Recommendations for Vaccination in Adult Patients with Systemic Inflammatory Rheumatic Diseases from the Portuguese Society of Rheumatology

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ABSTRACT

Background: Serious infections are a major cause of morbidity and mortality in systemic inflammatory rheumatic disease (SIRD) patients. Although vaccination may prevent numerous infections, vaccination uptake rates are low in this group of patients.

Objectives: To develop evidence-based recommendations for vaccination in SIRD patients.

Methods: We searched MEDLINE (until 31 October 2014) and EMBASE (until 14 December 2014) databases, as well as the ACR and EULAR congress abstracts (2011-2014). Patients with any systemic inflammatory rheumatic disease were included and all vaccines were considered. Any safety and efficacy outcomes were admitted. Search results were submitted to title and abstract selection, followed by detailed review of suitable studies. Data were subsequently pooled according to the type of vaccine and the SIRD considered. Results were presented and discussed by a multidisciplinary panel and systematic literature review (SLR)--derived recommendations were voted according to the Delphi method. The level of agreement among rheumatologists was assessed using an online survey.

Results: Eight general and seven vaccine-specific recommendations were formulated. Briefly, immunization status should routinely be assessed in all SIRD patients. The National Vaccination Program should be followed and some additional vaccines are recommended. To maximize the efficacy of vaccination, vaccines should preferably be administered 4 weeks before starting immunosuppression or, if possible when disease activity is controlled. Non-live vaccines are safe in SIRD, including immunosuppressed patients. The safety of live attenuated vaccines in immunosuppressed patients deserves further ascertainment, but might be considered in particular situations.

Discussion: The present recommendations combine scientific evidence with the multidisciplinary expertise of our taskforce panel and attained desirable agreement among Portuguese rheumatologists. Vaccination recommendations need to be updated on a regular basis, as more scientific data regarding vaccination efficacy and safety, emergent infectious threats, new vaccines as well as new immunomodulatory therapies become available.

Keywords: Antirheumatic agents; Immunosuppressive agents; Biological products; Rheumatic diseases; Vaccination; Recommendations

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INTRODUCTION

Patients with rheumatic diseases are at higher risk for infections, which contributes to increased morbidity and mortality[1-10]. Several factors have been associated

with increased susceptibility to infections, including disease activity and medication, in particular immunosuppressants[1-10]. Effective and safe vaccination is essential for the prevention of a significant number of these infections[11,12]. However, vaccination uptake rates among rheumatic patients are remarkably low[13-19]. Over the years, several scientific societies have developed practice guidelines and/or recommendations aiming to provide guidance on the optimal use of vaccines and improve vaccination adherence among patients with rheumatic diseases[20-23]. According to these recommendations, non-live vaccines can be given safely to patients treated with immunomodulators. The major differences among guidelines concern the safe use of live attenuated vaccines, due to the scarcity of data.

We aimed to develop evidence-based recommendations for the vaccination of adult patients with systemic inflammatory rheumatic diseases (SIRD), with a particular focus on safety and efficacy of vaccination in immunosuppressed SIRD patients.

METHODS

We performed a comprehensive systematic literature review (SLR), addressing the safety and efficacy of vaccination in systemic inflammatory rheumatic diseases (SIRD). We searched MEDLINE (until 31 October 2014) and EMBASE (until 14 December 2014) databases. Additionally, we searched the abstracts of the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) congresses (2011-2014) and performed a complementary hand search. Patients (both adults and children) with any SIRD were included and all vaccines were considered. Any safety and efficacy outcomes were admitted. Studies that assessed the simultaneous administration of two or more vaccines (except commercially available combinations), reviews and single case reports were excluded.

Title and abstract selection was performed by 8 independent reviewers. The selected studies were submitted to independent detailed review (view Figure 1). Translation was requested when needed. Study and patient characteristics, the use of glucocorticoids and immunosuppressants (both synthetic and biologic), type of vaccine, as well as safety and efficacy outcomes were independently extracted into piloted forms. Data were subsequently pooled according to the type of vaccine and the SIRD considered. The quality of individual studies was appraised using an adapted checklist of 13 items[24] (Appendix 1). Risk of bias was assessed using the Cochrane Collaboration Tool[25]. Subsequently, a descriptive analysis was performed.

SLR results were presented and discussed at a national meeting (63 participants) by a multidisciplinary panel that included rheumatologists, infectious disease specialists, experts on immunization, health professionals and patients' representatives. The taskforce formulated eight general recommendations and seven vaccine-specific recommendations for adult patients with SIRD. Preliminary statements were afterwards submitted to the appraisal of the entire group and voted according to the Delphi method. A minimum concordance rate of 80% was considered necessary for the approval of each individual statement as a final recommendation. When below this level of agreement, the content and phrasing of each statement were discussed until a suitable concordance rate was attained. The agreement with the final set of recommendations was assessed using an online survey (52 participants); participants were asked to score their level of agreement with each recommendation using a 10-point quantitative scale (from 0-total disagreement to 10-total agreement).

RESULTS

We retrieved 14594 abstracts. After title and abstract selection, followed by the detailed review of the most relevant results, 123 papers were identified. We initially planned to issue recommendations for both adults and children with SIRD, but at the time of this study another working group was preparing recommendations for the pediatric population; therefore, 28 pediatric studies were additionally excluded and a final total of 95 articles concerning adults with SIRD were reviewed (Figure 1).

We obtained 65 papers on influenza vaccination[26-91], 20 on pneumococcal[92-112], 4 on viral hepatitis[113-116], 2 on varicella zoster vaccine[117-119] and 4 papers on various other vaccines (including papillomavirus[120], poliomyelitis[121], diphtheria/tetanus/pertussis (DTP)[122] and yellow fever[123] vaccines). Studies focused on different SIRD, namely rheumatoid arthritis, systemic lupus erythematosus, spondyloarthritis, psoriathic arthritis, primary systemic vasculitis, systemic sclerosis, polymyositis, Sjögren's syndrome, antiphospholipid

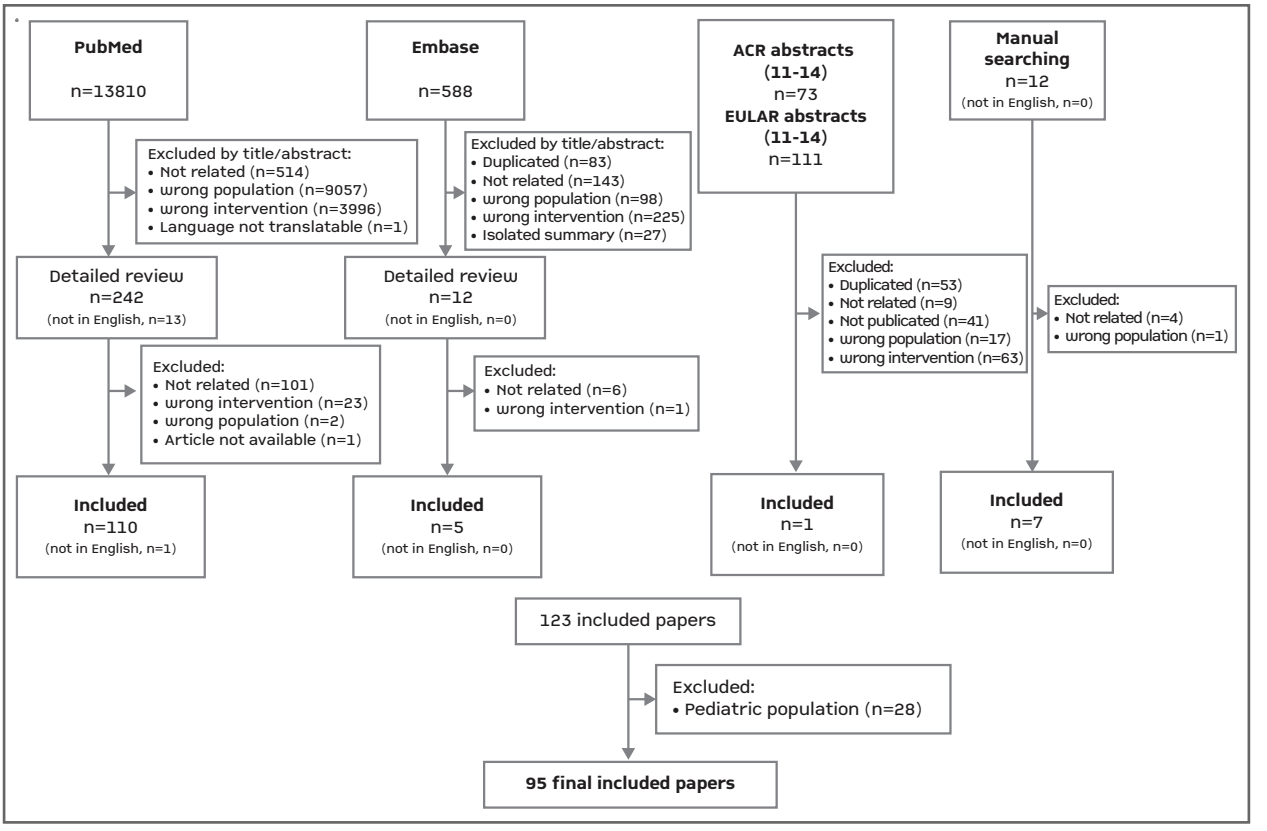

FIGURE 1. Search strategy for the systematic literature review

antibody syndrome and undifferentiated connective tissue disease. Table I summarizes the distribution of included studies according to the disease and vaccine considered.

RECOMMENDATIONS

Eight general principles and seven vaccine-specific recommendations were formulated, reaching a high level of agreement among Portuguese rheumatologists (Table II).

GENERAL PRINCIPLES

1. The initial assessment of all patients with systemic inflammatory rheumatic diseases (SIRD) should include immunization status and catch-up vaccination schedule, according to the National Vaccination Program, if necessary. Level of evidence[124] 2a; Grade of recommendation C; Agreement (mean and standard deviation (SD)): 9.4 (1.3).

Vaccination was proven to be safe and effective in the prevention of many infectious diseases[26-124]. However, particular safety and efficacy issues must be taken into consideration when vaccinating SIRD patients, especially those on immunosuppressants[30,31,36,38,93--95,98,101,102,109]. The taskforce considered that the vaccination status of all SIRD patients must ideally be assessed at the moment of diagnosis and always before starting immunosuppressive therapy.

2. Vaccines should be administered ideally at least 4 weeks before starting any immunosuppressive therapy and, when possible, disease activity should be controlled. Level of evidence 4; Grade of recommendation C; Agreement (mean (SD)): 8.5(1.9).

Early disease was considered a sensible time for vaccination, especially if live vaccines are considered. In general, vaccines are safe and effective, regardless of disease activity. A few studies included patients with active disease who were able to mount an adequate immune response and there was no consistent evidence that vaccines lead to an increased number of flares or

TABLE I. DISTRIBUTION OF THE INCLUDED STUDIES ACCORDING TO THE DISEASES AND VACCINES ASSESSED

Vaccine	RA	SLE	SpA/PsA	PSV	SSc/PM	Other
Influenza	25	23	8	10	9	7
Pneumococcus	9	9	3	–	–	1
Viral hepatitis	2	1	–	1	–	–
Varicella zoster	3	1	3	–	–	–
Papillomavirus	–	1	–	–	–	–
Polio (oral)	–	1	–	–	–	–
DTP/ Tetanus	1	1	–	–	–	–
Yellow fever	1	–	–	–	–	–

Please note that there is some overlap in the numbers because some studies included different SIRDs (≥1 patient) simultaneously. RA: Rheumatoid arthritis, SLE: systemic lupus erythematosus, SpA: spondyloarthritis, PsA: psoriathic arthritis, PSV: primary systemic vasculitis, SSc: systemic sclerosis, PM: polymyositis, JSIRD: juvenile systemic inflammatory rheumatic diseases, MMR - measles/mumps/ /rubella, DTP - diphtheria/tetanus/pertussis. Other diseases include: Sjögren's syndrome, antiphospholipid antibody syndrome, /undifferentiated connective tissue.

adverse effects[47,51,52,70,71,74,96,99,100,104,107,120,124]. An exception was lower immunogenicity of influenza vaccination in SLE patients, a trait frequently related with disease activity[49]. On the other hand, immunosuppressive therapies (conventional DMARDs, biologics and moderate to high doses of steroids) reduce the immunogenicity of non-live vaccines[27,29,38,49,51,64,69,94,95,101,106,109,123]. The use of immunosuppression was very consistently associated with lower efficacy of influenza and pneumococcal vaccines in RA, SpA and CTD[27,29,38,49,51,64,69,94,95,101,106,109]. This can reflect both a direct effect of the drugs and indirectly the effect of disease activity. Therefore, vaccines should preferably be administered to stable patients. Nonetheless, if stability cannot be achieved, it is safe to vaccinate and it should be done, as the risk of infection is likely to be increased in active SIRD[125,126].

3. Patients receiving Rituximab should ideally be vaccinated at least 4 weeks before the biological therapy is started. When this is not possible, vaccination should occur 6 months after the previous infusion (mean (SD)). Level of evidence 2a, Grade of recommendation B, Agreement: 8.8(1.4).

Rituximab is a chimeric IgG1CD20-specific monoclonal antibody that depletes peripheral blood B cells with subsequent reduction in differentiated plasma cells (responsible for immunoglobulin production). Patients receiving rituximab have an impaired response to inactivated or bacterial vaccines due to a reduction in protective antibodies[64,70,100,88,89,127,128]. This is particularly evident with pneumococcal vaccines, either conjugated or polysaccharide, where treatment with rituximab is associated with significantly lower antibody response[89,93,129]. In patients in whom vaccination is indicated, immunization should take place at least 4 weeks before drug administration. If a patient has already received rituximab, responses may be blunted at least until B cell recovery occurs, which takes between 6 to 9 months. Sometimes the ideal timing for vaccination cannot be accomplished, particularly in case of seasonal influenza, but in these situations the clinical benefit of vaccination still exists[46,88,89,129].

4. Post vaccination assessment of antibody titers is not routinely recommended except for hepatitis B. Level of evidence 5; Grade of recommendation D; Agreement (mean (SD)): 8.8(1.6).

In immunosuppressed patients, the response to hepatitis B immunization (measurement of anti-HBs titers) should be assessed 4 to 8 weeks after completion of the 3-dose schedule. A titer of anti-HBs above 10 IU/L should be considered protective. Titers of antibodies after measles, rubella, varicella, pertussis and mumps are neither reasonably specific nor sensitive. Pneumococcal, tetanus and influenza vaccines are acceptably effective in SIRD patients; therefore, we do not recommend the assessment of their post-vaccination titers in daily clinical practice.

5. Non-live vaccines can be safely administered during treatment with synthetic or biologic DMARDs. Level of evidence 1b, Grade of recommendation A; Agreement (mean (SD)): 9.3(1.0).

The efficacy and safety of several non-live vaccines

TABLE II. RECOMMENDATIONS FOR THE VACCINATION OF ADULT PATIENTS WITH SYSTEMIC INFLAMMATORY RHEUMATIC DISEASES

Recommendations	Level of evidence[124]	Grade	Agreement (0-10), mean(SD)
General			
The initial assessment of all patients with systemic inflammatory rheumatic diseases (SIRD) should include immunization status and catch-up vaccination schedule, according to the national vaccination program, if necessary.	2a	C	9.4 (1.3)
Vaccines should be administered ideally at least 4 weeks before starting any immunosuppressive therapy and, when possible, disease activity should be controlled.	4	C	8.5 (1.9)
Patients receiving rituximab should ideally be vaccinated at least 4 weeks before the biological therapy is started. When this is not possible, vaccination should occur 6 months after the previous infusion.	2a	B	8.8 (1.4)
Post vaccination assessment of antibody titers is not routinely recommended except for hepatitis B.	5	D	8.8 (1.6)
Non-live vaccines can be safely administered during treatment with synthetic or biologic DMARDs.	1b	A	9.3 (1.0)
Live attenuated vaccines may be considered for certain patients receiving immunosuppressive therapy.	4	D	7.9 (1.6)
Vaccination of close contacts should be strongly considered in certain situations, depending on patient characteristics, degree of immunosuppression and the infectious agent.	5	D	8.1 (2.0)
Patients with SIRD who wish to travel should attend a travel medicine consultation at least 6 months in advance.	2b	C	9.0 (1.6)
Specific			
Yearly anti-influenza vaccination is recommended to all patients with SIRD regardless of current therapy.	2c	B	8.7 (1.5)
Pneumococcal vaccination (PCV13 + PPSV23) is recommended for patients with iatrogenic immunosuppression, including systemic corticosteroids and synthetic or biologic DMARDs (*).	2b	B	9.0 (1.5)
The dosing schedule must take in consideration the patient's age and previous immunization.	2b	B	
All SIRD patients with negative serology for hepatitis B virus (HBsAg, AntiHBc, and AntiHBs negative) should be vaccinated.	2b	C	8.7 (1.4)
In the case of isolated AntiHBc antibody positivity and negative viral load, vaccination should be considered.	5	D	
The response to vaccination should be assessed 1-2 months after the third dose, and revaccination considered (0, 1 and 6 months) if seroprotection is not achieved.	2b	C	
Hepatitis A vaccination is recommended for SIRD patients travelling to endemic areas, preferably with 2 doses 6 months apart.	2b	B	8.9 (1.4)
Consider HPV vaccine with 3-dose series (0, 2 and 6 months) for young adults with SIRD if not vaccinated previously.	2b	C	8.6 (1.7)
Patients with SIRD should follow the recommended vaccination schedule in the national vaccine program for anti-tetanic, i.e., every 10 years.	2b	C	9.6 (1.0)
The individual assessment of the risk/benefit ratio of HZV is recommended for patients with SIRD who are 60 years of age and older.	4	D	8.7 (1.7)

(*) Systemic corticotherapy ≥20mg/day prednisolone or equivalent for ≥14 days; methotrexate > 0,4 mg/Kg/week; azathioprine > 3 mg/Kg/day; leflunomide, mycophenolate, cyclophosphamide, cyclosporine and tacrolimus. Biological therapy or DMARDs used in rheumatoid arthritis, systemic lupus erythematous, Sjögren's syndrome and inflammatory bowel disease, including anti-TNF (infliximab, etanercept, adalimumab, golimumab, certolizumab); anti-CD20 (rituximab); anti-IL6 (tocilizumab); CTLA-4-Ig (abatacept); anti-BLYS (belimumab); anti-IL12 e anti-IL23 (ustekinumab); IL-1 antagonist (anakinra/canakinumab).

in SIRD patients were assessed, namely influenza[29], pneumococcal[66], hepatitis A[115], hepatitis B[114], human papillomavirus vaccine[120] and tetanus toxoid[142]. Most studies assessed RA[51,70] and SLE[81,99] patients, with a lesser extent of patients with systemic sclerosis, spondyloarthritis and primary systemic vasculitis[29,52]. The immunosuppressants considered included glucocorticoids[87,101,110,120,127], various synthetic disease-modifying antirheumatic drugs (sDMARD)[69,101,110,120], cyclophosphamide[29,45,99,100], tumour necrosis factor (TNF) blocking agents[27,36,40,42,81-74,105], rituximab[30,39,69,88,89], tocilizumab[64,102,104], abatacept[59,60,104] and belimumab[91]. Although sufficiently powered studies are lacking, vaccination was globally safe. Most vaccine-related adverse events reported were mild local and systemic adverse events, apparently unrelated to either disease or immunosuppression. Serious adverse events were rare[94,129] and were associated neither to vaccination nor to immunosuppression[44].

The vast majority of studies support the idea that vaccination with non-live vaccines is not significantly associated with clinical or laboratorial flares comparing to healthy controls[70,81].

Thus, the taskforce considers that vaccination with non-live vaccines can be safely administered during immunosuppressant treatment, including sDMARD, cyclophosphamide, TNF blockers, rituximab, tocilizumab, abatacept and belimumab.

6. Live attenuated vaccines may be considered for certain patients receiving immunosuppressive therapy.

Level of evidence 4, Grade of recommendation D, Agreement (mean (SD)): 7.9(1.6).

Live vaccines are prepared from live microorganisms or viruses cultured under adverse conditions, leading to loss of their virulence but maintenance of their ability to induce protective and long lasting immunity. The administration of live vaccines bears the potential risk of invasive infection in immunosuppressed patients. The risk of infection is higher in live vaccines with a high potential of replication (e.g. yellow fever vaccine) rather than in vaccines with a low risk of replication (typhoid oral vaccine, varicella/herpes zoster vaccine). In most international guidelines, live vaccines are contraindicated during treatment with immunosuppressants[22,129-134]. Although sufficiently powered studies are lacking, there is growing evidence that live attenuated viral vaccines, such as live-attenuated influenza[136,136], varicella–zoster virus[118,119], MMR[140,11,142] and yellow fever virus[124] vaccines might actually be safe for immunosuppressed patients in well-defined situations.

Our taskforce considered that live attenuated vaccines may be used with caution in SIRD patients. If a live vaccine is indicated in a patient on immunosuppressive treatment, an individual assessment of the risk/benefit must be performed, which includes disease activity, medication, the replication potential of the vaccine and the risk of infection. The risk assessment by an infectious diseases or vaccination expert is encouraged.

7. Vaccination of close contacts should be strongly considered in certain situations, depending on patient characteristics, degree of immunosuppression and the infectious agent. Level of evidence 4, Grade of recommendation D, Agreement (mean (SD)): 8.1(2.0).

The aim of immunizing close contacts of SIRD patients is to counter the suboptimal immune responsiveness of immunosuppressed patients and to prevent the transmission of vaccine-preventable pathogens to these susceptible individuals[137]. Close contacts of immunosuppressed* patients, as well as health professionals participating in the care of immunocompromised[138] individuals*, should be offered routine annual immunizations with inactivated influenza vaccine in order to minimize disease spread[139]. Close contacts should also comply or catch-up with the recommended schedules for tetanus vaccination, pneumococcal, MMR and varicella zoster virus (VZV) vaccines[140,141]. Limited data are available on the risk of immunosuppressed individuals acquiring infection from a family member or close contact who receives a live vaccine[140]. Recent recommendations on primary immunodeficiency note that microorganism transmission from family contacts receiving vaccines is a rare but possible event[140]. Oral live polio vaccine is contraindicated in immunocompromised patients[142,143] and their household contacts[140]. An immunocompromised individual without previous exposure to varicella zoster virus is at minimal risk of transmission from a close-contact recently immunized for VZV, unless blisters develop at the site of administration. In this case, isolation of the patient is recommended and varicella zoster immunoglobulin could be given prophylactically[140].

(*) Systemic corticotherapy ≥20mg/day prednisolone or equivalent for ≥14 days; methotrexate > 0,4 mg/Kg/week; azathioprine > 3 mg/Kg/day; leflunomide, mycophenolate, cyclophosphamide, cyclosporine and tacrolimus. Biological

therapy or DMARDs used in rheumatoid arthritis, systemic lupus erythematous, Sjögren's syndrome and inflammatory bowel disease, including anti-TNF (infliximab, etanercept, adalimumab, golimumab, certolizumab); anti-CD20 (rituximab); anti-IL6 (tocilizumab); CTLA-4-Ig (abatacept); anti-BLYS (belimumab); anti-IL12 e anti-IL23 (ustekinumab); IL-1 antagonist (anakinra/canakinumab).

8. Patients with SIRD who wish to travel should attend a travel medicine consultation at least 6 months in advance. Level of evidence 2; Grade of recommendation C; Agreement (mean (SD)): 9.0(1.6).

Immunocompromised individuals are at greater risk of contracting disease while travelling than healthy persons, particularly in destinations where several vaccine-preventable infections are endemic. Anticipated planning is crucial to safe and successful travelling. A pre-travel consultation with a travellers' health, infectious diseases, tropical medicine or vaccination expert is encouraged, so as to assess the risk of exposure to infections and other hazards during travel and to implement adequate preventive strategies. The consultation must be performed timely because patients may require destination, transportation or accommodation adjustments, catch-up and/or additional vaccination and also disease chemoprophylaxis[131]. The taskforce considered appropriate a minimum advance of 6-months to allow time for completion of most multiple-dose vaccination schemes. Inactivated vaccines can be safely administered to patients on immunosuppression (view General Recommendation 5). These vaccines include those against viral hepatitis A and B, Japanese encephalitis, tick borne encephalitis and rabies, as well as the inactivated form of the typhoid and polio vaccines (view Specific Recommendations). Specific vaccination and chemoprophylactic strategies, including the administration of live attenuated vaccines in this context, should be based on an individual risk-benefit assessment (view General Recommendation 6).

B. VACCINE-SPECIFIC RECOMMENDATIONS

1. Influenza

Yearly anti-influenza vaccination is recommended to all patients with SIRD regardless of current therapy. Level of evidence: 2c, Grade of recommendation: B; Agreement (mean (SD)): 8.7(1.5).

Efficacy

Acute lower respiratory infections are a significant concern in SIRD patients[144-146]. Multiple cohort studies assessed the vaccine immunogenicity in different SIRD, comparing the efficacy of the vaccine in patients under different therapies or versus healthy controls. Most studies indicate preserved immunogenicity to the influenza vaccine in SIRD*.

Rheumatoid arthritis. Influenza vaccination in RA patients was proven globally effective and leads to a reduction in respiratory infections[37]. It was suggested that male gender, old age and smoking were related to worse vaccine responses[37,95,64]. Treatment with methotrexate (MTX), leflunomide and TNF inhibitors was also associated with lower efficacy, but reasonable values of seroprotection (SP) were obtained in the majority of studies (SP>60-70%)[26,36,38,40,47,51,70,73-75]. Impairment of the vaccine immunogenicity was more significant in patients on rituximab and abatacept (seroconversion (SC) 10-40%)[36,46,59,64,65,85]. Data on tocilizumab (TCZ) are scarce, but one study showed that patients under TCZ monotherapy have a better response to the vaccine in comparison with patients treated with the association TCZ+MTX[54].

Spondyloarthritis (SpA). In general, H1N1 vaccination induced a protective response in SpA patients (SP>60-70%). One sole study used the seasonal influenza vaccine, also with reasonable efficacy. There was a tendency for better responses in SpA patients when compared with RA patients. Within SpA patients, better responses were observed in Ankylosing Spondylitis (AS) versus Psoriatic Arthritis (PsA). Most studies suggest that TNF inhibitors reduce the vaccine responses. Older age (>60 years-old), smoking and methotrexate treatment were also associated with lower efficacy[27,29,52,55,64,73,74,95].

Connective tissue diseases (CTD) and primary systemic vasculitis (PSV). Influenza vaccination was less effective in SLE patients than in healthy controls. Nonetheless, in a majority of studies, seroprotection rate was close to 70%[49,52,69,71,72]. Steroid use (prednisolone in doses above 10-20mg) and treatment with other immunosuppressants (azathioprine, mycophenolate, etc.) were associated with lower efficacy[69,71,80,91]. Hydroxychloroquine might restore the immunogenicity in patients on immunosuppressants[71]. In a sub-analysis of the BLISS trial, patients on belimumab maintained the seroprotection over time likewise patients on placebo[91]. Furthermore, newly vaccinated patients during the trial had good vaccine responses independently of the treatment group. In a heterogeneous group of 16 CTD patients treated with rituximab, the seroprotection was not achieved in about half of cases[39]. Data concerning other CTDs, including PSV are considerably limited. However, data point to a similar efficacy to that observed in SLE patients[45,52,64].

Safety

Safety outcomes included all adverse events (including local and systemic effects), disease activity scores and autoantibody measurements in a variable time period after the vaccine administration.

RA. The influenza vaccine exhibited an excellent safety profile, in spite of past or present therapy. No serious adverse events were reported. Mild local reactions and flu-like symptoms were described in slightly higher frequencies of those observed in healthy population. Five studies reported elevation of disease activity after vaccine administration, but this result was contradicted in twelve other studies[22,26,28,29,46,47,50-52,54,59,60,64,65,70,72-75,77].

SpA. Safety issues were poorly described, as no studies specified the occurrence of adverse events. Vaccination does not seem to influence disease activity[27,29,36,52,55,64,73,74].

CTD and PSV. Vaccination in SLE patients is generally safe. Mild adverse events (local reaction and flu-like syndromes) occurred with variable frequency (5-41%). In all 17 studies which addressed safety issues, two serious events were reported (an acute myocardial infarction and a deep venous thrombosis), that were not considered to have a causal relationship with the vaccine. Some studies report a transitory rise in auto-antibody titers[40,43,44,49,61,63,69,71,78-80,87,90,91].Vaccination does not seem to influence disease activity[27,29,36,52,55,64,73,74].

There are conflicting results on the frequency of flares after vaccination, though eight out of twelve studies did not show an increased frequency of flares.

(*) European Guidelines propose that an efficacious influenza vaccine should confer a seroprotection (SP) rate >70% or a seroconversion (SC) rate >40% in adults between 18 and 60 years-old148.

2. PNEUMOCOCCAL

a) 23-valent Pneumococcal polysaccharide vaccine (VPP23) and 13-valent Pneumococcal conjugate vaccine (VPC13) are recommended in patients with iatrogenic immunosuppression, including systemic corticosteroids and synthetic or biological Disease--Modifying Antirheumatic Drugs (DMARDs)* Level of evidence 2b, Grade of recommendation B.

b) Schedule for pneumococcal vaccination must take into consideration patient s age and previous immunization status. Level of evidence 2b, Grade of recommendation B.

Agreement (all statements, mean (SD)): 9.0(1.5).

Indications

Streptococcus pneumoniae infection is responsible for substantial mortality and morbidity in elderly adults (aged ≥ 65 years) or with underlying chronic or immunosuppressive conditions[148-150]. Vaccination plays a crucial role in protection from infections caused by these bacteria[150]. At the moment, 2 pneumococcal vaccines are available: 23-valent polysaccharide vaccine (VPP23) and 13-valent conjugate vaccine (VPC13). VPP23 induces antibodies primarily by T-cell-independent mechanisms, therefore without development of immunological memory[151]. The levels of antibodies directed to most pneumococcal vaccine antigens remain elevated for at least 5 years and decrease progressively to prevaccination levels within 10 years. A more rapid decline may occur in immunosuppressed patients and in elderly persons[150-153]. For this reason, patients on immunosuppressants should be revaccinated with VPP23 a second time within 5 years from the first dose. However, more than one re-vaccination is not recommended since vaccination with pneumococcal polysaccharide antigens may induce hyporesponsiveness and a less robust antibody response may occur on the subsequent doses[152]. VPC13 has a conjugated protein in its formulation that is recognized by T-cells, stimulating serum antibody response and immunologic memory. Therefore, revaccination with VPC13 is not indicated. VPC13 also boosts the immunological response to VPP23, stimulates mucosal immunity and decreases nasal and oropharynx colonization[154].

Patients should be vaccinated according to the following schedule (Figure 2)[138,154,155]:

In patients **who have not been previously vaccinated**, a single dose of VPC13 should be given, followed by a dose of VPP23 at least 8 weeks later. Patients should be revaccinated with VPP23 at least 5 years from the first dose (this second those can be given either before 65 years old or after).

For individuals **who have already been vaccinated with VPP23**, a single dose of VPC13 should be given 1 or more years after the last dose of VPP23. Revaccination with VPP23 should occur 5 years after the last dose and no sooner than 8 weeks after VPC13.

Efficacy

In general, pneumococcal vaccination turned out to be as effective in patients with SIRD as in healthy controls. Regarding SLE patients, there are conflicting results, with two studies demonstrating lower efficacy[92,97] and a shorter seroprotection period (42% of SLE patients lost SP 3 years after immunizations[97]). However, treatment with methotrexate, TNF inhibitors and rituximab is associated with lower efficacy either with

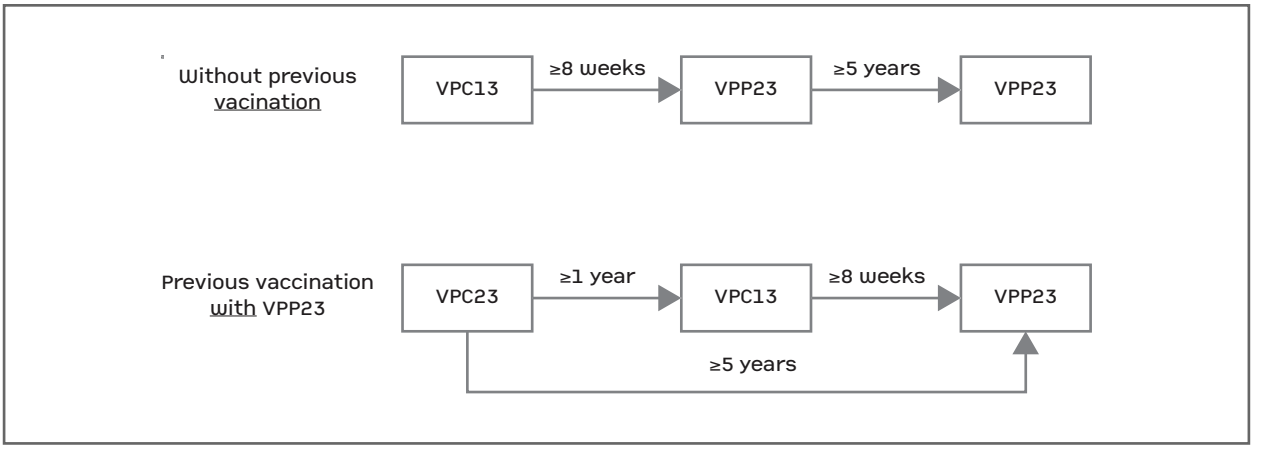

FIGURE 2. Pneumococcal vaccination schedule
Adapted from Froes F, Diniz A, Robalo Cordeiro C, Serrado M, Ramalho de Almeira A. Consensus document for the prevention of respiratory infections in adults. Sociedade Portuguesa de Pneumonologia. Rev Port de Pneumonologia. 2014;20(2):111-1114

VPP23 or VPC13, as it was demonstrated in three studies involving patients with SpA (including PsA)[94,106,110] and in seven studies in patients with RA[93,95,101,103,104,108,112]. Data on tocilizumab (TCZ) and abatacept (ABA) are scarce, with only two studies demonstrating no negative impact in seroprotection in RA patients receiving TCZ[101,104] and one study showing that ABA reduces the efficacy of VPC13 in RA patients[104]. With regard to belimumab, there is only one study available in patients with SLE, showing no immunological impairment after pneumococcal vaccination in patients receiving belimumab[91].

Safety

Several studies demonstrate that pneumococcal immunization is safe, with only one study in RA and SpA patients treated with anti-TNF reporting two serious adverse events (pneumonia and soft tissue infection)[94]. Both vaccines appear not to influence disease activity[96,99,104,107,108].

(*) Systemic corticotherapy ≥20mg/day prednisolone or equivalent for ≥14 days; methotrexate > 0,4 mg/Kg/week; azathioprine > 3 mg/Kg/day; leflunomide, mycophenolate, cyclophosphamide, cyclosporine and tacrolimus. Biological therapy or DMARDs used in rheumatoid arthritis, systemic lupus erythematous, Sjögren's syndrome and inflammatory bowel disease, including anti-TNF (infliximab, etanercept, adalimumab, golimumab, certolizumab); anti-CD20 (rituximab); anti-IL6 (tocilizumab); CTLA-4-Ig (abatacept); anti-BLYS (belimumab); anti-IL12 e anti-IL23 (ustekinumab); IL-1 antagonist (anakinra/canakinumab).

3. HEPATITIS B

a) All SIRD patients with negative serology for hepatitis B virus (HBsAg, AntiHBc, and AntiHBs negative) should be vaccinated. Level of evidence 2b; Grade of recommendation C.

b) In the case of isolated antiHBc antibody positivity and negative viral load, vaccination should be considered. Level of evidence 5; Grade of recommendation D.

c) The response to vaccination should be assessed 1-2 months after the third dose, and revaccination considered (0, 1 and 6 months) if seroprotection is not achieved. Level of evidence 2b; Grade of recommendation C. Agreement (all statements, mean (SD)): 8.7(1.4).

Indications

Universal hepatitis B (HB) vaccination is recommended for all Portuguese children and adults, according to the National Vaccination Program (PNV)[158]. This has resulted in a great decrease in HB incidence over the past two decades[159]. SIRD patients have an increased risk of liver disease due to drug toxicity (synthetic and biologic DMARDs, NSAIDs) and infectious diseases (including acute/chronic HB and reactivation of past HB due to severe immunosuppression).

Use

In order to prevent the development of a potential comorbidity that could seriously interfere with the treatment and outcome of SIRD patients, HB vaccination (3 doses: 0, 1 and 6 months) is recommended for all patients with negative serology (HBsAg, AntiHBc, and AntiHBs negative). One to two months after the third dose of the vaccine (*i.e.* 7-8 months after starting the vaccination scheme), AntiHBs titers should be mea-

sured so as to assess response to vaccination[113,114,116]. Seroprotection is defined as a serum titer above 10IU/L and, if it is not achieved, revaccination should be considered. Only one study addressed this question in two inactive SLE patients, not on DMARDs, that responded to vaccination only after a 4th dose[113]. However, based on expert recommendations, a repetition of the complete 3-dose scheme – 0, 1 and 6 months – should be preferred if patients fail to respond at first.

There is no available evidence concerning the effect of accelerated (0-1-2-12 months) or super accelerated schedules (0-7-21-360 days) of HB vaccination on SIRD patients and, therefore, no recommendations can be issued for these strategies. However, this might be an option if a rapid immune response is needed.

Efficacy

Despite the limited number of studies available, HB vaccination of SIRD patients was effective in 68-93% of cases[113,114,116]. Importantly, lower responses were reported in the study where most RA patients were treated with MTX, other sDMARDs and/or glucocorticoids[114]. There were no data available on the effect of biologics on vaccine efficacy.

Safety

There were no reports of safety or disease-worsening issues. Based on these data, on extrapolation from other vaccines and experts' opinion, HB vaccine can and should be administered in every SIRD patient without protective antibodies for HBV. Patients who present isolated positive AntiHBc due to previous contact with HBV may still benefit from vaccination, in order to generate AntiHBs antibodies that can be protective in the event of reexposure. Confirmation of undetectable viral load should be attained prior to immunization.

4. HEPATITIS A

a) Vaccination is recommended for SIRD patients travelling to endemic countries, preferably with 2 doses 6 months apart. Level of evidence 2b; Grade of recommendation B; Agreement: 8.9(1.4).

Indications

The incidence of hepatitis A (HA) has dramatically decreased in Portugal in the last 20 years due to major improvements in the overall environmental and socioeconomic conditions[159-161]. Universal HA vaccination is, thus, currently not recommended and is limited to individuals travelling to high prevalence countries (Africa, South and Central America, parts of Asia and Eastern Europe) or during an outbreak of disease[162,163]. In some patients with liver disease or at high risk for hepatotoxicity, due to the occurrence of occasional outbreaks of hepatitis A related to contamination of imported foods with hepatitis A virus, immunization should be considered even if travel is not expected[162,163]. Due to the decrease in the prevalence of HA in Portugal, the number of susceptible younger individuals has risen and this could lead to greater and more frequent outbreaks[163]. Protecting more vulnerable patients through immunization would prevent potentially serious liver disease or worsening of the SIRD due to suspension of hepatotoxic DMARDs.

Use

For SIRD patients, two doses of the vaccine should be administered (0 and 6 months) before travelling, in order to ensure adequate protection[115].

Efficacy and safety

In a cohort study of 53 RA patients treated with TNF blockers ± MTX, vaccination response was low after the first dose (6-20%), especially in patients exposed to MTX, and greatly increased after the second (82%)[115]. No adverse events were reported[115].

5. PAPILLOMAVIRUS

a) Consider HPV vaccine with 3 doses scheme (0, 2 and 6 months) in young adults with SIRD that have not been previously vaccinated. Level of evidence: 2b, Grade of recommendation: C, Agreement (mean (SD)): 8.6(1.7).

Indications

Quadrivalent human papillomavirus (HPV) vaccine is a recombinant vaccine against HPV serotypes 6, 11, 16 and 18. It is included in the Portuguese National Vaccination Plan and scheduled as a 2-dose series (0 and 2 months) for all girls between 10 to 13 years old; a 3-dose series (0, 2 and 6 months) is used for women between 18 and 25 years old[164]. Systemic Lupus Erythematosus (SLE) patients have an increased incidence of human papillomavirus (HPV) infection and cervical dysplasia. HPV clearance is also decreased comparing to the general population[165,166]. Experts suggest that HPV vaccination should also be extended to males in order to achieve universal immunity.

Use

In the opinion of our taskforce, young adult SIRD patients (both male and female) should be considered for HPV vaccination if not previously immunized.

Efficacy and safety

HPV vaccine is safe and effective in SLE patients with stable disease[120]. No evidence is available for other SIRD, but as with other non-live vaccines, HPV vac-

cine is considered safe in immunosuppressed patients (General Recommendation 5).

6. TETANUS

a) Patients with SIRD should follow the recommended vaccination schedule in the National Vaccine Program, i.e. tetanus and dyphteria (Td) every 10 years. Level of evidence 2b, Grade of recommendation B, Agreement (mean (SD)): 9.6(1.0).

Indications

SIRD patients should follow the National Vaccination Program schedule[168].

Efficacy

Tetanus toxoid vaccination (TTV) immunogenicity was shown to be reduced in RA and SLE patients comparing to healthy controls, independently of the use of glucocorticoids and immunosuppressants[123,127,167]. The efficacy of the vaccine when administered 2 weeks after rituximab was similar to methotrexate monotherapy[66]. Nevertheless, as immunogenicity might be decreased within 1-3 months after B-cell depleting therapy, it is recommended to vaccinate patients 4 weeks before initiation of therapy, or alternatively 6-8 months after the last infusion (General Recommendations 2 and 3).

Safety

TTV was demonstrated to be safe in RA and SLE patients[123,127,167].

7. HERPES ZOSTER

a) In patients with SIRD over 60 years it is recommended individual assessment of the risk/benefit of HZ vaccine. Level of evidence 4, Grade of recommendation D, Agreement (mean (SD)): 8.7(1.7).

Indications

Herpes zoster (HZ) has an incidence of 34/1000 people-year and will affect 1 in 3 adults. Following natural infection (varicella or chickenpox) or vaccination, varicella zoster viruses (VZV) reside, latent, on the dorsal root ganglia. Over time, reactivation may occur, mainly by changes in cell mediated immunity. The vaccine reduced the risk for developing zoster by 51% and prevented post-herpetic neuralgia (PHN) in 67% persons. In general, with increasing age at vaccination declines the vaccine efficacy, but the vaccine retained efficacy against severity of zoster better than against zoster itself. For persons older than 80 years the efficacy against zoster was 18%, but the efficacy against PHN was 39%[174].

Patients with SIRD have an increased risk for herpes zoster[169-173]. Immunosuppressed patients have a higher risk of severe rash, visceral dissemination or death, whereby prevention is desirable[175-177]. On the other hand, the administration of live vaccines, such as HZ vaccine bears the potential risk of invasive infection in susceptible individuals (General Recommendation 6).

According to the Center of Disease Control and Prevention Advisory Committee on Immunization Practices Recommendations (CDC-ACIP) and the American College of Rheumatology (ACR), herpes zoster vaccination should be considered in patients >60 years-old who are receiving: prednisone <20 mg/day, short term (<2 weeks) corticosteroids, topical or intraarticular corticosteroids, 'low dose' methotrexate (defined as <0.4 mg/kg/week), azathioprine (<3.0 mg/kg/day) or 6-mercaptopurine (<1.5 mg/kg/day). The guidelines do not address vaccine use when these agents are combined. They state the vaccine should not be given in the following circumstances: treatment with biologics (specifically naming adalimumab, infliximab and etanercept); high dose corticosteroids > 20 mg/day for more than two weeks; active leukemia, lymphoma, malignant neoplasm affecting bone marrow or lymphatics; AIDS/HIV patients and those with CD4 lymphocyte counts < 200 per mm^3 clinical or laboratory evidence of cellular immunodeficiency (patients with hypogammaglobulinemia or dysgammaglobulinemia can receive the zoster vaccine); hematopoetic stem cell transplantation; pregnancy and severe acute illness.

Efficacy

In our SLR, we found two large retrospective studies concerning VZV vaccination in SIRD patients, including patients receiving biologics[118,119]. VZV vaccine (single dose of 0.65mL subcutaneously) was administered to RA, PsA, SpA, psoriasis and inflammatory bowel disease patients treated with TNF inhibitors (n=553), non-TNF biologics (n=82), DMARDs and/or glucocorticoids (average dose 14.02 mg/day, range 2.5--50mg/day). Immunization was associated with a long--term (2 years of follow-up) protective effect[118,119].

Safety

HZV was not associated with an increase of HZV infections up to 42 days after vaccination (95%CI - 0-5.4 cases per 1000 anti-TNF users and 0-4.7 per 1000 biologic users)[118,119]. The vaccine also appears to be safe and well tolerated by SLE patients, but reduced effectiveness is a concern[117].

Use

In light of the available evidence, our taskforce con-

TABLE III. SUMMARIZED INFORMATION ON VACCINES, RECOMMENDED USE AND DOSING SCHEMES

Vaccine	Type	Use	Dosing schemes
Non-live vaccines			
Influenza	Inactivated	All SIRD patients[a]	Yearly administration
Pneumococcal - VPC13[b]	Conjugate	All SIRD patients[a]	Single dose (If previous PPSV23 vaccination, >1 year (y) interval is recommended)
Pneumococcal – PPSV23[c]	Inactivated	All SIRD patients[a]	First dose: ≥8 weeks after VPC13 Second dose: 5 y after 1st
Hepatitis B	Subunit	Negative serology for Hep B *or* Isolated antiHBc antibody positivity and negative viral load	Dosing: 0, 1 and 6 months[h] (mo) Assess Ac. Anti-Hbs titer 1-2 mo after the last dose Revaccinate if titer <10 IU/L
Hepatitis A	Inactivated	Susceptible travellers to endemic regions	0 and 6 mo[h]
Papillomavirus	Subunit	Young adults (female or male) not previously vaccinated	0, 2 and 6 mo
Tetanus/diphtheria[d]	Toxoid	All SIRD patients[a]	Every 10 y
Poliomyelitis (parenteral)[d]	Inactivated	Unvaccinated or incompletely vaccinated patients	Scheme: 0, 1 and 6-12 mo. Single booster ≥10y after scheme completion
Live attenuated viral vaccines (LAVV)[e]			
Varicella	LAVV	Susceptible persons (negative anti-VZV)	Dosing: 0 and 4 weeks
Varicella zoster (herpes zoster)	LAVV	SIRD patients ≥60 yo.[i]	Single dose
MMR[d,f]	LAVV	Selected SIRD patients[d]	Single dose
Yellow fever[g]	LAVV	Travelers to endemic regions	Single dose

a. Ideally ≥4 weeks before any immunosuppressive treatment or ≥6 months after rituximab, controlled disease activity is advised; b. VPC13: 13-valent Pneumococcal conjugate vaccine; c. VPP23: 23-valent Pneumococcal polysaccharide vaccine; d. SIRD patients should comply with the National Vaccination Program recommendations for adults ≥18 yo; e. The administration of live vaccines must be based in an individual assessment of the risk/benefit, which includes disease activity, medication, the replication potential of the vaccine and the risk of infection; f. MMR: measles, mumps, rubella; g. Previous consultation with a Traveller's Medicine Specialist is recommended; h. Accelerated (0-1-2-12 months) or super accelerated schedules (0-7-21-360 days) of HB vaccinationcan be used for people travelling on short notice that face imminent exposure or for emergency responders to disaster areas. A combined hepatitis A and hepatitis B vaccine can also be used on the same 3-dose schedule (0, 7, and 21–30 days), with a booster at 12 months. However, these vaccination schemes have not been tested in SIRD patients; i. Receiving prednisone <20 mg/day, short term (<2 weeks) corticosteroids, topical or intraarticular corticosteroids, 'low dose' methotrexate (defined as <0.4 mg/kg/week), azathioprine (<3.0 mg/kg/day) or 6-mercaptopurine (<1.5 mg/kg/day).

sidered that the risk/benefit of the HZV must be individually assessed, including patient age, disease activity, medication and the risk of infection.

Table III summarizes information on review vaccines, such as type of vaccine, recommended use and dosing schemes.

CONCLUSIONS

Thirteen evidence-based recommendations for vaccination in adult patients with SIRD were elaborated aiming to improve care for these patients.

The present recommendations combine scientific evidence with the expertise of a multidisciplinary panel and attaining desirable agreement among Portuguese rheumatologists. For dissemination purposes, the current paper will be published in a MEDLINE-indexed journal and will be freely available online at the SPR website. SPR members will be notified by email and/or newsletter after publication. However, there are still many areas deserving future research (Table IV). Most studies used surrogate markers of efficacy, such as seroprotection and seroconversion, instead of the oc-

TABLE IV. AREAS OF FUTURE RESEARCH

Areas of future research	
Live vaccines	Safety and efficacy on the context of ongoing immunosuppression;
Herpes Zoster Vaccine	A more permissive guideline might be issued if favourable safety, efficacy and cost/benefit relation could be established;
Meningococcal (tetravalent and serotype B) vaccines	No published data could be found until December 2014;
Primary systemic vasculitis and connective tissue diseases other than SLE and RA	The impact of disease activity and treatment in the safety and efficacy of vaccination;
Rituximab, tocilizumab, abatacept, belimumab, ustekinumab, secukinumab and kinase-targeted sDMARDs	The immunogenicity and safety of vaccinations in SIRD patients under such therapies;
Hepatitis B	The role of booster vs. revaccination in rituximab-treated patients whose AntiHBs titers decline after one or more infusions.

currence of infections as the primary study outcome. Definite conclusions on the impact of disease activity or immunosuppressive drugs on the safety of vaccination were limited by variability in the measures used in the assessments. Evidence was also scarce on various other contexts (Table IV).

The reader of these recommendations should keep in mind that many recommendations given in this article are based on clinical experience and expert opinion as scientific data are still scarce on many aspects.

Vaccination recommendations need to be updated on a regular basis, as more scientific data regarding vaccination efficacy and safety, emergent infectious threats, new vaccines as well as new immunomodulators become available.

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APPENDIX I – QUALITY ASSESSMENT OF VACCINATION STUDIES

DEFINITION OF STUDY POPULATION:

1. **Sufficient description of characteristics of study groups**
   A '1' is given when a paper describes at least setting and time period of the study, ages of patients (and its range), sex and ongoing medication
2. **Definition of diagnosis:**
   Rheumatic disease diagnosis
   diagnosis was according accepted classification criteria.
3. **Selection bias:**
   Clear description of selection of study subjects.

   When a paper described how the study subjects were selected (description of in- and exclusion criteria) from the population level to the study level, a '1' will be given.
4. **Follow-up:**

Follow-up time ≥ 6 weeks for rheumatic disease patients.

6 weeks was seen as an acceptable follow-up duration to assess antibody production

5. **Organization of follow-up**
   A '1' was given if there was a structured follow-up applied (efficacy and safety). So not only on patients request.
6. **Participation rate ≥ 80% for study groups**

   80% was an arbitrary margin chosen to determine the quality of the selection of study subjects.
7. **No differences in lost to follow-up (in both groups)**
   Including (quantitative and qualitative) information on completers and non-completers
8. **Assessment of the outcome:**
   Valid measures of vaccine efficacy *Reliable assays used for antibody titer measurement;*
   Immunologic outcome assessment was blinded to clinical data (at least treatment and symptom duration)

   A '1'is given if the observers were blinded to the intervention
9. **Safety assessment was performed using valid measures**
   For example A '1'is given if disease flare was according to accepted definitions
   Analysis and Data Presentation

10. **Frequencies of most important comorbidities were given**
11. **Immunosuppressant medication use and dosage was given**
12. **Frequencies of important outcomes studied were given**
13. **Appropriate analysis techniques with estimates were used**

TOTAL QUALITY RATE (x/13)

Adapted from: Kwok WY, Plevier JW, Rosendaal FR, Huizinga TW, Kloppenburg M. Risk factors for progression in hand osteoarthritis: a systematic review. Arthritis Care Res (Hoboken). 2013;65:552-562.