

## REVIEW

Pneumococcal vaccination in  
autoimmune rheumatic diseasesÉva Rákóczi,<sup>1,2</sup> Zoltan Szekanecz<sup>2</sup>

**To cite:** Rákóczi É, Szekanecz Z. Pneumococcal vaccination in autoimmune rheumatic diseases. *RMD Open* Published Online First: [please include Day Month Year]. doi:10.1136/rmdopen-2017-000484

Received 24 April 2017  
Revised 11 August 2017  
Accepted 14 August 2017

## ABSTRACT

*Streptococcus pneumoniae* is the leading cause of the community-acquired pneumonia. The mortality rate of invasive pneumococcal infections is high. Immunocompromised patients suffering from autoimmune inflammatory rheumatic diseases (AIRD) have a high risk for acquiring these infections. Protection against infection can be improved with vaccination. After using polysaccharide vaccines (PPV-23), in July 2013, a 13-valent conjugate vaccine (PCV-13) was approved for adults. Due to its conjugate form, this vaccine is the recommended choice in pneumococcal vaccine-naïve patients. PCV-13 is also recommended in patients previously receiving PPV-23. Vaccination in AIRD is very important and needs deliberate scheduling to coordinate with the immunosuppressive therapy. Here, based on international and national vaccine guidelines, we provide a current review of PPV-23 and PCV-13 vaccines for specialists following patients with AIRD.

INTRODUCTION: THE EPIDEMIOLOGY OF  
PNEUMOCOCCAL INFECTIONS

The most common pneumococcal infection, such as community-acquired pneumonia (CAP), has been a large global challenge for healthcare providers. CAP caused by *Streptococcus pneumoniae* may exert both invasive and non-invasive forms. In 2010, pneumonia was the most common invasive infection accounted for 70% of all cases<sup>1</sup>. In the USA, approximately 4 million cases of CAP are estimated annually among elderly patients<sup>1</sup> and 17%–41% of these cases are caused by *S. pneumoniae*.<sup>2,3</sup> The incidence of invasive pneumococcal disease (IPD) depends on geographic regions, age group, comorbidities and immunosuppressive conditions. In 2012, the incidence of IPD in Europe was 4.3/100 000, the highest rates were seen in Denmark (15.8/100 000), Sweden (14.6/100 000) and Finland (13.9/100 000). The lowest rates were observed in Luxembourg (0.19/100 000), Lithuania (0.23/100 000) and Bulgaria (0.26/100 000).<sup>4,5</sup> In children under the age of 1 year, this incidence was 10.9/100 000, while in adults aged ≥65 years the frequency of confirmed cases was 12.1/100 000 population.<sup>5</sup> *S. pneumoniae* is the most frequently

isolated bacterium in European patients with CAP.<sup>6</sup> The annual incidence of CAP in adults is 1.07–1.20/1000 person-years (PY), while in elderly aged ≥65 years it is 14/1000 PY.<sup>7</sup> Comparing the normal adult population to special immunocompromised patient groups, the incidence is very high in HIV-infected patients (12/1000 PY). Among patients with autoimmune inflammatory rheumatic diseases (AIRD) treated with tumour necrosis factor alpha (TNF-α) inhibitors, the incidence is 5.97/1000 PY.<sup>7</sup>

## LOWER RESPIRATORY TRACT INFECTIONS IN AIRD

Patients with AIRD are immunocompromised and exert increased risk for infections.<sup>8,9</sup> Infection is the major cause of death in patients with AIRD. In patients with rheumatoid arthritis (RA), after correction for age and gender, the mortality of respiratory infections is two to five times higher than that in the general population. Due to the severity of infections, hospital admissions of patients with RA are doubled.<sup>10,11</sup> Infection is one of the most common causes of deaths in systemic lupus erythematosus (SLE) and it causes the same number of deaths as the active disease itself during the first 5 years of illness.<sup>12,13</sup> Gharibdoost *et al*.<sup>14</sup> reviewed the mortality of 2021 Iranian patients with SLE. The retrospective analysis indicated that infection was the most common cause of death (12.1%) between 1991 and 2000. In a systematic review published by Falagas *et al*.<sup>15</sup> 29% of 5411 patients with connective tissue disease had serious infections leading to death in 24% of the cases. The most common disease manifestations were bacteraemia and pneumonia.<sup>15</sup>

PNEUMOCOCCAL INFECTION IS A VACCINE  
PREVENTABLE DISEASE: IMPORTANCE OF  
CAPSULAR SEROTYPES

The polysaccharide capsular serotypes of *S. pneumoniae* are virulence factors responsible for invasive infections.<sup>16</sup> This bacterium has



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<sup>1</sup>Institute of Infectious Diseases, University of Debrecen Faculty of Medicine, Kenézy University Hospital, Debrecen, Hungary

<sup>2</sup>Division of Rheumatology, Department of Medicine, University of Debrecen Faculty of Medicine, Debrecen, Hungary

## Correspondence to

Dr Zoltan Szekanecz, Division of Rheumatology, Department of Medicine, University of Debrecen Faculty of Medicine, Debrecen, Hungary; szekanecz.zoltan@med.unideb.hu

**Table 1** Timeline of pneumococcal vaccine development

| 1911          | Starting pneumococcal vaccine research development   |
|---------------|--|
| 1915–1945     | Description of chemical structure of pathogen, virulence factors, antigenicity and serotypes. In 1940 more than 80 serotypes were known. |
| 1977          | Introduction of pneumococcal polysaccharide vaccine with 14 serotypes (PPV-14) in USA  |
| 1983          | Introduction of pneumococcal polysaccharide vaccine with 23 serotypes (PPV-23)   |
| 2000          | First development of pneumococcal conjugate vaccine with seven serotypes (PCV-7)   |
| 2009          | Introduction of pneumococcal conjugate vaccine with 10 serotypes (PCV-10) received by European Commission authorisation                  |
| 2010          | Introduction of 13-valent pneumococcal conjugate vaccine (PCV-13) for children (6 weeks to 71 months)                                    |
| December 2011 | First application of PCV-13 in adults $\geq 50$ years  |
| June 2012     | ACIP recommendation of PCV-13 for adults aged $\geq 19$ years with immunocompromising conditions   |
| January 2013  | PCV-13 for teenagers (6–17 years)  |
| July 2013     | EMA recommendation of PCV-13 for all ages  |

ACIP, Advisory Committee on Immunization Practices; EMA, European Medicines Agency.

more than 90 serotypes. In humans, approximately 25–30 serotypes are responsible for 90% of invasive infectious cases.<sup>16</sup> The effectivity of vaccine is the reduction in incidence of a disease among those who have been vaccinated relative to the incidence in the unvaccinated. The efficacy of pneumococcal vaccines highly depends on the coverage of the most common serotypes, as well as on their immunogenicity.<sup>16,17</sup> The prevalence of serotypes is variable depending on age, chronic diseases, geographic region, administration of pneumococcal vaccines and the use of antibiotics.<sup>17</sup> For example, in 2010, the most common serotypes were 1, 3, 4, 7F, 8, 14, 12F, 19A, 19F and 22F in the European Union countries.<sup>17</sup> Immunogenicity refers to the ability of a vaccine to induce an immune response in a vaccinated individual. Protective pneumococcal antibody level has been established by the working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology: a twofold increase in the antibody level (baseline level before vaccination and after 4 weeks of vaccination) is an indicator of immune responsiveness.<sup>18</sup>

## PNEUMOCOCCAL VACCINE DEVELOPMENT

In 1977, the first pneumococcal polysaccharide vaccine (PPV) approved in the USA included 14 serotypes (table 1). Six years later, the number of serotypes expanded from 14 to 23.<sup>16</sup> The first pneumococcal conjugate vaccine (PCV) covering seven serotypes was developed in 2000.<sup>17,19</sup> During the development of pneumococcal vaccines, the 19A, 1, 7F, 3, 14, 22F, 8, 4, 12F and 19F serotypes were most commonly targeted.<sup>17,19</sup> Two PCVs containing 7 and 10 pneumococcal serotypes were licensed in 2000 and 2009, respectively. These vaccines were approved only for infants and children.<sup>17,19,20</sup> It has been established that PCVs exert higher immunogenicity compared with PPVs due to T cell-dependent immune

responses leading to stronger induction of memory B cells. PPVs are unable to trigger long-standing immunological memory.<sup>20</sup> The 7-serotype PCV has been gradually removed from the market as it had limited coverage of serotypes causing serious pneumococcal infections in most developing countries.<sup>17</sup> By 2010, a new PCV covering 13 serotypes had been developed and was first introduced only to children.<sup>21</sup> In December 2011, the Food and Drug Administration licensed the 13-valent PCV for prevention of pneumonia and invasive diseases in adults aged  $\geq 50$  years.<sup>22,23</sup> In June 2012, the Advisory Committee on Immunization Practices (ACIP) recommended the routine use of PCV-13 for immunocompromised adults.<sup>24,25</sup> Finally, the administration of this vaccine has been recommended from July 2013 for all ages in European countries as recommended by European Medicines Agency.<sup>24</sup>

The recently used pneumococcal vaccines are indicated in table 2. Most European countries have recommendations on immunisations for pneumococcal disease within their childhood vaccination schedule except for Croatia, Estonia and Malta. This routine use of PCVs in childhood has significantly reduced serotype-specific IPD in children.<sup>26</sup>

## PNEUMOCOCCAL VACCINATION: GENERAL CONSIDERATIONS

Childhood vaccination impacts the incidence of serious invasive infection in the adult population as well. Large proportion of pneumococcal vaccination in children can reduce transmission of the infection to others, for example, adult contacts. This phenomenon is called herd immunity: if unvaccinated individuals get in contact with vaccinated ones, there is a lower chance to be infected by the organism.<sup>24,27</sup> After 30-year experience with PPV-23, we know that the PPV-23, although it covers a high number of serotypes, lacks the booster effect of revaccination, which limits its use in all age groups.<sup>24,28</sup> As described above, the

**Table 2** Pneumococcal vaccines and serotypes

| Vaccines | Serotypes |    |    |    |     |     |     |     |    |     |
|----------|-----------|----|----|----|-----|-----|-----|-----|----|-----|
| PCV-7    | 4         | 6B | 9V | 14 | 18C | 19F | 23F |     |    |     |
| PCV-10   | 1         | 4  | 5  | 9V | 14  | 18C | 19F | 23F |    |     |
| PCV-13*  | 1         | 3  | 4  | 5  | 6A  | 6B  | 7F  | 9V  | 14 | 18C |
| PPV-23*  | 1         | 2  | 3  | 4  | 5   | 6B  | 7F  | 8   | 9N | 9V  |

\*Vaccines only for adult population.

PCV-7, pneumococcal conjugate vaccine with seven serotypes; PCV-10, pneumococcal conjugate vaccine with 10 serotypes; PCV-13, pneumococcal conjugate vaccine with 13 serotypes; PPV-23, pneumococcal polysaccharide vaccine with 23 serotypes.

PCV-13 exerts higher immunogenicity and induces B cell memory compared with PPV-23.<sup>24 27 28</sup> Based on these data, the WHO declared and hastened that PCV-13 was required to prevent severe pneumococcal disease.<sup>24 29–31</sup>

### PNEUMOCOCCAL VACCINATION IN IMMUNOCOMPROMISED POPULATION

There have been limited data available about immunogenicity and safety of PCV-13 administered in immunocompromised conditions.

A phase 3, open-label, single-arm study evaluated immunogenicity and safety of PCV-13 administered to 301 pneumococcal vaccine-naïve, HIV-infected individuals, who had CD4<sup>+</sup> T cell counts  $\geq 200$ /mL and viral load  $< 50\,000$  copies/mL. Among them, 151 adult patients received three doses of PCV-13 followed by one dose of PPV-23 after 1 month. In this group, the PCV-13 vaccine was effective and well tolerated. Significantly increased antibody responses were seen after the first dose of PCV-13.<sup>32</sup>

Pasiarski *et al*<sup>33</sup> investigated response to PCV-13 in 24 previously untreated adult patients with chronic lymphocytic leukaemia (CLL). Patients did not require anti-cancer therapy. Thirty days after vaccination, specific pneumococcal antibody titres showed twofold increase, an adequate response to vaccination, in 58.3% of patients with CLL.<sup>33</sup> Increased serum levels of IgG2 indicated effective immunogenicity of the PCV-13 vaccine in patients with CLL.<sup>33</sup>

### PNEUMOCOCCAL VACCINATION IN PATIENTS WITH AIRD: EFFICACY AND IMMUNOGENICITY OF VACCINATION

Patients with AIRD exert increased risk for pneumococcal infections. AIRD may be associated with secondary immunodeficiency and these patients also receive immunosuppressive drugs or biological agents that might affect protective immune responses to vaccination.<sup>9 10</sup> There have been limited amount of data with regard to the effectiveness and immunogenicity of pneumococcal vaccinations in patients with AIRD receiving immunosuppressive therapy. In a prospective, multicentre, double-blind, randomised, placebo-controlled trial, Izumi *et al*<sup>34</sup> used PPV-23 to vaccinate patients with RA. They found no differences in the incidence of pneumonia between corticosteroid, methotrexate (MTX) or biologically treated patients after a mean of 1.7 years postvaccination.<sup>34</sup>

There has been one systematic review and meta-analysis published in 2014 by Hua *et al*.<sup>9</sup> This meta-analysis included six studies related to pneumococcal vaccination. In four of these studies, patients were vaccinated by PPV-23 (n=232), while two studies included 114 patients vaccinated by PCV-7. Responsiveness to pneumococcal vaccines was impaired in patients with RA treated with MTX or rituximab, but the response was intact in patients receiving TNF- $\alpha$  inhibitors.<sup>9</sup> Nevertheless, this meta-analysis could not distinguish PPV-23 and PCV-7.<sup>9</sup> Kapetanovic *et al*<sup>35</sup> also reported that PPV-23 response

was normal in anti-TNF, but reduced in MTX-treated patient. In another study, the anti-interleukin-6 receptor antibody tocilizumab, in combination with MTX, slightly attenuated humoral responses to PPV-23 in comparison to MTX monotherapy.<sup>36</sup> Recently, Alten *et al*<sup>37</sup> published the results of two multicentre, open-label substudies, which evaluated antibody responses to PPV-23 administered to 125 abatacept-treated patients with RA. This study confirmed that the majority of patients with RA treated with abatacept had appropriate immune response to PPV-23 vaccine, with good safety profile. The concomitant use of MTX (irrespective of dose) or corticosteroids had no significant impact on the proportion of patients achieving protective antibody levels in patients receiving abatacept.<sup>37</sup>

There have been some studies that investigated the immunogenicity or effectiveness of PCVs in patients with AIRD.<sup>38–41</sup> Two studies confirmed that PCV-7, approved only for children, was immunogenic in adult patients with RA.<sup>38,39</sup> Kapetanovic *et al*<sup>39</sup> found reduced antibody responses to PCV-7 in MTX-treated patients, while the response was intact in patients receiving TNF- $\alpha$  inhibitors. Nagel *et al*<sup>40</sup> studied efficacy of a PCV-7 vaccine in adult patients with AIRD. They observed statistically non-significant reduction in the occurrence of serious infections in patients with RA and spondyloarthritis after immunisation with PCV-7. Recently, we have prospectively evaluated the immunogenicity of the PCV-13 vaccine in patients with RA receiving etanercept. Vaccination with PCV-13 was effectively immunogenic and safe. Higher age at vaccination was identified as a predictor of impaired antibody response.<sup>41</sup> In a recent study, 47 patients with SLE receiving belimumab given in addition to standard of care therapy were immunised with PCV-13. The study confirmed that the efficacy of PCV-13 was not impaired by belimumab.<sup>42</sup>

### LONG-TERM SAFETY OF PNEUMOCOCCAL VACCINES

Based on the literature on pneumococcal vaccine safety, there have been no appropriate epidemiological studies on serious side effects or postvaccination autoimmunity in patients with AIRD. Therefore, data are limited.

**Table 3** ACIP recommendation for categories of immunosuppression therapy dosing

| Immunosuppressive therapy | Definition of 'high-level immunosuppression' |
|---------------------------|--|
| Corticosteroids           | $\geq 20$ mg/day for $\geq 14$ days          |
| Azathioprine              | $> 3.0$ mg/kg/day                            |
| Methotrexate              | $> 0.4$ mg/kg/week                           |
| 6-Mercaptopurine          | $> 1.5$ mg/kg/day                            |
| TNF- $\alpha$ inhibitors  | Any dose                                     |
| Rituximab                 | Any dose                                     |

ACIP, Advisory Committee on Immunization Practices; TNF- $\alpha$ , tumour necrosis factor alpha.

Autoimmune inflammatory syndrome induced by adjuvants (ASIA) or Shoenfeld's syndrome has been most commonly reported after human papilloma and influenza vaccination, but there have also been scattered reports on Bacillus Calmette-Guerin, diphtheria-tetanus-perussis, hepatitis B and mumps-morbilli-rubella vaccinations.<sup>43</sup> Vaccines contain preservatives and adjuvants in order to ensure their sterility. Preservatives prevent contamination of multidose containers, while adjuvants enhance the immunogenicity of the vaccine antigen. PPV and PCV contain phenol preservative and aluminium salt adjuvant, respectively. The most common adjuvants, such as aluminium salts, may cause fever, pain at the injection site and malaise. So far there have been no data on pneumococcal vaccine-induced ASIA syndrome.<sup>43</sup>

Between 2003 and 2014, spontaneous reports of vasculitis as an adverse event following immunisation have been reported to three international spontaneous reporting systems (EudraVigilance, the Vaccine Adverse Event Reporting System and VigiBase). The most commonly reported pneumococcal vaccine-related event was Kawasaki disease. This type of vasculitis occurred mainly in children less than 1 year of age. There were no data about the type of pneumococcal vaccine triggering vasculitis in these reporting systems.<sup>44</sup>

Altogether 67 patients with cryopyrin-associated periodic syndromes (CAPS) treated with canakinumab were followed in the b-CONFIDENT (Clinical Outcomes and Safety Registry) global, long-term, prospective, observational study. Out of these patients, 19 had pneumococcal vaccination including 15 PPV and 2 PCV-vaccinated patients. In two cases, the nature of vaccine was unknown. Five PPV-related serious adverse events were reported (local inflammation, meningitis, progressive cellulitis), while two patients had systemic inflammation due to CAPS reactivation. After a period of 10–28 days, the adverse events resolved in all patients.<sup>45</sup>

### RECOMMENDATIONS ON PNEUMOCOCCAL VACCINATION IN PATIENTS WITH AIRD

Based on the data described above, four sets of clinical recommendations have become available on pneumococcal vaccination in AIRD. These include (1) the European League Against Rheumatism (EULAR) recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases<sup>46,47</sup>; (2) a WHO position paper on pneumococcal vaccines<sup>30,31</sup>; (3) ACIP recommendations on the use of 13-valent PCV and 23-valent PPV for adults with immunocompromising conditions<sup>25</sup>; and (4) Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for vaccination of the immunocompromised host: recommendations for vaccination of patients with chronic inflammatory diseases on immunosuppressive medications.<sup>48</sup>

In 2017, a systematic review of vaccination recommendations for adult immunosuppressed patients was published. In this review, authors summarised 12 years of



**Table 4** Sequential administrations of PCV-13–PPV-23 among immunocompromised adults based on ACIP recommendation

| Pneumococcal vaccine-naïve immunocompromised* adult persons                 |  |                |   |               |
|---|--|----------------|---|---------------|
| First vaccine   | Interval between two vaccines            |                | Second vaccine                            |               |
| PCV-13  | ≥8 weeks                                 |                | PPV-23                                    |               |
| Previously PPV-vaccinated immunocompromised adult persons ≥65 years         |  |                |   |               |
| First vaccine   | Interval between two vaccines            |                | Second vaccine                            |               |
| PPV-23  | ≥1 year                                  |                | PCV-13                                    |               |
| Previously received PPV-23 in immunocompromised adults, when aged <65 years |  |                |   |               |
| First vaccine before age 65   | Interval between first PPV-23 and PCV-13 | Second vaccine | Interval between PCV-13 and second PPV-23 | Third vaccine |
| PPV-23  | ≥1 year                                  | PCV-13         | ≥8 weeks                                  | PPV-23        |
| Interval between first and second PPV-23 vaccine: ≥5 years                  |  |                |   |               |

\*Immunocompromised conditions are defined as: congenital or acquired immunodeficiency, human immunodeficiency viral infection, chronic renal failure, nephrotic syndrome, leukaemia, lymphoma, Hodgkin disease, generalised malignancy, iatrogenic immunosuppression, solid organ transplant, multiple myeloma.

ACIP, Advisory Committee on Immunization Practices; PCV-13, pneumococcal conjugate vaccine with 13 serotypes; PPV-23, pneumococcal polysaccharide vaccine with 23 serotypes.

data on American, British, Canadian, Australian, French and German recommendations. Patients included those with primary immunodeficiency, solid organ and haematopoietic stem cell transplantation, inflammatory bowel diseases, rheumatic diseases, as well as patients who underwent splenectomy, with cancer and HIV.<sup>49</sup> This review recommended pneumococcal vaccinations universally following sequential administration protocols for patients with AIRD. In rituximab-treated subjects, the first pneumococcal vaccine should be administered 2–3 weeks before initiation of biological treatment.<sup>49</sup>

These recommendations can now be summarised and applied as the currently licensed PCV-13 vaccine has been available for immunocompromised patients and appropriate advice for sequential vaccination with PPV-23 has been developed. Both types of pneumococcal vaccines (PPV and PCV) are inactivated vaccines, so there is no risk of bacterial reactivation after vaccination. Before administration of the pneumococcal vaccine to a patient with AIRD, one should determine the optimal timing of vaccination, the type of vaccine (PCV-13, PPV-23) to be used and the strategy of vaccination (eg, sequential application).<sup>49</sup>

In 2011, EULAR developed the first evidence-based recommendations for vaccination in patients with AIRD. The committee included experts representing 11 European countries.<sup>46</sup> In 2014, the IDSA published the special vaccine recommendations for immunocompromised patients.<sup>48</sup> In the recommendation, the definitions of high-level versus low-level immunosuppression were established (table 3). High-level immunosuppression includes more than 20 mg daily use of corticosteroids for more than 14 days; more than 3.0 mg/kg daily use of azathioprine; more than 0.4 mg/kg weekly use of MTX; more than 1.5 mg/kg daily use of 6-mercaptopurine and any dose of TNF- $\alpha$  inhibitors and rituximab. These categories may determine the protocol of

vaccination<sup>48</sup>; however, vaccination is always recommended in these patients. ACIP recommended to administer pneumococcal vaccinations to adults with planned initiation of immunosuppressive therapy or in the status of low-level immunosuppression.<sup>25</sup>

ACIP also reviewed the best available evidence for sequential administrations of PCV-13 and PPV-23 to immunocompetent and immunocompromised adults.<sup>25</sup> This recommendation includes immunocompromised individuals also including patients with acquired immunodeficiency and those receiving immunosuppressive agents. The key issue is the determination of optimal intervals between the two vaccines. The sequence of administration is determined by the high immunogenicity of PCV-13 and the high number of covered serotypes of PPV-23. Recent studies suggested that the best clinical results could be achieved if PCV-13 was administered first to pneumococcal vaccine-naïve patients. Patients prevaccinated with PPV-23 should receive PCV-13 after 1 year.<sup>25</sup> ACIP does not recommend multiple revaccinations (booster) with PPV-23 in the normal population due to insufficient data regarding its clinical benefit, particularly the degree and duration of protection and safety but only in adults aged ≥19 years with immunocompromising conditions. In this group, PPV-23 vaccination should be repeated at least 5 years after the most recent dose of PPV-23, following administration of PCV-13.<sup>25</sup> Recommendations on sequential PCV-13 and PPV-23 vaccination are seen in table 4.

## SUMMARY

Summarised recommendations of pneumococcal vaccination in patients with AIRD:

- The best time to start immunisation is before the administration of immunosuppressive therapy (at least 2–3 weeks before initiation), in stable condition, without disease activity.

- ▶ In patients receiving disease-modifying antirheumatic drugs, the timing of vaccination has to be set in accordance with the status of immunosuppression. Ideally, the vaccine should be performed in patients with low-level immunosuppression but the vaccine should still be administered even if its efficacy might be decreased, so even in patients with high-level immunosuppression taking into account the following:
  - There is no requirement of treatment-free intervals before and after immunisation in patients receiving TNF- $\alpha$  blockers, abatacept or tocilizumab.
  - The vaccination must be started at least 2–3 weeks before initiation of rituximab treatment, or 5–7 months after completion of treatment; if not possible, at least 6 months after the start and 4 weeks before the next course.
- ▶ Pneumococcal vaccinations have to be administered in a sequential manner based on the previous PPV-23 vaccination status.
- ▶ The vaccination programme of patients with AIRD must be established by approach of multidisciplinary team (rheumatologists, infectious disease specialists, physicians expert in comorbidity management).

Patients with AIRD are prone to several infections, which may be a great challenge for the treating physician. Immunogenic PCV or PPV vaccines effectively reduce the risk of invasive infectious diseases and pneumonia mortality. In order to achieve an optimal response, the administrations of PCV-13 and PPV-23 are recommended as soon as possible following AIRD diagnosis. These vaccines are safe; serious adverse events have rarely been reported. There is an important role of all healthcare workers to suggest patients with AIRD and their family members to manage these vaccinations.

**Contributors** ÉR and ZS wrote and reviewed the manuscript.

**Funding** This work was supported by the European Union and the State of Hungary cofinanced by the European Social Fund in the framework of TAMOP-4.2.4/A/2-11/1-2012-0001 'National Excellence Program' (ZS).

**Competing interests** None declared.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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