

## ORIGINAL ARTICLE

## Incidence and prevalence of vaccine preventable infections in adult patients with autoimmune inflammatory rheumatic diseases (AIIRD): a systemic literature review informing the 2019 update of the EULAR recommendations for vaccination in adult patients with AIIRD

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**ABSTRACT**

**Objectives** The aims of this study were to update the evidence on the incidence and prevalence rates of vaccine preventable infections (VPI) in patients with autoimmune inflammatory rheumatic diseases (AIIRD) and compare the data to the general population when available.

**Methods** A literature search was performed using Medline, Embase and Cochrane library (October 2009 to August 2018). The primary outcome was the incidence or prevalence of VPI in the adult AIIRD population. Meta-analysis was performed when appropriate.

**Results** Sixty-three publications out of 3876 identified records met the inclusion criteria: influenza (n=4), pneumococcal disease (n=7), hepatitis B (n=10), herpes zoster (HZ) (n=29), human papillomavirus (HPV) infection (n=13). An increased incidence of influenza and pneumococcal disease was reported in patients with AIIRD. HZ infection-pooled incidence rate ratio (IRR) was 2.9 (95% CI 2.4 to 3.3) in patients with AIIRD versus general population. Among AIIRD, inflammatory myositis conferred the highest incidence rate (IR) of HZ (pooled IRR 5.1, 95% CI 4.3 to 5.9), followed by systemic lupus erythematosus (SLE) (pooled IRR 4.0, 95% CI 2.3 to 5.7) and rheumatoid arthritis (pooled IRR 2.3, 95% CI 2.1 to 2.6). HPV infection-pooled prevalence ratio was 1.6, 95% CI 0.7 to 3.4 versus general population, based on studies mainly conducted in the SLE population in Latin America and Asia. Pooled prevalence of hepatitis B surface antigen and hepatitis B core antibody in patients with AIIRD was similar to the general population, 3%, 95% CI 1% to 5% and 15%, 95% CI 7% to 26%, respectively.

**Key messages****What is already known about this subject?**

- The first EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases (AIIRD) were published in 2011, based on available literature through September 2009 and expert opinion.

**What does this study add?**

- Since 2009, a significant body of data has been published in the field of epidemiology of vaccine preventable infections (VPI) within AIIRD population, including influenza, pneumococcal disease, herpes zoster, hepatitis B and human papillomavirus infection.
- This systematic literature review provides an updated overview on the incidence and prevalence rates of VPI in patients with AIIRD.
- Patients with AIIRD are at increased risk of influenza, pneumococcal, herpes zoster and human papillomavirus infections, indicating the importance of their monitoring and use of vaccination to decrease the risk of these infections.

**How might this impact on clinical practice?**

- This systematic literature review informed the task force for the 2019 update of the EULAR recommendations for vaccination in adult patients with AIIRD.

**Conclusion** Current evidence shows an increased risk of VPI in patients with AIIRD, emphasising that prevention of infections is essential in these patients.

## INTRODUCTION

In 2011, the first EULAR evidence-based recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases (AIIRDs) were published,<sup>1</sup> with the main goal to reduce infection-related morbidity and mortality in the AIIRD population. Despite the well-established fact of a high burden of infections among patients with AIIRD,<sup>2</sup> limited evidence was available concerning the real incidence and prevalence of vaccine preventable infections (VPIs) in this population.<sup>3</sup> In light of the newly accrued data over the last decade, this paper presents the results of the systematic literature review (SLR) on the incidence and prevalence of VPI in adult patients with AIIRD. Together with the SLR on efficacy, immunogenicity and safety of vaccinations in patients with AIIRD,<sup>4</sup> it provided the EULAR task force an evidence-based rationale for the 2019 update on the recommendations for vaccination in this population of patients.

## METHODS

### Literature search

A systematic literature search was conducted via Medline (Ovid), Embase (Embase.com) and Cochrane (Wiley) databases, from 1 October 2009 up to 15 August 2018. Additionally, reference lists of included studies and additional papers considered relevant in the opinion of experts were screened. For all databases, we used free text terms describing our lists of AIIRD and VPI. Additionally, we searched with the corresponding Medical Subject Headings for Medline and Embase subject heading Emtree for Embase. We used a broad filter for locating incidence and prevalence studies, adapted from a previously published systematic review.<sup>5</sup> The full search strategy of all databases is documented in online supplementary file 1. We manually searched the references cited by the retrieved articles and reviewed articles for additional references.

### Search strategy

Our research question was formulated according to the PICO format (**P**opulation, **I**nterventions, **C**omparators, **O**utcomes) (box 1). The population was defined as patients with AIIRD, treated or untreated with immunosuppressive drugs (table 1, supplementary file). Interventions were not applicable to our research question. The comparators were healthy individuals or the general population when the data were available. Outcomes were defined as the incidence or prevalence rates for the following vaccine preventable infectious diseases: influenza, tetanus, diphtheria, pertussis, measles, mumps, rubella, varicella, herpes zoster (HZ), human

## Box 1 PICO-formulated research question.

### What is the incidence or prevalence of vaccine preventable infections (VPI) in adult patients with AIIRD?

- Population: Patients with AIIRD treated or untreated with immunosuppressive drugs
- Intervention: None
- Comparison: Healthy controls or general population
- Outcome: Incidence or prevalence of vaccine-preventable infections: influenza, tetanus, diphtheria, pertussis, measles, mumps, rubella, varicella, herpes zoster, human papillomavirus infection, *Streptococcus pneumoniae* infection, hepatitis A, hepatitis B, *Neisseria meningitidis* infection, *Haemophilus influenzae* infection, tick-borne encephalitis, typhoid fever, yellow fever.

AIIRD, autoimmune inflammatory rheumatic disease(s).

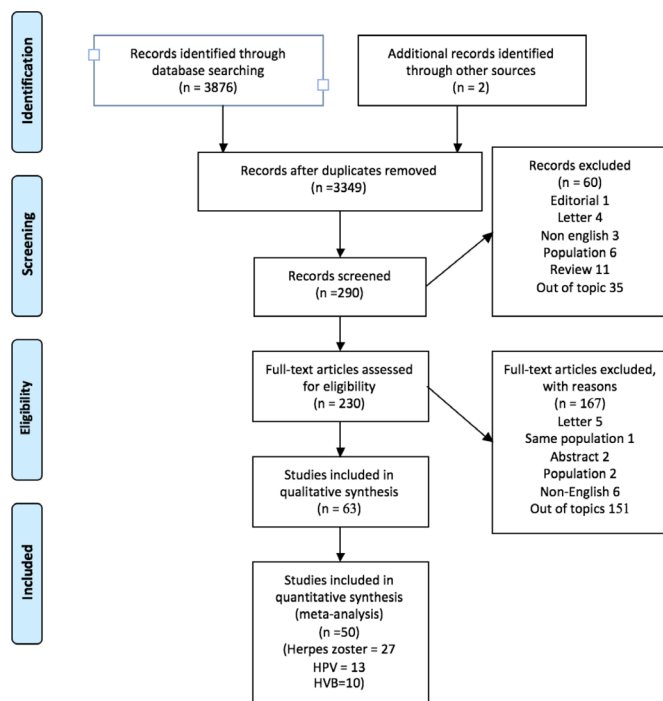
papillomavirus (HPV) infection, *Streptococcus pneumoniae* infection, hepatitis A, hepatitis B, *Neisseria meningitidis* infection, *Haemophilus influenzae* infection, tick-borne encephalitis, typhoid fever, yellow fever.

### Inclusion and exclusion criteria

Eligible studies were observational longitudinal studies/cohort studies, including registries and claims database studies, for the IRs and cross-sectional studies for the prevalence rates only, when the data on the disease incidence were unavailable. SLRs of cohort studies and meta-analyses were also included. For hepatitis B, only studies reporting the seroprevalence of hepatitis B surface antigen (HBsAg) and/or hepatitis B core antibody (anti-HBc) were included. Only articles in English on adult patients (≥18 years old) were included. Case-control studies, case reports, intervention studies, vaccination studies, abstracts presented in scientific meetings, in vitro and animal studies were excluded. Papers included in the previous recommendations were also excluded. Studies on patients with non-rheumatic autoimmune diseases, immunodeficiency, transplantation, atopic diseases and malignancies were excluded.

### Data extraction and quality assessment

Two reviewers (OE and VF) independently screened titles and abstracts to determine eligibility for inclusion, according to the predefined inclusion criteria, followed by full-text review when necessary. Data were extracted using a standardised form and included *study characteristics*: title, authors, journal, publication year, country, study design, study period; *population characteristics*: study population (AIIRD), controls (when available), number of patients, number of controls, age, gender, ethnicity, immunosuppressive medications; *outcome definitions*: number of VPI cases, diagnostic criteria used for the diagnosis/definition of infection, IRs and IRRs with 95% CI (when available) or HRs and prevalence rates and prevalence rate ratios (for infections for which IRs were not applicable) or ORs, and the risk of complications (when reported). For studies on incidence that did not report 95% CI, we computed exact 95% CI.



**Figure 1** Flow chart of the literature search. HPV, human papillomavirus; HVB, hepatitis B virus.

Quality assessment was performed for each study based on the study design: cohort studies were assessed by a critical appraisal adjusted for the specific infection, and cross-sectional studies were assessed by the New Castle Ottawa scale,<sup>6</sup> as specified in the online supplementary file 2. Based on the quality assessment, all studies were rated with a level of evidence according to the Oxford Level of Evidence.<sup>7</sup> The quality assessment was used to upgrade or downgrade the level of evidence. For example, low-grade quality cohort studies were downgraded from 2b to 4. The present SLR follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.<sup>8</sup>

### Data analysis

Statistical analysis including meta-analysis was performed for the studies reporting on the following diseases: herpes zoster (HZ), human papillomavirus (HPV) infection and hepatitis B (HBV). For HZ, meta-analysis included the original studies that reported the incidence of HZ by disease, whereas studies that reported the incidence of HZ by treatments only were excluded. A very small number of studies in case of influenza and the use of different outcomes in studies on influenza and pneumococcal diseases precluded the performance of meta-analysis. The statistical analysis and graphical presentation were performed using Stata V.12.1 (Stata Corp, College Station, Texas, USA).

For incidence studies (HZ), the incidence rate (IR) was calculated by dividing the number of new cases by the total person time (multiplied by 1000 to present the results per 1000 person-years). The pooled IR was estimated for each type of AIIRD and overall. In addition, the incident rate ratio (IRR) was calculated for HZ

studies that compared patients with AIIRD patients with the control group. The pooled IRR was estimated for each type of AIIRD and overall.

For prevalence studies (HBV and HPV), we used the metaprop command to pool the prevalence rate for each type of AIIRD and overall. For studies that compared the prevalence with the control group, the prevalence ratio (PR) was calculated and pooled for each type of AIIRD and overall.

Heterogeneity of the studies was explored using Cochrane's Q test of heterogeneity ( $p < 0.1$  considered statistically significant). Inconsistency in the studies' results was assessed by  $I^2$ , which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. When  $I^2 \geq 50\%$ , we assumed that there was more than moderate inconsistency. Random effects model (DerSimonian and Laird) was chosen if Cochrane's Q test  $p < 0.1$  or  $I^2 \geq 50\%$ . Otherwise, the fixed effects model (inverse variance methods) was chosen. For quality analysis, we explored the association between the effect size (prevalence, IR, IRR and so on) and the studies quality assessment via metaregression. Sensitivity analysis for HPV included subgroup analysis with and without outlier studies. Publication bias was explored via funnel plots and the Egger test for asymmetry.

## RESULTS

The literature search identified 3876 articles and two additional articles identified by experts (figure 1). After removal of duplicates, 3349 studies were screened by abstracts. A total of 230 articles underwent a full-text review. Sixty-three of these met the full inclusion criteria. Data on the incidence/prevalence rates were available for five VPI: influenza, pneumococcal disease, hepatitis B, HZ and HPV.

### Influenza

Annual incidence of influenza in the general population is estimated as 5%–10% of adults, according to the WHO. One in 10 unvaccinated adults are estimated to be infected by seasonal influenza annually, with rates of symptomatic influenza roughly half of these estimates.<sup>9</sup>

In the 2011 review, two large cohort studies from the USA confirmed a high risk for influenza and influenza-related complications in elderly patients ( $\geq 65$  years) with rheumatic diseases.<sup>3</sup> In the present review, four additional studies reported on the incidence of influenza in the AIIRD population (table 1). The diagnosis of influenza was based either on the patients' reports of influenza-like illness (ILI) or International Classification of Diseases (ICD) codes.

Two studies addressed the frequency of influenza among patients with rheumatoid arthritis (RA). A large administrative study from the USA provided the most detailed data on the rates of influenza in the RA population compared with controls: influenza IRR 1.2, 95% CI 1.1 to 1.4.<sup>9</sup> Influenza-related complications, including



**Table 1** Influenza studies characteristics, influenza incidence rates and incidence rate ratios

Author, Year	Country	Study design	AIIRD, Controls, Sample size	Influenza definition/ascertainment	IR AIIRD	IR Controls	IRR, 95% CI	Level of evidence
Dirven 2012 <sup>11</sup>	The Netherlands	Cross-sectional	879 RA	Influenza symptoms (patient-report)	5.9% of the cohort	NA	NA	4
Blumentals 2012 <sup>10</sup>	USA	Cohort (Marketscan)	46 030 RA; 46 030 controls	ICD-9	409.3/100 000 PY	306.1/100 000 PY	1.2 (1.1 to 1.4)	2b
Mohammad 2017 <sup>13</sup>	Sweden	Cohort	186 AAV; 744 age and gender-matched controls	ICD-10	*5010/100 000 PY	*1530/100 000 PY	*3.3 (2.2 to 4.8)	2b
Bello 2012 <sup>12</sup>	Italy	Cross-sectional	159 RA, PsA, AS, SpA on bDMARD	Influenza-like illness (patient-report)	17% of the cohort	NA	NA	4

\*Combined incidence of influenza and pneumonia.

AAV, ANCA-associated vasculitis; AIIRD, autoimmune inflammatory rheumatic disease(s); AS, ankylosing spondylitis; bDMARD, biologic disease-modifying antirheumatic drug(s); IR, incidence ratio; IRR, incidence rate ratio; NA, non-available/non-applicable; PsA, psoriatic arthritis; PY, patient years; RA, rheumatoid arthritis; SpA, spondyloarthropathy.

pneumonia, stroke and myocardial infarction, within 30 days of influenza diagnosis, were also more common in RA versus controls: IRR 1.8, 95% CI 1.2 to 2.8, translating into a 2.75-fold increase in incidence of influenza-related complications in RA.<sup>10</sup> Complications occurred most frequently in patients aged  $\geq 70$  years old. Notably, concomitant disease modifying anti-rheumatic drug (DMARD) or biological use did *not* significantly affect the rate of influenza or its complications.<sup>10</sup> A questionnaire-based study from the Netherlands reported a 5.9% incidence of ILI among patients with RA, a twofold higher rate compared with the general Dutch population.<sup>11</sup> The use anti-tumour necrosis factor (anti-TNF) therapy was associated with a higher risk of contracting influenza in this study. A questionnaire-based study from Italy reported a 17% incidence of ILI among patients with RA, psoriatic arthritis (PsA), ankylosing spondylitis (AS) and spondyloarthropathy (SpA) treated with biological treatments,<sup>12</sup> compared with a lower incidence of influenza in the general Italian population (9.7%). Notably, no significant influenza-related morbidity or hospitalisations were reported in this study. In a Swedish cohort of ANCA-associated vasculitis (AAV), the combined incidence of influenza and pneumonia was significantly higher in patients with vasculitis compared with the general population (IRR 3.3, 95% CI 2.2 to 4.8).<sup>13</sup> In summary, the present data suggest a higher risk for contracting influenza in patients with AIIRD compared with the general population.

### *Streptococcus pneumoniae*

Pneumococcal pneumonia is the most common clinical presentation of pneumococcal disease and the most common cause of hospitalisation for community-acquired pneumonia in the adult population.<sup>14 15</sup> Since 1998, the incidence of invasive pneumococcal disease (IPD) in the USA has significantly decreased from 100 to 9/100 000 persons in 2015, following the implementation of the vaccination policy for pneumococcal disease.<sup>16</sup>

In the 2011 review, four studies reported on the incidence of pneumococcal infection in patients with systemic lupus erythematosus (SLE), without comparison to the general population.<sup>3</sup> The present literature search yielded seven retrospective cohort studies conducted in the AIIRD population in Europe and USA<sup>17–23</sup> (table 2). A large study using the data from USA healthcare claims repositories (2006–2010) identified RA and SLE as risk conditions for both pneumonia and IPD in all age groups.<sup>17</sup> Compared with healthy controls, IRR for pneumococcal pneumonia was 4.4, 95% CI 3.8 to 5.2 in patients with RA and 4.3, 95% CI 3.8 to 4.7 in patients with SLE. The highest risk for IPD was reported in young patients of age 18–49 years old, IRR 7.1, 95% CI 4.9 to 10.1.<sup>17</sup> Another large study from the UK demonstrated that patients with AIIRD admitted to the hospital or receiving hospital-based care had an increased risk for IPD compared with controls.<sup>18</sup> IRR for IPD was highest in SLE 5.0, 95% CI 4.6 to 5.4 and polyarteritis nodosa 5.0, 95% CI 4.0 to

**Table 2** Pneumococcal disease studies characteristics, pneumococcal disease incidence rates and incidence rate ratios

Author, Year	Country	Study design	AIIRD, Controls, Sample size	Pneumococcal disease definition/ascertainment	IR AIIRD (100,000 PY)	IR Controls (100,000 PY)	IRR, 95% CI	LoE
Shea 2014 <sup>17</sup>	USA	Retrospective cohort (three integrated healthcare claims repositories)	RA, SLE, Crohn's disease, healthy controls (sample size NA)	Pneumonia and IPD/ICD-9	18–49 y – 13.0 50–64 y – 21.1 ≥65 y – 33.3	18–49 y – 1.8 50–64 y – 4.5 ≥65 y – 8.3	Pneumonia: 18 to 49 y – 4.4 (3.8 to 5.2) 50 to 64 y – 4.3 (3.8 to 4.7) ≥65 y – 4.0 (3.6 to 4.4) IPD: 18 to 49 y – 7.1 (4.9 to 10.1) 50 to 64 y – 4.7 (3.7 to 6) ≥65 y – 4 (3.0 to 5.3)	2b
Wotton 2012 <sup>18</sup>	UK	Retrospective cohort (English national linked Hospital Episode Statistics (1999–2008))	RA 247 414 AS 20 569 SLE 20 005 Sjögren 12 002 SSc 9308 DM/PM 5223 PAN 1839 Immunocompetent controls (sample size of controls NA)	Pneumonia, IPD, pneumococcal meningitis/ICD-10	NA	NA	RA 2.5 (2.4 to 2.5) AS 2.5 (2.3 to 2.8) SLE 5.0 (4.6 to 5.4) Sjögren 3.2 (2.9 to 3.5) SSc 4.2 (3.8 to 4.7) DM/PM 3.9 (3.4 to 4.5) PAN 5.0 (4.0 to 6.0)	4
Luijten 2014 <sup>20</sup>	Nether-lands	Retrospective cohort	260 SLE	Pneumonia leading to hospitalisation/ medical records+positive cx for S. pneumoniae	201	NA	NA	2b
Schurder 2018 <sup>21</sup>	France	Retrospective cohort	190 SLE	Pneumonia leading to hospitalisation: positive cx for S. pneumoniae or pneumococcal Ag in urine	236	NA	NA	2b
Shigayeva 2016 <sup>19</sup>	Canada	Population-based surveillance for IPD	20 427 AIIRD (SLE, SSc, Sjögren, PM/DM); 3 973 048 controls	IPD/Clinical diagnosis and positive cx for S. pneumoniae	20	4.8	NA	2b
Bachkhaus 2016 <sup>23</sup>	Sweden	Retrospective cohort	8500 RA, 830 SLE; controls (sample size NA)	IPD/Clinical diagnosis and positive cx for S. pneumoniae	RA – 72 SLE – 213	NA	RA 4.9 (3.9 to 6.1) SLE 14.2 (9.6 to 21.3)	2b
Weycker 2016 <sup>22</sup>	USA	Retrospective cohort (healthcare database claims repositories)	RA, SLE (sample size NA)	IPD/inpatients – ICD-9; outpatients – ICD-9 + HCPCS/NDC codes for antibiotic therapy	18–64 y – 17.8 ≥65 y – 33.3	18–64 y – 2.7 ≥65 y – 8.3	18 to 64 y – 6.6 (5.4 to 8.0) ≥65 y – 4 (4.0 to 5.3)	2b

Ag, antigen; AIIRD, autoimmune inflammatory rheumatic disease(s); AS, ankylosing spondylitis; cx, culture; DM, dermatomyositis; GCA, giant cell arteritis; HCPCS/NDC, Healthcare Common Procedure Coding System/ National Drug Codes; IR, incidence rate; IRR, incidence rate ratio; LoE, level of evidence; NA, non-available/non-applicable; PAN, polyarteritis nodosa; PM, polymyositis; PsA, psoriatic arthritis; PY, patient years; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; y, years.

6.0, followed by systemic sclerosis (SSc) 4.2, 95% CI 3.8 to 4.7, Sjögren's syndrome 3.2, 95% CI 2.9 to 3.5, and the lowest in RA 2.5, 95% CI 2.4 to 2.5.<sup>18</sup> Consistently, data from a Canadian population-based surveillance for IPD showed a substantially increased incidence rate of IPD among patients with SLE, SSc, Sjögren's syndrome and dermatomyositis/polymyositis (DM/PM) during 1995–2012.<sup>19</sup> Two studies focusing in particular on patients with SLE have confirmed the previously reported notion of a substantially high risk of pneumococcal pneumonia and IPD in this susceptible population.<sup>20 21</sup> Moreover, case-fatality ratio related to IPD in patients with SLE was higher compared with immunocompetent controls, OR 1.3, 95% CI 0.4 to 4.8.<sup>19</sup> In summary, the rates of pneumococcal disease are significantly higher in patients with AIIRD compared with immunocompetent controls.<sup>22</sup> Patients with SLE, including young patients, are particularly at increased risk for pneumococcal disease, with a more complicated course.<sup>23</sup>

### Herpes zoster (HZ)

The lifetime risk of developing HZ in the general population is between 25% and 30%, rising to 50% in those aged at least 80 years. The estimated average overall incidence of HZ is about 3.4–4.8/1000 person years, increasing to more than 11/1000 person years in those aged  $\geq 80$  years.<sup>24</sup>

In the 2011 review,<sup>3</sup> the incidence of HZ in RA ranged from 0.55 to 14.5/1000 person years in different studies. RA per se and the use of steroids, conventional synthetic DMARDs (csDMARDs) and anti-TNF therapies were identified as predisposing factors to develop HZ. In SLE, a significantly increased incidence of HZ was consistently reported, ranging from 16 to 91.5/1000 person years. The increased risk of HZ among patients with SLE was estimated as fivefold to 16-fold compared with the general population and as threefold compared with other musculoskeletal disorders. Immunosuppressive therapies were associated with the increased risk of HZ in SLE. Increased incidence of HZ was also observed in systemic vasculitis and PM/DM.<sup>3</sup>

The present review has contributed 29 studies,<sup>25–51</sup> among them 2 meta-analyses,<sup>52 53</sup> expanding the data on the incidence of HZ in AIIRD (table 3). Eleven studies included a control group.<sup>25 28 34 39 40 44–46 49–51</sup> Based on the analysis of 21 studies including 894 891 patients, pooled IR and pooled IRR were calculated for patients with AIIRD in general and for specific disease subtypes (figure 2; supplementary file table 1). In comparison to the general population, the risk of HZ infection in the AIIRD population was increased, pooled IRR 2.9, 95% CI 2.4 to 3.3, based on 11 studies, n=762 553 patients. The results of the studies were heterogeneous as reflected by Q test ( $p < 0.1$ ), except for studies in DM with a low heterogeneity (Q test  $p = 0.6$ ). Publication bias assessed by funnel plots of the IR and IRR (online supplementary figure 1) showed an asymmetric distribution of the results, whereas Egger's meta-regression tests with

quantitative and descriptive p values were non-significant ( $p > 0.1$ ).

In RA,<sup>25–40</sup> the incidence of HZ ranged from 6.7 to 21.3/1000 person years, with the highest incidence observed in the elderly patients.<sup>34</sup> The risk of HZ infection among patients with RA was estimated to be twofold compared with the healthy population within the same age range. Among patients with RA, the pooled IR (based on nine studies, n=726 711 patients with RA) was 11.6/1000 person years, 95% CI 9.4 to 13.9 vs 6.5, 95% CI 4.7 to 8.2/1000 person years among controls (based on four studies, n=473 406 controls); the pooled IRR 2.3, 95% CI 2.1 to 2.6 based on four studies (85 419 patients with RA and 473 406 controls). A meta-analysis of five studies further confirmed the increased risk of HZ in patients with RA, pooled IRR of 1.7, 95% CI 1.4 to 2.0.<sup>53</sup>

The rates of HZ-related complications were reported by a number of studies.<sup>25 27 29 37 38 40</sup> Overall, the rate of disseminated disease and HZ-related hospitalisation was low. The IR of disseminated HZ ranged from 0.2, CI 95% 0.1 to 0.6/1000 person years in a Japanese study<sup>40</sup> to 3, CI 95% 2 to 4/1000 person years in a pooled analysis of patients with RA exposed to tofacitinib in clinical trials.<sup>38</sup> Importantly, a study from Taiwan reported an increased risk of stroke in patients with RA with HZ compared with patients with RA without HZ (adjusted hazard rate (aHR) 1.3,  $p = 0.047$ ), particularly in those with HZ-related neurological complications (aHR 1.5,  $p = 0.015$ ).<sup>39</sup> The following risk factors for HZ infection in RA were identified: old age, high disease activity and dose-related use of glucocorticoids (GCs).<sup>25 26 29 30 32 37 54</sup> No clear association between the use of MTX and HZ infections in RA was established.<sup>55</sup> The role of anti-TNF and other biological therapies regarding the contribution to HZ risk in RA remains *controversial*. Some studies reported that treatment with anti-TNF agents significantly increased the risk of HZ compared with csDMARDs<sup>27 31 37 52</sup> and was associated with more severe HZ disease.<sup>27 54</sup> Others reported a similar risk of HZ in patients with RA treated with different csDMARDs and biologic DMARDs.<sup>29 30 32 33 40 56</sup> The use of an anti-JAK inhibitor, tofacitinib, doubled the risk of HZ in RA compared with other biologics.<sup>35 54</sup> Similarly to tofacitinib, baricitinib was also associated with a particular increased risk of HZ, which served the main reason for the treatment discontinuation in a clinical trial.<sup>57</sup>

In SLE, the incidence of HZ ranged from 6.4 to 37.7/1000 person years<sup>28 34 43–45</sup> and was estimated two fold to 10-fold higher compared with the general population.<sup>28 43–45</sup> The pooled IR of HZ infection was 18.9, 95% CI 8.1 to 29.6/1000 person years in SLE vs 5.1, 95% CI 4.5 to 5.6/1000 person years in controls. The pooled was IRR 4.0, 95% CI 2.3 to 5.7, based on three studies including 155 959 patients and 51 087 635 controls. Another meta-analysis of four studies confirmed the increased risk of HZ in patients with SLE: pooled RR of 2.1, 95% CI 1.4 to 3.2.<sup>53</sup> Importantly, patients with SLE aged 18–30 years had the highest risk for HZ infection compared with older patients with

**Table 3** HZ studies characteristics and HZ incidence rate (IR), incidence rate ratio (IRR) and HR according to AIIRD

Author, Year	Country	Study design	AIIRD, Controls, Sample size	HZ diagnosis / ascertainment	Incidence/ 1000 PY (95% CI) AIIRD	Incidence/ 1000 PY (95% CI) Controls	IRR (95% CI) or HR (95% CI)	LoE
<b>Rheumatoid arthritis</b>								
Galloway 2013 <sup>27</sup>	UK	Prospective cohort (BSRBR)	15554 RA; 3673nbDMARD; 11881 TNFi	Patient and/or physician report confirmed by medical records	TNFi 16 (1.3 to 2.0); nbDMARD 8 (0.6 to 1.1)	NA	NA	2b
Veetil 2013 <sup>25</sup>	USA	Retrospective, population- based cohort	830 RA 830 Controls	ICD-9 confirmed by medical records	12.1 (9.6 to 14.9)	5.4 (3.9 to 7.2)	HR 2.4 (1.7 to 3.5)	2b
Widdifield 2013 <sup>26</sup>	Canada	Retrospective, population- based cohort	86039 RA	ICD-9 or ICD-10	8.5 (8.3 to 8.8)	NA	NA	2b
Winthrop 2013 <sup>29</sup>	USA	Cohort (data claim)	36212 RA; 11828 nbDMARD 24384 TNFi	ICD-9 and use of antiviral medication within 30 days of the code	csDMARD: 12.7 (10.3 to 15.6) TNFi: 12.1 (10.7 to 13.6)	NA	NA	2b
Che 2014 <sup>52</sup>	Global	Systematic literature review and meta-analysis	163077 RA patient years	NA	NA	NA	Pooled risk ratio 1.6 (1.2 to 2.2)	2a
Chen SY 2014 <sup>28</sup>	USA	Cohort (data claim)	571555 RA	ICD-9	12.2 (12.0 to 12.5)	4.8 (4.8 to 4.8)	IRR/Comparison by age groups (yo): 50 to 59 vs 18 to 49 1.5 (1.5 to 1.6) 60 to 64 vs 18 to 49 1.8 (1.7 to 2.0) ≥65 vs 18 to 49 2.2 (2.1 to 2.3)	2b
Nakajima 2015 <sup>30</sup>	Japan	Cohort	7986 RA	Patient report confirmed by medical records	9.1 (6.2 to 12.9)	NA	NA	2b
Segan 2015 <sup>31</sup>	Australia	Cohort (survey)	1870 RA	Patient report confirmed by physician	15.9 (13.5 to 18.8)	NA	NA	4
Pappas 2015 <sup>32</sup>	USA	Cohort (CORRONA)	28852 RA	Rheumatologist report	7.7 (7.1 to 8.2)	NA	NA	2b
Yun 2015 <sup>33</sup>	USA	Cohort (data claim)	29129 RA (bDMARD only)	ICD-9 and claim for an antiviral medication within 30 days of the code	Range by specific drug: 16.1 (8.9 to 29.1) – 24.5 (15.7 to 38.5)	NA	NA	2b
Yun 2016 <sup>34</sup>	USA	Cohort (data claim)	50268 RA 328580 controls	ICD-9	Range by age groups: 6.6 to 21.3 (CI NA)	5.3 range by age groups: 2.7 to 10.6 (CI NA)	NA	2b
Curtis 2016 <sup>35</sup>	USA	Cohort (data claim)	69726 RA (bDMARD or tofacitinib only)	ICD-9 and antiviral drugs within 7 days of the diagnosis code	Range by specific drug: 4.79 (4.3 to 5.3) – 7.61 (6.1 to 9.6)	NA	NA	2b

Continued

Table 3 Continued

Author, Year	Country	Study design	AIIRD, Controls, Sample size	HZ diagnosis / ascertainment	Incidence/ 1000 PY (95% CI) AIIRD	Incidence/ 1000 PY (95% CI) Controls	IRR (95% CI) or HR (95% CI)	LoE
Burmester 2017 <sup>36</sup>	Global	Cohort (pooled analysis of RCT and extension studies of adalimumab)	15 152 RA (treated with adalimumab)	Adverse event as reported in clinical trials	17 (CI NA)	NA	NA	2b
Harada 2017 <sup>37</sup>	Japan	Cohort (REAL database)	1987 RA	Medical records and antiviral medication use	6.7 (4.9 to 8.8)	NA	NA	2b
Cohen 2017 <sup>38</sup>	Global	Cohort (pooled analysis of RCT and extension studies of tofacitinib)	6194 RA	Adverse event as reported in clinical trials	39.0 (36.0 to 42.0)	NA	NA	2b
Liao 2017 <sup>39</sup>	Taiwan	Retrospective, population- based cohort	27 609 RA	ICD-9	18.3 (CI NA)	7.2 (CI NA)	HR: 2.5 (2.4 to 2.7)	2b
Kawai 2017 <sup>53</sup>	Global	SLR and meta-analysis	RA	NA	NA	NA	Pooled risk ratio 1.7 (1.4 to 2.0)	2a
Sakai 2017 <sup>40</sup>	Japan	Cohort (data claim)	6712 RA 33 560 controls	ICD-10 and antiviral medication use	14.2 (11.1 to 14.9)	8.3 (7.6 to 9.0)	IRR: 1.7 (1.5 to 2.0)	2b
<b>Psoriatic Arthritis</b>								
Zisman 2016 <sup>41</sup>	Israel	Cohort (data claim)	3131 PsA	ICD-9 and antiviral medication use ( $\geq 5$ days course)	9.06 (7.8 to 10.5)	NA	NA	2b
Yun 2016 <sup>34</sup>	USA	Cohort (data claim)	2609 PsA 328 580 controls	ICD-9	Range by age groups: 8.5 to 19.4 (CI NA)	5.3 (range by age groups: 2.7 to 10.6) (CI NA)	NA	2b
<b>Ankylosing spondylitis</b>								
Yun 2016 <sup>34</sup>	USA	Cohort (data claim)	1011 AS 328 580 controls	ICD-9	Range by age groups: 5.1 to 26.3 (CI NA)	5.3 (range by age groups: 2.7 to 10.6) (CI NA)	NA	2b
Lim 2018 <sup>42</sup>	Korea	Cohort (data claim)	1079 AS	ICD-10 and antiviral medication use at the same time	11 (8.2 to 14.3)	NA	NA	2b
<b>Psoriatic arthritis, psoriasis, ankylosing spondylitis</b>								
Winthrop 2013 <sup>29</sup>	USA	Cohort (data claim)	12 137 PsA, psoriasis, AS (7047 csDMARD, 5090 TNFi)	ICD-9 and use of antiviral medication within 30 days of the code	csDMARDs: 6.9 (4.7 to 10.0) TNFi: 4.4 (2.8 to 7.0)	NA	NA	2b
<b>Systemic lupus erythematosus</b>								
Borba 2010 <sup>43</sup>	Brazil	Cohort	1145 SLE	Clinical diagnosis	6.4 (CI NA)	NA	NA	2b

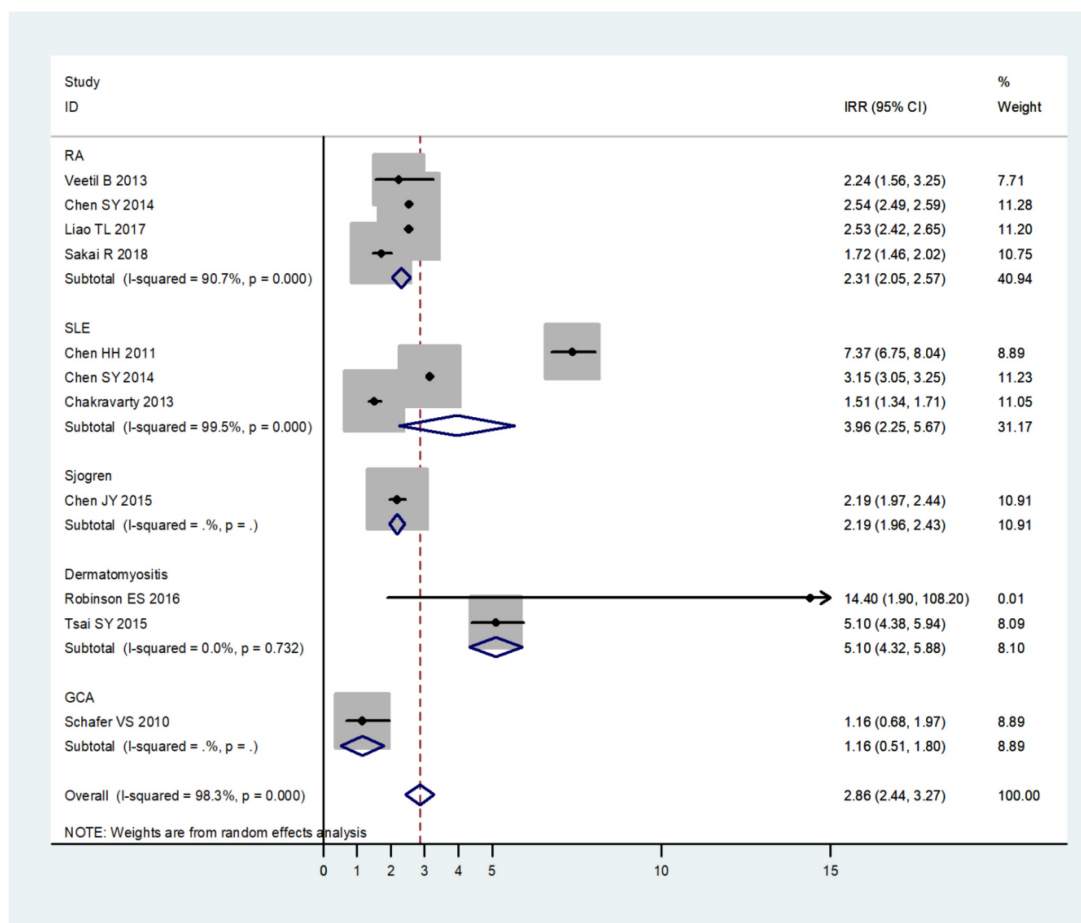
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Table 3 Continued

Author, Year	Country	Study design	AIIRD, Controls, Sample size	HZ diagnosis / ascertainment	Incidence/ 1000 PY (95% CI) AIIRD	Incidence/ 1000 PY (95% CI) Controls	IRR HR (95% CI) or HR (95% CI)	LoE
Chen HH 2011 <sup>44</sup>	Taiwan	Retrospective, population- based cohort	10337 SLE 62022 controls	ICD-9	37.7 (25.5 to 40.0)	5.1 (4.8 to 5.4)	IRR: 2.5 (1.8 to 3.4)	2b
Chakravarty 2013 <sup>45</sup>	USA	Cohort (National Data Bank for Rheumatic Diseases)	1485 SLE 2775 controls	Patient report	16.2 (12.4 to 21.1)	10.7 (7.6 to 15)	HR 1.7 (1.1 to 2.7)	2b
Chen SY 2014 <sup>28</sup>	USA	Cohort (data claim)	144 137 SLE	ICD-9	15.2 (14.7 to 15.7)	4.8 (4.8 to 4.8)	IRR/Comparison by age groups (yo): 50 to 59 vs 18 to 49 2 (1.1 to 1.2) 60 to 64 vs 18 to 49 1.5 (1.3 to 1.7) ≥65 vs 18 to 49 1.8 (1.6 to 2.0)	2b
Kawai 2017 <sup>53</sup>	Global	SLR and meta-analysis	SLE	NA	NA	NA	pooled risk ratio 2.10 (1.4 to 3.2)	2a
Yun 2016 <sup>34</sup>	USA	Cohort (data claim)	8395 SLE 328580 controls	ICD-9	19.9 (range by age groups: 15.2 to 24.6) (CI NA)	5.3 (range by age groups: 2.7 to 10.6) (CI NA)	NA	2b
<b>Sjögren</b>								
Chen JY 2015 <sup>46</sup>	Taiwan	Retrospective, population- based cohort	4287 Sjögren 25722 controls	ICD-9	18.74 (CI NA)	8.55 (CI NA)	HR 1.7 (1.5 to 1.9)	2b
<b>Polymyositis/Dermatomyositis</b>								
Fardet 2009 <sup>47</sup>	France	Retrospective inception cohort	121 DM	Physician report	33 (CI NA)	NA	NA	4
Marie 2011 <sup>48</sup>	France	Cohort	279 PM/DM	Medical records	33 (CI NA)	NA	NA	4
Tsai 2015 <sup>49</sup>	Taiwan	Retrospective, population- based cohort	2023 PM/DM 7409 controls	ICD-9	35.8 (CI NA)	7.01 (CI NA)	HR 3.9 (3.2 to 4.8)	2b
Robinson 2016 <sup>50</sup>	USA	Retrospective cohort	103 DM 152 controls	Medical records confirmed by dermatologist	55.4 (CI NA)	3.9 (CI NA)	NA	2b
<b>Giant cell arteritis</b>								
Schafer 2010 <sup>51</sup>	USA	Cohort (data claim)	204 GCA 407 controls	Healthcare provider report, ICD-9 code confirmed by medical records	Range by age groups: 11.3 to 14 (CI NA)	Range by age groups: 4.6 to 12.1 (CI NA)	HR 1.22 (0.7 to 2.1)	2b

AIIRD, autoimmune inflammatory rheumatic disease(s); BSRBR, The British Society for Rheumatology Biologics Register; CORRONA, The Consortium of Rheumatology Researchers of North America; DM, dermatomyositis; GCA, giant cell arteritis; IR, incidence ratio; IRR, incidence rate ratio; LoE, level of evidence; NA, non-available/non-applicable; nbdMARD, non-biologic disease modifying anti-rheumatic drug; PM, polymyositis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RCT, randomised controlled trial; SLE, systemic lupus erythematosus; SSC, systemic sclerosis; TNFi, tumour necrosis factor inhibitor(s).



**Figure 2** Forest plot of the meta-analysis of pooled incidence rate ratios (IRRs) of herpes zoster in patients with autoimmune inflammatory rheumatic diseases compared with the general population. GCA, giant cell arteritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

SLE.<sup>34 44</sup> Risk factors for HZ in the SLE populations mainly included use of GCs and immunosuppressive therapy in a dose-dependent manner.<sup>28 43 45 58</sup> Notably, the new pipeline medications for SLE including anti-interferon- $\alpha$  antibodies, anifrolumab<sup>59</sup> and sifalimumab,<sup>60</sup> also seem to contribute to the increased risk of HZ. To underline the burden of HZ in patients with SLE, a trend for increased hospitalisation rates due to HZ in SLE versus non-SLE patients was observed over the last decade.<sup>61</sup>

Among other AIIRD, a particularly high incidence of HZ was reported in patients with DM and PM compared with controls with a pooled IRR 5.1, 95% CI 4.3 to 5.9/1000 person years.<sup>47–50</sup> These studies were notable for a low heterogeneity (Q test p 0.6). Patients with primary Sjögren<sup>46</sup> and giant cell arteritis<sup>51</sup> also had a high risk to contract HZ, as reflected by a single study for each disease group. In summary, the present review demonstrates an increased risk of HZ infection in patients with AIIRD compared with the general population, with the highest risk in patients with inflammatory myositis and GCA, followed by SLE and RA.

### Human papillomavirus (HPV)

The global prevalence of HPV infection is estimated as 11.7%, 95% CI 11.6 to 11.7, with considerable regional

differences, with higher rates reported in sub-Saharan Africa (24%), Eastern Europe (21%) and Latin America (16%).<sup>62</sup> The highest HPV prevalence is observed at young ages, peaking in women younger than 25 years (24.0%; 23.5 to 24.5), then declining in older ages.<sup>62</sup> The majority of HPV infections (70%–90%) are asymptomatic and transient, resolving spontaneously in 1–2 years. Certain HPV serotypes ('high-risk') are responsible for cervical dysplasia, premalignant abnormalities and cervical cancer. HPV16 is the most frequent oncogenic type, followed by HPV18, HPV52, HPV31 and HPV58.<sup>63</sup>

In the 2011 review,<sup>3</sup> five studies reported on the increased prevalence of HPV cervical infection in female patients with SLE compared with the general population.<sup>64 65</sup> The present review has significantly expanded the knowledge on the genital HPV infection in SLE (n=11),<sup>66–76</sup> RA (n=2)<sup>69 77</sup> and SSc (n=1), including 1313 patients altogether<sup>78</sup> (table 4). Most studies on the SLE population were conducted in Latin America (n=9), followed by Asia (n=2). The HPV prevalence mainly ranged from 12% to 30% of HPV in patients with SLE, with two exceptions: a negligible prevalence in a small group of patients with SLE in Egypt<sup>73</sup> and a strikingly high prevalence in a Brazilian SLE cohort.<sup>70</sup> The authors

**Table 4** Genital human papillomavirus (HPV) infection studies characteristics and HPV incidence/prevalence rates

Author, Year	Country	Study design	Study outcome	AIIRD, Controls, Sample size	HPV definition /ascertainment	Incidence or prevalence, AIIRD	Incidence or prevalence, Controls	OR (95% CI) of HPV in SLE vs controls	LoE
Klumb 2010 <sup>66</sup>	Brazil	Cross-sectional	Prevalence	173 SLE, 216 controls	Cervical smear/ HPV DNA PCR	20%	7.3%	NA	3b
Tam 2010 <sup>67</sup>	Hong Kong, China	Cohort (3-year f/u)	Prevalence, incidence	150 SLE	Cervical smear/ HPV DNA PCR	Prevalence: Baseline: 12.5% 3-year f/u: 25% Incidence of new HPV: 17/1000 patient months	NA	NA	2b
Lee 2010 <sup>68</sup>	Korea	Cross-sectional	Prevalence	134 SLE, 4595 controls	Cervical smear/ Hybrid Capture II technology or HPV PCR DNA; cervical cytology	24.6%	7.9%	OR 3.8 (2.5 to 5.7)	3b
Rojo-Contreras 2012 <sup>69</sup>	Mexico	Cross-sectional	Prevalence	43 RA 34 SLE 146 controls	Cervical smear/ HPV DNA PCR	RA: 27.9% SLE: 14.7%	30.8%	NA	3b
Lyrio 2013 <sup>70</sup>	Brazil	Cross-sectional	Prevalence	88 SLE 70 controls	Cervical smear/ HPV nested DNA PCR	80.7%	35.7%	OR 7.2 (2.9 to 17.8)	3b
Mendoza-Pinto 2013 <sup>71</sup>	Mexico	Cross-sectional	Prevalence	148 SLE	Cervical smear/ HPV DNA PCR	29%	NA	NA	3b
García-Carrasco 2015 <sup>72</sup>	Mexico	Cross-sectional	Prevalence	67 SLE	Cervical smear/ HPV DNA PCR	28.4%	NA	NA	3b
Al-Sherbeni 2015 <sup>73</sup>	Egypt	Cross-sectional	Prevalence	32 SLE 20 controls	Cervical smear/ Immunostaining with HPV antibody	3.1%	0	NA	3b
Mendoza-Pinto 2017 <sup>74</sup>	Mexico	Cohort (3-year f/u)	Prevalence, incidence	127 SLE	Cervical smear/ HPV DNA PCR	Prevalence: 22.8 Incidence: 10.1/1000 patient months	NA	NA	2b
Amara 2017 <sup>75</sup>	Brazil	Cross-sectional	Prevalence	70 SLE	Cervical smear/ HPV DNA PCR	22.8%	NA	NA	3b

Continued

Table 4 Continued

Author, Year	Country	Study design	Study outcome	AIIRD, Controls, Sample size	HPV definition /ascertainment	Incidence or prevalence, AIIRD	Incidence or prevalence, Controls	OR (95% CI) of HPV in SLE vs controls	LoE
Méndez-Martínez 2018 <sup>76</sup>	Mexico	Cohort (2-year f/u)	Prevalence, Incidence	148 SLE	Cervical smear/HPV DNA (method not specified); cervical cytology	Prevalence: 29% Incidence of new infection: 13.2%	NA	NA	2b
Waisberg 2015 <sup>77</sup>	Brazil	Cross-sectional	Prevalence	50 RA 50 controls	Cervical smear/HPV DNA Hybrid Capture technology; cervical cytology	14%	30%	NA	3b
Martin 2014 <sup>78</sup>	France	Cross-sectional	Prevalence	25 SSC 50 controls	Cervical smear/HPV DNA PCR and serum antibodies against HPV16 and 18	32%	38%	NA	3b

AIIRD, autoimmune inflammatory rheumatic disease(s); f/u, follow-up; LoE, level of evidence; NA, non-available/non-applicable; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSC, systemic sclerosis.

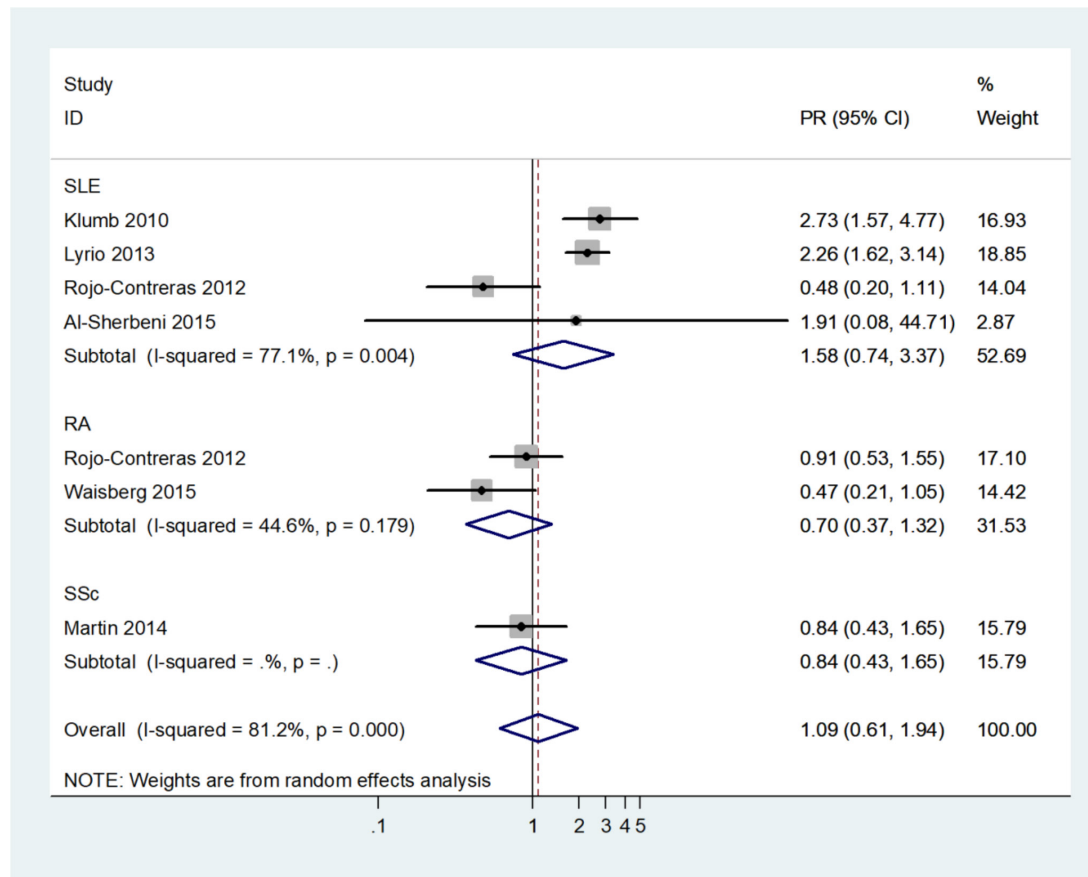
suggested that using a very sensitive technique of PCR (n-PCR) might have resulted in a significant increase in the detection of the virus.<sup>70</sup> Seven studies also reported the prevalence of cervical dysplasia, including the high-grade squamous intraepithelial lesions (HGSILs).<sup>67-70 72 76 77</sup> The pooled prevalence of HPV and pooled prevalence and prevalence ratios of HPV, high-risk HPV and HGSIL are summarised in table 2 in the supplementary file and depicted in figure 3. Most studies were heterogeneous as estimated by the Q test, with the exception of data on HGSIL. For publication bias assessment, a funnel plot of the prevalence of HPV, high-risk HPV and HGSIL was depicted (figure 2 in supplementary file), with Egger's meta-regression tests with quantitative and descriptive p values being non-significant (p>0.1).

A limited number of studies included a control group, reporting a higher prevalence of HPV in SLE compared with controls in two studies<sup>66 68</sup> and the opposite in a small Mexican cohort.<sup>69</sup> Compared with the general population, pooled prevalence ratio of HPV in SLE patients was 1.6, 95% CI 0.7 to 3.4. Excluding the study by Rojo-Contreras *et al*,<sup>69</sup> with an exceptionally high background HPV prevalence in the control group, from the analysis resulted in a statistically significant pooled PR for SLE – 2.4, 95% CI 1.8 to 3.2.

In patients with RA, no difference in the prevalence of HPV was found between patients and controls (pooled PR 0.7, 95% CI 0.5 to 1.1). Furthermore, important information on HPV persistence, clearance and incidence of de novo infection was obtained from cohort studies (n=3) of patients with SLE with a follow-up to 3 years.<sup>67 74 76</sup> In one study, the cumulative prevalence of HPV infection and specifically high-risk HPV infection significantly increased from 12.5% to 25.0% after 3 years (p=0.006) and from 11.1% to 20.8% after 3 years (p=0.02), respectively.<sup>67</sup> Overall, 90.6% of the preexisting infection and 14.7% of the incident infections were cleared,<sup>67</sup> consistent with a high clearance rate of 88.6% in another study.<sup>74</sup> The rate of acquisition of a new HPV infection was about 13%.<sup>76</sup> Risk factors for HPV infection among patients with SLE were similar to the general population, including multiple sexual partners,<sup>74</sup> previous HPV infection, previous sexually transmitted disease<sup>66</sup> and younger age.<sup>71</sup> The presence of SLE itself was found as an independent predictor for HPV infection,<sup>70</sup> and a risk factor for high-risk HPV types.<sup>68</sup> The impact of immunosuppressive therapy on the increased prevalence of HPV remains controversial, with some data supporting a causal relation, especially related to a high cumulative dose of corticosteroids, azathioprine and cyclophosphamide exposure.<sup>66 69 71 74</sup>

In RA, a lower prevalence of HPV infection was observed in pre-anti-TNF-treated patients compared with controls (14% vs 30 %, p=0.054).<sup>77</sup> Treatment with anti-TNF (for 6 months) did not increase a risk of exacerbation and/or progression of HPV in this small cohort.<sup>77</sup> In a small study of patients with SSC (n=25, 80% limited SSC), the prevalence of HPV was similar in patients and controls





**Figure 3** Forest plot of the meta-analysis of pooled prevalence ratio (PR) of human papillomavirus in patients with autoimmune inflammatory rheumatic diseases compared with the general population. RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

(32% vs 38%).<sup>78</sup> High-risk HPV52 was the most common genotype with a greater multi-HPV infection rate.<sup>78</sup>

In summary, the prevalence of genital HPV infection, including high-risk HPV serotypes and HGSIL, was increased in the female population with SLE from Latin America and Asia and comparable to the general population in patients with RA and SSc, based on the limited data.

### Hepatitis B (HBV)

The epidemiology of HBV infection widely varies around the globe. The seroprevalence of hepatitis B surface antigen (HBsAg), reflecting chronic infection with HBV, is estimated as 3.6% (95% CI 3.6% to 3.6%) worldwide, with the highest prevalence in countries of the African (total 8.8%, CI 8.8% to 8.8%) and Western Pacific regions (total 5.3%, CI 5.3% to 5.3%).<sup>79</sup> In the Americas and the WHO European region, the prevalence ranges from 0.2% to 13.6%.<sup>79</sup>

The scope of the SLR performed in 2011 did not include data on HBV infection. The present SLR retrieved 10 cross-sectional studies, conducted mainly in the Asian population (China, Japan, Taiwan) on the seroprevalence of HBV, defined by positive HbsAg and/or positive anti-hepatitis B core antibody (anti-HBc) among patients

with AIIRD.<sup>80–89</sup> All studies were of cross-sectional design with level of evidence 3b.

The documented HBV seroprevalence differed considerably between the studies (table 3 in the supplementary file). The lowest prevalence of HBsAg was reported in patients with SLE, followed by RA and SpA in the increasing order, with the highest prevalence detected in patients with AS.<sup>82–89</sup> The pooled seroprevalence of HBsAg was 3% (95% CI 1% to 5%) and for anti-HBc 15% (CI 95% 7% to 26%) (figure 4; table 4 in the supplementary file). There was a high heterogeneity among the studies,  $Q < 0.1$ . For publication bias assessment, a funnel plot of the seroprevalence results was depicted (figure 3 in the supplementary file) with Egger's meta-regression tests with quantitative and descriptive p values being non-significant ( $p > 0.1$ ). Overall, in the present studies, the prevalence of HBV in the AIIRD population seems to be similar, and in some studies even lower,<sup>80–86–87</sup> compared with the general population.

### DISCUSSION

This SLR presents the update on the incidence and prevalence of VPI among patients with AIIRD. The results of the SLR highlight the insufficient data on the

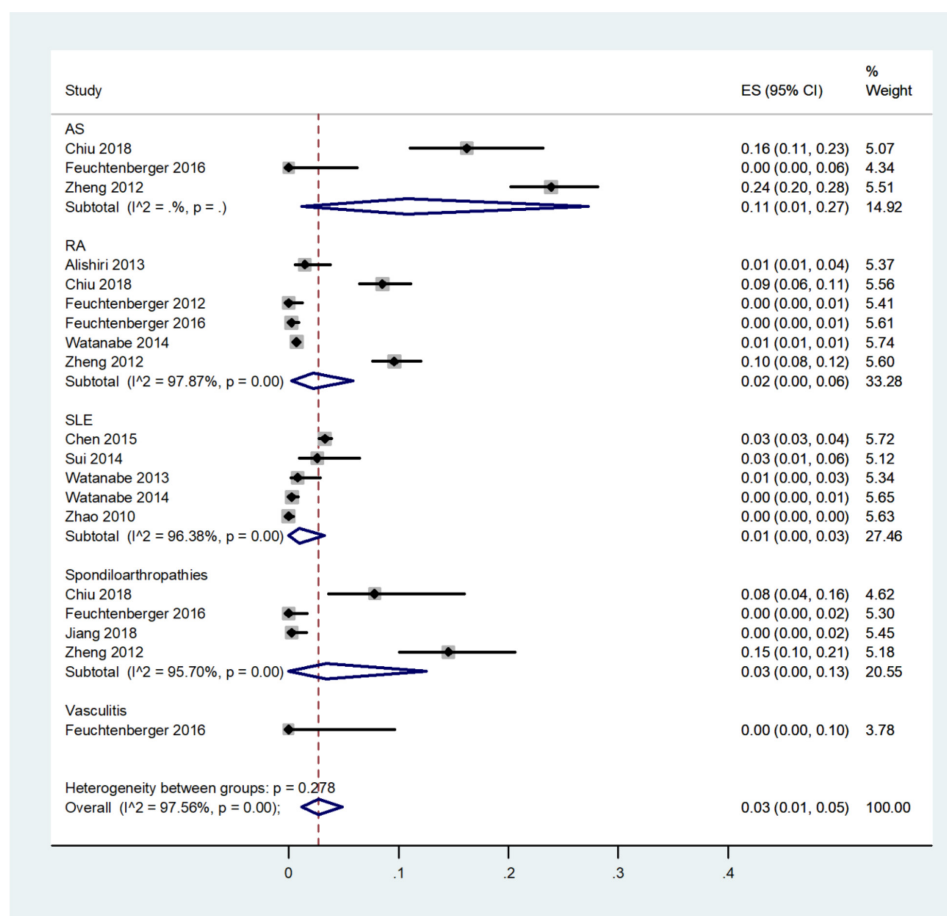
epidemiology of most VPI in the AIIRD population. In fact, data were available on only 5 out of 18 searched VPI: influenza, *S. pneumoniae*, HZ, HPV and HBV infections. Furthermore, there was a paucity of European studies addressing the epidemiology of HPV and HBV infections, with most studies being conducted in Latin America and Asia. However, this information was extremely useful in the process of formulation of the recommendations for vaccination in patients with AIIRD, since it emphasised the increased prevalence of influenza, *S. pneumoniae*, HZ and HPV among patients with AIIRD, especially encouraging vaccination against these agents. The observation of a similar prevalence of hepatitis B infection among patients with AIIRD and the general population supported the recommendation to vaccinate patients with AIIRD for HBV as indicated for the general population.

Concerning influenza, patients with AIIRD are prone for contracting influenza and influenza-related complications compared with the general population. A limited number of the eligible studies ( $n=4$ ) and their heterogeneous outcomes (patient reported ILI symptoms and ICD codes) precluded the performance of a meta-analysis. Lack of data concerning microbiological confirmation of the diagnosis of influenza should be noted

in all four studies. This limitation is pertinent to epidemiological studies on influenza in general, as the evaluation of the precise incidence of influenza represents a complex epidemiological challenge, due to lack of access to sensitive and specific diagnostic tests, difficulty obtaining specimens for testing, the unpredictability of influenza epidemics, and the complexity of assembling and following large cohorts.<sup>90</sup>

Concerning pneumococcal infection, patients with AIIRD are prone for contracting pneumococcal disease compared with the general population. Importantly, patients with SLE, including young patients, are at particular increased risk for pneumococcal disease.<sup>23</sup> In this dataset, heterogeneity of the outcomes and reporting the pneumococcal disease incidence for the combined groups of inflammatory diseases, including inflammatory bowel diseases in some studies, precluded conducting a meta-analysis.

With regard to HZ, the sample size of studies reporting the incidence of HZ infection, most of which were of moderate to good quality, permitted the performance of a meta-analysis, that unequivocally demonstrated that patients with AIIRD are at increased risk to contract HZ compared with the general population. This conclusion was consistent with the previous 2011 review results. A



**Figure 4** Forest plot of pooled prevalence of hepatitis B surface antigen virus in patients with autoimmune inflammatory rheumatic diseases. AS, ankylosing spondylitis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

particularly high risk for HZ was observed in patients with inflammatory myositis and SLE, including young patients with SLE, for whom vaccination for HZ has not been approved by the regulatory agencies but only for those aged 50 years and older. Importantly, the burden of HZ in SLE is also reflected by an increasing trend in hospitalisation for HZ in patients with SLE in the recent decade.<sup>61 91</sup>

The prevalence of HPV infection is significantly affected by both geographical distribution and socioeconomic status of the population, factors that may preclude extrapolation of the data retrieved in the present SLR to the European AIIRD population. Most studies included in the meta-analysis showed a tendency towards a higher prevalence of genital HPV, including high-risk serotypes of HPV, and HGSIL in patients in SLE but not in patients with RA and SSc. These data should be cautiously interpreted given the heterogeneity of the studies and their diverse geographical distribution (Latin America and Asia).

The common assumption is that the increased prevalence of influenza, pneumococcal disease, HZ and HPV is related to the status of immunodeficiency inherent to the nature of autoimmune diseases and immunosuppressive treatments. Concerning HPV, it has been suggested that the virus itself may be a trigger for the onset or exacerbation of SLE.<sup>92 93</sup>

The meta-analysis of the seroprevalence of chronic HBV infection in patients with AIIRD mirrored the global epidemiology of the disease in the general population.

This SLR reports an increased risk of VPI in patients with AIIRD, emphasising that prevention of infections is essential in these patients. In addition, it highlights the importance of the epidemiological research of the incidence and prevalence of VPI in patients with AIIRD. The proposed research agenda, therefore, includes the collection of reliable epidemiological data using standardised methodology of disease rates and development of prevention and control strategies for infectious diseases in patients with AIIRD.

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**Contributors** VF, with collaboration with OE, performed literature search and reviewed articles on the prevalence and/or incidence of vaccine preventable diseases in patients with autoimmune inflammatory rheumatic diseases. The systematic literature review (SLR) and meta-analysis, when applicable, was performed under the supervision by SvA, the expert in infectious diseases, and the methodologists, JmVL and RL. The results of the SLR were presented to all task force members, discussed and reviewed during the task force meetings. VF drafted and edited the manuscript, under the supervision of OE. All authors read and approved the final version of the manuscript.

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