

# Vaccination Recommendations for Adults With Autoimmune Inflammatory Rheumatic Diseases in Latin America

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**Background/Objective:** Patients with autoimmune inflammatory rheumatic diseases (AIRDs) are at increased risk of contracting severe infections and suffering complications, particularly when they are receiving immunomodulating therapy. Vaccination is an important means to prevent many potential infections and thereby reduce the morbidity and mortality associated with AIRD. The purpose of this consensus document is to provide health care professionals with recommendations for the vaccination of AIRD patients who reside in Latin America. The recommendations were developed by an expert committee from the region based on a review of the literature and their clinical experience.

**Methods:** The Americas Health Foundation (AHF) used PubMed and EMBASE to identify clinicians and scientists with an academic or hospital affiliation and who had published in the field of adult vaccination and rheumatic diseases since 2010. As a result of this effort, AHF convened an 8-member panel of clinical and scientific experts from Latin America. Both the AHF and panel members conducted a careful literature review to identify relevant publications in the areas of adult vaccination and rheumatology, and the sum of the articles identified was provided to the entire panel. Prior to the conference, panelists were each asked to prepare a written response to a salient issue on the subject, identified by AHF.

**Results and Conclusions:** During the conference, each response was edited by the entire group, through numerous drafts and rounds of discussion until a complete consensus on vaccination recommendations for adult patients with AIRDs was obtained, including 7 key recommendations.

**Key Words:** Autoimmune, immunosuppression, recommendations, rheumatic disease, vaccination

Patients with autoimmune inflammatory rheumatic diseases (AIRDs) are at increased risk of infectious diseases and their complications. Autoimmune inflammatory rheumatic disease comprises more than 2 dozen different diseases (e.g., rheumatoid arthritis [RA], systemic lupus erythematosus [SLE], systemic sclerosis, spondyloarthritis).<sup>1,2</sup> The heightened risk of infections in these patients is due to the nature of the diseases themselves, as well as the various immunomodulatory medications routinely prescribed. Some of the infectious complications, which in some cases even result in mortality, are vaccine-preventable diseases.<sup>3</sup> In patients with AIRD, the risk of acquiring a confirmed infection can be 1.7 times higher than in the general population. Also, the course of infection can be more severe; the risk of an infection requiring hospitalization has been shown to be 1.8 times higher than in healthy persons.<sup>4</sup>

Vaccination is both an individual right and a social responsibility; vaccination, in addition to providing direct personal benefit, is the responsibility of all citizens and their government because primary prevention of disease through vaccination also indirectly protects those who cannot be vaccinated. Vaccination is also one of the most cost-effective and cost-saving tools to reduce the burden of infections in a population. Adult vaccination, in particular, is often indicated for the primary prevention of infectious diseases or as a means to boost immunity when the previous immune response was insufficient. Special at-risk groups, such as patients with AIRD, require more attention.<sup>5</sup>

Thus, a robust and comprehensive adult vaccination program is extremely important. Although many reports have recently appeared<sup>2,6–8</sup> reviewing the safety and efficacy of vaccinations in adult patients with various rheumatic diseases, none have addressed the relatively unique needs and conditions in Latin America (e.g., yellow fever [YF], dengue, Argentine hemorrhagic fever) and specifically in patients with AIRD. One report from the Brazilian Society of Rheumatology recommended a vaccination strategy for patients with RA.<sup>5</sup> Other reports from Colombia addressed vaccination in patients with rheumatic diseases.<sup>9,10</sup> These initiatives are of great value because they stimulate the various rheumatology societies of other Latin American countries to develop the vaccination strategies for patients with rheumatic diseases.

In Latin America, it is difficult to find comprehensive epidemiological data that objectively evaluate the incidence of AIRD in all countries in the region. This uncertainty also extends to the incidence of vaccine-preventable diseases, the extent of which is very unclear.<sup>11</sup> The most frequently associated infectious agents in patients with AIRD, such as influenza virus, *Streptococcus pneumoniae*, and herpes zoster (HZ) virus, have established vaccination schemes. However, once again, information suggests that the vaccination coverage for these infectious diseases in patients with AIRD remains low.

Despite the worldwide shift from acute to chronic diseases that has occurred primarily because of improved sanitation and the advent of vaccination, the Latin American region still suffers

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from a large burden of infectious diseases. For example, the dengue virus disease represents one such case. The World Health Organization recommends that countries consider the introduction of the CYD-TDV vaccine in geographic environments (national or subnational) where epidemiological data indicate a high burden of the disease.<sup>12</sup> It is also worth mentioning other viral infectious diseases of epidemiological importance that are transmitted by mosquitoes (mosquito bites), such as Mayaro fever, chikungunya fever, and Zika fever, for which vaccines have not yet been developed. Another case is malaria disease; despite many decades of intense research and development effort, there is currently no commercially available malaria vaccine for adults.<sup>13,14</sup>

The aim of the present article is to provide health care professionals with a comprehensive and updated set of vaccination recommendations for the region. To achieve this goal, the Americas Health Foundation convened Latin American experts in rheumatic and infectious diseases and immunology to develop consensus recommendations for the vaccination of patients with AIRD. The authors of this report independently developed this consensus document, relying on a comprehensive review of the literature and their personal expertise.

## VACCINATION RECOMMENDATIONS

The 2 most important criteria when developing recommendations for vaccination are the safety and efficacy of the vaccine. Safety in AIRD is generally defined as the likelihood of the vaccine triggering either an adverse event or a flare of the autoimmune disease. Efficacy in AIRD is defined as the ability of the vaccine to prevent the disease for which the vaccine is given. For many vaccines, immunogenicity is a surrogate marker for efficacy. However, the timing of vaccination, the immunogenicity given by seroconversion, and the development of blocking antibodies in titers are all factors involved in conferring protection against infection, a result that does not happen in all vaccinated individuals. As a result, rheumatologists should consider the aforementioned variables when making vaccination decisions, as well as the activity or inactivity of the disease, and clinical conditions such as complement deficiency, hyposplenic/asplenic patients, therapy with or without immunosuppressive drugs, and immunosenescence, which is related to the chronicity and activity of the disease, as well with the chronological age of the patient. Following vaccination with some antigens, such as hepatitis B, it can be useful to request antibody titers to verify if protection has developed.<sup>15-17</sup> It is important to note, however, that no serological tests are commercially available to assess immune responses for some vaccines, including for those diphtheria, tetanus, and hepatitis A.

Because published studies regarding vaccine efficacy are often conducted in healthy subjects, few data exist on vaccine efficacy in patients with AIRD. Moreover, there are often no data on some of the diseases encompassed by AIRD. In this report, we extrapolated the data available for various rheumatic diseases to AIRD as a whole, because the diseases that fall under this category have many common features, and patients with AIRD receive many similar therapies.

Vaccines are generally safe for most patients with rheumatic diseases, considering that they neither worsen the activity nor reactivate manifestations of the disease. However, there are some concerns about the safety of live attenuated vaccines when administered in patients on immunosuppressive agents. In this context, the risk of vaccine-induced infection may be enhanced.

There are several kinds of vaccines available, such as inactivated (composed of killed whole viruses or bacteria, fractions of either, or toxoids), live attenuated viruses or bacteria, recombinant (produced by genetic engineering technology), and vaccines

developed in cell cultures (made by growing viruses in animal cell cultures). In addition, vaccines can be adjuvanted. An adjuvant is defined as a component that potentiates the immune response to an antigen and modulates it toward a desired immune response.<sup>18</sup>

Inactivated vaccines demonstrate a total lack of infectious potential and thus are safe.<sup>19</sup> Inactivated vaccines are not associated with a greater number of adverse events in AIRD patients or with the worsening of systemic inflammatory activity.<sup>5</sup> Inactivated or recombinant vaccines may have the disadvantage of inducing a less optimal immune response, sometimes requiring the use of adjuvants or transporting proteins (i.e., carriers) or the administration of booster shots.<sup>5,20-22</sup>

Live attenuated vaccines may be contraindicated in AIRD patients receiving immunosuppressive agents.<sup>2,6</sup> Vaccines in this group should preferably be administered before beginning immunosuppressive therapy to ensure that viral replication is over before immunosuppression occurs. When the patient is already receiving immunosuppressive treatment, vaccination should be postponed until therapy has been discontinued for an appropriate period of time (e.g., 1 month after glucocorticoids, 3 months after cytotoxic and human immunoglobulin treatment, 6 months after rituximab [RTX], or a period corresponding to 4 half-lives for other biologic agents).<sup>5</sup> Moreover, if a patient requires more than 1 live attenuated vaccine, to ensure vaccine efficacy, all such vaccines must either be administered at 1 time or be separated from each other by at least 4 weeks. Inactivated vaccines, however, may be administered at any interval independent of the administration of other inactivated or live attenuated vaccines.

In recent years, more data on the safety of live attenuated vaccines in patients with rheumatic diseases have been published, and there is increasing evidence to support vaccination with such vaccines in patients on immunosuppressive therapy. The use of immunosuppressive drugs such as methotrexate (MTX) (at a dose of <0.4 mg/kg per week) and azathioprine (at a dose of <3.0 mg/kg per day), low doses of glucocorticoids (<20 mg/d prednisone or equivalent), or short-term glucocorticoids (<14 days) or local glucocorticoid injections are not considered sufficiently immunosuppressive to question the safety of live attenuated vaccines. However, most of the time, these vaccines may still be contraindicated for patients on higher doses of immunosuppressive therapy.<sup>2</sup>

The first step in improving vaccination status in the individual patient is to assess his/her actual vaccination profile.<sup>23</sup> The vaccination history should be taken at the first visit, to the rheumatology outpatient clinic, and at regular intervals thereafter. At the initial visit, the patient should be reminded of the importance of vaccination, and this should be re-explained at office visits or by a paper reminder. For patients who did not receive the appropriate vaccination schedule for any particular vaccine, vaccination should continue with the missing doses and not restart the schedule. It is always beneficial to administer vaccines as soon as possible after the diagnosis of AIRD and prior to the initiation of immunosuppressive drugs.

What follows are the recommendations for the administration of specific vaccines in adults with AIRD in Latin America. The Table provides a synopsis of the recommendations discussed in the following sections.

## Influenza Vaccine

There are several types of influenza vaccines available including inactivated vaccine (trivalent or quadrivalent), live attenuated virus vaccine, recombinant vaccine, and a vaccine developed in cell culture. Latin American countries almost entirely use the inactivated influenza vaccine.

Many published studies have assessed the immunogenicity, efficacy, and safety of nonadjuvanted trivalent inactivated influenza (TIV) vaccine, adjuvanted TIV vaccine, or adjuvanted monovalent vaccine (A/H1N1) in RA patients or in patients with other AIRDs.<sup>24,25</sup> A small number of RA patients who were undergoing treatment with RTX and vaccinated with nonadjuvanted TIV did not achieve sufficient protection to prevent influenza.<sup>26</sup> Another study using nonadjuvanted TIV demonstrated that although the immune response was lower in RA patients treated with RTX, seroprotection was achieved for some influenza antigens.<sup>27</sup> Given that most studies achieved at least a partial response, the administration of nonadjuvanted TIV is not precluded in RA patients undergoing RTX treatment.<sup>27</sup> However, most experts agree that the response to influenza vaccination can be improved if the vaccine is given 4 weeks before, or 6 months after, RTX administration.<sup>24</sup> In studies that assessed the response to influenza vaccine in RA patients, MTX and therapy with tumor necrosis factor (TNF) inhibitors did not affect immunogenicity.<sup>28,29</sup>

Treatment with abatacept in RA patients has been found to significantly reduce the humoral immune response to influenza vaccination.<sup>30</sup> In contrast, a more recent study showed that abatacept-treated RA patients are able to develop an appropriate immune response after seasonal influenza vaccination.<sup>31</sup> Thus, it is unclear whether treatment with abatacept results in a diminished immune response to influenza vaccination.

Patients with RA undergoing treatment with tocilizumab (TCZ), with or without MTX, who were vaccinated against influenza, showed that the vaccine conferred protection and that neither severe adverse effects nor RA flares were observed.<sup>32</sup>

Tofacitinib showed no impairment of seroconversion after influenza vaccine administration in patients with RA, although seroprotection was not achieved in all treated patients.<sup>33,34</sup>

Another study showed that in many AIRDs vaccination with nonadjuvanted influenza H1N1 did not find either moderate or severe adverse effects after vaccination.<sup>35</sup> In order to improve the immunogenicity of influenza vaccines, adjuvanted vaccines have recently been developed. Most of the adjuvants, which are oil-in-water squalene based, helped produce an adequate immune response and had no adverse effect or impact on disease status.<sup>36–38</sup> However, some adjuvants have been implicated in the new syndrome named ASIA (autoimmune/inflammatory syndrome induced by adjuvants), which describes clinical features of 5 immune-mediated conditions.<sup>39,40</sup> In this regard, more studies are needed to evaluate this outcome in patients with AIRD.<sup>41</sup>

The above studies support the annual administration of influenza vaccine for all patients with AIRD. It is not possible to establish before vaccination which patient will respond better to influenza vaccine based on disease status or treatment. No flares of rheumatic disease have been clearly demonstrated after vaccination even with the use of adjuvanted vaccines. Timing of vaccination depends on local epidemiology and national guidelines. The influenza vaccine is considered very safe and has been used worldwide in annual campaigns.<sup>6,27,42</sup> To provide additional protection to AIRD patients against influenza, influenza vaccination of household contacts is recommended.

## Pneumococcal Vaccine

Respiratory tract infections are very common among patients with AIRD. *Streptococcus pneumoniae* is responsible for almost half of all cases of community-acquired pneumonia and many other invasive diseases such as meningitis and sepsis. There are 2 vaccines available for the adult population: 13-valent conjugated pneumococcal vaccine (PCV13) and 23-valent polysaccharide pneumococcal vaccine (PPV23). There are several studies that

evaluated the response of these vaccines in patients with AIRD undergoing different treatments.

Two studies show that TCZ administered as monotherapy to patients with RA does not impair antibody response after PPV23 vaccination.<sup>22,43</sup> Among patients starting tofacitinib, there is a decreased humoral response after PPV23 administration compared with placebo, particularly among those who also received MTX.<sup>33</sup> In those studies demonstrating a decreased humoral response, however, one should not conclude that the patients were not protected against pneumococcal infection. Regarding long-term protection, data show that antibody levels against PPV23 antigens are preserved for at least 10 years in patients with AIRD (across all ages) who are treated with TNF inhibitors, TCZ, and low-dose prednisone.<sup>44</sup> Another study showed that vaccination with PCV13 in patients receiving etanercept (ETN) for RA is safe and effective.<sup>45</sup>

There are few studies that assess actual protection against disease by vaccination. One such study showed that the first conjugated pneumococcal vaccine, the heptavalent vaccine, achieved favorable results reducing by nearly half the risk of serious pneumococcal infections in vaccinated compared with nonvaccinated AIRD patients.<sup>46</sup> Regardless of the impact of treatment or other factors (such as age) on the response to pneumococcal vaccines in patients with RA or other rheumatic diseases, these vaccines should be administered to all AIRD patients.

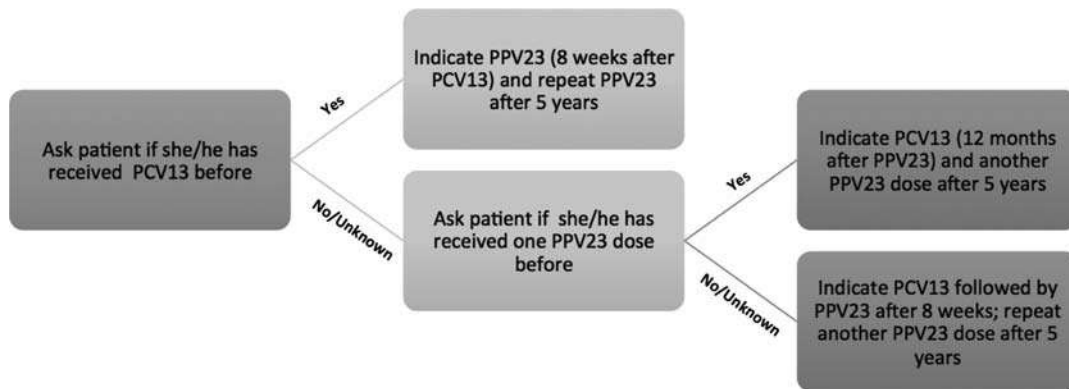
Considering that PCV13 showed an improved immune response against serotypes common to both vaccines and that PPV23 covers more pneumococcal serotypes than PCV13, it is recommended to use a sequential vaccination scheme that consists of PCV13 as priming and then PPV23 at least 8 weeks later for all immunocompromised patients, including those with rheumatic diseases.<sup>47</sup> A booster dose of PPV23 5 years after the first dose is also recommended. A third dose is recommended after age 65 years when more than 5 years has elapsed since the last dose. An algorithm for pneumococcal vaccination in AIRD patients is shown in the Figure 1.

With regard to safety, both vaccines PCV13 and PPV23 are well tolerated in patients with AIRD. The adverse events are mild and limited to the vaccine application site.<sup>43</sup> Moreover, data suggest that pneumococcal vaccines do not induce exacerbation of RA.<sup>48</sup>

## Herpes Zoster Vaccine

There is an increased risk of the development of HZ in AIRD patients.<sup>49</sup> Risk factors related to HZ infection include age, female sex, and the use of glucocorticoids, biologics, and tofacitinib (which doubled the risk compared with biologics).<sup>50</sup> A live attenuated vaccine is shown to be efficacious for preventing HZ in persons 50 years or older in the general population and even more so for avoiding postherpetic neuralgia.<sup>51,52</sup> There was no association of an increased incidence of HZ within 42 days after vaccination in AIRD patients, thus suggesting the vaccine is safe.<sup>53</sup> In addition, in this study, 2 years after vaccine administration, the incidence of HZ in vaccinated patients was less than that observed in unvaccinated individuals, thus demonstrating that the vaccine is effective. This observation suggests that HZ vaccination is indicated for use in patients with AIRD, subject to an individualized risk-benefit analysis. There is also an adjuvanted nonlive HZ vaccine under development that has demonstrated a 97% efficacy in a 2-dose schedule and that may be a useful tool to immunize immunosuppressed individuals in the future.<sup>54</sup>

The current recommendations for HZ live attenuated vaccine administration in patients with AIRD include those who receive low-dose, short-term, and local glucocorticoids, MTX (<0.4 mg/kg per week), or azathioprine (<3.0 mg/kg per day). In those who receive other immunosuppressive agents, the decision about vaccine



**FIGURE 1.** Recommended pneumococcal vaccination algorithm for patients with AIRD. Adapted from the Centers for Disease Control and Prevention (CDC).<sup>47</sup>

administration should be made on a case-by-case basis, and vaccination should either be administered at least 2 weeks before immunosuppression begins or be deferred until at least 4 half-lives after therapy discontinuation.<sup>55</sup> The recurrence of HZ infection can also be prevented by the use of the HZ vaccine.<sup>56</sup>

### Hepatitis B Vaccine

In most Latin American countries, among adults, hepatitis B vaccination is provided only to those at high risk. The vaccine is developed by recombinant DNA technology and is immunogenic and safe in patients with AIRD. In 1 study, 68% of immunized RA patients developed an adequate immune response, and their treatment with low-dose glucocorticoids, MTX, azathioprine, sulfasalazine, or antimalarial drugs did not affect the antibody response.<sup>57</sup> In addition, in SLE and Behçet disease patients, the vaccine also produced an adequate response regardless of treatment.<sup>58,59</sup>

In all AIRD patients, serologic status for hepatitis B should be assessed prior to treatment initiation with immunosuppressive drugs, particularly in those patients who are going to receive biological agents. Patients with negative serology for hepatitis B should receive a complete hepatitis B vaccination scheme (0, 1, and 6 months). In all AIRD patients, a serological test to assess vaccine response should be performed 1 to 2 months after the third dose; an antibody response of 10 IU/mL is adequate.<sup>60</sup> For those with an inadequate response, it is recommended to repeat the entire vaccination scheme and retest to determine the response.

The hepatitis B vaccine is also considered safe in patients with AIRD. In RA and SLE, for example, vaccination against hepatitis B has been associated with neither a significant deterioration of any clinical measure or laboratory test associated with disease activity nor other important adverse events.<sup>57,58</sup>

### Human Papillomavirus Vaccine

Patients with AIRD may be at a higher risk of cervical cancer because of their disease and the immunosuppressive medications they receive.<sup>61,62</sup> The human papillomavirus (HPV) vaccine is an inactivated virus vaccine. Studies on the immunogenicity and safety of the vaccine in patients with AIRD show that it is both safe and effective.<sup>63</sup> There are 2 vaccines available in Latin America. One vaccine is bivalent (HPV2), and the other is quadrivalent (HPV4); both are inactivated, virus-like particles. Both contain the 2 serotypes mostly associated with cervical cancer, 16 and 18, and the HPV4 also contains serotypes 6 and 11, which are associated with the development of genital warts. There is a nonavalent vaccine, soon to be available in Latin America, which includes 5 additional serotypes (31, 33, 45, 52, and 58) that are

associated with cervical and other HPV-related cancers.<sup>64</sup> Both of the available vaccines are highly efficacious to prevent anogenital lesions associated with HPV16 and HPV18 in men and women.

With regard to vaccine immunogenicity, in a study of women with inflammatory bowel disease undergoing biologic treatment with TNF inhibitors (infliximab or adalimumab), a high rate of seropositivity was obtained after 3 doses of HPV4 (100% for serotypes 6, 11, and 16 and 96% for serotype 18).<sup>65</sup> There are no data regarding the efficacy of HPV vaccines in RA patients. However, the HPV4 vaccine is well tolerated and reasonably effective in patients with stable SLE and does not induce an increase in disease activity. It is worth mentioning that although there is a 2-dose scheme for women younger than 15 years, in immunocompromised hosts of any age, the 3-dose vaccination schedule is the only one recommended. Based on the burden of illness, the risk of development of malignant HPV-associated disease in AIRD patients, and considering the safety and efficacy of the vaccine in studies of patients with AIRD,<sup>63,65</sup> the HPV vaccine is recommended for young women and men with AIRD.

### Hepatitis A Vaccine

Inactivated vaccines, such as hepatitis A virus vaccine, can be safely administered to immunosuppressed patients. This vaccine should be administered to AIRD patients who are seronegative for hepatitis A.<sup>5</sup> Regarding efficacy of hepatitis A virus vaccine in patients with AIRD undergoing treatment with MTX and TNF inhibitors, a 2-dose scheme with a 6-month interval provided 86% protection for RA patients.<sup>20</sup>

### Tetanus/Diphtheria and Tetanus/Diphtheria/Pertussis Vaccine

The vaccine is initially given in infancy as part of a basic vaccination schedule and, subsequently, to maintain protection against these diseases. In adults, the tetanus/diphtheria vaccine should be administered in all adults, including AIRD patients, as a booster dose every 10 years. Pertussis is not infrequent in adults, who are the main transmitters of this disease to infants, particularly breastfeeding infants who have a high risk of death from the disease.

The vaccine available to prevent pertussis is a denominated acellular, inactivated vaccine and is only available combined with diphtheria and tetanus (Tdap). As with all other inactivated vaccines, it is safe in AIRD patients.<sup>6</sup> In patients with AIRD receiving RTX in the preceding 6 months, protection against tetanus might be diminished, and immunoglobulin against tetanus should be administered in case of tetanus exposure.<sup>5,66</sup> In some countries of the region, Tdap is recommended for women in every pregnancy in

order to improve protection of the newborn against pertussis and tetanus. We recommend that Tdap be given in each pregnancy after week 20 in all patients with AIRD.

### Meningococcal Vaccine

Meningococcal monovalent (serogroup C) and tetravalent (serogroups A, C, W, Y) conjugated vaccines are available. Also, a vaccine against *Neisseria meningitidis* serogroup B developed by reverse vaccinology is available in some countries in Latin America. There are few data published on the efficacy of these vaccines in AIRD patients. One study showed that serogroup C conjugated vaccine does not produce flares of juvenile idiopathic arthritis (JIA) and generates adequate antibody levels, even in patients receiving high doses of immunosuppressive medication.<sup>67</sup> Meningococcal vaccines should be given every 3 to 5 years to AIRD patients who have functional or anatomical asplenia or complement deficiency. The type of vaccine administered depends on the epidemiology of the meningococcal diseases and serogroup distribution in each country.<sup>2</sup>

### Yellow Fever Vaccine

Yellow fever is endemic to limited areas within Latin America, primarily in tropical areas, has no effective treatment, and carries a high level of mortality. The national immunization schedules of some Latin American countries include YF vaccination in childhood for residents of endemic areas and recommend administration to travelers in these areas. Also, because of International Health Regulations,<sup>68,69</sup> YF vaccination may be a requirement for travelers from YF endemic countries to other countries free of the diseases, but where the vector is present. In this case, when there is no risk of acquiring the disease, AIRD patients can obtain a waiver for YF vaccination from the health authorities.

The YF vaccine is a live-attenuated vaccine that is highly immunogenic and provides lifelong protection.<sup>70</sup> Although the risk of serious adverse events is rare, reports indicate that YF vaccine can cause 2 clinically relevant syndromes known as YF vaccine-associated neurotropic disease and YF vaccine-associated viscerotropic disease (YEL-AVD).<sup>71</sup> Yellow fever vaccine-associated viscerotropic disease generally occurs 3 to 5 days after vaccination and is characterized by fever, malaise, jaundice, oliguria, cardiovascular instability, and hemorrhage secondary to a platelet disorder.<sup>72</sup> Increased risk of developing YEL-AVD might be associated with autoimmune diseases. Cases of YEL-AVD have been reported in patients with SLE, polymyalgia rheumatica, Crohn disease, ulcerative colitis, and other AIRDs.<sup>5,73</sup>

On the other hand, a Brazilian retrospective study evaluated 70 patients with AIRD who were inadvertently vaccinated against YF. The therapeutic schemes included MTX, glucocorticoids, sulfasalazine, leflunomide, cyclophosphamide, and biological agents. Among these patients, adverse reactions were no more frequent than among immunocompetent individuals.<sup>74</sup> Another Brazilian study included 17 RA patients revaccinated against YF (which is no longer necessary)<sup>75</sup> while receiving infliximab therapy, and there were also no relevant adverse events.<sup>76</sup> Thus, it seems that YF vaccination may be safe, but an individualized assessment of risk-benefit should be conducted.<sup>5</sup>

### Varicella Vaccine

History of varicella infection should be verified in persons with AIRD at the time of the disease's diagnosis. Those who have had varicella or were vaccinated against it can be considered immune to the disease. For those who are seronegative for varicella, the vaccine in a 2-dose schedule with an 8-week interval can be administered before the initiation of treatment for AIRD. It is worth remembering that this vaccine, like other live-attenuated

vaccines, may be contraindicated to immunosuppressed individuals, especially when the risks of acquiring the disease surpass the potential risks of vaccination.<sup>5</sup>

### Measles, Mumps, and Rubella Vaccine

This live attenuated virus vaccine is recommended in most Latin American countries and is generally administered in a 2-dose schedule after the first year of life and during early childhood; it provides protection for life. In adults with AIRD who have not received both doses at the appropriate times, a serological assessment should be performed. If serology is negative for any of the 3 diseases, 2 doses of the measles, mumps, and rubella (MMR) vaccine, separated by at least 4 weeks, should be administered after assessment of the risks and benefits, keeping in mind that it is a live attenuated vaccine.<sup>8</sup> While measles and rubella have been eliminated in Latin America, it is common for mumps outbreaks to appear in adolescents and young adults.

The MMR vaccine has a good safety profile and is well tolerated. The safety of the MMR vaccine was assessed in patients with JIA.<sup>77,78</sup> In a randomized trial, MMR booster vaccination, compared with no booster, did not result in worse JIA disease activity and was immunogenic in children with JIA who had undergone primary immunization.<sup>79</sup> There are no studies on the safety of the MMR vaccine in adults with AIRD.<sup>5</sup>

### Dengue Vaccine

Dengue is a viral infection transmitted by the mosquito of the genus *Aedes* that can affect a large proportion of the population that live in Latin America. There are 4 dengue virus serotypes (DEN1, DEN2, DEN3, and DEN4), and the disease is characterized by fever, rash, malaise, myalgia, headache, nausea, and vomiting and can evolve to severe dengue or death in a few cases, particularly in those individuals who have been previously infected. Recently, a recombinant, live attenuated vaccine that contains all of the virus serotypes has become available in some countries of the region and is mainly directed to adolescents and young adults who live in endemic areas. The vaccine is given in a 3-dose schedule (0, 6, and 12 months). The efficacy in adolescents is greater than 60% to prevent disease and is even more efficacious for the prevention of dengue complications.<sup>80</sup> There are no data available regarding efficacy and safety of this vaccine in AIRD, but considering that it is a live-attenuated vaccine, it may be contraindicated in those AIRD patients receiving high-dose immunosuppressive drugs.

### Argentine Hemorrhagic Fever Vaccine

Argentine hemorrhagic fever is a viral disease produced by the arenavirus Junin that is transmitted by rodents and is mainly observed in rural areas in the central region of Argentina. The live-attenuated vaccine (Candid 1) has been found to have 95% efficacy and should be given as 1 dose to persons 15 years or older who live or work in an endemic area.<sup>81</sup> No data are available regarding the administration of this vaccine in adults with AIRD. Considering that it is a live-attenuated vaccine, it may be contraindicated in patients receiving high doses of immunosuppressive drugs.

### Tuberculosis Vaccine

Tuberculosis is a very prevalent disease among adults in most Latin American countries; however, vaccination is not indicated in adults. Bacillus Calmette-Guérin vaccine, primarily used to prevent severe forms of tuberculosis in newborns, does not protect individuals already infected with *Mycobacterium tuberculosis*, and its administration in adults, which includes adult AIRD patients,

**TABLE 1. Immunization Recommendations for Adults With AIRD in Latin America**

Vaccines	Dosage	Can Treatment Adversely Impact Vaccination Efficacy?	Can Treatment Adversely Impact Vaccination Safety?	Caveats/Issues
Influenza (I) (inactivated, adjuvanted, and nonadjuvanted)	1 Annual dose	Yes, rituximab and abatacept may diminish	No	Vaccination of household contacts and pregnant women is important.
Pneumococcal vaccines				
13-Valent conjugated (PCV13) (I)	1 Dose	Yes, immunosuppressors may diminish	No	For immunization scheme, see Figure.
23-Valent polysaccharide (PPV23) (I)	2 Doses (5-y interval); additional dose after age 65 y (if last dose was given before age 60 y)			
Herpes zoster (LA)	1 Dose for persons aged >50 y	No	Yes, the assessment of risk-benefit is prudent	Live attenuated vaccines may be indicated in patients receiving low-dose <sup>a</sup> immunosuppressive drugs.
Hepatitis B (I)	3 Doses (0, 1, and 6 mo)	Yes, immunosuppressors may diminish	No	Check serology before and after vaccination.
HPV (I)	3 Doses (0, 1, and 6 mo) for bivalent; 3 doses (0, 2, and 6 mo) for quadrivalent	No	No	Women—no age limit; men—up to age 26 y (may also be beneficial at later ages).
Hepatitis A (I)	2 Doses, minimum interval of 6 mo	Yes, with TNF inhibitors and MTX, but very limited data	No	Vaccines should be given only in patients who are seronegative for hepatitis A.
Tdap or Td (tetanus/diphtheria) (I)	Basic vaccination schedule followed by booster shot with Td every 10 y	Yes, RTX may diminish	No	Vaccinate pregnant women after week 20 with Tdap.
Meningococcal vaccines (I)	Only for patients with functional or anatomical asplenia or complement deficiency: 1 dose every 3–5 y	No data	No	Recommendations vary across countries and year to year, depending on bacterial serogroup.
YF (LA)	1 Dose for those living in endemic areas or traveling to such areas	No (limited data)	Yes (limited data); assess risk-benefit	Live attenuated vaccines may be indicated in patients receiving low-dose <sup>a</sup> immunosuppressive drugs.
Varicella (LA)	2 Doses, 8-wk interval in patients with negative history for varicella zoster infection or vaccination	No data	Yes (limited data); assess risk-benefit	Live attenuated vaccines may be indicated in patients receiving low-dose <sup>a</sup> immunosuppressive drugs.
MMR (LA)	Two doses at least 4 wk apart in those with negative serology for any of the 3 diseases	No data	Yes (limited data); assess risk-benefit	Live attenuated vaccines may be indicated in patients receiving low-dose <sup>a</sup> immunosuppressive drugs. Patients aged >50 y are considered immune.
Dengue (LA)	Doses (0, 6, and 12 mo)	No data	No data; assess risk-benefit	Live attenuated vaccine may be contraindicated in persons receiving high-dose immunosuppressive drugs.

Argentine hemorrhagic fever (LA)	1 Dose given to persons aged ≥15 y	No data	No data; assess risk benefit	Vaccine administration limited to persons residing in endemic areas of Argentina. Live attenuated vaccine may be contraindicated in persons receiving high-dose immunosuppressive drugs.
Tuberculosis (bacillus Calmette-Guérin) (LA)	Not indicated for adults	No data	No data	—

<sup>a</sup>Low dose is defined as glucocorticoids (<20 mg/d prednisone or equivalent), short-term corticosteroids (<14 days), local corticosteroid injections, or MTX (<0.4 mg/kg per week) or azathioprine (<3.0 mg/kg per day) at the doses indicated.  
 I indicates inactivated; LA, live attenuated.

does not provide protection against disease.<sup>5</sup> Therefore, treatment against latent tuberculosis infection or early detection of the infection in immunosuppressed hosts such as AIRD patients is of the utmost importance. Since the development of TNF inhibitors, some immunosuppressive biologics have been associated with an increased risk of reactivation of latent tuberculosis infection and new cases of TB.<sup>8,2</sup>

**Other Vaccines**

There is a group of vaccines that may be considered in special situations and that deserve mention despite not being included in the Table 1.

- Polio  
*Bivalent oral polio vaccine.* This is a live attenuated vaccine and is contraindicated for AIRD patients and members of their household. Thus, AIRD patients and members of their household should instead receive the inactivated polio vaccine.  
*Inactivated polio vaccine.* Inactivated polio vaccine is a parenteral vaccine and is indicated for infant household members of patients with AIRD and for patients with AIRD who plan to travel to polio endemic areas.
- Rabies: The rabies vaccine is an inactivated virus vaccine and should be considered in special situations, such as:  
 pre-exposure: in case of occupational risk or for travelers who plan to spend long periods in countries or areas where the disease is endemic; and  
 postexposure: in case of an accident presenting the potential risk of contracting rabies disease, which is both rare and fatal.
- Typhoid fever  
 The inactivated vaccine is recommended (at least 2 weeks before travel) for travelers going to a destination with unfavorable sanitary conditions.
- *Haemophilus influenzae* type B  
 The *H. influenzae* type B inactivated vaccine is 1 dose given to AIRD patients who have functional or anatomical asplenia or complement deficiency.

**Other Considerations**

It is important to note that patients with AIRD who are planning to travel should consult an infectious disease specialist to receive the appropriate vaccination indications, based on the destination and conditions of travel, and at least 6 months prior to departure.

Finally, one especially vulnerable group to consider is pregnant women with AIRD. Both pregnant women and their fetuses are at an increased risk of infectious diseases and their complications. Therefore, it is essential that they receive the influenza vaccine in any trimester of gestation, as well as the Tdap vaccine after the 20th week of pregnancy. Both of these vaccines are inactivated, safe, and effective.

**KEY RECOMMENDATIONS**

1. Assess vaccination status upon diagnosis of AIRD.
2. Complete vaccination of household contacts is recommended to provide additional protection of immunocompromised persons.
3. Vaccinations should ideally be administered prior to initiating immunosuppressive therapy.

4. For patients who did not receive the appropriate vaccination schedule for any particular vaccine, continue with the missing doses and do not restart the schedule.
5. Vaccination with live attenuated vaccines may be permissible during treatment with immunosuppressive agents after an individualized risk-benefit analysis is performed. Vaccination with inactivated vaccines is safe.
6. Because of safety and efficacy, live attenuated vaccines should ideally be administered at least 2 weeks before immunosuppressive therapy begins or be deferred until at least 2 weeks after discontinuation of synthetic immunosuppressive drugs; 4 weeks after discontinuation of glucocorticoids; 12 weeks after discontinuation of immunoglobulins, cytotoxic drugs, or alkylating agents; and, in the case of biological agents, at least 4 half-lives after discontinuation of therapy.
7. If an AIRD patient requires more than 1 live attenuated vaccine, all such vaccines must either be administered at one time or be separated from each other by at least 4 weeks. Inactivated vaccines may be administered at any interval independent of the administration of other inactivated or live attenuated vaccines.

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