Present and future in prevention of pneumococcal disease

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frequently asked QUESTIONS

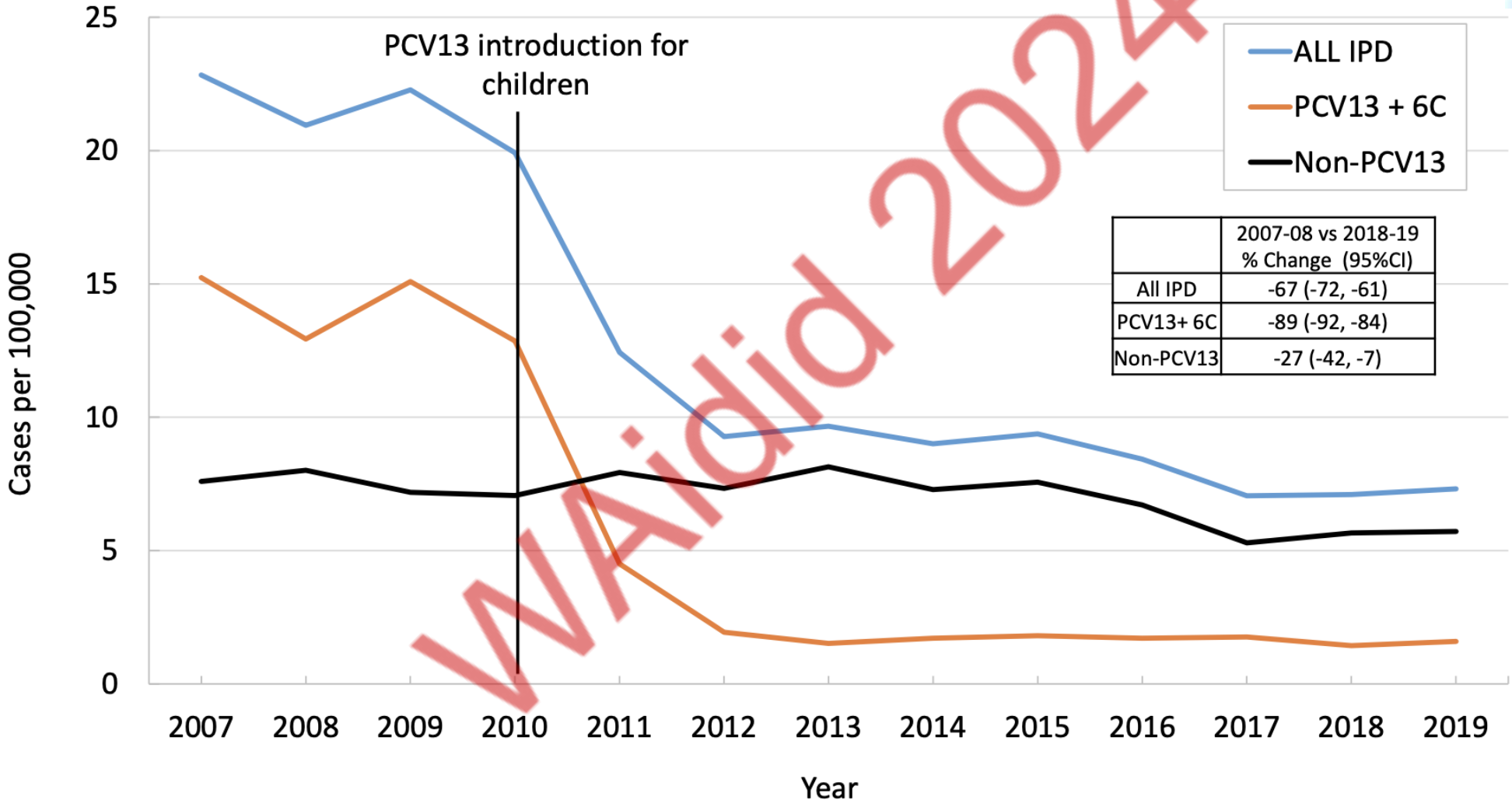
1. The impact of pneumococcal conjugate vaccines heritage of PCV13.
2. Epidemiological need for expanded valence PCVs.
3. The added value of PCV15/PCV20/PCV21.
4. The future vaccines.

New Pneumococcal Vaccines for children and Adult in Advanced Stages of Implementation

	1	3	4	5	6A	6B	7 F	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	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V																	
PCV20	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V												
PPV23	V	V	V	V		V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V								
PCV21		V			V		V				V			V	V	V	V	V	V			V	V	V	V	V	V	V	V	V	V	V

Kobayashi M, Leidner AJ, Gierke R, et al. Use of 21-Valent Pneumococcal Conjugate Vaccine Among U.S. Adults: Recommendations of the Advisory Committee on Immunization Practices — United States, 2024. MMWR Morb Mortal Wkly Rep 2024;73:793–798. DOI: http://dx.doi.org/10.15585/mmwr.mm7336a3

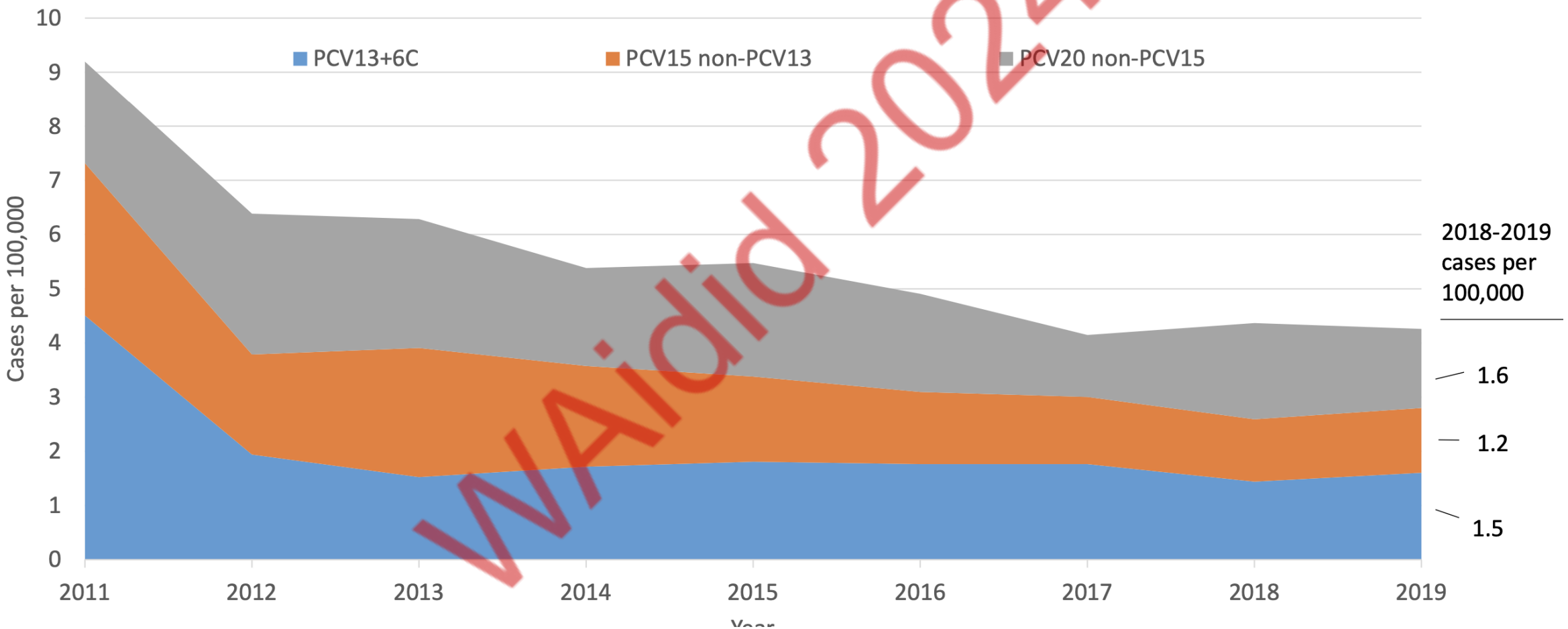
PCV13 IMPACT - Incidence rates of invasive pneumococcal disease (IPD) among children < 5 years old, 2007 - 2019 (US)



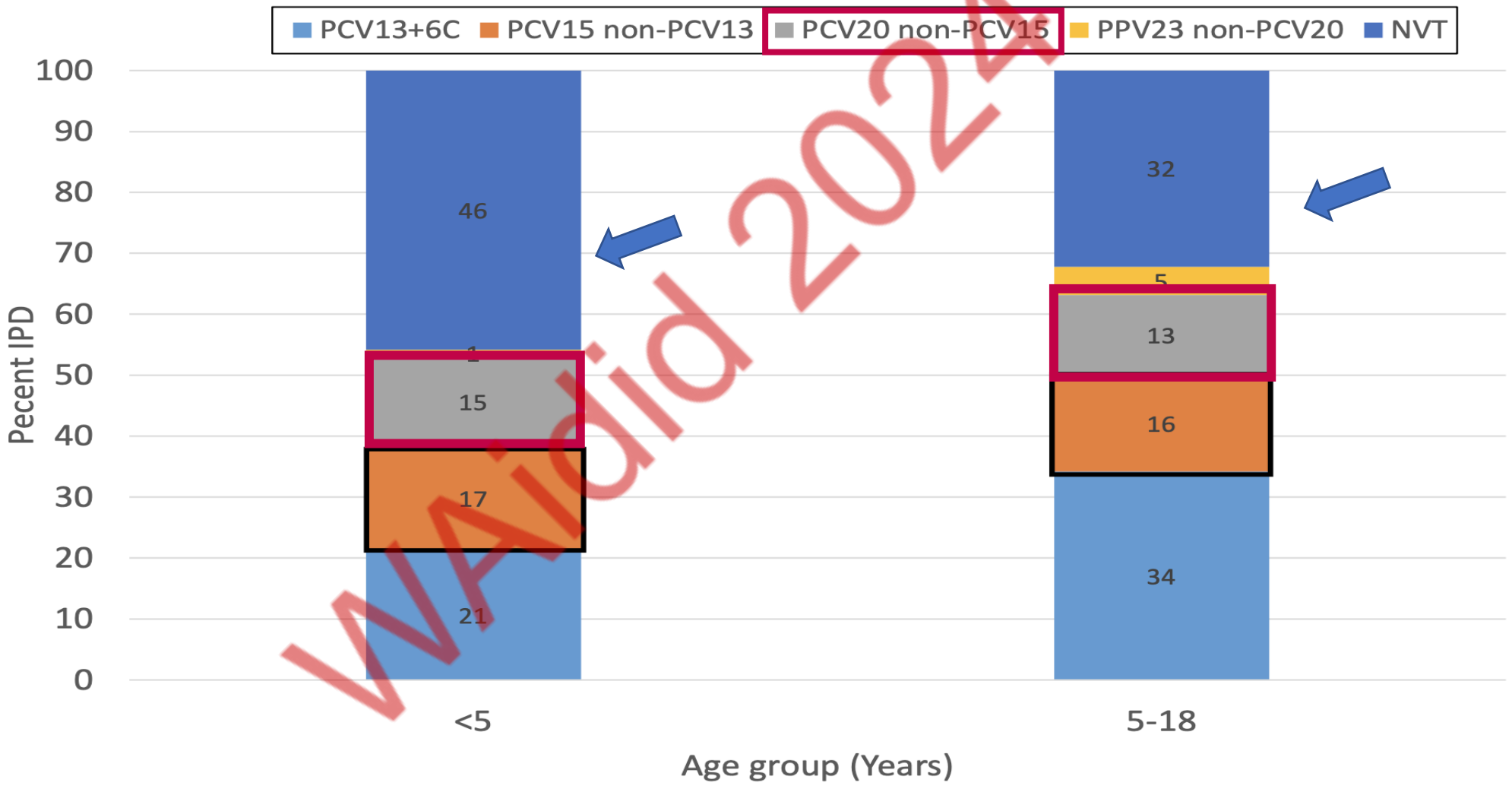
	2007-08 vs 2018-19 % Change (95%CI)
All IPD	-67 (-72, -61)
PCV13+ 6C	-89 (-92, -84)
Non-PCV13	-27 (-42, -7)

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

Incidence rates of IPD among children <5 years old, 2011 – 2019, by the various conjugate vaccine types



Proportion of IPD by vaccine-type and age group in 2018-2019



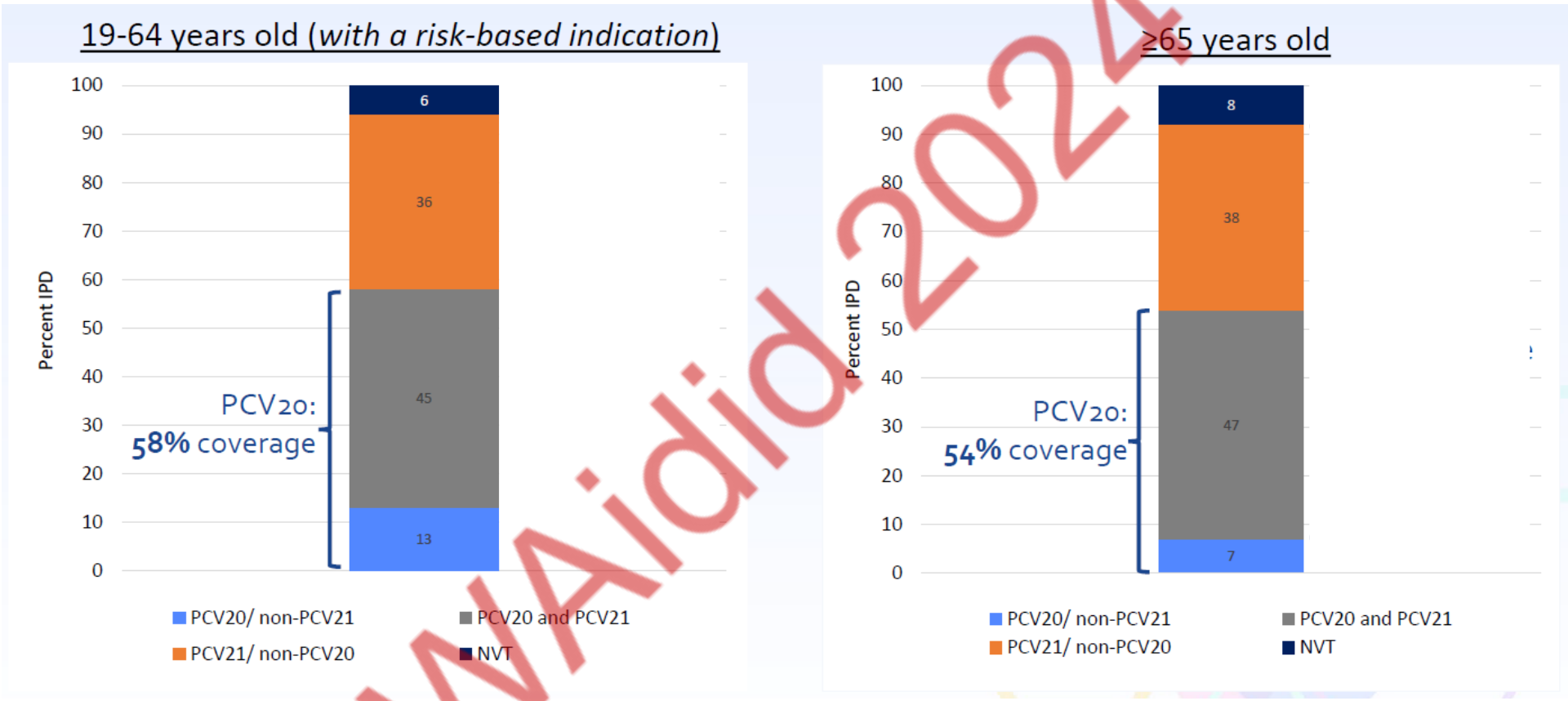
Current Epidemiology of Pneumococcal Disease and Pneumococcal Vaccine Coverage among Children, United States
Ryan Gierke, MPH Advisory Committee on Immunization Practices February 24th, 2022

PCV20 vs. PCV21

	1	3	4	5	6A	6B	7 F	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	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V												
PCV21		V			V		V				V			V	V	V	V	V	V			V	V	V	V	V	V	V	V	V	V

In certain populations in which ≥30% of pneumococcal disease is due to serotype 4, previously recommended pneumococcal vaccines that include serotype 4 (PCV20 alone or PCV15 and PPSV23 in series) are expected to provide broader serotype coverage against locally circulating strains than does PCV21

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



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

Gierke February 2024 ACIP meeting presentation

The innovation behind PCV21

- PCV21 is unique from other PCVs in that it was developed to prevent pneumococcal serotypes that commonly cause disease in adults.
- There is a plan to use of PCV21 in children aged 2–18 years with a risk condition for which there is a phase 3 trial currently in progress.
- PCV21 is not expect to offer similar indirect protection from its additional serotypes.

Use of 21-Valent Pneumococcal Conjugate Vaccine Among U.S. Adults: Recommendations of the Advisory Committee on Immunization Practices (ACIP) — United States, 2024

Weekly / September 12, 2024 / 73(36);793–798

- Adults aged 19–64 years with risk conditions for pneumococcal disease and those aged ≥65 years are recommended to receive either PCV15- or PCV20.
- On June 27, 2024, the Advisory Committee on Immunization Practices recommended 21-valent PCV (PCV21) as an option for adults aged ≥19 years who are currently recommended to receive PCV15 or PCV20. PCV21 contains eight serotypes not included in other licensed vaccines.
- Adding PCV21 as an option in the current PCV recommendation is expected to prevent additional disease caused by pneumococcal serotypes unique to PCV21.

The future vaccines

Whole cell pneumococcal vaccine

The whole cell pneumococcal vaccine componnents

- SPn whole-cell antigen bulk, from strain RM200 RX1E PdT ΔlytA (genetically modified to remove the lytA gene).
- The virulence factor pneumolysin gene was replaced with a gene encoding for a pneumolysoid containing 3 point mutations that abolish cytolytic activity and complement activation.
- Beta-propriolactone was utilized to inactivate cells during processing…
- The final formulation contained 0.6 mg of elemental aluminum per dose

A Phase 1 Randomized, Placebo-controlled, Observer-blinded Trial to Evaluate the Safety and Immunogenicity of Inactivated *Streptococcus pneumoniae* Whole-cell Vaccine in Adults

Cheryl A. Keech, MD, PhD,†, Royce Morrison, MD‡, Porter Anderson, PhD§, Andrea Tate, MBA*,†, Jorge Flores, MD*, David Goldblatt, MD, PhD¶, David Briles, PhD‖, John Hural, PhD**, Richard Malley, MD§, and Mark R. Alderson, PhD**

TABLE 1. Demographics and Treatment Compliance

	Treatment 1 (0.1 mg); N = 10	Treatment 2 (0.3 mg); N = 10	Treatment 3 (0.6 mg); N = 10	Placebo; N=12	Total; N = 42
Sex (N) female/male	3/7	4/6	7/3	8/4	22/20
Age (years) mean (standard deviation [SD]); N (%)	28.9 (5.4)	25.2 (6.1)	29.9 (6.8)	28.5 (7.0)	28.1 (6.4)
Weight (kg) mean (SD); N (%)	83.3 (17.8)	94.1 (26.2)	78.5 (21.4)	83.2 (26.1)	84.7 (23.1)
Systolic/diastolic blood pressure mean mm Hg (SD) at baseline; N (%)	114 (14.0)/71 (5.7)	116 (11.5)/71 (11.4)	109 (12.4)/74 (10.7)	118(10.0)/75 (8.7)	
Ethnicity (N) and race; Hispanic or Latino/non-Hispanic or Non-Latino (n/total)	2/8	3/7	2/8	2/10	9/11
Black or African American (n/total)	2/10	2/10	4/10	2/12	10/42
White/Caucasian (n/total)	7/10	7/10	5/10	10/12	29/42
Other (n/total)	1/10	1/10	1/10	0/12	3/42
Vaccinations completed N (%) At least 1	10 (100.0)	10 (100.0)	10 (100.0)	12 (100.0)	42 (100.0)
At least 2	9 (90.0)	8 (80.0)	9 (90.0)	10 (83.3)	36 (85.7)
All 3	9 (90.0)	8 (80.0)	9 (90.0)	9 (75.0)	35 (83.3)
Completed day 84 visit; N (%)	9 (90.0)	5 (50.0)	9 (90.0)	9 (75.0)	32 (76.2)
Completed 6-month safety phone call; N (%)	7 (70.0)	4 (40.0)	8 (80.0)	6 (50.0)	25 (59.5)
Lost to follow-up at day 84; N (%)	1 (10.0)	5 (50.0)	1 (10.0)	3 (25.0)	10 (23.8)
Total lost to follow-up by 6-month phone call; N (%)	3 (30.0)	6 (60.0)	2 (20.0)	6 (50.0)	17 (40.5)

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This study was conducted in 2013….

Conclusions:

wSp was safe and well tolerated in healthy US adults, eliciting pneumococcal antigen-specific antibody and T-cell cytokine responses.

- ….using formalin or beta-propriolactone is associated with cross-linking between proteins and reduced immunogenicity, while live attenuated vaccines pose a significant biological and health risk.
- The use of γ-irradiation has been reported as an effective alternative inactivation method for the development of highly immunogenic and safe WCVs

The Pediatric Infectious Disease Journal • Volume 39, Number 4, April 2020

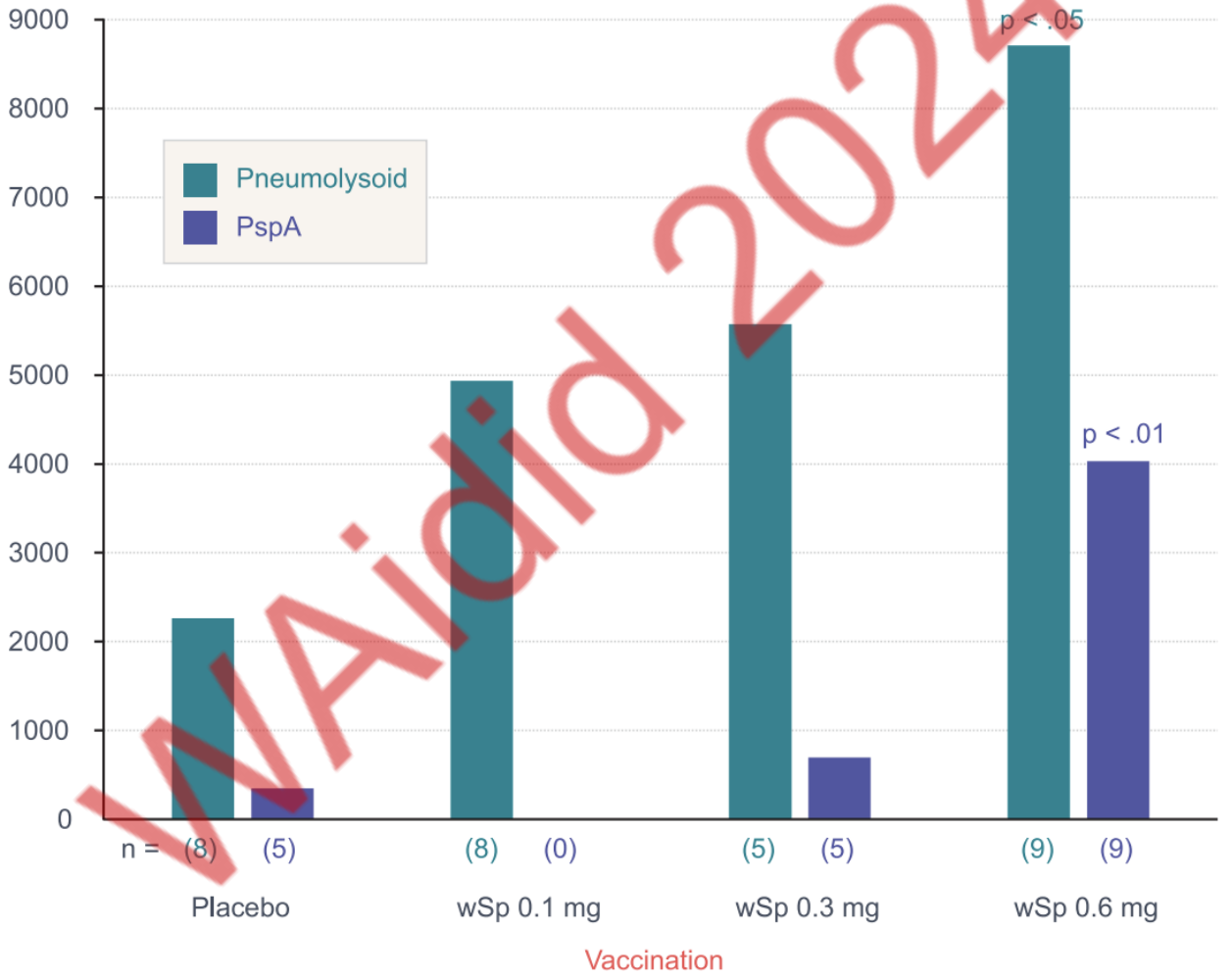
A Non-adjuvanted Whole-Inactivated Pneumococcal Vaccine Induces Multi-serotype Opsonophagocytic Responses Mediated by Nonc-apsule-Specific Antibodies

Geometric mean OI for rabbits immunized IM with PCV13, Gamma-PN, or Gamma-PN+Al[a]

Serotype	Pre-Bleed (pooled)	PCV13 $n = 3$	Gamma-PN $n = 6$	Gamma-PN+Al $n = 4$
2	< 4	< 4	16	< 4
3	< 4	15	4	4
6A	5	1,170	21,600	1,620
6C	5	273[b]	262	11
9N	306	393	34,700	955
11A	< 4	12	950	559
15A	< 4	13	3,240	206
22F	52	118	56,000	1,510
23A	< 4	371[b]	384	779
23B	< 4	4	26	7
23F	5	1,950	2,920	248
33F	< 4	4	237	43
35B	24	31	2,050	142

David SC, Brazel EB, Singleton EV, *et al*. A nonadjuvanted whole-inactivated pneumococcal vaccine induces multiserotype opsonophagocytic responses mediated by noncapsule-specific antibodies. *mBio* 2022; 13(5), e0236722.

Immunoglobulin G responses following vaccination with wSP measured by pneumolysoid and pneumococcal surface protein A enzyme-linked immunosorbent assays.



GPN VACCINES

PIPELINE

Disease	Product	Target Population	Developmental stage
			Discovery / Preclinical / Phase 1 / Phase 2 / Phase 3
Invasive Pneumococcal Disease	Gamma-PN	Adult	
		Pediatric	
Chronic Obstructive Pulmonary Disease	Gamma-HI	Adults	
Otitis Media	Gamma-OM *	Pediatric	
Invasive Group A *Streptococcus* Disease	Gamma-PY	Adult	
		Pediatric	
			Discovery / Early Phase / Late Phase
Streptococcus suis Infection	Gamma-SU	Veterinary	

**Gamma-OM is a combination vaccine, minimally comprising Gamma-PN and Gamma-HI.*

Completed

Safety, Tolerability and Immunogenicity of an Inactivated Whole-cell Pneumococcal Vaccine Gamma-PN3.

ClinicalTrials.gov ID NCT05667740

Sponsor GPN Vaccines

Information provided by GPN Vaccines (Responsible Party)

Last Update Posted 2024-09-05

A Phase 1, Randomised, Placebo-controlled, Double-blind, Sequential Ascending-dose Study to Evaluate the Safety, Tolerability, and Immunogenicity of an Inactivated Whole-cell Pneumococcal Vaccine (Gamma-PN3) in Healthy Adults

Study Overview

Brief Summary

This is a randomised placebo-controlled first-in-man dose-ranging study to determine safety and markers of efficacy.

Detailed Description

The study is of double-blind; parallel groups dose escalation design. In each cohort of 39 participants 30 will receive Gamma-PN3; 3 will receive Prevenar; 3 will receive Pneumovax and 3 saline placebo.

The doses of Gamma-PN3 will be 50mcg; 250 mcg and 1000 mcg of protein content.

Results Overview

No Study Results Posted on ClinicalTrials.gov for this Study

Study results have not been submitted. This may be because the study isn't done, the deadline for submitting results hasn't passed, this study isn't required to submit results, or the sponsor or investigator has requested or received a certification to delay submitting the results.

For more information:

FDAAA 801 and the Final Rule: Which trials must have results information submitted to ClinicalTrials.gov?

FDAAA 801 and the Final Rule: Delayed submission of results information

Recruitment Status	Actual Primary Completion Date	Actual Study Completion Date
Completed	2023-10-08	2023-10-08

Study Record Versions

- This table shows all the versions of this study record arranged in order by submitted date.
  - To view one version of the study record, click the submitted date.
  - To compare two versions, select them using the check boxes and click "Compare" at the bottom of the list.

	Version	Date submitted (YYYY-MM-DD)	Changes
☐	1	2022-12-19	• None (earliest version on record)
☐	2	2022-12-29	• Study Status • Study Identification
☐	3	2023-02-21	• Study Status • Contacts/Locations
☐	4	2024-09-02	• Recruitment Status • Study Status • Study Design

New Adult Pneumococcal Vaccines in Advanced Stages of Development

	1	3	4	5	6A	6B	7 F	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	7C
PCV15	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V																		
PCV20	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V													
PPSV23	V	V	V	V		V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V									
PCV21		V			V		V				V			V	V	V	V	V	V			V	V	V	V	V	V	V	V	V	V	V	
Pn- MAPS24V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V									
VAX-24		V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V									
VAX-31		V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V		V	V	V		V	V	V

- 24-valent pneumococcal vaccines:
  - Pn-MAPS24v (GSK): Completed phase 1/2 study for adults; Breakthrough Therapy Designation granted and next steps in preparation; undergoing phase 2 studies in infants1
  - VAX-24 (Vaxcyte): Completed enrollment for phase 2 studies in infants2; topline results anticipated in 2025

Chichili et al. Vaccine 2022; 2.Vaxcyte Completes Enrollment of Phase 2 Study Evaluating VAX-24 for the Prevention of Invasive Pneumococcal Disease (IPD) in Infants - Vaxcyte, Inc.; 3. VAX-31 Phase ½ Study Topline Results in Adults Aged 50 and Older. September 3, 2024

PCV24 + MAPS

- ASP3772, (re-named AFX3772,) is a novel 24-valent pneumococcal vaccine
- Developed based on a Multiple Antigen Presenting System (MAPS) platform, which has been shown to induce robust B-cell and T-cell immunity
- The MAPS platform takes advantage of the high affinity non-covalent binding between biotin and rhizavidin, a biotin-binding protein that has no significant predicted homology with human proteins
- ASP3772 contains 24 polysaccharides, including the 13 serotypes contained in PCV13 plus an additional 11 contained in PPSV23.

	1	3	4	5	6A	6B	7 F	9V	14	18C	19A	19F	23F	22F	33F	8	10A	11A	12F	15B	2	9N	17F	20
PCV13	V	V	V	V	V	V	V	V	V	V	V	V	V											
PPSV23	V	V	V	V		V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
Pn- MAPS24V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V

PCV24 + MAPS

- Each serotype is individually biotinylated and complexed with a unique fusion protein consisting of rhizavidin fused to two pneumococcal protein segments derived from genetically conserved surface protein genes (sp1500 and sp0785).
- Deletion of sp1500 and sp0785 resulted in significant reduction in virulence of a type 3 pneumococcus.
- In addition, fusion of the two proteins conferred protection against colonization and generated opsonic antibodies that assisted in the killing of pneumococcal strains.

PCV24

Contents lists available at ScienceDirect

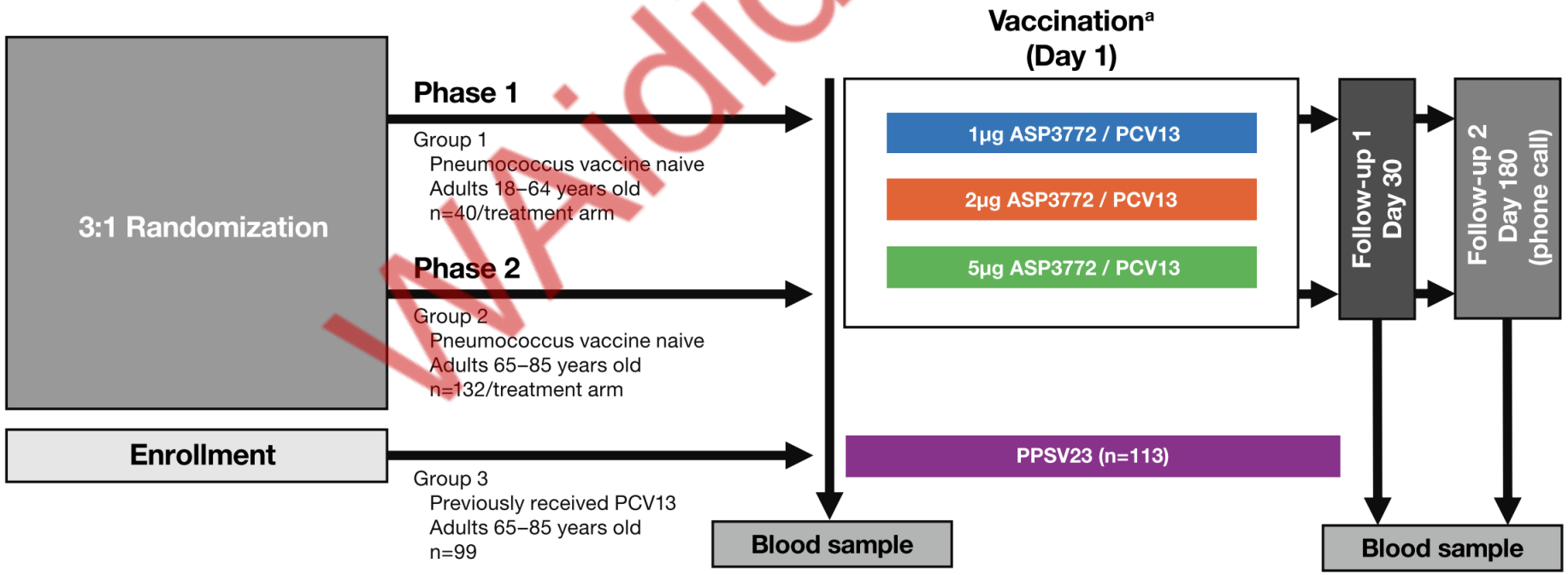
Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Phase 1/2 study of a novel 24-valent pneumococcal vaccine in healthy adults aged 18 to 64 years and in older adults aged 65 to 85 years

Gurunadh R. Chichili [a,*], Ronald Smulders [a], Vicki Santos [a], Beth Cywin [a], Laura Kovanda [a], Charles Van Sant [a], Frank Malinoski [b], Shite Sebastian [b], George Siber [b], Richard Malley [b]

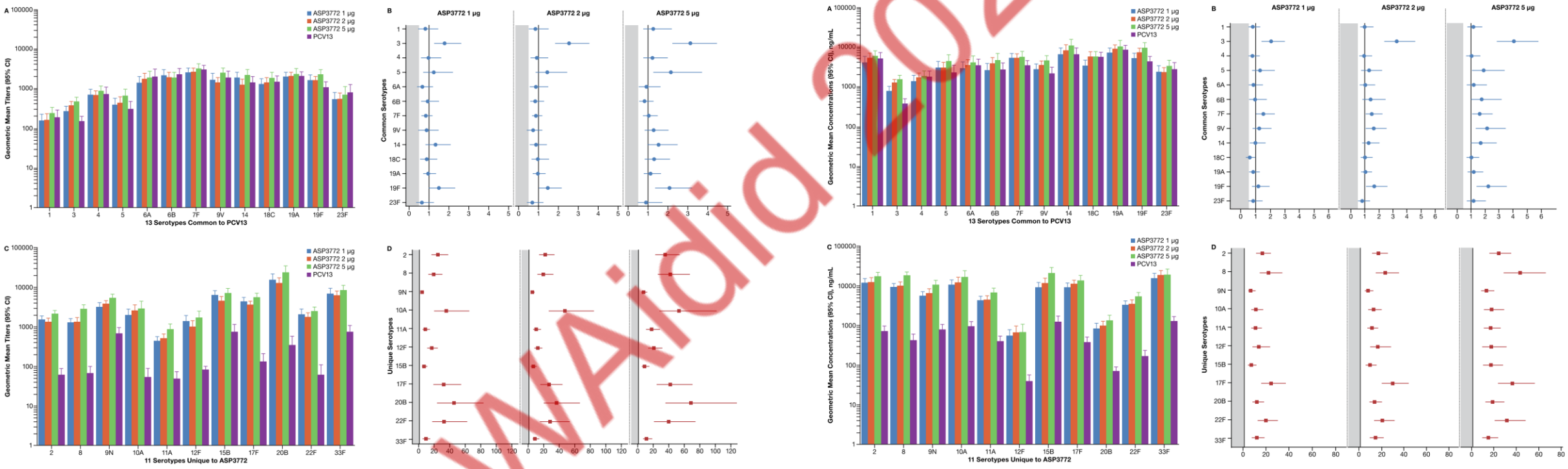
Study Schema.



PCV24

Postimmunization OPA Geometric Mean Titers

Postimmunization IgG Geometric Mean Concentrations (ng/mL)



(A) Titers and (B) Ratios for 13 Serotypes Common to PCV13. (C) Titers and (D) Ratios for 11 Serotypes Unique to ASP3772. Abbreviations

Gurunadh R Chichili et al. Vaccine . 2022 Jul 29;40(31):4190-4198.

Contents lists available at ScienceDirect

Vaccine

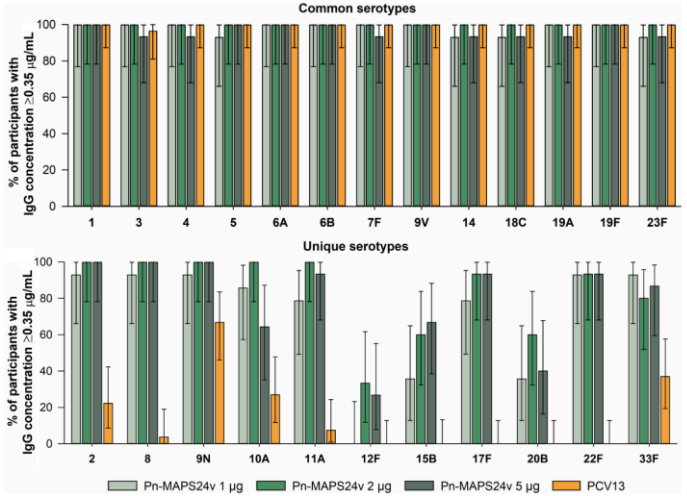
journal homepage: www.elsevier.com/locate/vaccine

Safety, tolerability and immunogenicity of a novel 24-valent pneumococcal vaccine in toddlers: A phase 1 randomized controlled trial

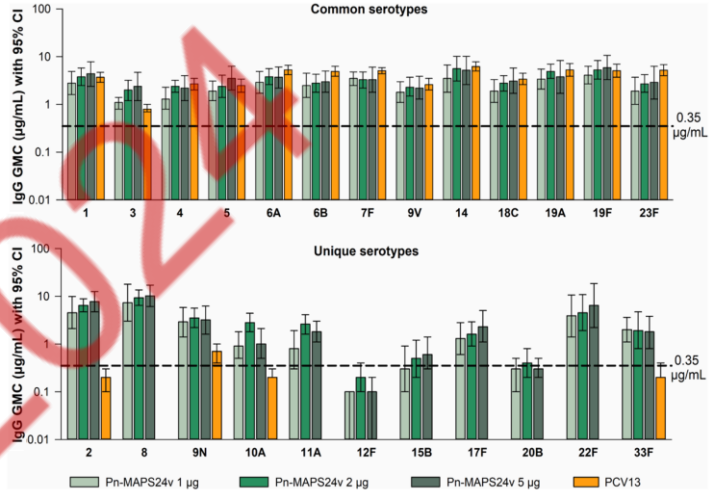
Dorota Borys [a,*], Richard Rupp [b], Ronald Smulders [c], Gurunadh R. Chichili [c], Laura L. Kovanda [c], Vicki Santos [c], Frank Malinoski [d,1], George Siber [d,2], Richard Malley [d,3], Shite Sebastian [d,4]

Vaccine Volume 42, Issue 10, 11 April 2024, Pages 2560-2571

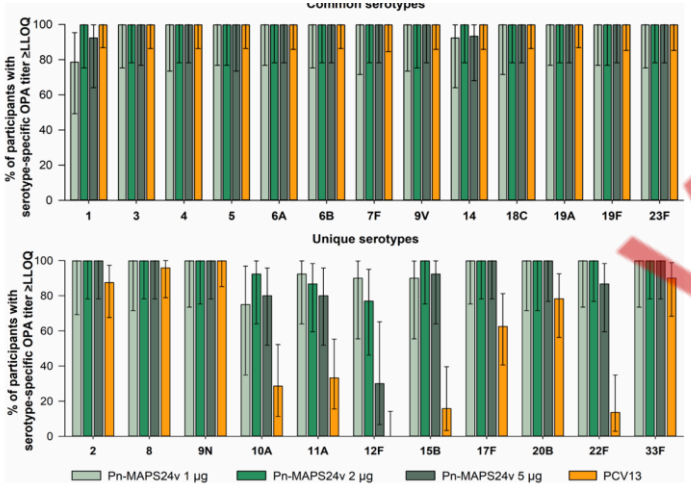
Percentages of participants with serotype-specific anti-capsular PS IgG concentration ≥0.35 µg/mL with 95 % CI at 30 days post-vaccination



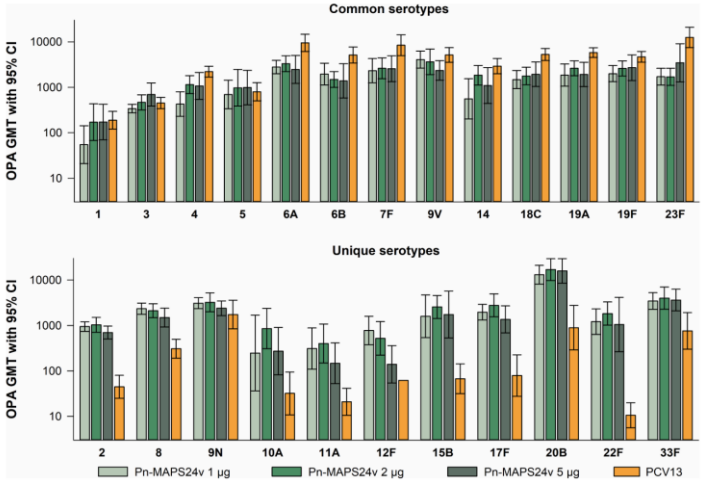
Pneumococcal serotype-specific anti-capsular PS IgG GMC levels with 95 % CI at 30 days post-vaccination.



Percentages of participants with serotype-specific OPA titer ≥ lower limit of quantitation; CI (LLOQ) with 95 % CI at 30 days post-vaccination.



Pneumococcal serotype-specific OPA GMTs with 95 % CI at 30 days after vaccination.



OPA, opsonophagocytic activity; GMT, geometric mean titer; CI, confidence interval; Pn-MAPS24v, 24-valent pneumococcal vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

Vaccine Volume 42, Issue 10, 11 April 2024, Pages 2560-2571

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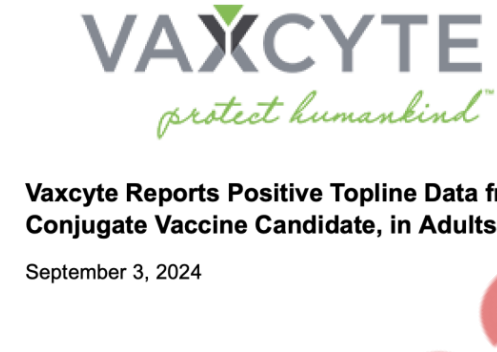
Safety, tolerability and immunogenicity of a novel 24-valent pneumococcal vaccine in toddlers: A phase 1 randomized controlled trial

Dorota Borys [a,*], Richard Rupp [b], Ronald Smulders [c], Gurunadh R. Chichili [c], Laura L. Kovanda [c], Vicki Santos [c], Frank Malinoski [d,1], George Siber [d,2], Richard Malley [d,3], Shite Sebastian [d,4]

Conclusions

- In toddlers aged 12–15 months and primed in infancy with three doses of PCV13, a single dose of Pn-MAPS24v demonstrated an acceptable safety and tolerability profile
- Each of the three Pn-MAPS24v dose levels elicited immune responses in terms of IgG concentrations and OPA titers against all common and most of the unique pneumococcal serotypes after a single dose.
- Based on these results, progression of clinical studies towards a lower age group (infants) is warranted.

PCV 31



- At All Doses Studied, VAX-31 Demonstrated Robust Opsonophagocytic Activity Immune Responses for All 31 Serotypes
- At Middle and High Doses, VAX-31 Met or Exceeded Regulatory Immunogenicity Criteria for All 31 Serotypes
- At All Doses Studied, VAX-31 Was Observed to be Well Tolerated and Demonstrated a Safety Profile Similar to Prevnar 20®

	1	3	4	5	6A	6B	7 F	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	7C
PCV15	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V																		
PPSV23	V	V	V	V		V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V									
VAX-31		V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V		V	V	V		V	V	V

VAXCYTE
protect humankind™

Vaxcyte Reports Positive Topline Data from Phase 1/2 Study of VAX-31, its 31-Valent Pneumococcal Conjugate Vaccine Candidate, in Adults Aged 50 and Older

September 3, 2024

- ….For Adult Indication, VAX-31 Selected to Advance to Phase 3 Program; Vaxcyte Plans to Initiate Phase 3 Pivotal, Non-Inferiority Study by Mid-2025 and Announce Topline Safety, Tolerability and Immunogenicity Data in 2026
- For Pediatric Indication, ….Company Plans to Initiate VAX-31 Infant Phase 2 Study in First Quarter of 2025….

Annual health economic burden attributable to PCV31-additional serotypes pneumococcal disease

	Costs in millions, 2022 USD (95 % CI)						
	Outpatient			Inpatient			Total[d]
Condition	*Medical*[b]	*Non-medical*[c]	*Total*[d]	*Medical*[e]	*Non-medical*[f]	*Total*[d]	
AOM	343.5 (226.8, 511.7)	228.4 (175.4, 295.9)	573.1 (418.8, 783.8)	2.0 (0.5, 5.7)	0.1 (0.1, 0.2)	2.2 (0.6, 5.9)	575.1 (421.1, 786.3)
Sinusitis	609.7 (298.1, 1125.5)	570.6 (347.5, 835.3)	1187.2 (686.6, 1881.2)	–	–	–	1187.2 (686.6, 1881.2)
Pneumonia	30.8 (18.3, 50.2)	435.3 (311.7, 607.1)	466.7 (335.8, 647.9)	668.9 (376.8, 1179.3)	2601.7 (2386.6, 2845.1)	3278.8 (2878.6, 3861.9)	3754.3 (3293.8, 4382.1)
All non-invasive	990.6 (615.1, 1578.5)	1241.0 (965.4, 1568.7)	2239.6 (1656.7, 3026.0)	671.2 (379.0, 1181.6)	2601.8 (2386.7, 2845.2)	3281.3 (2880.9 3864.5)	5538.1 (4741.7 6590.5)
Meningitis	–	–	–	43.2 (35.7, 54.5)	224.8 (211.1, 240.8)	268.4 (250.1, 290.1)	268.4 (250.1, 290.1)
Bacteremic pneumonia	–	–	–	334.3 (253.6, 458.6)	1083.5 (1018.0, 1160.2)	1420.4 (1301.5, 1575.3)	1420.4 (1301.5, 1575.3)
Bacteremia	–	–	–	31.8 (16.9, 55.0)	205.0 (192.6, 219.5)	237.4 (216.2, 265.4)	237.4 (216.2, 265.4)
All invasive	–	–	–	409.3 (306.4, 567.9)	1513.3 (1421.7, 1620.5)	1926.3 (1768.8, 2129.2)	1926.3 (1768.8, 2129.2)
Total	990.6 (615.1, 1578.5)	1241.0 (965.4, 1568.7)	2239.6 (1656.7, 3026.0)	1081.4 (721.7, 1708.6)	4115.3 (3829.5, 4445.3)	5209.2 (4693.3, 5940.8)	7467.3 (6586.1, 8627.0)

PCV31-additional serotypes

Total

7467.3 (6586.1, 8627.0)

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Conclusions

- Pneumococcal conjugated vaccines reduced dramatically serotype specific pneumococcal infections both in children and adults.
- In recent years three new PCVs 15/20/21 valent were approved for children and/or adults.
- New more valent vaccines are in development such as PCV24 and PCV31.
- A new approach using whole cell vaccines is being developed.

ALL YOU NEED IS LOVE

Oxygen can helps a bit too