Evidence to Recommendations Framework and Policy Options: Use of 20-valent Pneumococcal Conjugate Vaccine in U.S. Children

Miwako Kobayashi, MD, MPH

Pneumococcal Vaccines Work Group
Advisory Committee on Immunization Practices
June 22, 2023

PICO Question	Should PCV20 be recommended as an option for pneumococcal vaccination for U.S. children?	
Population	**All U.S. children aged <2 years**	**U.S. children aged 2–18 years with underlying medical conditions**
Intervention	**PCV20 according to currently recommended dosing and schedules**	**PCV20 (without PPSV23)**
Comparison	PCV13 or PCV15 according to currently recommended dosing and schedules	
Outcomes	VT-IPD, VT- pneumonia, VT- AOM, VT- pneumococcal deaths, serious adverse events following vaccination	

VT: vaccine-type, IPD: invasive pneumococcal disease, AOM: acute otitis media

PICO Question	Should PCV20 be recommended as an option for pneumococcal vaccination for U.S. children?	
Population	**All U.S. children aged <2 years**	**U.S. children aged 2–18 years with underlying medical conditions**
Intervention	**PCV20 according to currently recommended dosing and schedules**	**PCV20 (without PPSV23)**
Comparison	PCV13 or PCV15 according to currently recommended dosing and schedules	
Outcomes	VT-IPD, VT- pneumonia, VT- AOM, VT- pneumococcal deaths, serious adverse events following vaccination	

VT: vaccine-type, IPD: invasive pneumococcal disease, AOM: acute otitis media

PICO Question	Should PCV20 be recommended as an option for pneumococcal vaccination for U.S. children?	
Population	**All U.S. children aged <2 years**	**U.S. children aged 2–18 years with underlying medical conditions**
Intervention	**PCV20 according to currently recommended dosing and schedules**	**PCV20 (without PPSV23)**
Comparison	PCV13 or PCV15 according to currently recommended dosing and schedules	
Outcomes	VT-IPD, VT- pneumonia, VT- AOM, VT- pneumococcal deaths, serious adverse events following vaccination	

VT: vaccine-type, IPD: invasive pneumococcal disease, AOM: acute otitis media

Risk group/Condition
Children without immunocompromising conditions
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)
Diabetes mellitus
Cerebrospinal fluid leak
Cochlear implant
Children with immunocompromising conditions
On maintenance dialysis or nephrotic syndrome
Congenital or acquired asplenia, or splenic dysfunction
Congenital or acquired immunodeficiency¶
Diseases and conditions treated with immunosuppressive drugs or radiation therapy**
HIV infection
Sickle cell disease or other hemoglobinopathies
Solid organ transplant

† Recommendations are of particular importance for children with cyanotic congenital heart disease and cardiac failure.

¶ Includes B-(humoral) or T-lymphocyte deficiency; complement deficiencies, particularly C1, C2, C3, and C4 deficiency; and phagocytic disorders (excluding chronic granulomatous disease).

** Including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease.

Risk group/Condition
Children without immunocompromising conditions
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)
Diabetes mellitus
Cerebrospinal fluid leak
Cochlear implant
Children with immunocompromising conditions
On maintenance dialysis or nephrotic syndrome
Congenital or acquired asplenia, or splenic dysfunction
Congenital or acquired immunodeficiency[¶]
Diseases and conditions treated with immunosuppressive drugs or radiation therapy**
HIV infection
Sickle cell disease or other hemoglobinopathies
Solid organ transplant

[†] Recommendations are of particular importance for children with cyanotic congenital heart disease and cardiac failure.

[¶] Includes B-(humoral) or T-lymphocyte deficiency; complement deficiencies, particularly C1, C2, C3, and C4 deficiency; and phagocytic disorders (excluding chronic granulomatous disease).

** Including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease.

Risk group/Condition
Children without immunocompromising conditions
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)
Diabetes mellitus
Cerebrospinal fluid leak
Cochlear implant
Children with immunocompromising conditions
On maintenance dialysis or nephrotic syndrome
Congenital or acquired asplenia, or splenic dysfunction
Congenital or acquired immunodeficiency¶
Diseases and conditions treated with immunosuppressive drugs or radiation therapy**
HIV infection
Sickle cell disease or other hemoglobinopathies
Solid organ transplant

† Recommendations are of particular importance for children with cyanotic congenital heart disease and cardiac failure.

¶ Includes B-(humoral) or T-lymphocyte deficiency; complement deficiencies, particularly C1, C2, C3, and C4 deficiency; and phagocytic disorders (excluding chronic granulomatous disease).

** Including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease.

Rationale for updating indications for risk-based recommendations

- Improve harmonization between pediatric and adult recommendations
- Data supporting increased risk of pneumococcal disease in this population
  - Increased pneumococcal pneumonia[1] or IPD[1,2] risk in **children with asthma without long-term oral corticosteroid use**
  - Increased risk of IPD in children with **chronic kidney disease (regardless of stage)**[2,3]
  - Increased pneumococcal pneumonia[2] or IPD[2,4] risk in children with **chronic liver disease**

IPD=invasive pneumococcal disease

1. Talbot et al. NEJM 2005. Long-term oral corticosteroid use of ≥120 days defined as high risk
2. Pelton et al. CID 2014. Long-term oral corticosteroid use of ≥30 days defined as severe asthma
3. Hjuler et al. Pediatrics 2008.
4. Van Hoek et al. Journal of Infection 2012

Evidence to Recommendations (EtR) framework

EtR Domain	Question
Public Health Problem	• Is the problem of public health importance?
Benefits and Harms	• How substantial are the desirable anticipated effects? • How substantial are the undesirable anticipated effects? • Do the desirable effects outweigh the undesirable effects? • What is the overall certainty of this evidence for the critical outcomes?
Equity	• What would be the impact of the intervention on health equity?

Evidence to Recommendations (EtR) framework

EtR Domain	Question
Public Health Problem	• Is the problem of public health importance?
Benefits and Harms	• How substantial are the desirable anticipated effects? • How substantial are the undesirable anticipated effects? • Do the desirable effects outweigh the undesirable effects? • What is the overall certainty of this evidence for the critical outcomes?
Values	• Does the target population feel the desirable effects are large relative to the undesirable effects? • Is there important variability in how patients value the outcomes?
Acceptability	• Is the intervention acceptable to key stakeholders?
Feasibility	• Is the intervention feasible to implement?
Resource Use	• Is the intervention a reasonable and efficient allocation of resources?
Equity	• What would be the impact of the intervention on health equity?

EtR Domain: Public Health Problem

Pneumococcal disease epidemiology in children

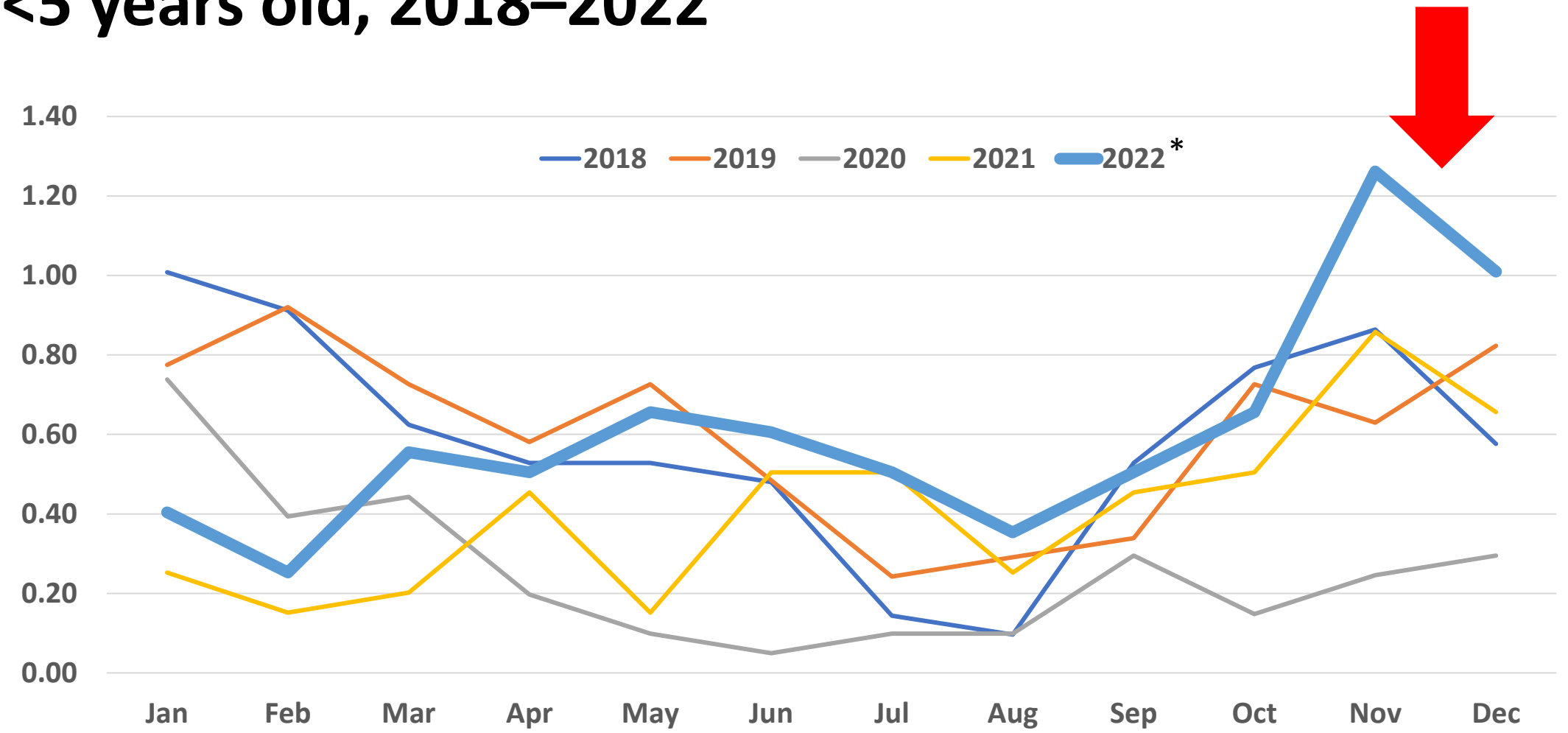
- **Use of PCVs (PCV7, PCV13) significantly decreased the incidence of pneumococcal disease in U.S. children.**
- **Outpatient ARIs caused by pneumococcus, such as AOM, sinusitis, and pneumonia, are common causes of outpatient visits and antibiotic prescribing.**
  - Estimated incidence of outpatient visits and antibiotic prescriptions attributable to PCV20, non-PCV13 serotypes: **4–5 times** PCV15, non-PCV13
- **In 2018–2019, the proportion of IPD caused by vaccine serotypes was:**
  - PCV20, non-PCV13: ~30% of IPD
  - PCV15, non-PCV13: ~15% of IPD
  - PPSV23, non-PCV20: 1–5% of IPD
- **Risk of pneumococcal disease remains high in children with underlying conditions that increase the risk of pneumococcal disease.**

AOM=acute otitis media; ARI= acute respiratory illness; IPD=invasive pneumococcal disease

Gierke. February 2023 ACIP meeting presentation

King. February 2023 ACIP meeting presentation

Monthly IPD rates (per 100,000) among children aged <5 years old, 2018–2022



IPD=invasive pneumococcal disease
CDC ABCs unpublished data. *2022 estimates are preliminary

Public Health Problem

Is pneumococcal disease of public health importance in U.S. children?

- ☐ No
- ☐ Probably no
- ☐ Probably yes
- ☐ Yes
- ☐ Varies
- ☐ Don’t know

EtR Domain: Benefits and Harms

Summary of evidence: Benefits, children <2 years

- **Informed by 2 randomized controlled trials (Phase II and III)[1,2]**
  - Healthy children randomized to either PCV13 or PCV20
  - PCVs given using 3+1 schedule
- **Summary of findings**
  - PCV20 had numerically **lower** IgG geometric mean concentrations vs. PCV13 for the 13 shared serotypes
  - **Post dose 3**:
    - PCV20 did **not** meet noninferiority criteria* vs. PCV13 for serotypes 1, 3, 4, 9V, 23F, and 12F*** for one of the outcomes
  - **Post dose 4**:
    - PCV20 **noninferior**** to PCV13 for all 13 shared serotypes
    - PCV20 **noninferior** to PCV13*** for all 7 additional serotypes

*Measured as lower bound of 2-sided 95% CI for percent difference proportion of participants (PCV20-PCV13) meeting IgG threshold value of >=0.35µg/mL for all serotypes except ≥ 0.23 µg/mL, ≥ 0.10 µg/mL and ≥ 0.12µg/mL for serotypes 5, 6B and 19A respectively

**Measured as lower bound of 2-sided 95% CI for IgG geometric mean concentration ratio (PCV20/PCV13) >0.5

***Compared with the serotype with lowest immune response among PCV13 serotypes except for serotype 3

1. Senders et al. PIDJ 2021
2. Pfizer unpublished data from B7471011

Summary of evidence: Safety, children <2 years

- **Serious adverse events (SAEs) across 3 studies (dose 1 through 6 months after dose 4)[1-3]:**
  - PCV20: 4.5% (101 of 2,232) vs PCV13: 3.7% (64 of 1,717)
- **None were considered to be vaccine-related**

1. Senders et al. PIDJ 2021
2. Pfizer B7471011, https://www.fda.gov/media/149987/download
3. Pfizer B7471013, https://www.fda.gov/media/149987/download

Should PCV20 be recommended as an option for pneumococcal conjugate vaccination according to currently recommended dosing and schedules, for U.S. children aged <2 years?

Type	Outcome	Importance	Included in evidence profile	Certainty of evidence
Benefits	VT-IPD	Critical	Yes	Moderate
	VT-pneumonia	Critical	Yes	Moderate
	VT-AOM	Critical	Yes	Moderate
	VT-pneumococcal deaths	Critical	Yes	Moderate
Harms	SAEs following vaccination	Critical	Yes	Moderate

AOM=acute otitis media, IPD=invasive pneumococcal disease, SAE=serious adverse events, VT=vaccine-type

Summary of evidence:
Benefits, children 2–18 years with underlying conditions

- **No studies conducted among children with underlying medical conditions**
- **Informed by 1 non-randomized trial (Phase III), no comparator**
  - Healthy children aged 15 months to 17 years received a dose of PCV20
    - Children aged <5 years received ≥3 doses of PCV13
- **Summary of findings**
  - PCV20 was immunogenic* for all 20 vaccine serotypes 1 month after vaccination vs. pre-vaccination.

*Measured as IgG GMCs and GMFR and OPA GMFRs
Pfizer unpublished data from B7471014

Summary of evidence:
Safety, children 2–18 years with underlying conditions

- **Serious adverse events (SAEs) :**
  - PCV20: 0.6% (5/831)
- **None were considered to be vaccine-related**

Pfizer unpublished data from B7471014

Should PCV20 without PPSV23 be recommended as an option for pneumococcal vaccination for U.S. children aged 2–18 years with underlying medical conditions that increase the risk of pneumococcal disease?

Type	Outcome	Importance	Included in evidence profile	Certainty of evidence
Benefits	VT-IPD	Critical	Yes	Very Low
	VT-pneumonia	Critical	Yes	Very Low
	VT-AOM	Critical	Yes	Very Low
	VT-pneumococcal deaths	Critical	Yes	Very Low
Harms	SAEs following vaccination	Critical	Yes	Very Low

AOM=acute otitis media, IPD=invasive pneumococcal disease, SAE=serious adverse events, VT=vaccine-type

Benefits and Harms

How substantial are the desirable anticipated effects?

- **Routine PCV20 use for children aged <2 years**
- **PCV20 without PPSV23 for children aged 2–18 years with underlying conditions**

□ Minimal
□ Small
□ Moderate
□ Large
□ Varies
□ Don't know

- PCV20 provides the broadest serotype coverage among available PCVs.
- Unknown how substantial the protection conferred from PCV20 will be based on available data.
- No PCV20 data among children with **underlying medical conditions**.

Benefits and Harms

How substantial are the undesirable anticipated effects?

- Routine PCV20 use for children aged <2 years
- PCV20 without PPSV23 for children aged 2–18 years with underlying conditions

- ☐ Minimal
- ☐ Small
- ☐ Moderate
- ☐ Large
- ☐ Varies
- ☐ Don’t know

Benefits and Harms

Do the desirable effects outweigh the undesirable effects?

- **Routine PCV20 use for children aged <2 years**
- **PCV20 without PPSV23 for children aged 2–18 years with underlying conditions**

□ Favors intervention*
□ Favors current recommendation
□ Favors both
□ Favors neither
□ Varies
□ Don't know

***Intervention:** PCV20 use
Comparison:

- **Children <2 years:** PCV13 or PCV15 use
- **Children 2–18 years with underlying conditions:** PPSV23 use after currently recommended PCV (PCV13 or PCV15) doses

EtR Domain: Equity

Summary of evidence

- **Disparities** in pneumococcal vaccine coverage by race/ethnicity, insurance coverage, and poverty level exist[1]
- Nationally representative PPSV23 vaccine coverage data among children with indications are limited[2–5]
  - Range ~20–60%, many reports from single institution
- **Disparities** in IPD rates by race and the percentage of census tract poverty remain[6,7]
  - Most of the remaining disparities were due to serotypes **not included in PCV20**

1. ChildVaxView Interactive Child Vaccination Coverage | CDC
2. Reeves et al. Pediatric Blood & Cancer, 2018
3. Tran et al. Frontiers in Pediatrics, 2021
4. Mirza et al. The Ochsner Journal, 2022
5. Harris et al. Pediatrics, 2022
6. Farrar February 2022 ACIP meeting presentation
7. Kobayashi February 2023 ACIP meeting presentation

Equity

What would be the impact of recommending PCV20 for U.S. children on health equity?

- ☐ Reduced
- ☐ Probably reduced
- ☐ Probably no impact
- ☐ Probably increased
- ☐ Increased
- ☐ Varies
- ☐ Don’t know

Equity

What would be the impact of recommending PCV20 for U.S. children aged <2 years on health equity?

Probably reduced:

- New interventions are likely to be accessible to wealthy communities, first

→VFC program mitigates inequities in access to recommended vaccines

Probably no impact:

- Remaining disparities in vaccine-type disease seem to be minimal

Probably increased:

- Post-PCV13 data showed that PCV13 reduced disparities in vaccine-type disease

VFC=Vaccines for Children

Equity

What would be the impact of recommending PCV20 without PPSV23 for U.S. children aged 2–18 years with underlying medical conditions on health equity?

Probably no impact:

- Risk-based recommendation is less likely to be equitable compared with routine vaccine recommendations.

Probably increased:

- PCV20 use without PPSV23 could simplify the pneumococcal vaccine recommendations and improve vaccine coverage.

EtR Domain: Values and Preferences

Values and Preferences

Criterion 1: Does the target population feel that the desirable effects from vaccination are large relative to undesirable effects?

- **Routine PCV20 use for children aged <2 years**
  - **Probably Yes**
- **PCV20 without PPSV23 for children aged 2–18 years with underlying conditions**
  - **Probably Yes/Yes**

Values and Preferences

Criterion 2: Is there important uncertainty about, or variability in, how much people value the main outcomes?

- **Routine PCV20 use for children aged <2 years**
  - **Probably important/not important** uncertainty or variability

- **PCV20 without PPSV23 for children aged 2–18 years with underlying conditions**
  - **Probably not important** uncertainty or variability

Values and Preferences

Uncertainties:

- No data assessing the public's perception of PCV20
- No data assessing efficacy/effectiveness of PCV20 against disease
- Benefits from PCV20 use alone without PPSV23 for children with underlying conditions are uncertain

Probably not important uncertainty or variability:

- >90% vaccine coverage for ≥3 PCV doses in children by age 24 months[1]
- Increased cases of invasive pneumococcal disease (late 2022): caregivers of the child will likely value the use of PCV20

1. Hill et al. MMWR 2023.

EtR Domain: Acceptability

Three healthcare provider surveys

- Web-based surveys among providers who administer pneumococcal vaccines to children
  - 1 by **Pfizer** (manufacturer of PCV13 and PCV20)[1]
  - 2 by **Merck** (manufacturer of PCV15 and PPSV23)[2,3]

1. Myers K, Pierce N, Poulos C, Arguedas A, Chilson E, Hauber B, et al. US Health Care Providers' Preferences for Pediatric Pneumococcal Conjugate Vaccines. Preliminary Findings. 2023.
2. OPEN Health. Provider Knowledge, Attitude, and Preferences Towards Pediatric Pneumococcal Vaccines. 2023.
3. Merck & Co. Inc. HCP Preferences Concerning Pediatric Pneumococcal Vaccines Report. 2023.

Key findings (Pfizer survey)

Vaccine profiles of PCV15 and PCV20 shown, emphasizing IPD serotype coverage.

Children aged <2 years with incomplete series:

- **76%** of providers responded that they would transition patients who started their PCV series with either PCV13 or PCV15 to PCV20
  - To provide protection against as many serotypes as possible (**94%**).

Children with underlying conditions:

- **43%** of providers responded that PCV20 alone without PPSV23 should be recommended.
  - Prefer/store only 1 vaccine instead of multiple vaccines (**61%**).
  - Prefer conjugated vaccines over unconjugated polysaccharide vaccines (**48%**).

1. Myers K, Pierce N, Poulos C, Arguedas A, Chilson E, Hauber B, et al. US Health Care Providers' Preferences for Pediatric Pneumococcal Conjugate Vaccines. Preliminary Findings. 2023.

Key findings (Merck surveys)

- **Importance of pneumococcal vaccination**
  - **>90%** of providers believed that it is important to administer pneumococcal vaccines to children aged <2 years.[1]

- **Important vaccine attributes**
  - **≥90%** of providers believed that it is important to have product-specific data for immunocompromised or premature children.[1]
  - Of the five vaccine attributes assessed for hypothetical vaccines, immune response for the serotypes covered in PCV13 was given the highest importance.[2]

1. Merck & Co. Inc. HCP Preferences Concerning Pediatric Pneumococcal Vaccines Report. 2023..
2. OPEN Health. Provider Knowledge, Attitude, and Preferences Towards Pediatric Pneumococcal Vaccines. 2023.

Acceptability

Is recommending PCV20 acceptable to key stakeholders?

- **Routine PCV20 use for children aged <2 years**
  - **Yes**
- **PCV20 without PPSV23 for children aged 2–18 years with underlying conditions**
  - **Probably Yes/Yes**
    - Simplifies storage, less prone to vaccine administration errors
    - Some providers may not feel comfortable recommending PCV20 alone without PPSV23

EtR Domain: Resource Use

Summary of evidence

- **Routine PCV20 use vs. PCV13 or PCV15 in children aged <2 years**
  - Base case ranged from cost-saving to $125,000 per QALY gained
  - Differences across models related to indirect effects on adult disease

- **PCV20 alone without PPSV23 use in children aged 2–18 years with underlying conditions**
  - PCV20 alone instead of PCV13/PCV15+PPSV23* was found to be cost-saving in most model scenarios
  - Addition of PPSV23 to PCV20 had high cost per QALY gained
    - Greater than $1.9 million per QALY gained among CMC
    - Between $200,000 to $690,000 per QALY gained among IC

CMC=chronic medical conditions, including chronic heart, lung, and liver disease, diabetes
IC=immunocompromising conditions, including chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosuppression, generalized malignancy, HIV, Hodgkin disease, leukemia, lymphoma, solid organ transplants, cochlear implants, CSF leaks, congenital or acquired asplenia, sickle cell disease, or other hemoglobinopathies
QALY= quality-adjusted life-years
*CMC received 1 dose of PPSV23, IC received 2 doses of PPSV23

Resource Use

Is the option a reasonable and efficient allocation of resources?

- **Routine PCV20 use for children aged <2 years**
- **PCV20 without PPSV23 for children aged 2–18 years with underlying conditions**

□ No
□ Probably no
□ Probably yes
□ Yes
□ Varies
□ Don't know

Yes:

- Protects against more pneumococcal serotypes.

Minority opinion:

- Expensive vaccine.
- Uncertainties in the effectiveness remain.
  - Only immunogenicity data.
  - No PCV20 data from children with underlying conditions.
- Challenging to interpret cost-effectiveness analyses findings that use different methods and assumptions (routine PCV20 use).
- Sensitive to launch price.

EtR Domain: Feasibility

Feasibility

Is recommending PCV20 feasible to implement?

- **Routine PCV20 use for children aged <2 years**
- **PCV20 without PPSV23 for children aged 2–18 years with underlying conditions**

- ☐ No
- ☐ Probably no
- ☐ Probably yes
- ☐ Yes
- ☐ Varies
- ☐ Don’t know

Routine PCV20 use for children aged <2 years:

- PCVs have been recommended for >20 years.

PCV20 without PPSV23 for children with underlying conditions:

- Simpler, streamlined recommendation.
- More feasible in general and are more likely to be followed in clinical practice.

Summary of Work Group Interpretation of the EtR Domains (Updated)

EtR Domains	PCV20, <2 years (routine)	PCV20, 2–18 years old
Public Health Problem	Yes	
Benefits and Harms		
a. Benefits	Moderate	
b. Harms	Minimal	
c. Benefit>Harm?	Favors intervention/Favors both (split)	
d. Overall certainty: effectiveness	2 (moderate)	4 (very low)
e. Overall certainty: safety	2 (moderate)	4 (very low)
Values		
a. Desirable>Undesirable?	Probably yes	Probably yes/yes (split)
b. Uncertainty?	Probably important uncertainty or variability/Probably no important uncertainty or variability (split)	Probably no important uncertainty or variability
Acceptability	Yes	Probably yes/yes (split)
Resource Use	Yes	
Equity	Probably increased (different opinions)	
Feasibility	Yes	

Summary: Work Group Interpretations

Should PCV20 be recommended as an option for pneumococcal conjugate vaccination according to currently recommended dosing and schedules for ***U.S. children aged <2 years****?*

Comparison: PCV13 or PCV15

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences is *closely balanced* or *uncertain*	**Desirable consequences *probably* outweigh undesirable consequences in most settings**	**Desirable consequences *clearly outweigh* undesirable consequences in most settings**	There is insufficient evidence to determine the balance of consequences

Summary: Work Group Interpretations

Should PCV20 be recommended as an option for pneumococcal conjugate vaccination according to currently recommended dosing and schedules for ***U.S. children aged <2 years****?*

In support of recommending PCV20:

- Additional serotypes covered by PCV20 are expected to prevent additional disease.

In support of recommending both PCV20 and PCV15*:

- We only have immunogenicity study data for both PCV20 and PCV15, clinical implications are unknown.
- Range in cost-effectiveness analysis findings.
- Good to have options for PCVs, in case of challenges with/delays in access to PCV20.

*PCV13 expected to be removed from market after a transition period

Summary: Work Group Interpretations

Should PCV20 without PPSV23 be recommended as an option for children aged 2–18 years with underlying medical conditions that increase the risk of pneumococcal disease?

Comparison: PCV13 or PCV15 + PPSV23 according to current dosing /schedule

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences is *closely balanced* or *uncertain*	**Desirable consequences *probably* outweigh undesirable consequences in most settings**	Desirable consequences *clearly outweigh* undesirable consequences in most settings	There is insufficient evidence to determine the balance of consequences

Summary: Work Group Interpretations

Should PCV20 without PPSV23 be recommended as an option for children aged 2 to 18 years with underlying medical conditions that increase the risk of pneumococcal disease?

In support of recommending PCV20 without PPSV23:

- Simplicity of PCV20 use without PPSV23, ease of vaccine storage.
- Immunologic advantages of PCVs over PPSV23.
- PCV20 provides the broadest serotype coverage among available PCVs.

In support of recommending BOTH PCV20 without PPSV23 AND PCV15* + PPSV23:

- No data on PCV20 use in children with underlying medical conditions.
- Harmonization with the updated adult pneumococcal vaccine recommendations (October 2022 ACIP meeting).

*PCV13 expected to be removed from market after a transition period

Proposed Policy Options for a Vote

1. Routine PCV use for all children aged <24 months

Use of either PCV15 or PCV20 is recommended for all children aged 2–23 months according to currently recommended PCV dosing and schedules.

Age at visit/ Health status	No. of previous PCV13/PCV15/PCV20 doses received	Recommended PCV15/PCV20 regimen†
All children (healthy and those with risk conditions)		
2–6 mos	1	3 additional doses: 2 doses, 8 wks apart; last dose at age 12–15 mos
	2	2 additional doses: 1 dose 8 wks after most recent dose; last dose ≥8 wks later at age 12–15 mos
	3	1 additional dose at age 12–15 mos
7–11 mos	1 or 2 (at age <7 mos)	2 additional doses: 1 dose 8 wks after most recent dose; last dose ≥8 wks later at age 12–15 mos
	3 (at age <7 mos)	1 additional dose at age 12–15 mos
	1 (at age ≥7 mos)	2 additional doses: 1 dose 8 wks after most recent dose; last dose ≥8 wks later at age 12–15 mos
	2 (at age ≥7 mos)	1 additional dose at age 12–15 mos
12–23 mos	1 (at age <12 mos)	2 additional doses: 1 dose ≥8 wks after most recent dose; last dose ≥8 wks later
	2 or 3 (at age <12 mos)	1 additional dose, ≥8 wks after most recent dose
	1 (at age ≥12 mos)	1 additional dose, ≥8 wks after most recent dose†

† Minimum interval between doses is 8 weeks except for children vaccinated at age <1 year, for whom minimum interval between doses is 4 weeks.

2. Catch-up PCV doses for children aged 24–71 months with an incomplete PCV vaccination status

For healthy children aged 24–59 months or through age 71 months for children with any underlying condition that increases the risk of pneumococcal disease (hereafter, risk condition)* with an incomplete PCV vaccination status, use of either PCV15 or PCV20 according to currently recommended PCV dosing and schedules is recommended.

*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 and other hemoglobinopathies).

Risk group/Condition
Children without immunocompromising conditions
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)
Diabetes mellitus
Cerebrospinal fluid leak
Cochlear implant
Children with immunocompromising conditions
On maintenance dialysis or nephrotic syndrome
Congenital or acquired asplenia, or splenic dysfunction
Congenital or acquired immunodeficiency[¶]
Diseases and conditions treated with immunosuppressive drugs or radiation therapy**
HIV infection
Sickle cell disease or other hemoglobinopathies
Solid organ transplant

[†] Recommendations are of particular importance for children with cyanotic congenital heart disease and cardiac failure.

[¶] Includes B-(humoral) or T-lymphocyte deficiency; complement deficiencies, particularly C1, C2, C3, and C4 deficiency; and phagocytic disorders (excluding chronic granulomatous disease).

** Including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease.

Age at visit/ Health status	No. of previous PCV13/PCV15/PCV20 doses received	Recommended PCV15/PCV20 regimen[†]
Healthy Children		
24–59 mos	No previous doses or any incomplete schedule by 24 mos	1 additional dose, ≥8 wks after most recent dose
5–18 yrs	No previous doses or any incomplete schedule by 24 mos	No additional dose
Children with risk conditions		
24–71 mos	No previous doses or any incomplete schedule and <3 doses by age 24 mos	2 doses: 1 dose ≥8 wks after most recent dose; last dose ≥8 wks later
	3 (all at age <12 mos)	1 additional dose, ≥8 wks after most recent dose

[†] Minimum interval between doses is 8 weeks except for children vaccinated at age <1 year, for whom minimum interval between doses is 4 weeks.

3. Children aged 2–18 years with any risk condition who have completed their recommended PCV doses before age 6 years

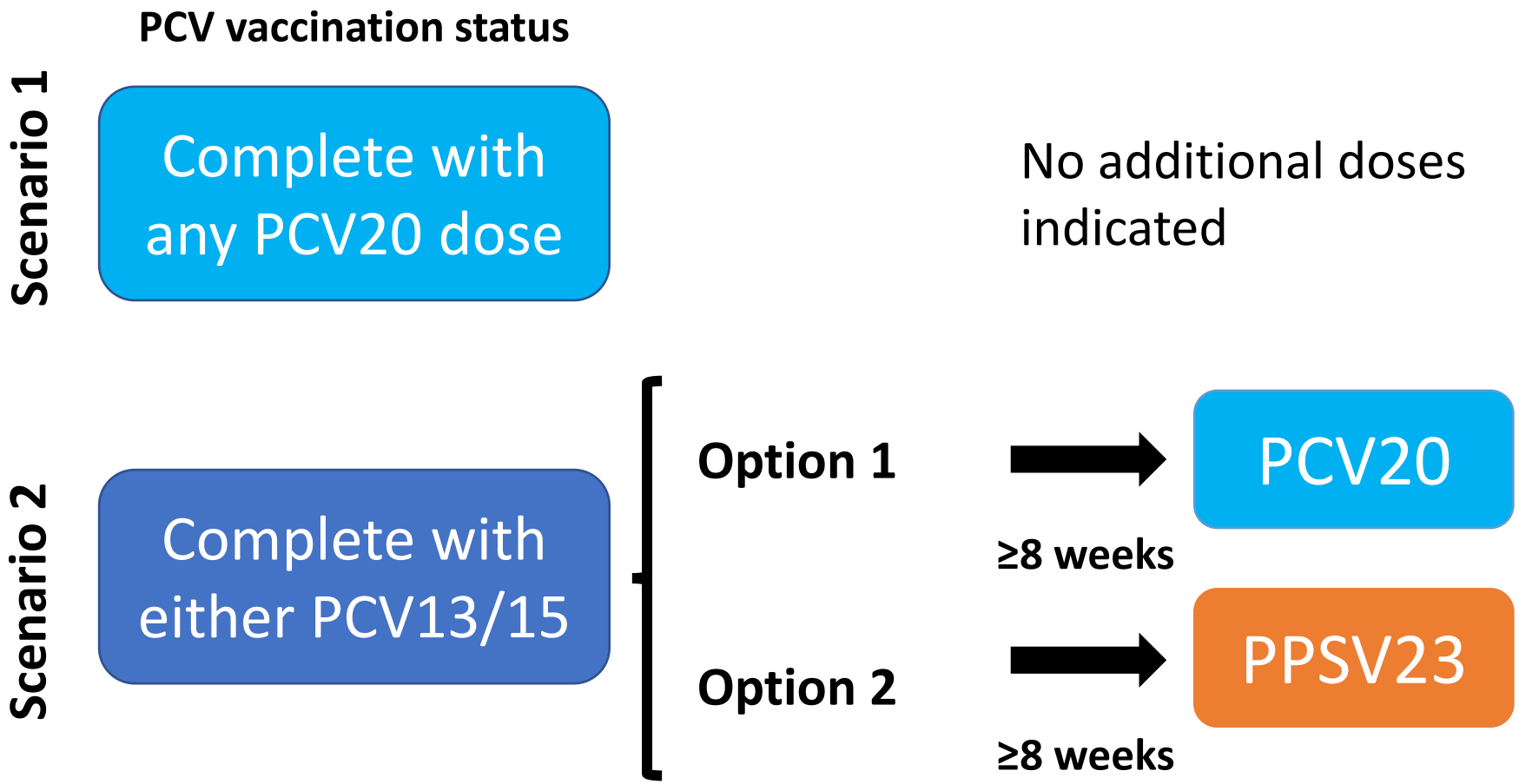
For children aged 2–18 years with any risk condition who have received all recommended doses before age 6 years

- **Using ≥1 dose of PCV20: No additional doses of any pneumococcal vaccine are indicated. This recommendation may be updated as additional data become available.**
- **Using PCV13 or PCV15 (no PCV20): A dose of PCV20 or PPSV23 using previously recommended doses and schedule is recommended.**

Children aged 2–18 years with CMC, CSF leak, or cochlear implant who have received all recommended PCV doses before age 6 years, current recommendations

CMC=chronic medical conditions, including chronic kidney disease (excluding maintenance dialysis and nephrotic syndrome, which are included in immunocompromising conditions), chronic heart disease, chronic liver disease, chronic lung disease (including moderate persistent or severe persistent asthma), diabetes mellitus; CSF=cerebrospinal fluid

Children aged 2–18 years with CMC, CSF leak, or cochlear implant who have received all recommended PCV doses before age 6 years, proposed recommendations

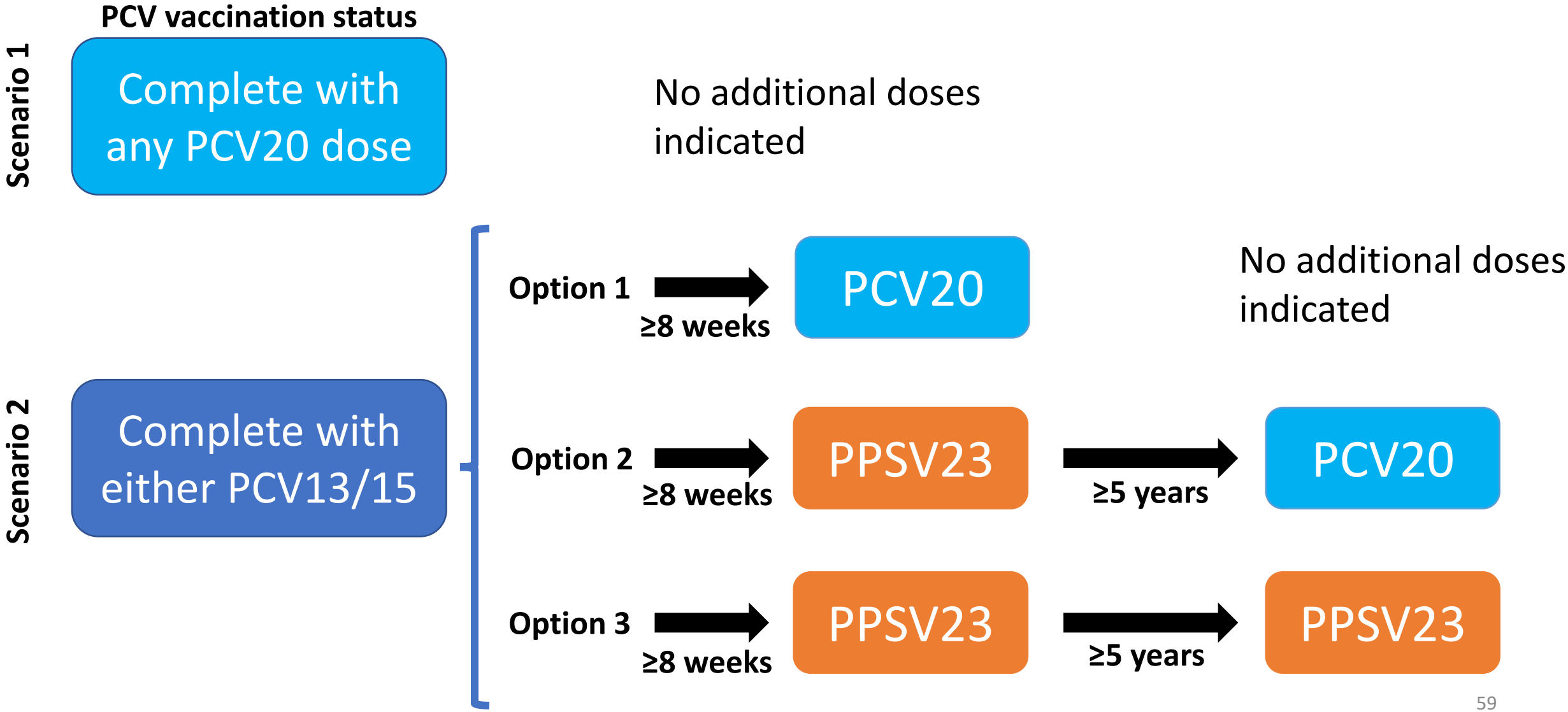


CMC=chronic medical conditions, including chronic kidney disease (excluding maintenance dialysis and nephrotic syndrome, which are included in immunocompromising conditions), chronic heart disease, chronic liver disease, chronic lung disease (including moderate persistent or severe persistent asthma), diabetes mellitus; CSF=cerebrospinal fluid

Children with an immunocompromising condition aged 2–18 years who have completed PCV doses before age 6 years, current recommendations

IC= immunocompromising condition

Children with an immunocompromising condition aged 2–18 years who have completed PCV doses before age 6 years, proposed recommendations



IC= immunocompromising condition

4. Children aged 6–18 years with any risk condition who have not received any dose of PCV

For children aged 6–18 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 at least 8 weeks after the most recent dose of pneumococcal vaccine. When PCV15 is used, it should be followed by a dose of PPSV23 at least 8 weeks later if not previously given.

Current risk-based pneumococcal vaccine recommendations for PCV unvaccinated children aged 6–18 years with risk conditions

	PCV13/15 recommended	PPSV23 Recommended	Single PPSV23 revaccination 5 yrs after first dose
Chronic heart disease		Y	
Chronic lung disease		Y	
Diabetes mellitus		Y	
Cerebrospinal fluid leak	Y	Y	
Cochlear implant	Y	Y	
Chronic renal failure or nephrotic syndrome	Y	Y	Y
Congenital or acquired asplenia, or splenic dysfunction	Y	Y	Y
Congenital or acquired immunodeficiency	Y	Y	Y
Diseases and conditions treated with immunosuppressive drugs or radiation therapy	Y	Y	Y
HIV infection	Y	Y	Y
Sickle cell disease or other hemoglobinopathies	Y	Y	Y
Solid organ transplant	Y	Y	Y

Proposed risk-based pneumococcal vaccine recommendations for PCV unvaccinated children aged 6–18 years with risk conditions

	PCV15/20 recommended	PPSV23 Recommended
Chronic heart disease	Y	Only if PCV15 used
Chronic kidney disease	Y	Only if PCV15 used
Chronic liver disease	Y	Only if PCV15 used
Chronic lung disease*	Y	Only if PCV15 used
Diabetes mellitus	Y	Only if PCV15 used
Cerebrospinal fluid leak	Y	Only if PCV15 used
Cochlear implant	Y	Only if PCV15 used
Maintenance dialysis or nephrotic syndrome	Y	Only if PCV15 used
Congenital or acquired asplenia, or splenic dysfunction	Y	Only if PCV15 used
Congenital or acquired immunodeficiency	Y	Only if PCV15 used
Diseases and conditions treated with immunosuppressive drugs or radiation therapy	Y	Only if PCV15 used
HIV infection	Y	Only if PCV15 used
Sickle cell disease or other hemoglobinopathies	Y	Only if PCV15 used
Solid organ transplant	Y	Only if PCV15 used

*including moderate persistent or severe persistent asthma

Clinical Guidance

PCV13 use for children aged <6 years

- If only PCV13 is available when the child is scheduled to receive a PCV, PCV13 may be given as previously recommended.
- 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.

Children aged 6–18 years with a risk condition who have received PCV13 only

For children who have previously received PCV13 only, either a dose of PCV20 at least 8 weeks later or PPSV23 based on previous dosing and schedules is recommended.

Children who have received hematopoietic stem cell transplant (HSCT)

Children who received HSCT are recommended to receive **three doses of PCV20**, 4 weeks apart starting 3–6 months after HSCT. **A fourth PCV20 dose** is recommended at least 6 months after the third PCV20 dose, or at least 12 months after HSCT, whichever is later. HSCT recipients who have started their pneumococcal vaccine series with PCV13 or PCV15 may complete their 4-dose pneumococcal vaccine series with PCV20 without giving extra doses.

If PCV20 is not available, **three doses of PCV15, followed by a dose of PPSV23** at least 12 months after HSCT may be given. For patients with chronic graft-versus-host disease who are receiving PCV15, a fourth dose of PCV15 can be given in place of PPSV23 since these children are less likely to respond to PPSV23.

A patient's clinical team is best positioned to determine the appropriate timing of vaccination.

Language aligned with clinical guidance for adults (October 2022 ACIP meeting)

Acknowledgements

- ACIP and the Pneumococcal Vaccines Work Group
- CDC contributors and consultants: Ryan Gierke, Jennifer Farrar, Kristin Andrejko, Lindsay Zielinski, Emma Accorsi, Adam Cohen, Alison Albert, Angela Jiles, Noele Nelson, Diepreye Ayabina, Andrew Leidner, Pedro Moro, Elizabeth Velazquez, Marc Fischer, Katie Hamilton, Noelle Sobotka, Rebecca Morgan, Doug Campos-Outcalt

Summary of voting language:
No change in PCV doses or schedule

1. Use of either PCV15 or PCV20 is recommended for all children aged 2–23 months according to currently recommended PCV dosing and schedules.

2. For healthy children aged 24–59 months or through age 71 months for children with any underlying condition that increases the risk of pneumococcal disease (hereafter, risk condition)* with an incomplete PCV vaccination status, use of either PCV15 or PCV20 according to currently recommended PCV dosing and schedules is recommended.

*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 and other hemoglobinopathies).

Summary of voting language: Modifications to schedule

3. For children aged 2–18 years with any risk condition who have received all recommended doses before age 6 years

- **Using ≥1 dose of PCV20: No additional doses of any pneumococcal vaccine are indicated. This recommendation may be updated as additional data become available.**
- **Using PCV13 or PCV15 (no PCV20): A dose of PCV20 or PPSV23 using previously recommended doses and schedule is recommended.**

4. For children aged 6–18 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 at least 8 weeks after the most recent dose of pneumococcal vaccination. When PCV15 is used, it should be followed by a dose of PPSV23 at least 8 weeks later if not previously given.

Supplementary Slides

GRADE Summary of Evidence

Search strategy: PCV20 use in children

Database	Strategy	No. identified	Included in GRADE

Clinicaltrials.gov	Inclusion: Relevant Phase 2, or 3 randomized controlled trials of PCV20
	• Involved human subjects
	• Reported primary data
	• Included infants and children (age ≤18 years)
	• Included data relevant to the efficacy or effectiveness or immunogenicity and safety outcomes being measured
	• Included data for the dosage and timing being recommended:
	  ○ 3+1 series for infants starting the vaccine series as currently recommended
	  ○ Catch-up vaccine schedule for older infants and children who did not start the 3+1 series in time
	  ○ Use of PCV20 to complete the PCV13 series
	  ○ Use of PCV20 in series with PPSV23 in older children with underlying conditions in series with PPSV23
		12	3*

Pubmed Medline	"PCV20" or "20-valent pneumococcal conjugate vaccine" Included studies using the criteria listed above	62	1
Additional resources	Unpublished and other relevant data by consulting with the vaccine manufacturer	2	3*

*Same trials. Unpublished data from these trials were obtained from pharmaceutical companies.

Included Studies: Routine PCV20 Use in Children Aged <2 years

Author, year	Study design	Intervention	Country	Age	Total population	N Intervention	N comparison	Outcomes	Funding source
Senders, 2021	Phase II RCT in healthy full-term infants	PCV20 @ 2, 4, 6, and 12 months of age	US	42–98 days of age at consent	460	232	228	Immuno-genicity and safety	Pfizer
B7471011	Phase III RCT in healthy full-term infants	PCV20 @ 2, 4, 6, and 12 – 15 months of age	US, Puerto Rico	42–98 days of age at consent	1998	1001	997	Immuno-genicity and safety	Pfizer
B7471013	Phase III RCT in healthy infants	PCV20 @ 2, 4, 6, and 12 – 15 months of age	US, Puerto Rico, Canada, Chile, Argentina, EU	42–98 days of age at consent	1511	1000	551	Safety	Pfizer

RCT=Randomized Controlled Trial

GRADE Summary of Findings: Routine PCV20 use in Children Aged <2 Years

Certainty assessment							№ of patients		Results		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	comparison	Relative (95% CI)	Absolute (95% CI)		
Vaccine effectiveness												
2[1-2]	RCT	Not serious	Not serious	Serious[a]	Not serious	Not serious	921-1022	910-989	• PCV20 had numerically lower immune responses compared with PCV13 for most of the 13 shared serotypes. • PCV20 did not meet one of the noninferiority endpoints[b] for some serotypes (1, 3, 4, 9V, 23F, and 12F) after dose 3. • PCV20 noninferior[c] to PCV13 for all 13 shared serotypes after dose 4. • PCV20 noninferior[c] to PCV13 for all 7 additional serotypes after dose 4.		Moderate	Critical

RCT=randomized clinical trial

a. These are all immunogenicity studies and there are no correlates of protection for some critical outcomes considered.

b. Noninferiority for difference in percentages of participants meeting predefined IgG threshold value was defined as the lower bound of 2-sided 95% confidence interval for percent difference (PCV20-PCV13)>-10%. Additional 7 serotypes contained in PCV20 but not in PCV13 were compared with a PCV13 serotype with the lowest percentage excluding serotype 3.

c. Noninferiority for GMC ratio was defined as the lower bound of 2-sided 95% confidence interval of IgG GMC ratio (PCV20/PCV13) >0.5. Additional 7 serotypes contained in PCV20 but not in PCV13 were compared with a PCV13 serotype with the lowest percentage excluding serotype 3.

References

1. Senders S, Klein NP, Lamberth E, Thompson A, Drozd J, Trammel J, Peng Y, Giardina PC, Jansen KU, Gruber WC, Scott DA, Watson W. Safety and Immunogenicity of a 20-valent Pneumococcal Conjugate Vaccine in Healthy Infants in the United States. Pediatr Infect Dis J. 2021 Oct 1;40(10):944-951. doi: 10.1097/INF.0000000000003277.

2.B7471011. A Phase 3, Randomized, double-blind trial to evaluate the safety and immunogenicity of a 20-valent pneumococcal conjugate vaccine in healthy infants

GRADE Summary of Findings: Routine PCV20 use in Children Aged <2 Years

Certainty assessment							№ of patients		Results		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparison	Relative (95% CI)	Absolute (95% CI)		
Serious Adverse Events (SAEs) following vaccination												
2[1-3]	RCT	Not serious	Not serious	Not serious	Serious[a]	Not serious	101/2232 (4.5%)	64/1717 (3.7%)	No vaccine-related serious adverse events reported		Moderate	Critical

RCT=randomized clinical trial

a. No vaccine-related serious adverse events reported

References

1.Senders S, Klein NP, Lamberth E, Thompson A, Drozd J, Trammel J, Peng Y, Giardina PC, Jansen KU, Gruber WC, Scott DA, Watson W. Safety and Immunogenicity of a 20-valent Pneumococcal Conjugate Vaccine in Healthy Infants in the United States. Pediatr Infect Dis J. 2021 Oct 1;40(10):944-951. doi: 10.1097/INF.0000000000003277.

2.B7471011. A Phase 3, Randomized, double-blind trial to evaluate the safety and immunogenicity of a 20-valent pneumococcal conjugate vaccine in healthy infants

3.B7471013. A Phase 3, Randomized, double-blind trial to evaluate the safety of a 20-valent pneumococcal conjugate vaccine in healthy infants. Data limited to U.S. and Puerto Rico sites.

Included Study: PCV20 Use in Children Aged 2–18 Years with Underlying Medical Conditions

Author, year	Study design	Intervention	Country	Age	Total population	N Intervention	N comparison	Outcomes	Funding source
B7471014	Phase III Clinical Trial in healthy children, some previously vaccinated	Single dose PCV20 @ 15m to <24m; **previous vaccination ≥3 doses of PCV13**	US	15m to <24m	209	209	N/A	Immuno-genicity and safety	Pfizer
		Single dose PCV20 @ 2y to <5y; **previous vaccination ≥3 doses of PCV13**		2y to <5y	216	216	N/A		
		Single dose PCV20 @ 5y to <10y		5y to <10y	201	201	N/A		
		Single dose PCV20 @ 10 to <18y		10y to <18y	205	205	N/A		

GRADE Summary of Findings: PCV20 Use in Children Aged 2–18 Years with Underlying Medical Conditions

Certainty assessment							№ of patients		Results		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	comparison	Relative (95% CI)	Absolute (95% CI)		
Vaccine effectiveness												
1[1]	Non-RCT	Very Serious[a]	Not applicable	Very Serious[b,c]	Not serious	Not serious	752-757	None	IgG GMCs were higher 1-month post-PCV20 dose compared to before vaccination for 13/13 shared serotypes and 7/7 additional serotypes, for all age groups		Very Low	Critical

RCT=randomized clinical trial

a. Study design is an open label non-randomized controlled trial with no comparator group. Downgraded for lack of randomization, lack of blinding, and lack of a comparison group.

b. Study population did not include children with underlying conditions

c. This is an immunogenicity study and there are no correlates of protection for some critical outcomes considered

References

B7471014. Safety and Immunogenicity Study of 20vPnC in Healthy Children 15 Months Through 17 Years of Age

GRADE Summary of Findings: PCV20 use in Children Aged 2–18 Years With Underlying Medical Conditions

Certainty assessment							№ of patients	Results		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV20 Intervention	Relative (95% CI)	Absolute (95% CI)		
Serious Adverse Events (SAEs) following vaccination											
1[1]	Non-RCT	Serious[a]	Not applicable	Serious[b]	Serious[c]	Not serious	5/831 (0.6%)	No vaccine-related SAEs reported		Very Low	Critical

RCT=randomized clinical trial

a. Study design is an open label non-randomized controlled trial with no comparator group
b. Study population did not include children with underlying conditions
c. No vaccine-related serious adverse events reported; relative risk crossing 1

Reference

B7471014. Safety and Immunogenicity Study of 20vPnC in Healthy Children 15 Months Through 17 Years of Age