**CURRENT OPINION**

**Vaccinations for rheumatoid arthritis**

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**Purpose of review**

Rheumatoid arthritis (RA) patients experience increased infectious disease-related morbidity and mortality, and vaccinations represent an important element in their care. However, vaccine immunogenicity can be affected by disease-modifying antirheumatic drug (DMARD) therapy, such that vaccine choice and timing can be clinically challenging. We review the indications, safety, and immunogenicity of vaccines in the setting of RA.

**Recent findings**

Recent recommendations highlight the use of influenza, pneumococcal, and shingles vaccines in RA patients. Studies suggest influenza and pneumococcal vaccines are underutilized, but well tolerated in RA patients and generally immunogenic during DMARD use with the exception of rituximab. Though data for other nonlive vaccines are more limited, hepatitis B virus and human papilloma virus vaccines also appear well tolerated and immunogenic in this population. Live vaccines for shingles and yellow fever remain contraindicated in some RA patients; however, limited data suggest they might be well tolerated in certain individuals.

**Summary**

The review updates rheumatologists on the optimal use and timing of routine vaccinations in the care of RA.

**Keywords**

influenza, pneumococcal pneumonia, rheumatoid arthritis, shingles, vaccine

**INTRODUCTION**

Patients with rheumatoid arthritis (RA) suffer greater infectious morbidity and mortality [1,2]. This is attributable both to disease-related abnormalities of the immune system and to the RA patient’s immunosuppressive medications [2]. Specific risk factors for infection in RA include older age, extraarticular disease, certain comorbidities, lymphopenia, and corticosteroid and disease-modifying antirheumatic drug (DMARD) use [3,4]. Pneumonia, skin, and soft tissue infections are among the most common infectious complications in this population, with some of these infections being presumably vaccine preventable [5,6]. Despite this risk, vaccination rates for pneumococcal pneumonia, influenza, and shingles are suboptimal. In the United States, 28.5% of RA patients were optimally vaccinated for pneumococcal pneumonia, and 45.8% were optimally vaccinated against influenza [7]. Shingles vaccination is even less common, with US estimates in 2012 suggesting only 4.0% of patients with rheumatic diseases over the age of 60 were vaccinated [8]. The reasons for this poor uptake of vaccinations are unclear, and it remains a clinical practice gap within RA.

**INFLUENZA VACCINATION**

**Background**

RA patients should use the intramuscular influenza vaccine, as the live intranasal vaccine is contraindicated. The traditional vaccine is trivalent protecting against two influenza A and one influenza B strains, although now a quadrivalent form is available offering protection to an additional B strain [9]. Both the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) recommend yearly vaccination of all RA patients [10,11]. Patients over the age of 65 should receive the high-dose vaccine (for now only the trivalent vaccine is available in high dose), which has been shown to be more effective than the standard dose.
KEY POINTS

- The yearly influenza vaccine should be given to all RA patients regardless of DMARD use, as the majority of DMARDs with the exception of rituximab have no significant impact on influenza vaccine immunogenicity.

- Anti-TNF therapy and most DMARDs do not significantly impact pneumococcal vaccine immunogenicity; however, rituximab, tofacitinib, and MTX negatively affect humoral response to PPSV-23; to date, no trials have evaluated PCV-13 in this population.

- For RA patients age more than 50 years on low-to-moderate doses of corticosteroids or traditional nonbiologic DMARDs, the shingles vaccine should be given as long as their immunosuppression is below the 2008 CDC thresholds; however, this vaccine remains contraindicated in the setting of biologic therapy.

- HBV and HPV vaccines have limited data in RA, however, should be given to RA patients when indicated.

- Primary yellow fever vaccinations is contraindicated in patients using immunosuppressives; however, limited studies of patients receiving booster vaccination in the setting of biologics or corticosteroid use have not shown adverse events; until further data are collected, this live vaccine remains contraindicated.

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Effect of DMARD therapy on vaccine effectiveness and safety

Influenza vaccine immunogenicity is evaluated with hemagglutinin inhibition antibody titers, where at least 1:40 is considered protective [14]. In the majority of studies [15,16,17*,18–24,25*] evaluating the effect of methotrexate (MTX) or biologics, vaccine immunogenicity suggest that hemagglutinin inhibition titers are similar or sometimes slightly lower in such patients, but that the proportion of patients reaching protective titers is generally similar in patients taking DMARDs compared with control RA patients. Rituximab, however, significantly reduce the humoral response [25*,26–29]. Longer delays between rituximab and the vaccine of at least 6 months results in better humoral response than shorter delays of 4–6 weeks [27,28]. Studies [30,31*] with tocilizumab and tofacitinib suggest no significant effect of either drug on influenza vaccine immunogenicity. Abatacept significantly reduced the humoral response to the 2009 influenza A/H1N1 vaccine; however, the seasonal trivalent and quadrivalent vaccines, which may be more immunogenic, were not evaluated [17*,32].

Summary and recommendations

The intramuscular influenza vaccine should be given annually to all RA patients regardless of immunosuppressive therapy. It is relatively unaffected by DMARD use, except for rituximab (Table 1). When giving this vaccine to patients using rituximab, it ideally should be given prior to therapy start or as long after therapy administration as compatible with the influenza season.

PNEUMOCOCCAL VACCINATION

Background

Two pneumococcal vaccines are approved in the United States; pneumococcal conjugate vaccine 13-valent (PCV-13) is a 13-valent conjugated vaccine and pneumococcal polysaccharide vaccine 23-valent (PPSV-23) is a 23-valent polysaccharide vaccine. Conjugated vaccines are generally more immunogenic than polysaccharide vaccines. Studies of the prior conjugated pneumococcal vaccine PCV-7, however, did not suggest greater immunogenicity than PPSV-23 in RA patients [42]. PCV-13 immunogenicity in RA has not yet been directly evaluated. In pneumococcal vaccine-naïve individuals, Center for Disease Control (CDC) recommends PCV-13 followed by PPSV-23 at least 8 weeks later. For those who have already received PPSV-23, PCV-13 should be given at least 1 year later with and additional PPSV-23 booster given as usual 5 years from the first [43*].

Effect of DMARD therapy on vaccine immunogenicity and safety

Antitumor necrosis factor (TNF) therapy does not appear to reduce humoral response to pneumococcal vaccinations [22,24,25*,33–36]. Several studies [37,38,39*] looking at tocilizumab’s effect on the vaccine have similarly shown either unchanged or lower but statistically insignificant differences in humoral responses. Rituximab, tofacitinib, and MTX, however, have been shown to decrease humoral responses [25*,27,31*,33,34,38,44]. MTX-treated RA patients who were vaccinated with PPSV-23 or PCV-7 were found to have 12–29% lower rates of patients achieving an adequate humoral response, with greater decreases
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Table 1. Impact of RA therapy on vaccine immunogenicity and indications for vaccination

|                  | MTX | TNF inhibitors | Rituximab | Abatacept | Tofacitinib | Tocilizumab | Indications                      |
|------------------|-----|----------------|-----------|-----------|-------------|-------------|---------------------------------|
| Influenza        | ±   | OK             | ↓ ↓ ↓     | ↓         | OK          | OK          | All patients regardless of immunosuppression, ideally before biologics or MTX, yearly |
| Pneumococcus*   | ↓   | OK             | ↓ ↓ ↓     | ↓ ↓ ↓     | ↓ ↓ ↓       | OK          | All patients regardless of immunosuppression, ideally before biologics or MTX |
| Hepatitis B      | ?   | ?              | ?         | ?         | ?           | ?           | All at-risk patients regardless of immunosuppression |
| Human papilloma virus | ?   | ?              | ?         | ?         | ?           | ?           | All patients age ≤26, regardless of immunosuppression |
| Herpes zoster    | ?   | ?              | ?         | ?         | ?           | ?           | All patients ≥50 not on biologics or high-dose corticosteroids; Should be given ≥2 weeks before starting biologics or ≥4 weeks after stopping biologics |
| Yellow fever     | ?   | ?              | ?         | ?         | ?           | ?           | Contraindicated for patients using immunosuppressives |

Indications for vaccination based on ACR and EULAR guidelines [10,11]. Methotrexate decreases humoral response to pneumococcal vaccine, and may also decrease humoral response to influenza vaccination [25*,33,34]. TNF inhibitors do not significantly impact response to influenza or pneumococcal vaccines, though two small studies showed a negative effect on hepatitis B vaccine response [15–24,25*,33–36,40,41]. Rituximab significantly decreases humoral response to both influenza and pneumococcal vaccines [25*,26–29]. Abatacept decreases humoral response to influenza and pneumococcal vaccines [17*,22,38]. Tofacitinib does not have a negative effect on influenza vaccine but does decrease immunogenicity of pneumococcal vaccines [31*]. Tocilizumab has shown to have no detrimental effect on influenza or pneumococcal vaccine immunogenicity [30,37,38,39*].

*No data regarding vaccine immunogenicity in this setting; +/-: Limited data suggests this medication might negatively impact immunogenicity, though more data is needed; MTX, methotrexate; OK, Vaccine does not impair immunogenicity; TNF, Tumor necrosis factor.

*Polyvalent pneumococcal vaccine data only, the 13-valent conjugate vaccine immunogenicity has not been evaluated in the setting of RA.

*Abatacept diminished immunogenicity to the H1N1 influenza vaccine. Seasonal trivalent or quadrivalent influenza vaccines were not evaluated.

for the 6B than the 23F strain [25*,33,34]. A recent study [38] of rituximab and PCV-7 found that of 29 patients on rituximab monotherapy only 10.3% had an adequate humoral response to the two antigens evaluated, and of 26 patients on rituximab plus MTX none achieved an adequate response to both antigens. Tofacitinib appears to lower immune responses to a similar extent to MTX, and greater reductions were noted when the drugs were used together. For patients already taking tofacitinib, however, the majority of patients achieve satisfactory responses and temporary drug discontinuation prior to vaccination had little effect upon humoral response [31*]. Very limited data exist with abatacept, and of 26 patients on rituximab plus MTX none achieved an adequate response to both antigens. Tofacitinib appears to lower immune responses to a similar extent to MTX, and greater reductions were noted when the drugs were used together. For patients already taking tofacitinib, however, the majority of patients achieve satisfactory responses and temporary drug discontinuation prior to vaccination had little effect upon humoral response [31*]. Very limited data exist with abatacept, and of 26 patients on rituximab plus MTX none achieved an adequate response to both antigens. Tofacitinib appears to lower immune responses to a similar extent to MTX, and greater reductions were noted when the drugs were used together. For patients already taking tofacitinib, however, the majority of patients achieve satisfactory responses and temporary drug discontinuation prior to vaccination had little effect upon humoral response [31*].

Summary and recommendations

TNF inhibitors and tocilizumab have little or no effect upon PPSV-23 immunogenicity. Rituximab, tofacitinib, and MTX negatively affect humoral response to PPSV-23 (Table 1). There are currently no data regarding the influence of RA medication on PCV-13, or on the efficacy of using PCV-13 to prime responses to PPSV-23 in the setting of RA. Lastly, the ACR guidelines stress that whenever possible the pneumococcal vaccines should be given prior to initiation of RA therapy [11].

SHINGLES VACCINATION

Background

Shingles is more common in older patients and those with compromised immune systems [45]. A recent study [46*] observed incidence rates between 1.61 and 2.45/100 person-years for RA patients, with similar risk observed for all biologics, although similar to other studies, a dose-dependent risk with corticosteroids was observed. The shingles vaccine is a live attenuated vaccine approved for immunocompetent patients over the age of 50 [47]. The CDC, however, recommends the vaccine only after age 60, citing difference in cost-effectiveness between the 50+ and 60+ age groups and concerns for decreased vaccine efficacy over time; however, no cost–benefit analysis has done specifically for RA [48]. Given the higher risk of shingles in RA, the 2015 ACR guidelines recommended shingles vaccinations for RA patients at least 50 years [11].

While few data exist regarding this vaccine’s safety during immunosuppressive use, the CDC advises that the vaccine can be used safely with:
MTX (<0.4 mg/kg/week, e.g. 25 mg/week), low-to-moderate doses of glucocorticoids (<20 mg/day prednisone or equivalent), intraarticular, bursal, or tendon corticosteroid injections, and azathioprine (<3.0 mg/kg/day). The CDC and Infectious Disease Society of America both currently recommended avoiding this vaccine in patients taking biologics or high-dose corticosteroids, and waiting at least 1 month after discontinuation of these drugs before giving the shingles vaccine [49,50]. The ideal time is to vaccinate prior to biologic start, and a gap of 2–4 weeks is recommended between vaccine and drug start.

Effect of DMARDs on shingles vaccine immunogenicity and safety

To this date, no prospective trials exist evaluating the safety or efficacy of the shingles vaccine in RA patients [51]. An observational study [8] using US Medicare data identified 633 patients who were inadvertently vaccinated while using biologics found no cases of shingles or varicella in the 6 weeks after vaccination, and long-term the patients vaccinated had approximately a 40% reduction in shingles risk. Another analysis of claims data from a nationwide US health plan looked at 47 patients with rheumatic conditions who were exposed to biologics (primarily anti-TNF) at the time of vaccination, and again found no cases of shingles within 30 days of vaccination [51].

Summary and recommendations

For RA patients aged at least 50 years on low-to-moderate doses of corticosteroids or traditional non-biologic DMARDs, the shingles vaccine should be given as long as their immunosuppression is below the 2008 CDC thresholds listed above. Even though early observational data suggest that vaccination in the setting of biologics may not result in shingles, more robust prospective data are needed to determine whether this is truly safe. For now, in the author’s opinion, it is optimal to vaccinate patients 4 weeks before starting a biologic or tofacitinib, or 1 month after discontinuing such therapy [11].

OTHER VACCINES: HUMAN PAPILLOMA VIRUS, HEPATITIS B VIRUS, AND YELLOW FEVER VACCINES

Human papilloma virus

There are three available human papilloma virus (HPV) vaccines: a bivalent vaccine approved only for women, a quadrivalent vaccine covering strains 6, 11, 16, and 18, and as of 2014, a 9-valent vaccine that covers strains 6, 11, 16, 18, 31, 33, 45, 52, and 58, which is now the preferred vaccine. The CDC recommends vaccination for boys and girls aged 11 or 12, previously unvaccinated females aged 13 through 26, and males aged 13 through 21, but extends the recommendation to age 26 in immunocompromised men [52].

The burden of disease of HPV in RA is not well established, though one population-based cohort study [53] showed an increased risk of high-grade cervical dysplasia and cervical cancer in women with RA compared with healthy controls, which was significant even after adjustment for immunosuppressant use. Higher rates of HPV and cervical cancer have been observed in inflammatory bowel disease and systemic lupus erythematosus (SLE) patients as well [54–57]. Data for HPV vaccine immunogenicity in rheumatic illnesses are limited. A prospective observational cohort of the bivalent HPV vaccine in juvenile idiopathic arthritis (JIA) patients, including nine on TNF inhibitors and 24 on MTX, found no difference in rates of seroconversion, though the JIA patients tended to have lower rates of antibody and B-cell responses [58]. In another study [59], 50 SLE patients receiving the quadrivalent vaccine compared with healthy controls found slightly lower seroconversion rates associated with SLE and that mycophenolate mofetil use was a risk factor for inadequate humoral response. A recent systematic review of the available data in SLE, JIA, and inflammatory bowel disease concluded that the vaccine is well tolerated and efficacious in most of these patients, though large studies evaluating the effect of medications on immunogenicity are lacking [60].

Both the ACR and EULAR recommend considering the HPV vaccine in selected patients where the vaccine is indicated, regardless of concurrent immunosuppressant [10,11]. More data are certainly needed regarding the disease burden of HPV in RA patients, and the role of immunosuppressive therapy on cervical cancer risk and vaccine immunogenicity.

Hepatitis B virus

The hepatitis B virus (HBV) vaccine is available in the United States for use in adults as either a single antigen vaccine, or as a combination vaccine with hepatitis A virus. Vaccination is recommended for all nonimmune adults who are at risk for HBV or request vaccination. At-risk individuals are persons with a household contact or sexual partner who is hepatitis B surface antigen (HBsAg) positive, more
than one sexual partner in the last 6 months, those seeking evaluation for treatment of a sexually transmitted disease, MSM, current or recent IV drug users, resident or staff of a facility for the developmentally disabled, healthcare workers, patients with end-stage renal disease, travelers to endemic areas, patients with chronic liver disease, diabetic patients using glucometers, and patients with HIV [61]. RA patients who contract or carry HBV may reactivate in the setting of RA therapy. Reactivation is well established during treatment with anti-TNF drugs and rituximab, more recently reported with abatacept and tocilizumab, and reported in a small number of cases with nonbiologic DMARDs [62–67]. Reactivation has been demonstrated mostly in HBsAg-positive patients, and less commonly in HBsAg-negative patients who lack hepatitis B surface antibody and are hepatitis B core antibody positive [68,69]. The CDC, American Association for the study of Liver Diseases, ACR, and National Institute of Health all recommend screening for HBV prior to initiation of immunosuppressive therapy [11,70–72]. Patients lacking natural or vaccine-induced immunity who are at risk for acquiring HBV should be vaccinated [73]. The impact of DMARDs upon this vaccine is largely unstudied, although limited data suggest that treatment with TNF inhibitors may impair humoral response [40,41] (Table 1).

Yellow fever
The yellow fever vaccine is a live vaccine that is recommended for all immunocompetent adults who travel or live in endemic areas, and is contraindicated in the setting of immunosuppressants [74]. During a recent outbreak in Brazil, a number of patients were inadvertently revaccinated while on immunosuppressive medications. These patients had been vaccinated previously, such that they had primary immunity at the time of booster. Of those vaccinated while using DMARDs or biologics (n = 31), including 23 with RA, investigators found no major adverse events and lower, yet adequate, antibody titers following vaccination [75]. In another group of patients using infliximab and MTX (n = 17) who were revaccinated, all but one achieved satisfactory antibody levels, and none experienced adverse reactions [76]. A separate study [77] of 34 travelers using 5–20 mg/day (median 7 mg/day, median duration 10 months) of corticosteroids receiving the vaccine, 18 of whom were vaccine naive, found an increase in local reactions to the vaccine but no major adverse events and satisfactory immunogenicity. Taken together, these small studies suggest yellow fever vaccine might be well tolerated in the setting of TNF blockers or corticosteroids when given to patients who have received prior immunization; however, both the CDC and EULAR recommend avoiding yellow fever vaccine in RA patients using biologics regardless of a prior history of vaccination [10].

CONCLUSION
There remain numerous gaps in our understanding of vaccinations in the RA population. At present, there are very few efficacy or effectiveness studies for vaccinations in this setting. With regard to immunogenicity, it is unclear how DMARDs affect PCV-13, HPV, and HBV vaccines. Although the live shingles and yellow fever vaccines are contraindicated in RA patients using biologics or tofacitinib, early data indicate that they might be safer in the setting of immunosuppression than previously thought, but large prospective trials are needed to evaluate this question. In RA where shingles risk is elevated, the ability to prevent disease represents an important clinical practice gap. There are nonlive shingles vaccines in development that might one day be useful in this setting [78]. Although the body of data available is growing, many recommendations are still dependent on small case series or expert opinion. In this review, we have discussed the available safety and immunogenicity data for influenza, pneumococcal, and shingles vaccines, as well as HPV, HBV, and yellow fever vaccine data, and important gaps in data leaving unanswered questions. Unfortunately, despite the high rates of infectious disease-related morbidity and mortality, vaccination rates in RA remain poor. It is extremely important for the treating rheumatologist to understand the safety and efficacy of these vaccinations to educate patients, advocate for vaccination in clinic, and ultimately help prevent serious infectious disease complications in this vulnerable population.

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