2012 Brazilian Society of Rheumatology Consensus on vaccination of patients with rheumatoid arthritis

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ABSTRACT

Objective: To elaborate recommendations to the vaccination of patients with rheumatoid arthritis (RA) in Brazil. **Method:** Literature review and opinion of expert members of the Brazilian Society of Rheumatology Committee of Rheumatoid Arthritis and of an invited pediatric rheumatologist. **Results and conclusions:** The following 12 recommendations were established: 1) Before starting disease-modifying anti-rheumatic drugs, the vaccine card should be reviewed and updated; 2) Vaccines against seasonal influenza and against H1N1 are indicated annually for patients with RA; 3) The pneumococcal vaccine should be indicated for all patients with RA; 4) The vaccine against varicella should be indicated for patients with RA and a negative or dubious history for that disease; 5) The HPV vaccine should be considered for adolescent and young females with RA; 6) The meningococcal vaccine is indicated for patients with RA only in the presence of asplenia or complement deficiency; 7) Asplenic adults with RA should be immunized against *Haemophilus influenzae* type B; 8) An additional BCG vaccine is not indicated for patients diagnosed with RA; 9) Hepatitis B vaccine is indicated for patients with RA who are negative for antibodies against HBsAg; the combined hepatitis A and B vaccine should be considered; 10) Patients with RA and at high risk for tetanus, who received rituximab in the preceding 24 weeks, should undergo passive immunization with tetanus immunoglobulin in case of exposure; 11) The YF vaccine is contraindicated to patients with RA on immunosuppressive drugs; 12) The above described recommendations should be reviewed over the course of RA.

Keywords: rheumatoid arthritis, vaccination, immunization, adult.

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INTRODUCTION

Patients with rheumatoid arthritis (RA) are at increased risk for infections.[1,2] Infectious outcomes in RA are among the major causes of death in those patients, and the mortality related to those events can be up to ten times that of the general population.[3] Patients with severe disease and/or comorbidities are most often affected.[1,4]

Several factors have been associated with that increased susceptibility to infections. One of those major factors is the use of immunomodulators for the treatment of the disease itself, in particular biologics, whose indication has been increasingly frequent and early in the course of disease. The introduction of new agents in the therapeutic arsenal of rheumatology interferes with several points of the immune system.[5]

Knowing that vaccination is the most effective preventive measure for reducing the occurrence of infection at any age group, the vaccine chart should be reviewed and updated before starting either synthetic or biological disease-modifying anti-rheumatic drugs (DMARDs) (Table 1). However, that is often neglected in routine rheumatological practice, leaving a large number of patients unprotected against infectious diseases that could be prevented. Several studies have shown that the vaccine coverage of patients with rheumatic diseases worldwide is suboptimal.[6–8]

Some of the vaccines available can have their immunogenicity reduced depending on the patient's immunosuppression status; however, international experience has shown that the administration of most vaccines comprised in the vaccine calendar is safe, considering that they neither worsen the activity nor reactivate manifestations of rheumatic diseases.[9]

The present consensus aimed at reviewing the literature and elaborating recommendations for the indication of vaccines in patients with RA, considering the epidemiological scenario and the resources of medical care in Brazil. The purpose of this document is to summarize the current position of the Brazilian Society of Rheumatology (SBR) on the subject, to guide Brazilian physicians, especially rheumatologists.

METHOD OF CONSENSUS ELABORATION

The method for elaborating the recommendations included a literature review and the opinion of expert members of the SBR Committee of Rheumatoid Arthritis and of an invited pediatric rheumatologist. The bibliographic survey included publications in the MEDLINE, SciELO, PubMed and EMBASE databases up to February 2012. The recommendations were written and reassessed by all participants during multiple rounds of questioning and corrections performed via internet. Based on the considerations, the experts provided recommendations on the vaccination of patients diagnosed with RA (Table 2).

Inactivated or Recombinant Vaccines

The great advantage of inactivated vaccines is the total lack of infectious potential of the pathogenic agent: such vaccines do not trigger the disease, but maintain the immunologic characteristics of the agent. Inactivated or recombinant vaccines, however, have the disadvantage of inducing a suboptimal immune response, requiring sometimes the association of adjuvants or transporting proteins and the administration of booster shots.

Adhesion to the Brazilian guidelines is recommended for the following vaccines that do not contain live organisms: influenza vaccine (intramuscular – IM); pneumococcal vaccine (13V-conjugated and 23-polysaccharide); tetanus vaccine; diphtheria vaccine; pertussis vaccine; *Haemophilus influenzae* type B (Hib) vaccine; hepatitis A and B vaccine; poliomyelitis vaccine (inactivated – VIP); meningococcal vaccine; human papillomavirus (HPV) vaccine; typhoid fever vaccine (IM); and rabies vaccine.[10] Such vaccines can be safely administered, preferentially 14 days before starting DMARDs, in an attempt to reach the expected immunogenicity. When the vaccine chart cannot be updated prior to the beginning of treatment, all those vaccines can be administered to patients with RA, even those on corticosteroids (CS) and/or synthetic or biological DMARDs, based on their safety demonstrated in several studies;[9,11] the response, however, might be impaired.

Influenza virus vaccine

Respiratory infections are common among patients with RA and have high mortality rate.[12] Vaccination against influenza has proved to reduce the number of hospital admissions and mortality due to respiratory infections in elderly patients, being effective even in patients on DMARDs.[13]

Response to the influenza vaccine seems not to be impaired in patients on anti-TNF agents, even when associated with methotrexate (MTX).[14–16] However, one author has reported a reduced response to that vaccine in patients on infliximab or etanercept associated with MTX.[17] Likewise, one study conducted in Brazil assessing the vaccine against H1N1 influenza has found, in addition to a good safety profile, a reduction in the seroprotection of patients with RA, regardless of disease activity. Methotrexate was the only DMARD associated with a reduced response to that vaccine.[11]

There is also evidence of an impaired response to pneumococcal and influenza vaccines when administered to patients on rituximab.[13,18,19] The response to the influenza vaccine (including vaccine against influenza A and H1N1) is particularly impaired when administered early, 4–8 weeks after the administration of rituximab. Thus, influenza vaccines should be administered before starting rituximab or 6 months after its first infusion and 4 weeks before its next dose.[20]

The influenza vaccine is considered safe, and has been used in Brazil in annual campaigns for the population aged 60 years and over and for adults and children over the age of 6 months in special clinical situations, such as patients with RA.[10] It is contraindicated only to patients with history of allergy to egg or to the vaccine itself, as well as to those who had Guillain-Barré syndrome up to 6 weeks after receiving that vaccine.

Seasonal and H1N1 influenza vaccines are indicated annually to patients with RA.

Pneumococcal vaccine

Bacterial infections of the respiratory tract are more common in patients diagnosed with RA as compared with the general population and contribute to increase morbidity and mortality.[21,22] Thus, vaccination against *Streptococcus pneumoniae* (pneumococcus) is highly relevant for patients with RA.

Table 1
Immunization schedule according to vaccine and age group for adults in Brazil

Vaccine	Age group (years)					Vaccine availability
	18–26	27–49	50–59	60–64	≥ 65	
Influenza¥	1 annual dose					Public health units/ CRIE
Tdap: tetanus, diphtheria, pertussis¥	Complete basic vaccination schedule: booster shot with Tdap and, then, one dose of dT every 10 years#				Booster shot of dT every 10 years	Public health units Acellular vaccine at private clinics
IPV (Salk)¥	Complete basic vaccination schedule: booster shot with 1 dose##					CRIE/private clinics
Tdap + IPVθ	Complete basic vaccination schedule: booster shot with Tdap from the age of 7 years onwards and, then, 1 dose of dT every 10 years#					Private clinics
HPV¥	3 doses (women) (0, 2 and 6 months)					Private clinics
Pneumococcal 23 (polysaccharide)*,¥	1 or 2 doses				1 dose	CRIE/private clinics
Conjugated pneumococcal 13**	1 dose or more**					CRIE/private clinics
Conjugated meningococcal¥	1 dose, even for individuals vaccinated during childhood or more than 5 years before					Public health units
Hepatitis A¥	2 doses, minimum interval of 6 months					CRIE/private clinics
Hepatitis B¥	3 doses (0, 1 and 6 months)					Public health units
Combined hepatitis A and Bθ	3 doses (0, 1 and 6 months)					Private clinics
Varicella***,¥	2 doses, 8-week interval (negative history for varicella-zoster virus infection or vaccination)					CRIE/private clinics
Yellow fever***	1 dose every 10 years for those living in endemic areas or traveling to such areas					Public health units
Herpes-zoster***,¥			1 dose			Private clinics
Measles, mumps, rubella***,¥	Single dose if the vaccination schedule is complete. Two doses (minimum interval of 30 days) for those who had received one previous dose		1 dose			Public health units

CRIE: reference center for special immunobiological drugs; dt: adult combined vaccine against diphtheria and tetanus; Tdap: combination vaccine with acellular pertussis of the adult type; IPV: inactivated polio vaccine; HPV: human papilloma virus.
¥For all individuals of that category who meet the age criteria and need immunization (with neither vaccination card nor evidence of previous infections).
θCombined vaccines, option: to reduce the number of injections.
*For patients with functional or anatomical asplenia or complement deficiency.
** For patients without a good response to the pneumococcal 23 vaccine.
*** Live, attenuated vaccines. Contraindicated to immunosuppressed individuals and pregnant women, except when the risks for acquiring the disease surpass the potential risks of vaccination. Greater care should be taken on the first vaccination.
#With incomplete or unknown basic vaccination schedule (fewer than 3 previous doses of dT, DTP or DTaP vaccines): complete the 3-dose schedule, administering 1 dose of Tdap and 1 or 2 doses of dT (schedule: 0–2–6 months) to provide 3 doses of the tetanus component. In both cases, if the Tdap vaccine cannot be used, replace it with the dT vaccine.
##Unvaccinated adults should receive primary vaccination with IPV. Adults without vaccination documentation should be considered unvaccinated. Two doses of IPV at 4–8-week interval are recommended; a 3rd dose should be administered 6–12 months after the 2nd dose. Household contacts of immunosuppressed patients should be vaccinated.

Table 2
Recommendations of the Brazilian Society of Rheumatology on vaccination of patients diagnosed with rheumatoid arthritis

Recommendation 1 Before starting synthetic or biological DMARDs, the vaccine card should be reviewed and updated.
Recommendation 2: influenza vaccine Vaccines against seasonal influenza and against H1N1 are indicated annually for patients with RA.
Recommendation 3: pneumococcal vaccine The pneumococcal vaccine should be indicated for all patients with RA and can be more effective when administered before starting synthetic or biological DMARDs. When patients are on immunosuppressive agents, the response to vaccine should be assessed.
Recommendation 4: HPV vaccine The HPV vaccine should be considered for adolescent and young females with RA, preferably before starting sexual life.
Recommendation 5: meningococcal vaccine The meningococcal vaccine is indicated for patients with RA only in the presence of asplenia or complement deficiency. It should also be considered in the presence of outbreaks and severe immunosuppression.
Recommendation 6: Haemophilus influenzae type B vaccine Asplenic adults with RA should be immunized against *Haemophilus influenzae* type B.
Recommendation 7: hepatitis A and B vaccine Hepatitis B vaccine is indicated for patients with RA who are negative for antibodies against HbsAg, preferably before starting treatment with biological DMARDs. The combined hepatitis A and B vaccine should be considered.
Recommendation 8: Combined vaccine against diphtheria, tetanus and acellular pertussis (DTaP/Tdap) and combined vaccine against diphtheria and tetanus (dT) Patients on immunosuppressive drugs should undergo the same vaccine schedule recommended for healthy individuals. Patients with RA and at high risk for tetanus, who received rituximab in the preceding 24 weeks, should undergo passive immunization with tetanus immunoglobulin in case of exposure.
Recommendation 9: BCG vaccine An additional BCG vaccine is not indicated for patients diagnosed with RA, because all the Brazilian population is already vaccinated right after birth.
Recommendation 10: vaccines comprising live attenuated viruses These vaccines should be administered 2–4 weeks before beginning immunosuppressive therapy, 2 weeks after discontinuation of synthetic DMARDs, 4 weeks after discontinuation of CS, 12 weeks after discontinuation of immunoglobulins, cytotoxic drugs or alkylating agents. For biological DMARDs, a period corresponding to 4 half-lives should be observed after drug suspension.
Recommendation 11: vaccine against varicella The vaccine against varicella should be indicated for patients with RA and a negative or dubious history for that disease and/or previous vaccination, preferably before starting immunosuppression, or when patients are on low CS doses and usual MTX doses.
Recommendation 12: vaccine against YF The YF vaccine is contraindicated for patients with RA on immunosuppressive drugs, such as synthetic and biological DMARDs. Physicians should provide their patients with information on endemic areas, individualized risk of infection, and each patient's immunosuppression status, so that the indication of vaccine to that population in specific and very particular situations can be assessed.
Recommendation 13 The above described recommendations should be reviewed over the course of RA. Whenever possible, the vaccine status should be updated, even when synthetic DMARDs are used and preferably before starting biological therapy.

DMARD: disease-modifying anti-rheumatic drug; RA: rheumatoid arthritis; HPV: human papilloma virus; CS: corticosteroid; YF: yellow fever; BCG: Bacillus Calmette-Guérin.

In Brazil, the pneumococcal vaccine available for adults is the 23-valent polysaccharide vaccine (Pn23), a polyvalent vaccine prepared from purified polysaccharides of the bacterial capsule, containing 23 serotypes of *Streptococcus pneumoniae*.[10] However, it is associated with low immune response when compared with conjugated formulations (pneumo 7, 10 and 13).

The isolated use of MTX or its combination with some anti-TNF agents (adalimumab, etanercept and infliximab) can reduce the efficacy of the vaccine, while the isolated use of those biologics does not influence the response to vaccine.[15,17] In 2011, that finding was confirmed by a study performed with conjugated vaccine against 7 pneumococcal serotypes (Pn7) in patients with RA and spondyloarthritides.[23] A single administration of the Pn23 vaccine offers up to 10-year protection against the development of pneumococcal pneumonia in patients with RA on MTX.[24] The safety profile seems appropriate, which was a conclusion common to all those studies.

The additional benefit of the association of the Pn23 vaccine with conjugated vaccines has not yet been shown in patients with RA, but the response to the Pn23 vaccine should be monitored, mainly when administered to patients on synthetic or biological DMARDs. When inappropriate, the administration of a conjugated vaccine should be indicated, knowing that it is much more immunogenic than the Pn23 vaccine.

Usually, the Pn23 vaccine is well tolerated. The adverse events are mild, of short duration and limited to the vaccine application site. More intense local reactions are most often observed after early revaccination, especially in individuals with high titers of antibodies against the pneumococcus.[10]

In Brazil, the Pn23 vaccine is used to immunize institutionalized individuals aged 60 years and over. In that population, a single dose of the vaccine is administered with only one booster shot 5 years after the initial dose. It can also be indicated to individuals with chronic diseases, such as heart diseases, lung diseases, diabetes, and other conditions considered to increase the risk for pneumococcal disease, such as functional or anatomical asplenia and complement deficiency.[10,25]

The pneumococcal vaccine should be indicated for all patients with RA, and can be more effective when administered before beginning synthetic or biological DMARDs.

HPV vaccine

The HPV is a sexually transmitted virus, highly prevalent in Brazil.[26] There are more than 100 types of HPV, of which approximately 30 types affect men and women. HPV infection is the major risk factor for uterine cervix cancer, being also associated with tumors of the penis, anus, mouth and throat. HPV also causes genital warts or condyloma acuminatum.[27]

The quadrivalent vaccine is highly effective to prevent infections by the subtypes 16 and 18 (the most oncogenic subtypes) and 6 and 11 (responsible for genital warts). Several countries recommend vaccination against HPV in young women, ideally before initiating sexual activity. The Brazilian Ministry of Health does not recommend that as a public health guideline,[28] but the Brazilian Agency of Sanitary Surveillance (ANVISA) indicates that vaccination in women aged 11 to 26 years. That vaccine is administered via IM, in 3 doses on the months 0, 1–2 and 6.[27] Few adverse events of that vaccine have been described, and some patients can have mild local reactions.

Unlike systemic lupus erythematosus, a condition in which the incidence of HPV infection is known to be increased,[26] in RA, data are less well-known. In 2008, a Mexican study showed that 1 in every 3 women with RA can have HPV infection, and more than 90% of the patients have the high-risk viral subtype.[29]

Studies on the efficacy and safety of the HPV vaccine in patients with RA or other rheumatic diseases still lack. However, because the vaccine contains no viral genetic material and its basis is L1 capsid proteins, it is considered safe for patients with autoimmune diseases, even when immunosuppressed. Other international societies of specialists have suggested that patients with autoimmune diseases might benefit from that vaccine.[9]

The HPV vaccine should be considered for adolescents and young women with RA, preferably before initiating their sexual life.

Meningococcal vaccine

Meningococcal vaccine is indicated to prevent invasive disease caused by *Neisseria meningitidis*, especially in conditions of particular susceptibility to meningococcus, such as patients with asplenia and complement deficiency. The meningococcal serogroup C conjugate vaccine is currently available at the Brazilian public health system. It can be administered via IM from the age of 2 months onward, with no upper age limit.[10] Although the incidence of meningococcal disease in adults is low, vaccination is recommended when possible or in case of outbreaks, or travels that entail risk. The quadrivalent meningococcal conjugate vaccine (types A.C, W135 and Y) should be considered an option to immunize adolescents and adults.

Studies on the efficacy and safety of the meningococcal vaccine in patients with RA still lack. The experience is higher with pediatric patients. It has been proven safe and effective in children and adolescents with juvenile idiopathic arthritis (JIA), even when on immunosuppressive drugs.[30,31] The adverse events that might occur in the general population are local reactions, low fever and irritability.

The meningococcal vaccine is indicated for patients with RA, mainly those with asplenia and complement deficiency.

Haemophilus influenzae type B vaccine

The Hib is a capsulate bacterium that causes invasive diseases, such as meningitis, epiglottitis, septicemia, osteomyelitis and arthritis. Patients with RA and other rheumatic diseases are at greater risk of developing infections related to that bacterium, having, thus, indication for immunization.[32]

Similarly to the meningococcal vaccine, the Hib vaccine is conjugated, comprises polysaccharides of the bacterial capsule, and is administered via IM. That vaccine is part of the Brazilian vaccination calendar, and should be administered to children and adolescents up to the age of 19 years.[33]

Patients with rheumatic disease and indication for vaccination against Hib should be immunized as soon as their diagnosis is made, preferentially before beginning the immunosuppressive therapy, because of the possible interference with vaccine response.[34]

In addition to the indication of Hib vaccination for children and adolescents with rheumatic disease, asplenic adults

with RA should also be immunized. Studies on safety and efficacy in patients with RA still lack.[13]

Hepatitis A and B vaccine

There is no evidence that infections by hepatitis A (HVA) or B (HVB) viruses are more prevalent in patients with RA. However, screening of liver diseases and preventive measures against liver diseases are highly recommended in that group of patients due to their frequent use of hepatotoxic drugs, and the fact that Brazil has changed its endemic situation of hepatitis A, being currently considered of intermediate risk, meaning an increase in the number of susceptible adult individuals.[35]

In Brazil, vaccines available against HVA and HVB are produced by using recombinant DNA technology, and the combined formulation of both exist. The hepatitis A and B vaccines are considered safe.[10] They might cause local reactions, fever in the first 24 hours, fatigue, headache, irritability and gastrointestinal discomfort.

In RA, the safety and efficacy of the hepatitis B vaccine have been assessed in a prospective study.[36] Vaccination against hepatitis B has been associated with neither a significant deterioration of any clinical or laboratory measure of the disease, nor other important adverse events. Regarding efficacy, 15 of 22 (68.2%) patients responded to vaccination, with titers of antibodies against HBsAg of 10 IU/L after 7 months. The response rate was lower than that of the general population (85%–95%). In addition, the use of anti-TNF agents might significantly reduce the vaccine response.[37] Studies of HVA in patients with RA still lack.

The hepatitis B vaccine should be indicated for patients with RA when their serology against HBsAg is negative, preferably before beginning treatment with biological DMARDs.

The hepatitis A vaccine should be indicated for patients with RA because of their increased susceptibility to infection by that virus in our population, and because of the additional risk of hepatitis A-associated macrophage activation syndrome (MAS) and fulminant hepatitis in patients on chronic non-steroidal anti-inflammatory drugs (NSAIDs).[38,39]

Combined vaccine against diphtheria, tetanus and acellular pertussis (DTaP/Tdap) and combined vaccine against diphtheria and tetanus (dT)

The DTaP is a combined vaccine against diphtheria, tetanus and pertussis, in which the pertussis component is acellular.[34] Adult and elderly individuals with a complete basic vaccination schedule should receive a booster shot with Tdap (combination vaccine with acellular pertussis of the adult type) every 10 years. The combined vaccine against diphtheria and tetanus (dT) is indicated for adolescents and adults.

Individuals with an incomplete basic vaccination schedule (who have received fewer than 3 doses of the tetanus component during their lives) should complete their 3-dose schedule, receiving 1 dose of Tdap and 1 or 2 doses of dT according to the 0–2–6-month schedule. The Tdap vaccine is strongly indicated for the elderly. Individuals who have received the dT vaccine at least 2 years before should receive 1 dose of the Tdap vaccine.[34]

The Brazilian Ministry of Health recommends the vaccine with whole cell pertussis (DTP for children or dT for adolescents and adults). The World Health Organization (WHO) and the Pan-American Health Organization continue to recommend the DTP vaccine for most countries, assuring its efficacy and safety. The DTaP vaccine is not part of the routine calendar. Several developed countries indicate the acellular forms as follows: DTaP for individuals < 7 years and Tdpa for adolescents and adults.

After completing the vaccination schedule, the vaccine should be administered every 10 years, and, in case of pregnancy or wounds suspected of causing tetanus, every 5 years.

The vaccines against tetanus, diphtheria and pertussis are safe for adults and children with rheumatic diseases. The same vaccination schedule of healthy individuals is recommended for patients on immunosuppressive drugs.

Patients with RA and at high risk for tetanus, who received rituximab in the preceding 24 weeks, should undergo passive immunization with tetanus immunoglobulin in case of exposure.[18,19]

LIVE ATTENUATED VACCINES

This group includes the following vaccines: MMR (measles, mumps and rubella) triple vaccine; Bacillus Calmette-Guérin (BCG) vaccine; vaccine against influenza (nasal); vaccine against varicella; vaccine against herpes zoster; typhoid fever vaccine; vaccine against poliomyelitis (oral polio vaccine – OPV); vaccine against smallpox; and vaccine against yellow fever (YF).

The Brazilian guidelines for vaccination with live attenuated vaccines against MMR, varicella and booster shot of YF should be applied to patients with RA, except when they are known to be immunosuppressed, on high doses of CS, alkylating agents and/or biologics, until further data are available. Those vaccines can be used for rheumatologic patients on usual doses of synthetic DMARDs.

Vaccines in this group should be preferably indicated 2–4 weeks before beginning the immunosuppressive therapy, to assure that viral replication is over before the change in the patient's immune competence due to the use of the medication. Otherwise, when the immunosuppressive treatment has already started, vaccination should be postponed for at least 1 month after CS therapy discontinuation, 3 months after cytotoxic and human immunoglobulin treatment discontinuation, and 6 months after rituximab discontinuation. For the other biological DMARDs, a period corresponding to 4 half-lives should be observed after drug suspension.

However, some specific situations, such as the occasional use of the YF vaccine in the population of endemic areas, should be considered.[40]

BCG vaccine

Mycobacterium tuberculosis infection remains the most lethal infectious disease in the world, accounting for approximately 1.7 million deaths per year. Brazil ranks the 17th position out of the 22 countries responsible for 80% of all cases of tuberculosis (TB) in the world.[10,41] Patients with RA are at increased risk for TB, especially with the advent of anti-TNF-alpha therapy.

Patients with RA on synthetic DMARDs have an incidence of TB 2- to 10-times greater than that of the general population. When patients are on TNF-alpha inhibitors, their incidence of TB is 6 to 10 times greater than that of patients who are not on biologics; in addition, their rate of TB is 30 times higher than that of the general population, reaching 144 per 100,000 person-years.[41] If preventive measures against TB are not adopted before the use of anti-TNF-alpha therapy, the risk is even higher.[43]

The BIOBADA Brasil, the Brazilian registry of patients with rheumatic diseases on biologics, shows 3 cases of TB out of 466 patients with RA on anti-TNF-alpha therapy.[22]

The BCG vaccine, the only licensed vaccine against TB, is elaborated from attenuated bacteria of bovine origin (*Mycobacterium bovis*), which is similar to the microorganism causing TB (*Mycobacterium tuberculosis*).[10]

In Brazil, the BCG vaccine is primarily indicated for children aged 0 to 4 years, being mandatory for those under the age of 1 year. According to most studies, its efficacy is 50% (range, 10%–66%) for all forms of the disease, but it is insufficient to protect against the pulmonary forms (efficacy lower than 50% in the majority of the most consistent studies). It protects against tuberculous meningitis, disseminated forms of the disease (range of efficacy, 68%–100%), and leprosy. The immunity is maintained for 10–15 years. The BCG vaccine does not protect individuals already infected with *Mycobacterium tuberculosis*.

An additional BCG vaccine for patients with RA is not indicated, because, in most of those patients, TB is due to disease reactivation or new infection, forms that the vaccine does not prevent. In addition, the efficacy of the BCG vaccine has not been proven in adults. The fact that it has an attenuated mycobacterium is another relevant factor supporting its contraindication in patients with RA.[10,41]

Vaccine against varicella and herpes zoster

Patients with RA are at higher risk of developing herpes zoster infection *versus* general population.[44] That risk is even greater in patients on CS therapy and biologics.[44,45]

The vaccine against varicella contains live attenuated viruses derived from the Oka strain, and is administered subcutaneously.[10] It has been proven to reduce the number of infections and complications, such as postherpetic neuralgia in immunosuppressed patients (on chemotherapy and post-transplantation), as compared to those reporting infection with the wild virus in childhood.[10,46]

The vaccine against herpes zoster, still not available in Brazil, also had its efficacy confirmed in adults over the age of 60 years[47] and in patients with chronic inflammatory diseases over the age of 50 years.[48] According to those studies, that vaccine is indicated for patients over the age of 50 years and diagnosed with rheumatic diseases based on the American College of Rheumatology criteria, even when they are on DMARDs at usually recommended doses.[49] The use of low doses of immunosuppressive drugs, such as MTX (< 0.4 mg/kg/week) and azathioprine (< 3.0 mg/kg/day), is not considered sufficiently immunosuppressive to jeopardize that vaccine's safety, not constituting a contraindication to its administration.[49]

The vaccine against varicella should be indicated for patients with RA and with a negative or dubious history for that disease and/or previous vaccination, preferably before starting immunosuppression. It is contraindicated when patients are immunosuppressed, receiving the following: high doses of systemic CS (> 20 mg of prednisone per day or equivalent) for 2 weeks or longer; pulse therapy; cytotoxic or alkylating agents; synthetic DMARDs at doses above those recommended; or immunobiological therapy.[50]

The vaccine against varicella might be indicated for patients with stable disease on low CS doses and usual MTX doses. If either the virus or infectious symptoms persist after vaccination, treatment with acyclovir is a possibility.[49,50]

Vaccine against yellow fever

Yellow fever is a noncontagious viral hemorrhagic febrile disease, transmitted by the bite of insects, especially those

of the *Aedes* and *Haemagogus* genera.[51] In Brazil, the endemic area comprises mainly the Northern and West-Central regions, corresponding to approximately 68% of the territory.[52] The overall lethality ranges from 5%–10%. It is estimated that only 10% of the cases are severe forms, associated with high lethality (range, 40%–60% of the cases). There is no specific treatment for the disease, the YF vaccine being the major preventive measure.[51]

The 17D vaccine against YF provides protection for at least 10 years, and even for the entire life.[52,53] Within 30 days, more than 90% of vaccinated individuals develop antibodies against the disease.[54] Of those individuals, 98%–100% become immunized.[55,56]

The YF vaccine is contraindicated to patients with RA on immunosuppressive drugs, because it is a live, attenuated vaccine, and there is risk of an uncontrolled vaccine viral replication.[9,54,57] Cases of YF vaccine-associated viscerotropic disease have been reported in patients with systemic lupus erythematosus and rheumatic polymyalgia.[58–60]

Another factor to be considered is the seroconversion ability of those patients, which is inversely proportional to the immunosuppression degree.[57]

Anaphylaxis secondary to the YF vaccine is another relevant aspect, occurring at the frequency of 0.8 to 1.8 per 100,000 doses, being attributed to allergy to egg or to the gelatin used in the vaccine's production.[61,62] The most relevant severe adverse events are YF vaccine-associated neurotropic and viscerotropic diseases,[52,54,63] having the latter an expected lethality of around 60%.[54]

Only 2 studies have assessed the response to YF vaccination in rheumatic patients on immunosuppressive agents and their adverse events.[40,64]

Regarding adverse events in rheumatic patients, the only existing study has reported a case series of 70 patients with several rheumatic diseases, who had been inadvertently immunized with the YF vaccine. All of them had already been previously vaccinated against YF. Of the 70 patients, 16 (22.5%) reported minor adverse events, a figure compatible with that expected for the healthy population.[40]

Regarding the immune response in rheumatic patients, a study has assessed 17 patients with RA on biological therapy, who received the YF vaccine. Comparing the antibody titers between patients and controls, a trend of reduced response in the group of patients with RA was observed, although a statistical analysis could not be performed because of the small number of patients.[64]

The WHO recommends vaccination of the population residing in endemic areas and of travelers to those regions, with a boost every 10 years.[53] The current recommendation is that immunosuppressed patients should not be vaccinated against the disease.[9,65] Thus, the YF vaccine is contraindicated to patients with RA on immunosuppressive drugs, including synthetic and biological DMARDs.

Vaccination against YF in patients with RA living in endemic areas, close to the wild or who will be exposed during work is controversial, and, so far, no consensus has been achieved. A risk-benefit analysis requires considering whether the risk of contracting the natural infection é higher than that of experiencing a severe adverse event.[57] Physicians should provide their patients with information on endemic areas, individualized risk of infection, and each patient's immunosuppression status, so that the indication of vaccine to that population in specific and very particular situations can be assessed; the decision to vaccinate, however, is up to each patient.[65]

Vaccine against measles, mumps and rubella (MMR or triple viral vaccine)

The triple viral vaccine is a combined vaccine containing live, attenuated viruses, and which protects against measles, mumps and rubella (MMR). It is administered subcutaneously. Usually, the MMR vaccine causes few adverse events, being well tolerated. All individuals should receive or have received 2 doses of the MMR vaccine, with a minimum interval of 1 month. More than 2 doses are not necessary.

It is worth noting that, as the MMR vaccine became part of the official Brazilian vaccination calendar only in 2003, most patients with RA might not have received that vaccine. The MMR vaccine is indicated to childbearing age women, because of the risk of congenital rubella, and to all patients with a negative serology or who travel to endemic areas, except for the restrictions applied to vaccines of live, attenuated viruses.

Only 2 studies have assessed the safety of the MMR vaccine (booster shot) to patients with JIA. Both studies evidenced appropriate safety and immunogenicity.[66,67] Studies on the safety of the MMR vaccine to adults with RA still lack.

CONCLUSIONS

Safe and effective vaccination is crucial for patients with RA, because of their increased risk of infection. Vaccination is no longer exclusive to children, and currently adolescents, adults, pregnant women and the elderly have specific and individualized immunization programs.

The vaccine chart should be updated as soon as the diagnosis of RA is established, preferably before starting DMARDs. The recommendations of the SBR Committee for RA followed

the Brazilian guidelines for vaccination, because those guidelines consider local epidemiology, resources and health policies. Vaccines against Hib, pneumococcus, meningococcus, HPV, hepatitis A, and varicella-zoster virus (VZV) are not universally recommended in the Brazilian guidelines, but are considered important in the management of those patients. There are specific recommendations for those vaccines.

Several recommendations proposed have not been based on the best degree of scientific evidence, and some limitations should be highlighted in the present study. To properly assess the efficacy of a certain vaccine, studies aimed at assessing the number of infections prevented with the intervention should have been conducted. That type of study cannot be performed because of the number of patients required, the follow-up time necessary, and ethical issues; thus, the results analyzed in this study were based on intermediate outcomes (immunogenicity).

Usually, vaccines have good immunogenicity in patients with RA, except for some conditions depending on the type and dose of the immunosuppressive treatment and the type of vaccine. Patients on MTX showed a reduced response to the Pn23, while the T-dependent response to conjugated or live, attenuated vaccines was considered adequate. Responses to several vaccines (influenza, VZV) were reduced in patients on high doses of either CS or azathioprine. The use of rituximab is related to a reduction in the T-dependent and T-independent responses to vaccines. To yield an adequate and safe immune response, vaccination should be ideally performed before the introduction of immunosuppressive drugs.

Regarding safety, both disease activity and adverse events were studied. It is worth emphasizing that there is no study with satisfactory statistical power to assess adverse events in patients with RA for most vaccines. However, the administration of inactivated vaccines during the use of CS, usual doses of DMARDs, and anti-TNF seems to be safe. Because data on vaccines with live components are still scarce, their indication is limited to booster doses of the varicella, YF and MMR vaccines, apparently safe in patients on regular doses of MTX and low doses of CS. The first dose of those vaccines should be administered before starting the treatment of patients with RA, observing the already described intervals.

This study aimed at establishing consensual guidelines for the vaccination of patients diagnosed with RA, by using evidence obtained from the best studies available, to standardize the indication of immunization by rheumatologists and other professionals managing those patients, considering specific aspects of the Brazilian reality. We believe that implementing those guidelines is perfectly feasible in Brazil, considering that the Brazilian Immunization Program (PNI) is one of the most successful public health initiatives in Brazil.

REFERENCES

1. Falagas ME, Manta KG, Betsi GI, Pappas G. Infection-related morbidity and mortality in patients with connective tissue diseases: a systematic review. Clin Rheumatol 2007; 26(5):663–70.
2. Michaud K, Wolfe F. Comorbidities in rheumatoid arthritis. Best Pract Res Clin Rheumatol 2007; 21(5):885–906.
3. Naz SM, Symmons DP. Mortality in established rheumatoid arthritis. Best Pract Res Clin Rheumatol 2007; 21(5):871–83.
4. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Predictors of infection in rheumatoid arthritis. Arthritis Rheum 2002; 46(9):2294–300.
5. Tak PP, Kalden JR. Advances in rheumatology: new targeted therapeutics. Arthritis Res Ther; 13 Suppl 1:S5.
6. Desai SP, Turchin A, Szent-Gyorgyi LE, Weinblatt M, Coblyn J, Solomon DH, et al. Routinely measuring and reporting pneumococcal vaccination among immunosuppressed rheumatology outpatients: the first step in improving quality. Rheumatology (Oxford) 2011; 50(2):366–72.
7. Lanternier F, Henegar C, Mouthon L, Blanche P, Guillevin L, Launay O. Low influenza-vaccination rate among adults receiving immunosuppressive therapy for systemic inflammatory disease. Ann Rheum Dis 2008; 67(7):1047.

8. Marchand-Janssen C, Loulergue P, Mouthon L, Mahr A, Blanche P, Deforges L, et al. Patients with systemic inflammatory and autoimmune diseases are at risk of vaccine-preventable illnesses. Rheumatology (Oxford); 50(6):1099–105.
9. van Assen S, Agmon-Levin N, Elkayam O, Cervera R, Doran MF, Dougados M, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis 2011; 70(3):414–22.
10. Brasil. Ministério da Saúde. Manual de vigilância epidemiológica de eventos adversos pós-vacinação. 2.ed. Brasília, 2008; p.184.
11. Ribeiro AC, Guedes LK, Moraes JC, Saad CG, Aikawa NE, Calich AL, et al. Reduced seroprotection after pandemic H1N1 influenza adjuvant-free vaccination in patients with rheumatoid arthritis: implications for clinical practice. Ann Rheum Dis 2011; 70(12):2144–7.
12. Coyne P, Hamilton J, Heycock C, Saravanan V, Coulson E, Kelly CA. Acute lower respiratory tract infections in patients with rheumatoid arthritis. J Rheumatol 2007; 34(9):1832–6.
13. van Assen S, Agmon-Levin N, Elkayam O, Cervera R, Doran MF, Dougados M, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis 2011; 70(3):414–22.
14. Kubota T, Nii T, Nanki T, Kohsaka H, Harigai M, Komano Y, et al. Anti-tumor necrosis factor therapy does not diminish the immune response to influenza vaccine in Japanese patients with rheumatoid arthritis. Mod Rheumatol 2007; 17(6):531–3.
15. Kaine JL, Kivitz AJ, Birbara C, Luo AY. Immune responses following administration of influenza and pneumococcal vaccines to patients with rheumatoid arthritis receiving adalimumab. J Rheumatol 2007; 34(2):272–9.
16. Fomin I, Caspi D, Levy V, Varsano N, Shalev Y, Paran D, et al. Vaccination against influenza in rheumatoid arthritis: the effect of disease modifying drugs, including TNF alpha blockers. Ann Rheum Dis 2006; 65(2):191–4.
17. Kapetanovic MC, Saxne T, Nilsson JA, Geborek P. Influenza vaccination as model for testing immune modulation induced by anti-TNF and methotrexate therapy in rheumatoid arthritis patients. Rheumatology (Oxford) 2007; 46(4):608–11.
18. Bingham CO, 3rd, Looney RJ, Deodhar A, Halsey N, Greenwald M, Codding C, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial. Arthritis Rheum 2010; 62(1):64–74.
19. Buch MH, Smolen JS, Betteridge N, Breedveld FC, Burmester G, Dorner T, et al. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis 2011; 70(6):909–20.
20. Buch MH, Smolen JS, Betteridge N, Breedveld FC, Burmester G, Dorner T, et al. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis 2011; 70(6):909–20.
21. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum 2002 Sep; 46(9):2287–93.
22. Titton DC, Silveira IG, Louzada-Junior P, Hayata AL, Carvalho HM, Ranza R, et al. Brazilian biologic registry: BiobadaBrasil implementation process and preliminary results. Rev Bras Reumatol 2011; 51(2):152–60.
23. Kapetanovic MC, Lindqvist E, Geborek P, Saxne T, Eberhard K. Long-term mortality rate in rheumatoid arthritis patients with disease onset in the 1980s. Scand J Rheumatol 2011; 40(6):433–8.
24. Coulson E, Saravanan V, Hamilton J, So KL, Morgan L, Heycock C, et al. Pneumococcal antibody levels after pneumovax in patients with rheumatoid arthritis on methotrexate. Ann Rheum Dis 2011; 70(7):1289–91.
25. Imunizações ABd. Calendário de Vacinação do adulto e do idoso 2011. Available from: http://www.sbim.org.br/calendario-de-vacinacao/adultos-e-idosos/. [Accessed on Feb/2012].
26. Klumb EM, Pinto AC, Jesus GR, Araujo M, Jr., Jascone L, Gayer CR, et al. Are women with lupus at higher risk of HPV infection? Lupus; 19(13):1485–91.
27. WHO position on HPV vaccines. Vaccine 2009; 27(52):7236–7.
28. Brasil. Ministério da Saúde. Relatório final do grupo de trabalho instituído pela portaria MS 310, de 10 de fevereiro de 2010. In: Ministério da Saúde INdC, editor. 2010.
29. Nath R, Mant C, Luxton J, Hughes G, Raju KS, Shepherd P, et al. High risk of human papillomavirus type 16 infections and of development of cervical squamous intraepithelial lesions in systemic lupus erythematosus patients. Arthritis Rheum 2007; 57(4):619–25.
30. Zonneveld-Huijssoon E, Ronaghy A, Van Rossum MA, Rijkers GT, van der Klis FR, Sanders EA, et al. Safety and efficacy of meningococcal c vaccination in juvenile idiopathic arthritis. Arthritis Rheum 2007; 56(2):639–46.
31. Silva CAA, Terreri MTRA, Barbosa CMPL, Hilário MOE, Pillegi GCS, Ferriani VPL, et al. Immunization consensus for children and adolescents with rheumatic diseases. Rev Bras Reumatol 2009; 49(5):562–89.
32. Davies K, Woo P. Immunization in rheumatic diseases of childhood: an audit of the clinical practice of British Paediatric Rheumatology Group members and a review of the evidence. Rheumatology (Oxford) 2002; 41(8):937–41.
33. Silva CA, Terreri MT, Aikawa NE, Carvalho JF, Pileggi GC, Ferriani VP, et al. Vaccination practice in children with rheumatic disease. Rev Bras Reumatol 2010; 50(4):351–61.
34. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Manual dos Centros de Referência para Imunobiológicos Especiais (CRIES). Brasília: Ministério da Saúde; 2006.
35. Migowski E. Hepatite A, uma doença benigna? Available from: www.apamt.org.br/anais_2008/jornada2008-anais/conferencias/hepatiteA-uma_doenca_benigna.pdf. [Accessed on 11, Feb 2012].
36. Elkayam O, Yaron M, Caspi D. Safety and efficacy of vaccination against hepatitis B in patients with rheumatoid arthritis. Ann Rheum Dis 2002 Jul; 61(7):623–5.
37. Garrido Lopez BC, Navarro Compain MV, Navarro Sarabia F. Vaccines and chemo-prophylaxis in rhemautoid arthritis: is a vaccine calendar necessary? Reumatol Clin 2011; 7(6):412–6.
38. Russo RA, Rosenzweig SD, Katsicas MM. Hepatitis A-associated macrophage activation syndrome in children with systemic juvenile idiopathic arthritis: report of 2 cases. J Rheumatol 2008; 35(1):166–8.
39. Pham H, Geraci SA, Burton MJ. Adult immunizations: update on recommendations. Am J Med 2011; 124(8):698–701.

40. Mota LM, Oliveira AC, Lima RA, Santos-Neto LL, Tauil PL. Vaccination against yellow fever among patients on immunosuppressors with diagnoses of rheumatic diseases. Rev Soc Bras Med Trop 2009; 42(1):23–7.
41. Manual de Recomendações para o Controle da Tuberculose no Brasil In: Saúde Md, editor. Brasília 2010.
42. Dixon WG, Hyrich KL, Watson KD, Lunt M, Galloway J, Ustianowski A, et al. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis 2010; 69(3):522–8.
43. Gomez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthritis Rheum 2003; 48(8):2122–7.
44. Smitten AL, Choi HK, Hochberg MC, Suissa S, Simon TA, Testa MA, et al. The risk of herpes zoster in patients with rheumatoid arthritis in the United States and the United Kingdom. Arthritis Rheum 2007; 57(8):1431–8.
45. Strangfeld A, Listing J, Herzer P, Liebhaber A, Rockwitz K, Richter C, et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. JAMA 2009; 301(7):737–44.
46. Brisson MEW, Gay NJ, Law B, De Serres G. Modelling the impact of immunization on the epidemiology of varicella zoster virus. Epidemiol Infect 2000; 125(3):651–69.
47. Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005; 352(22):2271–84.
48. Zhang J, Delzell E, Xie F, Baddley JW, Spettell C, McMahan RM, et al. The use, safety, and effectiveness of herpes zoster vaccination in individuals with inflammatory and autoimmune diseases: a longitudinal observational study. Arthritis Res Ther 2011; 13(5):R174.
49. Harpaz R, Ortega-Sanchez IR, Seward JF. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2008; 57(RR-5):1-30; quiz CE2-4.
50. Pileggi GS, de Souza CB, Ferriani VP. Safety and immunogenicity of varicella vaccine in patients with juvenile rheumatic diseases receiving methotrexate and corticosteroids. Arthritis Care Res (Hoboken) 2010; 62(7):1034–9.
51. Vasconcelos PF. Yellow Fever. Rev Soc Bras Med Trop 2003; 36(2):275–93.
52. Camara FP, Gomes AL, Carvalho LM, Castello LG. Dynamic behavior of sylvatic yellow fever in Brazil (1954–2008). Rev Soc Bras Med Trop 2011;44(3):297–9.
53. Barrett AD, Teuwen DE. Yellow fever vaccine – how does it work and why do rare cases of serious adverse events take place? Curr Opin Immunol 2009; 21(3):308–13.
54. Vellozzi C, Mitchell T, Miller E, Casey CG, Eidex RB, Hayes EB. Yellow fever vaccine-associated viscerotropic disease (YEL–AVD) and corticosteroid therapy: eleven United States cases, 1996–2004. Am J Trop Med Hyg 2006; 75(2):333–6.
55. Monath TP, Cetron MS, McCarthy K, Nichols R, Archambault WT, Weld L, et al. Yellow fever 17D vaccine safety and immunogenicity in the elderly. Hum Vaccin 2005; 1(5):207–14.
56. Bruyand M, Receveur MC, Pistone T, Verdiere CH, Thiebaut R, Malvy D. Yellow fever vaccination in non-immunocompetent patients. Med Mal Infect 2008; 38(10):524–32.
57. Whittembury A, Ramirez G, Hernandez H, Ropero AM, Waterman S, Ticona M, et al. Viscerotropic disease following yellow fever vaccination in Peru. Vaccine 2009; 27(43):5974–81.
58. Martin M, Tsai TF, Cropp B, Chang GJ, Holmes DA, Tseng J, et al. Fever and multisystem organ failure associated with 17D-204 yellow fever vaccination: a report of four cases. Lancet 2001; 358(9276):98–104.
59. Martins RM, Maia MLS, Santos EM, Cruz RLS, Santos PG, Carvalho SMD, et al. Yellow Fever Vaccine Post-marketing Surveillance in Brazil. Procedia in Vaccinology 2010; 2:178–83.
60. Hayes EB. Is it time for a new yellow fever vaccine? Vaccine 2010; 28(51):8073–6.
61. Lindsey NP, Schroeder BA, Miller ER, Braun MM, Hinckley AF, Marano N, et al. Adverse event reports following yellow fever vaccination. Vaccine 2008; 26(48):6077–82.
62. Vasconcelos PF, Luna EJ, Galler R, Silva LJ, Coimbra TL, Barros VL, et al. Serious adverse events associated with yellow fever 17DD vaccine in Brazil: a report of two cases. Lancet 2001; 358(9276):91–7.
63. Scheinberg M, Guedes-Barbosa LS, Mangueira C, Rosseto EA, Mota L, Oliveira AC, et al. Yellow fever revaccination during infliximab therapy. Arthritis Care Res (Hoboken) 2010; 62(6): 896–8.
64. Kavanaugh A. Infection prophylaxis in antirheumatic therapy: emphasis on vaccination. Curr Opin Rheumatol 2009; 21(4): 419–24.
65. Oliveira ACV ML, Santos-Neto LL, Tauil PL. What a Rheumatologist needs to know about yellow fever vaccine. Rev Bras Reumatol [In Press]. 2012
66. Heijstek MW, Pileggi GC, Zonneveld-Huijssoon E, Armbrust W, Hoppenreijs EP, Uiterwaal CS, et al. Safety of measles, mumps and rubella vaccination in juvenile idiopathic arthritis. Ann Rheum Dis 2007; 66(10):1384–7.
67. Borte S, Liebert UG, Borte M, Sack U. Efficacy of measles, mumps and rubella revaccination in children with juvenile idiopathic arthritis treated with methotrexate and etanercept. Rheumatology (Oxford) 2009; 48(2):144–8.