

ongoing contributions to the quality of health service provision in Australasia in the 21st century.

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## REVIEW

# A practical approach to vaccination of patients with autoimmune inflammatory rheumatic diseases in Australia

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## Key words

vaccination, rheumatic disease, infection, immunosuppression, biologics.

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## Abstract

Autoimmune inflammatory rheumatic diseases (AIIRD), such as rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis are often complicated by infection, which results in significant morbidity and mortality. The increased risk of infection is probably due to a combination of immunosuppressive effects of the AIIRD, comorbidities and the use of immunosuppressive conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs) and more recently, targeted synthetic DMARDs and biologic DMARDs that block specific pro-inflammatory enzymes, cytokines or cell types. The use of these various DMARDs has revolutionised the treatment of AIIRD. This has led to a marked improvement in quality of life for AIIRD patients, who often now travel for prolonged periods. Many infections are preventable with vaccination. However, as protective immune responses induced by vaccination may be impaired by immunosuppression, where possible, vaccination may need to be performed prior to initiation of

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immunosuppression. Vaccination status should also be reviewed when planning overseas travel. Limited data regarding vaccine efficacy in patients with AIIRD make prescriptive guidelines difficult. However, a vaccination history should be part of the initial work-up in all AIIRD patients. Those caring for AIIRD patients should regularly consider vaccination to prevent infection within the practicalities of routine clinical practice.

## Introduction

Autoimmune inflammatory rheumatic diseases (AIIRD), such as rheumatoid arthritis (RA), psoriatic arthritis and ankylosing spondylitis are often complicated by infection, which results in morbidity and mortality.<sup>1</sup> Increased infection may be due to the immunosuppressive effect of the AIIRD, comorbidities, hospitalisations, surgical procedures and therapeutic immunosuppression.<sup>2</sup> Vaccine-preventable infection accounts for much of this burden with influenza, pneumococcal, herpes zoster (HZ) and human papillomavirus (HPV) infection occurring more frequently in AIIRD patients than in the general population.<sup>3</sup>

## Immunosuppression

Immunosuppressants used to treat AIIRD include corticosteroids (CS), conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs)<sup>4</sup>, such as methotrexate (MTX), sulfasalazine, leflunomide and hydroxychloroquine. Targeted synthetic DMARDs (tsDMARDs),<sup>4</sup> such as the new oral agents tofacitinib or apremilast that target specific pro-inflammatory enzymes, and biologic DMARDs (bDMARDs), such as etanercept or rituximab that target specific pro-inflammatory mediators or cell types, respectively, have revolutionised the treatment of AIIRD (Table 1).

Live vaccines are usually contraindicated in severely immunocompromised patients due to possible vaccine-

induced disease from viral replication.<sup>5</sup> High dose prednisone (>2 mg/kg or ≥20 mg/day of prednisone, or equivalent), when administered for ≥2 weeks,<sup>6</sup> or > 60 mg/day of prednisone for >1 week<sup>5</sup> may be sufficiently immunosuppressive to raise concerns about live-virus vaccines. The Infectious Diseases Society of America considers a dose ≥20 mg/day of prednisone or equivalent for ≥14 days, or treatment with a bDMARD as 'high level immunosuppression', whereas a lower dose of prednisone or MTX ≤0.4 mg/kg/week or azathioprine ≤3 mg/kg/day is 'low level immunosuppression'.<sup>7</sup> *The Australian Immunisation Handbook* considers patients with haematological malignancy, recent chemotherapy, solid organ or bone marrow transplant and human immunodeficiency virus with CD4+ counts <15% as 'severely immunocompromised'.<sup>5</sup> Most rheumatologists would not regard DMARDs, tsDMARDs or bDMARDs at the doses used to treat AIIRD, as severely immunosuppressive.

The aim of this review is to prompt those involved in the care of AIIRD patients to assess vaccination status early, preferably before initiation of any DMARDs and to regularly consider vaccination to prevent infection. The first part of this review deals with vaccines, which are in widespread clinical use. While travel vaccines are an important aspect of vaccination, it is not possible to exhaustively discuss each one. We have therefore limited our discussion of travel vaccines in the second part of this review to the more commonly required travel vaccines. Due to the complexity of AIIRD patients and the wide range of vaccines available, management of individual cases may require close consultation with an infectious diseases (ID) physician.

**Table 1** Targeted synthetic and biologic DMARDs currently available on the Pharmaceutical Benefits Scheme in Australia for the treatment of inflammatory arthritis

Mechanism of action	Agent
Targeted synthetic DMARDs	
Janus kinase inhibitor	Tofacitinib
Phosphodiesterase-4 inhibition	Apremilast
Biologic DMARDs	
Tumour necrosis factor inhibition	Etanercept
	Adalimumab
	Infliximab
	Certolizumab pegol
	Golimumab
T-cell co-stimulation blockade	Abatacept
B-cell depletion	Rituximab
Interleukin 12/23 inhibitor	Ustekinumab

DMARDs, disease-modifying anti-rheumatic drugs.

## Methods

The literature search strategy used is outlined in Table 2.

## Influenza

### Epidemiology

Influenza A/B infection follows person-to-person transmission by virus-containing respiratory aerosols or by contact with respiratory fluids. The annual cost of influenza-related illness to the Australian healthcare system was approximately \$115 million.<sup>8</sup>

**Table 2** Search strategy used to arrive at recommendations

Medline (via PubMed) was searched from 2000 to July 2016 by combining MESH terms for the AIIRD, DMARDs, bDMARDs and vaccines. The search was limited to 'English' language and 'human' subjects. Other papers or conference abstracts considered relevant were used along with those found by citation tracking. Each Rheumatologist (PW, HB, CB, PH, AK, MM, PP, JR, RW, LY) was responsible for researching and writing one topic and presenting results to the combined group. Recommendations were made by consensus in light of current national guidelines from Australia and overseas considering the practicalities of routine clinical practice. These were then reviewed by two independent infectious diseases physicians (KL, DJ) whose suggestions/recommendations were considered by the group and incorporated, if appropriate

AIIRD, autoimmune inflammatory rheumatic diseases; bDMARDs, biologic disease-modifying anti-rheumatic drugs; DMARDs, disease-modifying anti-rheumatic drugs.

### Vaccine use in AIIRD patients

Influenza vaccines normally contain three circulating viral strains (trivalent). However, quadrivalent vaccines are a viable alternative in adults, with possibly a greater range of protection due to the additional influenza B subtype contained.<sup>9</sup>

While measured antibody responses are not necessarily the only marker of protection against clinical disease, most studies use these as a surrogate marker of clinical protection. A prospective cohort study examined the protective antibody response following influenza vaccination in 112 AIIRD patients treated with either a tumour necrosis factor inhibitor (TNFi,  $n = 64$ ) or without a TNFi ( $n = 48$ ) and a control group of 18 healthy individuals.<sup>10</sup> The proportion of patients (approximately 80%) with a protective antibody titre was not reduced in the presence of a TNFi.<sup>10</sup> There was no significant difference in antibody titre 4 weeks post-vaccination in patients on the TNFi, adalimumab versus those on placebo.<sup>11</sup> Patients with RA treated with MTX alone ( $n = 37$ ) had a better serological response to influenza vaccination compared to those on a TNFi alone ( $n = 62$ ), or in combination with MTX and/or other DMARDs ( $n = 50$ ). However, most patients had protective post-vaccination antibody titres.<sup>12</sup> A Japanese study of 194 RA patients found that the interleukin-6 receptor inhibitor, tocilizumab did not impair the antibody response to influenza vaccine.<sup>13</sup>

A prospective single centre study of 173 patients (82 with RA, 45 with spondyloarthritis, 46 with other AIIRD) and 138 control subjects found two doses of adjuvanted influenza vaccine administered 3–4 weeks apart were required to elicit a similar serologic response to that following one dose of vaccine in healthy controls.<sup>14</sup>

In contrast, post-vaccination sero-protection with a non-adjuvanted pandemic 2009 influenza A/H1N1 vaccine was reduced in a small study of 11 RA patients treated with the co-stimulatory inhibitor, abatacept (ABA) compared to MTX alone (9% versus 58%;  $P = 0.006$ ) or healthy controls (69%;  $P < 0.001$ ).<sup>15</sup> Influenza vaccination in 23 RA patients treated with the B-cell depleting antibody rituximab (RTX) failed to induce a protective antibody response.<sup>16</sup> While administration of a trivalent

influenza vaccine to 23 RA patients treated with RTX failed to induce seroconversion, a modestly restored humoral response was seen when vaccine was administered 6–10 months post-RTX.<sup>17</sup>

### Recommendations

- As immunosuppression is associated with an increased risk of influenza-related complications, free annual vaccination is available under the National Immunisation Programme (NIP).
- All immunocompromised AIIRD patients who receive the influenza vaccine for the first time should receive two vaccine doses, at least 4 weeks apart and one dose annually thereafter on an ongoing basis (Table 3).<sup>5</sup>
- A lower sero-protective response may be seen in the presence of ABA.<sup>15</sup>
- Influenza vaccination should occur as far as possible from a dose of RTX.<sup>16,17</sup>

## ***Streptococcus pneumoniae*** (Pneumococcus)

### Epidemiology

Invasive pneumococcal disease (IPD; bacteraemia, meningitis or pneumonia) is an important cause of morbidity and mortality in AIIRD patients.<sup>2</sup>

### Vaccine use in AIIRD patients

Two vaccine types are available – a conjugate vaccine (T-cell dependent) and a polysaccharide vaccine (T-cell independent). Most studies involving AIIRD patients have used the polysaccharide vaccine – the usual vaccine used in immunocompetent adults.

The currently used conjugate vaccine is a 13-valent vaccine (13vPCV) containing capsular polysaccharides from the commonest pneumococcal types, linked to a non-toxic diphtheria toxin-like protein that enhances

**Table 3** Recommendations for vaccination of patients with autoimmune inflammatory rheumatic diseases in Australia

Vaccine	Recommendations	Dosing	Frequency	Cost covered by NIP	Approx. cost if not covered by NIP	Reference
Influenza	Annually	Two doses 4 weeks apart for 1st year and then one dose annually	Annually	Yes	NA	<sup>5</sup>
Pneumococcus-vaccine-naïve	13vPCV, 23vPPV vaccines	13vPCV first, then 23vPPV after ≥8 weeks	Rpt in 5 years, then 3rd dose at age 65	For adults ≥65 years	Standard co-payment \$37.70 or \$6.10 for concession card holders	<sup>5</sup>
Pneumococcus-previously vaccinated	23vPPV at age 18 or at diagnosis of AIIRD, or 5 years after last dose	23vPPV at diagnosis of AIIRD, or 5 years after last dose	<2 More doses, 5 years apart	For adults ≥65 years	Standard co-payment \$37.70 or \$6.10 for concession card holders	<sup>5</sup>
Hepatitis B	Those at increased risk of contracting infection (see text)	3 doses in 6/12. Engerix-B day 0 – 1st dose, 2nd dose 1 month post-1st injection and 3rd dose, 6/12 after 1st injection	3 Doses over 6/12	Yes	\$25 Each vaccine × 3 = \$75	<sup>5</sup>
Twinrix (720/20)-combination Hep A/B	Those at risk of contracting Hep A and/or Hep B†	3 Doses in 6/12. Day 0 – 1st dose, 2nd dose 1 month post-1st injection and 3rd dose, 6/12 after 1st injection	3 Doses over 6/12	Yes	\$80 each vaccine × 3 = \$240	<sup>5</sup>
Human papilloma virus	Case-by-case basis (see text)	Three doses, second at least 1 month after the 1st, and 3rd at least 3 months after the 2nd	Once	No	\$450 for course	<sup>2,5</sup>
Herpes zoster	Consider in those aged ≥50 years with AIIRD Note: live vaccine	One dose	Once, re-vaccination interval unclear	Yes, 70–79 years from November 2016	\$220 for each dose	Consensus
Bacillus Calmette Guérin	Only if indigenous child <12 months or <5 years and travelling to high-risk country for extended period. Not recommended in immunocompromised as live vaccine	One dose	Once	Yes, if eligible	NA	<sup>2</sup>
Diphtheria, tetanus, pertussis (dTpa)	In ≥50 years without booster in last 10 years	One dose	Probably every 10 years	Yes	NA	<sup>2</sup>

†Those at increased risk of more severe disease or contracting Hep B and in addition – travellers to, and those living in mod-high endemic areas for hepatitis A and B, persons whose lifestyle puts them at risk of hepatitis A and B, those who attend or work at facilities for people with developmental disabilities, occupational risk for exposure to hepatitis A and B, those with chronic liver disease and/or hepatitis C. AIIRD, autoimmune inflammatory rheumatic diseases; NA, not applicable; NIP, National Immunisation Programme.

vaccine immunogenicity. This is important in infants and the immunocompromised.

The pneumococcal polysaccharide vaccine (23vPPV) covers 85–95% of pneumococcal disease and has been used in adults for many years but is poorly immunogenic in children. It contains 12 of the serotypes included in 13vPCV plus 11 other serotypes.<sup>5</sup> Fifty percent of IPD cases in immunocompromised adults were caused by serotypes contained in 13vPCV.<sup>18</sup> Another 21% of cases were caused by serotypes contained only in 23vPPV.<sup>18</sup> As a result, the 'prime and boost' strategy aims to provide broader protection through using both pneumococcal vaccines.<sup>5</sup>

Most studies in AIIRD patients have used the polysaccharide vaccine (23vPPV). Low-dose CS does not impair development of post-vaccination protective antibody.<sup>3</sup> As there were variable immune responses to polysaccharide vaccination following MTX,<sup>19–21</sup> pneumococcal vaccination should occur before starting MTX. The observed reduction in protective immunity following pneumococcal vaccination in patients receiving MTX + TNFi may be due to MTX.<sup>19,20</sup> In most studies, TNFi monotherapy did not impair the protective post-vaccination immune response.<sup>19,20</sup>

RTX impaired the immune response to both vaccines.<sup>22</sup> Tocilizumab had no effect on immune response following 23vPPV vaccination.<sup>23</sup>

While patients receiving ABA showed a reduced immune response to the vaccine, an adequate level of protective antibody still occurred.<sup>3</sup> Patients receiving tofacitinib (TFN) mounted a sub-optimal immune response to 23vPPV (45% vs 68% in the placebo group).<sup>24</sup>

## Recommendations

*The Australian Immunisation Handbook* recommends (Table 3):<sup>5</sup>

- pneumococcal vaccination as part of the NIP of childhood vaccination and for all ≥65 year olds;
- immunosuppressed adults should receive 23vPPV at age 18 or 5 years after the most recent dose, with up to two more doses 5 years apart;
- those newly diagnosed with a condition requiring immunosuppression and vaccine-naïve should receive 13vPCV followed by 23vPPV after at least 8 weeks. The dose of 23vPPV should be repeated in 5 years and a third dose given at 65 years (or 50 years in indigenous people);
- ideally, pneumococcal vaccination should be given before initiation of DMARDs (especially MTX).<sup>19,20</sup>

## Hepatitis B (HBV)

### Epidemiology

While over 207 000 people in Australia live with HBV, only 55% know they have chronic HBV infection.<sup>25</sup> Reactivation of HBV infection in AIIRD patients may occur following commencement of, or immediately after discontinuing immunosuppression.<sup>2</sup> Due to the risk of HBV reactivation, all AIIRD patients should be screened (both HBsAg and anti-HBc Ab) for HBV before immunosuppression.<sup>26</sup>

### Vaccine use in AIIRD patients

A recent study of 47 RA patients and 156 controls showed a reduced response to HBVAXPRO-10 (10 µg/L Hepatitis B vaccine) in patients on bDMARDs.<sup>27</sup> There was no difference in response between patients using a TNFi ( $n = 26$ ) or csDMARDs ( $n = 8$ ).<sup>27</sup> A better response was observed in a study of 44 RA patients on csDMARDs using the ENGERIX-B vaccine (20 µg/L Hepatitis B vaccine).<sup>28</sup> Fifteen of the 22 patients (68%) demonstrated a post-vaccination antibody level of more than 10 IU/L after 6 months.<sup>28</sup> This vaccine should probably be used in preference to HBVAXPRO-10 in RA patients on treatment although it is unclear whether response rates will remain robust in those on tsDMARDs or bDMARDs.

Vaccination is administered at month 0, 1 and 6. Anti-HBs Ab should be measured 4–8 weeks after the last dose. If adequate anti-HBs Ab levels ( $\geq 10$  mIU/mL) are absent, a booster dose (4th dose) of vaccine can be given. Non-responders after the 4th dose and in whom HBV infection has been excluded should have two further doses of vaccine (or a double dose of vaccine) at monthly intervals and be re-tested for anti-HBs Ab levels  $\geq 4$  weeks after the last dose. Persistent non-responders sometimes respond to intradermal vaccination, but should otherwise be considered unprotected against HBV and advised to minimise exposure and informed about the need for HBIG within 72 h of parenteral or mucosal exposure to HBV.<sup>5</sup> If anti-HBs Ab titres fall  $< 10$  IU/mL, a booster dose should be given for those with ongoing risk of exposure and the individual re-tested.

### Recommendations

Vaccination for HBV is recommended when (Table 3):<sup>5</sup>

- the patient is at higher risk of severe disease, for example, on immunosuppression;
- the risk of contracting HBV is increased, e.g. travel to, or residence in countries endemic for HBV;

- there is increased risk of exposure or proven exposure to HBV, for example, healthcare professionals, infected family member or contacts; or
- when protective HBV antibodies are absent.

## Human papilloma virus

### Epidemiology

Human papilloma virus types 16 and 18 are associated with cancer of the cervix, vagina, vulva, penis, anus and head/neck, while types 6 and 11 are associated with genital warts.<sup>29</sup> The cumulative incidence of HPV infection in college women was 40% within 24 months of first sexual intercourse.<sup>29</sup> The lower clearance rate of HPV in systemic lupus erythematosus (SLE) patients may affect the long-term risk of cervical cancer.<sup>30</sup>

### Vaccine use in AIIRD patients

Proteins from the HPV shell became the basis of the two commercially available vaccines – the quadrivalent HPV vaccine (4vHPV, Gardasil), which protects against types 16, 18, 6 and 11, and the bivalent HPV vaccine (Cervarix), which protects against types 16 and 18. Both have high efficacy for prevention of HPV vaccine type-related persistent infection.<sup>29</sup> As they are killed vaccines, there are no specific risks in AIIRD patients.

The HPV vaccine is included in the Australian NIP via school-based programmes for girls and boys aged 12–13 years.<sup>5</sup> There is limited vaccine experience in immunocompromised patients. The HPV-specific geometric mean titres were consistently lower in SLE patients compared with healthy controls.<sup>31,32</sup> A clinical trial assessing immunogenicity of the 4vHPV vaccine in 37 female patients with inflammatory bowel disease (mean age 15 years; 51% on TNFi, 49% on immunomodulators) reported sero-positivity after the third dose was 100% for types 6, 11 and 16 and 96% for type 18.<sup>33</sup>

### Recommendations

There are variable national guidelines regarding HPV vaccination.<sup>2,5</sup> The Australian Technical Advisory Group on Immunisation (ATAGI) recommends HPV vaccination for immunocompromised adults regardless of age.<sup>5</sup> The decision to vaccinate those with AIIRD should consider the likelihood of previous exposure to HPV, the future risk of HPV exposure and the extent/duration of immunosuppression. Adolescents with AIIRD who have not yet been vaccinated may be offered ‘catch-up’ as they may be more likely to develop persistent HPV infection, which may progress to HPV-related disease.<sup>30</sup> Patients

with AIIRD should be advised about HPV vaccination as per the general population, with primary prevention via the cervical screening programme. Vaccination is optional, at patient expense and costs approximately AU\$450 for three doses (Table 3).

## Herpes zoster

### Epidemiology

Most Australians have been infected with the varicella-zoster virus (VZV) and are therefore at risk of virus reactivation, leading to the usually painful HZ (shingles) rash. The incidence of HZ in Australia is approximately 10/1000 with the risk of viral reactivation increasing with age.<sup>34</sup> The mean age of HZ onset is 60 years, while half of those aged ≥85 years will probably develop HZ.<sup>35</sup> Post-herpetic neuralgia is a debilitating complication with 80% of cases occurring in those ≥50 years of age.<sup>36</sup> HZ ophthalmicus occurs in 15% of cases and can lead to blindness.<sup>36</sup>

There is an increased risk of HZ in AIIRD patients on DMARDs and CS.<sup>2</sup> The relative risk associated with tsDMARDs or bDMARDs is unclear, but there is an increased risk of HZ with TFN.<sup>37</sup>

### Vaccine use in AIIRD patients

Zostavax, the only currently available HZ vaccine, contains a live attenuated virus and is used in those with previous VZV to prevent shingles. (Varicella vaccine contains a lower dose of live attenuated virus and is used in those lacking VZV immunity to prevent chickenpox). Zostavax is registered in Australia for adults aged ≥50 years of age but only recommended in people aged ≥60 years, because the incidence of post-herpetic neuralgia is greater in this age group.<sup>5</sup> As of November 2016, Zostavax is included in the Australian NIP for ≥70 year olds (ongoing) and 71–79 year olds (catch-up).<sup>38</sup> These age groups were chosen because of compromise between cost, risk at different ages and reduced vaccine efficacy with increasing age. The risk of HZ in those aged 50–59 years with AIIRD approximates that of healthy people aged 70–79 years.<sup>39</sup> We therefore recommend HZ vaccination in patients with RA aged ≥50 years.

Current recommendations are that live virus vaccines should be avoided in the setting of immunosuppression.<sup>2,5,7</sup> Low-to-moderate doses of CS (dose equivalent to prednisone ≤ 10 mg/day), leflunomide, sulfasalazine and MTX (≤0.4 mg/kg per week) and AZA (≤3 mg/kg per day) are not a contraindication.<sup>40</sup> However, ATAGI suggests patients receive HZ vaccination 4 weeks prior to commencement of immunosuppression.<sup>5</sup>

There is evidence patients with AIIRD can be safely vaccinated with Zostavax. A retrospective US cohort

study of 463 541 patients aged  $\geq 60$  years with inflammatory arthritis and/or inflammatory bowel disease found a lower rate of early HZ (within 42 days of vaccination, and hence possibly vaccine related) in vaccine recipients (and no cases in the subset of 633 patients exposed to a TNFi or other bDMARDs at the time of vaccination).<sup>41</sup> Vaccine efficacy was maintained in this population (adjusted hazard ratio 0.61; 95% CI: 0.52–0.71 for HZ risk after 42 days).<sup>41</sup>

There were no reported infectious complications following administration of Zostavax to 142 patients aged  $\geq 50$  years receiving bDMARDs, including RTX.<sup>42</sup> All patients missed one dose of bDMARD prior to vaccination, with Zostavax given at the time of the missed dose and the bDMARD re-started 2 weeks later. Patients receiving RTX had the vaccination at least 6 months following the last dose of RTX, and 2–4 weeks before the next dose.<sup>42</sup>

Zostavax functions as a booster on the assumption patients have been previously exposed to VZV and in healthy patients there is no need to check immune status against the virus prior to vaccination. However, in the immunocompromised it is prudent to check serological VZV status. If negative, vaccination with the lower dose live attenuated Oka varicella vaccine (Varivax or Varilrix) to prevent chickenpox may be considered (two doses separated by  $>4$  weeks for those aged  $\geq 13$  years). A new recombinant HZ subunit vaccine appears promising, but is currently not licensed in Australia.<sup>43</sup>

## Recommendations

All patients aged 50–80 years should be considered for HZ vaccination before commencing tsDMARDs or bDMARDs (Table 3). (In Australia, Zostavax is free for all adults  $\geq 70$  years of age from November 2016.)<sup>38</sup> Those being treated with a TNFi should be vaccinated after discussion regarding the risks and benefits of vaccinating with a live vaccine. While most of us would miss  $\geq 1$  dose of the bDMARD prior to vaccination with Zostavax, there is some evidence suggesting this may not be necessary. However, more data are required.

## Bacillus Calmette Guérin (BCG)

This involves a live vaccine derived from an attenuated strain of *Mycobacterium bovis* given to prevent disseminated tuberculosis in young infants and complications, such as meningitis.<sup>5</sup> Vaccination is not recommended except for indigenous neonates  $<12$  months of age or if  $<5$  years old and travelling to a high-risk country for an extended period (Table 3).<sup>5</sup> It is not recommended in immunocompromised patients due to the possible, but low risk of disseminated infection post-vaccination.<sup>2</sup> This low risk also

occurs following intravesical BCG as treatment of bladder cancer, which can be associated with reactive arthritis.<sup>44</sup>

Patients being considered for a TNFi are screened for *Mycobacterium tuberculosis* by assessing previous exposure, usually by an Interferon Gamma-Release assay (e.g. Quantiferon Gold) and a chest X-ray. If these suggest previous TB exposure, specialist advice should be sought regarding isoniazid prophylaxis prior to the TNFi.

## Diphtheria, tetanus and pertussis

Adults aged  $\geq 50$  years without a booster dose of diphtheria and tetanus toxoid in the preceding 10 years should receive the dTpa (diphtheria-tetanus-pertussis acellular) formulation, which will also protect against pertussis.<sup>5</sup> This differs from the DTPa formulation, which is used in children and contains smaller amounts of antigen.

## Measles, mumps and rubella (MMR)

The MMR vaccine is a live preparation and not recommended in immunosuppressed patients. Post-exposure prophylaxis for non-immune exposed adults should be undertaken with normal human immunoglobulin administered within 6 days of exposure.<sup>5</sup>

## Vaccination for travellers with AIIRD<sup>5,45,46</sup>

The use of DMARDs has improved the quality of life for AIIRD patients, who often now travel for prolonged periods. Overseas travel should be planned well ahead of time to allow appropriate vaccination. Routine vaccinations should be reviewed and travel-specific vaccinations assessed on an individual basis. Unfortunately, this is often not done.<sup>47</sup>

Advice from a travel medicine/ID specialist may be required due to the requirements for destination-specific vaccination.

**1 Hepatitis A (HAV):** Vaccination should be considered in all patients as HAV may be severe in the immunocompromised. Two doses of vaccine 6 months apart are normally recommended: the first dose prior to travel provides adequate protection in healthy individuals; a second dose boosts the immune response to provide long-term immunity. A study of 53 RA patients treated with a TNFi ( $n = 15$ ), TNFi + MTX ( $n = 21$ ) or MTX ( $n = 17$ ) found that a single dose of vaccine did not reliably result in seroconversion, but two doses of HAV vaccine at a 6-month interval provided protection.<sup>48</sup> A larger Dutch study of 740 patients on immunosuppression to treat a range of conditions found the overall sero-

protection rate after a single HAV vaccination was only 60%, but increased to 95% after a second vaccination.<sup>49</sup> Those using a TNFi had sero-protection rates of 46 and 79% after a first and second vaccination respectively. Corresponding rates for those on csDMARDs were 62 and 98%.<sup>49</sup> Intramuscular Ig may be required in immunocompromised individuals lacking a serological response to vaccination or where there is insufficient time before travel to allow two vaccine doses.

**2 Salmonella typhi:** Parenteral polysaccharide vaccine is recommended prior to travel to endemic areas. The oral live attenuated vaccine is contraindicated in the immunocompromised.

**3 Polio:** One booster vaccination with inactivated polio vaccine (Salk) is advised in adulthood, if not already received. The live attenuated (Sabin) vaccine is contraindicated in the immunocompromised.

**4 Meningococcus:** Vaccination with a quadrivalent vaccine is recommended for those visiting the sub-Saharan African 'meningitis belt' and is a requirement for travellers to Mecca, Saudi Arabia. The meningococcal quadrivalent conjugate vaccine (4vMenCV) is associated with better immunogenicity than the polysaccharide vaccine and is recommended for immunocompromised patients. Administration of the recombinant multi-component meningococcal B vaccine (4CMenB) can also be considered in those at high risk for meningococcal infection. This includes young children <24 months, adolescents 15–19 years of age, patients with complement deficiency, functional or anatomical asplenia, HIV and patients post-haemopoietic stem cell transplant.<sup>5</sup>

**5 Rabies:** Vaccination is recommended following a risk assessment regarding the likelihood of animal exposure. Travellers should avoid contact with dogs, cats, monkeys and bats. Any wound should be washed with soapy water and antiseptic. Post-exposure vaccination and use of human rabies immunoglobulin should be discussed with an ID physician.

**6 Japanese encephalitis:** Inactivated vaccine is recommended if travelling to high-risk areas, for example, many parts of Asia, India and Papua New Guinea, particularly if staying >4 weeks. The live vaccine (Imojev) should not be used in immunosuppressed individuals.

**7 Yellow fever:** Live vaccine that is contraindicated in the immunocompromised. Specialist advice should be sought if planning travel to an area where evidence of receipt of this vaccine is required.

**8 Cholera:** The Dukoral vaccine comprises inactivated whole cell *Vibrio cholerae* O1, in combination with a recombinant cholera toxin B subunit. Administration should be considered in the immunocompromised as they have a higher risk of diarrhoeal disease, especially if planning to visit an area with endemic/epidemic cholera.

## Infant vaccinations

Limited data suggest exposure to the TNFi, infliximab *in utero* and via breastfeeding does not prevent newborns from generating an immune response to inactivated vaccines.<sup>50,51</sup> Infants exposed to bDMARDs or thiopurines *in utero* or through breastfeeding should receive inactivated vaccines according to the normal childhood NIP. However, as immune responses may be sub-optimal, serological evidence of immunity may need to be checked at 7 months and boosters considered if antibody titres are inadequate.<sup>52</sup>

The safety of live vaccines in infants with exposure to bDMARDs or thiopurines *in utero* or through breast milk is unclear. The TNFi's adalimumab, infliximab, etanercept and golimumab are likely to be transmitted to the infant.<sup>53</sup> Certolizumab pegol lacks an Fc portion and so does not cross the placenta, nor does it appear to enter breast milk.<sup>54</sup> Live attenuated vaccines should not be given in the first few months of life as the immature infant immune response may allow vaccine viral replication, which may lead to clinical symptoms.<sup>53</sup>

The rotavirus vaccine is the only live vaccine routinely administered to infants <12 months old.<sup>5</sup> The other live vaccines (MMR and varicella) are recommended at ≥12 months of age. As administration of rotavirus vaccine to children of immunosuppressed mothers might cause clinical disease, some experts recommend not giving it to infants <6 months old born to mothers who received bDMARDs during pregnancy.<sup>55</sup> The likelihood of rotavirus infection is less in infants >6 months old, so if the vaccine is omitted, a 'catch-up' dose may be unnecessary. As rotavirus vaccination is part of the NIP,<sup>5</sup> even an un-immunised infant may be protected by 'herd' immunity. Others believe infants exposed to certolizumab pegol *in utero* or through breastfeeding can safely receive the rotavirus vaccine, and suggest its use in high-risk infants who have been exposed to TNFi, particularly where serum levels of these agents can be measured.<sup>54</sup>

## Conclusion

The use of DMARDs, tsDMARDs and bDMARDs has revolutionised the treatment of AIIRD. Patients with these conditions are at increased risk of infection due to the immunosuppressive effect of the AIIRD, comorbidities, and the use of an increasing range of DMARDs. Many infections are preventable with vaccination. However, vaccination may need to be performed prior to immunosuppression. Limited data regarding vaccine efficacy in patients with AIIRD make prescriptive guidelines difficult. A vaccination history should be part of the initial work-up in all AIIRD patients. Those caring for AIIRD patients should regularly consider vaccination to prevent infection.



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