

# Italian recommendations for influenza and pneumococcal vaccination in adult patients with autoimmune rheumatic diseases

G. Guerrini<sup>1</sup>, F. Franzetti<sup>2</sup>, R. Giacomelli<sup>3</sup>, L. Meroni<sup>2</sup>, A. Riva<sup>2</sup>, C.A. Scirè<sup>1</sup>, R. Scrivo<sup>4</sup>, M. Tavio<sup>5</sup>, A. Agostinone<sup>6</sup>, P. Airò<sup>7</sup>, F. Atzeni<sup>8</sup>, F. Bartalesi<sup>9</sup>, L. Bazzichi<sup>10</sup>, O. Berardicurti<sup>3</sup>, G. Cassola<sup>11</sup>, A. Castagna<sup>12</sup>, F. Castelli<sup>13</sup>, A. Cattelan<sup>14</sup>, G. Citriniti<sup>15</sup>, F. Cristini<sup>16</sup>, F. De Rosa<sup>17</sup>, E. Fracassi<sup>18</sup>, J. Galloway<sup>19</sup>, G.M.C. La Paglia<sup>20</sup>, M.C. Moioli<sup>21</sup>, D. Ripamonti<sup>22</sup>, A. Saracino<sup>23</sup>, C. Tani<sup>10</sup>, C. Tascini<sup>24</sup>, T. Tieghi<sup>25</sup>, M. Tinelli<sup>26</sup>, A. Zabotti<sup>27</sup>, P. Sarzi-Puttini<sup>28</sup>, M. Galli<sup>2</sup>

---

## Abstract Objective

*To provide evidence-based recommendations for vaccination against influenza virus and S. pneumoniae in patients with autoimmune rheumatic diseases (ARDs).*

---

## Methods

*A Consensus Committee including physicians with expertise in rheumatic and infectious diseases was established by two Italian scientific societies, Società Italiana di Reumatologia (SIR) and Società Italiana di Malattie Infettive e Tropicali (SIMIT). The experts were invited to develop evidence-based recommendations concerning vaccinations in ARDs patients, based on their clinical status before and after undergoing immunosuppressive treatments.*

*Key clinical questions were formulated for the systematic literature reviews, based on the clinical pathway.*

*A search was made in Medline (via PubMed) according to the original MeSH strategy from October 2009 and a keyword strategy from January 2016 up to December 2017, updating existing EULAR recommendations.*

*Specific recommendations were separately voted and scored from 0 (no agreement with) to 100 (maximal agreement) and supporting evidence graded. The mean and standard deviation of the scores were calculated to determine the level of agreement among the experts' panel for each recommendation. Total cumulative agreement  $\geq 70$  defined consensus for each statement.*

---

## Results

*Nine recommendations, based on 6 key clinical questions addressed by the expert committee, were proposed. The aim of this work is to integrate the 2011 EULAR recommendations on vaccination against influenza and S. pneumoniae in ARDs patients. An implementation plan was proposed to improve the vaccination status of these patients and their safety during immunosuppressive treatments.*

---

## Conclusion

*Influenza and pneumococcus vaccinations are effective and safe in patients with ARDs. More efforts should be made to translate the accumulated evidence into practice.*

---

## Key words

disease-modifying anti-rheumatic drugs, autoimmune rheumatic diseases, influenza vaccine, pneumococcal vaccine

For the authors' affiliations, see page 254.

Giulio Guerrini, Fabio Franzetti, Roberto Giacomelli, Luca Meroni, Agostino Riva, Carlo Alberto Scirè, Rossana Scrivo, Marcello Tavio, Adriana Agostinone, Paolo Airò, Fabiola Atzeni, Filippo Bartalesi, Laura Bazzichi, Onorina Berardicurti, Giovanni Cassola, Antonella Castagna, Francesco Castelli, Annamaria Cattelan, Giorgia Citriniti, Francesco Cristini, Francesco De Rosa, Elena Fracassi, James Galloway, Giuliana M.C. La Paglia, Maria Cristina Moioli, Diego Ripamonti, Annalisa Saracino, Chiara Tani, Carlo Tascini, Tiziana Tieghi, Marco Tinelli, Alen Zabotti, Piercarlo Sarzi-Puttini, Massimo Galli.

Please address correspondence to: Massimo Galli,

Clinica delle Malattie Infettive, Department of Biomedical and Clinical Sciences L. Sacco, Via Giovanni Battista Grassi 74, 20157 Milano, Italy.

E-mail: massimo.galli@unimi.it

Received on February 22, 2019; accepted in revised form on May 20, 2019.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2020.

*Funding: this project was supported by The Italian group for the Study and Management of the Infections in patients with Rheumatic diseases (ISMIR group) and it is jointly promoted by the Italian Society of Rheumatology (SIR), and by the Italian Society of Infectious and Tropical Diseases (SIMIT)*

*Competing interests: none declared.*

## Introduction

Patients with autoimmune rheumatic diseases (ARDs) are at increased risk of infections. Vaccination is both an individual right and a societal responsibility. Vaccines provides personal benefits and, at the same time, indirectly protect the wider population including those who cannot be vaccinated. Over the years, scientific societies have developed clinical practice recommendations aiming to provide guidance on optimal use of vaccines and improve vaccination adherence among patients with ARDs in whom there is an increased morbidity and mortality attributable to infection.

In rheumatoid arthritis (RA), an exemplar ARDs, patients have double the rate of infections of matched non-RA controls, due to a combination of disease and drug-related immune system disturbances (1–3).

On this basis, preventative strategies such as vaccination, are especially relevant in ARDs patients. Many infections are either preventable using vaccination or, alternatively, vaccinations might make the clinical course less severe. To date, there is a general agreement that inactivated vaccines can be safely given to patients treated with immunosuppressive drugs, while concerns still exist on the safety of live attenuated vaccines in these patients, despite the absence of conclusive data.

Vaccination rates of RA patients are lower than in the general population, probably in part due to physician mis-counselling about vaccinations and the prejudices of vaccine-related side effects (4).

The objective of this study group was to reassess, through a systematic literature review (SLR), the efficacy and safety of influenza and pneumococcal vaccination in ARDs patients. The SLR has been restricted to these two vaccinations because they are directed against widespread diseases with a high rate of morbidity and mortality (5, 6).

A steering committee, including Italian experts in rheumatic and infectious diseases, convened to develop the recommendations, combining evidence from clinical studies with expert opinion, when adequate evidence was lacking,

according to the treatment status of the patients. These recommendations, although produced by the Italian scientific community, derive from available international literature and cover an important topic of general interest, providing an evidence-based medical behaviour in the setting of immunosuppression.

## Methods

### *Expert committee and key clinical questions*

A consensus committee including 35 physicians with expertise in rheumatic and infectious diseases was established by two Italian scientific societies (Società Italiana di Reumatologia: SIR, and Società Italiana di Malattie Infettive e Tropicali: SIMIT). The experts were invited to develop evidence-based recommendations concerning vaccinations against influenza and *S. pneumoniae* in ARDs patients, on the basis of their clinical status before and after immunosuppressive treatments. Six key clinical questions (KCQ) were formulated for the SLR (Table I).

### *Definitions*

Definition of ARDs and immunosuppressive drugs followed those reported in the “EULAR recommendations for vaccination in adult patients with systemic autoimmune rheumatic diseases” (7). In addition, targeted synthetic modifying anti-rheumatic drugs (tsDMARDs) were considered.

Vaccinations included any schedule and vaccination type for influenza and *S. pneumoniae*.

### *Systematic literature review*

Based on the KCQ and disease and treatment definitions, a general review question was formulated. According to the previously published SLR informing the 2011 EULAR recommendations (8), an updated literature search was performed. A total of 56 studies met the inclusion criteria and were included. The search was extended to include any paper referenced in previous reviews as well as papers identified from experts on the panel; in this way 45 articles were added (Fig. 1).

A search was made in Medline (via PubMed) according to the original

MeSH strategy from October 2009 and a keyword strategy from January 2016 up to December 2017 (See Supplementary online file).

Inclusion criteria include: patients with ARDs (inflammatory arthritis, connective tissue diseases, vasculitides); influenza or *S. pneumoniae* vaccine; data on safety or efficacy (seroconversion, infection rate); study design (randomised control trial: RCT, observational); publication in English.

The data were screened independently by two reviewers (CS and GG), recorded on a prespecified extraction form and summarised qualitatively. The results were sent to the committee before the second meeting, together with proposals for recommendations.

#### Development of recommendations

The recommendations summarised represent a consensus of published evidence and expert opinions (Table II). For each recommendation, we used a currently accepted hierarchy for categorising the available evidence and the strength of the recommendations (evidence categories A-D) (Suppl. file). Specific recommendations were separately voted and scored from 0 (no agreement with) to 100 (maximal agreement). The mean and standard deviation (SD) of the scores were calculated for each statement to estimate the strength of the recommendation (SOR) of the experts' panel. An agreement  $\geq 70$  defined consensus for each statement. In the case of lack of agreement, the statement was reworded according to the results of the discussion and then re-voted in further rounds.

## Results

### Recommendations

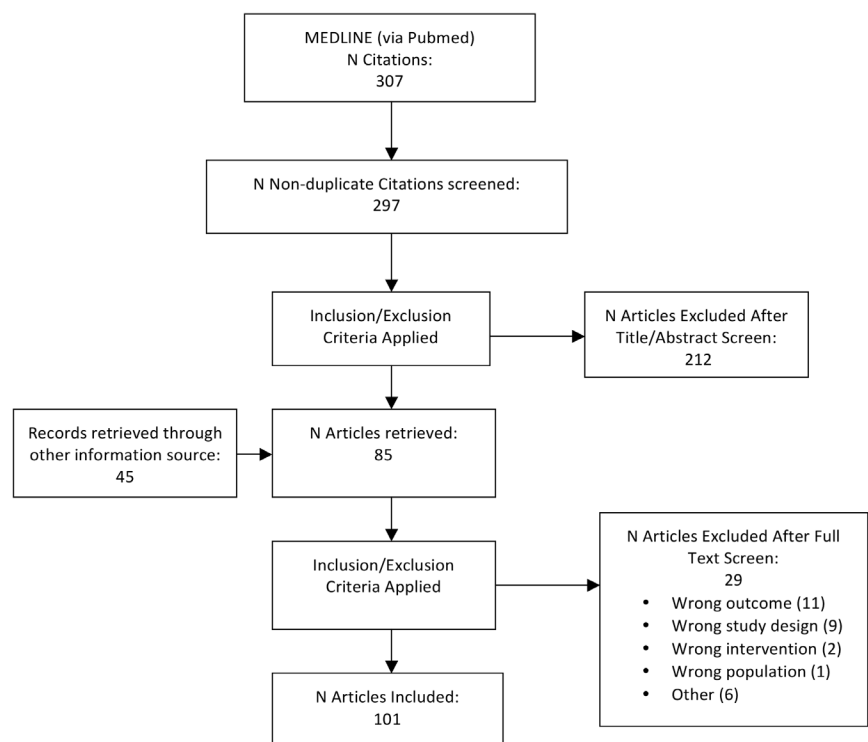
1. In patients with ARDs, the vaccination status for *S. pneumoniae* should be assessed in the initial investigation. [mean (SD) SOR: 87.00 (17.42); Grade IV (D)]

The initial assessment of ARDs patients, before starting immunosuppressive therapies, should include the evaluation of the immunisation status, according to the national vaccination programmes of each country. In accordance to the available literature, the

**Table I.** Key clinical questions.

ID	Key clinical questions
1	In patients with untreated ARDs, is vaccination against influenza virus or <i>S. Pneumoniae</i> equally effective and safe compared to the general population?
2	In patients with ARDs receiving csDMARDs, is vaccination against influenza virus or <i>S. pneumoniae</i> equally effective and safe compared to the general population?
3	In patients with ARDs receiving GCs, is vaccination against influenza virus or <i>S. pneumoniae</i> equally effective and safe compared to the general population?
4	In patients with ARDs receiving bDMARDs or tsDMARDs, is vaccination against influenza virus or <i>S. pneumoniae</i> equally effective and safe compared to the general population?
5	In patients with ARDs receiving a combination of cs- and bDMARDs or tsDMARDs, is vaccination against influenza virus or <i>S. pneumoniae</i> effective and safe compared to monotherapy?
6	In patients with ARDs receiving csDMARDs and/or tsDMARDs or bDMARDs and/or GCs is vaccination against influenza virus or <i>S. pneumoniae</i> effective and safe in active compared to inactive disease?

ARDs: autoimmune rheumatic diseases; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; GCs: glucocorticoids; bDMARDs: biological disease-modifying anti-rheumatic drugs; tsDMARDs: targeted synthetic disease-modifying anti-rheumatic drugs.



**Fig. 1.** Flow diagram.

vaccination status against *S. pneumoniae* should be assessed to select patients to be vaccinated.

Kapetanovic *et al.* have shown a good antibody response in arthritis patients following pneumococcal 7-valent conjugate vaccine (PCV-7), but 1.5 years after PCV-7 vaccination the antibody levels had reverted, in several cases, to pre-vaccination levels (9).

Other authors demonstrated that the efficacy of the 23-valent pneumococcal

polysaccharide vaccine (PPSV-23) was preserved for at least 10 years among patients with ARDs treated with methotrexate (MTX) and tumour necrosis factor (TNF) alpha or interleukin (IL)-6 receptor inhibitors (10). Consequently, the authors suggested that antibody levels should be considered to identify patients who may benefit from revaccination.

Recent international guidelines mostly agree on revaccination, suggesting a re-

**Table II.** Summary of the recommendations.

Record ID	mean	SD
1. In patients with ARDs, the vaccination status for <i>S. pneumoniae</i> should be assessed in the initial investigation.	87.00	17.42
2. In patients with ARDs, immunisation against influenza can be safely administered during the use of csDMARDs.	90.38	11.13
3. In patients with ARDs, immunisation against <i>S. pneumoniae</i> can be safely administered during the use of csDMARDs, even though a slight impairment of effectiveness is expected, in particular with methotrexate.	90.93	10.48
4. In patients with ARDs, immunisation against influenza and <i>S. pneumoniae</i> can be safely administered during the use of GCs, though a better response is expected at low GC dosage.	88.97	13.04
5. In patients with ARDs, immunisation against influenza or <i>S. pneumoniae</i> can be safely administered during the use of bDMARDs or tsDMARDs, even in combination with csDMARDs, though a slight impairment of effectiveness of pneumococcal vaccine is expected, in particular with rituximab, abatacept and tofacitinib.	89.83	9.75
6. Patients with ARDs should be actively immunised against influenza (yearly). Adjuvated vaccines may be more efficacious, in particular in patients on bDMARDs.	85.83	17.88
7. Patients with ARDs should be actively immunised against <i>S. pneumoniae</i> .	89.86	11.24
8. In patients with ARDs, vaccination should ideally be administered during stable disease.	82.17	20.74
9. In patients with ARDs, vaccination against <i>S. pneumoniae</i> should ideally be administered before starting any immunosuppressive treatment, in order to maximise effectiveness and safety. In particular, vaccination should be administered before starting abatacept and at least 4 weeks before starting rituximab.	92.69	8.23

ARDs: autoimmune rheumatic diseases; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; GCs: glucocorticoids; bDMARDs: biological disease-modifying anti-rheumatic drugs; tsDMARDs: targeted synthetic disease-modifying anti-rheumatic drugs.

call dose with PPSV-23 5 years after the first dose of PPSV-23. Only Australian Technical Advisory Group on Immunisation favours a second dose of PPSV-23 5 to 10 years after the previous one, and a third dose at 65 years (11).

In patients treated with rituximab (RTX), abatacept (ABA), golimumab (GOL), and tofacitinib (TOF), which may reduce immunogenicity against pneumococcal vaccines, testing the antibody titres should be considered 4-6 weeks after a completed primary course of vaccination. If serological threshold is not reached, additional doses may be necessary for achieving protection.

*2. In patients with ARDs, immunisation against influenza can be safely administered during the use of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs). [mean (SD) SOR: 90.38 (11.13); Grade II(B)]*

In patients with ARDs treated with csDMARDs, adverse events following influenza vaccination seem to be comparable to those occurring in the general population (7).

The disease activity does not seem to be significantly modified by the administration of the vaccine, regardless of the type (adjuvanted vs. not adjuvanted). No increased rates of serious adverse events (SAEs) have been reported after

influenza vaccination in patients with RA (12, 13), psoriatic arthritis (PsA) (14), systemic lupus erythematosus (SLE) (15-19), mixed connective tissue disease (20), dermatomyositis and polymyositis (21).

*3. In patients with ARDs, immunisation against S. pneumoniae can be safely administered during the use of csDMARDs, even though a slight impairment of effectiveness is expected, in particular with methotrexate. [mean (SD) SOR: 90.93 (10.48); Grade II (B)]*

The majority of data do not show the occurrence of severe adverse effects following pneumococcal vaccination in patients undergoing a csDMARDs regimen (22-24). Among csDMARDs, MTX significantly lowers the immunological response to the aforementioned vaccination (10, 23, 25-28).

However, in a small low-quality retrospective study, Coulson *et al.* stated that a single dose of PPSV-23 offers protection in patients with RA on MTX, on the basis of a 9.7 adjusted relative risk for developing pneumonia among non-vaccinated patients ( $p=0.0007$ ) (29).

Rezende *et al.* showed a reduced immunological response to PPSV-23 vaccination in SLE patients treated with mycophenolate mofetil (MMF), azathioprine (AZA) and cyclophosphamide (CYC) (30).

*4. In patients with ARDs, immunisation against influenza and S. pneumoniae can be safely administered during the use of glucocorticoids (GCs), though a better response is expected at low GC dosage. [mean (SD) SOR: 88.97 (13.04); Grade II (B)]*

Many studies support the safety of influenza vaccination in patients with ARDs treated with GCs (17, 31, 32).

Several reports indicate that GCs do not alter the effectiveness of influenza vaccination in patients with ARDs when administered at low-dose (12, 20, 21, 32-37), while high doses reduce the immunological response to vaccinations (31, 38, 39).

Borba *et al.* showed that, in patients suffering from SLE, a mean prednisone dose of >12 mg/day significantly reduced the seroconversion rate compared to untreated patients (18).

A meta-analysis showed that the seroprotection rate in patients with SLE treated with GCs was significantly reduced in comparison to the healthy control group (15).

Similar results apply to pneumococcal vaccinations. No increase in serious adverse effect rate was reported in patients with ARDs treated with GCs after the aforementioned vaccination. Low doses of GCs do not seem to reduce vaccination efficacy (25, 30).

In the study by Broyde *et al.*, the use

of low doses of GCs did not change the long-term efficacy of PPSV-23 in patients with RA, PsA and spondyloarthritis (SpA) (10).

In patients with ARDs treated with high doses of GCs, a reduction in the immunogenicity of the vaccination has been reported (40).

Paradoxically, in patients suffering from RA the use of GCs in association with anti-TNF-alpha or MTX was associated with a stronger immunological response to influenza and *S. pneumoniae* vaccines (25, 27).

*5. In patients with ARDs, immunisation against influenza or S. pneumoniae can be safely administered during the use of biological disease-modifying anti-rheumatic drugs (bDMARDs) or targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs), even in combination with csDMARDs, though a slight impairment of effectiveness of pneumococcal vaccine is expected, in particular with rituximab, abatacept, and tofacitinib. [mean (SD) SOR: 89.83 (9.75); Grade II (B)]*

The administration of influenza vaccination appears safe in patients receiving anti-TNF-alpha, ABA (41), tocilizumab (TCZ) (42) and RTX.

No SAEs have been reported in relation to a combined therapy with anti-TNF-alpha and csDMARDs in patients with RA and SpA (43-46). However, substantial studies to evaluate safety are not available.

The efficacy of influenza vaccination tends to be sustained or slightly reduced in RA (28, 33, 43-46) and SpA (44) patients receiving anti-TNF-alpha. In the study by Franca *et al.*, SpA patients receiving infliximab (IFX) or adalimumab (ADA) had a significantly reduced seroconversion rate after influenza vaccination compared to healthy controls (51.6% vs. 74.3%,  $p=0.002$ ), whereas no difference was observed for patients on etanercept (ETA) (86.7% vs. 74.3%,  $p=0.09$ ) (46).

Studies show that ABA can reduce the efficacy of influenza vaccination in ARDs patients (44). According to Ribeiro *et al.*, the efficacy of influenza vaccination in RA patients receiving ABA was considerably reduced in

comparison to patients receiving MTX (and to normal healthy controls) (41). However, other studies show that ABA cannot significantly change the efficacy of influenza vaccination. Alten *et al.* have evaluated 191 patients receiving ABA, and 82% of them developed clinically relevant antibody titres versus 2 or 3 antigens of trivalent influenza vaccine (47).

Limited data are available on the efficacy of TCZ in patients undergoing influenza vaccination. Mori *et al.* showed that the antibody response to influenza vaccine in RA patients was not affected by TCZ (42), and similar results can be found in the study by Tsuru *et al.* (48). RTX significantly minimises the antibody response and the success of influenza vaccine in RA patients (8, 31, 44, 49). Arad *et al.* revealed that humoral response was notably reduced in RA patients receiving RTX, compared to subjects receiving csDMARDs and to controls (26.4% vs. 68.4% vs. 47.1%). However, cellular response to vaccine was similar in patients treated with RTX and csDMARDs (50). The effect of RTX on influenza vaccine seems related to drug administration timing. Influenza vaccine should be given at least 4 weeks before or at least 6 months after treatment with RTX (51).

In 2012, Chatham *et al.* demonstrated that the antibody titre against the influenza vaccine antigens was preserved after 52 weeks since belimumab (BEL) onset. When vaccination was given during treatment, patients treated with BEL had a lower immunological response than the placebo arm (52).

An RCT evaluated the efficacy of tofacitinib on influenza and pneumococcal vaccines. Similar proportions of patients among those treated with tofacitinib or placebo showed a satisfactory immunological response to influenza vaccination (56.9% vs. 62.2%).

However, the seroprotection rate was significantly reduced in subjects treated with tofacitinib in association with MTX compared to patients receiving tofacitinib monotherapy (64.9% vs. 91.1%).

Temporary withdrawal of treatment with tofacitinib did not lead to an improvement in immunological response to vaccination (39).

Pneumococcal vaccination in ARDs patients treated with bDMARDs is generally safe and the rate of severe adverse events is not significantly increased. This can be seen in patients with RA and SpA treated with anti-TNF-alpha (25, 53), ABA (22) and RTX (54).

Efficacy of pneumococcal vaccines has been evaluated on the basis of clinical protection and of antibody response.

Protection against invasive pneumococcal disease (IPD) in patients with cs- and bDMARDs is controversial and data about clinical efficacy rely on few studies that show several limitations (Table III).

PPSV-23 has been evaluated in a multicentre RCT in Japanese patients treated with immunosuppressive agents, including biologic drugs. Seventeen (3.7%) of 464 patients in the vaccine group and 15 (3.4%) of 436 patients in the placebo group developed pneumonia. The authors concluded that the vaccine did not prevent against pneumonia overall in RA patients (55).

The only study investigating the occurrence of pneumococcal infections in RA and SpA patients after use of PCV-7 concluded that vaccination tend to reduce the risk of putative serious pneumococcal infections by about 45%, although the difference lacked statistical significance. The study had a retrospective design and the diagnosis of pneumococcal infection was presumed, because identification of bacteria in the site of infection was lacking. (56)

In conclusion, although a favourable trend was observed in vaccinated patients (PPSV-23 and conjugate vaccines), a more recent and better-designed study (on PPSV-23) did not confirm this suggestion.

The immunogenicity of pneumococcal vaccines varies depending on treatment. On this topic, only two RCTs are available, one demonstrating that the percentages of RA patients achieving a response to PPSV-23 were similar in the ADA and placebo groups (57), and a second one observing that IgG responses to GOL were lower than those in the MTX alone or control groups, whereas the opsonisation index (OI) responses were similar. (24)

The quality of the other non-ran-

**Table III.** Immunogenicity of pneumococcal vaccine.

		high dose GCs	MTX	DMARDs- ISS	TNFi	MTX + TNFi	RTX	ABA	TCZ	BEL	TOF
PPSV-23	RA		Reduced (27,93)	Reduced (95)	Good (27,55,56,82,96)	Reduced (27) <sup>[ns]</sup> , (93) <sup>[A/E/I]</sup> Reduced but good OI (24) <sup>[G]</sup>	Reduced (59,86)	Reduced but good OI (24) Good (47)	Good (48,58)		Reduced (39)
	ARDs	Reduced (10)	Reduced (10)		Good (10) <sup>[E/I]</sup> Reduced (91,97) <sup>[E/I]</sup>				Good (10)		
	SLE			Reduced (30)							Good (60)
	PsA		Reduced (98)		Good (98) <sup>[E]</sup>						
PCV-7	RA		Reduced (27,29)		Good (27,29) <sup>[ns]</sup>	Reduced (27,29) <sup>[ns]</sup>	Reduced (54)	Reduced (54)	Good (54)		
	SpA		Reduced (25)		Good (25) <sup>[ns]</sup>	Reduced (25) <sup>[ns]</sup>					
PCV-13	RA		Reduced (26)		Good (53) <sup>[E]</sup>						
	SLE/sV		Reduced (99)	Reduced (61,99)							Good (61)

ARDs: autoimmune rheumatic diseases; GCs: glucocorticoids; MTX: methotrexate; DMARDs: disease-modifying anti-rheumatic drugs; ISS: immunosuppressive therapy; ABA: abatacept; BEL: belimumab; OI: opsonisation Index; PsA: psoriatic arthritis; SpA: spondyloarthritis; sV: systemic vasculitis; TNFi: TNF inhibitors [<sup>[A]</sup>adalimumab (RCT)]; [<sup>[G]</sup>certolizumab pegol]; [<sup>[E]</sup>etanercept]; [<sup>[E/I]</sup>infliximab/etanercept]; [<sup>[G]</sup>golimumab (RCT)]; [<sup>[I]</sup>infliximab]; [<sup>[ns]</sup>not specified]; TCZ: tocilizumab; TOF: tofacitinib.

domised studies was low or very low. The results of these studies generally show that anti-TNF-alpha drugs do not reduce the efficacy of pneumococcal vaccine in patients with RA and SpA (10, 25, 28, 53).

At present, there are conflicting data on the efficacy of vaccination in patients treated with ABA. In 2013, Kapetanovic *et al.* showed a significantly reduced antibody response to PCV-7 in RA patients treated with ABA (54). Further works showed that the IgG response *versus* 6B serotype of PPSV-23 is reduced in subjects treated with ABA compared to controls, while OI is not impaired (22). These and other data suggest that immunisation with PPSV-23 results in a preserved immune response in RA patients treated with ABA (47).

Few studies evaluated the effect of anti-IL-6 therapy on the pneumococcal vaccine. In 2013, a RCT showed that a smaller percentage of patients treated with TCZ in association with MTX responds to PPSV-23 compared to those treated with MTX monotherapy (60% vs. 71%), although the difference was not statistically significant (58). On the contrary, another study evidenced that

immunogenicity of PPSV-23 performs better in patients with RA treated with TCZ than in controls treated with TCZ and MTX or MTX alone (42). Moreover, RA patients treated with TCZ had a sufficient antibody response after the administration of the pneumococcal 7-valent conjugate vaccine, in contrast to patients treated with RTX, ABA and MTX (54).

RTX reduces the efficacy of pneumococcal vaccine (28). Kapetanovic *et al.* showed a statistically significant reduction in IgG directed against 23F and 6B serotypes in patients with RA treated with RTX (54). In 2010, a controlled trial showed that patients treated with RTX and MTX had a reduced response to PPSV-23 compared to patients treated with MTX alone: 57% of patients treated with the combination of RTX and MTX achieved a 2-fold titre increase in at least 1 serotype compared to 82% in MTX monotherapy patients (59).

Several studies showed that treatment with BEL does not reduce the immunological response to pneumococcal vaccination in patients with SLE (52, 60, 61).

Tofacitinib has been shown reduce the efficacy of PPSV-23 in RA patients (39).

*6. Patients with ARDs should be actively immunised against influenza (yearly). Adjuvated vaccines may be more efficacious, in particular in patients on bDMARDs. [mean (SD) SOR: 85.83 (17.88); Grade II (B)]*

Influenza vaccination rate is below the level set by the WHO, both among healthy individuals and patients living with chronic diseases. Most authors largely attribute the poor uptake of influenza vaccination in patients with ARDs to the lack of its prescription by the rheumatologist or the general practitioner (62). The uptake is higher among those RA patients considered at highest risk for complicated influenza, such as the elderly and patients with severe co-morbidities (63). Whatever condition might hamper the increase of vaccination rate, a more practical goal may be to optimise the time of vaccine administration early before the onset of flu season to obtain maximal protection (64). Influenza vaccination significantly reduces mortality and infection-related complications in patients with

chronic obstructive pulmonary disease (COPD) (65), whereas among other categories of patients with chronic diseases, such as diabetes and cancer (66, 67), the actual benefits of flu vaccination are less clear.

The strength of recommendation for patients with ARDs is limited by small number of studies and low grade of evidence (68-70). Although more controlled trials would be desirable to better estimate the real clinical outcome of the influenza vaccination, the available data on safety and immunogenicity, as measured by surrogate markers of protection such as the geometric mean titre of haemagglutinin inhibition antibodies, justify routine recommendation. Each patient with ARDs should be vaccinated annually, before the onset of the influenza season, regardless the DMARDs regimen used.

Some authors suggest a temporary withdrawn of DMARDs in the time frame immediately preceding and following the administration of influenza vaccine to improve humoral responses, though such a strategy may promote flare of the rheumatologic disease (13, 39).

Patients with ARDs treated with DMARDs should receive the non-live inactivated formulation of influenza vaccine. There are no controlled studies performed with the live attenuated intranasally administered vaccines (71). In a recent meta-analysis, Huang *et al.* describe an overall better humoral response in RA patients comparable to healthy controls with the use of adjuvanted vaccine than with the non-adjuvanted formulation. Concerns exist with the use of adjuvanted form in patients with abnormal immunity, given the potential risk of autoimmune syndrome induced by adjuvants (ASIA). However, in the review by Huang *et al.*, the study attributing RA flare-up to adjuvant date back to 1979, and no studies have reported comparable adverse event since (72). To comment in detail on the immunogenicity of specific influenza strains in patients with ARDs is beyond the remit of this work. There are studies describing RA patients with a lower antibodies response either for H1N1 strain (72) or for H3N2 and B strains (39) compared to healthy controls. Expo-

sure to immunosuppression throughout a lifetime as well as environmental exposure to influenza conceivably condition vaccine specific immune responses. Virus strains encountered earliest in life have longer lasting effects and influenza responses to subsequent infection or vaccination. In addition, humoral responses to inactivated influenza vaccine are largely due to the boosting of pre-existing antibodies rather than new priming (73, 74) (Table IV).

*7. Patients with ARDs should be actively immunised against S. pneumoniae. [mean (SD) SOR: 89.86 (11.24); Grade II (B)]*

The available data show that immunogenicity of pneumococcal vaccines in ARDs patients is frequently decreased, but the majority of patients are able to mount immunogenic responses that achieve protective antibody titres (Table III).

Conjugate vaccines induce higher affinity antibody responses, longer lasting immune responses and memory responses than polysaccharide vaccines. Responses to PCV-7 are better than those observed for PPSV-23 in elderly (75,76) and HIV-infected patients (77-79), an additional benefit of the conjugated vaccine over the non-conjugated vaccine has not clearly documented in other immunosuppressed individuals. (80) The only study comparing the two vaccines in patients with RA receiving immunosuppressive treatment (primarily MTX and/or anti-TNF-alpha) showed that PCV-7 elicits similar antibody response as PPSV-23 (27).

Therefore, the standard of care supported by several guidelines in immunocompromised patients (11) as in general population is represented by pneumococcal 13-valent conjugate vaccine (PCV-13). However, no data are still available about the effectiveness of PCV-13 in ARDs patients.

Since PCV-13 and PPSV-23 cover different serotypes broader protection should be expected through use of both PCV-13 and PPSV-23 in series because conjugated vaccine might hypothetically prime the immune system for an enhanced secondary response to PPSV-23 (11). Despite recommended PPSV-

23 does not prevent pneumonia overall in RA patients at risk for infections (7). Consequently, sequential administration of PCV-13 and PPSV-23 has been advocated, even though no evidence supports this hypothesis in ARD population.

Based on the expert opinion, extrapolating data from other immunocompromised populations (78, 81-83) considering the high frequency of the invasive pneumococcal disease (IPD) cases in Italy covered by PPSV-23 (and not by PCV-13), the panel suggests a combined administration of the two pneumococcal vaccinations, in which conjugated vaccine should precede PPSV-23. In vaccination-naïve patients, the recommended schedule is a sequence of PCV-7 or PCV-13 followed by PPSV-23, with an interval of at least 8 weeks. This interval may be extended up to 12 months, depending on the patient's conditions.

In patients already vaccinated with PPSV-23, PCV-13 should be given at least 12 months later.

*8. In patients with ARDs, vaccination should ideally be administered during stable disease. [mean (SD) SOR: 82.17 (20.74); Grade IV (D)]*

There are few studies evaluating the efficacy of vaccination in patients with active ARDs. Likewise, studies comparing the efficacy of vaccination in patients with stable and unstable disease are rare. Ribeiro *et al.* pointed out that increased disease activity in RA patients does not preclude immune response to influenza vaccine and it is not linked to a higher rate of adverse events. (33)

Other studies record that the efficacy of influenza vaccination in SLE patients with increased disease activity seems to be reduced (18, 84).

Considering that the level of immunosuppression is high in patients with unstable disease and therefore the effectiveness of vaccination could be reduced, vaccination should be performed, preferentially, during stable phases of the disease.

*9. In patients with ARDs, vaccination against S. pneumoniae should ideally be administered before starting any immunosuppressive treatments, in order to maximise effectiveness and safety.*

**Table IV.** Immunogenicity of Influenza vaccine.

		GCs	HCQ	MTX	DMARDs - ISS	TNFi	MTX + TNFi	RTX	ABA	TCZ	BEL	TOF
Seasonal influenza (no adjuvanted)	RA	Good immunogenicity		Does not significantly attenuate humoral response (12,39,42) Reduced immunogenicity (13,33,41,46)	Good immunogenicity (50)	Good immunogenicity (33,46) Good to moderate immunogenicity. (43)		Reduced (49-51)	Reduced immunogenicity (41)	Good immunogenicity (42,48)		Does not significantly attenuate humoral response (39)
Seasonal influenza (adjuvanted)	RA	Good immunogenicity (31)(45)		Reduced immunogenicity (44)	Reduced immunogenicity (31)	Partially reduced immunogenicity* (44) Good immunogenicity (45)	Reduced immunogenicity (44)	Reduced immunogenicity (31,44)	Reduced immunogenicity (44)	Good immunogenicity (44)		
Seasonal influenza (adjuvanted)	ARDs	Good immunogenicity [106]		Reduced immunogenicity (100)	Good immunogenicity (100)	Good immunogenicity (100)	Reduced immunogenicity (100)	Reduced immunogenicity (100)	Reduced immunogenicity (100)			
Seasonal influenza (adjuvanted)	SpA	Good immunogenicity (31)		Reduced immunogenicity (44)	Reduced immunogenicity (31)	Good immunogenicity (44)	Reduced immunogenicity (44)	Reduced immunogenicity (31)				
Seasonal influenza (not adjuvanted)	SpA			Reduced immunogenicity (46)		Reduced immunogenicity (only for INF/ADA) (46)						
Seasonal influenza (not adjuvanted)	SLE/CTD/sV	Reduced immunogenicity (18,19,38) Good immunogenicity (20,21,32)	Good immunogenicity (18-20,32,38)	Reduced immunogenicity (18) Good immunogenicity (20)	Reduced immunogenicity (18,19,38,84) Does not significantly attenuate humoral response (20,21,32,101)							Reduced immunogenicity (52)
Seasonal influenza (adjuvanted)	SLE/CTD/sV	Good immunogenicity (31)			Reduced immunogenicity (31)			Reduced immunogenicity (31)				

ARDs: autoimmune rheumatic diseases; GCs: glucocorticoids; HCQ: hydroxychloroquine; MTX: methotrexate; DMARDs: disease-modifying anti-rheumatic drugs; ISS: immunosuppressive therapy; ABA: abatacept; BEL: belimumab; OI: Opsonisation Index; RA: rheumatoid arthritis; PsA: psoriatic arthritis; SpA: spondyloarthritis; sV: systemic vasculitis; SLE: systemic lupus erythematosus; CTD: connective tissue disease; TNFi: TNF inhibitors [I<sup>A</sup>] adalimumab (RCT); [I<sup>G</sup>] certolizumab pegol; [I<sup>E</sup>] etanercept; [I<sup>B</sup>] infliximab/etanercept; [I<sup>Q</sup>] golimumab (RCT); [I<sup>I</sup>] infliximab; [I<sup>M</sup>]not specified; TCZ: tocilizumab; TOF: tofacitinib.  
\*boosting with an additional dose improved antibody response.

*In particular, vaccination should be administered before starting abatacept and at least 4 weeks before starting rituximab. [mean (SD) SOR: 92.69 (8.23). Grade II(B)]*

Many studies show that the immunological response following pneumococcal vaccination in patients with ARDs is similar to that of healthy controls, while other studies show impaired efficacy, especially in patients with SLE (10, 30, 85). Immunosuppressive therapies can reduce the immunogenicity of pneumococcal vaccination, depending on the

type, total dose administered and timing (22, 23, 25, 26, 29, 47, 53, 54, 58). However, in some cases, the proportion of patients generating a response to pneumococcal vaccination does not depend on the time of administration of vaccine, as in the case of BEL (60). On the contrary, immune responses were severely reduced in healthy volunteers when pneumococcal vaccination was given 2 weeks after ABA (76) and patients vaccinated 6 months after RTX had worse outcomes than those vaccinated 6 days before (86). No dif-

ference was observed between patients vaccinated <180 days and >180 days after RTX administration (19). On this basis, in order to maximise the effectiveness of the vaccination, patients on immunosuppressive treatment should be vaccinated when the dosage of the therapy is tapered in stable disease or ideally before the introduction of the immunosuppressive drugs (87). This recommendation may not be feasible in everyday clinical practice under certain circumstances. Patients with ARDs in an active phase need to start



immunosuppressive therapies as soon as possible, often without the chance to vaccinate before the start of treatment. If it is advisable to vaccinate patients when the disease is in a stable clinical phase, it should not be overlooked that such a condition often occurs, in most cases, after the beginning of the immunosuppressive treatment.

It must be noted that this statement cannot be applied to influenza vaccinations, which follow a pre-established vaccination programme.

#### Implementation plan

The SIR and SIMIT societies plan to perform a baseline national survey on the vaccination status of patients with ARDs, and disseminate the present guidelines to the scientific society members. The same survey will be repeated on an annual basis to assess the implementation of the recommendations into practice.

#### Discussion

Vaccinations represent one of the most effective measure to prevent certain infections as well as to reduce morbidity and mortality (88).

Vaccines confer protection against infections by eliciting an immune response through the production of specific antibodies, thus their effectiveness requires an adequate immunologic status. Data from literature highlight the increased risk of infections in ARDs patients, which may be more severe when compared with the general population (89). This risk is due to the immunological dysfunction associated with the disease and the increased use of different immunosuppressive drugs. This study group reviewed the scientific evidence about the safety and efficacy of vaccination against influenza and *S. pneumoniae*, thus providing recommendations for clinical practice in ARDs patients.

We systemically reviewed the published data from 2009 to 2017 and, if the data were lacking expert opinions were taken into account. At present, only 1 RCT was published, exploring the role of PPSV-23 in preventing pneumococcal pneumonia in RA patients treated with bDMARDs. Surprisingly, PPSV-23 seems not to be effective to prevent pneumonia in vaccinated pa-

tients respect to non-vaccinated ones. The possible explanations for this paradox might be searched for some specific biases of the design study, including the short follow-up and the small sample size together with the difficulty in obtaining a definitive pathological cause of pneumonia (55).

Furthermore, the authors highlight the possibility that PPSV-23 alone may not be effective in protection against pneumonia, as reported in the guidelines for pneumococcal disease prevention (90). In fact, a sequential administration of PCV-13 (in vaccination-naïve patients can be used PCV-7 or PCV-13) and PPSV-23 could be a more appropriate approach for the prevention for pneumonia in RA patients receiving immunosuppressive treatments.

We pointed out the importance in assessing the patients' vaccination status for *S. pneumoniae*, in order to define the correct approach for each patient as well as the specific vaccination schedule at ARDs diagnosis, although this procedure is still not frequently met in clinical practice.

Data from literature show that PPSV-23 and PCV-7 may be safely administered in ARDs patients treated with csDMARDs. Among csDMARDs, MTX treatment regimen was associated with a decreased total immunoglobulin levels and impairment of vaccine-specific IgG levels following pneumococcal vaccination (26). On the other hand, some papers report the evidence of anti-pneumococcal antibodies in RA patients treated with MTX 10 years after specific vaccination (10, 29). As far as GCs therapy is concerned, low dosages seem unable to reduce the vaccine efficacy and safety (10, 25, 30), although a slightly impairment should be reported at prednisone dosage  $\geq 10$  mg/day (40). The introduction of bDMARDs for ARDs posed new questions about the safety and the efficacy of vaccination in general and about the pneumococcal vaccines specifically. Pre- and post-vaccination studies did not show increased adverse events in RA patients, irrespective of the type of bDMARD (22, 25, 53, 54, 57, 59, 91, 92)

In fact, anti-TNF-alpha molecules and TCZ used in monotherapy did not de-

crease the efficacy of pneumococcal vaccination. On the other hand, a combination therapy including MTX may reduce the immune response to the pneumococcal vaccinations, irrespective of the type of vaccine (27, 29, 93, 94). Furthermore, a special attention concerning the vaccination status of the patients should be paid before starting therapy with ABA and RTX.

RTX reduces the efficacy of pneumococcal vaccine (28) and still conflicting data are available about the effects of ABA. Despite the similar target for treatment, BEL, differently from RTX, seems to be unable to decrease the immunological response after pneumococcal vaccinations (52, 60, 61).

As far as the JAK inhibitors are concerned, emerging data highlight the possibility that tofacitinib may reduce the efficacy of PPSV-23 in RA patients, and this needs to be confirmed in larger cohorts.

In daily practice, influenza vaccination should be strongly recommended in ARDs patients before the onset of the immunosuppressive drugs, in order to maximise the effectiveness of the vaccination or, alternatively, when therapies are set at the lowest effective dosages (87). It has been shown that vaccine against influenza is effective and safe in ARDs patients treated with low dosage of GCs, csDMARDs, tsDMARDs and/or bDMARDs (12-21). Furthermore, it has been proposed that treatment with anti-malarial drugs (chloroquine) may improve the protective effect of the influenza vaccination (18). Its effectiveness is slightly reduced in patients treated with RTX (28, 31, 43, 44, 49). Furthermore, the effect of RTX on influenza vaccine seems to be related to RTX administration. In fact, influenza vaccine should be given at least 4 weeks before and at least 6 months after treatment with RTX to maximise the effect. Finally, data from a RCT evaluating the effectiveness of influenza vaccines in patients treated with tofacitinib showed a satisfactory immunological response to influenza vaccination and the sero-protection rate was significantly higher in those patients treated with tofacitinib in monotherapy when compared to subjects treated with tofacitinib and MTX (39).

## Acknowledgments

The Italian group for the Study and Management of the Infections in patients with Rheumatic diseases (ISMIR group), the Italian Society of Rheumatology (SIR) and the Italian Society of Infectious and Tropical Diseases (SIM-IT) for supporting this project.

## Authors' affiliations

<sup>1</sup>Dept. of Medical Sciences, Section of Rheumatology, University of Ferrara, Italy;

<sup>2</sup>Infectious Disease Unit, Dept. of Biomedical and Clinical Sciences L. Sacco, University of Milano, Italy;

<sup>3</sup>Rheumatology Unit, Dept. of Biotechnological and Applied Clinical Science, School of Medicine, University of L'Aquila, Italy;

<sup>4</sup>Rheumatology Unit, Dept. of Internal Medicine and Medical Specialties, Sapienza University of Rome, Italy;

<sup>5</sup>Division of Infectious Diseases, Azienda Ospedaliero Universitaria Ospedali Riuniti, Ancona, Italy;

<sup>6</sup>Unità di Malattie Infettive, Ospedale Civile Spirito Santo, Pescara, Italy;

<sup>7</sup>Rheumatology and Clinical Immunology Unit, Spedali Civili di Brescia, Italy;

<sup>8</sup>Dept. of Internal Medicine and Medical Therapy, Section of Rheumatology, University of Messina, Italy;

<sup>9</sup>Dept. of Experimental and Clinical Medicine, University of Florence, and Infectious and Tropical Diseases Unit, Careggi University Hospital, Florence, Italy;

<sup>10</sup>Rheumatology Unit, Dept. of Clinical and Experimental Medicine, University of Pisa, Italy.

<sup>11</sup>Infectious Diseases Unit, Galliera Hospital, Genoa, Italy;

<sup>12</sup>Clinic of Infectious Diseases, Vita-Salute San Raffaele University, Milano, Italy;

<sup>13</sup>University Department of Infectious and Tropical Diseases, University of Brescia and Spedali Civili General Hospital, Brescia, Italy;

<sup>14</sup>Division of Infectious and Tropical Diseases, Azienda Ospedaliera and University of Padova, Italy.

<sup>15</sup>Rheumatology Unit, Dept. of Medical and Surgical Science, University of Modena, Azienda Policlinico of Modena;

<sup>16</sup>Infectious Diseases Unit, Teaching Hospital S. Orsola-Malpighi, Alma Mater

Studiorum University of Bologna, Italy;

<sup>17</sup>Dept. of Medical Science, University of Turin, Infectious Diseases Amedeo di Savoia Hospital, Turin, Italy;

<sup>18</sup>Rheumatology Section, Dept. of Medicine, University of Verona, Italy;

<sup>19</sup>Academic Department of Rheumatology, King's College London, UK;

<sup>20</sup>Rheumatology Unit, University of Perugia, Italy;

<sup>21</sup>ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy;

<sup>22</sup>Division of Infectious Diseases, ASST Papa Giovanni XXIII, Bergamo, Italy;

<sup>23</sup>Clinic of Infectious Diseases, University of Bari, Italy;

<sup>24</sup>First Division of Infectious Diseases, Cotugno Hospital, Azienda Ospedaliera dei Colli, Napoli, Italy;

<sup>25</sup>Infectious Diseases Unit, Sapienza University, S.M. Goretti Hospital, Latina, Italy;

<sup>26</sup>Division of Infectious and Tropical Diseases, Hospital of Lodi, Italy;

<sup>27</sup>Rheumatology Clinic, Dept. of Medical and Biological Sciences, University Hospital Santa Maria della Misericordia, Udine, Italy;

<sup>28</sup>Rheumatology Unit, L. Sacco University Hospital, Milano, Italy.

## References

- BRENOL CV, AZEVEDO VF, BONVEHI PE *et al.*: Vaccination recommendations for adults with autoimmune inflammatory rheumatic diseases in Latin America. *J Clin Rheumatol* 2018; 24: 138-47.
- MERONI PL, ZAVAGLIA D, GIRMENIA C: Vaccinations in adults with rheumatoid arthritis in an era of new disease-modifying anti-rheumatic drugs. *Clin Exp Rheumatol* 2018; 36: 317-28.
- DORAN MF, CROWSON CS, POND GR, O'FALLON WM, GABRIEL SE: Frequency of infection in patients with rheumatoid arthritis compared with controls: A population-based study. *Arthritis Rheum* 2002; 46: 2287-93.
- SANDLER DS, RUDERMAN EM, BROWN T *et al.*: Understanding vaccination rates and attitudes among patients with rheumatoid arthritis. *Am J Manag Care* 2016; 22: 161-7.
- BLUMENTALS WA, ARREGLADO A, NAPAL-KOV P, TOOVEY S: Rheumatoid arthritis and the incidence of influenza and influenza-related complications: A retrospective cohort study. *BMC Musculoskelet Disord* 2012; 13: 158.
- SHEA KM, EDELSBERG J, WEYCKER D, FARKOUH RA, STRUTTON DR, PELTON SI: Rates of pneumococcal disease in adults with chronic medical conditions. *Open Forum Infect Dis* 2014; 1: ofu024.
- VAN ASSEN S, AGMON-LEVIN N, ELKAYAM O *et al.*: EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2011; 70: 414-22.
- VAN ASSEN S, ELKAYAM O, AGMON-LEVIN N *et al.*: Vaccination in adult patients with autoimmune inflammatory rheumatic diseases: A systematic literature review for the European League Against Rheumatism evidence-based recommendations for vaccination in adult patients with auto-immune inflammatory rheuma. *Autoimmun Rev* 2011; 10: 341-52.
- CRNKIC KAPETANOVIC M, SAXNE T, TRUEDSSON L, GEBOREK P: Persistence of antibody response 1.5 years after vaccination using 7-valent pneumococcal conjugate vaccine in patients with arthritis treated with different antirheumatic drugs. *Arthritis Res Ther* 2013; 15: R1.
- BROYDE A, ARAD U, MADAR-BALAKIRSKI N *et al.*: Longterm efficacy of an antipneumococcal polysaccharide vaccine among patients with autoimmune inflammatory rheumatic diseases. *J Rheumatol* 2016; 43: 267-72.
- LOPEZ A, MARIETTE X, BACHELEZ H *et al.*: Vaccination recommendations for the adult immunosuppressed patient: A systematic review and comprehensive field synopsis. *J Autoimmun* 2017; 80: 10-27.
- CHOUDHARY VR, JHA R: Acylation of nitrobenzene and substituted nitrobenzenes by benzoyl chloride using GaCl<sub>3</sub>- and GaAlCl<sub>3</sub>-grafted mesoporous Si-MCM-41 catalysts. *Microporous Mesoporous Mater* 2009; 119: 360-2.
- PARK JK, LEE MA, LEE EY *et al.*: Effect of methotrexate discontinuation on efficacy of seasonal influenza vaccination in patients with rheumatoid arthritis: A randomised clinical trial. *Ann Rheum Dis* 2017; 76: 1559-65.
- POLACHEK A, KOROBKO U, MADER-BALAKIRSKI N *et al.*: Immunogenicity and safety of vaccination against seasonal 2012 influenza virus among patients with psoriatic arthritis and psoriasis. *Clin Exp Rheumatol* 2015; 33: 181-6.
- HUANG Y, WANG H, WAN L, LU X, TAM WWS: Is systemic lupus erythematosus associated with a declined immunogenicity and poor safety of influenza vaccination? A systematic review and meta-analysis. *Med* 2016; 95: e3637.
- LIAO Z, TANG H, XU X, LIANG Y, XIONG Y, NI J: Immunogenicity and Safety of Influenza Vaccination in Systemic Lupus Erythematosus Patients Compared with Healthy Controls: A Meta-Analysis. *PLoS One* 2016; 11: e0147856.
- WIESIK-SZEWCZYK E, ROMANOWSKA M, MIELNIK P *et al.*: Anti-influenza vaccination in systemic lupus erythematosus patients: An analysis of specific humoral response and vaccination safety. *Clin Rheumatol* 2010; 29: 605-13.
- BORBA EF, SAAD CGS, PASOTO SG *et al.*: Influenza A/H1N1 vaccination of patients with SLE: Can antimalarial drugs restore diminished response under immunosuppressive therapy? *Rheumatol* 2012; 51: 1061-9.
- LAUNAY O, PAUL S, SERVETTAZ A *et al.*: Control of humoral immunity and autoimmunity by the CXCR4/CXCL12 axis in lupus patients following influenza vaccine. *Vaccine* 2013; 31: 3492-501.

20. MIOSSI R, FULLER R, MORAES J *et al.*: Immunogenicity of influenza H1N1 vaccination in mixed connective tissue disease: effect of disease and therapy. *Clinics* 2013; 68: 129-33.
21. SHINJO SK, DE MORAES JCB, LEVY-NETO M *et al.*: Pandemic unadjuvanted influenza A (H1N1) vaccine in dermatomyositis and polymyositis: Immunogenicity independent of therapy and no harmful effect in disease. *Vaccine* 2012; 31: 202-6.
22. MIGITA K, AKEDA Y, AKAZAWA M *et al.*: Effect of abatacept on the immunogenicity of 23-valent pneumococcal polysaccharide vaccination (PPSV23) in rheumatoid arthritis patients. *Arthritis Res Ther* 2015; 17: 357.
23. MORI S, UEKI Y, AKEDA Y *et al.*: Pneumococcal polysaccharide vaccination in rheumatoid arthritis patients receiving tocilizumab therapy. *Ann Rheum Dis* 2013; 72: 1362-6.
24. MIGITA K, AKEDA Y, AKAZAWA M *et al.*: Oposonic and antibody responses to pneumococcal polysaccharide in rheumatoid arthritis patients receiving golimumab plus methotrexate. *Med* 2015; 94: e2184.
25. KAPETANOVIC MC, ROSEMAN C, JÖNSSON G, TRUEDSSON L, SAXNE T, GEBOREK P: Antibody response is reduced following vaccination with 7-valent conjugate pneumococcal vaccine in adult methotrexate-treated patients with established arthritis, but not those treated with tumor necrosis factor inhibitors. *Arthritis Rheum* 2011; 63: 3723-32.
26. KAPETANOVIC MC, NAGEL J, NORDSTRÖM I, SAXNE T, GEBOREK P, RUDIN A: Methotrexate reduces vaccine-specific immunoglobulin levels but not numbers of circulating antibody-producing B cells in rheumatoid arthritis after vaccination with a conjugate pneumococcal vaccine. *Vaccine* 2017; 35: 903-8.
27. KAPETANOVIC MC, ROSEMAN C, JÖNSSON G, TRUEDSSON L: Heptavalent pneumococcal conjugate vaccine elicits similar antibody response as standard 23-valent polysaccharide vaccine in adult patients with RA treated with immunomodulating drugs. *Clin Rheumatol* 2011; 30: 1555-61.
28. HUA C, BARNETCHE T, COMBE B, MOREL J: Effect of methotrexate, anti-tumor necrosis factor  $\alpha$ , and rituximab on the immune response to influenza and pneumococcal vaccines in patients with rheumatoid arthritis: A systematic review and meta-analysis. *Arthritis Care Res* 2014; 66: 1016-26.
29. COULSON E, SARAVANAN V, HAMILTON J *et al.*: Pneumococcal antibody levels after pneumovax in patients with rheumatoid arthritis on methotrexate. *Ann Rheum Dis* 2011; 70: 1289-91.
30. DE REZENDE RPV, RIBEIRO FM, ALBUQUERQUE EMN, GAYER CR, ANDRADE LEC, KLUMB EM: Immunogenicity of pneumococcal polysaccharide vaccine in adult systemic lupus erythematosus patients undergoing immunosuppressive treatment. *Lupus* 2016; 25: 1254-9.
31. GABAY C, BEL M, COMBESURE C *et al.*: Impact of synthetic and biologic disease-modifying antirheumatic drugs on antibody responses to the AS03-adjuvanted pandemic influenza vaccine: A prospective, open-label, parallel-cohort, single-center study. *Arthritis Rheum* 2011; 63: 1486-96.
32. LU CC, WANG YC, LAI JH, LEE TSH, LIN HT, CHANG DM: A/H1N1 influenza vaccination in patients with systemic lupus erythematosus: Safety and immunity. *Vaccine* 2011; 29: 444-50.
33. RIBEIRO ACM, GUEDES LKN, MORAES JCB *et al.*: Reduced seroprotection after pandemic H1N1 influenza adjuvant-free vaccination in patients with rheumatoid arthritis: Implications for clinical practice. *Ann Rheum Dis* 2011; 70: 2144-7.
34. HOLVAST A, DE HAAN A, VAN ASSEN S *et al.*: Cell-mediated immune responses to influenza vaccination in Wegener's granulomatosis. *Ann Rheum Dis* 2010; 69: 924-7.
35. IWAMOTO M, HOMMAS, ONISHI S *et al.*: Low level of seroconversion after a novel influenza A/H1N1/2009 vaccination in Japanese patients with rheumatoid arthritis in the 2009 season. *Rheumatol Int* 2012; 32: 3691-4.
36. PASOTO SG, RIBEIRO AC, VIANA VST *et al.*: Short and long-term effects of pandemic unadjuvanted influenza A(H1N1)pdm09 vaccine on clinical manifestations and autoantibody profile in primary Sjögren's syndrome. *Vaccine* 2013; 31: 1793-8.
37. CROWE SR, MERRILL JT, VISTA ES *et al.*: Influenza vaccination responses in human systemic lupus erythematosus: Impact of clinical and demographic features. *Arthritis Rheum* 2011; 63: 2396-406.
38. HOLVAST A, VAN ASSEN S, DE HAAN A *et al.*: Effect of a second, booster, influenza vaccination on antibody responses in quiescent systemic lupus erythematosus: An open, prospective, controlled study. *Rheumatology* 2009; 48: 1294-9.
39. WINTHROP KL, SILVERFIELD J, RACEWICZ A *et al.*: The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis. *Ann Rheum Dis* 2016; 75: 687-95.
40. FISCHER L, GERSTEL PF, PONCET A *et al.*: Pneumococcal polysaccharide vaccination in adults undergoing immunosuppressive treatment for inflammatory diseases - A longitudinal study. *Arthritis Res Ther* 2015; 17: 151.
41. RIBEIRO AC, LAURINDO IM, GUEDES LK *et al.*: Abatacept and reduced immune response to pandemic 2009 influenza A/H1N1 vaccination in patients with rheumatoid arthritis. *Arthritis Care Res* 2013; 65: 476-80.
42. MORI S, UEKI Y, HIRAKATA N, ORIBE M, HIDAKA T, OISHI K: Impact of tocilizumab therapy on antibody response to influenza vaccine in patients with rheumatoid arthritis. *Ann Rheum Dis* 2012; 71: 2006-10.
43. SALEMI S, PICCHIANTI-DIAMANTI A, GERMANO V *et al.*: Influenza vaccine administration in rheumatoid arthritis patients under treatment with TNF- $\alpha$  blockers: Safety and immunogenicity. *Clin Immunol* 2010; 134: 113-20.
44. KAPETANOVIC MC, KRISTENSEN LE, SAXNE T, AKTAS T, MÖRNER A, GEBOREK P: Impact of anti-rheumatic treatment on immunogenicity of pandemic H1N1 influenza vaccine in patients with arthritis. *Arthritis Res Ther* 2014; 16: R2.
45. MILANETTI F, GERMANO V, NISINI R *et al.*: Safety and immunogenicity of co-administered MF59-adjuvanted 2009 pandemic and plain 2009-10 seasonal influenza vaccines in rheumatoid arthritis patients on biologics. *Clin Exp Immunol* 2014; 177: 287-94.
46. FRANÇA ILA, RIBEIRO ACM, AIKAWA NE *et al.*: Tnf blockers show distinct patterns of immune response to the pandemic influenza a h1n1 vaccine in inflammatory arthritis patients. *Rheumatol* 2012; 51: 2091-8.
47. ALTEN R, BINGHAM CO, COHEN SB *et al.*: Antibody response to pneumococcal and influenza vaccination in patients with rheumatoid arthritis receiving abatacept. *BMC Musculoskelet Disord* 2016; 17: 231.
48. TSURU T, TERAOKA K, MURAKAMI M *et al.*: Immune response to influenza vaccine and pneumococcal polysaccharide vaccine under IL-6 signal inhibition therapy with tocilizumab. *Mod Rheumatol* 2014; 24: 511-6.
49. WESTRA J, VAN ASSEN S, WILTING KR *et al.*: Rituximab impairs immunoglobulin (Ig)M and IgG (subclass) responses after influenza vaccination in rheumatoid arthritis patients. *Clin Exp Immunol* 2014; 178: 40-7.
50. ARAD U, TZADOK S, AMIR S *et al.*: The cellular immune response to influenza vaccination is preserved in rheumatoid arthritis patients treated with rituximab. *Vaccine* 2011; 29: 1643-8.
51. VAN ASSEN S, HOLVAST A, BENNE CA *et al.*: Humoral responses after influenza vaccination are severely reduced in patients with rheumatoid arthritis treated with rituximab. *Arthritis Rheum* 2010; 62: 75-81.
52. CHATHAM WW, WALLACE DJ, STOHL W *et al.*: Effect of belimumab on vaccine antigen antibodies to influenza, pneumococcal, and tetanus vaccines in patients with systemic lupus erythematosus in the BLISS-76 trial. *J Rheumatol* 2012; 39: 1632-40.
53. RÁKÓCZI É, PERGE B, VÉGH E *et al.*: Evaluation of the immunogenicity of the 13-valent conjugated pneumococcal vaccine in rheumatoid arthritis patients treated with etanercept. *Jt Bone Spine* 2016; 83: 675-9.
54. CRNKIC KAPETANOVIC M, SAXNE T, JÖNSSON G, TRUEDSSON L, GEBOREK P: Rituximab and abatacept but not tocilizumab impair antibody response to pneumococcal conjugate vaccine in patients with rheumatoid arthritis. *Arthritis Res Ther* 2013; 15: R171.
55. IZUMI Y, AKAZAWA M, AKEDA Y *et al.*: The 23-valent pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis: A double-blinded, randomized, placebo-controlled trial. *Arthritis Res Ther* 2017; 19: 15.
56. NAGEL J, GEBOREK P, SAXNE T *et al.*: The risk of pneumococcal infections after immunization with pneumococcal conjugate vaccine compared to non-vaccinated inflammatory arthritis patients. *Scand J Rheumatol* 2015; 44: 271-9.
57. KAINE JL, KIVITZ AJ, BIRBARA C, LUO AY: Immune responses following administration of influenza and pneumococcal vaccines to patients with rheumatoid arthritis receiving adalimumab. *J Rheumatol* 2007; 34: 272-9.
58. BINGHAM CO, RIZZO W, KIVITZ A, HASSANALI A, UPMANYU R, KLEARMAN M: Humoral immune response to vaccines in patients with rheumatoid arthritis treated with tocilizumab: Results of a randomised controlled trial (VISARA). *Ann Rheum Dis* 2015; 74: 818-22.

59. BINGHAM CO, LOONEY RJ, DEODHAR A *et al.*: Immunization responses in rheumatoid arthritis patients treated with rituximab: Results from a controlled clinical trial. *Arthritis Rheum* 2010; 62: 64-74.
60. CHATHAM W, CHADHA A, FETTIPLACE J *et al.*: A randomized, open-label study to investigate the effect of belimumab on pneumococcal vaccination in patients with active, autoantibody-positive systemic lupus erythematosus. *Lupus* 2017; 26: 1483-90.
61. NAGEL J, SAXNE T, GEBOREK P *et al.*: Treatment with belimumab in systemic lupus erythematosus does not impair antibody response to 13-valent pneumococcal conjugate vaccine. *Lupus* 2017; 26: 1072-81.
62. SANDLER DS, RUDERMAN EM, BROWN T *et al.*: Understanding vaccination rates and attitudes among patients with rheumatoid arthritis. *Am J Manag Care* 2016; 22: 161-7.
63. COSTELLO R, WINTHROP KL, PYE SR, BROWN B, DIXON WG: Influenza and pneumococcal vaccination uptake in patients with rheumatoid arthritis treated with immunosuppressive therapy in the UK: A retrospective cohort study using data from the clinical practice research datalink. *PLoS One* 2016; 11: e0153848.
64. BAKER DW, BROWN T, LEE JY *et al.*: A multifaceted intervention to improve influenza, pneumococcal, and herpes zoster vaccination among patients with rheumatoid arthritis. *J Rheumatol* 2016; 43: 1030-7.
65. HUANG HH, CHEN SJ, CHAO TF *et al.*: Influenza vaccination and risk of respiratory failure in patients with chronic obstructive pulmonary disease: A nationwide population-based case-cohort study. *J Microbiol Immunol Infect* 2019; 52: 22-29.
66. VINOGRAD I, A ZT, LEIBOVICI L, PAUL M: Influenza vaccines in immunosuppressed adults with cancer (Review). *Cochrane Database Syst Rev* 2015; Oct 29(10): CD008983.
67. GOEIJENBIER M, VAN SLO滕EN TT, SLOBBEL *et al.*: Benefits of flu vaccination for persons with diabetes mellitus: A review. *Vaccine* 2017; 35: 5095-101.
68. NICHOL KL, WUORENMAJ, VON STERNBERG T: Benefits of influenza vaccination for low-, intermediate-, and high- risk senior citizens. *Arch Intern Med* 1998; 158: 1769-76.
69. STOJANOVICH L: Influenza vaccination of patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). *Clin Dev Immunol* 2006; 13: 373-5.
70. HOUSDEN MM, BELL G, HEYCOCK CR, HAMILTON J, SARAVANAN V, KELLY CA: How to reduce morbidity and mortality from chest infections in rheumatoid arthritis. *Clin Med J R Coll Physicians London* 2010; 10: 326-9.
71. GLÜCK T, MÜLLER-LADNER U: Vaccines: Vaccination in Patients with Chronic Rheumatic or Autoimmune Diseases. *Clin Infect Dis* 2008; 46: 1459-65.
72. HUANG Y, WANG H, TAM WWS: Is rheumatoid arthritis associated with reduced immunogenicity of the influenza vaccination? A systematic review and meta-analysis. *Curr Med Res Opin* 2017; 33: 1901-8.
73. HUANG KYA, RIJAL P, SCHIMANSKI L *et al.*: Focused antibody response to influenza linked to antigenic drift. *J Clin Invest* 2015; 125: 2631-45.
74. LEE J, BOUTZ DR, CHROMIKOVA V *et al.*: Molecular-level analysis of the serum antibody repertoire in young adults before and after seasonal influenza vaccination. *Nat Med* 2016; 22: 1456-64.
75. NAMKOONG H, FUNATSU Y, OISHI K *et al.*: Comparison of the immunogenicity and safety of polysaccharide and protein-conjugated pneumococcal vaccines among the elderly aged 80 years or older in Japan: An open-labeled randomized study. *Vaccine* 2015; 33: 327-32.
76. TAY L, LEON F, VRATSANOS G, RAYMOND R, CORBO M: Vaccination response to tetanus toxoid and 23-valent pneumococcal vaccines following administration of a single dose of abatacept: A randomized, open-label, parallel group study in healthy subjects. *Arthritis Res Ther* 2007; 9: 1-11.
77. FRENCH N, GORDON SB, MWALUKOMO T *et al.*: A trial of a 7-valent pneumococcal conjugate vaccine in HIV-infected adults. *Malawi Med J* 2016; 28: 115-22.
78. FEIKIN DR, ELIE CM, GOETZ MB *et al.*: Randomized trial of the quantitative and functional antibody responses to a 7-valent pneumococcal conjugate vaccine and/or 23-valent polysaccharide vaccine among HIV-infected adults. *Vaccine* 2001; 20: 545-53.
79. FRENCH N, NAKIYINGI J, CARPENTER LM *et al.*: 23-Valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: Double-blind, randomised and placebo controlled trial. *Lancet* 2000; 355: 2106-11.
80. GOLOS M, ELIAKIM-RAZ N, STERN A, LEIBOVICI L, PAUL M: Conjugated pneumococcal vaccine versus polysaccharide pneumococcal vaccine for prevention of pneumonia and invasive pneumococcal disease in immunocompetent and immunocompromised adults and children. *Cochrane Database Syst Rev* 2016; 2016(8).
81. LESPRIT P, PÉDRONO G, MOLINA JM *et al.*: Immunological efficacy of a prime-boost pneumococcal vaccination in HIV-infected adults. *Aids* 2007; 21: 2425-34.
82. HO YL, BRANDÃO AP, DE CUNTO BRANDILEONE MC, LOPES MH: Immunogenicity and safety of pneumococcal conjugate polysaccharide and free polysaccharide vaccines alone or combined in HIV-infected adults in Brazil. *Vaccine* 2013; 31: 4047-53.
83. CHAN YC, MOLRINE DC, GEORGE S *et al.*: Pneumococcal conjugate vaccine primes for antibody responses to polysaccharide pneumococcal vaccine after treatment of Hodgkin's disease. *J Infect Dis* 1996; 173: 256-8.
84. MATHIAN A, DEVILLIERS H, KRIVINE A *et al.*: Factors influencing the efficacy of two injections of a pandemic 2009 influenza A (H1N1) nonadjuvanted vaccine in systemic lupus erythematosus. *Arthritis Rheum* 2011; 63: 3502-11.
85. PUGÈS M, BISCAY P, BARNETCHE T *et al.*: Immunogenicity and impact on disease activity of influenza and pneumococcal vaccines in systemic lupus erythematosus: A systematic literature review and meta-analysis. *Rheumatol* 2016; 55: 1664-72.
86. REHNBERG M, BRISSLERT M, AMU S, ZENDJANCHI K, HÁWI G, BOKAREWA MI: Vaccination response to protein and carbohydrate antigens in patients with rheumatoid arthritis after rituximab treatment. *Arthritis Res Ther* 2010; 12: R111.
87. BÜHLER S, EPERON G, RIBI C *et al.*: Vaccination recommendations for adult patients with autoimmune inflammatory rheumatic diseases. *Swiss Medical Weekly* 2015; 145: w14159.
88. MANDELL BF: Vaccination: An option not to be ignored. *Cleve Clin J Med* 2010; 77: 151.
89. WATAD A, SORIANO A, SHOENFELD Y: Vaccination in patients with autoimmune inflammatory rheumatic diseases. *Vaccines Autoimmun* 2014; 11: 113-26.
90. PILISHVILI T, BENNETT NM: Pneumococcal disease prevention among adults: strategies for the use of pneumococcal vaccines. *Am J Prev Med* 2015; 49: S383-90.
91. ELKAYAM O, CASPI D, REITBLATT T, CHARBONEAU D, RUBINS JB: The effect of tumor necrosis factor blockade on the response to pneumococcal vaccination in patients with rheumatoid arthritis and ankylosing spondylitis. *Semin Arthritis Rheum* 2004; 33: 283-88.
92. ELKAYAM O, PARAN D, CASPI D *et al.*: Immunogenicity and safety of pneumococcal vaccination in patients with rheumatoid arthritis or systemic lupus erythematosus. *Clin Infect Dis* 2002; 34: 147-53.
93. GELINCK LBS, VAN DER BIJL AE, VISSER LG *et al.*: Synergistic immunosuppressive effect of anti-TNF combined with methotrexate on antibody responses to the 23 valent pneumococcal polysaccharide vaccine. *Vaccine* 2008; 26: 3528-33.
94. KAPETANOVIC MC, SAXNE T, SJÖHOLM A, TRUEDSSON L, JÖNSSON G, GEBOREK P: Influence of methotrexate, TNF blockers and prednisolone on antibody responses to pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis. *Rheumatology* 2006; 45: 106-11.
95. FRENCH N, GORDON SB, MWALUKOMO T *et al.*: A trial of a 7-valent pneumococcal conjugate vaccine in HIV-infected adults. *Malawi Med J* 2016; 28: 115-22.
96. KROON FP, VAN DISSEL JT, RAVENSBERGEN E, NIBBERING PH, VAN FURTH R: Enhanced antibody response to pneumococcal polysaccharide vaccine after prior immunization with conjugate pneumococcal vaccine in HIV-infected adults. *Vaccine* 2000; 19: 886-94.
97. SALINAS GF, DE RYCKE L, BARENDREGT B *et al.*: Anti-TNF treatment blocks the induction of T cell-dependent humoral responses. *Ann Rheum Dis* 2013; 72: 1037-43.
98. MEASE PJ, RITCHLIN CT, MARTIN RW *et al.*: Pneumococcal vaccine response in psoriatic arthritis patients during treatment with etanercept. *J Rheumatol* 2004; 31: 1356-61.
99. NIVED P, NAGEL J, SAXNE T *et al.*: Immune response to pneumococcal conjugate vaccine in patients with systemic vasculitis receiving standard of care therapy. *Vaccine* 2017; 35: 3639-46.
100. ADLER S, KRIVINE A, WEIX J *et al.*: Protective effect of A/H1N1 vaccination in immune-mediated disease—a prospectively controlled vaccination study. *Rheumatology* 2012; 51: 695-700.
101. LITINSKY I, BALBIR A, ZISMAN D *et al.*: Vaccination against influenza in patients with systemic sclerosis. *Clin Exp Rheumatol* 2012; 30 (Suppl. 71): S7-11.