



# The Practice Guideline for Vaccinating Korean Patients With Autoimmune Inflammatory Rheumatic Disease

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To develop a clinical practice guideline for vaccination in patients with autoimmune inflammatory rheumatic disease (AIIRD), the Korean College of Rheumatology and the Korean Society of Infectious Diseases developed a clinical practice guideline according to the clinical practice guideline development manual. Since vaccination is unlikely to cause AIIRD or worsen disease activities, required vaccinations are recommended. Once patients are diagnosed with AIIRD, treatment strategies should be established and, at the same time, monitor their vaccination history. It is recommended to administer vaccines when the disease enters the stabilized stage. Administering live attenuated vaccines in patients with AIIRD who are taking immunosuppressants should be avoided. Vaccination should be considered in patients with AIIRD, prior to initiating immunosuppressants. It is recommended to administer influenza, *Streptococcus pneumoniae*, hepatitis A, hepatitis B, herpes zoster, measles-mumps-rubella virus, human papillomavirus, and tetanus-diphtheria-pertussis vaccines in patients with AIIRD; such patients who planned to travel are generally recommended to be vaccinated at the recommended vaccine level of healthy adults. Those who live in a household with patients with AIIRD and their caregivers should also be vaccinated at levels that are generally recommended for healthy adults. (*J Rheum Dis* 2020;27:182-202)

**Key Words.** Autoimmune inflammatory rheumatic disease, Vaccine, Immunization, Guideline

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## INTRODUCTION

Autoimmune inflammatory rheumatic disease (AIIRD) involves various organs due to immune dysregulation; although, causes have not been identified. In general, patients with AIIRD are at relatively high risk for infectious diseases compared to the general population [1-4]. This is due to loss of the normal immune response in the pathogenesis of the disease itself but is also associated with drug-related factors, such as glucocorticoid and other immunosuppressants, during treatment. In addition, comorbidities, such as Felty's syndrome and interstitial pneumonia, and disabilities caused by the diseases or operations are also identified as risk factors. As the causes of the diseases have recently started to be discovered, targeted therapies, such as biologic agents and small molecule inhibitors, have been developed and widely used which may increase the possibility of new opportunistic infections that are different from what are related to conventional immunosuppressants [5,6].

In general, vaccination is one of the most effective methods for preventing infectious diseases. However, patients with AIIRD have not been adequately vaccinated to date despite their necessity [7,8]. The most significant reason is potentially the lack of understanding of the necessity of vaccination among healthcare providers who treat the disease and the patients. Although they understand the necessity, there seems to be concern regarding the possibility that vaccination can worsen the AIIRDs' activity or that vaccination may not be effective for patients with AIIRD to acquire adequate immunity. Numerous clinical practice guidelines have been published around the world to promote the interest of doctors and patients and raise their awareness regarding the latest knowledge. Many efforts have been made to inform the global medical community regarding the latest information on the vaccination of patients with AIIRD and induce suitable changes in practice patterns.

In line with changes in clinical settings and the trends in the development of practice guidelines at home and abroad, there has also been a growing need for a practice guideline for vaccinating patients with AIIRD in Korea considering its health care system, practice patterns, and environmental characteristics. To develop a practice guideline for vaccination, the Korean Society of Infectious Diseases (KSID) and the Korean College of Rheumatology (KCR) formed a vaccination guideline development committee composed of rheumatologists who diagnose and

treat AIIRD, vaccine experts, and research methodologists. The total time for the guideline to be developed was 2 years and 6 months, between June 2017 and December 2019. This guideline is intended for experts in rheumatology and infectious diseases and for primary care providers who encounter patients with AIIRD intending to inform them of primary vaccines, methods to administer vaccines, and considerations in vaccination.

## DEVELOPMENT OF CLINICAL GUIDELINE

### Determination of targeted patients and vaccines of practice guideline

The targeted patients of this practice guideline include adults with AIIRD who are aged  $\geq 19$  years excluding children while targeting the following AIIRD diseases: rheumatoid arthritis; systemic lupus erythematosus; antiphospholipid syndrome; adult still's disease; systemic sclerosis; scleroderma; relapsing polychondritis; polymyalgia rheumatica; mixed connective tissue disease; spondyloarthritis; Behçet's disease; vasculitis; granulomatosis with polyangiitis (Wegener's granulomatosis); eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome); polyarteritis nodosa; Takayasu's arteritis; giant cell arteritis; Goodpasture syndrome; cryoglobulinemic vasculitis; dermatomyositis; polymyositis; amyopathic dermatomyositis; inclusion body myositis; antisynthetase syndrome; eosinophilic myositis; eosinophilic fasciitis; psoriatic arthritis; and periodic fever syndrome. The vaccines included in this practice guideline were limited to those primarily recommended for adults as follows: influenza vaccine; pneumococcal vaccine; hepatitis B vaccine; hepatitis A vaccine; human papillomavirus (HPV) vaccine; tetanus-diphtheria-pertussis vaccine; herpes zoster vaccine; and measles-mumps-rubella (MMR) vaccine.

### Formation of the practice guideline development committee and the working committee

A practice guideline development committee was formed, composed of four rheumatologists, four infectious disease specialists, and one preventive medicine specialist to determine targeted patients and vaccines, discuss methods to develop a detailed practice guideline, and key questions. A separate working committee was also formed, composed of seven rheumatologists and seven infectious disease specialists, to review key questions related to each vaccine and develop recommendations.

Those with a conflict of interest to any vaccine product were excluded from the committees.

As no sufficient evidence of the efficacy and safety of vaccination of patients with AIIRD was available, existing evidence-based practice guidelines were adapted. Additionally, to provide up-to-date information, we reviewed and incorporated the results of studies that were published after the search period of the most recent guideline. The additionally reviewed knowledge was limited to vaccines that have been recently and actively researched including the pneumococcal, HPV, and tetanus-diphtheria-pertussis vaccines. This practice guideline was developed as per the clinical practice guideline development manual distributed by the National Evidence-based healthcare Collaborating Agency [9].

### Selection of key questions for practice guideline

Key questions were developed by the practice guideline development committee through discussion based on questions that can be raised in clinical settings, and the developed key questions were divided into general questions related to vaccination and specific questions on individual vaccines. At first, 14 general questions about vaccination and 19 questions about individual vaccines were developed. Since the answers to some questions were not supported by evidence, existing practice guidelines and studies were reviewed and 18 key questions were selected and revised. They were secondarily reviewed by the Working Committee, and the final 15 key questions were selected considering the existence of evidence for the

questions and their applicability in Korea (Table 1).

### Searches and selection of existing practice guidelines

Practice guidelines were searched using combinations of keywords including vaccine, autoimmune inflammatory rheumatic disease and medication. Search terms included the following vaccines: influenza vaccine; pneumococcal vaccine; hepatitis B vaccine; hepatitis A vaccine; HPV vaccine; tetanus-diphtheria-pertussis vaccine; herpes zoster vaccine; and MMR vaccine. The rheumatoid diseases included in this guideline are as follows: rheumatoid arthritis; systemic lupus erythematosus; antiphospholipid syndrome; adult still's disease; systemic sclerosis; scleroderma; relapsing polychondritis; polymyalgia rheumatica; mixed connective tissue disease; spondylarthritis; Behçet's disease; vasculitis; granulomatosis with polyangiitis (Wegener's granulomatosis); eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome); polyarteritis nodosa; Takayasu's arteritis; giant cell arteritis; Goodpasture syndrome; cryoglobulinemic vasculitis; dermatomyositis; polymyositis; amyopathic dermatomyositis; inclusion body myositis; antisynthetase syndrome; eosinophilic myositis; eosinophilic fasciitis; psoriatic arthritis; and periodic fever syndrome. The drugs included in this guideline are: disease-modifying antirheumatic drugs (DMARD); tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) blocking agent; glucocorticoid; methotrexate; sulfasalazine; leflunomide; hydroxychloroquine; azathioprine; mycophenolate; cyclosporine; cyclopho-

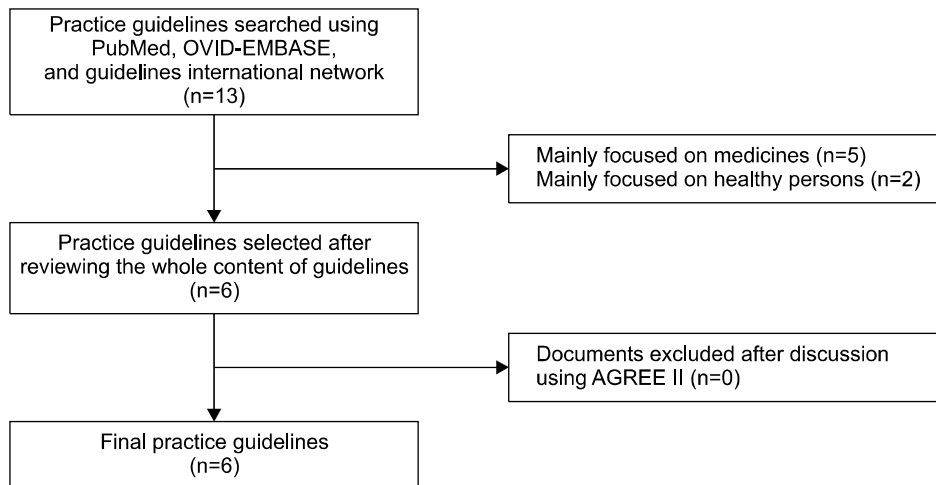
**Table 1.** List of Key Questions

Key Question 1. Does vaccination aggravate autoimmune inflammatory rheumatic disease (AIIRD)?
Key Question 2. Are live attenuated vaccines safe for patients with AIIRD?
2-1. Are live attenuated vaccines safe for patients who do not receive immunosuppressive therapies?
2-2. Are live attenuated vaccines safe for patients who receive immunosuppressive therapies?
Key Question 3. Is a survey on the vaccination history of AIIRD patients helpful in establishing treatment strategies?
Key Question 4. When should vaccines be administered to patients with AIIRD considering their treatment status?
Key Question 5. Is vaccination helpful in preventing endemic diseases for patients with AIIRD contemplating international travel?
Key Question 6. Should those who live in household members with patients with AIIRD and their caregivers receive vaccines?
Key Question 7. Are the vaccines recommended to patients with AIIRD and administering each vaccine safe and effective?
7-1. Are influenza vaccines safe and effective?
7-2. Are pneumococcal vaccines safe and effective?
7-3. Are hepatitis B vaccines safe and effective?
7-4. Are hepatitis A vaccines safe and effective?
7-5. Are human papillomavirus vaccines safe and effective?
7-6. Are tetanus-diphtheria-pertussis vaccines safe and effective?
7-7. Are herpes zoster vaccines safe and effective?
7-8. Are measles-mumps-rubella vaccines safe and effective?

sphamide; tacrolimus; cyclophosphamide; infliximab; etanercept; abatacept; adalimumab; golimumab; rituximab; belimumab; tocilizumab; certolizumab; ustekinumab; canakinumab; and anakinra. The documents published between January 2010 and August 2018 were searched and a total of 13 practice guidelines written in English were obtained from websites including PubMed, OVID-EMBASE, and Guidelines International Network.

We reviewed the content of 13 practice guidelines to preliminarily determine whether they fit the criteria to be included in the development of this practice guideline. Out of a total of 13 practice guidelines, five that were solely limited to medicines, and two that were mainly focused

on healthy individuals, rather than vaccination of patients with AIIRD, were excluded. Then, a secondary screening was performed on the guidelines that were initially searched to identify the authors, whether they were evidence-based guidelines, and whether the recommendation grades were described. For each practice guideline, three guideline development and working committee members, using the Appraisal of Guidelines Research and Evaluation (AGREE) II, an appraisal tool for practice guidelines, scored the following items: their scope and objective; management of conflicts of interest; rigidity of development; clarity of expressions; applicability; and independence of editing. Based on the results, a total of six



**Figure 1.** Procedure for searching and screening literature for adapting a practice guideline. AGREE: Appraisal of Guidelines Research and Evaluation.

**Table 2.** Final practice guidelines selected through an appraisal using AGREE II

	Title	Country/area	Organization	Year of publication
1	EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases	Europe	European League Against Rheumatism	2011
2	Canadian Rheumatology association recommendations for the pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs: part II safety	Canada	Canadian Rheumatology Association	2012
3	Clinical practice guideline for vaccination of the immunocompromised host	USA	Infectious Diseases Society of America	2013
4	2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis	USA	American College of Rheumatology	2015
5	Vaccination recommendations for adult patients with autoimmune inflammatory rheumatic diseases	Switzerland	The Federal Commission for Swiss Vaccination Issues	2015
6	Recommendations for vaccination in adult patients with systemic inflammatory rheumatic diseases from the Portuguese Society of Rheumatology	Portugal	Portuguese Society of Rheumatology	2016

AGREE: Appraisal of Guidelines Research and Evaluation, EULAR: European League Against Rheumatism.

practice guidelines suitable for adaptation were finally selected (Figure 1, Table 2).

### Review of the procedure for writing the practice guideline and up-to-datedness

The practice guideline development committee, comprehensively reviewed and collected recommendations provided in the selected six practice guidelines focusing on the key questions selected by the committee, while the working committee described recommendations for key questions and their evidence, based on the collected content and the latest studies. The level of evidence (LOE) of each recommendation was graded following the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology into high, moderate, low and very low, and the strength of recommendation (SOR) was classified into strong recommendation, weak recommendation, weak against, and strong against (Tables 3 and 4).

An additional literature review was conducted on the pneumococcal, HPV, and tetanus-diphtheria-pertussis vaccines, out of the eight vaccines addressed in this guideline because they have been actively researched on the targets of vaccines, immunogenicity, changes in vaccination methods and new vaccines. PubMed and EMBASE were used to search for data. Since the selected six practice guidelines were searched among publications released by October 2014, those published between November 2014 and October 2018 were additionally searched to review their up-to-datedness. We limited our search to systematic reviews, randomized controlled studies, cohort studies, case-control studies, and guidelines written in English. We applied the same keywords used to search the practice guidelines mentioned above. The title and abstract of the searched studies were reviewed by the practice guideline development committee

and their fitness for this study's purpose was cross-confirmed by two individuals. Those that failed to reach consensus were reviewed by two individuals together to determine whether to include them. Out of 445 studies first searched regarding the pneumococcal vaccine, six were included in the final review; out of 902 studies regarding the HPV vaccine, seven were included; out of 925 studies regarding the tetanus-diphtheria-pertussis vaccine, six were included. The selected studies were transferred to the working committee to be utilized in writing this practice guideline (Table 5).

### Survey on consensus of recommendations in the practice guideline

Data on general recommendations for vaccination and recommendations for each vaccine were shared online among 23 members of the practice guideline development and working committees who reviewed them. To reach a consensus on each recommendation among them, face-to-face meetings were additionally held. Prior to building consensus, it was confirmed whether those involved in the development of this guideline had received support regarding the targeted vaccines and medications. They expressed agreement and disagreement based on the existing practice guidelines, the latest findings, the current status of the Korean medical services, the benefits of the vaccines, and abnormal responses. They scored their agreement with each recommendation using a 9-point scale; when the score of over 80% of committee members reached between 7~9 points, it was considered that the recommendation reached a consensus. When they failed to reach a consensus on a certain recom-

**Table 3.** Definition of level of evidence (LOE)

LOE	Description
High	Very unlikely to change confidence in the estimate of effect by an additional study
Moderate	Likely to change confidence in the estimate of effect by an additional study
Low	Highly likely to change confidence in the estimate of effect by an additional study
Very low	Not sure about confidence in the estimate of effect

**Table 4.** Definition of strength of recommendation (SOR)

SOR	Description
Strong recommendation	Recommended to follow the course of action because there is sufficient evidence of desirable effects
Weak recommendation	Recommended to conditionally provide the course of action (test) or to provide it for certain individuals at the discretion of specialty providers
Weak against	Recommended not to follow the course of action, if feasible, because there is some evidence of undesirable effects
Strong against	Recommended not to follow the course of action because there is sufficient evidence of undesirable effects

**Table 5.** The literature reviewed to reflect the latest knowledge

	Title	Study design	Year of publication
1	Immunizations following solid-organ transplantation	Review	2014
2	Immunogenicity and safety of the bivalent human papilloma virus (HPV) vaccine in female patients with juvenile idiopathic arthritis: a prospective controlled observational cohort study	Case-control study	2014
3	Effect of abatacepton the immunogenicity of 23-valent pneumococcal polysaccharide vaccination (PPSV23) in rheumatoid arthritis patients	Randomized controlled study	2015
4	Opsonic and antibody responses to pneumococcal polysaccharide in rheumatoid arthritis patients receiving golimumab plus methotrexate	Randomized controlled study	2015
5	The risk of pneumococcal infections after immunization with pneumococcal conjugate vaccine compared to non-vaccinated inflammatory arthritis patients	Case-control study	2015
6	The association between antibody levels before and after 7-valent pneumococcal conjugate vaccine immunization and subsequent pneumococcal infection in chronic arthritis patients	Case-control study	2015
7	HPV vaccine trials and tribulations: clinical perspectives	Review	2015
8	Pertussis prevalence in Korean adolescents and adults with persistent cough	Retrospective observation study	2015
9	Evaluation of the immunogenicity of the 13-valent conjugated pneumococcal vaccine in rheumatoid arthritis patients treated with etanercept	Case-control study	2016
10	HPV infection and vaccination in Systemic Lupus Erythematosus patients: what we really should know	Review	2016
11	Recommended vaccinations for asplenic and hyposplenic adult patients	Review	2016
12	Prophylactic HPV vaccination: past, present, and future	Review	2016
13	Pneumococcal vaccination in autoimmune rheumatic diseases	Review	2017
14	Committee opinion no. 704: human papillomavirus vaccination	Guideline	2017
15	Practice alert: Advisory Committee on Immunization Practices (ACIP) vaccine update, 2017	Guideline	2017
16	Committee opinion no. 718: update on immunization and pregnancy: tetanus, diphtheria, and pertussis vaccination	Guideline	2017
17	Tdap vaccination coverage during pregnancy - selected sites, United States, 2006 ~ 2015	Retrospective observation study	2017
18	Prevention of pertussis, tetanus, and diphtheria with vaccines in the United States: recommendations of the ACIP	Guideline	2018
19	Infections in pregnancy and the role of vaccines	Review	2018

Tdap: tetanus-diphtheria-pertussis, ACIP: Advisory Committee on Immunization Practices.

mendation, they revised and adjusted its strength through discussion, ultimately voting on a new recommendation to reach a consensus.

### Final review, approval, and distribution of the practice guideline

The developed practice guideline was reviewed and approved by the external examiners selected by the KCR and the KSID. To receive feedback from patients with AIIRD who were vaccination targets, the guideline was shared with the Association of Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), Ankylosing

Spondylitis (AS) patients. The KCR and KSID agreed to jointly publish and distribute the final practice guideline. This guideline will be updated after 5 years according to newly published guidelines and studies.

## GENERAL RECOMMENDATIONS

### KQ 1. Does vaccination aggravate AIIRD?

Vaccination is unlikely to cause or aggravate AIIRD and generally recommended in AIIRD patients (LOE: Low/SOR: Strong recommendation).

The possibility that vaccination causes AIIRD is low; however, autoimmune responses such as Guillain-Barré syndrome and idiopathic thrombocytopenic purpura (ITP) were reported after vaccination. It has been rarely reported that adjuvants can be a potential cause of AIIRD [10-17]. The majority of studies, however, have reported that vaccines can be safely administered without worsening underlying diseases, and large-scale epidemiological studies also reported that the degree of abnormal responses observed in patients with AIIRD was not different from that observed in the general population [18-20].

**KQ 2. Are live attenuated vaccines safe for patients with AIIRD?**

KQ 2-1. Are live attenuated vaccines safe for patients who do not receive immunosuppressive therapies?

If AIIRD patients need to take live attenuated vaccines, they have to take vaccination while they are not taking immunosuppressive agents (LOE: Very low/SOR: Strong recommendation).

KQ 2-2. Are live attenuated vaccines safe for patients who receive immunosuppressive therapies?

AIIRD Patients on immunosuppressive agents should not take live attenuated vaccines (LOE: Very low/SOR: Weak against).

The live attenuated vaccine is created by reducing the virulence of germs and viruses to lower the potential risk of infection while keeping immunogenicity. Unless there is a specific prohibition, live attenuated vaccines can be administered to patients with AIIRD who do not take immunosuppressive medications. However, since concern exists regarding potential severe infections by administering live attenuated vaccines to patients with AIIRD who take immunosuppressants, delivering these vaccines to the aforementioned patients should be avoided, when feasible. Recently, several biologic agents targeting patients with AIIRD have been developed and widely used; however, they must be cautiously administered as they lower immunity. The majority of studies also prohibit the administration of live attenuated vaccines to patients with AIIRD who are taking immunosuppressants [21-26]. Still, MMR, varicella, and herpes zoster vaccines can be restrictively considered depending on the level of immunosuppression by performing a risk-benefit analysis for individual patients. The risk of infections that may be caused by administering live attenuated vaccines can

change depending on the type of vaccines and the level of immunosuppression. Herpes zoster vaccines can be considered for those who used a steroid for a short period within 2 weeks, and were given with a dose of >20 mg of prednisolone per day, a dose of  $\geq 0.4$  mg/kg of methotrexate per week, and a dose of >3.0 mg/kg of azathioprine per day [23].

**KQ 3. Is a survey on the vaccination history of AIIRD patients helpful in establishing treatment strategies?**

Once patients are diagnosed with AIIRD, their vaccination history needs to be surveyed while treatment strategies are being established (LOE: Expert opinion/SOR: Strong recommendation).

Vaccines should be safely administered to patients with AIIRD while keeping immunogenicity. Immunosuppressants are not often administered immediately after patients are diagnosed with AIIRD. In these cases, live attenuated vaccines can be safely administered to the patients prior to treatment initiation minimizing the reduction of immunogenicity caused by immunosuppressants. For this reason, it is important to check the vaccination history of patients with AIIRD prior to treatment of immunosuppressants. If any method to test antibodies related to target vaccines is available, the test needs to be conducted in the early stage of diagnosis and vaccination plans need to be established based on the test results.

**KQ 4. When should vaccines be administered to patients with AIIRD considering their treatment status?**

KQ 4-1. Vaccines need to be administered to patients when their AIIRD is in a stable state (LOE: Very low/SOR: Strong recommendation).

KQ 4-2. AIIRD patients have to get vaccinated, if feasible, before commencing immunosuppressive therapies (LOE: Very low/SOR: Strong recommendation).

Those who treat patients with AIIRD should recommend vaccination, if feasible, prior to the planned immunosuppression for proper immunity building and safe vaccination [21-23,25,26]. Since immunogenicity is generally created within 3 weeks after administering live attenuated vaccines, it is recommended to administer vaccines 4 weeks prior to planned immunosuppression (Table 6) [21]. The recommended timing, however, can

**Table 6.** Recommended timing of vaccination after discontinuing AIIRD treatment by the type of AIIRD medications

Drug category	Medication	Half-life period	Inactivated vaccine	Live attenuated vaccine
Glucocorticoid	Prednisone	3 ~ 4 hours	No limitation to vaccination*	1 month
	Synthetic DMARD			
	Methotrexate	3 ~ 10 hours		1 ~ 3 months
	Leflunomide	14 days		3 ~ 24 months
Biologic DMARD	Etanercept	4.3 days		1 month
	Adalimumab	14 days		3 month
	Certolizumab	14 days		
	Golimumab	12 days		
	Infliximab	8 ~ 10 days		
	Abatacept	13 days		3 month
	Tocilizumab	13 days		
	Rituximab	21 days	6 ~ 12 months	

AIIRD: Autoimmune Inflammatory Rheumatic Disease, DMARD: disease-modifying antirheumatic drugs. \*Although there is no limitation to vaccination, decisions should be made in consideration of the urgency of vaccination and the level of immunosuppression.

differ depending on the type of immunosuppressants. When administering live vaccines prior to anti-TNF and rituximab therapies, it is recommended to separate them by a 4-week interval, but in the case of administering abatacept or tocilizumab, an interval of 2 ~ 3 weeks is recommended [27-31]. Unlike them, inactivated vaccines can be relatively safely administered while administering conventional DMARDs or biologic agents [22,26]. However, since immune responses can be slightly different depending on the type of administered immunosuppressive medications, vaccinations should be carefully performed. Combination therapies with methotrexate or anti-TNF drugs were reported to reduce the immunogenicity of vaccines, while no issue associated with the immunogenicity of influenza and pneumococcal vaccines was reported in a group to which adalimumab was solely administered [32-34]. While it was reported that humoral immune responses were reduced when abatacept was administered, no significant effect was observed in the group of tocilizumab [35,36]. Rituximab, a monoclonal antibody against the protein CD20, significantly reduces humoral immune responses due to loss of B cells, and for this reason, it is recommended to vaccinate patients at least 4 weeks prior to treatment [22,37]. As such, since immunosuppression can impede immune responses after vaccination, vaccination is recommended in general prior to treatment, but it is not recommended to delay treatment for AIIRD for completing vaccinations [21].

Since a decrease in the immunogenicity of vaccines caused by immunosuppressive therapies is dependent on

the total amount of medications that a patient is taking, it would be better to administer vaccines to those who have already been receiving immunosuppressive therapies when the total amount of medications is the lowest [25]. In addition, the timing of administering live attenuated vaccines after discontinuation of immunosuppressive therapies differs depending on the type of medications and thus should be determined in consideration of the pharmacodynamic characteristics of medications [26]. In general, when taking  $\geq 10 \sim 20$  mg of prednisolone for over 2 weeks, it is recognized as a high-dose steroid, and it is recommended to separate discontinuation of the medication and vaccination by a 4-week interval [38,39]. When a large amount of medications were intravenously injected, it is recommended to suspend vaccination at least for 3 months [38]. When 0.4 mg/kg/week or 20 mg/week of methotrexate or more was administered, it is recommended to administer vaccines 1 ~ 3 months after discontinuation of the medication [25,40]. In the case of leflunomide, due to its long half-life period, it is recommended to separate discontinuation of the medication and vaccination by the interval of 3 ~ 6 months. However, it can remain in the body in an activated state for as long as 2 years; therefore, it is recommended to administer vaccines 2 years after discontinuation [25,38,40]. As etanercept, among anti-TNF drugs, has a relatively short half-life period compared to other medications, vaccination can be considered 1 month after administering the medication. Conversely, other medications including adalimumab, certolizumab, and infliximab should be discontinued for 3 months before administering vaccines

[25,38,40]. In the case of biologic agents like abatacept, tocilizumab, and ustekinumab, it is recommended to administer vaccines 3 months (5 times their half-life period) after discontinuation. Regarding rituximab, however, it is recommended to separate discontinuation of the medication and vaccination by the interval of 6~12 months both for live attenuated vaccines and inactivated vaccines considering the recovery period of B cells [22,25,26,28-30,40].

**KQ 5. Is vaccination helpful in preventing endemic diseases for patients with AIIRD contemplating international travel?**

Patients with AIIRD contemplating travel have to receive vaccines as is generally recommended for healthy persons (LOE: Low/SOR: Strong recommendation).

Immunocompromised patients are more likely than healthy individuals to contract infectious diseases when on vacation to places where infectious diseases are endemic. For this reason, it is important to consult their doctor regarding vaccination in advance. Since some vaccines require multiple doses over a certain period, it is recommended to have a consultation 6 months before traveling; but, in case of an unexpected vacation, it is necessary to have a consultation as early as possible to increase patients' safety and immunogenicity [22]. The vaccines that are recommended for those contemplating travel to the aforementioned places include hepatitis A and B, influenza, meningococcus, pneumococcus, tetanus, typhoid, cholera, rabies, tick-borne encephalitis virus, yellow fever, and MMR vaccines.

**1) Yellow fever vaccination**

Yellow fever is an endemic infectious disease in the tropical areas of Africa and the Central and South America, having a mortality rate of over 20% due to the absence of an effective cure. Therefore, those who contemplate travel to areas where yellow fever is endemic are required to receive yellow fever vaccines; however, since these vaccines, compared to other live attenuated vaccines, show a high virus replication capacity, patients who receive immunosuppressive therapies are not recommended to receive them due to their potential risk of infection [25]. In general, it is recommended for patients with AIIRD to avoid travel to areas where yellow fever is endemic; but, those who inevitably have to visit such areas should write

a waiver that states the reason why they cannot be vaccinated [41].

**KQ 6. Should those who live in a household with patients with AIIRD and their caregivers receive vaccines?**

Those who live in households with patients with AIIRD and their caregivers have to receive generally recommended vaccines. In particular, influenza, measles-mumps-rubella (MMR), varicella, and herpes zoster vaccines need to be administered based on the same schedules for healthy persons (LOE: Moderate/SOR: Strong recommendation).

Those who live in households with patients with AIIRD and are immunocompetent should be vaccinated according to the Korean guideline for vaccination. They should be vaccinated against influenza every year, and MMR, rotavirus, varicella, and herpes zoster vaccines should be administered according to their general recommendations [42-48]. In some cases, yellow fever and oral typhoid vaccines should be administered if necessary. However, as live vaccines can spread viruses after administration, those who received such vaccines, in general, need to be careful when in contact with patients who are receiving immunosuppressive therapies, for 2 weeks following vaccination. If there is any family member who was vaccinated against rotavirus, patients with AIIRD should avoid contacting the vaccinated family member's feces for 4 weeks and should maintain hand hygiene.

## VACCINATION RECOMMENDATIONS BY VACCINE

### Influenza vaccine

Patients with AIIRD have to take influenza vaccines every year (LOE: Moderate/SOR: Strong recommendation).

**1) Vaccination targets**

All patients with AIIRD should be vaccinated against influenza. There are only a few epidemiological studies on influenza infection targeting patients with AIIRD. A study that targeted individuals aged  $\geq 65$  years reported that the number of those who were hospitalized due to influenza infections and complications increased in the group of patients with chronic diseases including rheu-

matoid diseases and vasculitis [49]. A retrospective study, targeting 46,030 patients with rheumatoid arthritis reported that their influenza infection rate was high (409.33 vs. 306.12 persons/100,000 patients-days) and that the rate of complications was 2.75 times higher [50]. No relationship was observed between the increasing rates and the medications used for the patients. In general, since patients with AIIRD are judged to be more likely to contract influenza and complications, it is recommended to administer influenza vaccines to all patients with AIIRD, and most guidelines also recommend influenza vaccines as the highest priority vaccine.

## 2) Effects and efficacy of vaccine

The immunogenicity of patients with rheumatoid arthritis is similar to that of healthy individuals, and immunogenicity can be maintained even when conventional synthetic DMARDs (csDMARDs) or anti-TNF drugs [34,51-61] are administered. It has often been reported that the immunogenicity of patients with lupus is slightly decreased, and many studies reported no significant differences in immunogenicity between patients with lupus and healthy individuals [18,20,57,62-70]. Patients with granulomatosis with polyangiitis, systemic sclerosis, and Sjögren's syndrome were also reported to show no differences in immunogenicity compared to healthy persons [19,71-73]. Only few studies exist, regarding the effects of influenza vaccines on patients with AIIRD; however, a large-scale observational study that targeted patients with rheumatoid arthritis reported that the infection rate of the vaccinated group decreased by 17% (95% confidence interval [CI], 5%~29%) [74]. Another study that targeted patients with rheumatoid arthritis and systemic erythematosus lupus also reported that the share of those who contracted pneumonia, acute bronchitis, and virus infection in the vaccinated group was significantly lower than that of the non-vaccinated group [74,75]. The immunogenicity of influenza vaccines can differ, depending on the use of immunosuppressants and the type of medications. However, it was reported that the immunogenicity of patients with AIIRD was generally similar to or slightly lower than that of healthy individuals.

## 3) Safety of vaccine

Inactivated influenza vaccines can be safely administered, even in an immunocompromised state. Their side effects in patients with AIIRD are not different from those in healthy persons [51,57].

## 4) Vaccination methods

Since protective immunity to influenza can be sufficiently achieved when influenza vaccines are administered before influenza is prevalent, influenza vaccines should be administered prior to the prevalence of influenza, and even amid the prevalence of influenza, patients should be vaccinated as early as possible. In Korea, influenza is prevalent from November to April. A dose of intramuscular injection is administered in general, but the methods of administration can differ depending on the dosage of vaccines. Therefore, they should be administered following their respective instructions. When patients are receiving immunosuppressants, the timing of vaccination should be determined, considering the patients' disease, immunosuppression level, and half-life period of the medications.

## Pneumococcal vaccine

Patients with AIIRD have to take pneumococcal vaccines (LOE: Low/SOR: Strong recommendation).

## 1) Vaccination targets

*Streptococcus pneumoniae* accounts for about 30%~40% of community-acquired pneumonia. The infection of *S. pneumoniae* can cause severe complications or death particularly in persons aged  $\geq 65$  years, patients with chronic diseases, and immunocompromised patients. Although epidemiological data available on the infection of *S. pneumoniae* in patients with AIIRD are sufficient, it was reported that patients who used anti-TNF drugs showed a 5 times higher incidence of pneumonia (5.97/1,000 vs. 1.07~1.2/1,000 patients-days) than healthy persons [76]. The mortality rate of patients with rheumatoid arthritis from pneumonia increased by 2~5 times and the hospitalization rate of patients with rheumatoid arthritis is 2 times higher than that of general persons [77]. Since the share of those who contract infections and complications caused by *S. pneumoniae* among patients with AIIRD increases, all patients with AIIRD are recommended to be vaccinated against *S. pneumoniae*.

## 2) Effects and efficacy of vaccine

In general, the effects of *S. pneumoniae* vaccines on patients with AIIRD are nearly identical to those on healthy persons [78-84]. As for the effects of medications administered to patients with AIIRD on the immuno-

genicity of vaccines, csDMARDs did not show any effect, while methotrexate, rituximab, and abatacept were reported to decrease immunogenicity. The immunogenicity of pneumococcal vaccines differed depending on the type of anti-TNF drugs in early studies. In a randomized controlled trial that studied the effect of a pneumococcal polysaccharide vaccine 23 (PPSV23) in patients with rheumatoid arthritis, the effect of pneumonia prevention was unclear. However, it was conducted on a small number of patients with a severe immunocompromised condition. Furthermore, some reports show reduced immunogenicity in some patient groups. Therefore, efforts to optimize the effects such as adjusting the timing of inoculation are necessary [85].

### 3) Safety of vaccine

Pneumococcal vaccines, as inactivated vaccines, can be administered regardless of the state of immunity, and do not affect the activity of AIIRD. No valid epidemiological study has been conducted yet regarding the safety of pneumococcal vaccines for patients with AIIRD [77]. It was reported that the aluminum salts used as a vaccine adjuvant may cause fever, pain at the injection site, and malaise and can cause autoimmune/inflammatory syndrome induced by adjuvants (ASIA); however, no study has been reported on streptococcal vaccines [86]. Yet, it was reported that both strong local and excessive systemic inflammatory responses were observed in patients with Behçet's disease after vaccination, thus making it necessary to carefully observe patients after vaccination [87]. Another study reported that abnormal responses to pneumococcal vaccines were observed in infants who were less than 1 year old and had Kawasaki disease [88].

### 4) Vaccination methods

As of 2019, 2 pneumococcal vaccines are available for adults: pneumococcal conjugate vaccine 13 (PCV13) and PPSV23. PCV13 shows good immunogenicity and also proved to be effective in preventing pneumonia in healthy adults. The finding that it is cost-effective to give both vaccines to high-risk patients of pneumococcal infection is true; therefore it is safe to administer both the PCV13 and the PPSV23 to adult patients with AIIRD [89]. A booster effect is caused when administering the PCV13 first, while a hypo-responsiveness is caused when administering the PPSV23 first; therefore, it is advisable to administer the PCV13 first [90].

① Unvaccinated patients against pneumococcal vac-

cines: A dose of PCV13 should be administered first, and 1 dose of PPSV23 should be administered at least 8 weeks later. A dose of PPSV23 should be additionally administered 5 years after the last vaccination.

② Patients who were administered with 1 dose of PPSV23: A dose of PCV13 should be administered 1 year after the administration of PPSV23. A dose of PPSV23 should be additionally administered at least 8 weeks after the administration of PCV13 and 5 years after the previous administration of PPSV23.

③ Patients who were administered with 2 doses of PPSV23: A dose of PCV13 should be administered 1 year after the last vaccination.

④ Patients who were administered with a dose of PCV13 and 2 doses of PPSV23 before the age of 65: A dose of PPSV23 should be additionally administered after turning 65, and 5 years after the previous administration of PPSV23.

## Hepatitis B vaccine

AIIRD patients who have no hepatitis B antibody have to take Hepatitis B vaccines (LOE: Low/SOR: Strong recommendation).

### 1) Vaccination targets

The use of immunosuppressants in patients with AIIRD is likely to reactivate hepatitis B, causing a high risk of complications [91-93]. A retrospective study that targeted 123 HBsAg-positive patients with rheumatoid arthritis reported that hepatitis B was reactivated in 30 patients (24.4%) during treatment [94]. Multiple guidelines related to the vaccination of patients with AIIRD also recommend to vaccinate patients with AIIRD with no hepatitis B antibody (all HBsAg, anti-HBc, and anti-HBs-negative) and unvaccinated individuals. Hepatitis B vaccines are more actively recommended for high-risk groups. The guidelines published by the KSID and the Korean Association for the Study of the Liver, the American College of Rheumatology, and the Canadian Rheumatology Association define hepatitis B high-risk groups as: those who abuse injection drugs; those who have sexual relations with multiple partners; those who travel or stay for a long time in areas where hepatitis B is prevalent; those who are frequently administered with blood components; male homosexuals; those who contact patients with hepatitis B; health care providers and

laboratory workers who can be exposed to the hepatitis B virus [95,96]; patients with AIIRD who are being administered with biologic agents such as TNF-blockers and rituximab; and immunocompromised patients who are receiving high-dose steroid therapies [21].

## 2) Effects and efficacy of vaccine

It is generally recognized that the preventive effect of hepatitis B vaccines can be achieved when the serum antibody reaches 10 IU/L after vaccination. When patients with AIIRD who had no hepatitis B antibody (all HBsAg, anti-HBc and anti-HBs-negative) were administered with 3 doses of hepatitis B vaccines (0, 1, and 6 months), a relatively large percentage (68%~93%) showed an effective seroconversion rate. However, since those who are being administered with csDMARDs, biologic agents, and rituximab show a low seroconversion rate (70%, 50%, and 25% respectively), the generation of antibodies in those who receive immunosuppressants should be monitored after vaccination [97]. To monitor the generation of antibodies, the potency of anti-HBs antibodies should be measured 4~6 weeks after the last vaccination. In the case that antibodies are not generated against hepatitis B after vaccination, it is recommended to administer 3 doses of hepatitis B vaccines (0, 1, and 6 months).

Vaccination is expected to benefit patients with AIIRD at some extent, who are positive only for anti-HBc (negative for HBsAg and anti-HBs) thus suspecting a past hepatitis B virus exposure; however, no consistent practice guidelines are available that support it [98]. For those who are positive only for anti-HBc, the HBV DNA test should be performed to identify whether the state is false positive or latent infectious, and, if negative, vaccination can be considered [99].

## 3) Safety of vaccine

Inactivated hepatitis B vaccines can be safely administered when immunity is compromised. The side effects of hepatitis B vaccination in patients with AIIRD are not different from those in healthy persons. A study that compared 44 patients with rheumatoid arthritis with healthy controls reported no difference in the frequency of abnormal responses to vaccination [97,100]. Moreover, there is no study reporting that hepatitis B vaccines worsen AIIRD.

## 4) Vaccination methods

A 3-dose series (0, 1, and 6 months) of hepatitis B vac-

cines should be administered to patients with AIIRD who have no hepatitis B antibody. To non-responding patients not showing any sign of antibodies after administering 3 doses, it is recommended to administer another 3 doses of (0, 1, and 6 months). No clear evidence yet exists of an accelerated schedule of hepatitis B vaccines (for instance, 0, 1, 2, and 12 months) or a high dose immunization for patients with AIIRD.

## Hepatitis A vaccine

Hepatitis A vaccines should be considered for patients with AIIRD based on the same indication of healthy persons (LOE: Low/SOE: Weak recommendation).

### 1) Vaccination targets

There is no evidence that patients with AIIRD are more vulnerable to hepatitis A or have a higher risk of complications. Almost no statement regarding hepatitis A vaccination was observed in the guidelines for the vaccination of patients with AIIRD that was either published in-country or abroad [22,23]. However, it is generally recommended to administer hepatitis A vaccines to patients with AIIRD based on the same indication of healthy individuals. The KSID recommends administering hepatitis A vaccines to patients with chronic diseases; workers in childcare facilities; health care providers and laboratory workers in danger of being exposed to hepatitis A virus; restaurant workers; those who travel to or stay for a long time in areas where hepatitis A is prevalent; those who are frequently administered with blood components; male homosexuals; those who abuse narcotic injections; and those who contact patients with hepatitis A [96]. Considering the epidemiology of hepatitis A in Korea, it is recommended to administer vaccines to those aged <40 years without an antibody test, and to those aged ≥40 years only after conducting an antibody test and confirming that they are antibody-negative [101].

### 2) Effects and efficacy of vaccine

The aforementioned research findings indicate that the immunogenicity of patients with AIIRD is not significantly lower than healthy individuals. Yet, those who are taking immunosuppressant therapies may show lower immunogenicity; therefore, hepatitis A vaccines should be administered, if feasible, prior to or following the administration of immunosuppressants. If the risk of

infection is high due to exposure to the hepatitis A virus, hepatitis A vaccines should be administered even during immunosuppressive therapies.

### 3) Safety of vaccine

The indicated hepatitis A vaccines can be safely administered even in an immunocompromised state. Their side effects in patients with AIIRD are not different from those in healthy individuals [102].

### 4) Vaccination methods

In general, intramuscular injections are administered according to the instructions of the products. After the first vaccination, the second dose should be administered within 6~18 months. When patients are receiving immunosuppressants, the timing of vaccination should be determined considering the disease conditions of patients, the immunosuppression level, and the medications' half-life period.

## Human papillomavirus vaccine

Patients with AIIRD must be administered human papillomavirus (HPV) vaccines (LOE: Low/SOR: Strong recommendation).

### 1) Vaccination targets

A multi-center cross-sectional study conducted in Korea reported that patients with systemic lupus erythematosus showed a higher-risk human papilloma virus infection rate (24.6% vs. 7.9%, odds ratio [OR] 3.8) and a higher frequency of abnormalities in the results of a Pap smear test (16.4% vs. 2.8%, OR 4.4) than a control group [103]. The systemic lupus erythematosus itself was an independent risk factor of the observed abnormalities (OR 3.5, 95% CI 1.8~6.9), and there was no significant correlation with the use of immunosuppressants. The overall prevalence of HPV in patients with systemic lupus erythematosus was higher (11.8% vs. 7.3%), and that of multiple infections of HPV in patients with lupus was also higher (4.7% vs. 1.1%) [104]. Whereas, the virus's removal rate in patients with systemic lupus erythematosus was lower than that of a general group [105]. HPV vaccines are recommended for young adults with AIIRD, particularly females aged between 13 and 16 years before having their first sexual contact, and no later than the age of 26 years [23,25,106]. In the United States, HPV vac-

cines are allowed to be administered by the age of 45 years, but for those aged >26 years, vaccination should be determined considering their sexual contact history and immunosuppressive state. Patients with rheumatoid arthritis who are taking immunosuppressants, including biologic agents, are recommended to receive HPV vaccines when they are adapted [95]. Young male patients with AIIRD are also recommended to receive HPV vaccines should they have no vaccination history. Since many clinical studies reported that patients with systemic lupus erythematosus contracted HPV, vaccination should be highly considered.

### 2) Effects and efficacy of vaccines

The seroprevalence rate of HPV vaccines in patients with systemic lupus erythematosus is 76%, which is lower than that of unaffected individuals (93%). Those who were administered with a low-dose steroid showed significantly low potency of HPV-16 antibodies compared to those who were not administered with steroid (1,870 mMU vs. 3,818 mMU), and patients with systemic lupus erythematosus who were administered with the mycophenolate mofetil immunosuppressant tended to show a lower potency of HPV-6, -16, -18 antibodies [107]. These research results indicate that administering immunosuppressants, such as steroids and mycophenolate mofetil, can lower the HPV's immunogenicity.

### 3) Vaccine safety

Inactivated HPV vaccines can be safely administered to patients with AIIRD regardless of their immunity state or the use of immunosuppressants. A recent case-control study that assessed the efficacy and safety of HPV vaccines in patients with systemic lupus erythematosus reported that there was no change in the activity of systemic lupus erythematosus for 1 year after vaccination [107]. The frequency and severity of abnormal responses were not different from healthy individuals, while there is no sufficient evidence that they worsen AIIRD. It was reported that blood clots were created after vaccination (relative risk, 0.2/100,000); however, most cases had a relevant risk factor [108]. Patients with antiphospholipid antibody syndrome need to be carefully observed after administering vaccines.

### 4) Vaccination methods

A primary series of HPV vaccines should be administered to female children aged between 11 and 12

years. For those not vaccinated or with an incomplete 3-dose primary series, it is recommended to administer an HPV 4 or HPV 9 vaccine to females aged between 13 and 26 years and an HPV 2 vaccine to females aged between 13 and 25 years. In Korea, a three-dose series of human papilloma virus vaccines is recommended. The second dose should be administered 1 or 2 months after the first, and the third dose should be administered 6 months after the second. The first and second doses should be separated by at least 4 weeks, and the second and third doses should be separated at least by 5 months. Those who did not receive the second and third doses after the first dose and thus did not complete vaccination do not need the series again from the first dose, and additional doses should be administered according to the recommended vaccination schedule. In this case, they can be vaccinated even after their 26th birthday. Those who are taking immunosuppressants, including biologic agents, can also be administered HPV vaccines; but, vaccination is recommended when the disease's activity is stabilized.

### Tetanus-diphtheria-pertussis vaccine

Patients with AIIRD have to take tetanus-diphtheria-pertussis vaccines (LOE: Moderate/SOR: Strong recommendation).

#### 1) Vaccination targets

Patients with AIIRD should be vaccinated against tetanus-diphtheria-pertussis, according to the general recommendations. When a contaminated injury was found in patients who received a rituximab therapy within the last 24 weeks, immunoglobulin is administered for passive immunity [23].

#### 2) Effects and efficacy of vaccine

It is known that the immunogenicity of tetanus vaccines in patients with rheumatoid arthritis or systemic lupus erythematosus is lower than that of healthy individuals regardless of the administration of immunosuppressants [109]. There are various ways in which a decrease in the immunogenicity of vaccines caused by the use of immunosuppressants is observed, depending on the type of administered immunosuppressants. A slight decrease was observed in the case of methotrexate compared to healthy persons; however, the immunogenicity of vaccines in those who received combination therapies with

methotrexate and rituximab was similar to the immunogenicity in those who were only administered methotrexate [110]. Although there was no study on patients with rheumatoid arthritis, the immunogenicity of healthy individuals who were administered tetanus vaccines 2 weeks after administering abatacept was reduced [111]. Those who were administered tetanus vaccines 8 weeks after administering abatacept showed similar immunogenicity compared to those who were administered with tetanus vaccines 2 weeks after receiving abatacept; but, the level was lower than that of those who did not receive abatacept. Patients with rheumatoid arthritis who were administered methotrexate and tocilizumab showed no significant difference regarding the immunogenicity of tetanus vaccines compared to those who were only administered methotrexate [36]. Some studies reported that the effects of tetanus-diphtheria-pertussis vaccines decreased in patients with systemic lupus erythematosus who showed high disease activity, but others reported opposite results, thus requiring an additional study [84,112-114].

#### 3) Safety of vaccine

Tetanus-diphtheria (Td) vaccines for adults and inactivated tetanus-diphtheria-pertussis (Tdap) vaccines, can be safely administered to patients with AIIRD, regardless of their state of immunity or use of immunosuppressants. The frequency and severity of side effects are not different from that of healthy individuals, with no evidence that vaccination increases the activity of rheumatoid arthritis or systemic lupus erythematosus [84].

#### 4) Vaccination methods

Td and Tdap vaccines can be administered to patients with AIIRD based on the same schedules for general adults. Adults aged 18 years or older who are not vaccinated with childhood DTP (Diphtheria toxoid, whole cell pertussis, and tetanus toxoid vaccine), who have no clear vaccination record, or who were born before 1958 (when domestic DTP was introduced) should be administered with 3 doses. The Tdap vaccine should be administered first, and additionally given with the Td vaccine after 4~8 weeks and 6~12 months. If the Td vaccine is primarily administered, then the second or third schedule constitutes the Tdap vaccine. Thereafter, the Td vaccine should be additionally administered every 10 years. Pregnant women should be given a Tdap vaccine every 27~36 weeks of pregnancy, regardless of the previous Td vaccine history or a Tdap vaccine to prevent pertussis in newborns.

## Herpes zoster vaccine

Herpes zoster vaccines should be considered for patients with AIIRD who are aged  $\geq 50$  years (LOE: Very low/SOR: Weak recommendation).

### 1) Vaccination targets

The risk of herpes zoster infection in patients with AIIRD is increased by immunosuppressants or immune dysregulation. Not many epidemiological studies have been conducted on patients with AIIRD, but the risk of herpes zoster infection in patients with rheumatoid arthritis, systemic lupus erythematosus, granulomatosis with polyangiitis, polymyositis and dermatomyositis is known to be higher than healthy individuals [115]. The KSID fully recommends to administer herpes zoster vaccines to adults aged  $\geq 60$  years regardless of their history of herpes zoster. In addition, it is recommended to determine whether to administer herpes zoster vaccines to adults aged 50~59 years based on the conditions of individuals. Most practice guidelines for patients with AIIRD published in other countries recommend to administer herpes zoster vaccines to patients with AIIRD who are aged  $\geq 60$  years and are not severely immunocompromised [23,26,95]. Guidelines in Europe and the Centers for Disease Control and Prevention (CDC) of the United States state that herpes zoster vaccines can be administered even when using a low dose of methotrexate ( $<0.4$  mg/kg/week or  $<20$  mg/week), glucocorticoid (prednisolone,  $<20$  mg/day), azathioprine ( $<3.0$  mg/kg/day) and 6-mercaptopurine ( $<1.5$  mg/kg/day).

### 2) Effects and efficacy of vaccines

No prospective study exists regarding the clinical effects and safety of herpes zoster vaccines on patients with rheumatoid arthritis. Two large-scale retrospective studies were conducted regarding the effects of the herpes zoster vaccines on patients with AIIRD, including those who were administered with biologic agents. Their results reported that the prevalence of herpes zoster in those who were administered the vaccines was similar to the prevalence in those who did not; however, the risk of herpes zoster was reduced by 39% (29%~48%) [116,117]. Another retrospective study reported that those who were administered the herpes zoster vaccines showed a lower prevalence than those who were not; however, they found that the effects disappeared 5 years

after vaccination [118]. A prospective pilot study targeting 10 patients with systemic lupus erythematosus also reported that their immunogenicity was slightly reduced, but was not significant [119].

### 3) Safety of vaccine

Herpes zoster vaccines that are currently distributed are live attenuated; thus, it should be carefully administered to those who receive immunosuppressants. Guidelines in Europe and the CDC of the United States state that herpes zoster vaccines can be administered even when using a low dose of methotrexate ( $<0.4$  mg/kg/week or  $<20$  mg/week), glucocorticoid ( $<20$  mg/day prednisolone or equivalent), and azathioprine ( $<3.0$  mg/kg/day). However, herpes zoster vaccines should not be administered to those who receive a high-dose steroid or immunosuppressant or a low dose of more than 2 types of immunosuppressants or biologic agents (adalimumab, infliximab, etanercept, etc.).

### 4) Vaccination methods

Herpes zoster vaccines that are currently distributed in Korea are one-time subcutaneously administered. The biggest issue regarding the herpes zoster vaccines is the emergence of Shingrix (GlaxoSmithKline Biologicals, Rixensart, Belgium), the recombinant zoster vaccine. The vaccine is yet to be introduced in Korea, and it will be a while before it is distributed. The two-dose series of Shingrix are intramuscularly injected, and, as the vaccine is inactivated, it is expected to remedy the disadvantages of live attenuated vaccines. The Advisory Committee on Immunization Practices (ACIP) in the United States recommends Shingrix administration to patients with rheumatoid arthritis. It has, however, deferred recommending Shingrix for immunocompromised patients or those who are receiving moderate or severe immunosuppressants [120].

## Measles-mumps-rubella vaccine

AIIRD patients on biologics agents or immunosuppressants should avoid measles-mumps-rubella (MMR) vaccines (LOE: Very low/SOR: Weak against).

MMR vaccines can be considered for those who have not been vaccinated, depending on the risk of being exposed to MMR virus (LOE: Very low/SOR: Weak recommendation).

### 1) Vaccination targets

Live attenuated vaccines must not be administered to patients with AIIRD who are taking immunosuppressants; however, when the level of immunosuppressive therapies is low, MMR vaccines can be considered [23]. Epidemiological studies on MMR infections in patients with AIIRD are rare. Korea was certified by the World Health Organization as the country that eradicated measles in 2014. However, imported cases of measles have been intermittently reported. Since it is generally known that the risk of MMR infections and complications in patients with AIIRD is high, it is recommended to administer MMR vaccines to patients with AIIRD considering the state of immunity and the type of medications used when the risk of MMR infection is high and the risk of infections caused by live attenuated vaccines is low [23,121].

### 2) Effects and efficacy of vaccine

The efficacy of MMR vaccines on patients with AIIRD has not been researched. Studies that targeted patients with juvenile arthritis reported both a maintained immunogenicity well after vaccination and the ineffectiveness of biologic agents including methotrexate and anti-TNF drugs on immunogenicity [122,123]. In conclusion, the immunogenicity of MMR vaccines can differ depending on the use of immunosuppressants and the type of medications; but, the level is generally assumed to be similar to or slightly lower than that of healthy individuals.

### 3) Safety of vaccine

Administering MMR vaccines should be avoided, if feasible, to those who are using biologic agents and immunosuppressants or to patients with AIIRD who are immunocompromised. This is due to the immunocompromised persons administered with live attenuated vaccines being infected by vaccine injections [124]. Unlike herpes zoster vaccines, the possibility of vaccination depending on the use and the dose of immunosuppressants are not mentioned in detail.

### 4) Vaccination methods

Administering the MMR vaccines to those who are contemplating travel to countries where measles is prevalent but whose level of immunity is uncertain is recommended. It should be determined whether to administer the vaccines to patients with AIIRD after checking their vaccination history, use of immunosuppressants, and an im-

munocompromised state. After checking their vaccination history (not necessary to vaccinate those who contracted measles in the past or those whose measles antibodies are positive or those aged  $\geq 51$  years), those who did not complete a 2-dose series of MMR vaccines or those who are not certain about their vaccination history are recommended to be administered with a 2-dose series of vaccines (at least 4 weeks apart) before traveling. Patients with AIIRD who are expecting pregnancy should be tested for rubella antibodies and if they are found to be antibody negative, they should be administered with vaccines. Still, it is recommended to administer vaccines at least 4 weeks prior to initiating immunosuppressive therapies. For those who are using immunosuppressants, the timing of vaccination should be determined considering the disease conditions of patients, and the immunosuppression level and the half-life period of the immunosuppressants.

## DISCUSSION AND CONCLUSIONS

This practice guideline was developed to present the types of vaccines and the methods of vaccination suitable for Korean patients with AIIRD. This guideline is intended for clinicians and primary care providers. A practice guideline development committee was formed to review existing guidelines and adapt them to develop a proper guideline.

The content of this practice guideline is not far different from that of the existing practice guidelines. Since vaccination is the most effective way to prevent infectious diseases and the possibility that vaccinations may aggravate AIIRD is low, vaccinations should be actively considered for patients with AIIRD based on the guideline for vaccination of persons who are healthy and whose level of immunity is normal. To do so, the vaccination history of patients should be checked prior to initiating AIIRD treatment, and it is recommended to vaccinate them, if feasible, prior to the use of immunosuppressants. Most inactivated vaccines can be safely administered, but live attenuated vaccines should be avoided for patients with AIIRD who use immunosuppressants as much as possible. In addition, those who live in a household with patients with AIIRD and their care providers should be vaccinated based on the vaccination instructions for healthy individuals.

One of the limitations of these guidelines is the lack of evidence for developing this practice guideline. The prev-

alence of AIIRD itself is low and the immunosuppression level and health conditions of patients differ. There are also various types of medications used to treat underlying diseases. For this reason, only a few high-quality randomized controlled studies have been conducted, making it difficult to systematically conduct a literature review. Moreover, there is almost no study that surveyed the vaccination status of Korean patients with AIIRD or analyzed the effects and impact of vaccines. Moreover, the opinions and needs of different groups were not reflected in the process of developing this practice guideline. Involving users in the process of developing and writing a guideline is effective in raising their sense of responsibility for, and inducing their interest in the developed guideline. For this reason, professionals in the field, such as doctors at general hospitals, practitioners, and nurses should be engaged in the process of development. It is also necessary to involve and collect feedback from patients in the process. Third, the applicability of this practice guideline was not sufficiently reviewed. The unique characteristics of the Korean health care systems were not sufficiently considered, and its applicability was not analyzed due to limited resources; therefore, the cost-effectiveness of vaccinations was not analyzed. Additionally, the distribution and implementation methods of this guideline were not discussed.

This is the first practice guideline regarding the vaccination of patients with AIIRD; therefore, it needs to be periodically revised, considering that new AIIRD medications continue to be developed and that new vaccines are also introduced.

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## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

## AUTHOR CONTRIBUTIONS

Conceptualization: H.J.C., S.S.L. Data curation: C.H.J., S.J.J. Investigation: K.T.K., E.S.K., J.H.K., H.A.K., D.J.P., S.H.P., J.K.P., J.K.A., J.S.O., J.W.Y., J.H.L., H.Y.L., M.J.C.,

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## SUPPLEMENTARY DATA

Supplementary data containing Korean version of this article is online at <https://doi.org/10.4078/jrd.2020.27.3.182>.

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