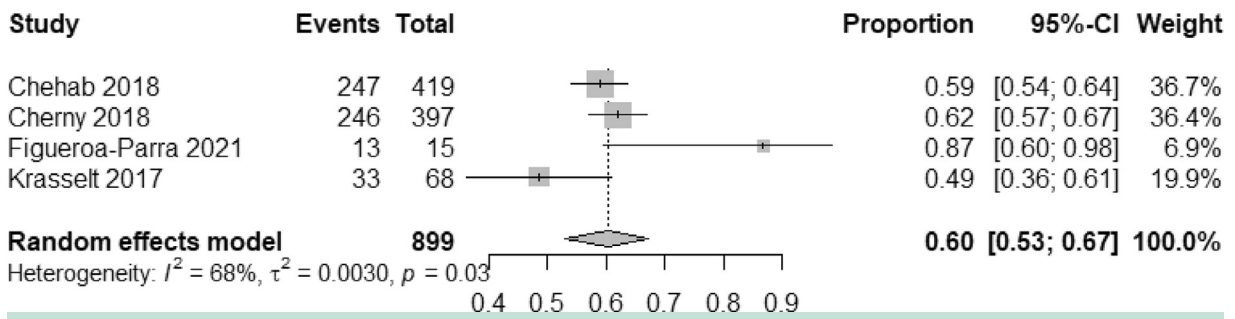
†Autoantibodies expressed as proportion of patients with autoantibody activity or expressed or autoantibody levels expressed as continuous data (mean ± SD for most studies except for Tarjan 2006 and Lu 2011 reported only as mean without SD). Units were as follow: aCL IgG (GPL U/mL), aCL IgM (MPL U/mL), Anti-dsDNA (IU/mL), Anti-Sm (U/mL), Anti-RNP (U/mL), Anti-Ro (U/mL), Anti-LA (U/mL), C3 (mg/dL), C4 (mg/dL), ANA titers, CD3+ (%), CD4+ (%), CD8+ (%), CD19+ (%), anti-histone IgG (AU/mL), anti-histone IgM (AU/mL), RF (IU/ml), CH50 (%), IFNα (IU/ml), aGPI IgG (U/mL), aGPI IgM (U/mL).

‡Flares and adverse events expressed as proportion of patients with events

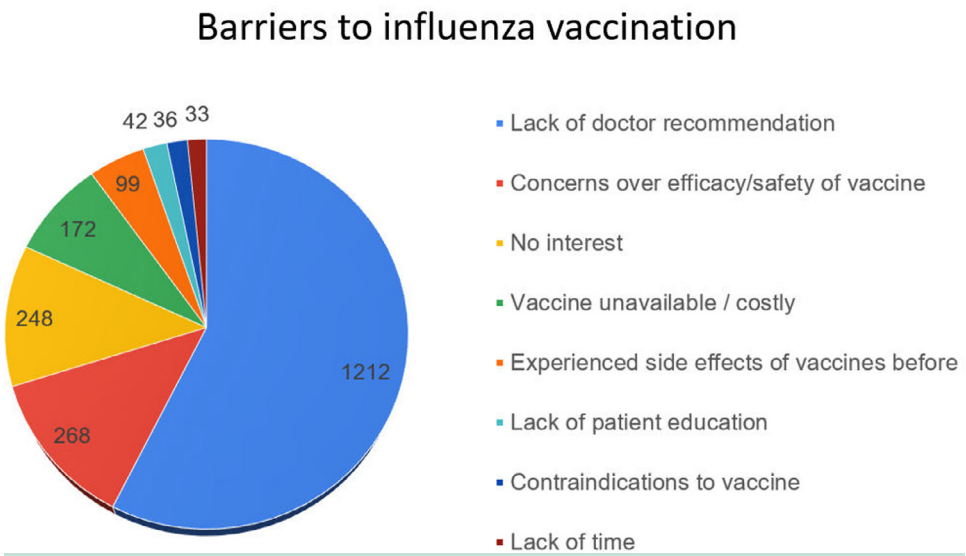
§Patients received a second dose of the influenza vaccination



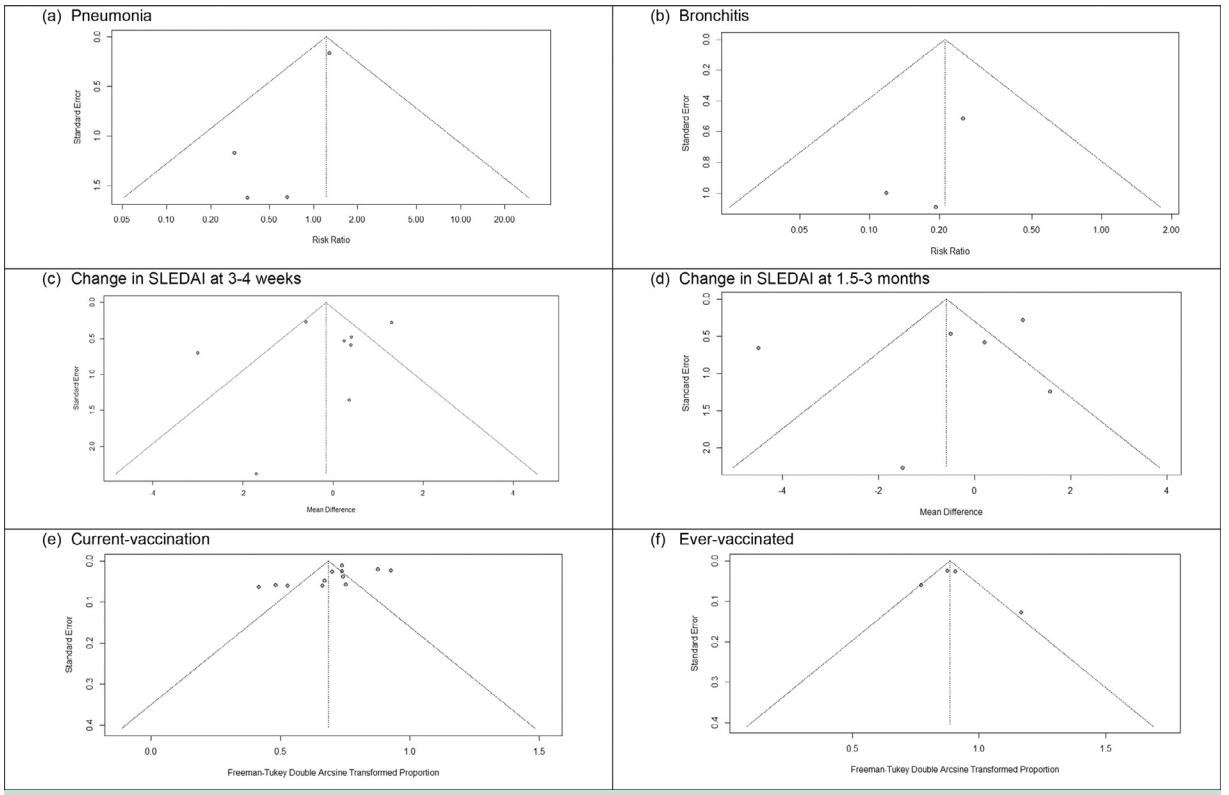
Supplementary Figure S1 Factors associated with current vaccination rates for influenza among systemic lupus erythematosus and lupus nephritis. Current influenza vaccination rates were significantly associated with **(A)** the gross domestic product of the country ($P = .002$) and **(B)** longer disease duration ($P = .02$).



Supplementary Figure S2 Proportion of patients with systemic lupus erythematosus ever vaccinated against influenza.



Supplementary Figure S3 Barriers to influenza vaccination among systemic lupus erythematosus and lupus nephritis.



Supplementary Figure S4 Funnel plots for influenza vaccination outcomes.
SLEDAI = Systemic Lupus Erythematosus Disease Activity Index