

Vaccination Guidelines for Patients With Immune-Mediated Disorders on Immunosuppressive Therapies

Kim A. Papp^{1,2}, Boulos Haraoui³, Deepali Kumar^{4,5}, John K. Marshall⁶, Robert Bissonnette⁷ , Alain Bitton⁸, Brian Bressler^{9,10}, Melinda Gooderham^{2,11}, Vincent Ho⁹, Shahin Jamal¹², Janet E. Pope^{13,14}, A. Hillary Steinhart^{5,15}, Donald C. Vinh^{8,16}, and John Wade^{9,17}

Journal of Cutaneous Medicine and Surgery
2019, Vol. 23(1) 50–74
© The Author(s) 2018



Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1203475418811335
journals.sagepub.com/home/jcms

Canadian Dermatology Association  Association canadienne de dermatologie



Abstract

Background: Patients with immune-mediated diseases on immunosuppressive therapies have more infectious episodes than healthy individuals, yet vaccination practices by physicians for this patient population remain suboptimal.

Objectives: To evaluate the safety and efficacy of vaccines in individuals exposed to immunosuppressive therapies and provide evidence-based clinical practice recommendations.

Methods: A literature search for vaccination safety and efficacy in patients on immunosuppressive therapies (2009-2017) was conducted. Results were assessed using the Grading of Recommendation, Assessment, Development, and Evaluation system.

Results: Several immunosuppressive therapies attenuate vaccine response. Thus, vaccines should be administered before treatment whenever feasible. Inactivated vaccines can be administered without treatment discontinuation. Similarly, evidence suggests that the live zoster vaccine is safe and effective while on select immunosuppressive therapy, although use of the subunit vaccine is preferred. Caution regarding other live vaccines is warranted. Drug pharmacokinetics, duration of vaccine-induced viremia, and immune response kinetics should be considered to determine appropriate timing of vaccination and treatment (re)initiation. Infants exposed to immunosuppressive therapies through breastmilk can usually be immunized according to local guidelines. Intrauterine exposure to immunosuppressive agents is not a contraindication for inactivated vaccines. Live attenuated vaccines scheduled for infants and children ≥ 12 months of age, including measles, mumps, rubella, and varicella, can be safely administered as sufficient time has elapsed for drug clearance.

Conclusions: Immunosuppressive agents may attenuate vaccine responses, but protective benefit is generally maintained. While these recommendations are evidence based, they do not replace clinical judgment, and decisions regarding vaccination must carefully assess the risks, benefits, and circumstances of individual patients.

Keywords

vaccination, immunosuppression, immune-mediated disease

Immunosuppressive treatments dysregulate immunity and increase the risk of infections and associated morbidity and mortality.¹⁻⁴ While immunization significantly mitigates these risks, vaccination rates in patients with immune-mediated diseases (IMDs) treated with immunosuppressants remain suboptimal, primarily due to the absence of physician recommendations.⁵⁻⁷ The reticence of physicians to vaccinate these patients may reflect the challenges of weighing the quality of protection achieved while on immunosuppressive treatment with the perceived risks of disease aggravation and vaccine-induced adverse events (AEs). This underscores the importance of improving physician awareness and the need for comprehensive guidelines for

the management of this patient population. This publication aims to critically evaluate evidence regarding the safety and efficacy of vaccinating individuals exposed to immunosuppressive therapies and provide evidence-based clinical practice recommendations.

Current knowledge of the safety and efficacy of vaccination in this setting is mainly derived from nonrandomized trials and observational studies using postimmunization antibody titres to vaccine antigens as surrogate markers of protection. Although it may be argued that this measure imperfectly reflects the magnitude and quality of the immune response, it is the best-characterized and most routinely used correlate of protective immunity for commercially available vaccines.⁸⁻¹⁴

As most vaccines mediate protection through humoral responses that block infection, viremia, or bacteremia,¹⁵ postimmunization serological titres and functional antibody characteristics are valuable indications of vaccine efficacy.

Methods

A multidisciplinary committee comprising gastroenterologists (J.K.M., A.B., B.B., A.H.S.), dermatologists (K.A.P., M.G., R.B., V.H.), rheumatologists (B.H., J.E.P., J.W., S.J.), and infectious disease specialists with expertise in vaccinology (D.K., D.C.V.) was assembled to develop guidelines on the practical management of patients considering vaccination while on immunosuppressive therapies. Synapse Medical Communications performed literature searches in accordance to the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) system across multiple databases (Embase, MEDLINE, PubMed).¹⁶ Major search terms included *vaccination*, *rheumatoid arthritis (RA)*, *inflammatory bowel disease (IBD)*, *psoriatic arthritis (PsA)*, *psoriasis (PsO)*, *autoimmune disease*, and concepts of interest such as specific vaccines, disease-modifying antirheumatic drugs (DMARDs), glucocorticoids, and biologic agents. The literature search identified clinical trials, meta-analyses, systematic reviews, observational studies, case series, and existing guidelines published from 2009 to 2017. Reference lists were manually searched to identify relevant articles and included based on the committee's discretion. Published studies were reviewed by the committee and assessed for content and GRADE evidence levels.¹⁶ The quality of evidence was rated as "high" (indicating that further research is unlikely to change the confidence in the estimate of effect), "moderate" (implying that further research is likely to have an impact on the confidence in the estimate of effect), "low" (suggesting that further research is likely to have a strong impact on the confidence in the estimate of

effect), or "very low" (meaning that any estimate of effect is very uncertain).

The Steering Committee (K.A.P. [chair], J.K.M., D.K., B.H.) developed the initial statements, which underwent 2 rounds of revisions according to feedback received from all authors. All 14 members voted on a web-based platform to determine the level of agreement for each statement using a 5-point scale (strongly agree, agree, neutral, disagree, strongly disagree). Statements achieving $\geq 75\%$ agreement were included in the guidelines. Of the 15 statements considered, 2 statements were rejected (see Appendix 1, available online).

The strength of a recommendation was evaluated according to GRADE and rated as "strong" when desirable consequences clearly outweighed undesirable consequences, "conditional" when desirable consequences probably outweighed undesirable consequences, or "weak" when the balance between desirable and undesirable consequences was closely balanced or uncertain. Clinical practice recommendations are listed in Table 1.

Good Clinical Practice Statement

Statement 1: In patients newly diagnosed with immune-mediated diseases, we recommend that immunization status be assessed and age- and condition-appropriate vaccines be administered prior to initiation of immunosuppressive treatment.

GRADE: Strong recommendation; moderate-level evidence

Vote: 64.3% strongly agree, 28.6% agree, 7.1% neutral

Evidence Summary

Studies in patients with type 1 diabetes, celiac disease, and IBD showed that individuals with these IMDs who are not

¹K Papp Clinical Research, Waterloo, ON, Canada

²Probit Medical Research, Waterloo, ON, Canada

³Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada

⁴University Health Network, Toronto, ON, Canada

⁵Faculty of Medicine, University of Toronto, Toronto, ON, Canada

⁶Department of Medicine and Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, ON, Canada

⁷Innovaderm Research, Inc, Montreal, QC, Canada

⁸McGill University Health Centre, Montreal, QC, Canada

⁹Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada

¹⁰St Paul's Hospital, Vancouver, BC, Canada

¹¹Faculty of Medicine, Queen's University, Kingston, ON, Canada

¹²Vancouver Coastal Health, Vancouver, BC, Canada

¹³Faculty of Medicine, University of Western Ontario, London, ON, Canada

¹⁴St Joseph's Health Care, London, ON, Canada

¹⁵Mount Sinai Hospital, Toronto, ON, Canada

¹⁶Research Institute, McGill University Health Centre, Montreal, QC, Canada

¹⁷Vancouver General Hospital, Vancouver, BC, Canada

Corresponding Author:

Kim A. Papp, K Papp Clinical Research and Probit Medical Research, 135 & 139 Union Street East, Waterloo, ON N2J 1C4, Canada.

Email: kapapp@probitmedical.com

Table 1. Recommendation Statements.

Statement 1: In patients newly diagnosed with immune-mediated diseases, we recommend that immunization status be assessed and age- and condition-appropriate vaccines be administered prior to initiation of immunosuppressive treatment.

Strong recommendation; moderate-level evidence.

Inactivated vaccines

Statement 2a: To optimize the immunogenicity of inactivated vaccines in treatment-naive patients with immune-mediated conditions, we suggest that immunization be performed at least 2 weeks prior to initiation of immunosuppressive therapy, whenever possible.

Conditional recommendation; moderate-level evidence.

Statement 2b: Among patients with immune-mediated diseases currently receiving immunosuppression, we recommend that immunosuppressive treatment not be interrupted for administration of inactivated vaccine.

Strong recommendation; moderate-level evidence.

Statement 2c: In patients with immune-mediated diseases treated with rituximab who require optimal vaccine immunogenicity, we recommend that immunization be deferred to ≥ 5 months after the last dose and at least 4 weeks prior to the subsequent dose of rituximab.

Strong recommendation; low-level evidence.

Live attenuated vaccines: Herpes zoster

Statement 3a: To optimize the immunogenicity of the live attenuated herpes zoster vaccine in treatment-naive patients with immune-mediated conditions, we suggest immunization be performed at least 2 to 4 weeks prior to initiation of immunosuppressive therapy.

Conditional recommendation; moderate-level evidence.

Statement 3b: In patients with immune-mediated diseases on immunosuppressive agents, the live attenuated herpes zoster vaccine can be safely administered to patients at risk, but the subunit vaccine is the preferred alternative. Individual situations should be assessed for patients treated with a combination of immunosuppressive drugs, if the live vaccine is being considered.

Strong recommendation; moderate-level evidence.

Other live attenuated vaccines

Statement 4a: In treatment-naive patients with immune-mediated diseases who are vaccinated with live attenuated vaccines, we recommend that the duration of viremia following immunization be considered when determining the optimal time to initiate immunosuppressive therapy.

Strong recommendation; very low-level evidence.

Statement 4b: In patients with immune-mediated diseases who interrupt immunosuppressive treatment prior to vaccination, we recommend that the duration of viremia following immunization be considered when determining the optimal time to reinstate immunosuppressive therapy.

Strong recommendation; very low-level evidence.

Statement 4c: In patients with immune-mediated diseases on immunosuppressive agents, we suggest that live attenuated vaccines be administered when individual benefits outweigh the perceived risks.

Conditional recommendation; low-level evidence.

Statement 4d: In situations where patient safety is a paramount concern and the clinical situation allows, we suggest that immunosuppressive treatment be interrupted for a duration based on drug pharmacokinetics prior to immunization with live vaccines.

Conditional recommendation; low-level evidence.

Vaccination of infants with early exposure to immunosuppressive agents

Statement 5a: In infants exposed to immunosuppressive agents in utero during the third trimester, we recommend that inactivated vaccines be administered according to the local immunization schedule.

Strong recommendation; very low-level evidence.

Statement 5b: In infants exposed to immunosuppressive agents in utero during the third trimester, we recommend that the MMR and varicella vaccines be administered according to the local immunization schedule.

Strong recommendation; low-level evidence.

Statement 5c: In infants breastfed by mothers on immunosuppressive regimens, we recommend that inactivated and live attenuated vaccines be administered according to the local immunization schedule without delay.

Strong recommendation; very low-level evidence.

Abbreviation: MMR, measles, mumps, rubella.

treated with immunosuppressive agents generally have comparable serologic responses to vaccination as healthy individuals.¹⁷⁻²⁰ As several DMARDs and biologic agents interfere with the immune response to vaccines (Figure 1, Figure 2, Table 2, and Table 3), it is imperative to assess the patient's immunization history at diagnosis and administer age- and disease-appropriate vaccines according to local guidelines prior to treatment initiation to optimize efficacy.

Concerns regarding the risk of disease exacerbation are unfounded as studies have shown that immunization did not generally cause clinically significant worsening of underlying IMDs (Tables 2 and 3). Indeed, a meta-analysis evaluating the impact of influenza and pneumococcal vaccination in systemic lupus erythematosus (SLE) demonstrated that immunization had no significant effect on the SLE disease activity index (SLEDAI) score.²¹ While some studies reported

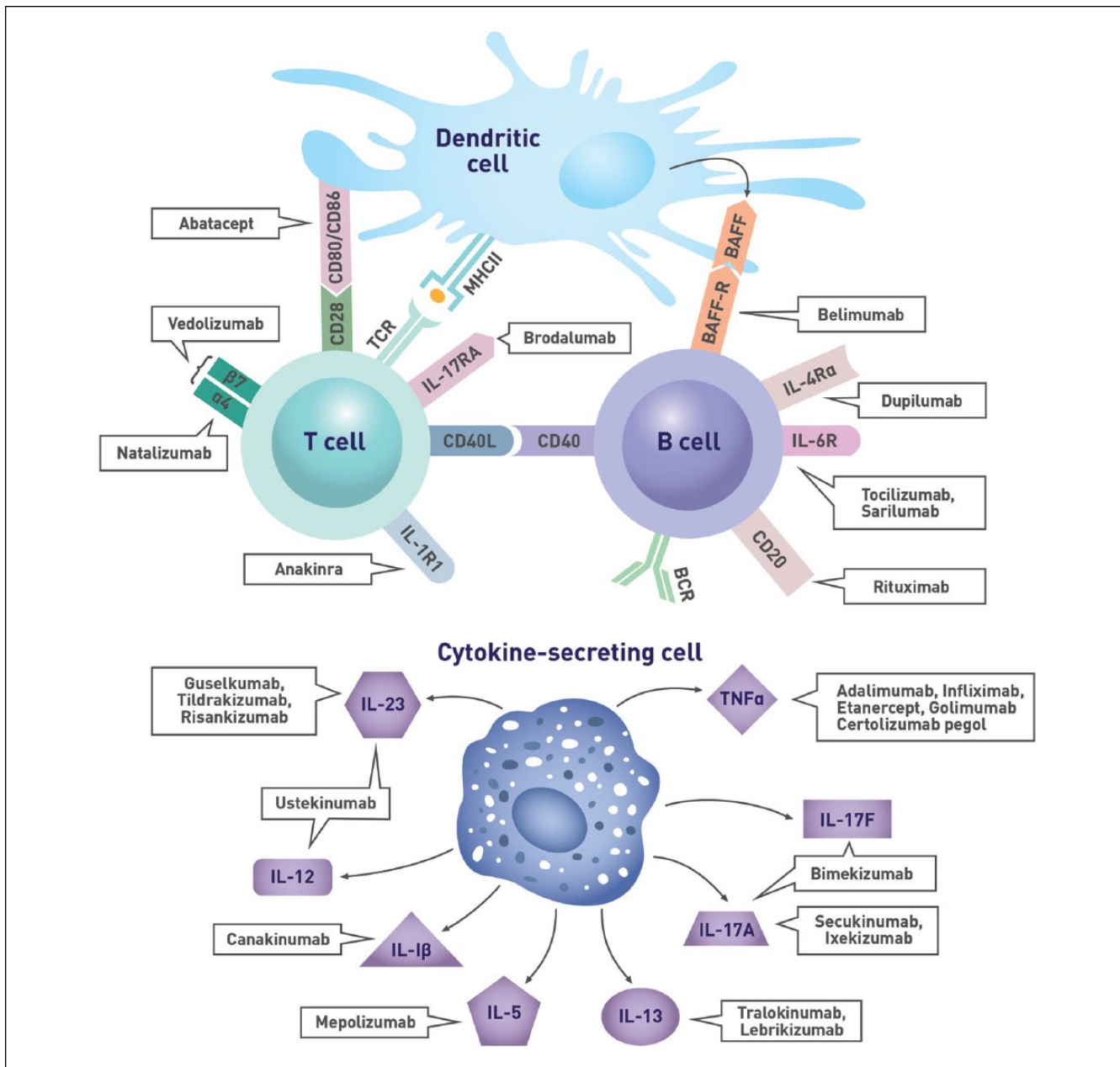


Figure 1. Immunological targets of biologic agents.

increased joint pain following the administration of pneumococcal or influenza vaccines to patients with RA, spondyloarthritis (SpA), or PsA,^{22,23} these symptoms were transient and self-resolving.

Biologics

Biologics may impede optimal immune responses to certain vaccines (Table 2). For example, patients with IBD receiving tumour necrosis factor α inhibitors (TNFi) tended to have attenuated humoral responses to influenza, pneumococcal, and hepatitis A virus (HAV) vaccines.^{18,24-30} A meta-analysis

of 9 studies (n = 728) revealed that patients with IBD on TNFi monotherapy had a significantly lower probability of achieving adequate immune responses to routine vaccinations, including those against hepatitis B virus (HBV), HAV, influenza, and pneumococcus, compared with untreated patients (odds ratio [OR], 0.32; 95% confidence interval [CI], 0.21-0.49; $P < .001$).³¹

Rituximab (RTX)-based B-cell depletion therapy also lowered antibody titres and seroprotection rates in response to influenza vaccines compared with DMARDs and/or prednisone.³²⁻³⁵ In addition, RTX treatment was often associated with failure to attain protective antibody titres against all

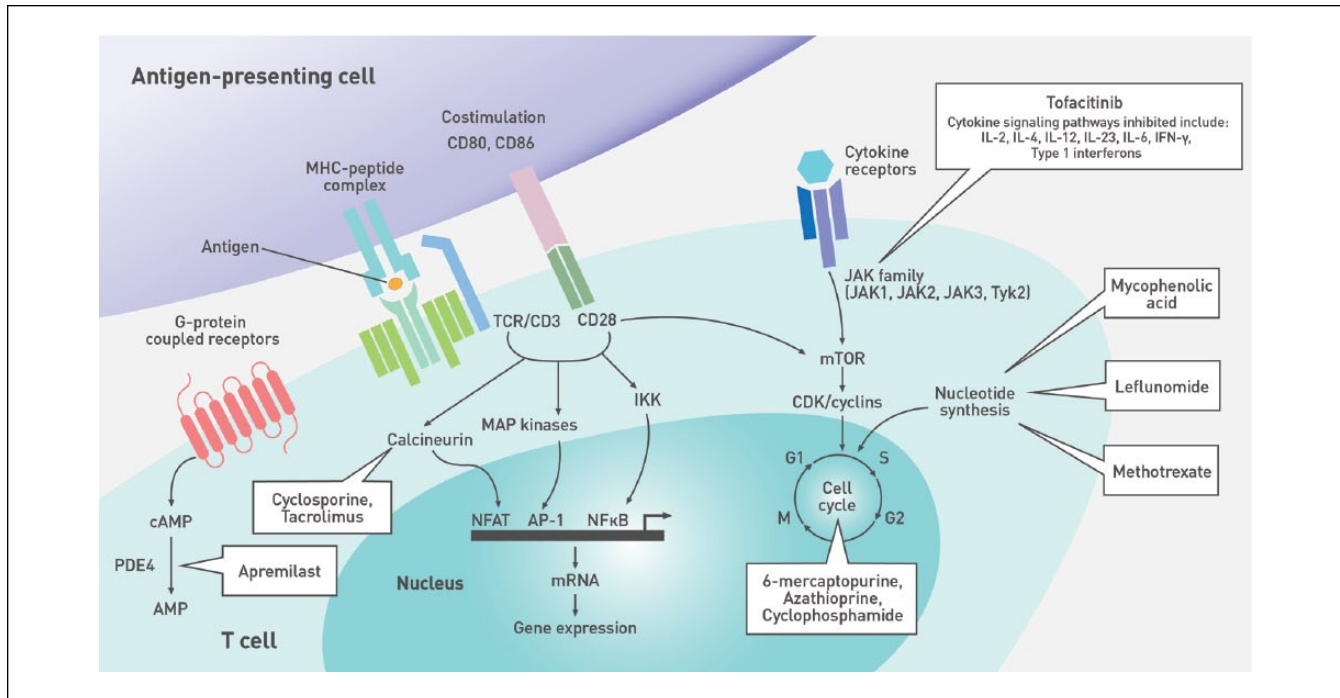


Figure 2. Immune pathways targeted by nonbiologic disease-modifying antirheumatic drugs.

Table 2. Safety and Efficacy of Vaccination in Patients on Biologic Agents.

Vaccine	Biologic Agent	Patient Population	Efficacy	Safety
Inactivated and subunit vaccines				
Cholera (oral)	Vedolizumab	Healthy individuals	No significant difference in seroconversion rates but diminished the magnitude of antibody titre increase ¹³¹	Well tolerated ¹³¹
Hepatitis A	TNFi (pooled)	RA	Diminished humoral response compared to healthy individuals, but 86% of patients achieved seroprotection with 2 vaccine doses ¹³²	Well tolerated and did not result in exacerbation of disease activity ¹³²
Hepatitis B	Infliximab	IBD	Diminished humoral response to the vaccine ²⁸	NA
	TNFi (pooled)	IBD	Reduced humoral response to the vaccine ¹³³	NA
	TNFi (pooled)	SpA	Diminished humoral response to the vaccine ¹³⁴	NA
Influenza	TNFi (pooled)	IBD	Humoral response unaffected by TNFi treatment; however, patients with IBD generally had lower responses than healthy controls regardless of treatment ¹³⁵	NA
	Vedolizumab	Healthy individuals	No significant difference ¹³¹	Well tolerated ¹³¹
	Abatacept	RA	Results are variable but may reduce humoral response to the vaccine ^{136,137}	Well tolerated ^{136,137}
Influenza	Adalimumab	RA	No significant effect ¹³⁸	Well tolerated ¹³⁸
	Belimumab	SLE	Lower fold-increase in titres for some influenza strains compared with controls ¹³⁹	NA
	Certolizumab pegol	RA	No significant effect ⁴⁵	Well tolerated ⁴⁵
	Infliximab	RA	No significant effect ¹⁴⁰	Well tolerated and did not exacerbate disease activity ¹⁴⁰
	Infliximab	IBD	Diminished humoral response ^{141,142}	Well tolerated, without incidence of serious adverse events ^{141,142}
	Rituximab	RA	Cellular responses maintained but diminished humoral response to the vaccine ³²⁻³⁶	Well tolerated ³²⁻³⁴
	Secukinumab	Healthy individuals	No significant effect among individuals who received a single secukinumab dose ¹⁴³	Well tolerated ¹⁴³
Tocilizumab	RA	No significant effect ^{43,144}	Well tolerated and did not result in exacerbation of disease activity ^{43,144}	

(continued)

Table 2. (continued)

Vaccine	Biologic Agent	Patient Population	Efficacy	Safety
Neisseria meningitidis Pneumococcal (polysaccharide or conjugate)	TNFi (pooled)	RA, PsO, PsA, SpA, and other immune-mediated diseases	Results are variable but may result in suppression of humoral response to the vaccine ^{44,46,58,145-147} TNFi monoclonal antibodies such as infliximab and adalimumab may have a greater suppressive effect than etanercept ⁵⁸	Generally well tolerated ^{44,58} May trigger short-lasting PsA exacerbation following vaccination ²² Higher incidence of mild, systemic reactions such as fever, arthralgia, and nasal congestion in TNFi-treated patients ⁵⁸
	Secukinumab	IBD Healthy individuals	Diminished humoral response to the vaccine ^{24,26,29} No significant effect among individuals who received a single secukinumab dose ¹⁴³	Well tolerated ²⁶ Well tolerated ¹⁴³
	Abatacept	RA	Results are variable but may reduce humoral response to the polysaccharide and conjugate vaccines ^{137,148,149}	Well tolerated ^{137,148,149}
	Adalimumab	RA	No significant effect on the immunogenicity of the polysaccharide vaccine ¹³⁸	Well tolerated ¹³⁸
	Certolizumab pegol	RA	No significant effect on the pneumococcal polysaccharide vaccine ⁴⁵	Well tolerated ⁴⁵
	Etanercept	RA	May reduce humoral response to the conjugate vaccine ¹⁵⁰	Well tolerated ¹⁵⁰
	Infliximab	RA	No significant effect on immunogenicity of the polysaccharide vaccine ¹⁵¹	NA
	Golimumab	IBD RA	Reduced humoral response to the polysaccharide vaccine ²⁷ Reduced fold-increase in vaccine-specific IgG titres in response to the polysaccharide vaccine but maintained opsonophagocytic function ¹⁵²	Well tolerated ²⁷ Well tolerated ¹⁵²
	Rituximab	RA	Diminished humoral response to the polysaccharide and conjugate vaccines ^{37,148,153}	Well tolerated ^{148,153}
	Tocilizumab	RA	No significant effect on the immunogenicity of the polysaccharide or conjugate vaccines ^{51,144,148,154}	Well tolerated ^{51,144,148,154}
Tetanus	TNFi (pooled)	RA, SpA	No significant effect on the immunogenicity of the polysaccharide and conjugate vaccines ^{23,37,47}	Well tolerated, but some patients treated with methotrexate or TNFi reported a transient worsening of joint pain 1 week after vaccination ²³
		IBD	Diminished humoral response to the polysaccharide and conjugate vaccines ^{18,25,27,30}	Well tolerated ^{25,27}
	Ustekinumab	PsO	No significant effect on the immunogenicity of the polysaccharide vaccine ¹⁵⁵	Higher incidence of mild injection site reactions in ustekinumab-treated patients but otherwise well tolerated ¹⁵⁵
	Abatacept	Type I diabetes	Achieved protective titres but diminished the magnitude of recall humoral response compared to controls ¹⁵⁶	NA
	Rituximab Tocilizumab	RA RA	Recall response not significantly affected ¹⁵³ No significant effect on recall humoral response to tetanus toxoid ¹⁵⁴	Well tolerated ¹⁵³ Well tolerated ¹⁵⁴
Pertussis	Ustekinumab	PsO	No significant difference ¹⁵⁵	Higher incidence of mild injection site reactions but otherwise well tolerated ¹⁵⁵
	TNFi (pooled)	IBD	TNFi monotherapy had no significant effect on the immunogenicity of booster vaccination ¹⁵⁷	Well tolerated, without incidence of disease flares ¹⁵⁷
	TNFi (pooled)	IBD	TNFi monotherapy had no significant effect on the immunogenicity of booster vaccination ¹⁵⁷	Well tolerated, without incidence of disease flares ¹⁵⁷
Live attenuated vaccines				
Herpes zoster	TNFi (pooled)	RA, PsA, PsO, AS, IBD	Vaccination effectively protected patients from disease ⁷⁴	Vaccination was not associated with short-term increase in herpes zoster risk ⁷⁴
Measles, mumps, rubella	Etanercept	JIA	No significant effect on humoral response to vaccination; insignificant trend toward lower cellular response ⁸⁰	Well tolerated and did not cause disease exacerbation ⁸⁰
	Vedolizumab	IBD	Single case report of a patient achieving a positive measles antibody index following revaccination ¹⁵⁸	No adverse effect observed ¹⁵⁸
Yellow fever	Infliximab	RA	Similar response rates following revaccination in infliximab-treated patients with RA and controls; trend toward lower titres in patients, but analysis limited by small study numbers ⁸¹	No adverse effect observed ⁸¹

Abbreviations: AS, ankylosing spondylitis; IBD, inflammatory bowel disease; IgG, immunoglobulin G; JIA, juvenile idiopathic arthritis; NA, not available; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SpA, spondyloarthritis; TNFi, tumour necrosis factor α inhibitor.

influenza strains contained within the vaccine.^{32,34,36} Similarly, a meta-analysis demonstrated the negative impact of RTX on pneumococcal vaccine response rates, with RTX-treated patients with RA (n = 88) having significantly poorer responses to both the 6B (OR, 0.25; 95% CI, 0.11-0.58; $P = .001$) and 23F (OR, 0.21; 95% CI, 0.04-1.05; $P = .06$) serotypes compared with controls.³⁷

Nonbiologic Agents

Corticosteroids and many DMARDs negatively affect vaccine immunogenicity (Table 3). For example, treatment with prednisone-equivalent doses ≥ 10 mg/d diminished humoral responses to influenza vaccines in patients with SLE.^{38,39} A meta-analysis of 15 studies demonstrated that, compared with healthy individuals, corticosteroid

Table 3. Safety and Efficacy of Vaccination in Patients on Nonbiologic DMARDs and Corticosteroids.

Vaccine	Drug	Patient Population	Efficacy	Safety
Inactivated and subunit vaccines				
Hepatitis A	Methotrexate	RA	Reduced humoral response to the vaccine among patients treated with a mean dose of 15 mg/wk ¹³²	NA
Hepatitis B	Corticosteroids	IBD	Reduced humoral response among patients who received ≥ 2 vaccine doses while on corticosteroid therapy ¹⁵⁹	NA
<i>Haemophilus influenzae</i> type b Human papillomavirus	Thiopurines	IBD	Reduced humoral response to the vaccine ¹³³	NA
	Thiopurines	IBD	No significant effect ¹⁶⁰	Vaccination did not exacerbate disease activity ¹⁶⁰
	Antimalarials	SLE	No significant effect ¹⁶¹	Well tolerated and did not result in exacerbation of disease activity ¹⁶¹
	Calcineurin inhibitors	SLE	No significant effect, but study limited by small sample size ¹⁶¹	Well tolerated and did not result in exacerbation of disease activity ¹⁶¹
	Corticosteroids	SLE	No significant effect among patients receiving a mean prednisolone dose of 4.8 mg/d ¹⁶¹	Well tolerated and did not result in exacerbation of disease activity ¹⁶¹
	Mycophenolate	SLE	Mycophenolate mofetil dose inversely correlated with vaccine-specific antibody titres for some serotypes following vaccination ¹⁶¹	Well tolerated ¹⁶¹
	Thiopurines	SLE	No significant effect ¹⁶¹	Well tolerated and did not result in exacerbation of disease activity ¹⁶¹
Influenza	Anti-malarials	RA, SpA, SLE	No significant effect ^{38,46,162} May restore influenza vaccine immunogenicity in patients with SLE receiving prednisone or other immune-suppressive therapy ³⁸	Well tolerated and did not result in exacerbation of disease activity ^{46,162}
	Calcineurin inhibitors	Solid organ transplant	Variable effect on vaccine immunogenicity but may reduce humoral response ¹⁶³⁻¹⁶⁷	Well tolerated without impact on allograft function ^{163,166,167}
	Corticosteroids	RA, SpA, IBD, Sjögren syndrome SLE	No significant effect, ^{44,45,142,168,169} particularly at mean prednisone-equivalent doses ≤ 10 mg/d ^{44,45,169} Reduced seroconversion rates observed, ^{38,40} particularly at prednisone-equivalent doses ≥ 10 mg/d ^{38,39}	Well tolerated ^{38,44,142,168,169} Increased incidence of disease flares and rise in autoantibody titres among patients with SLE with low response to the vaccine ³⁹
	Leflunomide	RA, PsA, AS, SLE	Reduced humoral response to vaccine compared to healthy controls ^{46,168}	Well tolerated and did not exacerbate disease activity ^{46,168}
	Methotrexate	RA, SpA	Reduced humoral response to the vaccine (mean dose in studies: 16-20 mg/wk) ^{44,46}	Well tolerated ^{43,44,46}
	Mycophenolate	Solid organ transplant	Reduced humoral response to the vaccine ^{166,167,170-174}	Well tolerated without incidence of allograft rejection ^{166,167,170-172,174}
	Sulfasalazine	RA, SpA, other inflammatory diseases	No significant effect ¹⁶²	Well tolerated ¹⁶²
	Thiopurines	Sjögren syndrome SLE Wegener granulomatosis	No significant effect ¹⁶⁹ Reduced seroconversion and seroprotection rates ^{40,175} No significant effect ¹⁷⁶	Well tolerated and did not result in exacerbation of disease activity ^{40,169,175,176}
		IBD	Reduced humoral response to H1N1 ¹⁴²	NA
		Tofacitinib	RA	Diminished humoral responses in patients treated with methotrexate + tofacitinib combination therapy but not in those treated with tofacitinib alone or methotrexate alone ⁵⁰
Pneumococcal (polysaccharide or conjugate)	Calcineurin inhibitors	Solid organ transplant RA	May diminish humoral response to some pneumococcal serotypes in the polysaccharide vaccine ¹⁶³ No significant effect on the immunogenicity of the polysaccharide vaccine ⁴⁹	Well tolerated without incidence of allograft rejection ¹⁶³ NA
	Corticosteroids	RA, SpA, and various inflammatory conditions	No significant effect on the immunogenicity of conjugate and polysaccharide vaccines, ^{23,45,47,138,154} particularly at mean prednisone-equivalent doses < 20 mg/d ^{23,45,47,138} Prednisone-equivalent doses ≥ 20 mg/d tended to result in poor serologic response to polysaccharide vaccine ¹⁷⁷	Well tolerated without incidence of disease exacerbation ^{23,138,177}
	Methotrexate	RA	Reduced humoral response to the conjugate and polysaccharide vaccines ^{23,45,47-52}	Well tolerated, ^{23,49,51} but some patients treated with methotrexate reported a transient worsening of joint pain 1 week after vaccination ²³
	Mycophenolate	Solid organ transplant	Reduced recall humoral response to the vaccine ¹⁷⁸	NA
	Thiopurines	IBD	No significant effect ²⁷	Well tolerated ²⁷
	Tofacitinib	RA	Diminished humoral response among patients on combination therapy with tofacitinib + methotrexate ⁵⁰	NA
Tetanus	Calcineurin inhibitors	Chronic uveitis	No significant effect, but study limited by small sample size ¹⁷⁹	NA
	Mycophenolate	Solid organ transplant	Reduced recall humoral response to the vaccine ¹⁷⁸	NA
	Sulfasalazine	Healthy individuals	Diminished fold-increase in antibody titres following booster vaccination ¹⁸⁰	NA

(continued)

Table 3. (continued)

Vaccine	Drug	Patient Population	Efficacy	Safety
Live attenuated vaccines				
Cholera (oral)	Antimalarials	Healthy individuals	Coadministration of chloroquine and live cholera vaccine reduced seroconversion rates ¹⁸¹	Well tolerated ¹⁸¹
Herpes zoster	Corticosteroids	RA, PsO, PsA, AS, IBD, various inflammatory conditions	Immunogenic and effectively protected vaccinated patients from disease for up to 2 years ^{74,182}	Vaccine was well tolerated with no incidence of vaccine-related varicella ^{75,182} . However, 1 study reported a 3-fold increased HZ risk in patients on immune-suppressive therapy ⁷⁵
	Methotrexate	RA	No significant effect among patients receiving 15-25 mg/wk ⁷²	Generally well tolerated, but 1 patient without existing immunity developed cutaneous dissemination of the vaccine strain 16 days after vaccination (2 days after initiating tofacitinib treatment) ⁷²
	Thiopurines	IBD	Low-dose thiopurine treatment blunted the cellular and humoral response to vaccine ¹⁸³	Well tolerated and did not result in disease exacerbation ¹⁸³
	Tofacitinib	RA	No significant effect among patients on background methotrexate vaccinated 2-3 weeks prior to starting tofacitinib treatment ⁷²	Generally well tolerated, but 1 patient without existing immunity developed cutaneous dissemination of the vaccine strain 16 days after vaccination (2 days after initiating tofacitinib treatment) ⁷²
Measles, mumps, rubella	Methotrexate	JIA	Nonsignificant trend toward reduced humoral and cellular recall responses among patients on a mean dose of ≤ 12 mg/m ² body surface area ⁸⁰	No disease exacerbation, need for increased treatment doses, or severe adverse events resulting from vaccination ^{76,80}
Typhoid + cholera (oral)	Antimalarials	Healthy Individuals	No significant effect ¹⁸¹	Well tolerated ¹⁸¹
Yellow fever	Calcineurin inhibitors	Solid organ transplant	NA	Well tolerated, but study limited by small sample size ⁷⁹
	Corticosteroids	RA and other inflammatory conditions	No significant effect on seroprotection rates among patients receiving a median prednisone-equivalent dose of 7 mg/d ⁷⁸	Vaccination did not result in serious adverse events; however, the frequency of moderate to severe local reactions was 8-fold higher among corticosteroid-treated patients compared with healthy adults ⁷⁸
	Methotrexate	RA, PsO, scleroderma, PsA	Methotrexate doses ranging from 10-30 mg/wk did not significantly affect humoral response as measured by plaque reduction neutralization test ⁸²	Well tolerated ⁸²

Abbreviations: AS, ankylosing spondylitis; HZ, herpes zoster; IBD, inflammatory bowel disease; JIA, juvenile idiopathic arthritis; NA, not available; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SpA, spondyloarthritis.

treatment lowered the probability of seroconversion in patients with SLE, with relative risk ratios (RRs) of 0.66 (95% CI, 0.53-0.82), 0.49 (95% CI, 0.26-0.91), and 0.51 (95% CI, 0.24-1.09) for influenza H1N1, H3N2, and B, respectively.⁴⁰ Similarly, methotrexate (MTX) suppressed humoral responses to both influenza⁴¹⁻⁴⁶ and pneumococcal vaccines.^{23,45,47-52} In 1 study, patients with RA without preexisting influenza or *Streptococcus pneumoniae* immunity receiving either placebo (n = 36) or placebo + MTX (n = 78; mean MTX dose of 17.2 mg/wk) were immunized with the influenza and 23-valent pneumococcal polysaccharide (PPSV23) vaccines.⁴⁵ Four weeks after vaccination, the placebo group achieved an influenza vaccine response rate of 84.6% (95% CI, 70.7%-98.5%) vs 50.9% (95% CI, 37.9%-63.9%) for the placebo + MTX group. Likewise, 89.3% (95% CI, 77.8%-100.0%) of placebo-treated patients achieved ≥ 2 -fold antibody titre increases to ≥ 3 of 6 pneumococcal antigens tested compared with only 50.0% (95% CI, 37.3%-62.7%) of MTX-treated patients. The suppressive effect of MTX was further exemplified in studies by Park et al,^{41,42} which

showed that patients with RA on MTX had a poorer vaccine response to the seasonal influenza vaccine than those in whom treatment was withheld for 2 weeks before and after vaccination and those who discontinued treatment for 2 to 4 weeks after vaccination.

Inactivated Vaccines

Statement 2a: To optimize the immunogenicity of inactivated vaccines in treatment-naive patients with immune-mediated conditions, we suggest that immunization be performed at least 2 weeks prior to initiation of immunosuppressive therapy, whenever possible.

GRADE: Conditional recommendation; moderate-level evidence

Vote: 71.4% strongly agree, 28.6% agree

Evidence Summary

To optimize efficacy, the length of time required to develop robust immune responses to administered vaccines should

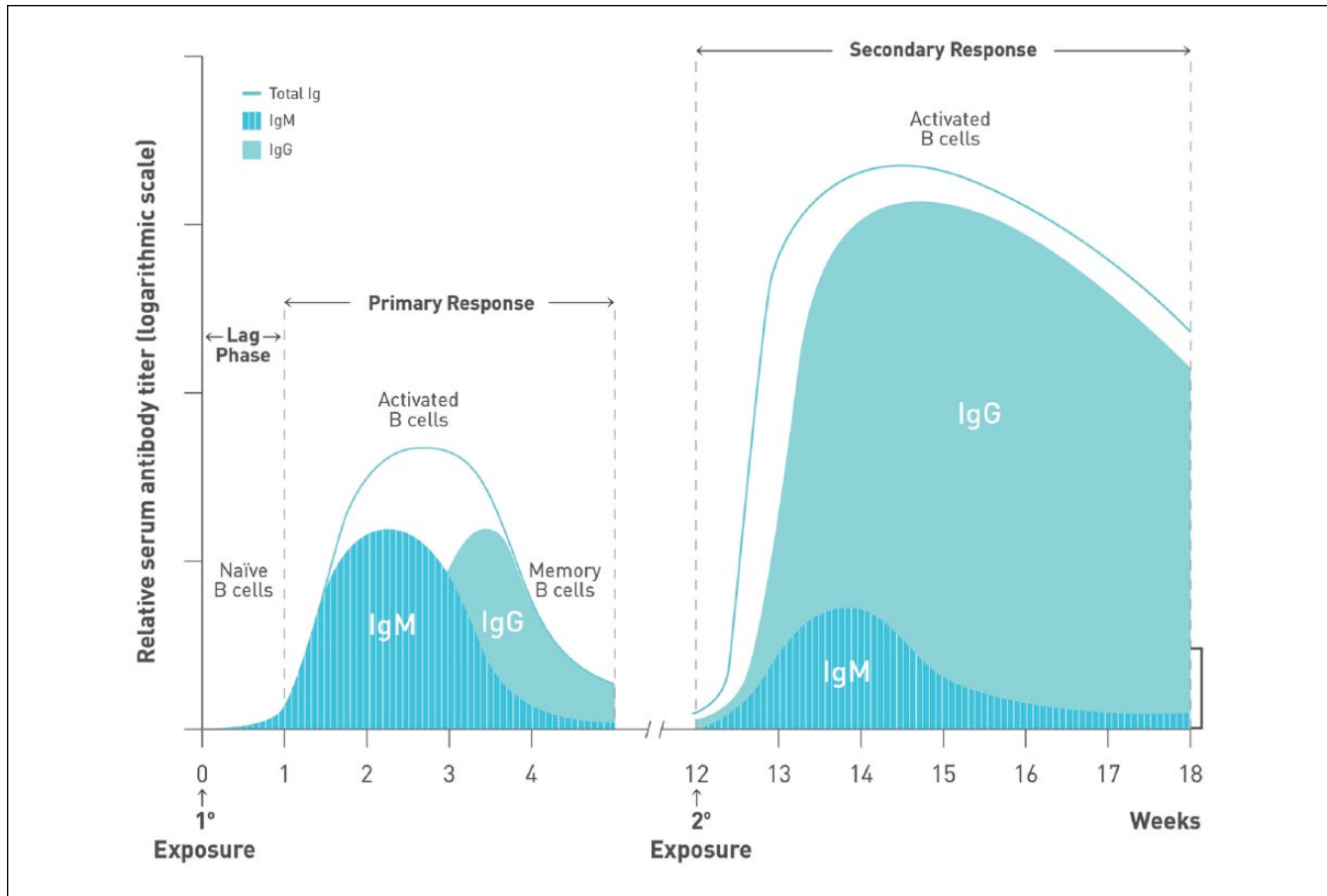


Figure 3. Kinetics of antibody response following immunization. The kinetics of B-cell activation and antibody (immunoglobulin M [IgM], immunoglobulin G [IgG]) production during primary and secondary responses to antigen are depicted. The primary response is characterized by a short lag phase lasting approximately 1 week, followed by the production of low-affinity IgM. IgG becomes detectable within 10 to 14 days after antigen exposure. Conversely, secondary responses reactivate memory B cells, resulting in quicker responses and higher IgG titres than those observed during a primary response.

be considered (Figures 3 and 4). Booster immunizations reactivate immune memory and induce high vaccine-specific IgG titres as quickly as 7 days after vaccination.⁵³⁻⁵⁵ In contrast, humoral responses to primary vaccination are characterized by the initial production of antigen-specific, low-affinity immunoglobulin M (IgM) antibodies after a lag phase lasting up to a week postimmunization.^{55,56} Higher affinity and avidity immunoglobulin G (IgG) antibodies eventually become detectable in the blood within 10 to 14 days⁵⁷ and may take up to 4 to 6 weeks to achieve maximum levels.^{53,56} It is therefore ideal to defer immunosuppressive treatment for ≥ 2 weeks after vaccination to allow sufficient time to develop a robust and protective humoral response.

One study demonstrated the benefit of deferring treatment following vaccination. In this study, humoral response to the seasonal influenza vaccine was compared between MTX-treated patients with RA who stayed on treatment and those who withheld treatment for 2 weeks postvaccination.⁴¹ Patients who discontinued treatment

for 2 weeks postvaccination had a significantly higher rate of satisfactory response to all 4 influenza antigens contained within the vaccine compared with those who stayed on MTX (46% vs 22%; $P < .001$). Similarly, another study compared the humoral response of patients with RA who continued MTX or withheld treatment for 2 weeks before and after vaccination or 4 weeks after vaccination.⁴² Compared to patients who remained on treatment, those who discontinued MTX for 2 weeks before and after vaccination (31.5% vs 51%; $P = .044$) or 4 weeks postvaccination (31.5% vs 46.2%; $P = .121$) tended to have greater response rates to all 3 influenza vaccine antigens.

Statement 2b: Among patients with immune-mediated diseases currently receiving immunosuppression, we recommend that immunosuppressive treatment not be interrupted for administration of inactivated vaccines.

GRADE: Strong recommendation; moderate-level evidence

Vote: 28.6% strongly agree, 64.3% agree, 7.1% neutral

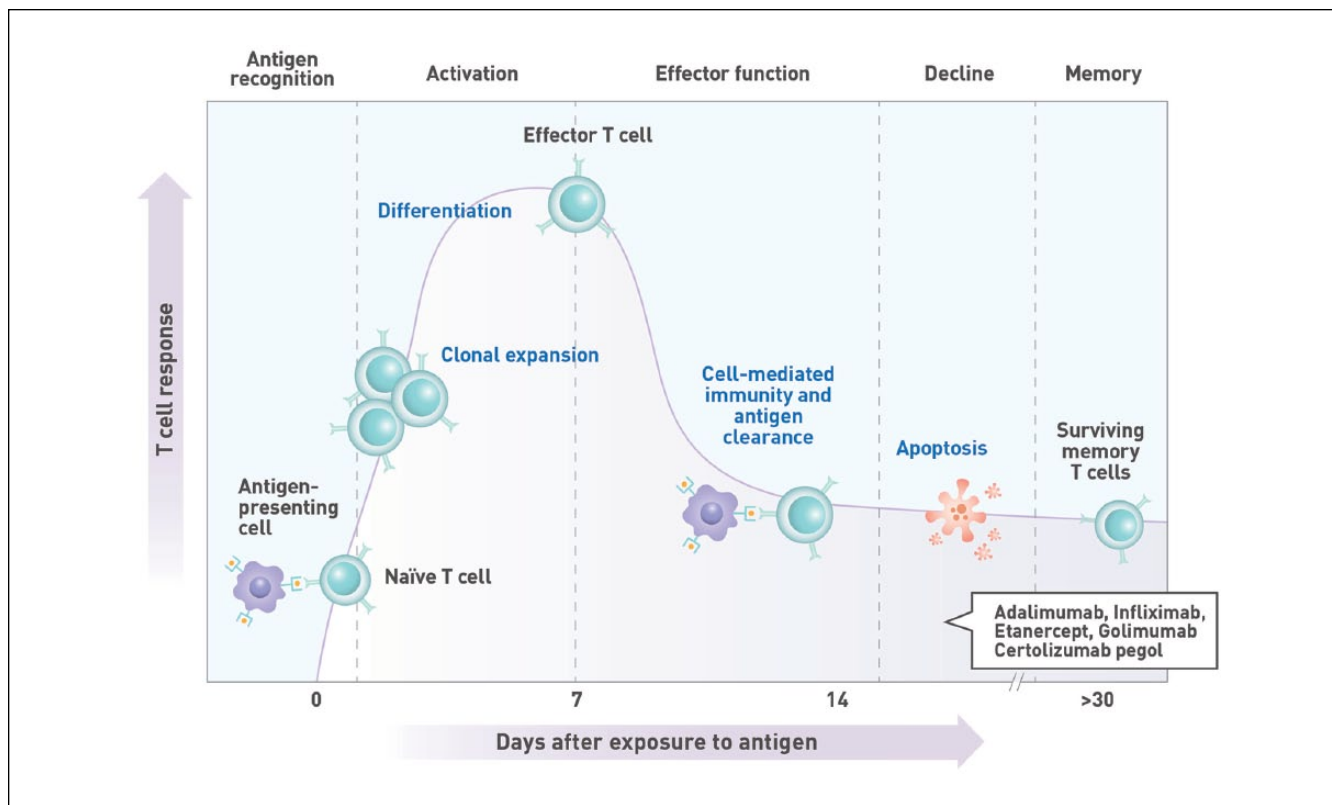


Figure 4. Kinetics of T-cell response. T-cell activation is initiated by the recognition of antigenic peptides displayed on the surface of antigen-presenting cells in the draining lymph nodes. This results in the clonal expansion of the activated T cell and the acquisition of effector cell function within approximately 1 week of antigen exposure. Cellular immunity plays a vital role in the clearance of intracellular pathogens and the development of robust T-cell-dependent humoral immune responses.

Evidence Summary

Treatment with immunosuppressive agents should not affect the decision to administer inactivated vaccines to patients with IMDs. While vaccine antigenicity may be attenuated compared with healthy individuals, humoral response is not abolished and significant increases in antigen-specific antibody titres, often reaching protective levels, are generally achieved. In a study by Adler et al,⁴⁴ DMARD-treated patients ($n = 28$) with RA, SpA, vasculitis, or connective tissue disease (CTD) achieved lower fold-increases in vaccine-specific antibody titres than healthy controls ($n = 40$) after receiving the influenza A/H1N1 vaccine (7.7 vs 13.3). Despite this, 79% of patients still achieved seroprotective titres $\geq 1:40$. While the seroprotection rate in DMARD-treated patients is reduced compared with healthy individuals (98%), the majority still benefitted from vaccination despite the negative effect of immunosuppressive treatment on vaccine immunogenicity.

Several studies established the safety and tolerability of inactivated vaccines in patients with IMDs on immunosuppressive therapies (Tables 2 and 3). No serious vaccine-related AEs have been reported, although differences in the incidence of mild AEs have been observed. One such study

noted higher rates of mild systemic reactions such as fever (8.3% vs 0.9%; $P = .01$), arthralgia (12.5% vs 4.3%; $P = .03$), and nasal congestion (13.3% vs 4.3%; $P = .014$) among patients treated with TNFi compared with healthy controls after receiving the A/H1N1 vaccine.⁵⁸

In patients receiving intermittent treatment in whom optimal vaccine immunogenicity is desired and the clinical situation allows, vaccination can be given at the nadir of immunosuppression. For immunosuppressive agents given as a bolus at intervals exceeding 4 weeks, such as infliximab (IFX) or cyclophosphamide, it is suggested that the vaccine be administered midcycle or 2 weeks prior to the next dose. Alternatively, immunosuppressive therapy may be temporarily discontinued prior to vaccination. The length of treatment discontinuation should take drug pharmacokinetics (Tables 4 and 5) and dosage into consideration.

Studies in RA have demonstrated that discontinuing MTX treatment until 2 weeks after immunization with the seasonal influenza vaccine increases vaccine response without increasing the risk of flares compared to those who stayed on treatment.⁴¹ However, flares tended to be more common among patients who received a 4-week MTX treatment break around the time of vaccination.⁴² Therefore, while a washout period before vaccine administration may improve the

Table 4. Pharmacokinetic Half-Lives of Biologic Agents.

Family	Biologic	Isotype	Target	Half-Life	Status
TNF inhibitors	Adalimumab	human IgG1	TNF α	10-20 days ¹⁸⁴	Approved
	Etanercept	IgG1 Fc domain + TNF receptor extracellular ligand-binding domain	TNF α , LT α (TNF β)	4.2 days ¹⁸⁵	Approved
	Certolizumab pegol	Humanized Fab' conjugated to polyethylene glycol	TNF α	14 days ¹⁸⁶	Approved
Interleukin inhibitors	Golimumab	Human IgG1 κ	TNF α	11-12 days ¹⁸⁷	Approved
	Infliximab	Chimeric IgG1 κ	TNF α	7.7-14.7 days ¹⁸⁸	Approved
	Dupilumab	Human IgG4	IL-4R α	NA ^{189,a}	Approved
	Mepolizumab	Humanized IgG1 κ	IL-5	16-22 days ¹⁹⁰	Approved
	Tocilizumab	Humanized IgG1 κ	IL-6R	11-13 days ¹⁹¹	Approved
	Sarilumab	Human IgG1	sIL-6R α , mL-6R α	Initial: 8-10 days Terminal: 2-4 days ¹⁹²	Approved
	Anakinra	IL-1 receptor antagonist	IL-1R1	4-6 hours ¹⁹³	Approved
	Canakinumab	Human IgG1 κ	IL-1 β	26 days ¹⁹⁴	Approved
	Tralokinumab	Human IgG4	IL-13	17.7 days ¹⁹⁵	In development
	Lebrikizumab	Humanized IgG4	IL-13	25 days ¹⁹⁶	In development
	Secukinumab	Human IgG1 κ	IL-17A	27 days ¹⁹⁷	Approved
	Ixekizumab	Humanized IgG4	IL-17A	13 days ¹⁹⁸	Approved
	Bimekizumab	Humanized IgG1	IL-17A, IL-17F	17-22 days ¹⁹⁹	In development
	Brodalumab	Human IgG2 κ	IL-17RA	NA ^{200,b}	Approved
	Ustekinumab	Human IgG1	IL-12, IL-23	15-32 days ²⁰¹	Approved
Guselkumab	Human IgG1 λ	IL-23	15-18 days ²⁰²	Approved	
Risankizumab	Human IgG1	IL-23	20-28 days ²⁰³	In development	
Tildrakizumab	Humanized IgG1 κ	IL-23	24.5 days ²⁰⁴	In development	
Nemolizumab	Humanized IgG2	IL-31RA	12.6-16.5 days ²⁰⁵	In development	
B-cell inhibitor	Rituximab	Chimeric IgG1 κ	CD20	20.8 days ⁵⁹	Approved
	Belimumab	Human IgG1 λ	BAFF (BLYS)	12.5-19.4 days ²⁰⁶	Approved
Integrin blockers	Vedolizumab	Humanized IgG1	α 4 β 7	25 days ²⁰⁷	Approved
	Natalizumab	Humanized IgG4 κ	α 4	9.6-11.1 days ²⁰⁸	Approved
Costimulatory modulator	Abatacept	CTLA-4 extracellular domain + modified IgG1 Fc domain	CD80, CD86	13.1-16.7 days ²⁰⁹	Approved

Abbreviations: BAFF, B-cell-activating factor; BLYS, B-lymphocyte stimulator; CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; Fab', fragment antibody binding; Fc, fragment constant; IgG, immunoglobulin G; IL, interleukin; IL-1R1, interleukin 1 receptor 1; IL-17RA, interleukin 17 receptor A; LT, lymphotoxin; mL-6R α , membrane-bound IL-6 receptor α ; NA, not available; sIL-6R α , soluble IL-6 receptor α ; TNF, tumour necrosis factor.

^aAs dupilumab has a distinct target-mediated phase and the instantaneous half-life decreases over time to values close to zero, its terminal half-life cannot be calculated or used for any practical purposes.

^bExpected be similar to endogenous IgG.

patient's immune response to the vaccine, clinicians should use their judgement to evaluate the risks vs benefits of treatment disruption.

Statement 2c: In patients with immune-mediated diseases treated with rituximab who require optimal vaccine immunogenicity, we recommend that immunization be deferred to ≥ 5 months after the last dose and at least 4 weeks prior to the subsequent dose of rituximab.

GRADE: Strong recommendation; low-level evidence

Vote: 14.3% strongly agree, 78.6% agree, 7.1% disagree

Evidence Summary

RTX pharmacokinetics does not directly correlate with B-cell reconstitution following treatment. Despite having a

half-life of approximately 21 days,⁵⁹ 1 study showed that B-cell reconstitution occurred after a mean of 8 months from the last RTX dose (n = 24; range of 5-13 months).⁶⁰ In line with this finding, patients immunized with the trivalent influenza vaccine >5 months after RTX infusion (n = 13) exhibited greater fold-increases in antibody titres for influenza H1N1 (2.1 vs 1.1; P = .02), H3N2 (1.7 vs 1.3; P = .23), and B (3.6 vs 1.6; P = .01) than patients vaccinated ≤ 5 months (n = 16) after their last RTX dose.³⁴ Similarly, another study reported that patients with RA vaccinated 6 to 10 months after their last RTX infusion (n = 12) exhibited modestly restored IgG responses and significant increases in antibody titres for the H3N2 and H1N1 vaccine strains compared with those vaccinated 4 to 8 weeks after RTX treatment (n = 11).^{33,35}

Table 5. Pharmacokinetic Half-Lives of Nonbiologic DMARDs.

Family	Drug	Half-Life
JAK family kinase inhibitor	Tofacitinib	3 hours ²¹⁰
Folate antagonist	Methotrexate	<30 mg/m ² : 3-10 hours ²¹¹ ≥30 mg/m ² : 8-15 hours ²¹¹
Calcineurin inhibitor	Tacrolimus	35 hours ²¹²
	Cyclosporine	18 hours ²¹³
Alkylating agent	Cyclophosphamide	7 hours ²¹⁴
Antimalarials	Chloroquine	40 days ²¹⁵
	Hydroxychloroquine	50 days ²¹⁶
Purine analog	6-Mercaptopurine	1.5 hours ^{217,a}
	Azathioprine	5 hours ^{218,b}
Sulfa drug	Sulfasalazine	6-8 hours ²¹⁹
Inosine monophosphate dehydrogenase inhibitor	Mycophenolate mofetil	17.9 hours for MPA ²²⁰
	Mycophenolate sodium	11.7 hours for MPA 15.7 hours for MPAG metabolite ²²¹
Glucocorticoid	Prednisolone	2-4 hours ²²²
Phosphodiesterase-4 inhibitor	Apremilast	8.9-9.7 hours ²²³
Isoxazole	Leflunomide	14 days ²²⁴

Abbreviations: JAK, Janus kinase; MPA, mycophenolic acid; MPAG, mycophenolic acid glucuronide.

^aActive metabolites have longer half-lives.

^bFor azathioprine's sulfur-containing metabolites.

For most IMDs, RTX is typically administered at most every 6 months, unless clinical evaluation indicates a need for alternative dosing (in RA, RTX is administered every 6 to >12 months, depending on response duration).⁶¹ Therefore, to allow for a degree of B-cell reconstitution, as well as provide sufficient time to mount an adaptive immune response to the vaccine, it is recommended that inactivated vaccines be given at least 5 months following the last RTX dose and approximately 1 month prior to subsequent B-cell depleting therapy. When feasible, titres assessing seroconversion should be considered.

Live Attenuated Herpes Zoster Vaccine

The live attenuated herpes zoster (HZ) vaccine is indicated for adults ≥50 years of age to prevent HZ and postherpetic neuralgia. It contains the Oka varicella-zoster virus strain (VZV), which is present at higher viral titres (19400 plaque-forming units [pfu]/dose) than that used for the primary prevention of chickenpox (1350 pfu/dose).^{62,63} Among those with previous exposure and immunologic memory to VZV, the vaccine mitigates disease risk by boosting the anti-VZV adaptive immune responses.

Typically, live vaccines are more immunogenic than their inactivated counterparts due to their ability to mimic natural infection and effectively activate the humoral and cellular arms of the immune system.⁵³ However, the HZ subunit vaccine (HZ/su) recently approved in Canada and the United States may actually provide a more effective alternative to the live attenuated vaccine. In 2 phase 3 clinical trials (ZOE-50, ZOE-70), the HZ/su vaccine efficacy over a mean

follow-up of 3.7 years was 97.2% (95% CI, 93.7-99.0; $P < .001$) in individuals aged ≥50 years and was 91.3% (95% CI, 86.8-94.5; $P < .001$) in those aged ≥70 years.^{64,65} These rates were greater than the 51.3% reduction in HZ incidence observed in individuals ≥60 years immunized with the live attenuated vaccine in the Shingles Prevention Study.⁶⁶ Furthermore, the subunit vaccine had an efficacy of 88.8% (95% CI, 68.7-97.1; $P < .001$) against postherpetic neuralgia in individuals ≥70 years old. In the Shingles Prevention Study, efficacy against postherpetic neuralgia was 66.8% in the same age group vaccinated with the live attenuated vaccine.^{64,66} To date, however, there are no studies directly comparing the 2 vaccines. There are also no published efficacy data on the use of the subunit vaccine in cohorts with IMDs.

As the adjuvant, AS01_B, is a component of the HZ/su vaccine, there has been some anecdotal concern regarding the risk of autoimmune/inflammatory syndrome induced by adjuvants (ASIA). However, pooled data from the clinical trials have shown no significant differences in the incidence of IMDs up to a year postvaccination between individuals receiving HZ/su (90/14645; 0.6%) and those receiving placebo (105/14660; 0.7%).⁶⁷ In addition, a subgroup analysis of patients with a history of IMD showed comparable incidences of possible postvaccination disease exacerbation in the HZ/su (27/983; 2.8%) and placebo (27/960; 2.8%) groups, suggesting that the vaccine is likely safe in this patient population.⁶⁷

Due to its safety and efficacy, the Centers for Disease Control and Prevention (CDC) now recommends the use of the HZ/su vaccine over the live attenuated version.⁶⁸ However, should the live vaccine be considered, the

following statements aim to address concerns regarding its use in patients with IMDs on immunosuppressive therapies.

Statement 3a: To optimize the immunogenicity of the live attenuated herpes zoster vaccine in treatment-naïve patients with immune-mediated conditions, we suggest immunization be performed at least 2 to 4 weeks prior to initiation of immunosuppressive therapy.

GRADE: Conditional recommendation; moderate-level evidence

Vote: 21.4% strongly agree, 78.6% agree

Evidence Summary

The live attenuated HZ vaccine should ideally be administered prior to initiation of immunosuppressive therapy. Some guidelines recommend HZ vaccination 3 to 4 weeks prior to starting therapy,^{69,70} likely due to evidence demonstrating the presence of the vaccine virus strain up to 4 weeks after vaccination.⁷¹ Further prospectively designed studies are needed; however, evidence from 1 study suggests that HZ vaccination is safe and effective when administered as early as 2 weeks before treatment initiation.⁷² HZ vaccine immunogenicity was assessed in patients with RA on MTX (15-25 mg/wk) who received tofacitinib (n = 55) or placebo (n = 57) 2 to 3 weeks postvaccination.⁷² Six weeks after immunization, the fold-increase in VZV-specific IgG titres (2.11 vs 1.74) and number of VZV-specific T cells (1.50 vs 1.29) were comparable between the tofacitinib and placebo groups, respectively, suggesting that tofacitinib did not interfere with humoral or cellular immune responses to the vaccine. Immunization was generally safe, with only a single case of cutaneous dissemination of the vaccine strain observed in a patient without preexisting VZV immunity.⁷²

Statement 3b: In patients with immune-mediated diseases on immunosuppressive agents, the live attenuated herpes zoster vaccine can be safely administered to patients at risk, but the subunit vaccine is the preferred alternative. Individual situations should be assessed for patients treated with a combination of immunosuppressive drugs, if the live vaccine is being considered.

GRADE: Strong recommendation; moderate-level evidence

Vote: 64.3% strongly agree, 21.4% agree, 14.3% neutral

Evidence Summary

According to the CDC, treatment with low-dose MTX (≤ 0.4 mg/kg/wk), azathioprine (≤ 3.0 mg/kg/d), 6-mercaptopurine (≤ 1.5 mg/kg/d), short-term steroid therapy lasting < 2 weeks, or prednisone-equivalent doses < 20 mg/d is not sufficiently immunosuppressive to preclude the use of live vaccines.⁷³ Conversely, treatment discontinuation lasting 1 or 3 months before live vaccine administration is recommended for patients on high-dose systemic steroid therapy lasting > 2 weeks or immunomodulatory biologics, respectively.⁷³ Data,

like those expected from the VERVE trial (NCT02538757) assessing the outcomes of HZ vaccination in TNFi users, are required to accurately assess the risks in specific patient populations. In the interim, retrospective analyses provided insights into the risks and benefits of HZ vaccination in patients with IMDs receiving immunosuppressive therapies.

A retrospective cohort study demonstrated the safety and efficacy of the HZ vaccine in patients ≥ 60 years with RA, PsA, ankylosing spondylitis (AS), PsO, or IBD treated with biologics (TNFi, abatacept, or RTX), DMARDs, and/or oral glucocorticoids (n = 463 541).⁷⁴ During the 42-day window in which infection risk with the vaccine strain is greatest, none of the patients exposed to biologics (n = 633) developed varicella or HZ. Furthermore, vaccination lowered the HZ incidence over a 2-year median follow-up in biologic-treated, vaccinated patients (incidence ratio [IR], 8.5; 95% CI, 5.1-14.4) vs unvaccinated patients (IR, 16.0; 95% CI, 15.2-16.8). Among the 551 patients on TNFi, the IR of HZ in vaccinated patients was 8.5 (95% CI, 4.8-15.0) vs 15.9 (95% CI, 15.1-16.8) for those unvaccinated. Similarly, among immunized DMARD- and glucocorticoid-treated patients, the IRs were 7.0 (95% CI, 4.7-10.3) and 10.3 (95% CI, 6.7-15.8), respectively, vs 13.6 (95% CI, 13.1-14.2) and 17.2 (95% CI, 16.5-17.9) for their respective unvaccinated counterparts.⁷⁴

Notably, 1 study reported that patients with IMDs on immunosuppressive therapy at the time of HZ vaccination (n = 4826) were at greater risk of HZ 42 days postvaccination (OR, 2.99; 95% CI, 1.58-5.70) than those who discontinued immunosuppressive treatment > 30 days before vaccination (n = 9728).⁷⁵ However, it is important to note that no cases of disseminated VZV from the vaccine strain were observed, and latent zoster virus reactivation was speculated to be the probable cause.

Taken together, studies on the use of the live attenuated HZ vaccine on patients with IMDs on immunosuppressive therapies suggest that it is generally safe and well tolerated. It is important to note that most patients receiving the HZ vaccine would have had previous VZV exposure and immunity, which decreases the risk of disseminated disease from the vaccine strain even in individuals on immunosuppressive treatment. However, caution may be warranted in patients without preexisting immunity to the virus. Serologic testing for VZV prior to immunization with the live attenuated vaccine should be considered.

Other Live Vaccines

Statement 4a: In treatment-naïve patients with immune-mediated diseases who are vaccinated with live attenuated vaccines, we recommend that the duration of viremia following immunization be considered when determining the optimal time to initiate immunosuppressive therapy.

GRADE: Strong recommendation; very low-level evidence

Table 6. Length of Viremia Following Vaccination With Live Attenuated Vaccines.

Vaccine	Length of Viremia
Varicella (Oka strain)	The vaccine strain could not be isolated up to 14 days postvaccination in children, ²²⁵ but 1 study detected the vaccine strain by PCR up to 5 weeks after immunization in 5 of 166 (3%) asymptomatic children given the varicella vaccine. ²²⁶
Herpes zoster (Oka strain)	Varicella zoster virus DNA can be detected by PCR analysis in 16% (11/67) of individuals 2 weeks postvaccination ²²⁷ and up to 4 weeks in 6% (2/36) of individuals >60 years old. ⁷¹
Yellow fever	Viremia after primary immunization wanes within 7 days postimmunization ²²⁸ and is generally cleared within 2 weeks of vaccination. ²²⁹
Measles	The vaccine strain has not been isolated from human blood after immunization of healthy children, ²³⁰ but a study on macaques has shown the persistence of the Schwarz vaccine strain 7 to 9 days postvaccination. ²³¹
Mumps	There is a low risk of viremia with the mumps vaccine strains; however, the incidence of aseptic meningitis occurring 2 to 3 weeks after vaccination suggests that the potential is maintained in some vaccine strains. The frequency of vaccine-associated aseptic meningitis varies from approximately 1 in 1.8 million doses for the Jeryl Lynn strain to as high as 1 in 336 for the Urabe AM9 strain. ²³²
Rubella	Viremia was documented 7 to 21 days postvaccination in some adults receiving the primary vaccination but not in children. ²³³
Live polio (type 2 Sabin)	In adults, free virus is present in the serum between 2 and 5 days after vaccine administration, with antibody-bound virus being present up to 8 days after vaccination. ²³⁴ In children aged ≤17 months, free virus can be detected up to 8 days after vaccination. ²³⁵

Abbreviation: PCR, polymerase chain reaction.

Vote: 21.4% strongly agree, 71.4% agree, 7.1% neutral

Statement 4b: In patients with immune-mediated diseases who interrupt immunosuppressive treatment prior to vaccination, we recommend that the duration of viremia following immunization be considered when determining the optimal time to reinstate immunosuppressive therapy.

GRADE: Strong recommendation; very low-level evidence

Vote: 21.4% strongly agree, 57.1% agree, 21.4% neutral

Evidence Summary

While there is currently no evidence regarding the optimal time to initiate immunosuppressive therapies after immunization with live attenuated vaccines, it is intuitive that risks would be mitigated if treatment is initiated after vaccine-induced viremia clears, whenever the clinical situation allows. Table 6 lists data regarding the length of viremia resulting from commercially available live vaccines.

Statement 4c: In patients with immune-mediated diseases on immunosuppressive agents, we suggest that live attenuated vaccines be administered when individual benefits outweigh the perceived risks.

GRADE: Conditional recommendation; low-level evidence

Vote: 14.3% strongly agree, 64.3% agree, 14.3% neutral, 7.1% disagree

Evidence Summary

The use of yellow fever (YF); measles, mumps, and rubella (MMR); and oral typhoid vaccines in patients on immunosuppressive therapy has not been extensively examined.

While further investigation is necessary, small observational studies provided insights into the safety and efficacy of live vaccines in this patient population.⁷⁶⁻⁸² Recall humoral and cellular responses to MMR in children with juvenile idiopathic arthritis (JIA) treated with etanercept + MTX (mean dose of 12 mg/m² body surface area [BSA] once weekly [QW]) (n = 5) or low-dose MTX alone (mean dose of 9 mg/m² BSA QW; n = 5) were not significantly different from healthy children (n = 22).⁸⁰ Moreover, the MMR vaccine was demonstrated to be safe for patients with JIA, with no reports of aggravated disease activity, increased medication use, or severe AEs following vaccination.^{76,80}

Primary or secondary YF vaccination also induced protective serologic responses in the majority of IFX-treated patients with RA (94% [16/17]),⁸¹ and adults with chronic inflammatory conditions receiving systemic corticosteroid therapy for a median of 10 months (100% [20/20 patients examined]; prednisone-equivalent dose: 5-20 mg/d).⁷⁸ In addition, patients with IMDs on MTX (n = 11), prednisolone (n = 1), leflunomide (n = 1), or etanercept (n = 2) achieved postvaccination neutralizing antibody titres comparable to healthy controls.⁸² In all studies, the YF vaccine was administered without adverse sequelae, although patients in 1 study experienced a higher frequency of transient local reactions (RR, 8.0; 95% CI, 1.4-45.9), including erythema, tenderness, and pain compared with healthy individuals.⁷⁸

A systematic review by Croce et al⁸³ noted that of the 253 YF vaccine doses administered to patients with IMDs or solid organ transplants, only 1 case of vaccine-related infection was reported. The fatal case of vaccine-associated viscerotropic disease occurred in a patient with SLE and RA treated with dexamethasone and possibly MTX.⁸³ While the patient was given a vaccine from a lot associated with >20 times the

risk of viscerotropic disease,⁸³ it is possible that the underlying autoimmunity and immunosuppressive treatment may have also contributed to the fatal outcome. Therefore, prudent assessment of the risks and benefits of vaccination in each individual patient is necessary to prevent potentially deleterious consequences. Whenever possible, physicians should assess the patient's risk of YF exposure and vaccinate accordingly prior to initiation of immunosuppressive regimens.

Statement 4d: In situations where patient safety is a paramount concern and the clinical situation allows, we suggest that immunosuppressive treatment be interrupted for a duration based on drug pharmacokinetics prior to immunization with live vaccines.

GRADE: Conditional recommendation; low-level evidence

Vote: 28.6% strongly agree, 64.3% agree, 7.1% neutral

Evidence Summary

There is evidence to suggest that live vaccines may be safely given to patients with IMDs treated with immunosuppressive agents. However, due to factors such as advanced age, disease severity, comorbidities, and potent immunosuppressive medications, some patients may be at greater risk of AEs or disseminated infection after receiving live attenuated vaccines. For instance, the risk of developing YF vaccine-associated viscerotropic disease increases with age, with elderly individuals having a 5000-fold increased incidence (0.05%) compared to children (0.00001%).⁸⁴ In situations where patient safety is of paramount concern and the decision is made to interrupt immunosuppressive therapy prior to immunization, the duration of the treatment break prior to vaccine administration should ideally take drug pharmacokinetics into consideration (Tables 4 and 5) to minimize the interference of immunosuppressive agents on vaccine response and their potential effect on risk of disseminated infection.

Vaccination of Infants With Early Exposure to Immunosuppressive Agents

Statement 5a: In infants exposed to immunosuppressive agents in utero during the third trimester, we recommend that inactivated vaccines be administered according to the local immunization schedule.

GRADE: Strong recommendation; very low-level evidence

Vote: 57.1% strongly agree, 42.9% agree

Evidence Summary

Biologics

Serological responses to routine childhood vaccinations in infants exposed to TNFi up to the third trimester (final dose

at 17-39 weeks' gestation) were described in 3 observational studies and 1 case report.⁸⁵⁻⁸⁸ Adequate and protective responses to tetanus, pneumococcal, and diphtheria vaccines were generally achieved, although some variability in *Haemophilus influenzae* type b (Hib) vaccine immunogenicity was observed.^{85,88} Furthermore, routine childhood vaccinations were well tolerated, resulting in no safety concerns or severe AEs.⁸⁵⁻⁹¹

More recently, data from the Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry comparing vaccine responses in infants born of mothers who were exposed to biologic therapies (IFX, adalimumab, vedolizumab, certolizumab pegol, golimumab, natalizumab, or ustekinumab) vs those unexposed during gestation revealed no significant differences in seroprotection rates to the Hib (21/38 [71%] vs 4/8 [50%]; $P = .41$) and tetanus toxoid vaccines (33/41 [80%] vs 6/8 [75%]; $P = .66$) between the 2 groups.⁹²

Three case reports examined the efficacy of routine childhood immunizations such as tetanus, diphtheria, and HBV among infants exposed to RTX up to the third trimester (last RTX dose at 30-34 weeks' gestation).⁹³⁻⁹⁵ Despite all infants exhibiting low⁹⁴ or undetectable^{93,95} B-cell counts at birth, protective antibody levels were generally achieved following vaccination without serious AEs.

DMARDs and Glucocorticoids

Two case-control studies examined HBV vaccine immunogenicity among infants born to mothers treated with dexamethasone, thiopurines, or cyclosporine for autoimmunity or CTD during pregnancy.^{96,97} Despite exposure to immunosuppressive drugs in utero, these infants achieved protective antibody titres and exhibited comparable IgG serum levels, lymphocyte counts, and other immune parameters to unexposed infants. Importantly, vaccination with inactivated vaccines was demonstrated to be safe. In a study involving 30 infants exposed to thiopurines due to maternal IBD during gestation, diphtheria, tetanus, pertussis, inactivated polio, Hib, and pneumococcal conjugate vaccines were safely administered without serious AEs or complications.⁹⁸

Exposure to higher doses of immunosuppressive agents in the solid organ transplant setting did not significantly affect the immune response to childhood vaccinations.⁹⁹ Of the 17 infants born to renal transplant recipient mothers treated with thiopurines, tacrolimus, prednisone, and/or cyclosporine during pregnancy, 82% exhibited B-cell numbers lower than the 10th percentile of normal Brazilian values (280/mm³) while 29.4% exhibited abnormalities in other lymphocyte populations at birth. Despite this, primary immunization with Hib, pneumococcal, and tetanus vaccines was safely administered and resulted in protective antibody titres that were comparable to those of infants unexposed to immunosuppressive agents in utero.

Statement 5b: In infants exposed to immunosuppressive agents in utero during the third trimester, we recommend that the MMR and varicella vaccines be administered according to the local immunization schedule.

GRADE: Strong recommendation; low-level evidence

Vote: 42.9% strongly agree, 57.1% agree

Evidence Summary

Live attenuated MMR and varicella vaccines are indicated for children 12 to 15 months of age.^{100,101} At this time, <1% of the initial biologic agent levels should be present in the infant based on the known half-life of 30 to 52.5 days of maternally derived IgG antibodies.¹⁰²⁻¹⁰⁴ In the case of in utero RTX exposure, continued presence of the biologic agent in the infant was shown to delay B-cell development in some cases. However, circulating CD20⁺ B-cell numbers were shown to normalize 3 to 6 months after birth, possibly suggesting integrity to adequately respond to vaccines given at later time points.^{93,94,105} In fact, studies demonstrated that infants exposed to either TNFi or RTX in utero achieved protective antibody levels without complications upon completion of the MMR vaccine regimen.^{85,90,93,95}

Similarly, nonbiologic immunomodulatory agents with relatively long half-lives such as leflunomide (14 days) and antimalarials (40-50 days) are expected to be cleared or present in minute concentrations that are unlikely to negatively affect the immunogenicity or safety of vaccines given \geq 12 months after birth.

Statement 5c: In infants breastfed by mothers on immunosuppressive regimens, we recommend that inactivated and live attenuated vaccines be administered according to the local immunization schedule without delay.

GRADE: Strong recommendation; very low-level evidence

Vote: 35.7% strongly agree, 57.1% agree, 7.1% neutral

Evidence Summary

Biologic Agents

Due to the inefficient transfer of IgG antibodies across the mammary epithelium, only low levels of IgG-based biologics are typically found in breastmilk.^{87,106-112} Any antibodies ingested by the infant are not taken up by the intact intestinal mucosa¹¹³ and are subject to degradation by proteolytic enzymes in the stomach and intestine.^{113,114} Consequently, breastfeeding while being treated with Ig-based biologics poses little to no risk of infant drug exposure, as evidenced by the continuous decline in serum levels of biologics acquired through gestational exposure in breastfed infants.^{87,110,115} For this reason, infants breastfed by mothers on biologic therapy should receive routine immunizations without delay according to local immunization guidelines.

Table 7. Exposure of Infants to Immunosuppressive Agents Through Breastmilk.

Drug	Estimated Infant Exposure
Chloroquine	0.55% ^{119,a}
Hydroxychloroquine	2% ^{118,b}
Tacrolimus	0.3% ^{123,b}
Cyclosporine	0.2%-1.1% ^{236,b}
Prednisolone	0.1% ^{120,a}
Azathioprine	6-MP metabolite: <0.09% ^{121,b}
Sulfasalazine	5.9% ^{119,a}
Methotrexate	NA ^{122,c}

Abbreviations: 6-MP, 6-mercaptopurine; NA, not available.

^aPercent of maternal dose ingested.

^bInfant drug exposure corrected for maternal and infant body weight (weight-adjusted dose).

^cExpected to result in minimal exposure of infant to methotrexate due to the low milk/plasma ratio (0.08) observed.

Of note, subtherapeutic IFX levels were observed in an infant exposed to the drug solely through breastfeeding.¹¹² Five days after maternal infusion with IFX, the biologic agent was detected in the infant (1700 ng/mL), despite being only partially breastfed. No AEs were observed in the child, and the level present in the infant's serum is below the therapeutic range and not expected to interfere with the safety or efficacy of childhood immunizations. However, the mechanism of infant absorption of the biologic in this case is unclear, and further investigation may be warranted.

Nonbiologic Agents

Hydrocortisones, antimalarials, azathioprine metabolites, sulfasalazine, MTX, cyclosporine, and tacrolimus have been detected in breastmilk at concentrations lower than maternal serum levels.¹¹⁶⁻¹²⁴ At these levels, the weight-adjusted exposure of the breastfed infant is estimated to be minimal (Table 7)¹²⁵ and would likely have little effect on vaccine immunogenicity and efficacy. However, live attenuated vaccines should be administered with caution to infants breastfed by mothers on cyclophosphamide as cases of neutropenia and hematopoiesis suppression were documented in infants exposed to this agent through breastmilk.^{126,127}

Discussion

Consensus Level

These guidelines present recommendations on general immunization practices for patients with IMDs treated with immunosuppressive therapies, as well as infants exposed to such agents during the third trimester of pregnancy or through breastfeeding. Consensus was reached on 13 statements, with 2 statements being rejected (Appendix 1).

Comparison With Other Guidelines

In contrast to the recommendations in this publication, several guidelines, including those from the National Advisory Committee on Immunization (NACI), Advisory Committee on Immunization Practices, American College of Gastroenterology, and European Crohn's and Colitis Organization, have suggested waiting at least 3 to 4 weeks after immunization with live vaccines prior to commencing immunosuppressive therapy.^{69,70,73,128} In addition, the 2014 NACI guidelines recommended that the live HZ vaccine not be given to individuals receiving high-dose corticosteroids or immune-suppressing medications, unless treatment has been discontinued for a period of 3 days to up to 1 year prior to vaccination, depending on the medication.¹²⁸

However, in individuals with prior exposure and immunity to VZV, the live attenuated HZ vaccine acts as a booster immunization, which elicits a secondary immune response with faster kinetics than primary vaccination. Studies on tofacitinib in patients with RA demonstrated that treatment initiation within 2 weeks of vaccination did not compromise the safety or efficacy of the vaccine.⁷² Furthermore, data from retrospective studies suggest that vaccination even while on immunomodulatory biologics (TNFi, abatacept, or RTX), DMARDs, and glucocorticoids is safe and effective,⁷⁴ potentially eliminating the need for long wait times between vaccination and treatment initiation. Presented with this evidence, the committee deemed the live attenuated HZ vaccine to be relatively safe for individuals with preexisting immunity to varicella, even in those on certain immunosuppressive treatments. In treatment-naïve patients, deferring the initiation of immunosuppressive therapy 2 to 4 weeks postvaccination should be sufficient to mount an effective adaptive response to the vaccine.

While this manuscript was being prepared for publication, the NACI released the 2018 recommendations on the use of HZ vaccines, which state that the HZ/su vaccine, not the live attenuated vaccine, may be considered for immunocompromised adults aged ≥ 50 years.¹²⁹ This echoes the CDC recommendation that the subunit vaccine be considered over the live attenuated vaccine for immunocompetent adults ≥ 50 years of age or those anticipating immunosuppression.⁶⁸ Aligned with the NACI and CDC guidelines, this publication preferentially recommends considering the subunit vaccine for patients with IMDs on immunosuppressive regimens until further data are available.

With regards to vaccinating patients on RTX, the Public Health Agency of Canada recommends that treatment be discontinued 6 to 12 months prior to vaccination with live or inactivated vaccines,¹³⁰ whereas a minimum washout period of 5 months preimmunization is recommended in this publication. While longer washout periods would be ideal and allow B-cell numbers to rebound following B-cell depletion therapy, extended treatment cessation is not always feasible if disease control is to be maintained. Thus, in patients requiring RTX infusion every 6 months, the

committee determined that immunizing patients 5 months following the last RTX dose and at least 4 weeks prior to the subsequent dose would allow for a degree of B-cell reconstitution and sufficient time to mount an adaptive immune response to the vaccine.

Limitations

While these guidelines were developed according to the best evidence available to date, the body of evidence regarding the safety and efficacy of vaccination among individuals receiving immunosuppressive therapy for IMDs remains incomplete. Large-scale clinical trials assessing the effectiveness of vaccines in this patient population have not been performed, and data regarding the safety and efficacy of immunization for patients on recently approved drugs and biologic agents are currently lacking. Furthermore, antibody thresholds may be an imperfect surrogate for vaccine-induced protection, and the lack of more accurate measures of vaccine efficacy may hinder our complete understanding of how immunosuppressive drugs and biological agents affect the immunological response to immunization.

Conclusions

The use of immunomodulatory biologics, DMARDs, and glucocorticoids may result in attenuation but not abolishment of the immune response to vaccines. The risks and benefits of immunization should be weighed to determine patient eligibility and appropriate timing of vaccine administration relative to immunosuppressive therapy.

While specialists endorse the importance of giving age- and disease-appropriate vaccines to patients with IMDs, primary care physicians (PCPs) are often tasked with carrying out immunizations in these patients. To ensure that necessary vaccines are given and patients receive consistent care across health care providers, communication between specialists and PCPs is imperative. Should the need arise, these guidelines may serve to inform not only specialists but also family physicians and other health care providers on issues regarding the safety and efficacy of vaccines in patients with IMDs on immunosuppressive therapies.

Acknowledgments

We thank Synapse Medical Communications, Oakville, Ontario, which provided medical writing assistance in the form of drafting and revising as per authors' directions and in accordance with the standards set out by the International Committee of Medical Journal Editors. Medical writing support was funded by the Dermatology Association of Ontario.

Declaration of Conflicting Interests


The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Kim Papp is an advisory board participant, steering

committee member, investigator, speaker, and/or consultant for AbbVie, Akros, Allergan, Amgen, Anacor, Astellas, AstraZeneca, Baxalta, Baxter, Boehringer Ingelheim, Bristol-Myers Squibb, CanFite, Celgene, Coherus, Dermira, Dow Pharma, Eli Lilly, Forward Pharma, Galderma, Genentech, GSK, Janssen, Kyowa Hakko Kirin, LEO Pharma, MedImmune, Meiji Seika Pharma, Merck (MSD), Merck Serono, Mitsubishi Pharma, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Takeda, UCB, and Valeant. Boulos Haraoui is an advisory board participant, speaker, consultant, and/or investigator for Amgen, AbbVie, Janssen, Lilly, Merck, Pfizer, Novartis, and UCB. Deepali Kumar is an advisory board participant, speaker, investigator, and/or consultant for Astellas, GSK, Janssen, Oxford Immunotec, Pfizer, Qiagen, and Sanofi. John K. Marshall is an advisory board participant, speaker, and/or consultant for AbbVie, Allergan, Celgene, Celltrion, Ferring, Hoffman-La Roche, Hospira, Janssen, Lilly, Merck, Pfizer, Procter & Gamble, Shire, and Takeda. Robert Bissonnette is an advisory board participant, investigator, speaker, and/or consultant for AbbVie, Amgen, Boehringer Ingelheim, BMS, Celgene, Eli Lilly, Galderma, GSK Stiefel, Immune, Incyte, Janssen, Kineta, Leo Pharma, Merck, Novartis, Pfizer, and Xenoport and is a shareholder of Innovaderm Research. Alain Bitton is an advisory board participant, speaker, and/or investigator for AbbVie, Janssen, Takeda, Shire, Ferring, Pfizer, Merck, and Pharmascience. Brian Bressler is an advisor and/or speaker for AbbVie, Actavis, Allergan, Amgen, Celgene, Ferring, Genentech, Janssen, Merck, Pendopharm, Pfizer, Shire, and Takeda and received research support from AbbVie, Alvine, Amgen, Atlantic Pharmaceuticals, Boehringer Ingelheim, BMS, Celgene, Genentech, GlaxoSmithKline, Janssen, Merck, Qu Biologic, Red Hill Pharma, and Takeda. Melinda Gooderham is an advisory board participant, investigator, consultant, and/or speaker for AbbVie, Actelion Pharmaceuticals, Akros Pharma, Amgen, Arcutis, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermira, Eli Lilly, Galderma, GSK, Janssen, LEO Pharma, MedImmune, Novartis, Pfizer, Regeneron Pharmaceuticals, Roche, Sanofi Genzyme, Sun Pharmaceutical Industries, UCB, and Valeant Pharmaceuticals. Vincent Ho is an advisory board participant, investigator, and/or speaker for Abbvie, Lilly, Novartis, Janssen, and Sanofi. Shahin Jamal is an advisory board participant for Abbvie, Amgen, BMS, Celgene, Eli Lilly, Janssen, Merck, Novartis, Pfizer, Roche, Sandoz, Sanofi Aventis, and UCB. Janet E. Pope is a consultant for Lilly, Merck, Novartis, Pfizer, Roche, Sanofi, Sandoz, and UCB and received research grants from Merck, Pfizer, Roche, UCB, and Seattle Genetics. A. Hillary Steinhart is an advisory board participant, speaker, investigator, and/or consultant for Abbvie, Amgen, Arena Pharmaceuticals, Celgene, Ferring, Genentech, Hoffmann-La Roche, Hospira, Janssen, Merck, Pfizer, Pharmascience, Red Hill Biopharma, and Takeda. Donald C. Vinh is an advisory board participant, speaker, consultant, and/or investigator for Cidara, CSL Behring Canada, Merck Canada, and Shire Canada. John Wade is an advisory board participant and consultant for Abbvie, Amgen, BMS, Celgene, Janssen, Lilly, Novartis, Roche, Sanofi, and UCB.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Development of the vaccination guidelines was funded by the Dermatology Association of Ontario.

ORCID iD

Robert Bissonnette  <https://orcid.org/0000-0001-5927-6587>

References

1. Yun H, Yang S, Chen L, et al. Risk of herpes zoster in auto-immune and inflammatory diseases: implications for vaccination. *Arthritis Rheumatol*. 2016;68:2328-2337.
2. Shigayeva A, Rudnick W, Green K, et al. Invasive pneumococcal disease among immunocompromised persons: implications for vaccination programs. *Clin Infect Dis*. 2016;62:139-147.
3. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. *Arthritis Rheum*. 2002;46:2287-2293.
4. McKinnon JE, Maksimowicz-McKinnon K. Autoimmune disease and vaccination: impact on infectious disease prevention and a look at future applications. *Transl Res*. 2016;167:46-60.
5. Assala M, Groh M, Blanche P, et al. Pneumococcal and influenza vaccination rates in patients treated with corticosteroids and/or immunosuppressive therapies for systemic autoimmune diseases: a cross-sectional study. *Joint Bone Spine*. 2017;84:365-366.
6. Lawson EF, Trupin L, Yelin EH, Yazdany J. Reasons for failure to receive pneumococcal and influenza vaccinations among immunosuppressed patients with systemic lupus erythematosus. *Semin Arthritis Rheum*. 2015;44:666-671.
7. Hua C, Morel J, Ardouin E, et al. Reasons for non-vaccination in French rheumatoid arthritis and spondyloarthritis patients. *Rheumatology (Oxford)*. 2015;54:748-750.
8. Taranger J, Trollfors B, Lagergård T, et al. Correlation between pertussis toxin IgG antibodies in postvaccination sera and subsequent protection against pertussis. *J Infect Dis*. 2000;181:1010-1013.
9. Amanna IJ, Messaoudi I, Slifka MK. Protective immunity following vaccination: how is it defined? *Hum Vaccin*. 2008;4:316-319.
10. Hobson D, Curry RL, Beare AS, Ward-Gardner A. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. *J Hyg (Lond)*. 1972;70:767-777.
11. Chen RT, Markowitz LE, Albrecht P, et al. Measles antibody: reevaluation of protective titers. *J Infect Dis*. 1990;162:1036-1042.
12. Andrews NJ, Waight PA, Burbidge P, et al. Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study. *Lancet Infect Dis*. 2014;14:839-846.
13. Käyhty H, Peltola H, Karanko V, Mäkelä PH. The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. *J Infect Dis*. 1983;147:1100.
14. Jack AD, Hall AJ, Maine N, Mendy M, Whittle HC. What level of hepatitis B antibody is protective? *J Infect Dis*. 1999;179:489-492.
15. Plotkin SA. Correlates of protection induced by vaccination. *Clin Vaccine Immunol*. 2010;17:1055-1065.
16. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924-926.

17. Marseglia GL, Scaramuzza A, d'Annunzio G, Comolli G, Gatti M, Lorini R. Successful immune response to a recombinant hepatitis B vaccine in young patients with insulin-dependent diabetes mellitus. *Diabet Med*. 1996;13:630-633.
18. Melmed GY, Agarwal N, Frenck RW, et al. Immunosuppression impairs response to pneumococcal polysaccharide vaccination in patients with inflammatory bowel disease. *Am J Gastroenterol*. 2010;105:148-154.
19. Zanoni G, Contreas G, Valletta E, Gabrielli O, Mengoli C, Veneri D. Normal or defective immune response to hepatitis B vaccine in patients with diabetes and celiac disease. *Hum Vaccin Immunother*. 2015;11:58-62.
20. Schappi MG, Meier S, Bel M, Siegrist CA, Posfay-Barbe KM. Protective antibody responses to influenza A/H1N1/09 vaccination in children with celiac disease. *J Pediatr Gastroenterol Nutr*. 2012;54:817-819.
21. Puges M, Biscay P, Barnetche T, et al. Immunogenicity and impact on disease activity of influenza and pneumococcal vaccines in systemic lupus erythematosus: a systematic literature review and meta-analysis. *Rheumatology (Oxford)*. 2016;55:1664-1672.
22. Caso F, Ramonda R, Del Puente A, et al. Influenza vaccine with adjuvant on disease activity in psoriatic arthritis patients under anti-TNF-alpha therapy. *Clin Exp Rheumatol*. 2016;34:507-512.
23. Kapetanovic MC, Roseman C, Jönsson G, Truedsson L, Saxne T, Geborek P. Antibody response is reduced following vaccination with 7-valent conjugate pneumococcal vaccine in adult methotrexate-treated patients with established arthritis, but not those treated with tumor necrosis factor inhibitors. *Arthritis Rheum*. 2011;63:3723-3732.
24. Launay O, Abitbol V, Krivine A, et al. Immunogenicity and safety of influenza vaccine in inflammatory bowel disease patients treated or not with immunomodulators and/or biologics: a two-year prospective study. *J Crohns Colitis*. 2015;9:1096-1107.
25. Lee CK, Kim HS, Ye BD, et al. Patients with Crohn's disease on anti-tumor necrosis factor therapy are at significant risk of inadequate response to the 23-valent pneumococcal polysaccharide vaccine. *J Crohns Colitis*. 2014;8:384-391.
26. Andrisani G, Frasca D, Romero M, et al. Immune response to influenza A/H1N1 vaccine in inflammatory bowel disease patients treated with anti TNF-alpha agents: effects of combined therapy with immunosuppressants. *J Crohns Colitis*. 2013;7:301-307.
27. Fiorino G, Peyrin-Biroulet L, Naccarato P, et al. Effects of immunosuppression on immune response to pneumococcal vaccine in inflammatory bowel disease: a prospective study. *Inflamm Bowel Dis*. 2012;18:1042-1047.
28. Park SH, Yang SK, Park SK, et al. Efficacy of hepatitis A vaccination and factors impacting on seroconversion in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2014;20:69-74.
29. Frasca D, Andrisani G, Diaz A, Felice C, Guidi L, Blomberg BB. AID in aging and autoimmune diseases. *Autoimmunity*. 2013;46:168-175.
30. Kantso B, Halkjaer SI, Thomsen OO, et al. Immunosuppressive drugs impairs antibody response of the polysaccharide and conjugated pneumococcal vaccines in patients with Crohn's disease. *Vaccine*. 2015;33:5464-5469.
31. Nguyen DL, Nguyen ET, Bechtold ML. Effect of immunosuppressive therapies for the treatment of inflammatory bowel disease on response to routine vaccinations: a meta-analysis. *Dig Dis Sci*. 2015;60:2446-2453.
32. Oren S, Mandelboim M, Braun-Moscovici Y, et al. Vaccination against influenza in patients with rheumatoid arthritis: the effect of rituximab on the humoral response. *Ann Rheum Dis*. 2008;67:937-941.
33. van Assen S, Holvast A, Benne CA, et al. Humoral responses after influenza vaccination are severely reduced in patients with rheumatoid arthritis treated with rituximab. *Arthritis Rheum*. 2010;62:75-81.
34. Arad U, Tzadok S, Amir S, et al. The cellular immune response to influenza vaccination is preserved in rheumatoid arthritis patients treated with rituximab. *Vaccine*. 2011;29:1643-1648.
35. Westra J, van Assen S, Wilting KR, et al. Rituximab impairs immunoglobulin (Ig)M and IgG (subclass) responses after influenza vaccination in rheumatoid arthritis patients. *Clin Exp Immunol*. 2014;178:40-47.
36. Eisenberg RA, Jawad AF, Boyer J, et al. Rituximab-treated patients have a poor response to influenza vaccination. *J Clin Immunol*. 2013;33:388-396.
37. Hua C, Barnetche T, Combe B, Morel J. Effect of methotrexate, anti-tumor necrosis factor alpha, and rituximab on the immune response to influenza and pneumococcal vaccines in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)*. 2014;66:1016-1026.
38. Borba EF, Saad CG, Pasoto SG, et al. Influenza A/H1N1 vaccination of patients with SLE: can antimalarial drugs restore diminished response under immunosuppressive therapy? *Rheumatology (Oxford)*. 2012;51:1061-1069.
39. Crowe SR, Merrill JT, Vista ES, et al. Influenza vaccination responses in human systemic lupus erythematosus: Impact of clinical and demographic features. *Arthritis Rheum*. 2011;63:2396-2406.
40. Huang Y, Wang H, Wan L, Lu X, Tam WW. Is systemic lupus erythematosus associated with a declined immunogenicity and poor safety of influenza vaccination? A systematic review and meta-analysis. *Medicine (Baltimore)*. 2016;95:e3637.
41. Park JK, Lee YJ, Shin K, et al. Impact of temporary methotrexate discontinuation for 2 weeks on immunogenicity of seasonal influenza vaccination in patients with rheumatoid arthritis: a randomised clinical trial. *Ann Rheum Dis*. 2018;77:898-904.
42. Park JK, Lee MA, Lee EY, et al. Effect of methotrexate discontinuation on efficacy of seasonal influenza vaccination in patients with rheumatoid arthritis: a randomised clinical trial. *Ann Rheum Dis*. 2017;76:1559-1565.
43. Mori S, Ueki Y, Hirakata N, Oribe M, Hidaka T, Oishi K. Impact of tocilizumab therapy on antibody response to influenza vaccine in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2012;71:2006-2010.
44. Adler S, Krivine A, Weix J, et al. Protective effect of A/H1N1 vaccination in immune-mediated disease—a prospectively controlled vaccination study. *Rheumatology (Oxford)*. 2012;51:695-700.
45. Kivitz AJ, Schechtman J, Texter M, Fichtner A, de Longueville M, Chartash EK. Vaccine responses in patients with rheumatoid arthritis treated with certolizumab pegol: results from a single-blind randomized phase IV trial. *J Rheumatol*. 2014;41:648-657.

46. Ribeiro AC, Guedes LK, Moraes JC, et al. Reduced seroprotection after pandemic H1N1 influenza adjuvant-free vaccination in patients with rheumatoid arthritis: implications for clinical practice. *Ann Rheum Dis*. 2011;70:2144-2147.
47. Kapetanovic MC, Saxne T, Sjöholm A, Truedsson L, Jönsson G, Geborek P. Influence of methotrexate, TNF blockers and prednisolone on antibody responses to pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis. *Rheumatology (Oxford)*. 2006;45:106-111.
48. Kapetanovic MC, Roseman C, Jönsson G, Truedsson L. Heptavalent pneumococcal conjugate vaccine elicits similar antibody response as standard 23-valent polysaccharide vaccine in adult patients with RA treated with immunomodulating drugs. *Clin Rheumatol*. 2011;30:1555-1561.
49. Migita K, Akeda Y, Akazawa M, et al. Pneumococcal polysaccharide vaccination in rheumatoid arthritis patients receiving tacrolimus. *Arthritis Res Ther*. 2015;17:149-157.
50. Winthrop KL, Silverfield J, Racewicz A, et al. The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis. *Ann Rheum Dis*. 2016;75:687-695.
51. Mori S, Ueki Y, Akeda Y, et al. Pneumococcal polysaccharide vaccination in rheumatoid arthritis patients receiving tocilizumab therapy. *Ann Rheum Dis*. 2013;72:1362-1366.
52. Kapetanovic MC, Nagel J, Nordstrom I, Saxne T, Geborek P, Rudin A. Methotrexate reduces vaccine-specific immunoglobulin levels but not numbers of circulating antibody-producing B cells in rheumatoid arthritis after vaccination with a conjugate pneumococcal vaccine. *Vaccine*. 2017;35:903-908.
53. Siegrist CA. Vaccine immunology. In: Plotkin SA, Orenstein WA, Offit PA, eds. *Vaccines*. 5th ed. Philadelphia, PA: Elsevier; 2008:17-36.
54. Halperin BA, Morris A, Mackinnon-Cameron D, et al. Kinetics of the antibody response to tetanus-diphtheria-acellular pertussis vaccine in women of childbearing age and postpartum women. *Clin Infect Dis*. 2011;53:885-892.
55. Murphy KP. *Janeway's Immunobiology*. 8th ed. New York, NY: Garland Science, Taylor & Francis Group, LLC; 2012.
56. Vauloup-Fellous C, Grangeot-Keros L. Humoral immune response after primary rubella virus infection and after vaccination. *Clin Vaccine Immunol*. 2007;14:644-647.
57. Flehmig B, Staedele H, Xueref C, Vidor E, Zuckerman J, Zuckerman A. Early appearance of neutralizing antibodies after vaccination with an inactivated hepatitis A vaccine. *J Infect*. 1997;35:37-40.
58. França IL, Ribeiro AC, Aikawa NE, et al. TNF blockers show distinct patterns of immune response to the pandemic influenza A H1N1 vaccine in inflammatory arthritis patients. *Rheumatology (Oxford)*. 2012;51:2091-2098.
59. Hoffmann-La Roche Limited. RITUXAN [product monograph]. October 31, 2014.
60. Leandro MJ, Cambridge G, Ehrenstein MR, Edwards JC. Reconstitution of peripheral blood B cells after depletion with rituximab in patients with rheumatoid arthritis. *Arthritis Rheum*. 2006;54:613-620.
61. 6-month interval dosing: Rituxan dosing schedule. <http://www.rituxanforra-hcp.com/dosing/6-month-interval>. Accessed November 29, 2017.
62. Merck Canada, Inc. ZOSTAVAX II [product monograph]. July 5, 2017.
63. Merck Canada, Inc. VARIVAX III [product monograph]. January 25, 2016.
64. Cunningham AL, Lal H, Kovac M, et al. Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. *N Engl J Med*. 2016;375:1019-1032.
65. Lal H, Cunningham AL, Godeaux O, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. *N Engl J Med*. 2015;372:2087-2096.
66. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. 2005;352:2271-2284.
67. GlaxoSmithKline Biologicals. SHINGRIX vaccines and related biological products advisory committee briefing document. <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVacBloodVaccinesandOtherB/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM575192.pdf>. Accessed November 29, 2017.
68. Centers for Disease Control and Prevention. Shingles (herpes zoster): vaccination. <https://www.cdc.gov/shingles/vaccination.html>. Accessed June 26, 2018.
69. Farraye FA, Melmed GY, Lichtenstein GR, Kane SV. ACG clinical guideline: preventive care in inflammatory bowel disease. *Am J Gastroenterol*. 2017;112:241-258.
70. Rahier JF, Magro F, Abreu C, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis*. 2014;8:443-468.
71. Pierson DL, Mehta SK, Gilden D, et al. Varicella zoster virus DNA at inoculation sites and in saliva after Zostavax immunization. *J Infect Dis*. 2011;203:1542-1545.
72. Winthrop KL, Wouters AG, Choy EH, et al. The safety and immunogenicity of live zoster vaccination in patients with rheumatoid arthritis before starting tofacitinib: a randomized phase II trial. *Arthritis Rheumatol*. 2017;69:1969-1977.
73. Kroger AT, Duchin J, Vazquez M. General best practice guidelines for immunization: best practices guidance of the Advisory Committee on Immunization Practices. <https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html>. Accessed April 20, 2017.
74. Zhang J, Xie F, Delzell E, et al. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. *JAMA*. 2012;308:43-49.
75. Cheetham TC, Marcy SM, Tseng HF, et al. Risk of herpes zoster and disseminated varicella zoster in patients taking immunosuppressant drugs at the time of zoster vaccination. *Mayo Clin Proc*. 2015;90:865-873.
76. Heijstek MW, Pileggi GC, Zonneveld-Huijssoon E, et al. Safety of measles, mumps and rubella vaccination in juvenile idiopathic arthritis. *Ann Rheum Dis*. 2007;66:1384-1387.
77. Oliveira AC, Mota LM, Santos-Neto LL, Simoes M, Martins-Filho OA, Tauil PL. Seroconversion in patients with rheumatic diseases treated with immunomodulators or immunosuppressants, who were inadvertently revaccinated against yellow fever. *Arthritis Rheumatol*. 2015;67:582-583.
78. Kernéis S, Launay O, Ancelle T, et al. Safety and immunogenicity of yellow fever 17D vaccine in adults receiving systemic corticosteroid therapy: an observational cohort study. *Arthritis Care Res (Hoboken)*. 2013;65:1522-1528.

79. Azevedo LS, Lasmar EP, Contieri FL, et al. Yellow fever vaccination in organ transplanted patients: is it safe? A multicenter study. *Transpl Infect Dis*. 2012;14:237-241.
80. Borte S, Liebert UG, Borte M, Sack U. Efficacy of measles, mumps and rubella revaccination in children with juvenile idiopathic arthritis treated with methotrexate and etanercept. *Rheumatology (Oxford)*. 2009;48:144-148.
81. Scheinberg M, Guedes-Barbosa LS, Manguiera C, et al. Yellow fever revaccination during infliximab therapy. *Arthritis Care Res (Hoboken)*. 2010;62:896-898.
82. Wieten RW, Jonker EF, Pieren DK, et al. Comparison of the PRNT and an immune fluorescence assay in yellow fever vaccinees receiving immunosuppressive medication. *Vaccine*. 2016;34:1247-1251.
83. Croce E, Hatz C, Jonker EF, Visser LG, Jaeger VK, Buhler S. Safety of live vaccinations on immunosuppressive therapy in patients with immune-mediated inflammatory diseases, solid organ transplantation or after bone-marrow transplantation: a systematic review of randomized trials, observational studies and case reports. *Vaccine*. 2017;35:1216-1226.
84. World Health Organization. Vaccine safety basics, module 2: types of vaccine and adverse reactions. <http://vaccine-safety-training.org/overview-and-outcomes-2.html>. Accessed May 19, 2017.
85. Bortlik M, Duricova D, Machkova N, et al. Impact of anti-tumor necrosis factor alpha antibodies administered to pregnant women with inflammatory bowel disease on long-term outcome of exposed children. *Inflamm Bowel Dis*. 2014;20:495-501.
86. Zelinkova Z, de Haar C, de Ridder L, et al. High intra-uterine exposure to infliximab following maternal anti-TNF treatment during pregnancy. *Aliment Pharmacol Ther*. 2011;33:1053-1058.
87. Vasiliasukas EA, Church JA, Silverman N, Barry M, Targan SR, Dubinsky MC. Case report: evidence for transplacental transfer of maternally administered infliximab to the newborn. *Clin Gastroenterol Hepatol*. 2006;4:1255-1258.
88. Sheibani S, Cohen R, Kane S, Dubinsky M, Church JA, Mahadevan U. The effect of maternal peripartum anti-TNF alpha use on infant immune response. *Dig Dis Sci*. 2016;61:1622-1627.
89. Steenholdt C, Al-Khalaf M, Ainsworth MA, Brynskov J. Therapeutic infliximab drug level in a child born to a woman with ulcerative colitis treated until gestation week 31. *J Crohns Colitis*. 2012;6:358-361.
90. Johnsson A, Avlund S, Grosen A, Julsgaard M. Chicken pox infection in a three months old infant exposed in utero to adalimumab. *J Crohns Colitis*. 2013;7:e116-e117.
91. de Lima A, Zelinkova Z, van der Ent C, Steegers EA, van der Woude CJ. Tailored anti-TNF therapy during pregnancy in patients with IBD: maternal and fetal safety. *Gut*. 2016;65:1261-1268.
92. Beaulieu DB, Ananthakrishnan AN, Martin C, Cohen RD, Kane SV, Mahadevan U. Use of biologic therapy by pregnant women with inflammatory bowel disease does not affect infant response to vaccines. *Clin Gastroenterol Hepatol*. 2018;16:99-105.
93. Mandal PK, Dolai TK, Bagchi B, Ghosh MK, Bose S, Bhattacharyya M. B cell suppression in newborn following treatment of pregnant diffuse large B-cell lymphoma patient with rituximab containing regimen. *Indian J Pediatr*. 2014;81:1092-1094.
94. Klink DT, van Elburg RM, Schreurs MW, van Well GT. Rituximab administration in third trimester of pregnancy suppresses neonatal B-cell development. *Clin Dev Immunol*. 2008;2008:271363.
95. Friedrichs B, Tiemann M, Salwender H, Verpoort K, Wenger MK, Schmitz N. The effects of rituximab treatment during pregnancy on a neonate. *Haematologica*. 2006;91:1426-1427.
96. Cimaz R, Meregalli E, Biggioggero M, et al. Alterations in the immune system of children from mothers treated with immunosuppressive agents during pregnancy. *Toxicol Lett*. 2004;149:155-162.
97. Biggioggero M, Borghi MO, Gerosa M, Trespidi L, Cimaz R, Meroni PI. Immune function in children born to mothers with autoimmune diseases and exposed in utero to immunosuppressants. *Lupus*. 2007;16:651-656.
98. de Meij TG, Jharap B, Kneepkens CM, van Bodegraven AA, de Boer NK. Long-term follow-up of children exposed intra-uterine to maternal thiopurine therapy during pregnancy in females with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2013;38:38-43.
99. Dinelli MI, Ono E, Viana PO, et al. Response to immunization in children born to renal transplant recipients using immunosuppressive drugs during gestation. *Vaccine*. 2016;34:404-407.
100. Public Health Agency of Canada. Canada's provincial and territorial routine (and catch-up) vaccination programs for infants and children. <http://healthycanadians.gc.ca/healthy-living-vie-saine/immunization-immunisation/schedule-calendrier/alt/infants-children-vaccination-enfants-nourrissons-eng.pdf>. Accessed October 5, 2016.
101. Centers for Disease Control and Prevention. 2017 Recommended immunizations for children from birth through 6 years old. <https://www.cdc.gov/vaccines/parents/downloads/parent-ver-sch-0-6yrs.pdf> 2017. Accessed June 6, 2017.
102. Shahid NS, Steinhoff MC, Hoque SS, Begum T, Thompson C, Siber GR. Serum, breast milk, and infant antibody after maternal immunisation with pneumococcal vaccine. *Lancet*. 1995;346:1252-1257.
103. Sarvas H, Seppälä I, Kurikka S, Sieberg R, Mäkelä O. Half-life of the maternal IgG1 allotype in infants. *J Clin Immunol*. 1993;13:145-151.
104. Wiener AS. The half-life of passively acquired antibody globulin molecules in infants. *J Exp Med*. 1951;94:213-221.
105. Decker M, Rothermundt C, Hollander G, Tichelli A, Rochlitz C. Rituximab plus CHOP for treatment of diffuse large B-cell lymphoma during second trimester of pregnancy. *Lancet Oncol*. 2006;7:693-694.
106. Grosen A, Julsgaard M, Kelsen J, Christensen LA. Infliximab concentrations in the milk of nursing mothers with inflammatory bowel disease. *J Crohns Colitis*. 2014;8:175-176.
107. Ben-Horin S, Yavzori M, Kopylov U, et al. Detection of infliximab in breast milk of nursing mothers with inflammatory bowel disease. *J Crohns Colitis*. 2011;5:555-558.
108. Ben-Horin S, Yavzori M, Katz L, et al. Adalimumab level in breast milk of a nursing mother. *Clin Gastroenterol Hepatol*. 2010;8:475-476.
109. Mahadevan U, Wolf DC, Dubinsky M, et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with

- inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2013;11:286-292.
110. Murashima A, Watanabe N, Ozawa N, Saito H, Yamaguchi K. Etanercept during pregnancy and lactation in a patient with rheumatoid arthritis: drug levels in maternal serum, cord blood, breast milk and the infant's serum. *Ann Rheum Dis*. 2009;68:1793-1794.
 111. Berthelsen BG, Fjeldsøe-Nielsen H, Nielsen CT, Hellmuth E. Etanercept concentrations in maternal serum, umbilical cord serum, breast milk and child serum during breastfeeding. *Rheumatology (Oxford)*. 2010;49:2225-2227.
 112. Fritzsche J, Pilch A, Mury D, Schaefer C, Weber-Schoendorfer C. Infliximab and adalimumab use during breastfeeding. *J Clin Gastroenterol*. 2012;46:718-719.
 113. Hurley WL, Theil PK. Perspectives on immunoglobulins in colostrum and milk. *Nutrients*. 2011;3:442-474.
 114. Ling J, Koren G. Challenges in vaccinating infants born to mothers taking immunoglobulin biologicals during pregnancy. *Expert Rev Vaccines*. 2016;15:239-256.
 115. Julsgaard M, Christensen LA, Gibson PR, et al. Concentrations of adalimumab and infliximab in mothers and newborns, and effects on infection. *Gastroenterology*. 2016;151:110-119.
 116. Khan AK, Truelove SC. Placental and mammary transfer of sulphasalazine. *BMJ*. 1979;2:1553.
 117. Akintonwa A, Gbajumo SA, Mabadeje AF. Placental and milk transfer of chloroquine in humans. *Ther Drug Monit*. 1988;10:147-149.
 118. Nation RL, Hackett LP, Dusci LJ, Ilett KF. Excretion of hydroxychloroquine in human milk. *Br J Clin Pharmacol*. 1984;17:368-369.
 119. Østensen M, Khamashta M, Lockshin M, et al. Anti-inflammatory and immunosuppressive drugs and reproduction. *Arthritis Res Ther*. 2006;8:209-227.
 120. Ost L, Wettrell G, Björkhem I, Rane A. Prednisolone excretion in human milk. *J Pediatr*. 1985;106:1008-1011.
 121. Moretti ME, Verjee Z, Ito S, Koren G. Breast-feeding during maternal use of azathioprine. *Ann Pharmacother*. 2006;40:2269-2272.
 122. Johns DG, Rutherford LD, Leighton PC, Vogel CL. Secretion of methotrexate into human milk. *Am J Obstet Gynecol*. 1972;112:978-980.
 123. Zheng S, Easterling TR, Hays K, et al. Tacrolimus placental transfer at delivery and neonatal exposure through breast milk. *Br J Clin Pharmacol*. 2013;76:988-996.
 124. Østensen M, Brown ND, Chiang PK, Aarbakke J. Hydroxychloroquine in human breast milk. *Eur J Clin Pharmacol*. 1985;28:357.
 125. Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis*. 2016;75:795-810.
 126. Durodola JI. Administration of cyclophosphamide during late pregnancy and early lactation: a case report. *J Natl Med Assoc*. 1979;71:165-166.
 127. Amato D, Niblett JS. Neutropenia from cyclophosphamide in breast milk. *Med J Aust*. 1977;1:383-384.
 128. National Advisory Committee on Immunization (NACI). Update on the use of herpes zoster vaccine. http://publications.gc.ca/collections/collection_2014/aspc-phac/HP40-92-2014-eng.pdf. Accessed June 26, 2018.
 129. National Advisory Committee on Immunization (NACI). *Updated Recommendations on the Use of Herpes Zoster Vaccines*. Public Health Agency of Canada; Ottawa, 2018.
 130. Public Health Agency of Canada. Canadian immunization guide: part 3—vaccination of specific populations. <https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-3-vaccination-specific-populations/page-8-immunization-immunocompromised-persons.html#a25>. Accessed June 26, 2018.
 131. Wyant T, Leach T, Sankoh S, et al. Vedolizumab affects antibody responses to immunisation selectively in the gastrointestinal tract: randomised controlled trial results. *Gut*. 2015;64:77-83.
 132. Askling HH, Rombo L, van Vollenhoven R, et al. Hepatitis A vaccine for immunosuppressed patients with rheumatoid arthritis: a prospective, open-label, multi-centre study. *Travel Med Infect Dis*. 2014;12:134-142.
 133. Andrade P, Santos-Antunes J, Rodrigues S, Lopes S, Macedo G. Treatment with infliximab or azathioprine negatively impact the efficacy of hepatitis B vaccine in inflammatory bowel disease patients. *J Gastroenterol Hepatol*. 2015;30:1591-1595.
 134. Salinas GF, De RL, Barendregt B, et al. Anti-TNF treatment blocks the induction of T cell-dependent humoral responses. *Ann Rheum Dis*. 2013;72:1037-1043.
 135. Belle A, Baumann C, Bigard MA, et al. Impact of immunosuppressive therapy on hepatitis B vaccination in inflammatory bowel diseases. *Eur J Gastroenterol Hepatol*. 2015;27:877-881.
 136. Ribeiro AC, Laurindo IM, Guedes LK, et al. Abatacept and reduced immune response to pandemic 2009 influenza A/H1N1 vaccination in patients with rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2013;65:476-480.
 137. Alten R, Bingham CO III, Cohen SB, et al. Antibody response to pneumococcal and influenza vaccination in patients with rheumatoid arthritis receiving abatacept. *BMC Musculoskelet Disord*. 2016;17:231-240.
 138. Kaine JL, Kivitz AJ, Birbara C, Luo AY. Immune responses following administration of influenza and pneumococcal vaccines to patients with rheumatoid arthritis receiving adalimumab. *J Rheumatol*. 2007;34:272-279.
 139. Chatham WW, Wallace DJ, Stohl W, et al. Effect of belimumab on vaccine antigen antibodies to influenza, pneumococcal, and tetanus vaccines in patients with systemic lupus erythematosus in the BLISS-76 trial. *J Rheumatol*. 2012;39:1632-1640.
 140. Fomin I, Caspi D, Levy V, et al. Vaccination against influenza in rheumatoid arthritis: the effect of disease modifying drugs, including TNF alpha blockers. *Ann Rheum Dis*. 2006;65:191-194.
 141. deBruyn J, Fonseca K, Ghosh S, et al. Immunogenicity of influenza vaccine for patients with inflammatory bowel disease on maintenance infliximab therapy: a randomized trial. *Inflamm Bowel Dis*. 2016;22:638-647.
 142. Hagihara Y, Ohfuji S, Watanabe K, et al. Infliximab and/or immunomodulators inhibit immune responses to trivalent influenza vaccination in adults with inflammatory bowel disease. *J Crohns Colitis*. 2014;8:223-233.
 143. Chioato A, Noseda E, Stevens M, Gaitatzis N, Kleinschmidt A, Picaud H. Treatment with the interleukin-17A-blocking antibody secukinumab does not interfere with the efficacy of influenza and meningococcal vaccinations in healthy subjects: results of an open-label, parallel-group,

- randomized single-center study. *Clin Vaccine Immunol.* 2012;19:1597-1602.
144. Tsuru T, Terao K, Murakami M, et al. Immune response to influenza vaccine and pneumococcal polysaccharide vaccine under IL-6 signal inhibition therapy with tocilizumab. *Mod Rheumatol.* 2014;24:511-516.
 145. Kapetanovic MC, Saxne T, Nilsson JÅ, Geborek P. Influenza vaccination as model for testing immune modulation induced by anti-TNF and methotrexate therapy in rheumatoid arthritis patients. *Rheumatology (Oxford).* 2007;46:608-611.
 146. Kubota T, Nii T, Nanki T, et al. Anti-tumor necrosis factor therapy does not diminish the immune response to influenza vaccine in Japanese patients with rheumatoid arthritis. *Mod Rheumatol.* 2007;17:531-533.
 147. Polachek A, Korobko U, Mader-Balakirski N, et al. Immunogenicity and safety of vaccination against seasonal 2012 influenza virus among patients with psoriatic arthritis and psoriasis. *Clin Exp Rheumatol.* 2015;33:181-186.
 148. Kapetanovic MC, Saxne T, Jönsson G, Truedsson L, Geborek P. Rituximab and abatacept but not tocilizumab impair antibody response to pneumococcal conjugate vaccine in patients with rheumatoid arthritis. *Arthritis Res Ther.* 2013;15:R171.
 149. Migita K, Akeda Y, Akazawa M, et al. Effect of abatacept on the immunogenicity of 23-valent pneumococcal polysaccharide vaccination (PPSV23) in rheumatoid arthritis patients. *Arthritis Res Ther.* 2015;17:357-366.
 150. Rákóczi É, Perge B, Végh E, et al. Evaluation of the immunogenicity of the 13-valent conjugated pneumococcal vaccine in rheumatoid arthritis patients treated with etanercept. *Joint Bone Spine.* 2016;83:675-679.
 151. Visvanathan S, Keenan GF, Baker DG, Levinson AI, Wagner CL. Response to pneumococcal vaccine in patients with early rheumatoid arthritis receiving infliximab plus methotrexate or methotrexate alone. *J Rheumatol.* 2007;34:952-957.
 152. Migita K, Akeda Y, Akazawa M, et al. Opsonic and antibody responses to pneumococcal polysaccharide in rheumatoid arthritis patients receiving golimumab plus methotrexate. *Medicine (Baltimore).* 2015;94:e2184.
 153. Bingham CO III, Looney RJ, Deodhar A, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial. *Arthritis Rheum.* 2010;62:64-74.
 154. Bingham CO III, Rizzo W, Kivitz A, Hassanali A, Upmanyu R, Kleerman M. Humoral immune response to vaccines in patients with rheumatoid arthritis treated with tocilizumab: results of a randomised controlled trial (VISARA). *Ann Rheum Dis.* 2015;74:818-822.
 155. Brodmerkel C, Wadman E, Langley RG, et al. Immune response to pneumococcus and tetanus toxoid in patients with moderate-to-severe psoriasis following long-term ustekinumab use. *J Drugs Dermatol.* 2013;12:1122-1129.
 156. Weinberg A, Boulware D, Dighero B, Orban T. Effect of abatacept on immunogenicity of vaccines in individuals with type 1 diabetes. *Vaccine.* 2013;31:4791-4794.
 157. Dezfoli S, Horton HA, Thepyasuwan N, et al. Combined immunosuppression impairs immunogenicity to tetanus and pertussis vaccination among patients with inflammatory bowel disease. *Inflamm Bowel Dis.* 2015;21:1754-1760.
 158. Wichmann A, Krugliak CN, Rubin DT. Safety and efficacy of live measles vaccine administered to a Crohn's disease patient receiving vedolizumab. *Am J Gastroenterol.* 2016;111:577.
 159. Sempere L, Almenta I, Barrenegoa J, et al. Factors predicting response to hepatitis B vaccination in patients with inflammatory bowel disease. *Vaccine.* 2013;31:3065-3071.
 160. Dotan I, Werner L, Vigodman S, et al. Normal response to vaccines in inflammatory bowel disease patients treated with thiopurines. *Inflamm Bowel Dis.* 2012;18:261-268.
 161. Mok CC, Ho LY, Fong LS, To CH. Immunogenicity and safety of a quadrivalent human papillomavirus vaccine in patients with systemic lupus erythematosus: a case-control study. *Ann Rheum Dis.* 2013;72:659-664.
 162. Gabay C, Bel M, Combescure C, et al. Impact of synthetic and biologic disease-modifying antirheumatic drugs on antibody responses to the AS03-adjuvanted pandemic influenza vaccine: a prospective, open-label, parallel-cohort, single-center study. *Arthritis Rheum.* 2011;63:1486-1496.
 163. Dengler TJ, Strnad N, Bühring I, et al. Differential immune response to influenza and pneumococcal vaccination in immunosuppressed patients after heart transplantation. *Transplantation.* 1998;66:1340-1347.
 164. Versluis DJ, Beyer WE, Masurel N, Wenting GJ, Weimar W. Impairment of the immune response to influenza vaccination in renal transplant recipients by cyclosporine, but not azathioprine. *Transplantation.* 1986;42:376-379.
 165. Willcocks LC, Chaudhry AN, Smith JC, et al. The effect of sirolimus therapy on vaccine responses in transplant recipients. *Am J Transplant.* 2007;7:2006-2011.
 166. Salles MJ, Sens YA, Boas LS, Machado CM. Influenza virus vaccination in kidney transplant recipients: serum antibody response to different immunosuppressive drugs. *Clin Transplant.* 2010;24:E17-E23.
 167. Siegrist CA, Ambrosioni J, Bel M, et al. Responses of solid organ transplant recipients to the AS03-adjuvanted pandemic influenza vaccine. *Antivir Ther.* 2012;17:893-903.
 168. Elkayam O, Amir S, Mendelson E, et al. Efficacy and safety of vaccination against pandemic 2009 influenza A (H1N1) virus among patients with rheumatic diseases. *Arthritis Care Res (Hoboken).* 2011;63:1062-1067.
 169. Pasoto SG, Ribeiro AC, Viana VS, et al. Short and long-term effects of pandemic unadjuvanted influenza A(H1N1) pdm09 vaccine on clinical manifestations and autoantibody profile in primary Sjogren's syndrome. *Vaccine.* 2013;31:1793-1798.
 170. Baluch A, Humar A, Eurich D, et al. Randomized controlled trial of high-dose intradermal versus standard-dose intramuscular influenza vaccine in organ transplant recipients. *Am J Transplant.* 2013;13:1026-1033.
 171. Azevedo LS, Gerhard J, Miraglia JL, et al. Seroconversion of 2009 pandemic influenza A (H1N1) vaccination in kidney transplant patients and the influence of different risk factors. *Transpl Infect Dis.* 2013;15:612-618.
 172. Scharpé J, Evenepoel P, Maes B, et al. Influenza vaccination is efficacious and safe in renal transplant recipients. *Am J Transplant.* 2008;8:332-337.
 173. Smith KG, Isbel NM, Catton MG, Leydon JA, Becker GJ, Walker RG. Suppression of the humoral immune response by mycophenolate mofetil. *Nephrol Dial Transplant.* 1998;13:160-164.
 174. Keshtkar-Jahromi M, Argani H, Rahnavardi M, et al. Antibody response to influenza immunization in kidney transplant recipients receiving either azathioprine or mycophenolate: a controlled trial. *Am J Nephrol.* 2008;28:654-660.

175. Holvast A, Huckriede A, Wilschut J, et al. Safety and efficacy of influenza vaccination in systemic lupus erythematosus patients with quiescent disease. *Ann Rheum Dis.* 2006;65:913-918.
176. Holvast A, Stegeman CA, Benne CA, et al. Wegener's granulomatosis patients show an adequate antibody response to influenza vaccination. *Ann Rheum Dis.* 2009;68:873-878.
177. Fischer L, Gerstel PF, Poncet A, et al. Pneumococcal polysaccharide vaccination in adults undergoing immunosuppressive treatment for inflammatory diseases—a longitudinal study. *Arthritis Res Ther.* 2015;17:151-161.
178. Struijk GH, Minnee RC, Koch SD, et al. Maintenance immunosuppressive therapy with everolimus preserves humoral immune responses. *Kidney Int.* 2010;78:934-940.
179. Palestine AG, Roberge F, Charous BL, Lane HC, Fauci AS, Nussenblatt RB. The effect of cyclosporine on immunization with tetanus and keyhole limpet hemocyanin (KLH) in humans. *J Clin Immunol.* 1985;5:115-121.
180. Trollmo C, Gudmundsson S, Feltelius N, Rogberg S, Smedegård G, Klareskog L. Sulphasalazine inhibits human antigen-specific immune responses in vivo. *Ann Rheum Dis.* 2007;66:481-485.
181. Kollaritsch H, Que JU, Kunz C, Wiedermann G, Herzog C, Cryz SJ Jr. Safety and immunogenicity of live oral cholera and typhoid vaccines administered alone or in combination with antimalarial drugs, oral polio vaccine, or yellow fever vaccine. *J Infect Dis.* 1997;175:871-875.
182. Russell AF, Parrino J, Fisher CL Jr, et al. Safety, tolerability, and immunogenicity of zoster vaccine in subjects on chronic/maintenance corticosteroids. *Vaccine.* 2015;33:3129-3134.
183. Wasan SK, Zullo S, Berg A, Cheifetz AS, Ganley-Leal L, Farraye FA. Herpes zoster vaccine response in inflammatory bowel disease patients on low-dose immunosuppression. *Inflamm Bowel Dis.* 2016;22:1391-1396.
184. AbbVie Corporation. HUMIRA [product monograph]. February 26, 2016.
185. Amgen Canada, Inc. ENBREL [product monograph]. October 19, 2015.
186. UCB Canada, Inc. CIMZIA [product monograph]. January 15, 2014.
187. Janssen, Inc. SIMPONI [product monograph]. November 25, 2014.
188. Janssen, Inc. REMICADE [product monograph]. July 22, 2015.
189. Kovalenko P, DiCioccio AT, Davis JD, et al. Exploratory population PK analysis of dupilumab, a fully human monoclonal antibody against IL-4R alpha, in atopic dermatitis patients and normal volunteers. *CPT Pharmacometrics Syst Pharmacol.* 2016;5:617-624.
190. GlaxoSmithKline, Inc. NUCALA [product monograph]. August 30, 2016.
191. Hoffmann-La Roche Limited. ACTEMRA [product monograph]. October 29, 2015.
192. Sanofi-Aventis Canada, Inc. KEVZARA [product monograph]. January 12, 2017.
193. Swedish Ophan BioVitrum AB. KINERET [product monograph]. December 23, 2010.
194. Novartis Pharmaceuticals Canada, Inc. ILARIS [product monograph]. July 14, 2016.
195. Baverel PG, Jain M, Stelmach I, et al. Pharmacokinetics of tralokinumab in adolescents with asthma: implications for future dosing. *Br J Clin Pharmacol.* 2015;80:1337-1349.
196. Noonan M, Korenblat P, Mosesova S, et al. Dose-ranging study of lebrikizumab in asthmatic patients not receiving inhaled steroids. *J Allergy Clin Immunol.* 2013;132:567-574.
197. Novartis Pharmaceuticals Canada, Inc. COSENTYX [product monograph]. February 27, 2015.
198. Eli Lilly Canada, Inc. TALTZ [product monograph]. May 25, 2016.
199. Glatt S, Helmer E, Haier B, et al. First-in-human randomized study of bimekizumab, a humanized monoclonal antibody and selective dual inhibitor of IL-17A and IL-17F, in mild psoriasis. *Br J Clin Pharmacol.* 2017;83:991-1001.
200. Valeant Pharmaceuticals North America LLC. SILIQ (brodalumab) [prescribing information]. February 2017.
201. Janssen, Inc. STELARA [product monograph]. March 9, 2015.
202. Janssen, Inc. TREMFYA [product monograph]. November 10, 2017.
203. Krueger JG, Ferris LK, Menter A, et al. Anti-IL-23A mAb BI 655066 for treatment of moderate-to-severe psoriasis: safety, efficacy, pharmacokinetics, and biomarker results of a single-rising-dose, randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol.* 2015;136:116-124.
204. Zandvliet A, Glasgow S, Horowitz A, et al. Tildrakizumab, a novel anti-IL-23 monoclonal antibody, is unaffected by ethnic variability in Caucasian, Chinese, and Japanese subjects. *Int J Clin Pharmacol Ther.* 2015;53:139-146.
205. Nemoto O, Furue M, Nakagawa H, et al. The first trial of CIM331, a humanized antihuman interleukin-31 receptor A antibody, in healthy volunteers and patients with atopic dermatitis to evaluate safety, tolerability and pharmacokinetics of a single dose in a randomized, double-blind, placebo-controlled study. *Br J Dermatol.* 2016;174:296-304.
206. GlaxoSmithKline. BENLYSTA [product monograph]. April 16, 2014.
207. Takeda Canada, Inc. ENTYVIO [product monograph]. January 25, 2015.
208. Biogen Canada, Inc. TYSABRI [product monograph]. August 31, 2016.
209. Bristol-Myers Squibb. ORENCIA [product monograph]. April 3, 2017.
210. Pfizer Canada, Inc. XELJANZ [product monograph]. April 16, 2014.
211. Apotex, Inc. APO-METHOTREXATE [product monograph]. November 27, 2014.
212. Astellas Pharma Canada, Inc. PROGRAF [product monograph]. April 27, 2011.
213. Novartis Pharmaceuticals Canada, Inc. NEORAL [product monograph]. January 9, 2015.
214. Baxter Corporation. PROCYTOX [product monograph]. September 7, 2012.
215. Browning DJ. *Hydroxychloroquine and Chloroquine Retinopathy.* New York, NY: Springer; 2014:35-63.
216. Mylan Pharmaceuticals ULC. Mylan-Hydroxychloroquine [product monograph]. February 4, 2016.
217. SteriMax, Inc. Mercaptopurine Tablets USP [product monograph]. November 19, 2014.

218. Triton Pharma, Inc. IMURAN [product monograph]. January 31, 2013.
219. Pfizer Canada, Inc. SALAZOPYRIN [product monograph]. December 5, 2013.
220. Hoffmann-La Roche Limited. CellCept/CellCept i.v. [product monograph]. March 9, 2015.
221. Novartis Pharmaceuticals Canada, Inc. MYFORTIC [product monograph]. December 17, 2014.
222. Sanofi-Aventis Canada, Inc. PEDIAPRED [product monograph]. May 1, 2006.
223. Celgene, Inc. OTEZLA [product monograph]. June 9, 2015.
224. Apotex, Inc. APO-LEFLUNOMIDE [product monograph]. February 9, 2016.
225. Asano Y, Itakura N, Hiroishi Y, et al. Viral replication and immunologic responses in children naturally infected with varicella-zoster virus and in varicella vaccine recipients. *J Infect Dis*. 1985;152:863-868.
226. Gomi Y, Ozaki T, Nishimura N, et al. DNA sequence analysis of varicella-zoster virus gene 62 from subclinical infections in healthy children immunized with the Oka varicella vaccine. *Vaccine*. 2008;26:5627-5632.
227. Levin MJ, Cai GY, Lee KS, et al. Varicella-zoster virus DNA in blood after administration of herpes zoster vaccine. *J Infect Dis*. 2018;217:1055-1059.
228. Reinhardt B, Jaspert R, Niedrig M, Kostner C, L'age-Steir J. Development of viremia and humoral and cellular parameters of immune activation after vaccination with yellow fever virus strain 17D: a model of human flavivirus infection. *J Med Virol*. 1998;56:159-167.
229. Wheelock EF, Sibley WA. Circulating virus, interferon and antibody after vaccination with the 17-D strain of yellow-fever virus. *N Engl J Med*. 1965;273:194-198.
230. Katz SL, Kempe CH, Black FL, et al. Studies on an attenuated measles-virus vaccine, VIII: general summary and evaluation of the results of vaccine. *N Engl J Med*. 1960;263:180-184.
231. van Binnendijk RS, Poelen MC, van AG, de VP, Osterhaus AD. Protective immunity in macaques vaccinated with live attenuated, recombinant, and subunit measles vaccines in the presence of passively acquired antibodies. *J Infect Dis*. 1997;175:524-532.
232. Rubin SA, Plotkin RA. Mumps vaccine. In: Plotkin SA, Orenstein WA, Offit PA, eds. *Vaccines*. 6th ed. Philadelphia, PA: Elsevier; 2013:419-446.
233. Balfour HH Jr, Groth KE, Edelman CK, Amren DP, Best JM, Banatvala JE. Rubella viraemia and antibody responses after rubella vaccination and reimmunization. *Lancet*. 1981;1:1078-1080.
234. Melnick JL, Proctor RO, Ocampo AR, Diwan AR, Ben-Porath E. Free and bound virus in serum after administration of oral poliovirus vaccine. *Am J Epidemiol*. 1966;84:329-342.
235. Horstmann DM, Opton EM, Klempferer R, Llado B, Vignec AJ. Viremia in infants vaccinated with oral poliovirus vaccine (Sabin). *Am J Hyg*. 1964;79:47-63.
236. Moretti ME, Sgro M, Johnson DW, et al. Cyclosporine excretion into breast milk. *Transplantation*. 2003;75:2144-2146.

JCMS CME Program

Earn Royal College Section 3 credits with the new *JCMS CME Program*

Obtenez des crédits de section 3 du Collège royal grâce au nouveau
Programme de DPC du JCMS

Each issue now provides an opportunity
to assess your understanding of selected
topic through a current article.

Chaque numéro vous permet d'évaluer
vos connaissances sur un sujet particulier
au moyen d'un article d'actualité.

This program is supported by an unrestricted educational grant from Eli Lilly made available through the CDA Corporate Supporter Program.
Ce programme bénéficie d'une subvention à l'éducation sans restriction d'Eli Lilly versée par le biais du Programme des sociétés commanditaires de l'ACD.