Adult Vaccination for Pneumococcal Disease: a Comparison of the National Guidelines in Europe

C. Bonnave[a+], D. Mertens[a+], W. Peetermans[b], K. Cobbaert[c], B. Ghesquiere[c], M. Deschodt[d,e*], J. Flamaing[a,d*§]

a Department of Geriatrics, University Hospitals Leuven, Belgium b Department of Internal Medicine, University Hospitals Leuven, Belgium c Department of Geriatrics, AZ Delta Roeselare, Belgium d Department of Chronic Diseases, Metabolism and Aging, University of Leuven, Belgium e Department of Public Health, University of Basel, Switzerland

[+] shared first authorship

[*] shared last authorship

§ Corresponding author: University Hospitals Leuven, Herestraat 49, 3000 Leuven.

Email: Johan.flamaing@uzleuven.be.

Telephone number: 003216332211

Abstract

Background: Pneumococcal disease constitutes a major global health problem. Adults aged over 50 and younger adults with specific chronic health conditions are at risk for invasive

pneumococcal disease, associated with substantial morbidity and mortality. In Europe, two vaccine types are used in adults for pneumococcal immunization: pneumococcal polysaccharide vaccine (PPV23) and pneumococcal conjugate vaccine (PCV13).

Aims: To provide an overview and to compare the national guidelines for pneumococcal immunization for adults in Europe.

Sources: In November 2016, national guidelines on pneumococcal vaccination for adults of 31 European countries were obtained by Google search, the website of European Centre for Disease Prevention and Control and contacting public health officials. In our analysis we distinguished between age-based and risk-based guidelines. In October 2017, we used the same method to retrieve guideline updates.

Content: We observed great variability regarding age, risk groups, vaccine type and use of boosters. In age-based guidelines, vaccination is mostly recommended in adults aged over 65 using PPV23. Boosters are generally not recommended. An upper age limit for vaccination is reported in three countries. In the immunocompromised population, vaccination with both vaccines and administration of a booster is mostly recommended. In the population with chronic health conditions, there is more heterogeneity according vaccine type, sequence and administration of boosters. Asplenia is the only comorbidity for which all countries recommend vaccination.

Implications: The great variability in European pneumococcal vaccination guidelines warrants European unification of the guidelines for better control of pneumococcal disease.

Keywords: Pneumococcal vaccination; Adults; Europe; Recommendations; PCV13; PPV23

Introduction

Pneumococcal infections constitute a major global health problem. It leads to a number of diseases like otitis media, pneumonia, meningitis and bacteremia. (1) The most frequent

manifestation of pneumococcal disease in adults is pneumonia, where *Streptococcus pneumoniae* is responsible for up to 60% of the cases of community-acquired pneumonia. (2)

In the United States, data of the Centers for Disease Control and Prevention showed 17 cases of invasive pneumococcal disease (IPD) per 100.000 persons in all age groups. (3) In England and Wales an incidence of IPD of 7 per 100.000 persons in all age groups is reported, and an incidence of 21 per 100.000 in persons aged 65 and older. (2)

Risk groups for developing pneumococcal infections and complications are children aged <2 years, adults aged 50 and older, and persons with specific comorbidities. (1) Case fatality rate of IPD may reach 15-20% in adults and even 30-40% in elderly. (4, 5)

The pneumococcus is a common human commensal in the nasopharynx, with asymptomatic carriage reported from 5% to 93% in all age groups. Carriage diminishes greatly with age: whereas up to 60% of the school-aged children may be colonized, only 5-10% of adults and <5% of nursing home residents are. (2, 3, 6, 7) *S. pneumoniae* is classified by the presence of capsular polysaccharides, with at least 93 different serotypes identified. Up to 60% of the IPD infections (in Belgium even up to 83%) are caused by serotypes covered by PPV23. (5, 8)

Currently, two different pneumococcal vaccines are approved for use in adults: the polysaccharide vaccine containing 23 different capsular polysaccharides (PPV23) and the conjugate vaccine containing 13 serotypes of *S. pneumoniae* (PCV13). (9) The PPV23 triggers a T-cell independent immune response with serotype-specific antibody formation. Although the PPV23 offers an extended serotype coverage, much of the antibody-response after vaccination is transitory, resulting in a decline in protection after 2-4 years. Also, immunogenicity is probably lower among young children, elderly, and immunocompromised persons. (10, 14) PCV13 triggers a T-cell dependent immune response, with formation of both serotype-specific antibodies and B memory cells, resulting in a better immune response. (10) As PCV13

stimulates the formation of mucosal antibodies and thus prevents acquisition of nasal carriage of vaccine types, a reduced spread by children of the serotypes included in PCV13 was observed, thereby protecting unvaccinated individuals in all age groups ('herd protection effect'). (3)

As the global burden of pneumococcal disease is high, most European countries have implemented national vaccination guidelines. However, the immunization guidelines vary greatly among countries in Europe in terms of age and risk groups for vaccination. (1) The aim of this review is to provide an overview and compare the national guidelines in Europe for pneumococcal immunization in adults.

Methods

Search strategy

A two-fold search strategy was conducted in November 2016 to identify the national guidelines on pneumococcal vaccination for adults aged ≥ 18 years in 31 European countries. Immunization schedules for patients with hematological stem cell transplantation were excluded, as this was outside the scope of our review. Firstly, we used the Vaccine Schedule on the website of the European Centre for Disease Prevention and Control (ECDC; www.ecdc.europa.eu), and searched the reference websites provided for each country to obtain their official immunization guidelines. If no vaccination guidelines could be retrieved for a country by using this method, we performed a Google search ("pneumococcal vaccination guidelines adult [Name of the country]", translated in the official language of this country by using Google Translate). In case both search strategies failed, we contacted the public health

officials of this country (as was the case for Bulgaria, Cyprus, Croatia and Estonia). In October 2017, we used the same method to retrieve guideline updates.

Data extraction

To translate the vaccination guidelines from their original language, Google Translate or interpreters were used.

Data were extracted in Word and Excel tables to synthesize information regarding study characteristics, vaccine type, sequence of vaccination, and use of boosters (supplementary tables 1-3 and tables 1-2). In our analysis, we distinguished between age-based and risk-based guidelines. In the risk-based guidelines, we beheld three different risk groups: patients with specific chronic health conditions, an immunocompromised group, and patients with other predisposing risk factors for pneumococcal disease. The risk factor-based guidelines concern all adults aged 18 years and older, unless otherwise specified in supplementary table 3.

Data synthesis and analysis

For the age-based guidelines and the different risk factors, we calculated the absolute numbers and percentages of vaccine and booster recommendation, and vaccine type used (table 1-2). This data extraction was performed by one researcher (CB) and verified by a second researcher (DM).

Results

Identification of national vaccination guidelines

We were able to identify guidelines for adult pneumococcal immunization for 28 of the 31 reviewed European countries (90%). No guidelines were found for Cyprus, Latvia, and Romania. In all of the 28 countries, risk-based guidelines were available, while age-based guidelines were available in 27 countries (96%). No age-based guidelines were found for Croatia. More than 90% of these countries (93%; n=26) updated their guidelines in 2014 or later.

In both age- and risk-based guidelines, a great variability was observed regarding to the age group eligible for vaccination and the type of recommended vaccine (see supplementary table 2-3 and table 1-2)

Age-based guidelines

France, Liechtenstein and Portugal do not recommend systematical vaccination in healthy adults. The remaining European countries with age-based guidelines (n=24; 89%) advise vaccinating healthy adults with a minimum age of 50 years (n=5; 18.5%), 59 years (n=1; 4%), 60 years (n=5; 18.5%) or 65 years (n=13; 48%). An upper age limit for vaccination was mentioned in Belgium and Luxembourg (both 85 years) and in the Netherlands (75 years).

For primary vaccination of the healthy adult, four out of ten countries recommends the use of PPV23 only (n=11; 40.7%). One country (Estonia) recommends the use of PCV13 only, while seven other countries (26%) recommended both PCV13 and PPV23 for primary vaccination. In four countries (15%), the type of vaccine recommended depends on the preference of the treating physician (Finland, Denmark, Lithuania, Slovenia). In Slovakia, the recommended vaccine type is not specified.

If both vaccines are recommended for primary vaccination, which is the case in nine countries, PCV13 is always administered first. The recommended interval between the two vaccinations (PCV13 and PPV23) differed between ≥8 weeks in Belgium, Denmark, Hungary, Luxembourg and Italy and ≥1 year in Finland, Greece and Austria. Slovakia recommends primary vaccination but did not specify the recommended vaccine type.

Twelve countries (44.4%) do not advise a booster in healthy adults. Five national guidelines recommend a booster (18.5%), and five countries consider a booster under certain conditions (e.g. patients aged > 65y, who received their first vaccine at least 5 years ago when < 65y). In five guidelines, administration of boosters was not reported (18.5%). If a booster is given, all countries use PPV23.

Risk-based guidelines

The *chronic disease group* includes vaccination guidelines for chronic kidney (n=25; 89%), lung (n=25, 89%), heart (n=24, 86%), and liver disease (n=22, 79%) and diabetes mellitus (n=21, 75%). Mostly PCV13 and PPV23 or only PPV23 are recommended (see table 2). PCV13 only is rarely used. A booster is recommended in 26 to 37% of the countries (depending on the underlying health condition), is considered in about 15% of the countries, and is not recommended in 26 to 35% of the countries, respectively. In one fifth of the countries, no booster guidelines were reported.

In the immunocompromised population vaccination is recommended in the majority of the countries. Asplenia is the only condition for which all countries advise vaccination. Immunization of patients with immunodeficiency is recommended in 23 countries. About 65% of the countries recommend vaccination for HIV-patients, hematologic malignancies, patients taking immunosuppressive drugs and patients after solid organ transplant. 32% of these countries, recommend pneumococcal immunization in patients with parenchymatous

malignancies. The majority of the countries that recommend vaccinations in these immunocompromised patients (58 to 72% depending on the underlying condition), would vaccinate with PCV13 and PPV23. 10 to 20% of the countries recommend immunization with PPV23 only. Again, PCV13 only is rarely recommended. A booster is recommended in 40% of the countries that report risk-based guidelines (depending on the underlying condition). A booster is recommended for patients with asplenia in six out of ten countries. In up to 25% of the risk-based guidelines, no booster guidelines are reported.

The third category includes *various risk factors* for pneumococcal disease. For patients with cerebrospinal fluid leak or a cochlear implant, most countries (89% and 82% respectively) recommend vaccination, mostly with PCV13 and PPV23 (64% and 62,5% respectively). Four out of ten countries advise a booster in this risk group. About 40% of the countries recommend vaccination for smokers and alcoholics, and two out of ten would vaccinate patients with occupational risk (such as welders), institutionalized patients and patients with neuromuscular disease. In these five previous risk groups, half of the countries vaccinates with PPV23 only, and roughly a quarter recommends administration of a booster. For patients with previous invasive pneumococcal disease or pneumococcal pneumonia, vaccination is only recommended in three countries. Sweden and Liechtenstein are the only countries that would vaccinate patients with BMI > 40 kg/m². Norway and the Netherlands would consider pneumococcal immunization for patients with celiac disease, homeless patient groups and drug addicts.

Discussion

In this study, comparing the European guidelines for pneumococcal vaccination of adult patients at elevated risk for pneumococcal infection, we observed a great variability in vaccine recommendation despite increasing evidence of pneumococcal vaccine being effective in older adults.

Although no concluding evidence about the efficacy of PPV23 was reported in a Cochrane review (probably due to a lack of statistical power), the benefit of PPV23 was more pronounced when limiting the analysis to trials that assessed the incidence of vaccine-serotype disease. (11) Also, two recent meta-analyses showed PPV23 vaccine efficacy. (9, 12) Falkenhorst et al (2017) found a significant vaccine efficacy of 73% for IPD and of 64% for pneumococcal pneumonia in patients aged ≥ 60 years. (9) Kraicer-Melamed et al. (2016) described a 50% vaccine efficacy for IPD in patients aged ≥ 50 years. (12) The authors state that the use of recent and high quality data led to this results, contrary to the Cochrane review.

Concerning PCV13, the most important study is the CAPITA trial (2015). This placebocontrolled study analyzed the vaccine efficacy of PCV13 in 85.000 patients aged ≥ 65 years. A vaccine efficacy of 45.6%, 45% and 75 % in the prevention of respectively vaccine-type community acquired pneumonia, non-bacteremic and non-invasive community-acquired pneumonia, and invasive pneumococcal disease was demonstrated. Efficacy persisted throughout the trial (mean follow-up 3,97 years) suggesting that PCV13 should be part of the vaccination program in older adults. (13) However, the results of the CAPITA-trial should be interpreted with caution as patients with immunodeficiency were excluded and as it took place before implementation of childhood pneumococcal immunization in the Netherlands. The latter thereby ignores the herd effect, and the study possibly overestimates the efficacy of PCV13. (9) The CAPITA-trial also examined the long-term immunogenicity of PCV13 in pneumococcal vaccine–naive older adults, demonstrating high antibody titers during the first two years following vaccination after a single dose of PCV13. In adults aged ≥80 years, weaker responses were observed, but antibody levels remained above baseline. (14)

Cost-effectiveness analysis are often issued by health authorities to substantiate inclusion of pneumococcal vaccination in the adult vaccination program with (partial) reimbursement of the

costs. In 2012, the Infection Prevention Institute in Poland performed a cost-effectiveness analysis on the implementation of a public vaccination program with PPV23 only in the elderly aged ≥65 years. When taking into account the medical and economic burden of pneumococcal disease of that time, presuming a PPV23-vaccine efficacy of 64% for IPD in elderly and assuming a 50% reimbursement of the PPV23 vaccine from their national health fund, they concluded that the use of PPV23 in healthy elderly, would be highly cost-effective. (4) A costeffectiveness analysis in the United Kingdom (2015) stated that adding PCV13 to the existing vaccination program with PPV23 in healthy elderly would substantially raise costs of immunization programs and would not be cost-effective. (15)

Despite some disadvantages of PPV23 (lack of development of an immune memory, reduced immunogenicity in the elderly), and some conflicting results on efficacy of this vaccine as mentioned above, the more recent systematic reviews and this cost-effectiveness analysis provide arguments for a vaccination strategy in the healthy elderly that includes PPV23.
Furthermore, as there is to our knowledge no study comparing the efficacy of PCV13 and PPV23 in elderly patients, and considering the economic aspect and weaknesses of the CAPITA-trial mentioned above, updating vaccination guidelines and recommending the use of both PCV13 and PPV23 for the healthy elderly (as done in the United States by the Advisory Committee on Immunization Practices (ACIP) in 2014), should be done cautiously. (16) More studies on pneumococcal vaccination of the healthy elderly are needed, including a new efficacy trial for PCV13 that takes into account the herd protection effect.

As vaccine-induced immunity wanes after a few years, considering the lack of development of an immune memory, a booster vaccine can be considered. The efficacy of boosters however is uncertain, mainly because a state of hypo-responsiveness or immune tolerance is described

following revaccination with PPV23. This especially seems relevant if a booster is administered within 5 years after primary vaccination. Musher et al. demonstrated that persons who received PPV23 within one year, almost did not respond to revaccination, and those who had received PPV23 within 1 to 5 years responded less well than those who had no previous or more remote vaccination. (17, 18) Another systematic review comparing the effectiveness, immunogenicity and safety of revaccination with PPV23 in persons aged ≥ 50 years, demonstrated a reduced antibody response during the first months after revaccination (thereafter, immunogenicity of primary and repeated vaccination was comparable). There were no major safety concerns regarding revaccination. (19) All of the studies mentioned above however, are immunogenicity studies that evaluate antibody responses after immunization, therefore lacking clinical endpoints or data about clinical effectiveness. As the available evidence concerning revaccination with PPV23 is not unambiguous, neither are the guidelines concerning the use of boosters in healthy elderly.

The strength of this article lies in the comprehensive overview of 31 European countries and the United States, which is to our knowledge the largest comprehensive overview up to present. A limitation of the study includes the use of Google Translate or interpreters, and thus the lack of a formal forward-backward translation. Although this could have led to incorrect translations or interpretations, the immunization guidelines were very straightforward, often written in bullet points.

Conclusion

Pneumococcal vaccination has greatly reduced incidence of vaccine-type pneumococcal morbidity and mortality. There is great variability in European pneumococcal vaccination guidelines for adults, regarding age, risk groups, and vaccine type. Most countries did not have clear recommendations about the administration of boosters. For ease of implementation, European unification of the immunization guidelines is needed. This remains difficult despite increasing evidence on pneumococcal vaccine effectiveness in elderly.

Compliance with Ethical Standards

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Table to be included in the manuscript

Table 1 – Resume age-based guidelines

	N	%	Countries
Age-based guidelines (healthy population) - n=27			
Recommended starting age of vaccination			
>/= 50y	5	18.5	Austria, Estonia, Hungary, Lithuania, Poland
>/= 59y	1	3.7	Slovakia
>/= 60y	5	18.5	Bulgaria, Germany, Iceland, the Netherlands, Spain
>/= 65y	13	48.1	Belgium, Czech Republic, Denmark, Finland, Greece, Ireland, Italy, Luxembourg, Malta, Norway, Slovenia, Sweden, United Kingdom
Vaccination not recommended	3	11.1	France, Liechtenstein, Portugal
Upper limit of age for vaccination reported :			
	3	11.1	Belgium, Luxembourg, the Netherlands
Vaccine type recommended in primary vaccination			
PCV13	1	3.7	Estonia
PPV23	11	40.7	Bulgaria, Germany, Iceland, Ireland, Malta, the Netherlands, Norway, Poland, Spain, Sweden, United Kingdom
PCV13 and PPV23	7	25.9	Austria, Belgium, Czech Republic, Greece, Hungary, Luxembourg
Several options possible	4	14.8	Denmark, Finland, Lithuania, Slovenia
Recommended but vaccine type not specified	1	3.7	Slovakia
Sequence and recommended interval if both vaccines recommended (primary vaccination)			
PCV13 first	9	100	

- Interval between the two vaccines > 8 weeks	5	55.6	Belgium, Denmark, Hungary, Luxembourg, Italy
- Interval between the two vaccines > 1 year	3	33.3	Austria, Finland, Greece
- Interval not specified	1	11.1	Czech Republic
PPV23 first	0	0	
Administration of booster			
Booster recommended	5	18.5	Czech Republic, Denmark, Estonia, the Netherlands, Norway
No booster recommended	12	44.4	Austria, Belgium, France, Germany, Iceland, Italy, Liechtenstein, Luxembourg, Malta, Portugal, Sweden, United Kingdom
Booster to consider	5	18.5	Bulgaria, Ireland, Lithuania, Slovenia, Spain
Not reported	5	18.5	Finland, Greece, Hungary, Poland, Slovakia
Type of vaccine used for booster			
PCV13	10	100	Bulgaria, Czech Republic, Denmark, Estonia, Ireland, Lithuania, the Netherlands, Norway, Slovenia, Spain
PPV23	0	0	

n: number of countries; PPV23: pneumococcal polysaccharide vaccine; PCV13 pneumococcal conjugate vaccine

Table to be included in the manuscript

Table 2 – Resume risk factor-based guidelines

Risk factor-based guidelines (n = 28)

	Vaccination recommended		Vaccination to consider		Vaccine type									
					PCV13		PPV23		PCV13 + PPV23		Several options			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Chronic disease														
Chronic kidney disease	25	89.3	2	7.1	1	3.7	7	25.9	14	51.9	5	18.5		
Chronic lung disease	25	89.3	2	7.1	1	3.7	8	29.6	12	44.4	6	22.2		
Chronic heart disease	24	85.7	2	7.1	1	3.8	7	26.9	12	46.2	6	23.1		
Chronic liver disease	22	78.6	2	7.1	1	4.2	7	29.2	11	45.8	5	20.8		
Diabetes mellitus	21	75	2	7.1	1	4.3	8	34.8	9	39.1	5	21.7		
Immunocompromising conditions														
Asplenia	28	100	0	0	1	3.6	4	14.3	18	64.3	5	17.9	16	57.1
Immunodeficiency	23	82.1	2	7.1	1	4	2	8	16	64	6	24	10	40
HIV	19	67.9	1	3.6	1	5	4	20	12	60	3	15	7	35
Hematological malignancy	18	64.3	1	3.6	1	5.3	3	15.8	11	57.9	4	21.1	7	36.8
Immunosuppressive therapy	18	64.3	2	7.1	1	5	3	15	12	60	4	20	7	35
Solid organ transplant	17	60.7	1	3.6	1	5.6	2	11.1	11	61.1	4	22.2	8	44.4
Parenchymatous malignancy	9	32.1	2	7.1	0	0	1	9.1	8	72.7	2	18.2	5	45.5
Other risk factors for pneumococcal disease														
CSF-leak	25	89.3	0	0	1	4	5	16	16	64	4	16	10	
Cochlear implant	23	82.1	1	3.6	1	4.2	4	16.7	15	62.5	4	16.7	10	4
Alcoholism	12	42.9	2	7.1	0	0	5	35.7	6	42.9	3	21.4	2	
Smoking	10	35.7	1	3.6	0	0	4	36.4	6	54.5	1	9.1	3	2
Occupational risk	6	21.4	1	3.6	0	0	3	42.9	3	42.9	1	14.3	2	2
Institutionalized patients	5	17.9	0	0	0	0	2	40	0	0	3	60	1	
Neuromuscular disease	5	17.9	0	0	0	0	3	60	1	20	1	20	1	
Medical history of IPD	3	10.7	2	7.1	0	0	0	0	4	80	1	20	3	
BMI > 40 kg/m²	2	7.1	0	0	1	50	1	50	0	0	0	0	0	
Celiac disease	0	0	2	7.1	0	0	0	0	1	50	1	50	0	
Homeless patients	0	0	2	7.1	0	0	0	0	1	50	1	50	0	
Drug addicts	0	0	2	7.1	0	0	0	0	1	50	1	50	0	

BMI: body mass index; CSF: cerebrospinal fluid; HIV: human immunodeficiency virus; IPD: invasive pneumococcal disease; n: number of countries; PPV23: pneumococcal polysaccharide vaccine; PCV13 pneumococcal conjugate vaccine