



# Vaccination and Pediatric Rheumatic Diseases: Current Recommendations

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## Editorial

Pediatric patients with rheumatic diseases are at increased risk of infections. Current aggressive treatments involving the early use of immunosuppressive drugs and biological agents have further increased the susceptibility to infections in this group of patients. The immunogenicity concept means the immune response induced by vaccination, and is often used to assess the efficacy of vaccination in children with rheumatic diseases. The response is evaluated by using vaccine-specific Geometric Mean Antibody Titers (GMT) or concentrations (GMC), seroconversion rates and/or seroprotection rates. The immunogenicity of a vaccine depends on protection and immunological response of each pathogen due to the interaction between the humoral and cellular immune system. Immunogenicity of a vaccine in patients with rheumatic diseases can differ from the healthy population, due to the disease or immunosuppressive treatment. Immunosuppression can be interpreted as “high level” and “low level”, according to the Infectious Diseases Society of American guidelines: Receiving daily corticosteroid treatment at a dose of 20 mg (or >2 mg/kg/day for patients <10 kg) of prednisone or equivalent for >14 days or receiving certain biologic drugs (i.e., adalimumab, certolizumab, infliximab, etanercept, golimumab, rituximab) are regarded as “high-level immunosuppression”. “Low-level immunosuppression” is accepted as receiving prednisone at a dose of 0.5 mg/kg/day, methotrexate at doses of less than 0.4 mg/kg/week or azathioprine at less than 3 mg/kg/day.

Biologics are disease modifying agents which cause high level immunosuppression. Their immune-modulating effects can last for weeks to months after discontinuation, depending on their half lives. Patients treated with biologics are at increased risk of infections caused by mycobacteria, molds, fungi, legionella and other intracellular pathogens.

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Recommendations for the vaccination of children with rheumatic diseases under the light of current literature are outlined as follows:

1. The vaccination schedule should be questioned at each visit and, be recorded to the vaccination card. Once a rheumatologic disease is diagnosed, the patient's vaccinations should be reviewed immediately and incomplete vaccinations should be completed. If the treatment has already been started, vaccinations should be administered during the period when the disease is at remission and the immunosuppression is at its lowest level.
2. Vaccination should be administered prior to immunosuppression, if possible.
3. Vaccines are effective and safe to prevent the risk of infection when they are administered in accordance with guidelines, and there is no evidence that vaccines lead to rheumatologic diseases or exacerbations in patients with pediatric RD. There is no contraindication for inactive or live vaccines in patients who do not receive immunosuppressive treatment.
4. Inactivated vaccines can be administered to pediatric patients with RD while using glucocorticosteroid, DMARDs and/or anti-TNF- $\alpha$  therapy.
5. Inactivated vaccines including inactive influenza virus (IIV), and live virus vaccines should be administered to patients prior to commencement of corticosteroid therapy as indicated on the annual immunization schedule for immunocompetent children, if possible. Inactivated vaccines should be completed  $\geq 2$  weeks before and live virus vaccines  $\geq 4$  weeks before the commencement of corticosteroid therapy.
6. To assure the adequate immune response, it is recommended to measure pathogen

specific antibody concentrations following vaccination in all pediatric patients with RD on high-dose glucocorticosteroids (>2 mg/kg/day or >20 mg/day for 2 weeks) or on rituximab. Measuring pathogen specific antibody concentrations should also be considered in patients receiving anti-TNF $\alpha$  treatment.

7. Hydroxychloroquine and sulfasalazine do not affect the immune response and are not considered as immunosuppressive agents. Non-biologic disease modifying agents other than corticosteroids or methotrexate do not significantly reduce the immune response to inactive vaccines, the response is usually sufficient.

8. It is recommended to adhere to national vaccination guidelines, which have specific focus on geographical conditions, closely interaction with the microflora. Related vaccination schemes would therefore include cholera, diphtheria, *Haemophilus influenzae* type B (Hib), hepatitis A virus (HAV), HBV, Japanese encephalitis, pertussis, pneumococci, poliovirus and meningococci, rabies, tetanus, tickborne encephalitis and typhoid fever, in children with RD.

9. Immunoglobulin administration may reduce the effectiveness of live vaccines. Therefore, it is necessary to apply live vaccines (i.e., measles, varicella vaccine) at least 3 months following the immunoglobulin administration. If immunoglobulin administration is required within 14 days of live vaccine administration, these vaccinations need to be repeated later.

10. Biologic drugs are considered as highly immunosuppressive. Live virus vaccines are contraindicated during and for weeks to months following discontinuation of the biologics. Inactivated vaccines including IIV are recommended during therapy as it is in the annual immunization schedule, and should not be withheld because of a concern for an exaggerated inflammatory response. Vaccination status should be documented, and inactivated vaccines (including annual IIV) should be administered 2 weeks before the initiation of biologic drugs, if required. Live virus vaccines should be administered at least 4 weeks before the initiation of biologic therapy, unless contraindicated by a condition or other therapies. Testing for Varicella zoster virus and Hepatitis B virus should also be considered.

11. Seasonal influenza vaccine is safe and immunogenic in adult and pediatric patients with RD. Seasonal influenza vaccine should be recommended annually to these patients.

12. Hepatitis B virus (HBV) vaccine is reported safe and immunogenic in most studies. It is important to check for antibody titers in the follow-up, since they may fall below their protective levels over time in pediatric patients with RD. A booster dose should be considered.

13. Hepatitis A vaccine is safe in patients with JIA. Its effectiveness is similar in both healthy and the ones with RD; however, children with active systemic JIA receiving anti-tumor necrosis factor alpha drugs should be checked for antibody titers.

14. Both PPV and PCV are safe and immunogenic in pediatric patients with RD, although anti-TNF $\alpha$  treatment may reduce antibody concentrations.

15. Meningococcal vaccine provides sufficient antibody levels, even in patients receiving intense immunosuppressive treatment. Hence, patients with JIA can be vaccinated safely and effectively with the MenC conjugated vaccine.

16. The tetanus and diphtheria toxoids, and anti-pertussis compound vaccines are safe for children and adults with RD, including immunosuppressive period. Vaccination schedule is the same for healthy children. Nevertheless, antibody titer may fall below the protective level in patients receiving high dose immunosuppressives such as glucocorticosteroid or biologic drugs. Anti-tetanus immunoglobulin may be considered in pediatric patients with RD receiving high-dose corticosteroid, immunosuppressants, or biologics.

17. Long-term protection against HPV infections in SLE patients is not clear. Larger, controlled studies in JSLE patients are needed to evaluate the immunogenicity of the HPV vaccine in this group. The immunogenicity of the bivalent HPV vaccine in JIA patients are found as adequate up to 12 months after vaccination. Despite lower antibody levels compared to controls, no statistical significant difference in results over time is observed.

18. In pediatric patients with RD living in endemic areas for tuberculosis, it is suggested to vaccinate prior to starting immunosuppressive therapy. However, BCG vaccination is contraindicated during immunosuppressive treatment. Live bacilli are observed at the site of inoculation at least for 6 months, which is a risk factor for disseminated infection in related patients.

19. Patients on immunosuppressive drugs such as systemic corticosteroids, should receive the inactive vaccine (Salk), according to the universal immunization schedule, but not the live vaccine (Sabin).

20. MMR vaccination appears to be safe in JIA according to recent literature. Protective antibody levels against mumps and rubella up to 10 years following MMR booster vaccination may fall under protective level. Therefore, the MMR booster vaccine may be needed in pediatric patients with RD over time.

All the patients with RD should be screened for sensitivity to the Varicella-zoster virus before the commencement of immunosuppressive drugs such as corticosteroids. should be considered in sensitive patients and, if possible, given at least 3 weeks before the inception of such medications. Several studies have found that VZV vaccine is immunogenic in patients using methotrexate, prednisone and/or biologic agents and no varicella infection is reported in these patients. On the other hand, vaccination with VZV vaccine is contraindicated in patients using high dose immunosuppressives.