

5 November 2019

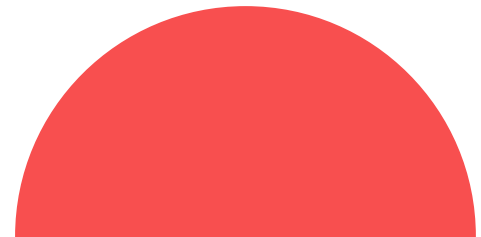
Update on global prevention of pneumococcal infection

Expanded conjugate vaccines and new pneumococcal protein vaccines, implications of Gavi graduation and serotype replacement

Mark Alderson



Photo: PATH/Gabe Bieneycki



Outline of Presentation

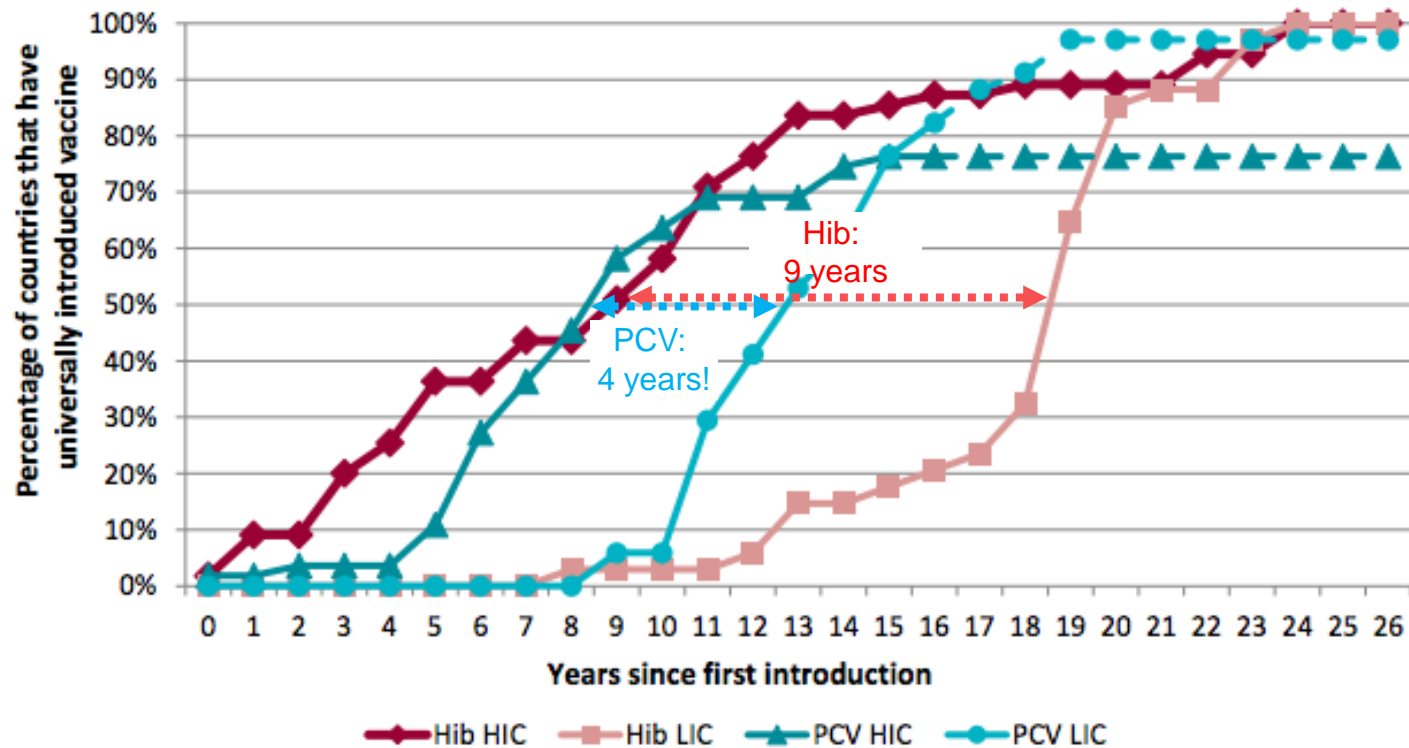
- What have we learned about PCVs in the last 20 years?
- Gaps with current pneumococcal vaccines.
- A new low-cost 10-valent PCV.
- Challenges with higher valency PCVs.
- Recent advances, future and challenges with pneumococcal protein vaccines.

What have we learned about PCVs in the past 20 years?

Substantial uptake in lower income countries only a few years after high income countries

Much shorter lag time than was seen with Hib vaccines

Figure 3: PCV and Hib vaccine introductions, by income group

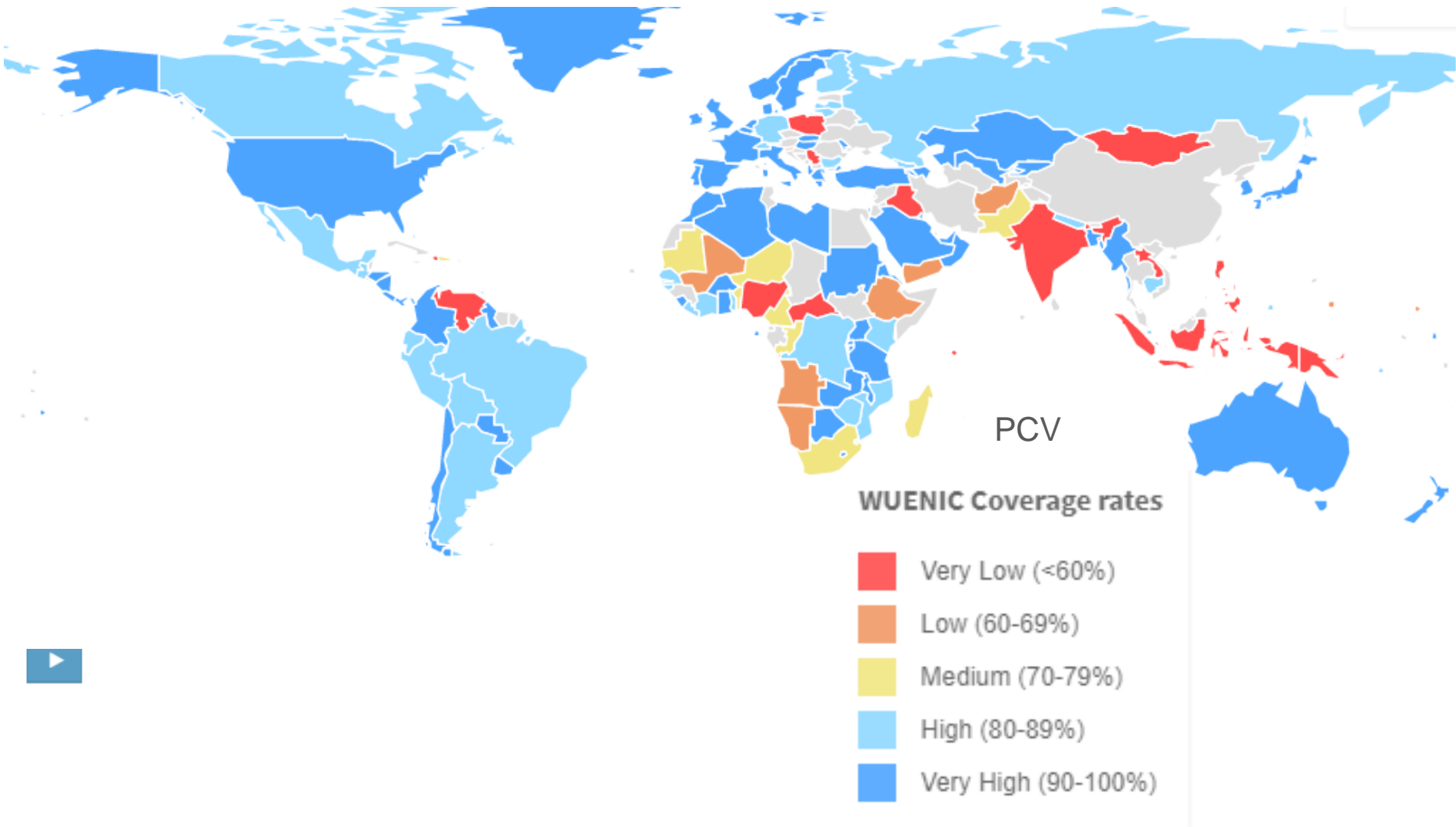


HIC: high-income country; LIC: low-income country

Note: Dashed lines represent projected introductions in the future. Projections are limited for HICs.

Source: IVAC, VIMS Global Vaccine Introduction Report, Dec 2015

But... some major LMICs have been slow or non-adopters of current PCVs



Source: IVAC/Johns Hopkins Univ View Hub; accessed 24 Oct 2019

<http://view-hub.org/viz/?YXBwaWQ9MSZpbmRpY2F0b3JpZD03Mg==>

What else have we learned about PCVs?

- In children, large overall IPD impact was only partially attenuated by replacement disease
 - ⇒ **Both PCV formulations are excellent and recommended by WHO**
 - “Insufficient evidence of a difference in the net impact ...on overall disease burden” (*WHO: WER Feb 2019*)
 - Likely differential impact on specific serotypes (19A, perhaps 3, maybe even NVT) (*Naucner CID, 2017*)
- In >50 year olds, PCV impact (via herd effect) less clear
 - Net decrease of IPD not universally observed due to extensive replacement disease (*Ladhani Lancet ID, 2018*)
- Almost all emerging NVT types show non-susceptibility to antibiotics
 - PCV impact on antibiotic resistant disease may be transient if antimicrobial pressure continues (*Hausdorff & Hanage, 2016*)

Gaps with Current Pneumococcal Vaccines

Coverage

- Only 10-13 of the 95+ serotypes + non-vaccine serotype replacement/emergence = significant residual disease burden.

Cost

- Driven primarily by PCV manufacturing complexity. Limits access/sustainability for LMICs, particularly Gavi graduating countries.

Carriage

- Complete serotype replacement in the nasopharynx promotes continued pneumococcal genetic evolution.

- ***We need more affordable and broader coverage vaccines against pneumococcus***

SI IPL 10-valent PCV

Serum Institute of India Pvt. Ltd.



SI IPL-PCV	1			5	6A	6B	7F	9V	14		19A	19F	23F
Synflorix	1		4	5		6B	7F	9V	14	18C		19F	23F
Prevenar 13	1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F

Polysaccharides: 2 µg for all except 6B (4 µg)

Carrier Protein: rCRM₁₉₇

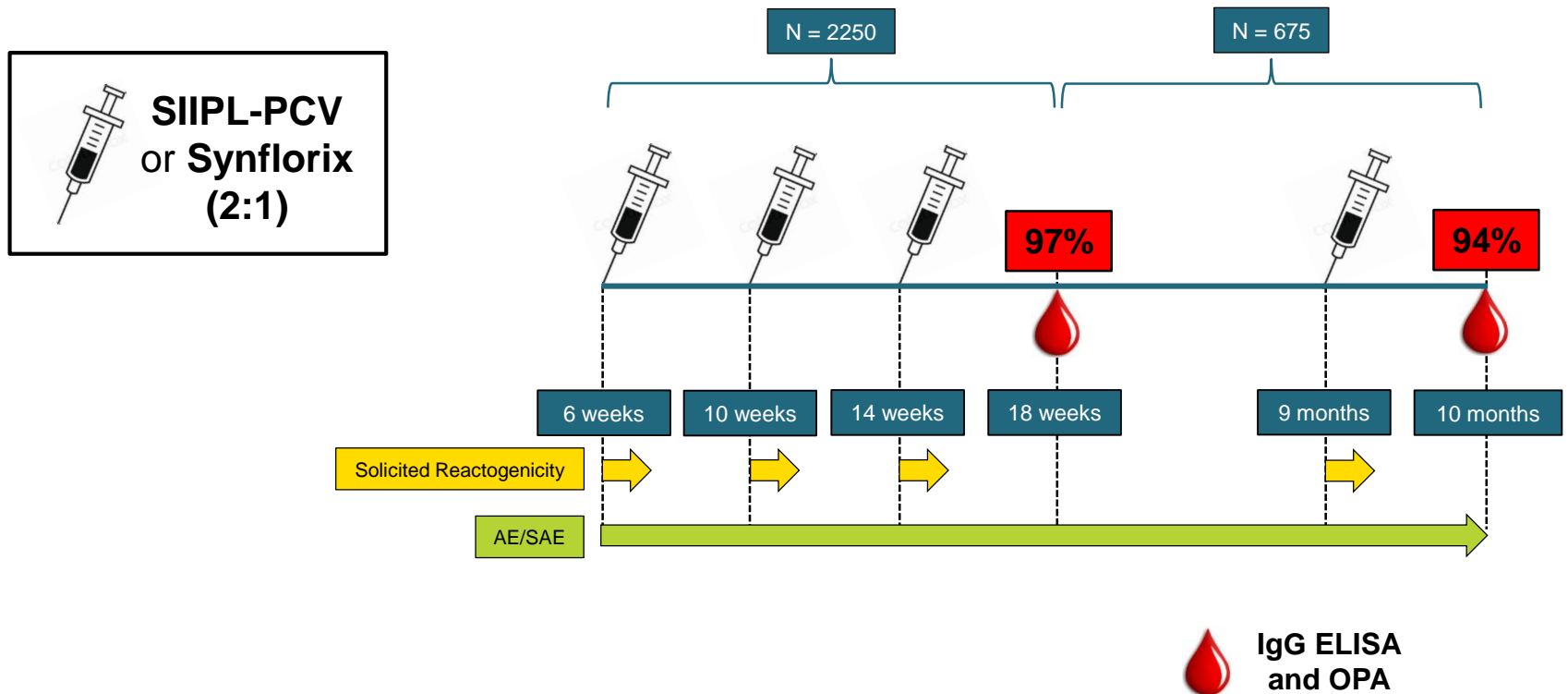
Conjugation Method: CDAP

VVM 30

1 and 5 dose vials

Phase 3 Trial Design

- Based on WHO Technical Report Series (TRS) for licensure of new PCVs



Primary Immunogenicity Objectives

1. Lot-to-Lot equivalence

- 3 manufacturing lots of SIIPL-PCV
 - Equivalence margin GMC ratio: 0.5-2.0 (lot1/lot2 etc.)



2. Non-inferiority of the post-primary immune responses to SIIPL-PCV compared to Synflorix

- Matched serotypes (or lowest responders for 6A and 19A)
- Seroresponse rates (IgG \geq 0.35 μ g/mL)
 - Non-inferiority margin: -10% (SIIPL-PCV-Synflorix)
- IgG GMC
 - Non-inferiority margin: 0.5 (SIIPL-PCV/Synflorix)

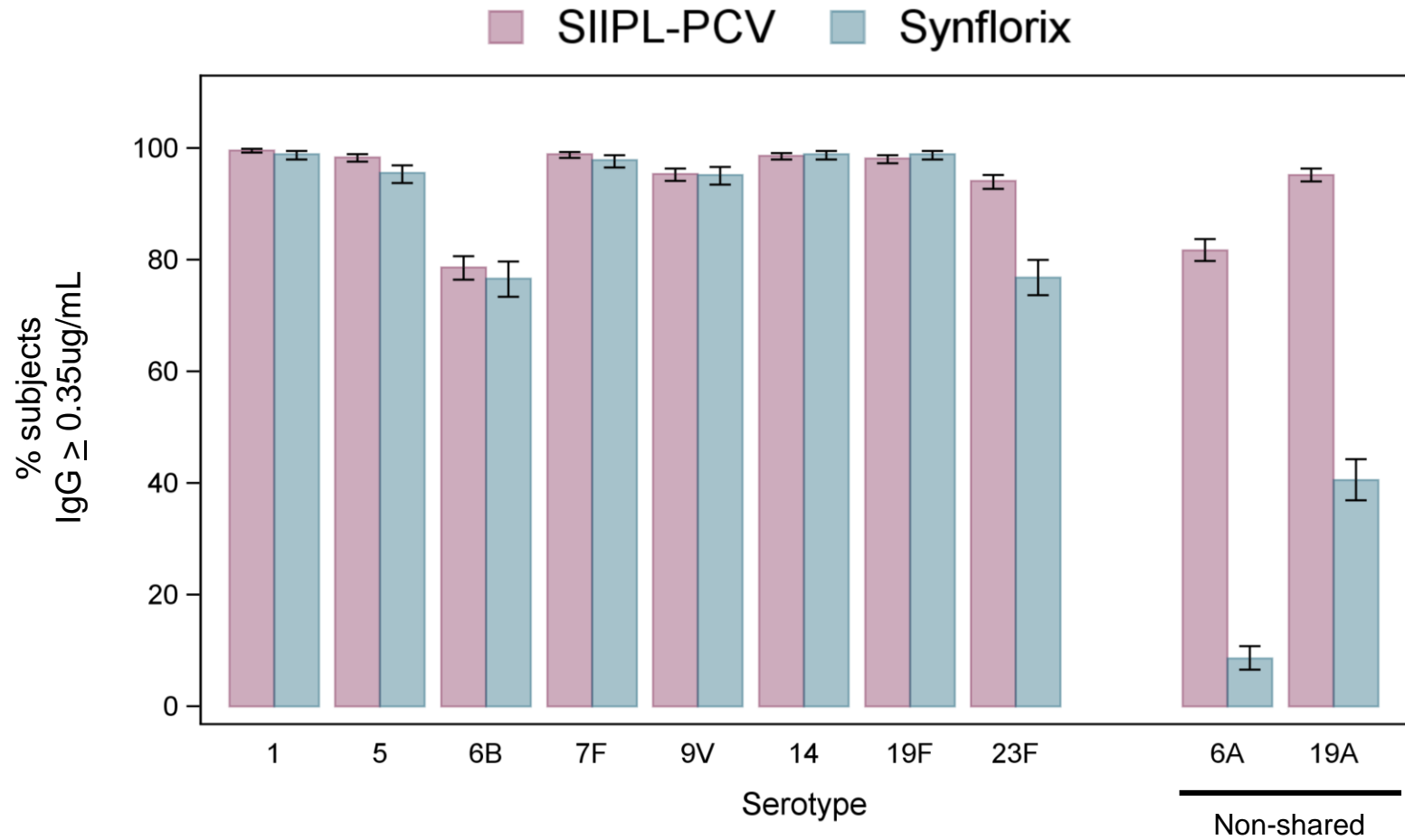


3. Non-interference with co-administered EPI vaccines

- Pentavalent, polio, rotavirus, MR and yellow fever
 - Non-inferiority of seroresponse rates or GMC

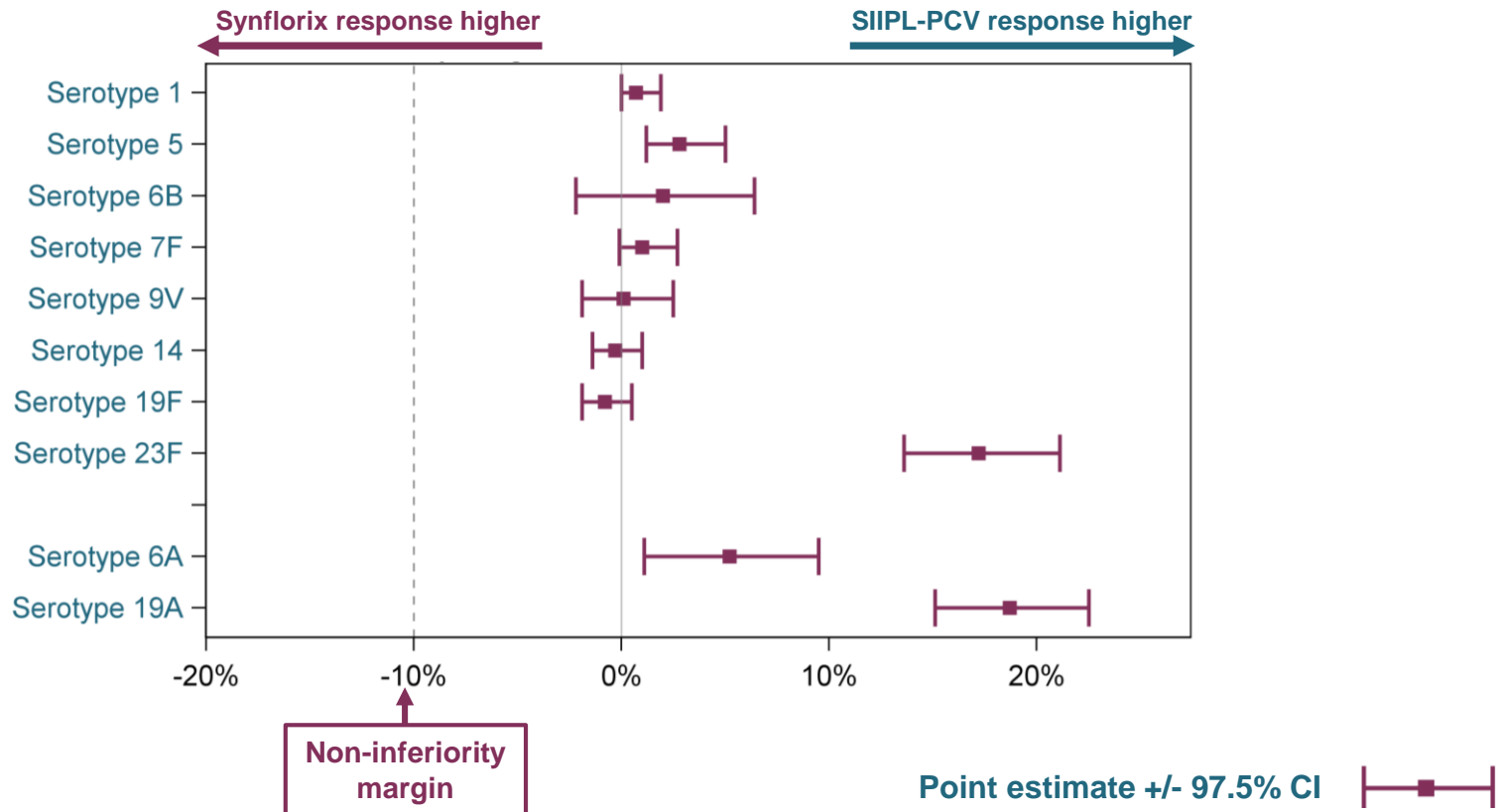


Seroresponse rates – IgG ELISA



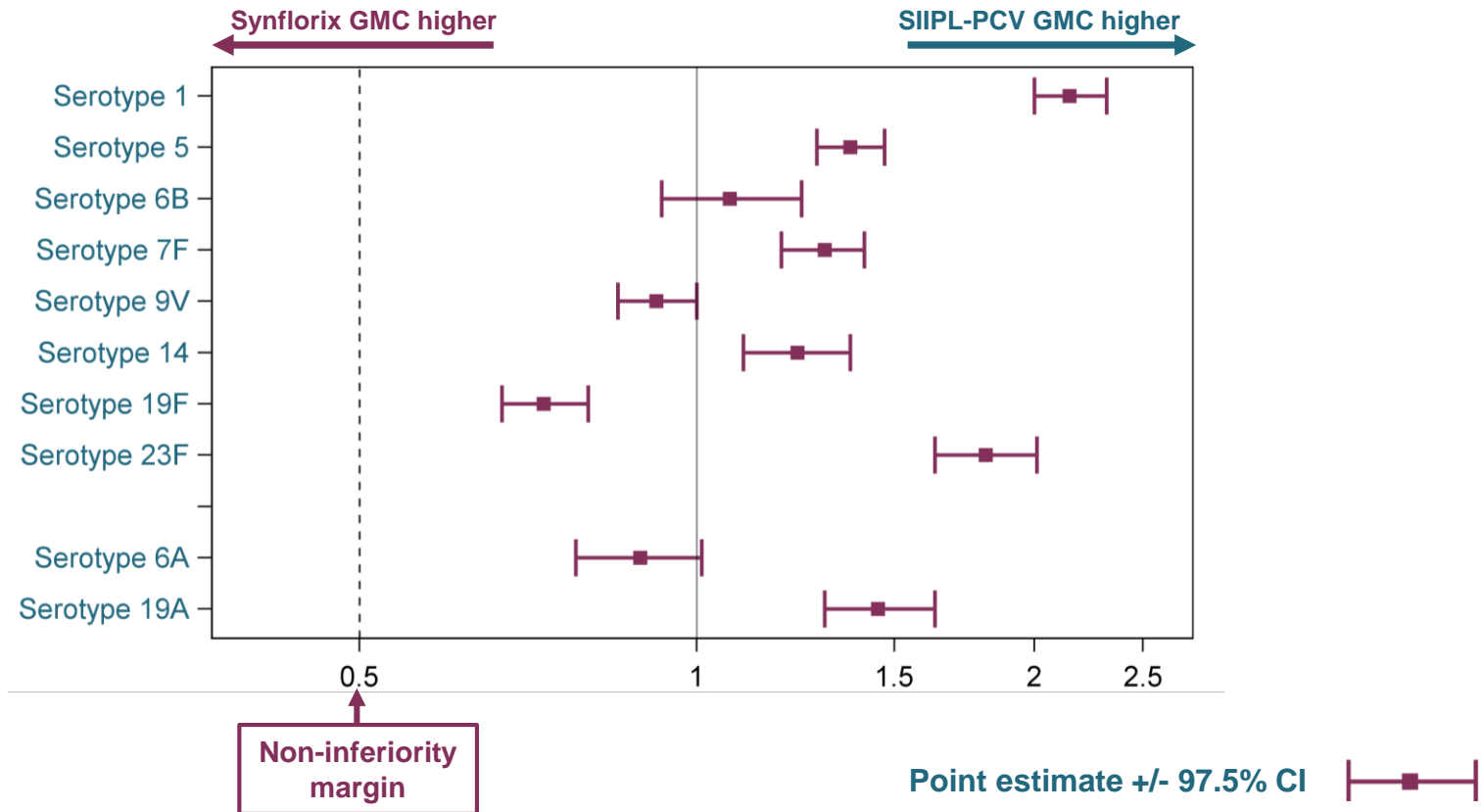
Non-inferior IgG seroresponse rates

Seroresponse rate (IgG ≥ 0.35 $\mu\text{g/ml}$)
(SIPL-PCV – Synflorix)

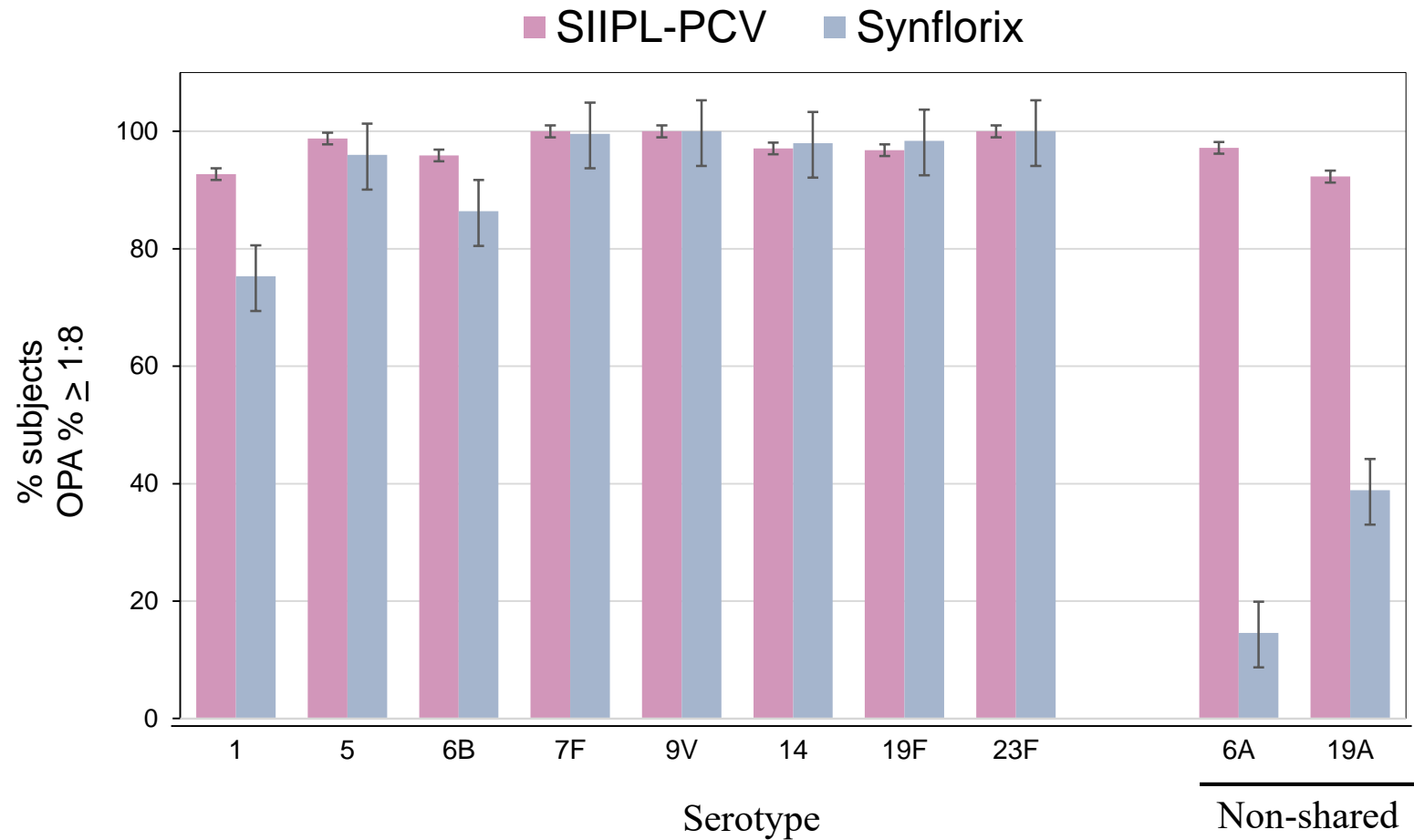


Non-inferior IgG geometric mean concentrations

- GMC ratio (SIIPL-PCV/Synflorix)



Seroresponse rates—Opsonophagocytic Activity



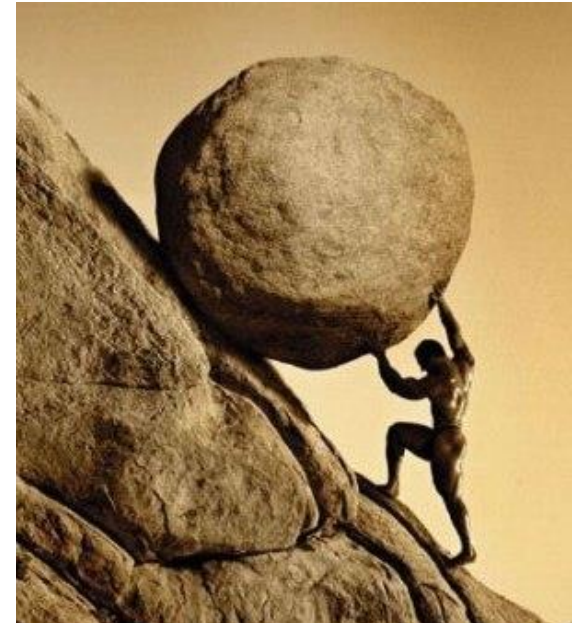
Ongoing SIPL-PCV Clinical Studies

Study/Comparators	Age group/design	Number of subjects	Safety and Immunogenicity	Status
Phase 3 India-3 +0 Prevenar 13 [®] and Synflorix [®]	Infants, 3 +0 Schedule (6, 10 and 14 weeks)	448 Infants (6 to 8 weeks inclusive on Day 0)	Safety and Immunogenicity	Ongoing
Phase 3 India-2 +1 Prevenar 13 [®] and Synflorix [®]	Infants, 2 +1 Schedule (6, 14 weeks and 9 month of age)	336 Infants (6 to 8 weeks inclusive on Day 0)	Safety and Immunogenicity	Ongoing
Phase 3 Gambia-2 +1 Prevenar 13 [®] and Synflorix [®]	Infants, 2 +1 Schedule (6, 14 weeks and 9 month of age)	660 Infants (6 to 8 weeks inclusive on Day 0)	Safety and Immunogenicity	Ongoing

WHO Prequalification anticipated in the near future

Challenges with Higher Valency PCVs

- Overarching challenge is manufacturing complexity
 - If it was routine there would be many licensed PCVs...
- Carrier suppression
 - Is 13-15 valent the maximum for a single carrier protein like CRM₁₉₇?
- What additional serotypes should be included?
 - Regional differences in distribution
- Further serotype replacement



QC Testing of PCVs

Polysaccharide

1. Identity
2. Polysaccharide composition
3. Moisture content
4. Protein impurity
5. Nucleic acid impurity
6. Pyrogen content
7. Molecular size distribution

Carrier Protein

1. Identity
2. Purity
3. Toxicity
4. Extent of derivatisation (if appropriate) NR

Activated Saccharide

1. Extent of activation
2. Molecular size distribution

Bulk Conjugate

1. Identity
2. Residual reagents
3. Saccharide:protein ratio & conjugation markers
4. Capping markers
5. Saccharide content NR
6. Conjugated v. free saccharide
7. Protein content
8. Molecular size distribution
9. Sterility
10. Specific toxicity of carrier (if appropriate)
11. Endotoxin content

Final Vaccine

1. Identity
2. Sterility
3. Saccharide content (of each)
4. Residual moisture
5. Endotoxin content
6. Adjuvant content (if used)
7. Preservative content (if used)
8. General safety test
9. pH
10. Inspection

WHO Recommendations for the production and control of pneumococcal conjugate vaccines, ECBS, October 2003. Updated 2009

13 valent PCV ~ 700 QC tests

Slide courtesy of Neil Ravenscroft

Higher valency PCVs in late stage development

- Pfizer 20 valent PCV
 - In Phase 3 in adults
 - US FDA Fast Track designation for infants and adults



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- **PF-06482077** -- In October 2017, Pfizer initiated a Phase 2 clinical trial to evaluate the safety and immunogenicity of PF-06482077, Pfizer's next-generation multi-valent pneumococcal conjugate vaccine candidate in healthy adults. PF-06482077 is being studied to potentially extend coverage beyond the thirteen serotypes covered by Prevnar 13 to include seven additional serotypes prevalent in causing pneumococcal disease in adults and children. Results from a previously completed Phase 1 trial demonstrated that the vaccine candidate was safe and well tolerated and induced functional immune responses that could kill all twenty serotypes. The FDA granted Fast Track designation for PF-06482077 in May 2017 for use in an infant population and in October 2017 for use in an adult population. The FDA's Fast Track approach is a process designed to facilitate the development and expedite the review of new drugs and vaccines intended to treat or prevent serious conditions and address an unmet medical need.

- Merck 15 and 24 valent PCVs

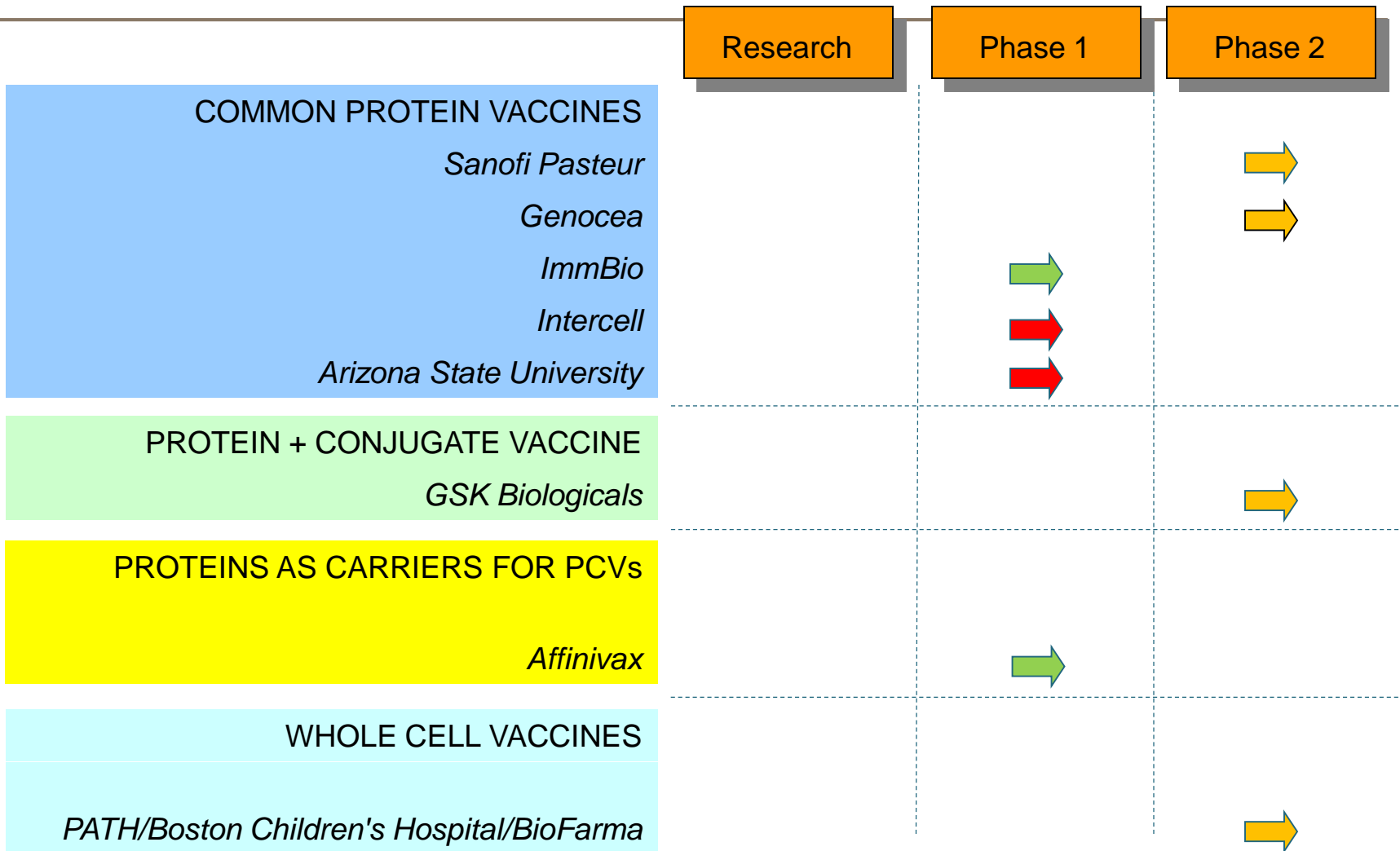
Novel PCV technologies

- Biotin-avidin complexes: Multiple Antigen Presenting System (MAPS - Affinivax)
 - Rapid, simple, high-yield complexing of Ps and carrier protein
 - Potential enhanced coverage using pneumococcal proteins as carriers
- Biosynthetic conjugates (Glycovaxyn, now LimmaTech/GSK)
 - Engineer *E. coli* to synthesize Ps, synthesize carrier protein and perform conjugation
- Cell free synthesis of protein carrier with synthetic amino acids for efficient conjugation (Sutrovax)
 - High PS to protein ratio may reduce carrier suppression
- Solid Phase glycation technology (PnuVax)
 - High efficiency conjugation

Where are we with pneumococcal protein vaccines?

- Preclinical data has been encouraging.
- A number of candidates have advanced to Phase 1 and 2 clinical trials.
- But... no clear evidence thus far of clinical efficacy against pneumococcal NP carriage or disease.
- A graveyard of pneumococcal protein vaccines in Phase 2 trials...

Protein vaccine pipeline (clinical stage)



Protein vaccine challenges

Regulatory pathway for licensure has not defined

- Correlates of protection need to be defined.

Disease endpoint clinical POC difficult for protein vaccines

- What impact on carriage is sufficient for POC?
- Concerns about elimination of pneumococcus from NP—what will replace?
- Placebo controlled trials may be difficult to justify.
- A Phase 3 trial with pneumonia/IPD endpoints will be large and expensive.

What about disease endpoints?

GSK Phase 2 with acute otitis media (AOM) endpoint

Two proteins (PhtD and Pld) co-administered with PCV-13 in Navajo Native American infants.

1,800 total subjects—PCV-13 (900), PCV-13 + Proteins (900).

Efficacy against AOM / acute lower respiratory infection (ALRI)—impact on NP carriage of non-PCV serotypes.

Primary endpoint—clinical AOM.

Secondary endpoints

- Healthcare-provider-diagnosed clinical AOM
- Clinical AOM (modified criteria)
- Recurrent healthcare-provider-diagnosed AOM
- Draining AOM (including pneumococcal AOM)
- Medically attended: ALRI; ALRI with fever; and healthcare-provider-diagnosed ALRI with fever.

Efficacy conclusions – GSK Phase 2 trial

- Incremental efficacy of dPly/PhtD vaccine against AOM (AAP definition) over PCV13 effect was not demonstrated.
- VE point estimates
 - 3.8% (-11.4, 16.9) for all episodes of AAP-defined AOM.
 - 2.9% – 5.2% for other AOM outcomes
 - -4.4% - 2.0% for ALRI outcomes
- **But...** VE tended to be higher for first than all episodes



Efficacy, safety and immunogenicity of a pneumococcal protein-based vaccine co-administered with 13-valent pneumococcal conjugate vaccine against acute otitis media in young children: A phase IIb randomized study

Laura L. Hammitt^{a,*}, James C. Campbell^a, Dorota Borys^b, Robert C. Weatherholtz^a, Raymond Reid^a, Novalene Goklish^a, Lawrence H. Moulton^a, Magali Traskine^b, Yue Song^c, Kristien Swinnen^b, Mathuram Santosham^a, Katherine L. O'Brien^a

VE against the first episode of clinical AOM or ALRI in children aged <12 months

		N	n	VE %	95% CI LL	UL
AAP-AOM	dPly/PhtD	808	165	16.9	-2.1	32.4
	Control	829 ^a	200			
Modified AAP-AOM	dPly/PhtD	808	222	9.3	-8.8	24.3
	Control	829 ^a	247			
HCP-AOM	dPly/PhtD	808	248	9.3	-7.7	23.6
	Control	829 ^a	275			
MA-ALRI	dPly/PhtD	808	44	32.0	0.5	53.6
	Control	829 ^a	66			
MA-ALRI with fever	dPly/PhtD	808	30	38.7	3.6	61.0
	Control	829 ^a	50			
MA-HCP-ALRI with fever	dPly/PhtD	808	89	27.4	4.6	44.7
	Control	829 ^a	123			

Thank you to the many SI IPL-PCV partners



Special thanks to Ed Clarke for slides

