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REVIEW

Recommendations for Pneumococcal Immunization Outside Routine Childhood Immunization Programs in Western Europe

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ABSTRACT

The global burden of pneumococcal diseases is high, with young children and adults ≥50 years of age at highest risk of infection. Two types of vaccine are available for the prevention of pneumococcal diseases caused by specific *Streptococcus pneumoniae* serotypes: the pneumococcal polysaccharide vaccine (PPV23) and the pneumococcal conjugate vaccine (PCV7, PCV10, and PCV13). Despite pneumococcal immunization programs in adults and children, the burden in adults has remained high. Most European countries have national or local/regional vaccination recommendations. The objective of this review was to provide an overview of the government recommendations for pneumococcal vaccination outside routine childhood vaccination programs for 16 Western European countries as of August 2014. We found that recommendations for pneumococcal immunization across Europe are complex and vary greatly among countries in terms of age groups and risk groups recommended for vaccination, as well as which vaccine should be administered. Clarifying or simplifying these recommendations and improving their dissemination could help to increase pneumococcal vaccine uptake and decrease the high burden of pneumococcal diseases in adults, both through a direct effect of the vaccine and via a herd effect in unvaccinated individuals.

Keywords: Age; Europe; Immunization; Infectious diseases; Pneumococcal conjugate vaccine; Pneumococcal diseases; Pneumococcal polysaccharide vaccine; Recommendations; Reimbursement; Risk

INTRODUCTION

Pneumococcal infection causes a spectrum of diseases from mild presentations such as sinusitis and otitis media, to more serious

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diseases such as meningitis, bacteremia, and pneumonia [1]. The 23-valent pneumococcal polysaccharide vaccine (PPV) was introduced in 1983 and is available in Europe for immunization against pneumococcal diseases caused by the 23 serotypes contained in the vaccine (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F) in adults and children aged ≥2 years [2]. The first pneumococcal conjugate vaccine (PCV7) was licensed in 2000 for immunization against pneumococcal diseases, including sepsis, meningitis, pneumonia, bacteremia, and acute otitis media (AOM) caused by the seven serotypes contained in the vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F) in infants and children aged 2 months to 5 years [3]. PCV10 (serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F) was approved in 2009 for protection against invasive pneumococcal disease (IPD), pneumonia, and AOM in infants and children aged from 6 weeks up to 5 years [4]. A higher-valent PCV, PCV13, comprising six additional serotypes to PCV7 (serotypes 1, 3, 5, 6A, 7F, and 19A) is now available in Europe for the prevention of IPD in adults aged ≥18 years, and for the prevention of IPD, pneumonia, and AOM in infants and children aged between 6 weeks and 17 years [5].

The global burden of pneumococcal diseases is high, with young children and adults ≥50 years of age at particular risk of infection. In the 1990s, the age groups with the highest incidence of IPD and highest case fatality rates were infants aged <2 years and adults aged >50 years [6]. Routine childhood pneumococcal immunization programs have helped to alleviate the burden of disease in children [7, 8]. Since 2006, the World Health Organization (WHO) has recommended that PCV be included in all routine childhood immunization programs [9]. Consequently, PCV use has increased from 1% of all WHO member states in 2000 to 44% in 2012, representing 31% of the global birth cohort [9]. Of the European region member states, 49% had introduced PCV by 2012 [9]. Over time the benefits of childhood vaccination with PCV in countries with high uptake have extended to unvaccinated children and adults as a result of the herd effect [10–13]. However, despite pneumococcal immunization programs covering adults and children, the burden in adults has remained high [14].

Recommendations for pneumococcal immunization across Europe are complex and are regularly updated. The objective of this review is to provide an overview of current government recommendations (not including scientific society recommendations), both national and regional where applicable, outside routine pneumococcal immunization programs for infants and children, in 16 individual countries across Western Europe (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Norway, Portugal, Spain, Sweden, and the United Kingdom [UK]), as of August 2014. A summary of the recommendations is provided in the text below, with more detailed information supplied for reference purposes in Table 1. To ensure the most up-to-date information for each country was included, Pfizer's country Medical Affairs offices provided information regarding national and regional recommendations for pneumococcal vaccination. This article is based on pre-existing source material and does not include any studies with human or animal subjects performed by the author.

Table 1 Comparison of the recommendations and funding for pneumococcal immunization outside routine vaccination programs for children in Western European countries

Country	Recommended vaccine	Region (date of recommendations)	Population (age, years)	Definition of risk	Funding	Additional information
Austria [28]	PCV13/PPV23	National (2014)	At risk and high risk (≥6)	High risk	Private	Naïve
				Asplenia (anatomical, functional)		PCV13 followed by PPV23 after ≥8 weeks
				Chronic renal insufficiency		Pre-vaccinated with PCV
				Cochlear implant		After interval of ≥8 weeks 1xPPV23
				Complement and properdin deficiency		Pre-vaccinated with PPV23
				Hematopoietic organ disorder		After interval of ≥8 weeks 1xPCV13 and after another interval of ≥8 weeks 1xPPV23 again (second PPV23 dose recommended ≥5 years after first PPV23 dose)
				HIV		
				Hypogammaglobulinemia		
				Immunodeficiency (congenital, acquired)		Investigations ongoing into necessity of further vaccinations
				Liquor fistula		
				Nephritic syndrome		
				Nephrotic syndrome prior to immunosuppressive therapy		
				Neurological disorder (in children)		
				Sickle-cell anemia		
				Transplantation (organ, subsequent to stem cell transplantation)		
				At risk		
				Body weight below third percentile (in infants and children)		
				Chronic cardiovascular disease (except hypertension)		
				Chronic respiratory disease		
				Cirrhosis		
				Diabetes		
				Metabolic disease		
				Neoplastic disease		
	PCV13/PPV23	National (2014)	All (≥50)	N/a	Private	Naïve
						PCV13 followed by PPV23 after 1 year
						Pre-vaccinated with PCV13
						After interval of ≥1 year 1xPPV23
						Pre-vaccinated with PPV23
						After interval of ≥2 years 1xPCV13
						Investigations ongoing into necessity of further vaccinations

Table 1 continued

Country	Recommended vaccine	Region (date of recommendations)	Population (age, years)	Definition of risk	Funding	Additional information
Belgium [29, 30]	PCV13/PPV23	National (2013)	High risk (≤17)	Asplenia	Private	PCV13 (schedule depending on age) followed by PPV23 (revaccination every 5 years for asplenia)
				Chronic disease (heart, lung, renal)		
				Cochlear implant		
				CSF leak		
				Diabetes (non-stable)		
				Immunodeficiency (congenital, immunosuppressant induced)		
				Metabolic disease		
			High risk (≥18)	Autoimmune disease/immune-mediated inflammatory disease	Private	High-risk populations PCV13 followed by PPV23 after at least 8 weeks and revaccination with PPV23 every 5 years Adults aged ≥50 years with certain co-morbidities and all ≥65 years Either PPV23 with 1 revaccination after 5 years or PCV13 followed by PPV23 after 8 weeks with 1 revaccination after 5 years (except >75 years who do not require revaccination)
				Asplenia		
				Cancer (hematological)		
				Cochlear implant		
				HIV		
				Immunodeficiency		
				Transplantation (organ)		
			At risk (≥50)	Alcoholism		
				Chronic disease (heart, kidney, liver, respiratory)		
				Smoking		
			All (≥65)	N/a		
Denmark [31]	PCV13	National (2012)	At risk (any age)	Asplenia (functional)	Limited subsidy (to cover vaccination of at-risk groups and some age groups)	For individuals at risk aged ≥6 years vaccination with PCV13 should be followed by 1 dose of PPV23 after ≥8 weeks
				Cochlear implant		
				CSF leak		
				History of IPD		
				HIV		
				Lymphoma		
				Splenectomy (completed/planned)		
				Transplantation (organ)		

Table 1 continued

Country	Recommended vaccine	Region (date of recommendations)	Population (age, years)	Definition of risk	Funding	Additional information
			At risk (<18)	Chronic lung disease		
				Cyanotic heart disease		
				Heart failure/insufficiency		
				Hypodynamic respiratory insufficiency		
				Immunodeficiency (excluding agammaglobulinemia and SCID)		
				Nephrotic syndrome		
				Palliative surgery for heart disease		
			At risk (18–65)	Chronic disease (heart, kidney, liver, lung)	Private	For individuals at risk vaccination with PCV13 should be followed by 1 dose of PPV23 ≥8 weeks after PCV13 vaccination
				Diabetes		
			All (≥65)	N/a		
Finland [32]	PCV13	National (2013)	High risk (≥5)	Asplenia (anatomical, functional)	Private (except stem cell transplantation patients)	PCV13 preferred in high-risk individuals (e.g., immunocompromised) and may be followed by PPV23. However, physicians can choose whether to give PCV13 or PPV23
				Cochlear implant		
				HIV		
				Immunodeficiency (congenital, acquired)		PCV13 is funded for stem cell transplantation patients of all ages
				Liquor fistula		
				Lymphoma		PCV13 may also be considered in healthy individuals of all ages
				Multiple myeloma		
				Nephrotic syndrome		
				Patients treated with systemic corticosteroids or other immunosuppressants		
				Transplantation (organ and tissue)		
	PPV23		At risk or in permanent institutional care (≥5)	Chronic disease (cardiac, pulmonary)		–
				Diabetes (type 1)		
				Hepatic insufficiency		
				Patients treated with systemic corticosteroids or other immunosuppressants		
				Renal insufficiency		
				Transplantation (organ, tissue)		
			All (≥65)	N/a		

Table 1 continued

Country	Recommended vaccine	Region (date of recommendations)	Population (age, years)	Definition of risk	Funding	Additional information
France [33]	PCV13	National (2013)	At risk (≥2)	Asplenia or hyposplenia	Public	For all at-risk individuals aged ≥2 years, PCV13 followed by PPV23 after ≥8 weeks In some cases the vaccination schedule may differ and there are slight differences for specific populations (for asplenic and immunosuppressed patients PCV is preferred), but PCV13 should be administered first in all cases For high-risk individuals aged ≥6 years to <50 years funding procedure ongoing
				Cancer treated by chemotherapy (solid tumor, hematological)		
				Cochlear implant or planned cochlear implant		
				HIV		
				Immunodeficiency (congenital)		
				Immunosuppressive therapy, biotherapy, or corticotherapy for autoimmune disease or chronic inflammation		
				Meningeal fistula		
				Nephrotic syndrome		
				Transplantation or waiting for transplantation (organ, hematopoietic stem cell)		
	PPV23		At risk (≥5)	Asthma (severe with continuous treatment)	Public	–
				Chronic liver disease (alcoholic or non-alcoholic origin)		
				Chronic respiratory failure		
				COPD		
				Cyanotic congenital heart disease		
				Diabetes (not balanced by diet)		
				Emphysema		
				Heart failure		
				Kidney failure		

Table 1 continued

Country	Recommended vaccine	Region (date of recommendations)	Population (age, years)	Definition of risk	Funding	Additional information
Germany [34]	PCV	Saxony [35] (updated January 2014)	At risk (>2)	Asplenia Autoimmune disease Bone marrow transplantation Chronic disease (heart, kidney, respiratory) CSF leaks, cochlea implant HIV Hematological diseases Immunodeficiency (primary) Metabolic disease Neurological diseases in children Occupational risk (laboratory personnel at risk of infection, medical personnel in contact with patients) Sickle-cell anemia Transplantation (organ)	Public	All infants from the age of 2 months to 5 years should receive PCV (vaccination should be started in the third month of life, according to schedule of vaccine manufacturer) PCV may be PCV10 or PCV13 for those aged 2–<5 years; PCV will be PCV13 for those aged ≥5 years. Children with persisting risk for pneumococcal infection should be vaccinated in the third year of life with PPV23 in addition to PCV (interval of at least 2 months after last vaccination with PCV) Non-vaccinated infants (aged ≥5 years), adolescents and adults should receive one dose of PCV or PPV23 (according to approval) PCV can be supplemented with PPV23 if protection against further serotypes is required (interval at least 4 years) In those pre-vaccinated with PPV23, catch-up vaccination with PCV is useful (interval at least 5 years) In at-risk individuals and those aged ≥60 years revaccination with PPV23 is possible (≥5 years for adults, ≥3 years for children aged <10 years)
			All (≥60)	N/a		
	PCV	National (PCV funding 2013; PCV recommendations 2014)	At risk (2–<5)	Chronic disease (e.g., heart, kidney, liver, respiratory diseases, metabolic disorders [e.g., diabetes], neurological diseases [e.g., cerebral pareses, seizure disorders]) Immunodeficiency (congenital, acquired, e.g., T cell, B cell or antibody deficiency, deficiency or functional disorders of myeloic cells [e.g., neutropenia, chronic granulomatosis, leukocyte adhesion or signal transduction defects], complement or properdin deficiency, functional hypersplenism or splenectomy, neoplastic diseases, HIV infection, bone marrow transplantation, immunosuppressive therapy [e.g., due to organ transplantation, autoimmune disease]) Anatomic risks, risks associated with foreign bodies for pneumococcal meningitis (e.g., liquor fistula, cochlea implant)		For this age group, PCV may be PCV10 or PCV13 For congenital or acquired immunodeficiencies, chronic renal diseases/nephrotic syndrome, revaccination can be considered every 5 years (for those aged >10 years) or every 3 years (for those aged <10 years)

Table 1 continued

Country	Recommended vaccine	Region (date of recommendations)	Population (age, years)	Definition of risk	Funding	Additional information
	PCV13/PPV23	National (PCV funding 2013; PCV recommendations 2014; PPV 1982)	At risk (≥5)	Chronic disease (e.g., heart, kidney, liver, respiratory diseases, metabolic disorders [e.g., diabetes], neurological diseases [e.g., cerebral pareses, seizure disorders]) Immunodeficiency (congenital, acquired, e.g., T cell, B cell or antibody deficiency, deficiency or functional disorders of myeloic cells [e.g., neutropenia, chronic granulomatosis, leukocyte adhesion or signal transduction defects], complement or properdin deficiency, functional hypersplenism or splenectomy, neoplastic diseases, HIV infection, bone marrow transplantation, immunosuppressive therapy [e.g., due to organ transplantation, autoimmune disease]) Anatomic risks, risks associated with foreign bodies (e.g., liquor fistula, cochlea implant)		For this age group, PCV will be PCV13 For congenital or acquired immunodeficiencies, chronic renal diseases/nephrotic syndrome, revaccination can be considered every 5 years (for those aged >10 years) or every 3 years (for those aged <10 years)
	PPV23	National (1998)	All (≥60)	N/a		
Greece [36]	PCV13	National (2011)	All (>50)	N/a	Public	–
Ireland [37]	PCV13/PPV23	National (2013)	Medium risk and high risk (2–<5)	Medium risk Children <5 years of age following IPD Chronic heart, lung, or liver disease Chronic renal disease or nephrotic syndrome Diabetes mellitus requiring insulin or oral hypoglycemic drugs Down syndrome High risk Asplenia, hyposplenia (including splenectomy, sickle-cell disease, hemoglobinopathies, and celiac disease) Candidates for, or recipients of, a cochlear implant Complement deficiency (particularly C1–C4) CSF leaks (congenital or complicating skull fracture or neurosurgery) Immunosuppressive conditions (e.g., some B and T cell disorders, HIV infection, leukemia, lymphoma) and those receiving immunosuppressive therapies Intracranial shunt Post-hematopoietic stem cell transplant Solid organ transplant	PCV13 supplied free of charge to all those in risk groups; individuals pay an administration fee	2–5 years: 1 or 2 doses of PCV13 at 2-month intervals followed by 1 dose of PPV23 ≥2 months after final PCV dose

Table 1 continued

Country	Recommended vaccine	Region (date of recommendations)	Population (age, years)	Definition of risk	Funding	Additional information
			High risk (5–<18; 18–64)	Asplenia, hyposplenia (including splenectomy, sickle-cell disease, hemoglobinopathies, and celiac disease)	PCV13 supplied free of charge to all those aged <18 years in risk groups; individuals pay an administration fee	>5–<18 years: 0, 1 or 2 doses of PCV13 followed by 1 dose of PPV23 ≥2 months after PCV
				Candidates for, or recipients of, a cochlear implant	PCV13 is not free of charge to those aged ≥18 years	
				Complement deficiency (particularly C1–C4)	PPV23 supplied free of charge to all those in risk groups; individuals pay an administration fee unless they have a medical or doctor-only card	
				CSF leaks (congenital or complicating skull fracture or neurosurgery)		
				Immunosuppressive conditions (e.g., some B and T cell disorders, HIV infection, leukemia, lymphoma) and those receiving immunosuppressive therapies		
				Intracranial shunt		
				Post-hematopoietic stem cell transplant		
				Solid organ transplant		
	PPV23		Medium risk (5–<18)	Children <5 years of age following IPD	Vaccine supplied free of charge to all those in risk groups; individuals pay an administration fee unless they have a medical or doctor-only card	1 Dose of PPV23
				Chronic heart, lung, or liver disease		
				Chronic renal disease or nephrotic syndrome		
				Diabetes mellitus requiring insulin or oral hypoglycemic drugs		
				Down syndrome		
			Medium risk (18–64)	Chronic heart, lung, or liver disease		–
				Chronic renal disease or nephrotic syndrome		
				Diabetes mellitus requiring insulin or oral hypoglycemic drugs		
				Smokers and alcoholics		
				Individuals with occupational exposure to metal fumes (i.e., welders)		
			All (≥65)	N/a		

Table 1 continued

Country	Recommended vaccine	Region (date of recommendations)	Population (age, years)	Definition of risk	Funding	Additional information
Italy	PCV13/PPV23	Basilicata [38] (2012)	At risk (any age)	Chronic disease (heart, liver [hepatic cirrhosis], respiratory)	Public	For at-risk adults aged <50 years, PCV13 is recommended in addition to PPV23. PPV23 should be administered after >8 weeks
				Metabolic disease		
			All (≥65)	N/a		
		Bolzano [39] (2013)	At risk (any age)	Alcoholism	Public	–
				Asplenia		
				Chronic disease (cardiac, liver, pulmonary)		
				Cirrhosis		
				Cochlear implant		
				Diabetes		
				HIV		
				Immunodeficiency		
				Immunosuppression (clinically significant)		
				Leukemia		
				Liquor fistula		
				Lymphoma		
				Multiple myeloma		
				Neoplastic spread		
				Nephrotic syndrome		
				SCID		
				Thalassemia		
				Transplantation (organ, bone marrow)		
			All (>65)	N/a		
		Cagliari (LHU Cagliari 8) [40] (2011)	At risk (≥50)	Asplenia	Public	PCV13 recommended in addition to PPV23
				Chronic disease (heart, kidney, liver, respiratory)		PPV23 to be administered 8 weeks following PCV13
				Cochlear implant		
				CSF leak		
				HIV		
				Immunodeficiency		
				Metabolic disease		
				Other pathologies predisposed to high IPD risk		
				Transplantation (organ)		

Table 1 continued

Country	Recommended vaccine	Region (date of recommendations)	Population (age, years)	Definition of risk	Funding	Additional information
		Emilia Romagna [41] (2014)	At risk and high risk (any age)	High risk	Public	High-risk individuals
				Asplenia		PCV13 recommended in addition to PPV23
				Chronic disease (kidney [renal failure])		PPV23 should be administered ≥8 weeks after PCV13; for bone marrow transplantation, 3 doses of PCV13 (interval 2 months); a fourth dose is recommended in case of chronic graft versus host disease
				Cochlear implant		
				CSF leak		
				Hemoglobinopathy		
				HIV		
				Immunodeficiency (acquired)		
				Immunosuppression (iatrogenic)		
				Leukemia		
				Lymphoma		
				Multiple myeloma		
				Neoplastic spread		
				Nephrotic syndrome		
				Transplantation (organ, bone marrow)		
				At risk		
				Alcoholism		
				Chronic disease (heart, liver [hepatic cirrhosis], respiratory)		
				Diabetes		
				Residents in an institution (e.g., nursing home) aged >65 years		
			In permanent institutional care (≥65)	N/a		
		Friuili–Venezia Giulia [42] (2012)	At risk (≥18)	Asplenia	Public	PCV13 recommended in addition to PPV23
				Chronic disease (heart, kidney [renal failure], liver [hepatic cirrhosis], respiratory)		At-risk individuals: PCV13, 2 doses 8 weeks apart (3 doses for bone marrow transplantation)
				CNS disease		
				Metabolic disease		
				Others		
			All (≥65)	N/a		

Table 1 continued

Country	Recommended vaccine	Region (date of recommendations)	Population (age, years)	Definition of risk	Funding	Additional information
		Lazio [43] (2012)	At risk (any age)	Asplenia	Public	–
				Chronic disease (heart, kidney [renal failure], liver [hepatic cirrhosis], respiratory)		
				CNS disease		
				Metabolic disease		
		Liguria [44] (2013)	At risk (any age)	Asplenia	Public	–
				Cancer (hematological)		
				Chronic disease (heart, kidney [renal failure], liver [hepatic cirrhosis], respiratory)		
				CSF leak		
				Diabetes		
				Immunodeficiency (congenital, acquired)		
				Neoplastic spread		
				Transplantation (organ, bone marrow)		
			All (>70)	N/a		
		Lombardia (LHU Milan) [45] (2012)	At risk and high risk (>18)	High risk	Public (PCV13 is available on medical prescription)	PCV13 recommended in addition to PPV23
				Asplenia		PPV23 should be administered 8 weeks after PCV13
				Chronic disease (renal)		Individuals already vaccinated with PPV23 should be vaccinated with PCV13 1 year after PPV23
				Cochlear implant		For adults aged <50 years PPV23 is recommended
				CSF leak		For adults aged ≥50 years PCV13 is recommended
				Hemoglobinopathy		
				HIV		
				Immunodeficiency (congenital, acquired)		
				Leukemia		
				Lymphoma		
				Multiple myeloma		
				Neoplastic spread		
				Previous IPD		
				Transplantation (organ, bone marrow)		
				At risk		
				Chronic disease (heart, liver, pulmonary)		
				Diabetes		

Table 1 continued

Country	Recommended vaccine	Region (date of recommendations)	Population (age, years)	Definition of risk	Funding	Additional information
			All (≥65)	N/a		PCV13 if not previously vaccinated
		Marche [46] (2013)	At risk (any age)	Asplenia	Public	–
				Chronic disease (heart, kidney disease [renal failure], respiratory)		
				Cochlear implant		
				CSF leak		
				Diabetes		
				Hepatic cirrhosis and chronic liver disease due to alcoholism		
				HIV		
				Immunodeficiency (congenital, acquired)		
				Immunosuppression (iatrogenic)		
				Leukemia		
				Lymphoma		
				Multiple myeloma		
				Neoplasia		
				Thalassemia		
				Transplantation (organ, bone marrow)		
		Piemonte [47] (2012)	At risk (>5)	Asplenia	Private	PCV13 + PPV23 6 months apart
				Chronic disease (heart [excluding hypertension], kidney [renal failure], liver, respiratory)		
				Cochlear implant		
				Complement deficiency		
				CSF leak		
				Diabetes (type 1)		
				Hemoglobinopathy		
				Immunodeficiency (congenital, acquired)		

Table 1 continued

Country	Recommended vaccine	Region (date of recommendations)	Population (age, years)	Definition of risk	Funding	Additional information
		Puglia [48] (2012)	At risk (≥50)	Asplenia	Public	–
				Chronic disease (heart, kidney [renal failure], liver [hepatic cirrhosis], respiratory)		
				Cochlear implant		
				CSF leak		
				Diabetes		
				Hemoglobinopathy		
				HIV		
				Immunodeficiency (congenital, acquired)		
				Leukemia		
				Lymphoma		
				Multiple myeloma		
				Neoplasia		
			Cohort (65, 70, 75)	N/a		
		Sicilia [49] (2012)	At risk (50–64)	Asplenia	Public	–
				Chronic disease (heart, kidney [renal failure], liver [hepatic cirrhosis], respiratory)		
				CNS disease		
				Metabolic disease		
			Cohort (65, 75)	N/a		
		Trento [50] (2012)	At risk or nursing home residents (any age)	Asplenia	Public	–
				Chronic cardiac disease		
				Chronic renal failure		
				Cochlear implant		
				COPD		
				Diabetes		
				HIV		
				Immunodeficiency (congenital)		
				Immunosuppression		
				Liquor leakage		
				Nephrotic syndrome		
				SCID		

Table 1 continued

Country	Recommended vaccine	Region (date of recommendations)	Population (age, years)	Definition of risk	Funding	Additional information
				All (>65)	N/a	
		Tuscany LHU [51] (Local Directive to GPs—April 2012) (2012)	At risk or in permanent institutional care (≥6)	Asplenia	Public	–
				Cardiac decompensation (severe)		
				Chronic disease (hematopoietic, liver)		
				Chronic renal failure		
				COPD		
				Diabetes		
				Immunodeficiency		
			All (≥50)	N/a		
		Umbria [52] (2012)	At risk or in permanent institutional care (≥50)	Asplenia	Public	–
				Chronic disease (heart, kidney [renal failure], liver [hepatic cirrhosis], respiratory)		
				CNS disease		
				Metabolic disease		
		Veneto [53] (2012)	At risk (any age)	Asplenia	Public	–
				Cancer (hematological, solid)		
				Chronic disease (heart, kidney [renal failure], liver [hepatic cirrhosis], respiratory)		
				CNS disease		
				Immunodeficiency (primary)		
				Metabolic disease		
				Transplantation (organ)		

Table 1 continued

Country	Recommended vaccine	Region (date of recommendations)	Population (age, years)	Definition of risk	Funding	Additional information
	PPV23	National [54] (2005)	At risk (any age)	Agammaglobulinemia	Public	–
				Asplenia		
				Asthma		
				Autoimmune disease		
				Cancer (hematological, solid tumor)		
				Chronic disease (heart, kidney, liver, respiratory)		
				Cyanotic heart disease		
				Immunodeficiency (primary)		
				Metabolic disease		
				SCID		
				Transplantation (organ)		
Luxembourg [55, 56]	PCV13	National (2011)	At risk (<5)	Asplenia	Private	–
				Chronic disease (heart, liver, renal, respiratory [excluding asthma])		
				Cochlear implant		
				CSF leak		
				Diabetes		
				HIV		
				Immunocompromised		
				Premature birth		

Table 1 continued

Country	Recommended vaccine	Region (date of recommendations)	Population (age, years)	Definition of risk	Funding	Additional information
	PPV23	National (2008)	At risk or in permanent institutional care (≥18)	Alcoholism		–
				Asplenia		
				Chronic disease (cardiovascular, renal, respiratory)		
				Cirrhosis		
				Cochlear implant		
				CSF leak		
				Diabetes		
				HIV		
				Liquor fistula		
				Lymphoma		
				Multiple myeloma		
				Nephrotic syndrome		
				Sickle-cell disease		
				Transplantation (organ)		
			All (>60)	N/a		
Netherlands [57]	PCV13/PPV23	National (2012)	At risk (any age)	Asplenia	Private	1 Dose of PCV13 followed by 1 dose of PPV23 after ≥8 weeks
						PPV23 should be repeated once after 5 years
Norway [58, 59]	PCV13	National (2013)	At risk (any age)	Asplenia	Public (for asplenia, HIV, and stem cell transplantation only)	PCV13 recommended only in addition to PPV23
				HIV		Administer PCV13 ≥8 weeks prior to PPV23
				Stem cell transplantation		For asplenia and HIV administer PPV23 in addition to PCV13
				Considered for following groups after collective evaluation of risk:		Repeat PPV23 every 5 years for asplenia and every 10 years for other risk groups
				B cell deficiency		
				Cancer (hematological)		
				Cochlear implant		
				CSF leak		
				Transplantation (organ, bone marrow)		

Table 1 continued

Country	Recommended vaccine	Region (date of recommendations)	Population (age, years)	Definition of risk	Funding	Additional information
	PPV23		At risk (any age)	Asplenia		
				B cell deficiency		
				Cancer (hematological)		
				Cochlear implant		
				CSF leak		
				HIV		
				Transplantation (organ, bone marrow)		
			All (≥65)	N/a		
Portugal [60]	PCV13	National (2010)	At risk and high risk (<5, 59 months)	High risk	Public	–
				Asplenia (anatomical, functional)		
				Cochlear implant or cochlear implant placement planned		
				Down syndrome		
				HIV infection		
				Premature birth (≤28 weeks)		
				Sickle-cell disease and other hemoglobinopathies		
				Presumable high risk		
				Acquired immunodeficiency		
				Immunosuppressive therapy, prolonged corticosteroid therapy, chemotherapy, or radiotherapy		
				Hematological cancer, mainly lymphocytic leukemia (acute and chronic), Hodgkin disease and multiple myeloma		
				Bone marrow donor		
				Chronic disease (cardiac [cyanotic congenital cardiopathy, heart failure], liver, pulmonary [excluding asthma, except patients on high doses of corticosteroids])		
				Chronic renal failure		
				Congenital immunodeficiency		
				Diabetes		
				CSF fistula (congenital malformation, cranial fracture, or neurosurgery procedure)		
				Nephrotic syndrome		
				Organ or bone marrow transplantation		

Table 1 continued

Country	Recommended vaccine	Region (date of recommendations)	Population (age, years)	Definition of risk	Funding	Additional information
	PPV23		At risk and high risk (2–17)	High risk		
				Asplenia (anatomical, functional)		
				Cochlear implant or cochlear implant placement planned		
				Down syndrome		
				HIV infection		
				Premature birth (≤28 weeks)		
				Sickle-cell disease and other hemoglobinopathies		
				Presumable high risk		
				Acquired immunodeficiency		
				Immunosuppressive therapy, prolonged corticosteroid therapy, chemotherapy, or radiotherapy		
				Hematological cancer, mainly lymphocytic leukemia (acute and chronic), Hodgkin disease and multiple myeloma		
				Bone marrow donor		
				Chronic disease (cardiac [cyanotic congenital cardiopathy, heart failure], liver, pulmonary [excluding asthma, except patients on high doses of corticosteroids])		
				Chronic renal failure		
				Congenital immunodeficiency		
				Diabetes		
				CSF fistula (congenital malformation, cranial fracture, or neurosurgery procedure)		
				Nephrotic syndrome		
				Organ or bone marrow transplantation		
Spain [61]	PCV13	National (2012)	At risk (≥50)	Cancer (hematological)	Public	–
				Chemotherapy or immunosuppressive treatment		
				HIV		
				Nephrotic syndrome		
				Renal insufficiency		
				Transplantation (organ, hematopoietic cell)		

Table 1 continued

Country	Recommended vaccine	Region (date of recommendations)	Population (age, years)	Definition of risk	Funding	Additional information
		Cataluña [62] (2014)	At risk (≥5)	Asplenia or asplenic dysfunction		
				Cancer (hematological)		
				Cochlear implant		
				CSF leak		
				HIV		
				Immunodeficiency (congenital, acquired)		
				Immunosuppressive treatment, including systemic steroids and radiotherapy		
				Nephrotic syndrome		
				Renal insufficiency		
				Sickle-cell disease		
				Transplantation		
		Galicia [63] (2012)	At risk (≥50)	Asplenia		
				Cancer (hematological)		
				Chemotherapy or immunosuppressive treatment		
				Chronic renal disease (stage ≥3)		
				Cochlear implant		
				CSF leak		
				HIV		
				Nephrotic syndrome		
				Transplantation (organ, hematopoietic cell)		
		Murcia [64] (2014)	At risk (≥6)	Asplenia or asplenic dysfunction		
				B or T cell deficiency		
				Cancer (hematological)		
				Chemotherapy or radiotherapy		
				Chronic liver disease (including cirrhosis)		
				Chronic renal insufficiency (advanced)		
				Complement deficiency		
				Hemodialysis		
				History of IPD		
				HIV		
				Phagocytosis dysfunction		
				Transplantation (organ, hematopoietic cell)		

Table 1 continued

Country	Recommended vaccine	Region (date of recommendations)	Population (age, years)	Definition of risk	Funding	Additional information
			At risk (6–50)	Cochlear implant		
				CSF leak		
		Basque Country [65] (2013)	At risk (≥50)	Asplenia		
				Cancer (hematological)		
				Chemotherapy or immunosuppressive treatment		
				Chronic renal insufficiency (advanced)		
				Cochlear implant		
				CSF leak		
				Hemodialysis		
				History of IPD		
				HIV		
				Immunodeficiency (congenital, acquired)		
				Transplantation (organ, hematopoietic cell)		
		Valencia [66] (2013)	At risk (≥18)	Asplenia or asplenic dysfunction		
				B or T cell deficiency		
				Cancer (hematological)		
				Chemotherapy or radiotherapy		
				Chronic renal disease (stage ≥3)		
				Complement deficiency		
				Cochlear implant		
				CSF leak		
				Hemodialysis		
				HIV		
				Nephrotic syndrome		
				Phagocytosis dysfunction		
				Transplantation (organ, hematopoietic cell)		

Table 1 continued

Country	Recommended vaccine	Region (date of recommendations)	Population (age, years)	Definition of risk	Funding	Additional information
		Madrid [67] (2013)	At risk (≥50)	Asplenia (including elective splenectomy and late complement component deficiency)		
				Cancer (hematological)		
				Chemotherapy or immunosuppressive treatment		
				Chronic alcoholism		
				Chronic liver disease		
				Cirrhosis		
				Coagulation factor concentrate recipients		
				Cochlear implant		
				CSF leak		
				Hemodialysis		
				HIV		
				Nephrotic syndrome		
				Renal disease (end-stage)		
				Renal insufficiency		
				Sickle-cell disease		
				Transplantation (organ, hematopoietic cell)		
		Navarra [68] (2013)	At risk (≥18)	Asplenia		
				Cancer (hematological)		
				Chemotherapy or immunosuppressive treatment		
				HIV		
				Nephrotic syndrome		
				Renal insufficiency (severe)		
				Transplantation (organ, hematopoietic cell)		
		Extremadura [69] (2013)	At risk (≥50)	Cancer (hematological)		
				Chemotherapy or immunosuppressive treatment		
				HIV		
				Nephrotic syndrome		
				Renal insufficiency		
				Transplantation (organ, hematopoietic cell)		

Table 1 continued

Country	Recommended vaccine	Region (date of recommendations)	Population (age, years)	Definition of risk	Funding	Additional information
	PPV23	All Spanish autonomous regions [70] (varies)	At risk or older adults in permanent institutional care (≥2 to ≤60/65)	Alcoholism Asplenia Cancer (hematological) Chronic disease (cardiovascular, respiratory) Cirrhosis Cochlear implant Diabetes HIV Nephrotic syndrome Renal insufficiency Sickle-cell disease Transplantation (organ)		Funded by Public Health of the different Spanish Regions Date of implementation differs between the 19 different autonomous regions
		Most Spanish autonomous regions [70] (varies)	All (≥60/≥65)	N/a		Recommended vaccination by age at time of influenza vaccination campaign Date of implementation varies between different regions
Sweden	PCV13/PPV23	Stockholm [71] (2013)	At risk (≥2)	Asplenia Cochlear implant Cystic fibrosis Immunosuppression (e.g., transplantation, receiving cytostatics or other medication severely affecting the immune system) Liquor fistula Nephrotic syndrome Transplantation (organ)	Public (for high-risk individuals)	Regional recommendations for high-risk individuals in Stockholm, PCV13 recommended followed by PPV23 after ≥8 weeks

Table 1 continued

Country	Recommended vaccine	Region (date of recommendations)	Population (age, years)	Definition of risk	Funding	Additional information
	PPV23	National [72] (1994)	At risk (≥2)	Agammaglobulinemia	Varies	Funding is decided by the local county council, in some areas vaccination of individuals aged ≥65 years is free of charge, in other areas it is partially subsidized, and in the remainder the full cost is paid by the individual
				Alcoholism		
				Asplenia		
				Asthma		
				Autoimmune disease		
				Cancer (hematological, solid tumor)		
				Chronic disease (heart, kidney, liver, respiratory)		
				Cyanotic heart disease		
				CNS disease		
				CSF leak		
				Hemodynamically significant residual lesion after surgery		
				Hemodynamic respiratory insufficiency		
				History of IPD		
				HIV		
				Immunodeficiency (primary)		
				Intracranial shunt		
				Metabolic disease		
				SCID		
				Sickle-cell disease and other hemoglobinopathies		
				Transplantation (organ)		
			All (≥65)	N/a		
United Kingdom	PCV13 [73]	National (2013)	At risk (<5)	Asplenia	Via the National Health Service	–
				Asthma (only if high-dose systemic steroids)		
				Cancer (hematological, solid tumor)		
				Chronic disease (heart, kidney, liver, respiratory)		
				Cochlear implant		
				CSF leak		
				Diabetes (excludes diet controlled)		
				HIV		
				Immunosuppression		
				Sickle-cell disease		
				Transplantation (organ)		

Table 1 continued

Country	Recommended vaccine	Region (date of recommendations)	Population (age, years)	Definition of risk	Funding	Additional information
			At risk—severely immunocompromised (≥5)	Genetic disorders severely affecting the immune system (e.g., IRAK-4, NEMO, complement deficiency)		
				Leukemia (acute, chronic)		
				Multiple myeloma		
				Transplantation (bone marrow)		
	PPV23 [73]	National (1992)	At risk (≥2)	Asplenia		
				Asthma (only if high-dose systemic steroids)		
				Cancer (hematological, solid tumor)		
				Chronic disease (heart, kidney, liver, respiratory)		
				Cochlear implant		
				CSF leak		
				Diabetes (excludes diet controlled)		
				HIV		
				Immunosuppression		
				Sickle-cell disease		
				Transplantation (organ)		
		National (2003)	All (≥65)	N/a		

CNS Central nervous system, *COPD* chronic obstructive pulmonary disease, *CSF* cerebrospinal fluid, *GPs* general practitioners, *HIV* human immunodeficiency virus, *IPD* invasive pneumococcal disease, *LHU* local health unit, *N/a* not applicable, *PCV* pneumococcal conjugate vaccine, *PPV* pneumococcal polysaccharide vaccine, *SCID* severe combined immunodeficiency

RECOMMENDATIONS OUTSIDE ROUTINE IMMUNIZATION PROGRAMS FOR CHILDREN FOR PNEUMOCOCCAL IMMUNIZATION IN WESTERN EUROPE

In addition to routine pneumococcal immunization programs in infants and children, most countries across Europe have further local or national recommendations (Table 1). Those without such recommendations may follow other guidelines, such as society guidelines or those from the Advisory Committee on Immunization Practices (ACIP; e.g., The Netherlands). Although generally falling within the prescribing information for the vaccines, pneumococcal immunization practices differ across Europe with regards to age groups and risk groups immunized, which vaccine (PPV versus PCV) is advised for which groups, and eligibility for reimbursement. The majority of the 16 Western European countries included in this article implement immunization programs with both age-based and risk-based elements. PPV23 is widely recommended across Western Europe; however, many countries have now included PCV in their pneumococcal immunization recommendations for certain groups of children and adults, either alone or in addition to PPV23. Figure 1 details the current adult national recommendations and reimbursement of PCV13.

Age-Based Elements of Pneumococcal Immunization Programs

Age-based recommendations (usually for older adults) form part of the full immunization programs across most countries in Western Europe. However, the recommended vaccine and the age group eligible for vaccination vary between countries (Table 1). For example, immunization programs recommending PPV23 are implemented in Luxembourg (age >60 years), Finland, Ireland, Norway, Sweden, UK (all age ≥65 years), and most autonomous regions of Spain (age ≥60/≥65 years). Immunization programs recommending PCV exist in Greece (PCV13; >50 years), Germany (Saxony only; PCV; ≥60 years), Denmark (PCV13; ≥65 years), and some regions of Italy, including Tuscany (PCV13; ≥50 years), Basilicata, Bolzano, and Trento (all PCV13; >65 or ≥65 years), Liguria (PCV13; >70 years), Puglia (PCV13; cohorts 65, 70, 75 years), and Sicilia (PCV13; cohorts 65, 75 years). Additionally, age-based immunization programs recommending PCV and/or PPV23 exist in Austria, Belgium, and some regions of Italy.

Risk-Based Elements of Pneumococcal Immunization Programs

Some countries/regions across Western Europe advise pneumococcal immunization in individuals with specific co-morbidities that are considered to place them at an increased risk of pneumococcal diseases, regardless of age. Such purely risk-based elements are implemented in the pneumococcal immunization programs in Denmark, Norway, Sweden, UK, and some regions of Italy (Basilicata, Bolzano, Emilia Romagna, Lazio, Liguria, Marche, Trento, and Veneto; see Table 1 for specific risk groups and recommended vaccines).

Risk-based elements of pneumococcal immunizations programs across Europe can be very complex. For example, the risk groups eligible for vaccination can vary by age group (e.g., Belgium, Denmark, France, Germany,

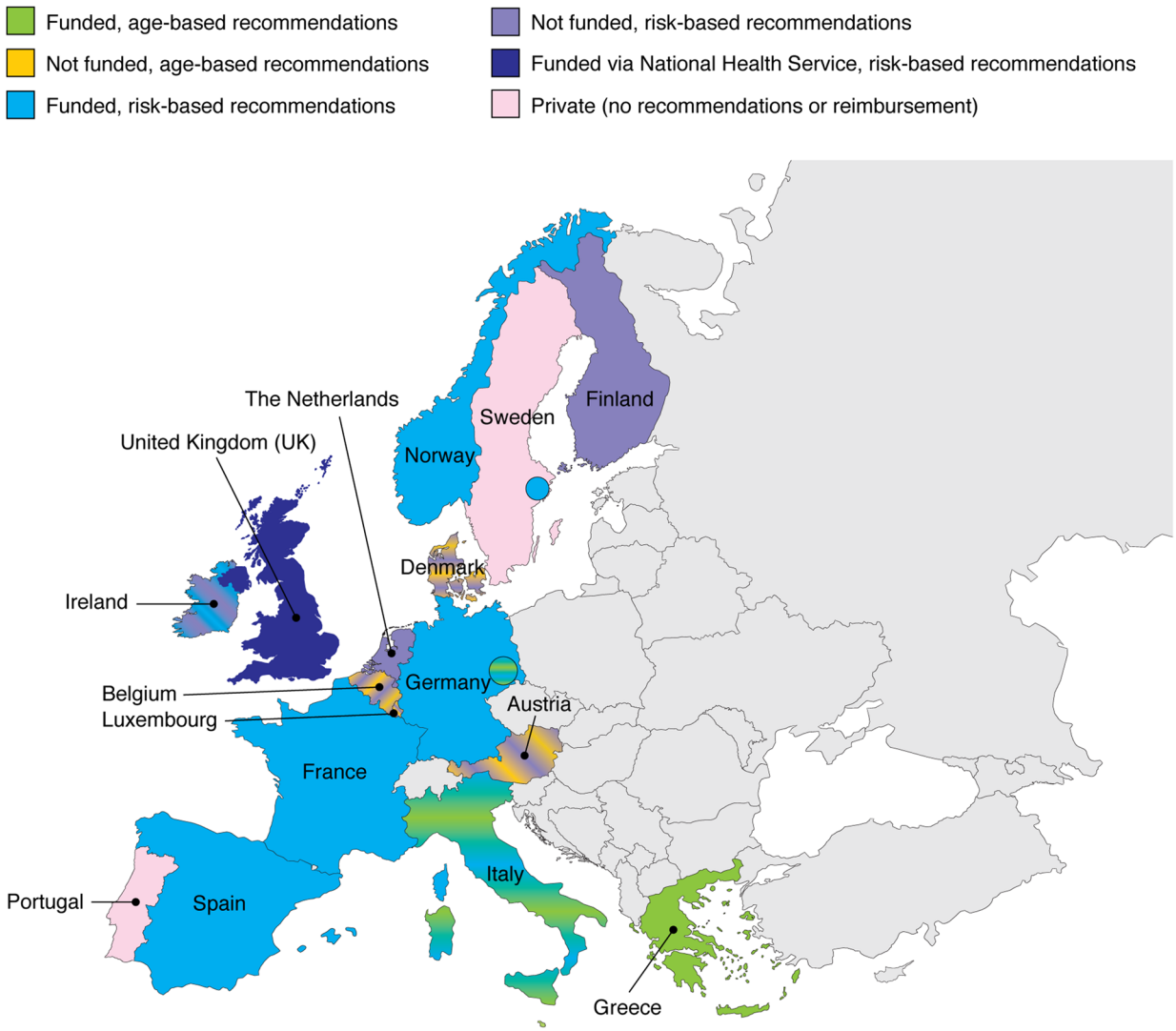

Fig. 1 European national recommendations and reimbursement of 13-valent pneumococcal conjugate vaccine (PCV13) in adults

Ireland, Luxembourg, Spain [Murcia], and the UK), different vaccines may be advised for different risk groups (e.g., Finland, France, Ireland, Norway, and the UK) or different vaccines may be advised in different age groups considered to be at risk of pneumococcal diseases (e.g., France, Germany, Ireland, Luxembourg, and Portugal). Many European countries/regions advise vaccination with both PCV and PPV23 in individuals at risk of pneumococcal diseases (see the Additional information column in Table 1). However, PCV is preferred over PPV23 in individuals at risk of pneumococcal diseases in Finland (all high-risk individuals) and France (immunosuppressed and asplenic individuals).

Heterogeneity in the Definition of Individuals Considered to be at Risk of Pneumococcal Diseases

There is a marked variation between countries concerning which individuals are considered to be at risk of pneumococcal diseases and their eligibility for immunization, with some countries including many more medical conditions (e.g., Austria, Ireland, and Portugal) than others (e.g., Norway and national recommendations for Spain). Consistent with the ACIP recommendations for immunization of children and adults at risk of pneumococcal diseases [15, 16], common conditions considered to place individuals at an increased risk in Europe include underlying co-morbidities such as chronic kidney (risk category in adults only), heart, liver or respiratory disease, metabolic diseases (e.g., diabetes mellitus), central nervous system diseases (e.g., cerebrospinal fluid leak) and immunocompromised individuals, including human immunodeficiency virus (HIV)-positive individuals, primary immunodeficiency, organ transplantation, asplenia (functional or anatomical), and hematological cancer. Other risk factors less commonly included are previous IPD (Denmark, Ireland [children under the age of 5 years], Italy [Lombardia], Spain [Murcia and Basque Country], and Sweden) and lifestyle risk factors such as alcoholism (Belgium, Ireland, Italy [Bolzano and Emilia Romagna], Luxembourg, Spain [Madrid and all autonomous regions], and Sweden), smoking (Belgium and Ireland), and residing in a nursing home or permanent institution (Finland, Italy [Emilia Romagna, Trento, Tuscany, Umbria], Luxembourg, and Spain [all autonomous regions]). Most European countries recommend initial vaccination with PCV13 for individuals at risk of pneumococcal diseases, followed by PPV23 vaccination ≥8 weeks later. Although broadly in line with ACIP recommendations [15, 16], age groups and timing of vaccination vary between countries.

Funding of Pneumococcal Immunization Programs

Further differences between countries across Europe also relate to public reimbursement for pneumococcal immunization. It is not funded for any age or risk groups in Austria, Belgium, or Luxembourg. Partial funding is available in Denmark, Finland (stem cell transplantation patients), Ireland (all individuals receiving PCV <18 years of age and some patients receiving PPV23 at risk of pneumococcal disease required to pay an administration fee; no funding for those aged ≥18 years), Norway (asplenia, HIV and stem cell transplantation), and Sweden (PCV13 funded in Stockholm county in individuals at high risk of pneumococcal diseases; PPV23 varies regionally between local councils). In contrast, full public funding is provided in France, Germany, Greece, Portugal, Spain, and Italy (except Piemonte).

Impact of Recommendations and Pneumococcal Immunization on Disease

The impact of pneumococcal immunization is highly dependent on vaccine uptake. Differences in pneumococcal immunization recommendations can impact the rates of immunization between countries. Risk-based immunization programs require the identification of individuals with specific diseases, while targeting of vaccination is simpler for age-based programs and thus they are easier to implement. Countries with age-based recommendations and public

reimbursement have demonstrated a higher uptake of PPV23 than countries immunizing only individuals at risk of pneumococcal diseases or countries without public reimbursement [17].

A meta-analysis of the efficacy of PPV in clinical trials demonstrated a high degree of heterogeneity between trials with little evidence of protection among elderly individuals or adults with chronic respiratory illness, for whom the vaccine was recommended [18]. Similarly, a meta-analysis of randomized controlled trials published up to June 2012 demonstrated the effectiveness of PPV in preventing IPD, but not all-cause pneumonia or mortality in the elderly [19]. However, data are conflicting. For example, in Japanese nursing home residents, PPV23 was shown to reduce the prevalence of pneumococcal pneumonia and all-cause pneumonia, as well as decrease mortality from pneumococcal pneumonia [20]. Although it is too early to assess the long-term impact of the inclusion of PCV in adult immunization programs, estimations can be made based on impact data from PCV7 childhood immunization programs, which have substantially reduced the burden of pneumococcal diseases in children [7, 8]. Emerging impact data in children show a decline in IPD due to serotypes contained in PCV13, following the introduction of PCV13 in Spain, England, and Norway [21–23]. Furthermore, it is anticipated that PCV13 will be cost-effective. Cost-effectiveness studies have predicted net savings of 102 million Euros over 5 years based on a model of a 65-year-old cohort immunization campaign in Spain [24], and between 7 million and 19 million Euros based on a model of an age-based PCV13 immunization program in adults aged ≥65 years in Italy [25].

CONCLUSION

Young children and adults aged ≥50 years are at particular risk of pneumococcal infection and despite childhood and adult immunization programs, burden of disease in adults remains high. Since the approval of PCV13 in adults aged ≥50 years in 2011, PCV13 is gradually being included in recommendations for adult pneumococcal immunization in addition to inclusion in childhood immunization programs within Western European countries. Ultimately, this should help to increase vaccine uptake and decrease the high burden of pneumococcal diseases in adults both through a direct effect of the vaccine and via a herd effect in unvaccinated individuals. Vaccine uptake and the effectiveness of pneumococcal immunization programs could be somewhat increased by raising awareness among healthcare professionals of the burden of pneumococcal diseases in adults, and improving the dissemination of recommendations for pneumococcal immunization. Moreover, the recommendations for pneumococcal immunization can be very complex and vary greatly between European countries in terms of age, risk, and which vaccine should be administered. When revising recommendations, public health officials should consider clarifying or simplifying recommendations, taking into account the merits of age-based versus risk-based recommendation for ease of implementation. This could help to increase vaccine uptake and thus reduce the burden of disease. Furthermore, the Community Acquired Pneumonia Immunization Trial in Adults (CAPiTA; ClinicalTrials.gov #NCT00744263), a randomized placebo-control trial involving >84,000 pneumococcal vaccination-naïve, community-dwelling adults ≥65 years of age, will provide valid data on the role of adult PCV13 vaccination in preventing vaccine-type

pneumococcal diseases, including pneumococcal community-acquired pneumonia and IPD, and thus has the potential to impact future pneumococcal vaccination recommendations [26, 27].

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