RHEUMATOLOGY

Rheumatology 2021;60:60–72
doi:10.1093/rheumatology/keaa478
Advance Access publication 25 October 2020

Systematic review and meta analysis

The risk of infections in adult patients with systemic lupus erythematosus: systematic review and meta-analysis

José María Pego-Reigosa[1,2], Lindsay Nicholson[3], Nick Pooley[3], Sue Langham[4], Nina Embleton[5], Zoe Marjenberg[3], Volkan Barut[6], Barnabas Desta[7], Xia Wang[8], Julia Langham[9] and Edward R. Hammond[10]

Abstract

Objectives. We conducted a systematic review and meta-analysis to determine the magnitude of infection risk in patients with SLE and evaluate the effect of general and SLE-related factors on infection risk.
Methods. We searched MEDLINE and Embase from inception to July 2018, screening for observational studies that evaluated infection risk in patients with SLE compared with the general population/healthy controls. Outcomes of interest included overall severe infection, herpes zoster infection/reactivation, opportunistic infections, pneumonia and tuberculosis. Random-effects models were used to calculate pooled risk ratios (RRs) for each type of infection. Sensitivity analysis assessed the impact of removing studies with high risk of bias.
Results. Eleven retrospective or prospective cohort studies were included in the meta-analysis: overall severe infection ($n = 4$), pneumonia ($n = 6$), tuberculosis ($n = 3$) and herpes zoster ($n = 2$). Pooled RRs for overall severe infection significantly increased for patients with SLE compared with the general population/healthy controls [RR 2.96 (95% CI 1.28, 6.83)]. Pooled RRs for pneumonia, herpes zoster and tuberculosis showed significantly increased risk compared with the general population/healthy controls [RR 2.58 (1.80, 3.70), 2.50 (2.36, 2.65) and 6.11 (3.61, 10.33), respectively]. Heterogeneity and evidence of publication bias were present for all analyses, except herpes zoster. Sensitivity analyses confirmed robustness of the results.
Conclusion. Patients with SLE have significantly higher risk of infection compared with the general population/healthy controls. Efforts to strengthen strategies aimed at preventing infections in SLE are needed.
Protocol registration. PROSPERO number: CRD42018109425.

Key words: SLE, infection, pneumonia, tuberculosis, herpes zoster, meta-analyses

CLINICAL SCIENCE

Rheumatology key messages

- Rates of infections are higher among persons with SLE compared with the general population.
- Pooled risk for overall severe infections is 3.0-fold, tuberculosis 6.1-fold, pneumonia 2.6-fold and herpes zoster 2.5-fold.
- SLE patients have significantly higher risk of infection compared with the general population/healthy controls.

[1]Rheumatology Department, University Hospital of Vigo, Vigo, [2]IRIDIS (Investigation in Rheumatology and Immune-Mediated Diseases) Study Group, IISGS (Instituto de Investigación Sanitaria Galicia Sur), Vigo, Spain, [3]Systematic Review Group, Maverex Limited, Manchester, [4]Health Economics Group, Maverex Limited, Manchester, [5]Statistical Group, Maverex Limited, Manchester, [6]Global Medical Affairs, AstraZeneca, Cambridge, UK, [7]Global Pricing and Market Access, AstraZeneca, Gaithersburg, MD, [8]Data Science & AI, AstraZeneca, Gaithersburg, MD, USA, [9]Epidemiology Group, Maverex Limited, Manchester, UK and [10]BioPharmaceuticals Medical, AstraZeneca, Gaithersburg, MD, USA

Submitted 2 March 2020; accepted: 24 June 2020

Correspondence to: Edward R. Hammond, AstraZeneca, 1 Medimmune Way, Gaithersburg, MD 20878, USA. E-mail: edr.hammond@gmail.com

Introduction

SLE is a chronic autoimmune disease that affects multiple organ systems, leading to a variety of clinical manifestations [1]. Increased disease activity, characterized by recurrent and unpredictable flares, can occur in patients with SLE and may be associated with organ damage and increased mortality [2]. SLE is associated with increased comorbidities [3], which may result from disease activity and CS use [4].

Infections are the leading cause of morbidity and mortality in patients with SLE [5, 6]. Approximately half of patients with SLE experience a severe infection during the course of their disease, and 11–23% of hospitalizations among patients with SLE are due to infections [6–8]. One-third of SLE-related deaths are attributable to an infectious organism [5, 9]. Bacterial infections are the most common aetiological agent in SLE. In a large registry study (The Registry of Systemic Lupus Erythematosus Patients of the Spanish Society of Rheumatology), bacterial infections accounted for 51.9% of all infections, followed by viruses (11.9%) and fungi (2.3%) [10]. In the same study, the most frequent infection sites were the respiratory tract (35.5%), urinary tract (15.0%) and soft tissues (13.3%) [10, 11].

Although many bacterial infections are more prevalent in patients with SLE than in healthy people, the causal organisms do not vary from the general population and include pathogens such as *Staphylococcus aureus*, *Streptococcus pneumonia* and *Escherichia coli* [12]. SLE disease activity, increased CS use and SLE-associated immunological abnormalities have all been associated with increased infections in patients with SLE [13]. Opportunistic infections are also underreported in patients with SLE due to their mimicry of active lupus [14].

Some studies have assessed risk of infection in patients with SLE; however, to date, no meta-analyses have been performed to provide a comprehensive overview of infection risk. We aimed to conduct a systematic review and meta-analysis to examine the magnitude of risk of opportunistic infections, tuberculosis and herpes zoster, as well as hospitalization rates due to infections. We also aimed to explore the impact of demographic factors (age and sex), SLE-related factors (treatment and time from SLE diagnosis) and study time period on infection risk.

Methods

Search strategy

This study was conducted in accordance with the Meta-analysis Of Observational Studies in Epidemiology and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for conducting and reporting systematic reviews [15, 16]. The study protocol is published via PROSPERO: International prospective register of systematic reviews (#CRD42018109425) [17]. We searched for full-text reports containing original data in MEDLINE and Embase, and in reference lists of included articles. The detailed search strategy is available in supplementary Table S1, available at *Rheumatology* online.

Eligibility criteria

We included full publications of observational studies (cohort, cross-sectional and case–control studies and analysis of hospital records/database) that evaluated risk of infection events in adult patients with an SLE diagnosis identified by International Classification of Diseases (ICD-7, ICD-8, ICD-9 or ICD-10) codes or ACR criteria [18, 19] compared with the general population (all individuals without reference to any specific characteristic) or healthy controls (patients without SLE or other autoimmune conditions). Outcomes reported in this manuscript include fatal (leading to death) and non-fatal (not leading to death) infection events for overall severe infection, pneumonia, herpes zoster, tuberculosis, bacteraemia and sepsis. Studies were included if they assessed risk using either hazard ratios, rate ratios, risk ratios (RRs), odds ratios, incidence rate ratios, proportionate morbidity ratios, standardized mortality rate or standardized incidence rate, with 95% CIs. Abstracts of unpublished studies were excluded as data were not reported in a form that could be used for formal comparison.

Screening and abstraction process

Two reviewers independently performed two-stage screening (title/abstract and full-text screening), data extraction and risk of bias assessment (N.P. and L.N.); disagreement was resolved by consensus involving a third reviewer (J.L.). Studies that met eligibility criteria and reported original data were included in the review. Data on study characteristics and the effect measure for outcomes of interest (fatal and non-fatal events) were extracted.

Risk of bias and quality assessment

Risk of bias for observational studies was assessed by an SLE-specific 12-point scale and the Newcastle-Ottawa scale [20].

The SLE-specific 12-point scale was used in previous SLE systematic reviews [21–27]. Each study was scored according to five domains: (i) source of the study sample, (ii) cohort type, (iii) SLE definition, (iv) length of SLE exposure and (v) ascertainment of outcome (supplementary Table S2, available at *Rheumatology* online).

The Newcastle-Ottawa scale assesses study quality in three domains: (i) selection of the study groups, (ii) comparability of cohorts on the basis of the design or analysis and (iii) ascertainment of outcomes of interest (supplementary Table S3, available at *Rheumatology* online). Studies were classified as having low, moderate or high risk of bias based on results from both scales.

Statistical analysis

Meta-analyses were conducted for all outcomes for which there were at least two studies with low risk of bias reporting useable data. When two studies reported findings from overlapping populations, one was selected based on study quality, population size and length of study period.

Odds ratios, hazard ratios and rate ratios, prevalence risk, standardized incidence ratios and standardized mortality ratios were treated as equal estimates assuming rare occurrence [28] and referred to as RRs throughout this report. A DerSimonian and Laird [29] random-effects model was fit to calculate the pooled RR and 95% CIs for all outcomes using the most adjusted RRs.

Heterogeneity was tested using the Cochran's Q statistic with statistical significance set at $P < 0.10$ and quantified by the I^2 test. Publication bias was assessed with funnel plots and the Egger's test [30].

Robustness of results was assessed using the leave1-out function, which examined the effect of removing individual studies on pooled estimates [31]. Several sensitivity analyses were performed, including least adjusted analysis; only studies published ≤5 years prior to 2018; only studies published >5 years prior to 2018; only studies with low risk of bias; excluding studies only reporting on non-fatal events; excluding studies only reporting on non-fatal or fatal events; and excluding cross-sectional studies. All analyses were conducted in R version 3.5.1 using the packages metafor and forestplot.

We describe reported RRs for patient subgroups for which data were available from specific studies (e.g. age, disease severity, types of SLE treatment). Due to the paucity of data, no meta-analyses were conducted for subgroups except examination for trends.

Results

Literature search

The initial search returned 4187 references after de-duplication. After title and abstract screening, 111 records were included for full-text review. Nineteen studies were included in the qualitative synthesis, and 11 studies were included in the quantitative synthesis (Fig. 1). Sixty-five of 92 studies were excluded because they did not have an appropriate comparison population or report a relevant outcome. A list of excluded studies and the reason for exclusion is outlined in supplementary Table S4, available at *Rheumatology* online.

Study characteristics

Nineteen studies were included in the qualitative synthesis [3, 32–49]; the study characteristics are summarized in Table 1. Fourteen were retrospective cohort studies, and there was one each of prospective cohort, single-centre cross-sectional, single-centre retrospective cohort, single-centre cohort/case–control and population-based cross-sectional studies. The 19 studies were conducted in Europe ($n = 7$), North America ($n = 6$), Asia ($n = 3$), Middle East ($n = 1$), South America ($n = 1$) and multiple countries ($n = 1$; centres in Europe, North America and Asia). Study periods ranged between <1 year [40] and 45 years [48]. Studies varied in outcomes reported: fatal outcomes only ($n = 6$), non-fatal only ($n = 1$), or both fatal and non-fatal events ($n = 12$). The percentage of female patients ranged from 78% [34] to 100% [40]. Average age ± S.D. (reported in 11 studies) ranged from 34.8 ± 14.3 [36] to 63.5 ± 18.4 years [47]. A total of 469 570 patients with SLE and 6 528 441 non-SLE/general population/healthy controls were reported across included studies. Not all studies reported the number of individuals evaluated. There were sufficient data for meta-analyses of overall severe infection, pneumonia, herpes zoster and tuberculosis, but not for bacteraemia, septicaemia and sepsis outcomes. No studies reported data on upper respiratory, gastrointestinal or CNS infections. All infection outcomes were defined by ICD codes, except four studies [3, 39, 40, 43] that did not describe how infections were identified (supplementary Table S5, available at *Rheumatology* online).

The overall risk of bias per study is shown in Table 1, and risk of bias assessments are summarized in supplementary Table S6, available at *Rheumatology* online. Seventeen studies were determined as having low risk of bias; one study (a population-based cross-sectional study) [39] had moderate risk of bias, and one (a single-centre cross-sectional study) had high risk of bias [40].

Risk of infections in SLE

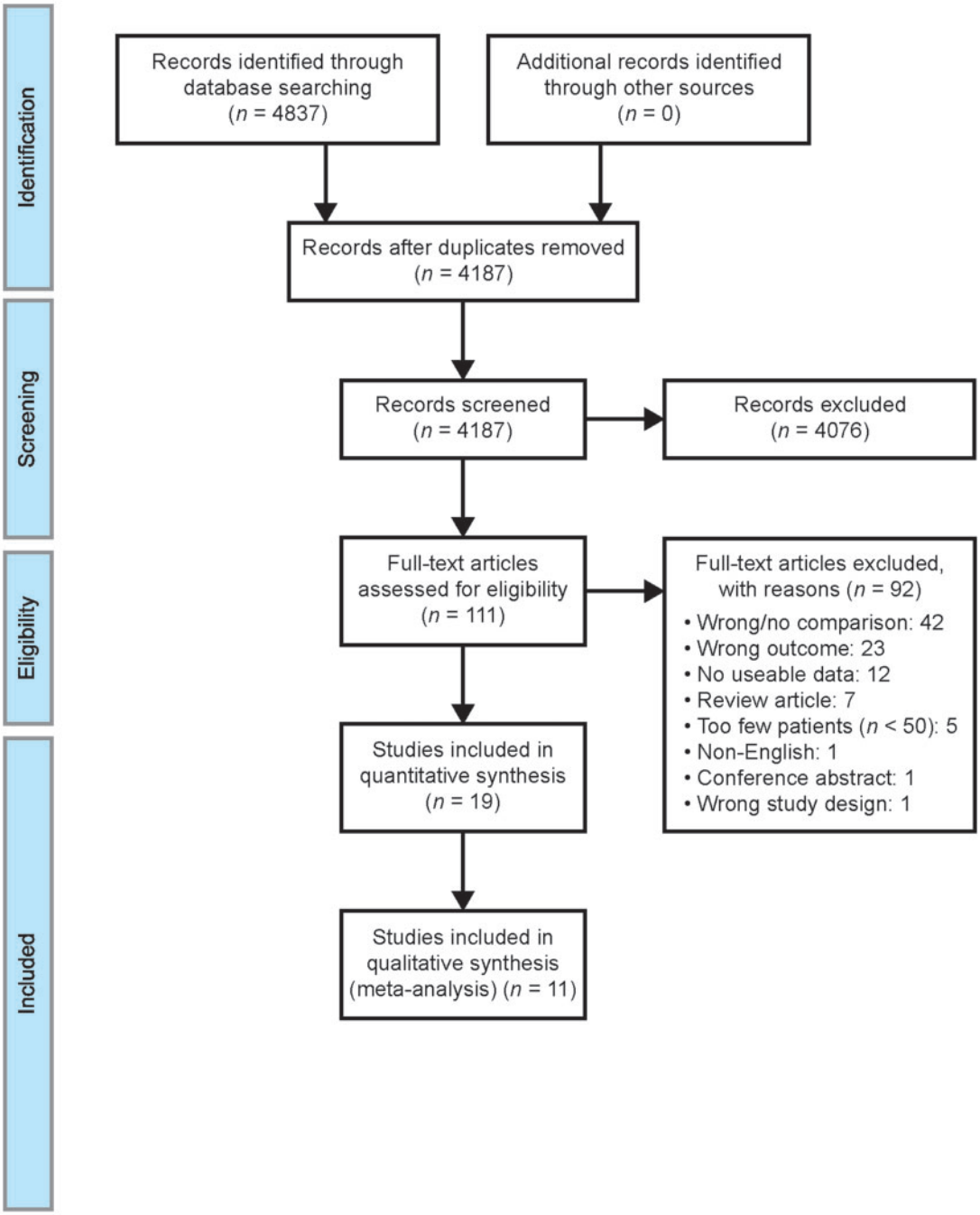
Eleven studies were included in the meta-analysis (Table 1). Eight studies were not used: three due to being stratified according to age [38, 44, 46], three due to being the only study to report that particular outcome [35, 39, 40], one stratified by treatment [37] and one stratified by study period [48].

Forest plots displaying risk of overall severe infection, pneumonia, herpes zoster and tuberculosis are shown in Fig. 2A–D. The findings suggest that SLE is associated with statistically significant increased risk of infections. For overall severe infection, RRs for each study ranged from 1.10 to 5.00, and pooled RR was 2.96 (95% CI 1.28, 6.83) (Fig. 2A). For pneumonia, RRs for each study ranged from 1.50 to 5.10, with a pooled RR of 2.58 (95% CI 1.80, 3.70) (Fig. 2B). For herpes zoster, individual study RRs ranged from 2.45 to 2.50, with a pooled RR of 2.50 (95% CI 2.36, 2.65) (Fig. 2C). For tuberculosis, RRs for each study ranged from 4.60 to 9.40, and pooled RR was 6.11 (95% CI 3.61, 10.33) (Fig. 2D).

Sensitivity analysis and heterogeneity

The leave1out method and sensitivity analyses confirmed the robustness of the results (Table 2 and supplementary Table S7, available at *Rheumatology* online). For overall severe infection, the removal of either Bjornadal *et al.* (2004) [34] or Thomas *et al.* (2014) [47] resulted in the formerly statistically significant increase

Fig. 1 Flow diagram of the systematic literature review process



in RR to become non-statistically significant. The removal of Rees *et al.* (2016) [3] resulted in an increase in RR from 2.96 (95% CI 1.28, 6.83) to 4.08 (95% CI 1.28, 6.83). For pneumonia, the leave1out analysis resulted in very little change in both significance and RR.

For the sensitivity analysis, for overall severe infection, limiting the studies to those published $\leq$5 years prior to 2018 reduced the main analysis RR from 2.96 (95% CI 1.26, 6.83) to 1.80 (95% CI 0.68, 4.74); conversely, limiting the studies to those published $>$5 years from 2018 increased the RR to 4.98 (95% CI 3.89, 6.37). Similarly, by limiting the studies to those only reporting fatal overall severe infection, RR increased to 4.08 (95% CI 2.75, 6.04). There was little impact on the significance level for pneumonia, tuberculosis and herpes zoster after altering any variables described (Table 2).

Table 1 Study characteristics: risk of infection in SLE compared with general population or healthy controls

Author/year Country	Study design	Study period	Definition of SLE	Source of SLE population	Source of comparison group	Inclusion of fatal/non-fatal events	Number of patients SLE; control	Mean/median age (years) SLE; control	Overall estimate risk of bias	Outcomes included in the meta-analysis	Outcomes not included in the meta-analysis	Relative risk measure reported
Barnado *et al*. (2018) [32] USA	Matched retrospective cohort study	NR	ICD-9	Vanderbilt's Synthetic Derivative	Same as SLE population	Fatal or non-fatal	270; NR	African American: 44; NR White: 53; NR	Low risk	Pneumonia	Skin, bacteraemia/ sepsis/septicaemia, bone, kidney, candidiasis	OR
Bernatsky *et al*. (2006) [33] Canada, USA, UK (England and Scotland), Iceland, Sweden, South Korea	Prospective cohort study	1958–2001	Clinician-confirmed[a]	Multi-site international (23 centres) SLE cohort	Population data	Fatal	9547; NR	NR	Low risk	Overall severe infection Pneumonia	NA	SMR
Bjornadal *et al*. (2004) [34] Sweden	Retrospective cohort study	1964–1994	ICD-7/8/9	The Hospital Discharge Register	Population data	Fatal	4737; NR	NR	Low risk	Overall severe infection	NA	SMR
Chang *et al*. (2017) [35] Taiwan	Retrospective cohort study	2001–2011	≥4 ACR (1997)	National Health Insurance Research Database	Same as SLE population	Fatal or non-fatal	12 102; 48 408	36.62; 36.63	Low risk	NA	Heart	HR
Chen *et al*. (2011) [36] Taiwan	Retrospective cohort study	1998–2006	≥4 ACR (1982/1997)	National Health Insurance Research Database	Same as SLE population	Fatal or non-fatal	10 337; 62 022	34.8; 34.8	Low risk	Herpes zoster	NA	RR
Herrinton *et al*. (2016) [37] USA	Retrospective cohort study	1 Jan 1997 to 31 Dec 2013	ICD-9	Kaiser Permanente Medical Care Program	Same as SLE population	Fatal or non-fatal	3030; NR	NR	Low risk	NA	Overall infection	HR
Lerang *et al*. (2014) [38] Norway	Retrospective cohort study	1 Jan 1999 to 1 Jan 2009	≥4 ACR (1997)	Inpatient/outpatient hospital discharges, local cohort from 1995, Systemic Connective Tissue Disease and Vasculitis Registry, private rheumatologists	Cause of Death Registry	Fatal	325; NR	NR	Low risk	NA	Overall infection	SMR
Mahroum *et al*. (2017) [39] Israel	Population-based cross-sectional study	NR	Clinician-confirmed[a]	Clalit Health Services	Same as SLE population	Fatal or non-fatal	5018; 25 090	50.2; 50.2	Moderate risk	NA	Hepatitis C	OR
Méndez-Martínez *et al*. (2017) [40] Mexico	Single-centre cross-sectional study	29 Jul 2014 to 4 Jan 2015	≥4 ACR (1997)	Regional General Hospital #36, Instituto Mexicano del Seguro Social, Puebla	Same as SLE population	Non-fatal	130; 94	45.8; 42.9	High risk	NA	Mycoplasma	OR
Murray *et al*. (2016) [41] USA	Retrospective cohort study	2000–2011	ICD-9	United States Healthcare Cost and Utilization Project National Inpatient Sample	Same as SLE population	Fatal or non-fatal	361 337; 668 267	51; 62	Low risk	Pneumonia, herpes zoster	Opportunistic, bacteraemia, cytomegalovirus	PR
Ramagopalan *et al*. (2013) [42] England	Retrospective cohort study	1999–2011	ICD-10	English Hospital Episode Statistics and Oxford Record Linkage Study	Same as SLE population	Fatal or non-fatal	27 519; NR	NR	Low risk	Tuberculosis	NA	RR

(continued)

TABLE 1 Continued

Author/year Country	Study design	Study period	Definition of SLE	Source of SLE population	Source of comparison group	Inclusion of fatal/non-fatal events	Number of patients SLE; control	Mean/median age (years) SLE; control	Overall estimate risk of bias	Outcomes included in the meta-analysis	Outcomes not included in the meta-analysis	Relative risk measure reported
Rees *et al*. (2016) [3] UK	Retrospective cohort study	1 Jan 1999 to 31 Dec 2012	Other validated criteria[b]	Clinical Practice Research Datalink	Same as SLE population	Fatal or non-fatal	7732; 28 079	48.1; 48.1	Low risk	Overall severe infection	NA	IRR
Rúa-Figueroa *et al*. (2014) [43] Spain	Single-centre cohort/case-control	1988–2009	≥4 ACR (1997)	Hospital Universitario de Gran Canaria Doctor Negrín, Las Palmas de Gran Canaria	Population data	Fatal or non-fatal	232; NR	45; NR	Low risk	Pneumonia	NA	SIR
Shea *et al*. (2014) [44] USA	Retrospective cohort study	2007–2010	ICD-9	Three large integrated health care claims repositories	Same as SLE population	Fatal or non-fatal	NR; NR	NR	Low risk	NA	Pneumonia, pneumococcal	Rate ratios
Souza *et al*. (2012) [45] Brazil	Retrospective cohort study	1985–2007	ICD-9/10	São Paulo State Data Analysis System Foundation	Population data	Fatal	4815; NR	35.8; NR	Low risk	Pneumonia, tuberculosis	Sepsis/septicaemia	O:E (95% CI)
Tektonidou *et al*. (2015) [46] USA	Retrospective cohort study	1996–2011	ICD-9	Nationwide Inpatient Sample, Healthcare Cost and Utilization Project	Same as SLE population	Fatal	NR; NR	NR	Low risk	NA	Pneumonia, skin, opportunistic, sepsis/septicaemia, urinary	Relative risk
Thomas *et al*. (2014) [47] France	Retrospective cohort study	2000–2009	Other validated criteria[c]	Epidemiological Center for the Medical Causes of Death	Same as SLE population	Fatal	1593; 5 395 754	63.5; NR	Low risk	Overall severe infection, pneumonia	Other infections	OR
Wotton and Goldacre (2012) [48] England	Retrospective cohort study	1963–2008	ICD-10	Oxford Record Linkage Study	Same as SLE population	Fatal or non-fatal	20 005; NR	NR	Low risk	NA	Pneumococcal	Rate ratios
Yang *et al*. (2017) [49] Singapore	Single-centre retrospective cohort study	1 Jan 2004 to 31 Dec 2011	ICD-9	Hospital discharge database of General Hospital	Same as SLE population	Fatal or non-fatal	841; 300 727	53.9; 44.7	Low risk	Tuberculosis	NA	OR

[a]Rheumatologist confirmed a definite diagnosis of SLE if four ACR criteria had been met.

[b]Based on Clinical Practice Research Datalink read codes.

[c]Based on death certificate. ACR: ACR 1982 or 1997 modified criteria; HR: hazard ratio; ICD: International Classification of Diseases; IRR: incident rate ratio; NA: not applicable; NR: not reported; O:E: observed to expected events; OR: odds ratio; PR: prevalence ratio; RR: risk ratio; SIR: standardized incidence ratio; SMR: standardized mortality ratio.

I^2 test results indicated heterogeneity was high in all meta-analyses, with the exception of herpes zoster (I^2 test 0.0%, $P = 0.90$), ranged from 89.30 to 98.50% and was statistically significant by the Cochran's Q statistic. Visual examination of funnel plots and Egger's test identified possible publication bias in all main analyses, except for herpes zoster. However, owing to the small number of studies included in each meta-analysis and the low power of the test, this may be due to chance [50].

Qualitative assessment of subgroups

Age

Five studies investigated the association of age with risk of infection in patients with SLE compared with the general population (supplementary Fig. S1, available at *Rheumatology* online) [36, 38, 39, 44, 47]. Infections assessed were hepatitis C [39], herpes zoster [36], 'other' infections (excluding pneumonia) [47], overall severe infection [38], pneumococcal disease [44] and pneumonia [47]. There was large variation in the age categories presented between studies, and no meta-analysis was carried out.

The comparative risk of infection (compared with the general population) was higher for the younger age groups, and risk of infection in older age groups was more comparable to the general population. This is particularly true in the herpes zoster infection study, with patients aged 18–24 years having higher risk than age-matched non-SLE controls [RR 8.78 (95% CI 3.08, 24.97)] and lower risk than older age groups [aged >65 years; RR 2.33 (95% CI 0.79, 6.87)] [36].

This pattern is similar in other studies reporting on pneumococcal disease [44]. There was no association between age and the risk of hepatitis C infection [39] or other infections [47] and overall severe infections [38, 47] in patients with SLE compared with the general population.

Sex

The association between sex and risk of infection in patients with SLE was investigated in three studies [36, 39, 47]. The percentages of female participants were 77% [47], 82% [39] and 90% [36]. When stratified by sex, there was no statistically significant difference in the RR of infection compared with sex-matched controls between female and male participants for herpes zoster [36], hepatitis C [39], overall severe infection, other infections or pneumonia [47].

SLE treatment

One study observed that patients with SLE had a 6- to 7-fold greater risk of serious infection than the general population [37]. Within the group of patients with SLE, this study also assessed effects of starting medications (antimalarials and glucocorticoids) on the risk of developing a serious infection. In comparison with patients with SLE starting antimalarials without glucocorticoids, the hazard ratio for the risk of serious infection was 3.9 (95% CI 1.7–9.2) for those starting glucocorticoids ≤15 mg/day without antimalarials- [37].

Time from SLE diagnosis

One study assessed the effect of time from first hospital admission for an SLE diagnosis on the risk of developing tuberculosis compared with the general population [42]. There was no difference between patients ≥1 year after first SLE admission [RR 9.1 (95% CI 7.0, 11.7)] and ≥5 years after first SLE admission [RR 9.1 (95% CI 6.3, 12.9)] [42].

Temporal trends of infections in SLE

One study evaluated age, sex, causes of death (including pneumonia, septicaemia and tuberculosis) and the observed/expected death ratio of patients with SLE 1985–1989 compared with 2003–2007 [45]. For SLE as an underlying cause, the main non-underlying causes of death were renal failure, circulatory system diseases, pneumonia and septicaemia. Over the period, the proportional mention of infectious causes and circulatory system diseases increased, whereas renal diseases decreased. The overall observed/expected death ratio was >1 for tuberculosis, septicaemia and pneumonia, with no statistically significant difference between both periods [45].

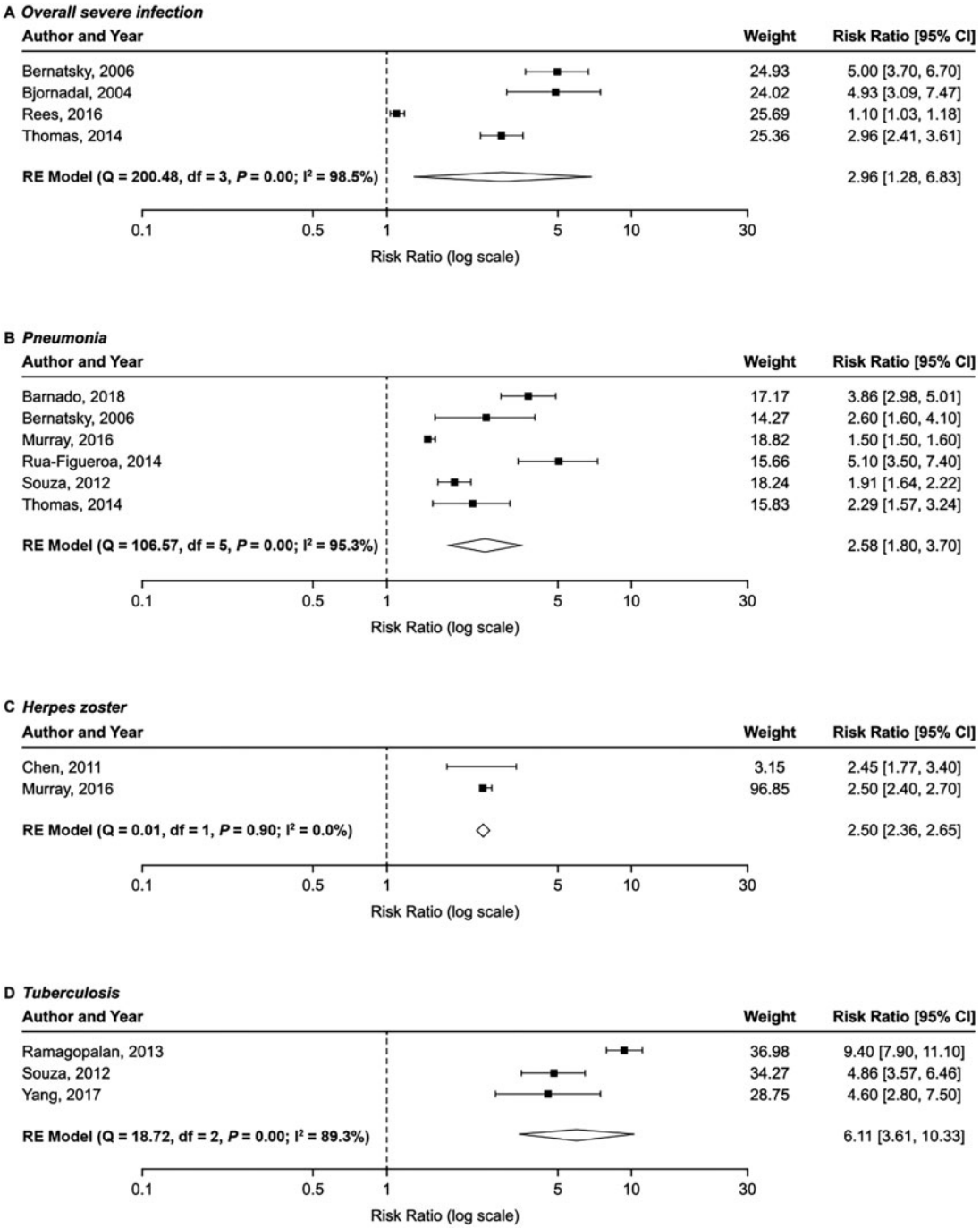
Discussion

Our findings suggest a 2- to 6-fold increase in relative risk of infection events in adult patients with SLE compared with the general population or healthy controls. To our knowledge, this is the first systematic literature review and meta-analysis conducted to assess risk of infection in patients with SLE. Multiple sensitivity analyses confirmed the robustness of the results even in the presence of heterogeneity.

Infections are common in patients with SLE and are associated with high morbidity and mortality [5, 9]. This susceptibility may result partly from immunosuppressive treatment [51] and aberrations in the immune system associated with SLE, predisposing patients to infection [52]. Our results further demonstrate this predisposition.

The effects of glucocorticoids and immunosuppressive treatment on risk of infection in patients with SLE have been extensively described in observational studies [6, 10, 53–56]. Rúa-Figueroa *et al.* [10] report significant association between any use of glucocorticoids ≥10 mg/day or immunosuppressors and a shorter time to severe infection. Increased disease activity has been associated with dysfunction of the immune system in patients with SLE, which increases risk of infection in comparison with patients with inactive SLE [6, 53]. Furthermore, a recent meta-analysis of clinical trial data demonstrated that high-dose glucocorticoid therapy was associated with a high risk of serious infections in patients with LN [57]. In the qualitative part of our study evaluating risk of infection in patients with SLE and the effect of general and SLE-related factors on that risk, we found limited evidence that included disease activity or glucocorticoid use.

FIG. 2 Forrest plots: meta-analyses of risk of overall severe infection, pneumonia, herpes zoster and tuberculosis in SLE



RE: random effects.

Nevertheless, in keeping with what is known about pathophysiology of infection in patients with SLE, the medical management of these patients should aim to achieve disease remission by using glucocorticoids at the lowest effective dosage and for the shortest possible time period. Consideration should also be given to reducing infection risk through different strategies such as general hygienic measures, vaccinations, detection of latent infections and antibiotic prophylaxis. Such approaches may include pneumococcal and influenza vaccinations in patients with stable disease [58, 59], screening for specific chronic viral infections or for tuberculosis before glucocorticoids and immunosuppressive treatment [60], or the use of appropriate

Table 2 Sensitivity analyses: risk of infection in SLE compared with general population or healthy controls

	Overall severe infection	Pneumonia	Tuberculosis	Herpes zoster
Base case	RR (95% CI): 2.96 (1.28, 6.83) $I^2 = 98.5\%$, $P > 0.001$ ($n = 4$)	RR (95% CI): 2.58 (1.80, 3.70) $I^2 = 95.3\%$, $P > 0.001$ ($n = 6$)	RR (95% CI): 6.11 (3.61, 10.33) $I^2 = 89.3\%$, $P > 0.001$ ($n = 3$)	RR (95% CI): 2.50 (2.36, 2.65) $I^2 = 0.0\%$, $P = 0.905$ ($n = 2$)
Leave1out (range)	RR (95% CI): 4.08 (2.75, 6.04) RR (95% CI): 2.48 (1.03, 5.95)	RR (95% CI): 2.93 (1.97, 4.36) RR (95% CI): 2.26 (1.62, 3.16)	RR (95% CI): 6.84 (3.58, 13.05) RR (95% CI): 4.79 (3.72, 6.18)	NA
Least adjusted analysis results	RR (95% CI): 3.17 (1.67, 6.04) $I^2 = 97.5\%$, $P > 0.001$ ($n = 4$)	NA	NA	RR (95% CI): 4.29 (1.49, 12.38) $I^2 = 99.752\%$, $P > 0.001$ ($n = 2$)
Published $\leq$5 years prior to 2018	RR (95% CI): 1.80 (0.68, 4.74) $I^2 = 98.793\%$, $P > 0.001$ ($n = 2$)	RR (95% CI): 2.84 (1.49, 5.41) $I^2 = 96.827\%$, $P > 0.001$ ($n = 4$)	NA	NA
Published >5 years prior to 2018	RR (95% CI): 4.98 (3.89, 6.37) $I^2 = 0\%$, $P = 0.959$ ($n = 2$)	RR (95% CI): 2.05 (1.59, 2.64) $I^2 = 33.145\%$, $P = 0.221$ ($n = 2$)	NA	NA
Only studies with low risk of bias	NA	NA	NA	NA
Only reporting on non-fatal/fatal	NA	RR (95% CI): 3.05 (1.32, 7.05) $I^2 = 97.775\%$, $P > 0.001$ ($n = 3$)	RR (95% CI): 6.84 (3.58, 13.05) RR (95% CI): 4.79 (3.72, 6.18) ($n = 2$)	NA
Only reporting on fatal	RR (95% CI): 4.08 (2.75, 6.04) $I^2 = 80.451\%$, $P = 0.006$ ($n = 3$)	RR (95% CI): 2.02 (1.75, 2.33) $I^2 = 4.013\%$, $P = 0.353$ ($n = 3$)	NA	NA
Excluding cross-sectional studies	NA	NA	NA	NA

NA: not applicable; RR: risk ratio.

prophylaxes (e.g. oral trimethoprim–sulfamethoxazole for prophylaxis of *Pneumocystis jiroveci* pneumonia) or drug modifications when indicated [60]. Additionally, there is increasing evidence on the potential role of antimalarial therapy in the protection against infections in patients with SLE [37, 61]. Smoking, on the other hand, has been associated with reduced effectiveness of antimalarials and shorter time to first severe infection [10, 62].

In our study, we did not find any significant differences between sex and risk of infection. It is noteworthy that there are not many studies addressing this topic. Data in the literature on the association between sex, clinical presentation and SLE outcomes are limited. The LUpus in MInorities, NAture versus nurture (LUMINA) Study Group described poor long-term prognosis among male patients with SLE compared with female patients, driven by their accelerated development of organ damage, particularly in early stages of the disease [63]. However, in the LUMINA study, there were no reports of an association between infection and organ damage or worse clinical outcomes. Although not specifically focused on infection, a review by Murphy and Isenberg [64] reported some clinical differences between male and female patients with SLE, but limited evidence to support a negative prognostic association between male gender and disease activity or mortality. Overall, the results of our research about infections in SLE are in line with the absence of significant differences in other clinical features of the disease.

The sensitivity analysis demonstrated a higher risk of overall severe infection in earlier studies compared with later studies (studies published >5 years prior to 2018 [33, 34] compared with studies published ≤ 5 years prior to 2018 [3, 47]). This difference may be attributable to changes in clinical practice during the time periods assessed, with the earlier studies including patient cohorts between 1958 and 2001 [33] and 1964 and 1994 [34], and the later studies between 1999 and 2012 [3] and 2000 and 2009 [47]. For pneumonia, studies published ≤ 5 years prior to 2018 show an increased risk compared with studies published >5 years prior. In the recent era, there have been more effective recognition and strategies to treat and limit infectious complications. An evaluation of SLE hospitalizations within the US National Inpatient Sample from 2000 to 2011 demonstrated increasing trends in the annual adjusted infections per hospitalization for pneumonia, bacteraemia, opportunistic fungal, varicella zoster and cytomegalovirus infections; however, infection rates for pneumocystis pneumonia (PCP) declined during this period [41]. The increasing trend of infections may be due to increasing use of immunosuppressive treatment and immune dysregulation from SLE [51, 52].

The observed decline in PCP may also reflect trends in clinical practice, such as use of prophylaxis or increasing use of MMF in preference to CYC [41, 65]. Although MMF has shown antimicrobial properties against PCP in renal transplantation trials and animal studies [66–68], such data in patients with SLE are limited. Findings from the Taiwan single-payer National Health Insurance Research Database from 1997 to 2013 showed increased odds of PCP infections with MMF, CYC and glucocorticoid use [69]. This study also identified that use of HCQ reduced the odds of PCP infections in patients with SLE.

Taken together, the evidence suggests modifiable infection risk factors and warrants increased research, including seeking to understand the role of disease activity, treatment and comorbidities. Well-designed trials and observational studies are needed to support the management and prevention of infection in patients with SLE, including identification of patients at high risk of infection and those who would benefit from vaccination, or patient monitoring to mitigate risk. Segura *et al.* [70] developed the SLE Severe Infection Score, an algorithm for predicting the risk of severe infection in patients with SLE. This tool is useful to monitor infection risk factors more closely in a weighted way and could contribute to the establishment of better strategies for the prevention, early diagnosis and treatment of severe infections in patients with SLE, with the goal of reducing morbidity and improving survival [70]. The findings from this current work fill an important evidence gap in understanding the risk posed to patients with SLE and have important strengths. They are generalizable to different SLE populations because we included populations from different age and sex groups, and geographic locations. This review was conducted to the highest standards, according to international guidelines on the conduct and reporting of systematic reviews and meta-analyses, including the Cochrane Handbook and Preferred Reporting Items for Systematic Reviews and Meta-Analyses statements [15, 71, 72].

Some limitations should be considered in interpreting our findings, primarily the limited number of studies that met the criteria to be included in both the meta-analysis and descriptive subgroup analyses. Few studies, in some instances no studies, were available to enable evaluation of age, sex, treatment regimen, disease severity and temporal trends of infections in patients with SLE. These limitations emphasize the need for more research.

Conclusion

Infection risk among patients with SLE increases 2- to 6-fold for overall severe infection, tuberculosis, pneumonia and herpes zoster compared with the general population or healthy controls. Demographics and SLE-related factors, including age, sex, the disease itself and treatment, are likely to be important in explaining this elevated risk. This should lead to strengthening the strategies aimed at prevention of infections in these patients, such as counselling on preventative measures, vaccinations, use of HCQ, or reduction of the dosage and duration of glucocorticoids and immunosuppressants.

Acknowledgements

Writing and editing assistance was provided by JK Associates Inc., a member of the Fishawack Group of Companies. This support was funded by AstraZeneca.

Funding: The current analysis was supported by funding from AstraZeneca. The funder of the study had a role in its design, interpretation of the data and in the writing of the manuscript. The funder had no role in the conduct, collection or analysis of the data. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosure statement: L.N., N.P., S.L., N.E., Z.M. and J.L. have received personal fees from AstraZeneca during the conduct of the study and outside the submitted work. V.B. and E.R.H. are employees of AstraZeneca. The other authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Manson JJ, Rahman A. Systemic lupus erythematosus. Orphanet J Rare Dis 2006;1:1–6.

2 Lopez R, Davidson JE, Beeby MD, Egger PJ, Isenberg DA. Lupus disease activity and the risk of subsequent organ damage and mortality in a large lupus cohort. Rheumatology (Oxford) 2012;51:491–8.

3 Rees F, Doherty M, Grainge M *et al.* Burden of comorbidity in systemic lupus erythematosus in the UK, 1999-2012. Arthritis Care Res (Hoboken) 2016;68:819–27.

4 Kaul A, Gordon C, Crow MK *et al.* Systemic lupus erythematosus. Nat Rev Dis Primers 2016;2:16039.

5 Wang Z, Wang Y, Zhu R *et al.* Long-term survival and death causes of systemic lupus erythematosus in China: a systemic review of observational studies. Medicine 2015;94:e794.

6 Goldblatt F, Chambers S, Rahman A, Isenberg DA. Serious infections in British patients with systemic lupus erythematosus: hospitalisations and mortality. Lupus 2009;18:682–9.

7 Petri M, Genovese M. Incidence of and risk factors for hospitalizations in systemic lupus erythematosus: a prospective study of the Hopkins Lupus Cohort. J Rheumatol 1992;19:1559–65.

8 Edwards CJ, Lian TY, Badsha H *et al.* Hospitalization of individuals with systemic lupus erythematosus: characteristics and predictors of outcome. Lupus 2003;12:672–6.

9 Hellmann DB, Petri M, Whiting-O'Keefe Q. Fatal infections in systemic lupus erythematosus: the role of opportunistic organisms. Medicine (Baltimore) 1987;66:341–8.

10 Rúa-Figueroa Í, López-Longo J, Galindo-Izquierdo M *et al.* Incidence, associated factors and clinical impact of severe infections in a large, multicentric cohort of patients with systemic lupus erythematosus. Semin Arthritis Rheum 2017;47:38–45.

11 Rúa-Figueroa I, López-Longo FJ, Del Campo V *et al.* Bacteremia in systemic lupus erythematosus in patients from a Spanish registry: risk factors, clinical and microbiological characteristics, and outcomes. J Rheumatol 2020;47:232–40.

12 Danza A, Ruiz-Irastorza G. Infection risk in systemic lupus erythematosus patients: susceptibility factors and preventive strategies. Lupus 2013;22:1286–94.

13 Gladman DD, Hussain F, Iban D, Urowitz MB. The nature and outcome of infection in systemic lupus erythematosus. Lupus 2002;11:234–9.

14 Zandman-Goddard G, Shoenfeld Y, Zandman-Goddard G, Shoenfeld Y. Infections and SLE. Autoimmunity 2005;38:473–85.

15 Higgins J, Green S. Cochrane handbook for systematic reviews of interventions. Version 5.1.0. London: The Cochrane Collaboration, 2011.

16 Stroup DF. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–12.

17 Nicholson L, Pooley N, Langham J. The risk of medically significant infections in adult patients with systemic lupus erythematosus: systematic review and meta-analysis. PROSPERO CRD42018109425. 2018. [updated 10 July 2018; cited 2020 March 2]. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018109425.

18 Tan EM, Cohen AS, Fries JF *et al.* The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–7.

19 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.

20 Wells GA, Shea B, O'Connell D, Peterson J. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2014. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

21 Avina-Zubieta JA, Thomas J, Sadatsafavi M, Lehman AJ, Lacaille D. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis 2012;71:1524–9.

22 Aviña-Zubieta JA, Choi HK, Sadatsafavi M *et al.* Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum 2008;59:1690–7.

23 Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand K. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. JAMA 2002;288:728–37.

24 Takkouche B, Etminan M, Montes-Martínez A. Personal use of hair dyes and risk of cancer. JAMA 2005;293:2516.

25 Holmqvist M, Simard JF, Asplund K, Arkema EV. Stroke in systemic lupus erythematosus: a meta-analysis of population-based cohort studies. RMD Open 2015;1:e000168.

26 Urowitz MB, Gladman DD, Tom BDM, Ibañez D, Farewell VT. Changing patterns in mortality and disease

outcomes for patients with systemic lupus erythematosus. J Rheumatol 2008;35:2152–8.

27 Yurkovich M, Vostretsova K, Chen W, Aviña-Zubieta JA. Overall and cause-specific mortality in patients with systemic lupus erythematosus: a meta-analysis of observational studies. Arthritis Care Res (Hoboken) 2014;66:608–16.

28 Greenland S. Quantitative methods in the review of epidemiologic literature. Epidemiol Rev 1987;9:1–30.

29 DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.

30 Stuck AE, Rubenstein LZ, Wieland D *et al.* Bias in meta-analysis detected by a simple, graphical test. Asymmetry detected in funnel plot was probably due to true heterogeneity. BMJ 1998;316:469; author reply 70–1.

31 Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw 2010;36:1–48.

32 Barnado A, Carroll RJ, Casey C, Wheless L *et al.* Phenome-wide association study identifies marked increased in burden of comorbidities in African Americans with systemic lupus erythematosus. Arthritis Res Ther 2018;20:1–11.

33 Bernatsky S, Boivin JF, Joseph L *et al.* Mortality in systemic lupus erythematosus. Arthritis Rheum 2006;54:2550–7.

34 Bjornadal L, Yin L, Granath F, Klareskog L, Ekbom A. Cardiovascular disease a hazard despite improved prognosis in patients with systemic lupus erythematosus: results from a Swedish population based study 1964-95. J Rheumatol 2004;31:713–9.

35 Chang YS, Chang CC, Chen YH, Chen WS, Chen JH. Risk of infective endocarditis in patients with systemic lupus erythematosus in Taiwan: a nationwide population-based study. Lupus 2017;26:1149–56.

36 Chen H-H, Chen Y-M, Chen T-J *et al.* Risk of herpes zoster in patients with systemic lupus erythematosus: a three-year follow-up study using a nationwide population-based cohort. Clinics 2011;66:1177–82.

37 Herrinton LJ, Liu L, Goldfien R, Michaels MA, Tran TN. Risk of serious infection for patients with systemic lupus erythematosus starting glucocorticoids with or without antimalarials. J Rheumatol 2016;43:1503–9.

38 Lerang K, Gilboe IM, Steinar Thelle D, Gran JT. Mortality and years of potential life loss in systemic lupus erythematosus: a population-based cohort study. Lupus 2014;23:1546–52.

39 Mahroum N, Hejly A, Tiosano S *et al.* Chronic hepatitis C viral infection among SLE patients: the significance of coexistence. Immunol Res 2017;65:477–81.

40 Méndez-Martínez S, García-Carrasco M, Cedillo-Ramírez ML *et al.* Genital Mycoplasma infection among Mexican women with systemic lupus erythematosus. Int J Gynaecol Obstet 2017;138:17–22.

41 Murray SG, Schmajuk G, Trupin L *et al.* National lupus hospitalization trends reveal rising rates of herpes zoster and declines in pneumocystis pneumonia. PLoS One 2016;11:e0144918.

42 Ramagopalan SV, Goldacre R, Skingsley A, Conlon C, Goldacre MJ. Associations between selected immune-mediated diseases and tuberculosis: record-linkage studies. BMC Med 2013;11:1.

43 Rúa-Figueroa I, Nóvoa J, García-laorden MI *et al.* Clinical and immunogenetic factors associated with pneumonia in patients with systemic lupus erythematosus: a case-control study. J Rheumatol 2014;41:1801–7.

44 Shea KM, Edelsberg J, Weycker D *et al.* Rates of pneumococcal disease in adults with chronic medical conditions. Open Forum Infect Dis 2014;1:ofu024.

45 Souza DCC, Santo AH, Sato EI. Mortality profile related to systemic lupus erythematosus: a multiple cause-of-death analysis. J Rheumatol 2012;39:496–503.

46 Tektonidou MG, Wang Z, Dasgupta A, Ward MM. Burden of serious infections in adults with systemic lupus erythematosus: a national population-based study, 1996–2011. Arthritis Care Res (Hoboken) 2015;67:1078–85.

47 Thomas G, Mancini J, Jourde-Chiche N *et al.* Mortality associated with systemic lupus erythematosus in France assessed by multiple-cause-of-death analysis. Arthritis Rheumatol 2014;66:2503–11.

48 Wotton CJ, Goldacre MJ. Risk of invasive pneumococcal disease in people admitted to hospital with selected immune-mediated diseases: record linkage cohort analyses. J Epidemiol Commun Health 2012;66:1177–81.

49 Yang Y, Thumboo J, Tan BH *et al.* The risk of tuberculosis in SLE patients from an Asian tertiary hospital. Rheumatol Int 2017;37:1027–33.

50 Higgins JP, Thompson SG. Controlling the risk of spurious findings from meta-regression. Stat Med 2004;23:1663–82.

51 Feldman CH, Hiraki LT, Winkelmayer WC *et al.* Serious infections among adult Medicaid beneficiaries with systemic lupus erythematosus and lupus nephritis. Arthritis Rheumatol 2015;67:1577–85.

52 Choi J, Kim ST, Craft J. The pathogenesis of systemic lupus erythematosus-an update. Curr Opin Immunol 2012;24:651–7.

53 Iliopoulos AG, Tsokos GC. Immunopathogenesis and spectrum of infections in systemic lupus erythematosus. Semin Arthritis Rheum 1996;25:318–36.

54 Jacobsen S, Petersen J, Ullman S *et al.* A multicentre study of 513 Danish patients with systemic lupus erythematosus. II. Disease mortality and clinical factors of prognostic value. Clin Rheum 1998;17:478–84.

55 Noël V, Lortholary O, Casassus P *et al.* Risk factors and prognostic influence of infection in a single cohort of 87 adults with systemic lupus erythematosus. Ann Rheum Dis 2001;60:1141–4.

56 Fessler BJ. Infectious diseases in systemic lupus erythematosus: risk factors, management and prophylaxis. Best Pract Res Clin Rheumatol 2002;16:281–91.

57 Singh JA, Hossain A, Kotb A, Wells G. Risk of serious infections with immunosuppressive drugs and glucocorticoids for lupus nephritis: a systematic review and network meta-analysis. BMC Med 2016;14:137.

58 Furer V, Rondaan C, Heijstek MW *et al.* 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis 2020;79:39–52.

59 Fanouriakis A, Kostopoulou M, Alunno A *et al.* 2019 Update of the EULAR recommendations for the management of systemic lupus erythematosus. Ann Rheum Dis 2019;78:736–45.

60 Gatto M, Zen M, Iaccarino L, Doria A. New therapeutic strategies in systemic lupus erythematosus management. Nat Rev Rheumatol 2019;15:30–48.

61 Sisó A, Ramos-Casals M, Bové A *et al.* Previous antimalarial therapy in patients diagnosed with lupus nephritis: influence on outcomes and survival. Lupus 2008;17:281–8.

62 Chasset F, Francès C, Barete S, Amoura Z, Arnaud L. Influence of smoking on the efficacy of antimalarials in cutaneous lupus: a meta-analysis of the literature. J Am Acad Dermatol 2015;72:634–9.

63 Andrade RM, Alarcón GS, Fernández M *et al.* Accelerated damage accrual among men with systemic lupus erythematosus: XLIV. Results from a multiethnic US cohort. Arthritis Rheum 2007;56:622–30.

64 Murphy G, Isenberg D. Effect of gender on clinical presentation in systemic lupus erythematosus. Rheumatology (Oxford) 2013;52:2108–15.

65 Gupta D, Zachariah A, Roppelt H, Patel AM, Gruber BL. Prophylactic antibiotic usage for Pneumocystis jirovecii pneumonia in patients with systemic lupus erythematosus on cyclophosphamide: a survey of US rheumatologists and the review of literature. J Clin Rheumatol 2008;14:267–72.

66 Ritter ML, Pirofski L. Mycophenolate mofetil: effects on cellular immune subsets, infectious complications, and antimicrobial activity. Transpl Infect Dis 2009;11: 290–7.

67 Husain S, Singh N. The impact of novel immunosuppressive agents on infections in organ transplant recipients and the interactions of these agents with antimicrobials. Clin Infect Dis 2002;35:53–61.

68 Oz HS, Hughes WT. Novel anti-Pneumocystis carinii effects of the immunosuppressant mycophenolate mofetil in contrast to provocative effects of tacrolimus, sirolimus, and dexamethasone. J Infect Dis 1997;175:901–4.

69 Yeo KJ, Chen HH, Chen YM *et al.* Hydroxychloroquine may reduce risk of Pneumocystis pneumonia in lupus patients: a nationwide, population-based case-control study. BMC Infect Dis 2020;20:112.

70 Segura BT, Rua-Figueroa I, Pego-Reigosa JM *et al.* Can we validate a clinical score to predict the risk of severe infection in patients with systemic lupus erythematosus? A longitudinal retrospective study in a British Cohort. BMJ Open 2019;9:e028697.

71 Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6:e1000097.

72 Moher D, Shamseer L, Clarke M *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.