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Pneumococcal vaccination among adults – updated Polish recommendations

ERNEST KUCHAR[1, A, D–F], ADAM ANTCZAK[2, A, D–F], ANNA SKOCZYŃSKA[3, A, D–F], ANDRZEJ FAL[4, 5, A, D–F],
ORCID ID: 0000-0002-7883-2427 ORCID ID: 0000-0003-3430-3088 ORCID ID: 0000-0002-2247-830X ORCID ID: 0000-0002-9675-7942
JACEK WYSOCKI[6, A, D–F], JOLANTA WALUSIAK-SKORUPA[7, A, D–F],
ORCID ID: 0000-0002-5360-5826 ORCID ID: 0000-0003-0836-6800
MAŁGORZATA CZAJKOWSKA-MALINOWSKA[8, A, D–F], AGNIESZKA MASTALERZ-MIGAS[9, A, D–F],
ORCID ID: 0000-0001-5661-3816 ORCID ID: 000-0001-6600-2760,
ROBERT FLISIAK[10, A, D–F], ANETA NITSCH-OSUCH[11, A, D–F]
ORCID - 0000-0003-3394-1635 ORCID ID: 0000-0002-2622-7348

[1] Department of Paediatrics with Clinical Assessment Unit, Medical University of Warsaw, Warsaw, Poland
[2] Department of General and Oncological Pulmonology, Medical University of Lodz, Lodz, Poland
[3] National Reference Centre for the Diagnostics of Bacterial Infections of the Central Nervous System (KOROUN), Department of Epidemiology and Clinical Microbiology, National Medicines Institute, Warsaw, Poland
[4] Department of Allergology, Lung Diseases and Internal Diseases, Central Clinical Hospital of the Ministry of Interior and Administration, Warsaw, Poland
[5] Faculty of Medicine, Collegium Medicum, Cardinal Stefan Wyszynski University, Warsaw, Poland
[6] Chair and Department of Health Prevention, Faculty of Health Sciences Poznan University of Medical Sciences, Poznan, Poland
[7] Department of Occupational Diseases and Environmental Health, Nofer Institute of Occupational Medicine, Lodz, Poland
[8] Department of Lung Diseases and Respiratory Failure, Centre of Sleep Medicine and Respiratory Care, Kujawy-Pomerania Pulmonology Centre, Bydgoszcz, Poland
[9] Department of Family Medicine, Faculty of Medicine, Wroclaw Medical University, Wroclaw, Poland
[10] Department of Infectious Diseases and Hepatology, Medical University of Bialystok, Bialystok, Poland
[11] Department of Social Medicine and Public Health, Medical University of Warsaw, Warsaw, Poland

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Summary Diseases caused by *Streptococcus pneumoniae* (*S. pneumoniae*) can be either invasive or non-invasive. In adults, pneumococcal infections most often occur as pneumonia, one of the leading causes of hospitalisation in these patients in Poland. Multiple factors predispose patients to the severe course of pneumococcal disease, including age, comorbidities, immune disorders and unhealthy behaviours, whereas the accumulation of coexisting conditions leads to risk stacking. Therefore, prophylactic vaccinations should be the preferred form of protection against pneumococcal infections in adults, based on high vaccination effectiveness and a relatively low risk of adverse events. Importantly, the current recommendations need to be updated in the context of epidemiological changes and the registration of new conjugate vaccines. This publication aims to present the current knowledge on the prevention of pneumococcal disease among adults and establish practical recommendations on the appropriate immunisation schedules used in Poland.
Key words: *Streptococcus pneumoniae*, immunization, evidence-based medicine, communicable diseases, public health, aged.

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Background

Pneumococcal disease caused by infection with Gram-positive bacteria *S. pneumoniae* (pneumococcus) is one of the major public health problems globally. The transmission of these bacteria occurs via respiratory droplets. *S. pneumoniae* produces a polysaccharide capsule that protects it against the immune system's activity and constitutes an important virulence factor. Importantly, not only people with symptoms constitute an infection source, but also numerous asymptomatic carriers. Pneumococci are a component of the nasopharynx's natural bacterial microbiota (microflora) and do not lead to infection in most asymptomatic carriers. Depending on the population, the presence of *S. pneumoniae* in the nasopharynx can be detected in up to 90% of children, which allows a rough estimation of the infection burden [1]. In the course of pneumococcal diseases, non-invasive or invasive forms could be differentiated. The former is generally mild and includes acute sinusitis, acute otitis media and pneumonia. The latter refers to invasive pneumococcal disease (IPD) when the presence of bacteria can be confirmed in originally sterile places (e.g. body fluids). IPD is a life-threatening disease that occurs most often in the adult population as pneumonia with bacteremia and less frequently as meningitis or sepsis [2, 3].

Universal immunisation against pneumococci in the infant population was introduced within the Polish National Immunisation Programme relatively recently (i.e. in January 2017). In contrast, in the adult population, an effective vaccination prophylaxis is still required [4]. The various forms of pneumococcal disease described above occur at different frequencies depending on the analysed age cohort. Acute otitis media is predominant in children, while pneumonia is most common among adult patients [5]. Studies including causative pathogen identification conducted before the COVID-19 pandemic show that 33–50% of community-acquired pneumonia (CAP) cases may be caused by *S. pneumoniae*. However, this percentage depends on the microbiological technique used [6].

Infections caused by pneumococci in Poland frequently result in visits to primary care physicians (PCP) and hospitalisation. In most cases, community-acquired pneumonia is treated on an outpatient basis. According to data from the National Health Fund (NHF), since 2019, almost 400,000 adults have been treated as part of primary health care. Nevertheless, it is estimated that in 2018, approximately 50% of acute respiratory disease-related hospitalisations in adults were caused by CAP. About 55,000 adults were hospitalised, which translates into an estimated cost to the NHF of PLN 169 million [7]. Additionally, in the case of pneumococcal infections in adults, it is also necessary to consider additional socio-economic costs, and thus the exact costs associated with it are difficult to estimate.

Objectives

The aim of this article is to describe the risk factors, Polish epidemiology and prevention of pneumococcal disease utilising the optimal vaccination schedules for adult patients. In addition, indicating the recommended vaccination schedules for adult patients in Poland, supported by practical remarks, should constitute an important tool for effective vaccine prophylaxis implementation in the context of diseases caused by *S. pneumoniae* in adult patients.

Risk factors on pneumococcal disease development

Pneumococcal pneumonia in adults is about three times more common without bacteremia, but it becomes invasive in about 25% of cases [8]. The elderly, patients with coexisting chronic diseases (including heart, lung, liver, kidney diseases and diabetes), people with impaired immunity and those with unhealthy behaviours (smoking and alcohol abuse) are particularly vulnerable to the development of invasive pneumococcal disease and pneumococcal pneumonia. The incidence of pneumococcal pneumonia increases proportionally when diverse risk factors coexist in a single patient [9]. There are numerous risk factors in the population of patients over 65 years of age, ranging from advanced age alone to the associated aging of the immune system and certain chronic conditions. Various risk factors can increase the risk of developing pneumococcal community-acquired pneumonia (pCAP) to a different degree. In the group of patients over 65 years of age, attention should be paid to chronic lung disease (relative risk (RR) 7.7, 95% CI: 7.3–8.0), chronic heart disease (RR 3.8, 95% CI: 3.6–3.9), chronic renal failure (RR 6.5, 95% CI: 6.1–6.9), chronic liver disease (RR 4.3, 95% CI: 3.6–5.0), diabetes (RR 2.8, 95% CI: 2.7–2.9), immunosuppressive conditions (RR 4.1, 95% CI: 4.0–4.3), alcoholism (RR 4.5, 95% CI: 3.6–5.7), as well as in case of smokers (RR 3.9, 95% CI: 3.6–4.3). It is noteworthy that as the patient's age increases, the risk of hospitalisation and death due to *S. pneumoniae* infection grows significantly [9]. Most often, the age threshold above which the risk of developing the disease is significantly elevated is the age of 50 or 65 (depending on the data source) [10, 11].

Table 1 lists known risk factors for developing pneumococcal disease according to the recommendations of the American Advisory Committee on Immunization Practices (ACIP) [12].

Table 1. Groups of patients at increased risk of pneumococcal disease, according to the ACIP recommendation [12]

Factors increasing the risk of pneumococcal disease development [12]	Rate ratios for patients ≥ 65 years (risk group patient in comparison to healthy counterparts) [9]	
	pCAP	IPD
Alcoholism	4.5	5.0
Chronic heart disease[§]	3.8	3.2
Chronic liver disease	4.3	6.4
Chronic lung disease[¶]	7.7	6.2
Smoking	3.9	4.2
Diabetes	2.8	2.5
Cochlear implant	3.9	10.5
Cerebrospinal fluid (CSF) leak	–	–
Congenital or acquired asplenia	10.5	14.0
Sickle cell disease or other hemoglobinopathies	–	–
Congenital or acquired immunodeficiencies**	9.4	14.2
Generalised malignancy	–	–
HIV infection	4.9	3.3
Hodgkin's disease	–	–
Iatrogenic immunosuppression[††]	4.1[#]	4.4[#]
Leukaemia	8.4[##]	13.3[##]
Lymphoma	–	–
Multiple myeloma	–	–
Nephrotic syndrome	–	–
Solid organ transplant	–	–

[§] Including congestive heart failure and cardiomyopathy.

[¶] Including chronic obstructive pulmonary disease (COPD), emphysema and asthma.

** Including deficiency of B- (humoral response) or T-lymphocytes, complement deficiencies (especially C1, C2, C3, and C4 deficiencies) and disorders of phagocytosis excluding chronic granulomatous disease.

[††] Diseases requiring treatment with immunosuppressants, including long-term systemic corticosteroid therapy or immunosuppression associated with radiotherapy.

[#] Rate ratio for the use of immunosuppressive drugs or clinical conditions causing immunosuppression.

[##] Rate ratio for diseases of white blood cells.

Pneumococci often cause superinfections in hospitalised patients with viral pneumonia. Although, in the case of influenza, about 35% of hospitalised patients develop pneumococcal co-infections [13], in COVID-19 patients, co-infections are less frequent [14]. Moreover, data on complications after pneumococcal infection should be considered in the long term, as evidenced by an increased risk of cardiovascular disease, which persists up to 5 years after the onset of pneumococcal pneumonia (adjusted hazard ratio (aHR) 1.87, 95% CI: 1.47–2.38) [15].

The impact of pneumococcal diseases on the mortality of the adult population is significant. According to data from 2019, the need for treatment in a hospital correlates with a high risk of death, which, in the case of community-acquired pneumonia, was 20.2% in the age group over 75 and was slightly lower

(10.9%) in patients within the age range of 65–74 years [7]. Research conducted in the US also showed that the mortality rates of adults hospitalised with pneumonia within one month and within a year of leaving hospital were 8.2% and 17.7%, respectively. Accordingly, hospital readmission within one month and a year occurred in 12.5% and 42.3% of patients [16]. The mean mortality rate of invasive pneumococcal infection exceeds 20% (95% CI: 17.5–24%). The presence of risk factors influences the mortality rate in selected patient groups. Risk factors associated with increased mortality comprised age (odds ratio (OR) 3.04, 95% CI: 2.5–3.68), chronic conditions (OR 2.34, 95% CI: 1.78–3.09), alcohol abuse (OR 3.14, 95% CI: 2.13–4.64), solid organ tumour (OR 5.34, 95% CI: 2.07–13.74) and septic shock (OR 13.35, 95% CI: 4.54–39.31) [17]. As shown by Polish data on IPD, the mortality rate differs for individual age groups. In 2021, it amounted to 65.5% (for patients over 65 years of age), 53.4% (in the 45–64 age group) and 28.9% (in the age range of 20–44 years) [18]. It is noteworthy that the mortality rate increases with age, and its highest values are recorded in the senior group.

Pneumococcal disease epidemiology

Invasive pneumococcal disease in Poland is monitored by the National Institute of Public Health – National Institute of Hygiene (NIZP PZH) and the National Reference Centre for Bacterial Meningitis (KOROUN). However, there is still a lack of accurate data on pCAP, which does not provide a complete overview of the burden of diseases caused by *S. pneumoniae*. Therefore, the most common serotypes causing invasive pneumococcal disease in adults in Poland, the rate of multi-drug resistant isolates (MDR) and the protection provided by individual vaccines are shown in Table 2. The table was created based on the available data for 2021 published by KOROUN [18].

In 2021, in Poland, 699 cases of IPD were reported, with the majority being related to the adult population. Of note, the number of IPD cases in the pre-pandemic year exceeded 1,000. Data published annually indicates that in 2021, the most common serotype responsible for invasive pneumococcal disease was serotype 3 (ST3), both in the general population and among adult patients. In the adult cohort, ST3 accounted for approximately 29% of IPD cases in Poland, being also the isolate responsible for the highest percentage of deaths in the general population. Serotypes 4 and 8 were the second and third causes of IPD in the adult population, accounting for 10% and 5% of cases, respectively. When analysing the percentage of antibiotic-resistant isolates of identified serotypes, three serotypes (6B, 19F and 19A) are especially interesting. Considering the data published by KOROUN, serotype 19A differs from the others. It is not only a common cause of IPD in the adult population (5% of cases), but it is also characterised by high antibiotic resistance. About 65% of ST19A isolates in the past year were resistant to at least three classes of antibiotics, which classified them as MDR (multidrug-resistant strains). Interestingly, the other two serotypes (6B, 19F) are much less likely to cause IPD in adult patients, even though they are characterised by an even higher level of antibiotic resistance (about 70% of isolates) [18].

Prevention of pneumococcal disease

Prophylactic vaccinations are the most effective way to prevent pneumococcal infections. Vaccines protect against pneumococcal disease caused by the most virulent *S. pneumoniae* serotypes, among which over 100 were identified [19]. When juxtaposing the differences in the mechanism of action of contemporary vaccines, they can be divided into two groups. The first group refers to Pneumococcal Conjugate Vaccines (PCV), and the second to unconjugated Pneumococcal Polysaccharide Vaccines (PPSV or PPV). More complex than unconjugated, the PCV-type vaccines are characterised by a robust immune response resulting from conjugating the polysaccharide antigen with the carrier protein [23]. Different types of vaccines (PCV and PPSV) are not equal. Considering the clinical practice, the important criteria are vaccine efficacy and effectiveness, authorised indications, further vaccination needs and availability on the market. The degree of vaccine protection may vary depending on the chosen vaccine type. Vaccines also differ in their availability to patients on the market. Ultimately, considering these factors allows for choosing the appropriate prophylaxis option.

There are four pneumococcal vaccines registered in Poland indicated for adult patients, comprising the 13-, 15- and 20-valent conjugated polysaccharide vaccines (PCV13, PCV15, and PCV20, respectively) and the 23-valent unconjugated polysaccharide vaccine (PPSV23 or PPV23). The composition of the *S. pneumoniae* polysaccharide antigens' serotypes contained in these vaccines is shown in Table 3. All preparations available in Poland cover serotypes 3 and 4, which cause the most identified cases of IPD in adults. Of note is that only the PCV20 and PPSV23 vaccines protect against serotype 8, which ranks third in Poland in terms of the number of IPD cases in the adult popula-

Table 2. *S. pneumoaniae* serotypes most frequently causing IPD in adults based on the KOROUN data for 2021. The percentage share of a given serotype among all reported IPD cases in Poland is given in parentheses. The table also shows the proportion of multi-drug resistant isolates (MDRs) and the coverage that each vaccine provides [18]

Serotype (% share) / Vaccine	3 (29%)	4 (10%)	8 (5%)	9N (5%)	19A (4%)	22F (4%)	6C (4%)	14 (4%)	23B (3%)	11A (3%)	19F (3%)	23A (2%)	9V (2%)	18C (2%)	35F (2%)
PCV13	■	■			■		*	■			■		■	■	
PCV15	■	■			■	■	*	■			■		■	■	
PCV20	■	■	■		■	■	*	■		■	■		■	■	
PPSV23	■	■	■	■	■	■		■		■	■		■	■	

PCV13 – pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed).
PCV15 – pneumococcal polysaccharide conjugate vaccine (15-valent, adsorbed).
PCV20 – pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed).
PPSV23 – pneumococcal polysaccharide vaccine (23-valent).
* Cross-reactive serotype (cross-protection) 6A-6C [20–22].
■ – low MDR percentage (< 20%).
■ – moderate MDR percentage (20–40%).
■ – high MDR percentage (> 40%).

Table 3. Polysaccharide antigen coverage of individual *S. pneumoniae* serotypes among pneumococcal vaccines indicated for use in adult patients

Vaccine	Vaccine type	Antigens of a given serotype of *S. pneumoniae*																							
		1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F	22F	33F	8	10A	11A	12F	15B	2	9N	17F	20
PCV13	Conjugated (PCV)	●	●	●	●	●	●	●	●	●	●	●	●	●											
PCV15		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●									
PCV20		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●				
PPV23	Unconjugated (PPSV, PPV)	●	●	●	●		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

tion. Each of the above-mentioned vaccines also provides coverage of the serotypes with the highest percentage of multi-drug resistant isolates (6B, 19F and 19A).

The PPSV23 vaccine provides protection against the broadest spectrum of *S. pneumoniae* serotypes; however, elicited immune response is based on T-independent polysaccharide antigens that only stimulate B lymphocytes without the activation of T lymphocytes and the subsequent formation of memory cells. Therefore, the PPSV23 vaccine primarily protects against the development of IPD, while the efficacy against pCAP and duration of protection is uncertain [24]. Conjugated vaccines (PCV), in turn, contain T-dependent antigens, presenting a more complex mechanism of action based on the activation of B- and T-lymphocytes and the subsequent production of memory cells. In addition, conjugated polysaccharide vaccines have been shown to induce a more effective immune response compared to unconjugated vaccines [25]. As a result of eliciting a T-dependent response and robust immunogenicity, just one dose of the PCV vaccine can provide adult patients with permanent and effective protection against pneumococcal infections. Additionally, the immune response produced by conjugate vaccines may reduce the carriage of *S. pneumoniae* [25, 26]. Considering all the above reasons, PCV-type vaccines should be used first, i.e. before unconjugated polysaccharide vaccines, if subsequent administration is justified [4].

Before 2022, the pneumococcal vaccination prophylaxis for adults in Poland was not reimbursed. As of 1 January 2022, the 13-valent conjugate vaccine (PCV13) became partially reimbursed, meaning it could be purchased with a 50% co-payment for people over 65 years of age with an increased (moderate to high) risk of pneumococcal disease [27]. PCV13 is the first reimbursed pneumococcal vaccine for adult patients in Poland, which constitutes an essential step toward an increase in the awareness of vaccination prophylaxis among adults. The 50% reimbursement is available to patients who meet both the age criterion and are at increased risk of developing the pneumococcal disease. A detailed list of clinical conditions entitling the patient to reimbursement is presented in the tabular form below (Table 4).

Numerous scientific societies have underlined the significance of pneumococcal vaccination in their recommendations for adult patients. The American Advisory Committee on Immunization Practices (ACIP) recommends the use of pneumococcal vaccinations in all adults over 65 years of age, as well as in younger individuals (19–64 years) with a moderate to high risk of *S. pneumoniae* infection [12, 28]. European [29, 30] and American [31] recommendations indicate the use of pneumococcal vaccination in patients treated for both solid tumours and proliferative blood diseases. In addition, numerous recommendations, created by both Polish and European scientific societies, emphasise the need for pneumococcal vaccination in HIV-infected patients, individuals suffering from AIDS [32], diabetes [33], COPD [34], heart failure [35], pulmonary hypertension [36], autoimmune inflammatory diseases [37] and in solid organ recipients [38].

Table 4. Reimbursement criteria for the PCV13 vaccine that qualifies a patient for a 50% reimbursement

PCV13 reimbursement criteria	Age criterion	Risk criterion (Factors increasing the risk of pneumococcal disease development)
Concomitant fulfilment of the age and risk criteria (presence of at least 1 factor)	above 65 years of age	chronic heart disease
		chronic liver disease
		chronic lung disease
		chronic renal failure
		diabetes
		cochlear implant
		CSF leak
		congenital or acquired asplenia
		sickle cell anaemia and other hemoglobinopathies
		congenital and acquired immunodeficiencies
		HIV infection
		leukaemia
		Hodgkin's disease
		generalised malignancy
		multiple myeloma
		iatrogenic immunosuppression
		solid organ transplant

Recommended vaccination schedules for adult patients in Poland

In the context of pneumococcal disease epidemiological changes and new vaccine authorisations in adult patients, the American Advisory Committee on Immunization Practices (ACIP) has developed new recommendations for vaccination prophylaxis. The latest ACIP document recommends pneumococcal vaccination for all people over 65 years of age (regardless of concomitant risk factors) and for younger adult patients (19–64 years) who are at increased risk of pneumococcal disease development [12].

Considering the epidemiological landscape changes in Poland, as well as the registration of new pneumococcal vaccines (PCV15 and PCV20), there is a need to formulate appropriate national recommendations indicating proper vaccination schedules. Depending on the patient's condition and previous vaccination history, practical schemes are recommended, which facilitate decision-making in vaccinations. Recommended vaccination schedules are summarised in Table 5.

Table 5. Recommended pneumococcal vaccination schedules for adult patients

Patient group	Vaccination history	Vaccination schedule		Remarks
		First vaccination	Second vaccination	
Patients over 65 years of age or adults aged 19–64 with risk factors*	Not vaccinated against pneumococcal or history unknown	PCV20	not necessary	a single dose of PCV20 is the complete vaccination course
		PCV15	PPSV23	the time interval between the first and second immunisation should be at least 8 weeks** or at least one year (in all other cases); in case PCV15 is not available, the schedule should begin with PCV13
		PCV13	PPSV23	the time interval between the first and second immunisation should be at least 8 weeks** or at least one year (in all other cases); in certain patients, PCV13 is partially reimbursed
	Documented	**Administered vaccine**	**Vaccine to be administered**	**Remarks**
		PCV13	PPSV23 or PCV20	PCV20 should be given when PPSV23 is not available; when using the PCV13 + PPSV23 regimen, the interval between the first and second immunisation should be at least 8 weeks** or at least one year (in all other cases); in clinical studies of the PCV13 + PCV20 schedule, the time interval between the first and second immunisations was at least 6 months
		PPSV23	PCV15 or PCV20	PCV20 vaccine provides broader serotype coverage than PCV15***; one dose of PCV15 or PCV20 at least one year after PPSV23 administration
		PCV13 and PPSV23	–	the vaccination course is completed, administration of another vaccine is not necessary

* Risk factors are described in Table 1.
** For adults with a medical condition that compromises the immune system, a cochlear implant, or a cerebrospinal fluid leak, shorter intervals, e.g. ≥ 8 weeks, may provide additional benefits.
*** Applies to five additional serotype antigens contained in the PCV20 vaccine (8, 10A, 11A, 12F, 15B) that are not contained in PCV15.

The new vaccination schedules include the administration of a single dose of the PCV20 vaccine or the use of a sequential vaccination schedule that includes one dose of PCV15 and one dose of PPSV23 at appropriate intervals. The above-described vaccination schedules can be considered equivalent, as each of them provides an adequate protection range. A single dose of PCV20, then, is sufficient without the need for a supplemental PPSV23 vaccination [12]. The schedule of sequential administration (PCV15 + PPSV23) allows, in turn, for obtaining an immune response to a slightly wider range of *S. pneumoniae* serotypes than the administration of PCV20 alone, but it takes a longer time for adequate protection to be developed. However, American data indicates that a significant percentage of patients do not sign up for the supplementary dose of PPSV23 if the sequential schedule is utilised. In the US, the percentage of patients reporting a second vaccination visit when using the sequential regimen was low [39]. Aiming to reduce of the time needed to protect a patient against pneumococcal diseases and to minimise the risk of low compliance with the sequential regimen, vaccination with a single dose of PCV20 seems to be more advantageous and easier to apply.

Contraindications for pneumococcal vaccination

When qualifying adults for pneumococcal vaccination, it should be remembered that there are only a few contraindications to vaccination, which can be divided into absolute, relative, permanent and temporary. The only absolute and permanent contraindication is the occurrence of anaphylactic shock after a previous dose of the vaccine or after the administration of any component contained in the vaccine to be administered. Temporary contraindications do not exclude the patient from the possibility of vaccination, but they do force the vaccination to be postponed. Vaccination should be postponed in the event of acute infectious disease (with or without fever) or upon exacerbation of a chronic disease (until stabilisation is achieved). Stable chronic diseases or mild infections do not constitute a contraindication to vaccination, which should especially be remembered in the case of immunising the elderly or patients with underlying conditions [28].

Practical remarks

Increasing the awareness of adult patients in the field of pneumococcal vaccination is a key task facing the Polish healthcare system. A patient's education cannot be viewed as the sole obligation of primary healthcare physicians, who should inform patients about the risks associated with pneumococcal infections and the prophylaxis possibilities with the use of available vaccines. It is certain that patients' education on this matter requires the support of doctors of other specialties. Considering that doctors of other specialists often stay in touch with patients at increased risk of developing pneumococcal disease (due to

concomitant risk factors), to protect their patient's health and life, they should inform them about the possibility of appropriate vaccination prophylaxis. A desirable practice is to include some vaccination advice in the hospital discharge recommendations to encourage vaccine uptake during the patient's next visit to the general practitioner.

All possible opportunities should be utilised to foster prophylactic vaccinations against pneumococci in adults, with particular emphasis on other vaccination visits. It is advisable to inform the patient about the possibility of additional pneumococcal vaccination during these visits. This practice is especially important considering pneumococcal co-infections in the course of influenza or COVID-19 [13, 40]. Of importance, none of the registered pneumococcal vaccines contain live microbes. As indicated by the Polish National Immunisation Programme (PSO), in this case, the time interval between different vaccines which do not contain live microorganisms is discretionary. Therefore, if the necessary time interval for avoiding any possible vaccine overlapping adverse reaction (NOP) with another vaccination is taken, the physician may decide to administer different vaccines (e.g. with the COVID-19 vaccine or influenza) during the same vaccination visit [4].

Conclusions

Pneumococcal pneumonia and invasive pneumococcal disease in adults pose a threat to the health (occurrence of complications, deterioration of quality of life, decompensation of the underlying disease) and life of a patient (especially for elderly patients and those with comorbidities) and also generate high socio-economic costs. Considering the increasing threats related to infections caused by *S. pneumoniae* in adults, vaccination is constantly gaining importance. At least a few factors should be considered when recommending the most optimal protection selection against pneumococcal diseases: vaccine efficacy, authorised indications, further vaccination need and availability on the market. In addition, the appropriate vaccination schedule should be individually selected for a given patient, considering, inter alia, previous vaccination history. The recommended vaccination schedules described in this publication can assist in the choosing of an optimal protection schedule for adult patients against pneumococcal diseases in a simple, effective and safe manner.

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Address for correspondence:
Ernest Kuchar, MD, PhD, Assoc. Prof.
Klinika Pediatrii z Oddziałem Obserwacyjnym
Warszawskiego Uniwersytetu Medycznego
Szpital Pediatryczny 0C
ul. Żwirki i Wigury 63A
02-091 Warszawa
Polska
Tel.: +48 22 317-92-31
E-mail: ernest.kuchar@wum.edu.pl