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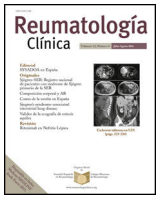

Special Article

Recommendations for prevention of infection in systemic autoimmune rheumatic diseases☆

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ABSTRACT

Objectives: To develop recommendations for the prevention of infection in adult patients with systemic autoimmune rheumatic diseases (SARD).
Methods: Clinical research questions relevant to the objective of the document were identified by a panel of experts selected based on their experience in the field. Systematic reviews of the available evidence were conducted, and evidence was graded according to the Scottish Intercollegiate Guidelines Network criteria. Specific recommendations were made.
Results: Five questions were selected, referring to prevention of infection by *Pneumocystis jirovecii* with trimethoprim/sulfamethoxazole, primary and secondary prophylactic measures against hepatitis B virus, vaccination against human papillomavirus, vaccination against *Streptococcus pneumoniae* and vaccination against influenza virus, making a total of 18 recommendations, structured by question, based on the evidence found for the different SARD and/or expert consensus.
Conclusions: There is enough evidence on the safety and efficacy of vaccinations and other prophylactic measures against the microorganisms reviewed in this document to specifically recommend them for patients with SARD.

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Recomendaciones SER sobre prevención de infección en enfermedades reumáticas autoinmunes sistémicas

Palabras clave:
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Hepatitis B
Virus del papiloma humano
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Streptococcus pneumoniae

R E S U M E N

Objetivo: Elaborar recomendaciones para prevención de infección en pacientes adultos con enfermedades reumáticas autoinmunes sistémicas (ERAS).
Métodos: Un panel de expertos, seleccionados en base a su experiencia, identificó preguntas clínicas de investigación relevantes para el objetivo del documento. Se realizaron revisiones sistemáticas de la evidencia, que se graduó de acuerdo con los criterios del Scottish Intercollegiate Guidelines Network. Tras ello se formularon las recomendaciones.
Resultados: Se seleccionaron cinco preguntas, referentes a la prevención de infección por *Pneumocystis jirovecii* con trimetoprim/sulfametoxazol, medidas profilácticas frente al virus de la hepatitis B, vacunación frente al virus del papiloma humano, vacunación frente al *Streptococcus pneumoniae* y vacunación frente al virus de la gripe. Se formularon un total de 18 recomendaciones, estructuradas por pregunta, con base en la evidencia encontrada para las diferentes ERAS y/o consenso de expertos.
Conclusiones: Existe suficiente evidencia sobre la seguridad y eficacia de las vacunaciones y otras medidas profilácticas frente a los microrganismos revisados en este documento para ser recomendadas específicamente en pacientes con ERAS.

Introduction

Severe infection is one of the major causes of morbidity and mortality in patients with systemic autoimmune rheumatic diseases (SARD).[1–4] In systemic lupus erythematosus (SLE), one of the most prevalent SARD, mortality secondary to infection is estimated to be up to five times higher than in the general population.[5] Although many of the risk factors for infection are shared with the general population, there are factors that are specific to SARD, such as genetic factors or characteristics inherent to the disease and its treatments.[6–9] The risk of severe infection is not uniform in all SARD, it is less frequent in primary Sjögren's syndrome (pSS) than in SLE.[10] In terms of treatments, immunosuppressants (IS) and glucocorticoids (GC) are well-known risk factors for infection.[6] The targeted therapies, biological and small molecule, although they have very specific molecular targets, can impair the immune response to infection and interfere with infection control. This is particularly relevant for therapies that target B-lymphocytes, such as rituximab (RTX).[11] On the other hand, controlling the immunopathogenic disease process using these therapies could, in turn, reduce the risk of infection intrinsic to SARD.[12]

The prevalence of preventable infections in SARD has not been well researched, although most studies suggest that it is higher than in the general population for influenza virus, *Streptococcus pneumoniae*, herpes zoster virus (HZV) and human papillomavirus (HPV).[13] Some infections, such as *S. pneumoniae* and HPV, appear to be more common in SARD, especially SLE, than in chronic inflammatory arthropathies, after adjusting for the level of immunosuppression.[9,13,14] Likewise, the prevalence of HZV appears to be higher in some SARD, such as inflammatory myopathies (IM) or giant cell arteritis (GCA).[13] Although there is little information on other viruses, such as hepatitis B virus (HBV) or hepatitis C virus (HCV), the prevalence of both seems to be similar or even lower in SARD than in the general population.[6,15,16]

Most serious infections in patients with SARD are caused by common microorganisms in the usual sites.[2,10] However, opportunistic infections, such as *Pneumocystis jirovecii* (PCJ), do occur, especially in patients treated with high doses of GC or other forms of intensive immunosuppression.[17–19] In the largest study published to date, conducted in Taiwan in 76,966 people with SARD and rheumatoid arthritis (RA), the risk of opportunistic infections was highest in the first year following diagnosis, highest in IM, followed by SLE, systemic sclerosis (SS), RA and pSS.[20]

Some infections, such as those caused by *S. pneumoniae* or influenza virus, have been reported to be more severe and fatal in immunocompromised SARD patients.[21–23] And finally, an infectious event can trigger flares of disease activity in SARD.[24–27]

Justification for specific recommendations for SARD

SARD are a group of complex and often severe diseases that share mechanisms and treatments that compromise the immune response, and therefore severe infections are common. Mortality due to infection is also higher than in other immune-mediated rheumatic diseases, which means infection prevention is an essential objective and a challenge for clinicians managing these diseases.

There is very little available evidence on the incidence and prevention of infections in SARD, and on the immunogenicity and safety of vaccines or other prophylactic measures in patients with these diseases.[13,28] Therefore, it is appropriate to develop specific recommendations for SARD, based on the best available evidence and the pooled opinion of multidisciplinary expert groups.

There are recently updated recommendations from the European League Against Rheumatism (EULAR) on vaccination in patients with immune-mediated rheumatic diseases,[29] but the scope of the objectives set means that the peculiarities of SARD have not been sufficiently addressed and questions have been left unanswered. Moreover, as only vaccine-preventable diseases are analysed, aspects that are specific to SARD have been excluded, such as PCJ chemoprophylaxis,[30,31] or the prevention of hepatitis B reactivation.[32]

Objective

To develop specific recommendations for the prevention of infection in adult patients with SARD, supported by systematic reviews (SR) and/or expert consensus, in questions considered a priority by the group of panellists, according to their clinical repercussions, the peculiarities of each infection in SARD and the availability of resources.

Methods

In developing these recommendations, we used a qualitative synthesis of the scientific evidence and consensus techniques, which reflect the agreement of experts based on the available evidence and their clinical experience.

The process to develop the project was as follows:

1 An expert panel was formed of six rheumatologists, two specialists in infectious diseases and one in preventive medicine. Two rheumatologists and two methodology specialists from the Research Unit of the Spanish Society of Rheumatology (UI-SER) were the coordinators.
2 The content and key aspects of the document were defined, and the clinical research questions with the greatest impact on clinical practice were set. The questions were reformulated in patient, intervention, comparison, and outcome (PICO) format.
3 A search was conducted of the scientific evidence published up to April 2019 using the PubMed (MEDLINE), EMBASE, and Cochrane Library (Wiley Online) databases. The process was completed with a manual search of the references of the studies found. The literature search strategies for the SR can be found in the Supplementary material.
4 The SR and synthesis of the scientific evidence were performed by SER rheumatologists who are experts in evidence review. The level of scientific evidence was assessed using the criteria of the Scottish Intercollegiate Guidelines Network (SIGN).[33]
5 The expert panel formulated the recommendations, based on formal evaluation or ïeasoned judgementöf the evidence, for each of the questions. They considered the quality, quantity and consistency of the scientific evidence, the generality of the results, their applicability, and their clinical impact. For questions where the evidence was insufficient, recommendations were formulated based on the consensus of the expert group. Two rounds of consensus were used to formulate the recommendations. Using the "reasoned judgement" consensus system, all the experts first drafted and discussed the recommendations. Then, in the presence of the methodologists, the degree of agreement among the experts on the content and wording of each of the recommendations was established using a modified nominal consensus technique. The SIGN[33] system was used to grade the recommendations (Appendix B Annex).
6 The draft document was submitted for external review to ensure the validity and accuracy of the recommendations and, after public exposure, to ensure that other SER partners and different potential stakeholder groups and entities could evaluate the document and make criticisms or suggestions.

Additional information

Full information on the results of the evidence review for each research question is available on the SER website (www.ser.es).

General preliminary considerations

We should emphasise that the recommendations developed in this document should be framed within a global strategy for infection risk management in SARD.

To address infection prevention in these diseases, it is first essential to estimate the individual risk of infection, which includes the recording of previous serious infectious events and the presence of chronic viral infections (hepatitis virus, HIV or HPV), or latent tuberculosis. It is beyond the scope of this document to make recommendations on infection screening strategies in SARD; the general recommendations apply for immunocompromised patients or those on the use of specific drugs such as the biological or targeted therapies. In estimating the risk of infection, factors such as age, ethnicity, type of SARD, smoking, comorbidities, severity of disease, active treatments, accumulated damage, etc. should be taken into account, as all of these condition the level of risk.[17,19] It is also essential to take the most accurate and reliable vaccination history possible (vaccines administered to date, valency, doses, booster, location in time, etc.), or previously completed tuberculosis prophylaxis. Lymphocyte subpopulation and/or immunoglobulin testing should be considered if a decrease is suspected, as a consequence of treatment or of the SARD itself.

This document does not address prevention of reactivation of latent *Mycobacterium tuberculosis* infection, as it is considered adequately reviewed in recent recommendations issued by other groups.[34,35]

General personal and oral hygiene measures[36] should be proactively promoted, as well as avoiding smoking or contact with patients with potentially serious active infectious diseases. Adequate adherence to vaccination programmes by household members can help reduce risks from exposure to infectious agents in the environment, in accordance with the c̈ocoon immunization strategy.:[37] Specific travel advice for geographic areas with special risks may be critical in terms of protection.

The panellists suggest the implementation of structured education programmes by trained nurses, where resources are available, given the effectiveness of these programmes in promoting vaccination,[38,39] always in collaboration with the preventive medicine services.

We should remember here that optimising or "fine tuning" IS treatment, minimising the dose of GC, is a widely accepted measure, on which there is agreement in clinical practice. In this regard, it is worth remembering that a daily dose of prednisone (or equivalent) equal or greater than 7.5 mg has been associated with an increased risk of serious infection in patients with SLE.[40] On the other hand, antimalarials have been consistently associated with a reduced risk of serious infection in patients with SLE,[17,41] and also in reducing its associated mortality.[42] It has even been suggested recently that their continued use may reduce the incidence of PCJ pneumonia.[43]

The panel believe it appropriate to highlight that the suggestions in this section of general preliminary considerations have not been subjected to the evidence review or the standardised expert consensus methodology followed in drafting the document. Finally, for situations in which the evidence has not been reviewed, the expert panel would defer to the recently updated EULAR recommendations on vaccination in immuno-mediated rheumatic diseases,[29] to the SER consensus on risk management of biological therapy in rheumatic diseases,[44] to the recommendations made by other groups for immunocompromised patients,[45] and, when applicable, those made for the general population should not be disregarded.

Terminology

- Immunogenicity: the capacity of a vaccine to elicit a measurable immune response.
- Seroconversion: an increase in antibody titre following administration of a vaccine until it becomes detectable when measured, or increases by a predetermined level from previous levels.
- Seroprotection: Serological evidence of immunity to an infectious disease, equal or above the cut-off level for the immunological correlate of protection.
- Seroreversion: Loss of immunological protection provided by a vaccine over time.
- Geometric mean concentrations (GMC): A measure of the average titre of antibodies generated by a vaccine in a group of individuals.

Results

A total of 18 recommendations were formulated that address the use of trimethoprim-sulfamethoxazole as prophylaxis against PCJ, primary and secondary prophylactic measures against HBV

Table 1
SER recommendations on infection prevention in SARD.

Recommendations	G R
Trimethoprim-sulfamethoxazole as prophylaxis against *Pneumocystis jirovecii*	
Recommendation: *Trimethoprim-sulfamethoxazole prophylaxis against Pneumocystis jirovecii infection is recommended in SARD patients treated continuously with glucocorticoids (≥ 20 mg/day). No minimum duration of glucocorticoid treatment beyond which prophylaxis is indicated can be established.*	*B √ C √*
Recommendation: *Irrespective of immunosuppressive therapy, in any patient with sustained CD4+ T-cell counts below 200/mm^3, prophylaxis with trimethoprim-sulfamethoxazole is also recommended.*	
Recommendation: *The trimethoprim-sulfamethoxazole dose of 400 mg/80 mg/day is recommended as it is the best documented regimen in terms of safety and efficacy for Pneumocystis jirovecii prophylaxis in patients with SARD.*	
Recommendation: *Folic acid supplementation is recommended in trimethoprim-sulfamethoxazole treatments that last longer than one month.*	
Primary and secondary prophylaxis measures against hepatitis B virus	
Recommendation: *In patients with SLE or Behçet's disease, vaccination against hepatitis B virus with 3 doses of recombinant vaccine (20 μg of purified HBsAg) is recommended in the inactive or low-activity phase and without immunosuppressive treatment.*	D√√√√
Recommendation: *In patients with other SARD, it is suggested that the above recommendations be applied. Although there is no direct evidence, this group of patients is considered to have enough similarities with SLE to extrapolate the recommendation.*	
Recommendation: *In all SARD patients who are immunosuppressed (due to previous or current treatment), it is suggested that vaccination schedules with 4 doses and/or higher antigen load (40 μg of purified HBsAg) be considered).*	
Recommendation: *It is recommended that the vaccination response to hepatitis B should be verified upon completion of the prescribed schedule, by determining antibody levels against surface antigen (anti-HBsAg), 1 month after vaccination.*	
Recommendation: *In all SARD patients with chronic HBV infection and who are to undergo immunosuppressive treatment, biological therapy (especially anti-CD20) or treatment with glucocorticoids (prednisone or equivalent ≥ 20 mg/day for 4 weeks), concomitant treatment with antivirals, preferably entecavir .5 mg/day, is recommended due to the high rate of resistance to lamivudine, to prevent reactivation of HBV infection.*	
Vaccination against human papillomavirus	
Recommendation: *The HPV vaccination recommendations for the general population should be followed for all SARD patients, i.e.:*	*D D √ C*
1. Universal vaccination is recommended for girls, ideally at 12 years of age.	
2. In older patients with cervical excisional treatment and/or WHIM syndrome (warts, hypogammaglobulinaemia, infections and myelokathexis syndrome), as well as in those under 26 years of age in prostitution, HIV infection and men who have sex with men.	
Recommendation: *In older patients with SARD, especially SLE who are not included in the above groups, the decision to vaccinate should be individualised, considering prior risk of exposure to papillomavirus and the risk of future contact with the virus.*	
Recommendation: *Vaccination is recommended before the onset of immunosuppression and in periods of remission or low disease activity to avoid the potential effect of immunosuppressants on response to the vaccine.*	
Vaccination against *Streptococcus pneumoniae*	
Recommendation: *Vaccination against Streptococcus pneumoniae is recommended for all SARD patients because, although it confers slightly lower immunogenicity compared to healthy individuals (especially in patients with SLE), it is sufficiently effective and safe.*	*B C √*
Recommendation: *It is recommended that the vaccine be administered before the onset of immunosuppression, particularly if with rituximab and in periods of remission or low disease activity, to prevent the use of immunosuppressants from diminishing the vaccine response.*	
Recommendation*: The recommended vaccination schedule for patients with SARD is that used in the general population, and consists of a sequential strategy, starting with a dose of conjugate vaccine and continuing with another dose of polysaccharide (or non-conjugate) vaccine, a minimum of 2 months later.*	
Vaccination against influenza virus	
Recommendation: *In patients with SLE, vaccination against influenza virus, with the AH1N1, AH3N2 strains and influenza B virus vaccine, preferably with adjuvant, is recommended.*	*B C C*
Recommendation: *In patients with a SARD other than SLE, the above recommendation is suggested. Although there is no direct evidence, it is considered that this group of patients has enough similarities with SLE patients to extend the recommendation.*	
Recommendation: *In SARD patients, a second booster dose 3–4 weeks after the first dose is suggested in the following circumstances:*	
Use of immunosuppressive drugs	
Treatment with rituximab in the previous 3 months.	

GR: Grade of recommendation (Appendix B Annexe); SARD: Systemic Autoimmune Rheumatic Diseases; SLE: Systemic Lupus Erythematosus.

and vaccination against HPV, *S. pneumoniae* and influenza virus (Table 1).

Prophylactic agents

Trimethoprim-sulfamethoxazole as prophylaxis against PCJ

What is the efficacy or effectiveness and safety of trimethoprim-sulfamethoxazole as prophylaxis against PCJ in SARD patients treated with GC or other immunosuppressive drugs?

Recommendation: PCJ prophylaxis with trimethoprim-sulfamethoxazole is recommended in SARD patients treated continuously with GC (≥20 mg/day). No minimum duration of GC treatment beyond which prophylaxis is indicated can be established (grade B recommendation).

Recommendation: irrespective of immunosuppressive therapy, in any patient with sustained CD4+ T-cell counts below 200/mm^3, prophylaxis with trimethoprim-sulfamethoxazole is also recommended (grade √ recommendation).

Recommendation: The trimethoprim-sulfamethoxazole dose of 400 mg/80 mg/day is recommended, as it is the best documented regimen in terms of safety and efficacy for PCJ prophylaxis in patients with SARD (grade C recommendation).

Recommendation: Folic acid supplementation is recommended in trimethoprim-sulfamethoxazole treatments that last longer than one month (grade √ recommendation).

PCJ pneumonia is a frequent opportunistic infection in immunocompromised patients.[46] It can cause respiratory failure and, in severe cases, death in both HIV and non-HIV patients. However, in the former group, anti-retroviral treatment and frequent use of PCJ prophylaxis has considerably reduced the rate of PCJ infection and mortality over the years.[47,48] The incidence of PCJ infection in SARD patients is generally considered to be very low.[49] However, there are insufficient data to reliably establish which patients are most at risk of developing this infection, although it is well established that GC at moderate-high doses constitute a clear independent risk factor.[50–52] Although a greater predisposition to PCJ infection has been described in patients with certain SARD, the studies are of limited quality, as they are retrospective and have confounding factors, such as combined immunosuppression and treatment time. On the other hand, multiple studies have shown that the course of the infection is poorer in immunosuppressed non-HIV patients, such as those with SARD, and that IS treatment contributes significantly to the risk of infection.[48,53,54] However, according to the results of a study conducted in the USA, the percentage is suboptimal of rheumatologists prescribing PCJ prophylaxis in at-risk situations, and up to 30% of respondents admitted to never prescribing PCJ prophylaxis.[55]

Although from the SR conducted for this recommendation, we can conclude that the intervention reduces the risk of PCJ pneumonia, no randomised clinical trial (RCT) was found that compared cotrimoxazole prophylaxis (TMT/SMX) vs. placebo. A case-control study, adjusting for a propensity score, showed that chemoprophylaxis was effective in reducing not only the incidence of PCJ pneumonia but also mortality (HR 0.08 [95% CI .0006–.71]) (*level of evidence 2+*).[56]

Regarding the dose of TMP/SMX used for chemoprophylaxis of PCJ, a RCT evaluated the efficacy of TMP-SMX at below the standard dose of 400 mg/80 mg daily and concluded that a daily dose of 200 mg/40 mg was equally effective as prophylaxis, with a lower rate of mild-moderate adverse events (AE) and a lower discontinuation rate[57] (*level of evidence 1+*). A retrospective study suggests that the d̈ose-escalationr̈egimen (initiating treatment at 10% of the 400 mg/80 mg dose of TMP-SMX and increasing it on successive days until reaching 100%) may be equally effective but with a lower discontinuation rate[58] (*level of evidence 3*). Other studies suggest that prophylactic regimens of two or three times a week could also be effective and result in fewer discontinuations and AE,[50,59] although the elevated risk of bias in these studies means we should exercise caution in basing a recommendation on them (*level of evidence 1-3*). To address this issue, further trials would be needed to compare the daily regimen with those of a less frequent weekly regimen at the same dose. Given the above, as there were no 200 mg/40 mg presentations in our setting, the drafting group would tend to recommend the 400/80 mg daily dose. However, in case of non-severe toxicity, lower dose TMP/SMX regimens could be used.

One study found a higher rate of AE in patients with SLE and mixed connective tissue disease (MCTD)[60] (*level of evidence 3*). The results of one of the studies reviewed suggested that the higher the dose of GC, the higher the likelihood of benefiting from PCJ prophylaxis, in terms of a better Number Needed to Treat/Number Needed to Harm ratio (NNT/NNH)[56] (*level of evidence 2+*).

In the different studies that have evaluated the safety of TMP-SMX, the most frequent AE are elevated transaminases, skin rash, thrombocytopenia, fever,[58,60] tachycardia and electrolyte disturbances.[51,56,57,59,61] The most serious AE are acute renal failure, thrombocytopenia, and Stevens-Johnson syndrome.[56–59,61]

No data were found to conclude the best time to initiate prophylaxis in patients with SARD. Extrapolating expert data and recommendations from other groups of immunocompromised patients, it is suggested that prophylaxis should start at a CD4 count of < 200/mm.[3,62,63] Regarding the duration of prophylaxis, ideally it should be maintained as long as the patient is considered at risk, i.e., when they are on high doses of prednisone or their CD4 is >200 mm,[3] but there are no studies that specifically assess this.

Finally, in patients with intolerance and/or allergy to TMP-SMX, the drafting group suggests considering other treatment regimens, extrapolating recommendations set out in consensus guidelines for other groups of immunocompromised patients. In short, these would be aerosolized pentamidine at a dose of 300 mg every four weeks, dapsone 100 mg/day or atovaquone 1500 mg/day, all of which are available in Spain.[30,49,64]

Full information on the results of the evidence review is available on the SER website (www.ser.es).

Primary and secondary prophylactic measures against hepatitis B virus

What is the efficacy or effectiveness and safety of primary and secondary prophylactic measures against HBV in patients with SARD?

Recommendation: In patients with SLE or Behçet's disease (BD), vaccination against hepatitis B virus with 3 doses of recombinant vaccine (20 μg of purified hepatitis B surface antigen [HBsAg]) in the inactive or low-activity phase and without immunosuppressive therapy is recommended (grade D recommendation).

Recommendation: In patients with other SARD, it is suggested that the above recommendations be applied. Although there is no direct evidence, this group of patients is considered to have enough similarities with SLE to extrapolate the recommendation (grade √ recommendation).

Recommendation: in all patients with SARD who are immunosuppressed (due to previous or current treatment), it is suggested that vaccination schedules with four doses and/or higher antigen load (40 μg of purified HBsAg) be considered (grade √ recommendation).

Recommendation: it is recommended that the vaccination response to hepatitis B should be checked upon completion of the

Table 2
Risk of HBV reactivation according to immunosuppressive therapy.

High risk (>10%)	Medium risk (1%–10%)	Low risk (<1%)
Anti-CD20 therapies	Other biological therapies (anti TNF)	Methotrexate
High doses of GC (≥20 mg/day for more than 4 weeks)	Moderate doses of GC (10–20 mg/day)	Azathioprine

GC: glucocorticoids; TNF: tumoral necrosis factor.

prescribed regimen, by determining levels of antibodies against surface antigen (anti-HBsAg), one month after vaccination (grade √ recommendation).

Recommendation: In all SARD patients with chronic HBV infection and who are to undergo immunosuppressive treatment, biological therapy (especially anti-CD20) or treatment with GC (prednisone or equivalent ≥ 20 mg/day for 4 weeks), concomitant treatment with antivirals, preferably entecavir .5 mg/day, is recommended due to the high rate of resistance to lamivudine, to prevent reactivation of HBV infection (grade recommendation: √).

HBV hepatitis B is one of the most prevalent infections worldwide, and therefore the World Health Organisation has been recommending universal vaccination for years.[65] Patients with SARD are in an immunosuppressive state, intrinsic to the disease and/or secondary to the treatments used, particularly RTX,[66] which could interfere with the efficacy of the HBV vaccine or facilitate HBV reactivation. Furthermore, there have been several reported cases of SARD attributed to the HBV vaccination.[67]

Primary prophylaxis: vaccination against HBV

Scant evidence was found, only two studies evaluated vaccination against HBV, one in patients with inactive SLE and one with BD. Both showed acceptable immunogenicity of the recombinant vaccine (>90%), using the standard schedule (three doses of 20 μg HBsAg)[68,69] (*level of evidence 3, 2-*).

Vaccination was not associated with reactivation of SLE or doses of prednisone or other IS, compared to the year prior to vaccination[68] (*level of evidence 3*). The same was true for BD, where only mild AE were observed, such as local injection site reactions[69] (*level of evidence 2-*).

In immunosuppressed SARD patients, the experts suggest considering vaccination schedules with four doses and/or with higher antigen load, as the immune response is presumed to be impaired in these individuals. Here it should be noted that in other immunocompromised patients, such as kidney transplantation recipients, the use of vaccines with a higher antigenic load has been shown to increase seroconversion rates.[29,70] It is recommended to verify the level of protective antibodies achieved.[29,70–72]

Secondary prophylaxis: use of antivirals

Some studies have shown a risk of HBV hepatitis reactivation in SARD patients receiving IS or prednisone treatment at doses > 5 mg/day, one with a fatal outcome[32,73–75] (*level of evidence 2, 3*).

Several low-quality studies, either small series or case reports, report a possible protective effect of lamivudine against HBV reactivation in SARD[76–81] (*level of evidence 3*).

In a series of 17 cases with HBsAg-positive HBV-associated cryoglobulinaemic vasculitis, none of the 7 patients treated with nucleotide analogue antivirals (entecavir, adefovir or lamivudine) had disease progression and viral DNA was undetectable[82] (*level of evidence 3*). Cases have also been reported of patients with SARD and HBV infection, treated with RTX or infliximab, whose viral load has remained stable, with no signs of progression of the infection, using antivirals.[83,84]

The drafting group concludes that initiation of secondary antiviral prophylaxis should be considered in all SARD patients on IS regimens who are at high and moderate risk, and those at low risk should be monitored.[85,86] Patients with SARD on IS treatment should be considered at risk of HBV reactivation in the presence of chronic or past infection (anti-HBc positive, with or without HBsAg positive). In addition to factors of the host and the virus, the type, degree, and duration of immunosuppression should be considered as a key risk factor for reactivation of infection[85,87] (Table 2). The level of risk for other IS not included in Table 2, such as mycophenolate mofetil (MMF), tacrolimus or cyclosporine, is unknown.

Full information on the results of the evidence review is available on the SER website (www.ser.es).

Vaccination against the human papillomavirus

What is the efficacy or effectiveness and safety of vaccination against the human papillomavirus in SARD patients?

Recommendation: The HPV vaccination recommendations for the general population should be followed in all patients with SARD, i.e.:

1 Universal vaccination is recommended for girls, ideally at 12 years of age (grade D recommendation).
2 In older patients with cervical excisional treatment and/or warts syndrome, hypogammaglobulinaemia, infections and myelokathexis syndrome (WHIM), and in patients under 26 years of age in prostitution, with HIV infection, and men who have sex with men (grade D recommendation).

Recommendation: In older patients with SARD, especially SLE, who are not included in the above groups, the decision to vaccinate should be individualised, considering prior risk of exposure to papillomavirus and future contact with the virus (grade √ recommendation).

Recommendation: Vaccination is recommended before the onset of immunosuppression and in periods of remission or low disease activity to avoid the potential effect of IS on response to the vaccine (grade C recommendation).

The risk of HPV infection is increased in patients with SARD, especially patients with SLE.[9,88,89] Accordingly, the prevalence of pre-invasive cervical lesions and cervical cancer increases consistently in patients with SLE,[90–95] and a higher prevalence of infection with oncogenic HPV genotypes has been found in some studies.[96,97] Although the same may occur in pSS,[98] there is insufficient data available for this or other diseases in the group to make this assertion.[99]

The studies identified evaluated the tetravalent vaccine (strains 6, 11, 16 and 18) against HPV only in patients with SLE. Also of note is that most of the patients in whom the vaccine was tested had low disease activity or remission of SLE.

Table 3
Seroconversion after vaccination against HPV.

Genotype VPH	Mok 2013[100]; 2018[101] (LE 2+) n = 100; population 100% China; mean age: 25.8 years % SCV (% of persistence at 5 years)	Dhar 2017[102] (LE 2+) n = 34; 79% Afro-American population; mean age: 38 years	Soybilgic 2013[163] (LE 2-) n = 20 mean age: 20.5 years
6	82% (89%)	100%	≥94%
11	89% (84%)	100%	≥94%
16	95% (94%)	100%	≥94%
18	75% (96%)	100%	≥94%

HPV: human papillomavirus; LE: level of evidence; SCV: seroconversion.

Immunogenicity after vaccination

In terms of immunogenicity, the seroconversion rate ranged from 75% to 100%, according to the study and vaccine serotype evaluated (Table 3):

Mok et al. also evaluated the persistence of protective antibodies five years after administering the vaccine, which ranged from 84% to 96%. A significant association was also found between seroreversion and cumulative doses of prednisone, MMF and tacrolimus[100,101] (*level of evidence 2+)*.

A 100% seroconversion rate was observed in a phase I clinical trial in mostly African American patients with inactive SLE at elevated risk of HPV infection. However, this trial only included patients with prednisone doses < 15 mg/day or equivalent and without IS[102] (*level of evidence 1+*). Unlike in the healthy individuals, no anamnestic vaccine response was observed in these patients. It is possible that the immune system dysfunction intrinsic to this disease plays a role in this. The authors conclude, therefore, that it is not useful to request HPV antibodies before administering the vaccine to patients with SLE[103] (*level of evidence 2+*).

Safety of vaccination

Regarding vaccine safety, the evidence indicates that AE are mild in most cases, and injection site reactions are relatively common (5%–62%)[101,102] (*level of evidence 2+,1+*). On the other hand, in a prospective, case-control study, the incidence of AE in SLE was like that of the general population[100] (*level of evidence 2+*). Regarding the possible increased risk of deep vein thrombosis, suggested based on isolated cases, the evidence published to date does not appear to support this risk[102] (*level of evidence 2+*).

Regarding disease activity, the systemic lupus erythematosus activity index (SLEDAI) was similar before and after vaccination in all the studies reviewed, with no difference in the number of flares compared to non-vaccinated subjects.[103] No serological changes or thrombosis were observed,[100–102] although these studies were mostly conducted in patients with mild activity or in remission. Interestingly, Mok et al. in their five-year study found a higher incidence of flares in patients who experienced seroreversion associated with the use of methylprednisolone[101] (*level of evidence 2+*). Finally, isolated case reports indicate the possibility of severe disease flares following vaccination[104,105] *(level of evidence 3*).

Full information on the results of the evidence review is available on the SER website (www.ser.es).

This vaccine is currently included in the Spanish vaccination schedule for the general female population,[106] in addition to being considered for people of both sexes with certain high-risk diseases or risky sexual behaviour.[106,107] Although the nonavalent vaccine extends protection against the strains of HPV that cause cervical cancer,[108,109] there is no evidence available on the efficacy and safety of this vaccine in SARD or data that would allow specific recommendations to be issued on its use in patients already vaccinated with the tetravalent vaccine.

Vaccination against S. pneumoniae

What is the efficacy of vaccination against *S. pneumoniae* in SARD patients?

Recommendation: Vaccination against *S. pneumoniae* is recommended for all SARD patients, because, although it confers slightly lower immunogenicity compared to healthy individuals (especially in patients with SLE), it is sufficiently effective and safe (grade B recommendation).

Recommendation: It is recommended that the vaccine be administered before the onset of immunosuppression, particularly if with RTX and in periods of remission or low disease activity, to prevent the use of immunosuppressants from diminishing the vaccine response (grade C recommendation).

Recommendation: The recommended vaccination schedule for patients with SARD is that used in the general population, and consists of a sequential strategy, starting with a dose of conjugate vaccine and continuing with another dose of polysaccharide (or non-conjugate) vaccine, a minimum of 2 months late (grade √ recommendation).

Invasive pneumococcal infection rates are higher in SARD patients.[8,110,111] Fourteen studies (two SR, four clinical trials, seven observational studies and one case), addressing both immunogenicity and safety of vaccination, were identified. Interestingly, most of the studies evaluated either the conjugate or polysaccharide vaccine in isolation and only three evaluated sequential combined vaccine strategies.

Patients with SLE

Efficacy of the vaccine

Several SR with meta-analyses of controlled and observational studies, which evaluated both the unconjugated (polysaccharide) 23-valent (PPV23) and the conjugated 7-valent and 13-valent (PCV13 and PCV7) vaccines, found no significant differences between SLE patients and healthy controls in immunogenic response[112,113] (*level of evidence 2++*). Two studies used the sequential vaccination strategy (conjugate followed by non-conjugate), one PCV13 followed by PPV23 and the other (one RCT) PPV23 alone vs. PCV7 followed by PPV23, concluding that the sequential schedule was not superior to the single vaccine in terms of immunogenicity and persistence. Despite the heterogeneity of the studies, their results indicate that the pneumococcal vaccine is generally immunogenic, although a proportion of patients may sero-revert in the long term[113] (*level of evidence 2+*).

Predictors of response to the vaccine

Different studies reported a lower immunogenic response in patients < 18 years or > 60 years and in those treated with IS. We can conclude from the results of these studies that it is advisable to vaccinate individuals with SLE preferably before starting treatment with IS[113] (*level of evidence 2-*). However, in the case of belimumab,

an RCT reported that treatment with this biological agent did not affect the response to the 23-valent vaccine[114] (*level of evidence 1+*).

In terms of safety, an SR by Adawi et al. reported no serious AE after pneumococcal vaccines, conjugated or non-conjugated. Neither did they find differences in flares of clinical or serological activity compared to the controls[113] (*level of evidence 2+*).

Patients with other diseases

Both PPV23 and PCV13 appear effective and safe in patients with pSS[115] (*level of evidence 1+*) with a possible poorer response in those treated with methotrexate (MTX)[116] *(level of evidence 2+*). Pneumococcal vaccines are also immunogenic in SS, although at least one study suggests decreased efficacy in patients treated with disease-modifying drugs (DMARDs)[117,118] (*level of evidence 2-, 2+*). In patients with anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis, the pneumococcal vaccine may not be effective if administered during remission induction periods, suggesting that high-intensity immunosuppression reduces its immunogenicity[119,120] (*level of evidence 2+*). In the maintenance phase, a study with a more heterogeneous group of systemic vasculitis also found a lower response to vaccination in patients undergoing IS, particularly with RTX[121] (*level of evidence 2+*). In patients with ANCA vasculitis and positive serology for cytomegalovirus (CMV), an RCT showed that the use of valacyclovir for six months, with the aim of suppressing CMV reactivation, increased the efficacy of PCV13[122] (*level of evidence 1+*). A retrospective study found a reduction in all-cause mortality in patients with ANCA vasculitis who had responded to pneumococcal vaccination, although other confounding factors, unrelated to the vaccination itself, could also explain this interesting result[121] (*level of evidence 2+*). Regarding safety, the vaccine has been found to be safe and well tolerated in patients with systemic vasculitis,[29,120] with no increase in the recurrence rate of vaccine-related vasculitis[121] (*level of evidence 2+*). In patients with BD, cases of local and/or febrile, non-severe, self-limiting inflammatory response, interpreted as a possible disproportionate activation of the inflammasome, consistent with the pathogenesis of BD itself, have been reported[123,124] (*level of evidence 3*).

Full information on the results of the evidence review is available on the SER website (www.ser.es).

Vaccination against the influenza virus

What is the efficacy or effectiveness and safety of vaccination against the influenza virus in SARD patients?

Recommendation: In patients with SLE, vaccination against influenza virus, with the AH1N1, AH3N2 strains and influenza B virus vaccine, preferably with adjuvant, is recommended (grade B recommendation).

Recommendation: In patients with a SARD other than SLE, the above recommendation is suggested. Although there is no direct evidence, it is considered that this group of individuals has sufficient similarities to those with SLE to extend the recommendation (grade C recommendation).

Recommendation: In SARD patients, a second booster dose three to four weeks after the first is suggested in the following circumstances (grade C recommendation):

- Use of IS drugs
- Treatment with RTX within the previous three months.

Patients with SARD, especially when undergoing IS therapy, are at increased risk of developing viral infections, which can sometimes become complicated and life-threatening. Vaccination is the principal measure to prevent infections such as influenza. However, influenza vaccination of patients with SARD may result in reduced production of protective antibodies against the virus or reactivation of SARD.[125–127]

Efficacy/effectiveness of influenza virus vaccination in SARD

Several meta-analyses have concluded[27,112,128] that the immunogenicity of influenza vaccination in SLE is generally adequate compared to healthy controls, although it depends on the virus strain, with a lower response for the H1N1 strain (*level of evidence 2++*). Other prospective studies in SLE patients showed the same trend[129,130] (*level of evidence 1+, 2+*), one of them also showed a booster effect after the second inoculation[130] (*level of evidence 2+*). Another study comparing vaccinated SLE patients with historical unvaccinated controls showed a significant difference in the ratio of antibody titres in favour of the vaccinated patients (n = 19, GMC: 141.05 vs. n = 11, GMC: 8.89, $P = .018$)[131] (*level of evidence 2+*). Finally, the pre-post study by Launay et al. reported a significant increase in antibody titres for all three strains after vaccination[132] (*level of evidence 2+*).

Regarding clinical outcome measures in SLE patients, at least one study showed a lower rate of influenza at six months post-vaccination (5% vs. 55% in non-vaccinated patients; $P < .01$), and, interestingly, a lower rate of other viral infections[131] (*level of evidence 2+*). Chang et al., using an administrative database, found that influenza vaccination was associated with a lower likelihood of hospitalisation, admission to the intensive care unit, bacteraemia, or septicaemia and death[133] (*level of evidence 2++*).

In patients with other SARD (SS, pSS, MCTD or IM), in general, no significant differences were found with respect to healthy controls in the immunogenicity of the influenza vaccine, or in seroprotection or seroconversion rates, which are reported to be similar or slightly lower in some cases in the different studies reviewed[134–141] (*level of evidence 2+*). The same is true for ANCA-associated vasculitis, although with a higher level of evidence, based on the results of two RCTs and one non-randomised study[142–144] (*level of evidence 1+, 2+*). Other studies in patients with SARD considered as a collective have shown seroprotection, seroconversion and sufficient GMC to meet the criteria of the Committee for Medicinal Products for Human Use (CHMP), although their levels were lower than those of the healthy controls.[129,145–147] Similarly, an open prospective study comparing the immunogenicity of the adjuvated influenza A/09/H1N1 vaccine in patients with SARD observed significantly lower seroconversion and seroprotection rates in the patient group. However, these levels equalised after a second inoculation of the vaccine[126] (*level of evidence 2+*).

Predictive factors of non-response to vaccination against the influenza virus

In patients with SLE, a meta-analysis and several of the studies reviewed suggest that IS treatment reduces the response to the influenza vaccine, this includes GC and the IS themselves (azathioprine [AZA], MMF, MTX and cyclophosphamide [CPM])[128,130,131] (*level of evidence 2+*). Likewise, several studies indicate that SLE patients treated with prednisone doses ≥10 mg/day or ≥.15 mg/kg/day have a lower rate of seroconversion[130,131,146] (*level of evidence 2+*). Although hydroxychloroquine does not seem to influence the efficacy of the vaccine[128] (*level of evidence 2+*), one study has suggested that the immunogenicity of the AH1N1/2009 vaccine in patients with prednisone at doses >20 mg with or without IS could be reinstated by antimalarials[148] (*level of evidence 2+*). Regarding belimumab treatment, a quasi-experimental study concluded that it did not affect the immune response to influenza vaccine[149] (*level of evidence 2+*).

Regarding SLE activity, several studies relate the level of disease activity to failure of seroconversion to influenza vaccine[130,131,146] (*level of evidence 2+*).

A meta-analysis indicates that the absence of adjuvant in the AH1N1 vaccine is associated with a lower rate of seroconversion and seroprotection when compared to adjuvanted vaccine[128] (*level of evidence 2+*).

Several studies on other SARD (SS, pSS, IM or MCTD) have failed to demonstrate that IS are a predictive factor of lower response to influenza vaccine[134,137,139–141] (*level of evidence 2+*). The same is true for patients with vasculitis, although with a higher level of evidence based on two RCTs and one non-randomised study[142–144] (*level of evidence 1+, 2+*). However, studies that have included patients with different rheumatic diseases, including SARD, observed that immunogenicity was significantly reduced by treatment with MTX, leflunomide or other IS (AZA, MMF and CPM)[126] (*level of evidence 2+*). In a clinical trial, Kostianovsky et al. found that biological therapy (RTX, etanercept, adalimumab and infliximab) was associated with a marked decrease in seroconversion rate, seroprotection and GMC[129] (*level of evidence 1+*). Adler et al. showed that patients with lower immune response to influenza vaccine compared to healthy controls were those receiving MTX, RTX or abatacept (P = .045)[145] (*level of evidence 2+*). In terms of disease characteristics, Litinsky et al. reported that patients with SS and diffuse interstitial lung disease had a lower response to the vaccine compared to those without the latter disease[135] (*level of evidence 2-*). In patients with IM, higher aldolase levels may be associated with a higher frequency of seroconversion failure[140] (*level of evidence 2+*).

Safety of influenza virus vaccination

In general, a very low frequency of serious AE in patients with SLE receiving influenza vaccines is found in the different studies. In a previously mentioned meta-analysis and other additional studies, no increased incidence of AE was found in SLE patients compared to healthy controls[27,128,131,149] (*level of evidence 2+*). Regarding a possible increase in disease activity, in the SR and meta-analysis by Pugès et al. the vaccine did not alter the SLEDAI[112] (*level of evidence 2++*). One study also found no significant difference in anti-DNA antibody titres or other autoantibodies.[150] In contrast, another study concluded that influenza vaccine can induce or increase anti-cardiolipin antibody titres, although not clinically significantly[151] (*level of evidence 2+*).

In studies conducted in patients with other SARD (SS, pSS, IM or MCTD), no differences were found in the percentages of AE compared to healthy controls[134–141] (*level of evidence 2+/2-*). Nor was there any significant clinical worsening of any of the abovementioned SARD after vaccination. As with SLE, two studies in pSS found an increase in certain proinflammatory cytokines (interferon, interleukin [IL]4 or IL17) and autoantibodies (anti-Ro and anti-La), none of which were associated with clinical worsening[137,138] (*level of evidence 2+*). In studies in patients with ANCA vasculitis, influenza vaccination has been shown to be safe, both in terms of adverse effects and disease activity, as estimated with the Birmingham Vasculitis Activity Score (BVAS)[142,144,152] (*level of evidence 1+, 2+*). An interesting observation in a cohort of 230 patients with ANCA-associated vasculitis was that the disease relapse rate per 100 patients was lower in subjects that were influenza vaccinated than in unvaccinated subjects (3.4% vs. 6.3%)[152] (*level of evidence 2+*).

Full information on the results obtained from the evidence review is available on the SER website (www.ser.es).

The drafting group considers that the results of the different studies are mostly consistent in terms of the efficacy/effectiveness of the influenza vaccine in SARD patients. It is important to note that although the degree of immunogenicity achieved in some cases, such as in SLE patients for certain strains, is often lower than in healthy individuals, it is still adequate. However, in certain patient profiles (e.g., active SLE, undergoing IS treatment or with daily doses of prednisone >10 mg, or other SARD on IS treatment), efficacy appears to be lower.

Discussion

Recommendations for infection prevention in SARD have been made in this document, based on SR of the available evidence, with a broader scope than that conducted by the EULAR experts in their update of vaccination recommendations[29] for a specific SARD subgroup. Where insufficient evidence was available, the SR were supplemented by the consensus opinion of the expert panel. To our knowledge, these are the first infection prevention recommendations specifically developed for SARD. They also include mentions of vaccines and chemoprophylaxis not covered in the PICO questions and general infection prevention measures, which should be part of the standard of infection risk management in all immunocompromised patients.

We can conclude overall that the vaccines studied are reasonably safe and effective in SARD patients, although their immunogenicity is not always at a level like that of the general population. For some of the vaccines assessed in SARD, we observed a negative influence of IS treatment, this is particularly reported in patients with SLE receiving influenza vaccine.[128] It is important to note that most of the studies that have not demonstrated a negative effect of IS on the immunogenicity of vaccines lack sufficient statistical power.

The vaccination booster strategy, using a second dose of influenza vaccine or more doses against HBV, to boost response, is a novel recommendation in SARD, which seeks to circumvent a possible suboptimal response due to IS treatment or high disease activity at the time of vaccination. This strategy is used successfully in other situations of compromised immunity, such as solid organ transplantation.[153]

Regarding chemoprophylaxis, only prevention of PCJ pneumonia was considered. Although the panel acknowledges that the incidence of this infection is low in SARD patients,[154] given its high mortality,[155–157] even higher than that observed in patients with HIV,[54] and the effectiveness and relative safety of TMT/SMX found in the SR, its use is recommended in at-risk subgroups. There is a cost-effectiveness analysis that would support its use, with favourable results, in patients with vasculitis.[158]

In addition to those contained in the body of evidence, developed from the PICO questions, it is relevant to highlight other potential advantages of chemoprophylaxis with TMT/SMX, such as the prevention of other serious respiratory infections, other than PCJ pneumonia, in patients with systemic vasculitis treated with RTX.[159]

Another potential beneficial effect of vaccination, linked to a reduction in infectious events, is its contribution to the control of SARD activity, as infections are known triggers of disease flares in these patients. This effect has been little studied and has only been described with influenza vaccine in SLE or ANCA-associated vasculitis.[152]

Among the limitations of these recommendations, we should first highlight their limited spectrum, as they do not include all infections for which preventive measures are available. In this regard, the opinion of the expert group was not to include recommendations for infections where changes are expected in the short term, such as varicella zoster virus (VZV).

Secondly, for improvements to vaccines, such as the nonavalent HPV vaccine (HPV-9), which broadens the antigenic spectrum above that of the previous tetravalent vaccine (HPV-4), it would be desirable to have specific safety data for SARD. There is no evidence on whether or not it is advisable to revaccinate with HPV-9 to extend protection to patients already vaccinated with HPV-4. It

may be reasonable to do so only if there are risk factors for the development of cervical cancer, or if, despite being vaccinated, the patient becomes infected with HPV. Studies are needed to assess whether this practice is safe and cost-effective in patients with SARD.

Thirdly, the information on safety and efficacy of the vaccines covered in the recommendations refers to patients in remission or low disease activity and therefore with low doses of GC, or maintenance or no immunosuppression as the most common scenario. Given the stimulation of immunity intrinsic to the vaccination process, there is a hypothetical possibility that the vaccines could trigger flares of SARD activity. However, the SR of the evidence suggest that, at least in remission or low disease activity situations, the vaccines reviewed do not significantly increase SARD activity. The data in this regard are particularly robust for SLE, but less so for the other SARD, where although consistent with those described in SLE, they are insufficient.

Fourthly, there is a limitation regarding the target population for certain vaccines, such as the HPV vaccine, which has been studied primarily in females. As there may be sex differences in immunogenicity,[160–162] these results are not directly applicable to men.

Finally, limited information was found in the SR to support these recommendations on the most relevant clinical outcomes, such as infectious event, hospitalisation, or mortality.

Conclusions

We present the first official SER document of recommendations for the prevention of infections in patients with SARD. These recommendations were made using a validated methodology, an SR of the scientific literature and expert consensus techniques. The recommendations can be directly applied to the Spanish healthcare system, as all the vaccines and chemoprophylactic agents included are available in Spain.

The SR of the evidence indicates that the vaccines and the chemoprophylaxis covered in these recommendations are reasonably safe and effective in SARD. It has been observed that some vaccines do not achieve the same level of immunogenicity as the general population, which seems to be related to IS treatment, but not exclusively. To avoid the risk of discontinuing therapy in patients with SARD, a booster strategy with a second dose has been recommended for some vaccines, such as influenza, given its satisfactory results in other immunosuppressed patient populations.

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Appendix A. Supplementary data

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References

1. Falagas ME, Manta KG, Betsi GI, Pappas G. Infection-related morbidity and mortality in patients with connective tissue diseases: a systematic review. Clin Rheumatol. 2007;26:663–70.
2. Lee YH, Choi SJ, Ji JD, Song GG. Overall and cause-specific mortality in systemic lupus erythematosus: an updated meta-analysis. Lupus. 2016;25:727–34.
3. Alarcón GS. Infections in systemic connective tissue diseases: systemic lupus erythematosus, scleroderma, and polymyositis/dermatomyositis. Infect Dis Clin North Am. 2006;20:849–75.
4. Garen T, Lerang K, Hoffmann-Vold AM, Andersson H, Midtvedt Ø, Brunborg C, et al. Mortality and causes of death across the systemic connective tissue diseases and the primary systemic vasculitides. Rheumatology (Oxford, England). 2019;58:313–20.
5. 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.
6. Kang I, Park SH. Infectious complications in SLE after immunosuppressive therapies. Curr Opin Rheumatol. 2003;15:528–34.
7. Ross SC, Densen P. Complement deficiency states and infection: epidemiology, pathogenesis and consequences of neisserial and other infections in an immune deficiency. Medicine. 1984;63:243–73.
8. Rúa-Figueroa I, Nóvoa J, García-Laorden MI, Erausquin C, García-Bello M, Rodríguez de Castro F, 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.

9. García-Carrasco M, Mendoza-Pinto C, Rojas-Villarraga A, Molano-González N, Vallejo-Ruiz V, Munguía-Realpozo P, et al. Prevalence of cervical HPV infection in women with systemic lupus erythematosus: a systematic review and meta-analysis. Autoimmun Rev. 2019;18:184–91.
10. Rúa-Figueroa I, Fernández Castro M, Andreu JL, Sanchez-Piedra C, Martínez-Taboada V, Olivé A, et al. Comorbidities in patients with primary Sjögren's syndrome and systemic lupus erythematosus: a comparative registries-based study. Arthritis Care Res (Hoboken). 2017;69:38–45.
11. Leandro MJ. Infections related to biologics: agents targeting B cells. Infect Dis Clin North Am. 2020;34:161–78.
12. Her M, Kavanaugh A. Alterations in immune function with biologic therapies for autoimmune disease. J Allergy Clin Immunol. 2016;137:19–27.
13. Furer V, Rondaan C, Heijstek M, van Assen S, Bijl M, Agmon-Levin N, et al. 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. RMD Open. 2019;5:e001041.
14. Bouza E, Moya JG, Muñoz P. Infections in systemic lupus erythematosus and rheumatoid arthritis. Infect Dis Clin North Am. 2001;15:335–61.
15. Sui M, Wu R, Hu X, Zhang H, Jiang J, Yang Y, et al. Low prevalence of hepatitis B virus infection in patients with autoimmune diseases in a Chinese patient population. J Viral Hepat. 2014;21:925–9.
16. Zhao J, Qiu M, Li M, Lu C, Gu J. Low prevalence of hepatitis B virus infection in patients with systemic lupus erythematosus in southern China. Rheumatol Int. 2010;30:1565–70.
17. Rúa-Figueroa Í, López-Longo J, Galindo-Izquierdo M, Calvo-Alén J, Del Campo V, Olivé-Marqués A, 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.
18. Juárez M, Misischia R, Alarcón GS. Infections in systemic connective tissue diseases: systemic lupus erythematosus, scleroderma, and polymyositis/dermatomyositis. Rheum Dis Clin North Am. 2003;29:163–84.
19. Cuchacovich R, Gedalia A. Pathophysiology and clinical spectrum of infections in systemic lupus erythematosus. Rheum Dis Clin North Am. 2009;35:75–93.
20. Hsu CY, Ko CH, Wang JL, Hsu TC, Lin CY. Comparing the burdens of opportunistic infections among patients with systemic rheumatic diseases: a nationally representative cohort study. Arthritis Res Ther. 2019;21:211.
21. Shigayeva A, Rudnick W, Green K, Chen DK, Demczuk W, Gold WL, et al. Invasive pneumococcal disease among immunocompromised persons: implications for vaccination programs. Clin Infect Dis. 2016;62:139–47.
22. Fiore AE, Uyeki TM, Broder K, Finelli L, Euler GL, Singleton JA, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Recomm Rep. 2010;59(Rr-8):1–62.
23. Mohammad AJ, Segelmark M, Smith R, Englund M, Nilsson J, Westman K, et al. Severe infection in antineutrophil cytoplasmic antibody-associated vasculitis. J Rheumatol. 2017;44:1468–75.
24. Torres-Aguilar H, Sosa-Luis SA, Aguilar-Ruiz SR. Infections as triggers of flares in systemic autoimmune diseases: novel innate immunity mechanisms. Curr Opin Rheumatol. 2019;31:525–31.
25. Torres-Ruiz J, Barrera-Vargas A, Ortiz-Hernández R, Alcocer-Varela J, Ponce-de-León A, Gómez-Martín D. Microbiological and immunological profile of patients with severe lupus flares related to bloodstream infections: a retrospective cohort study. Lupus. 2018;27:312–8.
26. Doria A, Canova M, Tonon M, Zen M, Rampudda E, Bassi N, et al. Infections as triggers and complications of systemic lupus erythematosus. Autoimmun Rev. 2008;8:24–8.
27. Liao Z, Tang H, Xu X, Liang Y, Xiong Y, Ni J. Immunogenicity and safety of influenza vaccination in systemic lupus erythematosus patients compared with healthy controls: a meta-analysis. PLoS One. 2016;11(2):e0147856.
28. Rondaan C, Furer V, Heijstek MW, Agmon-Levin N, Bijl M, Breedveld FC, et al. Efficacy, immunogenicity and safety of vaccination in adult patients with autoimmune inflammatory rheumatic diseases: a systematic literature review for the 2019 update of EULAR recommendations. RMD Open. 2019;5:e001035.
29. Furer V, Rondaan C, Heijstek MW, Agmon-Levin N, van Assen S, Bijl M, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2020;79:39–52.
30. Braga BP, Prieto-González S, Hernández-Rodríguez J. *Pneumocystis jirovecii* pneumonia prophylaxis in immunocompromised patients with systemic autoimmune diseases. Med Clin. 2019;152:502–7.
31. Tadros S, Teichtahl AJ, Ciciriello S, Wicks IP. *Pneumocystis jirovecii* pneumonia in systemic autoimmune rheumatic disease: a case-control study. Semin Arthritis Rheum. 2017;46:804–9.
32. Lin WT, Chen YM, Chen DY, Lan JL, Chang CS, Yeh HZ, et al. Increased risk of hepatitis B virus reactivation in systemic lupus erythematosus patients receiving immunosuppressants: a retrospective cohort study. Lupus. 2018;27:66–75.
33. Sign S. 50: A guideline developers' handbook. SIGN; 2011.
34. Mir Viladrich I, Daudén Tello E, Solano-López G, López Longo FJ, Taxonera Samso C, Sánchez Martínez P, et al. Consensus document on prevention and treatment of tuberculosis in patients for biological treatment. Arch Bronconeumol. 2016;52:36–45.
35. Sterling TR, Njie G, Zenner D, Cohn DL, Reves R, Ahmed A, et al. Guidelines for the treatment of latent tuberculosis infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020. MMWR Recomm Rep. 2020;69:1–11.
36. Pascual-Ramos V, Hernández-Hernández C, Soto-Rojas AE, Celis-Aguilar E, Sánchez-Guerrero J. Association between dental caries and pneumonia in patients with systemic lupus erythematosus. J Rheumatol. 2006;33:1996–2002.
37. Waszczuk K, Waszczuk E, Mulak A, Szenborn L, Paradowski L. A' cocoon immunization strategy' among patients with inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2015;27:249–53.
38. Naranjo A, Bilbao A, Erausquin C, Ojeda S, Francisco FM, Rúa-Figueroa I, et al. Results of a specific smoking cessation program for patients with arthritis in a rheumatology clinic. Rheumatol Int. 2014;34:93–9.
39. Serre J, François C, der Haegen MCV, Papo T, Goulenok T, Sacre K. Nurse-led vaccination program dramatically improves pneumococcal vaccination coverage among patients with autoimmune inflammatory disorders. Eur J Intern Med. 2017;43:e43–5.
40. Ruiz-Irastorza G, Olivares N, Ruiz-Arruza I, Martinez-Berriotxoa A, Egurbide MV, Aguirre C. Predictors of major infections in systemic lupus erythematosus. Arthritis Res Ther. 2009;11:R109.
41. Pimentel-Quiroz VR, Ugarte-Gil MF, Harvey GB, Wojdyla D, Pons-Estel GJ, Quintana R, et al. Factors predictive of serious infections over time in systemic lupus erythematosus patients: data from a multi-ethnic, multi-national, Latin American lupus cohort. Lupus. 2019;28:1101–10.
42. Teh CL, Wan SA, Ling GR. Severe infections in systemic lupus erythematosus: disease pattern and predictors of infection-related mortality. Clin Rheumatol. 2018;37:2081–6.
43. Yeo KJ, Chen HH, Chen YM, Lin CH, Chen DY, Lai CM, 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.
44. Gómez Reino J, Loza E, Andreu JL, Balsa A, Batlle E, Cañete JD, et al. [Consensus statement of the Spanish Society of Rheumatology on risk management of biologic therapy in rheumatic patients]. Reumatol Clin. 2011;7:284–98.
45. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58:309–18.
46. Thomas CF Jr, Limper AH. Pneumocystis pneumonia. N Engl J Med. 2004;350:2487–98.
47. Morris A, Lundgren JD, Masur H, Walzer PD, Hanson DL, Frederick T, et al. Current epidemiology of Pneumocystis pneumonia. Emerg Infect Dis. 2004;10:1713–20.
48. Mansharamani NG, Garland R, Delaney D, Koziel H. Management and outcome patterns for adult *Pneumocystis carinii* pneumonia, 1985 to 1995: comparison of HIV-associated cases to other immunocompromised states. Chest. 2000;118:704–11.
49. Wolfe RM, Peacock JE Jr. Pneumocystis Pneumonia and the rheumatologist: which patients are at risk and how can PCP be prevented? Curr Rheumatol Rep. 2017;19:35.
50. Ogawa J, Harigai M, Nagasaka K, Nakamura T, Miyasaka N. Prediction of and prophylaxis against Pneumocystis pneumonia in patients with connective tissue diseases undergoing medium- or high-dose corticosteroid therapy. Mod Rheumatol. 2005;15:91–6.
51. Vananuvat P, Suwannalai P, Sungkanuparph S, Limsuwan T, Ngamjanyaporn P, Janwityanujit S. Primary prophylaxis for *Pneumocystis jirovecii* pneumonia in patients with connective tissue diseases. Semin Arthritis Rheum. 2011;41:497–502.
52. Chew LC, Maceda-Galang LM, Tan YK, Chakraborty B, Thumboo J. *Pneumocystis jirovecii* pneumonia in patients with autoimmune disease on high-dose glucocorticoid. J Clin Rheumatol. 2015;21:72–5.
53. Yale SH, Limper AH. *Pneumocystis carinii* pneumonia in patients without acquired immunodeficiency syndrome: associated illness and prior corticosteroid therapy. Mayo Clin Proc. 1996;71:5–13.
54. Sepkowitz KA. Opportunistic infections in patients with and patients without Acquired Immunodeficiency Syndrome. Clin Infect Dis. 2002;34:1098–107.
55. Cettomai D, Gelber AC, Christopher-Stine L. A survey of rheumatologists' practice for prescribing pneumocystis prophylaxis. J Rheumatol. 2010;37:792–9.
56. Park JW, Curtis JR, Moon J, Song YW, Kim S, Lee EB. Prophylactic effect of trimethoprim-sulfamethoxazole for pneumocystis pneumonia in patients with rheumatic diseases exposed to prolonged high-dose glucocorticoids. Ann Rheum Dis. 2018;77:644–9.
57. Utsunomiya M, Dobashi H, Odani T, Saito K, Yokogawa N, Nagasaka K, et al. Optimal regimens of sulfamethoxazole-trimethoprim for chemoprophylaxis of Pneumocystis pneumonia in patients with systemic rheumatic diseases: results from a non-blinded, randomized controlled trial. Arthritis Res Ther. 2017;19:7.
58. Takenaka K, Komiya Y, Ota M, Yamazaki H, Nagasaka K. A dose-escalation regimen of trimethoprim-sulfamethoxazole is tolerable for prophylaxis against *Pneumocystis jiroveci* pneumonia in rheumatic diseases. Mod Rheumatol. 2013;23:752–8.
59. Yamamoto T, Hasunuma T, Takagi K, Akimoto K, Shikano K, Kaburaki M, et al. A feasibility study assessing tolerability of daily versus twice weekly trimethoprim-sulfamethoxazole regimen for prophylaxis against Pneumocystis pneumonia in patients with systemic autoimmune diseases on glucocorticoid therapy. Jpn J Clin Pharmacol Ther. 2014;45:89–92.

60. Maezawa R, Kurasawa K, Arai S, Okada H, Owada T, Fukuda T. Positivity for anti-RNP antibody is a risk factor for adverse effects caused by trimethoprim-sulfamethoxazole, a prophylactic agent for *P. jiroveci* pneumonia, in patients with connective tissue diseases. Mod Rheumatol. 2013;23:62–70.
61. Schmajuk G, Jafri K, Evans M, Shiboski S, Gianfrancesco M, Izadi Z, et al. *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis patterns among patients with rheumatic diseases receiving high-risk immunosuppressant drugs. Semin Arthritis Rheum. 2019;48:1087–92.
62. Stern A, Green H, Paul M, Vidal L, Leibovici L. Prophylaxis for Pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients. Cochrane Database Syst Rev. 2014;2014:Cd005590.
63. Suryaprasad A, Stone JH. When is it safe to stop *Pneumocystis jiroveci* pneumonia prophylaxis? Insights from three cases complicating autoimmune diseases. Arthritis Rheum. 2008;59:1034–9.
64. Cooley L, Dendle C, Wolf J, Teh BW, Chen SC, Boutlis C, et al. Consensus guidelines for diagnosis, prophylaxis and management of *Pneumocystis jirovecii* pneumonia in patients with haematological and solid malignancies, 2014. Intern Med J. 2014;44(12b):1350–63.
65. World Health Organization. Hepatitis B vaccines. Weekly epidemiological record. Relevé epidémiologique hebdomadaire. 2004;79:255–63.
66. Ogawa E, Wei MT, Nguyen MH. Hepatitis B virus reactivation potentiated by biologics. Infect Dis Clin North Am. 2020;34:341–58.
67. Maillefert JF, Sibilia J, Toussirot E, Vignon E, Eschard JP, Lorcerie B, et al. Rheumatic disorders developed after hepatitis B vaccination. Rheumatology (Oxford, England). 1999;38:978–83.
68. Kuruma KA, Borba EF, Lopes MH, de Carvalho JF, Bonfá E. Safety and efficacy of hepatitis B vaccine in systemic lupus erythematosus. Lupus. 2007;16:350–4.
69. Erkek E, Ayaslioglu E, Erkek AB, Kurtipek GS, Bagci Y. Response to vaccination against hepatitis B in patients with Behcet's disease. J Gastroenterol Hepatol. 2005;20:1508–11.
70. Ong KY, Wong HY, Khee GY. What is the hepatitis B vaccination regimen in chronic kidney disease? Clevel Clin J Med. 2018;85:32–4.
71. Epidemiology and Prevention of Vaccine-Preventable Diseases. 13th ed. Washington D.C.: Public Health Foundation; 2015.
72. Schillie S, Vellozzi C, Reingold A, Harris A, Haber P, Ward JW, et al. Prevention of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep. 2018;67:1–31.
73. Kato M, Atsumi T, Kurita T, Odani T, Fujieda Y, Otomo K, et al. Hepatitis B virus reactivation by immunosuppressive therapy in patients with autoimmune diseases: risk analysis in Hepatitis B surface antigen-negative cases. J Rheumatol. 2011;38:2209–14.
74. Xuan D, Yu Y, Shao L, Wang J, Zhang W, Zou H. Hepatitis reactivation in patients with rheumatic diseases after immunosuppressive therapy—a report of long-term follow-up of serial cases and literature review. Clin Rheumatol. 2014;33:577–86.
75. Koffas A, Dolman GE, Kennedy PT. Hepatitis B virus reactivation in patients treated with immunosuppressive drugs: a practical guide for clinicians. Clin Med. 2018;18:212–8.
76. Tse KC, Yung S, Tang C, Yip TP, Chan TM. Management of hepatitis B reactivation in patients with lupus nephritis. Rheumatol Int. 2009;29:1273–7.
77. Ghorbani Ga, Alishiri Gh, Pour Hk. High hepatitis B virus load in a patient with severe polyarthritis nodosa. Hepat Mon. 2010;10:306–9.
78. Zingarelli S, Airò P, Frassi M, Bazzani C, Scarsi M, Puoti M. Prophylaxis and therapy of HBV infection in 20 patients treated with disease modifying antirheumatic drugs or with biological agents for rheumatic diseases. Reumatismo. 2008;60:22–7.
79. Lau CF, Hui PK, Chan WM, Fung TT, Tung YM, Loo CK, et al. Hepatitis B associated fulminant polyarteritis nodosa: successful treatment with pulse cyclophosphamide, prednisolone and lamivudine following emergency surgery. Eur J Gastroenterol Hepatol. 2002;14:563–6.
80. Marinchev L, Antonov K, Peytcheva V, Kolarov Z. Outcome in a patient with systemic lupus erythematosus and concurrent chronic hepatitis B infection. BMJ Case Rep. 2010;2010:bcr0920092273.
81. Shibolet O, Ilan Y, Gillis S, Hubert A, Shouval D, Safadi R. Lamivudine therapy for prevention of immunosuppressive-induced hepatitis B virus reactivation in hepatitis B surface antigen carriers. Blood. 2002;100:391–6.
82. Mazzaro C, Dal Maso L, Urraro T, Mauro E, Castelnovo L, Casarin P, et al. Hepatitis B virus related cryoglobulinemic vasculitis: A multicentre open label study from the Gruppo Italiano di Studio delle Crioglobulinemie — GISC. Dig Liver Dis. 2016;48:780–4.
83. Abdulaziz S, Halabi H, Omair MA, Attar S, Alghamdi A, Shabrawishi M, et al. Biological therapy in arthritis patients with hepatitis B or C infection: a multicenter retrospective case series. Eur J Rheumatol. 2017;4:194–9.
84. Jalili A, Kinaciyan T, Barisani T, Peck-Radosavljevic M, Stingl G, Geusau A, et al. Successful treatment of refractory Behçet's disease with the TNF-alpha blocker infliximab. Iran J Immunol. 2009;6:55–8.
85. Pattullo V. Prevention of Hepatitis B reactivation in the setting of immunosuppression. Clin Mol Hepatol. 2016;22:219–37.
86. Gonzalez SA, Perrillo RP. Hepatitis B virus reactivation in the setting of cancer chemotherapy and other immunosuppressive drug therapy. Clin Infect Dis. 2016;62 Suppl 4:S306–13.
87. Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology. 2015;148:215–9.
88. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet (London, England). 2007;370:59–67.
89. Bosch FX, Manos MM, Muñoz N, Sherman M, Jansen AM, Peto J, et al. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group. J Natl Cancer Inst. 1995;87:796–802.
90. Santana IU, Gomes Ado N, Lyrio LD, Rios Grassi MF, Santiago MB. Systemic lupus erythematosus, human papillomavirus infection, cervical pre-malignant and malignant lesions: a systematic review. Clin Rheumatol. 2011;30:665–72.
91. Ladouceur A, Clarke AE, Ramsey-Goldman R, Bernatsky S. Malignancies in systemic lupus erythematosus: an update. Curr Opin Rheumatol. 2019;31:678–81.
92. Song L, Wang Y, Zhang J, Song N, Xu X, Lu Y. The risks of cancer development in systemic lupus erythematosus (SLE) patients: a systematic review and meta-analysis. Arthritis Res Ther. 2018;20:270.
93. Liu H, Ding Q, Yang K, Zhang T, Li G, Wu G. Meta-analysis of systemic lupus erythematosus and the risk of cervical neoplasia. Rheumatology (Oxford, England). 2011;50:343–8.
94. Zard E, Arnaud L, Mathian A, Chakhtoura Z, Hie M, Touraine P, et al. Increased risk of high grade cervical squamous intraepithelial lesions in systemic lupus erythematosus: A meta-analysis of the literature. Autoimmun Rev. 2014;13:730–5.
95. Kim SC, Glynn RJ, Giovannucci E, Hernández-Díaz S, Liu J, Feldman S, et al. Risk of high-grade cervical dysplasia and cervical cancer in women with systemic inflammatory diseases: a population-based cohort study. Ann Rheum Dis. 2015;74:1360–7.
96. Nath R, Mant C, Luxton J, Hughes G, Raju KS, Shepherd P, et al. High risk of human papillomavirus type 16 infections and of development of cervical squamous intraepithelial lesions in systemic lupus erythematosus patients. Arthritis Rheum. 2007;57:619–25.
97. Lee YH, Choe JY, Park SH, Park YW, Lee SS, Kang YM, et al. Prevalence of human papilloma virus infections and cervical cytological abnormalities among Korean women with systemic lupus erythematosus. J Korean Med Sci. 2010;25:1431–7.
98. Cirpan T, Guliyeva A, Onder G, Terek MC, Ozsaran A, Kabasakal Y, et al. Comparison of human papillomavirus testing and cervical cytology with colposcopic examination and biopsy in cervical cancer screening in a cohort of patients with Sjogren's syndrome. Eur J Gynaecol Oncol. 2007;28:302–6.
99. Raposo A, Tani C, Costa J, Mosca M. Human papillomavirus infection and cervical lesions in rheumatic diseases: a systematic review. Acta Reumatol Port. 2016;41:184–90.
100. Mok CC, Ho LY, Fong LS, To CH. Immunogenicity and safety of a quadrivalent human papillomavirus vaccine in patients with systemic lupus erythematosus: a case-control study. Ann Rheum Dis. 2013;72:659–64.
101. Mok CC, Ho LY, To CH. Long-term immunogenicity of a quadrivalent human papillomavirus vaccine in systemic lupus erythematosus. Vaccine. 2018;36:3301–7.
102. Dhar JP, Essenmacher L, Dhar R, Magee A, Ager J, Sokol RJ. The safety and immunogenicity of Quadrivalent HPV (qHPV) vaccine in systemic lupus erythematosus. Vaccine. 2017;35:2642–6.
103. Dhar JP, Essenmacher L, Dhar R, Magee A, Ager J, Sokol RJ. The effect of history of abnormal pap smear or preceding HPV infection on the humoral immune response to Quadrivalent Human Papilloma virus (qHPV) vaccine in women with systemic lupus erythematosus. Human Vaccin Immunother. 2018;14(9):2318–22.
104. Soldevilla HF, Briones SF, Navarra SV. Systemic lupus erythematosus following HPV immunization or infection? Lupus. 2012;21:158–61.
105. Anaya JM, Reyes B, Perdomo-Arciniegas AM, Camacho-Rodríguez B, Rojas-Villarraga A. Autoimmune/auto-inflammatory syndrome induced by adjuvants (ASIA) after quadrivalent human papillomavirus vaccination in Colombians: a call for personalised medicine. Clin Exp Rheumatol. 2015;33:545–8.
106. Moreno-Pérez D, Álvarez García FJ, Álvarez Aldeán J, Cilleruelo Ortega MJ, Garcés Sánchez M, García Sánchez N, et al. [Immunisation schedule of the Spanish Association of Paediatrics: 2019 recommendations]. An Pediatr (Barc). 2019;90:56.
107. Grupo de trabajo vacunación en población adulta y grupos de riesgo de laPonencia de Programa y Registro de Vacunaciones. Vacunación en grupos deriesgo de todas las edades y en determinadas situaciones. Comisión de Salud Pública del Consejo Interterritorial del Sistema Nacional de Salud. Ministeriode Sanidad, Consumo y Bienestar Social, julio 2018.
108. Stankiewicz Karita HC, Hauge K, Magaret A, Mao C, Schouten J, Grieco V, et al. Effect of human papillomavirus vaccine to interrupt recurrence of vulvar and anal neoplasia (VIVA): a trial protocol. JAMA Netw Open. 2019;2:e190819.
109. Mahumud RA, Alam K, Dunn J, Gow J. The cost-effectiveness of controlling cervical cancer using a new 9-valent human papillomavirus vaccine among school-aged girls in Australia. PLoS One. 2019;14:e0223658.
110. Shea KM, Edelsberg J, Weycker D, Farkouh RA, Strutton DR, Pelton SI. Rates of pneumococcal disease in adults with chronic medical conditions. Open Forum Infect Dis. 2014;1:ofu024.
111. 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 Community Health. 2012;66:1177–81.
112. Pugès M, Biscay P, Barnetche T, Truchetet M, Richez C, Seneschal J, et al. Immunogenicity and impact on disease activity of influenza and

pneumococcal vaccines in systemic lupus erythematosus: a systematic literature review and meta-analysis. Rheumatology (Oxford, England). 2016;55:1664–72.
113. Adawi M, Bragazzi NL, McGonagle D, Watad S, Mahroum N, Damiani G, et al. Immunogenicity, safety and tolerability of anti-pneumococcal vaccination in systemic lupus erythematosus patients: an evidence-informed and PRISMA compliant systematic review and meta-analysis. Autoimmun Rev. 2019;18:73–92.
114. Chatham W, Chadha A, Fettiplace J, Kleoudis C, Bass D, Roth D, et al. A randomized, open-label study to investigate the effect of belimumab on pneumococcal vaccination in patients with active, autoantibody-positive systemic lupus erythematosus. Lupus. 2017;26:1483–90.
115. Karsh J, Pavlidis N, Schiffman G, Moutsopoulos HM. Immunization of patients with Sjögren's syndrome with pneumococcal polysaccharide vaccine: a randomized trial. Arthritis Rheum. 1980;23:1294–8.
116. Nived P, Saxne T, Geborek P, Mandl T, Skattum L, Kapetanovic MC. Antibody response to 13-valent pneumococcal conjugate vaccine is not impaired in patients with rheumatoid arthritis or primary Sjögren's syndrome without disease modifying treatment. BMC Rheumatol. 2018;2:12.
117. Mercado U, Acosta H, Diaz-Molina R. Antibody response to pneumococcal polysaccharide vaccine in systemic sclerosis. J Rheumatol. 2009;36:1549–50.
118. Hesselstrand R, Nagel J, Saxne T, Geborek P, Skattum L, Kapetanovic MC. Immunogenicity and safety of pneumococcal vaccination in patients with systemic sclerosis. Rheumatology (Oxford, England). 2018;57:625–30.
119. Groh M, Puéchal X, Terrier B, Le Jeunne C, Batteux F, Launay O. Failure of pneumococcal immunization during remission induction treatment of ANCA-associated vasculitis: The Pneumovas Pilot 1 study. Joint Bone Spine. 2017;84:643–4.
120. Nived P, Nagel J, Saxne T, Geborek P, Jönsson G, Skattum L, et al. Immune response to pneumococcal conjugate vaccine in patients with systemic vasculitis receiving standard of care therapy. Vaccine. 2017;35:3639–46.
121. David Morgan M, Richter A, Al-Ali S, Flint J, Yiannakis C, Drayson M, et al. Association of low B cell count and IgG levels with infection, and poor vaccine response with all-cause mortality in an immunosuppressed vasculitis population. Arthritis Care Res. 2016;68:853–60.
122. Chanouzas D, Sagmeister M, Faustini S, Nightingale P, Richter A, Ferro CJ, et al. Subclinical reactivation of cytomegalovirus drives CD4+CD28null T-cell expansion and impaired immune response to pneumococcal vaccination in antineutrophil cytoplasmic antibody-associated vasculitis. J Infect Dis. 2019;219:234–44.
123. Hügle T, Bircher A, Walker UA. Streptococcal hypersensitivity reloaded: severe inflammatory syndrome in Behcet's disease following 23-valent polysaccharide Streptococcus pneumoniae vaccine. Rheumatology (Oxford, England). 2012;51:761–2.
124. Saeidinejad M, Kardash S, Connell L. Behcet's disease and severe inflammatory reaction to 23-valent pneumococcal polysaccharide vaccine: a case report and review of literature. Scottish Med J. 2018;63:119–21.
125. Elkayam O, Paran D, Caspi D, Litinsky I, Yaron M, Charboneau D, et al. Immunogenicity and safety of pneumococcal vaccination in patients with rheumatoid arthritis or systemic lupus erythematosus. Clin Infect Dis. 2002;34:147–53.
126. Gabay C, Bel M, Combescure C, Ribi C, Meier S, Posfay-Barbe K, et al. Impact of synthetic and biologic disease-modifying antirheumatic drugs on antibody responses to the AS03-adjuvanted pandemic influenza vaccine: a prospective, open-label, parallel-cohort, single-center study. Arthritis Rheum. 2011;63:1486–96.
127. Saad CG, Borba EF, Aikawa NE, Silva CA, Pereira RM, Calich AL, et al. Immunogenicity and safety of the 2009 non-adjuvanted influenza A/H1N1 vaccine in a large cohort of autoimmune rheumatic diseases. Ann Rheum Dis. 2011;70:1068–73.
128. Huang Y, Wang H, Wan L, Lu X, Tam WW. Is systemic lupus erythematosus associated with a declined immunogenicity and poor safety of influenza vaccination? A systematic review and meta-analysis. Medicine. 2016;95(19):e3637.
129. Kostianovsky A, Charles P, Alves JF, Goulet M, Pagnoux C, Le Guern V, et al. Immunogenicity and safety of seasonal and 2009 pandemic A/H1N1 influenza vaccines for patients with autoimmune diseases: a prospective, monocentre trial on 199 patients. Clin Exp Rheumatol. 2012;30 1 Suppl 70:S83–9.
130. Mathian A, Devilliers H, Krivine A, Costedoat-Chalumeau N, Haroche J, Huong DB, et al. Factors influencing the efficacy of two injections of a pandemic 2009 influenza A (H1N1) nonadjuvanted vaccine in systemic lupus erythematosus. Arthritis Rheum. 2011;63:3502–11.
131. Milanovic M, Stojanovich L, Djokovic A, Kontic M, Gvozdenovic E. Influenza vaccination in autoimmune rheumatic disease patients. Tohoku J Exp Med. 2013;229:29–34.
132. Launay O, Paul S, Servettaz A, Roguet G, Rozenberg F, Lucht F, et al. Control of humoral immunity and auto-immunity by the CXCR4/CXCL12 axis in lupus patients following influenza vaccine. Vaccine. 2013;31:3492–501.
133. Chang CC, Chang YS, Chen WS, Chen YH, Chen JH. Effects of annual influenza vaccination on morbidity and mortality in patients with Systemic Lupus Erythematosus: A Nationwide Cohort Study. Sci Rep. 2016;6:37817.
134. Sampaio-Barros PD, Andrade DCO, Seguro LCP, Pasoto SG, Viana VST, Ribeiro ACM, et al. Pandemic non-adjuvanted influenza A H1N1 vaccine in a cohort of patients with systemic sclerosis. Rheumatology (Oxford, England). 2018;57:1721–5.
135. Litinsky I, Balbir A, Zisman D, Mandelboim M, Mendelson E, Feld J, et al. Vaccination against influenza in patients with systemic sclerosis. Clin Exp Rheumatol. 2012;30 2 Suppl 71:S7–11.
136. Setti M, Fenoglio D, Ansaldi F, Filaci G, Bacilieri S, Sticchi L, et al. Flu vaccination with a virosomal vaccine does not affect clinical course and immunological parameters in scleroderma patients. Vaccine. 2009;27:3367–72.
137. Pasoto SG, Ribeiro AC, Viana VS, Leon EP, Bueno C, Neto ML, et al. Short and long-term effects of pandemic unadjuvanted influenza A(H1N1)pdm09 vaccine on clinical manifestations and autoantibody profile in primary Sjögren's syndrome. Vaccine. 2013;31:1793–8.
138. Brauner S, Folkersen L, Kvarnström M, Meisgen S, Petersen S, Franzén-Malmros M, et al. H1N1 vaccination in Sjögren's syndrome triggers polyclonal B cell activation and promotes autoantibody production. Ann Rheum Dis. 2017;76:1755–63.
139. Shinjo SK, de Moraes JC, Levy-Neto M, Aikawa NE, de Medeiros Ribeiro AC, Schahin Saad CG, et al. Pandemic unadjuvanted influenza A (H1N1) vaccine in dermatomyositis and polymyositis: immunogenicity independent of therapy and no harmful effect in disease. Vaccine. 2012;31:202–6.
140. Guissa VR, Pereira RM, Sallum AM, Aikawa NE, Campos LM, Silva CA, et al. Influenza A H1N1/2009 vaccine in juvenile dermatomyositis: reduced immunogenicity in patients under immunosuppressive therapy. Clin Exp Rheumatol. 2012;30:583–8.
141. Miossi R, Fuller R, Moraes JC, Ribeiro AC, Saad CG, Aikawa NE, et al. Immunogenicity of influenza H1N1 vaccination in mixed connective tissue disease: effect of disease and therapy. Clinics (Sao Paulo, Brazil). 2013;68:129–34.
142. Jeffs LS, Peh CA, Jose MD, Lange K, Hurtado PR. Randomized trial investigating the safety and efficacy of influenza vaccination in patients with antineutrophil cytoplasmic antibody-associated vasculitis. Nephrology (Carlton, Vic). 2015;20:343–51.
143. Holvast A, Stegeman CA, Benne CA, Huckriede A, Wilschut JC, Palache AM, et al. Wegener's granulomatosis patients show an adequate antibody response to influenza vaccination. Ann Rheum Dis. 2009;68:873–8.
144. Holvast A, de Haan A, van Assen S, Stegeman CA, Huitema MG, Huckriede A, et al. Cell-mediated immune responses to influenza vaccination in Wegener's granulomatosis. Ann Rheum Dis. 2010;69:924–7.
145. Adler S, Krivine A, Weix J, Rozenberg F, Launay O, Huesler J, et al. Protective effect of A/H1N1 vaccination in immune-mediated disease—a prospectively controlled vaccination study. Rheumatology (Oxford, England). 2012;51:695–700.
146. Crowe SR, Merrill JT, Vista ES, Dedeke AB, Thompson DM, Stewart S, et al. Influenza vaccination responses in human systemic lupus erythematosus: impact of clinical and demographic features. Arthritis Rheum. 2011;63:2396–406.
147. Muller RB, Maier R, Hoschler K, Zambon M, Ludewig B, Herrmann M, et al. Efficient boosting of the antiviral T cell response in B cell-depleted patients with autoimmune rheumatic diseases following influenza vaccination. Clin Exp Rheumatol. 2013;31:723–30.
148. Borba EF, Saad CG, Pasoto SG, Calich AL, Aikawa NE, Ribeiro AC, et al. Influenza A/H1N1 vaccination of patients with SLE: can antimalarial drugs restore diminished response under immunosuppressive therapy? Rheumatology (Oxford, England). 2012;51:1061–9.
149. Chatham WW, Wallace DJ, Stohl W, Latinis KM, Manzi S, McCune WJ, et al. Effect of belimumab on vaccine antigen antibodies to influenza, pneumococcal, and tetanus vaccines in patients with systemic lupus erythematosus in the BLISS-76 trial. J Rheumatol. 2012;39:1632–40.
150. Urowitz MB, Anton A, Ibanez D, Gladman DD. Autoantibody response to adjuvant and nonadjuvant H1N1 vaccination in systemic lupus erythematosus. Arthritis Care Res. 2011;63:1517–20.
151. Vista ES, Crowe SR, Thompson LF, Air GM, Robertson JM, Guthridge JM, et al. Influenza vaccination can induce new-onset anticardiolipins but not β2-glycoprotein-I antibodies among patients with systemic lupus erythematosus. Lupus. 2012;21:168–74.
152. Stassen PM, Sanders JS, Kallenberg CG, Stegeman CA. Influenza vaccination does not result in an increase in relapses in patients with ANCA-associated vasculitis. Nephrol Dial Transplant. 2008;23:654–8.
153. Cordero E, Roca-Oporto C, Bulnes-Ramos A, Aydillo T, Gavaldà J, Moreno A, et al. Two doses of inactivated influenza vaccine improve immune response in solid organ transplant recipients: results of TRANSGRIPE 1-2, a randomized controlled clinical trial. Clin Infect Dis. 2017;64:829–38.
154. Ognibene FP, Shelhamer JH, Hoffman GS, Kerr GS, Reda D, Fauci AS, et al. *Pneumocystis carinii* pneumonia: a major complication of immunosuppressive therapy in patients with Wegener's granulomatosis. Am J Respir Crit Care Med. 1995;151 3 Pt 1:795–9.
155. Li J, Huang XM, Fang WG, Zeng XJ. *Pneumocystis carinii* pneumonia in patients with connective tissue disease. J Clin Rheumatol. 2006;12:114–7.
156. Weng CT, Liu MF, Weng MY, Lee NY, Wang MC, Lin WC, et al. *Pneumocystis jirovecii* pneumonia in systemic lupus erythematosus from southern Taiwan. J Clin Rheumatol. 2013;19:252–8.
157. Mecoli CA, Saylor D, Gelber AC, Christopher-Stine L. *Pneumocystis jiroveci* pneumonia in rheumatic disease: a 20-year single-centre experience. Clin Exp Rheumatol. 2017;35:671–3.
158. Chung JB, Armstrong K, Schwartz JS, Albert D. Cost-effectiveness of prophylaxis against *Pneumocystis carinii* pneumonia in patients with Wegner's granulomatosis undergoing immunosuppressive therapy. Arthritis Rheum. 2000;43:1841–8.

159. Kronbichler A, Kerschbaum J, Gopaluni S, Tieu J, Alberici F, Jones RB, et al. Trimethoprim-sulfamethoxazole prophylaxis prevents severe/life-threatening infections following rituximab in antineutrophil cytoplasm antibody-associated vasculitis. Ann Rheum Dis. 2018;77:1440–7.
160. Fischinger S, Boudreau CM, Butler AL, Streeck H, Alter G. Sex differences in vaccine-induced humoral immunity. Semin Immunopathol. 2019;41:239–49.
161. Hillman RJ, Giuliano AR, Palefsky JM, Goldstone S, Moreira ED Jr, Vardas E, et al. Immunogenicity of the quadrivalent human papillomavirus (type 6/11/16/18) vaccine in males 16 to 26 years old. Clin Vaccine Immunol. 2012;19(2):261–7.
162. Giuliano AR, Isaacs-Soriano K, Torres BN, Abrahamsen M, Ingles DJ, Sirak BA, et al. Immunogenicity and safety of Gardasil among mid-adult aged men (27–45 years)—the MAM study. Vaccine. 2015;33:5640–6.
163. Soybilgic A, Onel KB, Utset T, Alexander K, Wagner-Weiner L. Safety and immunogenicity of the quadrivalent HPV vaccine in female Systemic Lupus Erythematosus patients aged 12 to 26 years. Pediatr Rheumatol Online J. 2013;11:29.