The role of pneumococcal vaccination in reducing cardiovascular risk in cardiac patients: Expert opinion of the Prevention Committee of the Polish Cardiac Society supported by the Polish Vaccinology Society

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ABSTRACT

Respiratory diseases have been the fourth most common cause of death in Poland in recent years. Respiratory infection, especially pneumonia, can lead to exacerbation of chronic cardiovascular disease. *Streptococcus pneumoniae* is the most common bacterial pathogen causing community-acquired pneumonia. Pneumococci are also the most common pathogen complicating the course of infection with the influenza virus. Pneumonia, especially invasive pneumococcal disease, is associated with risk of death in the course of respiratory failure or sepsis and also with worsening of the prognosis for existing cardiovascular disease. Despite those facts, recommendations for pneumococcal vaccination are still not well established in cardiovascular guidelines. This expert opinion aims to summarize current knowledge on the importance of preventing invasive pneumococcal disease in cardiac patients.

Key words: cardiovascular diseases, community-acquired pneumonia, invasive pneumococcal disease, pneumococcal vaccination

INTRODUCTION

Respiratory diseases have been the fourth most common cause of death in Poland in recent years [1]. These conditions, especially pneumonia, can lead to exacerbation of chronic cardiovascular disease. Through this mechanism, respiratory infections may be indirectly responsible for the most common cause of death in Poland, which is cardiovascular disease [1]. In 2019, 50% of hospital admissions for respiratory diseases — nearly 60 000 admissions — were related to community-acquired pneumonia (CAP) [2]. Microbiological diagnosis of CAP patients is a real challenge in clinical practice because sputum cultures are unfortunately not routinely collected and many blood culture results in hospitalized patients may be non-diagnostic due to previously started empiric antibiotic therapy (in outpatient or nursing homes, or care and treatment facilities). According to some studies, in as many as 40% of patients,

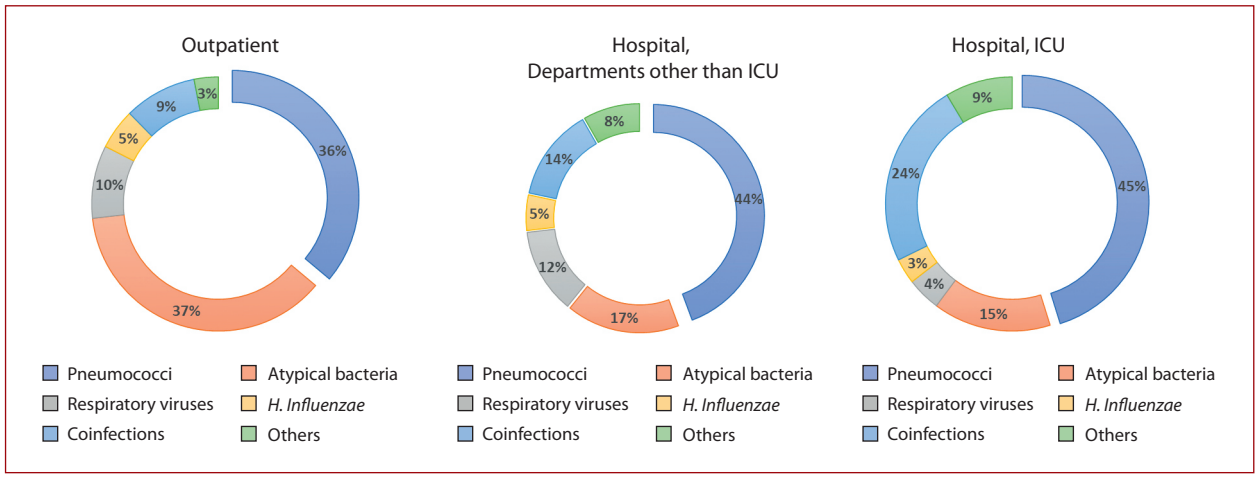

Figure 1. Etiology of CAP depending on the patient's location. Based on [4]
Abbreviations: CAP, community-acquired pneumonia; ICU, Intensive Care Unit

the pathogen causing CAP cannot be identified [3]. At the same time, in the case of confirmed etiology, regardless of the patient's location, the most common pathogen is *Streptococcus pneumoniae* (Figure 1) [4]. Pneumococci are also the most common pathogen complicating the course of influenza virus infection [5].

Bacterial co-infection affects 11%–35% of patients hospitalized for influenza, while influenza infection increases the risk of pneumococcal pneumonia in specific ways [5–7]. It has been observed that the influenza virus accelerates the proliferation of *S. pneumoniae*, facilitates the colonization of the respiratory tract, and promotes bacterial aspiration [5–7]. For years, educational campaigns have been conducted to convince the population about the benefits of annual influenza vaccination in reducing the risk of cardiovascular events [8]. This is an additional health bonus, apart from the possibility of reducing the risk of the infection itself or its severe course. The experience of the COVID-19 pandemic has been a painful reminder of how dangerous acute respiratory infections can be for patients with heart and vascular diseases [9–12]. Currently, there is no doubt that a severe course of coronavirus infection affected, among others, patients with a history of cardiovascular diseases, and vaccination against COVID-19 turned out to be the most effective weapon against the pandemic. It is worth emphasizing that, also in the case of coronavirus infection, pneumococci were the most common pathogen complicating the course of infection [13].

Regarding pneumococci, many studies in recent years have indicated that we should put more emphasis on preventing infection. This expert opinion aims to summarize current knowledge on the importance of preventing invasive pneumococcal disease (IPD) in cardiac patients.

COMMUNITY-ACQUIRED PNEUMONIA AND INVASIVE PNEUMOCOCCAL DISEASE

Polish data on the prevalence of pneumococcal infections come mainly from the National Reference Centre for Diagnostics of Bacterial Infections of the Central Nervous System (KOROUN), to which only community-acquired invasive forms of the disease are reported (all confirmed cases of invasive bacterial infections are reported, not only meningitis, and regardless of the ward where the patient was admitted). Therefore, it can be assumed that the incidence rates of (confirmed) pneumococcal pneumonia and CAP with sepsis are underestimated [14]. It is estimated that bacteremia accompanies about 25% of pneumonia cases, so this percentage of infections meets the definition of IPD (Figure 2) [14].

The course of infection is mainly influenced by the serotype of the bacteria. However, there are several risk factors related to the patient and his/her environment (Figure 3) [15, 16]. Many of these factors, such as age over 65, smoking, and coexisting diabetes or chronic kidney disease, are typical of patients with chronic cardiovascular diseases; they are also risk factors for a severe IPD course [17–21]. There is no doubt that advanced age is one of the most important risk factors. According to the KOROUN data, the IPD mortality rate in people over 65 years of age was over 65%, and this was the highest in the assessed age groups (Figure 4) [22].

Concomitant diseases affect both the risk of developing CAP and its course. Ramirez et al. [23], analyzing the incidence of CAP in the US in the years 2014–2016 in nearly 75 000 adults, emphasized the importance of the coexistence of comorbidities typical of patients with cardiovascular diseases [23]. In the general population, the incidence of CAP was 634/100 000: 1808/100 000 in patients with diabetes; 3456/100 000 in patients with heart failure; and 5832/100 000 in patients with COPD [23]. In-hospital mortality was 6.5%, but it increased with time from the beginning of hospitalization. The 30-day, 6-month, and 1-year mortality rates were 13%, 23.4%, and 30.6%, respectively [23]. Curcio et al. [24], on the other hand, demonstrated that the coexistence of typical cardiac diseases, such as COPD or diabetes, especially in the case of

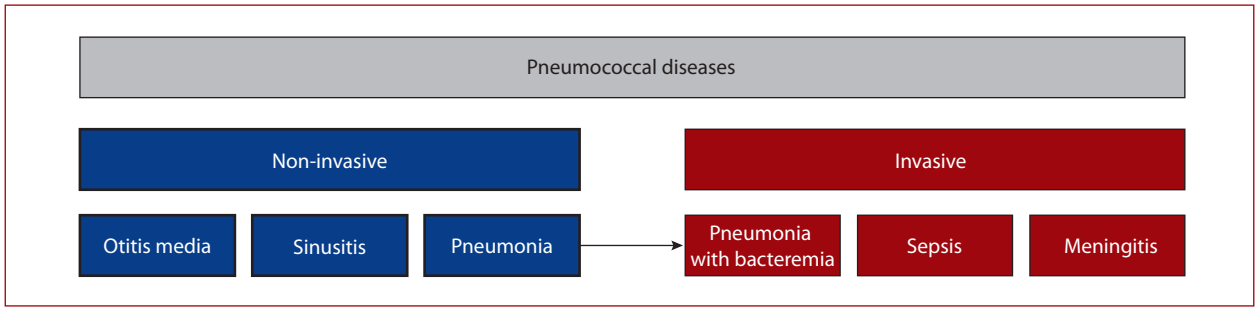

Figure 2. Types of pneumococcal infections divided into non-invasive and invasive. It is estimated that 75% of pneumococcal pneumonia cases are non-invasive, but in 25% of cases, it is accompanied by bacteremia, and these infections should be treated as invasive [14]

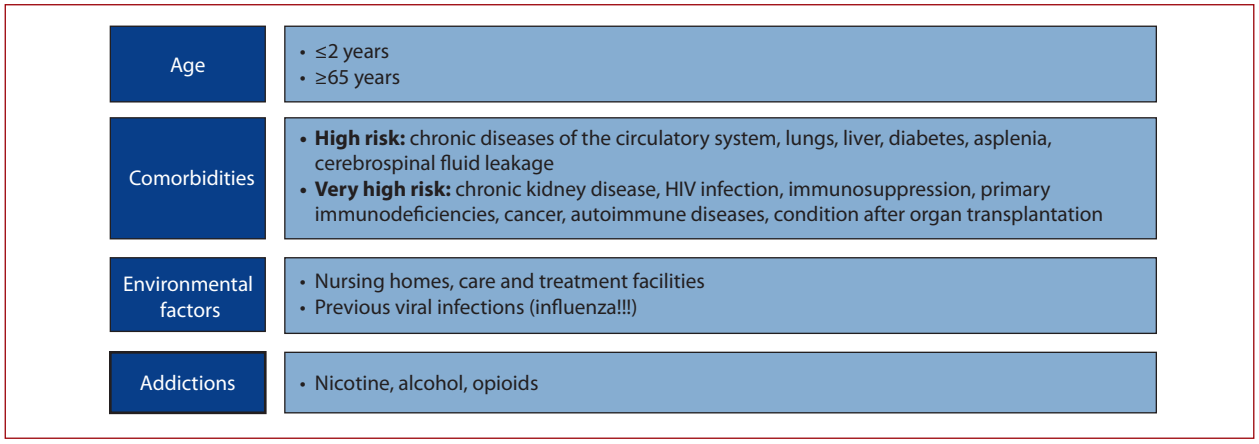

Figure 3. Factors increasing the risk of severe IPD [17–21]

Abbreviations: IPD, invasive pneumococcal disease

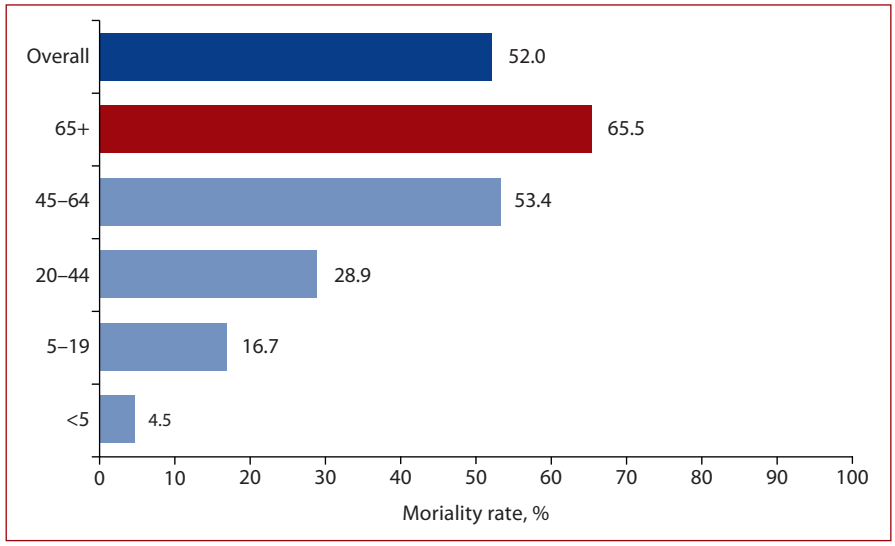

Figure 4. IPD-related mortality rate by age group [22]

Abbreviation: IPD, invasive pneumococcal disease

advanced age and active smoking, may multiply the risk of CAP, pneumococcal infection, and its invasive form. The authors commented on the observations made in earlier years by, among others, Shea et al. [25]. They showed that the coexistence of diseases such as diabetes, chronic heart disease, and chronic lung disease significantly increases the risk of pneumococcal pneumonia compared with healthy people, especially in people over 65 years of age (respectively 2.8 times, 3.8 times, and 7.7 times for diabetes, chronic heart disease, and chronic lung disease) [25].

However, Curcio et al. [24] suggest that the importance of the simultaneous occurrence of these factors may be underestimated. Polish epidemiological data, although still scarce, seem to indirectly confirm Curcio et al.'s observations. According to the information contained in the 2019 report "Pneumococcal pneumonia in adults — the situation in Poland. Epidemiology, consequences, prevention", nearly 605 000 cases of CAP were reported in Poland, of which almost 76 500 patients required hospitalization [26]. However, the incidence of CAP requiring

hospitalization per 100 000 people is clearly age-dependent and amounts to 36.2/100 000 among people aged 18–49 years; 141.3/100 000 among those aged 50–64 years; 318.7/100 000 in the case of people aged 65–74 years; and as many as 908.1/100 000 in the group over 75 years of age [26]. In 2019, 7676 patients died of CAP, with almost 20% of these deaths occurring in patients aged 65–74 and 65.8% in patients aged over 75 [26]. Therefore, when considering the utility of vaccinating cardiac patients against pneumococcal disease, the following facts should be considered:

- Pneumococcal infection is the leading cause of pneumonia;
- Risk of pneumonia increases manyfold in patients with coexisting typical internal and chronic cardiac diseases;
- Age and coexistence of chronic diseases (including heart failure, diabetes, COPD, etc.), as well as typical addictions (smoking, alcohol abuse), increase the risk of a severe course of infection;
- About 25% of pneumonia cases are associated with bacteremia, meeting the definition of IPD;
- IPD in patients over 65 years of age is associated with a 65% in-hospital mortality rate;
- In Poland, 20% of deaths from pneumonia occur in patients aged 65–74, and 65% in patients over 75 years of age.

THE LINK BETWEEN PNEUMONIA AND CARDIOVASCULAR DISEASE

A history of pneumonia, especially invasive pneumococcal disease, is associated not only with the risk of death in the course of respiratory failure or sepsis but also with the worsening of the prognosis of the existing cardiovascular disease. Already in 2015, Corrales-Medina and colleagues indicated, based on the analysis of data from the period 1987–1994 in the US, that in patients ≥65 years of age hospitalized for CAP, a significant increase in the risk of cardiovascular events persisted even at 10 years [27]. Bergh and colleagues, in turn, found that the risk of clinically manifested ischemic heart disease was more than 6-fold higher in individuals within a year of hospitalization for infection (CP or sepsis) than it was in the control group (hazard ratio [HR], 6.33; 95% confidence interval [CI] 5.65–7.09, adjusted for classical risk factors) [28]. The highest risk persists up to 3 years after infection but remains significantly elevated even 5 years after hospitalization [28].

Having an infection also increases the risk of heart failure. According to the analyses carried out by the Canadian team of Eurich et al. [29], within 90 days of infection, the risk of heart failure or death from heart failure was up to 50% higher than it was in the control group (HR, 1.53; 95% CI, 1.44–1.63). Interestingly, the highest relative risk of heart failure (HF) death was observed in subjects under 65 years of age (HR, 1.98; 95% CI, 1.55–2.53), and this effect was independent of the severity of CAP [29]. Recent studies suggest a significant relationship between the bacterial serotype responsible for infection and the risk of cardiovascular complications. In 2021, Africano's team published the results of a multicenter retrospective observational study that analyzed the relationship between the serotype of the bacteria causing invasive pneumococcal disease and the occurrence of a composite endpoint of the study, defined as myocardial infarction, heart failure, or arrhythmia [30]. The analysis included 310 microbiologically confirmed cases of IPD: 60% CAP with bacteriemia, 18% meningitis, and 21% primary sepsis. The average age of the subjects was 61 years. A composite endpoint occurred in 23% of all subjects and 28% of patients with CAP. Serotype 19A was the most common, bacteremia was present in 87% of patients with a major cardiovascular event, and infection with serotype 3 was an independent risk factor (OR, 1.48; 95% CI, 1.21–2.27; $P = 0.013$), as was infection with serotype 9n (OR, 1.29; 95% CI, 1.08–2.24; $P = 0.02$) [30].

Thus, there is scientific evidence to support the association between CAP, including CAP with confirmed pneumococcal etiology, and the risk of cardiovascular disease. The adverse impact on the cardiovascular prognosis is associated not only with the acute phase of infection (stimulation of inflammatory state, prothrombotic responses hypoxia) but also persists for many months/years after infection. Certain pneumococcal serotypes may specifically increase the risk of cardiovascular events. The arguments presented above justify interest in pneumococcal vaccination as a potential method of cardiovascular prevention.

ROLE OF PNEUMOCOCCAL VACCINATION IN THE PREVENTION OF CARDIOVASCULAR DISEASES

Recommendations for pneumococcal vaccination are still not well established in cardiovascular guidelines. The authors of these guidelines present an unambiguous position only on the diagnosis and treatment of pulmonary hypertension [31, 32]. Both 2015 and the latest 2022 European Society of Cardiology/Polish Cardiac Society guidelines recommend both annual influenza vaccination and pneumococcal vaccination (class of recommendation and level of evidence IC) [31, 32]. The authors of the guidelines for the diagnosis and treatment of heart failure from 2021 state that this vaccination should be considered (IIaB), while in the European Society of Cardiology (ESC) guidelines on cardiovascular prevention, vaccination recommendations are class IIbC, meaning vaccination can be considered (guidelines from 2016) and in the latest guidelines from 2021, experts do not refer to the issue of pneumococcal vaccination at all [33 -35]. This conservative attitude of guideline authors towards vaccines with proven efficacy may be misinterpreted. Thus, it should be made clear that the "cardiocentric" view of vaccine effectiveness is not about preventing CAP/ICD in general or reducing the risk of severe and fatal infections, but about the potential additional impact of vaccination on cardiovascular risk.

In the context of the potential beneficial effect of pneumococcal vaccination on the cardiovascular prognosis of

patients, it is worth paying attention to three meta-analyses of observational studies (cohort and case-control studies): Marra et al., Ren et al., and Vlachopoulos et al. [36–38]. The first of them included 18 studies in which the endpoint was the occurrence of a cardiovascular event, myocardial infarction, or stroke [36]. In terms of reducing the risk of a cardiovascular event, there was a 9% relative risk reduction (odds ratio [OR], 0.91; 95% CI, 0.84–0.99; $I^2 = 74.64\%$; $P < 0.0001$). The reduction in the risk of myocardial infarction was 12% (OR, 0.88; 95% CI, 0.79–0.98; $I^2 = 75.4\%$; $P < 0.0001$). Improved outcomes were observed due to the beneficial effects of vaccination in patients over 65 years of age [36]. Separate analyses for patients <65 years of age did not show statistically significant effects [36]. Pneumococcal vaccination also had no significant effect on the risk of stroke (OR, 0.96; 95% CI, 0.83–1.10; $I^2 = 74.3\%$; $P < 0.001$); however, there was a favorable trend (OR, 0.92; 95% CI, 0.81–1.04; $I^2 = 40.5\%$; $P = 0.15$) [36]. The meta-analysis by Marra et al. [36] therefore demonstrated that the pneumococcal polysaccharide vaccine (PPV23) may reduce the risk of cardiovascular events, including myocardial infarction, in patients over 65 years of age.

The other two meta-analyses included 9 and 13 observational studies with a polysaccharide vaccine [37, 38]. Ren et al. [37] also observed a reduction in the risk of myocardial infarction in patients over 65 years of age who were vaccinated (OR, 0.83; 95% CI, 0.71–0.97; $I^2 = 77\%$), while Vlachopoulos et al. [38] reported a 14% reduction in the risk of a cardiovascular event (RR, 0.86; 95% CI, 0.76–0.97; $P = 0.016$) and an 8% reduction in the risk of cardiovascular death (RR, 0.92; 95% CI, 0.86–0.98, $P = 0.01$) in favor of the vaccinated [37, 38]. So far, only Vlachopoulos et al. [38] have observed that it is possible to reduce the risk of stroke in people vaccinated against pneumococci only in patients over 65 years of age, and the effect was borderline statistically significant (RR, 0.86; 95% CI, 0.75–0.99; $P = 0.032$).

These meta-analyses, however, have all found that statistically significant benefits in the context of cardiovascular risk are obtained only in patients over 65 years of age. It should also be assumed from a technical point of view that the meta-analyses of Ren et al. [37] and Vlachopoulos et al. [38] are included in Marra et al.'s meta-analysis. A separate analysis of individual studies on the cardioprotective effects of the polysaccharide vaccine also allows us to see another regularity, apart from the age that predisposes to benefits. In studies whose methodology assumed a shorter observation period (3–6 months), the benefits in terms of reducing the risk of myocardial infarction were greater. In the study of Chang et al. in patients over 65 years of age, the RR was 0.71 (95% CI, 0.54–0.93). In the studies of Zahid et al. and Eurich et al. [39–41] in patients in all age groups, the respective RRs were 0.44 (95% CI, 0.22–0.88) and 0.46 (95% CI, 0.28–0.76). This observation is summarized by Vlachopoulos et al. [38], who stated that the protective effect of PPV23 in the cardiac context persists up to 1 year after vaccination. The trend towards cardiovascular benefits of vaccination was more pronounced in vaccinated patients with a history of greater disease burden. In this context, it is worth noting the outcomes of the meta-analysis by Jaiswal et al. [42], which included 15 studies, including 2 studies that evaluated the effectiveness of PPV23 in dialysis patients and patients with advanced renal failure (these studies were not included in the previously cited meta-analyses). Jaiswal et al. [42] showed that pneumococcal vaccination reduces all-cause mortality (HR, 0.76; 95% CI, 0.66–0.87; $P < 0.001$) and the risk of myocardial infarction (RR, 0.73; 95% CI, 0.56–0.96; $P = 0.02$) [41]. It is worth noting that in this meta-analysis, cardiac benefits were evident in patients with the highest baseline cardiovascular risk: namely, dialysis patients and patients with previously diagnosed coronary artery disease [42].

The authors also confirm their predecessors' observations that the cardioprotective effect of pneumococcal vaccination with PPV23 disappears over time [42]. Perhaps new data in this regard will be provided by the prospective double-blind AUSPICE study, which involves a 6-year comparative observation of patients vaccinated with PPV23 and patients receiving placebo in the context of the occurrence of fatal and non-fatal myocardial infarctions and strokes [43]. Preliminary outcomes from the first years of observation are available, regarding the presence and concentration of anti-pneumococcal antibodies in the IgG and IgM classes and anti-OxLDL antibodies in both classes [44]. This is one of the postulated potential mechanisms of the cardioprotective effect of pneumococcal vaccines [45]. Ren et al. [44, 45] showed that PPV administration generates a sustained increase in the titer of anti-pneumococcal antibodies in the IgG class, a less sustained increase in the IgM class, and only a transient increase in the titer of anti-OxLDL antibodies in the IgM class in the absence of an IgG reaction. Two years after PPV administration, the authors did not observe any significant differences in high sensitivity C-reactive protein (hs-CRP) level, pulse wave velocity, or intima-media thickness; all variables considered surrogates of the atherosclerotic process [44].

Given the interesting outcomes of the AUSPICE study on the polysaccharide vaccine available on the market since 1983, further observations of new pneumococcal conjugate vaccines may turn out to be even more interesting.

AVAILABLE PNEUMOCOCCAL VACCINATIONS

Currently, three conjugated vaccines (PCV) and one unconjugated polysaccharide vaccine (PPV23) are available on the Polish market. Of the conjugated vaccines, PCV10 is only licensed for children (up to 5 years of age), while PCV13, PCV20, and the PPV23 polysaccharide vaccine can be used in the adult population; the latter three are compared in Table 1.

PCV20 is the latest-generation vaccine, and the inclusion of 7 pneumococcal serotypes in addition to PCV13 is justified by the current global epidemiological situation [57]. Additional serotypes (all 7) are largely responsible for

Table 1. Comparison of key features of three pneumococcal vaccines registered for use in adults in Poland [46–56]

Type of vaccine	Conjugated (PCV)	Unconjugated (PPSV)
The latest vaccine	PCV20: 2021 (US), 2022 (UE)	PPSV23: 1983
Serotype coverage of the latest vaccine	20 serotypes	23 serotypes
Immunological memory [46]	+	–
Mucosal response [47]	+	–
The order of administration in adults according to PSO 2023 [48]	PCV13 as first or PCV20 first and only one	PPSV23 as second, after PCV13
Response to the next dose [49]	T-lymphocytes dependent (hyper-responsiveness)	T-lymphocytes independent (hypo-responsiveness)
Effectiveness in risk groups	PCV13 effective in the group 65–84 years of age [50], in immunocompromised patients and chronic diseases [51]	May be lower <2 years and ≥ 75 years and with chronic diseases [52, 54]
Protection time	At least 4–5 years for PCV13 [55, 56]	It is not known how long the protective titer of antibodies lasts; revaccination recommended in some elderly people [54]

Abbreviations: PCV, multi-valent pneumococcal conjugate vaccine, PCV20, 20-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PSO, Program Szczepień Ochronnych (Polish abbreviation for the governmental Protective Vaccination Program); PPSV23, 23-valent polysaccharide vaccine

The dates given refer to the year of vaccine registration. References given in the Table refer to the position of the source text in the collective study references

IPD occurrence. They are associated with the problem of increasing antibiotic resistance (11A, 15B, 22F, 33F) or higher mortality (almost all 7) [58–67]. In Poland, in 2019, IPD (according to the KOROUN data) was mainly caused by four serotypes: 3, 4, 19A, and 8 [22]. It is also worth emphasizing that PPV23 is effective in reducing the risk of developing IPD, and an additional benefit of conjugate vaccines is that they also reduce the risk of CAP. It should also be noted that, due to the already proven effectiveness of older-generation vaccines in reducing the risk of developing IPD or CAP, for ethical reasons, it is not possible to conduct direct studies comparing PCV20 with other vaccines or with placebo. The basis for the registration of the latest vaccine is confirmation of an acceptable safety profile and confirmation of equivalent immunogenicity compared with that observed with older vaccines. The studies carried out so far confirm the good tolerance of pneumococcal vaccines: side effects are rare, self-limiting, and usually mild or moderately severe (pain at the injection site, general malaise, fever).

According to the latest Polish expert recommendations, published in *Family Medicine & Primary Care Review,* pneumococcal vaccination should be recommended to all adults over 65 years of age and to those adults aged 19–64 who have additional risk factors [68]. Polish expert recommendations are consistent in this respect with the American recommendations [69]. These additional risk factors include, in addition to immunocompromised conditions, chronic heart disease, renal failure, diabetes, and chronic lung disease [68–69]. Therefore, it can be safely assumed that these criteria are met by the vast majority of patients hospitalized in cardiology and internal medicine wards. According to the Announcement of the Chief Sanitary Inspector from October 28, 2022, on the preventive vaccination program for 2023, two pneumococcal vaccination schemes are considered optimal for adults:

1. PCV20 administration without the need for a booster.
2. Administration of PCV13 followed by PPV23 after at least 8 weeks for those aged 18–64 (with risk factors) or after at least 1 year for those aged 65 and over.

In addition, the American Advisory Committee on Immunization Practices (ACIP) also recommends a regimen consisting of administration of the new PCV15 vaccine and then PPV23 after at least 8 weeks in the case of people aged 18–64 (with risk factors) or after at least 1 year in people over 65 years of age [68]. At the moment, however, PCV15 is not available in Poland.

CONCLUSIONS

Cardiac patients are particularly exposed to pneumococcal infection, especially CAP and its invasive form (pneumonia with sepsis). The number of such cases in Poland seems to be underestimated, considering the data on the incidence of CAP and its impact on cardiovascular prognosis. The problem of "low-quality" evidence regarding the benefit of pneumococcal vaccination for the cardiovascular prognosis (impact on major adverse cardiac events) may be due to the heterogeneous design of the analyzed studies, the fact that polysaccharide vaccines protected primarily against IPD and, to a lesser extent, against CAP, and the lower immunogenicity of older-generation vaccines compared with conjugate vaccines. However, the mere fact that the "average patient with cardiovascular disease" most often meets the definition of a patient for whom pneumococcal vaccination is currently recommended, even with only poor-quality evidence about the additional benefit of reduced risk of cardiovascular events in the vaccinated, should encourage cardiologists to actively recommend this vaccination. It is also worth emphasizing that, according to current recommendations, it is possible to fully vaccinate an adult with one dose of PCV20. Verbal encouragement or

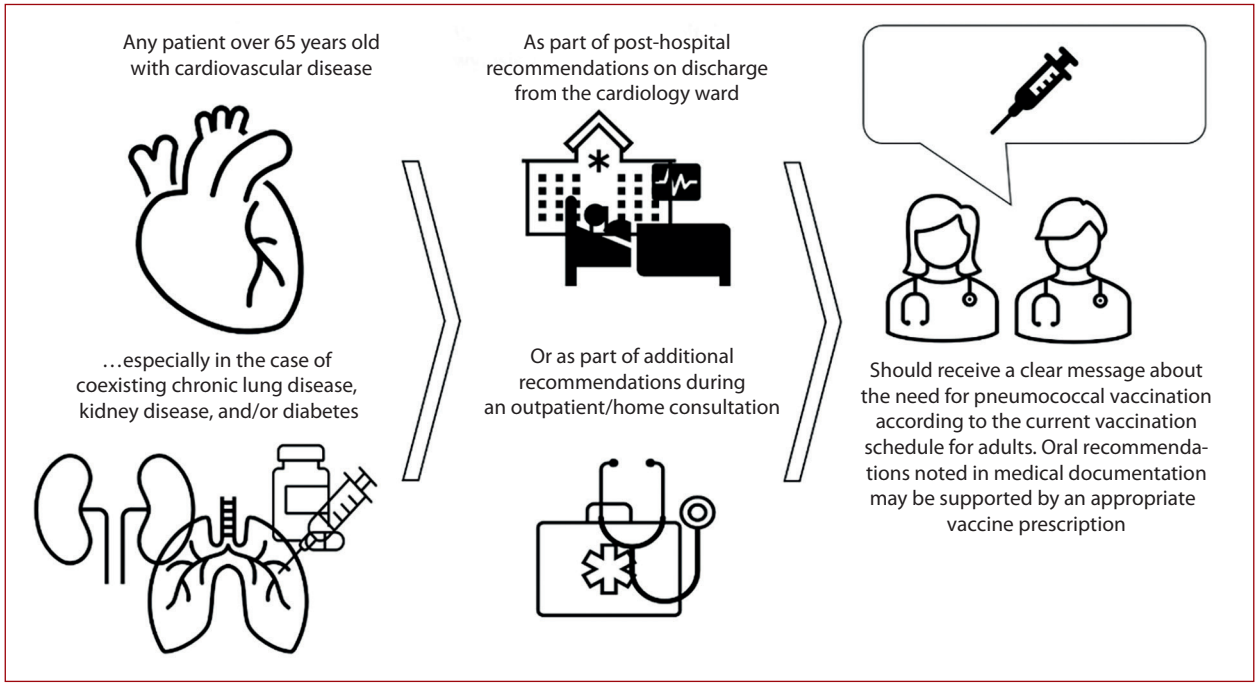

Figure 5. Summary of the strategy we propose to promote pneumococcal vaccination in the population of patients with cardiovascular disease

a recommendation to get vaccinated on the discharge card may be a good solution, but another is issuing a vaccine prescription to the patient when they leave the cardiology/ /internal medicine ward (Figure 5).

Article information

Conflict of interest: Honoraria for lectures and participation in advisory committees and/or clinical trials: MG, AM: Pfizer, MSD, Sanofi Pasteur. JW, EK: Pfizer, MSD, Sanofi Pasteur, GSK, AstraZeneca. PL, PM, JD: Pfizer. PJ: Pfizer, Sanofi Pasteur. MW: AstraZeneca, Pfizer, Sanofi.

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