CENTER FOR
INDIGENOUS HEALTH

The HibVax Study

Immunogenicity of *H. influenzae* type b PRP-OMP vaccines in American Indian and Alaska Native infants

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On behalf of the study team in Navajo Nation and Anchorage, Alaska

Disclosures/Disclaimers

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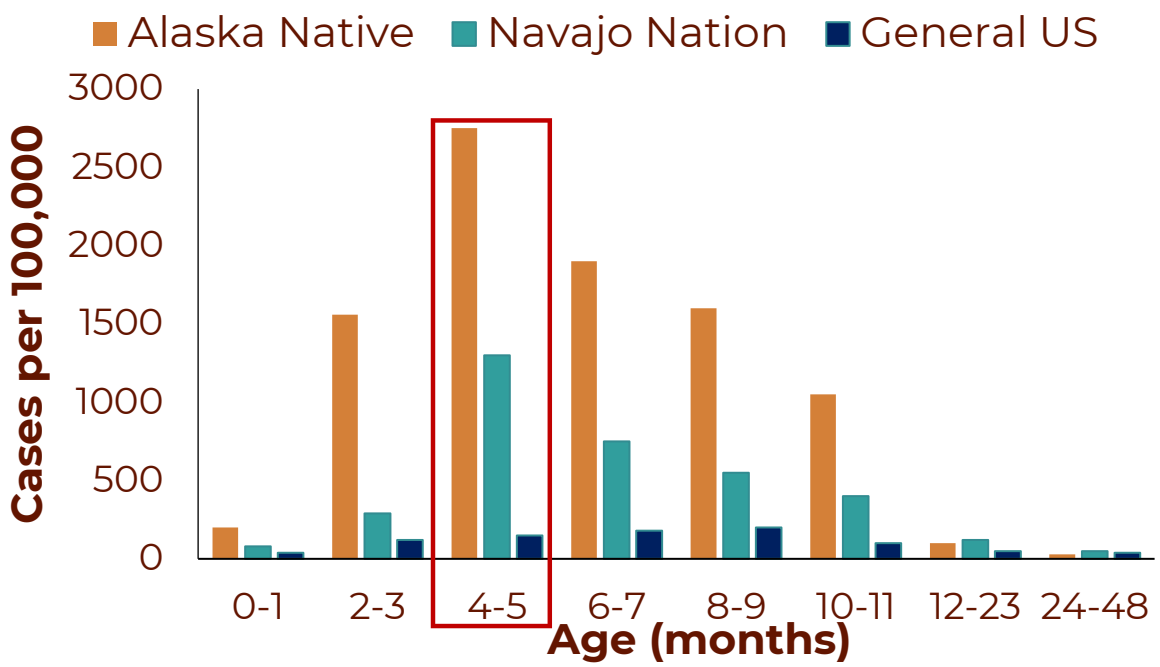
- The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Indian Health Service or the Centers for Disease Control and Prevention.

Preferential recommendation for PRP-OMP Hib conjugate vaccines in AI/AN infants

- Disease at a young age in the pre-vaccine era
- Robust protection following the first dose
  - Immunogenicity
  - Efficacy
- Re-emergence of Hib disease in AN infants following use of non-PRP-OMP vaccines

***H. influenzae* meningitis in children <5 years, 1971-1977**



Ward JI et al., *Lancet*, 1981; 1281-1284.

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Table 3. Efficacy Analysis of *H. influenzae* Type b OMPC Vaccine*

Time of Disease Onset	Cases of *H. influenzae* Vaccine (n/total)	Cases of *H. influenzae* Placebo (n/total)	Efficacy Estimate (%)	p-value	95% CI
At least 1 dose					
Onset before 18 mo.	1/2588	22/2602	95	<0.001	72-99
Onset before 15 mo.	0/2588	21/2602	100	<0.001	81-100
Onset before 2nd dose	0/2588	8/2602	100	0.005	41-100
Two doses					
Onset before 18 mo.	1/2056	14/2105	93	<0.001	53-98
Onset before 15 mo.	0/2056	13/2105	100	<0.001	67-100

*Intention-to-treat analysis - included all infants enrolled.

Santosham et al., *N Engl J Med* 1991; 324:1767-1772

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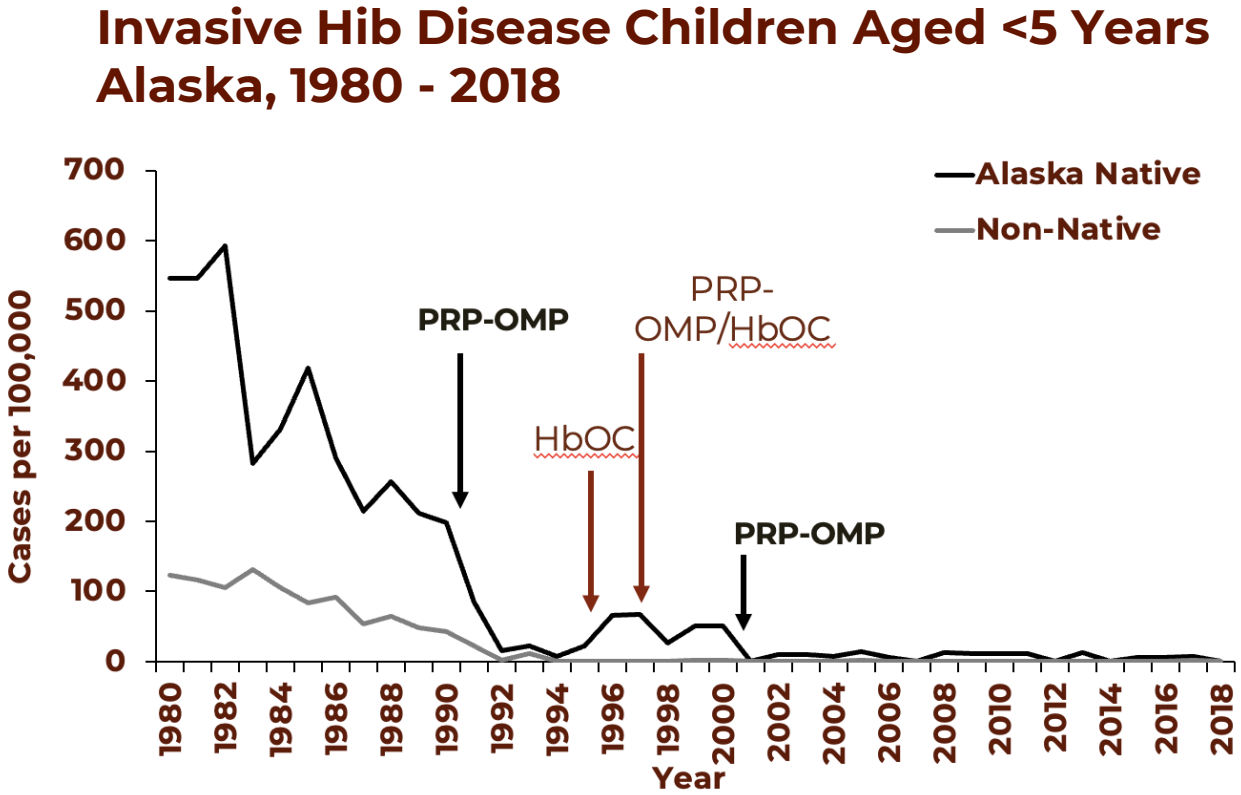
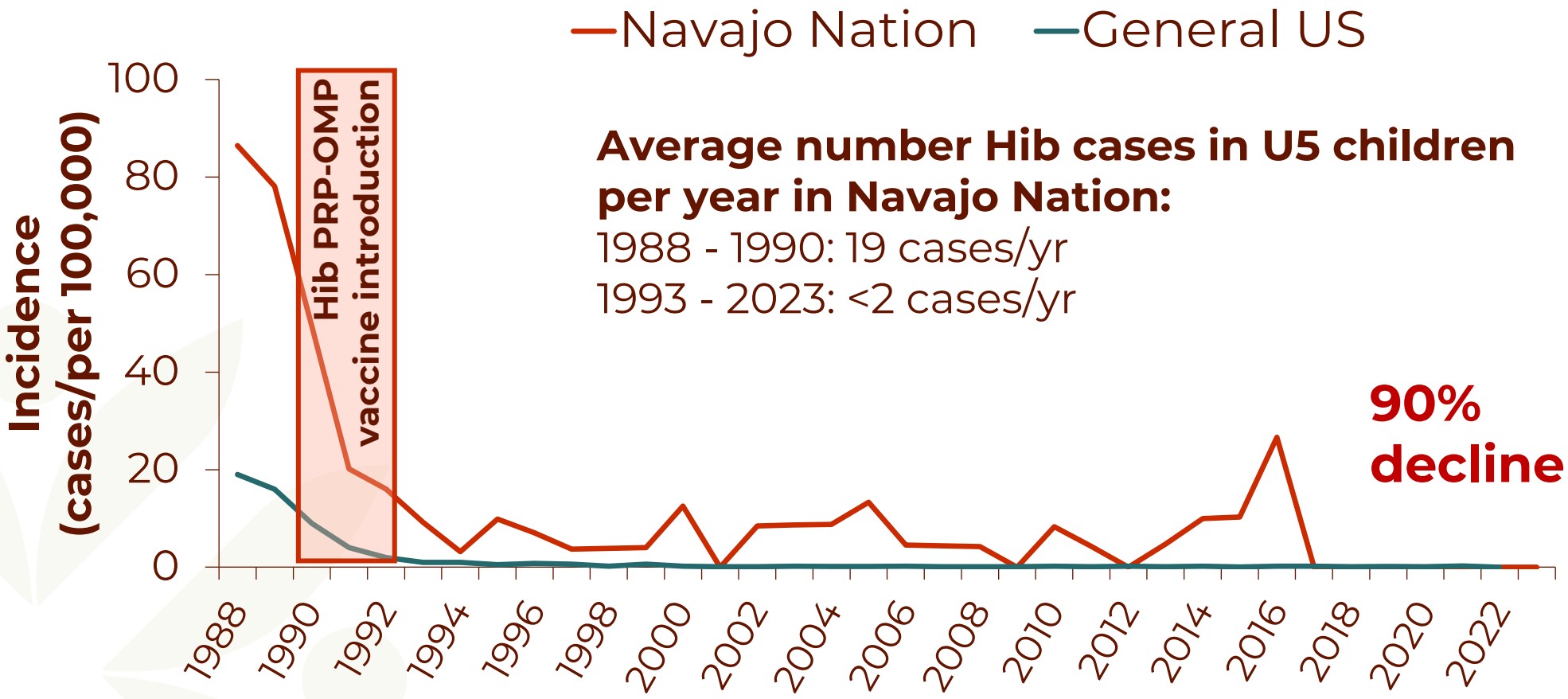


Figure courtesy of Rosalyn Singleton; Singleton, et al. J Pediatr 2000; 137:313-20

Invasive Hib disease in children <5 years

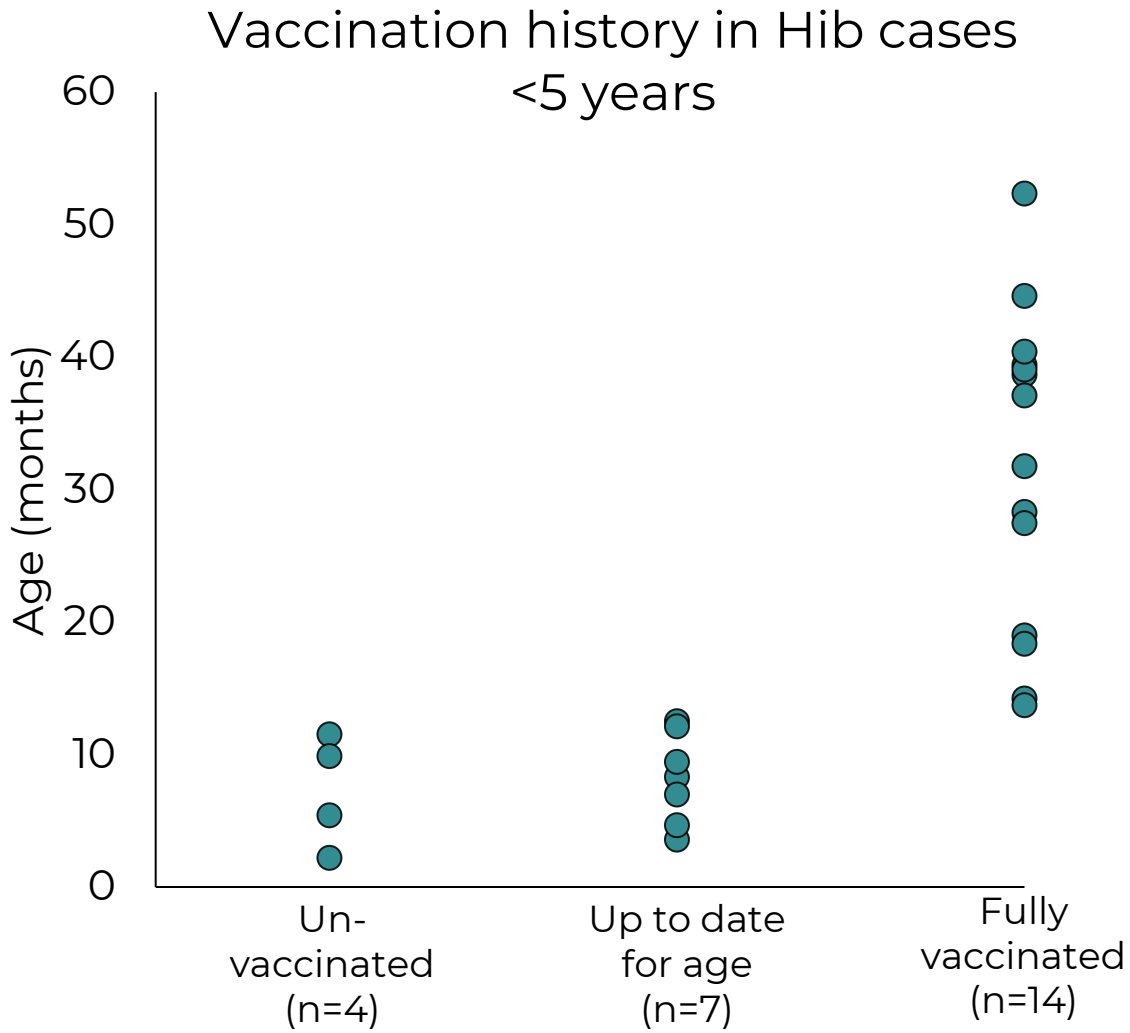


CIH/Navajo Epidemiology Center Active Bacterial Surveillance data; Navajo Research Conference 2021

Invasive Hib disease in AI/AN children <5 years Navajo Nation and White Mountain Apache Tribal Lands 2004-2023 (N=25)

Average age	21 months
Median age (IQR)	14 months (9-37 months)
Age range	2-52 months
Clinical syndrome	Meningitis: 28% Pneumonia: 40%

IQR: interquartile range



	PedvaxHIB® (PRP-OMP Hib vaccine)	Vaxelis® (DTaP-IPV-Hib-HepB)
Contents	Single Antigen	Hexavalent
Use in AI/AN infants	Currently recommended Hib vaccine for AI/AN infants	Currently recommended for general U.S. infants; not yet preferentially recommended for AI/AN infants
Hib Antigen and Conjugate	7.5 µg PRP OMP	3.0 µg PRP OMP
Primary Series	2-dose (2, 4 months)	3-dose (2, 4, 6 months)
Post-dose 1 immunogenicity	High	**???**

PRP: Hib polyribosylribitol phosphate; OMP: outer membrane protein of *Neisseria meningitidis*

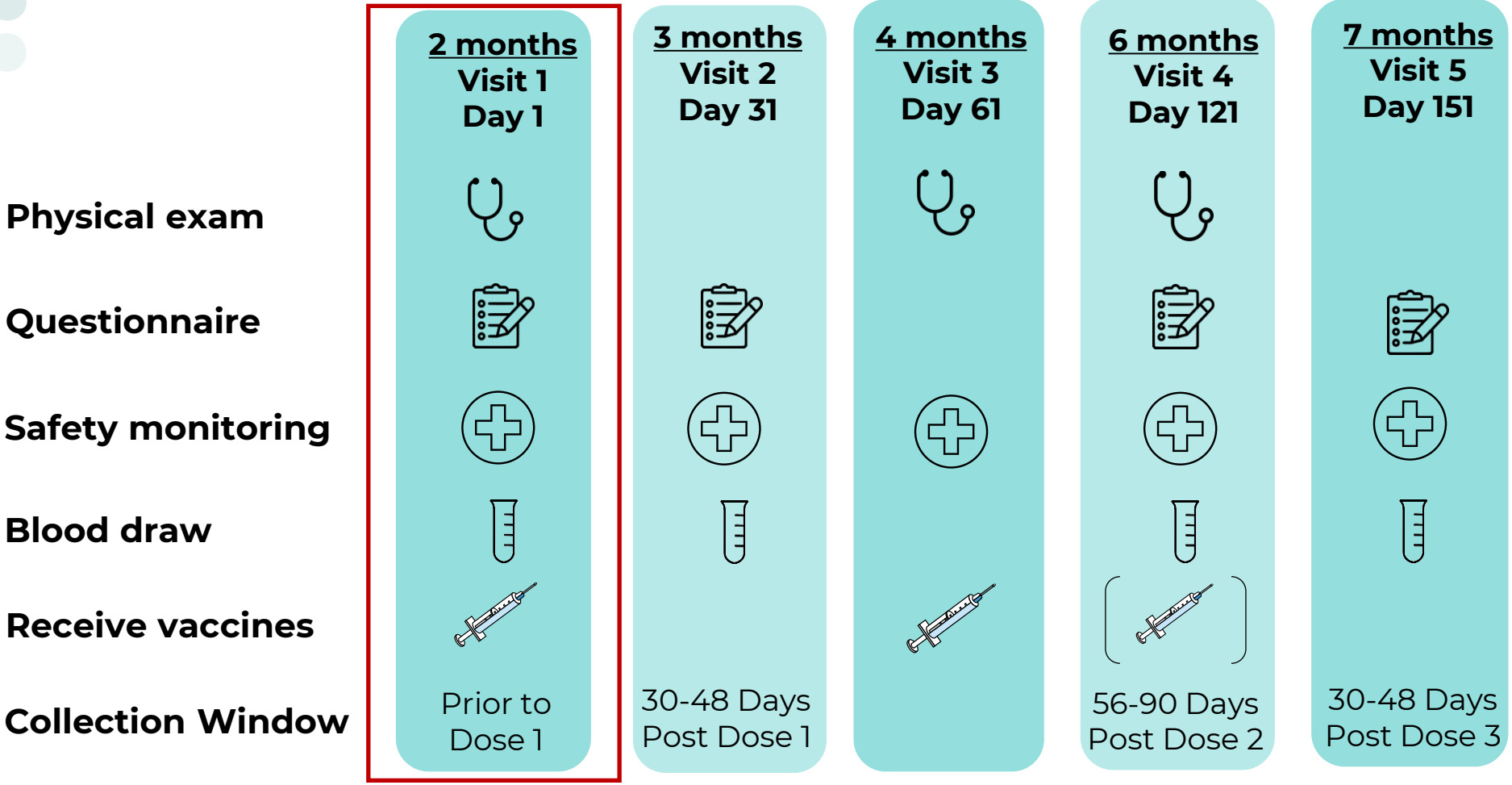
Combination vaccines → fewer shots, fewer missed doses, lower administrative burden

HibVax Study: Primary objective

Do **Hib antibody levels** in AI/AN infants meet **non-inferiority** criteria **30 days after dose 1** of Vaxelis® compared to PedvaxHIB®?

HibVax Study Overview

Phase IV, prospective, open label, RCT



NCT04978818; JHSPH IRB #11170; Navajo Nation Human Research Review Board #20.374; Alaska Area IRB #2020-20-011

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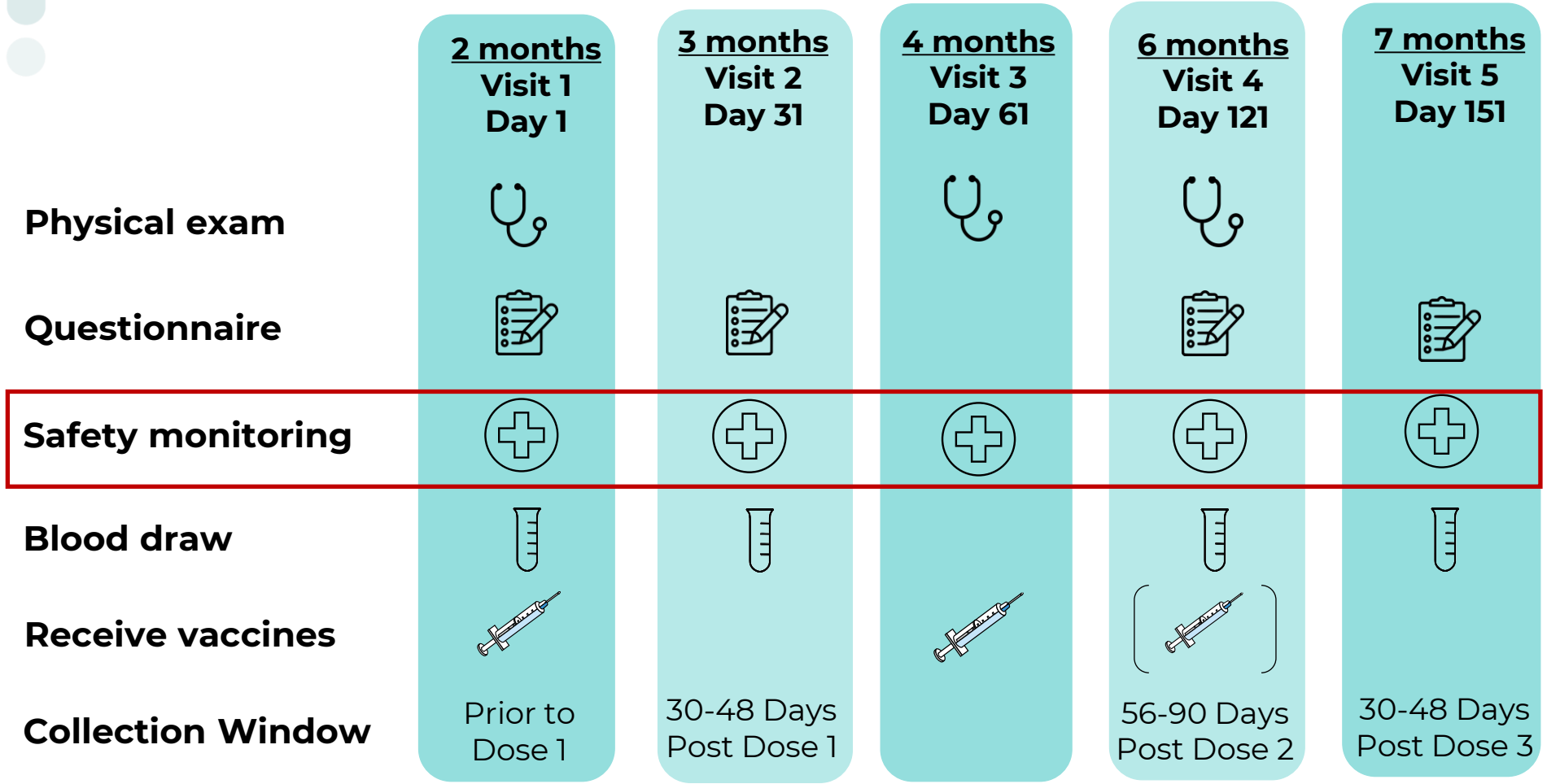

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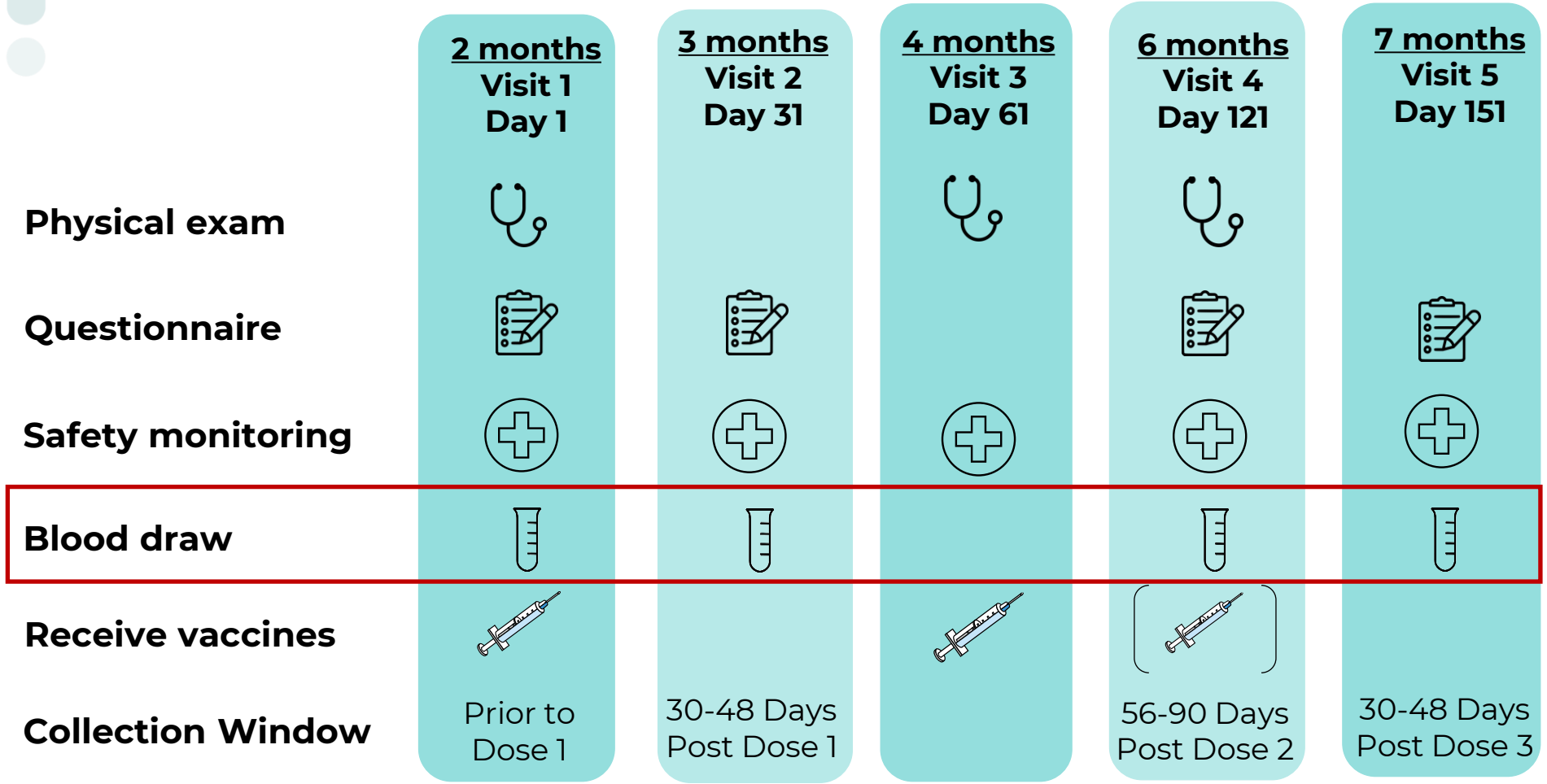

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Inclusion Criteria

- Healthy AI/AN infant born at gestational age of ≥35 weeks
- Between 6 to 12 weeks of age
- Written informed consent provided by parent(s)/Legally Authorized Representative(s)

Exclusion Criteria (selected)

- Prior receipt of infant vaccines other than birth dose hepatitis B vaccine
- History of receipt of blood, blood products, or antibody products
- Immunocompromised
- Allergy to any vaccine component, or to latex
- Acute illness and/or fever ≥38.0°C (time-limited exclusion)

Methods

- Anti-Hib IgG antibody levels measured by commercially available ELISA assay at CDC/Arctic Investigations Program, Anchorage, AK
- Geometric mean concentrations (GMCs) assessed using constrained longitudinal analysis (cLDA)
  - Assumes groups have equal anti-Hib GMC at baseline based on the randomized study design
- Results are presented for all evaluable participants complying with the procedures and intervals between primary doses, as defined in the protocol

Study Enrollment

- Enrollment began in Jan 2022 in Anchorage, AK and four sites in the Navajo Nation (Southwest US)
- All study visits competed by Oct 2023

Total enrollment	333
Anchorage, AK	26
Chinle, AZ	61
Fort Defiance, AZ	115
Gallup, NM	81
Shiprock, NM	50

Study Visit Completion

	2 months Day 1 N	3 months **Day 31** **N**	4 months Day 61 N	6 months Day 121 N	7 months Day 151 N
Completed Visit	333	319	314	300	296
Evaluable Sample	321	307	-	272	270
Evaluable Sample in ATP Cohort	321	298	-	255	245

ATP: According to protocol
No specimens were collected at Day 61, in accordance with the protocol

Participant Characteristics

	PedvaxHIB® (N=166)	Vaxelis® (N=167)
Median age in days at Dose 1, (interquartile range)	56 (45-63)	60 (46-63)
Male, n (%)	74 (44.6)	84 (50.3)
Site, n (%)		
Anchorage, AK	13 (7.8)	13 (7.8)
Chinle, AZ	30 (18.1)	31 (18.6)
Fort Defiance, AZ	57 (34.3)	58 (34.7)
Gallup, NM	40 (24.1)	41 (24.6)
Shiprock, NM	26 (15.7)	24 (14.4)

Serious Adverse Events (SAEs)

- 25 SAEs were detected during study follow up in 21 individuals.

	PedvaxHIB® N=166	Vaxelis® N=167	Total
SAEs, n	15	10	**25**
Participants, n (%)	12 (7%)	9 (5%)	**21 (6%)**

- No SAEs were associated with study participation.

- The most common SAE was acute respiratory infection (n=21).

Primary Outcome: Anti-Hib IgG Geometric Mean Concentration (GMC) 30 Days Post-Dose 1

		PedvaxHIB®	Vaxelis®
Anti-Hib Antibody GMC µg/mL (95% CI)	Observed Data	0.39 (0.31- 0.50)	0.41 (0.33 - 0.52)
	Modeled by cLDA	0.40 (0.31 - 0.50)	0.41 (0.33 - 0.51)

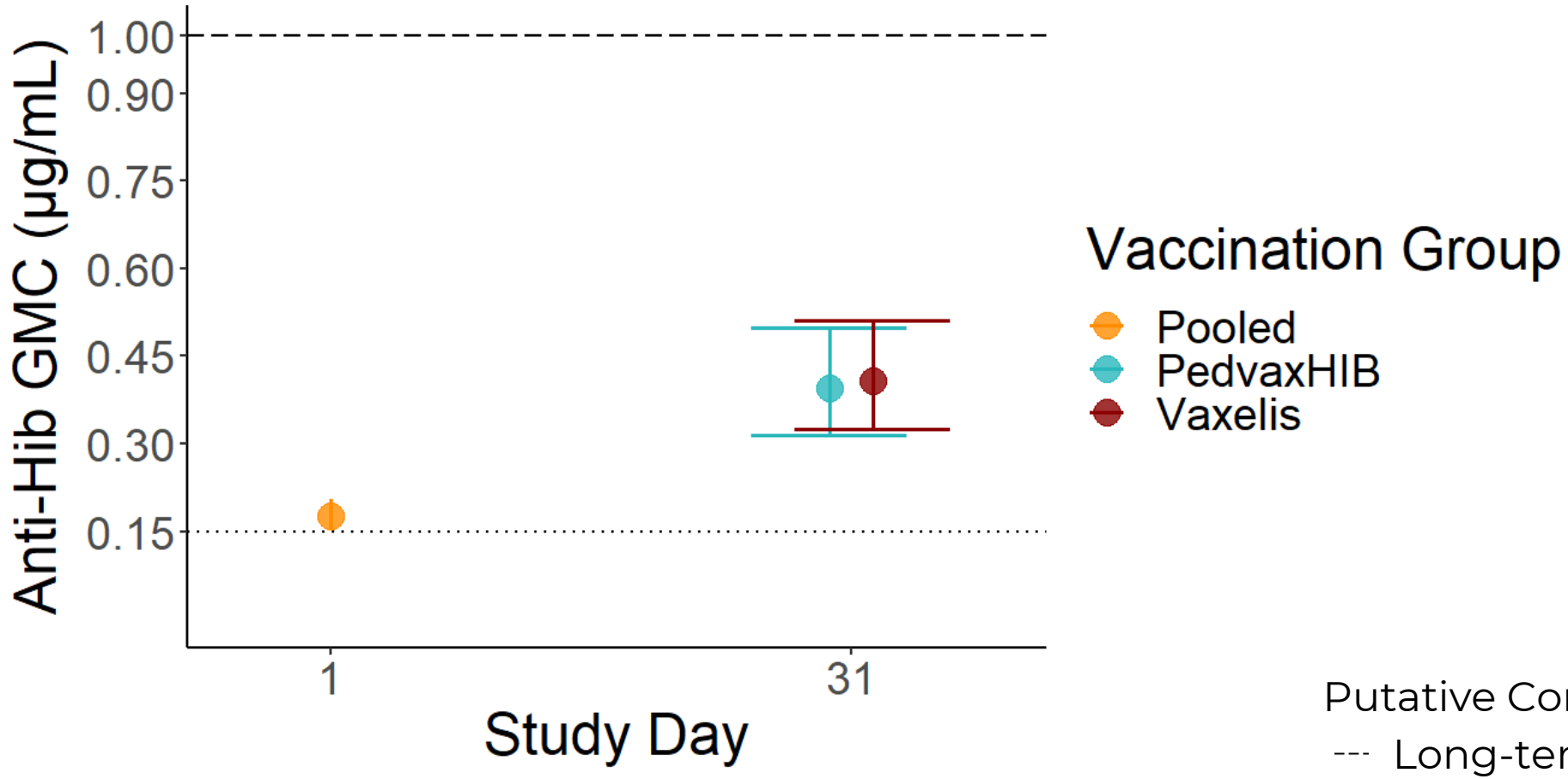
CI: confidence interval; cLDA: constrained longitudinal data analysis

Ratio of GMCs (Vaxelis : PedvaxHib)

1.03 (0.75 - 1.41)

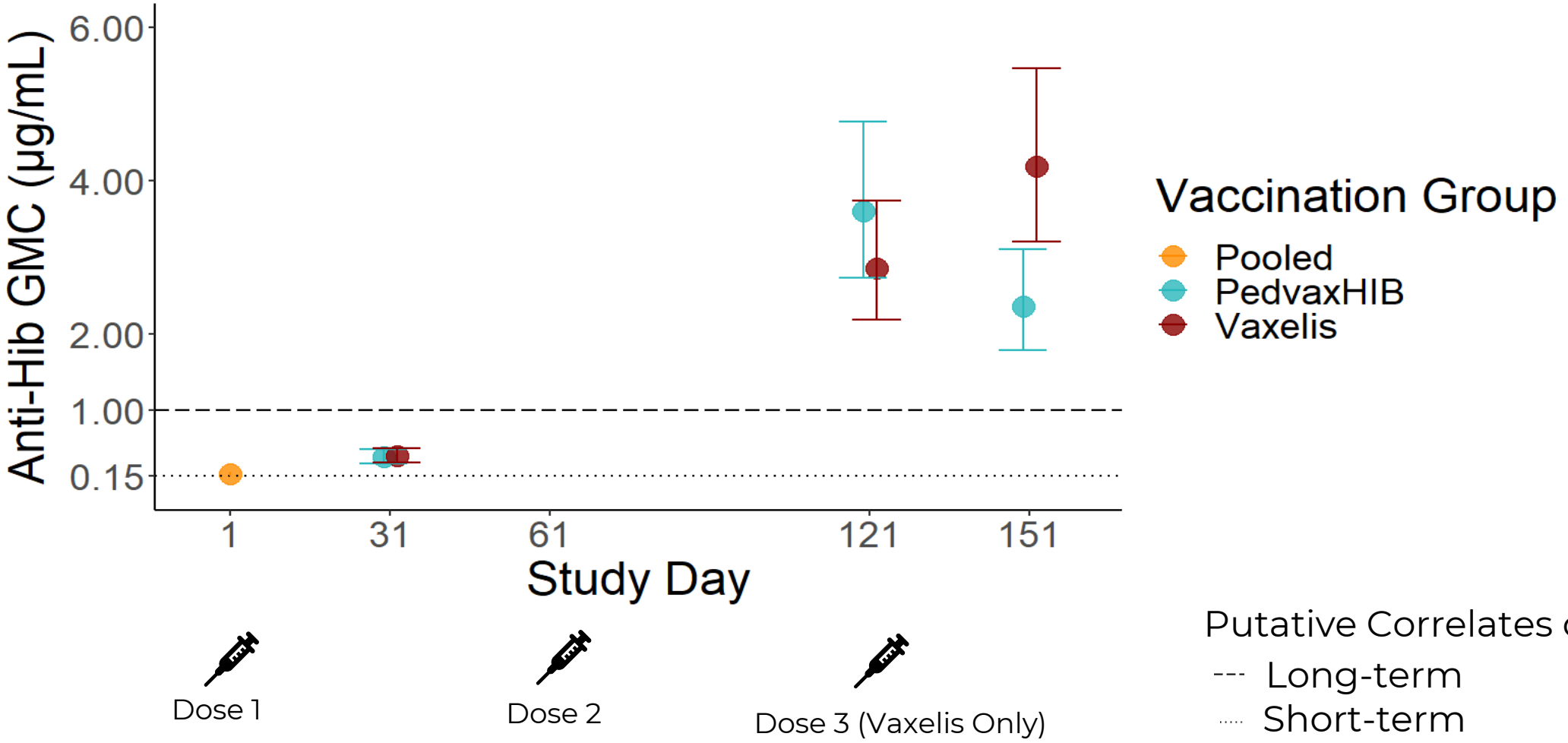
The pre-specified non-inferiority criterion was met based on the lower bound of the 95% confidence interval (CI) around the antibody concentration ratio [Vaxelis / PedvaxHIB] being > 0.67

Anti-Hib IgG Geometric Mean Concentration Day 1 and Day 31



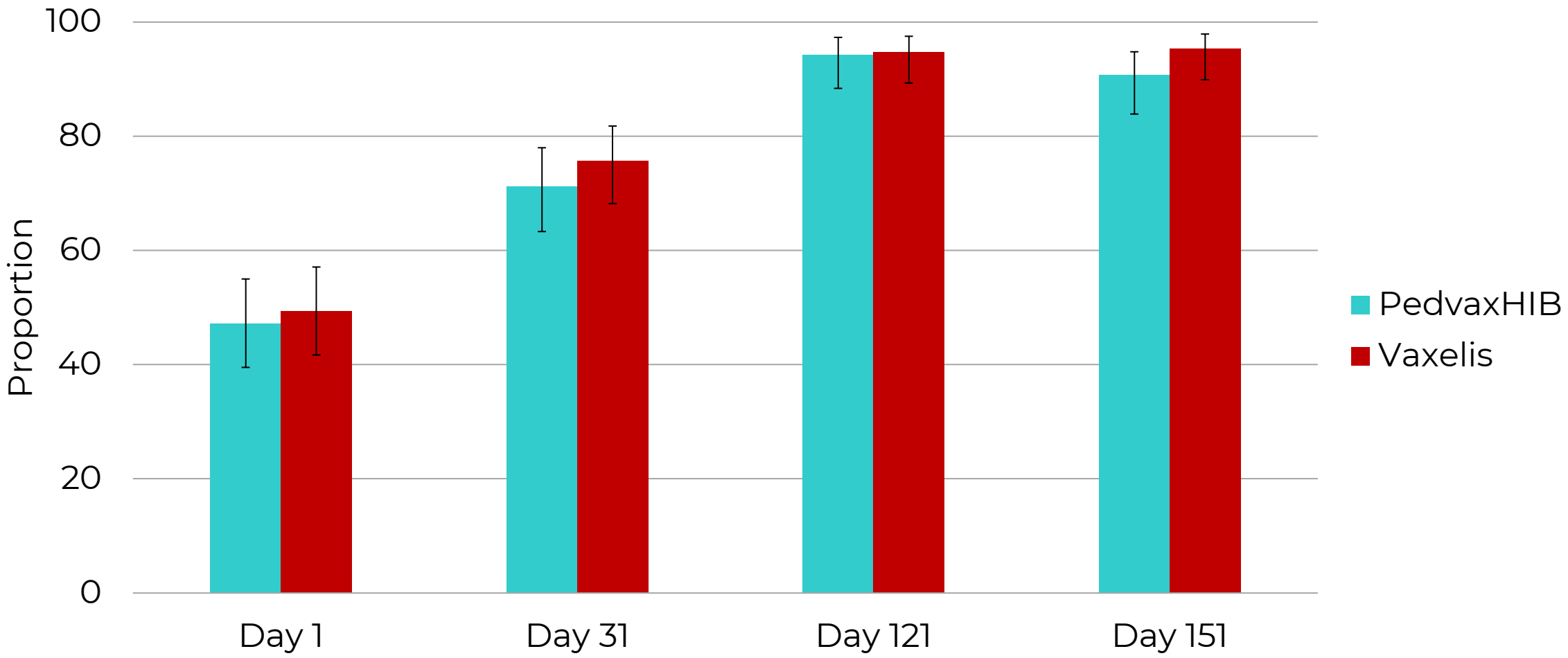
Output from constrained longitudinal data analysis

Anti-Hib IgG Geometric Mean Concentration Days 1, 31, 121, and 151

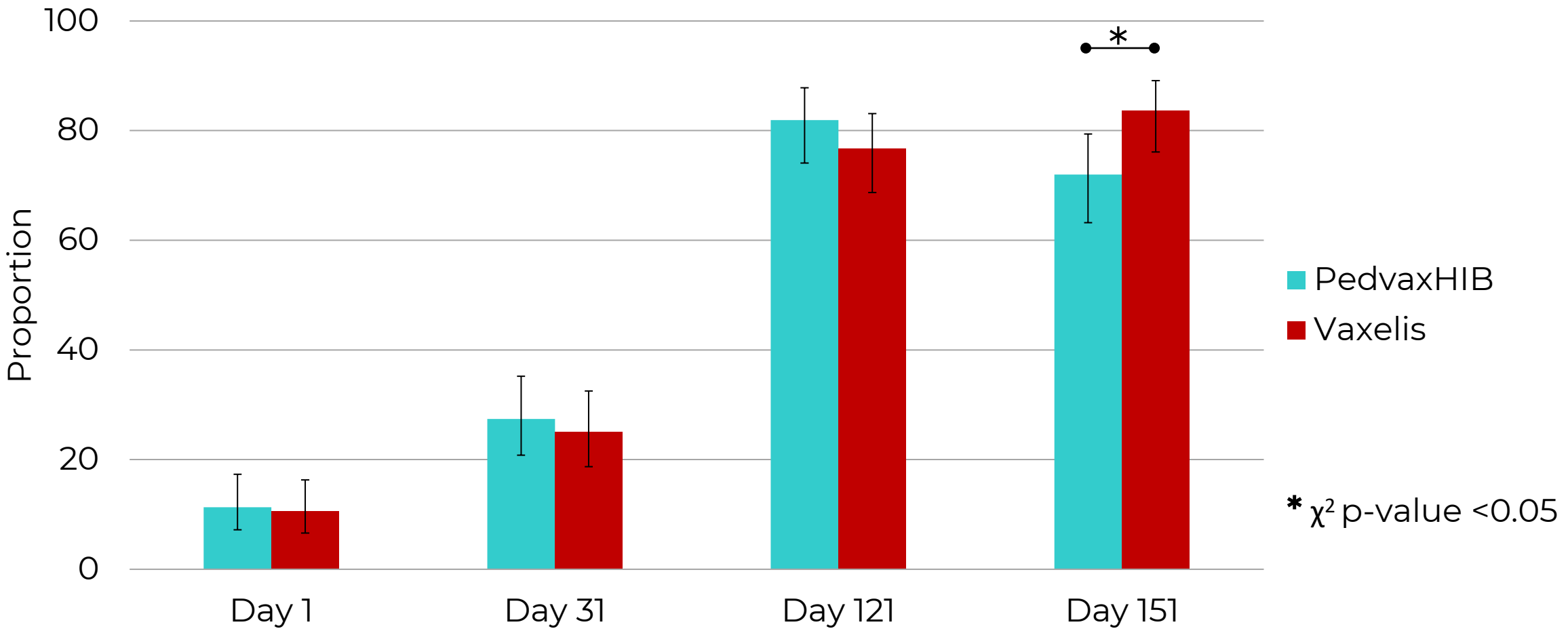


Output from constrained longitudinal data analysis

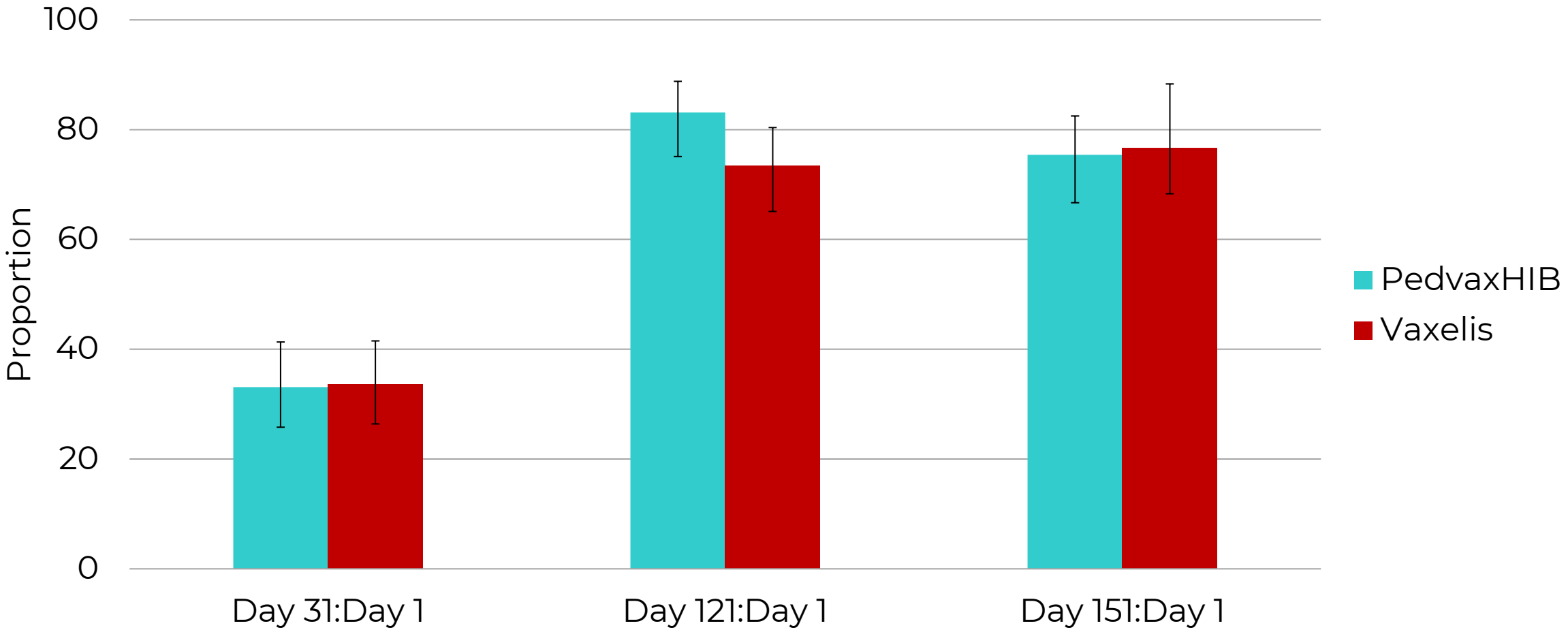
Proportion with Anti-Hib Concentration ≥0.15 µg/mL



Proportion with Anti-Hib Concentration ≥1.0 µg/mL



Proportion with 4-fold rise in Anti-Hib Concentration from Day 1



Limitations

- Participant follow-up ended at 7 months
  - Over 90% of participants had anti-Hib antibody above the putative correlate of short-term protection
  - The proportion of participants with anti-Hib antibody concentrations above the putative correlate of long-term protection and the anti-Hib GMC were greater in the Vaxelis® group

Protection Post-Booster

- Median age of Hib disease in AI/AN children in the Southwest US: 14 months
  - Majority of cases occur in fully vaccinated children
- Current booster strategy for AI/AN children: PedvaxHib at 12-15 months
- Robust immunogenicity seen in heterologous schedules of PRP-OMP followed by conjugate vaccines with different carrier proteins (e.g. PRP-TT, HbOC)

Reid *et al.*, 1993; Decker *et al.,* 1993; Decker and Edwards, 1998; Greenberg *et al*., 1995; Wilck *et al*., 2021

Vaxelis + PRP-TT

4 doses PRP-TT

Table 2
Protocol 006: Hib Response in American Indian (AI) Subset and All Races.

		American Indian	
		DTaP-IPV-Hib-HepB	Control
Time Point	Endpoint	Observed response (95% CI)	Observed response (95% CI)
Post-dose 3	% with titer ≥ 0.15 ug/mL (S/N)	100 (124/124) (97.1, 100)	100 (22/22) (84.6, 100)
	% with titer ≥ 1.0 ug/mL (S/N)	92.7 (115/124) (86.7, 96.6)	86.4 (19/22) (65.1, 97.1)
	GMC	7.8 (6.2, 9.9)	5.9 (3.1, 11.2)
Post-toddler Dose	% with titer ≥ 0.15 ug/mL (S/N)	100 (102/102) (96.5, 100)	100 (16/16) (79.4, 100)
	% with titer ≥ 1.0 ug/mL (S/N)	100 (102/102) (96.5, 100)	100 (16/16) (79.4, 100)
	GMC	55.4 (44.4, 69.1)	20.9 (13.8, 31.5)

Note: Toddler dose included DTaP + PRP-TT

Significantly higher post-booster anti-Hib GMC with a heterologous booster dose

Wilck MB et al. Vaccine. 2021;39(9):1428-1434. doi:10.1016/j.vaccine.2021.01.046

Conclusions

- Post-dose 1 anti-Hib GMCs following Vaxelis® met the pre-specified criteria for non-inferiority.
- Including Vaxelis® among the vaccines with a preferential recommendation would expand the available options for AI/AN children.

Acknowledgements

- Study participants and their families
- Institutional Review Boards
  - Navajo Nation Human Research Review Board (NNR-20.374)
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  - Alaska Native Tribal Health Consortium Human Research Review Committee
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