

2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases

Victoria Furer,^{1,2} Christien Rondaan,³ Marloes W Heijstek,⁴ Nancy Agmon-Levin,⁵ Sander van Assen,⁶ Marc Bijl,⁷ Ferry C Breedveld,⁸ Raffaele D'Amelio,⁹ Maxime Dougados,¹⁰ Meliha Crnkic Kapetanovic,¹¹ Jacob M van Laar,¹² A de Thurah,¹³ Robert BM Landewé,^{14,15} Anna Molto,¹⁶ Ulf Mueller-Ladner,¹⁷ Karen Schreiber,¹⁸ Leo Smolar,¹⁹ Jim Walker,²⁰ Klaus Warnatz,²¹ Nico M Wulffraat,²² Ori Elkayam²³

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For numbered affiliations see end of article.

Correspondence to

Victoria Furer, Rheumatology, Tel Aviv Sourasky Medical Center, Tel Aviv 62431, Israel; furer.rheum@gmail.com

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ABSTRACT

To update the European League Against Rheumatism (EULAR) recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases (AIIRD) published in 2011. Four systematic literature reviews were performed regarding the incidence/prevalence of vaccine-preventable infections among patients with AIIRD; efficacy, immunogenicity and safety of vaccines; effect of anti-rheumatic drugs on the response to vaccines; effect of vaccination of household of AIIRDs patients. Subsequently, recommendations were formulated based on the evidence and expert opinion. The updated recommendations comprise six overarching principles and nine recommendations. The former address the need for an annual vaccination status assessment, shared decision-making and timing of vaccination, favouring vaccination during quiescent disease, preferably prior to the initiation of immunosuppression. Non-live vaccines can be safely provided to AIIRD patients regardless of underlying therapy, whereas live-attenuated vaccines may be considered with caution. Influenza and pneumococcal vaccination should be strongly considered for the majority of patients with AIIRD. Tetanus toxoid and human papilloma virus vaccination should be provided to AIIRD patients as recommended for the general population. Hepatitis A, hepatitis B and herpes zoster vaccination should be administered to AIIRD patients at risk. Immunocompetent household members of patients with AIIRD should receive vaccines according to national guidelines, except for the oral poliomyelitis vaccine. Live-attenuated vaccines should be avoided during the first 6 months of life in newborns of mothers treated with biologics during the second half of pregnancy. These 2019 EULAR recommendations provide an up-to-date guidance on the management of vaccinations in patients with AIIRD.

INTRODUCTION

Patients with autoimmune inflammatory rheumatic diseases (AIIRD) have an increased burden of infections, attributed to the underlying autoimmune disease,^{1–4} comorbidities^{3,5} and immunosuppressive therapy, including glucocorticoids (GCs), disease-modifying antirheumatic drugs (DMARDs): conventional synthetic (csDMARDs), biological

(bDMARDs) and targeted synthetic DMARDs (tsDMARDs).^{3,6,7} As the 'treat to target' principle currently guides an intensive immunosuppressive therapy aimed at remission in most rheumatic diseases,^{8–10} these therapies are commonly applied, in particular at early disease stages. Thus, prevention of infections is crucial in the management of patients with AIIRD.

Vaccination prevents infections by inducing and/or enhancing protective immunity. Vaccination is particularly important in AIIRD patients, potentially translating into a lower rate of hospital admissions due to infections, emergency room visits and the rate of invasive infectious diseases.¹¹ Yet, the AIIRD population universally suffers from a suboptimal uptake of vaccinations,^{12–19} in part due to a low rate of referral for vaccination by rheumatologists²⁰ and other treating physicians,²¹ indicating that further interventions are needed to raise the awareness for vaccination among the rheumatology community and involved healthcare professionals. Another important factor for a low vaccination rate relates to concerns about efficacy, immunogenicity and safety of vaccinations,¹⁵ an important issue to be addressed by upcoming evidence.

Our aim was to update the present European League Against Rheumatism (EULAR) recommendations for vaccination in patients with AIIRD published in 2011 and to incorporate the new evidence on the incidence/prevalence of vaccine preventable infections (European League) among AIIRD patients, along with efficacy, immunogenicity and safety of vaccines provided to AIIRD patients under a wide range of immunosuppressive therapies. The update was conducted in line with the standard operating procedures (SOP) of the EULAR,²² combining evidence from clinical studies and expert opinion. Our recommendations target all healthcare professionals involved in the care for patients with AIIRD.

METHODS

Development of recommendations

The present update of the EULAR recommendations for vaccination in patients with AIIRD was a combined project for the adult and paediatric AIIRD populations. Following the 2014 updated EULAR SOP,²² the convenor (OE) first formed the



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Recommendation

Box 1. Research questions.

- ▶ What is the incidence or prevalence of vaccine-preventable infections in adult patients with autoimmune inflammatory rheumatic diseases (AIIRD)?
- ▶ What is the efficacy, immunogenicity and safety of available vaccines in adult AIIRD patients?
- ▶ Are vaccines efficacious and immunogenic in adult AIIRD patients, treated with immunosuppressive agents and disease-modifying antirheumatic drugs?
- ▶ What is the effect of vaccination of household of AIIRD patients, including newborns, on the prevention of vaccine preventable diseases and safety of the patients?

task force with a steering committee. The steering committee included the convenor (OE), co-convenor (ULM), methodologists (JvL and RL), three fellows who performed the systematic literature reviews (SLRs) (VF, CR, MH), one expert rheumatologist (MB) and one specialist in infectious diseases (SvA). The steering committee defined the research questions for the SLRs (Box 1) and organised a one-and-a-half-day meeting of the task force. Participants of the adult task force meeting represented seven European countries and Israel, included 10 adult rheumatologists, four clinical immunologists, one infectious disease specialist, one paediatrician/rheumatologist, two delegates of the EULAR young rheumatologists' network Emerging EULAR NETwork, one health professional in rheumatology (HPR) and two patients. Three fellows (VF, CR, MH) performed four SLRs covering the incidence of VPI, the efficacy, immunogenicity, safety of vaccination in patients with AIIRD, the effect of DMARDs on vaccination response and the effect of vaccination of household of AIIRDs patients, including newborns, on the prevention of VPI and safety of the patients. These SLRs focused on the studies published after the locking date of the SLRs for the previous update, that is, October 2009. MEDLINE (via PubMed), EMBASE and Cochrane were searched from 1 October 2009 to 1 August 2018. As search terms, the medical subject headings (MESH) terms for the defined AIIRD, immunosuppressive medications and vaccines were combined (Box 2). Only articles in English were included. Other papers that were considered relevant in the opinion of the experts could be added.

The first part of the meeting was shared by both adults and paediatric members of the task force, during which the preliminary results of the four SLRs were presented. Following the presentation, the group split in two in order to formulate the separate updated recommendations for vaccination in adults and children with AIIRD. In the adult group, the convenor (OE) proposed the wording of each recommendation. Each recommendation was discussed within the group and formulation was modified until agreement was reached among the members. In the second part of the meeting, the two groups rejoined and reviewed the two sets of recommendations, mainly in order to verify that there was no major discrepancy between them. Minor changes were made following this presentation and approved by all the members of the task force. The second meeting of the task force was then organised and included the presentation of the updated SLRs concerning the adult population with AIIRD. The results of the SLRs are reported in two articles, submitted for publication to RMD Open. Each recommendation was discussed and modified when necessary,

Box 2. Definition of autoimmune inflammatory rheumatic diseases (AIIRD), immunosuppressive agents and vaccines included in the literature search and recommendations

Autoimmune inflammatory rheumatic diseases

- ▶ Rheumatoid arthritis, juvenile idiopathic arthritis
- ▶ Adult Still's disease
- ▶ Systemic lupus erythematosus, Sjogren's syndrome, antiphospholipid syndrome
- ▶ Systemic sclerosis, mixed connective tissue disease
- ▶ Polymyositis, dermatomyositis, antisynthetase syndrome, clinically amyopathic dermatomyositis, inclusion body myositis, eosinophilic myositis, eosinophilic fasciitis
- ▶ Psoriatic arthritis, spondyloarthritis
- ▶ Polymyalgia rheumatica
- ▶ Giant cell arteritis, Takayasu arteritis
- ▶ Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis: granulomatosis with polyangiitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
- ▶ Polyarteritis nodosa
- ▶ Cryoglobulinemic syndrome
- ▶ Anti-glomerular basement membrane (GBM) antibody disease (Goodpasture disease)
- ▶ Behcet disease
- ▶ Relapsing polychondritis
- ▶ Periodic fever syndromes
- ▶ Familial Mediterranean fever

Immunosuppressive agents

- ▶ Glucocorticoids
- ▶ Synthetic disease-modifying antirheumatic drugs (DMARDs): methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, azathioprine
- ▶ Mycophenolic acid preparations
- ▶ Calcineurin inhibitors: cyclosporine, tacrolimus
- ▶ Alkylating agent: cyclophosphamide
- ▶ Biologic DMARDs: infliximab, etanercept, adalimumab, certolizumab, golimumab, abatacept, tocilizumab, rituximab, secukinumab, ixekizumab, belimumab, anakinra, canakinumab
- ▶ Targeted synthetic DMARDs: tofacitinib, baricitinib

Vaccines

Inactivated

- ▶ Diphtheria, hepatitis A, hepatitis B, Haemophilus influenzae b, human papillomavirus, influenza, Neisseria meningitidis, pertussis, parenteral poliomyelitis, *streptococcus pneumoniae* (polysaccharide and conjugated), tetanus toxoid, tick-borne encephalitis, parenteral typhoid fever

Live-attenuated

- ▶ Measles, mumps, oral poliomyelitis, oral typhoid fever, varicella zoster, yellow fever

followed by the second round of voting by all the members of the task force.

Six overarching principles and nine recommendations were formulated (tables 1 and 2). For each statement, the available evidence was critically appraised and the strength of the recommendations (SoR) was determined following the standards of the

Table 1 Overarching principles for vaccination in adult patients with AIIRD

Overarching principles	Level of Agreement (%)
1. The vaccination status and indications for further vaccination in patients with AIIRD should be assessed yearly by the rheumatology team.	100%
2. The individualised vaccination programme should be explained to the patient by the rheumatology team, providing a basis for shared decision-making, and be jointly implemented by the primary care physician, the rheumatology team and the patient.	94%
3. Vaccination in patients with AIIRD should preferably be administered during quiescent disease.	94%
4. Vaccines should preferably be administered prior to planned immunosuppression, in particular B cell depleting therapy.	100%
5. Non-live vaccines can be administered to patients with AIIRD also while treated with systemic glucocorticoids and DMARDs.	100%
6. Live-attenuated vaccines may be considered with caution in patients with AIIRD.	53%

AIIRD, autoimmune inflammatory rheumatic diseases; DMARDs, disease-modifying antirheumatic drugs.

Table 2 Recommendations for vaccination in adult patients with AIIRD with level of evidence for the incidence/prevalence of VPI, efficacy, immunogenicity and safety of vaccines, strength of recommendations (SoR) and level of agreement for each recommendation

Recommendation	Infection rate	Efficacy	Immuno-genicity	Safety	SoR*	Level of agreement: average/ range (0–10), %≥8
1. Influenza vaccination should be strongly considered for the majority of patients with AIIRD.	2b	2b	2a	2b	B	9.4 7–10 93%
2. Pneumococcal vaccination should be strongly considered for the majority of patients with AIIRD.	2b	4	2a	4	C	8.7 6–10 93%
3. Patients with AIIRD should receive toxoid tetanus vaccination in accordance with recommendations for the general population. Passive immunisation should be considered for patients treated with B cell depleting therapy.	NA	NA	2b	4	B D	9.5 8–10 100%
4. Hepatitis A and hepatitis B vaccination should be administered to patients with AIIRD at risk. In specific situations booster or passive immunisation is indicated.	HAV – NA HBV 2b	NA	2b	4	B C	9.6 8–10 100%
5. Herpes zoster vaccination may be considered in high-risk patients with AIIRD.	2b	2b	2b	4	B	9.1 7–10 93%
6. Vaccination against yellow fever should be generally avoided in patients with AIIRD.	NA	NA	2b	4	D	9.2 6–10 85.7%
7. Patients with AIIRD, in particular patients with SLE, should receive vaccinations against HPV in accordance with recommendations for the general population.	2b	NA	2b	4	C	9.5 8–10 100%
8. Immunocompetent household members of patients with AIIRD should be encouraged to receive vaccines according to national guidelines with the exception of the oral polio vaccines.	NA	NA	NA	NA	D	9.1 7–10 93%
9. Live-attenuated vaccines should be avoided during the first 6 months of life in newborns of mothers treated with biologics during the second half of pregnancy.	NA	NA	NA	NA	D	9.5 8–10 100%

*The strength of recommendation was primarily based on the efficacy data. If no efficacy data were available, immunogenicity was used as a major outcome. When immunogenicity outcomes did not directly correlate with protection, the strength of recommendation was downgraded. Few recommendations were primarily based on safety (especially live-attenuated vaccines) and here, the safety outcomes determined the strength of the recommendation.

AIIRD, autoimmune inflammatory rheumatic diseases; HAV, hepatitis A virus; HBV, hepatitis B virus; HPV, human papilloma virus; NA, non-available; SLE, systemic lupus erythematosus.

Oxford Centre for Evidence Based Medicine.²³ (online supplementary file 1)

After the second meeting, the final version of recommendations was disseminated among the members of the task force who electronically voted for agreement for each of the principles and recommendations. Each statement was separately voted on and given a score from 0 (absolutely no agreement with the proposed recommendation) to 10 (maximal possible support for the recommendation). The level of agreement for each recommendation was based on the mean vote score.

The final manuscript was drafted after the second meeting of the task force. The manuscript was structured according to the Appraisal of Guidelines for Research & Evaluation II principles,^{22 24} reviewed, revised and approved by all the task force

members, followed by final review and approval by the EULAR Executive Committee before submission to the journal.

Definitions

In the field of vaccination, several outcome measures are important. First, the capacity of vaccinations to prevent infections, referred to as 'efficacy'. Often, humoral responses to vaccines are considered as surrogate endpoints for efficacy, in particular for rare infections, that otherwise would require infeasible trials needing a very large number of patients to prove the vaccine's efficacy. The capacity of vaccines to induce humoral and/or cellular immune responses is referred to as 'immunogenicity'. These immune responses may correlate with clinical

Recommendation

efficacy for some vaccines, but not necessarily. This should be taken into account when interpreting the available evidence (primarily on immunogenicity) for these recommendations.

The SoR was primarily based on the level of evidence for efficacy of vaccination. In vaccine studies with only immunogenicity outcomes, the SoR was established based on the surrogate outcome (immunogenicity). In case there was no direct correlation between the immunogenicity outcomes and the level of protection, the SoR was downgraded.

Finally, the safety of vaccines is of great importance. Safe vaccination implies that vaccination has no severe adverse effects and does not aggravate the underlying disease. Especially for live-attenuated vaccines, safety is a major concern. For these vaccines, the safety outcomes primarily determined the SoR. The level of available evidence concerning efficacy, immunogenicity and safety provided the data was available, is presented for each recommendation.

RESULTS

Overarching principles

The task force endorsed the presentation of six general principles for vaccination of patients with AIIRD as overarching (table 1). Three new overarching principles were formulated. The other three principles originated from the recommendations #2 to #4 published in the 2011 version and were incorporated in the overarching principles due to their importance and generic nature.²⁵ The level of agreement of each overarching principle is presented in table 1.

The vaccination status and indications for further vaccination in patients with AIIRD should be assessed yearly by the rheumatology team

The force task endorsed an annual assessment of the vaccination status by the treating rheumatology team as a central principle guiding vaccinations in patients with AIIRD, constituting an overarching principle rather than a recommendation. In the 2011 version, the first recommendation referred to the assessment of the vaccination status of patients with AIIRD in the initial workup, without defining the responsible health-care provider. The current version emphasises the need for an *annual assessment*, delegating the responsibility to the treating rheumatologist or rheumatology team. The rheumatology team has an extended knowledge and expertise encompassing all aspects of AIIRD, including related treatment modalities applied to an individual patient. For patients with AIIRD, the treating rheumatology team commonly manages their medical care, communicates with a primary care physician and coordinates a multidisciplinary network when required. As stated in the 2011 version, an inventory of a vaccination history, adverse events and flares of the underlying AIIRD following earlier vaccinations should be included in the assessment and turned into the standard of care of patients with AIIRD.

The individualised vaccination programme should be explained to the patient by the rheumatology team, providing a basis for shared decision-making, and be jointly implemented by the primary care physician, the rheumatology team and the patient

This is a newly formulated principle, strongly endorsed by the patient representatives of the task force and supported by the other members. Shared decision-making and consideration of patient's needs, concerns and preferences have received the most prominent recognition in treatment of chronic diseases, as reflected in the updated EULAR recommendations.^{8–10}

Identifying barriers to immunisation and addressing patients' fears and concerns regarding adverse effects is a crucial step toward adherence with any immunisation programme. Having access to evidence-based information about vaccines and comprehension of risks and benefits of vaccination, enables patients to make a deliberate decision regarding the offered vaccination programme. The rheumatology team should inform patients about the risk of infections and the indications for vaccinations, educate patients about the risk/benefit ratio of vaccines and encourage patients to adhere to the appropriate vaccination schedule. Indeed, surveys among patients with AIIRD demonstrated that better knowledge about vaccination and recommendation for vaccination by a treating specialist were positively associated with improved vaccine uptake.^{15 26} Communication between the rheumatology and primary care teams further supports the implementation of the vaccination programme. A large survey of rheumatoid arthritis (RA) patients in the UK revealed that the majority of vaccination was undertaken in primary care,²⁷ supporting collaboration between primary and secondary care to maximise vaccine uptake.

Vaccination in patients with AIIRD should preferably be administered during quiescent disease

This statement, listed as the second recommendation in the 2011 version, was shifted into the third overarching principle. The rationale for this decision was the shared opinion by the majority of the members that this important message would benefit from being a fundamental general principle. Indeed, most vaccination studies conducted in the AIIRD population included patients with quiescent disease.^{28–33} The number of studies with AIIRD patients immunised at the active disease stage is too low to draw the conclusion that vaccinations during active phases of disease are effective or safe. One study has directly addressed the impact of underlying disease activity on the immunogenicity of vaccination.³⁴ In this study, patients with juvenile systemic lupus erythematosus (SLE) with high SLE activity had reduced seroconversion rates to influenza A H1N1 vaccination. Notably, in a study of 340 RA patients, high disease activity levels did not preclude immune response to influenza A H1N1 vaccination.³⁵ Yet, based on the limited knowledge on safety and immunogenicity of vaccinations in patients with active disease, vaccinations are preferentially administered during quiescent disease, according to expert opinion. In patients with active disease, immunisation should not be precluded and considered on the individual basis.

Vaccines should be preferably administered prior to planned immunosuppression, in particular B cell depleting therapy

This important concept, based on the fourth recommendation in the 2011 version, was further expanded to the initiation of csDMARDs, bDMARDs and tsDMARDs, prompting an early vaccination policy to ensure the optimal response to vaccines. Yet, it is important to emphasise that the intention of this principle is *not* to delay a necessary immunosuppressive treatment in severe cases. In such cases, initiation of the indicated immunosuppressive treatment is the main priority rather than early administration of vaccines.

A clear consensus was reached on the suppressive effect of rituximab (RTX) on humoral response to influenza and pneumococcal vaccination in patients with RA,^{36–47} spondyloarthropathies (SpA)⁴² and SLE,⁴⁸ explaining the rationale to provide vaccination *prior to the administration of rituximab*. Other bDMARD therapies have a variable impact on the response to

immunisation in the AIIRD population, with the majority of patients reaching a satisfactory serological response. The effect of specific DMARDs is broadly discussed in the extended SLR (submitted for publication in RMD Open).

In summary, vaccines should be ideally administered *before* the planned immunosuppression, with the emphasis on B cell-depleting biological therapy. In case of non-immunised patients on B cell-depleting therapy, vaccination should be provided at the following time window: at least *6 months after* the administration and *4 weeks before the next course* of B cell-depleting therapy, based on the state of clinical practice. In cases when this time window for immunisation is not possible, vaccination may be considered under B-cell depleting therapy, taking into consideration a potential suboptimal response to vaccine.

Non-live vaccines can be administered to patients with AIIRD during the use of glucocorticoids and DMARDs

Originally presented as the fourth recommendation in the 2011 version, this statement has been modified and upgraded to an overarching principle, in light of compelling evidence of the overall adequate efficacy and safety of vaccination during the use of GC and/or both csDMARDs, bDMARDs and tsDMARDs in a variety of rheumatic diseases. Accumulating data over the recent years have supported the administration of influenza, pneumococcal, tetanus toxoid, hepatitis B virus (HBV), hepatitis A virus (HAV), and human papilloma virus (HPV) vaccines to patients with AIIRD under immunosuppressive therapy. In the majority of studies adequate immunoprotection was achieved, with no major safety signals, though the follow-up period was short in most studies. The details of the relevant studies are provided in the SLR by Rondaan *submitted for publication in Open RMD*.

Live-attenuated vaccines may be considered with caution in patients with AIIRD

Administration of live-attenuated vaccines in patients with AIIRD warrants special attention. In the 2011 version, the third recommendation stated that live-attenuated vaccines should be *avoided* whenever possible in immunosuppressed patients with AIIRD. In light of the new evidence and experience on administering certain live-attenuated vaccines in patients with AIIRD, the task force has extensively discussed the modification of the original statement to formulate it in a more permissive mode. Agreement was reached to incorporate the new evidence in the updated recommendations with a detailed explanation of the rationale and the new evidence. In general, live-attenuated vaccines should be avoided in patients under immunosuppressive therapy, as these vaccines contain live-attenuated micro-organisms that theoretically might cause infections in the susceptible AIIRD population. Based on expert opinion, the preferable time window for vaccination with live vaccines is *4 weeks prior to treatment initiation*, based on the state of clinical practice. However, vaccinations such as measles, mumps, rubella (MMR) and live-attenuated herpes zoster vaccines may be an exception.

Following the Centers for Disease Control and Prevention (CDC) recommendations, the definition of the 'immunosuppressive therapy' includes GC usage for ≥ 2 weeks in dosages equivalent to prednisone of 20 mg/d or 2 mg/kg body weight are considered immunosuppressive, as is methotrexate (MTX) ≥ 0.4 mg/kg/week, azathioprine ≥ 3.0 mg/kg/day or 6-mercaptopurine ≥ 1.5 mg/kg/day, whereas dosages below these levels may be considered as a 'low grade' immunosuppression. The level of immunosuppression in case of a long-term treatment with low dose GC requires further investigation. In the field of

rheumatology, bDMARDs and tsDMARDs are likewise defined as immunosuppressive therapy.

The evidence on MMR is mainly derived from the observational data in the paediatric population of patients with AIIRD. With regard to immunogenicity, a retrospective study from the Netherlands reported a long-term persistent seroprotection for measles in a large group of patients with juvenile idiopathic arthritis (JIA).⁴⁹ The use of GCs or MTX did not influence the antigen-specific antibody concentration or seroprotection rates. Consistently, a similar outcome was reported in a small retrospective study performed in paediatric SLE patients in Brazil.⁵⁰ A prospective nested case-control study from Germany also reported a protective humoral response following 6 months after measles revaccination in 15 patients with JIA, treated with either low-dose MTX therapy alone or in combination with etanercept.⁵¹ Regarding safety, no increase in disease activity, measles flare or severe serious infections were seen, including JIA patients using etanercept.⁵¹ A randomised, open-label study from the Netherlands confirmed an appropriate immunogenicity and safety of the MMR booster provided to JIA patients, including 60 patients using MTX and a small number of patients using bDMARDs.⁵² Based on these safety data of the MMR booster vaccination, the measles virus booster vaccine (as opposed to neo-immunisation) can be considered in AIIRD patients on low grade of immunosuppression at risk of contracting measles infection (for example, travellers).

Concerning vaccination against herpes zoster (HZ), two studies evaluated the safety of the live-attenuated zoster vaccine in AIIRD patients using immunosuppressive drugs. A large cohort study of Medicare beneficiaries 60 years and older with AIIRD, treated with immunosuppressive therapies, including bDMARDs, did not show any increase in the incidence of herpes zoster during the first 42 days after vaccination.⁵³ Live-attenuated HZ vaccine was safely provided to a small cohort of SLE patients (n=10), followed for 12 weeks.⁵⁴ Based on these studies, the live-attenuated HZ vaccine may be considered in patients at risk. A non-live virus vaccine is now available in some countries. Both vaccines are discussed in the recommendation #5 below.

In summary, live-attenuated vaccines should be avoided during immunosuppression, with a possible exception of a cautious use of MMR booster and HZ vaccine under special circumstances, as discussed above.

Recommendations

A total of nine recommendations have been formulated. For each recommendation, the level of evidence for the incidence/prevalence of VPI in AIIRD, and efficacy/immunogenicity/safety of vaccination were stated, when available, followed by the strength of recommendation and the level of agreement (table 2). Six of these recommendations concerning influenza, pneumococcal, tetanus toxoid, HAV, HBV as well as HPV vaccinations originated from the 2011 recommendations with some modifications. Three recommendations (former #10, #12 in the 2011 version) concerning vaccination in hyposplenic/asplenic patients with AIIRD, BCG vaccination and travelling patients with AIIRD were deleted. The task force decided that the first two topics became irrelevant in a daily rheumatology practice. The recommendation for the travelling patients with AIIRD (former #13) to follow the national guidelines was omitted due to being non-specific. Two new recommendations (#8, #9) were formulated encompassing the vaccination in household members of patients with AIIRD and newborns treated with biologics during pregnancy. An SLR was performed on these topics which

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disclosed no relevant papers. Thus, these recommendations were based on expert opinion.

Influenza vaccination should be strongly considered for the majority of patients with AIIRD

This recommendation, listed #5 in the 2011 version, remained essentially unchanged, except for the remark that the vaccine should be considered for the *majority* of patients and not *all* patients. Patients with AIIRD have a higher risk of contracting influenza compared with the general population.^{55–57} The task force panel has extensively discussed the scope of patients for whom the vaccine should be recommended. As there is a substantial variability in national guidelines for influenza vaccination, ranging from the whole population vaccination in the USA to age-based and risk-based vaccination in other countries, the panel has taken into consideration different epidemiological and clinical aspects of influenza vaccination in patients with AIIRD. To date, there is no compelling epidemiological evidence to justify a universal influenza vaccination for the whole population of patients with AIIRD. For example, young patients with ankylosing spondylitis, treated with non-steroidal anti-inflammatory drugs only, are not considered immunosuppressed and thus are not at increased risk of influenza-related morbidity. Yet, the majority of the AIIRD population, in particular patients treated with immunosuppressive therapy, seems to benefit from the vaccine.^{33 58 59}

Regarding efficacy, seasonal trivalent subunit influenza vaccination has been shown to reduce the incidence and bacterial complications of influenza, admissions for and mortality from influenza/pneumonia in AIIRD.^{60–63} Most studies have focused on immunogenicity as surrogate outcome for efficacy. Influenza vaccination has been shown to be immunogenic in patients with RA, SLE, ANCA-associated vasculitis (AAV), SSc, and PsA, treated with all classes of DMARDs,^{33 59 64–98} except for rituximab.^{37 41 43 99 100} Temporary discontinuation of MTX was shown to improve immunogenicity of seasonal influenza vaccination in patients with RA, with the best results when MTX was suspended for 2 weeks before and 2 weeks after vaccination.^{101 102} However, it is currently not recommended to stop MTX before or after vaccinating for influenza. Adverse events of influenza vaccination in patients with AIIRD seem comparable to those in healthy controls, although there are no studies that are sufficiently powered with regard to safety.^{28 33 41 43 64 65 69 73–78 81 83–86 88–90 92 94–96 99 103 104}

Most studies investigating immunogenicity and safety of the pandemic monovalent influenza vaccine found reduced immunogenicity in AIIRD patients (mostly RA and SLE) and on most immunosuppressive medications, although protective antibody levels were reached in the majority of patients,^{34 35 38 40 59 89 105–116} except for those treated with rituximab and abatacept.^{38 42 117} A second booster dose of vaccine was shown to improve immunogenicity, leading to levels of seroprotection comparable to healthy controls.^{40 42 118} This has also been shown in SLE patients who received seasonal influenza vaccine for the first time.²⁹

Following vaccination with both seasonal and pandemic influenza vaccines, the disease activity was stable in the majority of studies and only mild adverse events, comparable with healthy controls, were reported.^{34 35 38 40 59 89 105–109 113–116 119} Based on the data of increased risk and morbidity of influenza infection in AIIRD patients, in combination with studies showing a decrease in influenza infections following vaccination, and a large body of evidence proving good influenza vaccine immunogenicity and safety in AIIRD patients, influenza vaccination should be strongly considered for the majority of patients.

Pneumococcal vaccination should be strongly considered for the majority of patients with AIIRD

This recommendation, listed #6 in the 2011 version, has been modified defining the scope of candidates to pneumococcal vaccine as the ‘majority’ of patients with AIIRD, in order to target patients at risk of pneumococcal disease. The task force panel has extensively discussed the types of pneumococcal vaccine, timing of vaccine administration, the scope of patients who will mostly benefit from vaccination and cost-effectiveness of the vaccine in order to target AIIRD patients at risk of pneumococcal disease.

The risk of pulmonary infection is particularly high for patients with AIIRD. In a study of US veterans with RA, the highest rate of hospitalisation for infection was due to pneumonia (37%).¹²⁰ RA and SLE were identified as additional at-risk conditions for pneumococcal disease.¹²¹ The incidence of invasive pneumococcal infection in SLE patients was 13 times higher compared with the Dutch general population.¹²²

Two pneumococcal vaccines are now available: the 23-valent pneumococcal polysaccharide vaccine (PPSV23) and the 13-valent pneumococcal conjugate vaccine (PCV13). Regarding efficacy, a randomised double-blind trial on the clinical efficacy of PPSV23 in preventing pneumonia in RA patients did not demonstrate an increased efficacy of the vaccine over placebo.¹²³ On the other hand, a retrospective study on the long-term effect of PPSV23 in RA patients treated with MTX showed a relative risk of 9.7 to develop pneumonia in non-vaccinated patients.¹²⁴ The humoral immunogenicity and safety of the PPSV23 has been demonstrated in RA,^{64 87 125–129} SLE,^{130–132} and to a limited extent in SpA and others.¹³³ The long-term immunogenicity of PPSV23 has been evaluated in two studies, in RA patients treated with MTX¹²⁴ and biologics, respectively.¹³⁴ Both have shown a long-term duration of protective antibodies, up to 7 years. The immunogenicity and safety of PCV13 has been evaluated in small groups of patients with RA and found to induce an appropriate humoral response,¹³⁵ although reduced under MTX,¹³⁶ in SLE¹³⁷ and systemic vasculitis patients.¹³⁸ None of the above-mentioned studies raised any safety concerns except for patients with cryopyrin associated periodic syndromes (CAPS), who may develop severe local reactions and systemic reactions to PPSV23.¹³⁹

Stepwise pneumococcal vaccination, a PCV13 prime-PPSV23 boost strategy, with an interval of at least 8 weeks between the two vaccinations, is now recommended based on the CDC and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommendations for young children, adults above 65 years old and patients at risk for pneumococcal disease (table 3). This is mainly based on expert opinion. Evidence from studies conducted in the general population^{140 141} and patients with HIV¹⁴² showed an augmented immunogenic response following the combined vaccination. On the other hand, the evidence for the efficacy of the combination of PCV13 and PPSV23 in patients with AIIRD is insufficient. A randomised controlled study in RA patients evaluated the serological response to PCV13 followed by PPSV23 after 16 to 24 weeks. The study demonstrated an adequate response (87% and 94% in RA patients on bDMARDs and csDMARDs, respectively), with a significantly decreased response in patients treated with RTX. A prime boosting strategy with PCV13 did not improve the response.⁴⁵ However, long-term follow-up studies addressing persistence of the humoral response and immunological memory are not available yet.

In view of the increased risk of non-invasive and invasive pneumococcal disease in patients with AIIRD, along with good

Table 3 Schedule of administration of pneumococcal vaccine in AIIRD patients under immunosuppressive therapy based on the CDC recommendations

History of prior vaccination	Schedule for administration of PCV13 and PPSV23
None or unknown	Administer PCV13 followed in 8 weeks by PPSV23 #1. Administer PPSV23 #2 at least 5 years after PPSV23 #1.
One dose PPSV23; zero or unknown PCV13	Administer PCV13 at least 1 year after PPSV23 #1. Administer PPSV23 #2 at least 5 years after PPSV23 #1 and at least 8 weeks after PCV13.
Zero or unknown PPSV23; one dose PCV13	Administer PPSV23 #1 at least 8 weeks after PCV13. Administer PPSV23 #2 at least 5 years after PPSV23 #1.
One dose PPSV23; one dose PCV13	Administer PPSV23 #2 at least 5 years after PPSV23 #1 and at least 8 weeks after PCV13.
Two doses PPSV23; 0 or unknown PCV13	Administer PCV13 at least 1 year after PPSV23 #2.

Reference: <http://www.immunize.org/catg.d/p3075.pdf>

AIIRD, autoimmune inflammatory rheumatic diseases; CDC, Centers for Disease Control and Prevention; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

efficacy, immunogenicity and favourable safety profile of pneumococcal vaccines in the healthy population, and in line with the present recommendations of the CDC^{143 144} and the ESCMID,¹⁴⁵ pneumococcal vaccination should be strongly considered for the majority of patients with AIIRD. Pneumococcal vaccination should be considered carefully in patients with CAPS given the potential risks of adverse events. The task force does not have a reason to recommend a specific pneumococcal vaccine based policy based on the present data on efficacy, immunogenicity and safety of available pneumococcal vaccines. Costs of vaccines may play a role in the decision of the vaccine choice.

Patients with AIIRD should receive tetanus toxoid vaccination in accordance to recommendations for the general population. Passive immunisation should be considered for patients treated with B cell depleting therapy.

The content of this recommendation remained essentially unchanged (*reference recommendation #7 in the 2011 version*), except of rephrasing of the second statement.

No studies evaluated infection rates of tetanus after vaccination. Humoral response to tetanus vaccination strongly correlates with disease prevention and therefore can be used as a clinical outcome measure. In general, patients with AIIRD are recommended to receive tetanus toxoid vaccination in accordance to recommendations for the general population.

Patients with RA and SLE show a satisfactory immunogenicity for tetanus toxoid vaccination comparable with healthy controls.^{146–148} This also holds true for patients with RA on immunosuppressive drugs,^{128 149} including those treated with rituximab 24 weeks earlier.³⁶ Treatment with belimumab did not affect the ability of patients with SLE to maintain antibody titers to previous tetanus immunisation.¹⁵⁰ Although no data are available regarding the efficacy of tetanus toxoid vaccine under the influence of B cell depleting therapy, the efficacy is assumed to be decreased in this situation, based on the data extrapolation from other vaccines. Therefore, passive immunisation with tetanus immunoglobulins should be considered in case of a high-risk exposure to tetanus in patients treated with B cell therapy, according to the expert opinion.

Hepatitis A and hepatitis B vaccines should be administered to AIIRD patients at risk — in specific situations, booster or passive immunisation is indicated

The original recommendation on HAV and HBV vaccination (#11 in the 2011 version) has been expanded regarding the indication for a booster or passive immunisation in specific cases. No data on the incidence/prevalence of HAV in AIIRD is available. Patients with AIIRD at risk of contracting hepatitis

A are recommended to receive vaccination against hepatitis A. Patients at risk include HAV-seronegative patients travelling to or resident in endemic countries. Data on the vaccine efficacy are lacking, but there is a strong correlation between antibody concentrations and seroprotection against infection. It should be emphasised that, as opposed to strong immunogenicity in healthy individuals, a single dose of HAV vaccine does not seem to afford a sufficient protection in RA¹⁵¹ and patients using immunosuppressive drugs.¹⁵² Therefore, second HAV vaccination after 6 months and determination of post-vaccination antibody titers is recommended. If this is not possible, as in the case of a last-minute traveller, one should be aware that an AIIRD patient may not be protected after a single dose of HAV vaccine, and consider passive immunisation prior to the specific journey.

Studies from the different geographical regions across the world reported a variable serological prevalence of HBV infection among AIIRD patients. Data on the efficacy of hepatitis B vaccination in AIIRD patients are lacking, but antibody concentrations are considered to correlate well with protection. Hepatitis B vaccination was immunogenic in most patients with AIIRD,^{153–156} although two open label small studies reported an insufficient humoral response to HBV vaccine in AIIRD patients treated with bDMARDs.^{157 158} Furthermore, high-dose HBV vaccination did not increase the humoral response rate.¹⁵⁸

In concordance with the previous recommendations, HBV vaccine should be administered only to patients at risk. Patients at risk include HBV-seronegative patients that travel to or are residents in endemic countries, and patients at increased risk of exposure to HBV (eg, medical personnel, household contacts or sexual partners of known persons with chronic HBV infection, intravenous drug users, men who have sex with men). In case of an exposure to HBV (for example percutaneous (needle stick, laceration, bite or permucosal) in an unvaccinated patient or a patient with an insufficient response to HBV vaccine, a booster or passive immunisation with hepatitis B immune globulin is indicated according to the CDC recommendations.¹⁵⁹

Herpes zoster vaccination may be considered in high-risk patients with AIIRD

This recommendation remained identical to the recommendation #8 in the 2011 version. The evidence accumulated over the last decade has further supported this recommendation.

AIIRD patients are at increased risk of HZ compared with the general population, with the highest risk of infection in patients with inflammatory myositis and SLE of all ages.¹⁶⁰ A live-attenuated HZ vaccine reduced the risk of HZ by 51% to 70% among immunocompetent individuals 50 years and older in two randomised blinded trials.^{161 162} In elderly AIIRD patients,

Recommendation

vaccination with HZ vaccine was associated with a reduced incidence of HZ over a median of 2 years follow-up, as reported in a retrospective large database study including patients with immune-mediated diseases (RA, PsA, AS, psoriasis, inflammatory bowel disease (IBD)). This effect was present regardless of medication use, including bDMARDs. HZ vaccination offered protection for about 5 years among patients with autoimmune diseases.⁵³ Furthermore, the vaccine seemed to be immunogenic and safe in a small sample of SLE⁵⁴ and in GC-treated patients.¹⁶³ Regarding safety, the vaccine was safe within 42 days of follow-up, including for patients on biologics.⁵³ Administration of HZ vaccine to active RA patients ≥ 50 years old treated with MTX, 2 to 3 weeks before starting tofacitinib, was reported to be safe and immunogenic at 14 weeks follow-up.¹⁶⁴ Large prospective trials sufficiently powered for assessing safety of this live-attenuated vaccine are lacking.

Based on the increased infection rates, the efficacy in healthy controls and documented efficacy and safety in one study including 463 541 AIIRD patients, including 633 patients on bDMARDs (predominantly tumour necrosis factor (TNF) blockers), the live-attenuated HZ vaccine may be considered in AIIRD patients. This vaccine is preferably administered 4 weeks prior to initiation of bDMARDs or tsDMARDs,¹⁶⁴ but not during the treatment with bDMARDs or tsDMARDs. In patients with uncertain varicella exposure, evaluation of varicella zoster serostatus may be considered before the administration of live-attenuated HZ vaccine in order to prevent primary varicella infection following the vaccine. There is not enough data on a long-term protection and the need for vaccine booster.

Importantly, a new non-live recombinant subunit adjuvant zoster vaccine called Shingrix was licensed in Europe since March 2018 and available in some countries. The vaccine is recommended for adults 50 years and older, including immunosuppressed patients, and administered in two intramuscular doses provided 2 to 6 months apart. Shingrix has been shown to be safe and more efficacious compared with live-attenuated vaccine in elderly adults.^{165 166} Safety and efficacy of the subunit zoster vaccine have not yet been investigated in AIIRD patients. Based on the fact that Shingrix is a non-live vaccine, it may replace the live-attenuated vaccine in patients with AIIRD.

Vaccination against yellow fever should be generally avoided in patients with AIIRD

This is a newly formulated recommendation. The rationale for specifically addressing the yellow fever vaccine stems from the fact that travelling to the endemic area for yellow fever in the South America and Africa has become popular in the European countries and the question of yellow fever vaccination in patients with AIIRD is commonly raised. A discussion was held regarding keeping the recommendation #12 from the 2011 version that referred to travelling patients with AIIRD. The majority of the panel agreed that the previous recommendation #12 was of a too general character advising to vaccinate travelling AIIRD patients according to general rules, with the exception of avoidance from live-attenuated vaccines. The addition of new, though limited, experience on administration of the vaccine to patients with AIIRD led to a special recommendation for the yellow fever vaccine.

The yellow fever vaccine is a live-attenuated vaccine. A single dose of which is sufficient to confer sustained immunity against yellow fever disease. Primary vaccines typically develop a low-level viraemia, which abates as anti-yellow virus immunoglobulin M (IgM) antibodies develop 4 to 7 days post-vaccination and can persist for several years following vaccination. The vaccine is

recommended for people who are travelling to or living in areas endemic for yellow fever virus in Africa and South America.¹⁶⁷

During the task force meeting, a discussion regarding the safety profile of the primary versus booster vaccination was held. Notably, the booster vaccine was administered without sequelae to 17 Brazilian patients with RA treated with infliximab¹⁶⁸ and 31 Brazilian patients with AIIRD (RA, SLE, SSC, AS), some of them treated with bDMARDs¹⁶⁹ with an adequate immunogenicity in both studies. Yet, these results cannot be extrapolated to immunocompromised individuals receiving yellow fever vaccine for the first time. Notably, 34 French travellers with autoimmune diseases treated with GCs (prednisone or equivalent dosage 7 mg/day) were vaccinated with yellow fever vaccine with an adequate immunogenicity 6 months after immunisation, with a notion of more frequent moderate-to-severe local responses to vaccination, without serious adverse events.¹⁷⁰

The force task also discussed the option to test for yellow fever immunity by measuring the serology (IgM and IgG specific to yellow fever) prior to the planned vaccination.¹⁷¹

In conclusion, patients with AIIRD under immunosuppression should avoid yellow fever vaccination due to the risk of inducing yellow fever infection. For patients with AIIRD travelling to the endemic countries, withholding immunosuppressive therapy to allow a safe vaccination or measuring serology in previously exposed patients may be considered. The duration of withholding of immunosuppressives should be based on the pharmacokinetics of each agent.

Patients with AIIRD, in particular patients with SLE, should receive vaccinations against HPV in accordance with recommendations for the general population

The recommendation concerning HPV vaccination (#9 in the 2011 version) has been modified: instead of considering the HPV vaccine for 'selected' patients with AIIRD, the wording was changed to 'patients with AIIRD, in particular patients with SLE' and the reference to the general population guidance was added. The main reason for this modification was based on the fact that the main bulk of evidence on the epidemiology of HPV in patients with AIIRD is based on studies in female patients with SLE.¹⁷²⁻¹⁷⁶ This population is at a particular high risk to contract genital HPV infection, including high-risk serotypes for cervical dysplasia.^{173 174} Whereas there is still no data on the efficacy of HPV vaccination in patients with AIIRD, new data on the vaccine immunogenicity in patients with SLE was published since 2010. Overall, the immunogenicity of the HPV vaccine was similar in patients with SLE and controls, without significant safety signals in patients with SLE.^{30 177-179} Notably, concerns regarding the safety of HPV vaccine have been raised based by case reports and case series on the onset of autoimmune diseases following HPV vaccination.¹⁸⁰⁻¹⁸⁵ Population based studies have consistently shown that quadrivalent HPV vaccine was not associated with increased incidence of new-onset autoimmune disease in girls and women with pre-existing autoimmune disease.¹⁸⁶⁻¹⁸⁸ Therefore, based on the present data, the task force agreed that HPV vaccination should be encouraged for patients with AIIRD, with a particular focus on patients with SLE, as indicated for the general population.

Immunocompetent household members of patients with AIIRD should be encouraged to receive vaccines according to national guidelines with the exception of the oral polio vaccine

This recommendation, mainly based on expert opinion, is new and follows guidelines of international societies, such as the

Infectious Diseases Society of America.¹⁸⁹ Immunocompetent individuals, who live in a household with immunosuppressed patients, should receive inactivated vaccines as well as live-attenuated vaccines such as MMR, rotavirus, varicella and zoster vaccine, according to national guidelines. Oral polio vaccine should be avoided due to a risk of transmission to household members, with a small risk of vaccine-associated paralytic poliomyelitis in immunosuppressed household members. Highly immunocompromised patients should avoid handling diapers of infants vaccinated against rotavirus for at least 4 weeks following the administration of the vaccine. Contact with persons developing skin lesions after varicella or zoster vaccines should be avoided.¹⁸⁹

Live-attenuated vaccines should be avoided during the first 6 months of life in newborns of mothers treated with biologics during the second half of pregnancy

Since IgG crosses the placenta during the third trimester,¹⁹⁰ anti-TNF biologics, except certolizumab pegol,^{191 192} are detectable in newborns of mothers treated with biologics until 6 months after birth.¹⁹³ Based on this data, live-attenuated vaccines should be avoided during the first 6 months of life in newborns of mothers exposed to anti-TNF biologics during the second half of pregnancy.^{194–199} Despite favourable data regarding the lack of certolizumab transfer to cord blood, it is limited to a small number of patients¹⁹¹ and there is no published data concerning live vaccination of the newborns of mothers treated with certolizumab during pregnancy.

A fatal case of disseminated tuberculosis in a newborn exposed to infliximab and vaccinated with Bacillus Calmette–Guérin (BCG) vaccine, underlines the importance to avoid live-attenuated vaccines for at least first 6 months of life.^{200 201} According to the EULAR points to consider for use of anti-rheumatic drugs before pregnancy, and during pregnancy and lactation, children exposed to biologics only before week 22, can receive vaccinations according to standard protocols including live vaccines. Children exposed to biologics at the late second and during the third trimester, can follow vaccination programme, but should not receive live vaccines in the first 6 months of life.²⁰² When available, measurement of child serum levels of the biologic in question could guide the decision for or against a live vaccine.²⁰²

DISCUSSION

The 2019 update of the EULAR recommendations for vaccination in adult patients with AIIRD was developed by 21 experts including patients, rheumatologists, immunologists, an infectious disease specialist and HPR representing eight countries. The original set of 13 recommendations published in 2011 was expanded and divided into six overarching principles, followed by nine recommendations. The EULAR task force defined the overarching principles as universal ones to guide vaccination in the AIIRD population, with the first two principles focusing on the responsibility for assessment, education and implementation of the individualised vaccination programme by a treating rheumatology team, jointly shared with and consented by patients. In light of the low uptake of vaccination among the AIIRD population worldwide, emphasising the role of the treating rheumatology team in education of patients and other healthcare professionals regarding vaccines benefits should improve the uptake of vaccination. The following overarching principles were based on the new data related to efficacy, immunogenicity and safety of vaccination under immunosuppressive therapies, specifically addressing the optimal timing of vaccination, the type of vaccine (non-live vs

live-attenuated) and the underlying disease activity at the time of vaccination. In line with the 2011 recommendations, vaccination should be ideally administered during quiescent disease, prior to the planned immunosuppressive therapy. Non-live vaccines seem to be safe and sufficiently immunogenic when provided under most immunosuppressive therapies, except for B cell depletion, and probably CTLA4-Ig therapy.

Different from the previous version, current recommendations advocate a more flexible approach to administration of certain live-attenuated vaccines, that is, MMR and HZ. New, but limited, data from the paediatric patients with AIIRD concerning MMR and adult AIIRD patients concerning HZ show efficacy and immunogenicity of both vaccines in patients treated under csDMARDs and bDMARDs.

The core set of recommendations was partially modified compared with the 2011 version, whereas for most recommendations the strength of recommendations remained unchanged, with the exception of HZ. Both influenza and pneumococcal vaccinations are now recommended for the *majority* of patients with AIIRD as opposed to *all* patients, emphasising the importance of an individual infection risk assessment in each case. For example, the risk to contract influenza in a young patient with AS treated with a nonsteroidal anti-inflammatory drug (NSAID) only is not equivalent to a patient with active SLE under immunosuppression. For pneumococcal vaccination, a prime-boost strategy (PCV13 followed by PPSV23 vaccination), a new approach adapted by the CDC for immunosuppressed patients, was presented and discussed. The lack of data on the implementation and efficacy of this regimen in patients with AIIRD was discussed. The choice and sequence of pneumococcal vaccination should be in concordance with local guidelines. The recommendations concerning tetanus, HAV and HBV were expanded to include passive immunisation for selected cases. In the case of HZ vaccination, the sufficient amount of a good-quality new clinical data accumulated over the last decade permitted to upgrade the strength of recommendation to B from C-D in the previous version. Furthermore, new items addressing the vaccination of an AIIRD patient's environment, including household members and newborns of mothers treated with biologics during pregnancy, were added and discussed. The recommendations regarding the BCG vaccine, which is no longer recommended in patients with AIIRD, an approach to hyposplenic/asplenic patients and to travellers with AIIRD were omitted from the present version. Instead, a separate item regarding the yellow fever vaccination in patients travelling to endemic areas was added.

The task force discussed current controversies in the field of vaccinations. In the era of personalised medicine, there is a strong need for a tool to estimate the risk of infection on an individual basis. A tool predicting the probability of contracting serious infections within a specified amount of time will indicate the patients who are most likely to benefit from preventive measures, and accordingly tailor the appropriate vaccination programme and antimicrobial prophylaxis. To date, three scoring systems of serious infection risk were developed in the field of RA, based on the Rochester cohort,²⁰³ large administrative US databases¹⁹ and German Biologics Register RABBIT.²⁰⁴ A patient's age, functional status, disease severity and activity, comorbidities, previous infections and treatments were considered as contributors to the future risk of infections, with each scoring system using a different model of risk assessment. Notably, the Rochester score did not include treatment with bDMARDs or non-biological DMARDs in contrast to the other two scores. Thus, given the differences in the scoring systems, no direct comparison between them can be performed.

Yet, these scores represent an important step toward personalised medicine in relation to prevention of infectious disease and avoidance of ‘unnecessary’ vaccination in AIIRD patients with low risk of infection. Further research is needed to optimise individual risk stratification, enabling physicians to personalise vaccination recommendations in the near future.

The following topics were in particular discussed during the task force: HZ vaccination in the young SLE population and safety of the HPV vaccine. Currently, the HZ vaccine is approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) only for individuals aged 50 years or older. Given the significantly elevated risk of HZ infection and related comorbidities, including the risk of disseminated disease, in the paediatric/young SLE population,^{160 205–208} clinical studies are required to evaluate the efficacy and safety of the vaccine in this vulnerable population. This topic may be solved in the future with the introduction of a non-live vaccine against HZ.

Concerns have been raised following the publication of several case reports and series on the onset and exacerbation of SLE after HPV vaccination^{185 209 210} and an up to 30% rate of flare in vaccinated patients with SLE in an open study.¹⁷⁷ On the other hand, large scale studies have not shown an increase in the incidence of autoimmune diseases among young females vaccinated against HPV and a case control study on HPV vaccination in SLE patients showed a similar rate of flares in both vaccinated and unvaccinated groups (30). These reports have led the task force to the present recommendation.

In conclusion, the evidence concerning safety, immunogenicity and efficacy of vaccination among patients with AIIRD has markedly grown during the last years allowing to adjust and upgrade the recommendations and guide physicians in the use of vaccinations in AIIRD.

Author affiliations

- ¹Rheumatology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
- ²Tel Aviv University Sackler Faculty of Medicine, Tel Aviv, Israel
- ³Rheumatology and Clinical Immunology, University Medical Centre Groningen, Groningen, Netherlands
- ⁴Pediatric Immunology, University Medical Center Utrecht, Utrecht, Netherlands
- ⁵Zabludowicz Center for Autoimmune Diseases, Chaim Sheba Medical Center, Tel HaShomer, Ramat Gan, Israel
- ⁶Department of Internal Medicine (Infectious Diseases), Treant Care Group, Hoogeveen, Netherlands
- ⁷Rheumatology and Clinical Immunology, University Medical Center Groningen, Groningen, Netherlands
- ⁸Rheumatology C4-r, University Hospital Leiden, Leiden, Netherlands
- ⁹Dipartimento di Medicina Clinica e Molecolare, Sapienza Università di Roma, Rome, Italy
- ¹⁰Hopital Cochin, Rheumatology, Université Paris Descartes, Paris, France
- ¹¹Section of Rheumatology, Department of Clinical Sciences Lund, Lund, Sweden
- ¹²Rheumatology & Clin Immunology, UMC Utrecht, Utrecht, Netherlands
- ¹³Rheumatology, Aarhus University Hospital, Aarhus, Denmark
- ¹⁴Amsterdam Rheumatology Center, AMC, Amsterdam, Netherlands
- ¹⁵Rheumatology, Zuyderland MC, Heerlen, Netherlands
- ¹⁶Rheumatology, Hopital Cochin, Paris, France
- ¹⁷Rheumatology and Clinical Immunology, Giessen University, Bad Nauheim, Germany
- ¹⁸Louise Coote Lupus Unit, St Thomas’ Hospital, London, UK
- ¹⁹Patient research partner, Tel Aviv, Israel
- ²⁰Patient Research Partner, Elgin, UK
- ²¹Center for Chronic Immunodeficiency (CCI), University Medical Center Freiburg, Freiburg, Germany
- ²²Pediatrics, University Medical Center Utrecht, Utrecht, Netherlands
- ²³Tel Aviv Medical Center, Tel Aviv, Israel

Contributors All listed authors of the manuscript are the members of the EULAR assigned task force dedicated to the update of recommendations of vaccination in adult patients with AIIRD. All authors contributed to the formulation of the recommendations. In details, the steering committee of the task force that included convenor (OE), co-convenor (ULM), an immunologist (MB), a specialist in infectious disease (SvA) and methodologists (JL and RL) defined the research

questions for the systematic literature reviews (SLRs), that were performed by three fellows (VF, CR, MH), under supervision of the experts in rheumatic diseases (MB) and infectious diseases (SvA). The manuscript was drafted by VF and revised by all task members.

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Vaccination for people with AIIRD

This is the lay version of the EULAR recommendations for vaccination in adults with autoimmune inflammatory rheumatic diseases (often shortened to AIIRD). The original publication can be downloaded from the EULAR website: www.eular.org.

Furer V, et al. 2019 Update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2020 Jan;79(1):39-52

Introduction

EULAR recommendations give advice to doctors, nurses and patients about the best way to treat and manage people with AIIRD. EULAR has updated its recommendations on vaccination in adults with AIIRD.

People with AIIRD are prone to infections because of the underlying autoimmune disease, as well as the use of medicines for AIIRD that work by suppressing the immune system. Preventing infections is important in the management of AIIRD. Vaccination can prevent infections, but people with AIIRD often avoid vaccinations because they are not aware how important they are, or because they have concerns about the efficacy and safety of vaccines.

Doctors, health professionals and patients worked together to develop these recommendations. Including patients in the team ensured that the patient point of view was integrated in the recommendations. The authors looked at the new evidence on the frequency of infections in people with AIIRD, and on the efficacy and safety of different vaccinations in these people. They discussed their expert opinion to achieve a level of agreement.

What do we already know?

People with AIIRD have a higher risk of infections compared to healthy people. Vaccinations can protect people with AIIRD from infections. There are two types of vaccines: non-live, composed of a non-live bacteria or virus, and live-attenuated, composed of a weakened bacteria or virus. Before decisions about vaccinations are made, information should be collected about any previous vaccinations, reaction to vaccination, the history of a person's disease, and what medicines are being used.

What do the recommendations say?

Overall, there are six overarching principles and nine recommendations. Each recommendation is based on available scientific evidence or expert opinion.

The overarching principles say that people with AIIRD should have their vaccination history and need for further vaccination reviewed yearly by their rheumatologist, and this should be discussed with them. A vaccination plan should be tailored for each person with AIIRD. Any decisions about vaccination should be based on a shared decision between the patient and doctor. Vaccination in people with AIIRD should be done when the underlying AIIRD is quiet or well controlled with treatment. Different drugs have a different impact on the response to vaccines. In general, vaccines should be given wherever possible before starting immunosuppressive treatment. It is particularly important to vaccinate before treatment with a medicine called rituximab. Non-live vaccines, such as those to protect against 'flu, pneumococcal disease, tetanus toxoid, hepatitis B virus, hepatitis A virus, and human papilloma virus (often shortened to HPV) vaccines can be given regardless of the type of treatment that a person is taking for their AIIRD. Live-attenuated vaccines, such as those to protect against herpes zoster or mumps-measles-rubella (the MMR vaccine), should be generally avoided in people taking immunosuppressive drugs, but in some cases they may be considered with caution.

The nine recommendations relate to particular vaccines, and to vaccination of household members of people with AIIRD.

Each recommendation is based on available scientific evidence and expert opinion. The more stars a recommendation has the stronger the evidence is.

One star (*) means there is very limited or no scientific evidence, but significant expert opinion.

Two stars (**) means it is a weak recommendation with some scientific evidence and significant expert opinion.

Three stars (***) means it is a strong recommendation with quite a lot of scientific evidence and expert opinion.

Four stars (****) means it is a strong recommendation supported with a lot of scientific evidence and expert opinion.

- **The flu vaccine should be strongly considered for most people with AIIRD.*****

People with AIIRD have a higher risk of getting influenza (often shortened to flu) and are more likely to have complications from the disease than healthy people. Many clinical studies have shown that the flu vaccine (a non-live vaccine) protects against flu in people with AIIRD, and is mostly safe. If you have AIIRD, your doctor will offer you an annual flu vaccination.

- **Vaccination against pneumococcal disease should be strongly considered for most people with AIIRD.****

The risk of lung infection is particularly high for people with AIIRD. There are two non-live vaccines available that protect from lung infection caused by pneumococcal bacteria. Studies have shown that pneumococcal vaccines are effective and safe in people with AIIRD. Your doctor will discuss the best options for you.

- **People with AIIRD should receive tetanus vaccination the same as the general population.*** A different type of tetanus prevention might be needed for people taking rituximab or belimumab.***

People with AIIRD should receive tetanus toxoid vaccination (a non-live vaccine) if they might have been exposed to tetanus. This is the same as for normal people in the general population in your country. The tetanus toxoid vaccine might not work as well as it should if you are taking drugs for your AIIRD called rituximab or belimumab. If you are taking one of these drugs, another form of tetanus protection (tetanus immunoglobulins) may be offered.

- **Hepatitis A and B vaccines should be given to people with AIIRD if they are at risk.*** In specific situations, booster or passive immunization is needed.****

Vaccines against hepatitis A and B are non-live. They are offered to people at risk for this type of infection.

People with AIIRD travelling to or who live in countries where hepatitis A is common should receive hepatitis A vaccination. For full protection, the vaccine is given in two separate doses 6 months apart.

Hepatitis B vaccine should be given only to people at risk. You may be at risk of getting hepatitis B if you travel to or live in a country where hepatitis B is common. You are also at increased risk if you work in healthcare, if people you live with have the virus, or if you have sexual partners who have chronic hepatitis B infection. Intravenous drug users and men who have sex with men are also at increased risk of getting hepatitis B. If it is possible that you have been exposed to the hepatitis B

virus and have not been vaccinated, or if you did not have a good enough response to a hepatitis B vaccine, you may need to have a vaccine booster.

- Herpes zoster vaccination may be considered in people with AIIRD if they are at high risk.****
People with AIIRD are at high risk for herpes zoster infection. This is especially true if you have polymyositis, dermatomyositis or Lupus. A live-attenuated herpes zoster vaccine decreases the risk of infection. However, the use of the vaccine is limited in people who have a weakened immune system, or people taking certain drugs that suppress the immune system, such as biologics. Your doctor will discuss this vaccine with you. A new non-live zoster vaccine has been available in Europe since March 2018, although it is not yet known how well it works in people with AIIRD. The vaccine is recommended for adults over the age of 50. It is given as two doses 2 to 6 months apart.
- People with AIIRD should not usually have vaccination against yellow fever.***
The yellow fever vaccine is a live-attenuated vaccine. The vaccine is generally recommended for people traveling to or living in areas where the yellow fever virus is common, such as in Africa or South America. If you have AIIRD and are taking immunosuppressive drugs you should not get the yellow fever vaccination as there is a risk that it could cause you to develop yellow fever infection. If you have AIIRD and are travelling to a country where yellow fever is common, you might need to stop taking your immunosuppressive drugs for a while beforehand so that you can be safely vaccinated.
- People with AIIRD, especially those with Lupus, should receive vaccination against human papilloma virus the same as for the general population.****
People with AIIRD should receive the human papilloma vaccine (HPV) as is recommended for healthy people. Many studies report that women with systemic lupus erythematosus (also called SLE or Lupus) are at particular high risk for HPV infection. If you have Lupus you should consider getting the HPV vaccine.
- If you have AIIRD, the people you live with should be up to date on their vaccinations according to the normal guidelines in your country – except for the oral polio vaccine.***
Healthy people living with people with AIIRD should get their vaccinations according to normal national guidelines. The only exception is that the oral polio vaccine should not be given to people you live with if you have AIIRD, as there is a risk that you could get polio from being close by them.

If you are taking immunosuppressive drugs, you should avoid handling the diapers of infants who have been vaccinated against rotavirus in the last 4 weeks.

Contact with people who develop skin lesions after taking the varicella or zoster vaccines should also be avoided if you have AIIRD.

- If you took biologic drugs during the second half of your pregnancy, your baby should not receive any live-attenuated vaccines until they are more than 6 months old.***
Newborn babies of mothers treated with some types of biologic drugs called the tumor necrosis factor inhibitors (often shortened to TNF) during pregnancy might have a small amount of the drug in their system after they are born, and until they are 6 months old. This is the case for all TNF inhibitors, except a drug called certolizumab. If you took a TNF inhibitor after week 22 of your pregnancy, your baby should not receive a live-attenuated vaccine until they are older than 6 months. If you took a TNF inhibitor before week 22 of your pregnancy, your baby can have the normal vaccinations recommended for newborns in your country.

Summary

Overall, the recommendations say that it is important for you and your doctor to work together to protect you from vaccine-preventable infections. If you have a rheumatic disease, these recommendations will guide you in the use of vaccination. If you have any questions or concerns about your disease or your medication, you should speak to your rheumatology team.