Centers for Disease Control and Prevention
National Center for Immunization and Respiratory Diseases

Preliminary Work Group Interpretations of EtR and Next Steps

February 2024, ACIP Meeting

February 29, 2024

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Policy Questions Being Considered by the Work Group

1. Should **PCV21** be recommended for U.S. adults aged ≥19 years who **currently have a recommendation to receive a PCV*?**

Comparison (current recommendations):

Adults aged ≥19 years who have **not received a PCV**

- One dose of PCV15 followed by PPSV23
- One dose of PCV20

Adults aged ≥19 years who have **received a PCV but have not completed the recommended series**

- One dose of PCV20
- ≥1 dose of PPSV23

*Includes,

- Adults aged ≥65 years who have never received a PCV
- U.S. adults aged 19-64 years with a risk condition, who have never received a PCV
- U.S. adults aged ≥19 year who have received a PCV (i.e., PCV7, PCV13, or PCV15), but have not completed the recommended series

Policy Questions Being Considered by the Work Group

2. Should **PCV21** be recommended for U.S. adults **aged 50-64 years** who currently do not have a risk-based pneumococcal vaccine indication?

3. Should **PCV21** be recommended for U.S. adults **aged 19-49 years** who currently do not have a risk-based pneumococcal vaccine indication?

Comparison (current recommendation):

- No vaccine

- Questions 2 and 3 imply a **new age-based recommendation** for these age groups.

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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EtR Public Health Problem

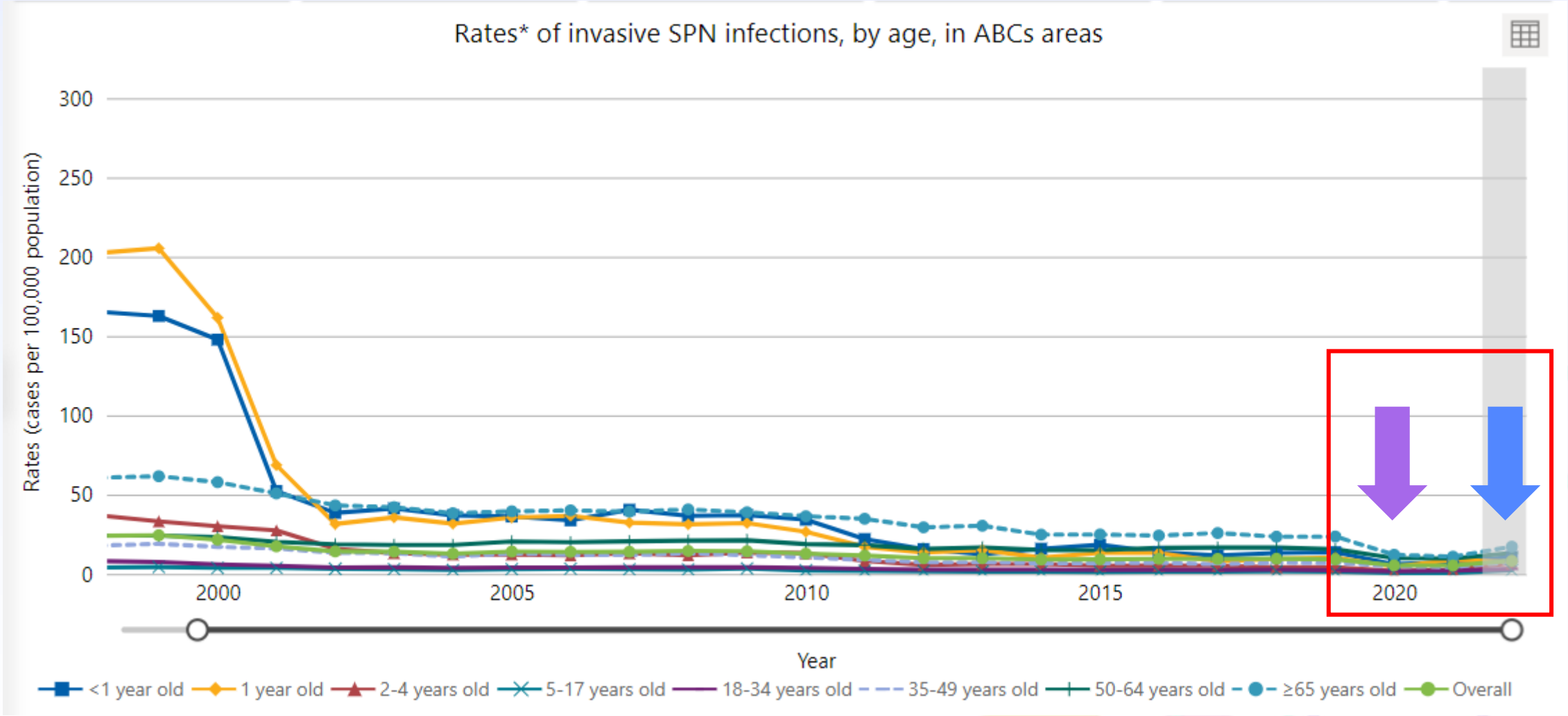
Is pneumococcal disease of public health importance?

Pneumococcal Disease Burden among U.S. Adults

- Prior to the COVID-19 pandemic, estimated to have caused every year[1]:
  - **≥100,000** non-invasive pneumococcal pneumonia hospitalizations
  - **≥30,000** invasive pneumococcal disease (IPD) cases (e.g., bacteremic pneumonia, pneumococcal bacteremia, meningitis)
    - **3,000** IPD deaths
- Risk of disease and severe outcomes is higher among older adults and adults with certain risk conditions.
  - **Over one-third** of adults aged ≥65 years hospitalized with community-acquired pneumonia in Louisville, KY died within 1 year[2]
  - **>80%** of IPD cases occurred among adults with risk-based indications[3]

1. Kobayashi M. October 20, 2021 ACIP Meeting Presentation. Considerations for Age-Based and Risk-Based Use of PCV15 and PCV20 among U.S. Adults and Proposed Policy Options.
2. Older Adults Hospitalized for Pneumonia in the United States: Incidence, Epidemiology, and Outcomes - Arnold - 2020 - Journal of the American Geriatrics Society - Wiley Online Library
3. CDC Active Bacterial Core surveillance unpublished data

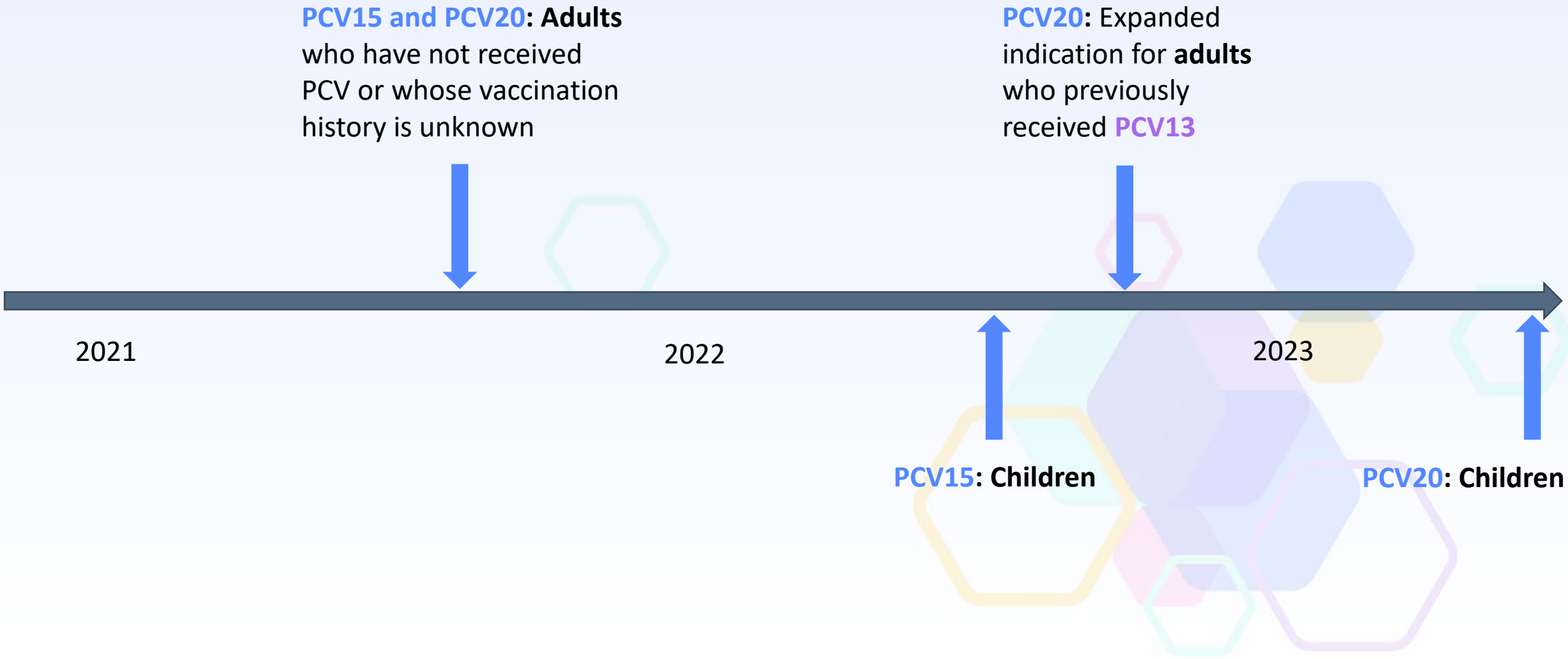
IPD incidence reached a historically low level early in the COVID-19 pandemic, but increasing toward pre-COVID levels



IPD=invasive pneumococcal disease; 2022 data in gray are preliminary

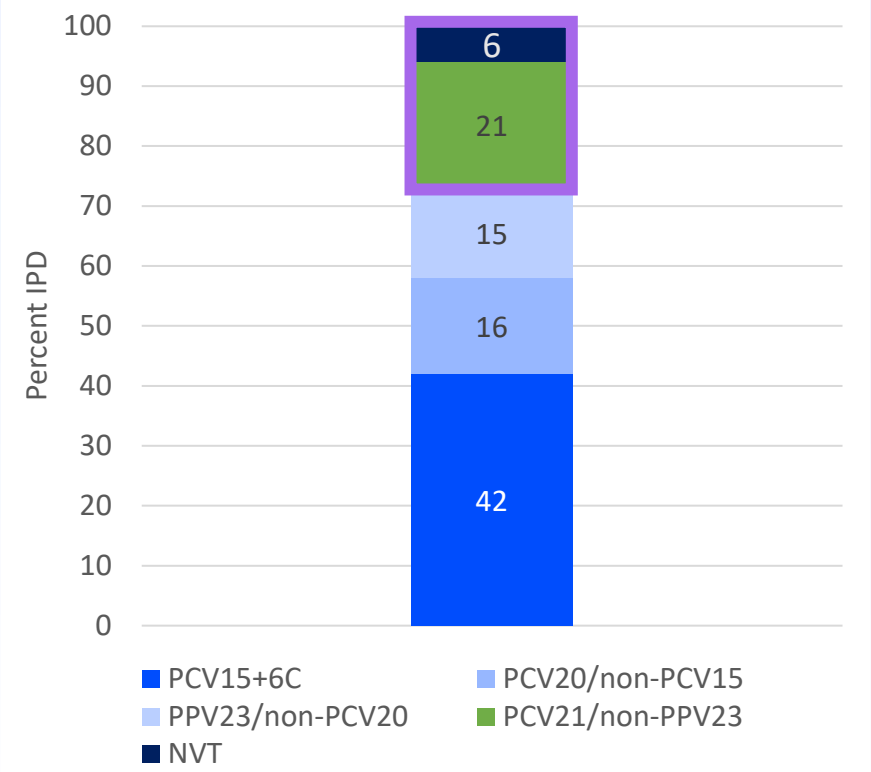
[ABCs Bact Facts Interactive Data Dashboard | CDC]

New pneumococcal conjugate vaccines, PCV15 and PCV20, were recommended for adults and children in recent years

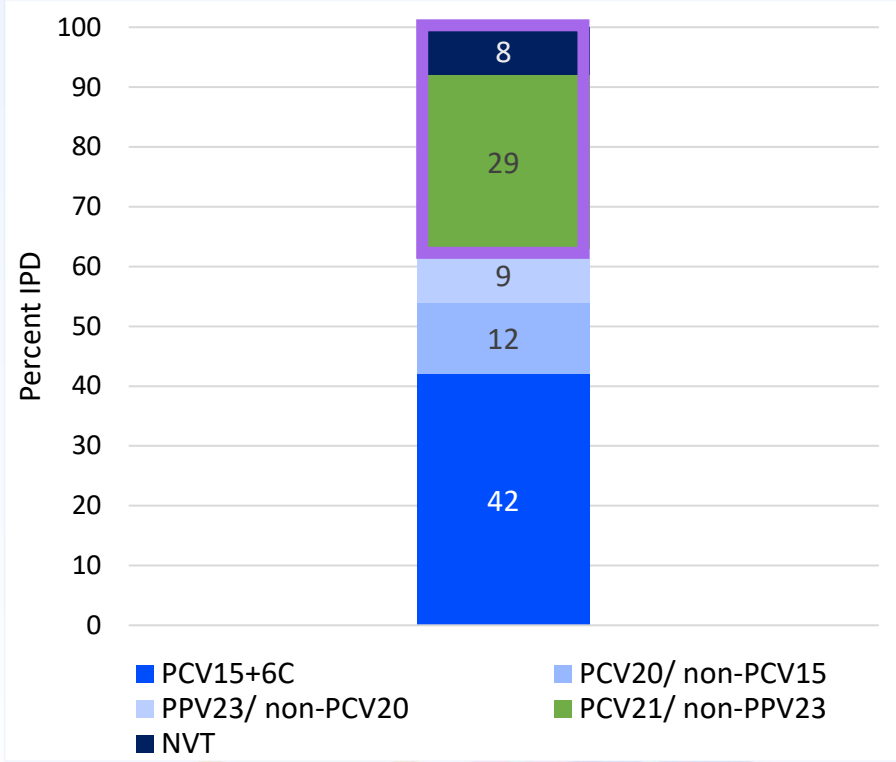


30–40% of adult IPD cases* are caused by serotypes not contained in currently available vaccines; PCV21 contains most of them.

Aged 19–64 years, with a risk-based indication



Aged ≥65 years



*Based on ABCs 2018–2022 data

Is pneumococcal disease of public health importance?

1. In adults **currently recommended to receive a PCV**? (group 1)

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

Minority opinion (probably yes):

- Pneumococcal disease burden has decreased from before
- Increase in disease incidence in recent years does not mean the incidence will continue to increase (i.e., may stabilize at pre-COVID-19 levels)

Is pneumococcal disease of public health importance?

2. In adults **aged 50–64 years who currently do not have a risk-based pneumococcal vaccine indication**? (group 2)

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

- Disease incidence in this age group overall is lower compared with adults aged ≥65 years (IPD incidence ~23% lower)

Is pneumococcal disease of public health importance?

3. In adults **aged 19–49 years who currently do not have a risk-based pneumococcal vaccine indication**? (group 3)

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

- The most common WG member responses were “No”(19%), “Probably No”(31%), and “Don’t know (25%)
- Adults aged 19–49 years have even lower disease incidence compared with adults aged 50–64 years

EtR Benefits and Harms

1. How substantial are the **desirable** anticipated effects of PCV21 vaccination?
2. How substantial are the **undesirable** anticipated effects of PCV21 vaccination?
3. Do the desirable effects of PCV21 vaccination outweigh the undesirable effects?
4. What is the overall certainty of this evidence for the critical outcomes?

Outcomes (Benefits)

Outcome	Importance*	Description
VT- IPD	**Critical**	Studies assessing PCV21 against these clinical outcomes are **currently not available** → PCV21 **immunogenicity studies** • OPA GMT • ≥4-fold rise in serotype-specific OPA responses
VT- non-bacteremic pneumococcal pneumonia	**Critical**	
VT- pneumococcal deaths	**Critical**	
All IPD	Important	
Non-bacteremic pneumococcal pneumonia	Important	
All-cause death	Important	

*Rated on a 1 to 9 scale, where 7–9 are critical, 4–6 are important, 1–3 are of limited importance

GMT= geometric mean titers; OPA=opsonophagocytic activity

See supplementary slides for details of methods

Outcomes (Harms)

Outcome	Importance*	Description
Serious adverse events (SAE)	**Critical**	Safety data for PCV21 are available.

*Rated on a 1 to 9 scale, where 7–9 are critical, 4–6 are important, 1–3 are of limited importance

See supplementary slides for details of methods

PCV21 Clinical Trials Included in Evidence Review

Last name first author, Publication year	Study design	Country	Age	Total population	N Intervention	N comparison	Outcomes	Funding source
Platt, Lancet ID 2023	RCT (Phase II)	U.S.	Adults ≥50 years	508	254	PPSV23: 254	Immunogenicity and Safety	MERCK
V116-003	RCT (Phase III); pivotal study	U.S., Australia, Belgium, Chile, Germany, Korea, New Zealand, Puerto Rico, Sweden, Taiwan, Turkey	Healthy adults ≥50 years, pneumococcal vaccine – naïve	2,663	1179	PCV20: 1,177	Immunogenicity and Safety	MERCK
			Healthy adults 18 - 49 years, pneumococcal vaccine – naïve		200	PCV20: 100		
V116-005	RCT (Phase III)	U.S.	Adults ≥50 years	1,080	(V116 + QIV, coadministered): 536	(QIV followed by V116) : 536	Immunogenicity and Safety	MERCK
V116-006	RCT (Phase III)	U.S., Canada, Israel, France, Italy, Japan, Korea, Spain, Taiwan	Adults ≥50 years, previous PPSV23 ≥1 year prior to enrollment	348	229	PCV15, n=119	Immunogenicity and Safety	MERCK
			Adults ≥50 years, previous PCV13 ≥1 year prior to enrollment	259	174	PPSV23 N=85		
			Adults ≥50 years, PCV13+PPSV23, PCV15+PPSV23, PCV15, PCV20, or PPSV23+PCV13 ≥1 year prior to enrollment	105	105	None		
V116-007	RCT (Phase III)	Belgium, Chile, France, South Africa, Thailand, United States	Adults living with HIV, ≥18 years; 36% prior PCV13 or PPSV23*	313	156	PCV15+PPSV23, n=157	Immunogenicity and Safety	MERCK
V116-004	RCT (Phase III)	U.S., Austria, Canada, Denmark, Finland, Israel, Poland, Spain	Adults 18 - 49 years with underlying chronic conditions	2,162	1,617	PPSV23:540	Safety	MERCK

GRADE Summary of Findings Table 1: Adults currently recommended to receive PCV

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV21	comparison	Relative (95% CI)	Absolute (95% CI)		
VT-IPD, VT-nonbacteremic pneumococcal pneumonia, VT-pneumococcal mortality outcome (Assessed with: Immunogenicity)												
5[1-5]	Randomized studies	Not serious	Not serious	Serious[a]	Not serious	Not serious	123 - 1161	58 - 1162	• PCV21 **met non-inferiority criteria**[b] for 9/9 shared and **superiority criteria**[c] for 12/12 unique serotypes vs. PPSV23 • PCV21 met **non-inferiority criteria**[d] for 10/10 shared and **superiority criteria**[e] 10/11 unique serotypes vs. PCV20 • PCV21 had numerically higher immune responses for 1-4/6 shared and all unique serotypes vs. PCV15		**Moderate**	Critical

a. These are all immunogenicity studies and there are no correlates of protection for some critical outcomes considered.
b. Noninferiority for GMT ratio was defined as the lower bound of the 95% CI of the estimated OPA GMT ratio ({PCV21:PPSV23} to be > 0.33.
c. Superiority for GMT ratio was defined as the lower bound of the 95% CI of the estimated OPA GMT ratio [PCV21:PPSV23] to be > 1.0.
d. Noninferiority for GMT ratio was defined as the lower bound of the 2 sided 95% CI of the OPA GMT ratio [PCV21 / PCV20] to be >0.5.
e. Superiority for GMT ratio was defined as the lower bound of the 2 sided 95% CI of the OPA GMT ratio [PCV21 / PCV20] to be >2.0.

References

1. Platt H, Omole T, Cardona J, Fraser NJ, Mularski RA, Andrews C, Daboul N, Gallagher N, Sapre A, Li J, Polis A, Fernsler D, Tamms G, Xu W, Murphy R, Skinner J, Joyce J, Musey L. Safety, tolerability, and immunogenicity of a 21-valent pneumococcal conjugate vaccine, V116, in healthy adults: phase 1/2, randomised, double-blind, active comparator-controlled, multicentre, U.S.-based trial. Lancet Infect Dis. 2023 Feb;23(2):233-246. doi: 10.1016/S1473-3099(22)00526-6. Epub 2022 Sep 15. PMID: 36116461.
2. V116-003. A clinical study to evaluate the safety, tolerability, and immunogenicity of V116 compared to PCV20 in pneumococcal vaccine-naïve adults
3. V116-006. A Phase 3 Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Pneumococcal Vaccine-Experienced Adults 50 Years of Age or Older
4. V116-007. A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator- Controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Adults Living With HIV
5. V166-005. A clinical study comparing the immunogenicity and safety of V116 when administered concomitantly with inactivated influenza vaccine

GRADE Summary of Findings Table
1: Adults currently recommended to receive PCV

Effect		Certainty	Importance
Relative (95% CI)	Absolute (95% CI)		
• PCV21 **met non-inferiority criteria**[b] for 9/9 shared and **superiority criteria**[c] for 12/12 unique serotypes vs. PPSV23 • PCV21 met **non-inferiority criteria**[d] for 10/10 shared and **superiority criteria**[e] 10/11 unique serotypes vs. PCV20 • PCV21 had numerically higher immune responses for 1-4/6 shared and all unique serotypes vs. PCV15		**Moderate**	Critical

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

GRADE Summary of Findings Table 1: Adults currently recommended to receive PCV

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№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV21	comparison	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events following immunization												
6[1-6]	Randomized studies	Not serious	Not serious	Not serious	Serious[f]	Not serious	**57/4445 (1.3%)**	**63/2962 (2.1%)**	Absolute % difference for SAEs across studies is **-0.8%;** two SAEs deemed vaccine-related[g] in the V116 group reported		**Moderate**	Critical

f. few vaccine-related serious adverse events reported.

g. Bronchospasm (V116-005): 50-year-old female in the sequential group with bronchospasm within 30 minutes after the 2ndvaccination (V116); duration 23 hours; resolved; Injection site cellulitis (V116-006): 67-year-old female in Cohort 1 (prior PPSV23) with injection site cellulitis on Day 6; duration 1.57 weeks; resolved (Merck, unpublished).

References

1. Platt H, Omole T, Cardona J, Fraser NJ, Mularski RA, Andrews C, Daboul N, Gallagher N, Sapre A, Li J, Polis A, Fernsler D, Tamms G, Xu W, Murphy R, Skinner J, Joyce J, Musey L. Safety, tolerability, and immunogenicity of a 21-valent pneumococcal conjugate vaccine, V116, in healthy adults: phase 1/2, randomised, double-blind, active comparator-controlled, multicentre, U.S.-based trial. Lancet Infect Dis. 2023 Feb;23(2):233-246. doi: 10.1016/S1473-3099(22)00526-6. Epub 2022 Sep 15. PMID: 36116461.
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5. V166-005. A clinical study comparing the immunogenicity and safety of V116 when administered concomitantly with inactivated influenza vaccine
6. V116-004. A Phase 3 Randomized, Double-blind, Active Comparator-controlled, Lot to-Lot Consistency Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Adults 18 to 49 Years of Age.

GRADE Summary of Findings Table
1: Adults currently recommended to receive PCV

№ of patients		Effect		Certainty	Importance
PCV21	comparison	Relative (95% CI)	Absolute (95% CI)		
57/4445 (1.3%)	63/2962 (2.1%)	Absolute % difference for SAEs across studies is -0.8%; two SAEs deemed vaccine-related[g] in the V116 group reported		**Moderate**	Critical

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See supplementary slides for details

1. How substantial are the desirable anticipated effects of PCV21 vaccination?

1. Adults currently recommended to receive PCV

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

2. Adults aged 50–64 years with no risk-based indication

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

3. Adults aged 19–49 years with no risk-based indication

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

2. How substantial are the *un*desirable anticipated effects of PCV21 vaccination?

- 1. Adults currently recommended to receive PCV
- 2. Adults aged 50–64 years with no risk-based indication
- 3. Adults aged 19–49 years with no risk-based indication

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

3. Do the desirable effects of PCV21 vaccination outweigh the *un*desirable anticipated effects?

1. Adults currently recommended to receive PCV

- □ Favors PCV21 use
- □ Favors current
- □ Favors both
- □ Favors neither
- □ Varies
- □ Don't know

2. Adults aged 50–64 years with no risk-based indication

- □ Favors PCV21 use
- □ Favors current (no vaccine)
- □ Favors both
- □ Favors neither
- □ Varies
- □ Don't know

3. Adults aged 19–49 years with no risk-based indication

- □ Favors PCV21 use
- □ Favors current (no vaccine)
- □ Favors both
- □ Favors neither
- □ Varies
- □ Don't know

- None selected by the majority
- "Favors current" and "favors PCV21 use" were the most common responses selected by similar number of members

Summary of Work Group Discussions: Comments in favor of PCV21 use

- Based on available data, no concerns about the risks outweighing the benefits of PCV21 vaccination
- For adults who currently have a PCV recommendation, PCV21 provides broader serotype coverage than currently recommended vaccines

Summary of Work Group Discussions:

In favor of lowering the age-based recommendation (question 2)

- We can expect a more robust immune response from administering PCV21 at age 50–64 years (vs. age ≥65 years) and before a portion of that population develops an immunocompromising condition

Summary of Work Group Discussions:

Concerns/uncertainties of lowering the age-based recommendation (especially question 3)

- The degree of benefits for adults who currently don't have vaccine recommendations is uncertain
- Epidemiology does not support expanding the vaccine indications to younger adults without a risk-based indication
- Younger adults (early 20s) would have received a PCV as a child
- We could miss the opportunity to provide protection against disease later in life if we lowered the age-based recommendation
  - Limited data on duration of protection or protection against disease from multiple PCV doses in adults
- Need to review cost-effectiveness analysis data

EtR: Equity

What would be the impact of recommending PCV21 use for adults on **health equity?**

Racial disparities exist in IPD incidence and vaccine coverage

- Racial disparities in IPD incidence exist
- White non-Hispanic adults tend to have highest vaccine coverage[1] compared with other race/ethnicity groups
- Remaining disparities in IPD incidence are primarily due to **non-PCV13-type** disease

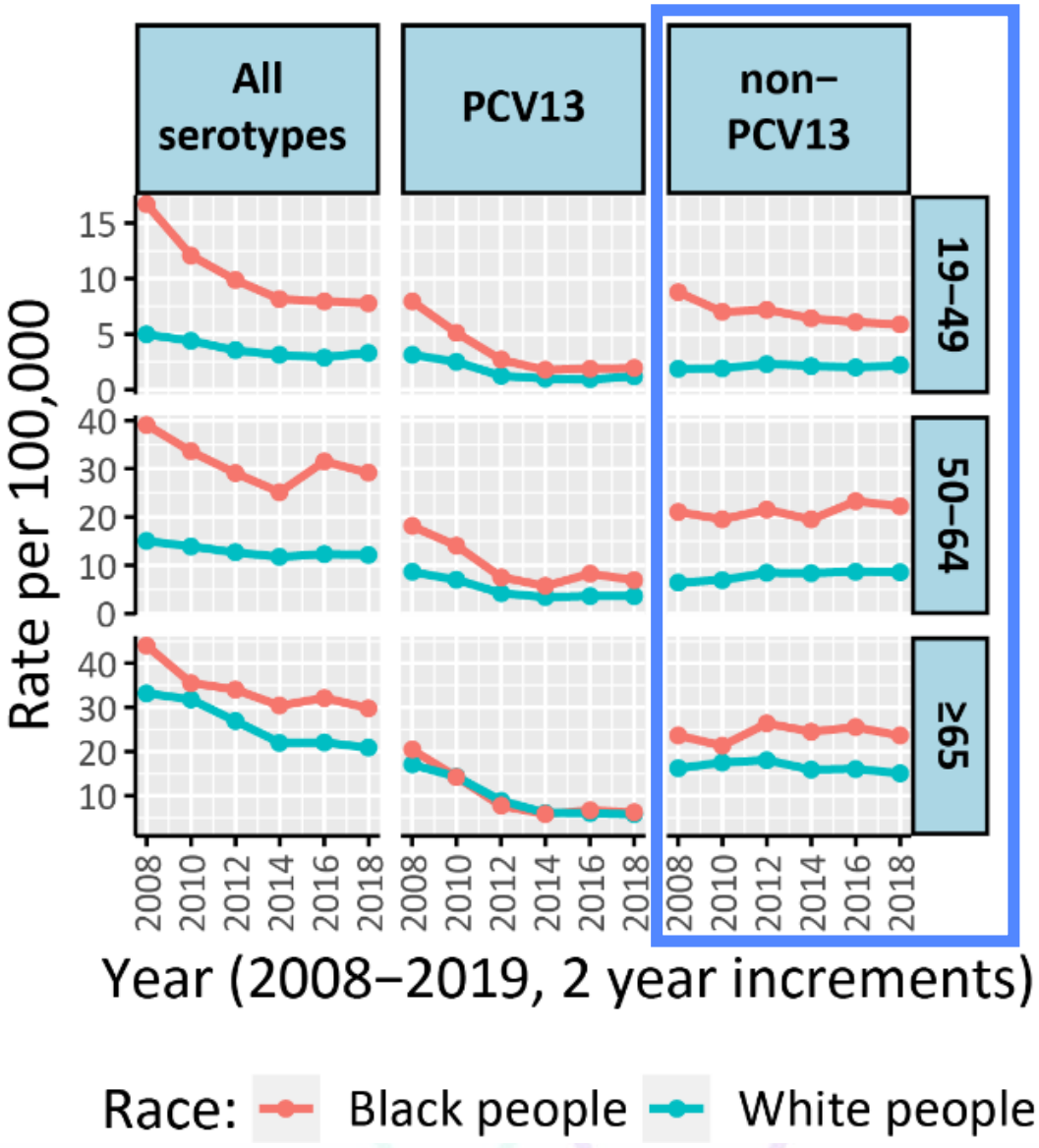


Figure: ABCs unpublished data

1. Vaccination Coverage among Adults in the United States, National Health Interview Survey, 2021 | CDC

Increase in serotype 4 (included in currently available vaccines, not in PCV21) IPD reported in certain subpopulations

- Adults experiencing homelessness (especially Western United States)
  - **100–300 times higher** serotype 4 IPD incidence reported in people experiencing homelessness (PEH) vs. non-PEH in the Western United States[1]
- Adults in Alaska (especially Alaska Native adults)
  - **88-fold increase** in serotype 4 IPD incidence reported in adults in Alaska, 2011–2018 vs. 2019–2020[2]

1. Upsurge of Conjugate Vaccine Serotype 4 Invasive Pneumococcal Disease Clusters Among Adults Experiencing Homelessness in California, Colorado, and New Mexico | The Journal of Infectious Diseases | Oxford Academic (oup.com)

2. Invasive Pneumococcal Disease and Potential Impact of Pneumococcal Conjugate Vaccines Among Adults, Including Persons Experiencing Homelessness—Alaska, 2011–2020 | Clinical Infectious Diseases | Oxford Academic (oup.com)

What would be the impact of recommending PCV21 use for adults on health equity?

1. In adults **currently recommended to receive a PCV**?

- Additional serotype coverage by PCV21 is expected to reduce racial disparities in remaining pneumococcal disease burden.
- For adults who have already received a PCV, recommending a second PCV dose to complete series might magnify the underlying disparities in vaccine coverage.

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

What would be the impact of recommending PCV21 use for adults on health equity?

2. In adults **aged 50–64 years who currently do not have a risk-based pneumococcal vaccine indication**?

3. In adults **aged 19–49 years who currently do not have a risk-based pneumococcal vaccine indication**?

- Probably more equitable to lower the age threshold for the age-based recommendation, which may improve vaccine coverage in those who currently have risk-based indications

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

Summary of Work Group Interpretation of the EtR Domains

EtR Domains	1. Adults with current PCV recommendations	2. Adults aged 50–64 years, no risk-based indication	3. Adults aged 19–49 years, no risk-based indication
Public Health Problem	Yes	Probably Yes	No/Probably No
Benefits and Harms			
a. Benefits	Moderate/Large	Small/Moderate	Minimal/Small
b. Harms		Minimal	
c. Benefit>Harm?		Favors PCV21 use	Favors PCV21/Favors no vaccine (split)
d. Overall certainty: effectiveness		Moderate	
e. Overall certainty: safety		Moderate	
Equity		Probably increased	

Work Group Next Steps

Work Group Next Steps

- Review findings from cost-effectiveness analyses
- Review evidence and discuss interpretations of remaining EtR domains (Values, Acceptability, Resource Use, Feasibility)
- Draft policy options on PCV21 use in U.S. adults for consideration by the committee
  - Including considerations for expanding the current risk-based vaccine indications to include adults with chronic kidney disease (CKD) who are not on maintenance dialysis

Considerations for including earlier stages of CKD for risk-based pneumococcal vaccine indications

Indications for risk-based pneumococcal vaccine recommendations	Children	Adults
Alcoholism		
Chronic heart disease[†]		
Chronic kidney disease (excluding maintenance dialysis and nephrotic syndrome)		
Chronic liver disease		
Chronic lung disease		
Cigarette smoking		
Diabetes mellitus		
Cerebrospinal fluid leak		
Cochlear implant		
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		

Risk-based pneumococcal vaccine indication was expanded to include earlier-stage CKD (i.e., those not on dialysis) in children. Does evidence support the change in adults as well?

Summary of Work Group Discussion to Date

In favor of expanding indications in adults:

- Pneumococcal disease risk is increased in earlier CKD stages
- Allows adults to receive vaccine when immune response is more robust

Concerned/cautious about expanding indications in adults

- Unlike children, CKD is more common in adults
- Inclusion of earlier stages, such as CKD stage 3a, could potentially result in expanding the risk-based indication to a much larger proportion of adults (unless they already have other risk-based indications)
- Would like to see a cost-benefit analysis

Questions for the Committee

Considering:

- Additional pneumococcal vaccines for adults are currently under investigation and may be approved in the near future, and
- Dynamic changes in pneumococcal disease incidence are anticipated post-COVID-19 and with increased uptake in PCV15/PCV20 in children and adults

1. Do you have any feedback on the policy questions being considered by the WG?

2. What additional data would be helpful to inform the discussions on PCV21 use in adults?

In addition,

3. What additional data would be needed to help inform the discussions on expanding the risk-based indications to include adults with CKD?

Acknowledgments

- ACIP and the Pneumococcal Vaccines Work Group
- CDC contributors and consultants: Ryan Gierke, Jennifer Farrar, Kristin Andrejko, Lindsay Zielinski, Emma Accorsi, Wei Xing, Adam Cohen, Alison Albert, Angela Jiles, Noele Nelson, Kimberly Fox, Pedro Moro, Elizabeth Velazquez, Janelle King, Fangjun Zhou, Marc Fischer, Cheryl Ward, Rebecca Morgan, Doug Campos-Outcalt
- Active Bacterial Core surveillance sites and program

Thank you!

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

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

GRADE Evidence Summary

Supplemental Slides

PICO 1: Adults currently recommended to receive PCV

Policy question:	Should PCV21 be recommended for U.S. adults aged ≥19 years who currently have a recommendation to receive a pneumococcal conjugate vaccine?
Population	• U.S. adults aged ≥65 years who have never received a PCV • U.S. adults aged 19–64 years with a risk condition, who have never received a PCV • U.S. adults aged ≥19 years who have received a PCV (i.e., PCV7, PCV13, or PCV15), but have not completed the recommended series
Intervention	One dose of PCV21 (V116)
Comparison	Adults who have not received a PCV • One dose of PCV15 followed by PPSV23 • One dose of PCV20 Adults who have received a PCV but have not completed the recommended series • One dose of PCV20 • ≥1 dose of PPSV23
Outcomes	Vaccine type (VT)-IPD, VT-non-bacteremic pneumococcal , VT-pneumococcal mortality, serious adverse events

PICO2: Adults aged 50–64 years, no risk-based indications

Policy question:	Should PCV21 be recommended for U.S. adults aged 50–64 years who currently do not have a risk-based pneumococcal vaccine indication?
Population	U.S. adults aged 50–64 years who currently do not have a risk-based pneumococcal vaccine indication
Intervention	One dose of PCV21
Comparison	No vaccination
Outcomes	Vaccine type (VT)-IPD, VT-non-bacteremic pneumococcal , VT-pneumococcal mortality, serious adverse events

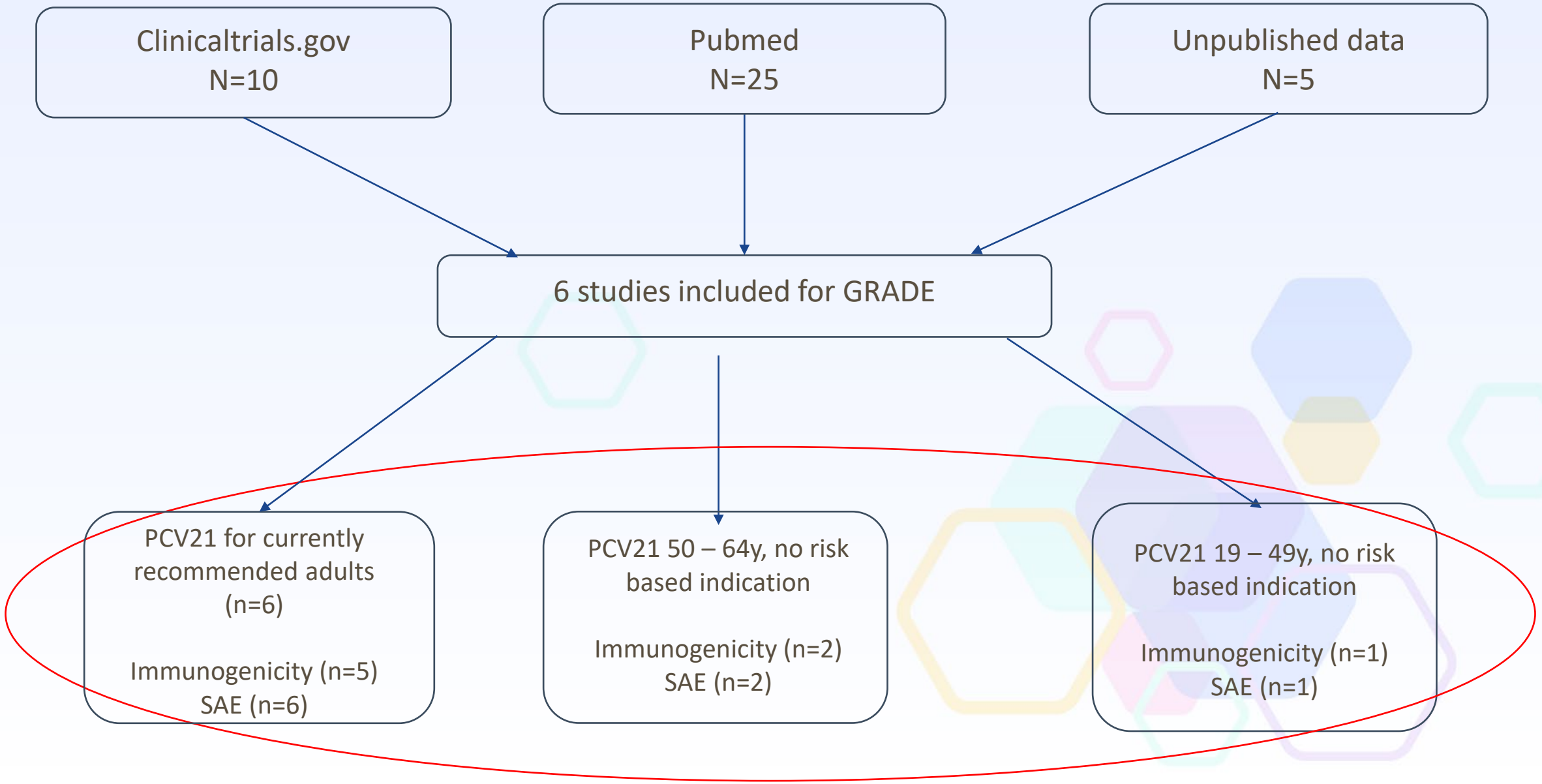
PICO3: Adults aged 19–49 years, no risk-based indications

Policy question:	Should PCV21 be recommended for U.S. adults aged 19–49 years who currently do not have a risk-based pneumococcal vaccine indication?
Population	U.S. adults aged 19–49 years who currently do not have a risk-based pneumococcal vaccine indication
Intervention	One dose of PCV21
Comparison	No vaccination
Outcomes	Vaccine type (VT)-IPD, VT-non-bacteremic pneumococcal , VT-pneumococcal mortality, serious adverse events

Search strategy

Database	Strategy	No. identified	Included in GRADE
clinicaltrials.gov	Search terms (searched separately): "V116"; "21-valent pneumococcal conjugate vaccine";"PCV21" Inclusion: Relevant Phase 2 or 3 randomized controlled trials of PCV21 • Involved human subjects • Reported primary data • Included adults (age ≥19 years) • Included data relevant to the efficacy or effectiveness or immunogenicity and safety outcomes being measured	10	6
Pubmed	"V116" or "21-valent pneumococcal conjugate vaccine" or "PCV21" Included studies using the criteria listed above	25	1
Additional resources	Unpublished and other relevant data by consulting with vaccine manufacturers and subject matter experts		5

Evidence Retrieval



PCV21 Clinical Trials included in Evidence Review

Last name first author, Publication year	Study design	Country	Age	Total population	N Intervention	N comparison	Outcomes	Funding source
Platt, Lancet ID 2023	RCT (Phase II)	U.S.	Adults ≥50 years	508	254	PPSV23: 254	Immunogenicity and Safety	MERCK
V116-003	RCT (Phase III); pivotal study	U.S., Australia, Belgium, Chile, Germany, Korea, New Zealand, Puerto Rico, Sweden, Taiwan, Turkey	Healthy adults ≥50 years, pneumococcal vaccine – naïve	2,663	1179	PCV20: 1,177	Immunogenicity and Safety	MERCK
			Healthy adults 18 - 49 years, pneumococcal vaccine – naïve		200	PCV20: 100		
V116-005	RCT (Phase III)	U.S.	Adults ≥50 years	1,080	(V116 + QIV, coadministered): 536	(QIV followed by V116) : 536	Immunogenicity and Safety	MERCK
V116-006	RCT (Phase III)	U.S., Canada, Israel, France, Italy, Japan, Korea, Spain, Taiwan	Adults ≥50 years, previous PPSV23 ≥1 year prior to enrollment	348	229	PCV15, n=119	Immunogenicity and Safety	MERCK
			Adults ≥50 years, previous PCV13 ≥1 year prior to enrollment	259	174	PPSV23 N=85		
			Adults ≥50 years, PCV13+PPSV23, PCV15+PPSV23, PCV15, PCV20, or PPSV23+PCV13 ≥1 year prior to enrollment	105	105	None		
V116-007	RCT (Phase III)	Belgium, Chile, France, South Africa, Thailand, United States	Adults living with HIV, ≥18 years; 36% prior PCV13 or PPSV23*	313	156	PCV15+PPSV23, n=157	Immunogenicity and Safety	MERCK
V116-004	RCT (Phase III)	U.S., Austria, Canada, Denmark, Finland, Israel, Poland, Spain	Adults 18 - 49 years with underlying chronic conditions	2,162	1,617	PPSV23:540	Safety	MERCK

GRADE Summary of Findings Table
PICO 1: Adults currently recommended to receive PCV

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV21	comparison	Relative (95% CI)	Absolute (95% CI)		
VT-IPD, VT-nonbacteremic pneumococcal pneumonia, VT-pneumococcal mortality outcome (Assessed with: Immunogenicity)												
5[1-5]	Randomized studies	Not serious	Not serious	Serious[a]	Not serious	Not serious	123 - 1161	58 - 1162	• V116 met non-inferiority criteria[b] for 9/9 shared and superiority criteria[c] for 12/12 unique serotypes vs. PPSV23 • V116 met non-inferiority criteria[d] for 10/10 shared and superiority criteria[e] 10/11 unique serotypes vs. PCV20 • V116 had higher immune responses for 1-4/6 shared and all unique serotypes vs. PCV15		Moderate	Critical

a. These are all immunogenicity studies and there are no correlates of protection for some critical outcomes considered.
b. Noninferiority for GMT ratio was defined as the lower bound of the 95% CI of the estimated OPA GMT ratio ({V116:PPSV23} to be > 0.33.
c. Superiority for GMT ratio was defined as the lower bound of the 95% CI of the estimated OPA GMT ratio [V116:PPSV23] to be > 1.0.
d. Noninferiority for GMT ratio was defined as the lower bound of the 2 sided 95% CI of the OPA GMT ratio [V116 / PCV20] to be >0.5.
e. Superiority for GMT ratio was defined as the lower bound of the 2 sided 95% CI of the OPA GMT ratio [V116 / PCV20] to be >2.0.

References

1. Platt H, Omole T, Cardona J, Fraser NJ, Mularski RA, Andrews C, Daboul N, Gallagher N, Sapre A, Li J, Polis A, Fernsler D, Tamms G, Xu W, Murphy R, Skinner J, Joyce J, Musey L. Safety, tolerability, and immunogenicity of a 21-valent pneumococcal conjugate vaccine, V116, in healthy adults: phase 1/2, randomised, double-blind, active comparator-controlled, multicentre, U.S.-based trial. Lancet Infect Dis. 2023 Feb;23(2):233-246. doi: 10.1016/S1473-3099(22)00526-6. Epub 2022 Sep 15. PMID: 36116461.
2. V116-003. A clinical study to evaluate the safety, tolerability, and immunogenicity of V116 compared to PCV20 in pneumococcal vaccine-naïve adults
3. V116-006. A Phase 3 Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Pneumococcal Vaccine-Experienced Adults 50 Years of Age or Older
4. V116-007. A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator- Controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Adults Living With HIV
5. V166-005. A clinical study comparing the immunogenicity and safety of V116 when administered concomitantly with inactivated influenza vaccine

GRADE Summary of Findings Table
PICO 1: Adults currently recommended to receive PCV

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV21	comparison	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events following immunization												
6[1-6]	Randomized studies	Not serious	Not serious	Not serious	Serious[f]	Not serious	57/4445 (1.3%)	63/2962 (2.1%)	Absolute % difference for SAEs across studies is -0.8%; two SAEs deemed vaccine-related[g] in the V116 group reported		Moderate	Critical

f. few vaccine-related serious adverse events reported.

g. Bronchospasm (V116-005): 50-year-old female in the sequential group with bronchospasm within 30 minutes after the 2ndvaccination (V116); duration 23 hours; resolved; Injection site cellulitis (V116-006): 67-year-old female in Cohort 1 (prior PPSV23) with injection site cellulitis on Day 6; duration 1.57 weeks; resolved (Merck, unpublished).

References

1. Platt H, Omole T, Cardona J, Fraser NJ, Mularski RA, Andrews C, Daboul N, Gallagher N, Sapre A, Li J, Polis A, Fernsler D, Tamms G, Xu W, Murphy R, Skinner J, Joyce J, Musey L. Safety, tolerability, and immunogenicity of a 21-valent pneumococcal conjugate vaccine, V116, in healthy adults: phase 1/2, randomised, double-blind, active comparator-controlled, multicentre, U.S.-based trial. Lancet Infect Dis. 2023 Feb;23(2):233-246. doi: 10.1016/S1473-3099(22)00526-6. Epub 2022 Sep 15. PMID: 36116461.
2. V116-003. A clinical study to evaluate the safety, tolerability, and immunogenicity of V116 compared to PCV20 in pneumococcal vaccine-naïve adults
3. V116-006. A Phase 3 Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Pneumococcal Vaccine-Experienced Adults 50 Years of Age or Older
4. V116-007. A Phase 3, Multicenter, Randomized, Double-blind, Active Comparator- Controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Adults Living With HIV
5. V166-005. A clinical study comparing the immunogenicity and safety of V116 when administered concomitantly with inactivated influenza vaccine
6. V116-004. A Phase 3 Randomized, Double-blind, Active Comparator-controlled, Lot to-Lot Consistency Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Adults 18 to 49 Years of Age.

GRADE Summary of Findings Table
PICO2: Adults aged 50–64 years, no risk-based indications

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV21	comparison	Relative (95% CI)	Absolute (95% CI)		
VT-IPD, VT-nonbacteremic pneumococcal pneumonia, VT-pneumococcal mortality outcome (Assessed with: Immunogenicity)												
2[1-2]	Randomized studies	Not serious	Not serious	Serious[a]	Not serious	Not serious	252 - 1161	254 - 1162	• V116 met non-inferiority criteria[b] for 9/9 shared and superiority criteria[c] for 12/12 unique serotypes vs. PPSV23 • V116 met non-inferiority criteria[d] for 10/10 shared and superiority criteria[e] 10/11 unique serotypes vs. PCV20		Moderate	Critical

a. These are all immunogenicity studies and there are no correlates of protection for some critical outcomes considered.
b. Noninferiority for GMT ratio was defined as the lower bound of the 95% CI of the estimated OPA GMT ratio ({V116:PPSV23} to be > 0.33.
c. Superiority for GMT ratio was defined as the lower bound of the 95% CI of the estimated OPA GMT ratio [V116:PPSV23] to be > 1.0.
d. Noninferiority for GMT ratio was defined as the lower bound of the 2 sided 95% CI of the OPA GMT ratio [V116 / PCV20] to be >0.5.
e. Superiority for GMT ratio was defined as the lower bound of the 2 sided 95% CI of the OPA GMT ratio [V116 / PCV20] to be >2.0.

References

1. Platt H, Omole T, Cardona J, Fraser NJ, Mularski RA, Andrews C, Daboul N, Gallagher N, Sapre A, Li J, Polis A, Fernsler D, Tamms G, Xu W, Murphy R, Skinner J, Joyce J, Musey L. Safety, tolerability, and immunogenicity of a 21-valent pneumococcal conjugate vaccine, V116, in healthy adults: phase 1/2, randomised, double-blind, active comparator-controlled, multicentre, U.S.-based trial. Lancet Infect Dis. 2023 Feb;23(2):233-246. doi: 10.1016/S1473-3099(22)00526-6. Epub 2022 Sep 15. PMID: 36116461.
2. V116-003. A clinical study to evaluate the safety, tolerability, and immunogenicity of V116 compared to PCV20 in pneumococcal vaccine-naïve adults

GRADE Summary of Findings Table
PICO2: Adults aged 50–64 years, no risk-based indications

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV21	comparison	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events following immunization												
2[1-2]	Randomized studies	Not serious	Not serious	Not serious	Serious[f]	Not serious	23/1431 (1.6%)	27/1429 (1.9%)	Absolute % difference for SAEs across studies is -0.3%; no vaccine-related serious adverse events reported		Moderate	Critical

f. No vaccine-related serious adverse events reported.

References

1. Platt H, Omole T, Cardona J, Fraser NJ, Mularski RA, Andrews C, Daboul N, Gallagher N, Sapre A, Li J, Polis A, Fernsler D, Tamms G, Xu W, Murphy R, Skinner J, Joyce J, Musey L. Safety, tolerability, and immunogenicity of a 21-valent pneumococcal conjugate vaccine, V116, in healthy adults: phase 1/2, randomised, double-blind, active comparator-controlled, multicentre, U.S.-based trial. Lancet Infect Dis. 2023 Feb;23(2):233-246. doi: 10.1016/S1473-3099(22)00526-6. Epub 2022 Sep 15. PMID: 36116461.
2. V116-003. clinical study to evaluate the safety, tolerability, and immunogenicity of V116 compared to PCV20 in pneumococcal vaccine-naïve adults

GRADE Summary of Findings Table
PICO3: Adults aged 19–49 years, no risk-based indications

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV21	comparison	Relative (95% CI)	Absolute (95% CI)		
VT-IPD, VT-nonbacteremic pneumococcal pneumonia, VT-pneumococcal mortality outcome (Assessed with: Immunogenicity)												
1[1]	Randomized studies	Not serious	Not serious	Serious[a]	Not serious	Not serious	184 - 198	550 - 575	V116 met criteria for immunobridging[b] to 50-64y for all serotypes		Moderate	Critical

a. These are all immunogenicity studies and there are no correlates of protection for some critical outcomes considered.
b. Immunobridging for GMT ratio was defined as the lower bound of the 2 sided 95% CI of the OPA GMT ratio [V116 18 to 49 group/V116 50 to 64 group] to be >0.5.

References

1. V116-003. A clinical study to evaluate the safety, tolerability, and immunogenicity of V116 compared to PCV20 in pneumococcal vaccine-naïve adults

GRADE Summary of Findings Table
PICO3: Adults aged 19–49 years, no risk-based indications

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV21	comparison	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events following immunization												
1[1]	Randomized studies	Not serious	Not serious	Not serious	Serious[c]	Not serious	1/200 (0.5%)	3/100 (3.0%)	Absolute % difference for SAEs is -2.5%; no vaccine-related serious adverse events reported		Moderate	Critical

c. No vaccine-related serious adverse events reported

References

1. V116-003. clinical study to evaluate the safety, tolerability, and immunogenicity of V116 compared to PCV20 in pneumococcal vaccine-naïve adults

PICO1: Adults currently recommended to receive PCV

Type	Outcome	Importance	Included in evidence profile	Certainty of evidence
Benefits	VT- IPD	Critical	No*	Moderate
	VT-pneumonia	Critical	No*	Moderate
	VT- pneumococcal deaths	Critical	No*	Moderate
Harms	Serious adverse events following immunization	Critical	Yes	Moderate

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

PICO2: Adults aged 50–64 years, no risk-based indications

Type	Outcome	Importance	Included in evidence profile	Certainty of evidence
Benefits	VT- IPD	Critical	No*	Moderate
	VT-pneumonia	Critical	No*	Moderate
	VT- pneumococcal deaths	Critical	No*	Moderate
Harms	Serious adverse events following immunization	Critical	Yes	Moderate

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

PICO3: Adults aged 19–49 years, no risk-based indications

Type	Outcome	Importance	Included in evidence profile	Certainty of evidence
Benefits	VT- IPD	Critical	No*	Moderate
	VT-pneumonia	Critical	No*	Moderate
	VT- pneumococcal deaths	Critical	No*	Moderate
Harms	Serious adverse events following immunization	Critical	Yes	Moderate

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