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Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of all Children

Policy Statement—Recommendations for the Prevention of *Streptococcus pneumoniae* Infections in Infants and Children: Use of 13-Valent Pneumococcal Conjugate Vaccine (PCV13) and Pneumococcal Polysaccharide Vaccine (PPSV23)

COMMITTEE ON INFECTIOUS DISEASES

KEY WORDS
pneumococcal vaccine, invasive pneumococcal disease, immunization, PCV7, PCV13, PPSV23

ABBREVIATIONS
PCV7—7-valent pneumococcal conjugate vaccine
IPD—invasive pneumococcal disease
PCV13—13-valent pneumococcal conjugate vaccine
AAP—American Academy of Pediatrics
PPSV23—23-valent pneumococcal polysaccharide vaccine
SIDS—sudden infant death syndrome

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abstract

Routine use of the 7-valent pneumococcal conjugate vaccine (PCV7), available since 2000, has resulted in a dramatic reduction in the incidence of invasive pneumococcal disease (IPD) attributable to serotypes of *Streptococcus pneumoniae* contained in the vaccine. However, IPD caused by nonvaccine pneumococcal serotypes has increased, and nonvaccine serotypes are now responsible for the majority of the remaining cases of IPD occurring in children. A 13-valent pneumococcal conjugate vaccine has been licensed by the US Food and Drug Administration, which, in addition to the 7 serotypes included in the original PCV7, contains the 6 pneumococcal serotypes responsible for 63% of IPD cases now occurring in children younger than 5 years. Because of the expanded coverage provided by PCV13, it will replace PCV7. This statement provides recommendations for (1) the transition from PCV7 to PCV13; (2) the routine use of PCV13 for healthy children and children with an underlying medical condition that increases the risk of IPD; (3) a supplemental dose of PCV13 for (*a*) healthy children 14 through 59 months of age who have completed the PCV7 series and (*b*) children 14 through 71 months of age with an underlying medical condition that increases the risk of IPD who have completed the PCV7 series; (4) "catch-up" immunization for children behind schedule; and (5) PCV13 for certain children at high risk from 6 through 18 years of age. In addition, recommendations for the use of pneumococcal polysaccharide vaccine for children at high risk of IPD are also updated. *Pediatrics* 2010;126:000

INTRODUCTION

Invasive disease attributable to *Streptococcus pneumoniae* remains a significant public health problem in children despite widespread use of the 7-valent pneumococcal conjugate vaccine (PCV7) in US infants 2 through 23 months of age. PCV7 was also recommended for certain children 24 through 59 months of age. After the introduction of PCV7, dramatic decreases in invasive pneumococcal disease (IPD) attributable to vaccine serotypes were noted in children. A significant decrease in adult pneumococcal disease attributable to vaccine sero-

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types was also seen. However, IPD attributable to serotypes not included in the PCV7 increased in frequency, which prompted the need for development of a pneumococcal conjugate vaccine with expanded coverage.[1]

On February 24, 2010, the US Food and Drug Administration licensed a new 13-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV13) (Prevnar 13 [Wyeth Pharmaceuticals Inc, Madison, NJ]) for use in children 2 through 71 months of age. This new vaccine will replace the previously recommended PCV7. PCV13 contains the same 7 pneumococcal capsular polysaccharides found in PCV7 and 6 additional pneumococcal serotypes, which are now responsible for substantial rates of IPD in US children. The 13 capsular polysaccharides included in the vaccine are 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.

The American Academy of Pediatrics (AAP), through its Committee on Infectious Diseases, actively participated in the development of the recommendations for use of the new PCV13 vaccine, which were approved by the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention.[2] PCV13 will replace PCV7 and use the same routine and catch-up immunization schedules recommended for PCV7 for healthy children through 59 months of age and for children at high risk through 71 months of age. In addition, a single supplemental dose of PCV13 is recommended for healthy children 14 through 59 months of age and children at high risk 14 through 71 months of age who were completely immunized with PCV7. No active recall of children is recommended, but the supplemental dose should be given at the next appropriate medical visit of the child who has been completely immunized with PCV7.

A single dose of PCV13 may be administered to children 6 through 18 years of age who are at increased risk of IPD because of sickle cell disease, anatomic or functional asplenia, HIV infection or another immunocompromising condition, or presence of a cochlear implant or cerebrospinal fluid leak. Children at high risk who are 2 years old or older should also receive 23-valent pneumococcal polysaccharide vaccine (PPSV23) at least 8 weeks after their last dose of PCV13. A second dose of PPSV23 is recommended 5 years after the first dose for children with sickle cell disease, anatomic or functional asplenia, HIV infection, or other immunocompromising conditions.

BACKGROUND

IPD is a leading cause of morbidity and mortality throughout the world, and an estimated 14.5 million episodes occurred in children younger than 5 years in the year 2000, resulting in an estimated 826 000 pediatric deaths representing 11% of all deaths in children 1 through 59 months of age.[3] In the United States, before introduction of PCV7, an estimated 16 250 cases of IPD occurred annually in children younger than 5 years, and 80% of cases of IPD in children were attributable to 1 of the 7 serotypes contained in PCV7.[4] After widespread use of PCV7, IPD attributable to all pneumococcal serotypes decreased by 75% in children younger than 5 years and decreased by 45% overall when all age groups were considered, secondary to herd immunity. The reduction in IPD attributable to serotypes contained in PCV7 was even more dramatic (100% in children younger than 5 years and 94% when people of all ages were considered). After accounting for the indirect effects on incidence of IPD, the cost per life-year saved (estimated at $10 400) made PCV7 immunization a cost-effective intervention.[5] In an analysis of 753 cases of IPD in children who had been completely immunized with PCV7, only 4% were true "vaccine failures." The remaining cases were attributable to serotypes not contained in PCV7.[6]

Rates of IPD attributable to serotypes not contained in PCV7 have increased for all age groups since 2000. By 2006–2007, only 2% of IPD cases in children younger than 5 years were caused by PCV7 types, but the 6 additional serotypes included in the new PCV13 vaccine caused 63% of IPD cases in this age group. A report published in the *Morbidity and Mortality Weekly Report* estimated that 4600 cases of IPD occurred in US children younger than 5 years in 2007. Approximately 2900 of these cases (63%) were attributable to serotypes contained in PCV13 and would be potentially preventable with widespread use of PCV13.[7]

DISCUSSION

PCV13 was licensed by the Food and Drug Administration on the basis of safety and immunogenicity. The vaccine is available in single-dose, prefilled syringes that do not contain latex. The vaccine is a sterile solution of 13 capsular polysaccharides of *S pneumoniae*, with each capsular polysaccharide conjugated to a nontoxic variant of diphtheria toxin carrier protein. The vaccine contains no thimerosal or other preservatives but does contain polysorbate 80 and 0.125 mg of aluminum (as aluminum phosphate adjuvant) and succinate buffer.

Vaccine safety was studied in 13 controlled trials involving 4700 healthy infants 6 weeks through 15 months of age who received PCV13 and 2700 infants who received PCV7 as the control population. PCV13 was given simultaneously with other recommended childhood vaccines. Rates of local reactions at the injection site were not different between the 2 groups. Systemic reaction rates (fever, irritability,

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sleep disturbances) were also not different between the PCV13 and PCV7 groups.

There were 3 deaths among the infants who received PCV13 (0.063%) and 1 death among the PCV7 recipients (0.036%). All infants died from sudden infant death syndrome (SIDS). The death rate from SIDS was consistent with the published background rates of SIDS in the United States.

Safety was also assessed in 354 patients 7 through 71 months of age who received at least 1 dose of PCV13 but had not previously received PCV7. An additional 284 children 15 through 59 months of age who had received at least 3 doses of PCV7 were given 1 or 2 doses of PCV13 and followed for adverse reactions. Vaccine was well tolerated in these groups, and no significant adverse events were reported.

Immunogenicity was assessed by measuring immunoglobulin G (IgG) antibody concentrations by enzyme-linked immunosorbent assay (ELISA) and by assessing functional antibody responses (opsonophagocytic activity). For 12 of the 13 serotypes, the percentage of children who achieved antibody responses of $\geq$0.35 μg/mL was similar to the percentage of children who achieved antibody responses of $\geq$0.35 μg/mL 1 month after the third dose of PCV7. For serotype 3 (not contained in PCV7), only 63.5% of children achieved an antibody concentration of $\geq$0.35 μg/mL. Functional opsonophagocytic antibody responses were elicited for all 13 serotypes. Responses after the fourth dose of PCV13 showed an increase in antibody concentrations measured by ELISA for all 13 serotypes.

PCV13 is currently being studied in children 72 months old and older with conditions that put them at high risk, but no data are currently available regarding safety or immunogenicity in this population of older children. However, on the basis of the experience with PCV7, it is likely that PCV13 will be as safe and effective in reducing the risk of pneumococcal disease in this high-risk, older population of children.

RECOMMENDATIONS

Children who have not previously received PCV7 or PCV13 or who are incompletely immunized with PCV7 or PCV13:

- PCV13 is recommended for all children 2 through 59 months of age and for children 60 through 71 months of age who have underlying medical conditions that increase their risk of pneumococcal disease or complications (Table 1).
- PCV13 is recommended as a 4-dose series given at 2, 4, 6, and 12 through 15 months of age (Table 2).
- For children within this age range who have received 1 or more doses of PCV7, the series should be completed with PCV13 when it is available in the office. Thus, previously administered PCV7 doses count toward completion of the recommended series (Table 3).
- The immunization schedule for infants and toddlers 2 through 59 months of age who have not received any previous PCV7 or PCV13 or who need "catch-up" immunization are the same as those published previously for PCV7, with PCV13 replacing PCV7 in the sched-

TABLE 1 Underlying Medical Conditions That Are Indications for Pneumococcal Immunization Among Children, According to Risk Group: Advisory Committee on Immunization Practices, United States, 2010

Risk Group	Condition
Immunocompetent children	Chronic heart disease[a]
	Chronic lung disease[b]
	Diabetes mellitus
	Cerebrospinal fluid leaks
	Cochlear implant
Children with functional or anatomic asplenia	Sickle cell disease and other hemoglobinopathies
	Congenital or acquired asplenia or splenic dysfunction
Children with immunocompromising conditions	HIV infection
	Chronic renal failure and nephrotic syndrome
	Diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease; or solid organ transplantation
	Congenital immunodeficiency[c]

[a] Particularly cyanotic congenital heart disease and cardiac failure.
[b] Including asthma, if treated with prolonged high-dose oral corticosteroids.
[c] Includes B- (humoral) or T-lymphocyte deficiency; complement deficiencies, particularly C1, C2, C3, and C4 deficiency; and phagocytic disorders (excluding chronic granulomatous disease).

TABLE 2 Recommended Routine Immunization Schedule for PCV13 Among Infants and Children Who Have Not Received Previous Doses of PCV7 or PCV13, According to Age at First Dose: Advisory Committee on Immunization Practices, United States, 2010

Age at First Dose, mo	Primary PCV13 Series, No. of Doses[a]	PCV13 Booster Dose at 12–15 mo of Age, No. of Doses[b]
2–6	3	1
7–11	2	1
12–23	2	—
24–59 (healthy children)	1	—
24–71 (children with certain chronic diseases or immunocompromising conditions[c])	2	—

[a] Minimum interval between doses is 8 weeks except for children vaccinated at 12 months of age or younger for whom the minimum interval between doses is 4 weeks. The minimum age for administration of the first dose is 6 weeks.
[b] Given at least 8 weeks after the previous dose.
[c] For a complete list of conditions, see Table 1.

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TABLE 3 Recommended Transition Schedule From PCV7 to PCV13 Vaccination Among Infants and Children, According to Number of Previous PCV7 Doses Received: Advisory Committee on Immunization Practices, United States, 2010

Infant Series			Booster Dose, ≥12 mo[a]	Supplemental PCV13 Dose, 14–59 mo[b]
2 mo	4 mo	6 mo		
PCV7	PCV13	PCV13	PCV13	—
PCV7	PCV7	PCV13	PCV13	—
PCV7	PCV7	PCV7	PCV13	—
PCV7	PCV7	PCV7	PCV7	PCV13

[a] No additional PCV13 doses are indicated for children 12 through 23 months of age who have received 2 or 3 doses of PCV before 12 months of age and at least 1 dose of PCV13 at 12 months of age or older.
[b] For children with underlying medical conditions (see Table 1), a single supplemental PCV13 dose is recommended through the age of 71 months.

ule (see Table 3.53 in *Red Book*[8] (p532)). The only addition to Table 3.53 is the extension of age in children with underlying medical conditions, for whom PCV13 is recommended through 71 months of age.

Supplemental dose recommendation:

- A single supplemental dose of PCV13 is recommended for all healthy children 14 through 59 months of age who are fully immunized with PCV7. The supplemental dose should be given at least 8 weeks after the last dose of PCV7.
- For children fully immunized with PCV7 who have underlying medical conditions that increase their risk of pneumococcal disease or complications, a single supplemental dose of PCV13 is recommended for children 14 through 71 months of age, including children who may have previously received PPSV23.
- No active recall of patients is recommended. The supplemental dose should be given at the next medical visit of the child.

Children 6 through 18 years of age with conditions that place them at high risk:

- A single dose of PCV13 may be administered to children 6 through 18 years of age who are at increased risk of IPD because of sickle cell disease, anatomic or functional asplenia, HIV infection or other immunocompromising condition, or presence of cochlear implant or cerebrospinal fluid leaks, regardless of whether they have previously received PCV7 or PPSV23.

Use of PPSV23 among children 2 through 18 years of age who are at increased risk of IPD:

- Children with an underlying medical condition that increases the risk of IPD should receive PPSV23 at 2 years of age or as soon as possible after a diagnosis of chronic illness is made after the age of 2 years.
- Doses of PCV13 should be completed before PPSV23 is given, with a minimum interval of 8 weeks between the last dose of PCV13 and the dose of PPSV23.
- If a child has previously received PPSV23, he or she should also receive the recommended doses of PCV13.
- A second dose of PPSV23 is recommended 5 years after the first dose in children with sickle cell disease or functional or anatomic asplenia, HIV infection, or other immunocompromising conditions, but no more than 2 total doses of PPSV23 are recommended at this time.

IMPLEMENTATION OF THE NEW RECOMMENDATIONS

The introduction of a new vaccine may have considerable impact on the practice. Therefore, the AAP has developed implementation guidance on supply, payment, coding, and liability issues; these documents can be found at www.aapredbook.org/implementation.

PCV13 is approved for the Vaccines for Children (VFC) program through 18 years of age, and the vaccine will be covered by the Vaccine Injury Compensation Program. PPSV23 is not covered by the Vaccine Injury Compensation Program.

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