Updates to the Evidence to Recommendation Framework: Use of 15-valent Pneumococcal Conjugate Vaccine in Children

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ACIP Meeting

June 22, 2022

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?

Evidence to Recommendations (EtR) Framework

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Equity	• What would be the impact of the intervention on health equity?

PICO Question	Should PCV15 be recommended as an option for pneumococcal conjugate vaccination according to currently recommended dosing and schedules, for U.S. children?	
Population	**U.S. children aged <2 years**	**U.S. children aged 2–18 years with underlying medical conditions**
Intervention	PCV15 according to currently recommended dosing and schedules	
Comparison	PCV13 according to currently recommended dosing and schedules	
Outcomes	VT-IPD, VT- pneumonia, VT- AOM, VT- pneumococcal deaths, serious adverse events following immunization	

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

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EtR Domain: Public Health Problem

(Unchanged)

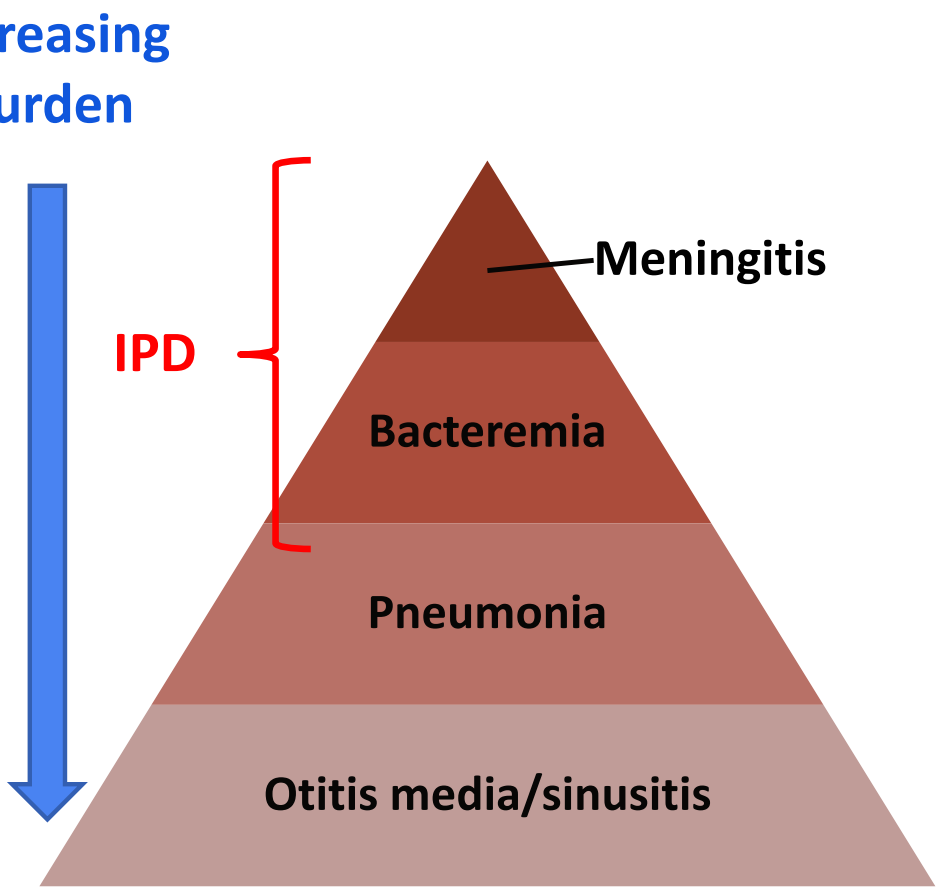
Pneumococcal disease

- Invasive pneumococcal disease (IPD)

  e.g., meningitis, bacteremia, bacteremic pneumonia

- Non-invasive disease

  e.g., non-bacteremic pneumonia, acute otitis media



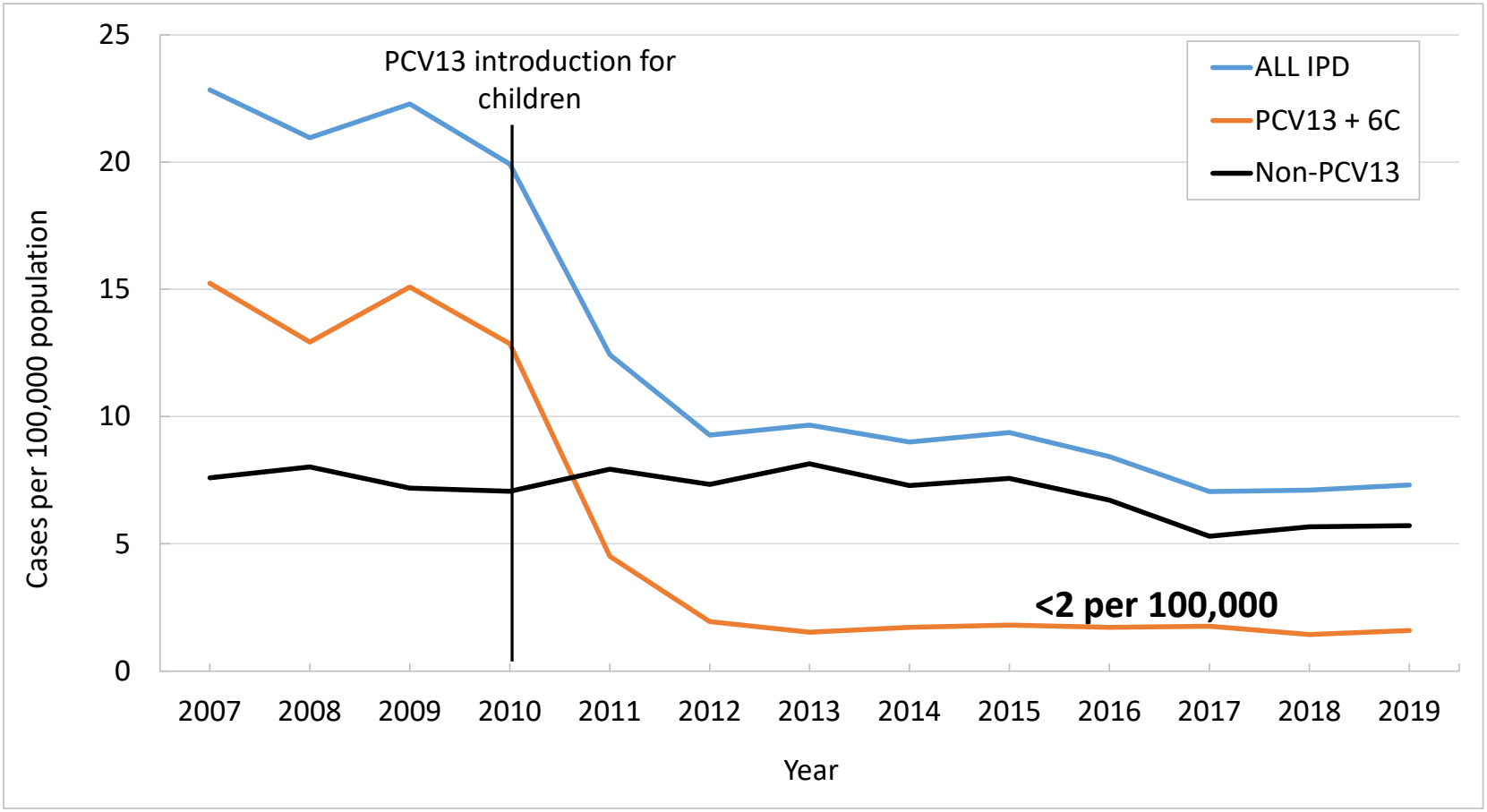
Estimated Burden of Acute Otitis Media (AOM) and Pneumonia in Children

- AOM one of most common reasons for outpatient care and antibiotic prescribing in children[1,2,3]
  - In 2018, approximately 75,000 (per 100,000 person years) AOM cases occurred in children aged <2 years[4]
  - Pneumococcus estimated to account for **24%** of clinically diagnosed AOM in children[5]
- In 2014, approximately 1,300 to 4,000 (per 100,000 person years) all-cause pneumonia occurred in children aged <17 years[6]
- Administrative data have shown decline in incidence of AOM and hospitalization of all-cause and pneumococcal pneumonia in children post-PCV introduction[4,7]

[1]Tong BMC Health Services Research 2018, [2]Lewnard CID 2021, [3]Hersh et al. Pediatric 2011, 4, Hu et al. BMCID, [5]Kaur et al. EJCMID 2022. [6]Tong BMC Health Services Research 2018, [7] Simmonsent, Lancet Resp Med 2014

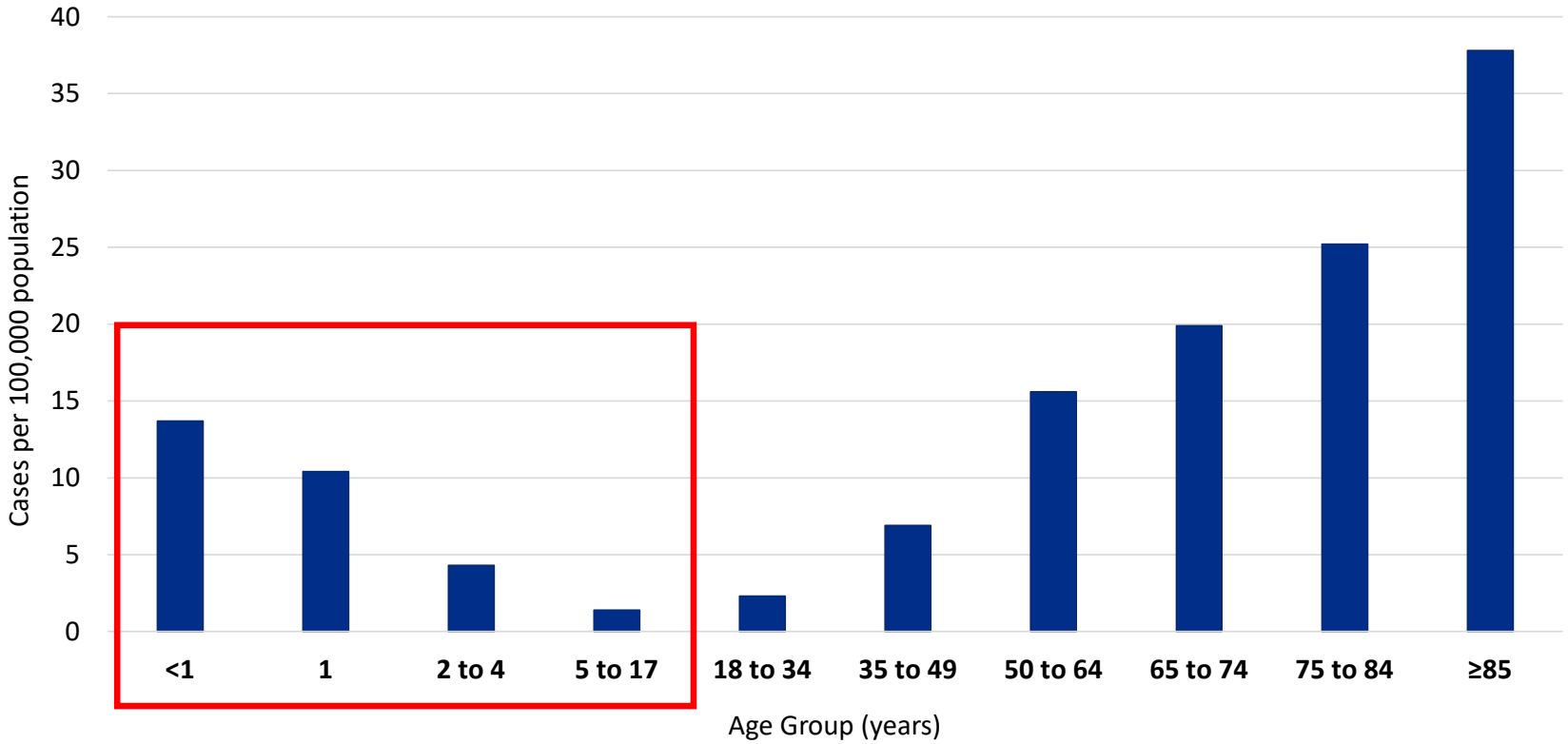
AOM: acute otitis media, IPD: invasive pneumococcal disease, PCV: pneumococcal conjugate vaccine

Incidence of invasive pneumococcal disease (IPD) among children aged <5 years decreased post-PCV13 introduction.



CDC ABCs, 2007 to 2019

In children, IPD incidence decreases with increasing age.



Active Bacterial Core Surveillance (ABCs) Report Emerging Infections Program Network Streptococcus pneumoniae, 2019. Available: SPN_Surveillance_Report_2019.pdf (cdc.gov)

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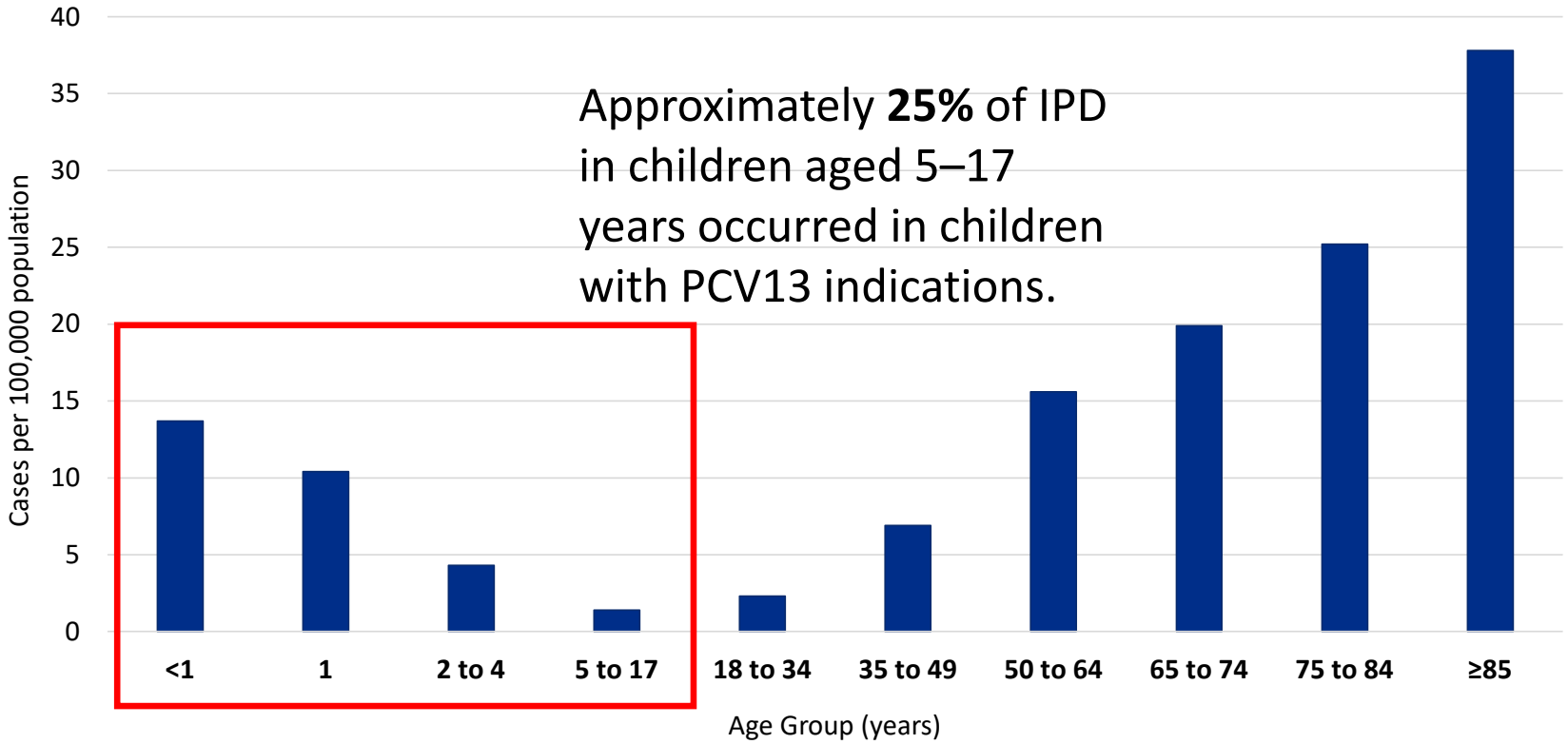

Active Bacterial Core Surveillance (ABCs) Report Emerging Infections Program Network Streptococcus pneumoniae, 2019. Available: SPN_Surveillance_Report_2019.pdf (cdc.gov)

Pneumococcal Serotype Distribution in Children

	Rochester Cohort, Children aged 3–36 mo with AOM	
	NP swabs (N=209)	MEF taps (N=98)
PCV13+6C type	**8.1%**	**9.3%**
ST3	1.4%	3.1%
ST19F	3.3%	3.1%
ST19A	1.4%	3.1%
PCV15, non-PCV13 type	**6.2%**	**8.2%**
All other serotypes	**85.6%**	**84.7%**

MEF= middle ear fluid, NP= nasopharyngeal

Adapted from Kaur et al. EJCMID 2022

Pneumococcal Serotype Distribution in Children

	Rochester Cohort, Children aged 3–36 mo with AOM (2015–2019)		ABCs, 2018–2019	
			Aged <5 yrs	Aged 5–18 yrs
	NP swabs (N=209)	MEF taps (N=98)	IPD	IPD
PCV13+6C type	**8.1%**	**9.3%**	**21%**	**34%**
ST3	1.4%	3.1%		
ST19F	3.3%	3.1%		
ST19A	1.4%	3.1%		
PCV15, non-PCV13 type	**6.2%**	**8.2%**	**17%**	**16%**
All other serotypes	**85.6%**	**84.7%**	**62%**	**50%**

MEF= middle ear fluid, NP= nasopharyngeal

Adapted from Kaur et al. EJCMID 2022

Public Health Problem

Is pneumococcal disease of public health importance in children?

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

No Change from February ACIP meeting

EtR Domain: Benefits and Harms

(Updated)

Benefits and Harms

How substantial are the desirable anticipated effects?

- **Routine PCV15 use for children aged <2 years**
- **PCV15 use for children aged 2–18 years with underlying medical conditions**

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

No change from February ACIP meeting.

Studies included in Evidence Review

Routine PCV15 Use for Children Aged <2 years

Author, year	Study design	Intervention	Country	Age	Total population	N Intervention	N comparison
Platt, 2020 (V114-008)	Phase 2 RCT (proof of concept); healthy children	PCV15 3+1 (2,4, 6, 12-15m)	Canada, Denmark, Finland, Israel, Spain, US	6-12 weeks at enrollment	1044	350 (Lot 1) 347 (Lot 2)	347
V114-029 Merck, unpublished	Phase 3 RCT (pivotal study); healthy children	PCV15 3+1 (2,4, 6, 12-15m); co-administration pentacel, recombivax, rotateq	Puerto Rico, Thailand, Turkey, US	42-90 days at enrollment	1714	858	856
V114-027 Merck, unpublished	Phase 3 RCT (product interchangeability); healthy children	Group 1: PCV13 @ 2,4,6, 12-15m Group 2: PCV13 + PCV13+ PCV13 + PCV15 (booster) Group 3: PCV13 + PCV13+ PCV15 + PCV15 (booster) Group 4: PCV13 + PCV15+ PCV15 + PCV15 (booster) Group 5: PCV15 @ 2,4,6, 12-15m	Puerto Rico, Thailand, Turkey, US	42-90 days at enrollment	896	Group 2 (n=181) Group 3 (n=178) Group 4 (n=179) Group 5 (n=179)	Group 1 (n=179)
V114-024 Merck, unpublished	Phase 3 RCT (catch up); healthy children	7-11m: 3 doses (dose 1 @ 0w, dose 2 @ 4-8w PD1, dose 3 @ 8-12w PD2 AND >12m 12-23m: 2 doses (dose 1 @ 0w, dose 2 @ 4-8w PD1) 2-17y: 1 dose (>8w after previous PCV)	Finland, Malaysia, Poland, Russia, Thailand	7 months – 17 years	606	2-11m (n=64) 12-23m (n=62) 2-17y (n=177)	2-11m (n=64) 12-23m (n=64) 2-17y (n=175)
V114-031 Merck, unpublished	Phase 3 RCT, full-term v. pre-term infants	PCV15 3+1 (2,4, 6, 12-15m)	Australia, Canada, Finland, Germany, Israel, Malaysia, Peru, Taiwan, Thailand, US	Full-term (>37 wks) and pre-term infants (<37 wks); 42-90 days at enrollment	2398	1965	433

Immunogenicity and Safety

All studies funded by Merck; comparator is PCV13 for all studies

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All studies funded by Merck; comparator is PCV13 for all studies

Summary of Evidence from PCV15 studies

Routine PCV15 Use for Children Aged <2 years

Benefits (VT-IPD, VT-AOM, VT-pneumonia, deaths)

Certainty assessment							№ of patients		Results		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PCV15 (intervention)**	**PCV13 (comparison)**	**Relative (95% CI)**	**Absolute (95% CI)**	
Vaccine effectiveness: Vaccine-type pneumococcal disease (assessed with immunogenicity data)											
4[1-4]	RCT	Not serious	Not serious	**Serious**[a]	Not serious	Not serious	2575	1685	• PCV15 **noninferior** to PCV13 for all 13 shared serotypes; **statistically significantly higher** immune response for st3 • PCV15 **statistically significantly higher** immune responses to PCV13 for 22F and 33F (unique st)		**2 Moderate**

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

References
1. Platt HL, Greenberg D, Tapiero B, Clifford RA, Klein NP, Hurley DC. A Phase II Trial of Safety, Tolerability and Immunogenicity of V114, a 15-Valent Pneumococcal Conjugate Vaccine, Compared With 13-Valent Pneumococcal Conjugate Vaccine in Healthy Infants. Pediatric Infectious Diseases Journal 2020.
2. V114-029. Safety, Tolerability, and Immunogenicity of V114 in Healthy Infants (V114-029)
3. V114-027. A Study to Evaluate the Interchangeability of V114 and Prevnar 13™ in Healthy Infants (V114-027/PNEU-DIRECTION)
4. V114-024. Safety and Immunogenicity of Catch-up Vaccination Regimens of V114 (V114-024)

RCT: Randomized Controlled Trial.
Please see GRADE summary tables for details

Studies included in Evidence Review

PCV15 Use for Children Aged 2–18 Years with Underlying Conditions

Author, year	Study design	Country	Age	Total population	N Intervention	N comparison
V114-023 Merck, unpublished	Phase 3 RCT (one dose of PCV15 vs. PCV13), children with sickle cell disease, 5–17 years	Brazil, Colombia, Dominican Republic, Greece, Italy, Panama, US	5-17 years	103	69	34
V114-030 Merck, unpublished	Phase 3 RCT (PCV15+PPSV23 vs. PCV13 + PPSV23), children living with HIV, 6 – 17 years	South Africa, Thailand, Ukraine	6-17 years	407	203	204

All studies funded by Merck

Summary of Evidence from PCV15 studies

PCV15 Use For Children Aged 2–18 Years with Underlying Conditions

Benefits (VT-IPD, VT-AOM, VT-pneumonia, deaths)

Certainty assessment							№ of patients		Results		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PCV15 intervention**	**PCV13 comparison**	**Relative (95% CI)**	**Absolute (95% CI)**	
Vaccine effectiveness: Vaccine-type pneumococcal disease (assessed with immunogenicity data)											
2[1,2]	RCT	Not serious	Not serious	**Serious**[a]	**Serious**[b]	Not serious	272	238	• **Post-PCV dose: PCV15 had higher immune responses (IgG GMC) vs. PCV13 for 6 - 7 PCV13 serotypes and unique serotypes (22F and 33F).** • **Post-PPSV23 dose: PCV15+PPSV23 had higher immune response (IgG GMC) vs. PCV13+PPSV23 for 3 of 13 PCV13 serotypes, but not for unique serotypes (22F and 33F).**		**3** **Low**

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

References
1. V114-023. A Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 in Children With Sickle Cell Disease (V114-023/PNEU-SICKLE)
2. V114-030. Safety and Immunogenicity of V114 in Children Infected With Human Immunodeficiency Virus (HIV) (V114-030/PNEU-WAY PED)

RCT: Randomized Controlled Trial. Please see GRADE summary tables for details

Benefits and Harms

How substantial are the undesirable anticipated effects?

- **Routine PCV15 use for children aged <2 years**

February 2022 ACIP meeting: **Minimal**

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

Benefits and Harms

How substantial are the undesirable anticipated effects?

- **Routine PCV15 use for children aged <2 years**
  - Uncertainty about higher reactogenicity in children who received PCV15
  - Descriptive safety analysis
    - Serious vaccine-related adverse events
    - Fever ≥104◦F post dose 4

Summary of Evidence from PCV15 studies

Routine Use for Children Aged <2 years

Harms: Serious Vaccine-Related Adverse Events

Certainty assessment							№ of patients		Results		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV15	PCV13	Relative (95% CI)	Absolute (95% CI)	
Serious adverse events following immunization											
5[1-5]	Randomized studies	Not serious	Not serious	Not serious	Very Serious[a]	Not serious	5/4540	0/2117	1.30 (0.22, 7.74)[b]	--	**3 Low**

a. Few vaccine-related serious adverse events reported, wide 95% CI of the relative risk cannot exclude the potential for increased harm or benefit.

b. Pooled estimate includes 3 of 5 studies where outcome occurred; two studies with no SAE were excluded.

References

1. Platt HL, Greenberg D, Tapiero B, Clifford RA, Klein NP, Hurley DC. A Phase II Trial of Safety, Tolerability and Immunogenicity of V114, a 15-Valent Pneumococcal Conjugate Vaccine, Compared With 13-Valent Pneumococcal Conjugate Vaccine in Healthy Infants. Pediatric Infectious Diseases Journal 2020.
2. V114-029. Safety, Tolerability, and Immunogenicity of V114 in Healthy Infants (V114-029)
3. V114-027. A Study to Evaluate the Interchangeability of V114 and Prevnar 13™ in Healthy Infants (V114-027/PNEU-DIRECTION)
4. V114-024. Safety and Immunogenicity of Catch-up Vaccination Regimens of V114 (V114-024)
5. V114-031. A Study to Evaluate the Safety and Tolerability of V114 and Prevnar 13™ in Healthy Infants (V114-031/PNEU-LINK)

Please see GRADE summary tables for details

Benefits and Harms

How substantial are the undesirable anticipated effects?

- **PCV15 use for children aged 2–18 years with underlying medical conditions**

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

No change from February ACIP meeting.

Summary of Evidence from PCV15 studies

Routine Use for Children Aged 2–18 Years with Underlying Conditions

Harms: Serious Vaccine-Related Adverse Events

Certainty assessment							№ of patients		Results		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PCV15**	**PCV13**	**Relative (95% CI)**	**Absolute (95% CI)**	
Serious adverse events following immunization											
2[1,2]	Randomized studies	Not serious	Not serious	Not serious	Very serious[a]	Not serious	0/272	0/238	not estimable	--	3 Low

a. No vaccine-related serious adverse events reported; sample size very small

References

1. V114-023. A Study to Evaluate the Safety, Tolerability, and Immunogenicity of V114 in Children With Sickle Cell Disease (V114-023/PNEU-SICKLE)
2. V114-030. Safety and Immunogenicity of V114 in Children Infected With Human Immunodeficiency Virus (HIV) (V114-030/PNEU-WAY PED)

Please see GRADE summary tables for details

Benefits and Harms

Do the desirable effects outweigh the undesirable effects?

- **Routine PCV15 use for children aged <2 years**
- **PCV15 use for children aged 2–18 years with underlying medical conditions**

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

February ACIP meeting:

- "**Favors intervention**" selected

Interpretation was updated after clarifying the comparison:
***Intervention:** PCV15 use
Comparison: PCV13 use

Benefits and Harms

Do the desirable effects outweigh the undesirable effects?

- What is the balance between the desirable effects relative to the undesirable effects?

- Uncertainty of the added impact from PCV15 use (vs. PCV13 use) given that we have no clinical efficacy data
- Uncertainty about reactogenicity from PCV15 use compared with PCV13 use

EtR Domain: Values and Preferences

(Unchanged)

High PCV13 vaccination coverage by age 24 months has been achieved.

Estimated PCV coverage by age 24 months, among children born during 2015–2018
National Immunization Survey-Child, United States, 2016–2020

PCV Doses	Born 2015-16	Born 2017-18
≥3 doses	91.9%	92.4%
≥4 doses	81.2%	82.3%

Hill et al. MMWR 2021

Values and Preferences

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

- **Routine PCV15 use for children aged <2 years**
- **PCV15 use for children aged 2–18 years with underlying medical conditions**

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

- Uncertainties remain about the magnitude of added benefit of PCV15 use compared with PCV13 use
- No change from February ACIP meeting

Values and Preferences

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

- **Routine PCV15 use for children aged <2 years**
- **PCV15 use for children aged 2–18 years with underlying medical conditions**

□ Important uncertainty or variability
□ Probably important uncertainty or variability
□ Probably not important uncertainty or variability
□ No important uncertainty or variability
□ No known undesirable outcomes

No change from February ACIP meeting

EtR Domain: Acceptability

Data source

- Merck's Provider Preferences Survey related to multi-valent pneumococcal conjugate vaccines
  - Administered Nov 2021
  - Included a sample of 600 healthcare providers (HCP) who prescribe/administer ≥10 pneumococcal vaccines per month (average 56)
    - Physicians (pediatrics, family medicine/general medicine): n=530
    - Physician assistant/nurse practitioner: n=70

Merck Unpublished Data, 2021

Key Findings

- About **40%** of HCPs believed the **risk of developing pneumococcal disease** is higher than the risk of developing other vaccine-preventable diseases* in children aged <24 months.
- Most HCPs (86–96%) believed that **pneumococcal vaccines are highly important** for children aged <24 months.
- **Important clinical features in pneumococcal vaccine choice** in children aged <24 months:
  - Invasive pneumococcal disease indication (63%)
  - Safety and side effects (47%)
  - Greater immune response to certain disease-causing serotypes (46%)
  - Overall immune response across vaccine serotypes (45%)

*measles, mumps, rubella, rotavirus, chickenpox, diphtheria, tetanus, or pertussis

Merck Unpublished Data, 2021

Acceptability

Is recommending PCV15 as an option for pneumococcal conjugate vaccination according to currently recommended dosing and schedules for children acceptable to key stakeholders?

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

EtR Domain: Resource Use

Summary of findings from cost-effective analyses

- PCV15 use reduces direct medical costs and improves health under the **following model assumptions**:
  - PCV15 and PCV13 have same VE for PCV13-type disease
  - PCV15 provides protective VE for two additional serotypes
  - The average cost for PCV15 is less than the cost of PCV13

Resource Use

Is the option a reasonable and efficient allocation of resources?

- **Routine PCV15 use for children aged <2 years**

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

Resource Use

Is the option a reasonable and efficient allocation of resources?

- **Routine PCV15 use for children aged <2 years**
  - Only immunogenicity studies available, and there are uncertainties around clinical efficacy of PCV15
  - There are uncertainties about the actual vaccine price
  - Possibility of increased healthcare utilization in the PCV15 recipients due to increased reactogenicity (e.g., fever)

Resource Use

Is the option a reasonable and efficient allocation of resources?

- **PCV15 use for children aged 2–18 years with underlying medical conditions**

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

EtR Domain: Equity

(Updated)

≥4 doses of PCV Coverage by age 24 months low among children who are uninsured, Black non-Hispanic, living in non-MSA, and living <133% FPL

Dimensions		Coverage (%)
Insurance Coverage	Private Insurance only	87.2
	Any Medicaid	77.3
	Uninsured	**62.2**
	Other	78.5
Race/Ethnicity	White, Non-Hispanic	83.6
	Black, Non-Hispanic	**76.5**
	Hispanic	80.4
	Other/Multiple Races, Non-Hispanic	80.7
Urbanicity	Living in MSA Principal City	81.3
	Living in MSA Non-Principal City	82.4
	Living in Non-MSA	**78.6**
Poverty	**<133% FPL**	**75.5**
	133% to <400% FPL	81.3
	>400% FPL	90.0

FPL=federal poverty level, MSA=metropolitan statistical area

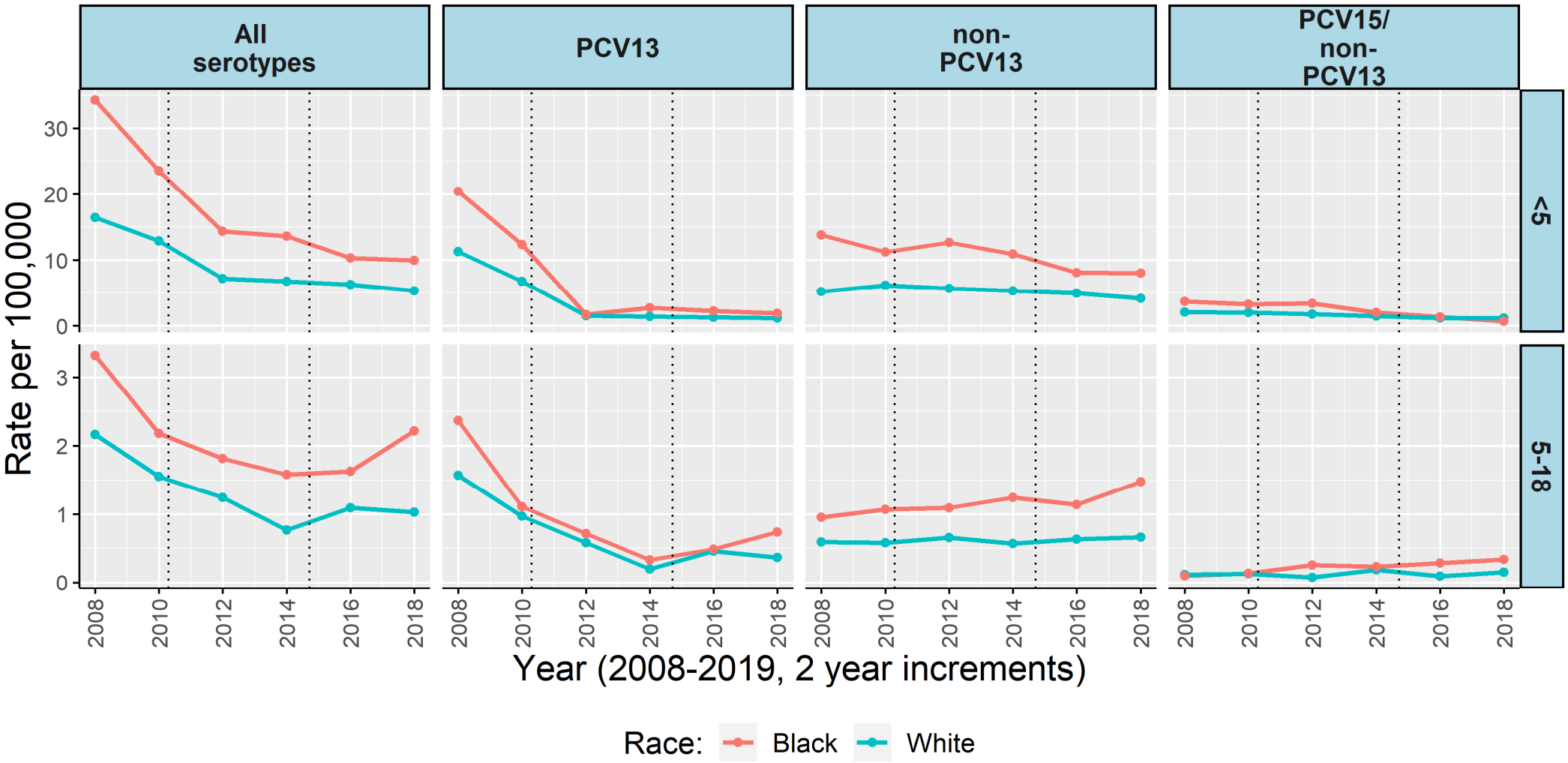
National Immunization Survey. 2020.

Pneumococcal disease burden remains higher in Native American/Alaskan Native children.

- IPD rates in Native American children <5 years remain approximately 4x higher compared to children of all races in 2018[1]
- Alaskan Native infant OM-associated outpatient visit rate 1.6-fold higher than general U.S. infant population[2]
- NA/AN experience cyclical outbreaks due to serotype 12F[3]
  - Serotype 12F not included in PCV13 or PCV15

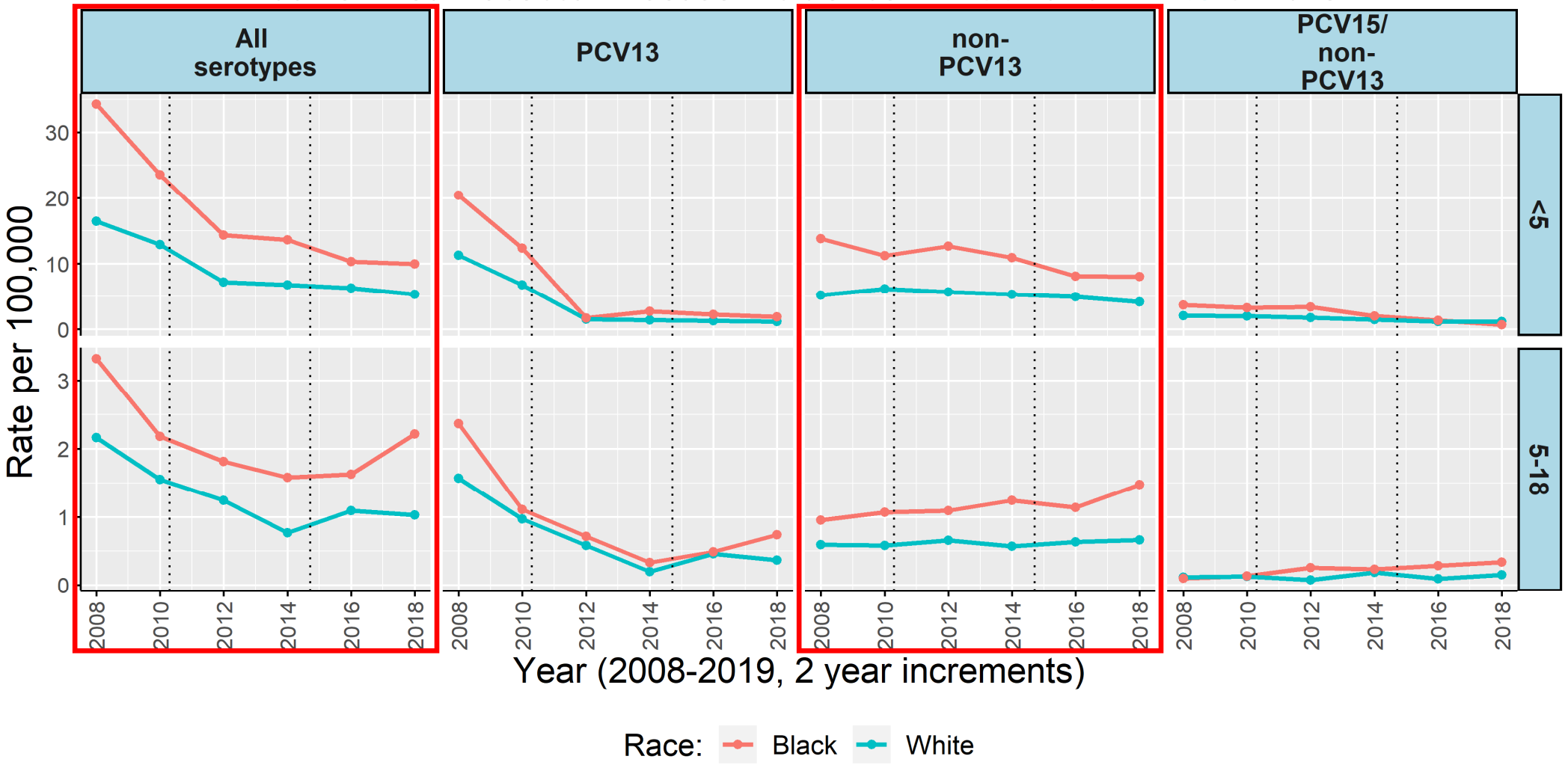
[1]Littlepage et al, 9th International Meeting on Indigenous Child Health, 2021
[2]Singleton et al. PIDJ 2018
[3]Zulz et al. JCM 2012

Invasive Pneumococcal Disease Incidence in Black and White Children



Unpublished CDC data, Active Bacterial Core surveillance

Invasive Pneumococcal Disease Incidence in Black and White Children



Unpublished CDC data, Active Bacterial Core surveillance

Invasive Pneumococcal Disease Incidence in Black and White Children

Unpublished CDC data, Active Bacterial Core surveillance

Equity

What would be the impact of recommending PCV15 for U.S. children on health equity?

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

February ACIP meeting:

- “**Probably increased**” selected

EtR Domain: Feasibility

Current private sector cost for PCV15 in adults is lower than that of PCV13 in children.

Vaccine	Brandname/ Tradename	NDC	Packaging	CDC Cost/ Dose	Private Sector Cost/ Dose	Contract End Date	Manufacturer
Pneumococcal 15-valent [5] Adults	Vaxneuvance™	00006-4329-03	10 pack – 1 dose syringe	$149.90	$216.086	6/30/2022	Merck
Pneumococcal 13-valent [5] (Pediatric)	Prevnar 13™	00005-1971-02	10 pack – 1 dose syringe	$158.18	$226.43	3/31/2023	Pfizer

- Vaccine for Children Program cost (public sector) is currently unknown

As of May 17, 20222. https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html

Feasibility

Is recommending PCV15 as an option for pneumococcal conjugate vaccination according to currently recommended dosing and schedules for children feasible to implement?

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

- PCV15 for children is likely to be priced similar to (or less than) PCV13
- PCV13 has achieved high coverage in children

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

EtR Domains	PCV15, <2 years	PCV15, 2–18 years old
Public Health Problem	Yes	
Benefits and Harms		
a. Benefits	Moderate	
b. Harms	Small	Minimal
c. Benefit>Harm?	Favors both	
d. Overall certainty: effectiveness	2 (moderate)	3 (low)
e. Overall certainty: safety	3 (low)	3 (low)
Values		
a. Desirable>Undesirable?	Yes/Probably Yes	
b. Uncertainty?	Probably not important uncertainty or variability	
Acceptability	Probably Yes	
Resource Use	Probably Yes/Yes	Probably Yes
Equity	Probably no impact	
Feasibility	Probably Yes	

Summary of Work Group Interpretation of the EtR Domains (New domains presented)

EtR Domains	PCV15, <2 years	PCV15, 2–18 years old
Public Health Problem	Yes	
Benefits and Harms		
a. Benefits	Moderate	
b. Harms	Small	Minimal
c. Benefit>Harm?	Favors both	
d. Overall certainty: effectiveness	2 (moderate)	3 (low)
e. Overall certainty: safety	3 (low)	3 (low)
Values		
a. Desirable>Undesirable?	Yes/Probably Yes	
b. Uncertainty?	Probably not important uncertainty or variability	
Acceptability	Probably Yes	
Resource Use	Probably Yes/Yes	Probably Yes
Equity	Probably no impact	
Feasibility	Probably Yes	

Summary: Work Group Interpretations

Should PCV15 be recommended as an option for pneumococcal conjugate vaccination according to currently recommended dosing and schedules for U.S. children

1. aged <2 years?

2. aged 2 to 18 years with underlying medical conditions?

Comparison: PCV13 use

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

ACIP Policy Statement for PCV15 Use

PCV15 may be used as an option to PCV13 for children aged <19 years according to currently recommended PCV13 dosing and schedules.

Acknowledgements

- ACIP and the Pneumococcal Vaccines Work Group
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GRADE tables

PICO – routine use in children aged <2 years

Outcomes and Rankings

Outcome	Importance*	Included in evidence profile
Vaccine-type invasive pneumococcal disease	Critical	No**
Vaccine-type pneumonia	Critical	No**
Vaccine-type acute otitis media	Critical	No**
Vaccine-type pneumococcal deaths	Critical	No**
Serious adverse events following immunization	Critical	Yes

*Three options: 1. Critical; 2. Important but not critical; 3. Not important for decision making
**No clinical evidence available; immunogenicity data used as proxy for vaccine effectiveness of outcomes

Summary of studies: immunogenicity

Author, year	Study design; population and age	Intervention	N intervention	N comparison	Comparator vaccine	IgG GMC ratios [range (serotype)][1]	Absolute difference in % seroresponders (serotype)[2]	Interpretation	Study limitations (Risk of Bias)
Platt, 2020 (V114-008)	Phase 2 RCT (proof of concept); healthy children, 6-12 weeks	PCV15 3+1 (2,4, 6, 12-15m)	350 (Lot 1) 347 (Lot 2)	347	PCV13	Post-dose 3 Lot 1: 0.54 (6A) to 1.98 (3) Lot 2: 0.57 (6A) to 1.93 (3) Post-dose 4 Lot 1: 0.67 (7F) to 1.44 (3) Lot 2: 0.66 (6A) to 1.48 (3)	Post-dose 3 Lot 1: -5.6 (6A) to 24.3 (3) Lot 2: -0.8 (19F) to 22.4 (3) Post-dose 4 Lot 1: -1.1 (23F) to 8.6 (3) Lot 2: 0 (4, 5, 6A, 7F, 9V, 14, 18C) to 9.6 (3)	GMC ratios Post-dose 3 • PCV15 > PCV13 for 3/13 (Lot 1) and 4/13 (Lot 2) shared serotypes; significantly higher for st3 (Lot 1 and 2) and 23F (Lot 2) • PCV15 (Lot 1 and 2) > PCV13 for 22F and 33F Post-dose 4 • PCV15 > PCV13 for st3 and 6B (Lot 1) and st3 and 18 (Lot 2); significantly higher for st3 only (Lot 1 and 2) • PCV15 (Lot 1 and 2) > PCV13 for 22F and 33F %seroresponders Post-dose 3 • PCV15 (Lot 1 and Lot 2) noninferior[3] to PCV13 for all 13 shared serotypes • PCV15 > PCV13 for 9/13 (Lot 1) and 8/13 (Lot 2) shared st; significantly higher for st3 only (Lot 1 and 2) • PCV15 (Lot 1 and 2) > PCV13 for 22F and 33F Post-dose 4 • PCV15 > PCV13 for 5/13 (Lot 1) and 6/13 (Lot 2) shared st; significantly higher for st3 only (Lot 1 and 2) • PCV15 = PCV13 for 5/13 (Lot 1) and 7/13 (Lot 2) shared st • PCV15 (Lot 1 and 2) > PCV13 for 22F and 33F	Not serious

Summary of studies: immunogenicity

Author, year	Study design; population and age	Intervention	N intervention	N comparison	Comparator vaccine	IgG GMC ratios [range (serotype)][1]	Absolute difference in % seroresponders (serotype)[2]	Interpretation	Study limitations (Risk of Bias)
V114-029 Merck, unpublished	Phase 3 RCT (pivotal study); healthy children, 42-90 days	PCV15 3+1 (2,4, 6, 12-15m); co-administration pentacel, recombivax, rotateq	858	856	PCV13	Post-dose 3: 0.52 (6A) to 1.73 (3) Post-dose 4: 0.60 (6A) to 1.35 (3)	Post-dose 3 -5 (6A) to 16 (3) Post-dose 4 Not reported	**GMC ratios** **Post-dose 3** • PCV15 noninferior[4] to PCV13 for 12/13 (no for 6A) shared serotypes; statistically significantly higher for st3 • PCV15 statistically significantly higher to PCV13 for 22F and 33F (unique st) • PCV15 > PCV13 for st3 only (statistically significant) • PCV15 > PCV13 for 22F and 33F **Post-dose 4** • PCV15 noninferior[4] to PCV13 for all 13 shared serotypes; statistically significantly higher for st3 • PCV15 statistically significantly higher to PCV13 for 22F and 33F (unique st) • Non-inferiority met for concombinant use • PCV15 > PCV13 for st3 (statistically significant) • PCV15 > PCV13 for 22F and 33F **%seroresponders** **Post-dose 3** • PCV15 noninferior[5] to PCV13 for all 13 shared serotypes; statistically significantly higher for st3 • PCV15 statistically significantly higher to PCV13 for 22F and 33F (unique st) • PCV15 > PCV13 for st 3 (statistically significant) • PCV15 = PCV13 for 14 and 23F • PCV15 > PCV13 for 22F and 33F **Post-dose 4** • Not reported	Not serious

1. Ratio calculated as [GMC (PCV15)]/[GMC (comparator vaccine)]; blood draws occurred 30 days or 1 month post-dose.
2. Seroresponse: proportion of participants meeting IgG threshold value of >=0.35µg/mL; blood draws occurred 30 days or 1 month post-dose.
3. Noninferiority requires the lower bound of the 2-sided 95% CI for the difference in response rates (V114 –PCV13) to be >-15 percentage points for the shared serotypes.
4. Noninferiority requires the lower bound of the 2-sided 95% CI for IgG GMC ratio (V114/PCV13) to be >0.5 (1-sided p-value <0.025
5. Noninferiority requires the lower bound of the 2-sided 95% CI for the difference in response rates (V114 –PCV13) to be >-10 percentage points (1-sided p-value <0.025

Summary of studies: immunogenicity

Author, year	Study design; population and age	Intervention	N intervention	N comparison	Comparator vaccine	IgG GMC ratios [range (serotype)][1]	Absolute difference in % seroresponders (serotype)[2]	Interpretation	Study limitations (Risk of Bias)
V114-027 Merck, unpublished	Phase 3 RCT (product interchangeability); healthy children, 42-90 days	Group 2: PCV13 + PCV13+ PCV13 + PCV15	181	179	Group 1: PCV13 @ 2,4,6, 12-15m	0.83 (1) to 1.51 (18C)	0 (6A, 7F, 9V, 14, 19F) to 6.5 (23F)	**GMC ratio (post-dose 4):** • PCV15 > PCV13 for 7/13 shared st; significant for 6B, 14, 18C **% seroresponders (post-dose 3):** • PCV15 > PCV13 for 8/13 shared st; significant for 14 and 23F • PCV15 = PCV13 for 5/13 st • PCV15 >PCV13 for 33F	Not serious
		Group 3: PCV13 + PCV13+ PCV15 + PCV15	178	179	Group 1: PCV13 @ 2,4,6, 12-15m	0.84 (4 and 19A) to 1.44 (18C)	-4.9 (4) to 5.9 (3)	**GMC ratio (post-dose 4):** • PCV15 > PCV13 for 6/13 shared st; significant for 14 and 18C **% seroresponders (post-dose 3):** • PCV15 > PCV13 for 4/13 shared st; significant for st4 • PCV15 = PCV13 for 7F • PCV15 >PCV13 for 22F and 33F	
		Group 4: PCV13 + PCV15+ PCV15 + PCV15	179	179	Group 1: PCV13 @ 2,4,6, 12-15m	0.77 (23F) to 1.08 (6B)	-91.4 (23F) to 8.7 (3 and 6B)	**GMC ratio (post-dose 4):** • PCV15 > PCV13 for 4/13 shared st **% seroresponders (post-dose 3):** • PCV15 > PCV13 for 5/13 shared st; significant for st3 • PCV15 >PCV13 for 22F	
		Group 5: PCV15 @ 2,4,6, 12-15m	179	179	Group 1: PCV13 @ 2,4,6, 12-15m	0.67 (7F) to 1.22 (3)	-4.7 (19A) to 20.7 (3)	**GMC ratio (post-dose 4):** • PCV15 > PCV13 for 2/13 shared st; significant for st3 **% seroresponders (post-dose 3):** • PCV15 > PCV13 for 6/13 shared st; significant for st3 • PCV15 > PCV13 for 22F and 33F	

Summary of studies: immunogenicity

Author, year	Study design; population and age	Intervention	N intervention	N comparison	Comparator vaccine	IgG GMC ratios [range (serotype)][1]	Absolute difference in % seroresponders (serotype)[2]	Interpretation	Study limitations (Risk of Bias)
V114-024 Merck, unpublished	Phase 3 RCT (catch up); heathy children, 7 months – 17 years	PCV15 (7-11m: 3 doses (dose 1 @ 0w, dose 2 @ 4-8w PD1, dose 3 @ 8-12w PD2 AND >12m)	64	64	PCV13 (3 doses)	0.52 (6A) to 1.55 (3)	-3.3 (6A and 6B) to 3.4 (3)	**GMC ratio (post-dose 3):** • PCV15 > PCV13 for st3 (significant) • PCV15 >PCV13 for 22F and 33F **% seroresponders (post-dose 3):** • PCV15 > PCV13 for st3 • PCV15 = PCV13 for 8/13 shared st • PCV15 >PCV13 for 22F and 33F	Not serious
		PCV15 (12-23m: 2 doses (dose 1 @ 0w, dose 2 @ 4-8w PD1))	62	64	PCV13 (2 doses)	0.54 (6A) to 1.76 (3)	-11.1 (6A) to 8.2 (3)	**GMC ratio (post-dose 2):** • PCV15 > PCV13 for 5/13 shared st; significant for st3 and 18C • PCV15 >PCV13 for 22F and 33F **% seroresponders (post-dose 2):** • PCV15 > PCV13 for 6/13 shared st; significant for st3 and 4 • PCV15 = PCV13 for 19F • PCV15 >PCV13 for 22F and 33F	
		PCV15 (2-17y: 1 dose (>8w after previous PCV)	177	175	PCV13 (1 dose)	0.48 (4) to 1.60 (18C)	-1.2 (4) to 8 (3)	**GMC ratio (post-dose 1):** • PCV15 > PCV13 for 6/13 shared st; significant for st3 and 18C • PCV15 >PCV13 for 22F and 33F **% seroresponders (post-dose 1):** • PCV15 > PCV13 for 5/13 shared st; significant for st3 • PCV15= PCV13 for 4/13 st • PCV15 >PCV13 for 22F and 33F	

Summary of studies: safety

Author, year	Study Design; population and age		N intervention	N comparison	Comparator vaccine	Absolute % difference (% SAE PCV15 – % SAE comparator)*	N related to vaccine	Study limitations (Risk of Bias)
Platt, 2020 (V114-008)	Phase 2 RCT (proof of concept); healthy children, 6-12 weeks		697 (lots 1 and 2 combined)	347	PCV13	1	2	Not serious
V114-029 Merck, unpublished	Phase 3 RCT (pivotal study); healthy children, 42-90 days		858	855	PCV13	0.8	0	Not serious
V114-027 Merck, unpublished	Phase 3 RCT (product interchangeability); healthy children, 42-90 days	Group 2: PCV13 + PCV13+ PCV13 + PCV15 (booster)	181	179	Group 1: PCV13 @ 2,4,6, 12-15m	1.6	0	Not serious
		Group 3: PCV13 + PCV13+ PCV15 + PCV15	178	179	Group 1: PCV13 @ 2,4,6, 12-15m	-3.3	1	
		Group 4: PCV13 + PCV15+ PCV15 + PCV15	179	179	Group 1: PCV13 @ 2,4,6, 12-15m	-1.6	0	
		Group 5: PCV15 @ 2,4,6, 12-15m	179	179	Group 1: PCV13 @ 2,4,6, 12-15m	0	0	
V114-024 Merck, unpublished	Phase 3 RCT (catch up); heathy children, 7 months – 17 years	PCV15 (7-11m: 3 doses (dose 1 @ 0w, dose 2 @ 4-8w PD1, dose 3 @ 8-12w PD2 AND >12m)	64	64	PCV13 (3 doses)	3.1	0	Not serious
		PCV15 (12-23m: 2 doses (dose 1 @ 0w, dose 2 @ 4-8w PD1))	62	64	PCV13 (2 doses)	0.2	0	
		PCV15 (2-17y: 1 dose (>8w after previous PCV)	177	175	PCV13 (1 dose)	0	0	
V114-031 Merck, unpublished	Phase 3 RCT, full-term v. pre-term infants, 41 – 90 days		1965	433	PCV13	-0.6	2	Not serious

Summary of Evidence for outcomes of interest

Outcome	Importance	Included in profile	Certainty
VT- invasive pneumococcal disease	Critical	No*	2
VT- pneumonia	Critical	No*	2
Vaccine-type acute otitis media	Critical	No*	2
Vaccine-type pneumococcal deaths	Critical	No*	2
Serious adverse events following immunization	Critical	Yes	3

*No clinical evidence available; immunogenicity data used as proxy for vaccine effectiveness of outcomes

GRADE tables

PICO – children aged 2–18 years with underlying medical conditions

Outcomes and Rankings

Outcome	Importance*	Included in evidence profile
Vaccine-type invasive pneumococcal disease	Critical	No**
Vaccine-type pneumonia	Critical	No**
Vaccine-type acute otitis media	Critical	No**
Vaccine-type pneumococcal deaths	Critical	No**
Serious adverse events following immunization	Critical	Yes

*Three options: 1. Critical; 2. Important but not critical; 3. Not important for decision making
**No clinical evidence available; immunogenicity data used as proxy for vaccine effectiveness of outcomes

Summary of studies: immunogenicity

Author, year	Study design; population and age	N intervention	N comparison	Comparator vaccine	IgG GMC ratios [range (serotype)] *	Absolute difference in % seroresponders (serotype)	Interpretation**	Study limitations (Risk of Bias)
V114-023 Merck, unpublished	Phase 3 RCT (one dose of V114 vs. PCV13), children with sickle cell disease, 5 – 17 years	69	34	PCV13	0.54 (4) to 1.67 (6B)	Not reported	GMC ratio (post-dose 1): • PCV15 > PCV13 for 6/13 shared st • PCV15 > PCV13 for 22F and 33F	Not serious
V114-030 Merck, unpublished	Phase 3 RCT (V114+PPSV23 vs. PCV13 + PPSV23), children living with HIV, 6 – 17 years	203	204	PCV13 followed by PPSV23 8 weeks later	Post-PCV: 0.61 (4) to 1.65 (6B) Post-PPSV23: 0.65 (4) to 1.43 (6B)	Not reported	Post-PCV: • PCV15 > PCV13 for 7/13 shared st; significant for st3 and 6B • PCV15 = PCV13 for 18C • PCV15 > PCV13 for 22F and 33F Post-PPSV23: • PCV15+PPSV23 > PCV13+PPSV23 for 3/13 shared st; significant for 6B • PCV15+PPSV23 < PCV13+PPSV23 for 22F and 33F	Not serious

* IgG GMC ratio = [GMC (PCV15)] / [GMC (comparator vaccine)]

**Blood draws occurred 30 days post-dose

Summary of studies: safety

Author, year	Study Design; population and age	N intervention	N comparison	Comparator vaccine	Absolute % difference (% SAE PCV15 – % SAE comparator)*	N related to vaccine	Study limitations (Risk of Bias)
V114-023 Merck, unpublished	Phase 3 RCT, children with sickle cell disease, 5 – 17 years	69	34	PCV13	-4.7	0	Not serious
V114-030 Merck, unpublished	Phase 3 RCT, children living with HIV, 6 – 17 years	203	204	PCV13	0	0	Not serious
		203	202	PCV13 + PPSV23	0	0	

*Reported serious adverse events include those that occurred after dose 1 through completion of study participation.

Summary of Evidence for outcomes of interest

Outcome	Importance	Included in profile	Certainty
VT- invasive pneumococcal disease	Critical	No*	3
VT- pneumonia	Critical	No*	3
Vaccine-type acute otitis media	Critical	No*	3
Vaccine-type pneumococcal deaths	Critical	No*	3
Serious adverse events following immunization	Critical	Yes	3

*No clinical evidence available; immunogenicity data used as proxy for vaccine effectiveness of outcomes