Pneumococcal vaccine side-by-side comparison

Updated November 2024

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What’s new?

The pneumococcal vaccine side-by-side comparison was last updated in December 2023. The November 2024 update includes the following changes:

- Removal of Prevnar 13 (PCV13) from the side-by-side table
- Addition of information for Capvaxive (PCV21)
- Updated ACIP recommendations from June and October 2024
- Updated pipeline information

Executive summary

Introduction

Pneumococcal vaccines have contributed to a substantial reduction in invasive pneumococcal disease (IPD) since they were first introduced in the late 1970s. The first vaccines were unconjugated pneumococcal polysaccharide vaccines (PPSV). PPSV23 (Pneumovax 23, Merck) was the primary pneumococcal vaccine on US market until 2000, when the first pneumococcal conjugate vaccine (PCV) was approved, PCV7 (Prevnar, Pfizer). PCVs stimulate antibody production through a different mechanism than PPSVs and provide a more robust and sustained immune response. PCV7 was later replaced by PCV13 (Prevnar 13, Pfizer) in 2013.

Two new PCVs were approved for use in adults in 2021, PCV15 (Vaxneuvance, Merck) and PCV20 (Prevnar 20, Pfizer). Both vaccines have since received expanded approval for use in pediatric patients. Following the expanded indication of PCV20 to pediatric patients, Pfizer discontinued PCV13 in early 2024. In June 2024, a third new PCV vaccine was approved – PCV21 (Capvaxive, Merck) – for use in adults 18 years of age and older only. The 3 new PCVs offer expanded serotype coverage compared with previously approved PCVs. PCV15 covers 2 additional serotypes compared with PCV13, while PCV20 covers 7 serotypes not found in PCV13. These 7 serotypes account for approximately 30% of the overall IPD in US adults and 29% to 32% in children. Despite covering 1 more total serotype than PCV20, PCV21 covers 11 unique serotypes not covered by PCV20. These serotypes uniquely covered by PCV21 account for approximately 37% of IPD in adults based on data from 2018 to 2022. Collectively, PCV20 covers serotypes responsible for approximately 56% of IPD in adults, while PCV21 provides coverage against roughly 83% of the serotypes causing IPD in adults. However, the serotypes responsible for IPD vary geographically and according to patient risk factors. Notably, PCV21 does not provide protection against serotype 4 which is responsible for at least 30% of IPD in certain adult populations in Alaska, Colorado, New Mexico, Oregon, and the Navajo Nation.

ACIP recommendations for pneumococcal vaccines

Recommendations on the use of pneumococcal vaccines in adult and pediatric patients from the Advisory Committee on Immunization Practices (ACIP) are published in *Morbidity and Mortality Weekly Report (MMWR).* However, more recent recommendations from the October 2024 ACIP meeting have not yet been published. See Table 2 and Table 3 in the summary of evidence section below for a synopsis of current guideline recommendations in adults. Table 4 provides an overview of current guideline recommendations of PCV-naïve pediatric patients.

Adult

- Use of PCV21 vaccine in adults (September 2024 *MMWR*)
- Pneumococcal vaccine for adults aged ≥ 19 years (September 2023 *MMWR*)

Pediatric

- Recommendations for use of PCV20 vaccine in children (September 2023 *MMWR*)
- Use of PCV15 vaccine among children (September 2022 *MMWR*)

Efficacy

The approval of PCV15, PCV20, and PCV21 were based on immunogenicity data. There are currently no published data evaluating the impact of these pneumococcal vaccines on clinical outcomes, such as IPD. An immune correlate of protection for clinical outcomes in adults has also not been established. In the absence of such a correlate, the Center for Biologics Evaluation and Research accepts demonstration of statistical noninferiority of opsonophagocytic activity (OPA) geometric mean titers (GMT) as evidence to support the approval of new pneumococcal vaccines. In vaccine studies in children, OPA titers are not typically the primary immunogenicity outcome of focus. Instead, an immunoglobulin G (IgG) concentration of greater than or equal to 0.35 mcg/mL is used as a threshold for determining adequate immune response. The test level of 0.35 mcg/mL is recommended by the World Health Organization as an immunogenicity bridge to the efficacy against IPD as demonstrated by PCV7.

Adult

PCV15 was compared with PCV13 in healthy adults 50 years of age and older in the PNEU-AGE trial. Noninferiority was demonstrated to all 13 shared serotypes based on OPA GMTs 30 days following vaccination. One shared serotype, and

both unique serotypes in PCV15, met the criteria for superiority compared with PCV13. PCV15 and PCV13, each followed by PPSV23 were evaluated in healthy adults 50 years of age and older (PNEU-PATH) and in adults 18 to 49 years of age at risk for pneumococcal disease (PNEU-DAY). Immune responses were numerically similar for most shared serotypes between PCV15 and PCV13, while the unique serotypes in PCV15 were numerically higher 30 days following vaccination. Immune responses for all 15 serotypes in PCV15 were comparable between groups following PPSV23, administered 6 to 12 months later.

PCV20 was compared with PCV13, each followed by placebo or PPSV23, respectively, 1 month later in patients 60 years of age and older. Noninferiority, based on OPA GMT, was demonstrated for all 13 shared serotypes between PCV20 and PCV13 and for 6 out of 7 shared serotypes between PCV20 and PPSV23. Noninferiority was also evaluated in a post hoc analysis in a phase 3 lot consistency study in adults 18 to 49 years of age. PCV20 was noninferior to PCV13 for all 13 shared serotypes 30 days following vaccination. In a phase 2 trial, adults 60 to 64 years of age received PCV20 or PCV13 followed 1 month later by either placebo or PPSV23, respectively. OPA GMTs 30 days following vaccination 1 were similar, but numerically lower for PCV20 compared with PCV13 for all 13 shared serotypes. OPA GMTs following vaccination 2 were numerically higher for PCV20 compared with PPSV23 for 6 out of 7 shared serotypes.

PCV21 was compared with PCV20 in adults 50 years of age and older. Noninferiority of PCV21 was demonstrated for the 10 shared serotypes in PCV20 based on OPA responses 30 days following vaccination. Superiority was demonstrated for all unique serotypes, with the exception of 15C, in PCV21 compared with PCV20. The predefined criterion for an immunobridging assessment (compared with the cohort of patients 50 years of age and older) was also met for all 21 serotypes in PCV21 in a cohort of patients 18 to 49 years of age. The immunogenicity of PCV21 has also been compared with PCV15 and PPSV23 in various patient populations including pneumococcal vaccine-experienced adults 50 years of age and older, adults 18 years of age and older with HIV, and adults 18 to 64 years of age at increased risk of pneumococcal disease. PCV21 elicited similar immune responses to comparator vaccines for shared serotypes and higher immune response to unique serotypes in each of these studies.

Pediatric

PCV15 was compared with PCV13 in infants, children, and adolescents for use as a 4-dose primary series (PNEU-PED). Interchangeability (PNEU-DIRECTION) and use in catch-up immunization series (PNEU-PLAN) were also evaluated. PCV15 demonstrated similar IgG responses for the 13 shared serotypes with PCV13 and higher responses to serotypes 22F and 33F across studies. PCV15 has also been evaluated in children with human immunodeficiency virus and recipients of hematopoietic stem cell transplant (HSCT).

PCV20 was evaluated in 3 key immunogenicity studies in pediatric patients. The pivotal phase 3 efficacy trial compared a 4-dose series with PCV20 with a 4-dose series of PCV13 at 2, 4, 6, and 12 to 15 months. Noninferiority of PCV20 was demonstrated for 8/13 shared serotypes with PCV13 and for 6/7 unique serotypes for the predefined IgG levels. Noninferiority of PCV20 was demonstrated for all 20 serotypes based on IgG concentration following dose 3 and dose 4. IgG responses were similar for the 13 shared serotypes, and higher for the 7 unique serotypes, between PCV20 and PCV13 when measured 1 month following dose 3 and dose 4 in a separate phase 2 study in infants given a 4-dose series. In a single-dose study in pediatric patients 15 months to < 18 years of age, immune response based on IgG was demonstrated for all vaccine serotypes following administration of PCV20.

Safety

Adult

PCV15, PCV20, and PCV21 were all generally well tolerated in clinical studies in adults. The most frequent adverse reactions common to each of these vaccines include injection-site reactions, myalgia, and fatigue. Injection-site reactions occurred more frequently with PCV15 vs. PCV13 in several studies. The reason for this difference is unknown; however, this difference was not considered to be clinically significant by the study authors as the reactions were generally mild in severity and of short duration. The overall rate of serious adverse events was low with each of the 3 vaccines in clinical studies. No serious adverse events were attributed to PCV15 or PCV20 in clinical studies in adults. Two serious adverse events, bronchospasm and injection-site cellulitis, were attributed to PCV21 in clinical studies.

Pediatric

Both PCV15 and PCV20 were generally well-tolerated in clinical studies in pediatric patients. The most common adverse reactions in infants reported with both vaccines were injection-site reactions and somnolence/drowsiness. The most common adverse reactions in children and adolescents reported with both vaccines are injection-site reactions and myalgia. The overall rate of serious adverse events was low and similar with control groups in clinical studies with both vaccines.

Summary

PCV15, PCV20, and PCV21 offer expanded serotype coverage compared with previously approved PCVs – PCV13 has been discontinued. PCV15 and PCV20 cover similar serotypes, with PCV20 covering 5 additional serotypes compared with PCV15; however, PPSV23 which is given in combination with PCV15, when used outside of the childhood immunization series, provides coverage for these 5 serotypes. PCV21 covers 11 unique serotypes compared with PCV20. Based on recent epidemiological data, PCV21 provides coverage against approximately 83% of serotypes responsible for IPD in adults compared with 56% with PCV20. However, the serotypes responsible for IPD vary by geography and patient risk factors. Notably, PCV21 does not provide protection against serotype 4 which is responsible for at least 30% of IPD in certain adult populations in Alaska, Colorado, New Mexico, Oregon, and the Navajo Nation. Additionally, the future epidemiological impact of the lack of coverage for the serotypes covered by PCV20 compared with PCV21 is unknown. Clinical trials have demonstrated noninferiority for immunogenicity endpoints for both PCV15 and PCV20 compared with PCV13 for each of the 13 shared serotypes and for PCV21 compared with the 10 serotypes shared with PCV20. PCV21 has also demonstrated comparable immune responses when compared with PCV15 in combination with PPSV23. Data on clinical outcomes for the new pneumococcal vaccines are not available. PCV15 and PCV20 are approved for use in both adults and pediatric patients greater than or equal to 6 weeks of age, while PCV21 is only approved for use in adults. ACIP does not specify a preferred PCV vaccine for any indication, except for hematopoietic stem cell transplant. ACIP recently lowered the age for the universal pneumococcal vaccination from 65 years of age to 50 years of age; this recommendation is specific to PCVs in PCV-naïve individuals and does not apply to PPSV23, unless given in combination with PCV15.

Looking forward

A clinical trial is currently underway to evaluate the use of PCV21 in children 2 through 17 years of age. Therefore, it is possible that the indication for this vaccine could be expanded in the future to include children in this age range with risk factors for IPD. However, Merck currently has no plans to pursue the expansion of PCV21 to include routine childhood immunization. Additional PCVs are in various stages in the pipeline. Another PCV21 vaccine (SP0202) from Sanofi is currently in phase 2 studies. Unlike, Merck's Capvaxive, the PCV21 from Sanofi covers the same 20 serotypes as Prevnar 20 with the addition of 1 extra serotype. Two 24-valent PCVs from GlaxoSmithKline (Pn-MAPS24v) and Vaxcyte (VAX-24) are currently in phase 2 studies. Vaxcyte is also evaluating a 31-valent PCV (VAX-31) with plans to begin a phase 2 study in the first quarter of 2025.

Pneumococcal vaccine side-by-side comparison

	Generic name (brand name)			
	PPSV23 (Pneumovax 23)[1]	**PCV20 (Prevnar 20)[2]**	**PCV15 (Vaxneuvance)[3]**	**PCV21 (Capvaxive)[4]**
Manufacturer	Merck	Pfizer	Merck	Merck
Approval date	1983	2021	2021	2024
FDA-approved indications				
Approved population	≥ 2 y	≥ 6 wks	≥ 6 wks	≥ 18 y
Indications	Active immunization for the prevention of pneumococcal disease caused by the 23 serotypes contained in the vaccine in adults ≥ 50 y or in persons ≥ 2 y at increased risk of pneumococcal disease.	• Active immunization for prevention of invasive disease caused by the 20 *S. pneumoniae* serotypes contained in the vaccine in individuals ≥ 6 wks. • Active immunization for prevention of pneumonia caused by the 20 *S. pneumoniae* serotypes contained in the vaccine in adults ≥ 18 y. • Active immunization for prevention of otitis media caused by *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F in children 6 wks to 5 y. *The indication for the prevention of pneumonia caused by serotypes 8, 10A, 11A, 12F, 15B, 22F, and 33F (ie, non-PCV13 serotypes) in individuals ≥ 18 y is approved under and accelerated approval pathway. Continued approval for this indication may be contingent on the verification and description of clinical benefit in a confirmatory trial.*	Active immunization for the prevention of invasive disease caused by the 15 *S. pneumoniae* serotypes contained in the vaccine in individuals ≥ 6 wks.	• Active immunization for prevention of invasive disease caused by the 21 *S. pneumoniae* serotypes, as well as 15C (due to cross protection), contained in the vaccine in adults ≥ 18 y. • Active immunization for prevention of pneumonia caused by all *S. pneumoniae* serotypes covered in the vaccine, except for 15B, in adults ≥ 18 y. *The indication for the prevention of pneumonia caused by the S. pneumoniae serotypes covered by PCV21 is approved under accelerated approval based on immune responses as measured OPA. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.*

	Generic name (brand name)			
	PPSV23 (Pneumovax 23)[1]	**PCV20 (Prevnar 20)[2]**	**PCV15 (Vaxneuvance)[3]**	**PCV21 (Capvaxive)[4]**
Pharmacology				
Mechanism of action	Induction of opsonophagocytic activity against the serotypes included in the vaccine			
Vaccine composition	Capsular polysaccharide antigen	Capsular polysaccharide conjugated to CRM197 carrier protein		
Immunology				
Antibody production mechanism[5]	T-cell independent	T-cell dependent		
Memory B cell production[5]	No	Yes		
Serotypes – see Table 1 below for full comparison of serotype coverage				
Shared	3, 7F, 19A, 22F, 33F			
Non-PPSV23	NA	6A		6A, 15A, 15C, 16F, 23A, 23B, 24F, 21, 35B
Non-PCV21	1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F, 2, 15B	1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F, 15B	1,4, 5, 6B, 9V, 14, 18C, 19F, 23F	NA
PCV21 unique	NA	NA	NA	15A, 15C (deOAc 15B), 16F, 23A, 23B, 24F, 21, 35B
Vaccination schedule				
Dose	0.5 mL	0.5 mL	0.5 mL	0.5 mL
Schedule	Please consult ACIP immunization schedules for recommended vaccine schedules for each of the available pneumococcal vaccines. **See addendums within immunization schedules for 2024 recommendations not yet reflected on the current schedules.** *These addendums are a new addition to immunization schedules that allows CDC to post official recommendations ahead of the typical annual February publication cycle.* • Child and adolescent immunization schedule (birth to 18 years of age) • Adult immunization schedule			
Preparation and administration				
Dilution required	No	No	No	No
Preparation	• Single-dose vial: Withdraw 0.5 mL using a sterile needle and syringe.	Shake single-dose, prefilled syringe to obtain a homogenous suspension. Attach a sterile needle to the prefilled syringe.		Attach a sterile needle to the prefilled syringe.

	Generic name (brand name)			
	PPSV23 (Pneumovax 23)[1]	**PCV20 (Prevnar 20)[2]**	**PCV15 (Vaxneuvance)[3]**	**PCV21 (Capvaxive)[4]**
	• Single-dose, prefilled syringe: Attach a sterile needle to the prefilled syringe.			
Administration	Intramuscular or subcutaneous	Intramuscular	Intramuscular	Intramuscular
Co-administration with other vaccines				
ACIP recommendations[6]	ACIP provides the following general guidance (not specific to the pneumococcal vaccines) on the spacing of inactivated vaccines: • Two or more inactivated vaccines may be administered simultaneously or at any interval between doses. • An inactivated vaccine may be administered simultaneously or at any interval between doses with a live vaccine. **Important exceptions** to the general guidance above may exist. These exceptions in addition to other available vaccine-specific information are summarized below.			
Influenza vaccine	May be co-administered			
Other pneumococcal vaccines	See Table 3 in text summary			
Other vaccines	• A reduced immune response to herpes zoster vaccine live (Zostavax) was observed with concurrent administration of PPSV23. **Separate administration of herpes zoster vaccine live and PPSV23 by at least 4 wks.** • Evaluation of coadministration of PPSV23 with COVID-19 vaccines is ongoing.[7]	• Concomitant administration of DTaP-HBV-IPV (Pediarix), *Haemophilus influenzae* type b (Hiberix), MMR (M-M-R II), or varicella virus vaccine, live (Varivax) did not demonstrate interferences with antibody responses to the concomitantly administered vaccines. • In adults ≥ 65 y who received 2 doses of Pfizer-BioNTech mRNA COVID-19 vaccine, slightly lower pneumococcal-specific OPA GMTs were reported when PCV20 was concomitantly administered; however the difference did not reach statistical significance. Data are not available on the use of PCV20 with other COVID-19 vaccines. Evaluation of concomitant administration	• Concomitant administration with the following vaccines were allowed in clinical trials evaluating a 4-dose series in infants and toddlers: DTaP-IPV-Hib (Pentacel), HepB recombinant (Recombivax HB), rotavirus vaccine (RotaTeq), HepA (VAQTA), MMR (M-M-R II), varicella virus vaccine (Varivax), and haemophilus influenzae type b (Hiberix). • No data are available in adults for the use with vaccines other than what is described above. • Evaluation of coadministration of PCV15 with COVID-19 vaccines is ongoing.[7]	• Data with concomitant administration of vaccines other than the influenza vaccine are not available. However, ACIP recommends that routine administration of pneumococcal vaccines with other age-appropriate vaccines at the same visit is acceptable in adults without contraindications.[8]

	Generic name (brand name)			
	PPSV23 (Pneumovax 23)[1]	**PCV20 (Prevnar 20)[2]**	**PCV15 (Vaxneuvance)[3]**	**PCV21 (Capvaxive)[4]**
		with PCV15 with other COVID-19 vaccines among adults ≥ 50 y is ongoing.[7]		
Injection-site	For vaccines given simultaneously, administer each injection at a different site and in separate syringes.			
Special Populations				
Pregnancy or lactation	• Human data from clinical trials have not established whether a vaccine-associated risk in pregnancy exists. Developmental toxicity studies in animals have not been conducted. • Data are not available for use in lactation.	• Human data in pregnancy are insufficient. A developmental toxicity study in rabbits found no evidence of fetal harm using a dose of 0.5 mL. • Data are not available for use in lactation.	• Human data in pregnancy are insufficient. Developmental toxicity studies in rats have not found evidence of fetal harm using a dose of 0.5 mL. • Data are not available for use in lactation.	• Human data in pregnancy are insufficient. Developmental toxicity studies in rats have not found evidence of fetal harm using a dose of 0.25 mL. • Data are not available for use in lactation.
Pediatric	PPSV23 is not approved for use in children < 2 y. Children in this age group do not develop an adequate immune response to the capsular types contained in this vaccine.	PCV20 is not approved for use in patients < 6 wks. The safety and effectiveness below this age have not been established.	PCV15 is not approved for use in patients < 6 wks. The safety and effectiveness below this age have not been established.	PCV21 is not approved for use in patients < 18 y. The safety and effectiveness below this age have not been established.
Safety				
Contraindications	Severe allergic reaction (eg, anaphylaxis) after a previous dose of or to any component of the vaccine.	• Severe allergic reaction (eg, anaphylaxis) after a previous dose of or to any component of the vaccine. • Severe allergic reaction (eg, anaphylaxis) to any diphtheria toxoid-containing vaccine.		
Precautions	• Appropriate treatment to manage immediate allergic reactions must be available. • Immunocompromised persons may have a diminished response to vaccination.			
	• Defer vaccination in persons with moderate to severe acute illness. • Use caution in persons in whom a systemic reaction would pose a significant risk, including individuals with severely compromised	Apnea has been observed in some infants born prematurely following vaccination		--

	Generic name (brand name)			
	PPSV23 (Pneumovax 23)[1]	**PCV20 (Prevnar 20)[2]**	**PCV15 (Vaxneuvance)[3]**	**PCV21 (Capvaxive)[4]**
	cardiovascular or pulmonary function. • This vaccine is not intended as a replacement for patients who require penicillin (or other antibiotic) prophylaxis against pneumococcal infection. • This vaccine may not effectively prevent pneumococcal meningitis in persons with chronic cerebrospinal fluid leakage.			
Adverse reactions	Most common are injection-site pain (60%), injection-site swelling/induration (20%), headache (18%), injection-site erythema (16%), asthenia and fatigue (13%), and myalgia (12%).	Most common are: • Children who received the 4-dose series at 2,4,6,12-15 mo: irritability (>60%), pain at the injection-site (>30%), drowsiness (>30%), decreased appetite, injection-site redness (>20%), injection site swelling (>10%), and fever (>10%). • Children 15 mo to 17 y who received a single dose: irritability (>60% in children < 2 y), pain at the injection-site (>50%), drowsiness (>40% in children <2 y), fatigue and muscle pain (>20% in children ≥ 2 y), decreased appetite (>20% in children < 2 y), injection-site swelling and injection-site redness (>10%), headache (>10% in children ≥ 5 y), and fever (>10% in children < 2 y). • Adults 18 to 59 y: injection-site pain (>70%), myalgia (>50%), fatigue (>40%), headache	Most common are: • Children who received the 4-dose series at 2,4,6,12-15 mo: irritability (57-63%), somnolence (24-48%), injection- site pain (26-40%), fever (13-20%), decreased appetite (14-19%), injection-site induration (13-15%), injection- site erythema (13-21%), and injection- site swelling (11-13%). • Children 2 to 17 y who received a single dose: between the ages of 2 and 17: injection site pain (55%), myalgia (24%), injection-site swelling (21%), injection-site erythema (19%), fatigue (16%), headache (12%), and injection-site induration (7%). • Adults 18 to 49 y: injection-site pain (76%), fatigue (34%), myalgia (29%), headache (27%), injection-site swelling (22%), injection-site erythema (15%) and arthralgia (13%).	Most common are: • Adults 18 to 59 y: injection-site pain (73%), fatigue (36%), headache (28%), myalgia (16%), injection-site erythema (14%), and injection-site swelling (13%). • Adults ≥ 50 y: injection-site pain (41%), fatigue (20%), and headache (11%)

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		(>30%), arthralgia (>10%), and injection-site swelling (>10%). • Adults ≥ 60 y: injection-site pain (>50%), myalgia (>30%), fatigue (>30%), headache (>20%), and arthralgia (>10%).	• Adults ≥ 50 y: injection-site pain (67%), myalgia (27%), fatigue (22%), headache (19%), injection-site swelling (15%), injection-site erythema (11%) and arthralgia (8%).	
Drug-drug interactions	• Immunosuppressive therapies: May reduce the response to immunization. • See *Co-administration with other vaccines* above for information specific to concomitant vaccine administration.	• Immunosuppressive therapies: May reduce the response to immunization. • See *Co-administration with other vaccines* above for information specific to concomitant vaccine administration.	• Immunosuppressive therapies: May reduce the response to immunization. • See *Co-administration with other vaccines* above for information specific to concomitant vaccine administration.	• Immunosuppressive therapies: May reduce the response to immunization. • See *Co-administration with other vaccines* above for information specific to concomitant vaccine administration.
How supplied				
Pre-filled syringe	0.5 mL	0.5 mL	0.5 mL	0.5 mL
Single-dose vial	0.5 mL	--	--	--
Formulation	Solution	Suspension	Suspension	Solution
Preservatives	0.25% phenol	None	None	None
Latex	No	No	No	No
Storage prior to use	2˚C to 8˚C	2˚C to 8˚C	2˚C to 8˚C	2˚C to 8˚C
Pre-filled syringe Cost (WAC)[9]	$117.08	$269.76	$236.36	$287.75
CPT code[10]	90732	90677	90671	90684
Medicare coverage[10]	Part B	Part B	Part B	Part B
Vizient contract	Yes	Yes	Yes	Yes

Abbreviations: ACIP = Advisory Committee on Immunization Practices; DTaP-HBV-IPV = diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B (recombinant) and inactivated poliovirus vaccine, combined; DTaP-IPV-Hib = diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus vaccine, Haemophilus influenzae type b, combined; COVID-19 = coronavirus disease 2019; CPT = Current Procedural Terminology; GMT = geometric mean titers; HepA = hepatitis A vaccine, inactivated; HepB = hepatitis B; mRNA = messenger ribonucleic acid; OPA = opsonophagocytic activity; PCV = pneumococcal conjugate vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine; PCV15 = 15-valent pneumococcal conjugate vaccine; PCV20 = 20-valent pneumococcal conjugate vaccine; PCV21 = 21-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine; WAC = wholesale acquisition cost

Summary of evidence

Introduction

Pneumococcal disease, caused by *Streptococcus pneumoniae,* is categorized as either invasive or non-invasive. Invasive pneumococcal disease (IPD) involves the infection of normally sterile sites and includes meningitis, septic arthritis, osteomyelitis, pneumonia with bacteremia, and bacteremia without a focus of infection. Common noninvasive infections include otitis media, sinusitis, and pneumonia without bacteremia. Pneumococcal pneumonia is the most common presentation of pneumococcal disease seen in adults. Pneumococci are also a common cause of bacterial pneumonia and otitis media in children. Approximately 150,000 hospitalizations occur annually in the United States (US) as a result of pneumococcal pneumonia.[11] The incidence of IPD is highest among children less than 2 years of age and adults 50 years of age and older.[12] Persons who are immunocompromised or who have certain chronic medical conditions, such as heart disease, lung disease, diabetes mellitus, alcoholism, liver disease, and smoking cigarettes, are also at increased risk of IPD.[11] Over 90% of IPD in adults occurs in persons 19 to 64 years of age with risk-based indications and in persons 65 years of age and older. Approximately 30,000 cases and 3,000 deaths related to IPD occurred in 2019.[13]

Pneumococcal vaccines have contributed to a substantial reduction in IPD. The first pneumococcal vaccine was approved in the US in 1977 and contained purified capsular polysaccharide antigens from 14 different serotypes**.** Six years later, a 23-valent pneumococcal polysaccharide vaccine (PPSV23, Pneumovax 23) was approved in the US, replacing the 14-valent vaccine. PPSV23 is 60% to 70% effective in preventing IPD from the serotypes contained in the vaccine.[11] However, there is a lack of consensus on the protection PPSV23 provides against nonbacteremic pneumonia.[11,14,15] PPSV23 was the primary pneumococcal vaccine on the US market until 2000, when the first pneumococcal conjugate vaccine (PCV) was approved, PCV7 (Prevnar). PCVs stimulate antibody production through a different mechanism than PPSVs and provide a more robust and sustained immune response.[11,13,16] Following the introduction of PCV7, IPD in children caused by the 7 serotypes covered by the vaccine declined by 99%. In 2010, PCV7 was replaced by a 13-valent PCV (PCV13, Prevnar 13). PCV13 contains the serotypes in PCV7, in addition to 6 other serotypes. IPD related to the 13 serotypes in PCV13 has declined by 90% in children since 2010. Adults 65 years and older have also benefited from the introduction of PCV13 through indirect effects, which account for over a 60% reduction in IPD in this population.[11] The direct effects of PCV13 were evaluated in approximately 85,000 adults 65 years of age and older in the CAPITA trial.[17] PCV13 demonstrated a 45.6% relative efficacy against vaccine-type community acquired pneumonia, a 45% relative efficacy against vaccine-type nonbacteremic pneumonia, and a 75% relative efficacy against vaccine-type IPD.

More than 100 immunologically distinct pneumococcal serotypes exist, of which a smaller subset are responsible for the majority of pneumococcal disease.[11,18] In 2021, 2 new PCVs – PCV15 (Vaxneuvance) and PCV20 (Prevnar 20) – were approved by the Food and Drug Administration (FDA) for use in adults 18 years of age and older. In June 2022, the labeled indications for PCV15 were expanded to include pediatric patients aged 6 weeks and older; PCV20 was expanded to include pediatric use in April 2023.[2,3] Following the expanded indication of PCV20 to include pediatric patients, Pfizer discontinued PCV13 at the beginning of 2024. In June 2024, a third new PCV vaccine was approved – PCV21 (Capvaxive) – for use in adults 18 years of age and older.[4] All 3 vaccines are indicated for the prevention of IPD; PCV20 and PCV21 are also indicated for prevention of pneumococcal pneumonia in adults ≥ 18 years of age. Prior to PCV20 and PCV21, PCV13 was the only pneumococcal vaccine in which prevention of pneumonia was a separate indication.[19] The approval of this indication for PCV20 for the 7, non-PCV13 serotypes contained in PCV20 was granted via an accelerated approval pathway – continued approval for this indication is contingent upon the results of a confirmatory phase 4 trial.[2] Similarly, this indication for PCV21 was approved via accelerated approval for all covered serotypes with the exception of serotype 15B.[4] The 3 new PCV vaccines offer expanded serotype coverage compared with previously approved PCVs. PCV15 covers 2 additional serotypes compared with PCV13. These serotypes, 22F and 33F, have been associated with increased rates of IPD in recent years.[20-24] Serotype 33F has also been associated with multi-drug resistance.[25] PCV20 covers 7 serotypes not found in PCV13, which account for approximately 30% of the overall IPD in US adults and 29% to 32% in children.[26-28] Despite covering 1 more total serotype than PCV20, PCV21 covers 11 unique serotypes not covered by PCV20. These serotypes uniquely covered by PCV21 account for approximately 37% of IPD in adults based on data from 2018 to 2022. Collectively, PCV20 covers serotypes responsible for approximately 56% of IPD in adults, while PCV21 provides coverage against roughly 83% of the serotypes causing IPD in adults. Conversely, PCV20 protects against 9 to 10 serotypes (15B is included in PCV20 but not PCV21; however, PCV21 includes de-O-acetylated 15B

which is structurally similar to 15C and expected to induce immune response to 15B and 15C) not covered by PCV21 which account for approximately 10% of IPD in adults.[29] While PCV21 on average, provides broader coverage against the currently prominent serotypes responsible for IPD in adults, there is variation based on geographic regions and other risk factors. For example, serotype 4 is notably not covered by PCV21, while it is covered by PCV15, PCV20, and PPSV23. In the overall US adult population, serotype 4 is responsible for approximately 4% of IPD.[30] However, in certain adult populations, serotype 4 accounts for at least 30% of IPD. Examples of such geographic regions include Alaska, Colorado, New Mexico, Oregon, and the Navajo Nation. Risk factors for serotype 4 IPD within these geographic areas include adults less than 65 years of age with underlying conditions such as chronic lung disease, cigarette smoking, injection drug use, alcoholism, and homelessness.[8] PPSV23 contains 4 serotypes not covered by PCV15 or PCV20 and 1 serotype (serotype 2) not covered by any of the PCV vaccines. However, these serotypes (2, 9N, 17F, 20) are less commonly associated with IPD in the US, collectively accounting for 3% to 14% of IPD depending on the age group.[16,21,23,27] Table 1 compares the serotype coverage provided by the 4 available pneumococcal vaccines in the US. The estimated proportion of IPD covered by vaccine-type and age-group in pediatric patients is illustrated in Figure 1. Figure 2 illustrates the proportion of IPD covered by PCV21 and PCV20 by age-group in adults.

Table 1. Pneumococcal vaccine serotypes[a]

	Serotype coverage																													
	1	3	4	5	6A[b]	6B	7F	9V	14	18C	19A	19F	23F	22F	33F	8	10A	11A	12F	15B[c]	2	9N	17F	20[d]	15A	15C[c]	16F	23A	23B	24F	31	35B
PCV15	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■																	
PCV20	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■												
PPSV23	■	■	■	■		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■								
PCV21		■			■		■				■			■	■	■	■	■	■			■	■	■	■	■	■	■	■	■	■	■

[a] Adapted from Loehr. ACIPJune 27, 2024 Meeting.[29]

[b] Cross-protection against 6C is expected from 6A

[c] PCV21 includes de-O-acetylated (deOAc) polysaccharide form of serotype 15B, which is structurally similar to serotype 15C; deOAc 15B induces OPA against both serotype 15B and serotype 15C

[d] PCV21 covers serotype 20A specifically

Guidelines

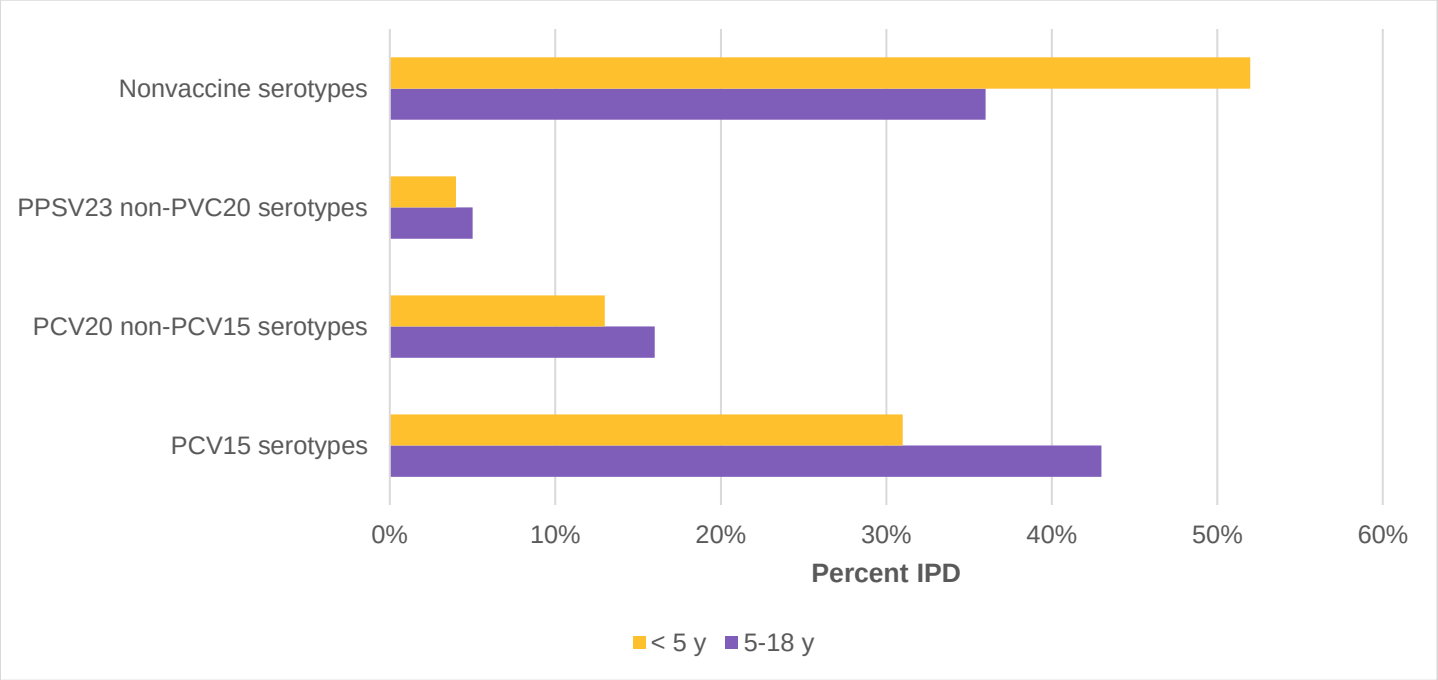
The Advisory Committee for Immunization Practices (ACIP) and Centers for Disease Control and Prevention (CDC) provide recommendations on the use of pneumococcal vaccines. These recommendations are published in *Morbidity and Mortality Weekly Report (MMWR)*. However, new recommendations following recent ACIP meetings may not yet be captured in current *MMWR* publications. This section will summarize the complete recommendations published in the current *MMWR* publications for pneumococcal vaccines as well as those recommendations made by ACIP that may not yet be reflected in *MMWR* publications. Recommendations for adults and pediatric patients will be reviewed separately.

Adult

Current pneumococcal recommendations in adults are addressed in the September 2023 *MMWR* and September 2024 *MMWR.*[7,8] These publications capture recommendations made by ACIP through June 2024. However, at the October 2024 ACIP meeting, a new recommendation was made regarding the use of pneumococcal vaccines in adults which is not yet reflected in *MMWR.* ACIP voted to lower the age for universal pneumococcal vaccination from 65 years of age and older to 50 years and older, specifically for *PCV-naïve individuals*.[31] The decision to lower the age to 50 years of age and older was based on a number of considerations including health equity, the prevalence of adults 50 to 64 years of age already with an indication for risk-based vaccination (estimated to be around 33% to 54%), simplicity of a uniform

recommendation (as compared with shared-clinical decision making for example), and data from economic modeling studies.[32] Table 2 summarizes the current recommendations for PCV-naïve adults. Table 3 summarizes current recommendations for individuals who have previously received pneumococcal vaccines.

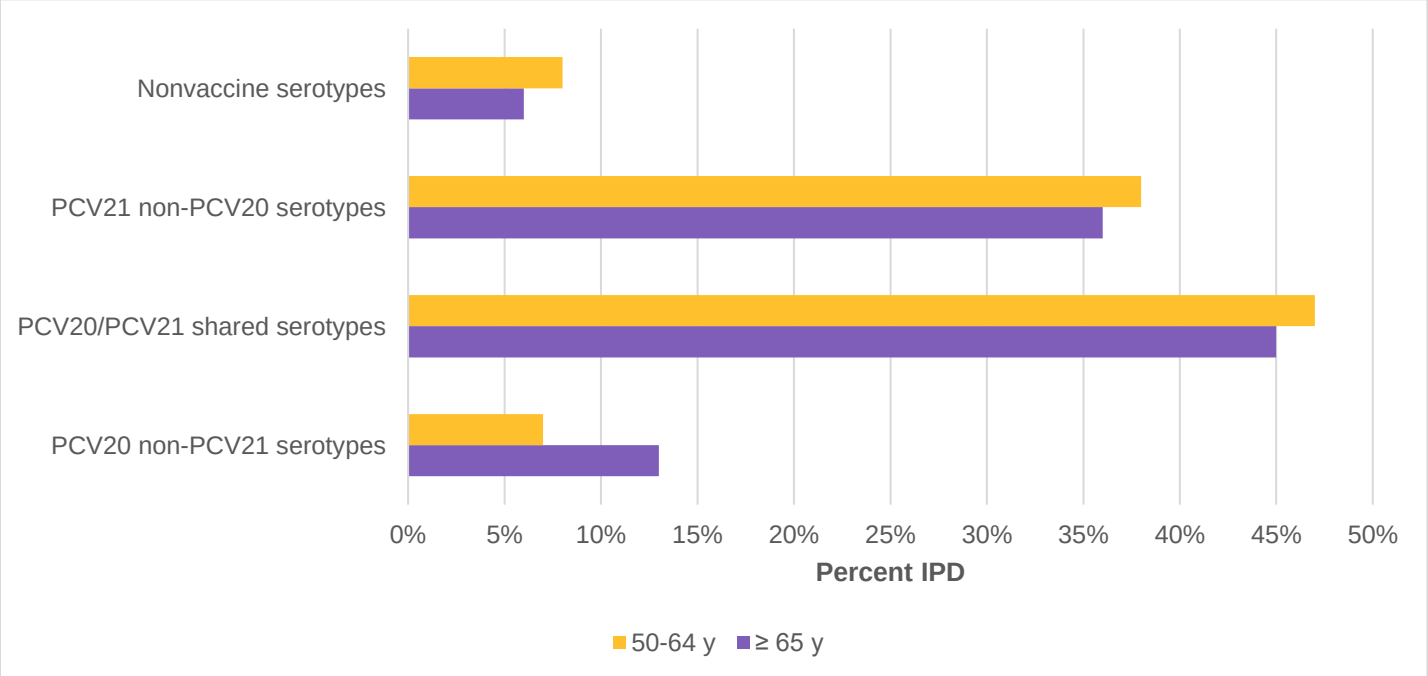
Figure 1. Proportion of IPD in pediatric patients by age-group and vaccine serotype coverage[a]



PPSV23 non-PCV20 serotypes = 2, 9N, 17F, 20; **PCV20 non-PCV15 serotypes** = 8, 10A, 11A, 12F, 15B **PCV15 serotypes:** 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F 22F, 33F, +6C (cross-protection from 6A)

[a] Pediatric data (2020-21) adapted from Gierke. ACIP February 22, 2023 meeting.[33]

Figure 2. Proportion of IPD in adults by age-group and vaccine serotype coverage[a]



PCV20 non-PCV21 serotypes = 1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F, 15B; **PCV20/PCV21 shared serotypes:** 3, 6A, 7F, 19A, 22F, 33F, 8, 10A, 11A, 12F, +6C (cross-protection from 6A); **PCV21 non-PCV20 serotypes:** 9N, 17F, 20A, 15A, 15C (deOAc 15B), 16F, 23A, 23B, 24F, 31, 35B

[a] Adult data (2018-2022) adapted from Loehr. ACIP June 27, 2024 meeting.[29]

Table 2. ACIP pneumococcal vaccine recommendations for PCV-naïve adults (or adults with unknown history)[7,8]

Risk Group	19 - 49 years	≥ 50 years
None or PCV7 at any age	No recommendation	PCV21 **or** PCV20 **or** PCV15 followed by PPSV23
Chronic medical condition[a]	PCV21[c] **or** PCV20[c] **or** PCV15 followed by PPSV23[c,d]	
Cochlear implant, cerebrospinal fluid leak		
Immunocompromising condition[b]		

[a] Includes chronic heart disease, chronic lung disease, diabetes mellitus, alcoholism, chronic liver disease, cirrhosis, cigarette smoking

[b] Includes functional or anatomic asplenia, sickle cell disease or other hemoglobinopathy, congenital or acquired immunodeficiency, human immunodeficiency virus infection, chronic renal failure, nephrotic syndrome, leukemia, lymphoma, Hodgkin disease, generalized malignancy, iatrogenic immunosuppression, solid organ transplant, multiple myeloma

[c] If administered prior to age 50 years, these vaccine doses do not need to be repeated in patients ≥ 50 years of age. *Note: this recommendation has not yet been explicitly stated since the recommended age has been lowered to ≥ 50 years, but it is assumed based on the previous recommendation in the September 2023 MMWR that these vaccines do not need to be repeated in individuals over ≥ 65 years*

[d] PPSV23 should be administered ≥ 1 year following PCV15. An interval of ≥ 8 weeks may be used in adults with immunocompromising conditions, cochlear implants, or cerebrospinal fluid leak.

Table 3. ACIP pneumococcal vaccine recommendations for pneumococcal vaccine-experienced adults[7,8]

Age or Risk Group	Vaccine previously received	Recommendation
Adults ≥ 65 years	PPSV23 only	A single dose of PCV21, PCV20, or PCV15 ≥ 1 year after PPSV23
	PCV13 only	A single dose of PCV21, PCV20, or PPSV23 ≥ 1 year after PCV13[a]
	PCV13 (any age) and PPSV23 < 65 years	A single dose of PCV21, PCV20, or PPSV23[b]
	PCV13 (any age) and PPSV23 ≥ 65 years	May give a single dose of PCV21 or PCV20 based on shared clinical decision-making (*optional*)[c]
Adults 19-64 years with chronic medical conditions[d]	PPSV23 only	A single dose of PCV21, PCV20, or PCV15 ≥ 1 year after PPSV23
	PCV13 only	A single dose of PCV21, PCV20, or PPSV23 ≥ 1 year after PCV13
	PCV13 and 1 dose of PPSV23	No vaccine recommended
Adults 19-64 years with an immunocompromising condition[e], cochlear implant, or cerebrospinal fluid leak	PPSV23 only	A single dose of PCV21, PCV20, or PCV15 ≥ 1 year after PPSV23
	PCV13 only	A single dose of PCV21 or PCV20 ≥ 1 year following PCV13 **or** a single dose of PPSV23 ≥ 8 weeks following PCV13[f]
	PCV13 and 1 dose of PPSV23	A single dose of PCV21, PCV20, or PPSV23 ≥ 5 years following the last pneumococcal vaccine[g]
	PCV13 and 2 doses of PPSV23	May administer a single dose of PCV21 or PCV20 ≥ 5 years following the last pneumococcal vaccine (*optional*)[h]

[a] When PPSV23 is used for adults with an immunocompromising condition, cochlear implant, or cerebrospinal fluid leak, administered PPSV23 ≥ 8 weeks following PCV13

[b] Administer PCV21 or PCV20 ≥ 5 years following the last pneumococcal dose. If PPSV23 is used, administer ≥ 1 year after PCV13 (may be ≥ 8 weeks for medical conditions outlined in footnote a) and ≥ 5 years following the previous dose of PPSV23

[c] Administer ≥ 5 years following last pneumococcal vaccine dose

[d] Includes chronic heart disease, chronic lung disease, diabetes mellitus, alcoholism, chronic liver disease, cirrhosis, cigarette smoking

[e] Includes functional or anatomic asplenia, sickle cell disease or other hemoglobinopathy, congenital or acquired immunodeficiency, human immunodeficiency virus infection, chronic renal failure, nephrotic syndrome, leukemia, lymphoma, Hodgkin disease, generalized malignancy, iatrogenic immunosuppression, solid organ transplant, multiple myeloma

[f] When PPSV23 is used instead of PCV21 or PCV20, another dose of either PCV21, PCV20, or PPSV23 is recommended ≥ 5 years after the first PPSV23 dose

[g] When PPSV23 is used, it should be given ≥ 8 weeks after PCV13 and ≥ 5 years after the first PPSV23 dose

[h] Specific to immunocompromised individuals

In the September 2023 *MMWR* specific recommendations are provided for multiple-dose series of PCV vaccine for adults who receive hematopoietic stem cell transplant (HSCT). These regimens are not reflected in the table above. HSCT was not specifically addressed in the current guidance issued for PCV21, but it is likely that PCV21 may be substituted in place of PCV20 outlined in the September 2023 *MMWR*; however, this has not been explicitly stated in ACIP guidance to date. Currently, adults who undergo HSCT are recommended to receive 3 doses of PCV20, 4 weeks apart starting 3 to 6 months after HSCT. A fourth dose of PCV20 is recommended ≥ 6 months after the third dose of PCV20 or ≥ 12 month after HSCT, whichever is later. If the pneumococcal vaccine series was started with PCV13 or PCV15, the 4-dose series can be completed by using PCV20 for the remaining doses (extra doses are not needed). If PCV20 is not available, 3 doses of PCV15 followed by PPSV23 ≥ 12 months following HSCT can be administered. A fourth dose of PCV15 can replace PPSV23 in patients with chronic graft-versus-host disease (GVHD) because these patients are less likely to respond to PPSV23.[7]

Pediatric

ACIP met in June 2022 to vote on recommendations for the use of PCV15 in pediatric patients.[34] In September 2022, the ACIP recommendations for the use of PCV15 in children were published in *MMWR.*[35] ACIP recommended PCV15 as an option alongside PCV13, without preference, across all clinical scenarios in which PCV13 was previously recommended.[34,35] In June 2023, ACIP voted to recommend the use of PCV20 as an option to PCV15.[36] These recommendations were subsequently published in *MMWR* in September 2023. Based on these latest recommendations, PCV15 and PCV20 are now the preferred PCV vaccines in pediatric patients.[37] PCV13 is no longer available in the US.

Additionally, indications for risk-based recommendations for PCV vaccines in pediatric patients were expanded in the most recent guidance from ACIP to include children with chronic kidney disease, chronic liver disease, and moderate persistent or severe asthma.[37] Previous risk conditions included cerebrospinal fluid leak; chronic heart disease; chronic lung disease; cochlear implant; diabetes mellitus; immunocompromising conditions (chronic renal failure or nephrotic syndrome; congenital or acquired asplenia or splenic dysfunction; congenital or acquired immunodeficiencies; diseases and conditions treated with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, Hodgkin disease, and solid organ transplant; human immunodeficiency virus (HIV) infection; and sickle cell disease and other hemoglobinopathies).[35]

The following are the current ACIP recommendations for the use of PCV15 and PCV20 in pediatric patients:[37]

- All children aged 2 to 23 months with no previous PCV vaccination are recommended to receive either PCV15 or PCV20 according to currently recommended PCV dosing and schedules (includes 4-dose series at ages 2, 4, 6, and 12 to 15 months; catch-up vaccination to complete primary PCV series in infants aged 7 to 11 months; and catch-up vaccination to complete primary PCV series in infants aged 12 to 23 months).
- Children aged 24 to 71 months with an incomplete vaccination status using either PCV13, PCV15, or PCV20 are recommended to receive either PCV15 or PCV20 according to currently recommended PCV dosing and schedules.
    - Healthy children aged 24 to 59 months with any incomplete PCV vaccination status are recommended to receive a single dose of either PCV15 or PCV20 ≥ 8 weeks after the last PCV dose.
    - Children aged 24 to 71 months with any risk condition who have not previously received a PCV or received any incomplete schedule of < 3 doses by age 24 months are recommend to receive 2 doses of either PCV15 or PCV20 ≥ 8 weeks apart between PCV doses.
    - Children aged 24 to 71 months with any risk condition who have received 3 doses of PCV, all before 12 months, are recommended to receive 1 dose of either PCV15 or PCV20 ≥ 8 weeks after the last PCV dose.
- For children 2 to 18 years with any risk condition who completed the recommended PCV series before age 6 years, if the recommended PCV doses were completed with ≥ 1 dose of PCV20, no additional doses of any pneumococcal vaccine are indicated. This recommendation may be updated as additional data become available. If the recommended PCV doses were completed using PCV13 or PCV15 (no PCV20), either a dose of PCV20 or ≥ 1 dose of PPSV23 is recommended (≥ 8 weeks following PCV13 or PCV15) to complete the recommended vaccine series. When PPSV23 is used instead of PCV20 for children aged 2 to 18 years with an immunocompromising condition, either PCV20 or a second PPSV23 dose is recommended ≥ 5 years after the first PPSV23 dose.

- For children aged 6 to 18 years with any risk condition who have not received any dose of PCV13, PCV15 or PCV20, a single dose of PCV15 or PCV20 is recommended ≥ 8 weeks after the most recent dose of pneumococcal vaccination (ie, if only PCV7 or PPSV23 previously given). When PCV15 is used, it should be followed by a dose of PPSV23 ≥ 8 weeks after the last PCV dose, if not previously given.

Table 4 summarizes the number of recommended PCV doses in PCV-naïve pediatric patients by age group and risk condition. PCV15 or PCV20 are the preferred PCV vaccines when available. For complete recommendations, refer to the September 2023 *MMWR*.[37]

Table 4. ACIP recommended PCV doses for PCV-naïve pediatric patients[37]

Age Group	Healthy[a]	Risk Condition[a,b]
2 to 6 months	**4 doses**: 3 doses 8 weeks apart; last dose at 12 to 15 months	
7 to 11 months	**3 doses**; 2 doses 8 weeks apart; last dose at age 12 to 15 months	
12 to 23 months	**2 doses**; 2 doses 8 weeks apart	
24 to 71 months	**1 dose** (up to 59 months only; routine use of PCV not recommended in healthy children ≥ 5 years of age)	**2 doses**; doses given ≥ 8 weeks apart[c]
6 to 18 years	**None**	**1 dose**[d]

[a] This table provides a summary of the number of recommended PCV doses for *PCV-naïve* pediatric patients by age group and risk condition for reference. Recommended doses may vary depending on receipt of previous PCV vaccines. For complete recommendations, refer to the September 2023 *MMWR*.

[b] Risk conditions include: cerebrospinal fluid leak; chronic heart disease; chronic kidney disease (excluding maintenance dialysis and nephrotic syndrome, which are included in immunocompromising conditions); chronic liver disease; chronic lung disease (including moderate persistent or severe persistent asthma); cochlear implant; diabetes mellitus; immunocompromising conditions (on maintenance dialysis or with nephrotic syndrome; congenital or acquired asplenia or splenic dysfunction; congenital or acquired immunodeficiencies; diseases and conditions treated with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, Hodgkin disease, and solid organ transplant; HIV infection; and sickle cell disease or other hemoglobinopathies).

[c] These children are also recommended to receive either a dose of PCV20 or ≥ 1 dose of PPSV23 if PCV20 is not given as part of their recommended PCV doses.

[d] When PCV15 is used, it should be followed by a dose of PPSV23 ≥ 8 weeks after the PCV15 dose if not previously given. When PCV20 is used, it does not need to be followed by a dose of PPSV23.

In addition to the above recommendations from ACIP, CDC provided the following additional guidance in the September 2023 *MMWR*:[37]

- If a child started the PCV series with PCV13, the child may complete the series with PCV15 or PCV20 without giving additional doses; the PCV series does not need to be restarted.
- For healthy children aged 24 to 59 months who completed the recommended PCV vaccination series with PCV13 (ie, 4 doses of PCV13 or another age-appropriate PCV13 schedule), a supplemental dose of PCV15 or PCV20 is not indicated.
- For children aged 6 to 18 years with a risk condition who have received PCV13 only at or after age 6 years, either a dose of PCV20 or ≥ 1 dose of PPSV23 is recommended ≥ 8 weeks after the last PCV13 dose. When PPSV23 is used instead of PCV20 for children aged 6 to 18 years with an immunocompromising condition, either PCV20 or a second PPSV23 dose is recommended ≥ 5 years after the first PPSV23 dose.
- Children aged < 19 years who are HSCT recipients are recommended to receive 4 doses of PCV20, starting 3 to 6 months after HSCT. Administer 3 doses of PCV20, 4 weeks apart starting 3 to 6 months after HSCT. Administer a fourth PCV20 dose ≥ 6 months after the third dose of PCV20 or ≥ 12 months after HSCT, whichever is later. If PCV20 is not available, 3 doses of PCV15 4 weeks apart, followed by a single dose of PPSV23 ≥ 1 year after HSCT, can be administered. For patients with GVHD who are receiving PCV15, a fourth dose of PCV15 can be administered in place of PPSV23 because these children are less likely to respond to PPSV23. These recommendations are consistent with the PCV recommendations in adult HSCT patients. These recommendations also update the recommendations from the September 2022 *MMWR* in which the PCV15/PPSV23 regimen was recommended. Based on these recommendations, PCV20 is preferentially recommended in this patient population when available.

For a complete tabular view of the updated pediatric pneumococcal vaccine recommendations outlined above, please refer to the September 2023 *MMWR*.

Clinical efficacy

A literature review was conducted using PubMed, Embase, and ClinicalTrials.gov to identify key studies evaluating immunogenicity of PCV15 and PCV20 in both adults and children and PCV21 in adults. Product labeling and FDA Medical Reviews for each vaccine were also reviewed to identify additional studies of interest. Studies evaluating the efficacy of PCV13 and PPSV23 were not included, as the place in therapy for these vaccines has been previously well-established by ACIP; additionally, PCV13 is no longer available in the US.

There are currently no studies that evaluate the impact of PCV15, PCV20, or PCV21 on clinical outcomes, such as nonbacteremic pneumonia or IPD. Instead, the efficacy data for these new vaccines are focused on immunogenicity outcomes. The primary immunogenicity outcome of interest across trials in adults for PCV vaccines was most commonly opsonophagocytic activity (OPA). Opsonin-dependent phagocytosis is the primary mechanism of protection against pneumococcal infection. OPA provides a functional measure of activity of anti-pneumococcal antibodies and is considered a strong *in vitro* correlate of protection.[18,38,39] However, an immune correlate of protection for clinical outcomes (eg, IPD) has not been established. In the absence of such a correlate, the Center for Biologics Evaluation and Research accepts demonstration of statistical noninferiority of OPA titers as evidence to support the approval of new pneumococcal vaccines.[18,38] OPA titers for PCV vaccines in clinical trials were commonly compared using the OPA geometric mean titer (GMT) ratios for the different shared serotypes with an active-control. Other measures of immunogenicity commonly evaluated in trials for pneumococcal vaccines in adults include the geometric mean concentration (GMC) of serotype-specific antibodies, geometric mean fold rise (GMFR) in the OPA titer or GMC, and the proportion of patients who demonstrated a 4-fold or greater rise in the OPA titer for the different serotypes. Historically, a 4-fold rise over baseline values in antibody titers has been defined as an adequate immune response.[40] In vaccine studies in children, OPA titers are not typically the primary immunogenicity outcome of focus. Instead, an immunoglobulin G concentration of greater than or equal to 0.35 mcg/mL is used as a threshold for determining adequate immune response. The test level of 0.35 mcg/mL is recommended by the World Health Organization as an immunogenicity bridge to the efficacy against IPD as demonstrated by PCV7.[41] Most immunogenicity outcomes were evaluated 30 days following vaccination. For studies that included PPSV23, the time frame for evaluating immunogenicity ranged from 2 to 13 months. As a result, long-term immunogenicity data are not available.

PCV15 (Vaxneuvance)

Adult

The majority of studies for PCV15 evaluated vaccine immunogenicity in healthy adults with stable medical conditions. Patients were generally excluded if they had previously received any other pneumococcal vaccine, had a history of IPD, or were immunocompromised. Noninferiority was demonstrated for all 13 shared serotypes based on OPA GMT ratios 30 days following vaccination in the PNEU-AGE trial[42], a phase 3 trial that compared PCV15 with PCV13 in 1,202 healthy adults 50 years of age and older. Additionally, the OPA GMT for serotype 3, a shared serotype, also met the criteria for superiority, along with the 2 unique serotypes, 22F and 33F. Serotype 3 is one of the more common serotypes covered by PCV13 that is associated with IPD.[27] PNEU-AGE is the only published trial in adults that was designed to evaluate noninferiority. The immunogenicity outcomes evaluated in other key trials were descriptive in nature. PNEU-PATH[12] compared PCV15 with PCV13, each followed by PPSV23 12 months later, in 652 healthy adults 50 years of age and older. PCV15 and PCV13 elicited comparable immune responses, assessed via OPA GMT ratios, for all 15 serotypes included in PCV15 at 30 days following PPSV23. PNEU-DAY[43] evaluated PCV15 vs. PCV13, each followed by PPSV23 at 6 months, in 1,515 immunocompetent adults 18 to 49 years of age at increased risk of pneumococcal disease. OPA GMTs at 30 days following PCV were similar for the 13 shared serotypes. Two serotypes were numerically lower in the PCV15 group compared with individuals who received PCV13. OPA GMTs for all 15 serotypes in PCV15 were similar between treatment groups following PPSV23. One phase 2 trial[24] compared PCV15 with PCV13 in 253 adults 65 years and older who had previously received PPSV23 at least 1 year ago. Immunogenicity, assessed via OPA GMT and GMC, was similar for the 13 shared serotypes and higher with PCV15 compared with PCV13 for the 2 unique serotypes. PNEU-WAY[44] compared PCV15 and PCV13, each followed by PPSV23 8 weeks later, in 302 adults 18 years of age and older with HIV infection who were on stable antiretroviral therapy. OPA GMTs at 30 days following PCV were comparable for 10 out of 13 shared serotypes. The OPA GMT for serotype 4 was numerically lower, while serotypes 3 and 18C had

numerically higher OPA GMTs for PCV15 compared with PCV13. OPA GMTs for nonshared serotypes were higher with PCV15. Following PPSV23, immune responses were comparable between the 13 shared serotypes.

Pediatric

PNEU-PED[45] is the pivotal trial that compared PCV15 versus PCV13 for use as a 4-dose primary series in 1,720 healthy infants. The primary efficacy outcomes were the noninferiority for IgG response rate (IgG ≥ 0.35 mcg/mL) at day 30 following dose 3 (lower bound of the 95% CI had to exceed -10%) and IgG GMC 30 days following dose 3 and 4 (lower bound of the 95% CI for the IgG GMC ratio for PCV15/PCV13 had to be > 0.5). PCV15 was non-inferior to PCV13 for all 13 shared serotypes based on IgG response rate; IgG response for serotypes 22F and 33F was superior with PCV15. Noninferiority for the IgG GMC was also demonstrated for 12 of the 13 shared serotypes following dose 3; following dose 4, noninferiority criteria were met for all 13 shared serotypes. PNEU-DIRECTION[46] evaluated the interchangeability of PCV15 and PCV13 as part of the 4-dose primary immunization series in 900 infants randomized 1:1:1:1:1 to a mixture of vaccine regimens. The primary immunogenicity outcome was the IgG GMC 30 days following dose 4 in the vaccine series. Based on IgG GMC ratios, the serotype-specific IgG GMCs were generally comparable across the 5 groups administered mixed vaccine regimens. Serotype-specific immune responses, assessed by the proportion of patients achieving IgG ≥ 0.35 mcg/mL, was also similar across groups. PNEU-PLAN[47] compared PCV15 with PCV13 for catch-up vaccination in 606 health infants, children, and adolescents. The primary immunogenicity outcome was the IgG GMC, evaluated in the per protocol population, at 30 days following PCV15 or PCV13. Across the age groups, IgG GMC following PCV15 was generally comparable for the 13 shared serotypes and higher for 22F and 33F. PNEU-WAY PED[48] compared PCV15 with PCV13, each followed by PPSV23 8 weeks later, in 400 children and adolescents with human immunodeficiency virus aged 6 to 17 years. The primary immunogenicity outcome, evaluated in the per protocol population, was the IgG GMC at 30 days following PCV15 or PCV13. IgG GMC following PCV15 was generally comparable for the 13 shared serotypes and higher for 22F and 33F. PCV15 was also compared with PCV13 in 277 children and adults who were recipients of allogenic hematopoietic stem cell transplant (allo-HSCT) in PNEU-STEM PED.[49] In this study, patients were administered PCV15 or PCV13 at day 1, 30, and 60 following allo-HSCT. PPS23 was given 12 months following allo-HSCT in both groups. The primary endpoint was the IgG GMC at 30 days following dose 3 of PCV15 or PCV13. IgG GMC was comparable for shared serotypes and higher for serotypes 22F and 33F. OPA GMTs, IgG GMFRs, and OPA GFMRs were also comparable.

PCV20 (Prevnar 20)

Adult

Similar to PCV15, studies for PVC20 primarily evaluated vaccine immunogenicity in healthy adults with stable medical conditions. Patients were generally excluded if they had previously received any other pneumococcal vaccine, had a history of IPD, or were immunocompromised. PCV20 was compared with PCV13 in a pivotal trial[50] of 3,880 adults 18 years of age and older. Study participants were divided into 1 of 3 age-based cohorts. Cohort 1 patients (60 years of age and older) were randomized to receive PCV20 or PCV13 followed by placebo or PPSV23 1 month later, respectively. Cohort 2 (50 to 59 years of age) and Cohort 3 (18 to 49 years of age) patients received PCV20 or PCV13 alone. The primary immunogenicity objectives were to evaluate noninferiority for the 13 shared serotypes between PCV20 and PCV13 and for the 7 shared serotypes between PCV20 and PPSV23 in Cohort 1. Noninferiority was demonstrated for all 13 shared serotypes between PCV20 and PCV13 and for 6 out of 7 shared serotypes between PCV20 and PPSV23 in Cohort 1. Noninferiority criteria were not met for serotype 8; however, 77.8% of patients achieved a 4-fold or greater rise in the OPA titer. Interestingly, OPA GMTs for PCV20 were numerically lower for all but 1 of 13 shared serotypes compared with PCV13, while OPA GMTs were numerically higher for all but 1 of 7 shared serotypes compared with PPSV23. The clinical significance of these differences is unclear. OPA GMTs to all 20 serotypes in both Cohort 2 and Cohort 3 were noninferior to the response observed in Cohort 1 in patients who received PCV20.[2,38,50] A phase 3, lot consistency study[51] was conducted in 1,710 healthy adults 18 to 49 years of age who were randomized to received 1 of 3 lots of PCV20 or PCV13. The primary objective in this trial was to evaluate equivalency in immune response across the 3 lots of PCV20. However, an exploratory post-hoc analysis to evaluate noninferiority of PCV20 compared with PCV13 was also performed. Noninferiority was demonstrated for all 13 shared serotypes based on OPA GMT ratios 30 days following vaccination. Finally, a phase 2 trial[16] in 444 healthy adults 60 to 64 years of age compared PCV20 with PCV13 followed by either placebo or PPSV23 1 month later. Immunogenicity analyses were descriptive in nature. OPA GMT and GMFR at

30 days following vaccination 1 were similar, but numerically lower for PCV20 compared with PCV13 for all 13 shared serotypes. For the 7 shared serotypes between PCV20 and PPSV23, OPA GMT and GMFR 30 days following vaccination 2 were numerically higher for PCV20 compared with PPSV23 for all serotypes except serotype 8.

Pediatric

Three key studies[52-54] evaluated the immunogenicity of PCV20 in pediatric patients. Senders et al[52] conducted a phase 2, double-blind, active-controlled study in 460 infants randomized to receive a 4-dose series with either PCV20 or PCV13 at 2, 4, 6, and 12 months of age. Immunogenicity, assessed by serotype-specific IgG concentrations, was evaluated as a secondary endpoint. IgG GMCs were similar for the 13 shared serotypes between PCV20 and PCV13 when measured 1 month following dose 3 and dose 4. Responses to individual serotypes were generally numerically lower with PCV20 compared with PCV13; however the IgG GMC was ≥ 0.35 mcg/mL, the accepted threshold for defining adequate immune response to pneumococcal vaccines in pediatric patients, for all 13-shared serotypes with PCV20. The IgG GMC to the 7 unique serotypes was higher with PCV20 compared with PCV13 following dose 3 and dose 4, as expected. The pivotal phase 3 efficacy trial[53] was a multicenter, randomized, double-blind study comparing a 4-dose series with PCV20 with a 4-dose series of PCV13 at 2, 4, 6, and 12-15 months in 1,997 infants. Noninferiority of the percent of participants with IgG above predefined levels (≥ 0.35 mcg/mL for most serotypes) was evaluated following dose 3, using a noninferiority margin of -10%. Noninferiority of PCV20 was demonstrated for 8/13 shared serotypes with PCV13 and for 6/7 unique serotypes for the predefined IgG levels. Noninferiority of PCV20 was demonstrated for all 20 serotypes for the IgG concentration GMR following dose 3 and dose 4. PCV20 was also evaluated in a single-dose study[54] in 831 pediatric patients 15 months to < 18 years of age previously vaccinated with ≥ 3 doses of PCV13. IgG GMC was evaluated 1 month following PCV20; immune responses were demonstrated for all vaccine serotypes.

PCV21 (Capvaxive)

Adult

Studies for PCV21 primarily evaluated vaccine immunogenicity in healthy adults with stable medical conditions. Patients were generally excluded if they had previously received any other pneumococcal vaccine, had a history of IPD, or were immunocompromised. STRIDE-3[55] was the pivotal study which evaluated PCV21 in 2,663 adults 18 years of age and older with or without stable medical conditions who were pneumococcal vaccine naïve. Study participants were enrolled in 1 of 2 cohorts. Cohort 1 consisted of adults 50 years of age and older randomized to receive either PCV21 or PCV20. Cohort 2 included patients 18 to 49 years of age randomized to PCV21 or PCV20. The primary outcomes assessed immunogenicity based on OPA responses 30 days following vaccination. In cohort 1, the criteria for noninferiority compared with PCV20 for the 10 shared serotypes were met. Criteria for superiority were met for 10 of the 11 serotypes, with the exception of 15C, unique to PCV21 compared with PCV20 based on GMT ratios. Similarly, superiority was demonstrated for 10 of the 11 unique serotypes, with the exception of 15C, for the 4-fold rise in OPA response. Immune response in cohort 2 was compared with cohort 1 via an immunobridging assessment, in which the predefined criterion was met for all 21 serotypes in PCV21. STRIDE-6[56] evaluated 717 adults 50 years of age and older who were pneumococcal vaccine experienced, which was defined as receipt of a pneumococcal vaccine at least 1 year prior to study enrollment. Individuals were split into 3 cohorts. Cohort 1 previously received PPSV23 and were randomized to receive PCV21 or PCV15. Cohort 2 previously received PCV13 and were randomized to receive PCV21 or PPSV23. Cohort 3 previously received PPSV23 followed by PCV13, PCV13 followed by PPSV23, PCV15 followed by PPSV23, or PCV15 alone. Individuals in cohort 3 all received open-label PCV21. Immunogenicity was evaluated descriptively 30 days following vaccination using OPA GMTs and IgG GMCs for PCV21 serotypes. PCV21 was immunogenic across all 3 cohorts. Immune responses were similar to PCV15 in cohort 1 and PPSV23 in cohort 2 and higher for the unique serotypes in PCV21. STRIDE-1[57] was a phase 1/2 study that evaluated PCV21 in 90 adults aged 18 to 49 years (phase 1) and 508 adults aged 50 years and older (phase 2). Immunogenicity of PCV21 was compared with PPSV23 in phase 2. PCV21 demonstrated a noninferior immune response to the 12 shared serotypes with PPSV23 and a superior immune response to the 9 unique serotypes in PCV21 compared with PPSV23. STRIDE-7 and STRIDE-8 are unpublished trials which evaluated PCV21 in adults 18 years of age and older with HIV and vaccine-naïve adults 18 to 64 years of age at increased risk of pneumococcal disease, respectively. Both studies compared PCV21 with PCV15 followed by PPSV23 and found that PCV21 elicited comparable immune responses to the 13 shared serotypes with PCV15 followed by

PPSV23 and greater immune responses to the 8 unique serotypes in PCV21 based on OPA GMTs and IgG GMCs at day 30 following vaccination in their respective patient populations.[58-61]

Safety

Adult

PCV15, PCV20, and PCV21 were all generally well-tolerated in clinical studies in adults. The most common adverse reactions reported in studies of PCV15 include injection-site pain, fatigue, myalgia, headache, injection-site swelling, injection-site erythema, and arthralgia.[3] Injection-site reactions occurred more frequently with PCV15 compared with PCV13 in several studies. The reason for this difference is unknown; however, this difference was not considered to be clinically significant by the study authors as the reactions were generally mild in severity and of short duration (ie, 1 to 3 days).[12,42] The rate of serious adverse events (SAE) ranged from 1.6% to 4.3% in clinical studies. No SAE were considered to be related to vaccination.[18] The most common adverse reactions reported in trials of PCV20 include injection-site pain, myalgia, fatigue headache arthralgia and injection-site swelling.[2] The rate of SAE ranged from 0.3% to 4.2% in clinical studies.[50,51,62] No SAE were considered to be related to vaccination.[38] The most common adverse reactions reported in trials for PCV21 include injection-site pain, fatigue, headache, myalgia, injection-site erythema, and injection-site swelling.[4] The rate of SAE across clinical studies reviewed by FDA was 1.4%, of which 2 SAE were considered to be related to study vaccine. These included 1 case of bronchospasm and 1 case of injection-site cellulitis.[63]

Pediatric

Both PCV15 and PCV20 were generally well-tolerated in clinical studies in pediatric patients. The most common adverse reactions reported in studies of PCV15 in infants were irritability, somnolence, and injection-site reactions. In children aged 6 to 17 years, the most common adverse reactions with PCV15 were injection-site reactions and myalgia.[3] In the PNEU-PLAN study,[47] children between the ages of 12 to 23 months old showed a greater rate of adverse reactions after receiving PCV15 compared with PCV13; however, reactions were generally mild in intensity and limited to less than 3 days. Additionally, in the PNEU-DIRECTION study,[46] the treatment group that received PCV13 for their first and second doses and PCV15 for their third and fourth doses experienced more injection-site pain compared with the group that received PCV13 for all doses. Again, the majority of adverse reactions were mild to moderate and severity and lasted less than 3 days. There were no differences in SAE in any of the studies.[45-49] The most common adverse reactions reported in trials of PCV20 in infants include pain at the injection site, drowsiness, decreased appetite and injection site redness, injection site swelling, and fever. In children 15 months to 17 years of age, the most common adverse reactions with PCV20 were irritability (in children < 2 y), pain at the injection-site, drowsiness (in children <2 y), fatigue and muscle pain (in children ≥ 2 y), decreased appetite (in children < 2 y), injection-site swelling and injection-site redness, headache (in children ≥ 5 y), and fever (in children < 2 y).[2] Safety was the primary outcome in the phase 2 trial by Senders et al.[52] Rates of local adverse reactions as well as reported systemic events were similar between groups. SAE were reported in 5.2% of patients who received PCV20 compared with 2.2% of patients who received PCV13; however, no SAE were considered vaccine related. A unpublished phase 3 trial[64] also compared the safety of PCV20 and PCV13, administered as a 4-dose series, in 1,511 infants 42 to 98 days of age at study entry. AE and SAE were similar in the PCV20 and PCV13 groups. The event rate of SAE was low (4.4% with PCV20 and 5.6% with PCV13), and no SAE was considered vaccine related.

Conclusion

PCV15, PCV20, and PCV21 offer expanded serotype coverage compared with previously approved PCVs – PCV13 has been discontinued. PCV15 and PCV20 cover similar serotypes, with PCV20 covering 5 additional serotypes compared with PCV15; however, PPSV23 which is given in combination with PCV15, when used outside of the childhood immunization series, provides coverage for these 5 serotypes. PCV21 covers 11 unique serotypes compared with PCV20. Based on recent epidemiological data, PCV21 provides coverage against approximately 83% of serotypes responsible for IPD in adults compared with 56% with PCV20. However, the serotypes responsible for IPD vary geographically and according to patient risk factors. Notably, PCV21 does not provide protection against serotype 4 which is responsible for at least 30% of IPD in certain adult populations in Alaska, Colorado, New Mexico, Oregon, and the Navajo Nation. Additionally, the future epidemiological impact of the lack of coverage for the serotypes covered by PCV20 compared with PCV21 is unknown. Clinical trials have demonstrated noninferiority for immunogenicity endpoints for both PCV15 and PCV20 compared with PCV13 for each of the 13 shared serotypes and for PCV21 compared with the 10 serotypes shared with PCV20. PCV21 has also demonstrated comparable immune responses when compared with PCV15 in

combination with PPSV23. Data on clinical outcomes for the new pneumococcal vaccines are not available. PCV15 and PCV20 are approved for use in both adults and pediatric patients greater than or equal to 6 weeks of age, while PCV21 is only approved for use in adults. ACIP does not specify a preferred PCV vaccine for any indication, except for HSCT. ACIP recently lowered the age for the universal pneumococcal vaccination from 65 years of age to 50 years of age; this recommendation is specific to PCVs in PCV-naïve individuals and does not apply to PPSV23, unless given in combination with PCV15.

Looking forward

A clinical trial[65] is currently underway to evaluate the use of PCV21 in children 2 through 17 years of age. Therefore, it is possible that the indication for this vaccine could be expanded in the future to include children in this age range with risk factors for IPD. However, Merck currently has no plans to pursue the expansion of PCV21 to include routine childhood immunization. Additional PCVs are in various stages in the pipeline. Another PCV21 vaccine (SP0202) from Sanofi is currently in phase 2 studies. Unlike, Merck's Capvaxive, the PCV21 from Sanofi covers the same 20 serotypes as Prevnar 20 with the addition of 1 extra serotype. Two 24-valent PCVs from GlaxoSmithKline (Pn-MAPS24v) and Vaxcyte (VAX-24) are currently in phase 2 studies. Vaxcyte is also evaluating a 31-valent PCV (VAX-31) with plans to begin a phase 2 study in the first quarter of 2025.[29,66]

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