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

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ACIP Meeting

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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

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?

Public Health Problem

Is pneumococcal disease of public health importance in children?

Public Health Problem

- AOM one of most common reasons for outpatient care in children[1,2]
  - Pneumococcus one of most common bacterial causes
- Administrative data have shown AOM and pneumonia rates in children decreased over time
- IPD rates decreased after PCV introduction in children, but young children are at increased risk of pneumococcal disease
  - Among children aged <5 years, overall and PCV13-type IPD incidence plateaued since 2013-2014
    - Incidence of IPD caused by PCV15 serotypes has remained stable
    - Two additional PCV15 serotypes caused 17% of IPD in 2018–2019
  - Overall IPD rates in children aged ≥5 years remained small; 25% IPD in children aged 6-18 years was in children with immunocompromising conditions

[1]Tong BMC Health Services Research 2018
[2]Lewnard CID 2021

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

Public Health Problem

Is pneumococcal disease of public health importance in children?

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

Benefits and Harms

How substantial are the desirable anticipated effects?

- How substantial is the anticipated effect for:

Vaccine-type IPD

Vaccine-type non-bacteremic pneumococcal pneumonia

Vaccine-type acute otitis media

Vaccine-type death?

Benefits and Harms

How substantial are the <u>undesirable</u> anticipated effects?

- How substantial is the anticipated effect for **serious adverse events?**

Benefits and Harms

Do the desirable effects outweigh the undesirable effects?

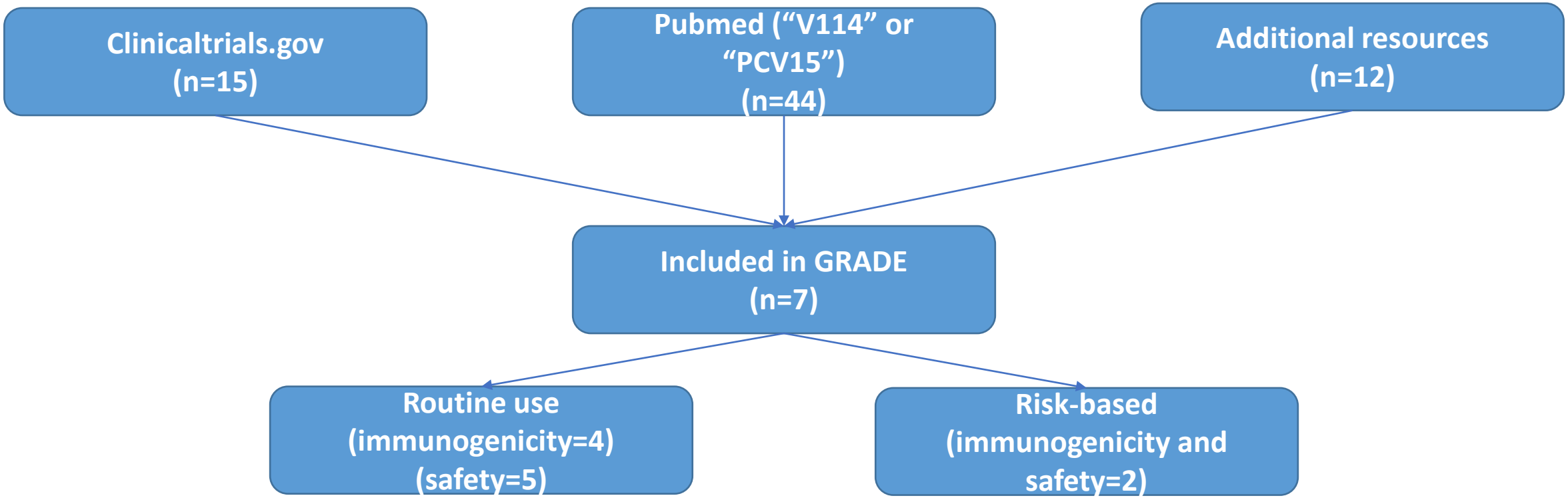
- What is the balance between the desirable effects relative to the undesirable effects?

Benefits and Harms

What is the overall certainty of this evidence for the critical outcomes?

- Effectiveness of the intervention
- Safety of the intervention

Search Strategy



No PCV15 studies directly assessed vaccine effectiveness against the critical outcomes

Studies included in Evidence Review

PICO – Routine Use

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

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

Studies included in Evidence Review

PICO – Routine Use

Author, year	Study design	Intervention	Country	Age	Total population	N Intervention	N comparison
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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)
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All studies funded by Merck; comparator is PCV13 for all studies

Summary of Evidence from PCV15 studies – Routine use: Benefits (VT-IPD, 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]	Randomized studies	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

a. These are all immunogenicity studies and there are no correlates of protection

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)

Please see GRADE summary tables for details

Benefits and Harms

How substantial are the desirable anticipated effects?

- PCV15 routine use in children <2 years of age?

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

Benefits and Harms

How substantial are the desirable anticipated effects?

- PCV15 routine use in children <2 years of age?

- No PCV15 studies directly assessed clinical outcomes
- Improved immunogenicity against serotype 3 unknown
- PCV15 provides additional coverage for 2 additional serotypes compared with PCV13, if improved immune response against these two serotypes translates to clinical effectiveness

Summary of Available Evidence from PCV15 studies- Routine Use: Harms

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	Serious[a]	Not serious	5/4540	0/2117	1.30 (0.22 -7.74)[b]	--	2

a. Few vaccine-related serious adverse events reported
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 routine use in children <2 years of age?

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

Benefits and Harms

Do the desirable effects outweigh the undesirable effects?

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

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

***Intervention:**

- PCV15 use as an additional option to PCV13 in children <2 years of age

Benefits and Harms

Do the desirable effects outweigh the undesirable effects?

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

- Responses split between “favors intervention” and “favors both”
- Some WG members thought the option “favors PCV15 use” gave the impression that a preferential recommendation was being proposed when intention is to assess whether PCV15 could be used as an option in addition to PCV13

Benefits and Harms

What is the overall certainty of this evidence for the critical outcomes?

- Effectiveness of the intervention: 2 (moderate)
- Safety of the intervention: 2 (moderate)

Studies included in evidence review

PICO – Children with underlying medical 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

Benefits and Harms

How substantial are the desirable anticipated effects?

- PCV15 routine use in children with underlying medical conditions 2 - 18 years of age?

- No PCV15 studies directly assessed clinical outcomes
- WG split between “moderate” and “large” responses
  - Some uncertainty around added benefit from PCV15 (not just from additional serotypes, but also against serotype 3)
- Improved immunogenicity against serotype 3 unknown
  - PCV15 provides additional coverage for 2 additional serotypes compared with PCV13, if improved immune response against these two serotypes translates to clinical effectiveness

Summary of Available Evidence from PCV15 studies- Underlying medical conditions: Harms

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

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

How substantial are the undesirable anticipated effects?

- PCV15 routine use in children with underlying medical conditions 2 - 18 years of age?

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

Benefits and Harms

Do the desirable effects outweigh the undesirable effects?

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

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

***Intervention:**

- PCV15 use as an additional option to PCV13 in children with underlying medical conditions 2 – 18 years of age

Benefits and Harms

Do the desirable effects outweigh the undesirable effects?

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

- Responses split between “favors intervention” and “favors both”
- Some WG members thought the option “favors PCV15 use” gave the impression that a preferential recommendation was being proposed when intention is to assess whether PCV15 could be used as an option in addition to PCV13

Benefits and Harms

What is the overall certainty of this evidence for the critical outcomes?

- Effectiveness of the intervention: 2 (moderate)
- Safety of the intervention: 3 (low)

Values and Preferences

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

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

Values and Preferences of PCV15 use in Children

- Data on values and preferences of PCV15 as an option for pneumococcal vaccination among U.S. children and caregivers not identified.
- **High vaccination coverage (92.4%) for ≥3 doses of PCV by age 24 months** demonstrates that the target population feels that the desirable effects of PCV vaccination outweigh the undesirable effects.

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?

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

- PCV15 routine use in children <2 years of age
- PCV15 use in children with underlying medical conditions 2 – 18 years of age

Values and Preferences

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

- WG split in responses likely due to small potential added impact of PCV15 use over PCV13 use, not uncertainty about whether vaccine is able to prevent serious pneumococcal disease

Values and Preferences

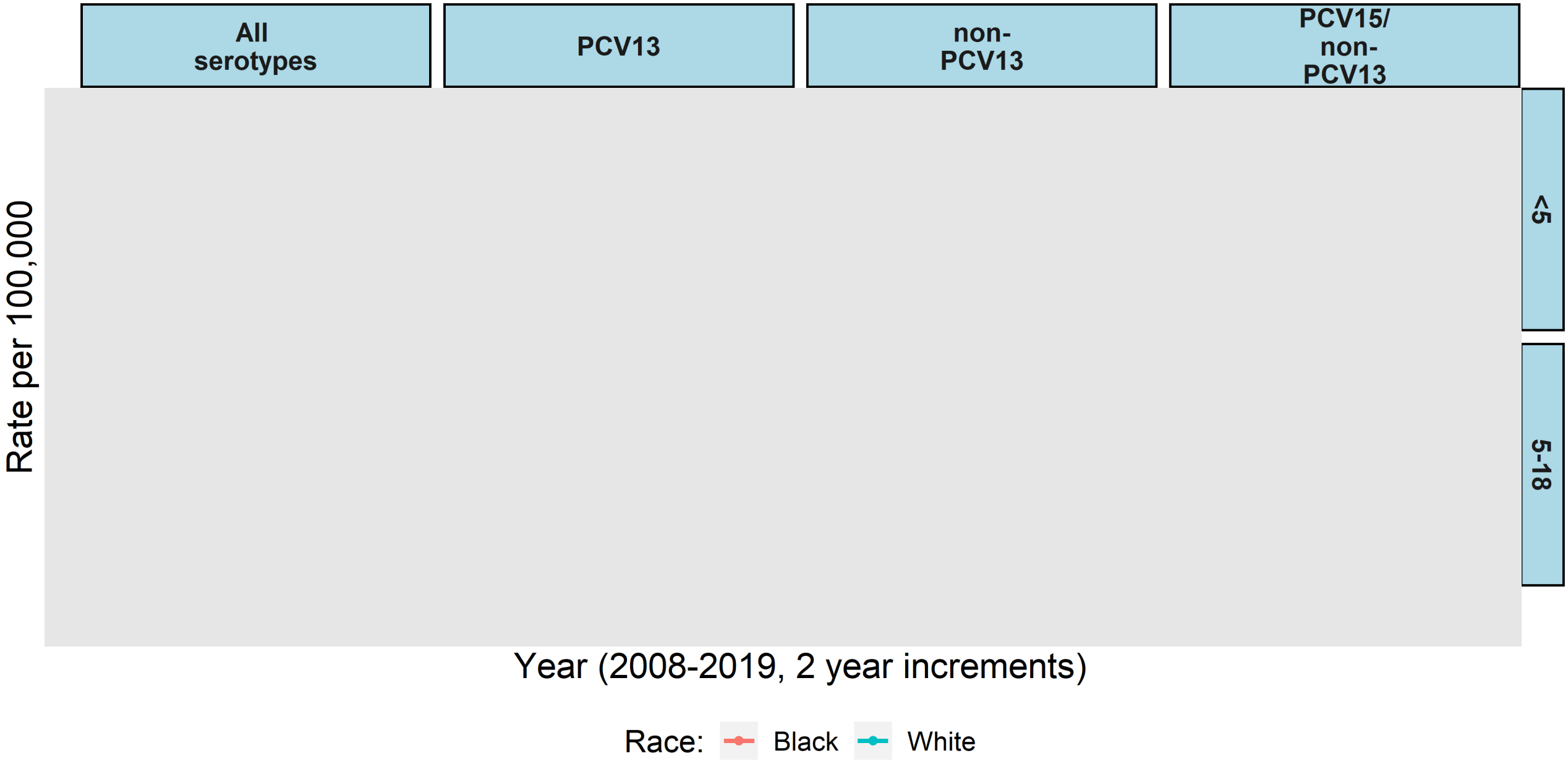
Criterion 2: Is there important uncertainty about, or variability in, how much people value the main outcomes?

- PCV15 routine use in children <2 years of age
- PCV15 use in children with underlying medical conditions 2 – 18 years of age

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

Equity

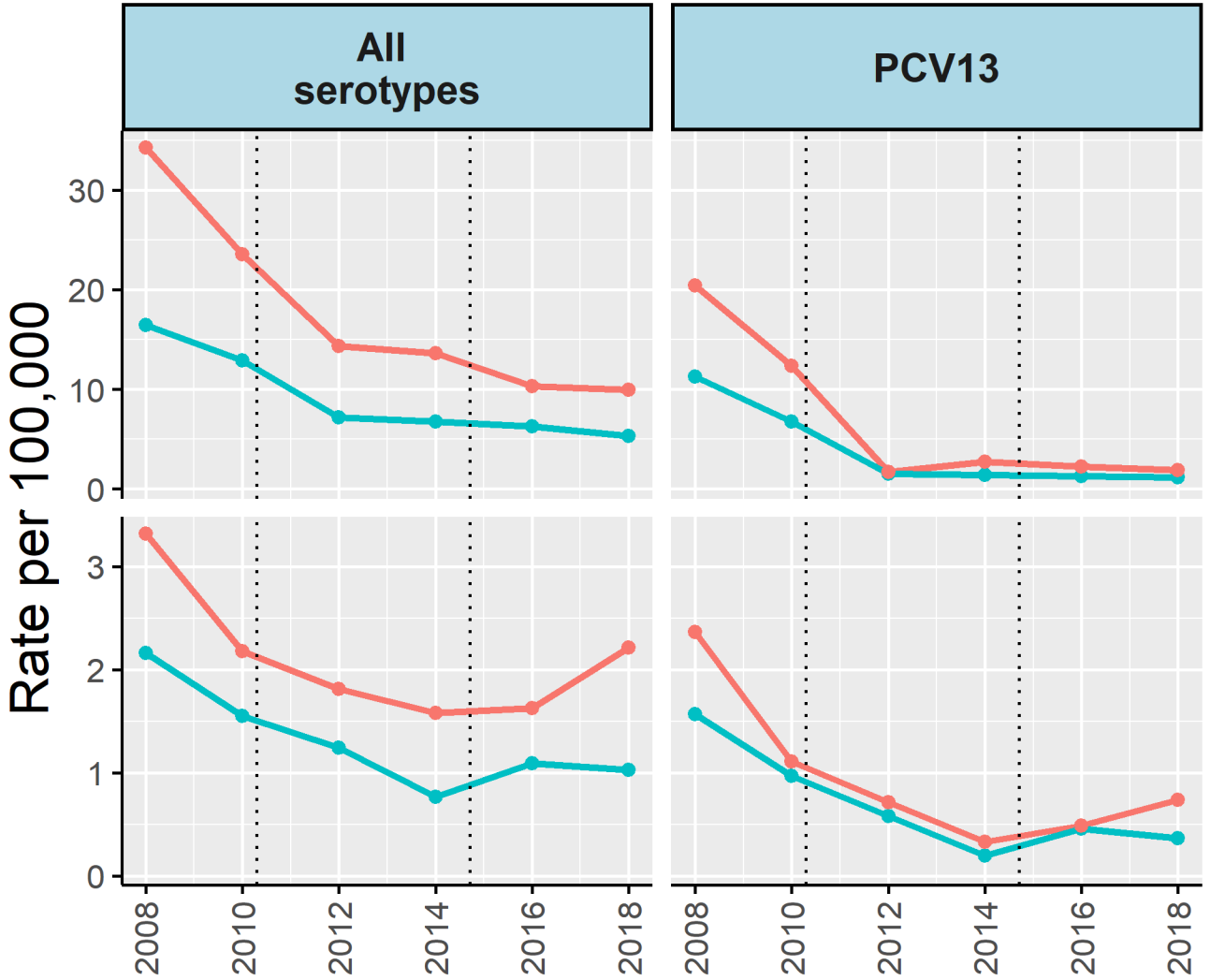
What would be the impact on health equity?



Unpublished CDC data, Active Bacterial Core surveillance

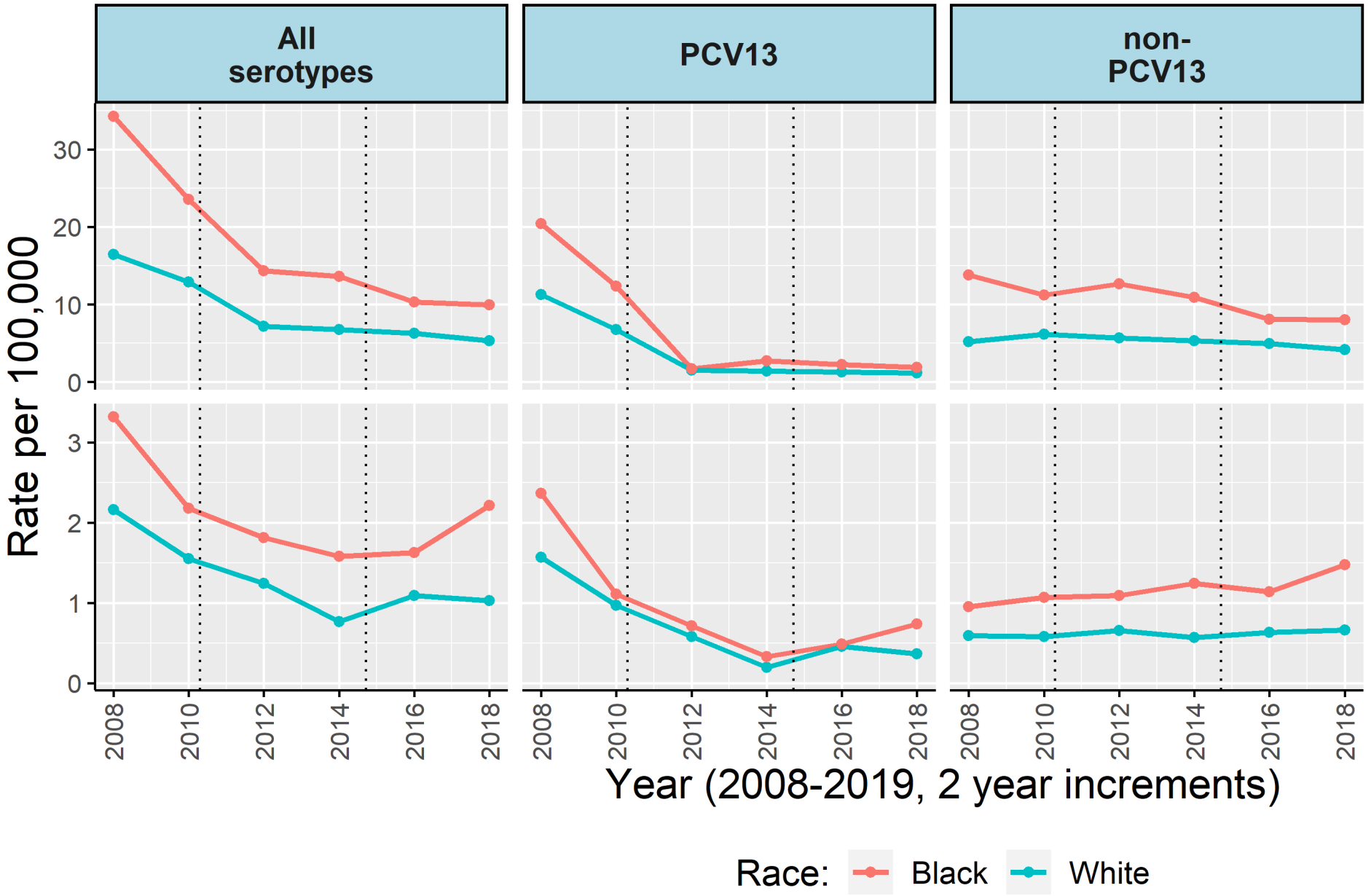
Age Group	RR 2008	RR 2018
<5	2.08 (1.81, 2.41)	1.87 (1.43, 2.43)
5-18	1.54 (1.16, 2.03)	2.15 (1.53, 3.02)

Unpublished CDC data, Active Bacterial Core surveillance



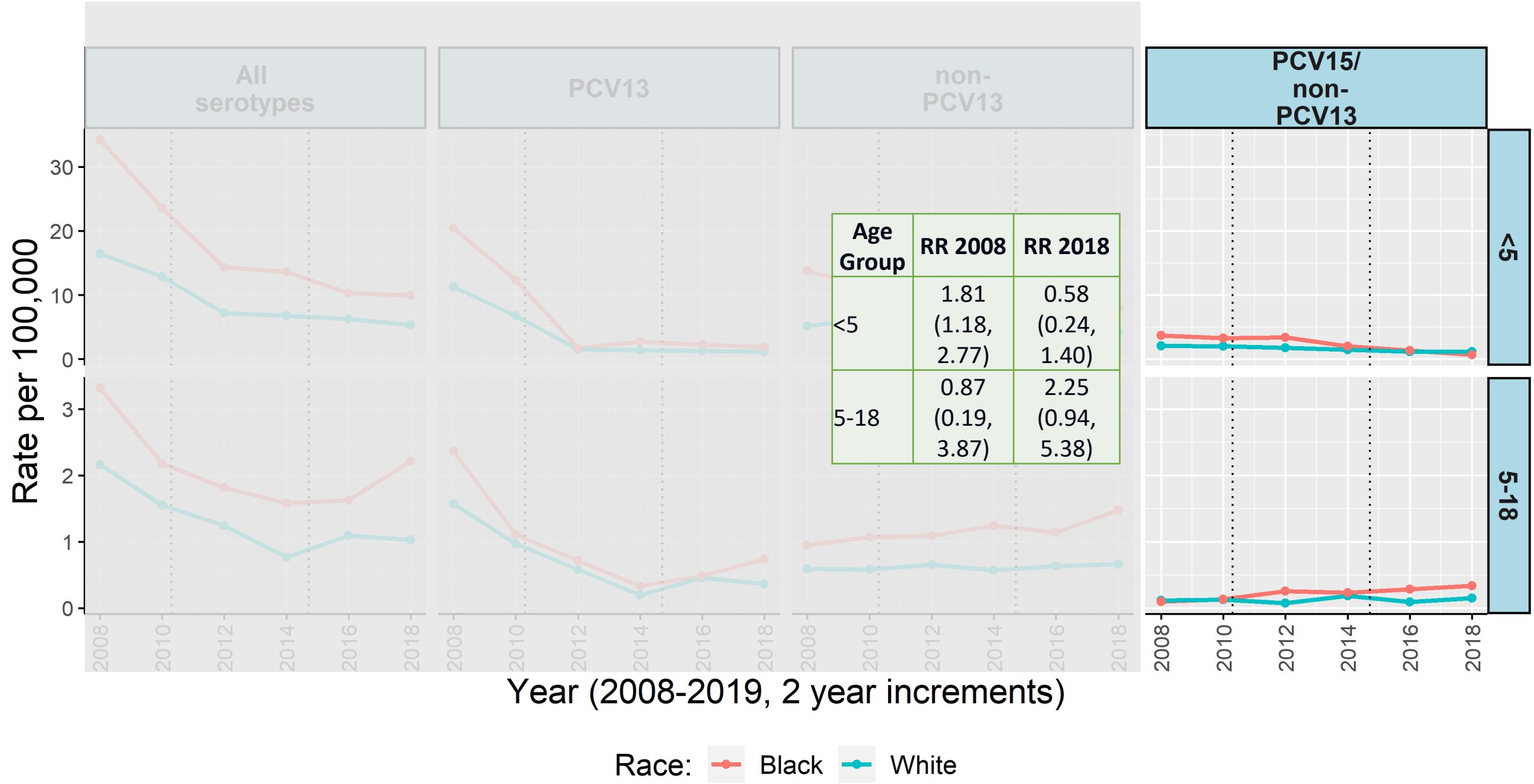
Age Group	RR 2008	RR 2018
<5	1.81 (1.51, 2.18)	1.64 (0.90, 2.96)
5-18	1.51 (1.08, 2.09)	2.03 (1.14, 3.63)

Unpublished CDC data, Active Bacterial Core surveillance



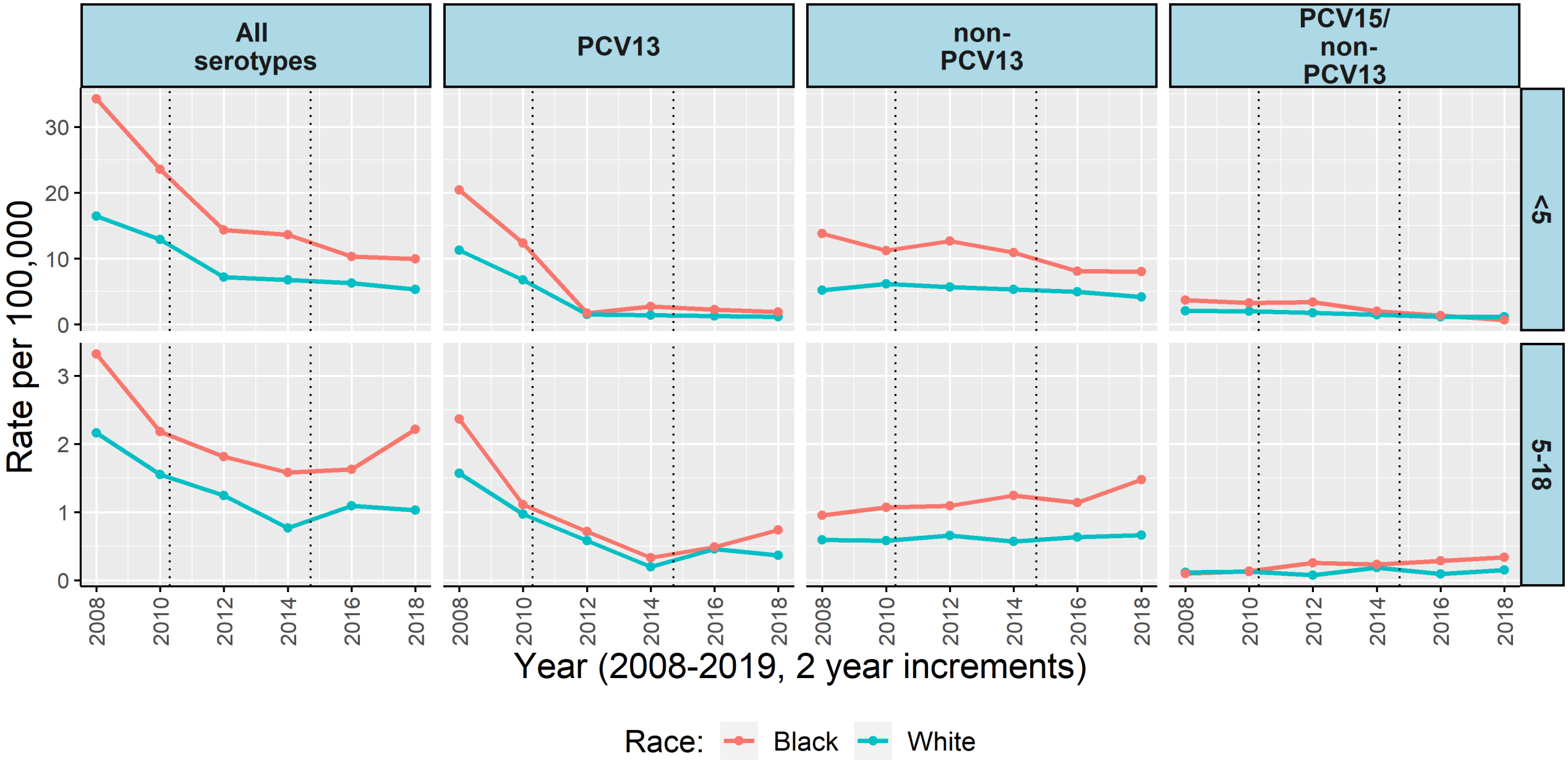
Age Group	RR 2008	RR 2018
<5	2.67 (2.11, 3.39)	1.93 (1.44, 2.60)
5-18	1.62 (0.96, 2.72)	2.22 (1.46, 3.37)

Unpublished CDC data, Active Bacterial Core surveillance



Age Group	RR 2008	RR 2018
<5	1.81 (1.18, 2.77)	0.58 (0.24, 1.40)
5-18	0.87 (0.19, 3.87)	2.25 (0.94, 5.38)

Unpublished CDC data, Active Bacterial Core surveillance



Unpublished CDC data, Active Bacterial Core surveillance

Equity: Native American/Alaskan Native children

- IPD rates in Native American children decreased after PCV13 use, but remain 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; included in PPSV23

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

Foreign-born children aged 19–35 months significantly lower pneumococcal vaccine coverage vs. U.S.-born children

National Immunization Survey, 2010–2012, ≥4 doses of PCV

	Coverage (%)	P-value
Foreign-born	46.4	p<0.001
US-born	83.9	Reference

Varan, AK et al. 2017. J Immigr Minor Health.

Fewer **Native American** children aged 19–35 months up-to-date with ≥4 PCV doses compared with White children in North Dakota

	2014	2015	2016	2017	2018
Native American Coverage %	70.6	67.4	69.1	67.8	66.3
White Coverage %	80.4	80.2	80.7	81.9	80.1

Woinarowicz, M & Howell, M. 2020. Public Health.

≥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.

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

Equity

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

- WG split in responses likely due to uncertainty regarding whether PCV15 use will improve healthy equity compared to PCV13 use

Summary of Work Group Interpretation on EtR Domains

EtR Domains	PCV15, <2 years	PCV15, 2 – 18 years old
Public Health Problem	Yes	
Benefits and Harms		
a. Benefits	Moderate	
b. Harms	Minimal	
c. Benefit>Harm?	Favors intervention	
d. Overall certainty: effectiveness	2 (moderate)	
e. Overall certainty: safety	2 (moderate)	3 (low)
Values		
a. Desirable>Undesirable?	Yes/Probably Yes	
b. Uncertainty?	Probably not important uncertainty or variability	
Equity	Probably Increased	

Acknowledgements

- ACIP and the Pneumococcal Work Group
- CDC contributors and consultants: Miwako Kobayashi, Tamara Pilishvili, Ryan Gierke, Emma Accorsi, Namrata Prasad, Heather Walker, Chukwuebuka Nsofor, Lana Childs, Heidi Moline, Pedro Moro, Sarah Schillie, Marc Fischer, Wei Xing, Rebecca Morgan, Doug Campos-Outcalt

Thank you

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

EXTRA SLIDES

GRADE tables

PICO – routine use

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

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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

Ratio calculated as [GMC (PCV15)]/[GMC (comparator vaccine)]; blood draws occurred 30 days or 1 month post-dose.
Seroresponse: proportion of participants meeting IgG threshold value of >=0.35µg/mL; blood draws occurred 30 days or 1 month post-dose.
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.
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
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	2

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

GRADE tables

PICO – children 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.