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Immunogenicity, safety and tolerability of anti-pneumococcal vaccination in systemic lupus erythematosus patients: An evidence-informed and PRISMA compliant systematic review and meta-analysis

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ABSTRACT

The immunological perturbations associated with systemic lupus erythematosus (SLE) put many patients at a higher risk of infections, including pneumococcal pneumonia. However, the uptake and utility of anti-pneumococcal vaccines in SLE patient is both controversial and not completely agreed upon. Indeed, several epidemiological studies of anti-pneumococcal vaccine safety and efficacy in SLE have reported short-term immunogenicity with elevated anti-pneumococcal antibody titres but inconsistent long-term findings, with some studies finding poor responses, mainly for long-term immune protection. Moreover, the safety and efficacy of the pneumococcal vaccine in SLE patients remains controversial due to the different types of anti-pneumococcal vaccines, and the heterogeneity of SLE patients. Several reviews addressing anti-pneumococcal vaccination in SLE patients exist, however, to the best of our knowledge, the present is the first systematic review and meta-analysis. To better understand the efficacy and safety of pneumococcal vaccination in SLE, a comprehensive literature search was performed identifying 18 studies, which have been included in the present systematic review and meta-analysis. All studies were designed as longitudinal investigations, 2, in particular, were of high quality, being randomized, double-blind trials (RCTs). Four studies had control groups. Total sample size included 601 participants. Vaccine immunogenicity in terms of subjects with protective antibody titers ranged from 36% to 97.6%. According to our systematic review and metanalysis, high erythrocyte sedimentation rate (ESR), older age, earlier SLE onset, high disease activity, and immunosuppressive therapy were predictors of poor immunogenicity, although belimumab was found to have no significant impact. With regard to safety, no serious adverse events were found, with up to one third of cases reporting mild/low-grade complaints.

In conclusion, due to the high risk of pneumococcal infection in SLE patients and given the safety and, at least partial, effectiveness, according to our systematic review and meta-analysis, in such patients, preventive

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strategies mainly by immunization, are required in all age groups and, in those needing immunosuppressive therapy, immunization should be given prior the initiation of the treatment.

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1. Introduction

Systemic lupus erythematosus (SLE) is a prototypic chronic, multi-organ autoimmune disease characterized by immune complex deposition and vasculopathy, and, therefore, can affect any organ and tissue of the human body. As a complex autoimmune disease [1], it is characterized by clinical heterogeneity, is more common among women [2], and has an estimated prevalence of 20 to 150 cases per 100,000 population [3,4]. The pathogenesis of SLE is not fully understood and is believed to be a result of a complex interplay between genetic susceptibility [5] and environmental factors in subjects with primary dysregulation in both innate and adaptive immune system, with dysregulation of type − 1 interferon being a common denominator [6–9].

In the face of autoimmune diseases, SLE patients are, somewhat paradoxically, at a higher risk of infections, in particular bacterial infections, representing one of the leading causes of morbidity and mortality in disease [10]. Infections account for 25–50% of overall mortality and half of SLE patients may experience severe infection, with > 20% of hospitalizations being due to infections [11–14].

The higher rate of infections in SLE can be attributed to various factors including the disease itself characterized by aberrant immune responses, complement dysregulation, and immunosuppressant therapy, such as corticosteroids and cytotoxic drugs commonly used in SLE management [10,15]. *Streptococcus pneumoniae* (*S. pneumoniae* or Pneumococcus) is a gram-positive diplococcus bacterium and the most frequent pathogen to involve the respiratory tract in SLE patients and remains an important cause of morbidity and mortality in patients with SLE [15,16]. Indeed, SLE patients are highly susceptible to *S. pneumoniae*. Invasive pneumococcal infection has an estimated incidence ranging from 201/100.000 to 236/100,000 patient-years among SLE patients, an incidence 13 times higher with respect to the general population [17,18].

Therefore, according to the European League Against Rheumatism (EULAR), vaccination status should be assessed in the initial workup of patients with autoimmune conditions including SLE [19]. However, controversy concerning the vaccination coverage, efficacy and safety in patients with SLE has existed for over 50 years. There are two types of pneumococcal vaccines available, pneumococcal conjugate vaccine or PCV and pneumococcal polysaccharide vaccine or PPSV [20].

The 13-valent PCV or PCV13 includes the most common pathogenic capsular polysaccharides: namely, 1, 3, 4, 5, 6A, 6B, 7F, 9 V, 14, 18C, 19A, 19F, and 23F, all of which are conjugated with the carrier protein CRM197, a non-toxic diphtheria toxin mutant. Because of the carrier protein conjugation, the vaccine is able to induce T-cell dependent immunological reactions, including higher affinity antibodies and an immunological memory.

The PPSV is a vaccine derived from a capsular polysaccharide: the polysaccharide antigens are used to induce type-specific antibodies that can enhance opsonization, phagocytosis, and killing of *S. pneumoniae*. The PPSV is, indeed, able to activate B-cells and to elicit T-cell independent immune responses, but is not able to induce mucosal immunity and, as such, has negligible impact on naso-pharyngeal carriage. The PPSV is widely recommended and used in high-risk adults, to prevent invasive pneumococcal disease. The 4-valent PPSV was the first vaccine introduced, replaced in the 1970's by the 14-valent formulation, further evolved into the 23-valent preparation in the 1980's [21]. There are currently two 23-valent PPSPV23 formulations: one used in the United States and in Europe (Pneumovax® 23) and one used in Europe and Canada (Pneumo® 23). In 2000, a further formulation was licensed: the protein conjugate heptavalent vaccine (PCV7).

With regard to anti-pneumococcal agents in SLE, several epidemiological studies have been conducted to assess their safety and efficacy with the reporting of inconsistent findings. Indeed, various studies found poor and impaired responses in terms of antibody titers, mainly for long-term immune protection following pneumococcal immunization in SLE patients [22–24], whereas others found anti-pneumococcal vaccines to be immunogenic with up to 79.2% having relevant protective antibody titres [25,26]. Furthermore, the safety of the pneumococcal vaccine in SLE patients remains controversial due to the different types of anti-pneumococcal vaccines, and the heterogeneity of SLE patients.

Several reviews addressing anti-pneumococcal vaccination in SLE patients exist, however, to the best of our knowledge, the present is the first systematic review and meta-analysis. The review and meta-analysis by Pugès and coworkers [27] was derived from data extracted from only three studies. To get a better understanding of the efficacy of pneumococcal immunization as well as its safety in patients with SLE, a broader and more comprehensive literature search was performed.

2. Material and methods

2.1. Systematic review and meta-analysis protocol and development

The present systematic review and meta-analysis has been conducted in compliance with the “Preferred Reporting Items for Systematic Reviews and Meta-analyses” (PRISMA) guidelines [28]. The study protocol has been devised according to the “PRISMA-Protocol” (PRISMA-P) guidelines [29] and is available upon request to the corresponding author.

This systematic review and meta-analysis has been registered in the International prospective register of systematic reviews (PROSPERO) of the Centre for Reviews and Dissemination of the York's University (UK; registration code CRD42018103605).

2.2. Search strategy

For the comprehensive literature search, a string made up of relevant keywords such as SLE, *S. pneumoniae*, vaccine and immunization, properly connected by Booleans operators, was utilized. This string was adapted according to the database searched. Target journals were hand-searched and reference lists of all included studies were scanned in order to increase the chance of getting potentially related articles. In accordance with the Cochrane recommendations, the gray literature was also independently mined *via* Google Scholar. No time or language filters were applied: scholarly databases were searched from inception and mined in any language. Studies were selected based on the following Patients/Intervention/Comparisons/Outcomes/Study design (PICOS) criteria: P (SLE patients with a diagnosis according to the ARA/ACR criteria), I (administration of an anti-pneumococcal vaccine), C (comparisons between vaccinated SLE patients and healthy controls; between SLE patients and SLE subjects who have refused the immunization), O (outcomes, anti-pneumococcal vaccine safety, tolerability and immunogenicity among SLE patients), and S (original investigation reporting sufficient quantitative details). Articles devised as clinical case-report, case-series, editorial, letter to editor, expert opinion, commentary, review article were excluded. Further details concerning the literature search strategy adopted are reported in Fig. 1 and Table 1.

Two authors (NLB, AW) independently extracted the following information using an *ad hoc* designed Excel spreadsheet: surname of first

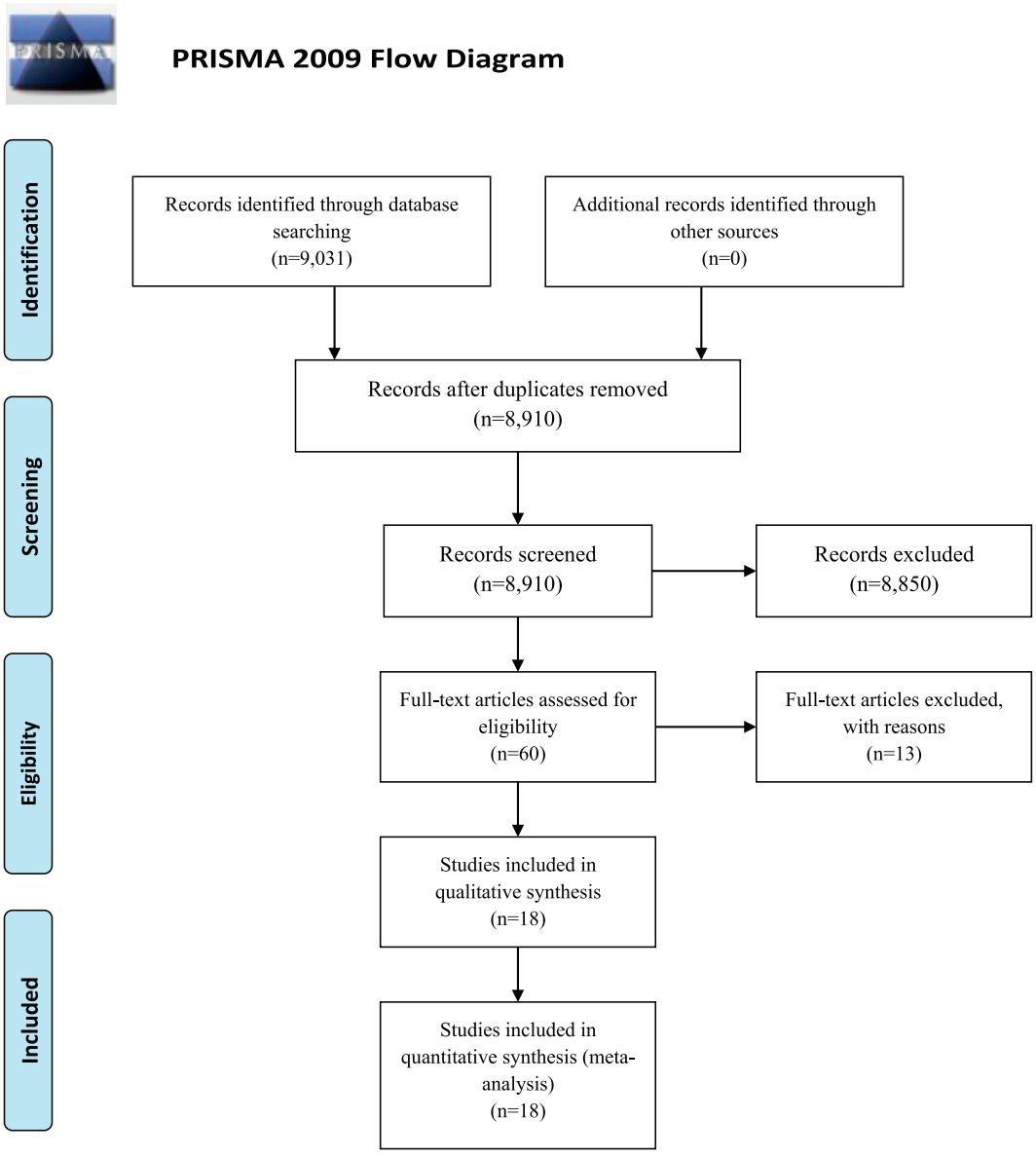

Fig. 1. Flowchart of the process of search strategy adopted in the present systematic review and meta-analysis.

Table 1
The search strategy adopted in the present systematic review and meta-analysis.

Search strategy item	Details
String of keywords	(systematic lupus erythematosus OR SLE) AND (Streptococcus pneumoniae OR S. pneumoniae OR pneumococcal OR anti-pneumococcal) AND (vaccine OR vaccination OR immunization)
Databases searched	PubMed/MEDLINE, Scopus, ISI/Web of Science, DOAJ, Google Scholar
Inclusion criteria	P: SLE patients I: immunized against pneumococcal pathogen C: between cases and controls (if a control group is available) O: safety, immunogenicity S: original research
Exclusion criteria	Case-report, case-series, editorial, letter to editor, expert opinion, commentary, review article Original research not meeting with inclusion criteria as stated by PICOS
Time filter	None
Language filter	None
Hand-searched target journals	Arthritis and Rheumatism; Autoimmunity; Autoimmunity Reviews; Clinical Infectious Diseases; Human Vaccines and Immunotherapeutics; Journal of Autoimmunity; Journal of Rheumatology; Lupus; Rheumatology (Oxford); Scandinavian Journal of Rheumatology; Vaccine

Abbreviations. DOAJ (Directory of Open Access Journals); ISI (Institute of Scientific Information); PICOS (Patients; Intervention/exposure; C: Comparator(s); O: Outcome(s); S: Study design); SLE (systemic lupus erythematosus).

Table 2
List of articles excluded with reason and reason for exclusion.

Excluded article with reason	Reason for exclusion
Azoicai et al., 2018 [30]	Review article/expert opinion/commentary
Bragazzi et al., 2017 [31]	Review article
Chehab et al., 2018 [32]	Not pertinent with the scope of the present systematic review
Elkayam et al., 2007 [26]	Review article
Krasselt et al., 2017 [33]	Not pertinent with the scope of the present systematic review
Lawson et al., 2015 [34]	Not pertinent with the scope of the present systematic review
Mathian et al., 2018 [35]	Review article
Mehta et al., 2014 [36]	Not pertinent with the scope of the present systematic review
Murdaca et al., 2014 [37]	Review article
Murdaca et al., 2016 [38]	Review article
Pugès et al., 2016 [27]	Review article
Rákóczi et al., 2017 [21]	Review article
Tarasova et al., 2014 [39]	The group includes 2 SLE pediatric patients together with children suffering from diverse rheumatologic disorders, but it is not possible to extrapolate data related to SLE only
Yazdany et al., 2010 [40]	Not pertinent with the scope of the present systematic review

Abbreviations. SLE (systemic lupus erythematosus).

author, year of publication, country, study design, type of vaccine (7-, 13-, 14- or 23-valent vaccine), sample size, drop-out rate, control group and type of controls (if present), mean duration of disease, activity of disease as assessed by the SLEDAI, SELENA-SLEDAI or SLEDAI-2 K score, drugs administered, safety concerns in terms of adverse events (AEs), immunogenicity (in terms of protective antibody titers), predictors of safety and/or immunogenicity, and main observations and conclusions.

2.3. Quality assessment

The quality of each included study was critically appraised using the Down & Black's modified checklist, which includes three main sections: reporting, external and internal validity. Quality appraisal was performed by 2 authors (NLB, AW) independently. Inter-rater agreement was excellent (Cohen's $\kappa > 0.90$).

2.4. Meta-analysis

Meta-analyses were carried out using the commercial software MedCalc Statistical Software version 16.8.4 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016) and Comprehensive Meta-Analysis CMA v3.

Prevalence ratios were calculated as effect size (ES) estimates. The 95% confidence intervals (CIs) were also generated. More in detail, the logit transformation (l) approach was utilized in the current meta-analysis, being one of the possible approaches for pooling together raw prevalence data. The following equation was used to compute l:

$$l = ln\left(\frac{p}{1-p}\right)$$

where p is the prevalence proportion.

Variance was computed using the equation:

$$Var(l) = \frac{1}{N \bullet p} + \frac{1}{N \bullet (1-p)}$$

where N is the population size.

The pooled l was subsequently back-transformed to a proportion using the equation:

$$p = \frac{e^l}{e^l + 1}$$

Statistical heterogeneity has been assessed using the I^2 statistic. $I^2 > 50\%$ was regarded as substantial heterogeneity. To identify sources of variation, further stratification was performed relative to study quality and to performance of confirmatory tests. In addition, for the sensitivity analyses, the stability of the pooled estimates with respect to each study was investigated by excluding individual studies from the analysis. Concerning publication bias, potential publication bias has been extensively investigated in the current systematic review and meta-analysis. First, we have visually inspected the funnel plot, looking at asymmetry of the graph. If asymmetry was present based on visual assessment, we performed exploratory analyses to investigate and adjust this using the Duval and Tweedie's trim-and-fill analysis. In addition, the probability of publication bias has been tested using the Egger's linear regression test.

3. Results

The initial search yielded a pool of 9031 items. After deleting the duplicates, 8910 unique results were retained. After the screening of the title and/or abstract, 8850 items were discarded. The full-text of 60 investigations was assessed and 14 texts were excluded with reasons (as reported in Table 2) [21,26,27,30–40]. Finally, 22 articles were included (4 studies had overlapping populations) in the present systematic review and meta-analysis.

It should be, however, noted, that some of these studies are follow-up studies and investigated, at least partially, overlapping patients cohorts. Table 3 provides a list of these redundant investigations [18,21,37–42], that have been utilized in the systematic review part but excluded in the meta-analysis. For this reason, data represent the synthesis of 18 investigations ($k = 18$), from 22 articles [18–21,37–58]. Their main features are tabulated in Tables 4–7.

Studies retained in the present systematic review have been conducted between 1979 and 2018. More in detail, 8 and 2 studies were undertaken in the USA and in Israel, respectively, 3 further investigations in France and other 2 in Russia, with 1 study in Argentina, Brazil, Iran, Hungary, Mexico, and Sweden. One study was a multi-center collaboration, performed in various countries of the North America and Europe.

The quality of retained studies as assessed with the modified Down & Black's checklist was generally good, with scores ranging from 8 to 10

Table 3
Overlapping studies.

Original study	Overlapping with
Elakayam et al., 2002 [25]	Elkayam et al., 2005 [41]
Jarrett et al., 1980 [22]	Mcdonald et al., 1984 [42]
Tarasova et al., 2016 [43]	Tarasova et al., 2018 [44]
Tratenberg et al., 2015 [45]	Prakash et al., 2017 [46]

Table 4
The main features of studies included.

Authors	Study year	Study design	Country	Type of vaccine	Sample size	Drop-out rate	Age
Alyasin et al. [47]	2016	Longitudinal case-control (convenient sampling)	Iran	23-valent	30	None	13.2 [3–18]
Battafarano et al. [48]	1998	Longitudinal (consecutive patients)	USA	23-valent vaccine administered simultaneously with tetanus toxoid and HIB vaccines	73	Out of 81 eligible patients, 6 patients lost at the follow-up (7.4%), 2 declined participation (2.5%). In total, 9.9% of subjects not taking part into the full study	43 [18–76]
Chatham et al. [49]	2012	Phase III, randomized, double-blind, placebo-controlled trial	North America, Europe (from 136 medical centers)	23-valent	86 for the on-study part (from a 204 cohort)	10 (12.7%) withdrew (patient request, $n = 3$; AE, $n = 3$; lost to follow-up, n = 2; other, $n = 2$)	42.0 (41.6 for the on-study part)
Croft et al. [50]	1984	Longitudinal	USA	14-valent	18	None	34.8 ± 10
Elkayam et al. [25]	2002	Longitudinal (consecutive patients)	Israel	23-valent	24	None	39.0 [23–58]
Elkayam et al. [41]	2005	Longitudinal (consecutive patients)	Israel	23-valent	24	None	39.0 [23–58]
Gonzalez et al. [51]	2017	Longitudinal	USA	13-valent	20 pediatric SLE patients	None	NR
Grabar et al. [52]	2017	Phase IIb randomized placebo-controlled double-blind trial	France (multi-center study)	23-valent or 7-valent +23-valent (sequential administration)	17 SLE patients (PnCj7–PPS23 cohort)	Out of 47 patients initially screened, 1 patient was not randomized, 2 withdrew consent, 1 had bleeding disorders, 1 started Ig infusions, 1 subject lost in the control group (12.8%)	41.4 [36.4–50.7]
Jarrett et al. [22]	1980	Longitudinal	USA	14-valent	38 SLE patients for the analysis at 4 w; 31 SLE patients for the analysis at 1 y	None at 4 w; 18.4% at 1 y	33
Klippel et al. [53]	1979	Randomized controlled double-blind trial	USA	14-valent	20 SLE patients	None	32 [14–61]
Lipnick et al. [54]	1985	Longitudinal randomized controlled double-blind study	USA	14-valent	38 SLE patients	None	36 [9–71]
Mcdonald et al. [42]	1984	Longitudinal	USA	14-valent	19 (21 patients being a sub-group of the population studied initially by Jarrett et al., 1980)	None	NR
Mercado [55]	2013	Longitudinal	Mexico	23-valent administered together with HIB conjugate vaccine	11 (out of 12 potentially eligible patients) at 4 w; 9 patients at 8 mo	8.3% at 4 w; 25.0% at 8 mo	31.8 [17–55]
Nagel et al. [56]	2017	Longitudinal (some consecutive and some randomly chosen patients)	Sweden	13-valent	47	None	50.8 [19.3–81.3]
Pisoni et al. [57]	2003	Longitudinal	Argentina	23-valent	35	2 patients lost at follow-up (5.4%)	40.0 ± 13.02 (42 [17–80])
Prakash et al. [46]	2017	Longitudinal	USA	23-valent	21 SLE patients	None	NR
Rezende et al. [24]	2016	Longitudinal, prospective open-label (consecutive patients)	Brazil	23-valent	54	None	39.3
Sacre et al. [23]	2018	Longitudinal, prospective study (consecutive patients)	France	13-valent +23-valent after 8 w	21 SLE patients (out of 37)	8 refused the vaccination, 7 patients lost in the follow-up, 1 refused the vaccination	40.0 [25–75]
Tarján et al. [58]	2002	Longitudinal (random-chosen patients)	Hungary	23-valent	18	None	43 [25–66]
Tarasova et al.	2016	Longitudinal	Russia	23-valent	24	None	19–62
Tarasova et al.	2018	Longitudinal	Russia	23-valent	30	None	19–62
Tratenberg et al. [45]	2015	Longitudinal	USA	23-valent	8 SLE patients	None	NR

Authors	Inclusion criteria	Exclusion criteria	Female (%)	SLE score	Disease duration	Drugs	Changes in auto-antibodies after vaccine
Alyasin et al. [47]	1997 revised ACR-SLE diagnosis	Fever, pregnancy, recent immunization, history of previous pneumococcal vaccination, history of hypersensitivity	76.7%	6.6 [0−22], NR post-immunization Active disease in 36.7%,	3.2 [0.25–15]	Hydroxychloroquine (83%), prednisolone (100%), azathioprine (10%), methotrexate (16.7%),	53.3% high levels of anti-dsDNA NR after immunization

(*continued on next page*)

Table 4 (*continued*)

Authors	Inclusion criteria	Exclusion criteria	Female (%)	SLE score	Disease duration	Drugs	Changes in auto-antibodies after vaccine
		reaction to vaccination, platelet level < 50,000, mixed connective tissue disorders and intra-venous immunoglobulin injection in the last 3 mo		active proteinuria in 13.3% of SLE patients		cyclophosphamide (16.7%), cellcept (10%), Rituximab (13.3%). Prednisolone was consumed 5.8 mg/day [1.25–15]. Methotrexate was consumed 6 mg/week [2.5–20]. Prednisolone < 10 mg/day 90%, > 10 mg/day 10%	
Battafarano et al. [48]	Revised ACR-SLE diagnosis	Immunization within 6 mo. No exclusion based on disease activity or demographic parameters	94.5%	2.5, 1.8 post immunization (after 12 w). Mild increase in SLEDAI observed in 8% of cases, stable values in 84% of cases, a decrease was observed in 8% of patients	NR	Antimalarials (48%), NSAIDs (34%), prednisone (74%), azathioprine (10%), cyclophosphamide (10%), methotrexate (1%). Prednisone < 10 mg/day 63%, > 10 mg/day 11%	↔ anti-dsDNA
Chatham et al. [49]	Active autoantibody-positive SLE (antinuclear antibody titer ≥1:80 or anti-dsDNA antibodies ≥30 IU/mL) with SLEDAI score ≥ 6, receiving a stable regimen of standard therapy for ≥30 days; immunization within 5 years	Severe active lupus nephritis or central nervous system lupus	94.6% (90.7% for on-study part)	9.2 (8.7 for the on-study part)	NR	Standard therapy + belimumab 1 mg/kg (38.2%) or 10 mg/kg (30.9%) *versus* placebo (30.9%); 58.3% with immunosuppressive therapy (59.3% for the on-study part)	NR
Croft et al. [50]	ACR-SLE diagnosis	NR	94.4%	NR ↔ disease activity before and after immunization	NR	Prednisone 83.3%, azathioprine 22.2%. Mean dose consumed of prednisone was 18.9 ± 16 mg/day [0–60 mg/day]. Mean dose consumed of azathioprine was 81.3 ± 20 mg/day	NR
Elkayam et al. [25]	ACR-SLE diagnosis	Pregnancy, a history of past vaccination allergy, and previous pneumococcal vaccination.	83%	4.41 ± 2.92 4.47 ± 3.22 after 2mo	6.9 [1 − 20]	Prednisone 62.4% (< 10 mg/day 45.8%, > 10 mg/day 16.6%), NSAIDs 8.3%, methotrexate 16.7%, azathioprine 16.7%, cyclophosphamide 4.2% and hydroxychloroquine 66.7%. Mean weekly dose consumed of methotrexate was 11.6 mg/week [7.5–15.0]	NR
Elkayam et al. [41]	Revised ACR-SLE diagnosis	Pregnancy, a history of past vaccination, allergy and previous pneumococcal vaccination	83%	4.41 ± 2.92 4.47 ± 3.22 after 2 mo	6.9 [1–20]	Prednisone 62.4% (< 10 mg/day 45.8%, > 10 mg/day 16.6%), NSAIDs 8.3%, methotrexate 16.7%, azathioprine 16.7%, cyclophosphamide 4.2% and hydroxychloroquine 66.7%. Mean weekly dose consumed of methotrexate was 11.6 mg/week [7.5–15.0]	↔ anti-Sm ↔ anti-dsDNA ↔ anti-RNP ↔ anti-Ro/SSA ↔ anticardiolipin IgM A single patient developed aCL IgG and another one turned anti-nRNP negative
Gonzalez et al. [51]	NR	NR	NR	NR	NR	Some patients under rituximab or mycophenolate	NR
Grabar et al. [52]	1997 ACR-SLE diagnosis, aged 18–75 y, with stable disease (no	HIV, HBV or HCV infection, medical history of allergy to	82%		7.6 [3.1–18.6]	41% with immunosuppressive therapy,	↔ anti-dsDNA

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Table 4 (*continued*)

Authors	Inclusion criteria	Exclusion criteria	Female (%)	SLE score	Disease duration	Drugs	Changes in auto-antibodies after vaccine
	modification of treatment within 2 mo), being treated at least with hydroxychloroquine, 5 mg or more of daily prednisone or equivalent, systemic glucocorticoid in combination at least with an immunosuppressant (mycophenolate mofetil, azathioprine or Methotrexate)	vaccine contents, immunization within 5 y or any vaccine received in the previous mo, intravenous immunoglobulin infusion within last 3 mo, splenectomy, bleeding disorders, active malignancy, cirrhosis, acute infection in the previous mo, treatment with rituximab in the previous y, pregnancy		18% with SLEDAI ≥4, 82% with SLEDAI < 4. SLEDAI remained stable over the time		anti-malarials 88%, corticosteroids 82%. Mean daily prednisone was 7 ± 2 mg/day. Prednisone > 10 mg/day 29%	
Jarrett et al. [22]	ARA-SLE diagnosis	NR	97.4%	No patient with major disease activity. Disease inactive in 73.7% at the period of immunization, renal disease in 63.2% of cases	NR	Prednisone alone 76.3%, prednisone + azathioprine 23.7%. Mean daily dose consumed of prednisone was 14–20 mg/day. Mean daily dose consumed of azathioprine was 78 mg/day	↔ anti-dsDNA
Klippel et al. [53]	ACR-SLE diagnosis	NR	97.5%	NF	NR	Corticosteroids 77.5%, NSAIDs 50%, antimalarials 42.5%. Mean daily dose of consumed prednisone was < 25 mg/day	
Lipnick et al. [54]	Revised ACR-SLE diagnosis, doses of prednisone < 0.5 mg/kg/day, doses of azathioprine or cyclophosphamide < 4 mg/kg/day	Pregnancy, history of surgical splenectomy, recent acute or chronic infection	94.8%	Inactive disease in 49.4%, mild in 41.6%, moderate-severe in 9.1% of SLE patients		Prednisone (66.2%), cyclophosphamide (6.5%), azathioprine (3.9%), cyclophophamide and azathioprine (11.7%). Mean daily dose of consumed prednisone was 16 mg/day [6–30] taken every day in 31.2% of patients. Mean daily dose of consumed prednisone was 14 mg/day [4–40] taken on alternate days in 35.1% of patients	↔ anti-dsDNA A 10% increase was reported in 8% and 16% of patients at 1 and 6 mo, *versus* 10% and 15% of controls, respectively
Mcdonald et al. [42]	ACR-SLE diagnosis	NR	NR	NR	NR	NR	NR
Mercado [55]	ACR-SLE diagnosis	NR	100.0%	NR ↓ Mex-SLEDAI (p = .0002)	8 [1–14]	Prednisone (mean 18.1 mg, range 5–50 mg per day). 2 patients were receiving cyclophosphamide, 1 danazol, 4 anti-malarials, 5 NSAIDs	↔ anti-dsDNA
Nagel et al. [56]	ACR-SLE diagnosis, never received vaccine or before 5 y	Pregnancy, ongoing infection or known hypersensitivity to the vaccine contents	93.6%	1.9 [0–8]	16.1 [0–58]	Prednisolone 68.1%, no DMARDs 14.9%, belimumab 23.4%, hydroxychloroquine only 21.3%, azathioprine or DMARDs other than hydroxychloroquine 19.1%, azathioprine + hydroxychloroquine 21.3%	NR
Pisoni et al. [57]	ACR-SLE diagnosis, with a disease activity of at least 1 y	SLEDAI greater than15, diabetes, transplantation, HIV	100.0%	↔ SLEDAI 5.42 ± 3.54 [4, 0–15]0.54,	NR		

(*continued on next page*)

Table 4 (*continued*)

Authors	Inclusion criteria	Exclusion criteria	Female (%)	SLE score	Disease duration	Drugs	Changes in auto-antibodies after vaccine
				4.82 ± 3.41 [4, 0–12] after 12w		Anti-malarials 37.1%, NSAIDs 31.4%, no treatment 17.1% of cases	↑ anti-dsDNA (in 8.5% of cases) ↔ ANA
Prakash et al. [46]	NR	NR	NR	NR	NR	Mycophenolate mofetil, prednisone (generally < 10 mg/day)	NR
Rezende et al. [24]	ACR-SLE diagnosis, age > 18 y	NR	90.7%	Median 4 in the immunosuppressive therapy patients and median 0 in those not receiving immunosuppressive therapy [0–15] ↔ SLEDAI-2 K score before and after immunization	10.5	51.9% with immunosuppressive therapy	NR
Sacre et al. [23]	ACR-SLE diagnosis, treatment administered at a stable dose for at least 3 mo, receiving steroids (for example, > 7.5 mg/day of prednisone for > 3 mon), immunosuppressive drugs or biologics	Immunization against Pneumococcus within 5 y	85.7%	Median in the range 0–2 [0–4]	9.7 [1 − 32]	Glucocorticoids in 90.5% of patients for 5 [0.5–26] years. 57.1% were still receiving prednisone at a daily dose of 10 [7–15] mg at study time. 71.4% had received immunosuppressive drugs for 4 [1–14] years and 42.9% patients were still under immunosuppressive drugs at study time. All patients were treated with daily hydroxychloroquine.. No patient under rituximab	NR
Tarján et al. [58]	ACR-SLE diagnosis, mild stable SLE	SLE diagnosed within one year, daily steroid dose above 20 mg, SLEDAI higher than 20, recent lupus flare defined as an acute 3 point increase of the SLEDAI score and the existence of an actual infection	88.9%	5.56 [0–18] ↔ SLEDAI after immunization Disease inactive in 100.0% of patients	9 [1–20]	Methylprednisolone dose: 5.9 mg (0 − 20), azathioprine 100 mg/day administered to 2 patients	↔ anti-dsDNA
Tarasova et al.	NR	NR	91.7%	Low activity in 75% moderate in 12.5% and remission in 12.5% of cases		Glucocorticoids 95.8%, biological DMARDs 33.3% (rituximab 20.8%, belimumab 12.5%)	NR
Tarasova et al.	NR	NR	90.0%	2 [2–4], 2 [0–4] post-immunization. Low activity in, high in 3.3%, moderate in 13.3%, low in 66.7% of cases. 16.7% of patients in remission		Glucocorticoids 96.7%, hydroxychloroquine 76.7%, cytostatics 46.7%, biological DMARDs 30.0% (rituximab 13.3%, belimumab 16.7%)	↔ anti-dsDNA
Tratenberg et al. [45]	NR	NR	NR	NR		Methotrexate, hydroxychloroquine	NR

Authors	Other immunological parameters before and after vaccine	Control group	Immunogenicity	Safety	Study follow-up	Predictors of safety/ immunogenicity	Main observations/ conclusions
Alyasin et al. [47]			↑ antibody titer from 68.8 [5.79–326.59] to 244.7	No AEs	3 w	ESR (p = .04 between poor and good responders; r = 0.4, p = .03	Generally immunogenic in children, even though a

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Table 4 (*continued*)

Authors	Other immunological parameters before and after vaccine	Control group	Immunogenicity	Safety	Study follow-up	Predictors of safety/ immunogenicity	Main observations/ conclusions
	Hypocomplementemia in 33.3% of SLE patients 8,3% abnormal Ig level	30 sex- and age-matched asthmatic children	[27.58–687.3] *versus* 71.88 [6.13–269.74] to 341.6 [22.7–964.6] in the control group Mean fold increase in antibody titer of 7.01 [1.13–33.4] *versus* 9.6 [1.3–47.4] in the control group Mean increase in antibody titer 175.8 [7.8–649.3] *versus* 269.7 [13.05–820.5] in the control group 77.8% (two-fold response criterion), 63.0% (three-fold response criterion), 55.6% (four-fold response criterion) *versus* 86.2%, 72.4%, 65.5% in the controls after 3 w			with pre-immunization antibody titer), age ($r = 0.30$, $p = .02$ with post-immunization antibody titer), SLE onset ($r = 0.43$, $p = .02$ with post-immunization antibody titer), SLEDAI score (8.9 [1.1–33.4] in low SLEDAI sub-group *versus* 3.2 [1.25–9.7] in the high SLEDAI sub-group, $p = .012$)	small group may exhibit impaired immunological response. Immunogenicity of anti-pneumococcal vaccination among SLE and asthmatic patients is comparable. Immunosuppressive therapy does not impair immunological response to anti-pneumococcal vaccination
Battafarano et al. [48]	↔ C3 ↔ C4 ↔ Ig	None	74% (two-fold response criterion), 59% (three-fold response criterion), 47% (four-fold response criterion)	No serious AEs: in 8% mild/low-grade (local tenderness, erythema, fever, malaise)	12 w	No significant predictors	Anti-pneumococcal vaccination is safe and immunogenic among SLE patients. Simultaneous immunization with other vaccines does not exacerbate SLE disease activity and does not result into AEs
Chatham et al. [49]	NR	None	97.6% in the belimumab cohort *versus* 97.0% in the pre-belimumab cohort. Over 85% of patients in both cohorts responded to ≥10 of serotypes, approximately 80% responded to ≥12 serotypes, and approximately two-thirds responded to ≥16 serotypes.	No serious AEs, eight (23.5%) patients experienced a treatment-related AE in the pre-belimumab cohort and four (8.9%) in the belimumab-concurrent cohort; seven patients experienced non-fatal serious AEs (pre-belimumab cohort, 11.8% [$n = 4$]; concurrent-belimumab cohort, 6.7% [n = 3]). No deaths were reported	4 w	NR	Treatment with belimumab does not impair immunological response to anti-pneumococcal vaccination
Croft et al. [50]	↔ complement levels	8 not immunized SLE patients +7 healthy volunteer controls from laboratory	Increase of antibody titer from 238.3 ± 273 to 1661.4 ± 1252 in the immunized group *versus* increase from 273.4 ± 254 to 1704.1 ± 693 in the immunized controls *versus* 335.7 ± 264 to 394.7 ± 272 in the SLE non immunized group Polyclonal B cell activation as response to pneumococcal vaccination	No AEs	4–6 w	No significant predictors	SLE patients appear to have a specific antibody response to antigenic stimulation with pneumococcal polysaccharide
Elkayam et al. [25]	↔ C3 ↔ C4 ↔ Ig	Age- and institution-matched controls	36–86% according to vaccine serotype Fold increase in antibody titer was significant only for serotype 2 (2.51, p < .05). Geometric mean	No serious AEs, only 1 patient complained of clinical pleuritic pain	2 mo	No significant predictors	Generally safe and immunogenic, even though a fraction of SLE patients may remain unprotected

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Table 4 (*continued*)

Authors	Other immunological parameters before and after vaccine	Control group	Immunogenicity	Safety	Study follow-up	Predictors of safety/ immunogenicity	Main observations/ conclusions
			concentration increase in antibody titer was significant only for serotype 8 (3.95, $p < .05$) Serotype 14 appeared to be the most immunogenic and serotype 4 the least immunogenic 20.8% responded to either none or only 1 of the 7 pneumococcal polysaccharides				
Elkayam et al. [41]	↔ C3 ↔ C4 ↔ Ig	Age- and institution-matched controls	NR	No serious AEs	2 mo	NR	Clinical safe, not triggering the formation of auto-antibodies
Gonzalez et al. [51]	NR	None	75% after 4 w	NR	4 w	Therapeutics (patients with rituximab or higher dose mycophenolate failed to achieve protective antibody level)	Generally immunogenic in the pediatric SLE population
Grabar et al. [52]	↔ C3 ↔ C4	25 in the placebo group (placebo-PPS23 cohort)	76% in the PnCj7–PPS23 cohort *versus* 72% in the placebo-PPS23 cohort after 28 w; 58.8% in the PnCj7–PPS23 cohort *versus* 52.0% in the placebo-PPS23 cohort after 52 w	No serious AEs. At least 1 mild/ low-grade AE (pain, headache) reported by 88% of cases. Nine SLE flares (including mild polyarthritis) were reported in 6 patients (4 in the placebo-PPS and 2 in the PnCj-PPS groups respectively, $p = .70$)	28–52 w	No significant predictors	The sequential administration of anti-pneumococcal vaccines is safe but not superior to the administration of a single vaccine alone. Furthermore, the immunosuppressive therapy does not impair the immunological response to anti-pneumococcal vaccination
Jarrett et al. [22]	↔ C3 ↔ C4	23 non vaccinated SLE patients +17 healthy volunteers used in a previous study +5 controls from laboratory	73.7% (2-fold response criterion) in cases *versus* 82.4% (2-fold response criterion) in controls, after 4 w Increase of antibody titer 918 ± 405 *versus* 1787 ± 694 in controls *versus* 1871 in laboratory controls after 4 w Immunological response against serotypes 3, 9 N, 12F, 19F did not differ between cases and controls Antibody titer 778.5 in SLE patients *versus* 1340 in laboratory controls	No serious AEs, however 3 subjects reported fever after immunization, 3 patients developed major clinical flares necessitating major immunosuppressant therapy after 1 y. 3 deaths (myocarditis; persistent fever, CNS disease and Gram negative sepsis; nephrotic syndrome) have occurred among vaccinees	Outcomes assessed at 4 w intervals, up to 24 w; 4 w-1 y	Not significant predictors	SLE patients have a lower and impaired immunological response to anti-pneumococcal vaccination with respect to healthy controls. Vaccine is generally safe
Klippel et al. [53]		20 SLE patients treated with placebo		No serious AEs, mild/low-grade in 85% of cases		NR	Immunosuppressive therapy does not impair with immunological response to anti-pneumococcal vaccination among SLE patients
Lipnick et al. [54]	Hypocomplementemia in 32.5% of SLE patients	39 SLE patients treated with placebo	With respect to placebo, antibody titer increased significantly against each Pneumococcus serotype Increase of antibody titer (2-fold response criterion) in 72% of patients at 1 mo, in 54% of	NR	1–6 mo	No significant predictors	Immunosuppressive therapy does not impair with immunological response to anti-pneumococcal vaccination among SLE patients

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Table 4 (*continued*)

Authors	Other immunological parameters before and after vaccine	Control group	Immunogenicity	Safety	Study follow-up	Predictors of safety/ immunogenicity	Main observations/ conclusions
			patients at 6 mo *versus* 5% and 6%, respectively in the placebo group				
Mcdonald et al. [42]	NR	5 healthy volunteers	57.9% after 3y With respect to controls, 2-y post-immunization antibody titer was lower for serotypes 4 ($p < .025$), 7F ($p < .005$), 18C ($p < .025$), 3-y post-immunization was lower for serotypes 1 ($p < .05$), 7F ($p < .0025$), 9 N ($p < .01$), 18C ($p < .025$)	No serious AEs, one patient developed pneumonia after 3y	1–2-3 y	NR	Immunological response to anti-pneumococcal vaccine is not persistent throughout time, SLE patients may remain unprotected against *S. pneumonia*
Mercado [55]	↑ C3 ($p = .019$) ↓ IgG ($p = .0193$)	None	Increased antibodies titer from 412.1 ± 202.5 to 1255 ± 1472.4 after 4 w ($p = .0005$) 45.5% with an increase antibody titer (4-fold response criterion) at 4 w No protective antibodies at 8 mo ↑ IgG antibody titer from 143.7 ± 189.1 to 674.0 ± 472.2 ($p = .0033$) against Pneumococcus serotype 1 ↑ IgG antibody titer from 78.5 ± 76.4 to 572.6 ± 607.4 ($p = .020$) against Pneumococcus serotype 12 ↑ IgG antibody titer from 146.8 ± 158.8 to 577.4 ± 584.4 ($p = .035$) against Pneumococcus serotype 6 ↑ IgG antibody titer from 57.0 ± 31.4 to 214.5 ± 182.8 ($p = .0094$) against Pneumococcus serotype 14	No AEs	4 w-8 mo	NR	Concurrent administration of various vaccines, including anti-pneumococcal vaccine, is safe among SLE patients, Increases in antibodies titer and decreases in the Mex-SLEDAI score were observed. However, protective antibody titer was short-lived
Nagel et al. [56]	NR	21 sex- and age-matched healthy volunteers	Increased antibodies titer upon vaccination, decreased after vaccination	No serious AEs (pain, redness around injection site, fever, headache), only one case of diarrhea, nausea and leucopenia		Older age (associated with lower antibody levels post-immunization, $p < .001$), prednisolone dosage (associated with antibody response to Pneumococcus serotype 9 V)	Treatment with belimumab does not impair immunological response to anti-pneumococcal vaccination among SLE patients. Vaccine is safe and well-tolerated
Pisoni et al. [57]	↓ CH50 (in 5.7% of cases)	None	Increase in antibodies titer from 82.34 ± 62.39 (73, [9–270]) in 85.0% of cases	No serious AEs, mild/low-grade (pain, local erythema, fever, dysphonia, lipothymia) in 25.7% of cases	12 w	NR	Generally immunogenic, persistent throughout time and safe
Prakash et al. [46]	NR	12 SLE controls	40% in the cases group *versus* 60% in the control group with statistically significant differences concerning serotypes 51 and 4 ($p = .05$ and $p = .025$, respectively). 2-fold increase was observed in	NR		Immunosuppressive therapy	Immunosuppressive therapy impairs the immunological response to anti-pneumococcal vaccine among SLE patients

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Table 4 (*continued*)

Authors	Other immunological parameters before and after vaccine	Control group	Immunogenicity	Safety	Study follow-up	Predictors of safety/ immunogenicity	Main observations/ conclusions
			20% of cases *versus* 50% of controls				
Rezende et al. [24]	NR	None	↑ IgG response to Pneumococcus serotupes ($p < .001$) 38.8% 29.6% (four-fold response criterion)	No AEs	4 w, 6 w	Immunosuppressive therapy (seroconversion response rate in the range 43.7–77.7% in the patients under immunosuppressants *versus* 52.3–90.0% in the group without immunosuppressive therapy; 4-fold increase in the range 25.0–57.1% in the patients under immunosuppressants *versus* 38.4–73.0% in the group without immunosuppressive therapy)	Poorly immunogenic, especially among SLE patients under immunosuppressive therapy
Sacre et al. [23]	NR	None	81.0% after 2 mo, 57.1% after 1 y	No AEs	2 mo, 1 y	B-cell defects, immunosuppressive therapy, serotype 19 F IgG titer measured 2 mo after the administration of the 13-valent (sensitivity of 100% [95%CI 47.8–100]; specificity of 91.7% [95%CI 61.5–99.8]) Immunological parameters such as a lower IgG2 serum level and a higher ratio of pre-germinal/post-germinal centre B cells are predictive of short-term protection	Poorly immunogenic, impaired long-term immune protection against *S. pneumoniae* following sequential vaccine administration among SLE patients.
Tarján et al. [58]	↓ C3 ↓ C4 ↔ immune-complexes ↔ CD8+ lymphocytes ↔ CD21+ lymphocytes ↔ CD3+/DR+ lymphocytes ↔ CD4+ lymphocytes ↔ CD19+ lymphocytes ↔ CD56+ lymphocytes ↔ opsonophagocytic activity ↓ serum total IgG levels, remaining however within normal ranges ↓ serum total IgA levels, remaining however within normal ranges	9 healthy volunteers (some data collected on 6 subjects)	Data collected on 6 patients Antigen-specific IgM and IgG responses against Pneumococcus serotype 6B and 23F were weaker among SLE patients with respect to healthy controls 66.7% of subjects had 2-fold increase in IgM titer against 6B. 33.3% of patients reacted to 23F. Among the controls, 50% and 16.7%, respectively, responded to 6B and 23F 0% and 50% had two-fold increase in IgG titer against 6B and 23F. Among the controls, 50% reported a 4-fold increase in antibody titer against 6B, while 83.3% reported high titers against 23F 66.7% of controls responded only to one antigen	No serious AEs, generally low/ mild-grade AEs (pain and/or swelling at the site of injection, low-grade fever under 38.0C, new or worsened arthralgia, myalgia, facial edema, vomitus, headache, axillary pain without lymph node enlarge- ment). Symptoms other than local pain or swelling were reported by 1/3 of patients. No clinical flares	6 d, 13 d and 28 d	NR	No short-term immunological effect of anti-pneumococcal vaccination among SLE patients, with striking individual differences in terms of protective antibodies titer. Vaccine is generally safe
Tarasova et al.	NR	None	NR	No serious AEs, well-tolerated in 41.7% patients	1 y	NR	Generally immunogenic, safe and well-tolerated among SLE patients
Tarasova et al.	↔ C3 ↔ C4	None	NR	No serious AEs. Pain was reported by 63.3% of patients. One patient	1 y	NR	

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Table 4 (*continued*)

Authors	Other immunological parameters before and after vaccine	Control group	Immunogenicity	Safety	Study follow-up	Predictors of safety/ immunogenicity	Main observations/ conclusions
				developed hypersensitivity reaction (Arthus phenomenon-type)			Generally immunogenic, safe and well-tolerated among SLE patients
Tratenberg et al. [45]	NR	3 SLE patients	40% in the cases group *versus* 60% in the control group with statistically significant differences concerning serotypes 51 and 4 (p = .05 and p = .025, respectively). 2-fold increase was observed in 20% of cases *versus* 50% of controls	NR	8 w	Immunosuppressive therapy	Immunosuppressive therapy impairs immunological response to anti-pneumococcal vaccination. Immunization should be given prior to initiation of immunosuppression

(- median 8.5), as shown in Table 5. Concerning the different sections, reporting was generally good while external and internal validity were good, being higher for the RCTs.

All studies were designed as longitudinal investigations, 4 (18.2% of all included studies), in particular, were of high quality, being randomized, double-blind trials (RCTs) – Chatham et al. [49], Grabar et al. [52], Klippel et al. [53], and Lipnick et al. [54].

Drop-out rate ranged from 0.0% to 25.0%. Study follows-up/timings ranged from few days to 3 years: in particular, most studies investigated the short-term immunological protection, with few investigations addressing the long-term protection. One study assessed the antibody titer after 6 months, 3 after 1 year, and 1 study after 2 years. A further study explored the immunological protection 3 years after the vaccine administration.

Fourteen studies had control groups: more in detail, 3 studies – McDonald et al. [42], Nagel et al. [56] and Tarján et al. [58] – utilized healthy volunteers, whereas 2 investigations – Croft et al. [50] and Jarrett et al. [22] – both SLE patients and healthy controls. Alyasin et al. [47] utilized asthmatic children as control group. All studies were conducted among adult SLE patients, except for Alyasin et al. [47] and Gonzalez et al. [51], who investigated pediatric patients. Sample size ranged from 12 to 86 participants with a total of 601 subjects. Female percentage went from 76.7% to 100.0%. Patients under immunosuppressive therapy ranged from 38.0% to 58.3%.

Concerning disease activity index, most studies utilized the SLEDAI score, apart from 2 studies, which used the SELENA-SLEDAI and the SLEDAI-2 K, respectively. At baseline, the mean disease activity score went from 2.5 to 9.2. Mean disease duration varied from 3.2 to 10.5 years. Disease was inactive in 49.4–100.0% of recruited SLE patients. The SLEDAI/SELENA-SLEDAI/SLEDAI-2 K score remained stable before and after immunization. Battafarano et al. [48] documented a mild increase in the score in 8% of cases, whereas stable values and a decrease in the score were observed in 84% and in 8% of patients, respectively.

Most studies (15/22) investigated the administration of the 23-valent anti-pneumococcal vaccine, whereas 5 and 3 studies evaluated the administration of the 14- and 13-valent formulations, respectively. Only 1 study investigated the administration of the 7-valent formulation. Two studies assessed the concurrent administration of the anti-pneumococcal vaccine with the *Haemophilus influenzae* type b (HIB) vaccine and/or the tetanus toxoid, whereas 2 studies investigated the sequential administration of different anti-pneumococcal vaccines (2 various formulations, each 1 administered as a single dose at 8-week interval).

Concerning immunogenicity of the anti-pneumococcal vaccine among SLE patients in terms of protective antibodies titer determinations, 15 (68.2%) studies judged found a general good immunological response, whereas 7 (31.8%) studies reported an immunological impairment or a poor response. Among the latter studies, McDonald et al. [42] reported that 57.9% of immunized SLE patients had protective antibody titer 3 years after receiving the anti-pneumococcal vaccine. With respect to controls, 2-year post-immunization antibody titer was lower for serotypes 4 ($p < .025$), 7F ($p < .005$), 18C ($p < .025$), 3-year post-immunization was lower for serotypes 1 ($p < .05$), 7F ($p < .0025$), 9 N ($p < .01$), 18C ($p < .025$). Tarján et al. [58] reported that antigen-specific IgM and IgG responses against Pneumococcus 6B and 23F serotypes were weaker among SLE patients with respect to healthy controls. From a quantitative standpoint, 66.7% of patients had 2-fold increase in IgM titer against 6B. serotype, 33.3% of them reacted also to 23F serotype and 50% had two-fold increase in IgG titer against 6B and 23F serotypes. Among the controls, 50% reported a 4-fold increase in IgG antibody titer against 6B, while 83.3% reported high IgG titers against 23F, while IgM response to vaccine was not different from that of SLE patients (50% and 16.7%, respectively, of controls reacted to 6B and 23F). Prakash et al. [46] found a good immunological response to vaccine only in 40% of SLE patients *versus* 60% of the subjects in the control group with statistically significant

differences specifically concerning Pneumococcus serotypes 51 and 4 ($p = .05$ and $p = .025$, respectively). A 2-fold increase in the antibody titer was observed in 20% of SLE patients *versus* 50% of controls.

Overall, immunogenicity of the vaccine went from 36.0% to 97.6%, depending also on the technique used and the timing when the assessment was performed. According to Elkayam et al. [25,41], 20.8% of SLE patients responded to either none or only 1 of the 7 pneumococcal polysaccharides.

Stratifying immunogenicity based on the anti-pneumococcal formulation administered, one third of the studies on the 13-valent and another third of the studies on the 23-valent vaccine found poorly immunogenic responses.

It should be, incidentally, noted that the antibody titer, which is a proxy of the seroprotection against *S. pneumoniae*, can be measured with different laboratory assays and utilizing different cut-offs and criteria. This may contribute to explain, at least partially, the heterogeneity found. More in detail, most studies utilized enzyme immunoassays, whereas Croft et al. [50] and Lipnick et al. [54] exploited radioimmunoassays and Jarrett et al. [22] and McDonald et al. [42] used radial immunodiffusion assays. Chatham et al. [49] and Nagel et al. [56] utilized multiplex fluorescent microsphere immunoassays (MFMIs). Furthermore, Grabar et al. [52], Nagel et al. [56] and Tarján et al. [58] investigated also the opsonophagocytic activity. Tarján et al. [58] performed also cellular assays on blood lymphocyte populations. Further details can be found in Table 5.

Concerning safety, no serious AEs were reported: they were generally mild/low-grade and with 8–88% of the participants reporting such reactions. SLE flares were rarely reported and only by two studies. Jarrett et al. [22] reported 3 subjects complaining of major clinical flares necessitating major immunosuppressant therapy 1 year after the vaccine administration. Three deaths (due to myocarditis; persistent fever, central nervous system disease and gram negative sepsis; nephrotic syndrome) occurred among SLE vaccinees. On the other hand, in the non-vaccinated SLE control group, 2 patients developed clinically major flares, 1 had active nephritis and another 1 severe hemolytic anemia. Furthermore, 1 death occurred secondary to acute pneumococcal meningitis (Pneumococcus serotype 14). Grabar et al. [52] reported that 9 SLE flares (including mild polyarthritis) occurred in 6 patients (4 in the placebo-PPS and 2 in the PnCj-PPS groups respectively, statistically not significant with a *p*-value of 0.70).

Only 7 studies investigated the changes in auto-antibodies (anti-dsDNA) after anti-pneumococcal immunization among SLE patients, showing no changes before and after immunization. Pisoni et al. [57] reported an increase of anti-dsDNA antibodies in 8.5% of the studied population. Lipnick et al. [54] reported a 10% increase in 8% and 16% of patients at 1 and 6 months *versus* 10% and 15% of controls, respectively.

Other auto-antibodies (anti-Sm, anti-Ro/SSA, anti-cardiolipin IgM, anti-RNP, anti-nuclear antibodies or ANA) have been investigated only by Elkayam et al. [25,41]. The same study documented that a single patient developed aCL IgG and another 1 turned anti-nRNP negative.

Concerning complement levels, which represent an important biomarker of SLE activity, only 8 studies addressed this topic and documented stability of complements before and after vaccination. Battafarano et al. [48], Croft et al. [50], Elkayam et al. [25], Elkayam et al. [41], Grabar et al. [52], and Jarrett et al. [22] reported no statistically significant differences between and after vaccination. Pisoni et al. [57] reported a post-immunization decrease of total complement activity measured as CH50 in 5.7% of SLE patients. Tarján et al. [58] found that C3 and C4 levels significantly decreased 13 days after vaccine administration: more in detail, C3 decreased from 1.29 g/L down to 1.14 g/L ($p = .0082$), whereas C4 from 0.24 g/L down to 0.20 g/L ($p = .004$). On the other hand, Mercado [55] documented a statistically significant increase in C3 levels post immunization ($p = .019$).

Few studies – including Mercado [55] and Tarján et al. [58] – assessed the changes in immunoglobulin levels before and after immunization, which were found to be generally stable. For example, Tarján et al. [58] found that in SLE vaccinees serum total IgG and IgA levels diminished by Day 28 compared to Day 0 in which immunization was given in a statistically significant way (IgG levels decreased from 12.9 g/L down to 12.22 g/L, $p = .047$; IgA levels decreased from 2.57 g/L down to 2.37 g/L, $p = .0003$), even though all the values remained in the normal range. On the other hand, Mercado [55] documented a statistically significant decrease in the IgG levels after immunization ($p = .0193$).

Concerning cellular immunological parameters, Tarján et al. [58] found that different cellular populations (namely, CD8+, CD21+, CD3+/DR+, CD4+, CD19+ and CD56+ lymphocyte populations) remained practically unchanged before and after the anti-pneumococcal vaccination.

Regarding opsonophagocytic activity, the few available data seem to suggest that anti-pneumococcal vaccination does not impair it.

Predictors of poor immunogenicity were found to be a high erythrocyte sedimentation rate (ESR, differing between poor and good responders in a statistically significant fashion with a *p*-value of 0.04, and correlating with pre-immunization antibody titer, $r = 0.4$, $p = .03$) [47], older age (correlating with post-immunization antibody titer, $r = 0.30$, $p = .02$) [47], SLE onset (correlating with post-immunization antibody titer, $r = 0.43$, p = .02, in other words earlier disease onset was associated with poorer immunological response) [47], high SLEDAI/SELENA-SLEDAI/SLEDAI-2 K score, immunosuppressive therapy (more in detail, prednisolone dosage, rituximab or mycophenolate mofetil) [24,45,46,51,56].

Concerning immunosuppressive therapy, Rezende et al. [24] documented a seroconversion response rate in the range 43.7–77.7% in the patients under immunosuppressants *versus* 52.3–90.0% in the group without immunosuppressive therapy, and, similarly, a 4-fold increase in the range 25.0–57.1% in the patients under immunosuppressants *versus* 38.4–73.0% in the group without immunosuppressive therapy). According to Tratenberg et al. [45], Prakash et al. [46], and Gonzalez et al. [51], treatment with mycophenolate mofetil interferes with immunization. Nagel et al. [56] found that prednisolone dosage was statistically associated with low antibody response to Pneumococcus serotype 9 V. On the contrary, according to the studies of Chatham et al. [49] and Nagel et al. [56], Belimumab treatment did not impair immunological response to anti-pneumococcal vaccination. The former investigation found an immunological response of 97.6% in the belimumab cohort *versus* 97.0% in the pre-belimumab cohort.

However, only few studies managed to obtain statistically significant determinants, whereas the majority of studies failed to report any significant predictor. Sacre et al. [23] found that B-cell defects (altered germinal centres, impaired production of immunoglobulins) predict poor response, whilst a lower IgG2 serum level and a higher ratio of pre-germinal/post-germinal centre B cells are predictive of short-term protection. Interestingly, the same group [23] found that Pneumococcus 19F serotype IgG titer measured 2 months after the administration of the 13-valent vaccine was a predictive biomarker of immunogenicity, with a sensitivity of 100% [95%CI 47.8–100] and a specificity of 91.7% [95%CI 61.5–99.8]).

No evidence of publication bias could be found, both by inspecting the funnel plot and conducting the Egger's linear regressiion test.

4. Discussion

Initially, rheumatologists and immunologists were reluctant to vaccinate SLE patients [59], especially after the first reports of autoimmune disorders diagnosed or worsened after vaccinations [60–62], even though the causal link could not be established. However, vaccination is a well-accepted strategy in SLE based on studies showing a decreased risk of infection following vaccination. Our analysis proves that anti-pneumococcal vaccination is safe in SLE patients and generally immunogenic, even though a fraction of subjects could remain

Table 5
Quality assessment using the modified Downs & Black's checklist.

Reference	Item 1	Item 2	Item 3	Item 6	Item 7	Item 10	Item 11	Item 12	Item 18	Item 20
Alyasin et al., 2016 [47]	1	1	1	1	1	1	0	0	1	1
Battafarano et al., 1998 [48]	1	1	1	1	1	1	1	0	1	1
Chatham et al., 2012 [49]	1	1	1	1	1	1	1	1	1	1
Croft et al., 1984 [50]	1	1	1	1	1	1	0	0	1	1
Elkayam et al., 2002 [25]	1	1	1	1	1	1	1	0	1	1
Elkayam et al., 2005 [41]	1	1	1	1	1	1	1	0	1	1
Gonzalez et al., 2017 [51]	1	1	1	1	1	1	0	0	1	1
Grabar et al., 2017 [52]	1	1	1	1	1	1	1	1	1	1
Jarrett et al., [22]	1	1	1	1	1	1	0	0	1	1
Klippel et al., 1979 [53]	1	1	1	1	1	1	1	1	1	1
Lipnick et al., 1985 [54]	1	1	1	1	1	1	1	1	1	1
Mcdonald et al., 1984 [42]	1	1	1	1	1	1	0	0	1	1
Mercado, 2003 [55]	1	1	1	1	1	1	0	0	1	1
Nagel et al., 2017 [56]	1	1	1	1	1	1	1	0	1	1
Pisoni et al., 2003 [57]	1	1	1	1	1	1	0	0	1	1
Prakash et al., 2017 [46]	1	1	1	1	1	1	0	0	1	1
Rezende et al., 2016 [24]	1	1	1	1	1	1	1	0	1	1
Sacre et al., 2018 [23]	1	1	1	1	1	1	1	0	1	1
Tarján et al., 2002 [58]	1	1	1	1	1	1	1	0	1	1
Tarasova et al., 2016 [43]	1	1	1	1	1	1	0	0	1	1
Tarasova et al., 2018 [44]	1	1	1	1	1	1	0	0	1	1
Tratenberg et al., [45]	1	1	1	1	1	1	0	0	1	1

Table 6
Relevant laboratory assays performed in the studies included in the present systematic review and meta-analysis and definitions of immunogenicity used by the authors.

Reference	Laboratory assay	Immunogenicity definition
Alyasin et al., 2016 [47]	Enzyme immunoassay	Fold increase
Battafarano et al., 1998 [48]	Enzyme immunoassay	Only total antibody levels, fold-increase
Chatham et al., 2017 [49]	Microsphere-based multianalyte immunoassay	Antibody levels for each Pneumococcus serotype
Croft et al., 1984 [50]	Radioimmunoassay	Only total antibody levels reported
Elkayam et al., 2002 [25]	Enzyme immunoassay	Antibody levels for each Pneumococcus serotype, cutoff 1 μg/mL
Elkayam et al., 2005 [41]	NA	NA
Gonzalez et al., 2017 [51]	Enzyme assay	Antibody levels for at least70% of Pneumococcus serotypes ≥1.3 μg/dl
Grabar et al., 2017 [52]	Enzyme immunoassay, opsonophagocytic activity	Responders to at least 5 serotypes, responders to all 7 serotypes, responders by number of serotypes, titer ≥1 μg/mL, ratio titer/week 0 ≥ 2
Jarrett et al., [22]	Radial immunodiffusion assay	Antibody levels for each Pneumococcus serotype, fold increase
Klippel et al., 1979 [53]		
Lipnick et al., 1985 [54]	Radioimmunoassay	Antibody levels for each Pneumococcus serotype, fold increase
Mcdonald et al., 1984 [42]	Radial immunodiffusion assay	Antibody levels for each Pneumococcus serotype, fold increase
Mercado, 2003 [55]	Enzyme immunoassay (EIA)	Total antibody level against S. pneumoniae, fold increase (4-fold response criterion), protective antibody titer ≥1:40
Nagel et al., 2017 [56]	Multiplex fluorescent microsphere immunoassay, opsonophagocytic assay	Fold-increase
Pisoni et al., 2003 [57]	Enzyme immunoassay	Only total antibody levels reported
Prakash et al., 2017 [46]	Enzyme immunoassay	Antibody titers or > 1.3 μg/mL or either a 4-fold, 3-fold, or 2-fold increase in the stimulation index (post-immunization titer/pre-immunization titer) for 70% of the 14 pneumococcal polysaccharides
Rezende et al., 2016 [24]	Enzyme immunoassay	Antibody titers > 1.3 μg/mL, fold-increase (4-fold response criterion)
Sacre et al., 2018 [23]	Enzyme immunoassay	Antigen-specific IgG concentration ≥ 1.3 μg/mL for at least 70% of 7 pneumococcal serotypes (4, 6 B, 9 V, 14, 18C, 19 F, 23 F)
Tarján et al., 2002 [58]	Enzyme immunoassay, phagocyte chemiluminescence, cellular assays on blood lymphocyte populations	
Tarasova et al., 2016 [43]	Enzyme immunoassay	Antibody levels against *S. pneumoniae*
Tarasova et al., 2018 [44]	Enzyme immunoassay	Antibody levels against *S. pneumoniae*
Tratenberg et al., [45]	Enzyme immunoassay	Antibody concentration ≥ 1.3μg/mL in at least 70% of the 14 pneumococcal serotypes, fold increase

Table 7
Synthesis of the major methodological features and outcomes studied in the present systematic review.

Studied outcome	Number of studies	References
Study design		
Longitudinal – convenience sample	1	Alyasin et al., 2016 [47]
Longitudinal – consecutive patients	5	Battafarano et al., 1998 [48] Elkayam et al., 2002 [25] Elkayam et al., 2005 [41] Rezende et al., 2016 [24] Sacre et al., 2018 [23]
Longitudinal – random-chosen patients	1	Tarján et al., 2002 [58]
Longitudinal – consecutive + random-chosen patients	1	Nagel et al., 2017 [56]
Longitudinal – no better specified	11	Croft et al., 1984 [50] Gonzalez et al., 2017 [51] Jarrett et al., 1980 [22] Lipnick et al., 1985 [54] McDonald et al., 1984 [42] Mercado, 2003 [55] Pisoni et al., 2003 [57] Prakash et al., 2017 [46] Tarasova et al., 2016 [43] Tarasova et al., 2018 [44] Tratenberg et al., 2015 [45]
Longitudinal – RCT	4	Chatham et al., 2017 [49] Grabar et al., 2017 [52] Klippel et al., 1979 [53] Lipnick et al., 1985 [54]
Case-control	14	Alyasin et al., 2016 [47] Battafarano et al., [48] Croft et al., 1984 [50] Elkayam et al., 2002 [25] Elkayam et al., 2005 [41] Grabar et al., 2017 [52] Jarrett et al., 1980 [22] Klippel et al., 1979 [53] Lipnick et al., 1985 [54] McDonald et al., 1984 [42] Nagel et al., 2017 [56] Prakash et al., 2017 [46] Tarján et al. 2002 [58] Tratenberg et al., 2015 [45]
Study follow-up/timing		
6 days	1	Tarján et al., 2002 [58]
13 days	1	Tarján et al., 2002 [58]
3 weeks	1	Ayasin et al., 2016 [47]
4 weeks/1 month	8	Chatham et al., 2017 [49] Croft et al., 1984 [50] Gonzalez et al., 2017 [51] Jarrett et al., 1980 [22] Lipnick et al., 1985 [54] Mercado, 2003 [55] Rezende et al., 2016 [24] Tarján et al. 2002 [58]
6 weeks	2	Croft et al., 1984 [50] Rezende et al., 2016 [24]
8 weeks/2 months	4	Elkayam et al., 2002 [25] Elakayam et al., 2005 [41] Sacre et al., 2018 [23] Tratenberg et al., 2015 [45]
12 weeks/3 months	1	Pisoni et al., 2003 [57]
6 months	1	Lipnick et al., 1985 [54]
28 weeks/7 months	1	Grabar et al., 2017 [52]
8 months	1	Mercado, 2003 [55]
1 year	5	Jarrett et al., 1980 [22] McDonald et al., 1984 [42] Sacre et al., 2018 [23] Tarasova et al., 2016 [43] Tarasova et al., 2018 [44]
52 weeks/13 months	1	Grabar et al., 2017 [52]
2 years	1	McDonald et al., 1984 [42]
3 years	1	McDonald et al., 1984 [42]
Anti-pneumococcal vaccine formulation		
7-valent	1	Grabar et al., 2017 [52]
13-valent	3	Gonzalez et al., 2017 [51] Nagel et al., 2017 [56] Sacre et al., 2018 (23)
14-valent	5	Croft et al., 1984 [50] Jarrett et al., 1980 [22] Klippel et al., 1979 [53] Lipnick et al., 1985 [54] McDonald et al., 1984 [42]
23-valent	15	Alyasin et al., 2016 [47] Battafarano et al., 1998 [48] Chatham et al., 2017 [49] Elkayam et al., 2002 [25] Elkayam et al., 2005 [41] Grabar et al., 2017 [52] Mercado, 2003 [55] Pisoni et al., 2003 [57] Prakash et al., 2017 [46] Rezende et al., 2016 [24] Sacre et al., 2018 [23] Tarasova et al., 2016 [43] Tarasova et al., 2018 [44] Tarján et al., 2002 [58] Tratenberg et al., 2015 [45]
Anti-pneumococcal vaccine administration		
Single administration	11	Alyasin et al., 2016 [47] Chatham et al., 2017 [49] Elkayam et al., 2002 [25] Elkayam et al., 2005 [41] Pisoni et al., 2003 [57] Prakash et al., 2017 [46] Rezende et al., 2016 [24] Tarasova et al., 2016 [43] Tarasova et al., 2018 [44] Tarján et al., 2002 [58] Tratenberg et al., 2015 [45]
Simultaneous administration of various vaccines	2	Battafarano et al., 1998 [48] Mercado, 2003 [55]
Sequential administration of various anti-pneumococcal vaccines	2	Grabar et al., 2017 [52] Sacre et al., 2018 [23]
Safety and tolerability		
Mild/low-grade AEs	20	Alyasin et al., 2016 [47] Battafarano et al., 1998 [48] Chatham et al., 2017 [49] Croft et al., 1984 [50] Elkayam et al., 2002 [25] Elkayam et al., 2005 [41] Jarrett et al., 1980 [22] Klippel et al., 1979 [53] Lipnick et al., 1985 [54] McDonald et al., 1984 [42] Mercado, 2003 [55] Nagel et al., 2017 [56] Pisoni et al., 2003 [57] Prakash et al., 2017 [46] Rezende et al., 2016 [24] Sacre et al., 2018 [23] Tarján et al., 2002 [58] Tarasova et al., 2016 [43] Tarasova et al., 2018 [44] Tratenberg et al., 2015 [45]
SLE flares and major AEs	2	Grabar et al., 2017 [52] Jarrett et al., 1980 [22]
Stability of auto-antibody levels	7	Battafarano et al., 1998 [48] Elkayam et al., 2005 [41] Grabar et al., 2017 [52] Jarrett et al., 1980 [22] Mercado, 2003 [55] Tarján et al., 2002 [58] Tarasova et al., 2018 [44]
Stability of complement levels	8	Battafarano et al., 1998 [48] Croft et al., 1984 [50] Elkayam et al., 2002 [25] Elkayam et al., 2005 [41]

(*continued on next page*)

Table 7 (*continued*)

Studied outcome	Number of studies	References
		Grabar et al., 2017 [52] Jarrett et al., 1980 [22] Mercado, 2003 [55] Tarasova et al., 2018 [44]
Immunogenicity		
Immunogenic	15	Alyasin et al., 2016 [47] Battafarano et al., 1998 [48] Chatham et al., 2012 [49] Croft et al., 1984 [50] Elkayam et al., 2002 [25] Elkayam et al., 2005 [41] Gonzalez et al., 2017 [51] Grabar et al., 2017 [52] Klippel et al., 1979 [53] Lipnick et al., 1985 [54] Mercado, 2003 [55] Nagel et al., 2017 [56] Pisoni et al., 2003 [57] Tarasova et al., 2016 [43] Tarasova et al., 2018 [44]
Poorly immunogenic	7	Jarrett et al., 1980 [22] McDonald et al., 1984 [42] Prakash et al., 2017 [46] Rezende et al., 2016 [24] Sacre et al., 2018 [23] Tarján et al., 2002 [58] Tratenberg et al., 2015 [45]
Predictors of immunogenicity		
Age	2	Alyasin et al., 2016 [47] Nagel et al., 2017 [56]
Clinical chemistry	1	Alyasin et al., 2016 [47]
Disease activity – SLEDAI/SELENA-SLEDAI/SLEDAI-2 K score	1	Alyasin et al., 2016 [47]
Disease onset	1	Alyasin et al., 2016 [47]
Immunosuppressive therapy	4	Nagel et al., 2017 [56] Prakash et al., 2017 [46] Rezende et al., 2016 [24] Tratenberg et al., 2015 [45]

Abbreviations. AE (adverse event); RCT (randomized-controlled trial); SELENA (Safety of Estrogens in Lupus National Assessment); SLEDAI (Systemic Lupus Erythematosus Disease Activity Index); SLEDAI-2 K (Systemic Lupus Erythematosus Disease Activity Index 2000).

unprotected against *S. pneumoniae*. A recently published meta-analysis carried out by Pugès and collaborators [27] has proven that, among SLE patients, the pneumococcal vaccine against Pneumococcus 23F serotype has a good preserved immunogenicity.

Determinants of immunological response to the anti-pneumococcal vaccination are poorly known. However, according to our study, high ESR levels, high SLEDAI/SELENA-SLEDAI/SLEDAI-2 K score, some immunological parameters such as B cell defects and immunosuppressive therapy (rituximab, mycophenolate mofetil, or prednisolone/prednisone) were found to be predictors of low immunogenicity.

The mechanism by which rituximab, an anti-CD20, increasingly and commonly used for diverse autoimmune conditions, such as SLE and primary systemic vasculitis [63,54], can induce low immunogenicity may be related to its mechanisms of action through the achievement of complete peripheral blood B cell depletion for a relatively long period [65,66]. In one study, following rituximab therapy, 34% patients had IgG < 6 g/L [63,64]. However, higher rates of hypogammaglobulinaemia have been reported in patients treated with rituximab due to lymphoproliferative disorders, especially in those receiving rituximab in combination with chemotherapy [67,68]. A study of Oren et al. [69] aimed to assess the impact of rituximab on the efficacy of influenza vaccination in patients with rheumatoid arthritis showing response to the vaccine was significantly lower among rituximab-treated patients. Another study conducted on ITP patients showed that 21.4% of patients treated with rituximab failed to respond to vaccines by any criteria [70]. Therefore, extra vigilance for infection in the 3-month window post starting rituximab in SLE patients is required by physicians and patients [71].

Interestingly, belimumab also exerts its effects on B cells, as a human monoclonal antibody directed against the B-cell activating factor, also known as B-lymphocyte stimulator, approved worldwide for the treatment of SLE [72,73]. However, in contrast to rituximab, the former seems to have no significant impact on the immunogenicity of anti-pneumococcal vaccines in SLE patients. One study assessing the effect of belimumab on antibodies levels against influenza, pneumococcal, and tetanus vaccines in patients with SLE found no significant effect [74]. Similar results were found in another study evaluating the impact of belimumab on the response to pneumococcal vaccination in SLE patients showing no significant differences between the pre-belimumab and belimumab-concurrent cohorts [45].

However, only few studies have found statistically significant predictors of anti-pneumococcal vaccine immunogenicity, and, moreover, determinants of poor immunological response have not been replicated by other studies. As such, there is a dearth of reliable information concerning biomarkers of immunogenicity and future studies should try to address this crucial question.

SLE patients are at high risk for developing pneumococcal pneumonia [75]. According to a retrospective survey conducted on data from 3 healthcare claims repositories, rates of all-cause pneumonia among subjects aged 18 years and older with chronic medical conditions were approximately 3 times the rates in age-matched healthy controls [76]. SLE represented an additional at-risk condition for pneumococcal disease [76].

As such, among SLE patients, anti-pneumococcal vaccination is considered of crucial importance in all age groups, in that it mitigates the burden related to infections and co-morbidities. It prevents invasive pneumococcal disease and improves the quality of life of SLE patients. For instance, in a nationwide study, Mehta and collaborators [32] analyzed a total of 193,293 SLE adult patients. Of these, 1755 (0.91%) patients received pneumococcal vaccination during the hospitalization. Mortality rates among the non-vaccinated lupus nephritis patients was 1.2% (208 out of 16,824), whereas no deaths were reported in the

Table 8
Take-home messages.

Main conclusions
Anti-pneumococcal vaccination is generally safe among SLE patients.
SLE flares after anti-pneumococcal vaccination have been rarely reported.
Anti-pneumococcal vaccination is generally immunogenic among SLE patients.
Immunization should be given prior initiation of immunosuppressive therapy (treatment with rituximab, prednisone/prednisolone high doses, and mycophenolate mofetil).
Treatment with belimumab does not interfere with the immunological response to anti-pneumococcal vaccination.
Sequential administration of anti-pneumococcal vaccines does not seem to confer particular benefits in terms of immunological protection.
Although a minority, a certain fraction of SLE patients remain unprotected against *S. pneumoniae*. More immunogenic vaccines should be produced
Predictors of poor immunological response to anti-pneumococcal vaccination remain unknown and further researches should explore this aspect
Coverage rate among SLE patients remains still low and unsatisfactory
Physicians and workers in the field of preventive medicine should elaborate new strategies for promoting anti-pneumococcal vaccine uptake

Abbreviations. SLE (systemic lupus erythematosus).

vaccinated patients. A total of 3390 (1.75%) SLE patients died during hospitalization, 3380 patients had not received pneumococcal vaccination. Mortality percentage of SLE patients who did not receive vaccination was 1.76% (3380/191,538) whereas mortality percentage in patients who received vaccination was 0.56% (10/1755), ($p < .001$). Pneumococcal vaccination was associated with decreased in-hospital mortality in SLE and lupus nephritis patients [32]. Thus, immunization against pneumococcal agents is required in SLE patients regardless of treatment and diseases activity, due to the high mortality rate reported in such patients.

However, despite the importance of anti-pneumococcal immunization, vaccine coverage among SLE patients remains low and unsatisfactory. For example, the cross-sectional analysis of the German long-term study (LuLa cohort) has analyzed the vaccination status of 579 SLE patients. Vaccination uptake was low for pneumococcus, being 32.2%. Older age was found to be predictive of receiving anti-pneumococcal vaccination [28]. According to the survey carried out by Malysheva and coworkers [77], only 12 patients (19%) of the total sample and 30% in the age group > 60 years have ever received the pneumococcal vaccination.

Innovative approaches to improve the vaccine uptake have been developed and implemented, including, for example, the use of Electronic Health Record Best Practice Alert or pre-visit and counselling, especially among SLE pediatric patients [78,79]. Further initiatives and techniques should be explored.

5. Strengths and limitations

The present systematic review and meta-analysis has a number of strengths, including its novelty and its broad and comprehensive literature search, free from any time and language constraints, and conducted in a rigorous, transparent and reproducible fashion. It has to be emphasized that also the gray literature has been systematically mined and that both fully published and unpublished/partially published (in congress proceedings) findings have been collected. This has enabled us to overcome any potential publication bias.

On the other hand, it is not without any limitations, which should be properly acknowledged. The main shortcoming is given by the high amount of heterogeneity among studies, which calls for caution in interpreting results.

6. Conclusions

To the best of our knowledge, the present systematic review and meta-analysis, synthesizing 22 primary studies, represents the first comprehensive review addressing the topics of immunogenicity, safety and tolerability of anti-pneumococcal vaccination in SLE patients.

According to our findings, anti-pneumococcal vaccines can be safely administered in SLE patients. They confer good immunological protection, even though a non-negligible percentage of vaccinees remains unprotected against pneumococcal bacterium. Determinants of poor response are still unknown with known relevant risk factors including older age, higher disease activity index, low complement levels, low immunoglobulins levels, and lymphocyte function being poorly evaluated in the available studies. Given the above-mentioned limitations, further high-quality RCTs investigating more immunogenic products are needed. It is, however, highly recommended to immunize SLE patients prior the initiation of immunosuppressive therapy. Furthermore, coverage rate among SLE patients remains still low and unsatisfactory: physicians and workers in the field of preventive medicine and public health should elaborate new strategies for promoting anti-pneumococcal vaccine uptake.

Due to the high risk of pneumococcal infection in SLE patients and given the safety and, at least partial, effectiveness in such patients preventive strategies mainly by immunization are required in all age groups of SLE patients.

Abbreviations. ACR (American College of Rheumatology); ANA (anti-nuclear antibodies); ARA (American Rheumatism Association); CD (cluster of differentiation); d (day/days); DMARDs (disease-modifying anti rheumatic drugs); dsDNA (double-strand DNA); HIB (*Haemophilus influenzae* type b); Ig: immunoglobulin; mo (month/months); NR (not reported); NSAIDs (nonsteroidal anti-inflammatory drugs); SELENA (Safety of Estrogens in Lupus National Assessment); SLEDAI (systemic lupus erythematosus disease activity index); SLEDAI-2 K (systemic lupus erythematosus disease activity index 2000); w (week/weeks); y (year/years).

Foot note.

Section Reporting. Item 1. Is the hypothesis/aim/objective of the study clearly described? Item 2. Are the main outcomes of the study clearly described? Item 3 Are the characteristics of the patients included in the study clearly described? Item 6 Are the main findings of the study clearly described? Item 7 Does the study provide estimates of the random variability in the data for the main outcomes? Item 10 Have actual probability values been reported (*e.g.* 0.035 rather than < 0.05) for the main outcomes except where the probability value is < 0.001?

Section External validity. Item 11 Were the subjects asked to participate in the study representative of the entire population from which they were recruited? Item 12 Were those subjects who were prepared to participate representative of the entire population from which they were recruited?

Section Internal validity. Item 18. Were the statistical tests used to assess the main outcomes appropriate? Item 20 Were the main outcome measures used accurate (valid and reliable)?

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