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

Pneumococcal Vaccines

February 2024, ACIP Meeting

February 29, 2024

Pneumococcal Vaccine Work Group Chair

James Loehr, MD, FAAFP

Pneumococcal Vaccines Work Group

ACIP Members

- Jamie Loehr (Chair, acting)
- Sarah Long

Ex Officio Members

- Jeffrey Kelman (CMS)
- Lucia Lee (FDA)
- Tina Mongeau (FDA)
- Uzo Chukwuma (IHS)
- Mamodikoe Makhene (NIH, primary)
- Meenu Upadhyay (NIH, alternate)

Liaison Representatives

- Lynn Fisher (AAFP)
- James Campbell (AAP/COID)
- Jason Goldman (ACP)
- David Nace (AGS/AMDA)
- Cora Hoover (AIM, primary)
- Risa Claytor (HRSA)
- James McAuley (IDSA)
- Eva Wong (NACI)
- Robert Hopkins (NFID, primary)
- William Schaffner (NFID, alternate)
- Virginia Caine (NMA)

Consultants

- Monica Farley (VAMC/Emory)
- Keith Klugman (BMGF)
- Kathy Poehling (Wake Forest)
- Arthur Reingold (UC Berkley)
- Lorry Rubin (CCMC)
- Richard Zimmerman (U. of Pittsburgh)

CDC Contributors and Consultants

Division of Bacterial Diseases
- Diepreye Ayabina
- Adam Cohen
- Ryan Gierke
- Jennifer Farrar
- Noele Nelson

Immunization Safety Office
- Pedro Moro

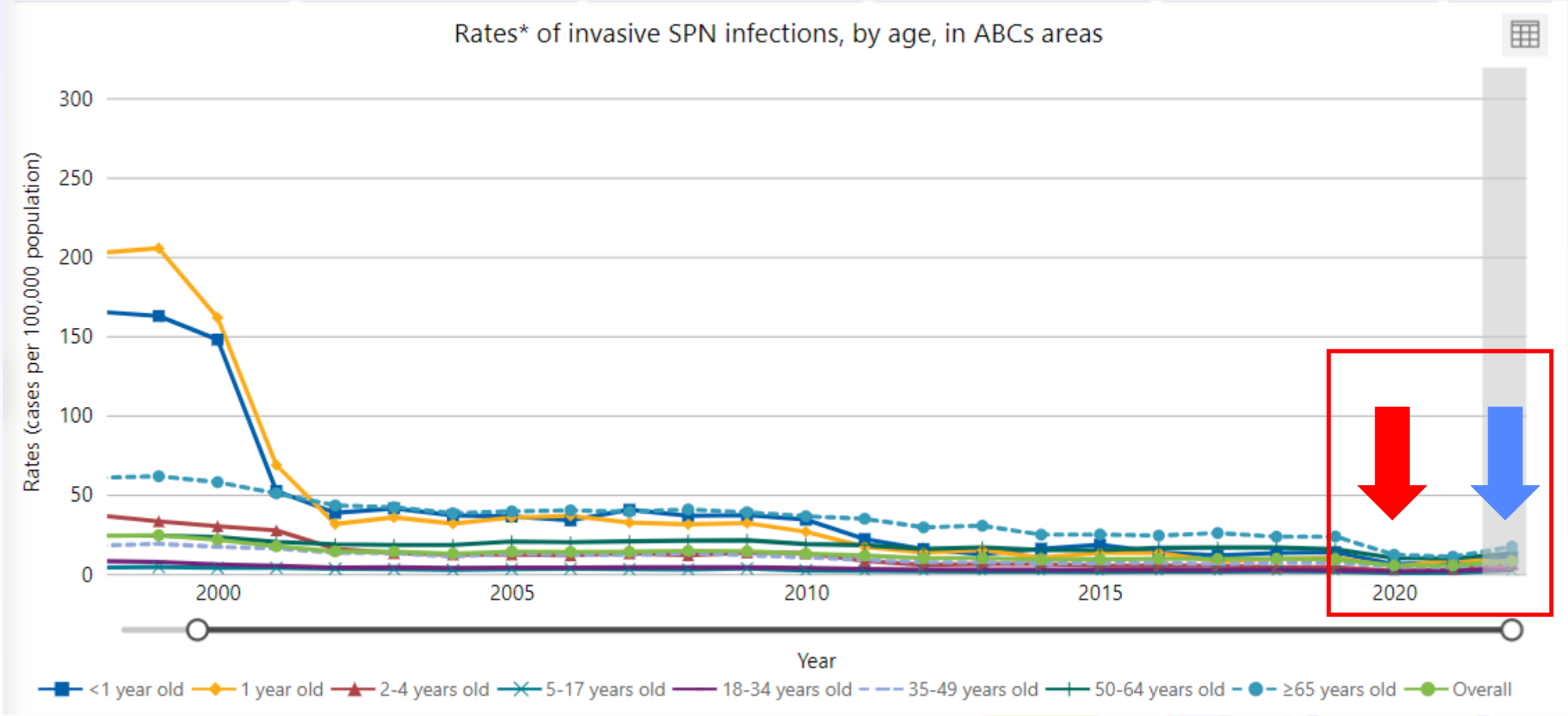
Immunization Services Division
- Janelle King
- Andrew Leidner
- Liz Velazquez

Arctic Investigations Program
- Marc Fischer

CDC Lead
- Miwako Kobayashi

GRADE/EtR consultants
- Doug Campos-Outcalt
- Rebecca Morgan

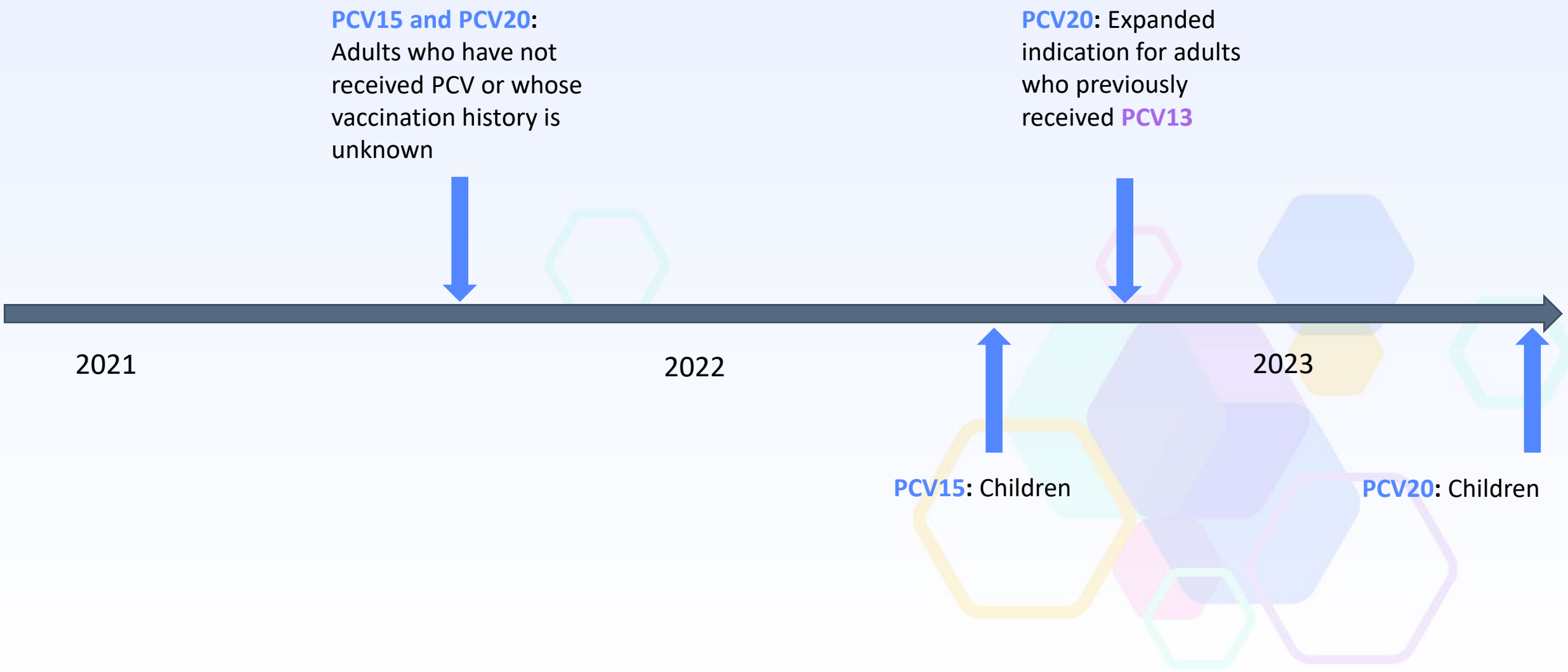
Invasive pneumococcal disease incidence reached a historically low level early in the COVID-19 pandemic but is returning toward pre-COVID levels



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

[ABCs Bact Facts Interactive Data Dashboard | CDC]

Around the same time, pneumococcal conjugate vaccines PCV15 and PCV20 were recommended for both adults and children



Additional Pneumococcal Vaccines in Advanced Stages of Development

	1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F	22F	33F	8	10A	11A	12F	15B	2	9N	17F	20	15A	15C	16F	23A	23B	24F	31	35B
PCV15																																
PCV20																																
PPSV23																																
Pn-MAPS24v																								20B								
VAX-24																								20B								
V116																								20A								

24-valent pneumococcal vaccines:

- **Pn-MAPS24v (GSK):** Completed phase 1/2 study for adults; Breakthrough Therapy Designation granted and Phase 3 study in preparation; undergoing phase 2 studies in infants[1]
- **VAX-24 (Vaxcyte):** Completed phase 1/2 studies for adults, undergoing phase 2 studies in infants[2]

21-valent pneumococcal conjugate vaccine (V116, Merck):

- **BLA accepted by the FDA for priority review[3]**

1. Chichili et al. Vaccine 2022; GSK Pipeline assets and clinical trials appendix Q4 2023 2. Wassil et al. Lancet ID 2023, ClinicalTrials.gov ID: NCT05297578, and NCT05844423; 3. FDA Grants Priority Review to Merck's New Biologics License Application for V116, an Investigational, 21-valent Pneumococcal Conjugate Vaccine Specifically Designed to Protect Adults - Merck.com.

Additional Pneumococcal Vaccines Under Development

- **25-valent** pneumococcal vaccine candidate (IVT PCV-25, Iventprise)
  - Completed Phase 2 dose ranging study in young adults[1]
- **31-valent** pneumococcal conjugate vaccine candidate (VAX-31, Vaxcyte)
  - Completed enrollment of Phase 1/2 study in adults aged ≥50 years[2]

1. Inventprise Completes Vaccination of Participants in a Phase 2 Dose Ranging Study of its 25 Valent Pneumococcal Vaccine Candidate – Inventprise
2. Vaxcyte Completes Enrollment of Phase 1/2 Study Evaluating VAX-31 for the Prevention of Invasive Pneumococcal Disease (IPD) in Adults Aged 50 and Older - Vaxcyte, Inc.

Current Pneumococcal Vaccine Recommendations for Adults and Vaccine Coverage

- The following groups are currently recommended to receive a dose of pneumococcal conjugate vaccine (PCV):
  - Adults aged ≥65 years who have not received a PCV[1]
  - Adults aged 19–64 years with certain underlying conditions or risk factors[2] who have not received a PCV[1]
  - Certain adults who have received PCV13 but have not received PCV20[3]

1. Excludes PCV7
2. alcoholism; chronic heart, liver, or lung disease; chronic renal failure; cigarette smoking; cochlear implant; congenital or acquired asplenia; CSF leak; diabetes mellitus; generalized malignancy; HIV infection; Hodgkin disease; immunodeficiency; iatrogenic immunosuppression; leukemia, lymphoma, or multiple myeloma; nephrotic syndrome; solid organ transplant; or sickle cell disease or other hemoglobinopathies
3. Adults who have not completed the recommended vaccine series, or shared clinical decision-making for adults aged ≥65 years who have completed the recommended vaccine series

Pneumococcal Vaccine for Adults Aged ≥19 Years: Recommendations of the Advisory Committee on Immunization Practices, United States, 2023 | MMWR (cdc.gov)

Adults with risk-based vaccine recommendations have lower vaccine coverage compared with those with age-based recommendations

- Coverage of ≥1 dose of any pneumococcal vaccine
  - Adults aged 19–64 years with risk-based indication: **22.2%**
  - Adults aged ≥65 years: **65.8%**

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

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*?

   *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

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?

   - Questions 2 and 3 would result in a new age-based recommendation for these groups.

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?

Today's Session

Introduction	Dr. Jamie Loehr (ACIP, WG Chair)
Current epidemiology of invasive pneumococcal disease among adults in the United States	Mr. Ryan Gierke (CDC, NCIRD)
Interim results from the Pneumococcal pNeumonia Epidemiology, Urine serotyping, and Mental Outcomes (PNEUMO) US study	Dr. Wesley Self (Vanderbilt University Medical Center)
Phase 3 clinical trial data of PCV21	Dr. Heather Platt
Post-licensure PCV20 safety data	Dr. Pedro Moro (CDC/NCEZID) Dr. Richard Forshee (FDA)
Preliminary WG interpretations of EtR and Next Steps	Dr. Miwako Kobayashi (CDC, NCIRD)

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

Current Epidemiology of Pneumococcal Disease among Adults, United States

February 2024, ACIP Meeting

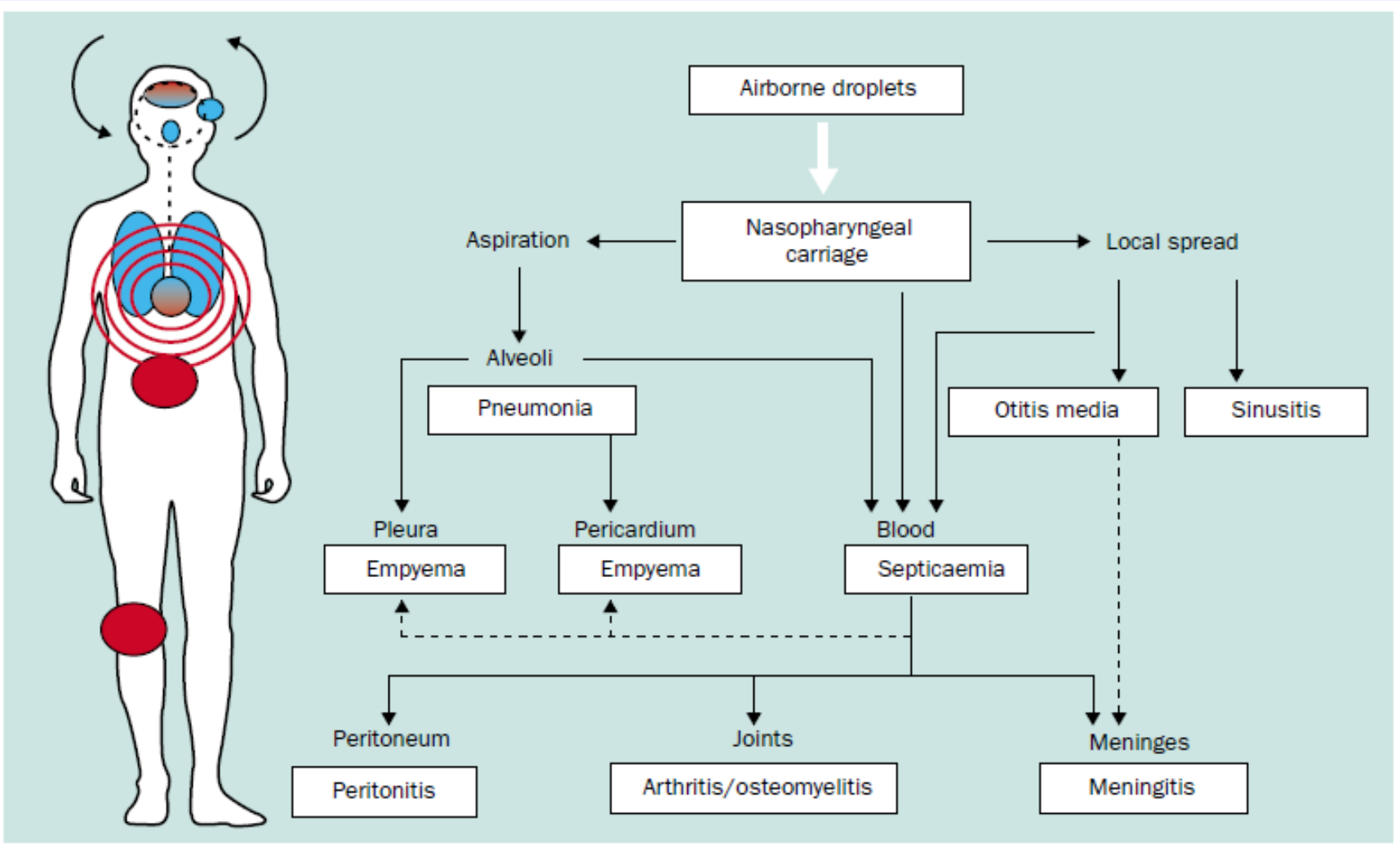
February 29, 2024

Ryan Gierke, MPH

Outline

- Background on pneumococcal disease
- Pneumococcal vaccine coverage in adults
- Pneumonia incidence estimates in adults
- Invasive pneumococcal disease (IPD)
  - Impact of COVID-19
  - Incidence by vaccine type
  - Serotype distribution

Pneumococcal carriage is precursor to pneumococcal disease



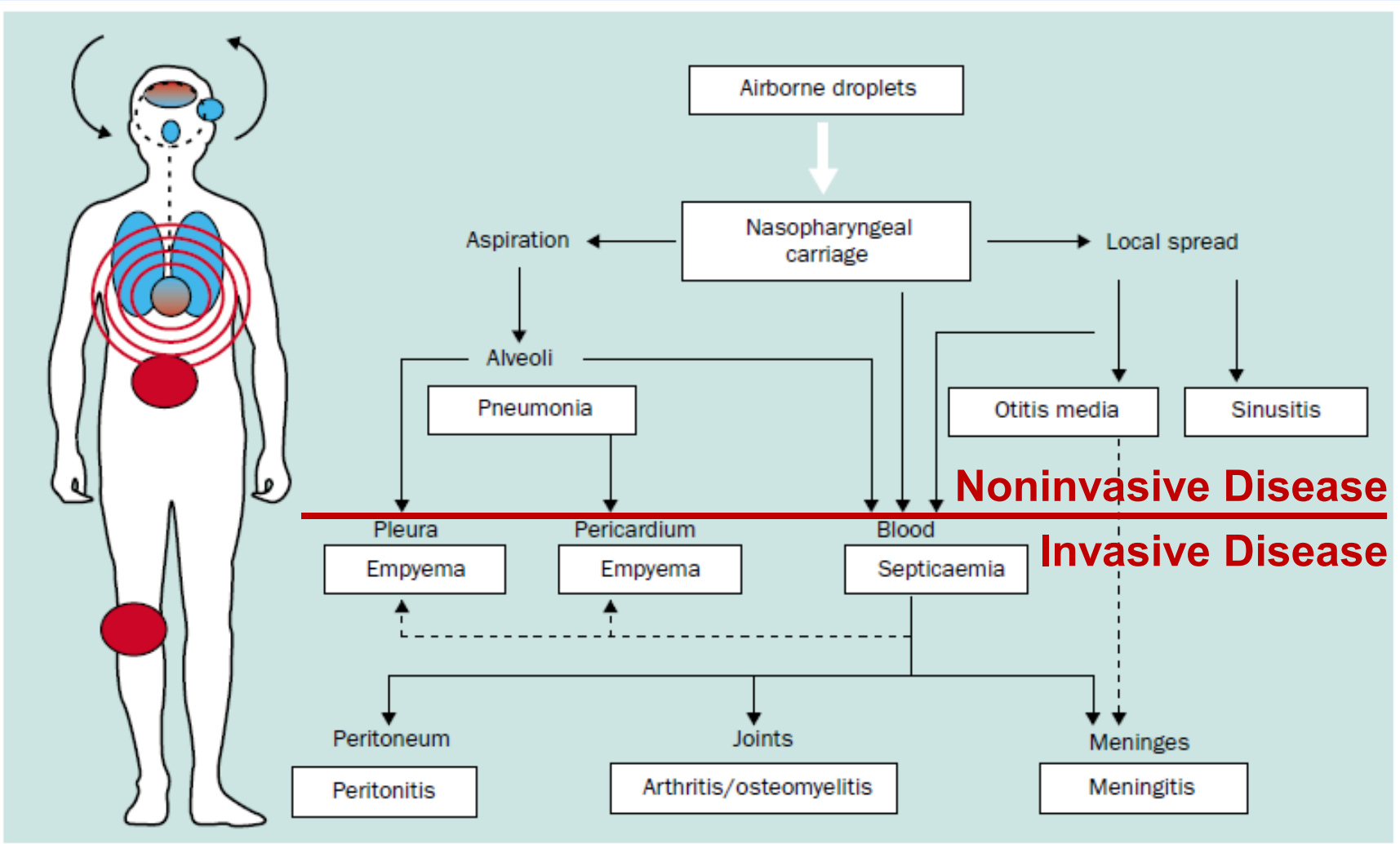
More frequent

Less frequent

Figure 1. Pathogenic route for S pneumoniae infection. Redrawn from reference 2. Organs infected through the airborne and haematogenic routes are depicted in blue and red, respectively.

Bogaert, Lancet Infect Dis 2004;4:144-54

Pneumococcal carriage is precursor to pneumococcal disease



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Less frequent

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PCV15 and PCV20 coverage among Medicare Part A/B beneficiaries aged ≥65 years[1], Oct 1, 2021 – Dec 31, 2023

- PCV20 coverage: **12%**
  - Ranged from **9%** (adults aged ≥85 years) to **25%** (adults aged 65 years)
- PCV15 coverage: **0.2%**
  - Less than **1%** across all ages

1. Based on age at the end of 2022

Unpublished data courtesy of CDC ISD. Based on CMS data from January 17, 2024.

Estimated proportion of adults who ever received any pneumococcal vaccination, National Health Interview Survey, 2021

Age group	%	(95% CI)
Overall (≥65 years)	65.8	(64.4-67.2)
Overall (19–64years *with risk-based indication*)	22.2	(21.0-23.5)
White	23.3	(21.7-24.9)
Black	22.6	(19.2-26.4)
Hispanic	19.0	(15.9-22.6)*
Asian	16.9	(12.0-23.2)*
Other	22.7	(16.3-30.7)

*p<0.05 for comparisons with white as the reference

https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/pubs-resources/vaccination-coverage-adults-2021.html#summary

Estimated incidence of pneumococcal disease in adults aged ≥65 years

Disease	Estimated incidence (per 100,000 population)
All-cause hospitalized pneumonia[1]	847–3,365
Hospitalized noninvasive pneumococcal pneumonia[2]	105
Invasive pneumococcal disease (IPD)[3]	24

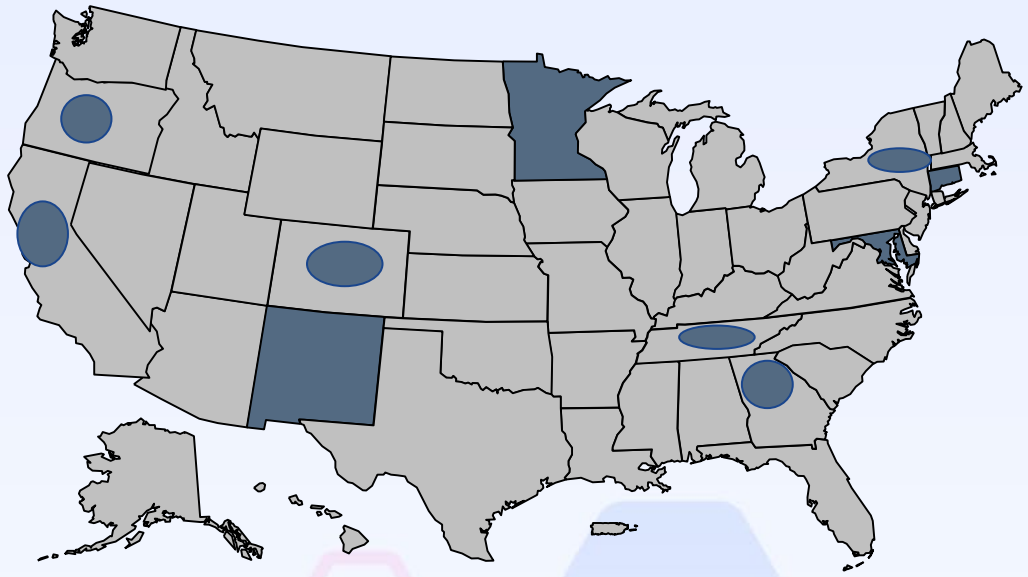
Case fatality ratio from IPD: 14%[3]

1. McLaughlin et al. Vaccine 2020 (limited to studies that collected data during or after 2010)
2. Gierke et al. IDweek 2020. CDC's **S**urveillance for **N**on**I**nvasive **P**neumococcal **P**neumonia (SNiPP), 2017
3. CDC ABCs, 2018–2019

IPD Incidence and Serotype Distribution Among Adults in the United States

Methods

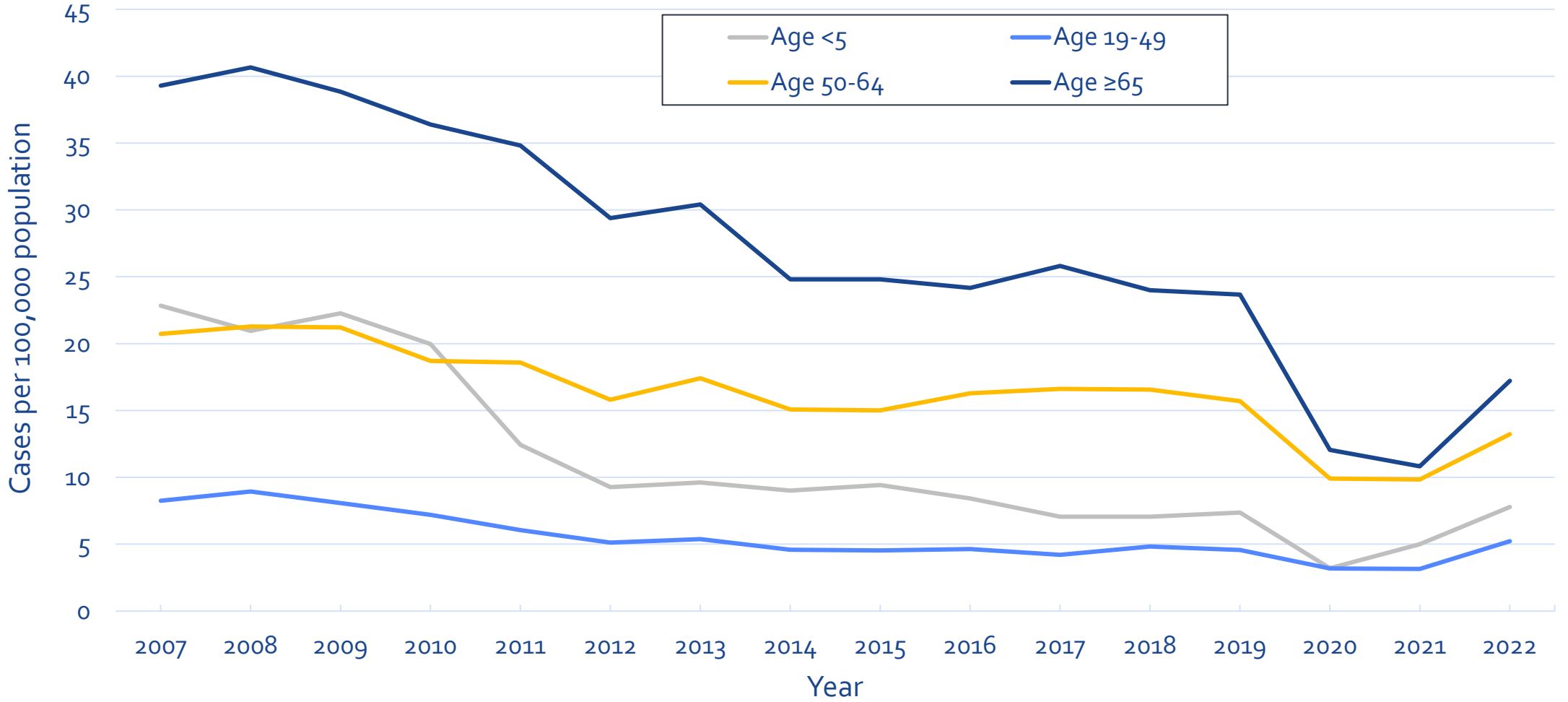
- **Active Bacterial Core surveillance (ABCs):**
  - Active laboratory and population-based surveillance, 10 sites
  - Pneumococcus isolation from sterile site



- **Isolates serotyped by whole-genome sequencing, Quellung, or PCR at reference labs and grouped for analysis by vaccine type**
- **US Census Bureau race-bridged post-census population estimates used as denominators**
- **Overall and serotype-specific IPD incidence rates (cases per 100,000 population)**

https://www.cdc.gov/abcs/methodology/surv-pop.html

IPD incidence rates, by age group, 2007 – 2022



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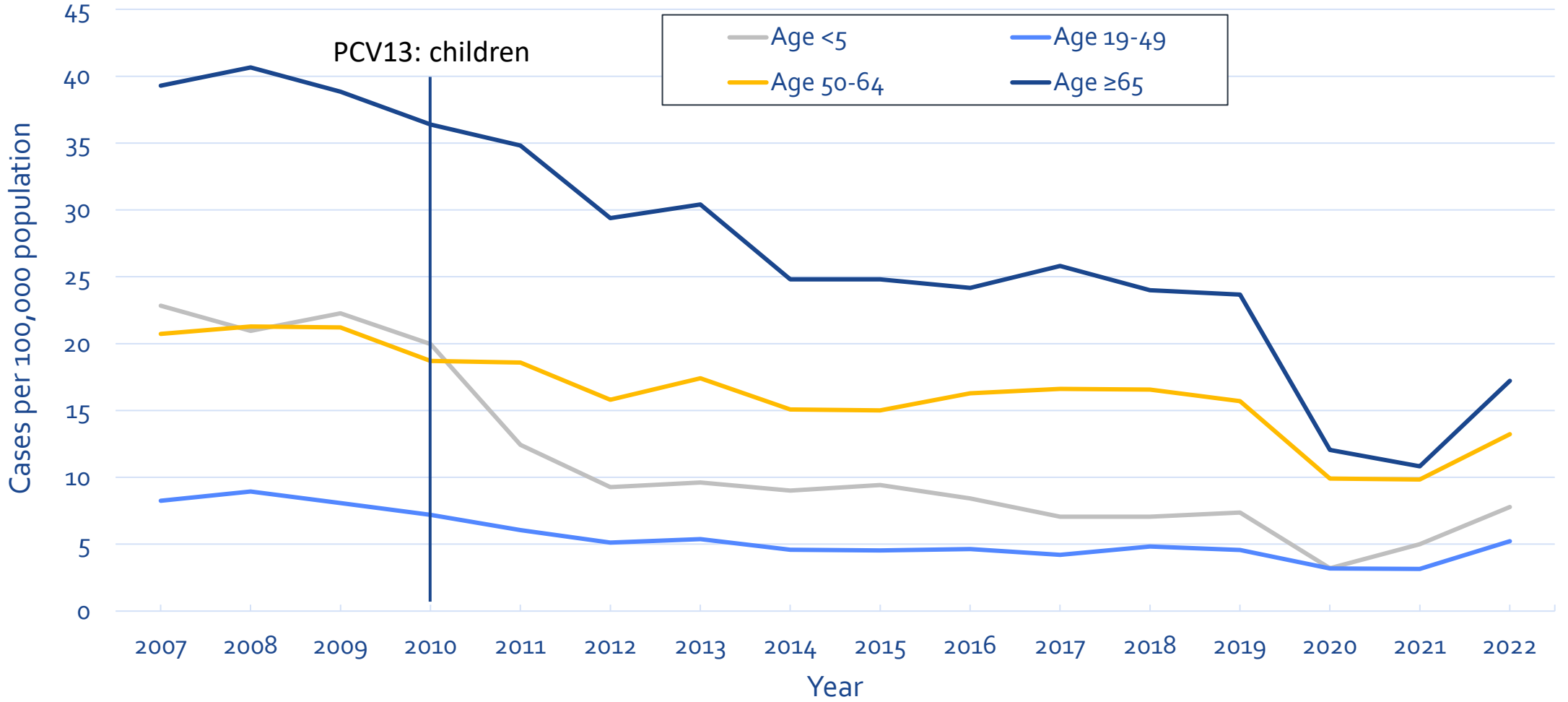

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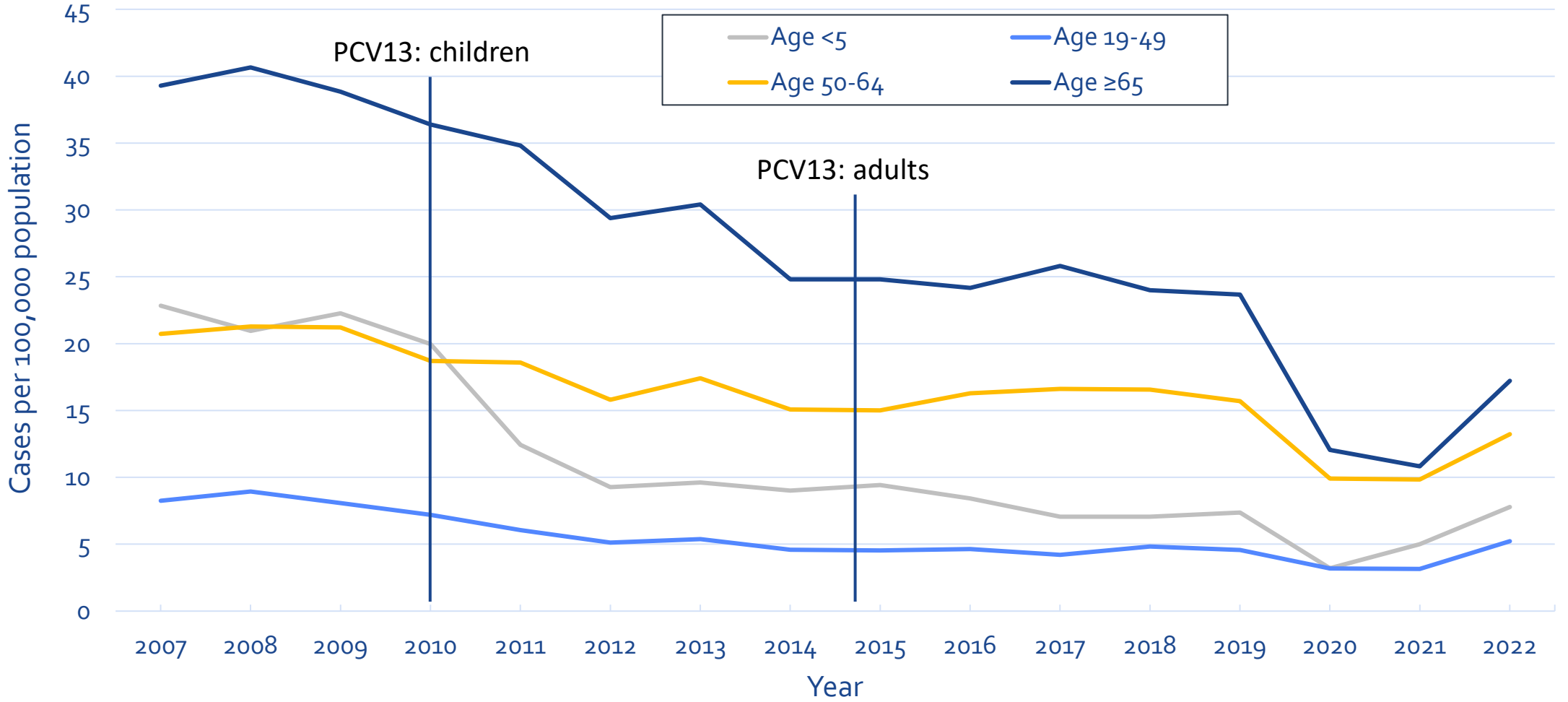

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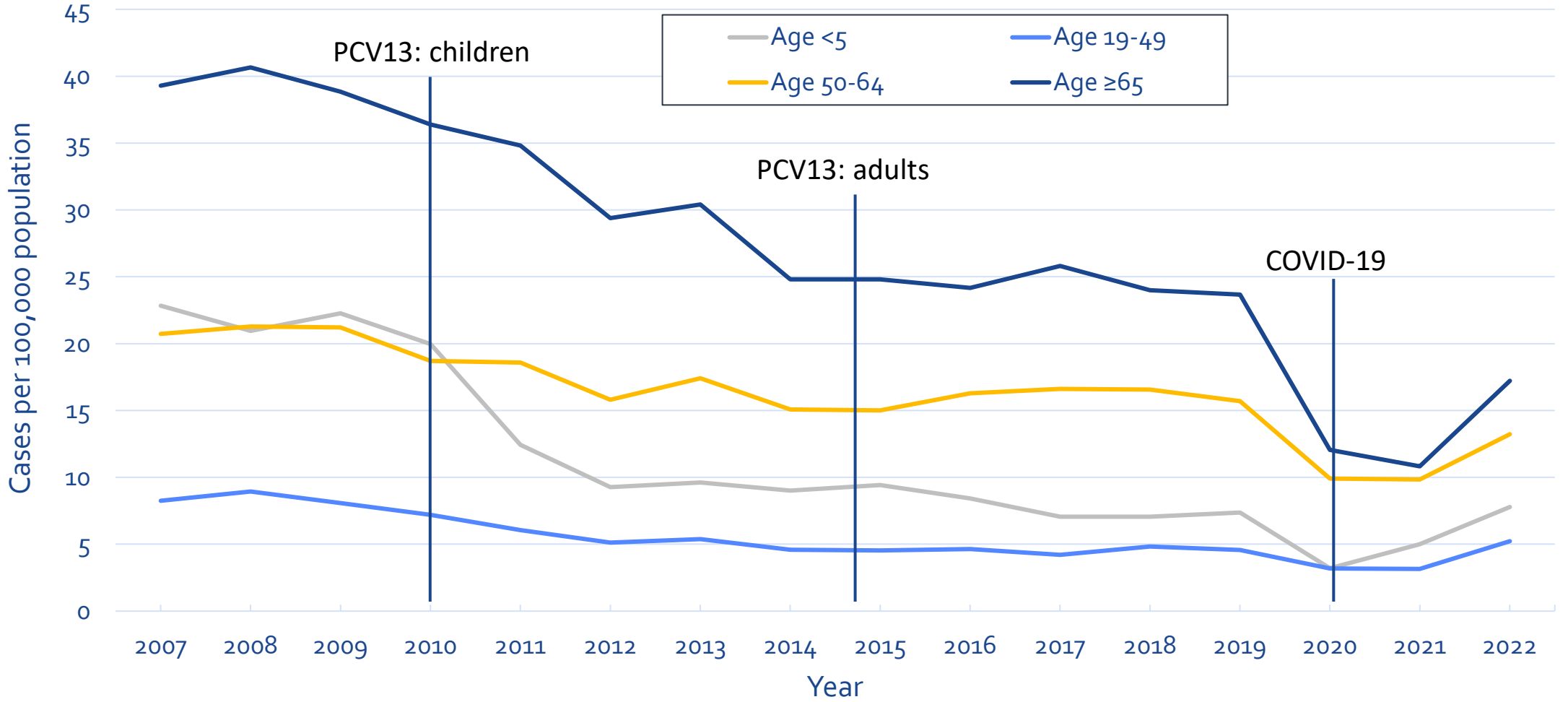

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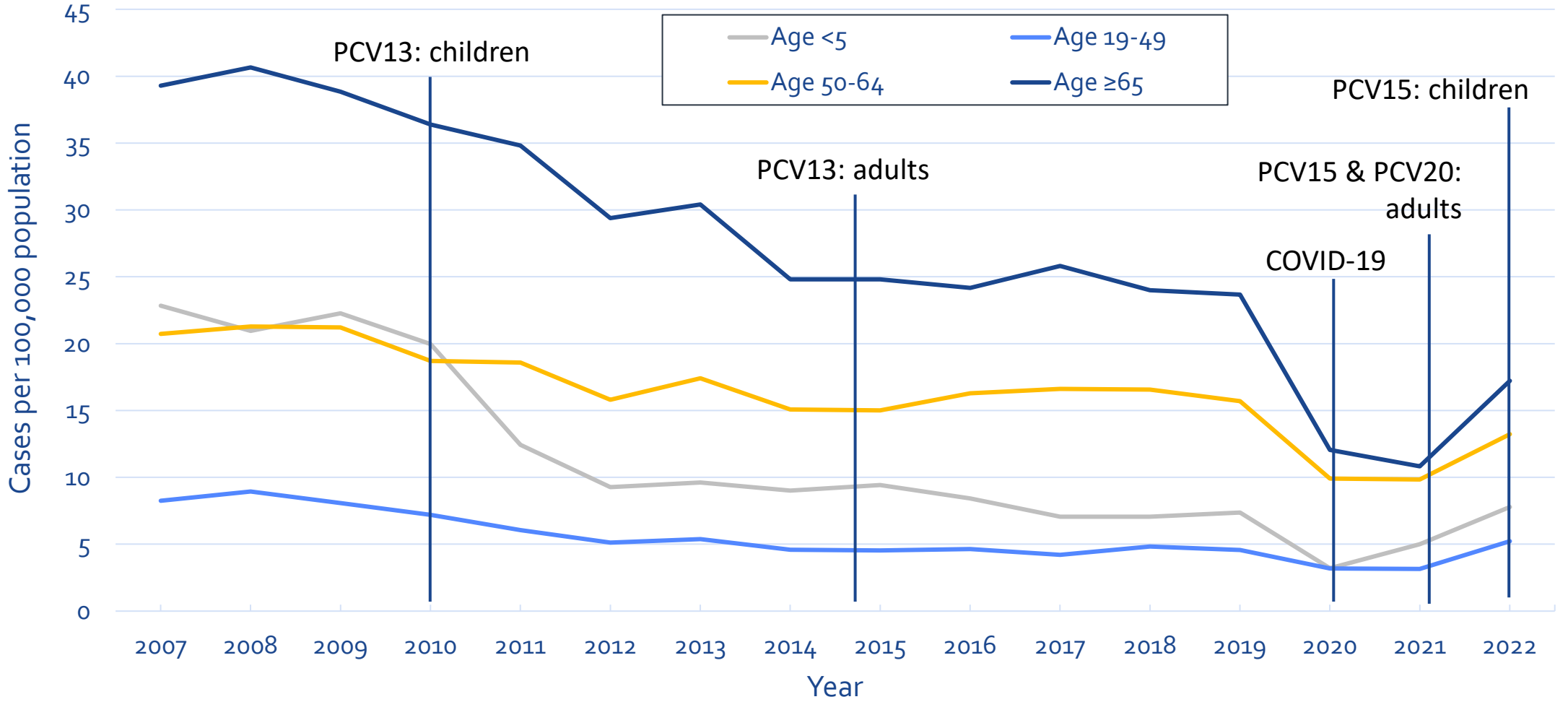

Proportion of adult IPD cases, with a risk-based indication, 2018 – 2021

- Among adult IPD cases, **82% – 87%** had at least one risk-based indication for pneumococcal vaccination
  - Age 19-49 years: **82%**
  - Age 50-64 years: **87%**
  - Age ≥65 years: **87%**

Serotypes contained in current and new pneumococcal vaccines

	1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F	22F	33F	8	10A	11A	12F	15B	2	9N	17F	20	15A	15C	16F	23A	23B	24F	31	35B
PCV15	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■																	
PCV20	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■												
PPSV23	■	■	■	■		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■								
PCV21		■			■		■				■			■	■	■	■	■	■			■	■	■	■	■	■	■	■	■	■	■

Serotypes contained in PCV20 and PCV21

	1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F	22F	33F	8	10A	11A	12F	15B	2	9N	17F	20	15A	15C	16F	23A	23B	24F	31	35B
PCV20																																
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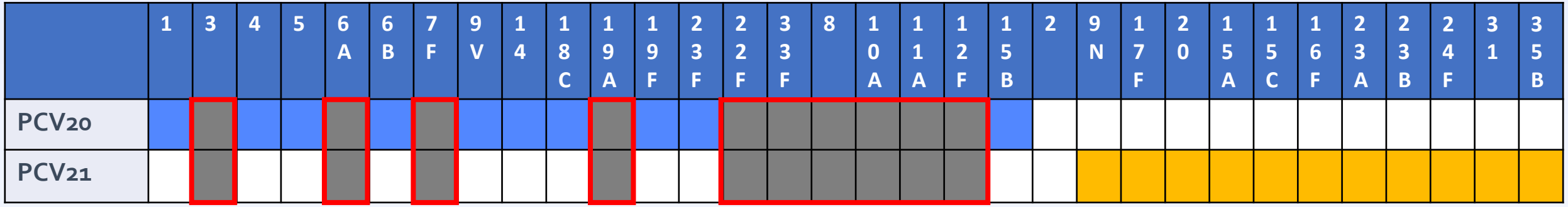
PCV20	■		■	■		■		■	■	■		■	■							■												
PCV21																						■	■	■	■	■	■	■	■	■	■	■

For analysis purposes:

- **PCV20 non-PCV21**: includes serotypes **1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F, 15B**

Serotypes contained in PCV20 and PCV21



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- **PCV20 non-PCV21**: includes serotypes **1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F, 15B**
- **PCV20 and PCV21**: includes serotypes **3, 6A, 7F, 19A, 22F, 33F, 8, 10A, 11A, 12F, +6C**

Serotypes contained in PCV20 and PCV21

	1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F	22F	33F	8	10A	11A	12F	15B	2	9N	17F	20	15A	15C	16F	23A	23B	24F	31	35B
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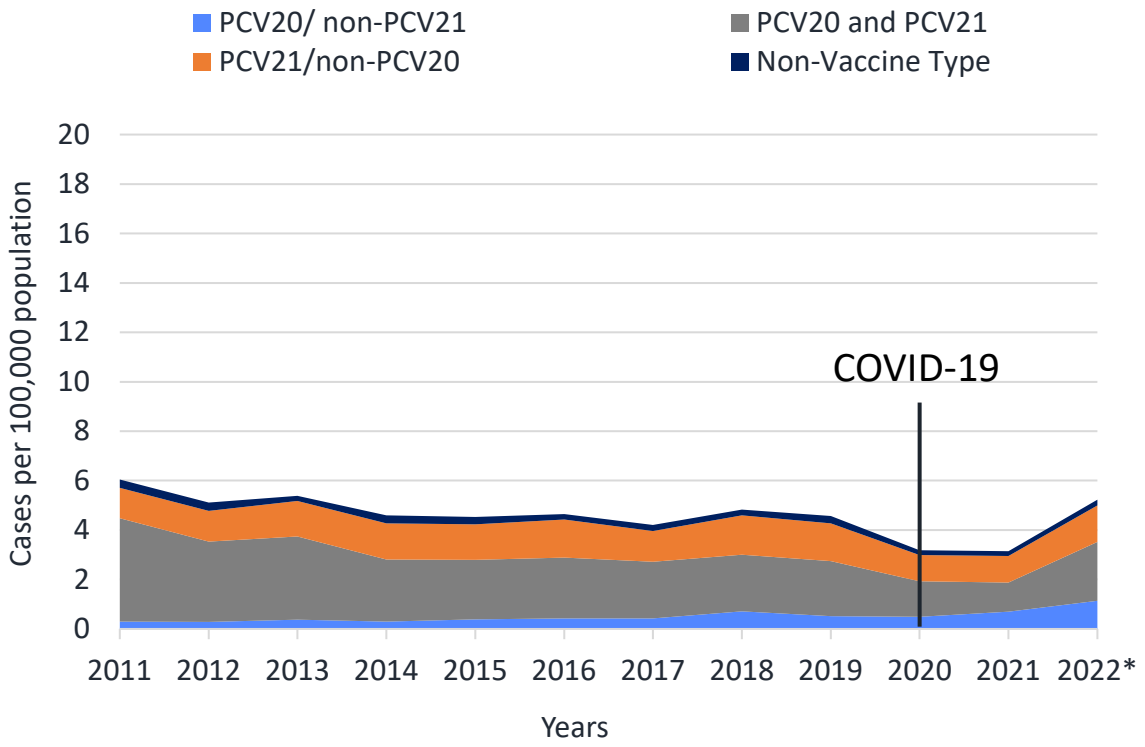
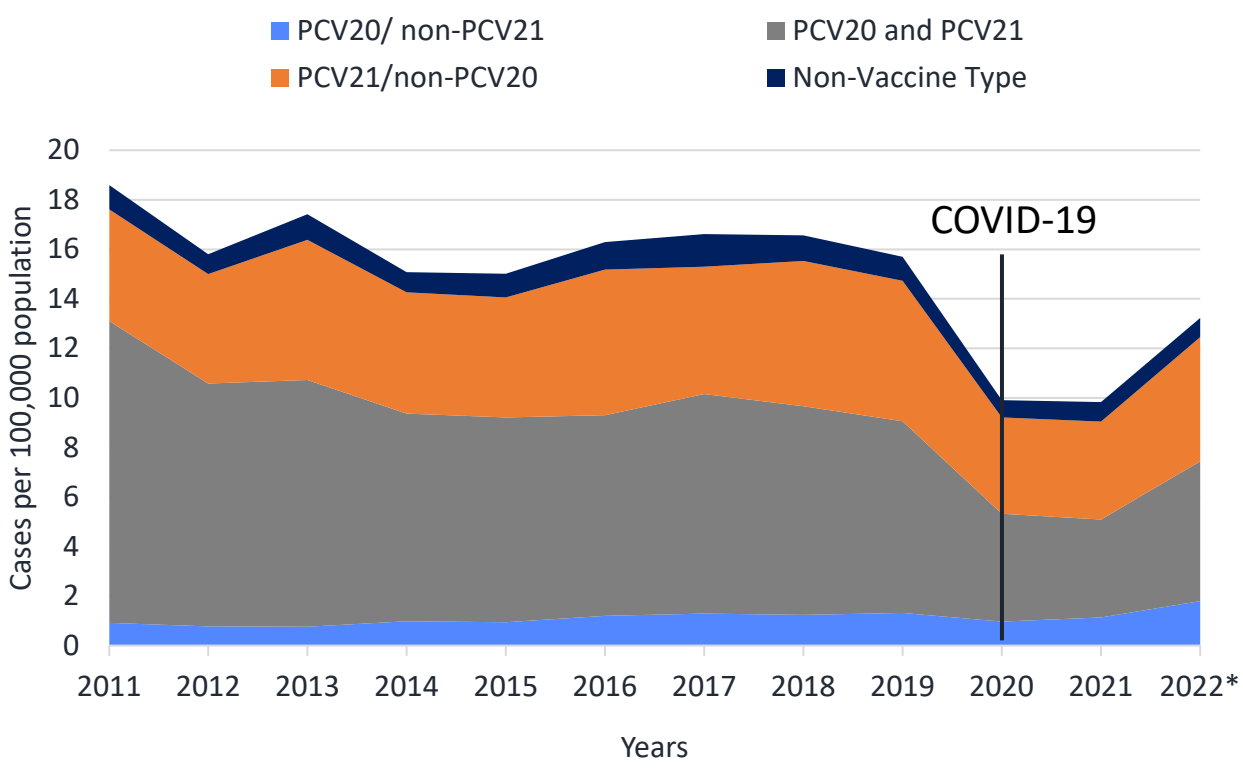
- **PCV21 non-PCV20:** includes serotypes **9N, 17F, 20, 15A, 15C, 16F, 23A, 23B, 24F, 31, 35B**

IPD incidence rates among adults 19-64 years old, by vaccine type, 2011 – 2022

19-49 years old



50-64 years old



PCV20/ non-PCV21 serotype: 1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F, 15B
PCV20/ in-PCV21 serotypes: 3, 6A, 7F, 19A, 22F, 33F, 8, 10A, 11A, 12F, +6C
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*2022 estimates are not finalized

IPD incidence rates among adults 19-64 years old, by vaccine type, 2011 – 2022

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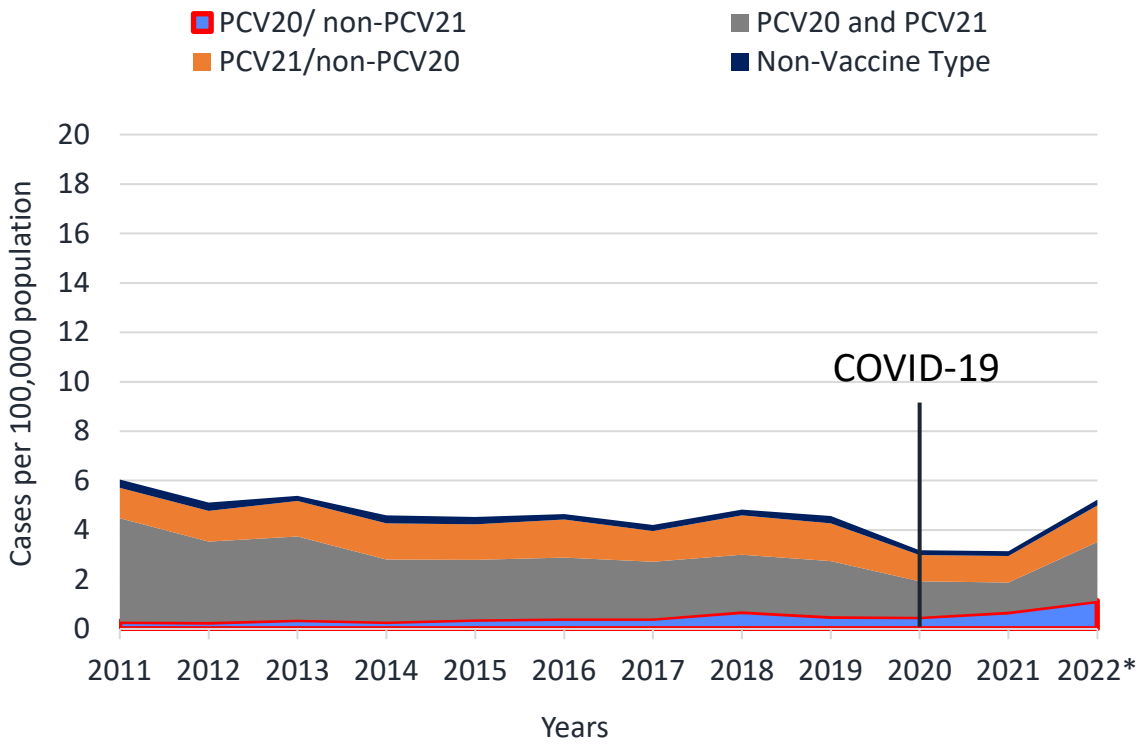
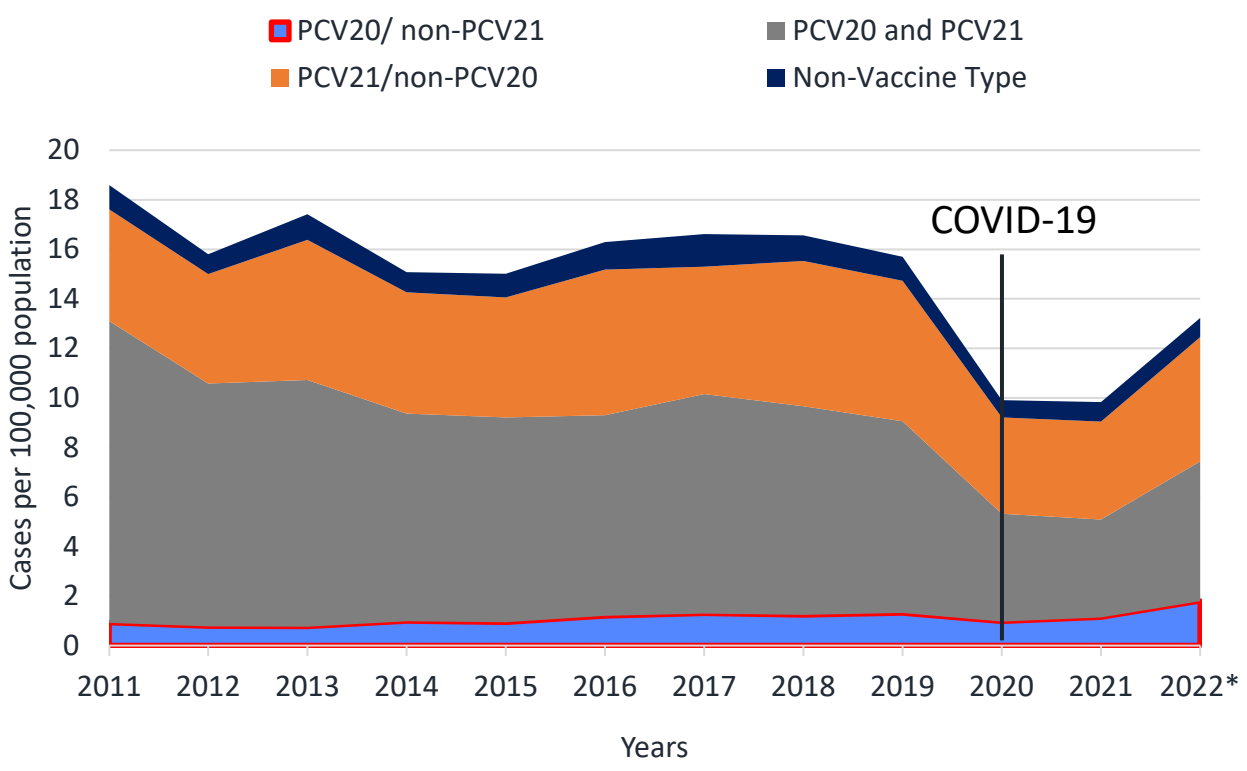


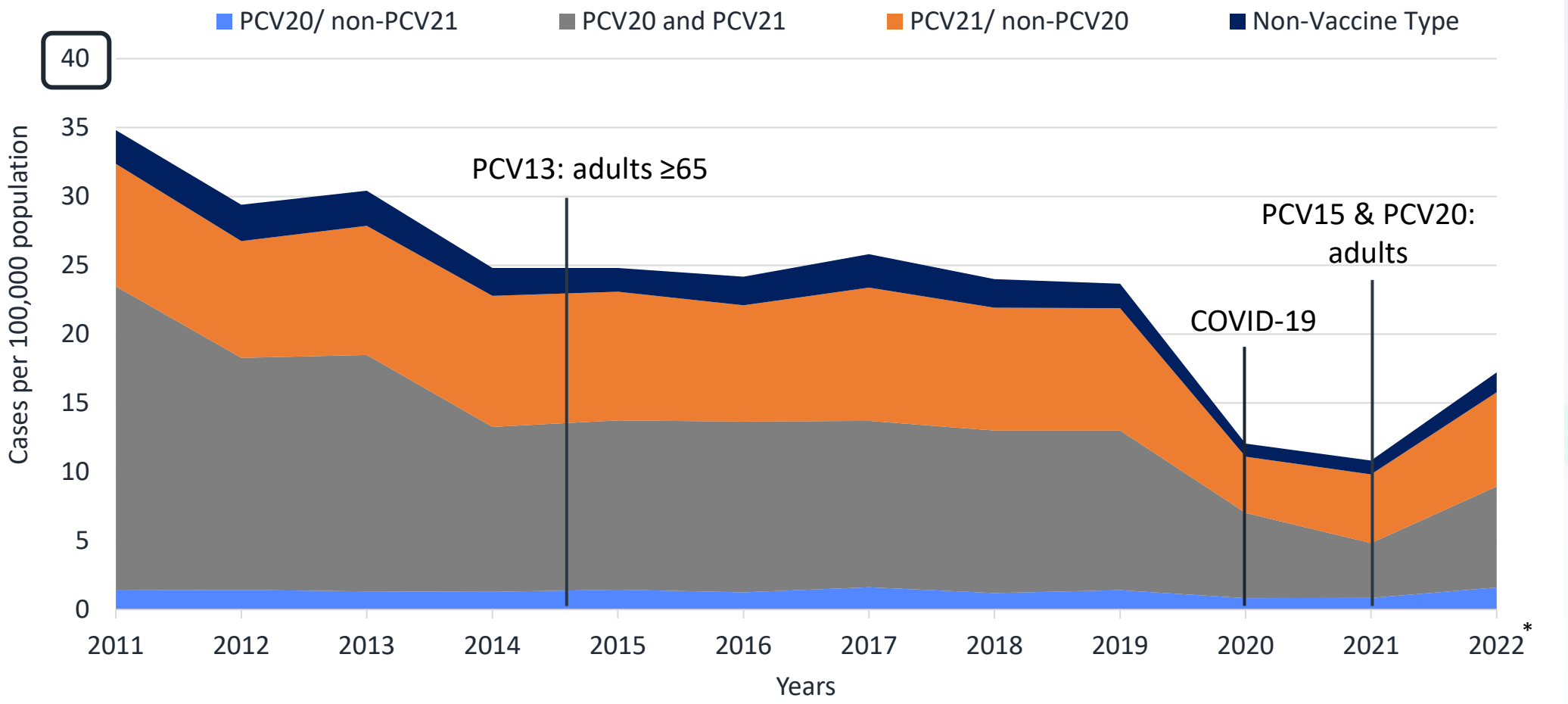
50-64 years old



PCV20/ non-PCV21 serotype: 1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F, 15B
PCV20/ in-PCV21 serotypes: 3, 6A, 7F, 19A, 22F, 33F, 8, 10A, 11A, 12F, +6C
PCV21/ non-PCV20 serotypes: 9N, 17F ,20, 15A, 15C, 16F, 23A, 23B, 24F, 31, 35B

*2022 estimates are not finalized

IPD incidence rates among adults ≥65 years old, by vaccine type, 2011 – 2022

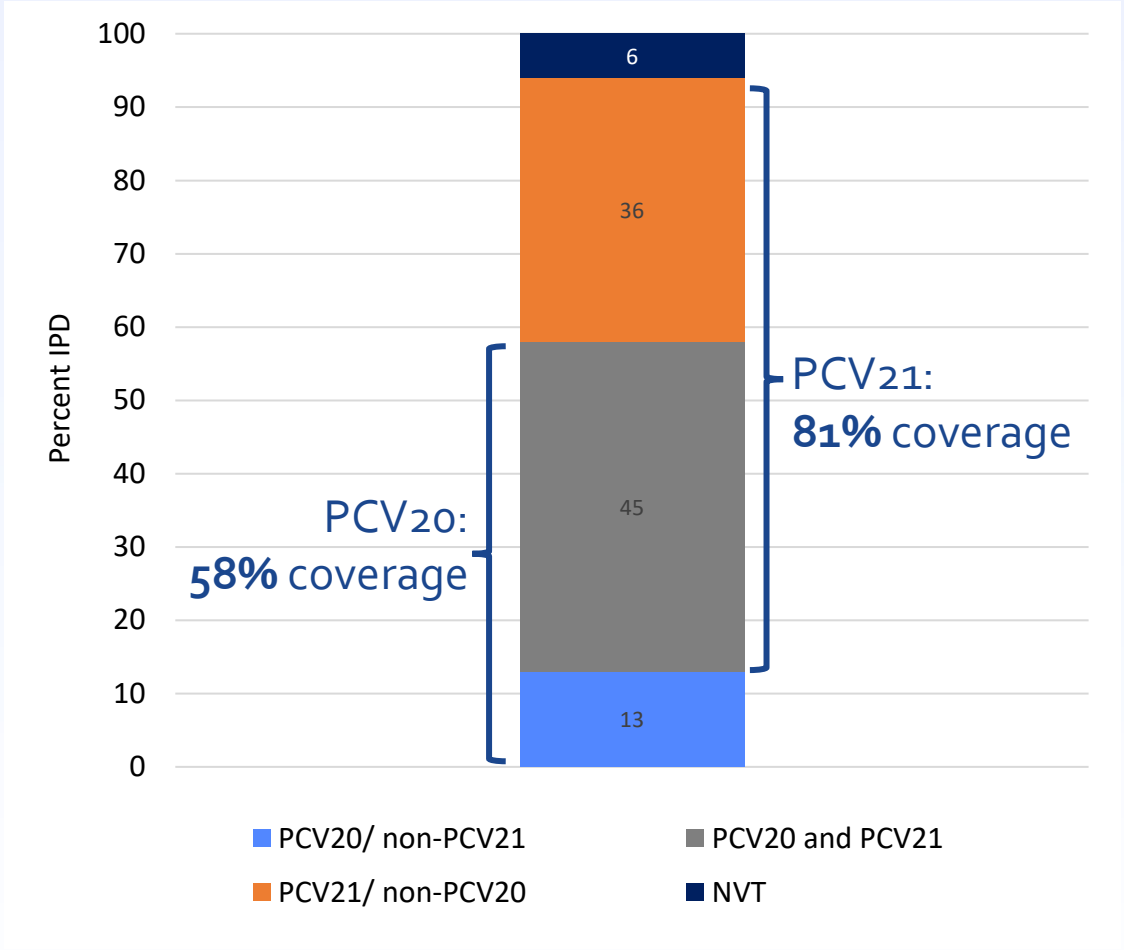


PCV20/ non-PCV21 serotype: 1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F, 15B
PCV20/ in-PCV21 serotypes: 3, 6A, 7F, 19A, 22F, 33F, 8, 10A, 11A, 12F, +6C
PCV21/ non-PCV20 serotypes: 9N, 17F ,20, 15A, 15C, 16F, 23A, 23B, 24F, 31, 35B

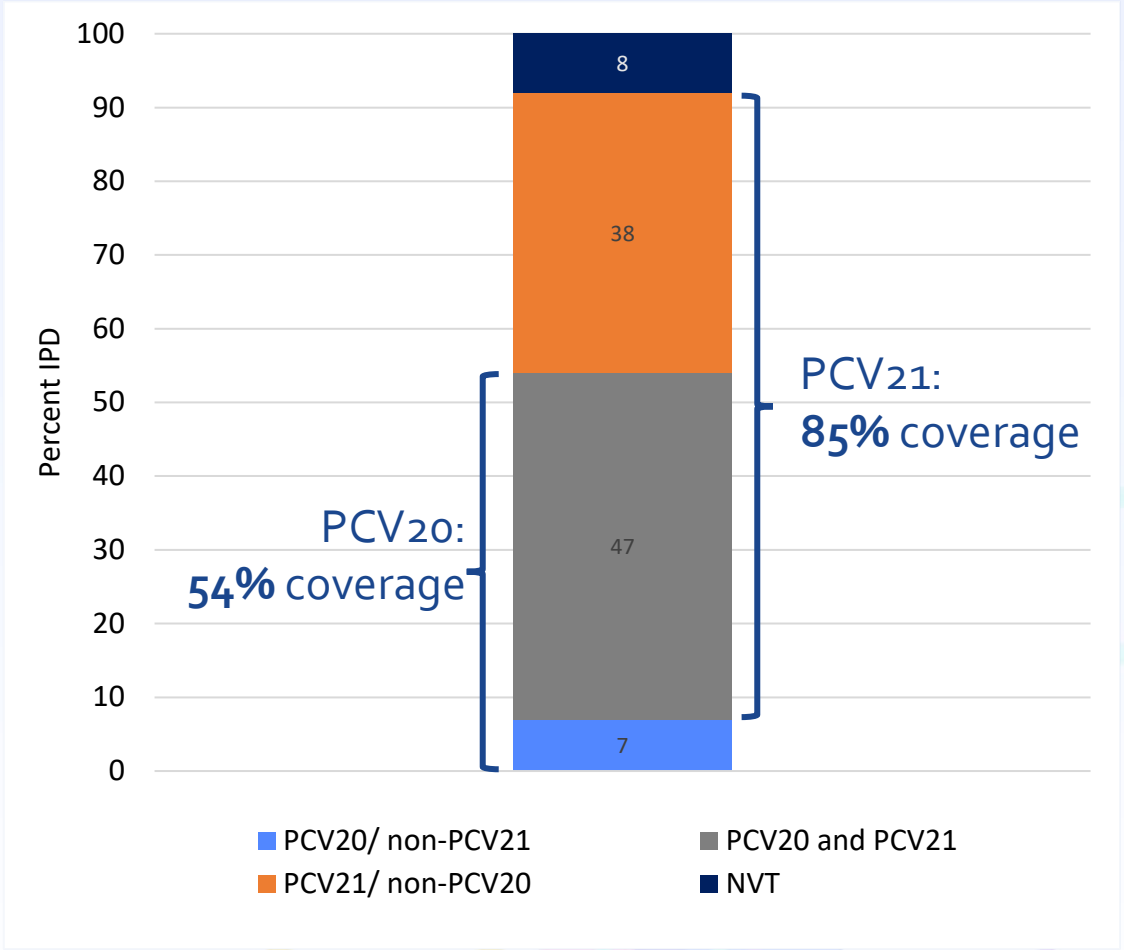
*2022 estimates are not finalized

Proportion of IPD by vaccine-type among adults with a pneumococcal vaccine indication, 2018 – 2022

19-64 years old (*with a risk-based indication*)



≥65 years old



PCV20/ non-PCV21 serotype: 1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F, 15B
PCV20/ in-PCV21 serotypes: 3, 6A, 7F, 19A, 22F, 33F, 8, 10A, 11A, 12F, +6C
PCV21/ non-PCV20 serotypes: 9N, 17F ,20, 15A, 15C, 16F, 23A, 23B, 24F, 31, 35B

Conclusion

- During the COVID-19 pandemic, rates of IPD declined but are now returning to pre-pandemic levels
- >80% of adult IPD cases have a risk-based indication for vaccination
- PCV21 has greater coverage of the serotypes causing IPD in adults compared to PCV20
  - PCV20 covers 54–58% of adult IPD
  - PCV21 covers 81–84% of adult IPD

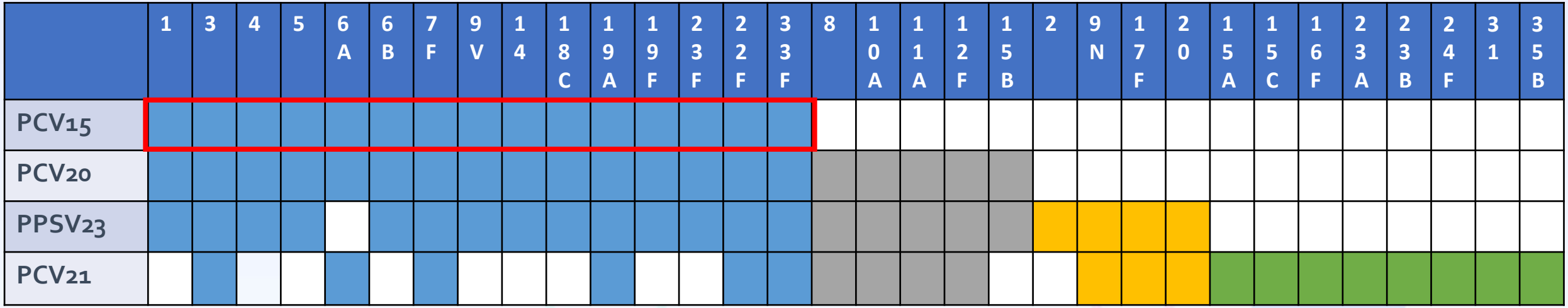
Questions

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.

Supplemental slides

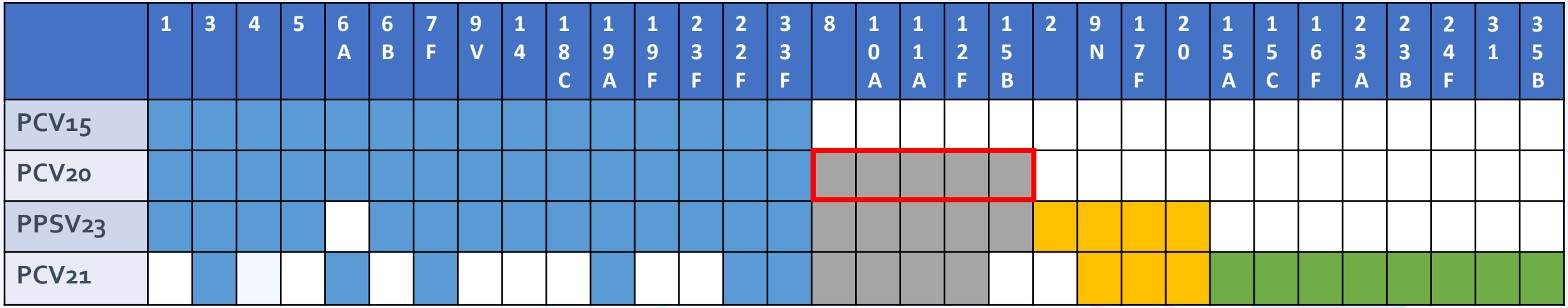
Serotypes contained in current and new pneumococcal vaccines



For analysis purposes:

- **PCV15+6C** includes serotype **6C** with PCV15 types due to cross protection from 6A antigen

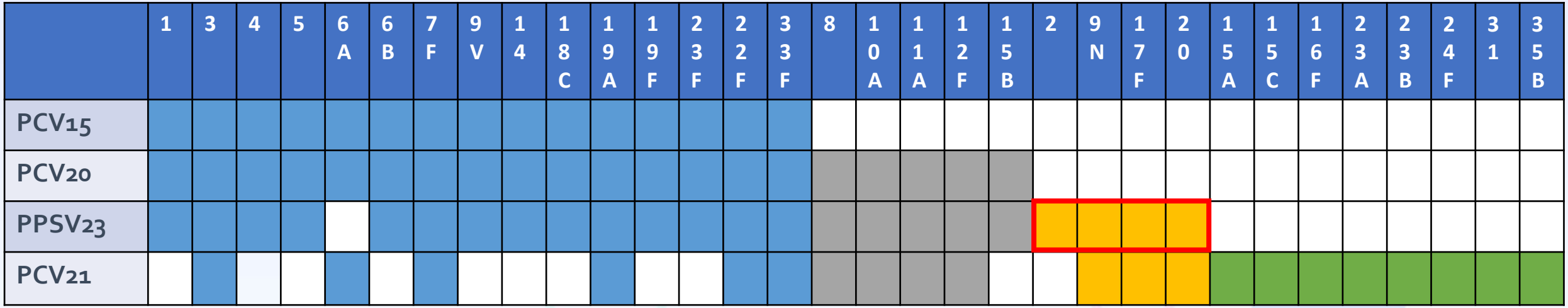
Serotypes contained in current and new pneumococcal vaccines



For analysis purposes:

- **PCV15+6C** includes serotype **6C** with PCV15 types due to cross protection from 6A antigen
- **PCV20/ non-PCV15**: includes serotypes **8, 10A, 11A, 12F, and 15B**

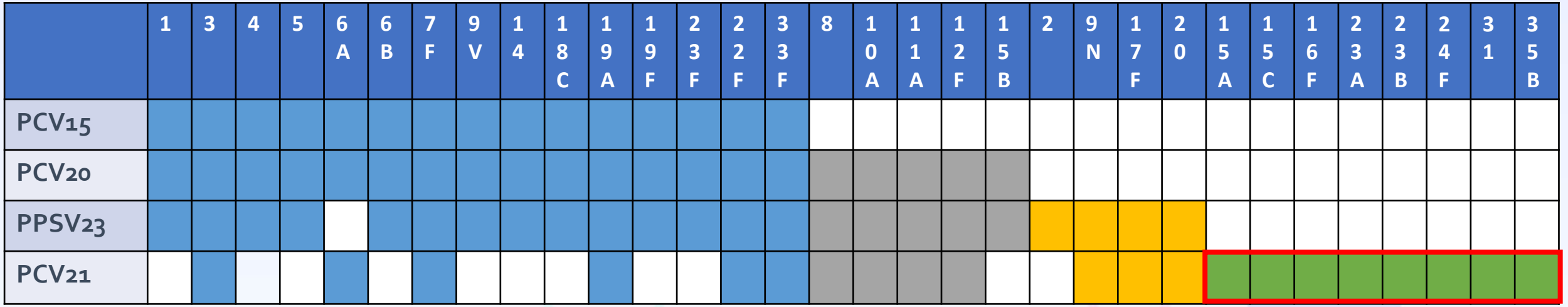
Serotypes contained in current and new pneumococcal vaccines



For analysis purposes:

- **PCV15+6C** includes serotype **6C** with PCV15 types due to cross protection from 6A antigen
- **PCV20/ non-PCV15**: includes serotypes **8, 10A, 11A, 12F, and 15B**
- **PPSV23/ non-PCV20**: includes serotypes **2, 9N, 17F, and 20**

Serotypes contained in current and new pneumococcal vaccines

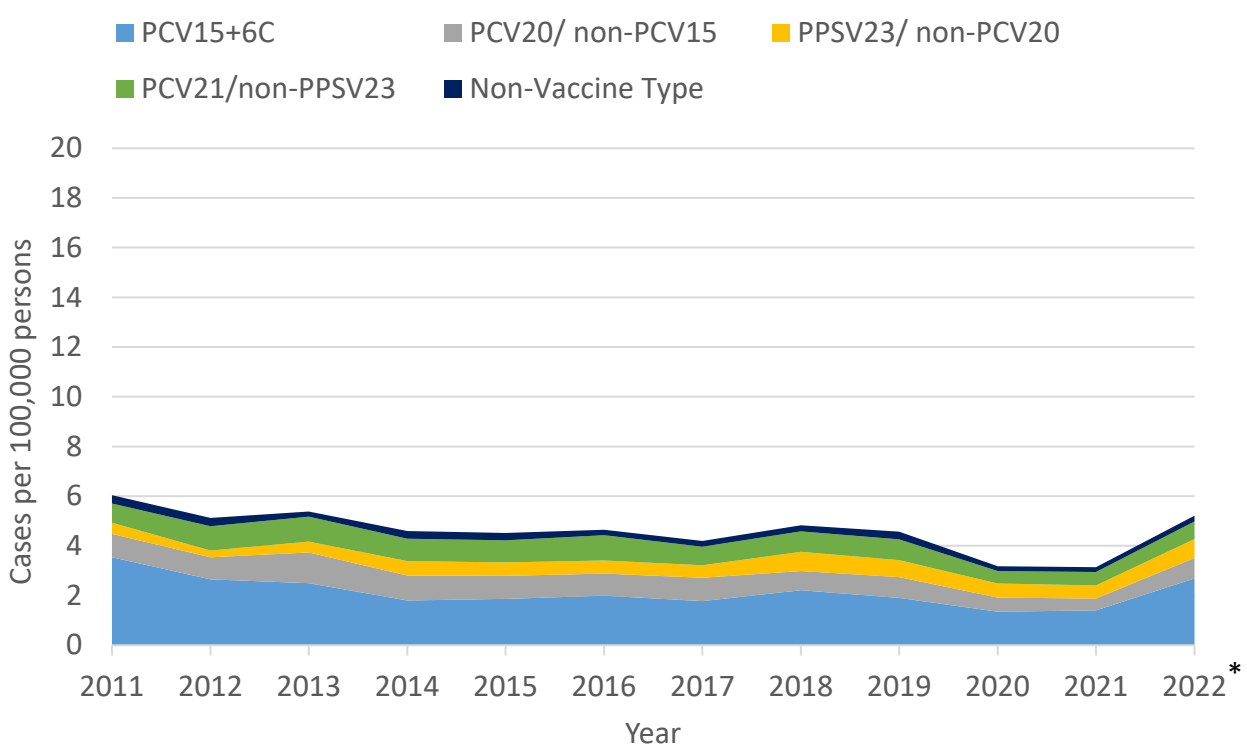


For analysis purposes:

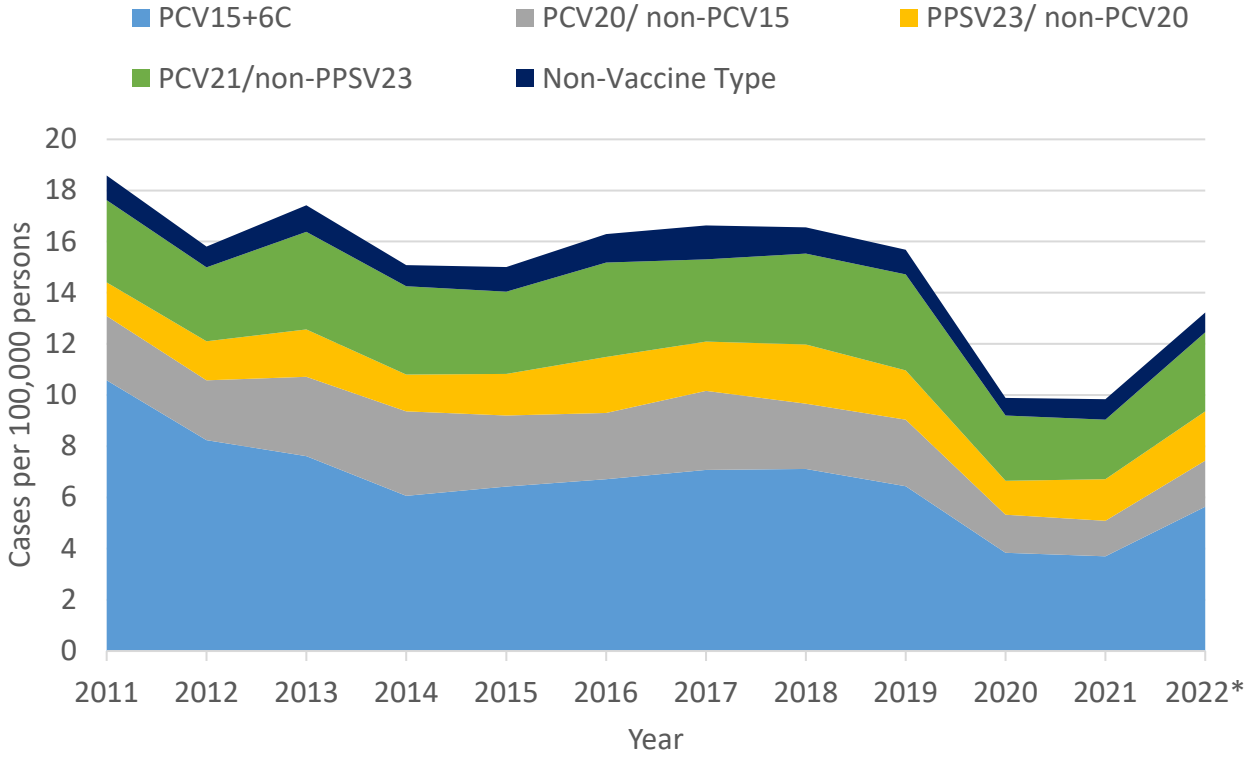
- **PCV15+6C** includes serotype **6C** with PCV15 types due to cross protection from 6A antigen
- **PCV20 non-PCV15**: includes serotypes **8, 10A, 11A, 12F, and 15B**
- **PPSV23 non-PCV20**: includes serotypes **2, 9N, 17F, and 20**
- **PCV21 non-PPSV23:** includes serotypes **15A, 15C, 16F, 23A, 23B, 24F, 31, 35B**

IPD incidence rates among adults 19-64 years old, by vaccine type, 2011 – 2022

19-49 years old



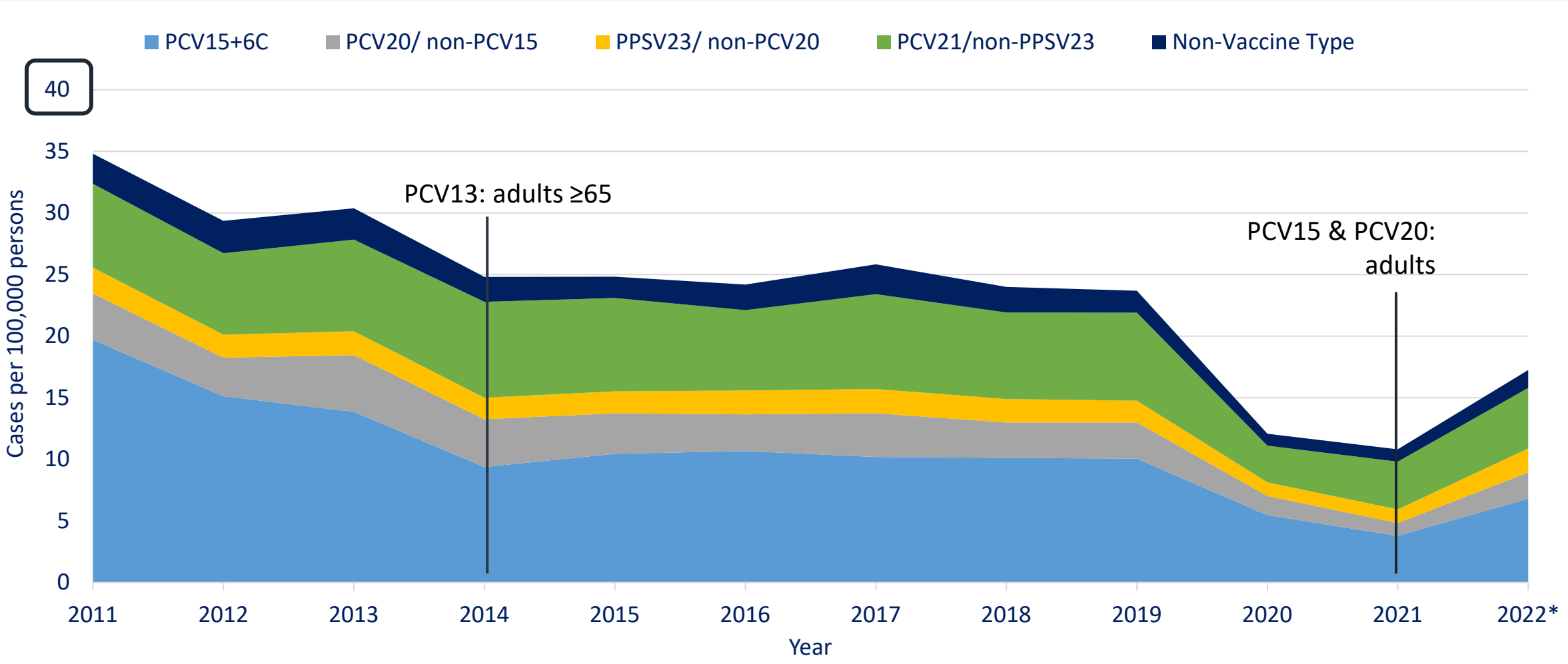
50-64 years old



PCV20 non-PCV15 serotypes: 8, 10A, 11A, 12F, 15B
PPSV23 non-PCV20 serotypes: 2, 9N, 17F, 20
PCV21 non-PPSV23 serotypes: 15A, 15C, 16F, 23A, 23B, 24F, 31, 35

*2022 estimates are not finalized

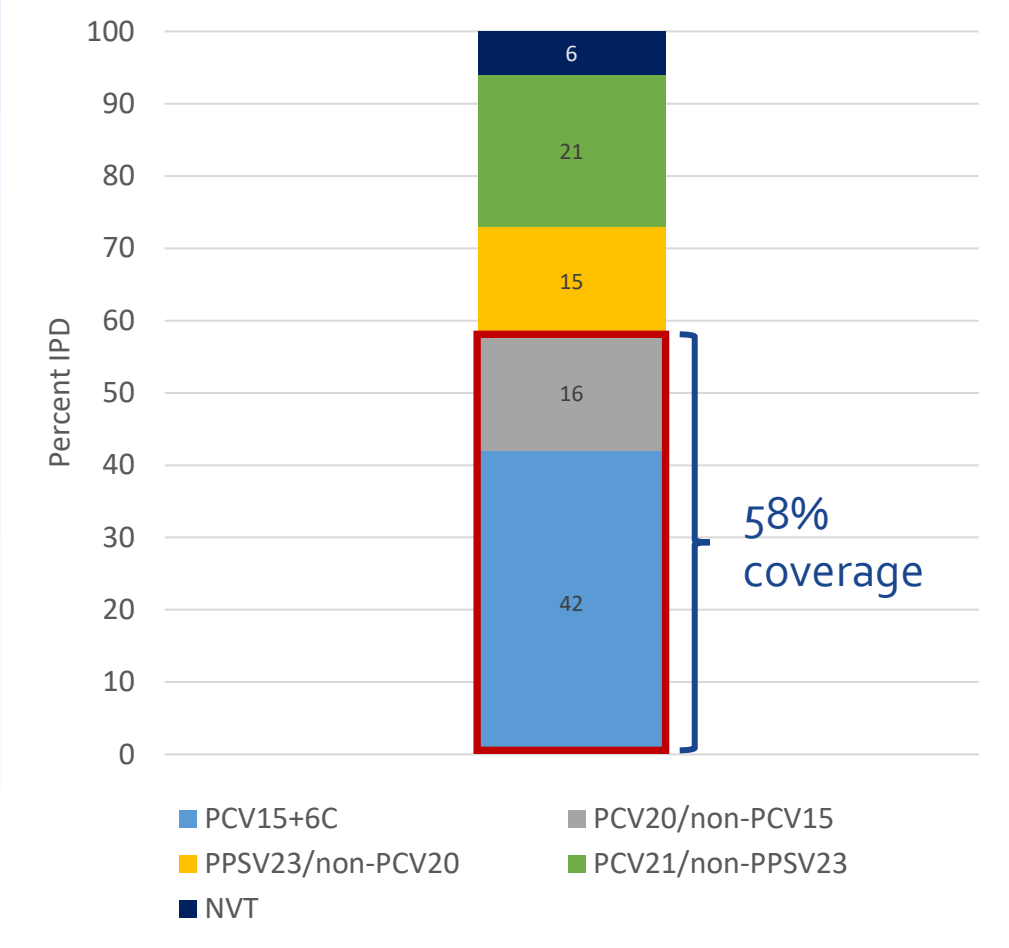
IPD incidence rates among adults ≥65 years old, by vaccine type, 2011 – 2022

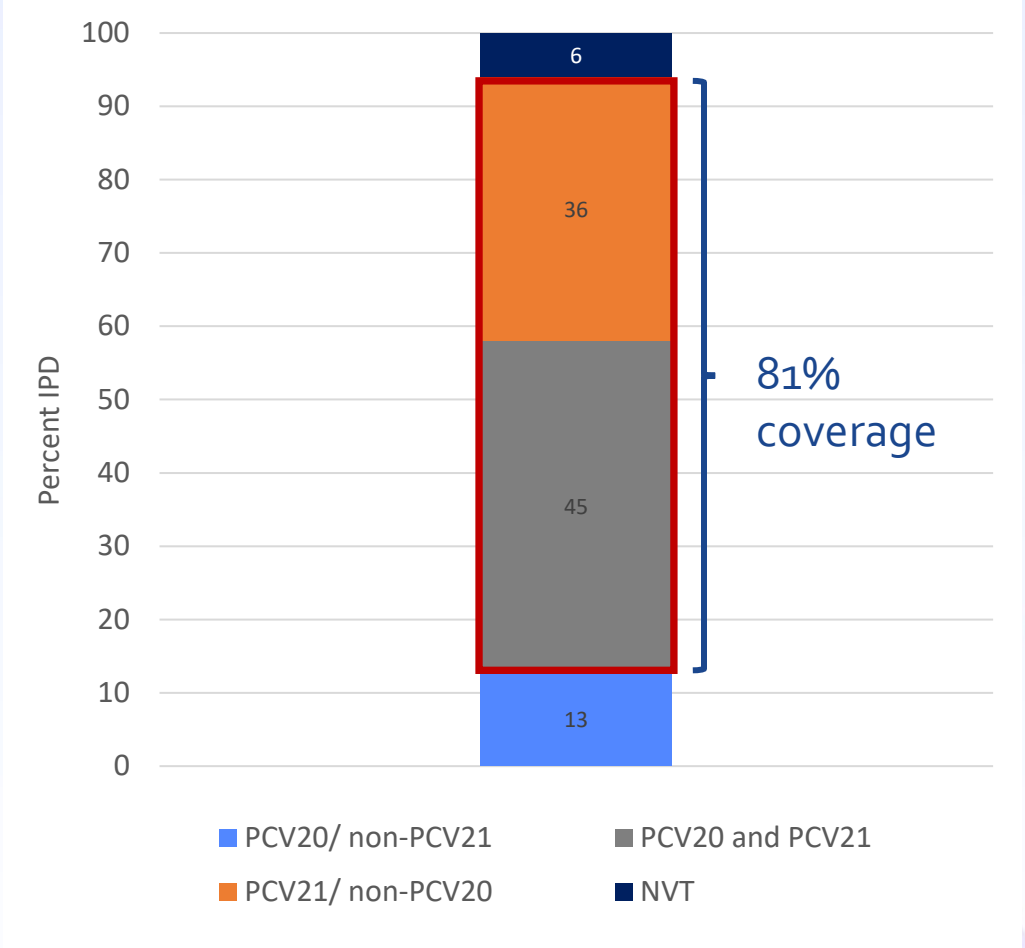


PCV20 non-PCV15 serotypes: 8, 10A, 11A, 12F, 15B
PPSV23 non-PCV20 serotypes: 2, 9N, 17F, 20
PCV21 non-PPSV23 serotypes: 15A, 15C, 16F, 23A, 23B, 24F, 31, 35

*2022 estimates are not finalized

Proportion of IPD by vaccine-type among adults aged 19-64 years, with a risk-based indication, 2018-2022

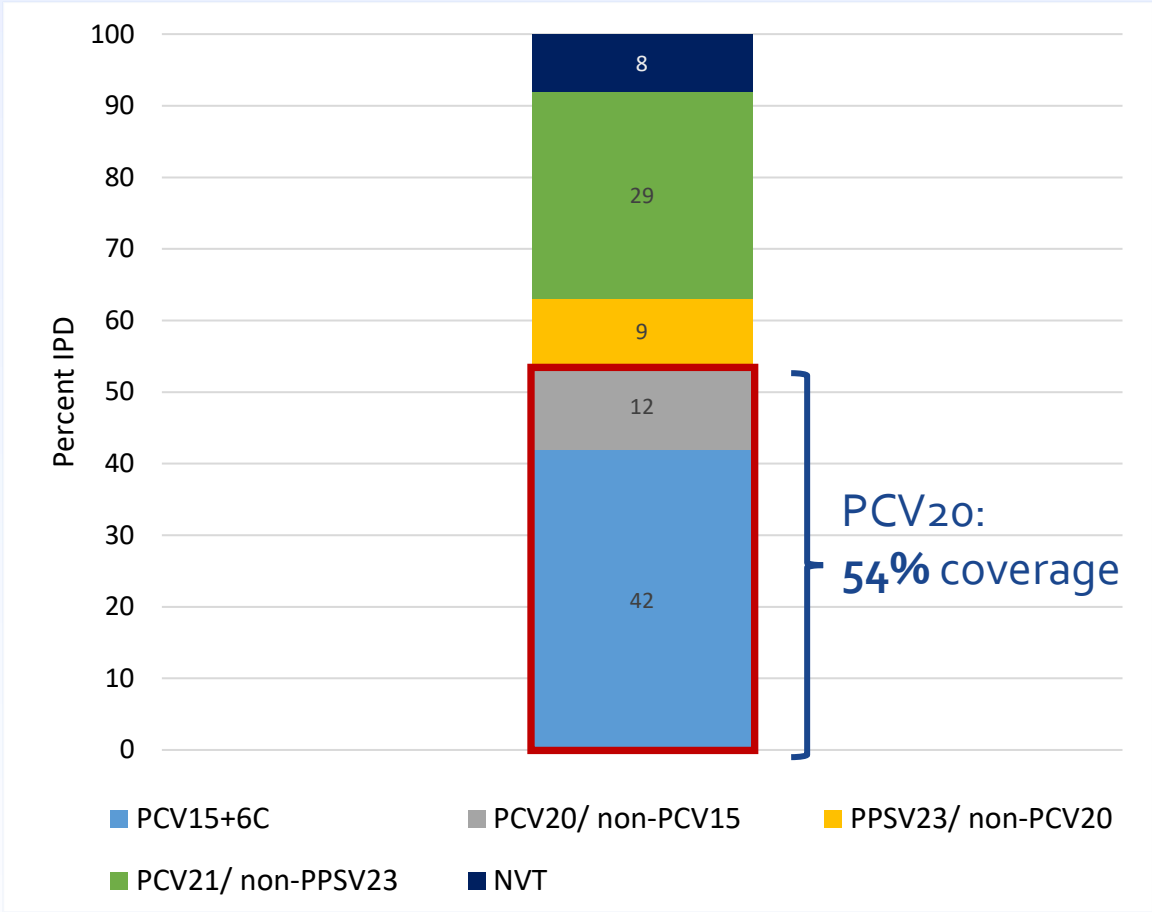


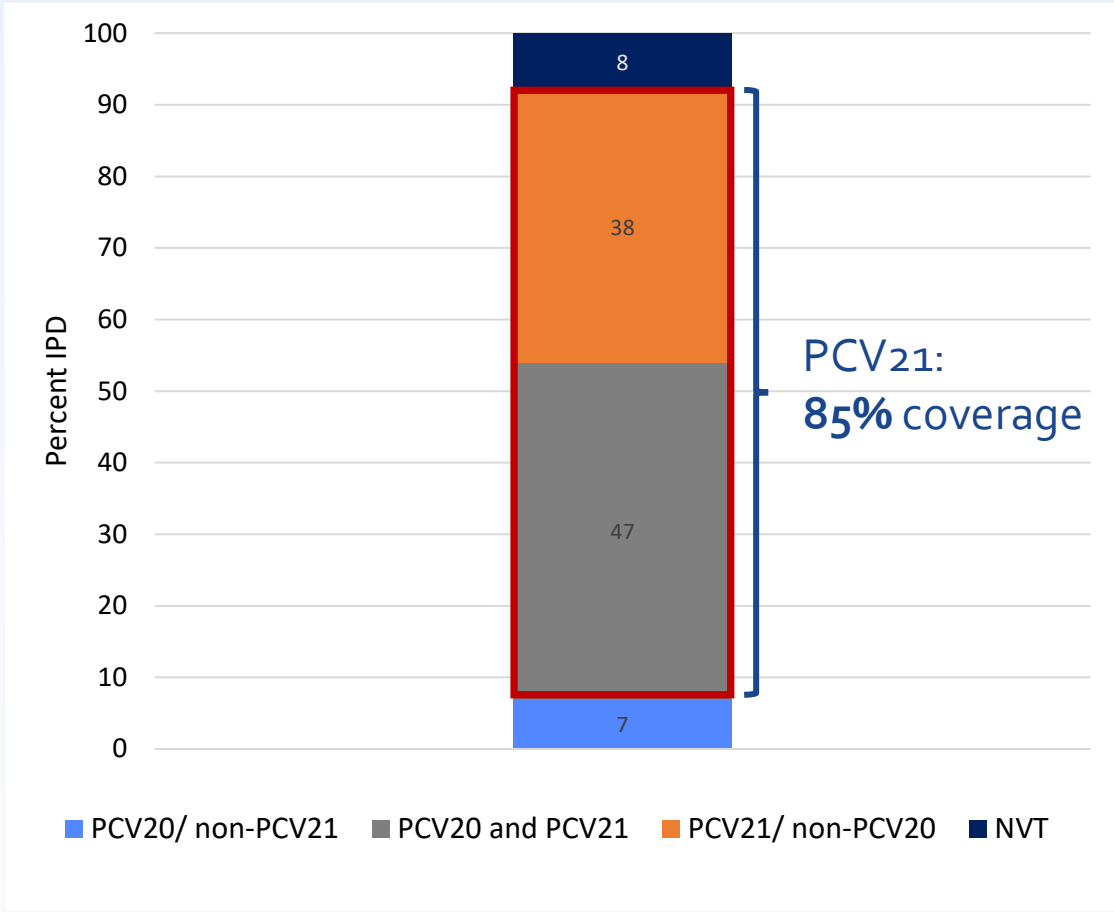


PCV20/ non-PCV15 serotypes: 8, 10A, 11A, 12F, 15B
PPSV23/ non-PCV20 serotypes: 9N, 17F ,20
PCV21/ non-PPSV23 serotypes: 15A, 15C, 16F, 23A, 23B, 24F, 31, 35

PCV20/ non-PCV21 serotype: 1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F, 15B
PCV20/ in-PCV21 serotypes: 3, 6A, 7F, 19A, 22F, 33F, 8, 10A, 11A, 12F, +6C
PCV21/ non-PCV20 serotypes: 9N, 17F ,20, 15A, 15C, 16F, 23A, 23B, 24F, 31, 35

Proportion of IPD by vaccine-type among adults age ≥65 years, 2018-2022





PCV20/ non-PCV15 serotypes: 8, 10A, 11A, 12F, 15B
PPSV23/ non-PCV20 serotypes: 2, 9N, 17F ,20
PCV21/ non-PPSV23 serotypes: 15A, 15C, 16F, 23A, 23B, 24F, 31, 35

PCV20/ non-PCV21 serotype: 1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F, 15B
PCV20/ in-PCV21 serotypes: 3, 6A, 7F, 19A, 22F, 33F, 8, 10A, 11A, 12F, +6C
PCV21/ non-PCV20 serotypes: 9N, 17F ,20, 15A, 15C, 16F, 23A, 23B, 24F, 31, 35

Interim Results from the PNEUMO Study

Pneumococcal pNeumonia Epidemiology, Urine serotyping, and Mental Outcomes study

February 29, 2024

Study Leadership

Wesley H. Self, MD
Vanderbilt University

Nadine Rouphael, MD
Emory University

J. Jackson Resser, MS
Vanderbilt University

Kelly D. Johnson, PhD
Merck & Co., Inc.

Funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA

PNEUMO study overview

Target Population

- Adults 18+ years hospitalized with community acquired pneumonia (CAP)

Design

- Multi-country, prospective, population-based active surveillance study

Objectives

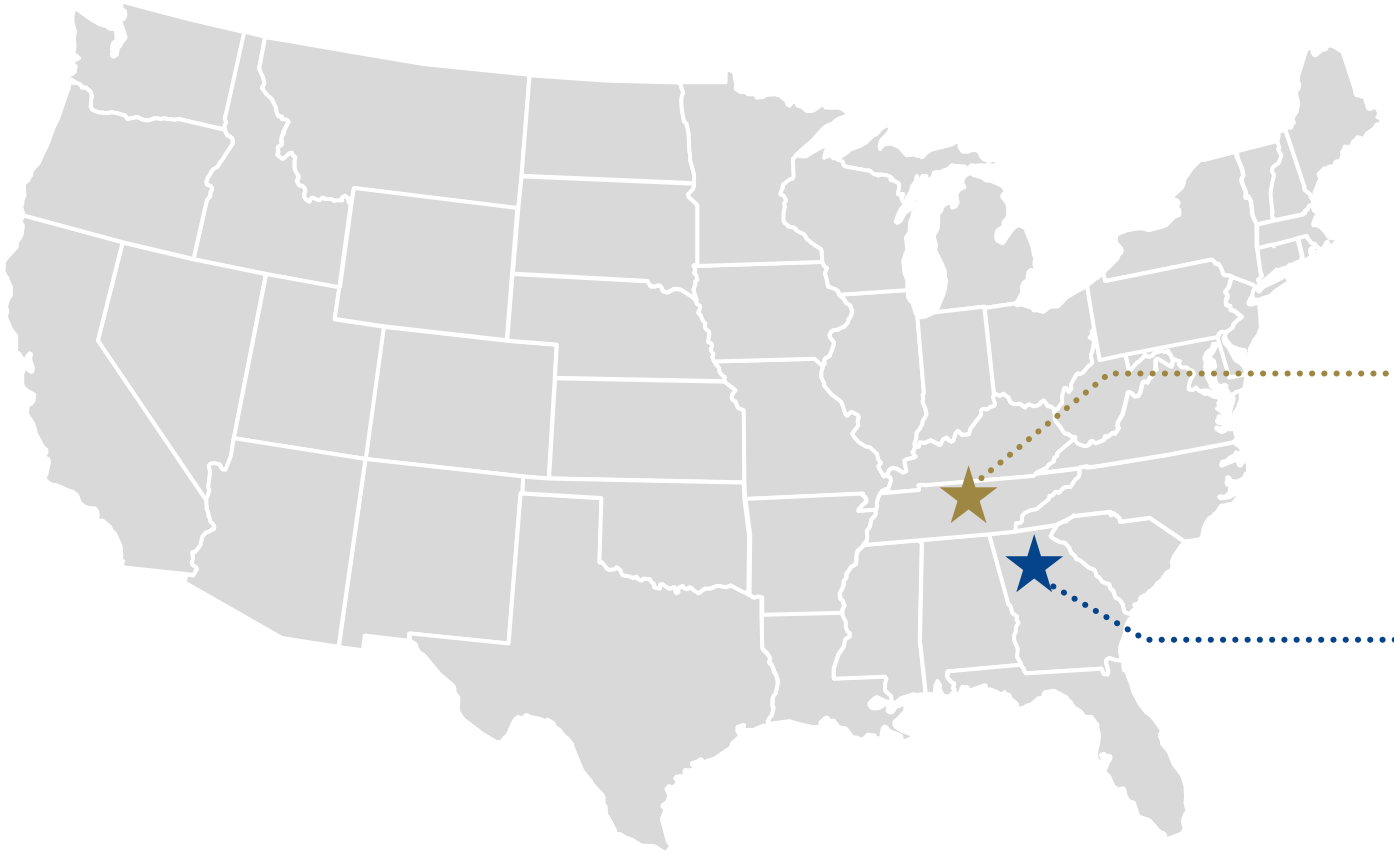
- Estimate pneumococcal pneumonia incidence and serotype prevalence (using Merck PCV15 and V116 SSUADs), with longitudinal evaluation of functional status, quality of life and cost

- Incidence hospitalized pneumococcal CAP
- Incidence hospitalized PCV15- and V116- type pneumococcal CAP
- Direct medical cost
- Work loss
- Functional status
- Cognitive status
- Quality of Life (EQ-5D)

Up to 6 months post-discharge

US PNEUMO sites: enrollment Sept 2018 - present

Pneumonia surveillance with prospective, real-time enrollment of adults hospitalized with CAP (including HCAP)



VANDERBILT UNIVERSITY MEDICAL CENTER

Nashville, Tennessee

EMORY UNIVERSITY HOSPITAL

(2 hospitals) Atlanta, Georgia

HCAP, healthcare associated pneumonia

Eligibility criteria

Inclusion Criteria

1. Age ≥ 18 years old
2. Hospitalized
3. Clinical signs and/or symptoms of an acute respiratory illness (e.g., new shortness of breath, cough)
4. Clinical signs and/or symptoms of an acute infection (e.g., fever, leukocytosis)
5. Radiologic evidence of pneumonia interpreted by a radiologist (x-ray or CT)

Exclusion Criteria

1. Prior enrollment in this study within the past 30 days (to avoid multiple enrollments for same episode of pneumonia).
2. Development of pneumonia >72 hours after hospital admission
3. Inability to obtain consent within 72 hours of hospital admission
4. Inability or unwillingness of the patient to provide a urine sample within 72 hours of hospital admission.
5. Non-pneumonia illness completely explains the patient's acute symptoms.

Tests for *S. pneumoniae*

- Urine collection from patients at enrollment

  (1) BinaxNow pneumococcal urinary antigen test (local testing by research team)

  (2) Serotype-specific urinary antigen detection (SSUAD) assays:
  - Developed and performed by Merck laboratory
  - 30 serotypes:
    - 1, 3, 4, 5, 6A*, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15A, 15C#, 16F, 17F, 18C, 19A, 19F, 20A, 22F, 23A, 23B, 23F, 24F, 31, 33F, 35B
      - All serotypes in PCV15, PCV20, and V116 included except 15B

- Results of clinically-obtained bacterial cultures:
  - Sterile sites: blood, pleural fluid, BAL fluid, CSF, synovial fluid
  - Non-sterile sites: high-quality respiratory samples (>25 WBC, <10 epi)
    - sputum, endotracheal aspirate

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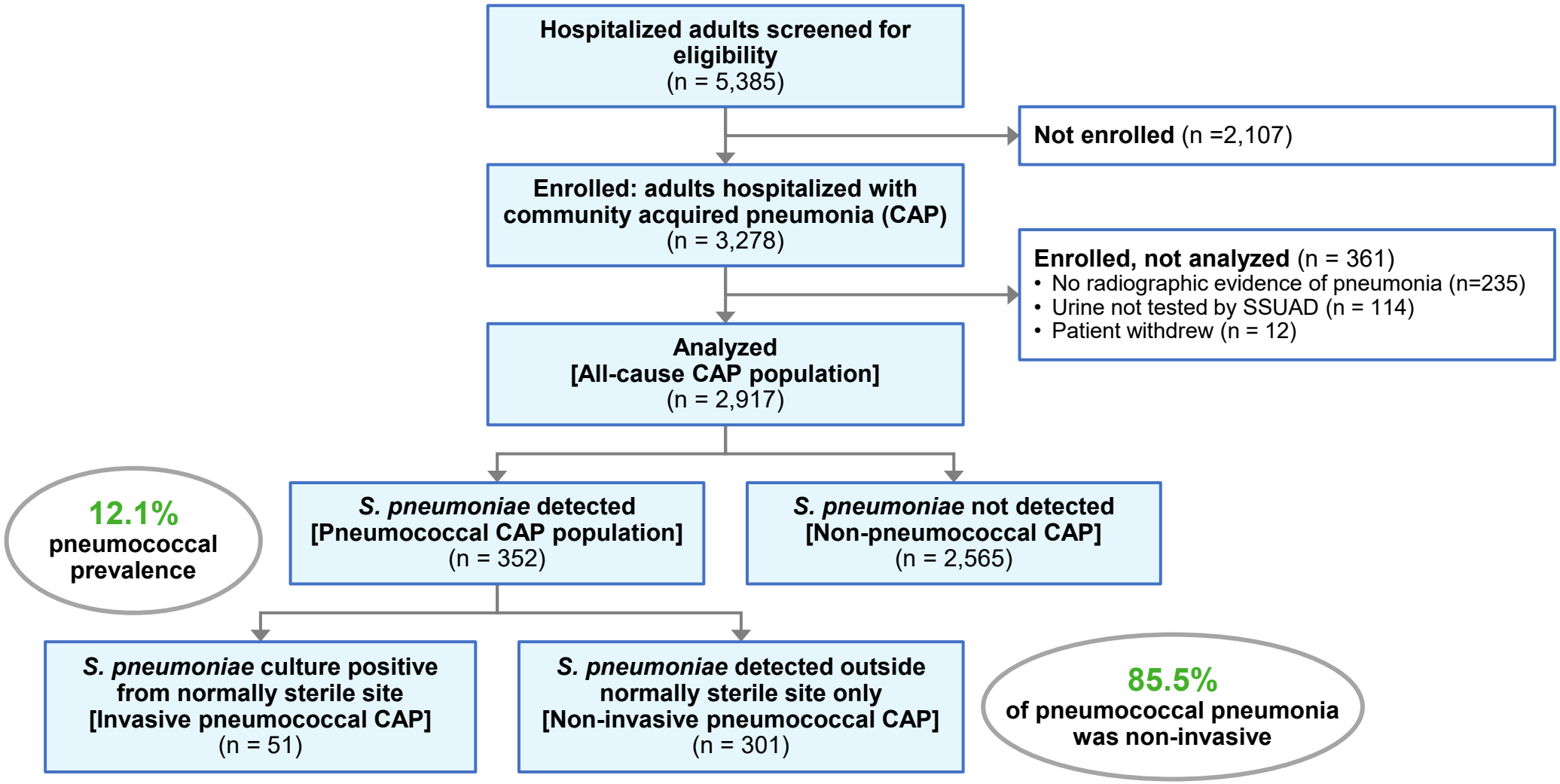
* assay for serotype 6A has cross-reactivity with serotype 6C

assay for serotype 15C has mild cross-reactivity with serotype 15B

Enrolled Patients



Patient Characteristics: Demographics

Characteristic	Pneumonia with *S. pneumoniae* detected (n= 352)	Pneumonia without *S. pneumoniae* detected (n= 2565)	P-value
Age in years, median (IQR)	60.3 (50.6, 70.2)	60.5 (46.8, 70.2)	0.34
Age category, n (%)			0.01
18-49 years	85 (24.1%)	767/2564 (29.9%)	
50-64 years	141 (40.1%)	817/2564 (31.9%)	
≥65 years	126 (35.8%)	980/2564 (38.2%)	
Female sex assigned at birth, n (%)	167/350 (47.7%)	1147/2558 (44.8%)	
Race, n (%)			<0.01
White	198 (56.2%)	1771 (69.0%)	
Black	145 (41.2%)	703 (27.4%)	
Asian	1 (0.3%)	38 (1.5%)	
American Indian/Native Alaskan	2 (0.6%)	14 (0.5%)	
Native Hawaiian/Pacific Islander	2 (0.6%)	6 (0.2%)	
Other	6 (1.7%)	54 (2.1%)	
Ethnicity, n (%)			0.95
Not Hispanic	328 (93.2%)	2394 (93.3%)	
Hispanic	14 (4.0%)	94 (3.7%)	
Unknown	10 (2.8%)	77 (3.0%)	

Patient Characteristics: Social History

Characteristic	Pneumonia with *S. pneumoniae* detected (n= 352)	Pneumonia without *S. pneumoniae* detected (n= 2565)	P-value
Type of home before illness, n (%)			0.27
Community dwelling	320 (90.9%)	2382 (92.9%)	
Nursing Home	6 (1.7%)	43 (1.7%)	
Assisted Living	6 (1.7%)	33 (1.3%)	
Rehabilitation hospital	1 (0.3%)	13 (0.5%)	
School housing	0 (0.0%)	0 (0.0%)	
Homeless/shelter	12 (3.4%)	40 (1.6%)	
Other	3 (0.9%)	33 (1.3%)	
Unknown	4 (1.1%)	21 (0.8%)	
Ever regularly smoked tobacco, n (%)	205/349 (58.7%)	1232/2554 (48.2%)	<0.01
Alcohol use >3 days/week, n (%)	30/348 (8.6%)	145/2543 (5.7%)	0.03
Use of opioids at least weekly, n (%)	68/339 (20.1%)	438/2462 (17.8%)	0.31
Interacts with child <5 years old at least once per week, n (%)	122/340 (35.9%)	682/2468 (27.6%)	<0.01
Lives with children, n (%)	83/346 (24.0%)	517/2534 (20.4%)	

Patient Characteristics: Chronic Medical Conditions

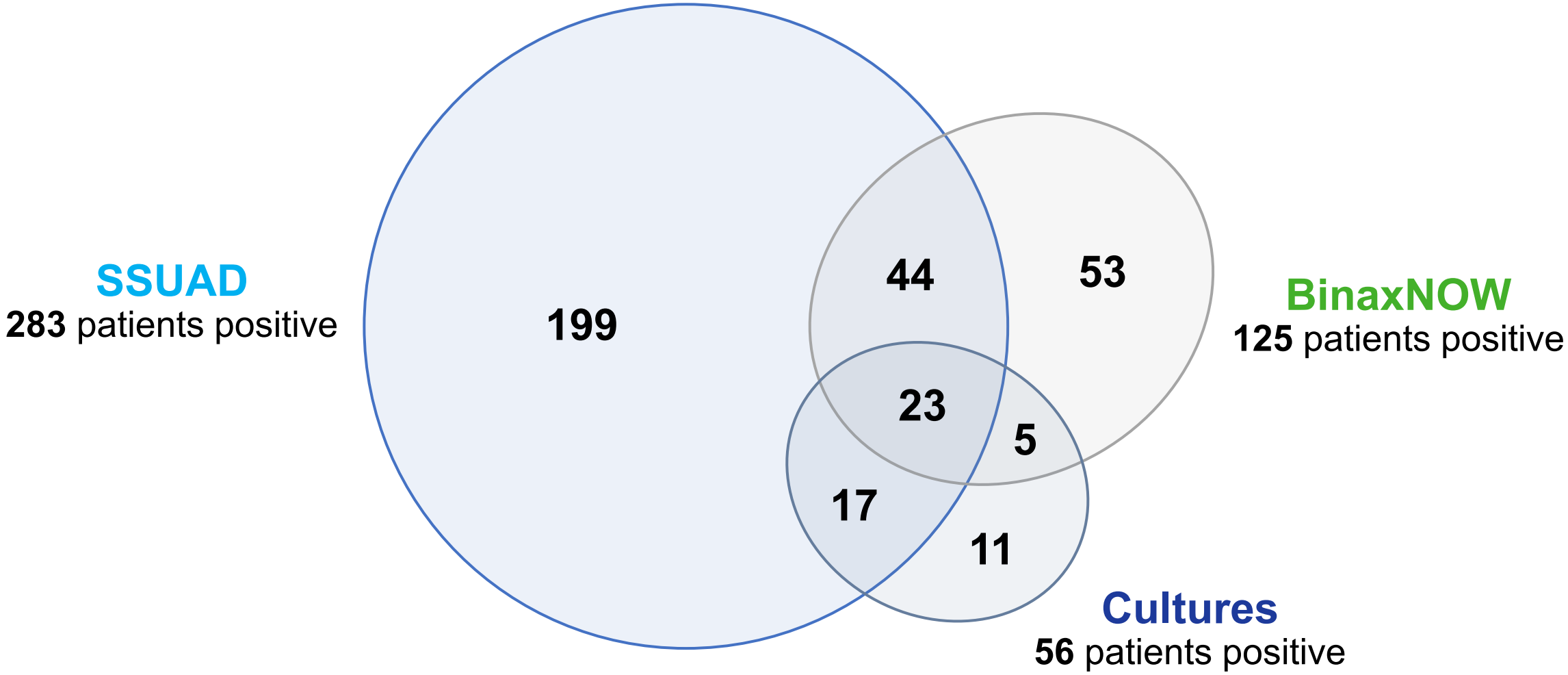
Characteristic	Pneumonia with *S. pneumoniae* detected (n= 352)	Pneumonia without *S. pneumoniae* detected (n= 2565)	P-value
Chronic medical conditions, n (%)			
Dementia	11/349 (3.2%)	65/2528 (2.6%)	0.362
COPD	97/346 (28.0%)	487/2510 (19.4%)	<0.001
Asthma	72/346 (20.8%)	474/2518 (18.8%)	0.413
Heart failure	61/340 (17.9%)	446/2509 (17.8%)	0.824
Prior MI	37/344 (10.8%)	231/2525 (9.1%)	0.359
Prior stroke	38/347 (11.0%)	255/2516 (10.1%)	0.651
End stage kidney disease with chronic kidney replacement	14/342 (4.1%)	125/2515 (5.0%)	0.424
Diabetes mellitus	82/348 (23.6%)	684/2525 (27.1%)	0.159
Chronic liver disease	30/343 (8.7%)	173/2508 (6.9%)	0.254
Immunosuppression	72/343 (21.0%)	529/2499 (21.2%)	0.983
Solid organ cancer	80/348 (23.0%)	589/2501 (23.6%)	0.981
Hematologic cancer	30/346 (8.7%)	193/2511 (7.7%)	0.598
Solid organ transplant	25/347 (7.2%)	205/2528 (8.1%)	0.545
Pregnant	0/348 (0.0%)	22/2533 (0.9%)	0.081
Obesity with body mass index >30 kg/m^2	89/355 (25.9%)	1009/2479 (40.7%)	<0.001

Patient Characteristics: Acute Illness

Characteristic	Pneumonia with *S. pneumoniae* detected (n= 352)	Pneumonia without *S. pneumoniae* detected (n= 2565)	P-value
Received antibiotics for current illness before hospitalization, n (%)	71/328 (21.6%)	613/2297 (26.7%)	0.05
Duration of acute illness prior to hospital admission [days], median (IQR)	2.6 (1.3, 5.0)	2.7 (1.1, 5.7)	0.36
CURB-65* score at hospital admission, n (%)			0.17
0 (low risk)	123/345 (35.7%)	943/2523 (37.4%)	
1 (low risk)	126/345 (36.5%)	869/2523 (34.4%)	
2 (moderate risk)	60/345 (17.4%)	547/2523 (21.7%)	
3 (high risk)	31/345 (9.0%)	150/2523 (5.9%)	
4 (high risk)	5/345 (1.4%)	14/2523 (0.6%)	
5 (high risk)	0/345 (0.0%)	0/2523 (0.0%)	
Timing of Enrollment			<0.01
Before COVID-19 in US (October 2018 – February 2020)	231/345 (67.0%)	1249/2519 (49.6%)	
After COVID-19 in US (March 2020 – October 2022)	114/345 (33.0%)	1270/2519 (50.4%)	

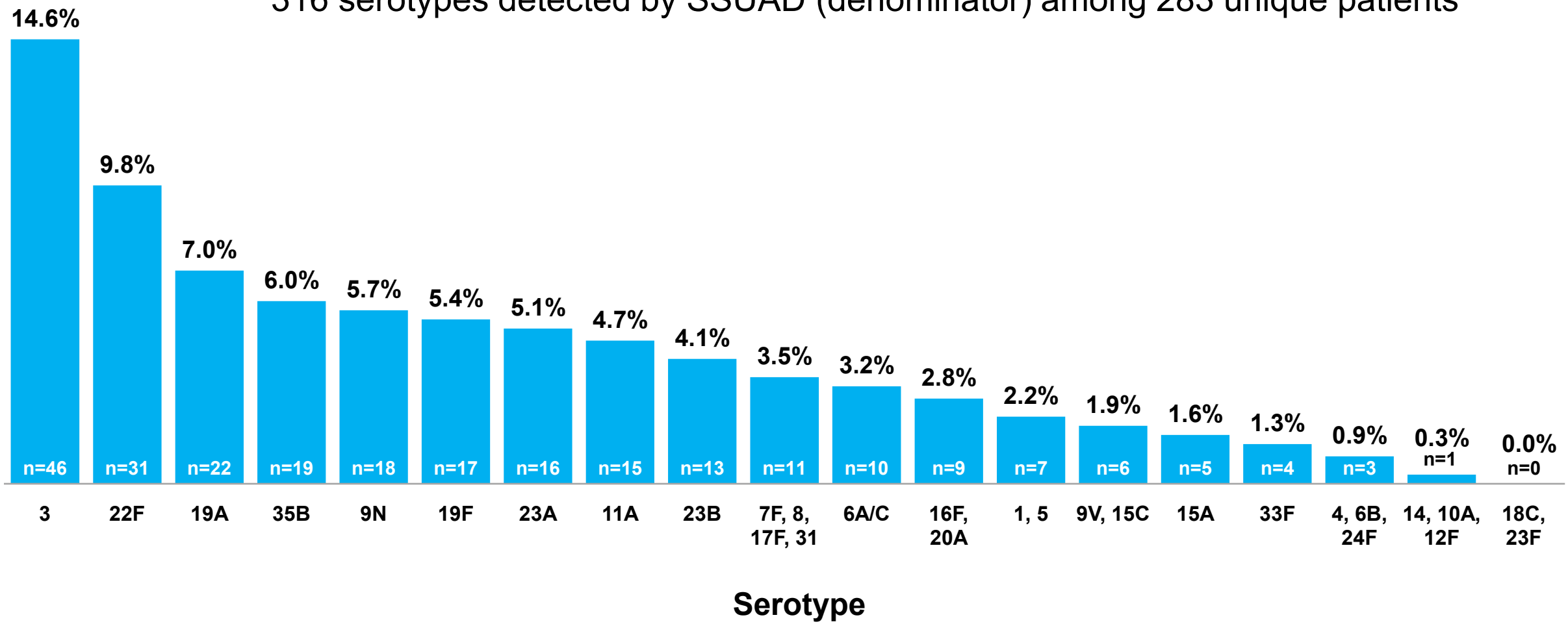
* CURB-65: pneumonia severity scoring system, consisting of the following variables: confusion, uremia, respiratory rate, blood pressure, age >65

352 Patients with ≥1 Positive Pneumococcal Test

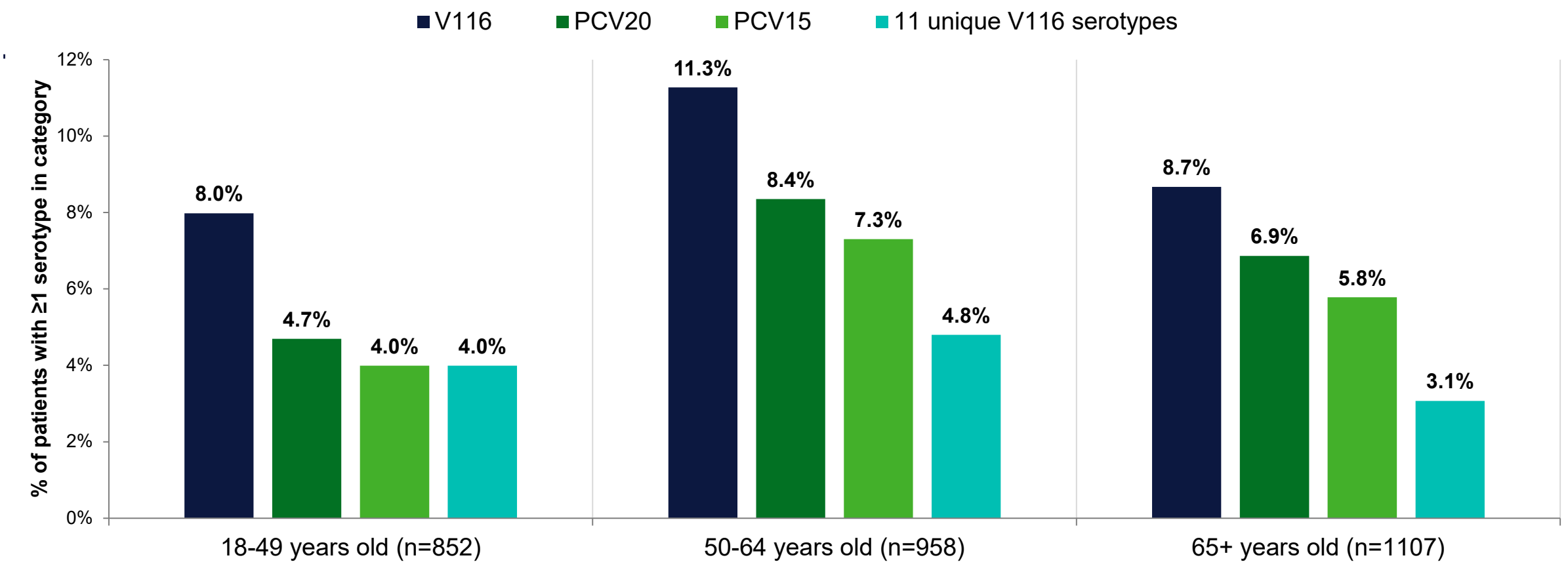


Percentage of Pneumococcal Serotype Detections

316 serotypes detected by SSUAD (denominator) among 283 unique patients



Percentage of Pneumococcal Serotype by Vaccine in Adults Hospitalized with CAP



Vaccine Category	Pneumococcal serotypes	% of serotypes in adults hospitalized with CAP (n=2917)
V116 (21 serotypes)	3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, 35B	**9.3%**
PCV20 (19 serotypes; serotype 15B not tested)	1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 18C, 19A, 19F, 22F, 23F, 33F	**6.7%**
PCV15 (15 serotypes)	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F	**5.8%**
V116 and not PCV15 or PCV20 (11 serotypes)	9N, 15A, 15C, 16F, 17F, 20A, 23A, 23B, 24F, 31, 35B	**4.1%**

Conclusions

- Pneumococcal CAP remains a major cause of adult hospitalizations
- SSUAD assays greatly increase *S. pneumoniae* detection over traditional testing
- Among adults hospitalized with CAP:
  - 12.1% with *S. pneumoniae* detected
  - 9.3% with a pneumococcal serotype in V116
  - 4.1% with a serotype unique to V116 (not PCV15 or PCV20)
    - Most commonly detected serotypes unique to V116: 35B, 9N, 23A, 23B

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INVENTING FOR LIFE

V116: An Investigational Adult Specific Pneumococcal Conjugate Vaccine

Key Results from the Phase 3 Clinical Development Program

ACIP Meeting, 29-Feb-2024

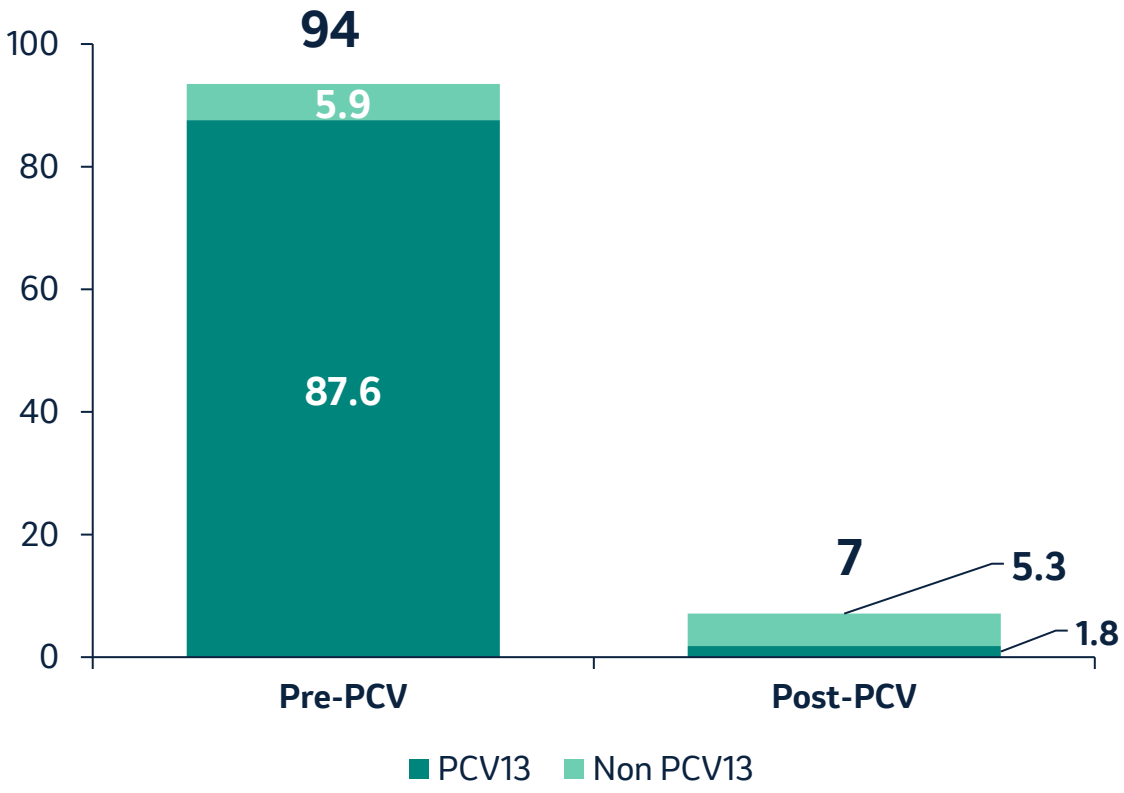
Heather Platt, M.D., on behalf of the V116 team
Distinguished Scientist, Global Clinical Development
Merck Research Laboratories
Merck & Company, Inc.

Presentation

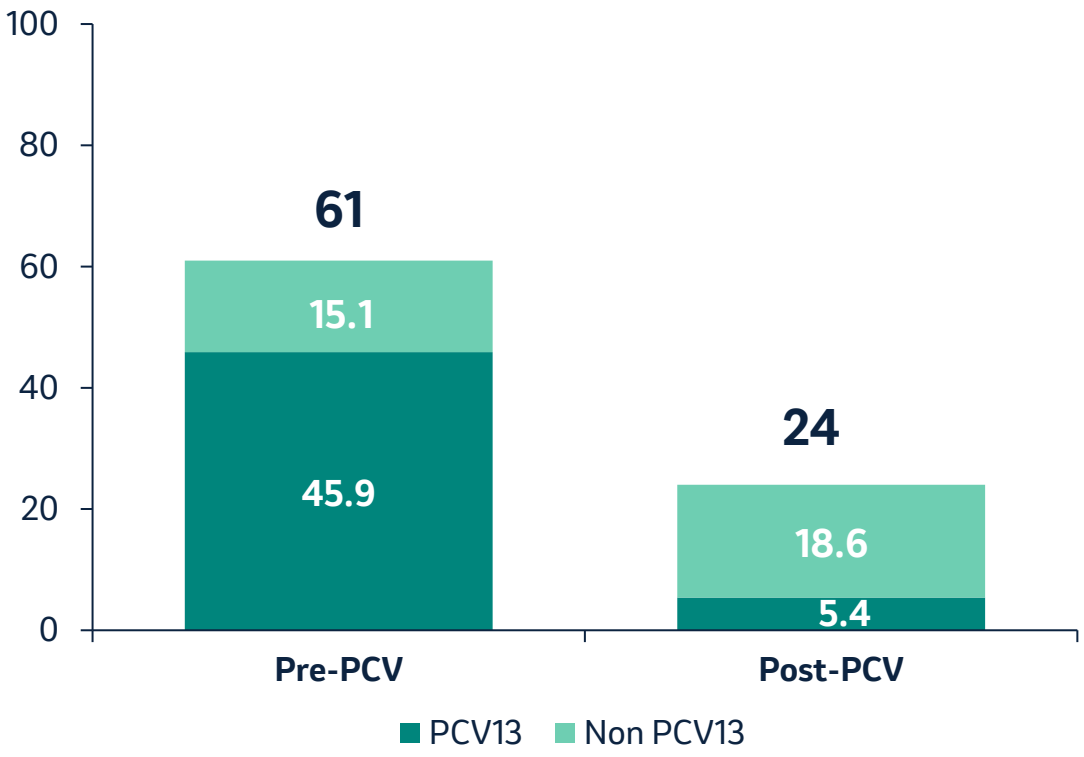
- Rationale for Development of V116
- Overview of V116 Adult Clinical Development Program
- Immunogenicity Results
  - Vaccine naïve adults ≥ 18 years of age
  - Vaccine experienced adults ≥ 50 years of age
- Integrated Summary of Safety
  - Vaccine naïve and vaccine experienced adults ≥ 18 years of age
- Supportive Studies
  - V116 in individuals living with HIV
  - V116 administered with concomitant influenza vaccine
  - V116 lot consistency
- Conclusions
- Questions

The introduction of PCVs has significantly decreased disease incidence in children and changed epidemiology of IPD in adults in the US

IPD cases per 100K in US by serotype, children <5



IPD cases per 100K in US by serotype, adults ≥65

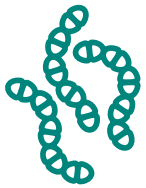


*Centers for Disease Control and Prevention, IPD serotype data 2019, as compiled from data provided through Active Bacterial Core surveillance (ABCs).

Rationale for Development of V116

Indirect protection through pediatric vaccination

PCV use in infants has significantly decreased the burden of disease in adults through **indirect protection**.

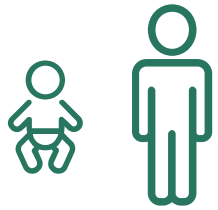


Unmet medical need in adults

The burden of disease in adults remains high; IPD due to **non-vaccine serotypes** has increased in adults.

Population-specific vaccination

V116 being developed as a **population-specific vaccine** to prevent invasive disease and pneumonia in adults.



Complementary to pediatric PCVs

V116 is designed to **complement PCV pediatric immunization** programs.

V116 is an **adult specific** pneumococcal conjugate vaccine (PCV)

- Includes **21 pneumococcal serotypes**, 4µg/PnPs individually conjugated to CRM197 formulated without an adjuvant
- Single dose, 0.5mL **pre-filled syringe**, intramuscular injection for adults 18+
- The serotypes in V116 accounted for **~85% of IPD** and the **8 unique serotypes accounted for ~30%** of IPD in US adults ≥65 years in 2019
- V116 is currently under **Priority Review** by the FDA for the prevention of IPD and pneumonia in adults ≥18 years of age with target action date of June 17, 2024.

	Serotype Composition																													
PCV13	4	6B	9V	14	18C	19F	23F	1	3	5	6A	7F	19A																	
PCV15	4	6B	9V	14	18C	19F	23F	1	3	5	6A	7F	19A	22F	33F															
PPSV23	4	6B	9V	14	18C	19F	23F	1	3	5		7F	19A	22F	33F	2	8	9N	10A	11A	12F	15B	17F	20						
PCV20	4	6B	9V	14	18C	19F	23F	1	3	5	6A	7F	19A	22F	33F		8		10A	11A	12F	15B								
V116									3		6A	7F	19A	22F	33F		8	9N	10A	11A	12F		17F	20A	15A	15C	16F	23A	23B	24F	31	35B

IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine; PCV13, pneumococcal conjugate vaccine, 13-valent; PCV15 pneumococcal conjugate vaccine, 15-valent, PCV20, pneumococcal conjugate vaccine, 20-valent.

1. **CDC**, IPD Serotype Data 2019, as compiled from data provided through Active Bacterial Core surveillance (ABCs).
2. 2. **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, US-based trial. Lancet Infect Dis. 2023 Feb;23(2):233-246. https://pubmed.ncbi.nlm.nih.gov/36116461/

15C is denoted here to represent the serotype protection proposed with deOAc15B as the molecular structures for deOAc15B and 15C are similar (Jones C, Lemercinier X. 2005. Full NMR assignment and revised structure for the capsular polysaccharide from Streptococcus pneumoniae type 15B. *Carbohydr Res* 340:403-409.)

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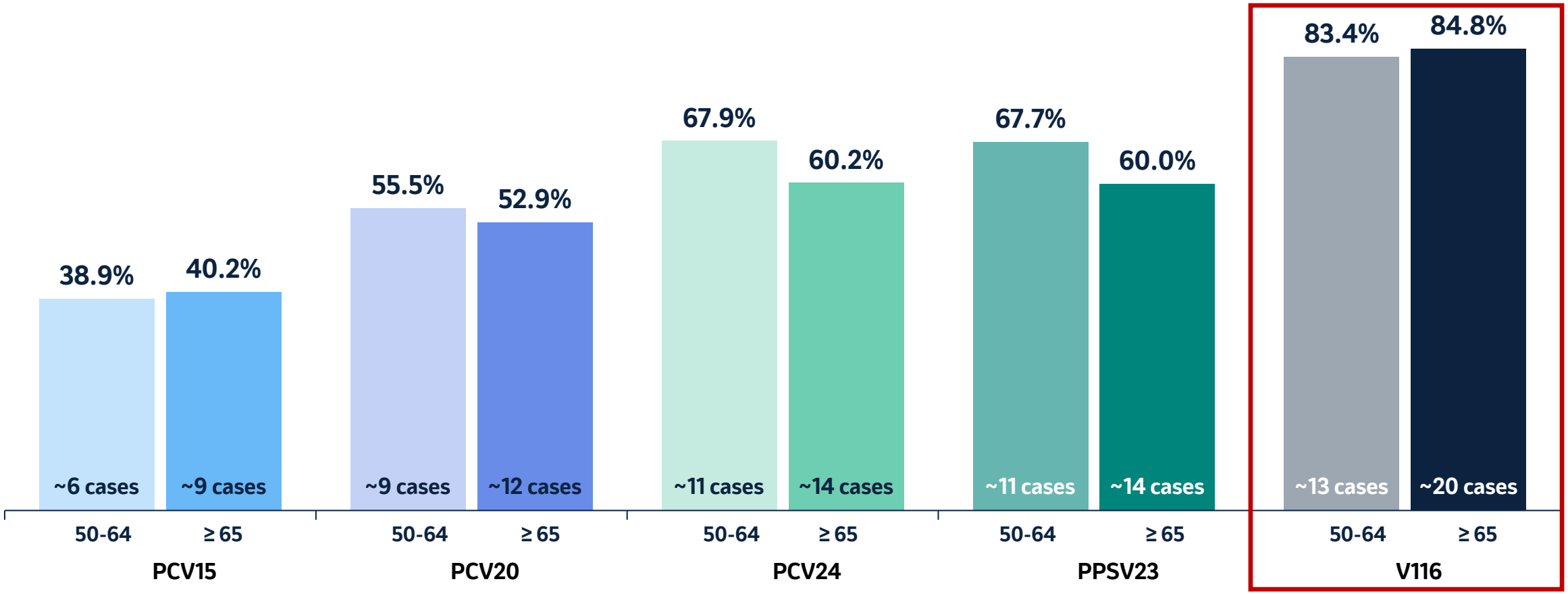
In adults 50–64 and ≥65 years of age, serotypes in V116 are responsible for the majority of residual IPD in adults

IPD coverage (% of serotypes and cases per 100,000) in US Adults 50–64 and ≥65 years of age, 2019



Source: US Centers for Disease Control and Prevention, IPD serotype data 2019, as compiled from data provided through Active Bacterial Core surveillance (ABC).

V116 Phase 3 Clinical Development Program

V116 Clinical Development Program focused on enrolling participants at risk for pneumococcal disease

V116-P004 **Clinical Lot Consistency** **(n=2040)**	**V116-P003** **Pivotal** **(n=2600)**	**V116-P005** **Concomitant Flu** **(n=1000)**	**V116-P006** **Vaccine Experienced** **(n=700)**
18 – 49 years old	**≥ 18 years old**	**≥ 50 years old**	

V116-007 **High Risk (HIV)** **(n=300)**	**V116-008** **At-Risk Adults** **(n=900)**	**V116-013** **Pediatric with Increased Risk** **(n=820)**
≥ 18 years old	**18 – 64 years old**	**≥ 2 - <18 years old**

4 Studies in the V116 BLA submission represent a broad, diverse patient population

V116-P004 Clinical Lot Consistency (n=2040)	V116-P003 Pivotal (n=2600)	V116-P005 Concomitant Flu (n=1000)	V116-P006 Vaccine Experienced (n=700)
18 – 49 years old	≥ 18 years old	≥ 50 years old	

Immunogenicity & Safety Endpoints in the V116 Program

Immunogenicity Endpoints

OPA responses supported primary objectives:

- Serotype specific OPA Geometric Mean Titers (GMTs)
- Proportion of participants with ≥4-fold rise in OPA responses from baseline to Day 30 postvaccination

OPA and IgG responses supported secondary objectives:

- Serotype specific IgG Geometric Mean Concentrations (GMCs)
- Proportion of participants with ≥4-fold rise in IgG responses from baseline to Day 30 postvaccination
- Geometric Mean Fold Rise (GMFR) of OPA and IgG responses
- Reverse Cumulative Distribution Curves (RCDCs) for OPA and IgG responses

Immune responses were assessed in validated multiplex opsonophagocytic (OPA) and electrochemiluminescence (ECL IgG) assays

Safety Endpoints

Primary Safety Endpoints:

- Solicited injection site events Day 1-5 postvaccination: erythema, swelling, injection-site pain
- Solicited systemic events Days 1-5 postvaccination: headache, myalgia, fatigue
- Serious vaccine-related events Day 1 through the duration of participation in the study

Additional Safety Endpoints:

- Unsolicited AEs, Vaccine related AEs, Any SAE
- Maximum temperature Day 1-5 postvaccination

Participants reported adverse events on an electronic vaccine report card.

V116-003

A Phase 3, Randomized, Double-blind, Active Comparator-controlled Clinical Study to Evaluate the Safety, Tolerability, and Immunogenicity of V116 in Pneumococcal Vaccine-naïve Adults

V116-003 Study Design

Cohort 1 (≥50 years of age)
N=2362 Participants
randomized 1:1,V116 to PCV20

(Stratified by age: 50-64, 65-74, 75-84, ≥85)

Cohort 2 (18-49 years of age)
N=301 Participants
randomized 2:1,V116 to PCV20

1	2	3	4	5
Day 1	Day 5 Day 7	Day 30	Day 90	Month 6

V116 or **PCV20**

Immunogenicity assessment

- **Prevaccination Immunogenicity (Day 1)**
- **Postvaccination Immunogenicity (Day 30)**

Safety assessment

- **eVRC, solicited AEs**
- **Serious and nonserious AEs**
- **Serious AEs**

V116-003: Primary study objectives

Primary immunogenicity

In adults ≥50 years:

- Demonstrate that V116 is **noninferior** to PCV20 for 10 common serotypes
  - Lower bound of the 2-sided 95% CI of the OPA GMT ratio (V116/PCV20) to be **>0.5**
- Demonstrate that V116 is **superior** to PCV20 for 11 unique serotypes
  - Lower bound of the 2-sided 95% CI of the OPA GMT ratio (V116/PCV20) to be **>2.0**
  - 2-sided 95% CI of the differences (V116 – PCV20) between the proportions of participants with a ≥4-fold rise to be **>10%**

In adults 18–49 years:

- Demonstrate V116 **immunobridges** to adults 50-64 years of age for 21 serotypes in V116
  - Lower bound of the 2-sided 95% CI of the OPA GMT ratio (V116 18-49/V116 50–64 years) to be **>0.5**

Primary safety

- To evaluate the safety and tolerability of V116 as assessed by the proportion of participants with adverse events (AEs)
  - **Solicited injection site** events Day 1–5 postvaccination: erythema, swelling, injection-site pain
  - **Solicited systemic events** Days 1–5 postvaccination: headache, myalgia, fatigue
  - **Serious vaccine-related events** Day 1 through the duration of participation in the study

V116-003 Baseline Characteristics

In each cohort, baseline characteristics were balanced between the treatment groups

	Cohort 1 (Age ≥50 years)		Cohort 2 (Ages 18-49 years)	
	V116, N=1179	PCV20, N=1177	V116, N=200	PCV20, N=100
Sex				
Female	687 (58.3)	670 (56.9)	137 (68.5)	64 (64.0)
Age (yr)				
Median (min to max)	65 (50-91)	65 (50-97)	36 (18-49)	34 (18-49)
18-49, n (%)	0 (0)	0 (0)	200 (100)	100 (100)
50 to 64, n (%)	589 (50.0)	587 (49.9)	0 (0)	0 (0)
65 to 74, n (%)	464 (39.4)	464 (39.4)	0 (0)	0 (0)
75-84, n (%)	112 (9.5)	113 (9.6)	0 (0)	0 (0)
≥ 85, n (%)	14 (1.2)	13 (1.1)	0 (0)	0 (0)
Race				
Asian	148 (12.6)	168 (14.3)	38 (19.0)	15 (15.0)
Black or African American	116 (9.8)	115 (9.8)	13 (6.5)	14 (14.0)
Multiple	26 (2.2)	30 (2.5)	9 (4.5)	6 (6.0)
White	867 (73.5)	844 (71.7)	139 (69.5)	62 (62.0)
Other	21 (1.8)	19 (1.6)	1 (0.5)	3 (3.0)
Ethnicity				
Hispanic or Latino	259 (22.0)	242 (20.6)	58 (29.0)	24 (24.0)
Pneumococcal Risk Factors				
1 Risk Factor	347 (29.4)	328 (27.9)	45 (22.5)	18 (18.0)
2 or More Risk Factors	100 (8.5)	81 (6.9)	3 (1.5)	1 (1.0)

Risk Factors includes prespecified medical history conditions: Alcoholism, Chronic Heart Disease, Chronic Kidney Disease, Chronic Liver Disease, Chronic Lung Disease, Diabetes, Smoking.

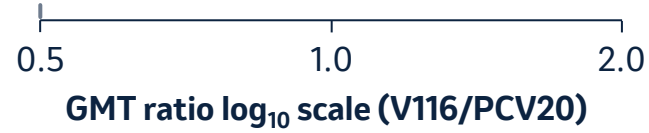
V116-003 Cohort 1: ≥50 years of age
V116 is noninferior to PCV20 for the 10 common serotypes

Primary immunogenicity objective

- V116 is noninferior to PCV20 for the 10 common serotypes.
- The lower bounds of the two-sided 95% confidence intervals (CIs) are greater than 0.5 for all 10 common serotypes.

Postvaccination OPA GMT Ratios for **Common Serotypes**

Pneumococcal serotype	V116 n	V116 GMT	PCV20 n	PCV20 GMT	GMT ratio (95% CI)
3	1154	274.0	1161	176.7	1.55 (1.40, 1.72)
6A	1148	2,302.0	1153	2,972.5	0.77 (0.68, 0.88)
7F	1152	3,637.4	1158	3,429.9	1.06 (0.95, 1.18)
8	1155	2,501.3	1158	1,811.1	1.38 (1.25, 1.53)
10A	1161	3,893.4	1159	4,678.0	0.83 (0.75, 0.93)
11A	1145	3,232.6	1150	2,092.8	1.54 (1.39, 1.72)
12F	1160	2,641.2	1161	2,499.6	1.06 (0.92, 1.21)
19A	1159	2,136.1	1162	2,817.8	0.76 (0.69, 0.84)
22F	1147	3,874.5	1154	4,770.1	0.81 (0.72, 0.92)
33F	1154	13,558.9	1157	11,742.1	1.15 (1.01, 1.32)



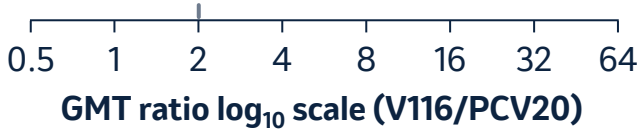
V116-003 Cohort 1: ≥50 years of age
V116 is superior to PCV20 for 10 of 11 unique serotypes

Primary immunogenicity objective

- V116 is superior to PCV20 for 10 of 11 unique serotypes in V116.
- The lower bounds of the two-sided 95% CIs are >2.0 for 10 of 11 unique serotypes in V116.
- For serotype 15C, the lower bound of the 95% CI is 1.77.

Postvaccination OPA GMT Ratios for **Unique Serotypes**

Pneumococcal serotype	V116 n	V116 GMT	PCV20 n	PCV20 GMT	GMT ratio (95% CI)
9N	1147	7,470.7	1150	1,640.4	4.55 (4.12, 5.04)
15A	1107	5,237.2	1102	1,589.0	3.30 (2.91, 3.74)
15C	1153	4,216.2	1158	2,072.3	2.03 (1.77, 2.34)
16F	1151	4,868.2	1153	846.3	5.75 (5.16, 6.41)
17F	1148	7,764.9	1156	460.4	16.86 (14.90, 19.09)
20A	1161	6,099.2	1155	631.1	9.66 (8.66, 10.79)
23A	1132	3,737.2	1104	461.5	8.10 (6.86, 9.55)
23B	1160	1,082.5	1160	107.3	10.09 (8.48, 12.00)
24F	1153	2,728.6	1130	70.5	38.71 (33.87, 44.25)
31	1153	3,132.5	1154	144.4	21.69 (18.68, 25.18)
35B	1153	8,527.8	1159	1,383.0	6.17 (5.59, 6.80)

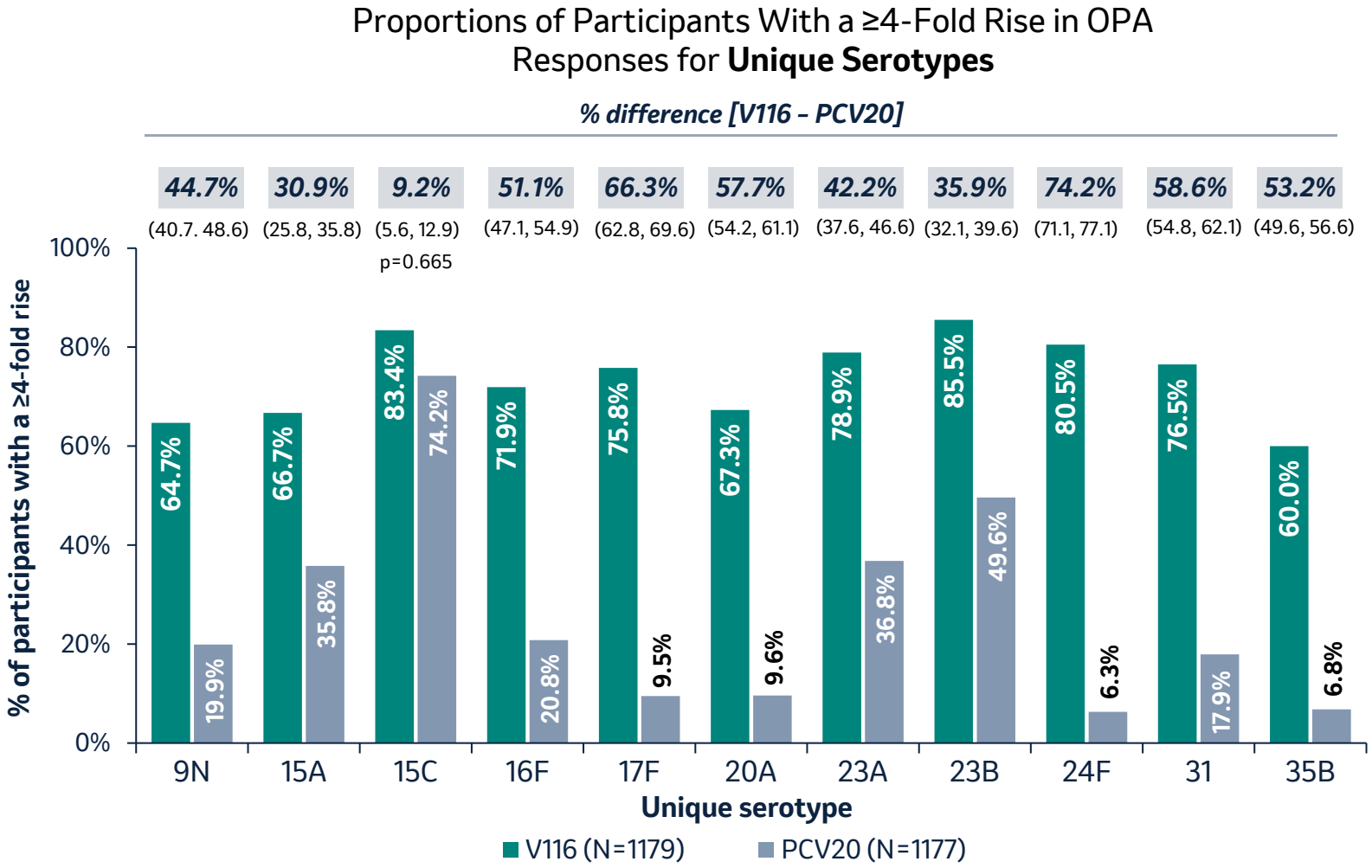


Superiority criteria met if the lower bound of the 95% CI is >2.0

V116-003 Cohort 1: ≥50 years of age
V116 is superior to PCV20 for 10 of 11 unique serotypes

Primary immunogenicity objective

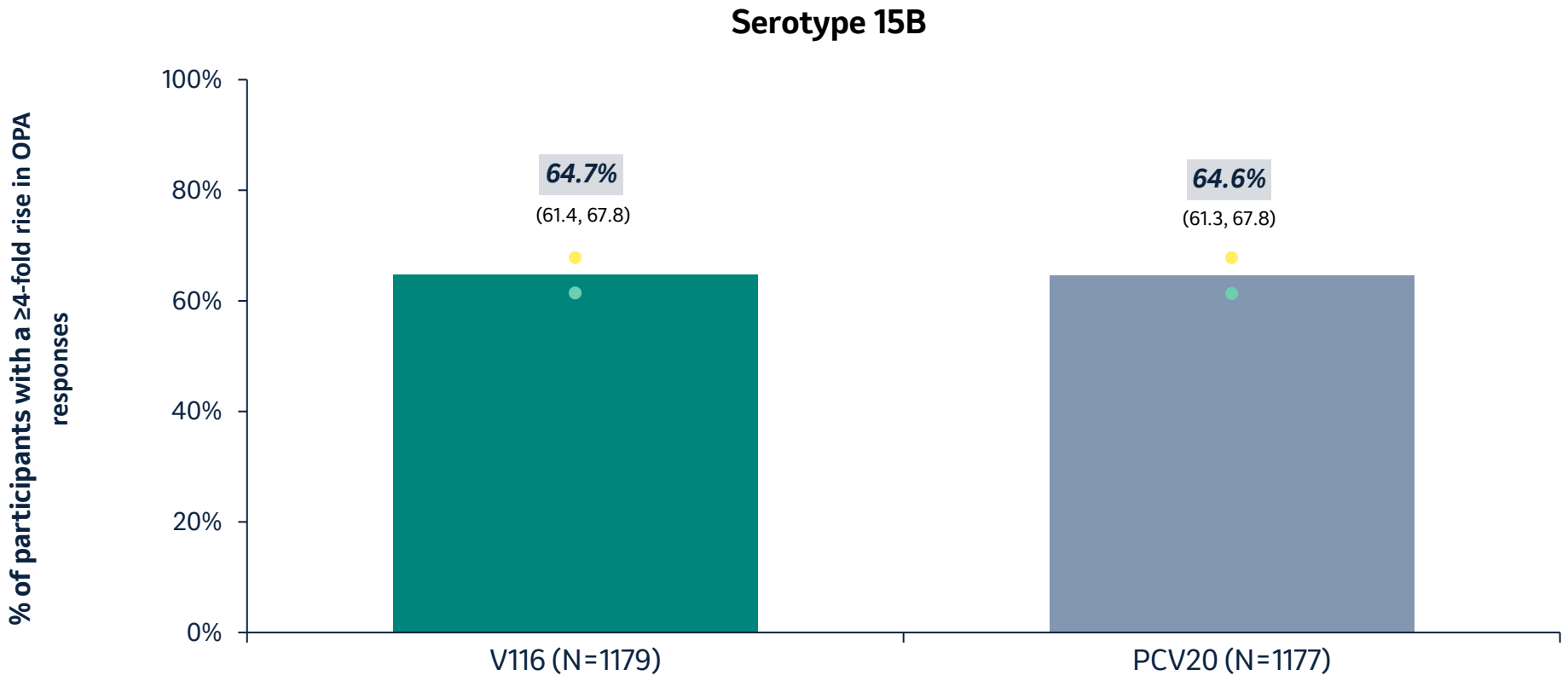
- V116 is superior to PCV20 for 10 of 11 unique serotypes in V116.
- The lower bounds of the 2-sided 95% CIs are > 10 percentage points for 10 of 11 serotypes.



Pivotal Study

V116-003 Cohort 1: ≥50 years of age

V116 elicits robust cross reactive antibody responses to serotype 15B



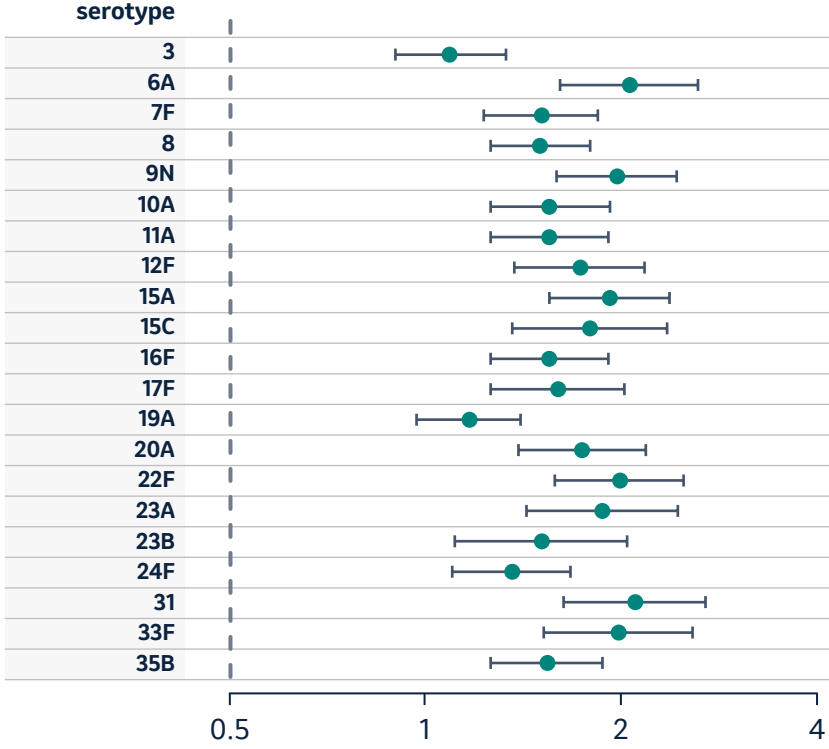
V116 includes serotype 15C and elicited cross-reactive immune responses to 15B

PCV20 includes serotype 15B

V116-003: Cohort 2: 18-49 years of age
V116 immunobridges to participants 50-64 years of age for all 21 serotypes

Primary immunogenicity objective

- V116 in participants 18 to 49 years of age immunobridges to V116 in participants 50 to 64 years of age for the 21 serotypes in V116.
- The lower bound of the two-sided 95% CIs is >0.5 for all 21 serotypes in V116.



Pneumococcal serotype	V116 18-49 years (N = 200) n	V116 18-49 years (N = 200) GMT	V116 50-64 years (N = 589) n	V116 50-64 years (N = 589) GMT	GMT ratio[a] (V116 18-49 years/ V116 50-64 years) (95% CI)
3	194	308.6	572	282.7	1.09 (0.90, 1.33)
6A	196	5,289.6	569	2,572.9	2.06 (1.61, 2.62)
7F	198	6,447.2	571	4,278.8	1.51 (1.23, 1.84)
8	197	4,516.0	571	3,004.7	1.50 (1.26, 1.79)
9N	197	17,283.2	570	8,791.4	1.97 (1.59, 2.43)
10A	197	6,808.1	575	4,382.6	1.55 (1.26, 1.92)
11A	196	5,871.6	564	3,785.8	1.55 (1.26, 1.91)
12F	196	6,150.4	574	3,561.2	1.73 (1.37, 2.17)
15A	184	11,319.2	550	5,901.2	1.92 (1.55, 2.37)
15C	195	10,194.0	570	5,708.0	1.79 (1.36, 2.35)
16F	193	8,877.0	571	5,720.0	1.55 (1.26, 1.91)
17F	194	16,070.6	568	10,068.0	1.60 (1.26, 2.02)
19A	198	2,773.2	574	2,374.6	1.17 (0.97, 1.40)
20A	197	13,150.0	575	7,562.7	1.74 (1.39, 2.18)
22F	198	9,299.6	568	4,683.6	1.99 (1.58, 2.49)
23A	192	8,848.7	561	4,739.5	1.87 (1.43, 2.44)
23B	198	2,140.1	575	1,420.9	1.51 (1.11, 2.04)
24F	197	4,137.6	570	3,047.2	1.36 (1.10, 1.67)
31	195	8,005.6	570	3,820.7	2.10 (1.63, 2.69)
33F	197	34,805.5	570	17,607.4	1.98 (1.52, 2.57)
35B	198	13,933.4	573	9,053.9	1.54 (1.26, 1.87)

GMT ratio $\log_{10}$ scale (V116 18-49/V116 50-64)

V116-006

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

Vaccine-experienced

V116-006 Study Design

	Visit	1	2	3	4	5
	Time	Day 1 Screening/vaccination	Day 7	Day 30	Day 90	Day 180
Cohort 1 : Prior PPSV23 only N=300; Randomized 2:1 (V116:PCV15)		V116 or PCV15				
Cohort 2 : Prior PCV13 only N=300; Randomized 2:1 (V116:PPSV23)		V116 or PPSV23				
Cohort 3 : Prior PCV15, PCV20, PCV13+PPSV23, PCV15+PPSV23 or PPSV23+PCV13 N=100; Open-label V116		V116				
Immunogenicity assessment		Prevaccination Immunogenicity (Day 1)		Postvaccination Immunogenicity (Day 30)		
Safety assessment		eVRC, solicited AEs; Serious and nonserious AEs		Serious AEs		

Participants used an electronic Vaccine Report Card (eVRC) to report solicited AEs Days 1-5 postvaccination and other AEs through Day 30 postvaccination

V116-006 Primary study objectives

Primary immunogenicity

In adults ≥50 years:

To evaluate the serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) at 30 days postvaccination for all serotypes included in V116

Primary safety

- To evaluate the safety and tolerability of V116 as assessed by the proportion of participants with adverse events (AEs)
  - **Solicited injection site** events Day 1–5 postvaccination: erythema, swelling, injection-site pain
  - **Solicited systemic events** Days 1–5 postvaccination: headache, myalgia, fatigue
  - **Serious vaccine-related events** Day 1 through the duration of participation in the study

Vaccine-experienced

V116-006 Participant Characteristics

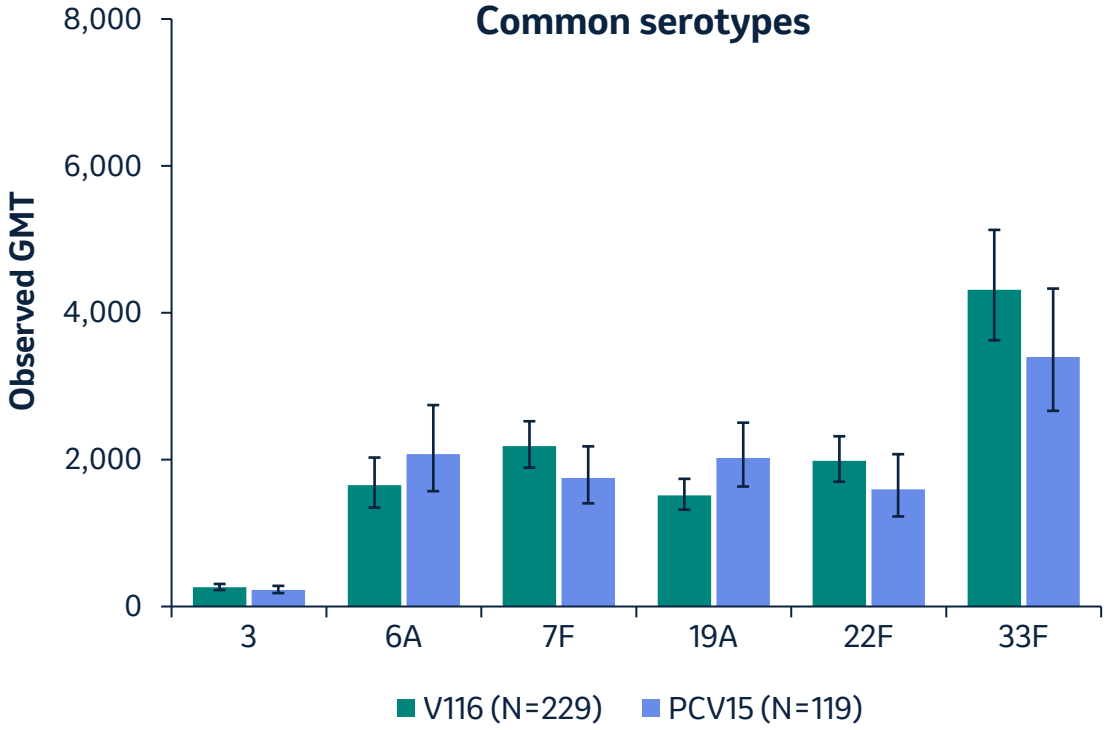
Enrollment is balanced in each cohort and reflects the pneumococcal vaccination history

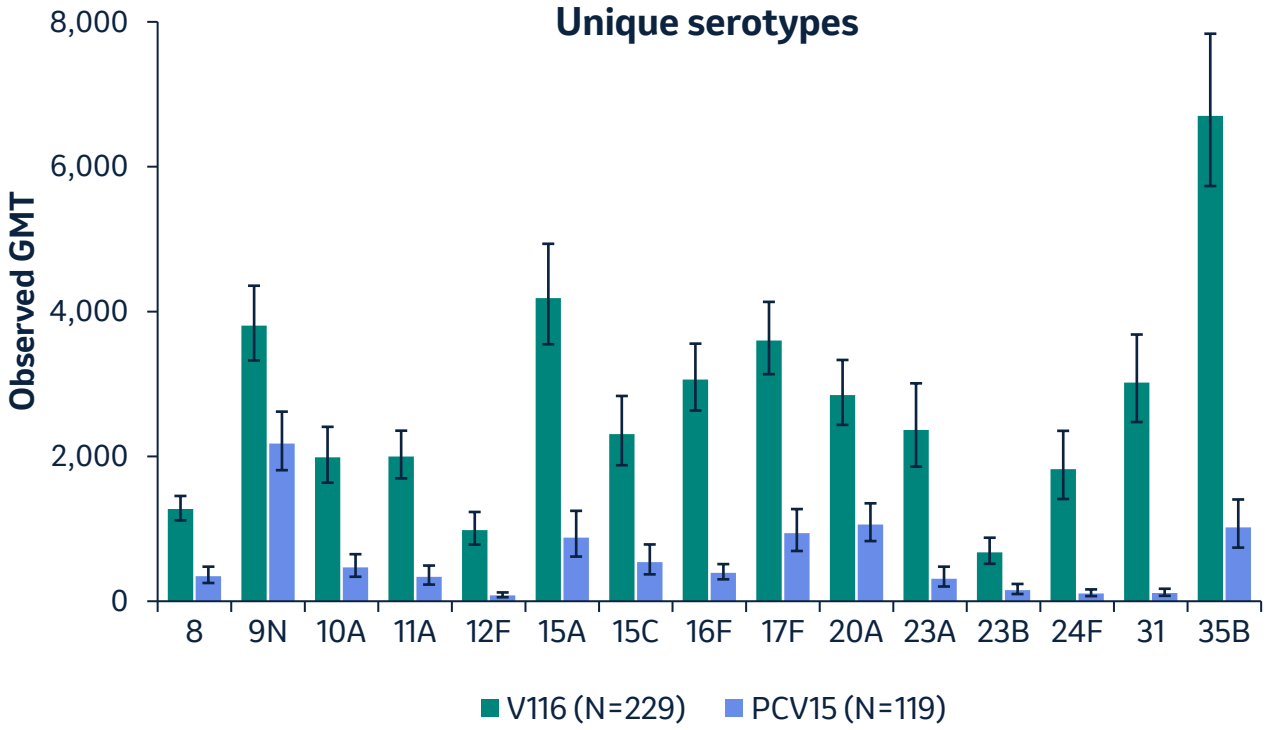
	Cohort 1 (prior PPSV23)		Cohort 2 (prior PCV13)		Cohort 3
	V116 N=229	PCV15 N=119	V116 N=174	PPSV23 N=85	V116 N=105
Sex					
Male	112 (48.9)	59 (49.6)	74 (42.5)	36 (42.4)	50 (47.6)
Female	117 (51.1)	60 (50.4)	100 (57.5)	49 (57.6)	55 (52.4)
Age (yr)					
50 to 64	48 (21.0)	25 (21.0)	80 (46.0)	39 (45.9)	17 (16.2)
≥65	181 (79.0)	94 (79.0)	94 (54.0)	46 (54.1)	88 (83.8)
Mean ± SD	68.7 ± 7.5	69.0 ± 7.1	65.5 ± 7.8	65.4 ± 6.6	71.0 ± 7.6
Median (range)	69.0 (50 to 86)	69.0 (51 to 88)	66.0 (50 to 83)	65.0 (51 to 81)	71.0 (53 to 91)
Race					
Asian	96 (41.9)	47 (39.5)	55 (31.6)	25 (29.4)	13 (12.4)
Black or African American	6 (2.6)	3 (2.5)	3 (1.7)	1 (1.2)	6 (5.7)
Multiple	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
White	125 (54.6)	69 (58.0)	116 (66.7)	59 (69.4)	85 (81.0)
Ethnicity					
Hispanic or Latino	21 (9.2)	17 (14.3)	34 (19.5)	16 (18.8)	14 (13.3)
Time since last pneumococcal vaccination					
1 to 4 years	108 (47.2)	54 (45.4)	135 (77.6)	66 (77.6)	78 (74.3)
5 to 9 years	85 (37.1)	45 (37.8)	33 (19.0)	18 (21.2)	27 (25.7)
≥10 years	36 (15.7)	20 (16.8)	6 (3.4)	1 (1.2)	0 (0.0)

Vaccine-experienced

V116-006 Cohort 1: ≥50 years of age who previously received PPSV23

V116 elicits comparable immune responses to PCV15; higher immune responses for serotypes unique to V116

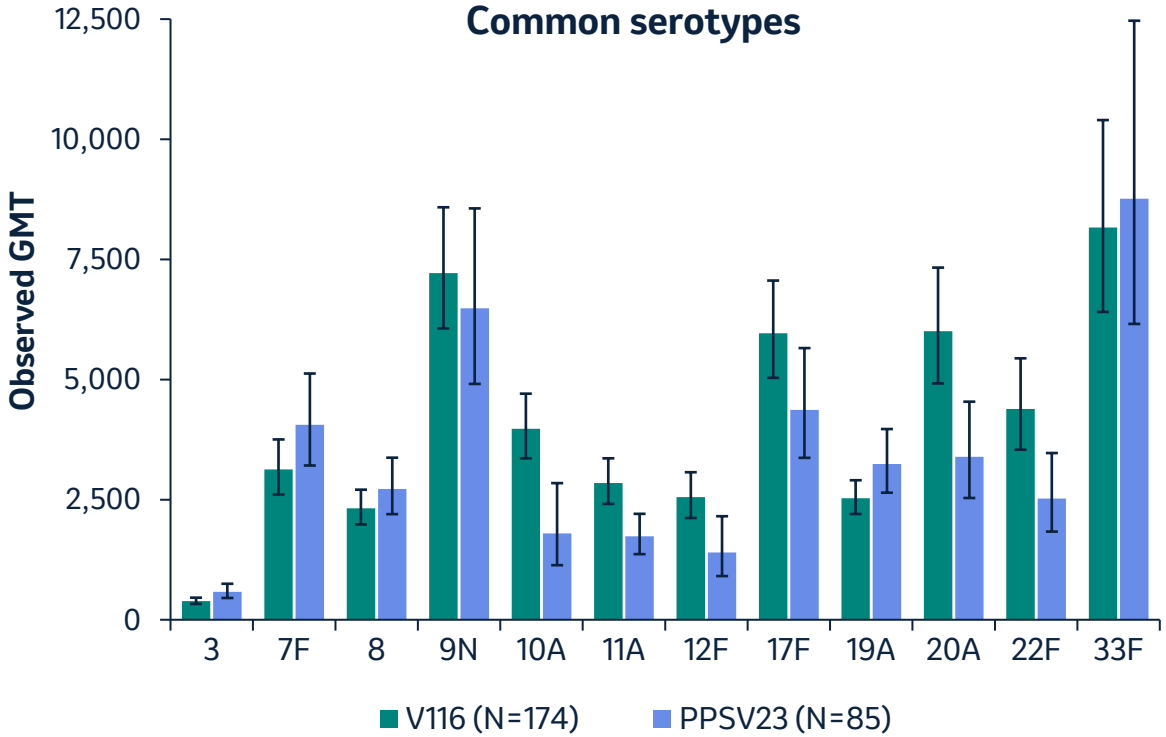


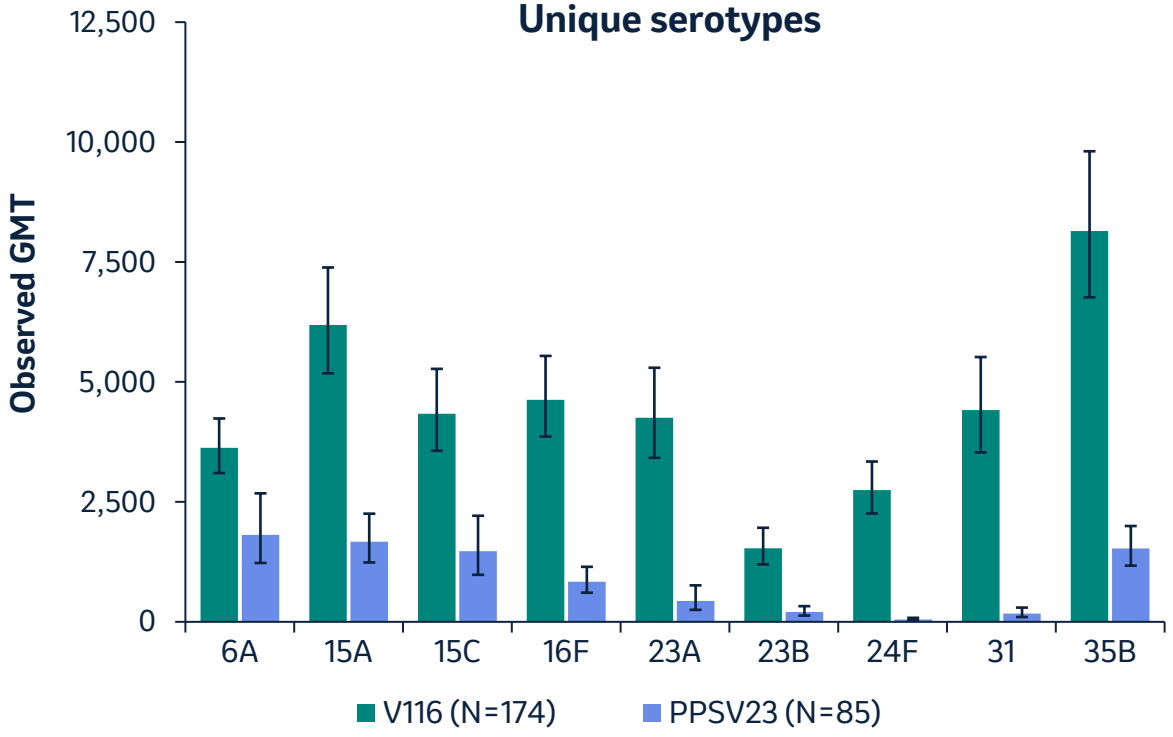


Vaccine-experienced

V116-006 Cohort 2: ≥50 years of age who previously received PCV13

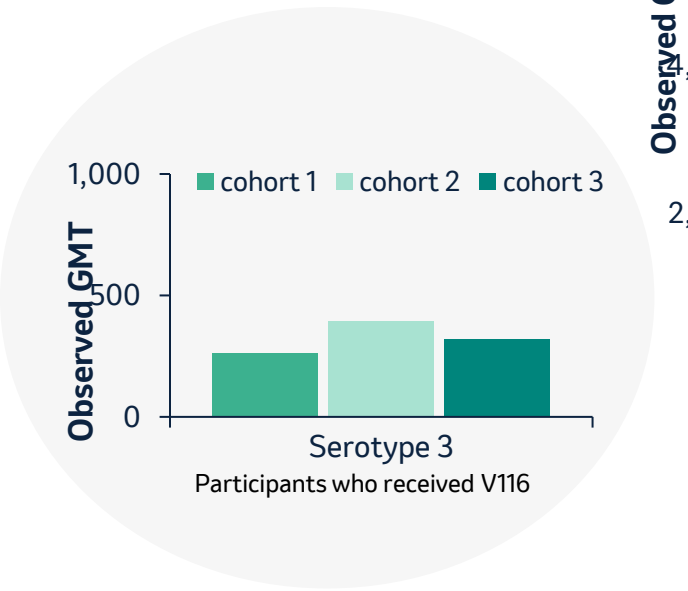
V116 elicits comparable immune responses to PPSV23; higher immune responses for serotypes unique to V116

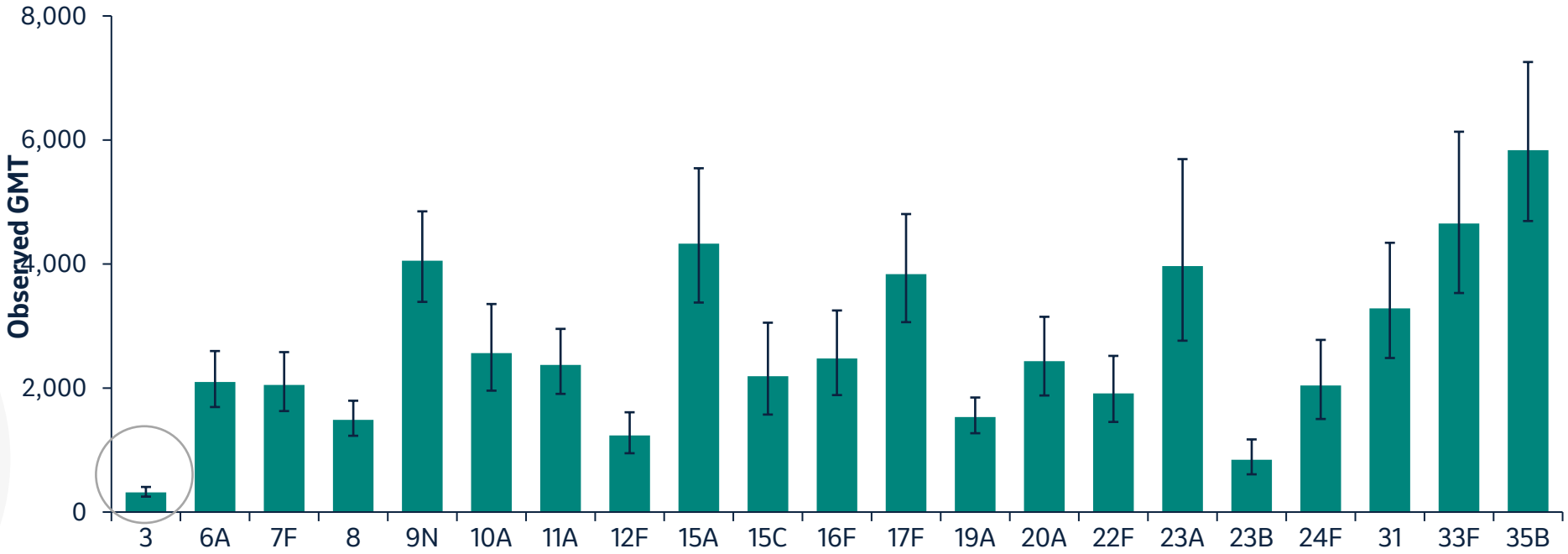




V116-006 Cohort 3: ≥50 years of age who previously received other pneumococcal vaccine(s)*

V116 is immunogenic in individuals who previously received a pneumococcal vaccine





*Prior PCV13+PPSV23 [n=45], PCV15+PPSV23 [n=5], PPSV23+PCV13 [n=54], PCV15 [n=1], or PCV20 [n=0]

Integrated Summary of Safety

Integrated Analysis of Safety in the
Phase 3 Clinical Development Program

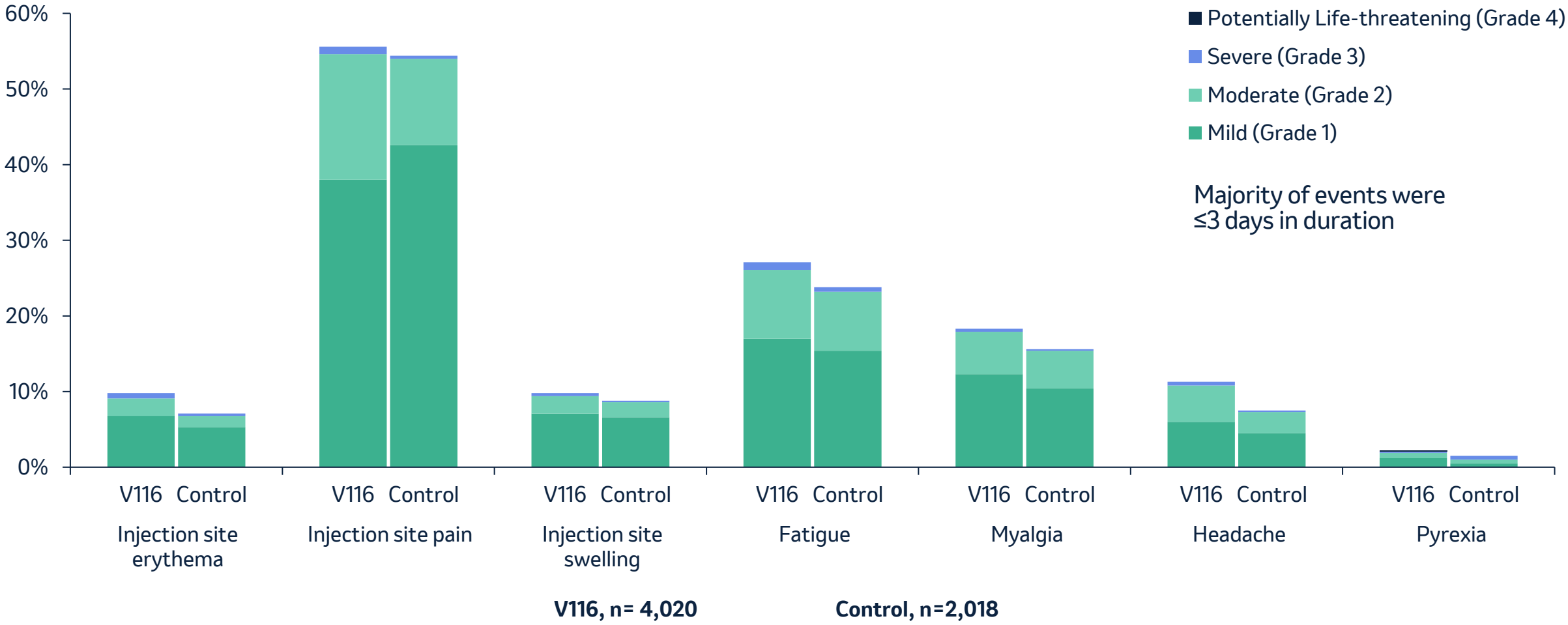
V116 is well tolerated in adults ≥ 18 years of age with a safety profile comparable to currently licensed pneumococcal vaccines

Adverse Event Summary (V116-003, V116-004, V116-005[a], V116-006)	V116 (N=4,020)		Control [b] (N=2,018)	
	n	(%)	n	(%)
With adverse events (Day 1 – 30)	2695	(67.0)	1386	(68.7)
With vaccine-related adverse events (Day 1-30)[c]	2555	(63.3)	1297	(64.3)
Solicited	2516	(62.6)	1279	(63.4)
Unsolicited	313	(7.8)	123	(6.1)
with SAEs (Day 1 - Day 30)	14	(0.3)	7	(0.3)
with vaccine-related SAEs (Day 1 - Day 30)	2	(0.0)	0	(0.0)
with SAEs within 30 minutes postvaccination	1	(0.0)	0	(0.0)
Who died[d]	6	(0.1)	3	(0.1)
with vaccine-related deaths[c]	0	(0.0)	0	(0.0)

[a] Only participants from V116-005 vaccinated with V116 in the sequential group are included in the V116 group.
[b] Control group includes participants vaccinated with PCV15, PCV20, or PPSV23
[c] As determined by the investigator; all injection site adverse events are assessed as vaccine-related
[d] 6 deaths in the V116 group in the Integrated Safety Summary; 7 deaths in the V116 group across the Phase 3 studies when the concomitant group from P005 is included.

Frequency and intensity of solicited adverse events were comparable in V116 and control groups

Solicited adverse events by intensity (%)



Solicited events include erythema, injection site pain, injection site swelling, fatigue, headache, and myalgia were solicited from Day 1 through Day 5 postvaccination. Pyrexia was defined as temperature ≥ 100.4 °F (38.0 C) solicited from Day 1 through Day 5 postvaccination.

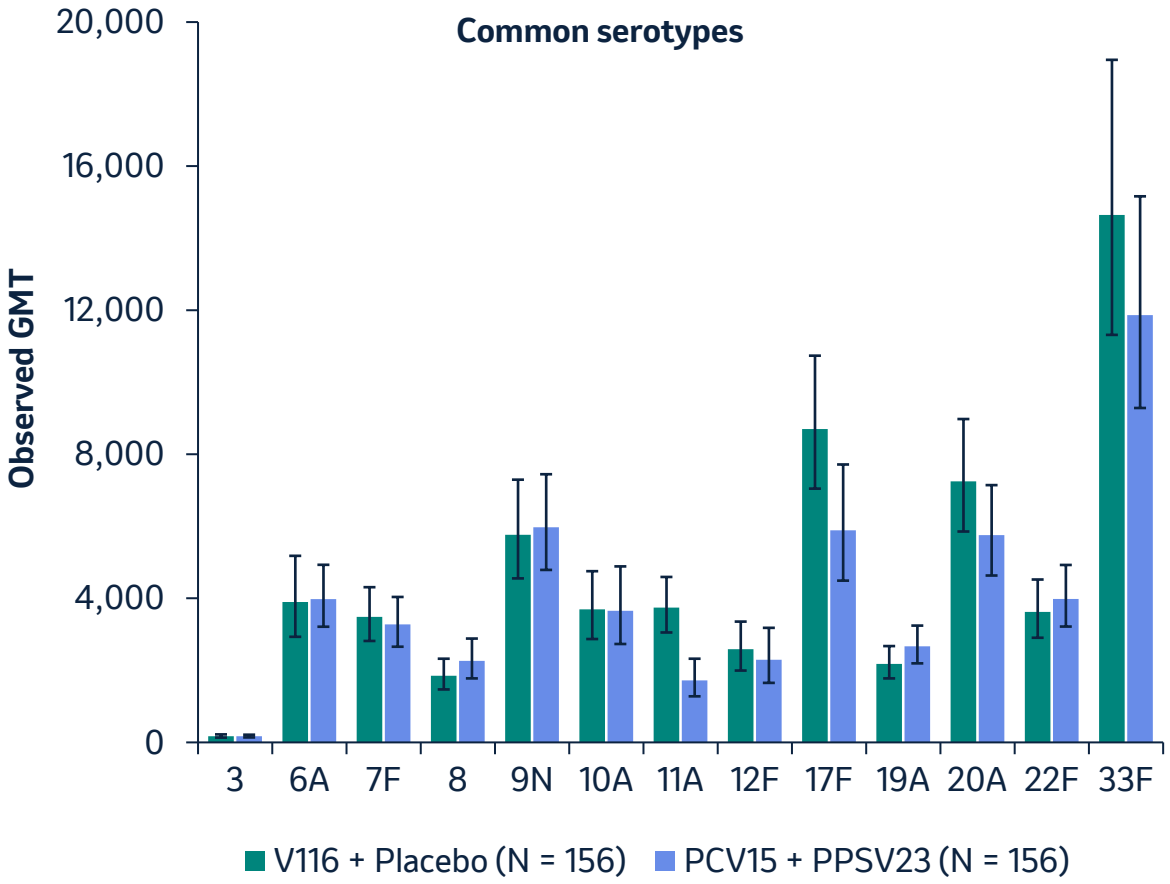
Phase 3 Supportive Studies

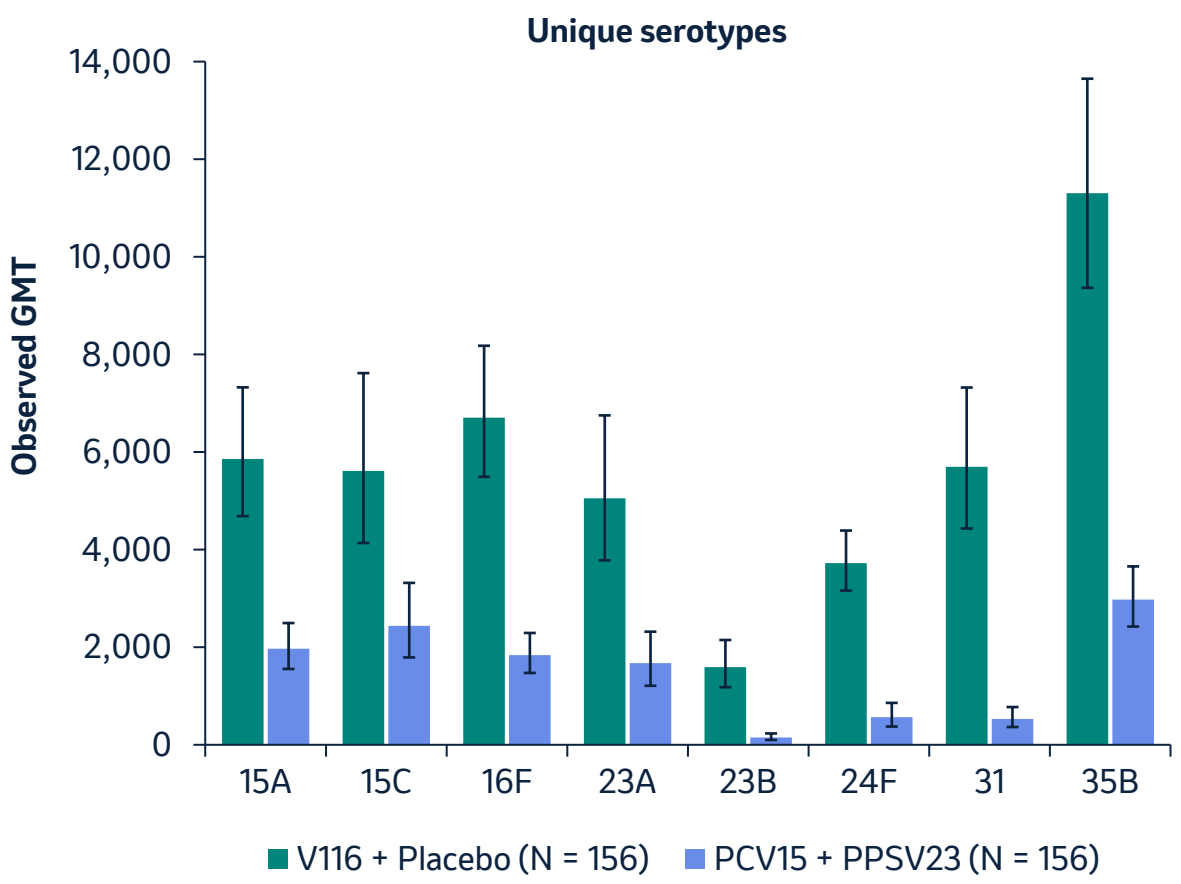
V116-007: V116 in Adults Living with HIV

V116-005: V116 with Concomitant Quadrivalent Influenza Vaccine (QIV)

V116-004: V116 Lot Consistency

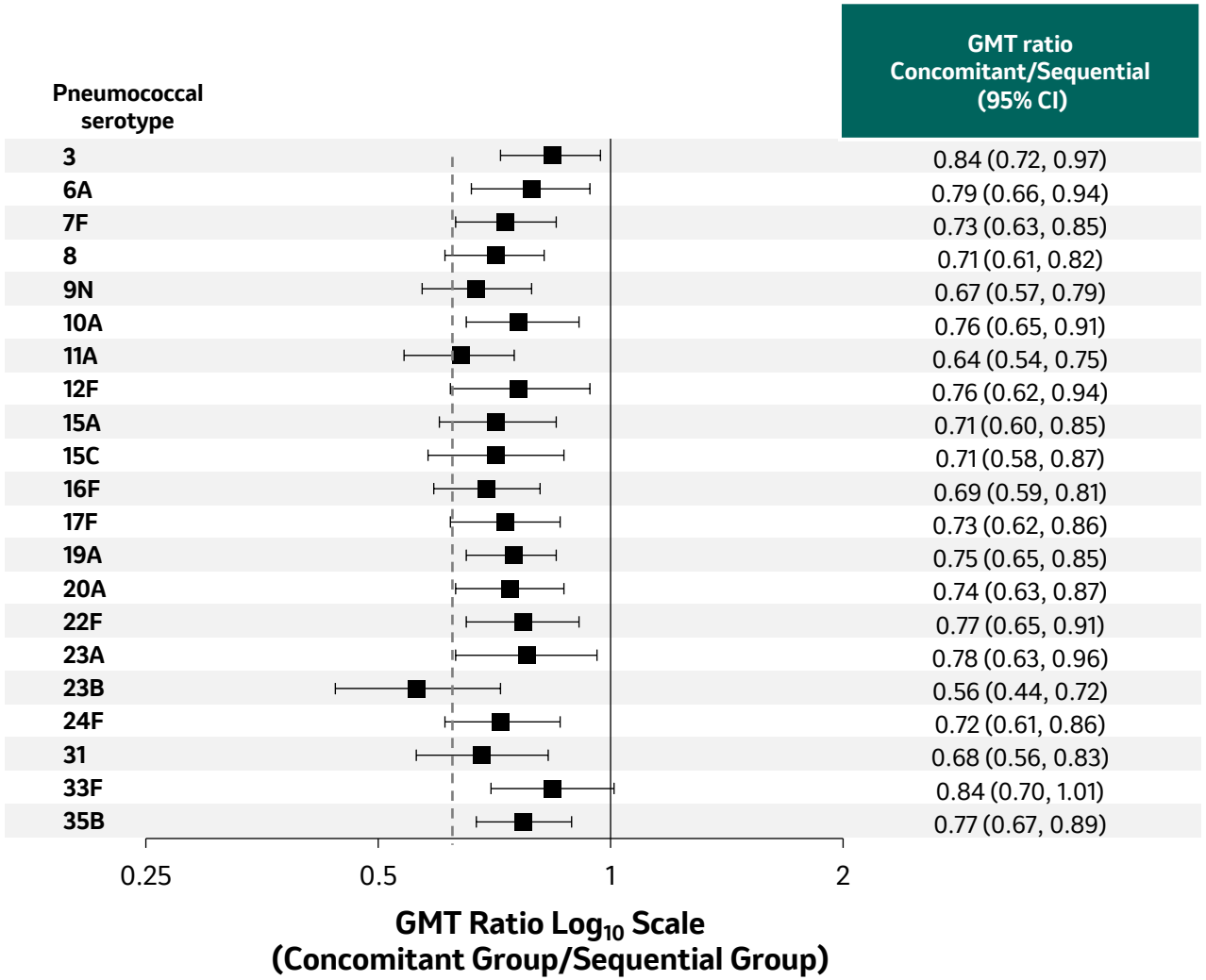
V116-007: In adults living with HIV, V116 elicits comparable immune responses to PCV15+PPSV23, & higher immune responses for unique serotypes



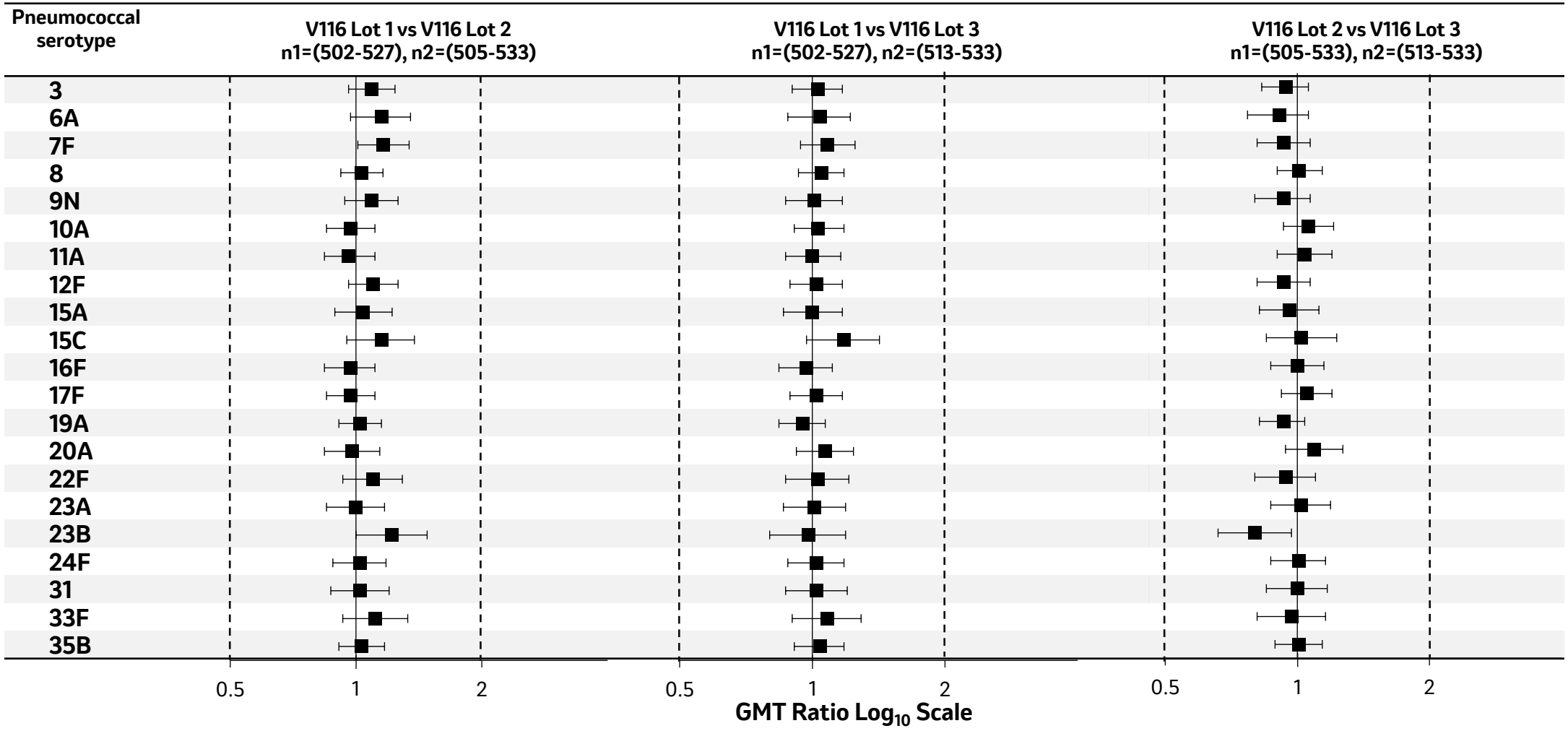


V116-005: V116 elicits robust immune responses when administered concomitantly with influenza vaccine

- V116 administered concomitantly with influenza vaccine is noninferior to V116 administered sequentially with influenza vaccine for 20 of 21 serotypes
- QIV administered concomitantly is noninferior to QIV administered sequentially for 3 of 4 strains



V116-004: V116 Immune responses were equivalent across 3 manufacturing lots



Note: dashed lines indicate the margins for the equivalence test

Phase 3 Summary & Conclusions

V116 Phase 3 Clinical Development Summary

In adults ≥18 years of age, who are pneumococcal vaccine-naïve and vaccine experienced, with and without risk conditions:

- V116 elicits **robust immune responses** to all 21 serotypes contained in the vaccine
- V116 is **noninferior to PCV20** for all common serotypes and **superior to PCV20** for 10 of 11 serotypes unique to V116 in pneumococcal vaccine-naïve adults ≥50 years of age.
- V116 is immunogenic in pneumococcal **vaccine experienced adults**, regardless of the prior vaccine received
- V116 is immunogenic when administered concomitantly with inactivated **influenza vaccine**.
- V116 is **well-tolerated** with a safety profile generally comparable to currently licensed pneumococcal vaccines.

V116 is the first adult specific PCV with the potential for broad public health impact through the prevention of invasive disease and pneumonia due to *S. pneumoniae*.

Thank you

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Post-licensure safety surveillance of 20-valent pneumococcal conjugate vaccine (PCV20) among U.S. adults in the Vaccine Adverse Event Reporting System (VAERS)

Advisory Committee on Immunization Practices (ACIP)
February 29, 2024

Pedro L. Moro, MD, MPH
Immunization Safety Office
Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention (CDC)

Disclaimer

- The findings and conclusions in this presentation are those of the author and do not necessarily represent the official position of the CDC
- The use of product trade names is for identification purposes only

Topics

- Background on pre-licensure safety of 20-valent pneumococcal conjugate vaccine (PCV20)
- Adverse events following PCV20 reported to the Vaccine Adverse Event Reporting System (VAERS)
- Adverse events of special interest: Guillain-Barré Syndrome (GBS)
- Summary

Background: Pre-licensure clinical trials PCV20

- Pre-licensure clinical trial data of PCV20 in adults has been reassuring
  - Six randomized controlled trials in adults aged ≥ 18 years, which included more than 6,000 participants[1,2]
  - Most common adverse reactions were injection site pain, muscle pain, fatigue, headache, and joint pain[2,3]
  - Serious adverse events (SAEs) balanced among vaccinees and controls[2]
  - No SAEs or deaths considered to be related to study vaccines[3]
  - No cases of Guillain-Barré Syndrome (GBS) identified in prelicensure studies[2,3]

[1] Pfizer's Adult and Pediatric Clinical Trial Programs for 20-Valent Pneumococcal Conjugate Vaccine Presented at IDWeek 2020. October 21, 2020.

[2] Kobayashi M, Farrar JL, Gierke R, et al. Use of 15-Valent Pneumococcal Conjugate Vaccine and 20-Valent Pneumococcal Conjugate Vaccine Among U.S. Adults: Updated Recommendations of the Advisory Committee on Immunization Practices — United States, 2022. MMWR Morb Mortal Wkly Rep 2022;71:109–117. DOI: http://dx.doi.org/10.15585/mmwr.mm7104a1

[3] Prevnar20 vaccine insert https://www.fda.gov/vaccines-blood-biologics/vaccines/prevnar-20

Introduction

- June 8, 2021 – PCV20 approved for adults aged ≥ 18 years by the FDA
- October 20, 2021 – ACIP recommendation
  - PCV20 for adults aged ≥65
  - PCV20 for adults aged 19–64 years with underlying medical conditions

FDA: Food and Drug Administration
ACIP: Advisory Committee on Immunization Practices

Objectives

- Describe the safety profile of reports submitted to the Vaccine Adverse Event Reporting System (VAERS) following PCV20 in
  - Adults aged ≥65 years
  - Adults aged 19–64 years

VAERS

Strengths

- National data
- Accepts reports from anyone
- Rapidly detects safety signals
- Can detect rare adverse events
- Data available to public

Limitations

- Reporting bias
- Inconsistent data quality and completeness
- Lack of unvaccinated comparison group or denominator
- Generally cannot assess causality

- VAERS accepts all reports from all reporters without making judgments on causality or judging clinical seriousness of the event
- As a hypothesis generating system, VAERS identifies potential vaccine safety concerns that can be studied in more robust data systems

Methods – 1: PCV20

- Searched VAERS database for U.S. PCV20 reports during:
  - October 21, 2021 through December 31, 2023 for adults aged ≥ 19 years (19–64 years and ≥ 65 years)
- Signs and symptoms of AEs coded using Medical Dictionary for Regulatory Activities (MedDRA)[1] Preferred Terms (PTs)
  - PTs are not mutually exclusive
  - A single report may be assigned more than one PT
- Review of serious[2] reports and medical records; categorized main diagnosis in a MedDRA system organ class
- Case definitions for AESIs: Guillain-Barré Syndrome[3]

[1] https://www.meddra.org/ ; [2] Based on the Code of Federal Regulations 21 CFR 600.80 ; [3]Sejvar JJ, et al. Brighton Collaboration GBS Working Group. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2011 Jan 10;29(3):599-612. doi: 10.1016/j.vaccine.2010.06.003. Epub 2010 Jun 18. PMID: 20600491

Methods – 2: PCV20

- Reporting rates
  - Use of doses distributed of PCV20 in the United States during 2022 and 2023 (20,579,720 doses)
- Empirical Bayesian data mining (FDA)*
  - Used to detect disproportional reporting for the entire post marketing period for each product
  - Identifies adverse events reported more frequently than expected after vaccine of interest compared with other vaccines in the VAERS database
  - Analysis by age groups and serious reports.**

*The presence of disproportionality may not suggest a safety signal. Conversely, the absence of disproportionality does not confirm the absence of a safety signal nor negate a signal detected by other methods.

**A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that meets any of the following criteria: 1. Results in death; 2. Is life-threatening; 3. Requires inpatient hospitalization or prolongation of existing hospitalization; 4. Results in persistent or significant disability/incapacity; 5. Is a congenital anomaly/birth defect. [FDA regulatory definition; U.S. Code of Federal Regulations, 21 CFR 600.80. Postmarketing reporting of adverse experiences (2014). Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=600.80]

PCV20 reports to VAERS, October 2021–December 2023

	19 – 64 years	≥ 65 years	≥ 19 years	All[2]
Characteristics[1]	N (%)	N (%)	N (%)	N (%)
Total reports	798	1,178	1,976	2,393
Female	582 (72.9)	846 (71.8)	1,428 (72.3)	1,598 (66.7)
Male	212 (26.6)	330 (28.0)	542 (27.4)	680 (28.4)
Unknown sex	4 (0.5)	1 (0.1)	5 (0.3)	115 (4.8)
Serious reports[3]	49 (6.1)	70 (5.9)	119 (6)	149 (6.2)
Deaths	2 (0.3)	9 (0.8)	11 (0.6)	20 (0.8)
Median age [IQR] in years	54 [45,60]	69 [66,75]		65 [56,70]
Median onset interval [IQR] in days	1 [0,2]	1 [0,2]	1 [0,2]	1 [0,1]
Received PCV20 alone	438 (54.9)	711 (60.4)	1,149 (58.1)	1,412 (59.0)

[1] U.S. primary reports (foreign reports excluded) ; [2]Includes reports in adults aged ≥19 years and 176 reports in persons aged 0-18 years and 241 reports of unknown age

[3] Based on the Code of Federal Regulations if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization or permanent disability

Most common signs and symptoms[1] in reports to VAERS following PCV20 in adults aged 19–64 years, October 2021–December 2023

PCV20 Non-serious (N=749)	N (%)
Injection site reaction	227 (30)
Pain	129 (17)
Erythema	117 (16)
Fever	103 (14)
Pain in extremity	90 (12)
Peripheral swelling	77 (10)
Headache	59 (8)
Skin warm	59 (8)
Fatigue	56 (7)
Arthralgia	52 (7)

PCV20 Serious (N=49)	N (%)
Fever	14 (29)
Dyspnea	12 (25)
Condition aggravated	10 (20)
Cough	10 (20)
Pain	10 (20)
Nausea	9 (18)
Pain in extremity	8 (16)
Dizziness	7 (14)
Fatigue	7 (14)
Headache	7 (14)

[1] Coded using the MedDRA Preferred Terms; more than one MedDRA Preferred Term may be assigned to a single report (i.e., not mutually exclusive)

Most common signs and symptoms[1] in reports to VAERS following PCV20 in adults aged ≥65 years, October 2021–December 2023

PCV20 non-serious (N=1,108)	N (%)
Injection site reaction	417 (35)
Pain	180 (15)
Pain in extremity	162 (14)
Erythema	158 (13)
Fever	135 (12)
Peripheral swelling	103 (9)
Rash	99 (8)
Fatigue	96 (8)
Headache	88 (7)
Pruritus	78 (7)

PCV20 Serious (N=70)	N (%)
Pain	14 (20)
Asthenia	13 (19)
Gait disturbance	11 (16)
Guillain Barre Syndrome	11 (16)
Dyspnea	8 (11)
Fatigue	8 (11)
Fever	8 (11)
Chest pain	7 (10)
Death	7 (10)
Dysphagia	7 (10)

[1] Coded using the MedDRA Preferred Terms; more than one MedDRA Preferred Term may be assigned to a single report (i.e., not mutually exclusive)

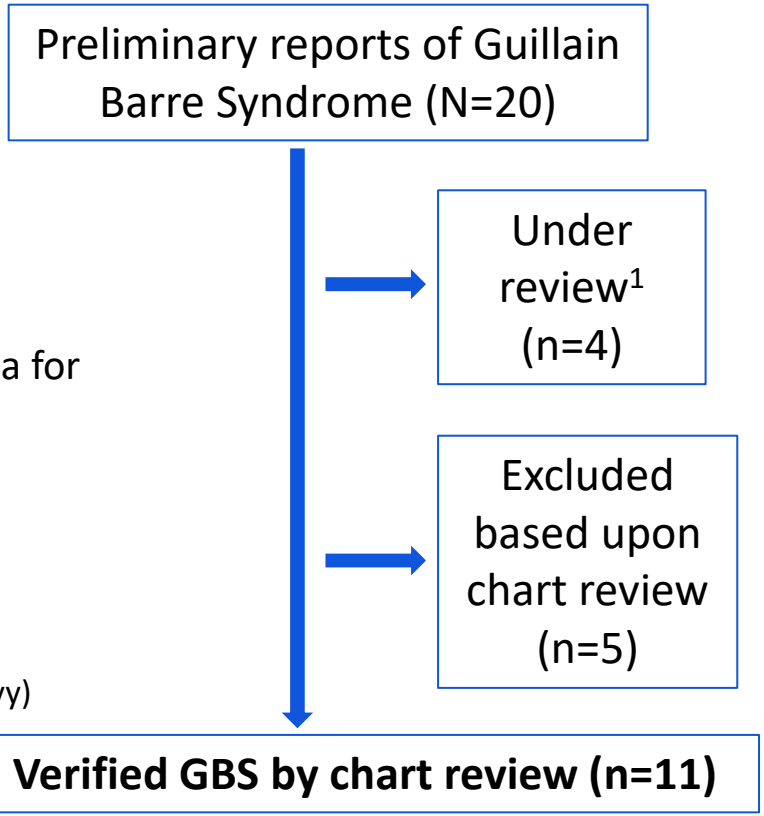
Empirical Bayesian data mining (as of January 26, 2024)

- Disproportional reporting observed for:
  - PT for “Guillain-Barré Syndrome” when limited to serious reports (EB05=3.6)[1]
    - When not limited to serious reports EB05=1.87

[1] EB05 = Empirical Bayesian data mining threshold for statistical alert; alert considered if EB05 >2.0

Reports to VAERS of Guillain Barre Syndrome after PCV20 vaccination among adults aged ≥19 years (as of December 31, 2023)

- 11 verified reports of Guillain Barré Syndrome[2]
  - Median age (range), years: 66 years (46-79 years)[3]
  - Median time to onset (range), days: 14 days (0-23)
  - 4 males, 7 females
  - All verified reports met Brighton Collaboration criteria for GBS:
    - 2 were Brighton level 1, 6 were level 2 and 3 were level 3
  - Other vaccines during same visit (5 of 11):
    - Two RZV (Shingrix)
    - One Fluad quadrivalent
    - One bivalent mRNA COVID-19 (Pfizer), HD-IIV4, RSV (Arexvy)
    - One Tdap (Boostrix)



[1] Awaiting medical records

[2] One patient had a norovirus infection 1-2 days before neurological symptoms

[3] No GBS reports in persons aged <19 years

Reporting rate for GBS after PCV20, 2022–2023

- Reporting rate: 0.5 cases per million doses distributed or 0.9 cases per 100,000 person-years (background rate 1.72 cases per 100,000 persons-years) [1]

[1]Gubernot D, et al. U.S. Population-Based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines. Vaccine. 2021;39:3666–3677.

Summary

- VAERS received 1,976 reports after PCV20 in adults during October 2021–December 2023
  - 798 in adults aged 19–64 years; 93.9% non-serious
  - 1,178 in adults aged ≥65 years; 94.1% non-serious

- Most commonly reported adverse events were injection site (e.g. injection site erythema) and systemic reactions (e.g. fever, headache); consistent with findings from pre-licensure studies

Summary (continued)

- Disproportionate reporting for Guillain-Barré Syndrome (GBS) identified in VAERS after PCV20 vaccine (11 verified GBS cases in adults)
- Potential safety signals detected in VAERS need to be evaluated in more robust population-based active systems such as the Vaccine Safety Datalink (VSD) or Center for Medicaid Services (CMS)
- Separate studies currently in progress in the VSD (CDC) and CMS (FDA) to assess PCV20 vaccine safety
- CDC and FDA will continue to closely monitor the safety of PCV20

Acknowledgements

- CDC Immunization Safety Office
  - VAERS Team
  - Clinical Immunization Safety Assessment (CISA) Project
- Food and Drug Administration
  - Office of Biostatistics and Pharmacovigilance, Center for Biologics Evaluation and Research
- Butantan Institute, Sao Paulo, Brazil

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

Photo credit: James Gathany (https://phil.cdc.gov/Details.aspx?pid=8876)

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.

FDA CBER:
Safety Assessment of 20-valent Pneumococcal Conjugate Vaccine (PCV20)

ACIP February 2024

Richard Forshee, PhD
Office of Biostatistics and Pharmacovigilance
Center for Biologics Evaluation and Research
US Food and Drug Administration

Disclaimer

- The BEST Initiative and its studies are funded by the U.S. Food and Drug Administration (FDA)
- There are no potentially conflicting relationships to disclose
- The findings and conclusions in this presentation are those of the authors and do not necessarily represent the official position of FDA, the Centers for Medicare & Medicaid Services, or Acumen, LLC

Is there an elevated risk for the listed health outcomes* following PCV20 vaccination?

- Acute Myocardial Infarction
- Myocarditis/Pericarditis
- Anaphylaxis
- Atrial Fibrillation
- Bell's Palsy
- Cardiomyopathy; Heart Failure
- Cellulitis and Infection
- Cholecystitis or Cholelithiasis
- Guillain-Barré syndrome
- Immune Thrombocytopenia
- Thrombocytopenia
- Transient Ischemic Attack

* The list of health outcomes were identified via literature review

Near Real-Time Monitoring: Medicare Fee-for-Service (FFS) Population (Age ≥ 65 years)

Design	Concurrent Comparator Cohort Design[1] for Near Real-Time Sequential Analysis Self-controlled case series planned to verify detected signals
Data Sources	Centers for Medicare & Medicaid Services (CMS) – Shared Systems Data (SSD)
Study Population	Medicare FFS beneficiaries (age ≥ 65 years) receiving one dose of PCV 15 or PCV 20 on or after the licensing date for the product - Two product populations analyzed separately
Study Period	Licensing date (PCV 15 = July 16, 2021 and PCV 20 = July 1, 2021) through the end of each calendar month (most recent update through November 30, 2023)
Health Outcomes	The 12 pre-specified health outcomes identified by claims algorithms and monitored within the follow-up window for each vaccinated beneficiary

1. Klein, N.P., et al., Surveillance for Adverse Events After COVID-19 mRNA Vaccination. JAMA, 2021. 326(14): p. 1390-1399.

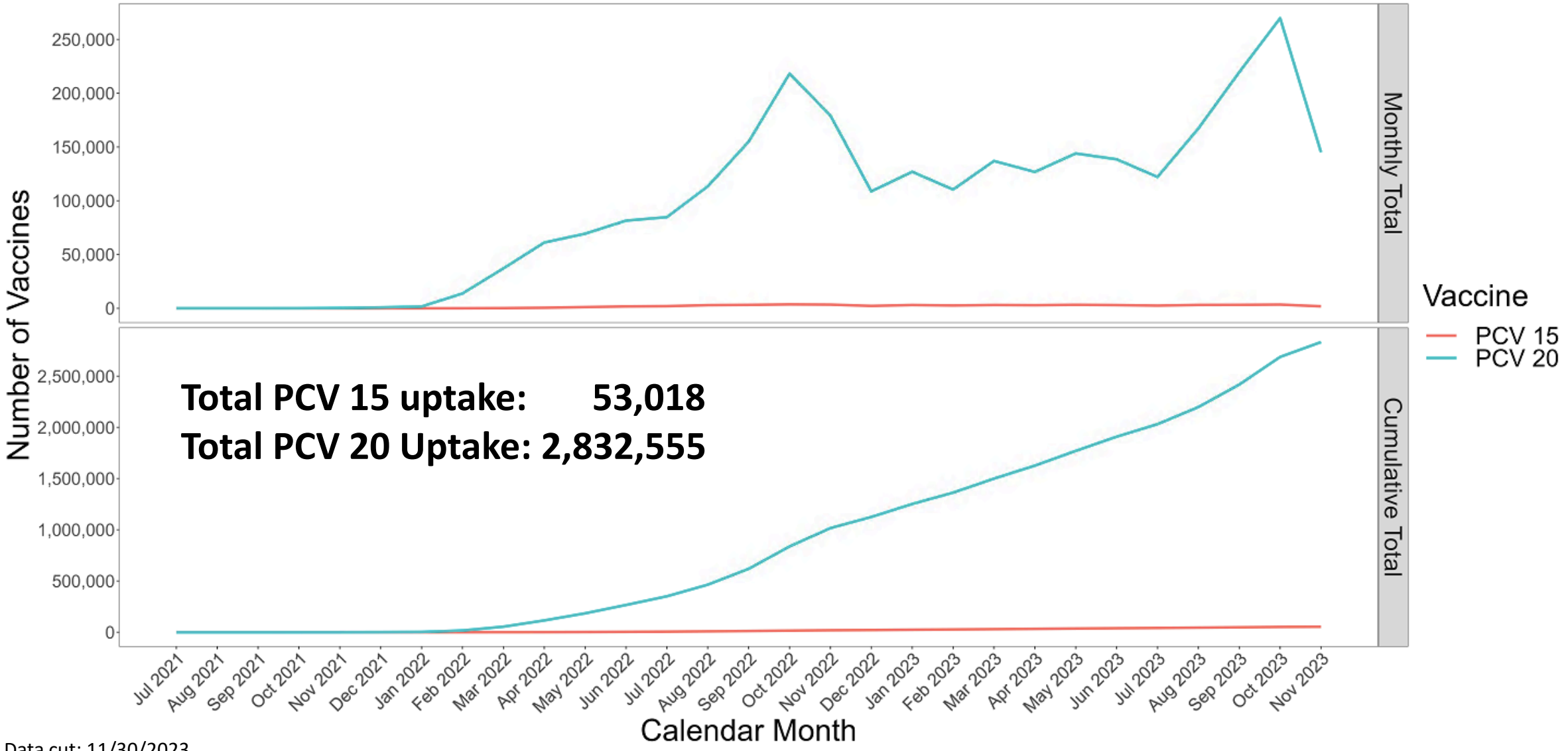
Near Real-Time Monitoring: Medicare Fee-for-Service (FFS) Population (Age ≥ 65 years)

Statistical Analyses	• Descriptive and Sequential analyses were performed monthly
	
	• Bayesian Poisson Regression was used to estimate the posterior distribution of incidence rate ratio (IRR) between pre-specified post-vaccination risk and comparison windows for each outcome
	  • Age, Sex, Immunocompromised Conditions*, Concomitant Influenza Vaccination**, and Months Post-Surveillance Start Date were included as adjustment covariates
	  • Adjustment for claims delay was made
	
	• Safety signal was assessed by evaluating if:
	  • The 95% Credible Interval (CI) exceeds 1 – Weak Signal
	  • The 98% Credible Interval (CI) exceeds 1 – Strong Signal

* Immunocompromised conditions was identified using administrative codes indicating presence of immunocompromising conditions or use of immunosuppressive therapies[2]
** Concomitant influenza vaccination is defined as seasonal influenza vaccination events that happened on or within 42 days prior to PCV 20 vaccination date

2. Greenberg JA, et al., Validation of a Method to Identify Immunocompromised Patients with Severe Sepsis in Administrative Databases. Ann Am Thorac Soc. 2016;13(2):253-258.

Uptake of PCV15 or PCV20 Vaccines in the Medicare FFS 65+ years Population; Monthly (top) and Cumulative (bottom) Counts*



* Data cut: 11/30/2023

Descriptive Characteristics of PCV 20 Vaccinees (N = 2,832,555)

Beneficiary Characteristics	Number of Vaccinees	% of Vaccinees
Race/Ethnicity		
Asian	70,416	2.49%
Black	155,878	5.50%
Hispanic	41,611	1.47%
Alaska Native/American Indian	6,964	0.25%
White	2,410,290	85.09%
Other	57,163	2.02%
Missing/Unknown	90,233	3.19%
Age (years)		
65-69	1,242,140	43.85%
70-74	599,077	21.15%
75-79	461,978	16.31%
80-84	291,753	10.30%
85-89	154,499	5.45%
90-94	64,176	2.27%
95+	18,932	0.67%

Beneficiary Characteristics	Number of Vaccinees	% of Vaccinees
Sex		
Female	1,614,235	56.99%
Male	1,218,320	43.01%
Urban/Rural		
Urban	2,375,807	83.88%
Rural	455,787	16.09%
Missing/Unknown	961	0.03%
Immunocompromised Status		
Yes	144,510	5.10%
No	2,688,045	94.90%
Medicare-Medicaid Dual Eligibility Status**		
Yes	264,266	9.33%
No	2,568,289	90.67%
Concomitant Influenza Vaccination***		
Yes	496,007	17.51%
No	2,336,548	82.49%

* Data cut: 11/30/2023

** Medicare-Medicaid dual eligibility status is defined as ever being dual eligible within the 3 months prior to the vaccination date

*** Concomitant influenza vaccination is defined as seasonal influenza vaccination events that happened on or within 42 days prior to PCV 20 vaccination date

Outcome Count and Incidence Rate (IR) among PCV20 vaccinated population*

Health Outcome	Risk Window** (days)	Comparison Window (days)	Total N (IR***)	Risk Window N (IR****)	Comparison Window N (IR****)
Acute Myocardial Infraction	1-28	29-56	3,274 (970)	1,699 (965)	1,575 (975)
Myocarditis/Pericarditis	1-21	22-42	80 (31)	43 (32)	37 (29)
Anaphylaxis	0-1	3-16	25 (20)	- (26)	- (20)
Atrial Fibrillation	1-42	43-84	17,925 (3,879)	9,709 (3,908)	8,216 (3,845)
Bell's Palsy	1-42	43-84	1,090 (207)	624 (220)	466 (191)
Cardiomyopathy; Heart Failure	1-42	43-84	16,263 (3,503)	8,778 (3,518)	7,485 (3,486)
Cellulitis and Infection	1-7	8-14	3,187 (3,548)	1,660 (3,685)	1,527 (3,410)
Cholecystitis or Cholelithiasis	1-28	29-56	665 (195)	323 (182)	342 (210)
Guillain-Barré Syndrome	1-42	43-84	29 (6)	- (8)	- (4)
Immune Thrombocytopenia	1-42	43-84	49 (10)	30 (11)	19 (8)
Thrombocytopenia	1-28	29-56	3,552 (1,053)	1,787 (1,015)	1,765 (1,093)
Transient Ischemic Attack	1-28	29-56	621 (182)	318 (179)	303 (186)

* Data cut: 11/30/2023, # of PCV 20 total uptake: 2,832,555
** Risk and comparison windows are defined as the number of days post vaccination
*** All IRs expressed as IR per 100,000 person-years
**** For the health outcome that has risk or comparison windows count less than 11, the counts for both windows are masked by "-"

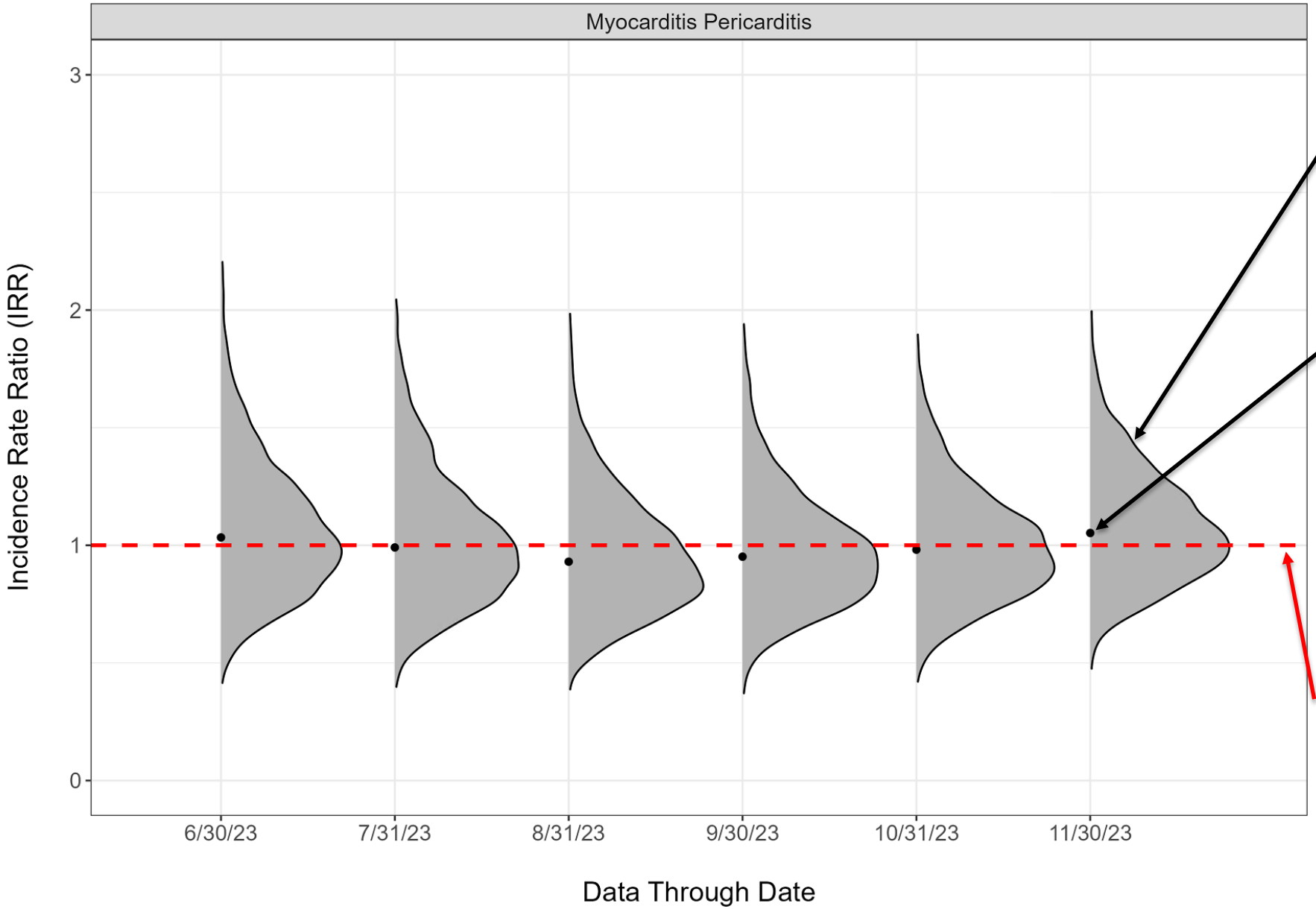
IRR between Risk and Comparison Windows with 95% and 98% CI among PCV20 Vaccinated Population*

Health Outcome	IRR**	95% CI	98% CI
Acute Myocardial Infraction	0.95	(0.89, 1.02)	(0.87, 1.03)
Myocarditis/Pericarditis	1.05	(0.69, 1.64)	(0.64, 1.77)
Anaphylaxis	1.11	(0.31, 3.12)	(0.22, 3.78)
Atrial Fibrillation	0.98	(0.95, 1.01)	(0.95, 1.02)
Bell's Palsy	1.13	(1.00, 1.29)	(0.97, 1.32)
Cardiomyopathy; Heart Failure	0.96	(0.93, 0.99)	(0.92, 1.00)
Cellulitis and Infection	1.06	(0.99, 1.14)	(0.97, 1.15)
Cholecystitis or Cholelithiasis	0.85	(0.73, 1.00)	(0.71, 1.03)
Guillain-Barré Syndrome	2.19	(0.97, 5.42)	(0.82, 6.50)
Immune Thrombocytopenia	1.35	(0.75, 2.50)	(0.67, 2.78)
Thrombocytopenia	0.89	(0.83, 0.95)	(0.82, 0.97)
Transient Ischemic Attack	0.94	(0.80, 1.11)	(0.78, 1.14)

No statistically significant elevated risk was detected

* Data cut: 11/30/2023, # of PCV 20 total uptake: 2,832,555
** IRR = Incidence rate ratio

Estimated Posterior Distributions of IRR from Sequential Analyses at Different Data Cuts – Myocarditis/Pericarditis

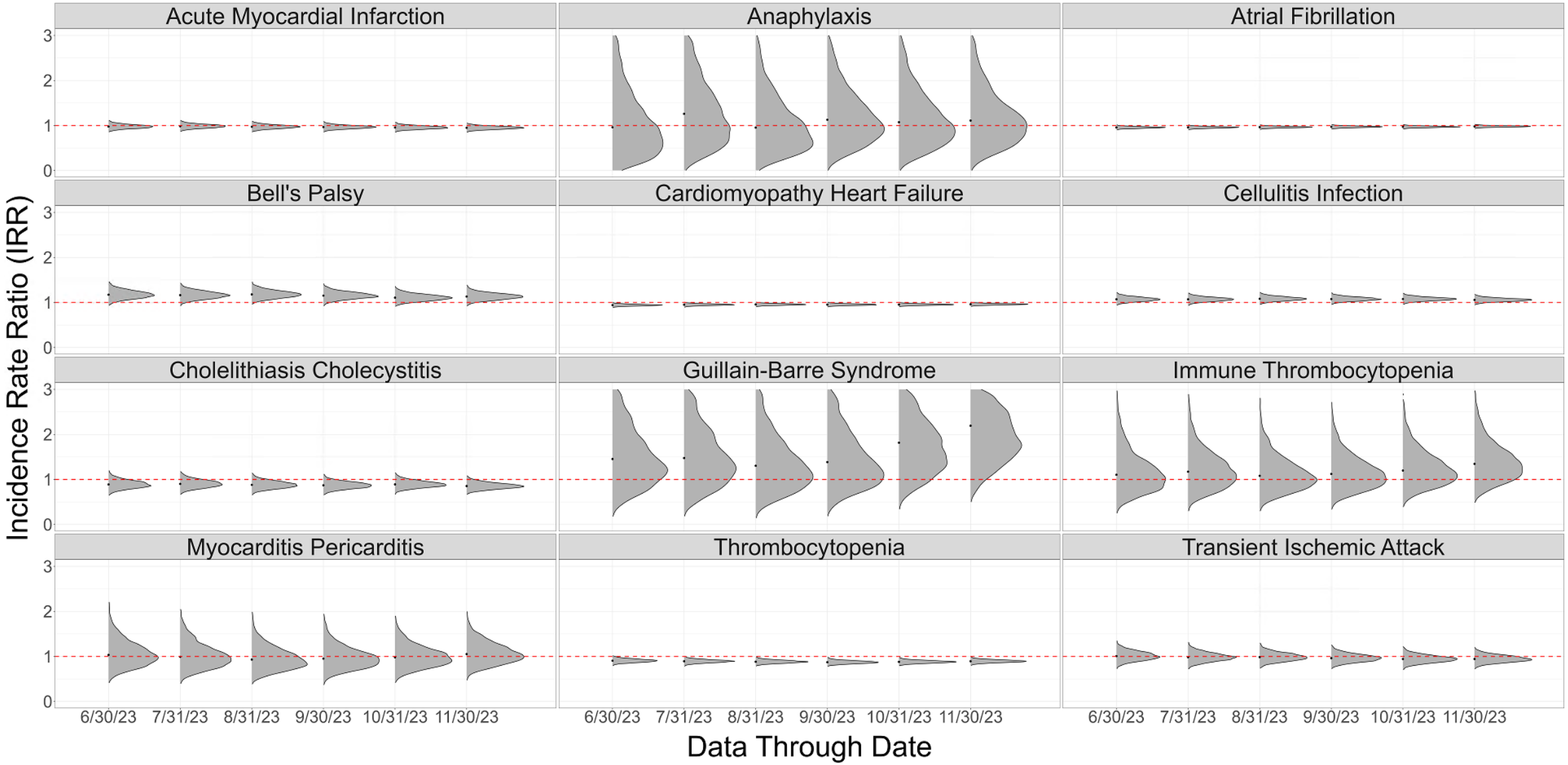


IRR posterior distribution from Bayesian model using data through November 2023

Median of the Posterior Distribution (IRR = 1.05)

IRR = 1, meaning no rate difference in the health outcome between risk and comparison windows

Estimated Posterior Distributions of IRR from Sequential Analyses at Different Data Cuts – All Health Outcomes



Summary

- Incidence rates post PCV 20
  - Incidence rates for Myocarditis/Pericarditis, Anaphylaxis, Guillain-Barré Syndrome and Immune Thrombocytopenia are less than 100 cases per 100,000 person-years

- Signal detection
  - The estimated IRRs and CIs did not identify statistically significant risk elevation following PCV 20 vaccination for any of the outcomes (no significant evidence that IRR > 1)
    - We continue to monitor and evaluate the health outcomes

Note: Summary based on results from data cut: 11/30/2023

Limitations for Sequential Monitoring

- Statistically significant results may appear and disappear from month to month due to use of Bayesian methods.
- Events were not chart-confirmed and the Positive Predictive Value (PPV) for some outcomes are likely low, e.g. The PPV for Bell's Palsy was 12.66% and the PPV for ITP was 4.00% in a recent study.
- Residual confounding may still exist given the limited number of variables being adjusted in the regression model
- Large uncertainty of incidence rate ratios for certain outcomes
  - Small number of events, wide credible intervals

Future Planning

- Active monitoring to continue monthly
- End of surveillance analysis may be performed using the self-controlled case series (SCCS) method for each outcome where there is sufficient sample size for a powered analysis

Summary of Evidence

- No GBS signal in clinical trials
- GBS signal for PCV20 in VAERS
- Currently no GBS signal in Medicare sequential monitoring. Monitoring is ongoing.
- Significant uncertainty because of the small number of cases observed
- Limitations in VAERS and Medicare studies

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National Center for Immunization and Respiratory Diseases

Preliminary Work Group Interpretations of EtR and Next Steps

February 2024, ACIP Meeting

February 29, 2024

Miwako Kobayashi, MD, MPH, FACP, FIDSA

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

EtR Public Health Problem

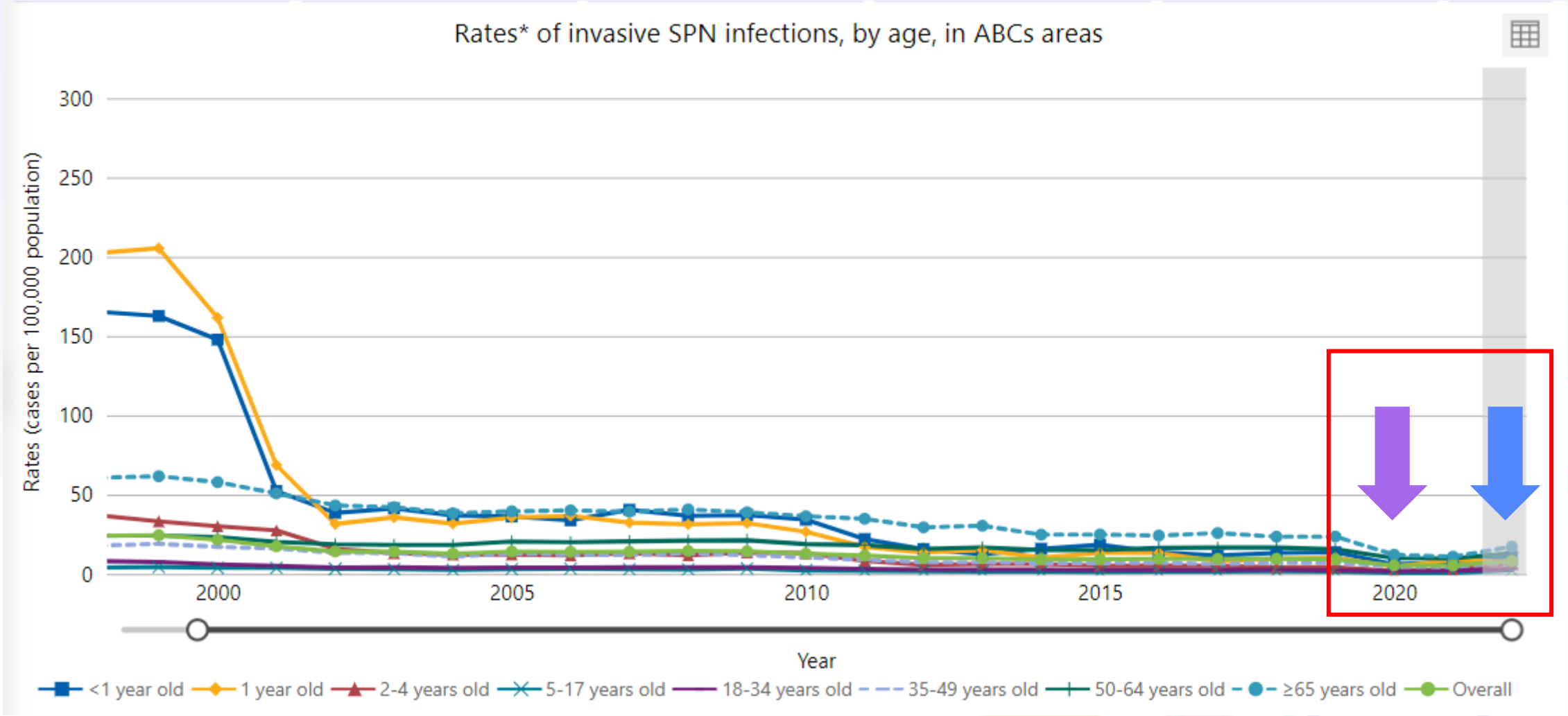
Is pneumococcal disease of public health importance?

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

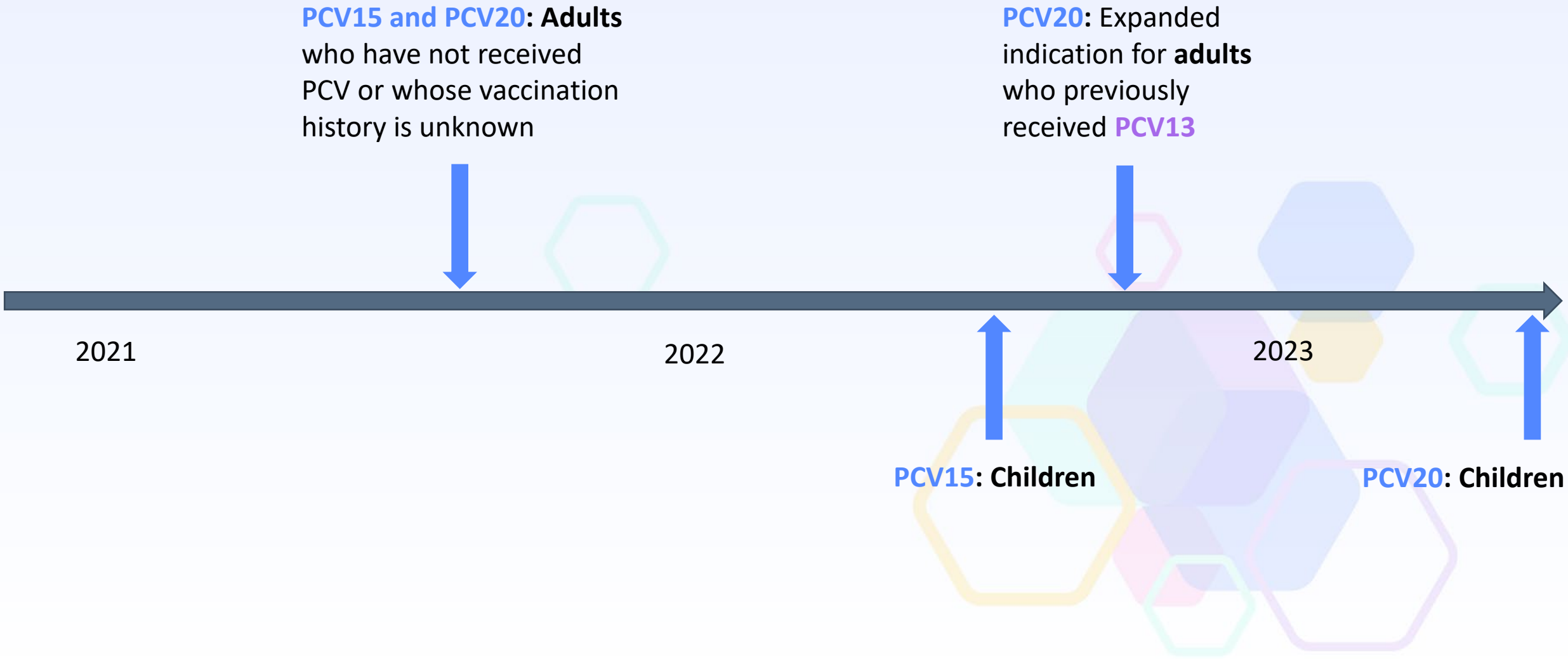
IPD incidence reached a historically low level early in the COVID-19 pandemic, but increasing toward pre-COVID levels



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

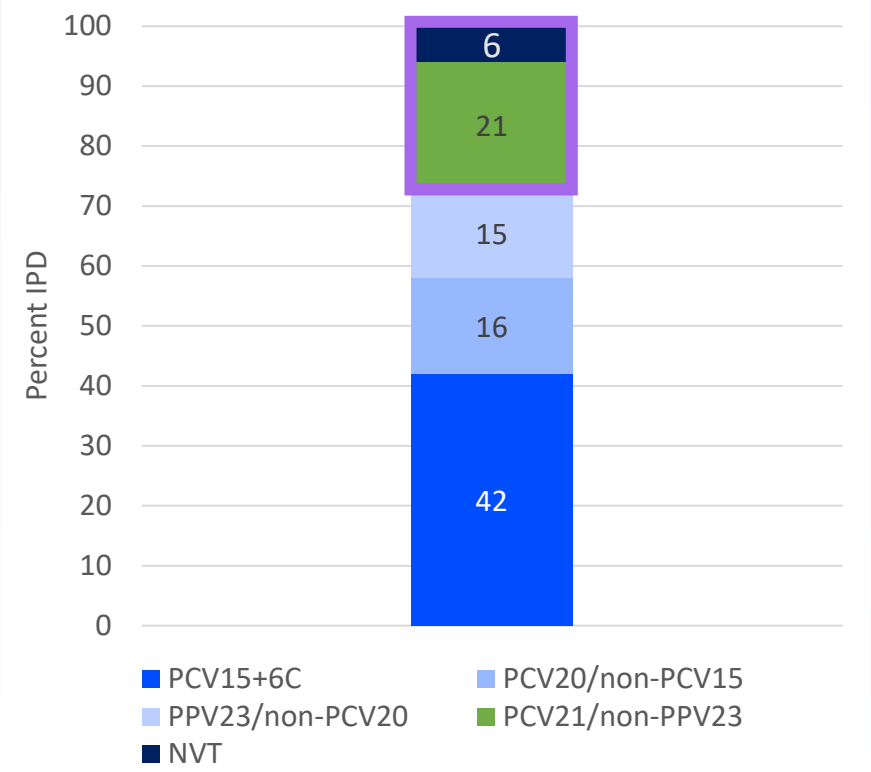
[ABCs Bact Facts Interactive Data Dashboard | CDC]

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

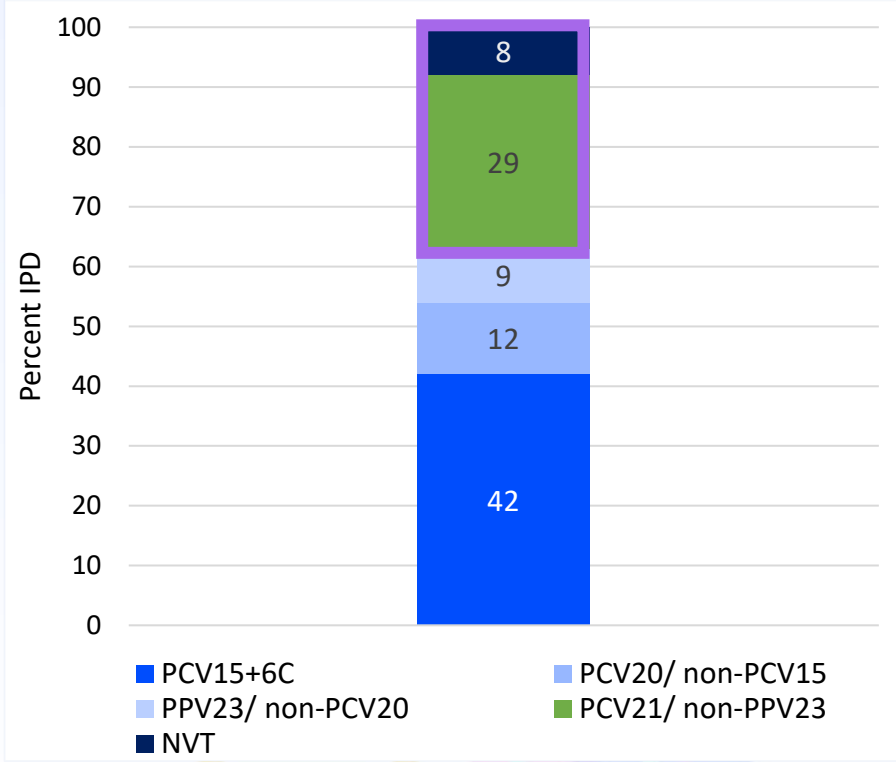


30–40% of adult IPD cases* are caused by serotypes not contained in currently available vaccines; PCV21 contains most of them.

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)		
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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

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.
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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
1: Adults currently recommended to receive PCV

№ of patients		Effect		Certainty	Importance
PCV21	comparison	Relative (95% CI)	Absolute (95% CI)		
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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

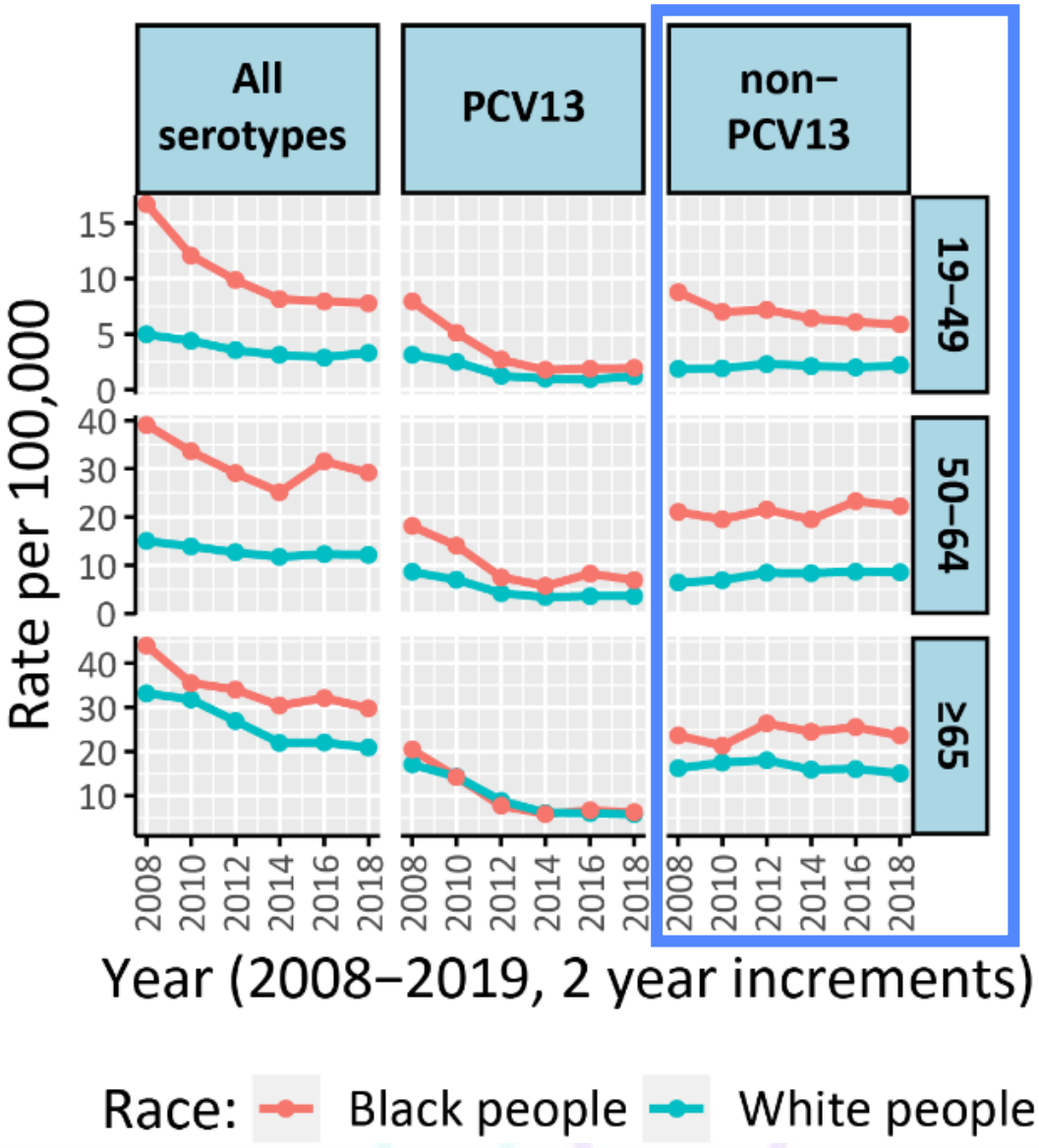


Figure: ABCs unpublished data

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

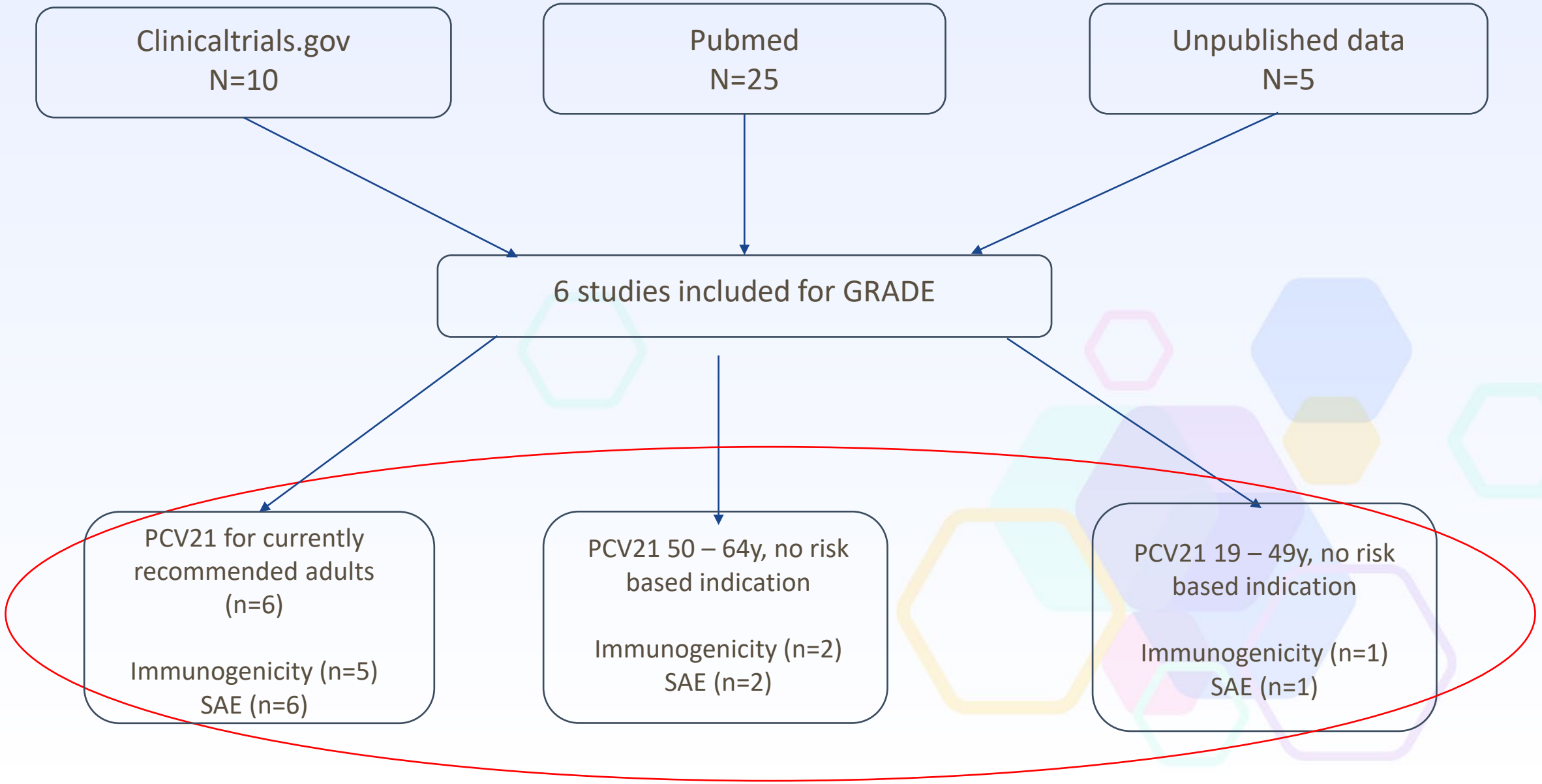
PICO3: Adults aged 19–49 years, no risk-based indications

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