

## *Immunization consensus for children and adolescents with rheumatic diseases*

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### ABSTRACT

Incidence of infectious diseases is higher in children and adolescents with rheumatic diseases than in the general population due to disease activity, possible immune deficiency secondary to the disease itself, or the use of immunosuppressive drugs. Vaccination is effective in reducing morbidity and mortality in those patients. The objective of this study was to establish an evidence-based consensus on the efficacy and safety of vaccination in children and adolescents with rheumatic diseases. Passive immunization of patients and guidelines for people who live with immunosuppressed patients were also included. The 32 pediatric rheumatologists of the Rheumatology Department of the Pediatrics Society of São Paulo, (SPSP, from the Portuguese), São Paulo, SP, Brazil, and/or the Commission on Pediatrics Rheumatology of the Brazilian Society of Rheumatology are responsible for this consensus; some of those professionals are involved on research and scientific publications in this field. The words efficacy and/or safety of different vaccines in children and adolescents with rheumatologic diseases were searched in Medline and Scielo data bases from 1966 to March 2009, including reviews, controlled studies, and case reports. The degree of recommendation and the scientific evidence of the studies were classified in four levels for each vaccine. As a rule, inactive and protein components vaccines are safe for patients with rheumatologic diseases, even in the presence of immunosuppressive therapy. However, live attenuated vaccines are, in general, contraindicated for immunosuppressed patients.

**Keywords:** immunization, vaccination, children, systemic lupus erythematosus, idiopathic juvenile arthritis, rheumatic disease.

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## INTRODUCTION

The risk of infections in patients with chronic rheumatologic diseases is twice that of normal individuals.<sup>1,2</sup> This increased risk is related to conditions inherent to the disease process and the immunosuppressive therapy required to control the disease. Besides, specific susceptibilities, such as functional asplenia, seen in some patients with systemic lupus erythematosus (SLE), resulting in a higher risk of infections with encapsulated bacteria like pneumococcus, meningococcus, and *Haemophilus influenzae* type b, can be present.<sup>3,4</sup> Facó *et al.* (2004) evaluated, on a retrospective study, the death of Brazilian children and adolescents with SLE over a 10-year period, and confirmed that infections represented the main cause of death in those patients.<sup>5</sup>

The growing use of more aggressive treatments in rheumatologic diseases like immunosuppressive drugs and biological agents increases the susceptibility of those patients to infections. In this context, safe administration of vaccines against infectious agents and development of adequate response to vaccination have a great impact in the prevention of infections.

However, manuals on the indications of currently available vaccines do not have specific recommendations for immunization of children and adolescents with rheumatologic diseases.<sup>5</sup> The lack of consensus generates a large variety of prescriptions among professionals, resulting in a gap between clinical practice and the academia.<sup>6,7</sup>

As a rule, recent publications on immunization of adult patients with rheumatologic diseases follow the recommendations for immunosuppressed patients, which contraindicate the administration of live vaccines in patients with rheumatologic diseases using immunosuppressive drugs.<sup>3,4,7,8</sup> This is also the recommendation of the British Pediatric Rheumatology Group.<sup>6</sup>

Twenty-six pediatric rheumatologists members of the Pediatric Rheumatology Department of the Pediatrics Society of São Paulo, (SPSP, from the Portuguese) met to establish to established a consensus on the immunization of patients with rheumatologic diseases of infancy and adolescence. Some of those professionals are involved in research and scientific publications in this field. Besides, 11 pediatric rheumatologists, members of the Pediatric Rheumatology Commission of the Brazilian Society of Rheumatology, also participated in this consensus. Five of them are from São Paulo (they participate in both commissions) and six come from other states, namely Bahia, Goiás, Pará, Mato Grosso do Sul, and Rio de Janeiro. All are certified in

Pediatric Rheumatology and/or Rheumatology, being active in teaching, patient care, and research. Coordinators of this study: CAAS and MTRAT.

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## OBJECTIVE

The objective of this study was to develop evidence-based recommendations for vaccines and passive immunization of children and adolescents with rheumatologic diseases.

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## METHODS

Those participating in this study were divided in work groups, each one responsible for reviewing the literature available on the efficacy and safety of individual vaccines currently recommended by the Brazilian Immunization Calendar for this group of patients.

The words efficacy and/or safety of the different vaccines in children and patients with rheumatologic diseases were searched in the Medline and Scielo data bases from 1966 to March 2009, including reviews of the subject, controlled studies, series, and case reports. For each vaccine, the “degree of recommendation” and “strength of the evidence” of the studies were classified in four levels:

- A:** Major experimental and observational studies.
- B:** Minor experimental and observational studies.
- C:** Case reports (non-controlled studies).
- D:** Opinion without critical evaluation based on consensus, physiological studies, or animal models.

## General considerations on immunization of children and adolescents with rheumatologic diseases

The first relevant question refers to the safety of administering attenuated live vaccines to patients with rheumatologic diseases on immunosuppressants due to the possibility that they can induce the development of infections instead of protection. However, it should be emphasized that we did not find, in the literature, reports on viral dissemination after the administration of attenuated live vaccines in individuals with immunosuppression secondary to rheumatologic diseases or their treatment.

On the other hand, all prospective studies evaluating the efficacy and safety of vaccines in patients with rheumatologic diseases only evaluated inactive vaccines. In addition, most studies are not controlled and included a limited number of

patients<sup>3,4,8</sup>. Consequently, recommendations on the use of vaccines in this group of patients are frequently based on the recommendations for other group of patients with other conditions, such as malignancies, who use higher doses of drugs than those prescribed in rheumatology. As such, based on the information currently available and on the opinion of specialists, the present consensus does not recommend the use of live attenuated virus in patients with rheumatologic autoimmune diseases (**evidence D**).

Some drugs commonly used in the treatment of rheumatologic diseases like corticosteroids (CS), methotrexate (MTX), azathioprine (AZA), cyclosporine A (CYA), cyclophosphamide (CPM), and tumor necrosis factor inhibitors (anti-TNF) are potential immunosuppressants.<sup>9</sup> The degree of immunosuppression caused by those drugs varies according to the duration and dose used (**evidence C**).<sup>7</sup>

Corticosteroid-induced immunosuppression is dose-dependent, although a consensus on the dose in which this immunosuppression would be enough to contraindicate the administration of live attenuated vaccines does not exist.<sup>7,10,11</sup> According to the American Academy of Pediatrics, vaccination with live vaccines is contraindicated when doses of prednisone equal or above 2 mg/kg/day or greater than 20 mg/day are used for more than one week (**evidence D**).<sup>12</sup> In 2002, Davies & Woo observed that, in the opinion of 24 rheumatologists of the British Pediatric Rheumatology Group, a dose of 0.2 to 1 mg/kg/day of CS contraindicates the use of chicken pox vaccine (live attenuated virus) in children with rheumatologic diseases (**evidence D**).<sup>6</sup>

The possibility that vaccination can trigger or reactivate rheumatic diseases also raises doubts on the safety of immunization in patients with those disorders. Although sporadic cases of the temporal association between the use of some vaccines, including hepatitis B, and reactivation of rheumatoid arthritis (RA) have been reported (**evidence D**),<sup>9</sup> prospective studies did not confirm this association.

In addition, recent studies suggest that infections and immunizations can induce modulation of the immune system, promoting protection against autoimmune phenomena (**evidence D**).<sup>13</sup> Issues about reactivating or triggering the disease has resulted, on several occasions, in inadequate vaccine coverage.

Those considerations will be discussed in more details with each one of the vaccines currently recommended by the Brazilian Society of Pediatrics.

This paper will be divided on the following vaccines: hepatitis A and B; human papillomavirus (HPV); influenza; pneumococcus; meningococcus; *Haemophilus influenzae*

type B (Hib); yellow fever; bacillus Calmette-Guérin (BCG); rotavirus; varicella; measles, mumps, rubella (MMR); tetanus and diphtheria; and poliomyelitis (Salk and Sabin). The use of immunoglobulins for passive immunization and orientation for contacts of immunodepressed patients are also included.

## Hepatitis A vaccine

Viral hepatitis are still a serious public health problem, both in the world and in Brazil. The main route of transmission of hepatitis A virus is fecal-oral, and parenteral transmission is rare. Thus, the dissemination is related to the socio-economic level of the population, and with the degree of sewage and water treatment, sanitary education, and hygiene of the population. Usually, the disease is self-limited and less than 1% of the cases progress to fulminating hepatitis (**evidence A**).<sup>14</sup>

Hepatitis A vaccine is an inactive vaccine that can be used in children one year old and older, in two doses with a 30-day interval, and it is available at the Special Immunobiological Agents Reference Centers (CRIEs, from the Portuguese) and the public health system (SUS, from the Portuguese). It is very safe, with rare adverse events, such as: pain, edema, and erythema at the injection site, and low grade fever.<sup>14</sup>

The Health Ministry indicates this vaccine in the following cases: individuals with chronic liver disease susceptible to hepatitis A; receptors of allogeneic or autologous grafts after bone marrow transplants; candidates for autologous bone marrow transplant, before harvesting, donors of allogeneic bone marrow grafts, and after splenectomy.<sup>14</sup>

Studies demonstrating the safety and efficacy of this vaccine in rheumatic diseases are lacking in the literature (**evidence D**). We found only one report of a patient with a diagnosis of hepatitis of unknown origin that developed lethargy, jaundice, increase of transaminases, hypergammaglobulinemia, positive antinuclear and anti-double strand DNA antibodies 10 days after receiving the hepatitis A vaccine and progressed with remission of the disease after treatment with corticosteroids.<sup>15</sup>

## Hepatitis B vaccine

The hepatitis B virus (HBV) is transmitted parenterally, especially through sex. Vertical transmission (maternal-fetal) is also a frequent cause of dissemination of this virus. During infancy, 70 to 90% of infections before age 5 become chronic, and 20 to 25% of chronic infections with evidence of viral replication progress to advanced liver disease (cirrhosis and hepatocarcinoma) (**evidence A**).<sup>14</sup>

The hepatitis B vaccine can be administered at any age and simultaneously with other vaccines of the basic calendar.

It requires three doses with a one-month interval between the 1<sup>st</sup> and 2<sup>nd</sup> doses, and a six-month interval between the 2<sup>nd</sup> and 3<sup>rd</sup> doses (0, 1, and 6 months). A special schedule should be used for some individuals, such as immunosuppressed patients, those with renal failure on hemodialysis, and some premature newborns.

This vaccine is available at SUS (public health service) for the following cases: newborns younger than one year, especially in the first 12 hours of life; children and adolescents from one to 19 years of age; frequent blood donors; native Brazilian populations; household contacts of patients with hepatitis B; hepatitis C; patients with end-stage renal disease on hemodialysis; multiple transfusions, hemophilia, thalassemia, sickle cell anemia; malignant tumors; HIV (symptomatic and asymptomatic), and users of injected and inhaled drugs; large concentration of confined individuals (prisons, psychiatric hospitals, institutions for the underaged, military etc.), jail and penitentiary workers; homosexuals, prostitutes; health care professionals; garbage collectors of hospital and household wastes; and firemen, police officers, and marshals involved in rescue activities.<sup>14</sup>

The literature is controversial on the safety of HBV vaccine in autoimmune diseases. Unlike hepatitis A, several autoimmune manifestations have been described after HBV vaccine, such as vasculitis, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), seronegative arthropathies, autoimmune thrombocytopenia, myasthenia gravis, Evans syndrome, uveitis, transverse myelitis, erythema nodosum, peripheral polyneuropathy, seizures, glomerulonephritis, Gianotti-Crosti syndrome, erythema multiforme, bullous pemphigus, and lichen planus (**evidence C**).<sup>16-18</sup>

A case-control study using the Vaccine Adverse Events Reporting System (VAERS) data base found a significant increase in the risk of autoimmune diseases after hepatitis B vaccine when compared to controls who received the tetanus vaccine (**evidence B**).<sup>19</sup> Another study, using the same data base, reported 465 cases of recurrence or worsening of rheumatologic diseases after HBV revaccination, including four cases of SLE (**evidence B**).<sup>20</sup> One should not forget that this data base includes millions of vaccinated individuals and, therefore, the number of cases reported is expressively reduced.<sup>21</sup>

On the other hand, a case control study with 260 SLE patients failed to identify the HBV vaccine as a risk factor for the development of this disease (**evidence A**).<sup>22</sup>

The effectiveness of the HBV vaccine in SLE is controversial. In a study evaluating 23 patients with juvenile SLE on dialysis, patients did not show seroconversion after

vaccination (**evidence C**).<sup>23</sup> It should be emphasized that this study was conducted in the 1990s, and it used a different HBV antigen than the one used for the current vaccine.

In a study undertaken in São Paulo, Kuruma *et al.* analyzed, prospectively, 28 females with SLE without disease activity, taking less than 20 mg/day of prednisone and without any other immunosuppressants who received the recombinant HBV vaccine, demonstrating the efficacy and safety of this vaccine in this population (**evidence A**).<sup>18</sup> An Australian study evaluated the administration of the hepatitis B vaccine in 39 patients with IJA in remission, and reactivation of the disease was not observed (**evidence B**).<sup>24</sup>

### HPV vaccine

Human papillomavirus is the most common viral agent in anogenital infections worldwide (**evidence B**).<sup>24</sup> The virus is usually eliminated spontaneously, without sequelae, but, if this does not happen, it can be responsible for clinical changes ranging from mild cervical dysplasia to cervical cancer (**evidence D**).<sup>25</sup> Types 16 and 18 are responsible for 70% of the cases of cervical cancer, while types 6 and 11 cause approximately 90% of the cases of anogenital condyloma (**evidence B**).<sup>26</sup>

The tetravalent vaccine against HPV types 6, 11, 16, and 18 was recently developed for the prevention of anogenital diseases and highly malignant cervical lesions. It requires three (0, 2, and 6 months) IM doses of 0.5 mL of the vaccine (containing viral particles). Two large phase III studies were undertaken to evaluate the efficacy of the vaccine in a large number of women ages 15 to 26 years, susceptible to this agent (**evidence A**).<sup>27,28</sup> The vaccine was also tested in more than one thousand children and adolescents of both genders, ages 10 to 15, with seroconversion rates of 99% for the four types of HPV (**evidence A**).<sup>26</sup> The vaccine is well tolerated, but it can cause mild local reaction or low fever.

With the evolution of the knowledge on rheumatologic diseases and the development of new immunosuppressive therapies, growing survival rates have been observed in those pathologies, with a proportional improvement in the quality of life of patients. Thus, pediatric patients have achieved adolescence and become sexually active, with the consequent risk of acquiring sexually transmitted diseases, vaginitis, and cervical dysplasia.

Several studies have demonstrated that women with SLE have an increased risk of developing cervical dysplasia, which was much higher than that of the control group (**evidence B**).<sup>29</sup> In a Brazilian study with adolescents with juvenile SLE

**(evidence B)**, inflammatory changes in the cervicovaginal cytology were significantly associated with disease activity, both in sexually active and inactive patients. In this study, condyloma secondary to HPV infection was identified in two sexually active control patients (6.4%) and in none of the patients with juvenile SLE.<sup>30</sup>

There are no systematic publications on HPV infection, cervicovaginal cytology, and cervical cancer in adolescents with juvenile idiopathic arthritis or juvenile dermatomyositis.

Considering that the anti-HPV vaccine is safe and effective in normal children and adolescents, the higher risk of immunodepressed patients of acquiring HPV infection, and the efficacy and safety of other inactive vaccines in those patients, the authors suggest vaccinating children and adolescents with rheumatic diseases against HPV, especially patients with SLE **(evidence D)**. However, the efficacy and safety of this vaccine has not been tested in immunodepressed patients in general. Besides, the vaccine is not available at CRIEs and SUS and its cost is elevated.

### Influenza vaccine

There are two types of influenza vaccine: dead, inactive virus vaccine, and live attenuated vaccines. The dead virus vaccine is available in Brazil.

The inactive trivalent influenza vaccine has two influenza A antigens and one influenza B antigen. One or more antigens might be modified every year, according to the worldwide prevalence of strains of the influenza virus or the development of new strains. It is recommended for individuals older than 6 months. Children aged 6 to 8 months should receive a second dose after four weeks.<sup>31</sup>

The influenza vaccine should be stored at temperatures between 2 and 8°C and administered intramuscularly. In children younger than two years of age, it should be administered in the *vastus lateralis* muscle of the thigh, and in children older than two years, the deltoid, *gluteus*, or *vastus lateralis* muscle of the thigh can be used. Children aged 6 to 35 months should receive a dose of 0.25 mL, and those older than 36 months, 0.5 mL.<sup>31</sup> The vaccine is not available at the SUS, but it is available at the CRIEs.

This vaccine is recommended for individuals at risk of developing complications of the influenza infection and contacts of individuals exposed to the same risk. The indications include: children aged 6 months to 5 years; pregnant women; individuals older than 50 years; patients with diabetes, cardiac diseases, chronic lung diseases, including asthma, chronic kidney diseases; anatomical or

functional asplenia and related diseases; chronic use of acetyl salicylic acid (including IJA and Kawasaki disease); institutionalized patients; drug- or neoplasia-induced immunosuppression, contacts of individuals at risk for influenza complications; contacts and caretakers of children younger than 6 months; and health care professionals.<sup>31,32</sup> Besides, the vaccine can be used by any person, older than 6 months of age, who does not want to catch the flu and develop its complications.

The influenza vaccine should not be administered to individuals with severe allergy to eggs or influenza vaccine; those who developed Guillain-Barré syndrome within six weeks after influenza vaccination; children younger than 6 months; and individuals with acute moderate and severe febrile illness.<sup>131,32</sup> It has an efficacy of 97% in adults.

Several studies, most involving a small number of patients, suggest that the response to the vaccine in patients with SLE is less effective than in healthy individuals **(evidences B and C)**.<sup>33,36</sup> Two studies demonstrated that 38 to 63% of 24 patients with SLE responded to the influenza vaccine. This response was lower in patients older than 50 years, taking more than 10 mg of prednisone, and treated with azathioprine.<sup>33,34</sup> On the other hand, two studies described that the response to the influenza vaccine of individuals with SLE was similar to that of healthy individuals **(evidences B and C)**.<sup>37,38</sup>

A prospective study demonstrated protective levels of antibodies in 95% of 34 children with idiopathic juvenile arthritis (IJA), with an incidence of local side effects comparable to that of the control group **(evidence B)**.<sup>39</sup> In another prospective study with 49 patients with IJA on long-term immunosuppressive treatment (CS, MTX, AZA, CYA), the authors observed that seroconversion rates varied from 80-100%, depending on the strain analyzed, and serious adverse events or reactivation of the disease were not observed **(evidence B)**.<sup>40</sup>

Several studies assessed the effects of the drugs used in the treatment of RA and IJA on the immunogenicity of the influenza vaccine. They demonstrated that CS, gold salts, MTX, and AZA did not affect significantly the production of protective antibodies in those diseases. Studies on RA have demonstrated that patients treated with anti-TNF drugs, such as infliximab, can show reduced levels of post-vaccination antibodies when compared to those that are not treated with this class of drugs, although the levels of antibodies remained within seroprotective levels, suggesting that those patients can be vaccinated **(evidence B)**.<sup>41,43</sup>

Inactive vaccines do not cause symptoms of influenza infection. Mild adverse events include pain, edema, and

erythema at the injection site, low grade fever, and myalgia for approximately 1 to 2 days.<sup>31</sup>

Most individuals with SLE described so far did not show relevant adverse reactions and the vaccine was considered safe (**evidences B and C**).<sup>43,44</sup> However, rare cases of renal activity in patients who received the influenza vaccine have been reported (**evidence C**).<sup>45</sup> It was also observed that the influenza vaccine did not induce the production of anti-double strand DNA antibodies (**evidence C**).

Studies in adults with SLE have not demonstrated a deterioration of clinical or laboratorial parameters of disease activity. In addition, evidence indicating an increase in disease activity triggered by the immunization is lacking. Besides being considered safe, the vaccine is capable of inducing a satisfactory immune response and should, therefore, be encouraged in patients with SLE to reduce the morbimortality associated with the influenza virus in this group of immunodepressed patients. Controlled studies on influenza vaccination in juvenile dermatomyositis (JDM) are lacking.

### Pneumococcal vaccine

Children with specific rheumatologic diseases, especially IJA and juvenile SLE, are at an increased risk of developing severe pneumococcal infection,<sup>46</sup> and they are more prone to a fast decline in the levels of post-vaccination anti-pneumococcal antibodies due to the compromised immune response induced by the disease and its treatment.<sup>5</sup>

The polysaccharide vaccine (Pn23) is composed of a suspension of 23 serotypes of purified *Streptococcus pneumoniae* capsular polysaccharides in phenol-preserved saline solution: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F.<sup>47,48</sup>

The conjugated 7-valent pneumococcal vaccine (Pnc7) has seven *S. pneumoniae* capsular polysaccharides, each associated with a non-toxic variant of the diphtheria toxin, CRM19. The vaccine contains serotypes 4, 9V, 14, 19F, and 23F capsular polysaccharides and 18C and 6B oligosaccharides, the carrier protein CRM197, and aluminum phosphate as adjuvant. It does not have preservers.<sup>47,48</sup>

The literature does not have any studies on the efficacy of the pneumococcal vaccine in pediatric populations with rheumatic diseases. Studies with children and adolescents after transplant demonstrated more than 70% efficacy for the conjugated vaccine and Pn23 (**evidence A**).<sup>49,50</sup> The use of MTX was associated with significantly lower levels of anti-23F and anti-6B IgG in adults. On the other hand, anti-TNF $\alpha$  agents were not associated with worse vaccine response in

rheumatoid arthritis and psoriatic arthritis (**evidence A**).<sup>49,50</sup> In SLE, the polysaccharide vaccine was effective in 74% of the patients, with a trend for lower humoral responses in patients treated with immunosuppressants (CPM, AZA, and MTX) or with active disease (**evidence B**).<sup>51</sup> Patients with primary or secondary Sjögren syndrome who received the multivalent polysaccharide vaccine (12 capsular antigens) showed significant elevations in the levels of antibodies against the 12 serotypes (**evidence A**).<sup>52</sup>

As a rule, the pneumococcal vaccine is well tolerated in rheumatic patients. Side effects associated with the vaccine include mild local hyperemia and pain, low grade fever, or malaise, usually for up to 72 hours, which does not require any therapeutic measures (**evidences A and B**).<sup>51,52</sup> In adult patients with RA, SLE, or Sjogren syndrome, clinical and laboratorial disease activity does not seem to change significantly after the administration of the pneumococcal vaccine (**evidence A**).<sup>49,52,53</sup> Studies with children with leukemia and other malignancies also demonstrated the safety of inactive vaccines, such as the pneumococcal vaccine (**evidence A**).<sup>49,54,55</sup>

The administration of the pneumococcal vaccine (Pnc7 and Pn23) is indicated in children and adolescents with rheumatic diseases, preferentially before the introduction of the immunosuppressive therapy, but it is not contraindicated during immunosuppressive therapy (**evidences A and B**).<sup>49,50,56</sup> In cases of elective splenectomy in juvenile SLE, the vaccine should be administered at least two weeks before surgery.

The conjugated 7-valent vaccine (Pnc7) is administered in a dose of 0.5 mL IM. Patients aged 2 to 6 months should receive three doses of Pnc7, with at least a 2-month interval between doses, followed by an additional dose of 12-15 months. Patients 7 to 59 years old should receive two doses of Pnc7, with a 2-month interval, followed by a dose of Pn23 several months after the second dose of Pnc7 (**evidence D**).<sup>57</sup>

The polysaccharide vaccine (Pn23) should be administered at a dose of 0.5 mL IM or, occasionally, subcutaneous (SQ). It is indicated for patients older than 2 years. Patients who have received the Pnc7 vaccine before 2 years of age should receive the polysaccharide vaccine with an interval  $\geq 2$  months after the last dose of the Pnc7 vaccine. Patients aged 2 to 10 years, including those who have already received the Pnc7 vaccine, should receive two doses of Pn23 with a 3- to 5-year interval between the doses. Patients older than 10 years should receive two doses of the Pn23 vaccine, and the second dose should be administered  $\geq 5$  years after the first dose. Patients should not receive more than 2 doses of the Pn23 vaccine (**evidence D**).<sup>57</sup>

The pneumococcal vaccine is not included among the mandatory vaccines of the SUS, but it is available at the CRIEs.

## Meningococcal vaccine

The conjugated group C meningococcal vaccine is indicated for active immunization of children older than 2 months, adolescents, and adults, for the prevention of invasive disease caused by group C *Neisseria meningitidis*. It is safe for children with rheumatologic diseases, including those on immunosuppressants, and the vaccine schedule should be the same used for healthy children (**evidence D**).<sup>58</sup>

Patients with asplenia, deficiency of C3 or terminal components of the complement (C5, C6, C7, C8, and C9) are at increased risk of developing meningococcal infection and should, therefore, be vaccinated (**evidence D**).<sup>58</sup> Individuals with compromised immune response secondary to immunosuppressants have an adequate antibody response to active immunization. Besides, the meningococcal vaccine neither increase the activity of IJA, nor triggers a relapse of the disease (**evidence B**).<sup>59</sup>

Each dose of the vaccine contains the polysaccharide of C meningococcus conjugated with tetanus toxoid or the *Corynebacterium diphtheriae* CRM197 protein. The IM route should be used, and 2 to 3 doses, according to the manufacturer, should be administered from the 2<sup>nd</sup> month of life on. A booster dose is administered at 12 months of age. In children older than 12 months, a single dose of the vaccine is administered.<sup>58</sup>

Although symptoms of meningism have been reported, such as rigidity of the neck or photophobia, there is no evidence that the vaccine causes meningococcus C meningitis. However, one should be attentive for the possibility of occasional concomitant meningitis.

This vaccine is not available in the public health care system, but it can be found at the CRIEs.

## Haemophilus influenzae B vaccine

Patients with rheumatic diseases are at a higher risk of developing invasive *Haemophilus influenzae* type B (Hib) diseases (meningitis, epiglottitis, sepsis, osteomyelitis, and arthritis), and, therefore, immunization is indicated in those patients (**evidence B**).<sup>6</sup>

According to the Committee on Infectious Disease of the American Academy of Pediatrics and the British Society for Rheumatology, the Hib vaccine is indicated in immunosuppressed patients.<sup>6,60</sup>

This is a conjugated vaccine, composed of the capsular polysaccharide of the bacteria, and its administration is IM. It is available in the public health system, since it is included in the official Brazilian immunization calendar, and at the CRIEs. Children and adolescents up to 19 years should be vaccinated:

up to one year of age – three doses (2, 4, and 6 months, with a booster at 15 months); non-vaccinated children, or those who received only one dose, younger than 5 years – 2 doses with a one- to two-month interval; patients who received two doses before 12 months of age – only one additional dose.<sup>60</sup>

Since the response to the vaccine can be influenced by immunosuppressive therapy, those patients should receive the vaccine as early as possible after the diagnosis and, preferentially, before beginning the treatment (**evidence D**).<sup>61</sup>

Efficacy data on children, adolescents, and adults with chronic diseases are not available. There is evidence that patients with SLE develop protective levels of antibodies against Hib (**evidence B**).<sup>51</sup>

## Yellow fever vaccine

The yellow fever vaccine, made of live attenuated virus, is indicated for children 9 months and older and adults who live or travel to areas endemic for the disease. It is available in the public health system.

It is administered as a single IM dose 10 days or more before traveling. A booster should be administered every 10 years in the case of continuous exposure.

Vaccination with live attenuated virus determines a sustained and highly protective immune response, but immunosuppressed patients have a reduced response and are at a higher risk of developing active infection.

Children and adolescents with rheumatic diseases who receive immunosuppressants should not receive live vaccines, despite reports of patients with those pathologies on immunosuppressants receiving the yellow fever vaccine who did not develop significant adverse events (**evidence C**).<sup>62</sup>

Besides the contraindication for live vaccines described previously, one should not forget that conditions like allergies to egg protein and pregnancy represent contraindications for the yellow fever vaccine. Severe adverse events, such as hypersensitivity reactions, and vaccine-related viscerotropic disease and neurotropic disease, have been reported (**evidence C**).<sup>63,64</sup>

## BCG vaccine

The BCG vaccine is prepared with live attenuated *Mycobacterium bovis* bacilli. In Brazil, healthy newborns weighing 2 kg or more are routinely vaccinated intradermally (**evidence B**).<sup>65</sup> It is available at the SUS and CRIEs.

Metanalysis and case control studies to evaluate the protective effect of BCG against severe clinical forms of tuberculosis (military and meningeal) in children, demonstrated

a high protection rate, above 80% (**evidence A and B**).<sup>66-68</sup> This protection can last for 10-15 years (**evidence B**).<sup>69</sup>

In Brazil, according to the norms of the Health Ministry, the BCG vaccine is contraindicated in the following situations (**evidence B**):<sup>70</sup> relative contraindication (newborns weighing  $\leq 2$  kg, generalized dermatologic disorders or at the site of administration, use of immunosuppressants) and absolute contraindication (adult with symptomatic or asymptomatic HIV infection, children with symptomatic HIV infection, and patients with congenital immunodeficiency).

In patients with rheumatologic disorders, BCG vaccination is contraindicated in the presence of immunosuppressive treatment (**evidence B**).<sup>70</sup> However, the BCG vaccine is not contraindicated for contacts of immunosuppressed patients.

Although BCG vaccination often results in local adverse effects, long term severe complications are rare (**evidence B**).<sup>70</sup> Patients may develop non-suppurative axillary adenomegaly during the normal evolution of the vaccine lesion, which remit spontaneously, without clinical or surgical treatment. Severe complications, such as abscesses at the site of administration, ulcers, and regional suppurative and fistulized lymphadenitis are rare. Osteomyelitis is rare and it is usually associated with immune deficiency.

### Rotavirus vaccine

Rotavirus is the main etiological agent of acute diarrhea in children younger than 5 years worldwide.<sup>71,72</sup> The infection varies from asymptomatic or mild, with liquid diarrhea of limited duration, to severe cases with dehydration, fever, vomiting, and hospitalization, affecting mainly infants from 3 to 24 months of age.<sup>72,73</sup> Immunocompromised children and adults develop severe or prolonged rotavirus gastroenteritis.<sup>72</sup>

Currently, two rotavirus vaccines have been licensed in Brazil. The monovalent vaccine [GIP(8)], which provides crossed immunity (heterotypical) against other serotypes of rotavirus, is available in the public and private health care system since 2006, and the recently licensed pentavalent vaccine [G1, G2, G3, G4, and P(8)]. Both are live vaccines.<sup>72,74</sup>

Those vaccines are administered orally; the first dose at 2 months of age (6 to 14 weeks and 6 days), and the second at 4 months (14 to 25 weeks), with at least a 1-month interval between them, and it should not be administered after 8 months of life.<sup>74</sup>

Rotavirus vaccines provide 74% to 87% protection against any severity of rotavirus gastroenteritis, and 85% to 98% against severe forms of the disease (**evidence A**).<sup>71,72</sup>

To obtain the best immunological response and avoid the risk of vaccine-induced disease, vaccination should not be done during the period of immunosuppression.

Data on the efficacy of the rotavirus vaccine in patients with rheumatologic diseases, as well as the development of auto-immunity after it, are lacking<sup>3</sup>. Although cases of Kawasaki disease have been reported after vaccination, the causal relationship still cannot be established.<sup>75</sup>

### Varicella vaccine

The varicella vaccine is made with live, attenuated virus derived from the OKA strain, and it is applied subcutaneously. In immunocompetent individuals, it is usually well tolerated and immunogenic. Immunosuppressed patients can develop more intense, although rarely severe, adverse reactions. The vaccine has an 85% effectiveness against all types of the disease and 99% against severe forms of the disease.

The vaccine is not in the official vaccine calendar of the Brazilian public health system, but it is available at the CRIEs. The vaccine schedule proposed by the Brazilian Society of Pediatrics is as follows: one dose for children 1 year old and a second dose at the age of 4 or 6 years. Adolescents, from 13 years on, who have not been vaccinated, or immunodepressed individuals older than one year, should receive two doses with a 4-week interval between them.

Currently, three commercial presentations of the varicella vaccine are available, and one of the manufacturers recommends a single dose for adolescents (**evidence D**).<sup>77</sup> The varicella vaccine suffers influence of other parenteral live vaccines, and they should be administered on the same day in different sites or with a 30-day interval.

A recent study to evaluate the immunization status against varicella in children and adolescents with rheumatologic diseases demonstrated that 50% of 98 patients (2 to 16 years) with a negative history of varicella infection were susceptible (**evidence B**).<sup>76</sup> In this study, 25 susceptible patients were selected (16 with IJA, 4 with JDM, 3 with scleroderma, and one with vasculitis) to receive the varicella vaccine. All patients were treated with MTX and 11 also received corticosteroids. Patients did not develop post-vaccine varicella and/or severe adverse events. Besides, a worsening of the rheumatologic disease was not observed by the authors (**evidence B**).<sup>76</sup>

Evidence on the immunogenicity and safety of the varicella vaccine in patients with SLE (3) is lacking.<sup>78</sup>

Patients with rheumatologic diseases are at a higher risk of developing severe cases of varicella, besides the additional risks related to the chronic use of anti-inflammatories, and

possible induction of macrophage activation syndrome. For children and adolescents with rheumatologic diseases, the ideal would be to indicate this vaccine to susceptible patients before starting pharmacological immunosuppression or three months after its discontinuation. When it is not possible to follow this recommendation, the indication of the varicella vaccine during immunosuppression should be evaluated for each patient considering the regional epidemiologic situation and the type and activity of the baseline disease, as well as the treatment, since a considerable percentage of those patients can be susceptible.<sup>76</sup> If the vaccine is used in this context, strict vigilance of adverse events in the first four weeks after vaccination is recommeAbsolute contraindications for patients with rheumatologic diseases include: doses of CS greater than 2 mg/kg/day or greater than 20 mg/day; monthly pulses of CPM; biological agents; and severe disease activity. When the vaccine is formally contraindicated, one should be attentive for situations of exposure to the varicella virus, at which time passive immunization and acyclovir, if necessary, are indicated, besides vaccination of all susceptible contacts.<sup>74</sup>

Special care should be taken in patients in chronic use of acetyl salicylic acid (only vaccinate one month after discontinuation of this drug) and human immunoglobulin (three months after discontinuation).<sup>74</sup>

### Measles, mumps, and rubella (MMR) vaccine

The MMR is a combined vaccine with live attenuated virus that protects against measles, mumps, and rubella, and it is administered by subcutaneous injection. Currently, three commercial presentations are available. As a rule, they cause little reaction and are well tolerated. Adverse events can be secondary to hypersensitivity reactions to any component of the vaccine or clinical manifestations similar to those caused by the wild virus (vaccine viral replication), usually milder. The vaccine is in the official calendar of the public health system, and the proposed schedule of the Brazilian Pediatrics Society for susceptible patients includes one dose at one year of age and a second dose from 4 to 6 years of age. All children and adolescents should receive or should have received two doses of MMR with at least one-month interval. It is not necessary to administer more than two doses.<sup>79</sup>

Only two studies in the literature evaluated the safety of the MMR vaccine (booster dose) in patients with IJA (**evidence B**).<sup>79,80</sup> The first evaluated prospectively a cohort of 207 patients with IJA, and cases of post-vaccine viral dissemination or higher rate of disease reactivation were not observed.<sup>79</sup> The

other prospective study evaluated the immunogenicity and safety of the vaccine in 15 patients with IJA treated with MTX and etanercept. None of the patients developed vaccine reaction or worsening of the baseline disease, and the response was not influenced by the drugs.<sup>80</sup> The indication of this vaccine for patients with IJA seems to be safe.

As for the indication of the MMR vaccine in other rheumatologic diseases, we suggest that the same guidelines described for the varicella vaccine should be followed.

### Acellular triple (DTaP/Tdap) and double (TT/Td) vaccines

The tetanus and diphtheria toxoids, and anti-pertussis compounds vaccines are safe for children and adults with rheumatologic diseases, including those on immunosuppressants, and the same vaccine calendar for healthy individuals should be used (**evidence A**).<sup>7,60</sup> As for the pertussis fraction, the classical vaccine (DPT) has cellular components capable of triggering the development of adverse reactions, it is also not specifically contraindicated in patients with rheumatic diseases, even those on immunosuppressive therapy (**evidence A**).<sup>81,82</sup> Patients with an incomplete vaccine schedule should be oriented to complete it normally; in those who completed the schedule, a booster dose in adolescence is recommended, since, along with infants and adults, this age group is one of the most affected by whooping cough (**evidence C**).<sup>83</sup>

Commercial presentations of DTaP with 3 and 5 pertussis components, with similar clinical efficacy, are available (**evidence A**).<sup>84</sup> This vaccine is indicated for: a) children up to 6 years who, after receiving any dose of the triple bacterial vaccine with whole cells (DTP or tetravalent – DTP + Hib), developed severe adverse events (seizures in the first 72 hours after vaccination or hypotonic hyporesponsive episode in the first 48 hours after vaccination) (**evidence D**); b) children at increased risk of developing severe reactions to the DTP or tetravalent vaccine (younger than 2 years with: chronic lung or heart disease, with a higher risk to decompensate with fever, and incapacitating chronic neurologic diseases) (**evidence D**); c) newborns who remain in the neonatal unit at the age of vaccination; extremely premature (less than 1,000 g or 31 weeks) at the time of the first dose of the tetravalent vaccine or as long as they remain in the neonatal unit, and chronic seizures (**evidence D**).<sup>85</sup>

The Td (pediatric type) is indicated in children younger than 7 years who presented encephalopathy in the first seven days after the administration of the DPT, tetravalent, or DTaP (contraindication for pertussis vaccine) (**evidence D**).<sup>85</sup>

The Td vaccine (adult type) is indicated for adolescents and adults. The Tda vaccine, in two commercial presentations with similar immunological response, highly immunogenic and safe, is used in adolescents and adults (**evidence A**).<sup>84</sup>

The vaccine schedule include 3 doses with a 60-day interval between each dose, beginning on the 2<sup>nd</sup> month of life. The first booster dose is administered at 15 months of age, the second between 4 and 6 years of age (**evidence A**), and the third between 11 and 19 years with the Td vaccine (**evidence D**).<sup>85</sup> The Brazilian Pediatric Society and the Centers for Disease Control and Prevention recommend the vaccination of adolescents with the Tda vaccine (**evidence D**).<sup>83,85</sup>

All acellular presentations are composed of the tetanus and diphtheria toxoids associated with chemically inactivated, or obtained by genetic engineering, pertussis toxin and other antigenic bacterial components. Their efficacy and immunologic response is similar to the whole cell DTP (**evidence A**). In Brazil, the Health Ministry recommends whole cell vaccines (DTP, for children, and Td, for adolescents and adults) in its official vaccine calendar,<sup>83</sup> although the Brazilian Pediatrics Society, as well as many developed countries, advocates the use of acellular vaccines (DTaP, for < 7 years of age, and Tdap, for adolescents and adults) (**evidence D**).<sup>84</sup>

When the three-dose (IM) schedule is completed, with a booster after 6 to 12 months, is maintained for 6 to 12 years (**evidence A**). Booster doses are administered every 10 years, which should be anticipated for 5 years in cases of pregnancy and wounds that could cause tetanus.<sup>60</sup> In the latter, the need of passive immunization, along with the vaccine, will depend on the number of vaccine doses received previously, the length of time since the last dose, and type of wound (**evidence A**).<sup>85</sup>

### Inactive (Salk) and active (Sabin) poliomyelitis vaccines

The Salk and Sabin vaccines are highly immunogenic and effective in the prevention of poliomyelitis. The Salk vaccine provides seroconversion for the three serotypes of the polio virus in 95%, with two doses, and 100% of the patients, with three doses. The Salk virus is not associated with fecal-oral dissemination. A vaccine schedule with at least three doses of the Sabin vaccine induces excellent antibody response, high intestinal immunity, and probable perennial protection. It is associated with fecal dissemination of the virus, which might lead to vaccination of contacts (**evidence A**).<sup>86</sup>

Children and adolescents with inflammatory diseases on immunosuppressants, including systemic corticosteroids, should receive the inactive vaccine (Salk), according to the universal

immunization schedule, but not the live vaccine (Sabin).<sup>6</sup> Live vaccine should not be administered to patients with SLE.<sup>78</sup>

In 1978, after a national vaccination campaign in Israel, four out of 73 SLE patients vaccinated developed a reactivation of their disease. However, prospective studies to confirm this report were not undertaken (**evidence D**).<sup>78</sup>

In controlled studies with patients undergoing bone marrow transplants, in Finland, the vaccine schedule of three doses of the inactive polio vaccine was equally immunogenic when instituted 6 or 18 months after the bone marrow transplant.<sup>87</sup>

On a vaccine campaign in Finland in 1985 to control an outbreak of poliomyelitis, it was observed that immunocompromised patients, who received the Salk vaccine (inactivated virus) instead of the Sabin vaccine (of the campaign), were protected against poliomyelitis during the outbreak, with protective titles of neutralizing antibodies against the poliomyelitis virus.<sup>87</sup>

The Sabin vaccine is administered at the SUS and CRIEs and the Salk vaccine at the CRIEs.

### Immunoglobulins for passive immunization

Vaccines with live attenuated virus against measles (monovalent or combined) and varicella are contraindicated in patients with congenital or acquired immunosuppression. Similarly, in children and adolescents with rheumatologic diseases on immunosuppressants or high doses of corticosteroids, vaccination should be postponed for at least 3 months after discontinuation of the drugs. To prevent or modify the course of the disease, prophylaxis after the contact through passive immunization with polyvalent, hyperimmune, or heterologous human immunoglobulins (Ig) after the contact is indicated in those cases. It has a fast response, within three days, and the protection lasts for three to four weeks (**evidence D**).<sup>58-74</sup>

In cases of exposure to measles, 0.5 mL/kg (up to 15 mL), double of the dose used for immunocompetent individuals, of human Ig is administered IM up to six days after exposure. Immunocompromised individuals who receive regular doses of Igs are considered protected. An additional dose (100-400 mg/kg) should be recommended if the individual is exposed to measles three or more weeks after the last dose (**evidence D**).<sup>58-74</sup>

Prophylaxis after exposure to varicella is indicated in the case of contact with patients with varicella or the contagious phase of herpes zoster. Specific hyperimmune human Ig, which contains high titers of anti-varicella antibodies (VZIG), at a dose of 1.25 mL (125 U) for each 10 kg of weight (up to 625 U) IM, should be administered up to 96 hours after exposure.

In high risk patients, the association with an antiviral agent might be necessary.<sup>58-74</sup>

Prophylaxis after contact with hepatitis B is indicated in immunosuppressed patients, even those previously vaccinated. The recommended dose of anti-hepatitis B human Ig (HBIG) is 0.06 mL/kg (10 mg IgG/kg) IM, administered as early as possible (no more than 14 days after exposure). For non-vaccinated patients or those with negative serology (anti-HBs), immediate vaccination, besides Ig, is recommended.<sup>58-74</sup>

Table 1 shows some situations in which passive immunization is indicated.

### Contacts of immunosuppressed patients

Individuals who are in contact with immunosuppressed patients, family members or health care professionals, are involuntary source of pathogens, which are often immunologically preventable and, therefore, they should

be adequately vaccinated to reduce the risks of disease transmission. Since the literature does not specify the degree of immunosuppression induced by the doses of the drugs used to treat rheumatologic diseases, we will use the guidelines for contacts of immunosuppressed patients (Table 2 and 3) (**evidence D**).<sup>74</sup> Table 4 shows the evidence for the use of the different vaccines in patients with SLE and IJA.

### CONCLUSIONS

As a rule, inactive vaccines and vaccines with protein components (against hepatitis A and B, HPV, influenza, pneumococcus, meningococcus, Hib, Salk, tetanus, and diphtheria) are effective and safe for patients with rheumatologic diseases, even those on immunosuppressants. However, live vaccines (yellow fever, BCG, rotavirus, varicella, MMR, and Sabin) are, usually, contraindicated in immunosuppressed children and adolescents.

**Table 1**  
Immunoglobulins in infectious diseases: passive immunizati

Disease/Indication	Composition	Administration	Schedule
<b>Measles</b> / Exposure to an infected person	Polyvalent human Ig	Up to 6 days after exposure	0.5 mL/kg, up to 15 mL, IM
<b>Varicella</b> /Significant contact with a patient with varicella or herpes zoster during the infectious stage	Specific human Ig with high titers of antibodies against varicella (VZIG)	Up to 96 h after exposure	1.25 mL (125 IU) for each 10 kg (up to 625 U), IM. Consider use of antiviral drugs
<b>Hepatitis B</b> /Accidental percutaneous or mucous exposure to blood; sexual contact with acute cases of hepatitis B; victims of sexual abuse, even those previously vaccinated	Specific human Ig with high titers of anti-HBsAg antibodies *	As early as possible (no more than 14 days after exposure)	Single dose, 0.06 mL/kg. In infants, 0.5 mL, IM
<b>Hepatitis A</b> /Contact	Polyvalent human Ig	Before and up to 14 days after exposure	Single dose, 0.02 mL/kg, IM
<b>Tetanus</b> /Susceptible individuals with severe injuries (extensive, multiple, or deep) with contaminated material (soil, contaminated water, dust)	Hyperimmune heterologous serum*; Specific human Ig with high titers of anti-tetanus antibodies*	As early as possible (up to 2 weeks after exposure)	Single dose, 5,000 IU, IM; single dose of 250 IU to 500 IU, depending on the severity, IM
<b>Rabies</b> /Exposure	Specific human Ig with high titers of anti-rabies antibodies *	As early as possible. Use even after a delay of several days	Single dose of 20 IU/kg infiltrated in the wound (as much as possible) and the remainder IM

\*Associate with the vaccine; IM = intramuscular

**Table 2**  
Vaccines recommended for patients with malignancies and/or need chemo-, radio-, or corticotherapy, and contacts of those patients<sup>1</sup>

Vaccines	Patients		Contacts	
	Before treatment	After treatment	Household	Hospital
BCG	No	No	Yes <sup>2</sup>	Yes <sup>2</sup>
Diphtheria/ tetanus/ whooping cough	Yes <sup>3</sup>	Yes <sup>3</sup>	Yes <sup>2</sup>	Yes <sup>2</sup>
Oral poliomyelitis	No	No	No	No
Inactivated poliomyelitis	Yes	Yes	Yes	Yes
Hepatitis B	Yes	Yes	Yes <sup>2</sup>	Yes <sup>2</sup>
Measles/mumps/ rubella	Yes <sup>4</sup>	No	Yes <sup>2</sup>	Yes <sup>2</sup>
Varicella Zoster	No	No	Yes, if susceptible	Yes, if susceptible
Haemophilus influenza	Yes, if < 19 years	Yes, if > 19 years	Yes <sup>2</sup>	Yes <sup>2</sup>
Influenza	Yes	Yes	Yes	Yes
Hepatitis A	Yes	Yes	No	No
Meningococcus	Yes	Yes	No	No
Pneumococcus (according to age) Pnc7/Pn23	Yes	Yes	No	No

<sup>1</sup> Whenever possible, follow the interval of the vaccine calendar of the national immunization program. <sup>2</sup> According to the norms of the national immunization program. <sup>3</sup> Preferentially DTaP. <sup>4</sup> If the patient does not have any pathology that contraindicates live vaccines.

**Table 3**  
Vaccine schedule for contacts of immunosuppressed patients.

Vaccine	Vaccine Schedule
Influenza	Yearly
Varicella	1st dose with 1 year of age
	2nd dose at 4 to 6 years
	2 doses with a 30-day interval if > 13 years
Poliomyelitis	Substitute the oral vaccine (OPV) by the inactive vaccine (IPV) on children beginning or finishing the vaccine schedule
MMR	1st dose at 1 year of age
	2nd dose at 4 to 6 years
	1 dose if not vaccinated

**Table 4**

Vaccination of patients with systemic lupus erythematosus (SLE) and idiopathic juvenile arthritis (IJA) according to scientific evidence

Vaccine	Type	SLE		IJA	
		Evidence of efficacy	Evidence of safety	Evidence of efficacy	Evidence of safety
BCG	Live attenuated	D	D	D	D
Haemophilus influenza	Conjugated	B	B	D	D
Hepatitis A	Inactivated	D	D	D	D
Hepatitis B	Recombinant DNA	A	A	D	D
Rotavirus	Live attenuated	0	0	0	0
Influenza	Inactive component	B	B	B	B
MMR	Live attenuated	0	0	B	B
Meningococcus C	Polysaccharide component	D	D	B	B
Pneumococcus	Polysaccharide component	B	B	D	D
Poliomyelitis	Oral: live attenuated	D	D	D	D
	Parenteral: inactive	D	D	D	D
Varicella	Live attenuated	0	0	B	B
Pertussis	Whole cell inactive	D	D	D	D
Tetanus	Toxoid	B	B	D	D
Diphtheria	Toxoid	D	D	D	D
Yellow fever	Live attenuated	0	C	0	0
HPV	Inactivated	0	0	0	0

MMR: measles, mumps, rubella; HPV: human papillomavirus; A: major experimental and observational studies; B: minor experimental and observational studies; C: case reports (non-controlled studies); D: opinion without critical analysis, based on consensus, or physiological studies or animal models; and 0: absence of studies.

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