Evidence to Recommendation Framework: Risk-based Use of 15-valent and 20-valent Pneumococcal Conjugate Vaccines in Adults

Miwako Kobayashi, MD, MPH

ACIP Meeting

September 29, 2021

Summary of Age-Based Policy Options Being Considered

- PCV15 option
  - Should PCV15 be routinely recommended to US adults aged ≥65 years in series with PPSV23?

- PCV20 options
  - Should PCV20 be routinely recommended to US adults aged ≥50 years?
  - Should PCV20 be routinely recommended to US adults aged ≥65 years?

Current and Proposed Options for Adults Aged ≥65 years

<table>
<tr><th></th><th>Current Policy</th><th>New Policy Options Considered</th></tr>
<tr><td>None of the conditions listed below</td><td rowspan="2">PCV13* based on shared clinical decision making, PPSV23 for all</td><td rowspan="3">1.PCV15 and PPSV23

2. PCV20</td></tr>
<tr><td>Chronic medical conditions† (CMC)</td></tr>
<tr><td>Cochlear implant, CSF leak</td><td rowspan="2">Both PCV13* and PPSV23</td></tr>
<tr><td>Immunocompromising conditions</td><td></td></tr>
</table>

PCV13: 13-valent pneumococcal conjugate vaccine, PCV15: 15-valent pneumococcal conjugate vaccine, PCV20: 20-valent pneumococcal conjugate vaccine, PPSV23: 23-valent pneumococcal polysaccharide vaccine

*If not previously given; †Examples include alcoholism, chronic heart/liver/lung disease, diabetes, cigarette smoking

https://www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf

Current and Proposed Options for Adults Aged ≥50 years

	Current policy		New Policy Option Considered for ≥50 Years
	50-64 Years	≥65 Years	
None of the conditions listed below	No recommendation	PCV13* based on shared clinical decision making, PPSV23 for all	PCV20
Chronic medical conditions† (CMC)	PPSV23		
Cochlear implant, CSF leak	Both PCV13* and PPSV23	Both PCV13* and PPSV23	
Immunocompromising conditions	Both PCV13* and PPSV23, repeat PPSV23 after 5 years		

*If not previously given; †Examples include alcoholism, chronic heart/liver/lung disease, diabetes, cigarette smoking

https://www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf

Summary of Updated WG Interpretation:

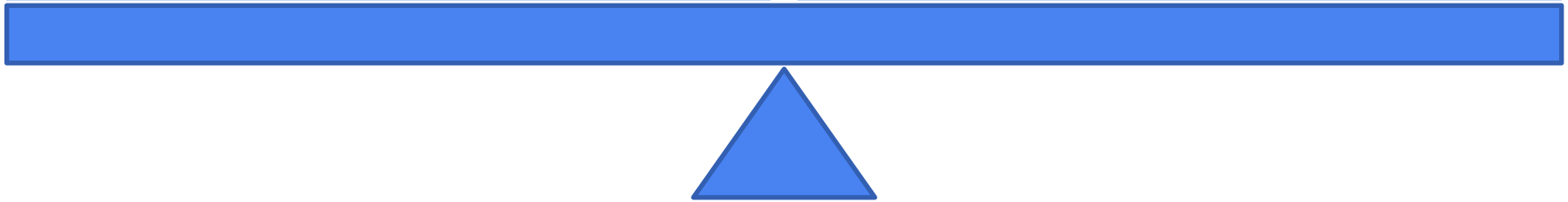
PCV15+PPSV23, Age ≥65 Years vs. Current Recommendations

Desirable

- Will prevent more disease (2 additional serotypes)
- Potential for improved protection vs. serotype 3 disease (uncertain)
- Simplified recommendation if routine PCV15+PPSV23 use is recommended (vs. shared clinical decision-making)
- Cost-saving* in updated CDC model

Undesirable

- Routine use of PCV15-PPSV23 series more likely to disadvantage those with limited access to vaccines
- May be less acceptable and feasible for some providers



*Intervention yielded better health outcomes and lower costs compared to the current recommendation.

Summary of Updated WG Interpretation:

PCV15+PPSV23, Age ≥65 Years vs. Current Recommendations

Desirable

- Will prevent more disease (2 additional serotypes)
- Potential for improved protection vs. serotype 3 disease (uncertain)
- Simplified recommendation if routine PCV15+PPSV23 use is recommended (vs. shared clinical decision-making)
- Cost-saving* in u[illegible]

Undesirable

- Routine use of PCV15-PPSV23 series more likely to disadvantage those with limited access to vaccines
- May be less acceptable and feasible for some providers

The balance between desirable and undesirable consequences is *closely balanced* or *uncertain*

*Intervention yielded better health outcomes and lower costs compared to the current recommendation.

Summary of Updated WG Interpretation:

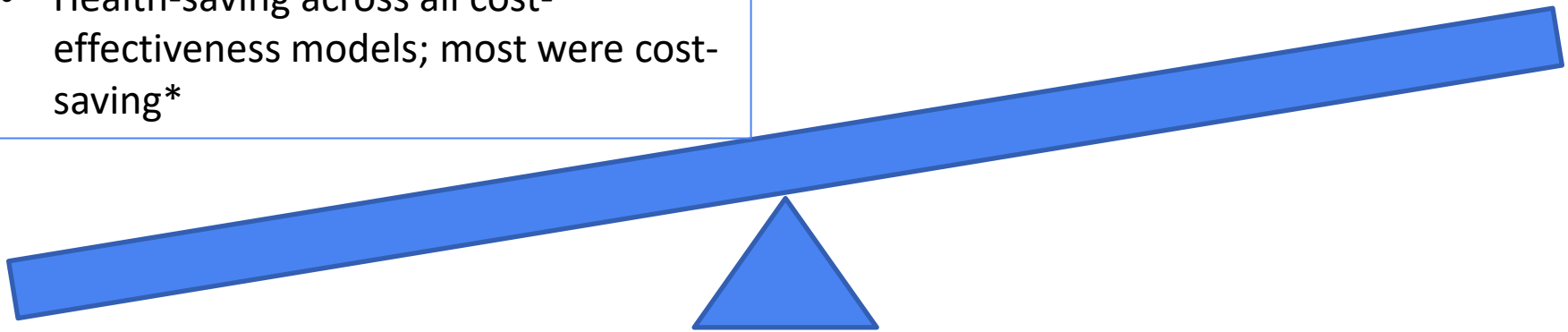
PCV20, ≥65 Years vs. Current Recommendations

Desirable

- Expect more protection (7 additional serotypes)
- Simplified recommendation—likely more acceptable and feasible, may increase vaccine coverage
- Health-saving across all cost-effectiveness models; most were cost-saving*

Undesirable

- Clinical significance of lower immunogenicity vs. PCV13 unknown (met non-inferiority criteria)
- Impact of losing coverage against 4 PPSV23 serotypes unknown



*Intervention yielded better health outcomes and lower costs compared to the current recommendation.

Summary of Updated WG Interpretation:

PCV20, ≥65 Years vs. Current Recommendations

Desirable

- Expect more protection (7 additional serotypes)
- Simplified recommendation—likely more acceptable and feasible, may increase vaccine coverage
- Health-saving across all cost-effectiveness models; most were cost-saving*

Undesirable

- Clinical significance of lower immunogenicity vs. PCV13 unknown (met non-inferiority criteria)
- Impact of losing coverage against 4 PPSV23 serotypes unknown

Desirable consequences *clearly* outweigh undesirable consequences in most settings

*Intervention yielded better health outcomes and lower costs compared to the current recommendation.

Summary of Updated WG Interpretation:

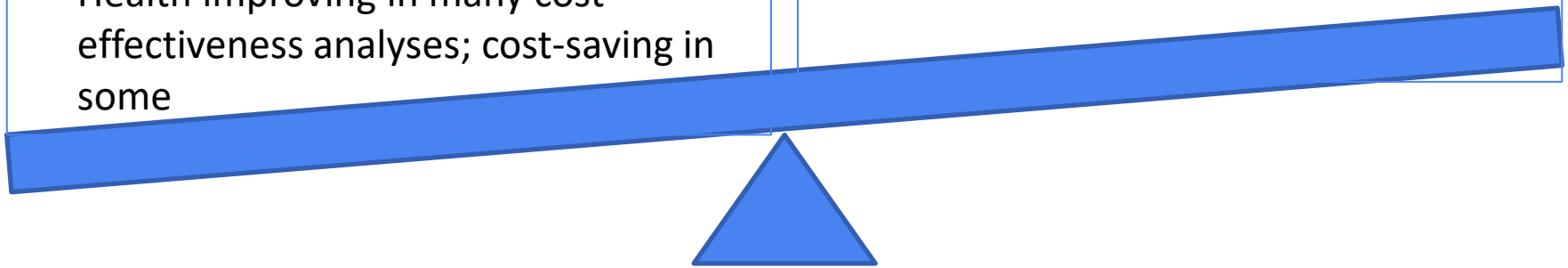
PCV20, ≥50 Years vs. Current Recommendations (differences from ≥65 Years)

Desirable

- May improve coverage in adults aged 50–64 years with underlying conditions, which are more prevalent in certain populations→may be more equitable
- Opportunity to vaccinate adults before they develop underlying conditions
- Health improving in many cost-effectiveness analyses; cost-saving in some

Undesirable

- Vaccine may not provide sufficient protection later in life when risk of disease increases (waning); worse health outcome in some CDC scenarios
- May have initial implementation challenges since this is a new age group



*Intervention yielded better health outcomes and lower costs compared to the current recommendation.

Summary of Updated WG Interpretation:

PCV20, ≥50 Years vs. Current Recommendations (differences from ≥65 Years)

Desirable

- May improve coverage in adults aged 50–64 years with underlying conditions, which are more prevalent in certain populations→may be more equitable
- Opportunity to vaccinate adults before they develop underlying conditions
- Health improving in many cost-effectiveness analyses; cost-saving in some

Undesirable

- Vaccine may not provide sufficient protection later in life when risk of disease increases (waning); worse health outcome in some CDC scenarios
- May have initial implementation challenges since this is a new age group

Desirable consequences *probably* outweigh undesirable consequences in most settings

*Intervention yielded better health outcomes and lower costs compared to the current recommendation.

Current and Proposed Options for Risk-Based Recommendation

	Current policy	New Policy Options Considered
None of the conditions listed below	No recommendation	No recommendation
Chronic medical conditions† (CMC)	**PPSV23**	**1. PCV15+PPSV23** **2. PCV20**
Cochlear implant, CSF leak	**Both PCV13* and PPSV23**	
Immunocompromising conditions	**Both PCV13* and PPSV23, repeat PPSV23 after 5 years**	

PCV13: 13-valent pneumococcal conjugate vaccine
PPSV23: 23-valent pneumococcal polysaccharide vaccine

*If not previously given; †Examples include alcoholism, chronic heart/liver/lung disease, diabetes, cigarette smoking
https://www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf

Classification of Risk Groups: CMC vs. Immunocompromising Conditions

	19–64 years	≥65 years
None of the conditions listed below	No recommendation	
Chronic medical conditions† (CMC)	**PPSV23**	CMC
Cochlear implant, CSF leak	**Both PCV13* and PPSV23**	Immunocompromising conditions (IC)
Immunocompromising conditions	**Both PCV13* and PPSV23, repeat PPSV23 after 5 years**	

PCV13: 13-valent pneumococcal conjugate vaccine
PPSV23: 23-valent pneumococcal polysaccharide vaccine

*If not previously given; †Examples include alcoholism, chronic heart/liver/lung disease, diabetes, cigarette smoking
https://www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf

CMC adults comprise 90% of adults eligible for the risk-based recommendations.

	Current policy 19–64 years old	New Policy Option Considered
Chronic medical conditions (CMC)	PPSV23 90%*	PCV15+PPSV23
Cochlear implant, CSF leak	Both PCV13 and PPSV23	
Immunocompromising conditions	Both PCV13 [illegible] 10%* [illegible] eat PPSV23 after 5 years	

†National Health Interview Survey, 2017–2018

Question	Should PCV15 in series with PPSV23 be recommended for US adults aged 19–64 years with CMC or IC?
Population	US adults aged 19–64 years with CMC or IC
Intervention	**One dose of PCV15 followed by PPSV23**
Comparison	• PPSV23 (adults with CMC*) • PCV13 followed by PPSV23 (immunocompromised adults**)
Outcomes	VT-IPD, VT-NBPP, deaths, serious adverse events

CMC: chronic medical conditions, IC: immunocompromising conditions, IPD: invasive pneumococcal disease, NBPP: non-bacteremic pneumococcal pneumonia, VT: vaccine-type

*alcoholism, chronic heart/liver/lung disease, cigarette smoking, diabetes mellitus

**immunocompromised adults include adults with immunocompromising condition (chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosuppression, generalized malignancy, human immunodeficiency virus, Hodgkin disease, leukemia, lymphoma, multiple myeloma, solid organ transplants, congenital or acquired asplenia, sickle cell disease, or other hemoglobinopathies), CSF leak, or cochlear implant; immunocompetent adults are those without these conditions.

Questions	Should PCV20 be routinely recommended for US adults with CMC/IC aged…	
	19–49 years?	**19–64 years?**
Population	US adults aged **19–49 years with CMC/IC**	US adults aged **19–64 years with CMC/IC**
Intervention	**One dose of PCV20**	
Comparison	PPSV23 only (adults with CMC*)	
	PCV13 followed by PPSV23 (immunocompromised**)	
Outcomes	VT-IPD, VT-NBPP, deaths, serious adverse events	

CMC: chronic medical conditions, IC: immunocompromising conditions, VT: vaccine-type, IPD: invasive pneumococcal disease, NBPP: non-bacteremic pneumococcal pneumonia

*CMC includes chronic heart/lung/liver disease, cirrhosis, diabetes mellitus, alcoholism, and cigarette smoking
**immunocompromised adults include adults with immunocompromising condition (chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosuppression, generalized malignancy, human immunodeficiency virus, Hodgkin disease, leukemia, lymphoma, multiple myeloma, solid organ transplants, congenital or acquired asplenia, sickle cell disease, or other hemoglobinopathies), CSF leak, or cochlear implant; immunocompetent adults are those without these conditions.

Evidence to Recommendations (EtR) Framework

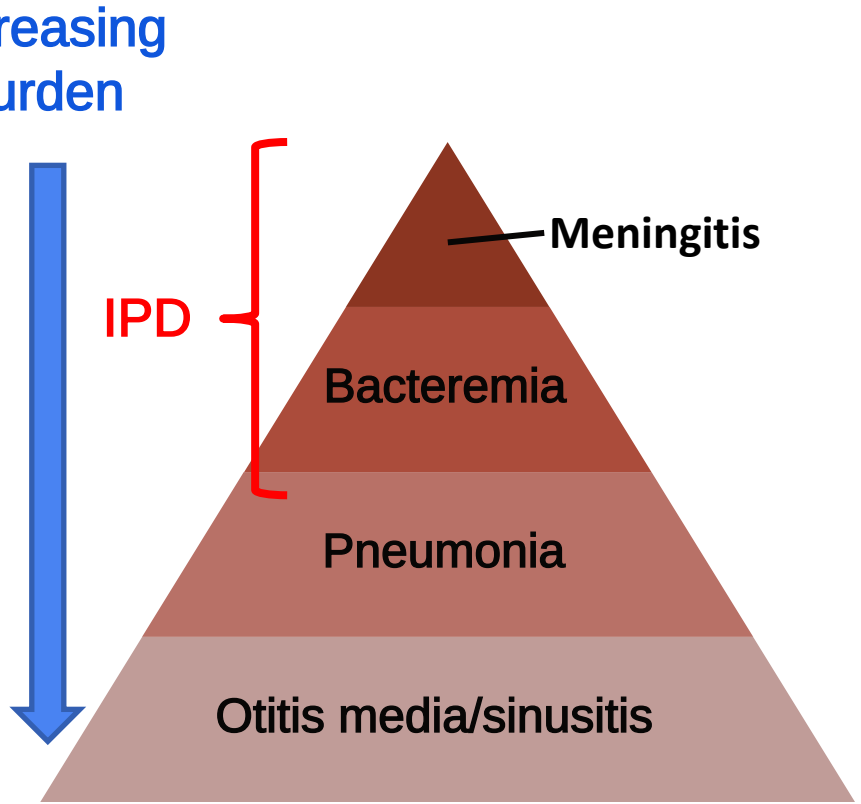
EtR Domain	Question
Public Health Problem	• Is the problem of public health importance?
Benefits and Harms	• How substantial are the desirable anticipated effects? • How substantial are the undesirable anticipated effects? • Do the desirable effects outweigh the undesirable effects?
Values	• Does the 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

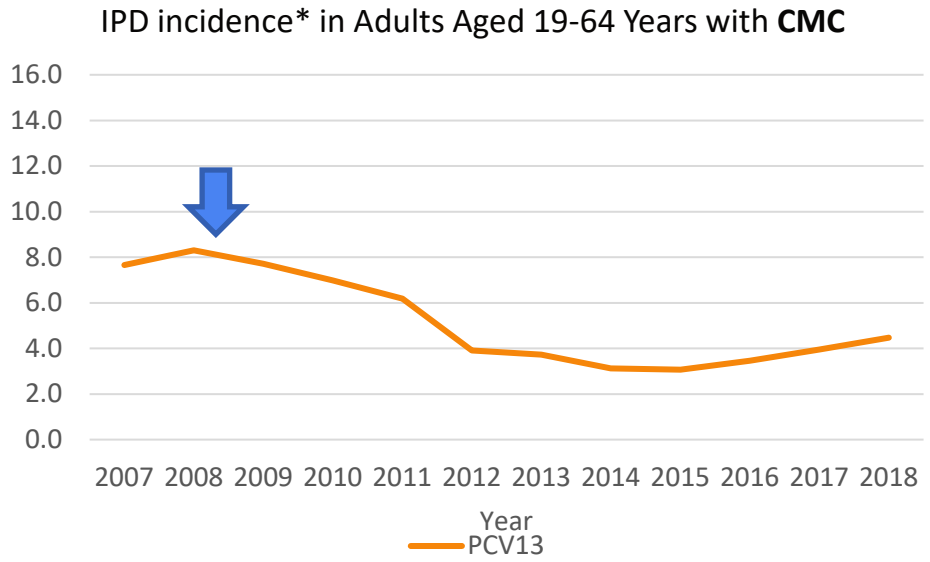
Is pneumococcal disease of public health importance in adults aged 19–64 years with CMC or IC?

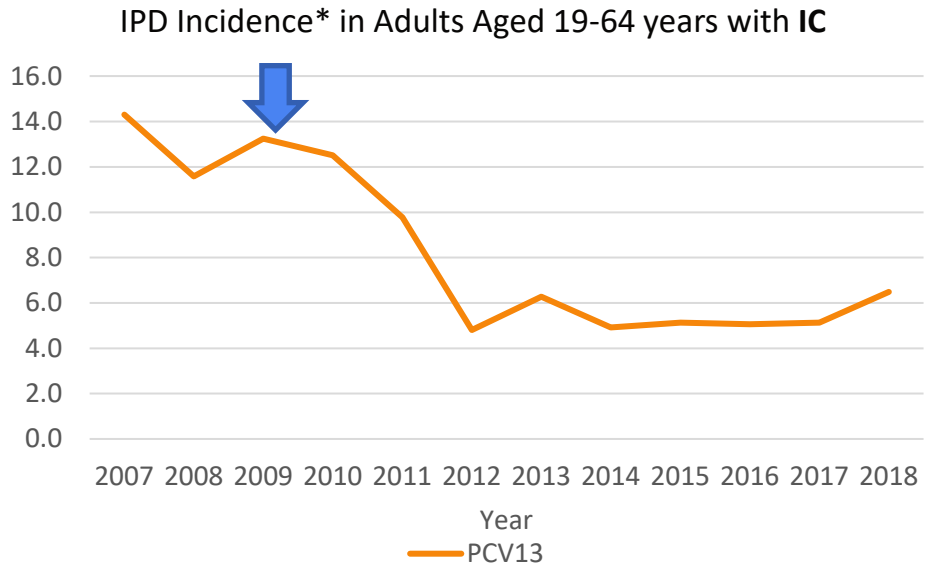
Pneumococcal disease

- Invasive pneumococcal disease (IPD)
  - e.g., meningitis, bacteremia, bacteremic pneumonia
- Non-invasive disease
  - e.g., non-bacteremic pneumonia



PCV13-type IPD incidence declined in adults aged 19–64 years with CMC/IC since PCV13 introduction in children in 2010.

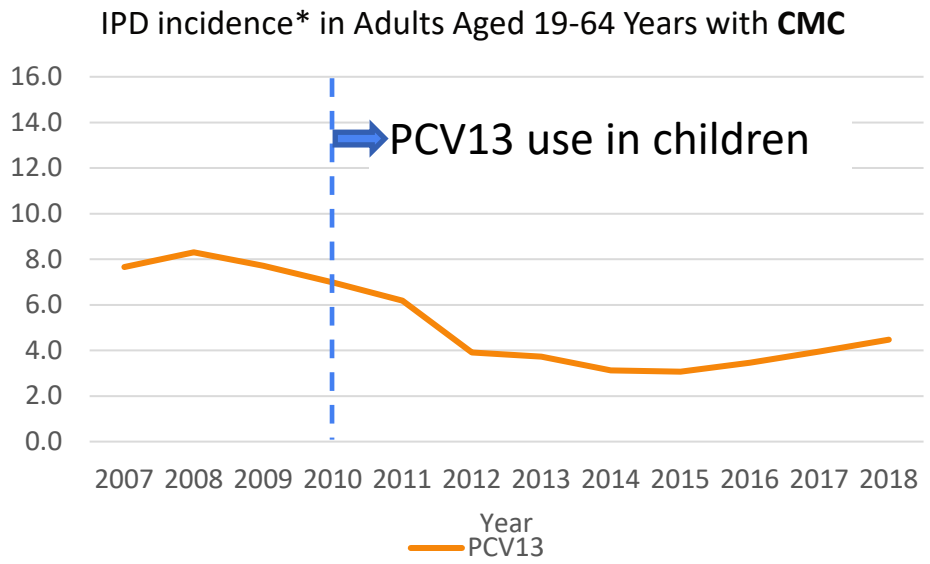


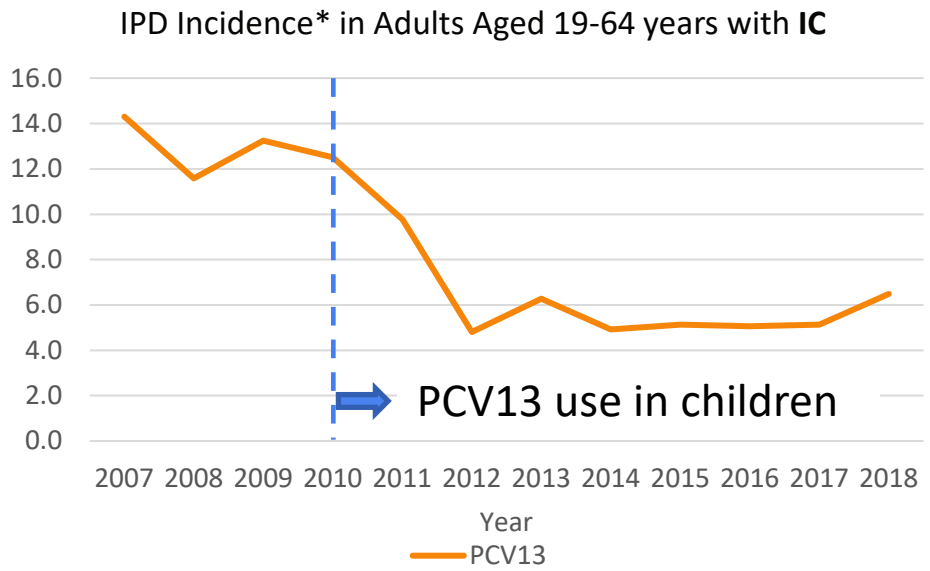


*per 100,000 population

ABCs, 2007–2018

PCV13-type IPD incidence declined in adults aged 19–64 years with CMC/IC since PCV13 introduction in children in 2010.

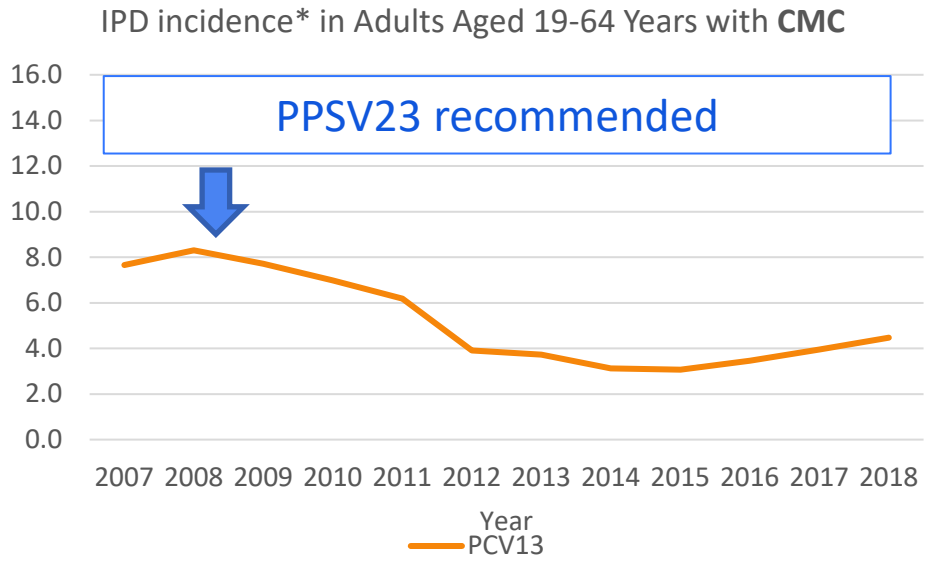


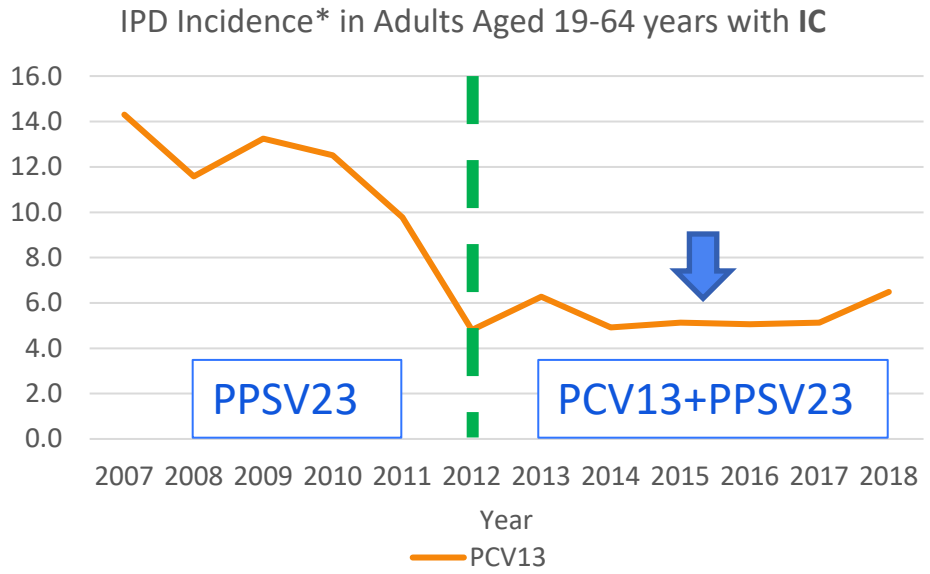


*per 100,000 population

ABCs, 2007–2018

PCV13-type IPD incidence remained stable in adults aged 19–64 years with IC since PCV13 introduction in 2012.

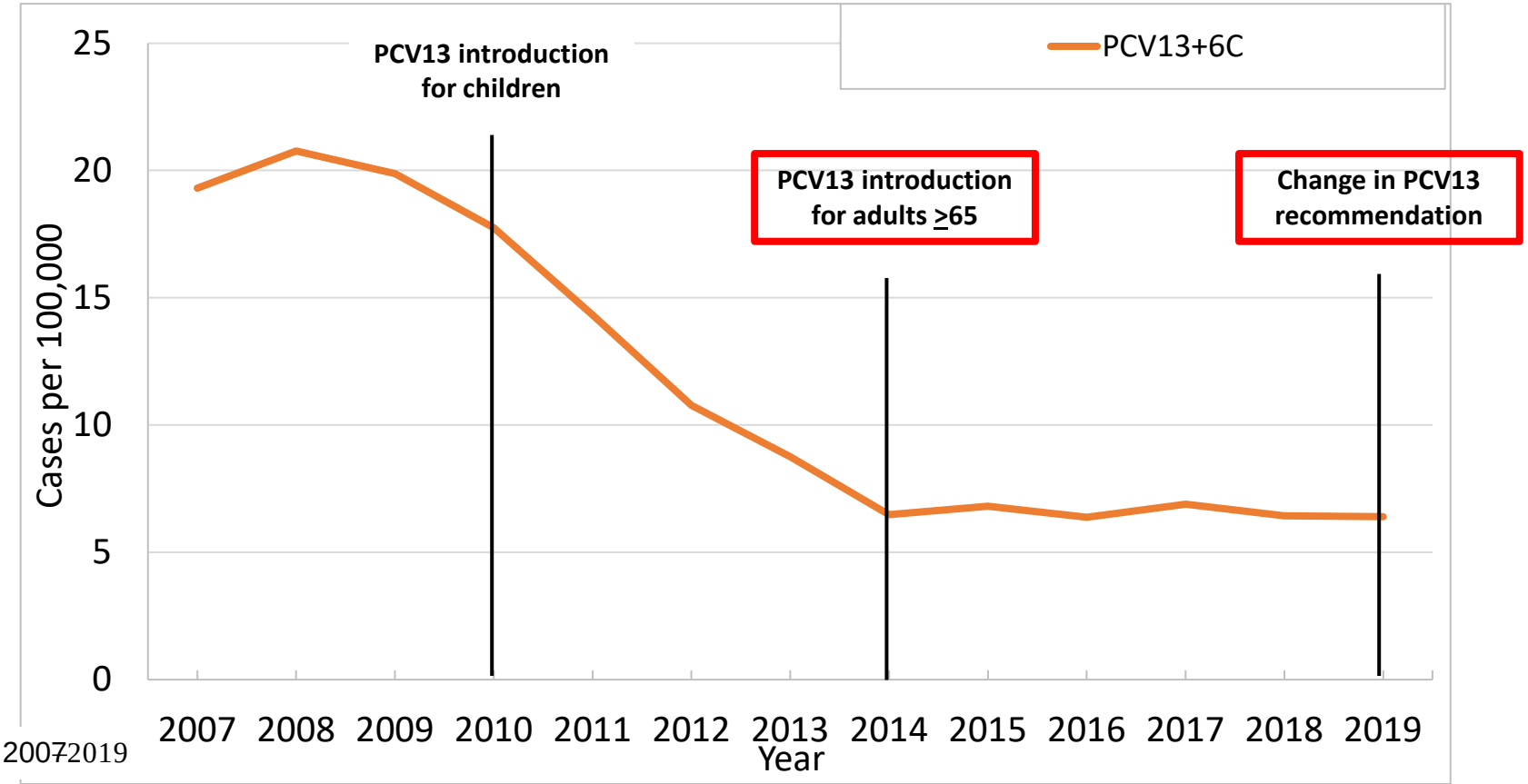




*per 100,000 population

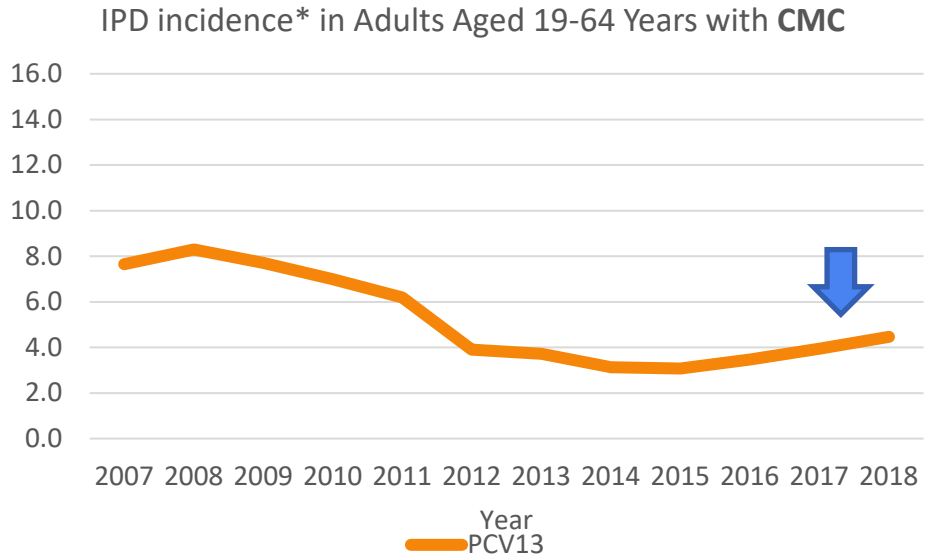
ABCs, 2007–2018

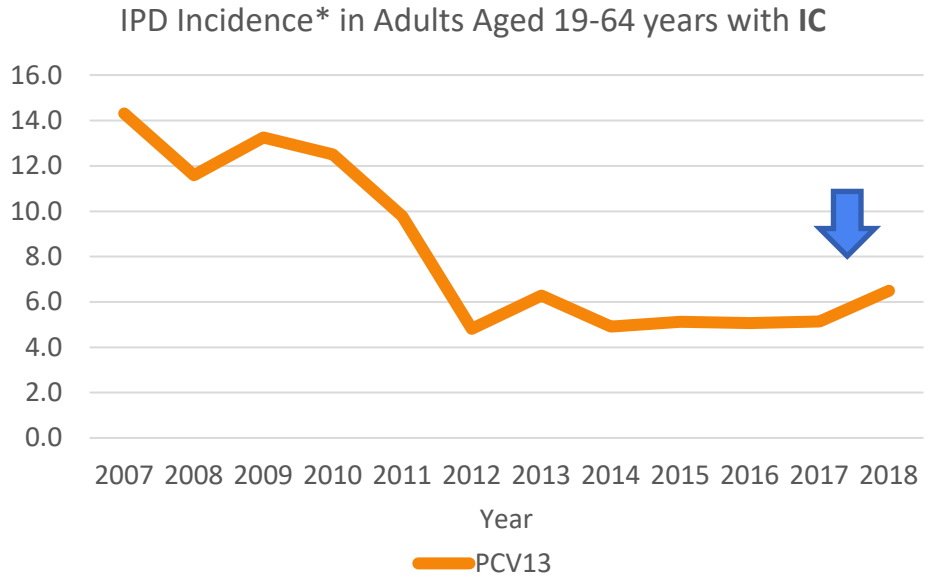
Routine PCV13 use had minimal impact against VT-IPD at the population level in adults aged ≥65 years, likely due to pediatric indirect effects.



ABCs 2007–2019

In 2017–2018, approximately 50% of the remaining PCV13 type IPD in adults aged 19–64 years with CMC/IC was due to serotype 3.

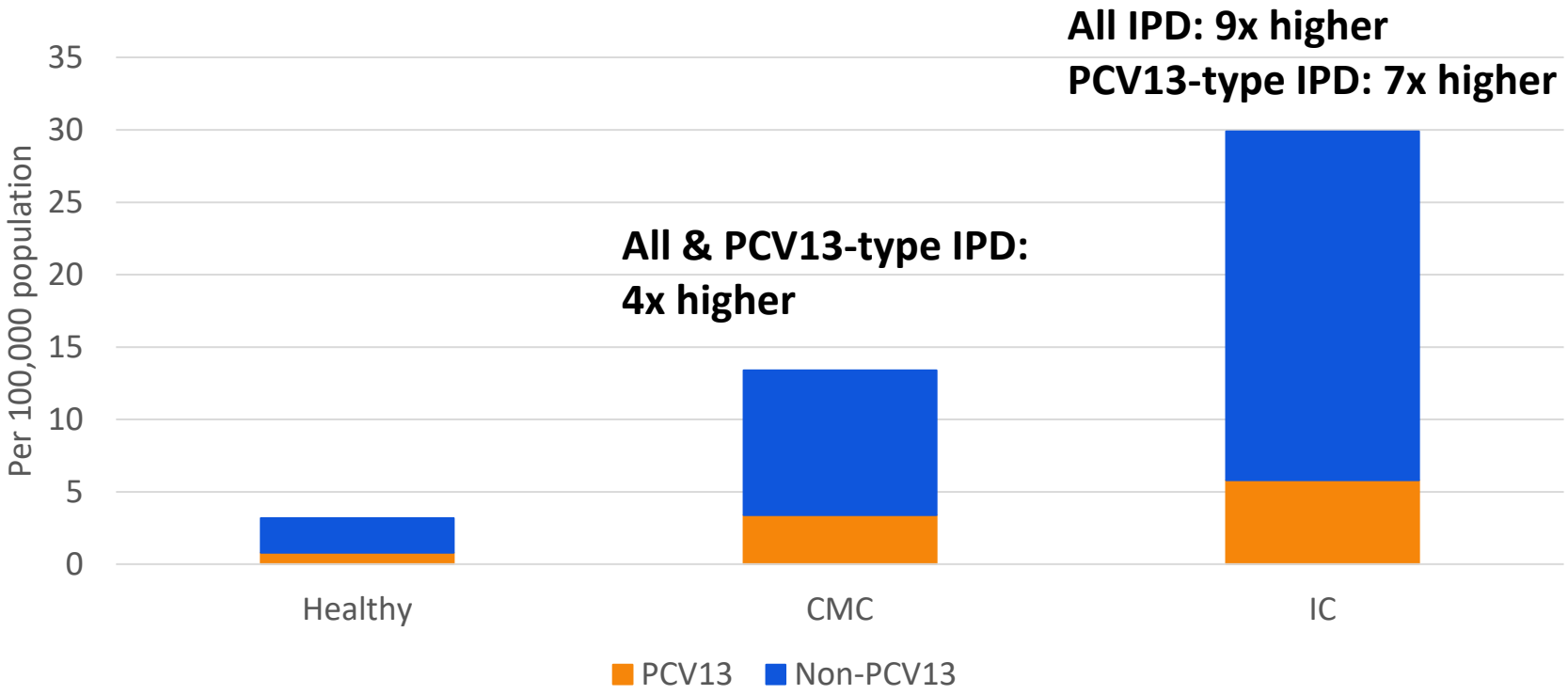




*per 100,000 population

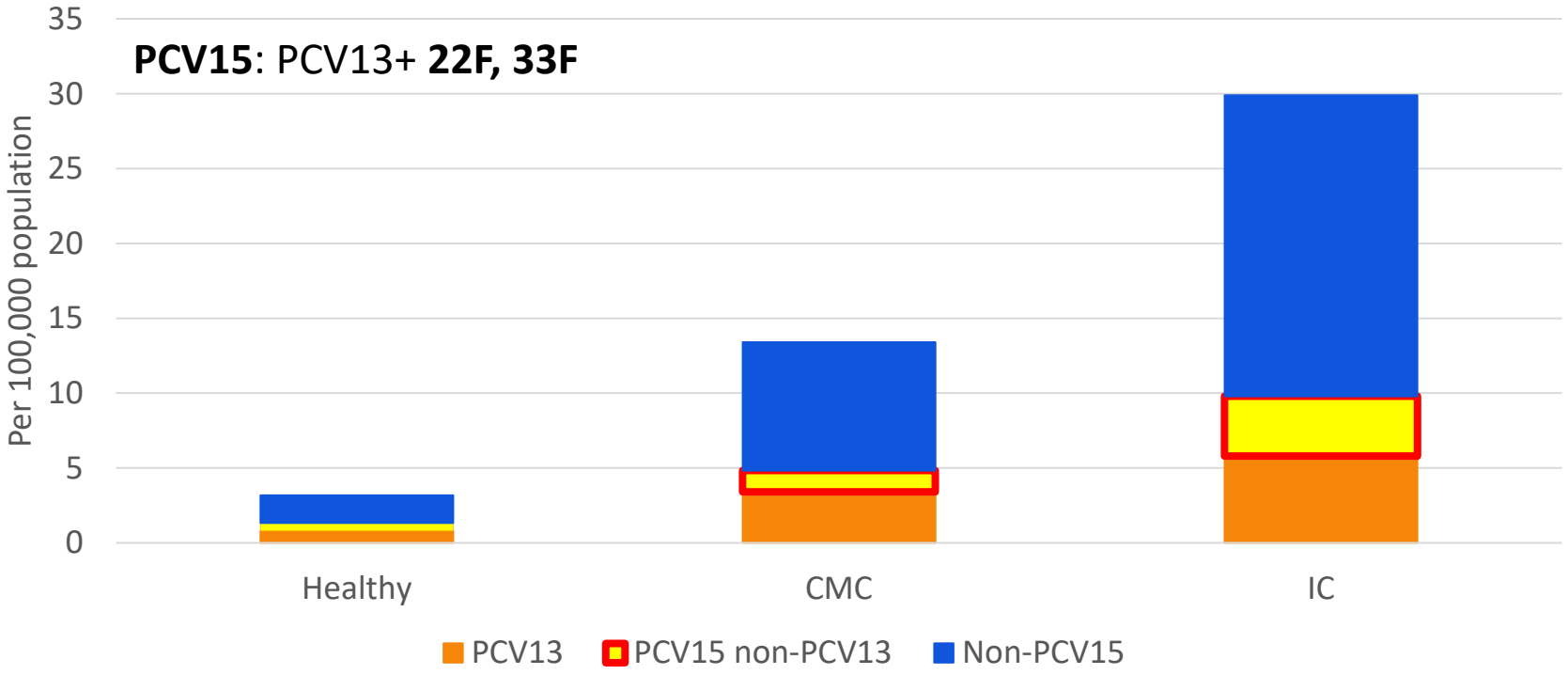
ABCs, 2007–2018

In 2017–2018, adults 19–64 years with CMC/IC had 4 to 9 times higher risk of all IPD, and 4 to 7 times higher risk of PCV13-type IPD compared with those without conditions.



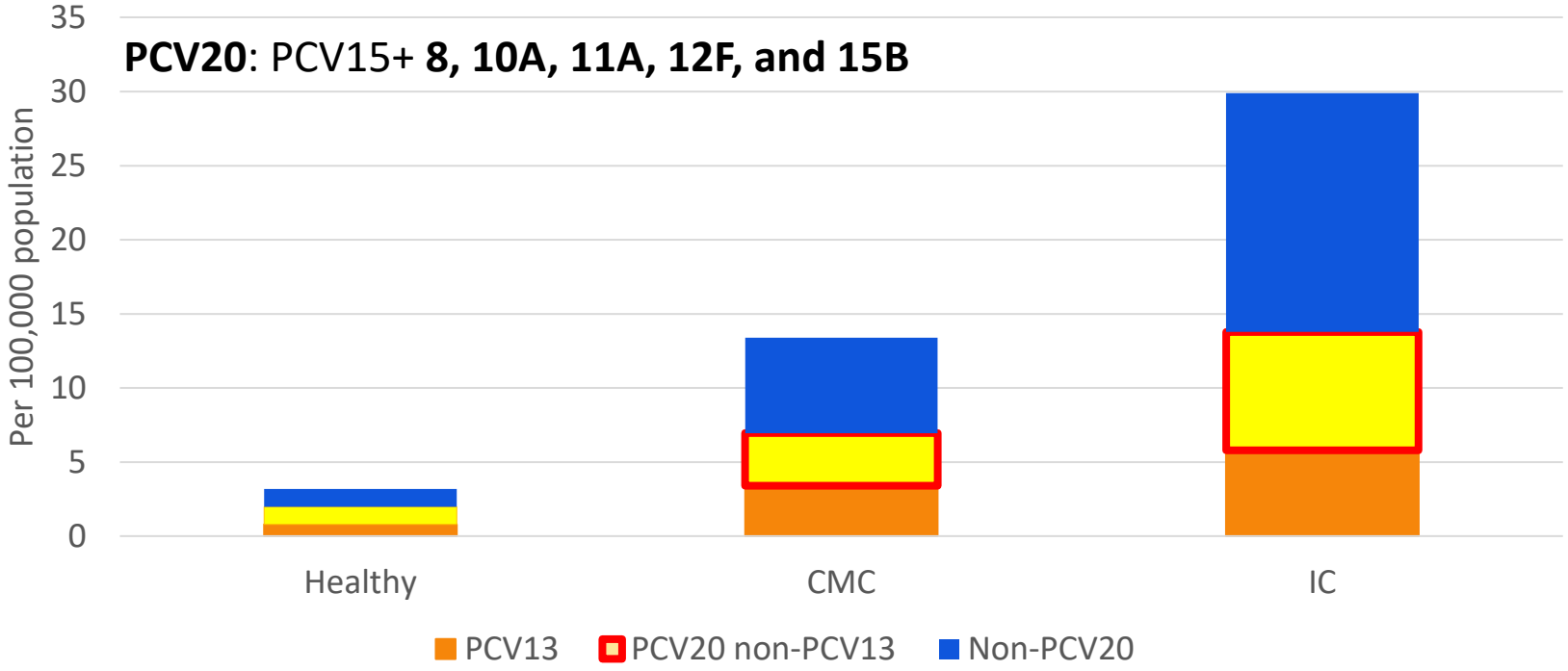
ABCs and NHIS, 2017–2018

Two additional serotypes included in PCV15 comprise 11 to 13% of remaining IPD burden in adults aged 19–64 years with CMC/IC.



ABCs and NHIS, 2017–2018

Seven additional serotypes included in PCV20 comprise 27% of remaining IPD burden in adults aged 19–64 years with CMC/IC.



ABCs and NHIS, 2017–2018

In 2013–2015, adults with CMC had 4 to 5 times higher rates of pneumococcal pneumonia hospitalizations vs. those without conditions.

	Hospitalized pneumococcal pneumonia per 100K person -years (95% CI), 2013–2015	Rate Ratio (95% CI) vs. Healthy
18–49 years		
Healthy	1.2 (1.1, 1.3)	**Ref**
CMC (at-risk)	6.0 (5.1, 6.9)	**5.0 (4.1, 6.0)**
IC (high-risk)	21.1 (17.9, 24.9)	**17.6 (14.4, 21.5)**
50–64 years		
Healthy	3.9 (3.5, 4.2)	**Ref**
CMC (at-risk)	14.8 (13.7, 16.0)	**3.8 (3.4, 4.3)**
IC (high-risk)	43.0 (39.7, 46.6)	**11.1 (9.9, 12.6)**

Pelton et al. CID 2019

In 2013–2015, adults with IC had 11 to 18 times higher rates of pneumococcal pneumonia hospitalizations vs. those without conditions.

	Hospitalized pneumococcal pneumonia per 100K person -years (95% CI), 2013–2015	Rate Ratio (95% CI) vs. Healthy
18–49 years		
Healthy	1.2 (1.1, 1.3)	Ref
CMC (at-risk)	6.0 (5.1, 6.9)	5.0 (4.1, 6.0)
IC (high-risk)	21.1 (17.9, 24.9)	17.6 (14.4, 21.5)
50–64 years		
Healthy	3.9 (3.5, 4.2)	Ref
CMC (at-risk)	14.8 (13.7, 16.0)	3.8 (3.4, 4.3)
IC (high-risk)	43.0 (39.7, 46.6)	11.1 (9.9, 12.6)

Pelton et al. CID 2019

Public Health Problem

Is pneumococcal disease of public health importance in adults aged 19–64 years with CMC or IC?

- □ 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 death?

Benefits and Harms

How substantial are the undesirable anticipated effects?

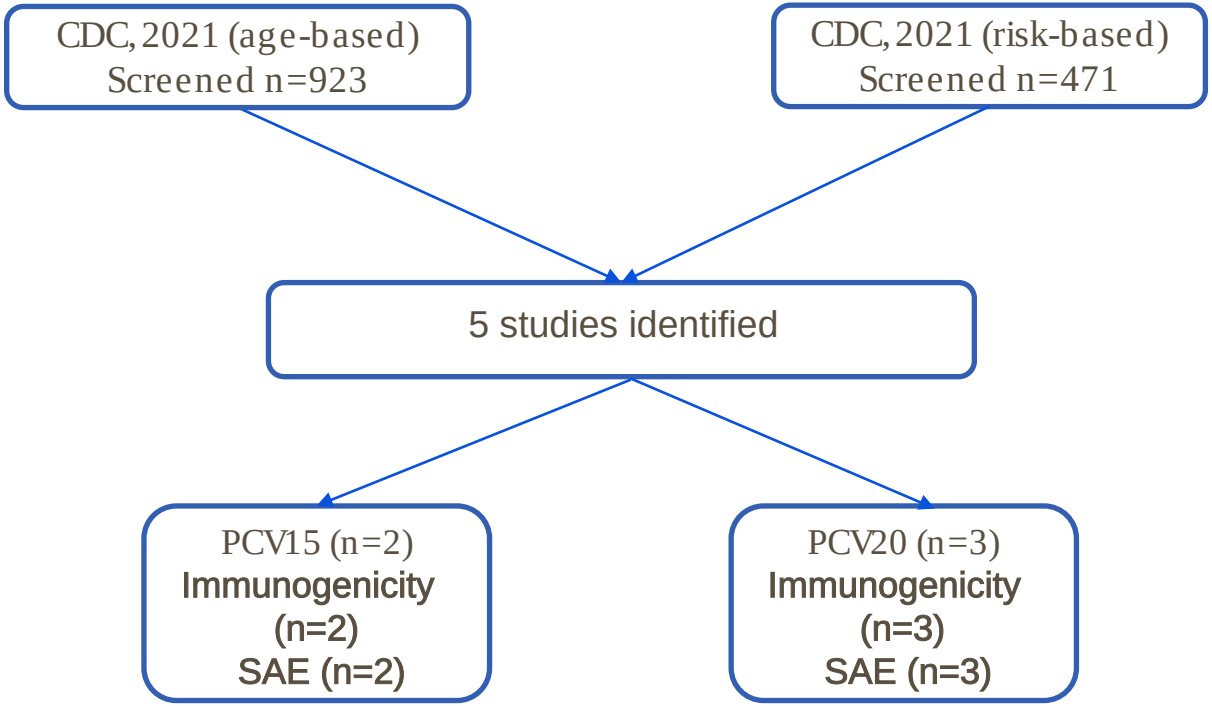
- How substantial is the anticipated effect for **serious adverse events?**

Benefits and Harms

Do the desirable effects outweigh the undesirable effects?

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

Evidence Retrieval



No PCV15 or PCV20 studies directly assessed vaccine effectiveness against the critical outcomes

Summary of Evidence, PCV15-PPSV23 series

Study	Age or other characteristic of importance	N intervention	N comparison	Comparator vaccine
V114-017, Phase III RCT	Immunocompetent adults 18-49 years of age at risk of pneumococcal disease	1035	346	PCV13 + PPSV23 (6-month interval)
V114-018, Phase III RCT	Adults ⩾18 years of ag with HIV	150	148	PCV13 + PPSV23 (8-week interval)

Please see GRADE summary tables for details

Summary of Available Evidence: PCV15 in series with PPSV23

Certainty assessment							№ of patients		Results		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**comparison[b]**	**Relative effect**	**Absolute effect**	
Vaccine effectiveness (Vaccine-type invasive pneumococcal disease, Vaccine-type non-bacteremic pneumococcal pneumonia, Vaccine-type pneumococcal mortality)											
2	Randomized studies	Not serious	Not serious	**Serious [a]**	Not serious	Not serious	844	352	**PCV15+PPSV23 had higher immune responses vs. PCV13+PPSV23 for 12 of 13 common serotypes across both studies. Of all comparisons across studies, only one serotype in a single study was found to be significantly higher by GMTs (ST18C).**		2 moderate

a. These are all immunogenicity studies and there are no correlates of protection
b. Patient no. based on minimum number of patients included in immunogenicity comparisons presented; some comparisons may have had more patients than this minimum

Please see GRADE summary tables for details

Summary of Available Evidence: PCV15 in series with PPSV23

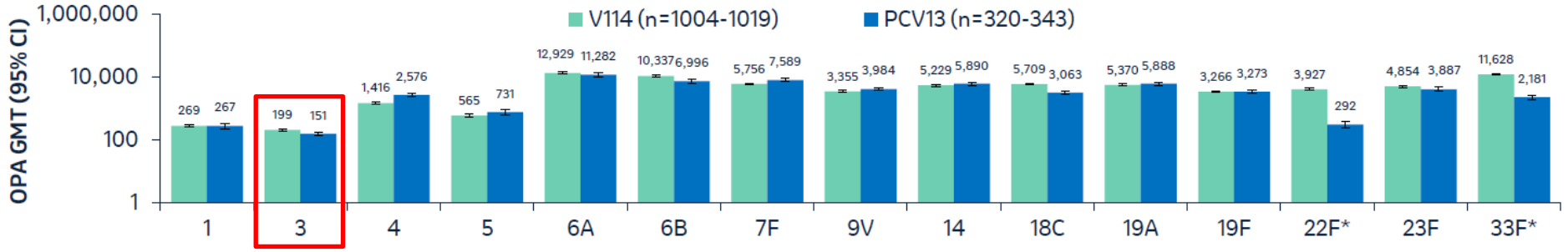
Certainty assessment							№ of patients		Results		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**comparison[b]**	**Relative effect**	**Absolute effect**	
Vaccine effectiveness (Vaccine-type invasive pneumococcal disease, Vaccine-type non-bacteremic pneumococcal pneumonia, Vaccine-type pneumococcal mortality)											
2	Randomized studies	Not serious	Not serious	**Serious [a]**	Not serious	Not serious	844	352	PCV15+PPSV23 had higher immune responses vs. PCV13+PPSV23 for 12 of 13 common serotypes across both studies. Of all comparisons across studies, only one serotype in a single study was found to be significantly higher by GMTs (ST18C).		**2 moderate**

a. These are all immunogenicity studies and there are no correlates of protection
b. Patient no. based on minimum number of patients included in immunogenicity comparisons presented; some comparisons may have had more patients than this minimum

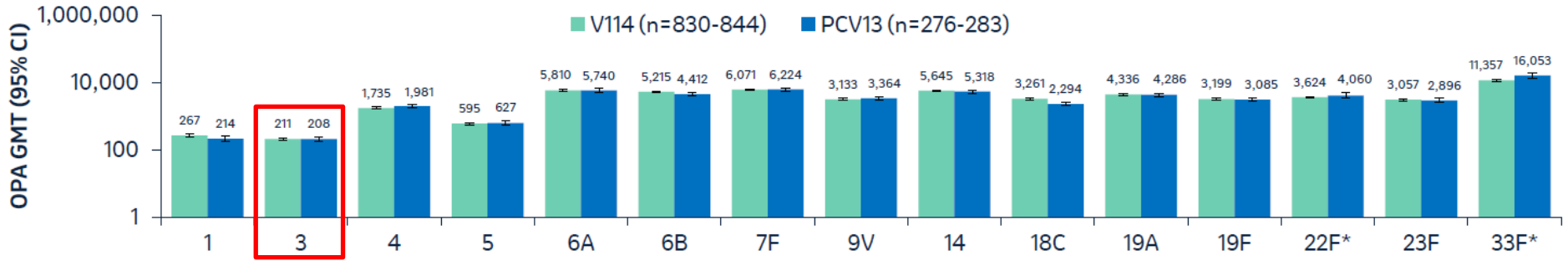
Please see GRADE summary tables for details

OPA GMTs against Serotype 3: V114-017

OPA GMTs 30 days postvaccination with V114/PCV13 (Day 30)



OPA GMTs 30 days postvaccination with PPSV23 (Month 7)



Merck February 2021 ACIP presentation, *Serotypes not included in PCV13, OPA: opsonophagocytic activity

Benefits and Harms

How substantial are the desirable anticipated effects?

- PCV15 use in series with PPSV23 in adults aged 19 –64 years with CMC/IC?

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

Benefits and Harms

How substantial are the desirable anticipated effects?

- PCV15 use in series with PPSV23 in adults aged 19 –64 years with CMC/IC?

- Added benefit in CMC (currently PPSV23 only) may be large.
  - Assuming improved VE against disease (esp. pneumonia) in PCV15 vs PPSV23
- Added benefit may be greater if PCV15 provides improved protection against ST3 disease, though clinical benefits unknown.
- PCV13-type disease declined from pediatric indirect effects.
- PCV15 contains 2 additional serotypes vs. PCV13 (11–13% of remaining IPD).

Summary of Available Evidence: PCV15 in series with PPSV23

Certainty assessment							№ of patients		Results		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**comparison[b]**	**Relative effect**	**Absolute effect**	
Serious adverse events											
2	Randomized studies	Not serious	Not serious	Not serious	Serious [c]	Not serious	**0/1186**	**0/493**	non estimable	---	2 moderate

a. These are all immunogenicity studies and there are no correlates of protection
b. Patient no. based on minimum number of patients included in immunogenicity comparisons presented; some comparisons may have had more patients than this minimum
c. No vaccine-related serious adverse events reported

Please see GRADE summary tables for details

Summary of Available Evidence: PCV15 in series with PPSV23

Certainty assessment							№ of patients		Results		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**comparison[b]**	**Relative effect**	**Absolute effect**	
Serious adverse events											
2	Randomized studies	Not serious	Not serious	Not serious	**Serious** [c]	Not serious	0/1186	0/493	non estimable	---	**2 moderate**

a. These are all immunogenicity studies and there are no correlates of protection
b. Patient no. based on minimum number of patients included in immunogenicity comparisons presented; some comparisons may have had more patients than this minimum
c. No vaccine-related serious adverse events reported

Please see GRADE summary tables for details

Benefits and Harms

How substantial are the undesirable anticipated effects?

- PCV15 use in series with PPSV23 in adults aged 19–64 years with CMC/IC?

□ 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 in series with PPSV23 for persons aged 19–64 years with CMC/IC

Summary of Evidence, PCV20

Study	Age or other characteristic of importance	N intervention	N comparison	Comparator vaccine
B7471007, Phase III RCT	Adults ≥ 18-49 years, **no IC** (mean 34.0, SD 8.8)	336	112	PCV13
	Adults ≥ 50-59 years, **no IC** (mean 54.9, SD 2.8)	334	111	PCV13
	Adults ≥ 60 years, **no IC** (mean 64.6, SD 4.8)	1507	1490	PCV13+PPSV23 (1-month interval)
Hurley 2020, Phase II RCT	Adults 60 - 64 years, **no IC** (mean 62.0,SD 1.4)	222	222	PCV13+PPSV23 (1-month interval)
Klein 2021, Phase III RCT	Adults 18-49 years, **no IC** (mean 35.3, SD 9.0)	1463	245	PCV13

Please see GRADE summary tables for details

Summary of Evidence from PCV20 studies: Benefits (VT-IPD, pneumonia, deaths)

- **PCV20 vs. PCV13 (comparison of 13 shared serotypes)**:
  - PCV20 recipients had **lower** responses by GMT and % seroresponders (12–13/13 serotypes)
    - Met noninferiority criteria for all shared serotypes by GMT ratio in both phase 3 trials.

	1	3	4	5	6 A	6B	7 F	9V	14	18 C	19 A	19 F	23 F	22 F	33 F	8	10 A	11 A	12 F	15 B	2	9N	17 F	20
PCV13																								
PCV20																								

*No overlap in 95% CI of % seroresponders
Please see GRADE summary tables for details

Summary of Evidence from PCV20 studies: Benefits (VT-IPD, pneumonia, deaths)

- **PCV20 vs. PCV13+PPSV23[†] (comparison of 13 shared serotypes)** :
  - In one phase 2 RCT, PCV20 recipients had lower responses by GMT in all serotypes
    - Significantly* lower in 9/13 serotypes

[†]The PCV13–PPSV23 interval used in this study (1 month) is different from the currently recommended interval

*no overlap in 95% CI
Please see GRADE summary tables for details

Summary of Evidence from PCV20 studies: Benefits (VT-IPD, pneumonia, deaths)

- **PCV20 vs. PPSV23 (comparison of 7 shared serotypes)** :
  - PCV20 recipients had **higher** responses by GMT and % seroresponders in all serotypes except serotype 8.
    - Met noninferiority criteria for 6/7 shared serotypes (not met for serotype 8) by GMT ratio in the phase 3 study

	1	3	4	5	6 A	6B	7 F	9V	14	18 C	19 A	19 F	23 F	22 F	33 F	8	10 A	11 A	12 F	15 B	2	9N	17 F	20
PCV20																								
PPSV23																								

*no overlap in 95% CI
Please see GRADE summary tables for details

Summary of Evidence from PCV20 studies: Benefits (VT-IPD, pneumonia, deaths)

- **PCV20 in age 18–49 years vs. 60–64 years**:
  - In one Phase 3 trial, larger immune response in 18–49 years by both GMT (all serotypes) and % seroresponders (18/20 serotypes).
    - Noninferiority criteria met for all 20 serotypes by GMT ratio.

Please see GRADE summary tables for details

Summary of Evidence from PCV20 studies: Benefits (VT-IPD, pneumonia, deaths)

Certainty assessment							№ of patients		Results		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	comparison[e]	Relative effect	Absolute effect	
Vaccine effectiveness (Vaccine-type invasive pneumococcal disease, Vaccine-type non-bacteremic pneumococcal pneumonia, Vaccine-type pneumococcal mortality)											
2 [1,2,3]	Randomized studies	Not serious	Not serious	Very serious [a,b,c,d]	Not serious	Not serious	3417	2802	PCV20 vs. PCV13: Across all studies non-inferiority met for all 13 shared serotypes PCV20 had slightly lower immune responses vs. PCV13 for all 13 shared serotypes. PCV20 vs. PPSV23 (non-PCV13 serotypes): Non-inferiority met for all serotypes in at least one study, but ST8 inferior in some studies. PCV20 had greater immune responses vs. PPSV23 for 6 of 7 non-PCV13 shared serotypes.		3 Low

a. These are all immunogenicity studies and there are no correlates of protection.
b. B7471007, Klein et al., and Hurley et al. enrolled healthy adults (some with chronic stable conditions, but focus is not those with immunocompromising or chronic medical conditions).
c. B7471007 provided primary PCV20 vs PCV13 immunogenicity outcomes for adults ≥60 and then showed non-inferiority for PCV20 in 18-49 year-olds compared to PCV20 in 60-64 year-olds. Did not directly compare immunogenicity of PCV20 vs PCV13 in 18-49 year-olds.
d. Hurley et al. only enrolled 60-64 year -olds.
e. Patient no. based on minimum number of patients included in immunogenicity comparisons presented; some comparisons may have had more patients than this minimum.
f. No vaccine-related serious adverse events reported; sample size relatively small

Benefits and Harms

How substantial are the desirable anticipated effects?

- PCV20 use for persons aged 19–49 years with CMC/IC
- PCV20 use for persons aged 19–64 years with CMC/IC

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

Benefits and Harms

How substantial are the desirable anticipated effects?

- PCV20 use for persons aged 19–49/19–64 years with CMC/IC

- PCV20 contains 7 additional serotypes vs. PCV13 (27% of remaining IPD)
- A simplified recommendation may improve vaccine coverage
- Concerns about the lower immunogenicity observed vs. PCV13
  - Met non-inferiority criteria in Phase 3 trials, clinical significance unknown
  - PCV13-type disease declined from pediatric indirect effects
- Concerns about fewer serotypes covered by PCV20 vs. PPSV23
  - Cost-effectiveness analyses showed improved health outcomes compared to the current recommendations

Summary of Available Evidence from PCV20 studies: Harms

Certainty assessment							№ of patients		Results		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	comparison[e]	Relative effect	Absolute effect	
Serious adverse events											
2 [1,2,3]	Randomized studies	Not serious	Not serious	Not serious	Serious[f]	None	0/4073	0/2421	non estimable	---	2 Moderate

a. These are all immunogenicity studies and there are no correlates of protection.
b. B7471007, Klein et al., and Hurley et al. enrolled healthy adults (some with chronic stable conditions, but focus is not those with immunocompromising or chronic medical conditions).
c. B7471007 provided primary PCV20 vs PCV13 immunogenicity outcomes for adults ≥60 and then showed non-inferiority for PCV20 in 18-49 year-olds compared to PCV20 in 60-64 year-olds. Did not directly compare immunogenicity of PCV20 vs PCV13 in 18-49 year-olds.
d. Hurley et al. only enrolled 60-64 year -olds.
e. Patient no. based on minimum number of patients included in immunogenicity comparisons presented; some comparisons may have had more patients than this minimum.
f. No vaccine-related serious adverse events reported; sample size relatively small

Please see GRADE summary tables for details

Benefits and Harms

How substantial are the undesirable anticipated effects?

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

- PCV20 use for persons aged 19–49 years with CMC/IC
- PCV20 use for persons aged 19–64 years with CMC/IC

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:**

- PCV20 use for persons aged 19–49 years with CMC/IC
- PCV20 use for persons aged 19–64 years with CMC/IC

Values and Preferences

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

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

Values: Published Literature

- Pubmed search on U.S. studies published in the past 5 years in adults who qualify for risk-based pneumococcal vaccine recommendations
- One online cross-sectional survey in March–April 2019
- Assessed vaccine-related beliefs, reasons for hesitancy, external influences on vaccination, and prior vaccination
- Residents in Tennessee aged 19–64 years with CMC/IC (n=1,002, 12% response rate)
  - Mostly female (75%), White (68%), non-Hispanic (95%), at least some college education (72%)
  - Most common qualifying conditions: current smoker (28%), asthma (26%), diabetes (19%)

Gatwood et al. AJHP 2021 (funded by Merck)

Values: Key Findings

- Pneumococcal vaccine offered in the past 5 years: **19%**
- Indicated that vaccines can prevent serious disease: **92%**
- Reluctant, hesitant, or resistant to a recommended vaccine: **32%**
  - Not knowing it was needed **(36%)**
  - Fear of needles **(29%)**
  - Concerns about safety **(24%)**
- The odds of vaccine hesitancy/resistance greater in:
  - Minorities (OR 1.6)
  - Those believing others like them do not get vaccinated (OR:1.8)
  - Those recalling negative media about vaccines (OR: 2.6)

Gatwood et al. AJHP 2021 (funded by Merck)

Values and Preferences

Criterion 1: Do adults feel that the desirable effects from vaccination are large relative to undesirable effects?

- PCV15 use in series with PPSV23 in persons aged 19–64 years with CMC/IC

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

Values and Preferences

Criterion 1: Do adults feel that the desirable effects from vaccination are large relative to undesirable effects?

- PCV13 and PPSV23 have been used in series and considered to be safe.
- Some believed that acceptance of pneumococcal vaccines is higher than other vaccines.
- Most adults with conditions that increase their risk of pneumococcal disease would value individual protection from vaccination.

Values and Preferences

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

- PCV15 used in series with PPSV23 in persons aged 19–64 years with CMC/IC

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

Values and Preferences

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

- PCV15 use in series with PPSV23 in persons aged 19–64 years with CMC/IC

- Some believed that increase in recommended vaccine doses in adults with CMC was an important source of uncertainty or variability.
- Most adults would probably perceive the desirable effects outweigh the undesirable effects.

Values and Preferences

Criterion 1: Do adults feel that the desirable effects from vaccination are large relative to undesirable effects?

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

- PCV20 use in persons aged 19–49 years with CMC/IC
- PCV20 use in persons aged 19–64 years with CMC/IC

Values and Preferences

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

- PCV20 use in persons aged 19–49 years with CMC/IC
- PCV20 use in persons aged 19–64 years with CMC/IC

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

Values and Preferences

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

- PCV20 use in persons aged 19–49 years with CMC/IC
- PCV20 use in persons aged 19–64 years with CMC/IC

- There may be some uncertainties in how changing from PPSV23→PCV20 (adults with CMC), or PCV13+PPSV23→PCV20 only (adults with IC) would be perceived.
- Most adults would probably perceive that desirable effects outweigh the undesirable effects

Acceptability

Is the option acceptable to key stakeholders?

Acceptability: Available Evidence Presented in June

- Healthcare Provider (HCP) Surveys
  - Vaccine Policy Collaborative Initiative (VPCI) Survey on **PCV13 shared clinical decision-making (SCDM)** recommendation (internet and mail)[1]
  - Pfizer's survey on HCP preferences web-based survey
    - Asked to rank **hypothetical vaccine recommendations** for adults aged ≥65 years and adults 19–64 years with underlying conditions
- Association of Immunization Managers (AIM) web-based survey
    - Primarily immunization program managers/directors
    - Option to provide narrative responses

Kobayashi June 2021 ACIP meeting presentation

1. Hurley et al. 2021

Acceptability: Review of Available Evidence

- Healthcare Provider (HCP) Survey
  - Merck's survey on HCP preferences
    - Online questionnaire sent by email
    - Physicians (family/general medicine, internal medicine, infectious diseases), physician assistants, pharmacists

Key Findings

- Preference for a **simplified** pneumococcal vaccine recommendation[1,2]
  - Same recommendation across age- and risk-groups[1]
- Mixed responses on use of **PCV in series with PPSV23**
  - A single vaccine was preferred over a sequential vaccine regimen, primarily for patient convenience[3]
  - Routine PCV-PPSV23 use was the most preferred among provided options in another survey[2]
  - Implementation/communication challenges, health equity issues (in hard-to-reach population) expressed in the AIM survey[1]

1. AIM survey 2021; 2. Pfizer HCP preference survey 2021; 3. Merck survey 2021

Key Findings

- When respondents were asked to score two hypothetical vaccine profiles with different attributes and levels, the following yielded the highest probability of preference[1]:
  - Immunogenicity
  - total additional coverage of serotypes associated with remaining pneumococcal disease

1. Merck survey 2021

Acceptability

Is recommending PCV15 in series with PPSV23 in persons aged 19–64 years with CMC/IC acceptable to key stakeholders?

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

Acceptability

Is recommending PCV15 in series with PPSV23 in persons aged 19–64 years with CMC/IC acceptable to key stakeholders?

- May add more burden to providers; larger population targeted for PCV-PPSV23 series
- Aligning CMC and IC recommendations will be a simplification
- Cost-effectiveness analyses showed that the new intervention will prevent more disease compared with the current recommendation.

Acceptability

Is recommending PCV20 for persons with CMC/IC acceptable to key stakeholders?

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

- For those aged 19–49 years?
- For those aged 19–64 years?

Acceptability

Is recommending PCV20 for persons with CMC/IC acceptable to key stakeholders?

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

- Simplification of the current risk-based recommendations.
- Cost-effectiveness analysis models showed that the new intervention will prevent more disease compared to the current recommendation.

Resource Use

Is the option a reasonable and efficient allocation of resources?

All strategies, PCV15+PPSV23

Summary of results

- Age-based analysis
  - Improved health indicated in all main results
  - Cost-savings[a] indicated by the CDC model (4 of 4 scenarios)
- Risk-based
  - Improved health and higher costs indicated in all main results
  - Risk-based only strategies yield a broad range of possible value
    - $250,000 to $656,000 per QALY gained
- Combined age- and risk-based assessments indicate values that were more favorable than risk-based alone, CDC model
    - $338,000 per QALY gained

[a] Cost-saving indicates an intervention strategy yielded higher health outcomes (more QALYs, fewer episodes of disease) and lower costs than the comparator.

Resource Use

Is recommending PCV15 in series with PPSV23 in adults aged 19–64 years with CMC/IC a reasonable and efficient allocation of resources?

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

- Initially split between “probably no” and “probably yes”.
- Determined that the additional health benefits from the new intervention was potentially sufficient to outweigh the additional cost associated with the intervention.

Risk-based and combined strategies, PCV20

Summary of results

- Improved health indicated in all risk-based strategies and models
- PCV20 19-64
  - Risk-based assessments indicate a broad range of possible value
    - $11,000 to $292,000 per QALY gained
  - Combined age- and risk-based assessments indicate cost-savings[a] in 2 of 2 models
- PCV20 19-49
  - Risk-based assessments indicate a broad range of possible value
    - Cost-saving[a,b] to $483,000 per QALY gained
  - Combined age- and risk-based assessments indicate more favorable value
    - CDC model indicates cost-savings
    - Pfizer model indicates costs of $11,000 per QALY gained

[a.] Cost-saving indicates an intervention strategy yielded higher health outcomes (more QALYs, fewer episodes of disease) and lower costs than the comparator.

[b.] In the Pfizer model with no potential pediatric indirect effects, estimate for 19-49 risk-based use was cost-saving.

Resource Use

- **Is recommending PCV20 for persons aged 19–49 years/19–64 years with CMC/IC a reasonable and efficient allocation of resources?**

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

- Additional health benefits from the new intervention was sufficient to outweigh the additional cost associated with the intervention.
- Cost-saving in some combined age- and risk-based assessments.

Equity

What would be the impact on health equity?

Pneumococcal Vaccine Coverage in adults aged 19–64 years with indications has been low.

	Sample size	%	(95% CI)
Overall	5,851	23.3%	(22.0, 24.6)
White	4,048	23.6%	(22.1, 25.2)
Black	696	25.7%	(21.8, 30.0)
Hispanic	656	18.5%	(15.2, 22.4)*
Asian	192	25.0%	(17.3, 34.5)
Other	259	25.8%	(19.3, 33.5)

National Health Interview Survey, 2018

*p<0.05 for comparisons with white as the reference.

Compared to Whites, Hispanics had significantly lower proportion of those who ever received pneumococcal vaccines.

	Sample size	%	(95% CI)
Overall	5,851	23.3%	(22.0, 24.6)
White	4,048	23.6%	(22.1, 25.2)
Black	696	25.7%	(21.8, 30.0)
Hispanic	656	18.5%	(15.2, 22.4)*
Asian	192	25.0%	(17.3, 34.5)
Other	259	25.8%	(19.3, 33.5)

National Health Interview Survey, 2018

*p<0.05 for comparisons with white as the reference.

Influence of social determinants of health on vaccine uptake and time to pneumococcal vaccination

- Nationwide convenience samples of commercial insurance claims data (MarketScan), 2013–2016
- Adults aged 18–64 years with no prior pneumococcal vaccination before CMC/IC diagnosis (n=173,712)
  - **25%** vaccinated within 1 year of CMC/IC diagnosis
  - Odds of vaccination lower among:
    - Areas of higher poverty (OR: 0.14)
    - Areas with limited internet access (OR: 0.14)
    - Adults not receiving a seasonal influenza vaccine (OR: 0.05)
  - Time to vaccination lower in rural communities and communities with less internet access

Gatwood et al. Vaccine 2021

Equity

What would be the impact of recommending PCV15 in series with PPSV23 in persons aged 19–64 years with CMC/IC on health equity?

- ☐ Reduced
- ☐ Probably reduced
- ☐ Probably no impact
- ☐ Probably increased
- ☐ Increased

Equity

What would be the impact of recommending PCV15 in series with PPSV23 in persons aged 19–64 years with CMC/IC on health equity?

- Alignment of CMC and IC recommendations may increase vaccine coverage
- Will prevent more disease and reduce disparity in vaccine-type disease
- A routine PCV-PPSV23 series recommendation is more likely to disadvantage populations with limited vaccine access

Equity

What would be the impact of recommending PCV20 in persons aged 19–49/19–64 years with CMC/IC be on health equity?

- □ Reduced
- □ Probably reduced
- □ Probably no impact
- □ Probably increased
- □ Increased

- A single risk-based vaccine recommendation may increase vaccine uptake, and reduce disparity in vaccine-type disease
- Some believed that introduction of any new effective adult vaccine may decrease equity at least in the short-term

Feasibility

Are the options feasible to implement?

Feasibility

Is recommending PCV15 in series with PPSV23 for persons aged 19–64 years with CMC/IC PPSV23 feasible to implement?

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

Feasibility

Is recommending PCV15 in series with PPSV23 for persons aged 19–64 years with CMC/IC PPSV23 feasible to implement?

- PCV13–PPSV23 series currently recommended for IC
- Extending PCV-PPSV23 series recommendation to CMC will result in a larger number of people targeted for the vaccine series.
    - May increase logistical and financial burden

Feasibility

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

- **Is recommending PCV20 for persons aged 19–49 years feasible to implement?**
- **Is recommending PCV20 for persons aged 19–64 years feasible to implement?**

Summary of Work Group Interpretation on EtR Domains

EtR Domains	PCV15+PPSV23, 19–64 yo	PCV20, 19–49 yo	PCV20, 19–64 yo
Benefits and Harms			
a. Benefits	Moderate	Large	Large
b. Harms		Minimal	
c. Benefit>Harm?		Favors intervention	
d. Overall certainty: effectiveness	Moderate	Low	Low
e. Overall certainty: safety		Moderate	
Values			
a. Desirable>Undesirable?		Probably Yes	
b. Uncertainty?	Probably important uncertainty/variability	Probably not important uncertainty/variability	Probably not important uncertainty/variability
Acceptability	Varies	Probably yes	
Resource use	Probably Yes	Yes	Yes
Equity	Probably no impact	Probably increased	Probably increased
Feasibility	Probably yes	Yes	Yes

Summary: Work Group Interpretations

Should PCV15 be recommended in series with PPSV23 for persons aged 19–64 years with CMC/IC?

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

- Desirable:
  - Alignment between current recommendations for CMC and IC
  - Potential for additional disease prevention, especially in CMC
- May not be desirable:
  - Acceptability, Feasibility, Resource use
- Unknown: impact against serotype 3 disease

Summary: Work Group Interpretations

Should PCV20 be recommended for persons aged 19–49 years with CMC/IC?

Should PCV20 be recommended for persons aged 19–64 years with CMC/IC?

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

Next Steps

Current PICO questions for PCV15

Age-based:

- Should **PCV15** be routinely recommended to US adults **≥65 years in series with PPSV23?**

Risk-based:

- Should **PCV15 in series with PPSV23** be recommended for U.S. adults aged **19–64 years** with chronic medical conditions* or immunocompromising conditions**?

*Alcoholism, chronic heart/liver/lung disease, diabetes, cigarette smoking

**Chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosuppression, generalized malignancy, human immunodeficiency virus infection, Hodgkin disease, leukemia, lymphoma, multiple myeloma, solid organ transplants, congenital or acquired asplenia, sickle cell disease, or other hemoglobinopathies, CSF leak, or cochlear implant

Current PICO questions for PCV20

If age-based recommendation at age ≥50 years:

- Should **PCV20** be routinely recommended to US adults aged **≥50 years?**

- Should **PCV20** be recommended for U.S. adults aged **19–49 years** with chronic medical conditions* or immunocompromising conditions**?

If age-based recommendation at age ≥65 years:

- Should **PCV20** be routinely recommended to US adults aged **≥65 years?**

- Should **PCV20** be recommended for U.S. adults aged **19–64 years** with chronic medical conditions* or immunocompromising conditions**?

*Alcoholism, chronic heart/liver/lung disease, diabetes, cigarette smoking

**Chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosuppression, generalized malignancy, human immunodeficiency virus infection, Hodgkin disease, leukemia, lymphoma, multiple myeloma, solid organ transplants, congenital or acquired asplenia, sickle cell disease, or other hemoglobinopathies, CSF leak, or cochlear implant

Current PICO questions

- At this time, revaccination strategies **are not** being considered
- Example:
  - If PCV15+PPSV23 or PCV20 is recommended for an adult aged 49 years with indication (**risk-based** strategy), no additional doses are being considered at age 50 (or 65) years (**age-based** strategy)

Questions for the Committee

- Does the Committee agree with the policy options being proposed for the October meeting?
- Are there additional data the Committee would like to see before deciding on policy options?

Current PICO questions

PCV15 Age-based:

- Should **PCV15** be routinely recommended to US adults **≥65 years in series with PPSV23?**

PCV15 Risk-based:

- Should **PCV15 in series with PPSV23** be recommended for U.S. adults aged **19–64 years** with chronic medical conditions* or immunocompromising conditions**?

If age-based PCV20 recommendation at age ≥50 years:

- Should **PCV20** be routinely recommended to US adults aged **≥50 years?**
- Should **PCV20** be recommended for U.S. adults aged **19–49 years** with chronic medical conditions* or immunocompromising conditions**?

If age-based PCV20 recommendation at age ≥65 years:

- Should **PCV20** be routinely recommended to US adults aged **≥65 years?**
- Should **PCV20** be recommended for U.S. adults aged **19–64 years** with chronic medical conditions* or immunocompromising conditions**?

*Alcoholism, chronic heart/liver/lung disease, diabetes, cigarette smoking

**Chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosuppression, generalized malignancy, human immunodeficiency virus infection, Hodgkin disease, leukemia, lymphoma, multiple myeloma, solid organ transplants, congenital or acquired asplenia, sickle cell disease, or other hemoglobinopathies, CSF leak, or cochlear implant

Next Steps

- Review available data to evaluate the interval for PCV15 use in series with PPSV23
- Review available data to draft guidance on use of PCV15/PCV20 for adults who already received PCV13 or PPSV23

Acknowledgements

- ACIP and the Pneumococcal Work Group
- CDC contributors and consultants: Tamara Pilishvili, Ryan Gierke, Jennifer Loo Farrar, Lana Childs, Amadea Britton, Chukwuebuka Nsofor, Brittany White, Fahmina Akhter, Mahamoudou Ouattara, Penina Haber, Pedro Moro, Sarah Schillie, Tammy Zulz, Marc Fischer, Andrew Leidner, Tandin Dorji, Wei Xing, Nong Shang, Rebecca Morgan, Doug Outcalt-Campos

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.