

# Vaccinations in juvenile chronic inflammatory diseases: an update

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**Abstract** | Vaccination is a powerful tool to reduce the burden of infectious diseases in paediatric patients with chronic rheumatic diseases. Live attenuated vaccines are not recommended for profoundly immunosuppressed patients, but nonlive vaccines have adequate safety and efficacy profiles in the few (admittedly underpowered) studies published to date. No severe vaccine-specific or disease-specific adverse events have been observed in patients with juvenile idiopathic arthritis (JIA) or childhood-onset systemic lupus erythematosus (SLE) who have been vaccinated with live or nonlive agents. The immune response to live vaccines is variable in these patients but generally adequate, despite concomitant use of immunosuppressive and biologic agents. The proposal that onset of autoimmune rheumatic diseases could be induced by vaccination is controversial and primarily based on case reports; however, patients with mevalonate kinase deficiency can experience febrile attacks after immunizations. Adequately powered studies of live and nonlive vaccination in patients with paediatric rheumatic diseases are necessary to clarify safety and efficacy issues. This narrative Review discusses vaccination in patients with JIA, childhood-onset SLE, juvenile dermatomyositis, juvenile systemic sclerosis, primary vasculitis and autoinflammatory syndromes. Vaccine safety, short-term and long-term changes in disease parameters, and the immunogenicity and influence of immunosuppressive agents are outlined for each combination of disease and vaccine.

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## Introduction

Children and adolescents with chronic rheumatic diseases, including juvenile idiopathic arthritis (JIA), childhood-onset systemic lupus erythematosus (SLE), juvenile dermatomyositis (JDM), primary vasculitis and autoinflammatory syndromes are particularly susceptible to infections, as a result of both the disease itself and immunosuppressive therapies. Vaccination is highly specific, inexpensive and safe in healthy paediatric populations and is, therefore, one of the main tools used to reduce the morbidity associated with viral and bacterial infections.<sup>1,2</sup> Live and nonlive vaccines are included in routine paediatric vaccination programs worldwide. However, immunization of patients with childhood inflammatory conditions is somewhat controversial, particularly because of concerns over vaccine safety and effectiveness, related to the distinct disease manifestations and their respective treatments.<sup>3–5</sup> Moreover, in some patients, vaccines that require administration with adjuvants have induced autoantibodies, and even overt autoimmune disease—a condition termed autoimmune/inflammatory syndrome induced by adjuvants (ASIA).<sup>3</sup> This condition is caused by environmental factors with an immune adjuvant effect such as silicone, aluminium, pristane, and infectious components that can induce autoimmune disease. ASIA is characterized by muscular and joint

manifestations, chronic fatigue, sleep disturbances, cognitive impairment and memory loss, and the possible emergence of a demyelinating autoimmune disease.<sup>3</sup>

The lack of a clear definition of vaccine immunogenicity and safety among children and adolescents with rheumatic diseases hampered the identification of indications and contraindications for vaccination, with consequently inadequate surveillance of vaccinated patients by paediatric rheumatologists.<sup>6–9</sup> In 2011, a European League Against Rheumatism (EULAR) task force published a systematic review<sup>10</sup> and an article in which the Delphi voting procedure was used to determine the level of agreement on 15 evidence-based recommendations<sup>1</sup> for vaccinating patients with paediatric rheumatic diseases. Both publications reinforced the need for regular updates, as the majority of recommendations were weak. Nonlive vaccines are, however, highly recommended for patients with JIA, childhood-onset SLE, JDM or juvenile systemic sclerosis.<sup>1</sup> By contrast, live attenuated vaccines are not recommended in profoundly immunosuppressed patients.<sup>1</sup> According to the American Academy of Pediatrics and The Committee of Immunization Practices of the Centers for Disease Control and Prevention in the USA, profound immunosuppression was defined as current use or use in the past 3 months of any dose of mycophenolate mofetil, cyclophosphamide or methylprednisolone; ciclosporin (>3.0 mg/kg daily), azathioprine (>1.5 mg/kg daily), methotrexate (>0.4 mg/kg or 28 mg weekly) or

## Competing interests

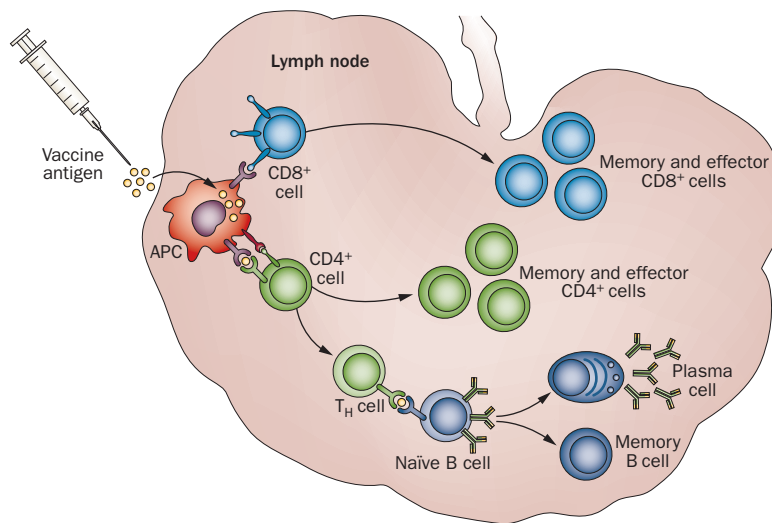
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**Key points**

- Nonlive vaccines have adequate safety profiles and are highly recommended for use in paediatric patients with rheumatic diseases
- Live attenuated vaccines are generally not recommended for profoundly immunosuppressed patients, including those receiving high doses of ciclosporin, azathioprine, methotrexate or corticosteroids
- Most published studies of vaccination in paediatric patients with rheumatic diseases were not adequately powered to assess immunogenicity and safety
- No serious adverse events have been reported in patients with juvenile idiopathic arthritis or childhood-onset systemic lupus erythematosus immunized with either live or nonlive vaccines
- The immune response to vaccination with nonlive agents in these two groups of patients was variable but generally adequate, despite concurrent use of immunosuppressive and biologic agents
- The proposal that autoimmune rheumatic diseases could be induced after vaccination is controversial, although patients with mevalonate kinase deficiency might experience febrile attacks after immunizations



**Figure 1** | The immune response to vaccination. Vaccine antigens are recognized by APCs in the lymph nodes. The antigens are then presented to T cells, inducing their activation and the clonal expansion of CD4<sup>+</sup> and CD8<sup>+</sup> T cells that can differentiate into effector and memory cells respectively. The CD4<sup>+</sup> T cells can also differentiate into T<sub>H</sub> cells that assist in the activation of B cells. The naïve B cells differentiate into memory B cells or antibody-secreting B cells. Memory B and T cells guarantee long-term immunity. Abbreviations: APC, antigen presenting cell; T<sub>H</sub>, T helper.

corticosteroids (>2.0 mg/kg or >20 mg daily for more than 1 week); or combinations of these drugs with other immunosuppressive agents.<sup>11,12</sup> The EULAR task force did not discuss a consensus opinion on the potential role of immunization in inducing or aggravating paediatric rheumatic diseases.<sup>1,10</sup>

The results of appropriately powered studies that calculated sample sizes on the basis of immunogenicity,<sup>3,13,14</sup> and data on vaccination of patients with paediatric autoimmune rheumatic and autoinflammatory diseases,<sup>13–32</sup> suggest that a consolidated approach to vaccinating patients with these conditions is needed. This Review focuses on each disease individually, examines the short-term and long-term safety of live attenuated and nonlive composite vaccines, and discusses whether the immunogenicity of each vaccine is influenced by disease-related

factors or treatment with immunosuppressive agents. However, no data exist regarding live attenuated vaccines for poliovirus or yellow fever or nonlive inactivated vaccines against poliovirus, *Haemophilus influenzae* type b or human papilloma virus in paediatric patients with rheumatic diseases; these vaccines are, therefore, not discussed in this Review.

**The developing immune system**

The immune response in children, especially young children (<5 years old), is weaker than in adults.<sup>33</sup> Indeed, infants who are born prematurely (<37 weeks gestation) or have a low birth weight (<2.5 kg) consequently have an increased risk of morbidity and mortality from vaccine-preventable diseases.<sup>34</sup> The adaptive immune system is underdeveloped *in utero* owing to restricted exposure to antigens. Neonates are, therefore, largely dependent on the innate immune system to ward off disease;<sup>35</sup> the attenuated type 1 T-helper (T<sub>H</sub>1) response alters the effectiveness of the response to vaccines in infants and increases their susceptibility to intracellular infections compared with older children.<sup>33,35</sup> T<sub>H</sub>1 cell-mediated immunity increases rapidly from 6 months after birth and the immune system continues to mature until the child is 5 years old, when the T<sub>H</sub>1 cell-driven immune response is comparable to that of adults.<sup>33</sup> Nonetheless, the total T-cell count in neonates, including CD4<sup>+</sup> and CD8<sup>+</sup> T cells, is twice that in adults. The number of CD4<sup>+</sup> T cells increases and the CD8<sup>+</sup> T-cell count remains stable until the age of 2 years, when both start to decline, reaching adult levels during adolescence.<sup>33</sup> During early infancy, the B-cell response is also less than that of adults, with a delayed onset, a shorter antibody response, lower IgG<sub>2</sub> titres and reduced immunoglobulin affinity.<sup>35</sup> Consequently, the humoral response to vaccines administered during the first 2 months of life does not always guarantee protective antibody titres.

An adequate immune response to vaccines depends mainly on B-cell responses, although T cells could also have important roles.<sup>6,36</sup> Vaccine administration induces adaptive immune responses through the activation of antigen-presenting cells (APCs) such as dendritic cells. In the lymph nodes, the antigens are presented to T cells by the APCs, resulting in the activation and the clonal expansion of CD4<sup>+</sup> and CD8<sup>+</sup> T cells. CD8<sup>+</sup> T cells can differentiate into memory and effector cells, and CD4<sup>+</sup> T cells differentiate into several T-helper cell subtypes and assist in the activation of B cells. Naïve B cells differentiate into memory B cells and antibody-secreting plasma cells. Memory B and T cells provide long-term immunity in the blood, lymph nodes and the bone marrow (Figure 1).

Indeed, both B-cell and T-cell defects can influence the effectiveness of immunization in patients with primary immunodeficiencies or those who are being treated with immunosuppressive therapy.<sup>13,35,36</sup> These children usually have a reduced immune response to vaccines and could also develop active infections after immunization with live agents.<sup>37</sup> Furthermore, if onset of paediatric rheumatic diseases (such as childhood-onset SLE and

**Table 1** | Live vaccines in patients with JIA

Study	Participants	Vaccine	Safety	Immunogenicity and influence of immunosuppressive agents
Linnemann <i>et al.</i> (1975) <sup>38</sup>	85 patients with JIA 85 healthy controls	Rubella	NA	Similar GMTs in patients with JIA and controls
Heijstek <i>et al.</i> (2007) <sup>39</sup>	207 patients with JIA (49 treated with methotrexate)	MMR	9 patients had joint complaints or disease aggravation 6 patients had fever or malaise No measles, mumps or rubella	NA
Borte <i>et al.</i> (2009) <sup>40</sup>	15 patients with JIA 22 healthy controls	MMR	No increase in disease activity within 6 months of vaccination No overt measles, mumps or rubella	No influence of low-dose methotrexate or etanercept on generation of virus-restricted T cells and protective IgG antibodies
Korematsu <i>et al.</i> (2009) <sup>41</sup>	1 patient with JIA	Rubella	Relapse of systemic JIA and congestive heart failure 5 days after vaccination	Increase in anti-rubella IgG and IgM antibodies
Kiray <i>et al.</i> (2009) <sup>42</sup>	115 patients with JIA 45 healthy controls	BCG	NA	Considerably lower response to PPD (induration size and antibody positivity rates) in patients with JIA than controls Glucocorticoid or methotrexate use had no effect on PPD test response
Pileggi <i>et al.</i> (2010) <sup>43</sup>	17 patients with JIA 18 healthy controls	Varicella-zoster	3 patients with JIA had a self-limited varicella-like rash No worsening of disease parameters, serious adverse events or overt varicella	8 of 17 patients were still positive for anti-varicella IgG after 1 year No changes in immunogenicity associated with methotrexate, ciclosporin or leflunomide therapy
Heijstek <i>et al.</i> (2012) <sup>20</sup>	400 patients with JIA 2,176 healthy controls	MMR	NA	Lower GMT and seroprotection rate against mumps and rubella and higher GMT against measles in patients with JIA than in controls Methotrexate and glucocorticoid use had no effect on vaccine response

Abbreviations: BCG, bacillus Calmette–Guérin; GMT, geometric mean titre; JIA, juvenile idiopathic arthritis; MMR, measles, mumps and rubella; NA, not available; PPD, purified protein derivative.

JDM)<sup>27,30</sup> occurs during the development of the immune system, the pathogenic processes underlying these diseases could influence both the specific T-cell response to vaccination and the resulting memory B-cell population.

## Juvenile idiopathic arthritis

### Live vaccines

#### Vaccine safety

Possible adverse events related to vaccination could involve either worsening of the pre-existing rheumatic disease or reactions to the vaccination itself, including localized or systemic anti-inflammatory reactions as well as overt disease (for live attenuated vaccines). Live attenuated vaccines, including those based on measles, mumps and rubella (MMR), varicella-zoster and bacillus Calmette–Guérin (BCG), seem to be safe to use in patients with JIA (Table 1).<sup>20,38–43</sup>

The MMR vaccine is usually administered at 14–15 months of age with a booster at 8–10 years of age.<sup>20,39</sup> A retrospective observational study was performed to evaluate the MMR vaccine booster in 207 patients with JIA.<sup>39</sup> Disease-specific and vaccine-specific safety of this vaccine was adequate, with no evidence of increased JIA activity or vaccine-related severe adverse events (including overt measles, mumps or rubella) during the 6 months after immunization;<sup>39</sup> similar results

were also reported in a small prospective study.<sup>40</sup> Moreover, no deterioration in erythrocyte sedimentation rate was observed after MMR vaccination in 49 patients with JIA who were being treated with methotrexate.<sup>39</sup> However, a mild exacerbation of JIA within the 8 weeks following rubella-only vaccination was reported in 85 patients with JIA.<sup>38</sup> To our knowledge, only one case report describes a relapse of JIA temporally associated with vaccination. Relapse occurred 5 days after administration of a live attenuated rubella-only vaccine in a patient with systemic-onset JIA who was in long-term remission.<sup>41</sup>

In a prospective, controlled study,<sup>43</sup> 25 patients with juvenile rheumatic diseases, 17 of whom had JIA, received a single dose of varicella-zoster vaccine. All patients were being treated with methotrexate and five patients with JIA were also receiving prednisone (up to 10 mg daily).<sup>43</sup> None of the 25 patients with a juvenile rheumatic disease or the 18 healthy children in this study developed varicella after immunization.<sup>43</sup> One patient with a juvenile rheumatic disease and one healthy child had a low-grade fever, and three patients with JIA developed a self-limited, varicella-like rash.<sup>43</sup> No disease activity parameter worsened during the 3 months after vaccination.<sup>43</sup> Of note, the number of active joints in the patients with JIA decreased significantly after immunization ( $P = 0.009$ ).<sup>43</sup>

*Immunogenicity and immunosuppressive agents*

The immunogenicity of live attenuated vaccines is generally reduced in patients with JIA compared with healthy children; however, therapy does not seem to account for this deleterious effect.<sup>1</sup> In a controlled study,<sup>40</sup> lower antibody titres were produced in response to the measles component of the MMR vaccine in patients with JIA compared with healthy children, 6 months after immunization. The immune response to the MMR vaccine comprises both humoral and cell-mediated elements,<sup>44</sup> but neither humoral nor cellular immune responses were substantially altered by low doses of methotrexate, alone or in combination with anti-TNF therapy, in patients with JIA who received the MMR vaccine.<sup>40</sup> The long-term antibody response to MMR and diphtheria vaccines was evaluated in a retrospective cross-sectional study of 400 patients with JIA and 2,176 healthy children.<sup>20</sup> Up to 5 years after vaccination, the patients with JIA had lower seroprotection rates as well as lower geometric mean titres (GMTs) of antibodies against mumps, rubella and diphtheria than those of the healthy children. By contrast, the measles-specific GMT was substantially higher in patients with JIA than healthy children, and seroprotection rates were comparable to those in healthy patients. Immunogenicity of the measles vaccine was not affected by treatment with immunosuppressive agents, particularly methotrexate or glucocorticoids.<sup>20</sup>

The humoral immune response in 17 patients with JIA of all subtypes was similar to that of controls after one dose of a live attenuated varicella-zoster vaccine.<sup>43</sup> Eight patients with JIA maintained seroprotective levels of virus-specific IgG antibodies 1 year after immunization.<sup>43</sup>

The (tuberculin) purified protein derivative skin test was performed in 115 children with JIA who had been vaccinated with BCG.<sup>42</sup> Immunogenicity (in terms of both induration size and test positivity rate) was significantly lower in immunized patients with JIA than in healthy, immunized children.<sup>42</sup>

**Nonlive vaccines***Vaccine safety*

Adequate safety profiles for vaccines against influenza, pneumococcal and meningococcal infections, hepatitis B and hepatitis A have been observed in patients with JIA (Table 2).<sup>15,22,25,26,45–50</sup> In general, clinical and laboratory disease activity parameters remained stable after influenza immunization.<sup>14,16,45–47</sup> A prospective evaluation of 34 paediatric patients with chronic arthritis found no significant increase in disease activity parameters after seasonal influenza vaccination.<sup>45</sup> Likewise, in a study of influenza vaccination in children with rheumatic diseases (including 49 patients with JIA) who were being treated with long-term immunosuppressive therapy, no patients had disease flares 1, 3, or 6–8 months after vaccination.<sup>47</sup> These observations, which indicate the safety of seasonal influenza vaccination, have been reinforced by the findings of a study in 31 patients with stable JIA,<sup>21</sup> in which no safety concerns were reported 1 month or 5 months after immunization. Additionally, the safety profile of the vaccine

administered with MF59 adjuvant was no worse in children and adolescents with JIA than in healthy individuals.<sup>16</sup> The most frequent adverse events related to this vaccine were mild, local reactions.<sup>14,21,22,45</sup>

Notably, autoantibody induction by seasonal influenza vaccine was assessed in one study of 49 children and adolescents with JIA; no increase in autoantibody titre was observed.<sup>47</sup> Likewise, rheumatoid factor levels remained stable in 60 patients with JIA who were immunized with seasonal influenza vaccine.<sup>16</sup> By contrast, a trend towards increased levels of anticardiolipin IgG after receiving seasonal influenza vaccination was observed in a prospective study of 31 patients with JIA: such antibodies were present in 10%, 20% and 32% of patients before, 1 month after, and 6 months after immunization, respectively.<sup>21</sup> No changes were observed in the levels of antinuclear antibodies, antineutrophil cytoplasmic antibodies, anti- $\beta$ 2 glycoprotein I antibodies or lupus anticoagulant.

In one case report,<sup>23</sup> a 3-year-old patient with systemic-onset JIA relapsed after receiving two doses of influenza vaccine. However, short-term severe adverse events and disease exacerbation were not observed after influenza vaccination in 27 paediatric patients with systemic-onset JIA who were being treated with tocilizumab.<sup>24</sup> The use of adjuvant-free pandemic influenza A H1N1/2009 vaccine also had a satisfactory disease-specific safety profile; patients with JIA had stable disease parameters before and after immunization.<sup>14</sup>

Pneumococcal infections are associated with increased morbidity and mortality in patients being treated with anti-TNF agents.<sup>49</sup> Vaccination against pneumococcal and meningococcal infections, as well as hepatitis A and B, is safe in patients with JIA. Only mild, local reactions in response to vaccination against pneumococcal infections were reported in 31 patients with JIA who were receiving conventional DMARDs along with anti-TNF therapy and in 32 age-matched patients treated only with conventional DMARDs.<sup>49</sup> In a multicentre study,<sup>50</sup> 234 patients with JIA aged 1–19 years received a meningococci serogroup C conjugate vaccine. Clinical and laboratory parameters of disease activity remained stable in these patients throughout the 6 months before and 6 months after vaccination.<sup>50</sup> In the only study that has evaluated hepatitis B vaccination in patients with JIA who were in disease remission at the time of vaccination,<sup>48</sup> none of the 39 patients (aged 4–16 years) had clinical deterioration or any other adverse event related to the vaccine. Similar findings were reported in a study of the effect of administering two doses of hepatitis A vaccine in 47 children with JIA.<sup>25</sup>

*Immunogenicity and immunosuppressive agents*

Antibody production induced by nonlive vaccines is variable in patients with JIA, and reduced antibody titres have been found in children with JIA after receiving nonlive vaccines.<sup>47,48,50</sup> Antibody responses to these vaccines were generally not affected by therapy with glucocorticoids or conventional DMARDs, including methotrexate, with the exception of anti-TNF therapy, which mildly decreased the antibody response.<sup>1,16,25,49</sup>



**Table 2** | Nonlive vaccines in patients with JIA

Study	Participants	Vaccine	Safety	Immunogenicity and influence of immunosuppressive agents
Malleson <i>et al.</i> (1993) <sup>45</sup>	34 patients with JIA 13 healthy controls	Seasonal influenza	No significant disease exacerbation No serious adverse events	Comparable antibody titres and seroconversion rates between patients with JIA and controls No influence of glucocorticoids or DMARDs
Olson <i>et al.</i> (1994) <sup>46</sup>	21 patients with JIA (14 vaccinated)	Seasonal influenza	Joint pain and systemic symptoms in 2 of 14 vaccinated patients	NA
Kanakoudi-Tsakalidou <i>et al.</i> (2001) <sup>47</sup>	49 patients with JIA 5 healthy controls	Seasonal influenza	Stable disease activity and autoantibody profile No serious adverse events	13 patients with JIA did not develop protective antibody titres to influenza B virus
Kasapçopur <i>et al.</i> (2004) <sup>48</sup>	39 patients with JIA 41 healthy controls	Hepatitis B	No disease exacerbation No adverse events	Adequate seroprotection rates in patients with JIA and controls, significantly lower antibody titres in patients with JIA than controls No influence of prednisone or methotrexate
Zonneveld-Huijssoon <i>et al.</i> (2007) <sup>50</sup>	234 patients with JIA	Meningococci	No disease exacerbation (6-month follow-up)	Adequate immune response (98% seroprotection rate) regardless of the use of immunosuppressive drugs
Farmaki <i>et al.</i> (2010) <sup>49</sup>	63 patients with JIA	Pneumococci	No disease flares No serious adverse events	87–100% seroprotection rate Significantly lower GMT against serotypes 4, 14 and 23F in patients treated with anti-TNF agents
Quartier <i>et al.</i> (2011) <sup>26</sup>	12 patients with JIA	Pneumococci	NA	Adequate and persistent antibody response in patients treated with anakinra, similar to placebo
Erguven <i>et al.</i> (2011) <sup>25</sup>	47 patients with JIA 67 healthy controls	Hepatitis A	No disease flares No adverse events	Significantly lower antibody response in patients with JIA (possibly associated with systemic onset and use of anti-TNF agents)
Ogimi <i>et al.</i> (2011) <sup>15</sup>	23 patients with JIA 36 patients with other diseases	Seasonal influenza	Disease flare in 1 patient Local adverse events No serious adverse events	Low seroconversion rate throughout the study (but comparable between patients with JIA and controls) No influence of glucocorticoids or immunosuppressive drugs (methotrexate, mycophenolate mofetil, azathioprine, ciclosporin, infliximab) on seroconversion
Miraglia <i>et al.</i> (2011) <sup>22</sup>	83 patients with JIA	Pandemic influenza	Local pain in 34%, headache in 26%, myalgia in 23%, malaise in 20% and arthralgia in 18% 0–3 days after vaccination	Adequate seroprotection rate (85.5%), seroconversion rate (78.3%) and GMT
Shimizu <i>et al.</i> (2012) <sup>23</sup>	1 patient with JIA	Seasonal influenza	Mild disease flare with oligoarthritis	NA
Shinoki <i>et al.</i> (2012) <sup>24</sup>	27 patients with JIA 17 healthy controls	Seasonal influenza	No disease exacerbation No serious adverse events	Similar GMT, seroprotection rate and seroconversion rate between patients and controls
Dell'Era <i>et al.</i> (2012) <sup>16</sup>	60 patients with JIA 30 healthy controls	Seasonal influenza	No disease exacerbation Similar safety and tolerability profile in patients with JIA and controls	Significantly lower GMT and significantly lower seroprotection and seroconversion rates to influenza B virus in patients with JIA treated with etanercept than in those treated with DMARDs or controls
Toplak <i>et al.</i> (2012) <sup>21</sup>	31 patients with JIA 14 healthy controls	Seasonal influenza	Disease flare in 13% of patients 1 month after vaccination and in 23% of patients in the following 5 months 32% of patients with JIA had a local reaction and 3% had a mild systemic reaction Trend towards increased rate of anticardiolipin IgG antibody positivity	Comparable and protective antibody titres between patients with JIA and controls, 6 months after vaccination
Heijstek <i>et al.</i> (2012) <sup>20</sup>	400 patients with JIA 2,176 healthy controls	Diphtheria and tetanus toxoid	Not examined (retrospective study)	Lower GMT and seroprotection rate in patients with JIA than in controls No influence of methotrexate or glucocorticoids on vaccine response
Aikawa <i>et al.</i> (2012) <sup>13</sup>	95 patients with JIA 91 healthy controls	Pandemic influenza	No disease exacerbation Mild arthralgia significantly more frequent after vaccination in patients with JIA No serious adverse events	Significantly lower seroconversion rates in patients with JIA than in controls No influence of glucocorticoids, methotrexate, leflunomide, ciclosporin, anti-TNF therapy

Abbreviations: GMT, geometric mean titre; JIA, juvenile idiopathic arthritis; NA, not available.

Immunization against seasonal influenza produced adequate seroprotection rates in a short-term assessment.<sup>16,21,45</sup> Protective antibody titres in patients with JIA were comparable to those in healthy controls 6 months after vaccination.<sup>21</sup> The vaccine was adequately tolerated in children with JIA who were concomitantly treated with immunosuppressive drugs;<sup>16</sup> however, this vaccine had reduced immunogenicity in patients treated with etanercept compared with healthy controls.<sup>16</sup> The use of MF59 adjuvant vaccines resulted in comparable seroprotection and seroconversion rates to seasonal influenza A (H1N1 and H2N3 strains) in 30 patients with JIA treated with conventional DMARDs, 30 patients with JIA treated with etanercept and 30 healthy children.<sup>16</sup> However, seroconversion and seroprotection rates, as well as GMTs to the influenza B strain, were significantly lower in individuals receiving anti-TNF therapy than in patients receiving conventional DMARDs or healthy individuals ( $P < 0.05$ ).<sup>16</sup> Therapy duration did not affect these immunogenicity end points.<sup>16</sup>

No significant differences in immunogenicity after immunization against influenza were observed between patients with systemic-onset JIA treated with an anti-IL-6 agent (tocilizumab) and healthy individuals.<sup>24</sup> Moreover, the duration of anti-IL6 therapy and the dose of glucocorticoids used did not influence the immune response in this subgroup of patients with JIA.<sup>24</sup>

Pandemic influenza vaccines are approved for use in patients with juvenile rheumatic diseases if the following three current immunologic standards proposed by the European Medicines Agency (EMA) and FDA are met: seroprotection rate  $>70\%$ , seroconversion rate  $>40\%$  and a GMT increase of  $>2.5$ -fold from baseline.<sup>51–53</sup> In a prospective study including 95 patients with JIA and 91 healthy people, the patients with JIA had an adequate seroprotection rate (88.4%) but the seroconversion rate was lower than that in healthy controls (83.2% and 95.6%, respectively, still within the EMA and FDA criteria) after vaccination with a pandemic influenza A H1N1/2009 vaccine.<sup>14</sup> Importantly, JIA subtype and treatment with immunosuppressive drugs, including methotrexate and anti-TNF agents, did not influence these immunogenicity parameters.

A septivalent pneumococcal conjugate vaccine generated protective titres of antibodies in 87–100% of patients with JIA who were treated with both an anti-TNF agent and DMARDs, and in 93–100% of those treated solely with conventional DMARDs.<sup>49</sup> Nevertheless, the GMTs against serotypes 4, 14 and 23F were significantly lower in patients treated with an anti-TNF agent plus DMARDs than in those treated with DMARDs alone ( $P < 0.05$ ).<sup>49</sup> All patients with systemic-onset JIA were immunized using a 23-valent pneumococcal polysaccharide vaccine in a randomized, placebo-controlled study of the IL-1 receptor antagonist anakinra.<sup>26</sup> An adequate and persistent antibody response was mounted by immunized patients treated with anakinra, but the antibody response in patients treated with placebo was not sustained 12 months after immunization.<sup>26</sup> The immune response to meningococci serogroup C

conjugate vaccine was adequate in a prospective study,<sup>50</sup> as seroprotective antibody titres were achieved in 153 (98%) patients with JIA, in spite of the concurrent use of immunosuppressive drugs.

In a controlled study of hepatitis B immunization,<sup>25</sup> 38 (97%) patients with JIA of all subtypes developed effective humoral responses, albeit with considerably lower GMTs than were obtained in healthy children. Patients vaccinated at 0, 1 and 6 months of age had a trend towards better responsiveness than those vaccinated at 0, 1 and 3 months of age.<sup>25</sup> Similarly, significantly lower levels of IgG antibodies against hepatitis A virus were produced in response to immunization in patients with JIA than in healthy individuals.<sup>25</sup> Of note, all four patients in this study who did not undergo seroconversion had active systemic-onset JIA and were being treated with anti-TNF therapy.<sup>25</sup>

## Childhood-onset SLE

### Live vaccines

#### *Vaccine safety*

The safety of live attenuated vaccines in patients with childhood-onset SLE has only been evaluated for varicella-zoster vaccine (Table 3).<sup>19</sup> A prospective and controlled study was carried out in 54 patients with childhood-onset SLE who were randomly assigned to receive or not receive varicella-zoster vaccine, along with 28 healthy children (all of whom were immunized).<sup>19</sup> No differences in adverse events or flares were observed between the vaccinated groups. During follow up, four cases of herpes zoster were reported in the nonvaccinated patients with childhood-onset SLE, whereas no cases of herpes zoster were reported in the vaccinated group.<sup>19</sup>

#### *Immunogenicity and immunosuppressive agents*

Data on the immunogenicity of live attenuated vaccines in patients with childhood-onset SLE are scarce (Table 3). In the varicella-zoster vaccination study described above,<sup>19</sup> the production of IFN- $\gamma$  by T cells stimulated *ex vivo* with varicella-zoster virus antigen was lower in immunized patients with childhood-onset SLE than in the immunized healthy individuals, who were not taking immunosuppressive drugs. IFN- $\gamma$  could be involved in the pathogenesis of SLE and could also interfere with the response to vaccination with varicella-zoster virus antigen.

A 2011 study evaluated the immunogenicity of a measles vaccine in 18 patients with childhood-onset SLE and 11 people who completed all their childhood vaccinations before the onset of SLE.<sup>18</sup> The levels of measles antibodies were similar between these groups.<sup>18</sup>

### Nonlive vaccines

#### *Vaccine safety*

Influenza, hepatitis B and tetanus vaccines are safe to use in patients with childhood-onset SLE (Table 3).<sup>15,18,27–29,47,54</sup> Seasonal influenza vaccine was well tolerated, and no severe adverse effects were documented in a few studies with small samples of patients with childhood-onset SLE.<sup>15,47</sup> An adjuvant-free pandemic influenza A

**Table 3** | Vaccines in patients with childhood-onset SLE

Study	Participants	Vaccine	Safety	Immunogenicity and influence of immunosuppressive agents
<b>Live vaccines</b>				
Miyamoto <i>et al.</i> (2011) <sup>18</sup>	18 patients with childhood SLE 11 healthy controls	Measles	NA	Comparable antibody titres and seroprotection rates between patients with childhood SLE and controls No influence of glucocorticoids or other immunosuppressive drugs (azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil)
Barbosa <i>et al.</i> (2012) <sup>19</sup>	54 patients with childhood SLE (28 vaccinated, 26 unvaccinated) 28 healthy controls	Varicella-zoster	No differences in disease flares or adverse events between immunized and nonimmunized patients with childhood SLE	Number of virus-specific T cells was lower in patients with childhood SLE than in controls (30 days after vaccination)
<b>Nonlive vaccines</b>				
Kanakoudi-Tsakalidou <i>et al.</i> (2001) <sup>47</sup>	11 patients with childhood SLE 5 healthy controls	Seasonal influenza	Stable disease activity and autoantibody profile No serious adverse events	One patient with childhood SLE did not develop protective antibody titres to influenza B virus
Kashef <i>et al.</i> (2008) <sup>54</sup>	40 patients with childhood SLE 60 healthy controls	Tetanus	NA	Similar antibody titres and seroprotection rate between patients with childhood SLE and controls No influence of glucocorticoids or other immunosuppressive agents (azathioprine, cyclophosphamide, mycophenolate mofetil)
Miyamoto <i>et al.</i> (2011) <sup>18</sup>	18 patients with childhood SLE 11 healthy controls	Tetanus	NA	Lower tetanus antibody levels in patients with childhood SLE than controls, but similar seroprotection rates No influence of glucocorticoids or other immunosuppressive drugs
Ogimi <i>et al.</i> (2011) <sup>15</sup>	12 patients with childhood SLE 36 healthy controls	Seasonal influenza	Local adverse effects, no serious adverse events	Low seroconversion rates (but comparable to that of controls) No influence of glucocorticoids or immunosuppressive drugs on seroconversion
Aytac <i>et al.</i> (2011) <sup>28</sup>	20 patients with childhood SLE 24 healthy controls	Hepatitis B	Stable disease activity (SLEDAI score) after three doses of vaccine No adverse events	Similar seroconversion rates but lower GMTs in patients with childhood SLE than in controls No influence of prednisone, azathioprine or mycophenolate mofetil
Long <i>et al.</i> (2012) <sup>29</sup>	20 patients with childhood SLE 20 healthy controls	Pandemic and seasonal influenza	NA	Lower humoral and cellular response in patients with childhood SLE than in controls
Campos <i>et al.</i> (2013) <sup>27</sup>	118 patients with childhood SLE 102 healthy controls	Pandemic influenza	Stable SLEDAI-2000 score up to 3 weeks after immunization Higher frequency of local reactions and arthralgia in patients with childhood SLE than in controls	GMT, seroprotection and seroconversion rates generally reduced in patients with childhood SLE; reduced seroconversion rate mainly associated with SLEDAI-2000 score $\geq 8$ and high mean current glucocorticoid dose

Abbreviations: GMT, geometric mean titre; NA, not available; SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index.

H1N1/2009 vaccine was examined in a prospective study including 118 patients with childhood-onset SLE and 102 healthy children of comparable age.<sup>27</sup> No change in the median SLE Disease Activity Index (SLEDAI)-2000 score was found 21 days or 4 months after immunization compared to preimmunization scores.<sup>27</sup> The frequencies of articular, neuropsychiatric and haematological abnormalities in these patients also remained stable, although a significant decrease in renal involvement and a significant increase in mucocutaneous lesions were observed 4 months after vaccination ( $P < 0.05$ ).<sup>27</sup> No serious adverse events attributable to the vaccine were reported.<sup>27</sup> These patients had stable autoantibody profiles (no change in the levels or specificities of autoantibodies) before and after vaccination;<sup>27</sup> similar results were also observed in 11 patients with childhood-onset SLE who were immunized against seasonal influenza.<sup>47</sup>

Only one study has assessed hepatitis B vaccination in patients with childhood-onset SLE.<sup>28</sup> In this study,<sup>28</sup> 20 patients with SLEDAI scores  $< 10$  and 24 healthy people were vaccinated with three doses of a recombinant hepatitis B vaccine at 0, 1 and 6 months. Disease flare frequency was comparable to that in a nonvaccinated group of patients with childhood-onset SLE (15% versus 18%, respectively), and the mean SLEDAI score was constant after the vaccination scheme was completed.<sup>28</sup> No adverse events related to the vaccine were observed.<sup>28</sup>

#### *Immunogenicity and immunosuppressive agents*

Antibody production induced by nonlive vaccines is variable in patients with childhood-onset SLE. Adequate seroconversion rates were observed in patients who received hepatitis B and tetanus vaccines.<sup>28,54</sup> Immunosuppressive therapy had no effect on the immunogenicity

of influenza vaccines, however humoral and cell-mediated immune responses to both pandemic influenza A H1N1 vaccine and trivalent seasonal influenza vaccine were lower in high-risk immunosuppressed children and adolescents than in healthy individuals.<sup>29</sup> The high-risk group included 20 patients with childhood-onset SLE, 80% of whom were treated with prednisone and 35% with mycophenolate mofetil.<sup>29</sup> The pandemic influenza vaccine achieved seroprotection in only 45% of patients with childhood-onset SLE;<sup>29</sup> moreover, although 60% of patients with childhood-onset SLE responded to the seasonal vaccine initially, these individuals had a more rapid decline in antibody titres than occurred in healthy children or patients with asthma.<sup>29</sup> Of note, patients with childhood-onset SLE had a lower cell-mediated response to the H1N1/2009 pandemic influenza vaccine than patients with asthma, sickle cell disease, or recipients of solid-organ graft, as measured by enzyme-linked immunosorbent spot assay.<sup>29</sup>

Likewise, immunogenicity parameters were also generally reduced in patients with childhood-onset SLE relative to their levels in healthy individuals after receiving the pandemic influenza vaccine.<sup>27</sup> The main factors associated with a lack of seroconversion were a SLEDAI-2000 score  $\geq 8$  and a high mean current glucocorticoid dose.<sup>27</sup> After multivariate logistic regression analysis, high SLEDAI-2000 score was the most important variable associated with the lack of seroconversion.<sup>27</sup>

By contrast, the immunogenicity of a hepatitis B vaccine was adequate in a prospective controlled study of a small population of patients with childhood-onset SLE.<sup>28</sup> Seroconversion rates were similar in patients with childhood-onset SLE and healthy individuals 1 month after the third vaccine dose (80% and 100%, respectively), despite reduced GMTs in the patients with childhood-onset SLE.<sup>28</sup> Vaccine immunogenicity was not influenced by immunosuppressive treatment.<sup>28</sup>

The humoral response to tetanus vaccine was evaluated in a controlled study including 40 patients with childhood-onset SLE and 60 healthy people matched for age and sex.<sup>54</sup> Protective titres of antitetanus antibody were produced in both patients and controls, and GMTs were also similar in both groups, despite the use of glucocorticoids and other immunosuppressive drugs in 90% of the patients with childhood-onset SLE.<sup>54</sup> Reinforcing this finding, in another study that evaluated the immunogenicity of tetanus vaccine,<sup>18</sup> patients who had received all their childhood vaccinations before onset of SLE had a comparable seroprotection rate to that in patients with childhood-onset SLE and healthy people.

### Juvenile dermatomyositis

The hypothesis that immunization can induce JDM is controversial. The temporal relationship between vaccinations against hepatitis B, diphtheria, pertussis, tetanus, poliomyelitis, smallpox and tuberculosis and the onset of JDM symptoms is restricted to a few case reports, and no causal relationship has been proven (Table 4).<sup>55–58</sup>

Data regarding the safety of live attenuated vaccines in patients with JDM are scarce. In the only report to

date,<sup>43</sup> no worsening of disease activity and no serious vaccine-related adverse effects occurred in four patients with JDM who received a live attenuated vaccine against varicella-zoster. Two of these patients produced protective levels of antibodies.<sup>43</sup> All four patients were taking prednisone (up to 10 mg daily) and methotrexate.<sup>43</sup>

Vaccine-induced antibody production was reduced in patients with JDM who received a nonlive vaccine against pandemic influenza, although vaccine-specific and disease-specific safety were both adequate.<sup>15,30</sup> The largest study to evaluate vaccination using nonlive agents in patients with JDM was a prospective, open-label, controlled study that included 30 patients with JDM and 81 healthy children and adolescents who were vaccinated against the pandemic influenza A strain H1N1/2009.<sup>30</sup> No clinical or laboratory findings suggestive of increased disease activity were reported 3 weeks after vaccination, and only mild adverse events were observed.<sup>30</sup> After immunization, seroconversion rates were markedly lower in patients with JDM than in healthy individuals, despite similar seroprotection rates, GMTs and increases in GMTs in both groups.<sup>30</sup> Lack of seroconversion was associated with a chronic disease course, prednisone doses  $>20$  mg daily and use of a combination of prednisone, methotrexate and ciclosporin.<sup>30</sup> Another study including six patients with JDM immunized with a nonlive vaccine against seasonal influenza also reported no vaccine-related severe adverse events or disease flares.<sup>15</sup>

### Juvenile systemic sclerosis

Rare case reports suggest a temporal relationship between hepatitis B, diphtheria, pertussis, tetanus and MMR vaccinations and the onset of juvenile systemic sclerosis, particularly deep morphea.<sup>59–61</sup> Whether these associations represent a causal relationship is not currently known. However, no worsening of disease parameters and no serious adverse events were reported in three patients with juvenile systemic sclerosis who received live attenuated varicella-zoster vaccine (Table 4).<sup>43</sup> Protective antibody levels were reached in two of the three patients, all of whom were taking prednisone (up to 20 mg daily) and methotrexate.<sup>43</sup>

Furthermore, in 237 patients with juvenile rheumatic diseases, only the 11 patients with juvenile systemic sclerosis produced titres of vaccine-induced antibodies that were comparable to those of healthy patients in response to vaccination (using a nonlive agent) against pandemic influenza.<sup>13</sup> A reduced immune response was observed in patients with JIA, childhood-onset SLE, JDM or primary vasculitis.<sup>13</sup> No severe adverse events related to vaccination were observed in any patient in this study.<sup>13</sup>

### Juvenile primary vasculitis

Several reports describe the onset of primary vasculitis, especially Henoch–Schönlein purpura (HSP)<sup>31,62–67</sup> and Kawasaki disease,<sup>68,69</sup> after administration of either live or nonlive vaccines. However, no increase in the incidence or recurrence of HSP was observed within 30 days



**Table 4** | Vaccines in patients with other paediatric rheumatic diseases

Study	Participants	Vaccine	Safety	Immunogenicity and influence of immunosuppressive agents
<b>JDM</b>				
Pileggi <i>et al.</i> (2010) <sup>43</sup>	4 patients with JDM 18 healthy controls	Varicella-zoster (live vaccine)	No disease exacerbation No overt varicella-zoster infection No serious adverse events	3 patients maintained IgG seropositivity after 4–6 weeks No influence of methotrexate, ciclosporin or leflunomide
Ogimi <i>et al.</i> (2011) <sup>15</sup>	6 patients with JDM 36 controls with other diseases	Seasonal influenza (nonlive vaccine)	Local adverse effects, no serious adverse events	Low seroconversion rates (but comparable to controls) No influence of glucocorticoids or immunosuppressive drugs on seroconversion
Guissa <i>et al.</i> (2012) <sup>30</sup>	30 patients with JDM 81 healthy controls	Pandemic influenza (nonlive vaccine)	No clinical or laboratory (strength or muscle enzymes) deterioration up to 3 weeks after vaccination Mild adverse events (local pain in 30%, headache in 17%), no serious adverse events	Patients had significantly lower seroconversion rates than controls Reduced seroconversion associated with high prednisone dose (>20 mg daily) and combination of prednisone, methotrexate and ciclosporin
<b>Juvenile SSC</b>				
Pileggi <i>et al.</i> (2010) <sup>43</sup>	3 patients with juvenile scleroderma 18 healthy controls	Varicella-zoster (live vaccine)	No disease exacerbation No overt varicella-zoster infection, no serious adverse events	2 patients maintained IgG seropositivity after 1 year No influence of methotrexate, ciclosporin or leflunomide
Aikawa <i>et al.</i> (2012) <sup>13</sup>	11 patients with juvenile scleroderma 91 healthy controls	Pandemic influenza (nonlive vaccine)	No disease exacerbation	Similar GMT, seroprotection and seroconversion rates in patients and controls
<b>Primary vasculitis</b>				
Ogimi <i>et al.</i> (2011) <sup>15</sup>	2 patients with Takayasu arteritis, 2 with Kawasaki disease, 1 with granulomatosis with polyangiitis 36 healthy controls	Seasonal influenza (nonlive vaccine)	Disease flare in one patient with Takayasu arteritis Local adverse effects, no serious adverse events	Patients had low seroconversion rates (but comparable to that of controls) No influence of glucocorticoids or immunosuppressive drugs on seroconversion
Aikawa <i>et al.</i> (2012) <sup>13</sup>	5 patients with Henoch–Schönlein purpura, 3 with Takayasu arteritis, 3 with granulomatosis with polyangiitis, 3 with polyarteritis nodosa, 1 with Kawasaki disease, 1 with Behçet disease 91 healthy controls	Pandemic influenza (nonlive vaccine)	No disease exacerbation	Lower seroconversion rates in patients than in controls
<b>Autoinflammatory syndromes</b>				
Bodar <i>et al.</i> (2011) <sup>80</sup>	3 patients with mevalonate kinase deficiency	Diphtheria, tetanus, pertussis	Typical fever attack	NA
Abbreviations: GMT, geometric mean titre; JDM, juvenile dermatomyositis; NA, not available; SSC, systemic sclerosis.				

after administration of a nonlive vaccine against group B meningococci in a New-Zealand-wide immunization campaign involving children aged 6 weeks to 10 years.<sup>70</sup> Similarly, in a retrospective analysis of data from a vaccine safety database, no new cases of HSP were found within the 42 days after administration of a total of 49,027 doses of meningococcal polysaccharide vaccine to a population of adolescents and young adults 16–20 years old.<sup>62</sup> Additionally, two retrospective studies found no association between the onset of Kawasaki disease and vaccinations, including with septivalent pneumococcal conjugate vaccine<sup>71</sup> and live rotavirus oral vaccine.<sup>72</sup>

Induration and inflammation at a previous BCG immunization site has aided in the diagnosis of complete and incomplete Kawasaki disease.<sup>73–78</sup> Indeed, in a nationwide Japanese epidemiological survey, redness or crust formation at a prior BCG inoculation site was

observed in 50% of the 15,524 patients with Kawasaki disease who had a history of BCG vaccination.<sup>79</sup>

The immunogenicity and safety of an adjuvant-free, nonlive influenza A H1N1/2009 vaccine has been studied in patients with juvenile autoimmune rheumatic diseases (Table 4).<sup>13</sup> The participants included 16 patients with a primary vasculitis: HSP ( $n = 5$ ), Takayasu arteritis ( $n = 3$ ), granulomatosis with polyangiitis ( $n = 3$ ), polyarteritis nodosa ( $n = 3$ ), Kawasaki disease ( $n = 1$ ) and Behçet disease ( $n = 1$ ).<sup>13</sup> Seroconversion rates were considerably lower in the patients with primary vasculitis than in healthy individuals, 3 weeks after vaccination, despite comparable seroprotection rates, GMTs and factor increases in GMT.<sup>13</sup> No severe vaccine-related adverse events were reported.<sup>13</sup> In another study of five paediatric patients with primary vasculitis, a disease flare occurred in one patient with Takayasu arteritis within 2 weeks of receiving a nonlive vaccine against seasonal

influenza.<sup>15</sup> The flare stabilized after the patient's dosage of prednisolone was increased.

### Autoinflammatory syndromes

Patients with mevalonate kinase deficiency (hyper IgD syndrome) might experience an inflammatory episode, especially a febrile attack, after receiving childhood immunizations (Table 4).<sup>80</sup> In a prospective observational study of 11 patients with mevalonate kinase deficiency,<sup>32</sup> anakinra treatment prevented the attacks of fever associated with diphtheria, tetanus and pertussis vaccination in three of these patients, without inhibiting antibody induction.

### Conclusions

The majority of studies of vaccination in paediatric patients with rheumatic diseases have been performed in small populations and were, therefore, insufficiently powered to determine the immunogenicity and safety of the vaccine. Most such studies were performed using nonlive vaccines in patients with JIA or childhood SLE, among whom no severe adverse events relating to either the vaccine or the underlying disease were reported. The vaccine-induced immune response was variable but generally adequate, despite the concurrent use of immunosuppressive and biologic agents. Studies of live vaccines in paediatric patients with rheumatic diseases are scarce, but no serious adverse events have been reported in patients with either JIA or childhood-onset SLE.

The suggestion that onset of autoimmune rheumatic diseases might be triggered by vaccination is controversial, and no causal relationship has yet been demonstrated. Patients with mevalonate kinase deficiency could, however, experience febrile attacks after immunizations. Adequately powered studies of the immune response to live and nonlive vaccines, and further evaluation of disease-specific and vaccine-specific safety profiles and the influence of immunosuppressive therapy are necessary in populations of patients with all paediatric rheumatic diseases.

### Review criteria

We searched for original articles focusing on immunization in patients with paediatric rheumatic diseases in MEDLINE and PubMed, published between 1970 and 2012. The search terms we used, in various combinations, were "vaccine", "immunization", "paediatric rheumatic diseases", "children", "juvenile idiopathic arthritis", "juvenile rheumatoid arthritis", "juvenile systemic lupus erythematosus", "childhood-onset systemic lupus erythematosus", "juvenile dermatomyositis", "scleroderma", "vasculitis", "Henoch-Schönlein purpura", "Kawasaki syndrome", "polyarteritis nodosa", "granulomatous polyangiitis", "Wegener granulomatosis", "Behçet disease", "Takayasu arteritis", "autoinflammatory syndromes", "immunogenicity" and "safety". All articles identified were English-language full-text papers. We also searched the reference lists of identified articles for further papers.

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#### Author contributions

All authors researched data for the article, discussed its content, wrote, reviewed and edited the manuscript.