

Vaccination of immune-compromised patients with the focus on patients with autoimmune-inflammatory diseases

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ABSTRACT

Among immunocompromised patients morbidity and mortality due to vaccine-preventable infections is high. Although vaccination seems indicated, controversy exists about which vaccines should be offered, at what moment, and to whom. Guidelines are needed as the number of immunocompromised individuals increases due to the wider use of immunosuppressive drugs and, in particular, because since the introduction of biological agents, the spectrum of immunosuppressive drugs is rapidly expanding. In this review we will highlight controversies about vaccination in immunocompromised patients and will discuss indications for the several vaccines available to prevent infectious diseases with the focus on patients with autoimmune-inflammatory diseases.

KEYWORDS

Vaccination, immunocompromised, infection, autoimmunity

INTRODUCTION

Patients with a deficient immune response have an increased morbidity and mortality due to vaccine-preventable diseases. For example, in two large retrospective studies an increased risk for influenza-related morbidity and mortality was demonstrated in groups of elderly patients (≥ 65 years) with rheumatic diseases, vasculitis, chronic renal failure, dementia or stroke (all considered at intermediate risk of contracting influenza). Measured over a period spanning six seasons, the odds ratio (OR) in this group was 1.6 (95% confidence interval [CI] 1.2 to 2.0) for admission for pneumonia or

influenza and 2.7 (CI 2.3 to 3.2) for death compared with low-risk elderly.¹ Another study reported that 4.5 to 7% of unvaccinated patients with rheumatic diseases, vasculitis, dementia or stroke were admitted for pneumonia/influenza or died, compared with 0.8% in unvaccinated healthy controls.² Based on these data vaccination in patients at risk seems indicated. However, clear vaccination guidelines are not available. This can be attributed to several factors.

First, a clear definition of an immunocompromised state is lacking. In general, it includes conditions commonly classified as primary immunodeficiency and secondary immunodeficiency. Primary immunodeficiencies are generally inherited and include conditions defined by an absence or quantitative deficiency of cellular and/or humoral components of the immune system such as X-linked agammaglobulinaemia, severe combined immunodeficiency disease, and chronic granulomatous disease. These diseases are relatively rare. The vast majority of immunocompromised patients have a secondary immunodeficiency. This is generally acquired and defined by a deficiency in humoral and/or cellular immunity that occurs as a result of a disease process or its therapy. Examples of secondary immunodeficiency include HIV infection, haematopoietic malignancies, and treatment with cytostatic/immunosuppressive drugs as given to patients with malignancies, after (solid organ) transplantation, and to patients with autoimmune inflammatory rheumatic disorders (AIIRD). The level of immunosuppression within this very heterogeneous group of patients varies largely between but also within certain patient categories. For example, in HIV-infected individuals the response on vaccination is related to the number of circulating CD4⁺-T cells and the treatment with combination antiretroviral

therapy (cART).³⁻⁶ cART-induced suppression of HIV replication is associated with an increase in CD4⁺-T cell and B-cell numbers. As a result, cART improves the efficacy of the immune response to vaccination in these patients, although responses in many patients remain suboptimal.^{7,8} Also, the degree to which immunosuppressive drugs cause clinically significant immunodeficiency varies by drug and is generally dose-related.

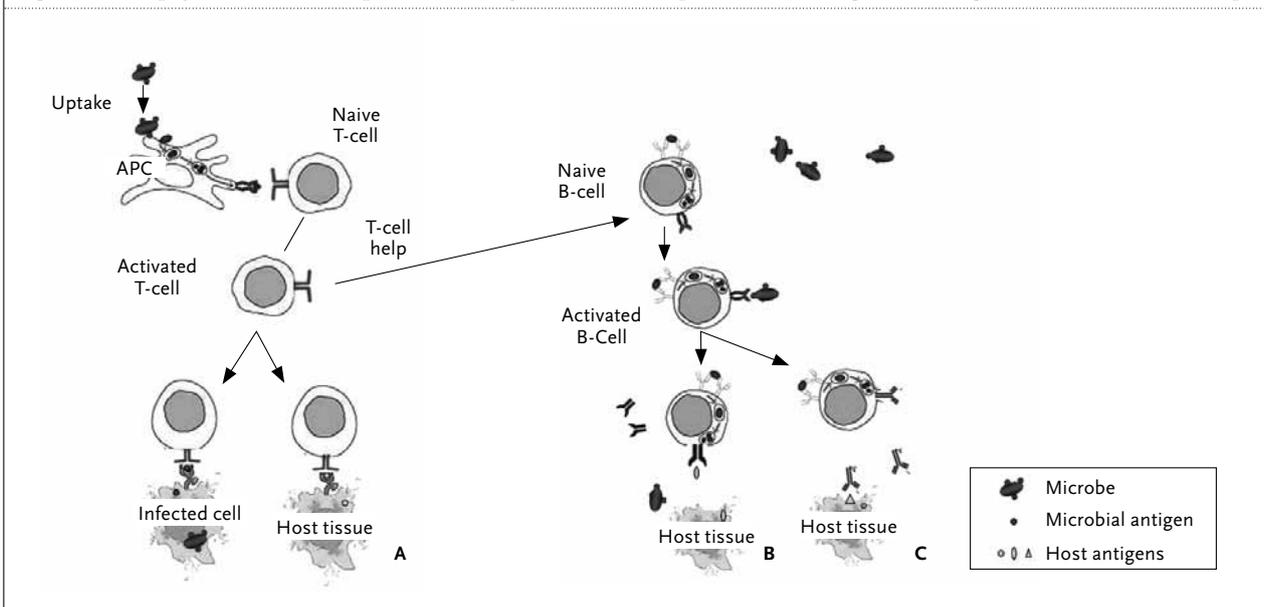
Secondly, although the risk for (severe) infection in these immunocompromised patients is increased and vaccination therefore seems indicated, due to the hampered immune response vaccination might not result in the level of protection aimed at. Moreover, administration of live-attenuated vaccines to immunocompromised individuals might result in infection because of reduced ability to mount an effective immune response. Not only infectious disease might be introduced, debate is also ongoing on whether vaccination might be responsible for the induction of certain diseases, including autoimmune disease, or might reactivate underlying disease through molecular mimicry, epitope spreading, bystander activation, or polyclonal activation (*figure 1*).⁹

Finally, apart from the retrospective studies mentioned above, only limited data on the incidence of vaccine-preventable infections (VPI) in immunocompromised patients are available and, moreover, most vaccination studies performed in these groups of patients did not have contraction and outcome of VPI as a primary study endpoint. Nearly all studies used humoral (antibody) response on vaccination as an outcome parameter. Except for a few vaccinations such as those against influenza and hepatitis B, no generally accepted definitions of protective antibody levels are available.¹⁰ Furthermore, it is still a matter of debate whether antibody response as a surrogate endpoint is valid. For example, in the elderly it has been demonstrated that the cellular response after influenza vaccination might be a better correlate of protection than the antibody response (*table 1*).^{11,12}

PRIMARY IMMUNODEFICIENCY

Most patients with primary immunodeficiency have a defect in the humoral immune response (X-linked

Figure 1. Simplified schematic representation of mechanisms by which microorganisms might induce autoimmunity



After invasion, microbes will be internalised by antigen-presenting cells (APCs). The microbes will be processed and microbial antigens will be presented by MHC molecules to T cells. These T cells can react with (virus) infected cells presenting the viral antigen (panel A, left). Whenever there is sufficient homology with certain self-antigens (molecular mimicry) these T cells can cross-react with self-antigens expressed by host tissue, leading to (reactivation of) autoimmune disease (panel A, right). B lymphocytes in themselves can be directly activated by microbes when polysaccharide microbial antigens are recognised by the B-cell receptor. Otherwise T-cell help is needed for B-cell activation. Activated B cells produce antibodies directed to microbial antigen, but, via a process of so-called epitope spreading also antibodies to structurally related subdominant (cryptic) epitopes may be produced which might be directed to self-antigens. Epitope spreading is a common characteristic of the adaptive immune responses mounted against different pathogens and describes the ability of the B- and T-cell immune response to diversify, at the level of specificity, from a single determinant to many different sites on a given antigen (panel B). In particular when the immune system is activated for a longer period (repetitive or constantly) the spectrum of B cells that are activated can expand and B cells with other specificity will proliferate. In some of these cases, a monospecific response can emerge, accompanied by circulating immune complexes and eventually resulting in damage to self tissues (panel C). Finally, underlying disease might reactivate through bystander activation. Bystander activation occurs whenever the initial immune response to an antigen induces tissue damage and the release of sequestered antigens which then in turn can activate autoreactive lymphocytes that were not directly involved in the initial response.

Table 1. Controversies to overcome for the development of vaccination guidelines for immunocompromised individuals

Problem	Example
Definition of immunocompromised state is lacking	Not clear at what time (depending on dosage and duration of use) individual immunosuppressive drugs hamper the immune response
Vaccination might induce harm	Vaccination studies are underpowered for safety Researchers are reluctant to perform studies with live-attenuated vaccines in immunocompromised patients
Data of incidence and outcome of most vaccine preventable infections is lacking	Data on contracting infectious, vaccine preventable infections after vaccination are lacking
Correlates of protection are not present or do not represent true protection	For most vaccine preventable infections no generally accepted definitions for seroprotection are available Moreover, discussion exists whether cellular instead of humoral (antibody) responses might not be a better correlate of protection

upper and lower respiratory tract infections. Although these patients seem to be at risk for complicated influenza and infections with encapsulated micro-organisms, the prevalence, morbidity and mortality of influenza, pneumococcal, meningococcal and *Haemophilus influenzae* B infections in these patients is unknown. One might question any efficacy of vaccination in patients with primary immunodeficiency. Indeed, mononuclear cells from X-linked agammaglobulinaemia patients do not mount any response to influenza vaccination. However, it has been shown that peripheral blood mononuclear cells from a subset of CVID patients are capable of producing antibodies in response to influenza antigen.^{13,14} Antibody responses to polysaccharide and polypeptide vaccines have been demonstrated in 18 and 23%, respectively, of CVID patients.¹⁵ Therefore, although data on safety of and response to other vaccines is lacking, it seems reasonable to offer patients with a primary immunodeficiency at least the seasonal flu vaccine and pneumococcal vaccine. For an overview see *table 2*.

agammaglobulinaemia (XLA), autosomal recessive agammaglobulinaemia, IgA deficiency (IgAD), common variable immunodeficiency (CVID), IgG-subclass deficiency (IgGSD), and specific antibody response deficiency) and frequently experience recurrent bacterial

SECONDARY IMMUNODEFICIENCY

As stated, the spectrum of patients with a secondary immunodeficiency is broad and covers many different disease entities. In order to present a condensed overview, we will focus on patients with autoimmune-inflammatory

Table 2. Vaccination in immunocompromised patients

Defect	Specific immunodeficiency	Recommended vaccines	Contraindicated vaccines	Comments
Innate				
Complement deficiency	Deficiency of early components (C1-C4)	Influenza Pneumococcal Meningococcal	None	All routine vaccines probably effective
	Deficiency of late components (C5-C9, properdin, factor B)	Influenza Pneumococcal Meningococcal	None	All routine vaccines probably effective
Phagocyte deficiency	Chronic granulomatous disease, leukocyte adhesion defect, myeloperoxidase deficiency	Influenza Pneumococcal	Live bacterial vaccines	All inactivated vaccines and live viral vaccines safe and probably effective
Adaptive				
Humoral (B-lymphocyte)	X-linked and autosomal recessive agammaglobulinaemia, CVID, selective IgA deficiency, IgG subclass deficiency, selective antibody response deficiency	Influenza Pneumococcal	Oral poliovirus Smallpox BCG Live oral typhoid	The effectiveness of any vaccine will be uncertain if it depends only on the humoral response
Cellular (T-lymphocyte)	SCID, DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia teleangiectasia	Influenza Pneumococcal Meningococcal <i>Haemophilus influenzae type b</i>	All live vaccines	Vaccines may be ineffective, depending on the degree of immune suppression
* Adapted from vaccination of persons with primary immune deficiencies, in: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). MMWR Recomm Rep 2006 Dec 1;55(RR-15):1-48. CVID = common variable immunodeficiency; SCID = severe combined immunodeficiency; BCG = Bacillus Calmette-Guérin.				

rheumatic diseases (AIIRD). Vaccination of HIV-positive individuals¹⁶ and renal transplant candidates and recipients¹⁷ has been recently reviewed elsewhere and general recommendations for immunocompromised adults can be found on the website of the Centres for Disease Control and Prevention.¹⁸

The group of AIIRD consists of a variety of disorders (table 3). These patients are at increased risk of contracting infectious diseases,¹⁹⁻²² resulting in significant morbidity and mortality. The increased susceptibility to infection can be contributed to several factors. Risk increases due to the underlying disease itself (such as hypocomplementaemia and lymphopenia in systemic lupus erythematosus (SLE) or neutropenia in Felty's syndrome in rheumatoid arthritis (RA)), but mostly because of treatment with immunomodulatory or immunosuppressive drugs such as (high-dose) corticosteroids, disease-modifying

antirheumatic drugs (DMARDs) or biological agents. Even stem cell transplantations are performed for treatment of several AIIRD.²³ Biologicals are of particular interest since more indications are being recognised for these agents, they are increasingly used earlier in the course of AIIRD, and new agents become available.²⁴ Importantly, the administration of these drugs aims to reduce disease activity but might also influence the response on vaccination. In the remaining part of this review we will discuss per VPI the literature available concerning the efficacy and safety of vaccination in AIIRD and the influence of immunosuppressive drugs on the vaccination response. Most studies included RA or SLE patients.

INFLUENZA VACCINE

As mentioned before, in two retrospective studies, elderly patients (≥ 65 years) with chronic underlying diseases (including rheumatic diseases and vasculitis) showed an increased risk for influenza resulting in admission for pneumonia or death in comparison with healthy controls.^{1,2} Whether this risk in patients with AIIRD can be reduced by influenza vaccination has not been addressed. All but one of the studies performed²⁵ have used the humoral response, that is the development of a protective level of antibodies to influenza (≥ 40 , as measured by the haemagglutination inhibition assay) as outcome measure but have not used the contraction and severity of influenza infection as a primary endpoint.

Rheumatoid arthritis

In RA patients the majority of studies evaluating efficacy of influenza vaccination have shown similar efficacy compared with healthy controls. Use of DMARDs did not diminish the humoral response.²⁶⁻³⁷ In several studies anti-tumour necrosis factor (TNF) treatment did not decrease the response to influenza vaccination either.^{31-33,35} Only one study reported a modestly impaired response in anti-TNF users, not resulting in a lower percentage of seroprotection.³⁴ The combination of anti-TNF and methotrexate, however, might act synergistically and in patients on this combination a somewhat reduced response to influenza vaccination has been reported.³⁸ B-cell depleting therapy using rituximab severely hampers the immune response:^{37,39,40} influenza vaccination in the first eight weeks after treatment with rituximab did not result in an antibody response. Six to ten months after rituximab treatment a partial restoration of the response could be observed.³⁷ None of the studies showed a significant increase in disease activity in RA patients following vaccination. However, it should be noted that none of these studies has been powered for safety.

Table 3. Autoimmune inflammatory rheumatic diseases (AIIRD) and vaccines

Disease	Vaccines
Adult Still's disease	Bacillus Calmette-Guérin (BCG)#
Antiphospholipid syndrome	Cholera
Anti-synthetase syndrome	Diphtheria
Behçet disease	Hepatitis A
Churg-Strauss syndrome	Hepatitis B
Clinically amyopathic dermatomyositis	<i>Haemophilus influenzae</i> b
Dermatomyositis	Human papillomavirus
Eosinophilic fasciitis	Influenza
Eosinophilic myositis	Japanese encephalitis
Giant cell arteritis	Measles*
Goodpasture's disease	Mumps*
Microscopic polyangiitis	<i>Neisseria meningitidis</i> (A/C/Y/W135, C conjugated)
Mixed connective tissue disease	Pertussis
Mixed essential cryoglobulinaemia	Poliomyelitis (parenteral and oral*)
Periodic fever syndromes	Rabies
Polyarteritis nodosa	Rubella*
Polychondritis	<i>Streptococcus pneumoniae</i> (polysaccharide and conjugated)
Polymyalgia rheumatica	Tetanus toxoid
Polymyositis	Tick-borne encephalitis
Rheumatoid arthritis	Typhoid fever (parenteral and oral#)
Scleroderma	Varicella zoster*
Sjögren's syndrome	Yellow fever*
Spondylarthropathies	
Sporadic inclusion body myositis	
Systemic lupus erythematosus	
Takayasu arteritis	
Wegener granulomatosis	

contains live bacteria; * contains live virus

Systemic lupus erythematosus

In SLE several controlled studies on the efficacy of subunit influenza vaccine have shown a similar humoral response in patients compared with healthy controls.^{27,41-44} In one RCT⁴⁵ and three controlled studies⁴⁶⁻⁴⁸ a modestly reduced response to influenza vaccination in SLE patients was found. In two other studies SLE patients showed a similar³⁰ or a slightly reduced *in vitro* response to immunisation, compared with disease controls (RA patients).²⁸ In most of the aforementioned studies that also addressed the influence of the use of immunosuppressive drugs on efficacy, no effect on the vaccination response was found.^{41,43,45,46} Others, however, did find a lower response to vaccination in SLE patients on azathioprine,^{47,49} steroids,²⁷ and hydroxychloroquine.⁵⁰ Occasionally, disease flares in SLE patients after influenza vaccination have been reported.^{42,43} However, most of these reports originate from uncontrolled studies. Although disease flares have also been reported in controlled studies, this frequency is not increased in vaccinated patients compared with unvaccinated patient controls, and therefore represents the natural course of the disease.^{25,30,45,49,51}

Other AIIRD

In two studies including patients with Wegener granulomatosis^{52,53} and one study in patients with systemic sclerosis (SSc)⁵⁴ humoral responses following influenza vaccination were similar between patients and healthy controls. Use of immunosuppressive drugs did not affect the humoral response and disease flares developed at the same, low, frequency compared with unvaccinated patients.

PNEUMOCOCCAL VACCINE

The efficacy of pneumococcal vaccination is even more difficult to determine as no generally accepted response criteria are available. Moreover, different vaccines (polysaccharide and conjugated pneumococcal vaccines) are available containing different numbers of antigens of pneumococcal serotypes.

Rheumatoid arthritis

In RA, similar as well as reduced responses to pneumococcal vaccination have been reported.^{55,56} Although small studies in RA patients on TNF-blocking agents suggested a reduction of efficacy by the use of these drugs,^{56,57} such an effect could not be demonstrated in larger studies.^{32,58,59} Two studies reported an impaired response to pneumococcal vaccination only in patients on the combination of methotrexate and anti-TNF, but not in those on these individual drugs.^{58,60} Probably, the combination of methotrexate and anti-TNF results in a synergistic immunosuppressive effect. Finally, rituximab

reduced the response to pneumococcal polysaccharide vaccine in patients vaccinated 28 weeks after rituximab administration.⁶¹ Safety has only been addressed in uncontrolled trials. In these studies, no increase in disease activity following pneumococcal vaccination has been reported.^{32,55,56,60, 61}

Systemic lupus erythematosus

Similar responses,^{62,63} as well as reduced responses,^{55,64-66} were observed in several controlled studies comparing SLE patients with healthy controls. Also in uncontrolled studies results vary. In one study all 20 patients showed a significant rise in antibodies to pneumococcal antigens,⁶⁷ whereas another study reported that only half of the patients developed a fourfold antibody rise.⁶⁸ In the studies that addressed the effect of immunosuppressive drugs, the combination of steroids and azathioprine or cyclophosphamide did not hamper the responses.^{55,63,64,66} With respect to safety, in all studies that compared SLE patients with to those without pneumococcal vaccination the disease activity after vaccination did not differ between groups.^{62,64,67} Also in uncontrolled studies no increase in SLE activity could be demonstrated following pneumococcal vaccination.^{55,63,66,68,69}

Other AIIRD

In patients with psoriatic arthritis and ankylosing spondylitis similar responses after pneumococcal vaccination were found in patients with or without use of TNF-blocking agents.^{66,70} In an uncontrolled study in 18 SSc patients, pneumococcal vaccination resulted in a protective level of antibodies to at least three out of four serotypes tested in 83% of the patients.⁷¹ An increase in disease activity after vaccination was not reported in any of these studies.

HEPATITIS B VACCINE

A few studies addressed the efficacy of hepatitis B vaccination in AIIRD patients (SLE,⁷² RA,⁷³ ankylosing spondylitis⁵⁷ and Behçet's disease⁷⁴). In the majority of patients, irrespective of the underlying AIIRD, an adequate response to vaccination could be demonstrated; however, a clear conclusion can not be drawn due to low numbers and absence of controls in these studies. Influence of steroids or DMARDs was absent. In contrast, use of TNF-blocking agents severely hampered the response to hepatitis B vaccine in ankylosing spondylitis patients.⁵⁷ Hepatitis B vaccine (HBV) vaccination did not lead to more RA disease flares in 22 vaccinated RA patients compared with 22 unvaccinated RA patients.⁷³

One uncontrolled prospective study regarding HBV vaccination in SLE patients revealed no significant change

in disease activity, as measured by SLE disease activity index (SLEDAI) score after vaccination.⁷²

In a study of 13 Behçet patients, three developed aphtae following HBV vaccination but no severe flares were present.⁷⁴

TETANUS TOXOID VACCINE

Rheumatoid arthritis

Tetanus toxoid vaccination also seems to be as efficacious in RA patients as in healthy controls.^{26,75} The use of steroids or DMARDs did not reduce efficacy. Also treatment with RTX did not diminish response to tetanus vaccine in RA patients when administered 24 weeks after RTX treatment.⁶¹ Adverse events occurred in comparable frequency in RTX-treated patients (22%) and in eight patients on methotrexate monotherapy (24.2%). These included itching, rash, soreness at the injection site, and malaise. No data are available regarding the efficacy of tetanus toxoid vaccine within 24 weeks after treatment with RTX.

Systemic lupus erythematosus

Controlled studies in SLE patients revealed a similar response to tetanus toxoid in comparison with healthy controls.⁷⁵⁻⁷⁷ In a larger, uncontrolled study, comprising 73 SLE patients, >90% of patients achieved protection after vaccination.⁶⁸ Side effects of immunisation (mild local tenderness or erythema, low-grade fever, or malaise) were noted in only six (8%) of patients and none of the side effects required systemic treatment or change in medical therapy for SLE. Only one small study (nine patients) showed a diminished response to tetanus vaccination in SLE patients.⁷⁸ The use of steroids or DMARDs did not reduce efficacy.

OTHER VACCINES

In an uncontrolled study on vaccination responses in SLE patients, next to tetanus toxoid, also *Haemophilus influenzae* B (HIB) vaccine was administered. This resulted in protection in 88% of the 73 included patients. A trend towards a lower response was observed in patients on immunosuppressive drugs.⁶⁸

Severe complications, such as vaccine-associated poliomyelitis, have followed vaccination with live-attenuated viral and live-attenuated bacterial vaccines among persons with altered immunocompetence.⁷⁹⁻⁸⁴ Based on these data live vaccines are considered contraindicated in AIIRD patients under immunosuppressive therapy⁸⁵ including biological DMARDs.²⁴ However, these recommendations are based on case reports from decades ago, in the

majority dealing with severely immunocompromised HIV-infected individuals, before the introduction of cART.^{79,81,83,84} Although the risk of administrating live virus by vaccination can not be denied, it has to be acknowledged that people with a reduced immune response are at increased risk of natural severe, even life-threatening infections with for example measles and Varicella.⁸⁶ The risk-benefit ratio might be in favour of vaccination. To address this question studies with live-attenuated virus vaccines have been undertaken in immunosuppressed patients including HIV-infected patients, those with renal failure, and other medical conditions associated with reduced immunocompetence. These studies showed safety of varicella vaccine and as a consequence in the USA the use of this vaccine in HIV-infected children with CD4+T cell counts $\geq 15\%$ of normal for their age can be considered.⁸⁷ Recently in 25 children and adolescents with juvenile rheumatic diseases varicella vaccine was administered, despite the use of methotrexate, steroids and other DMARDs.⁸⁸ A small proportion (20%) of patients developed a mild varicella rash in the first two weeks after immunisation; none of the patients had worsening of their underlying disease in the three months after vaccination as compared with the three months before vaccination. Efficacy was similar compared with a group of age-matched healthy controls. In a retrospective cohort study vaccination with live measles, mumps and rubella vaccine in children with juvenile idiopathic arthritis (JIA), the majority receiving methotrexate, did not result in an increase of disease activity, nor did it lead to measles, mumps or rubella infection.⁸⁹ In a prospective nested case-control study in JIA patients treated with methotrexate alone or in combination with etanercept these results could be confirmed.⁹⁰ Although no definite conclusions can be drawn from these studies for reasons as sample size and heterogeneity of the patients included, results are encouraging, and expanding of such studies in a broader group of even more immunocompromised patients is advocated.⁹¹

ADVISED VACCINATIONS IN AIIRD

Based on systematic literature review and expert opinion a working party of the European League Against Rheumatism recently formulated vaccination recommendations for patients with AIIRD.⁹² As can be appreciated from the studies discussed above, influenza and pneumococcal vaccination should be strongly considered in this category of patients. As data on other vaccines are limited, the working party refers to national vaccination guidelines (for adults) concerning tetanus toxoid vaccination, hepatitis A and B vaccination, and for vaccines indicated for those who plan to travel. Two exceptions were

defined. First, patients with contaminated wounds who received rituximab within the last 24 weeks should get passive immunisation with tetanus immunoglobulins. Secondly, although it is advised to avoid live-attenuated vaccines whenever possible in immunosuppressed patients with AIIRD, herpes zoster vaccination may be considered in a subgroup of immunocompromised patients based on the prevalence of herpes zoster and burden of disease (post-herpetic neuralgia). A short overview of the major recommendations is given in *table 4*.

SUMMARY

Immunocompromised patients have an increased risk for morbidity and mortality due to (vaccine preventable) infectious diseases and vaccination for these patients seems indicated. However, comprehensive, generally accepted guidelines are lacking. This is due to the absence of a clear definition of an immunocompromised state, doubts about efficacy and safety (in particular with live-attenuated virus), and the lack of clear definitions of correlate of protection after vaccination. More studies with appropriate endpoints are needed to develop evidence-based vaccination guidelines and to allow their implementation. Until then, although merely based on expert opinion, patients at risk might be vaccinated according to the proposal as presented in this overview.

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Table 4. Vaccine choice in immunodeficient patients

Defect	Specific immunodeficiency	Vaccines to be considered*	Vaccines to be avoided	Comments
AIIRD	No immunosuppressive drugs	Strongly considered: influenza and 23-valent pneumococcal vaccine		
	On DMARDs	Strongly considered: influenza and 23-valent pneumococcal vaccine	Live-attenuated vaccines	Vaccination can be administered during DMARD therapy
	On TNF-blocking agents	Strongly considered: influenza and 23-valent pneumococcal vaccine	Live-attenuated vaccines	Vaccination can be administered during TNF-blocking therapy
	On B-cell depleting agents	Strongly considered: influenza and 23-valent pneumococcal vaccine	Live-attenuated vaccines	Vaccination ideally should be administered before starting B-cell depleting therapy
AIIRD	Hyposplenic/asplenic patients	Recommended: influenza, pneumococcal, Hib, meningococcal	Live-attenuated vaccines	

*For other vaccines (hepatitis B, HPV, tetanus toxoid, etc) it is recommended to adhere to national vaccination guidelines.
AIIRD = autoimmune inflammatory rheumatic disorders; DMARD = disease-modifying antirheumatic drugs.

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