Haemophilus influenzae type b in Native American children

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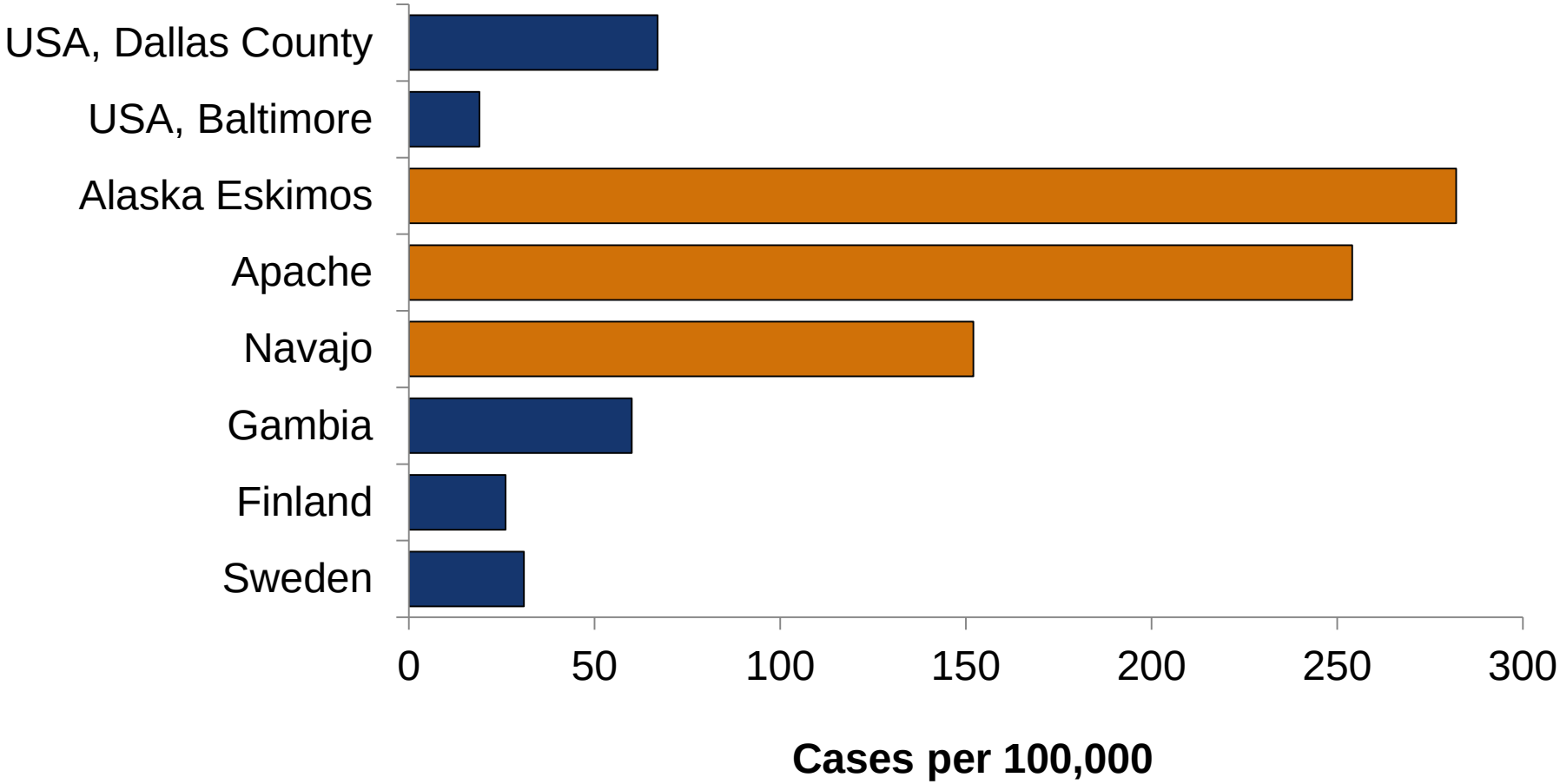
Disclosures

- Research funding to my institution from GSK, Merck, Novavax, Pfizer

Overview

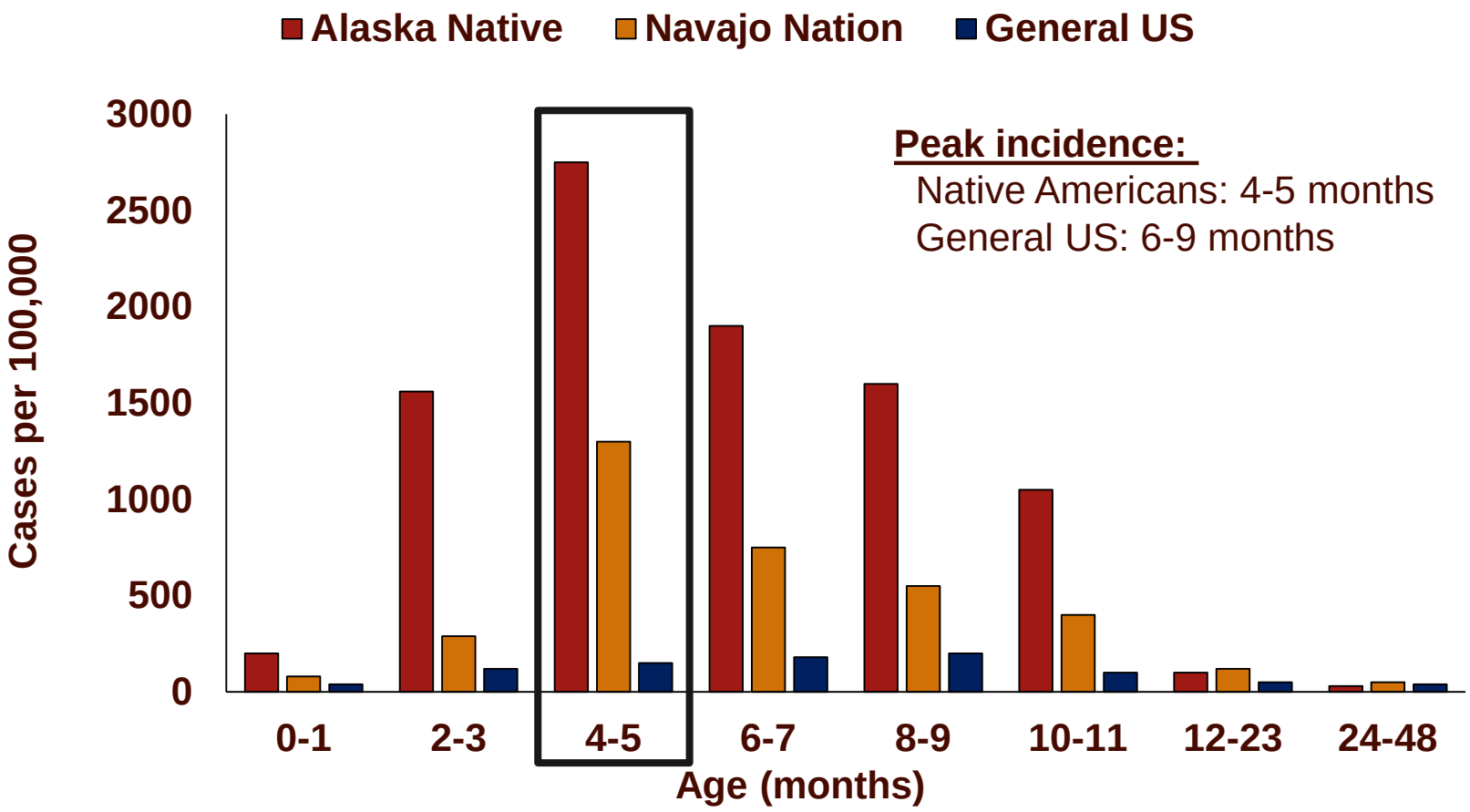
- *H. influenzae* type b (Hib) disease epidemiology in Native American children
- Rationale for preferential recommendation for PRP-OMP Hib vaccine for Native American children
- Considerations around Hexavalent use

H. influenzae type b (Hib) disease in children <5 years old: pre-vaccine era, 1965-1990



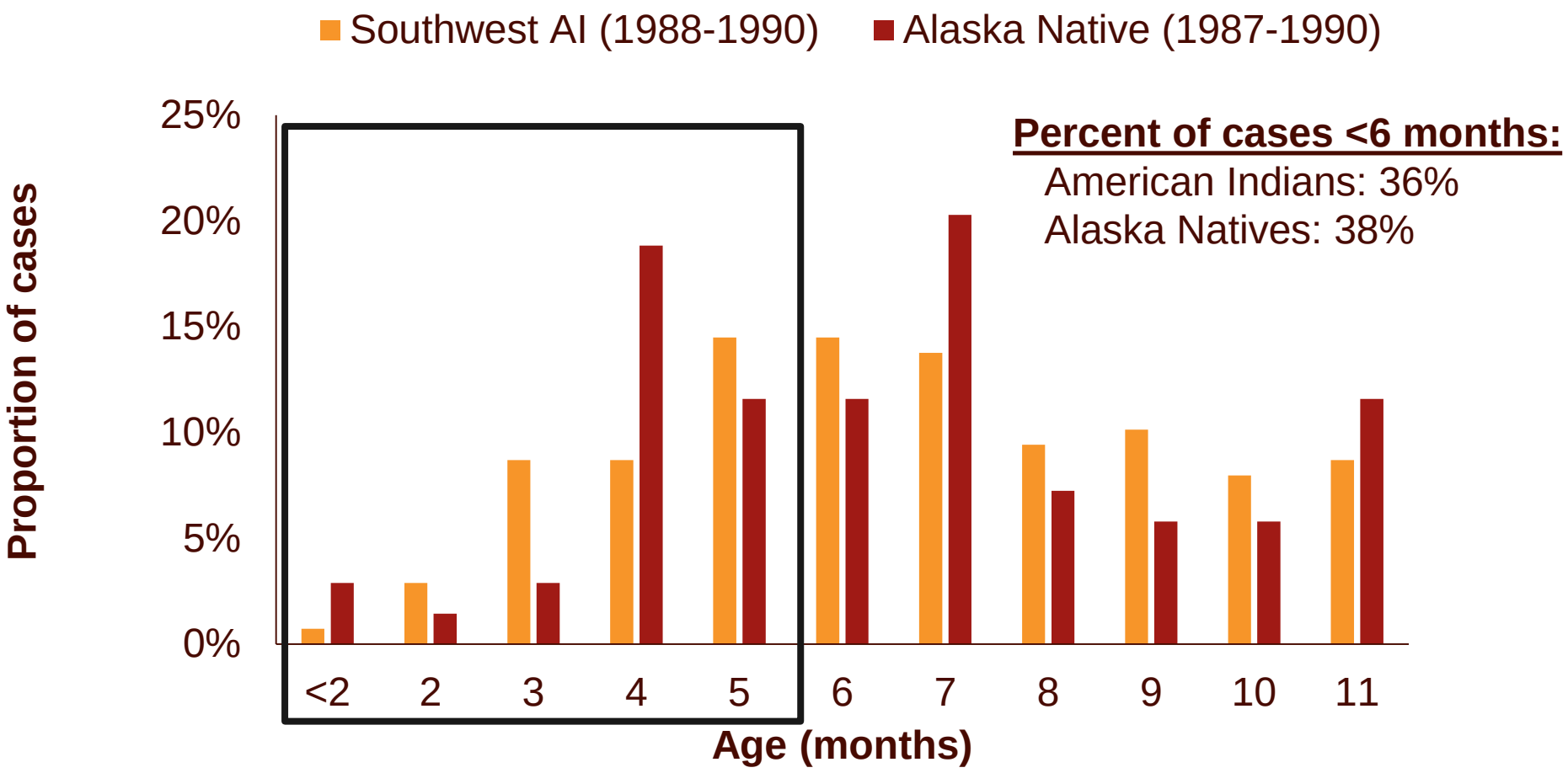
Modified from Bijlmer et al., *Vaccine*, 1991; 9(suppl.):S5

H. influenzae meningitis in children <5 years – Native Americans vs. General US, 1971-1977



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

Hib disease in Native American children <1 year, pre-vaccine era



Hib conjugate vaccines for use in infants

- **PRP-D**
  - PRP-diphtheria toxoid (ProHibit)
- **HbOC**
  - Hib oligosaccharide-CRM_{197} (Hibtiter)
- **PRP-T**
  - PRP-tetanus toxoid (ActHib; Hiberix)
- **PRP-OMP**
  - PRP *N. meningitidis* outer membrane protein (OMP) (PedvaxHIB)

PRP = Polyribosylribitol phosphate

Hib conjugate vaccine correlates of protection

- Based on serum anti-PRP antibody geometric mean concentrations (GMCs)
- GMC ≥0.15 µg/mL: predicts *short-term* protection against invasive disease
- GMC ≥1.0 µg/mL: predicts *long-term* protection against invasive disease

Käyhty et al., *J Infect Dis*; 1983, 147:1100

Immunogenicity of 2 or 3 Hib conjugate vaccine doses in Alaska Native infants

Age (mos) of serum collection	HbOC (2, 4, 6 months)				PRP-D (2, 4, 6 months)				PRP-OMP (2, 4 months)			
	n	GMC (µg/ml)	≥0.15 µg/ml (%)	≥1.0 µg/ml (%)	n	GMC (µg/ml)	≥0.15 µg/ml (%)	≥1.0 µg/ml (%)	n	GMC (µg/ml)	≥0.15 µg/ml (%)	≥1.0 µg/ml (%)
2	55	0.15	30 (55)	3 (5)	56	0.06	14 (25)	2 (4)	44	0.16	20 (45)	6 (14)
4	54	0.07	13 (24)	0 (0)	55	0.04	6 (11)	1 (2)	44	1.37	40 (91)	25 (57)
6	56	0.59	44 (79)	24 (43)	55	0.06	15 (27)	6 (11)	43	2.71	43 (100)	34 (79)
7	53	13.72	53 (100)	50 (94)	40	0.55	31 (78)	18 (45)	--	--	--	--
9-12	52	3.7	50 (96)	42 (81)	42	0.19	27 (64)	9 (21)	39	0.53	34 (87)	13 (33)
15-18	35	1.53	32 (91)	24 (69)	32	0.08	14 (44)	1 (3)	28	0.23	20 (71)	4 (14)

GMC: geometric mean concentration. Results for PRP-T not shown.

Bulkow et al., *Pediatr Infect Dis J* 1993;12:484-92

THE EFFICACY IN NAVAJO INFANTS OF A CONJUGATE VACCINE CONSISTING OF *HAEMOPHILUS INFLUENZAE* TYPE b POLYSACCHARIDE AND *NEISSERIA MENINGITIDIS* OUTER-MEMBRANE PROTEIN COMPLEX

Mathuram Santosham, M.D., M.P.H., Mark Wolff, Ph.D., Raymond Reid, M.D., Matt Hohenboken, M.D., Ph.D., Massee Bateman, M.D., Julius Goepp, M.D., Margaret Cortese, M.D., David Sack, M.D., Janné Hill, B.S., Wendy Newcomer, M.P.H., Linda Capriotti, M.P.H., Jeanne Smith, M.P.H., Marjorie Owen, M.S., Sheila Gahagan, M.D., Diana Hu, M.D., Renee Kling, B.A., Linda Lukacs, B.S., Ronald W. Ellis, Ph.D., Philip P. Vella, Ph.D., Gary Calandra, M.D., Ph.D., Holly Matthews, M.S., and Vincent Ahonkhai, M.D.

Table 2. Antibody Responses in Infants Vaccinated with *H. influenzae* type b OMP Vaccine or Placebo

Time of Measurement	Vaccine					Placebo				
	No. of infants	Mean age	Antibody Levels			No. of infants	Mean age	Antibody Levels		
			≥0.15 µg	≥1.0 µg	GMT*			≥0.15 µg	≥1.0 µg	GMT*
	(n)	(mos)	(%)	(%)	(µg/mL)	(n)	(mos)	(%)	(%)	(µg/mL)
Before vaccination	982	1.8	45	10	0.16	991	1.8	44	8	0.16
2 mo. after 1st dose	879	4.2	90	51	0.97†	905	4.2	19	1	0.09
2 mo. after 2nd dose	735	6.3	91	59	1.35†	735	6.3	13	1	0.08
8 mo. after 2nd dose	331	11.7	76	24	0.40†	336	11.8	24	4	0.1
2nd follow-up visit‡	108	17.7	69	24	0.40†	113	17.7	29	6	0.11

*The serum antibody response to the capsular polysaccharide of *H. influenzae* type b. GMT denotes geometric titer.

†$p<0.001$ for the comparison with placebo values.

‡Serum samples were obtained between 15 and 18 months of age.

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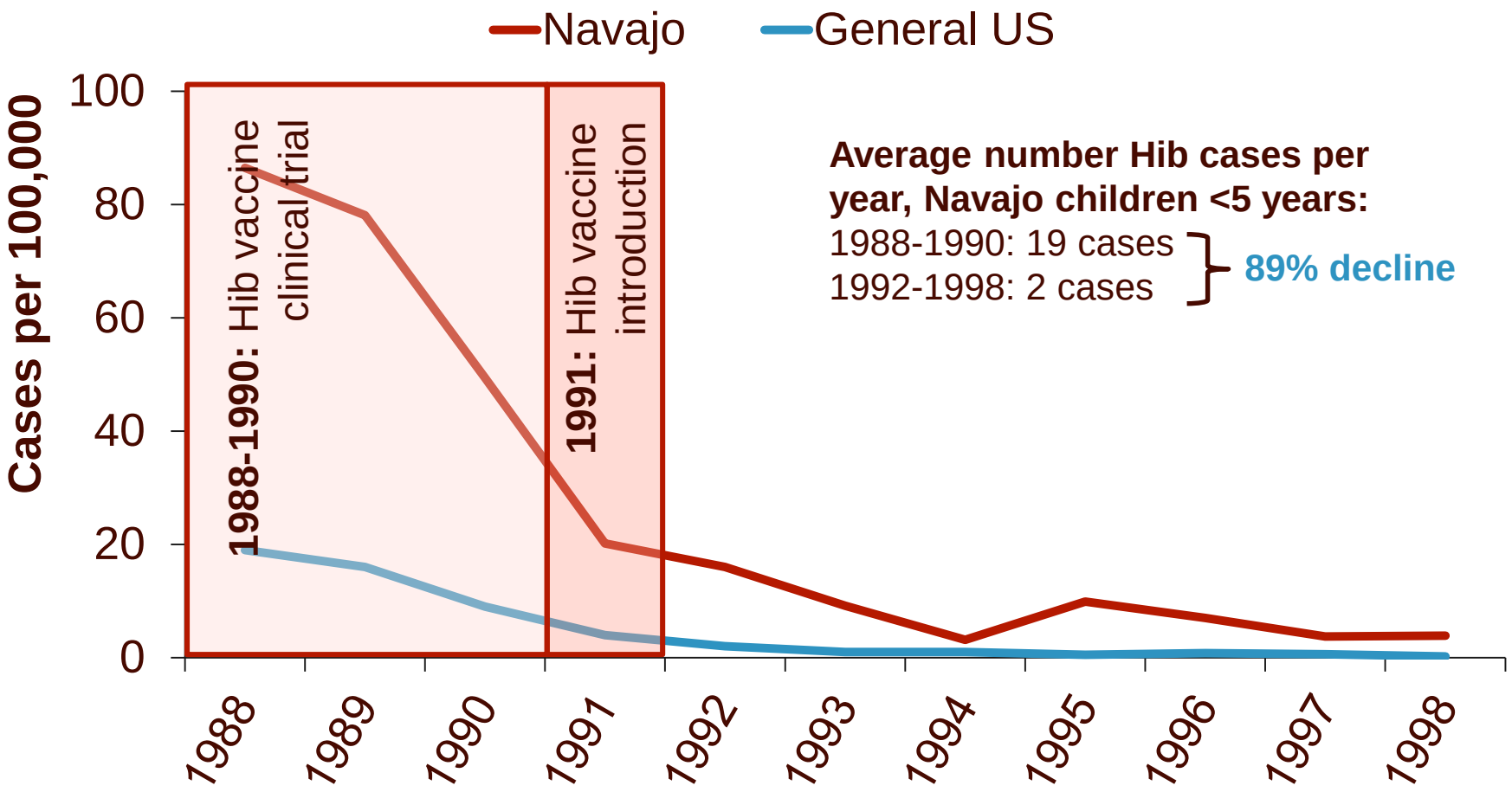
Table 3. Efficacy Analysis of *H. influenzae* Type b OMPC Vaccine*

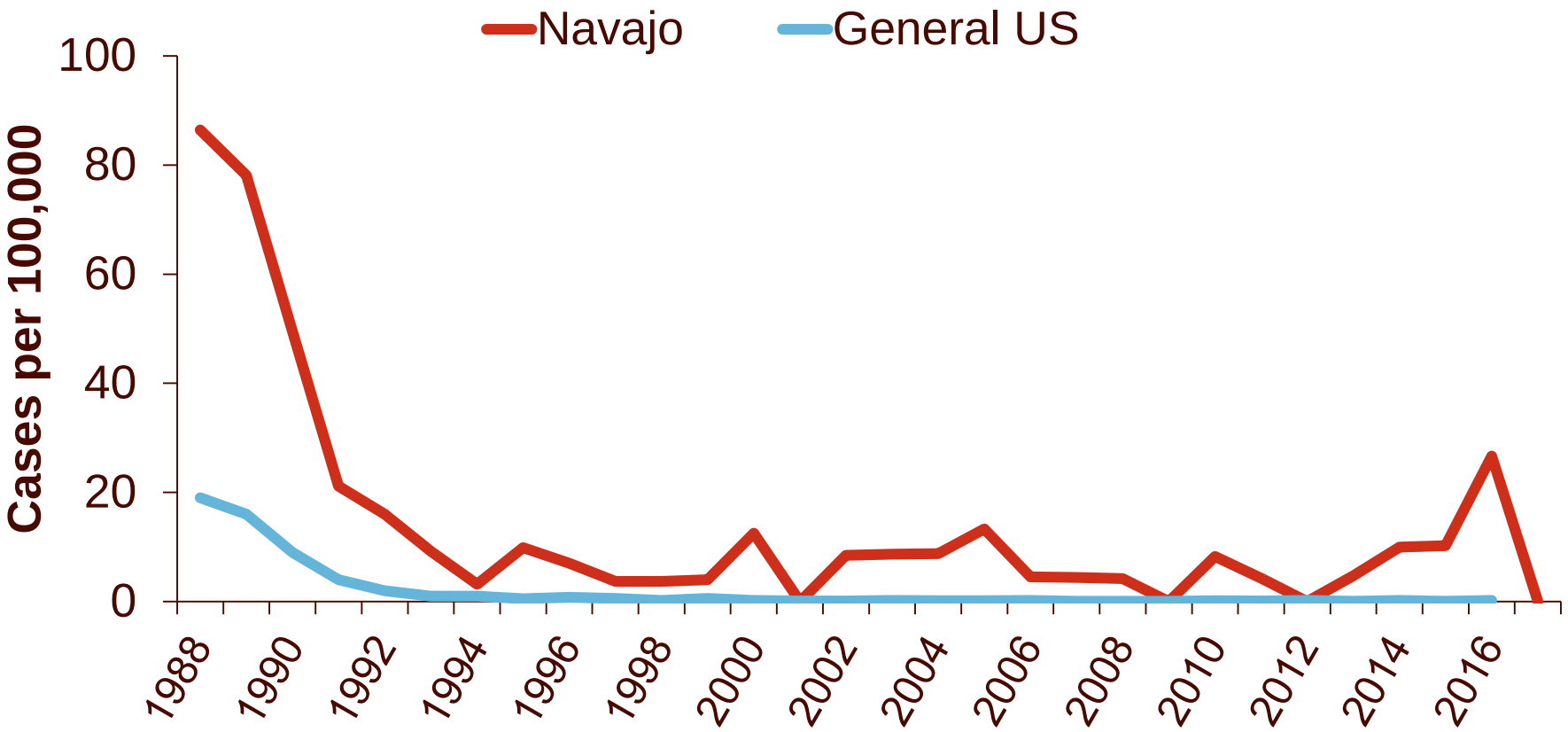
Time of Disease Onset	Cases of *H. influenzae* (n/total)		Efficacy Estimate (%)	p-value	95% Confidence Interval
	Vaccine	Placebo			
At least 1 dose					
Onset before 18 mo.	1/2588	22/2602	95	<0.001	72-99
Onset before 15 mo.	0/2588	21/2602	100	<0.001	81-100
Onset before 2nd dose	0/2588	8/2602	100	0.005	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.

Introduction of PRP-OMP vaccine reduces Hib disease in Navajo children <5 years

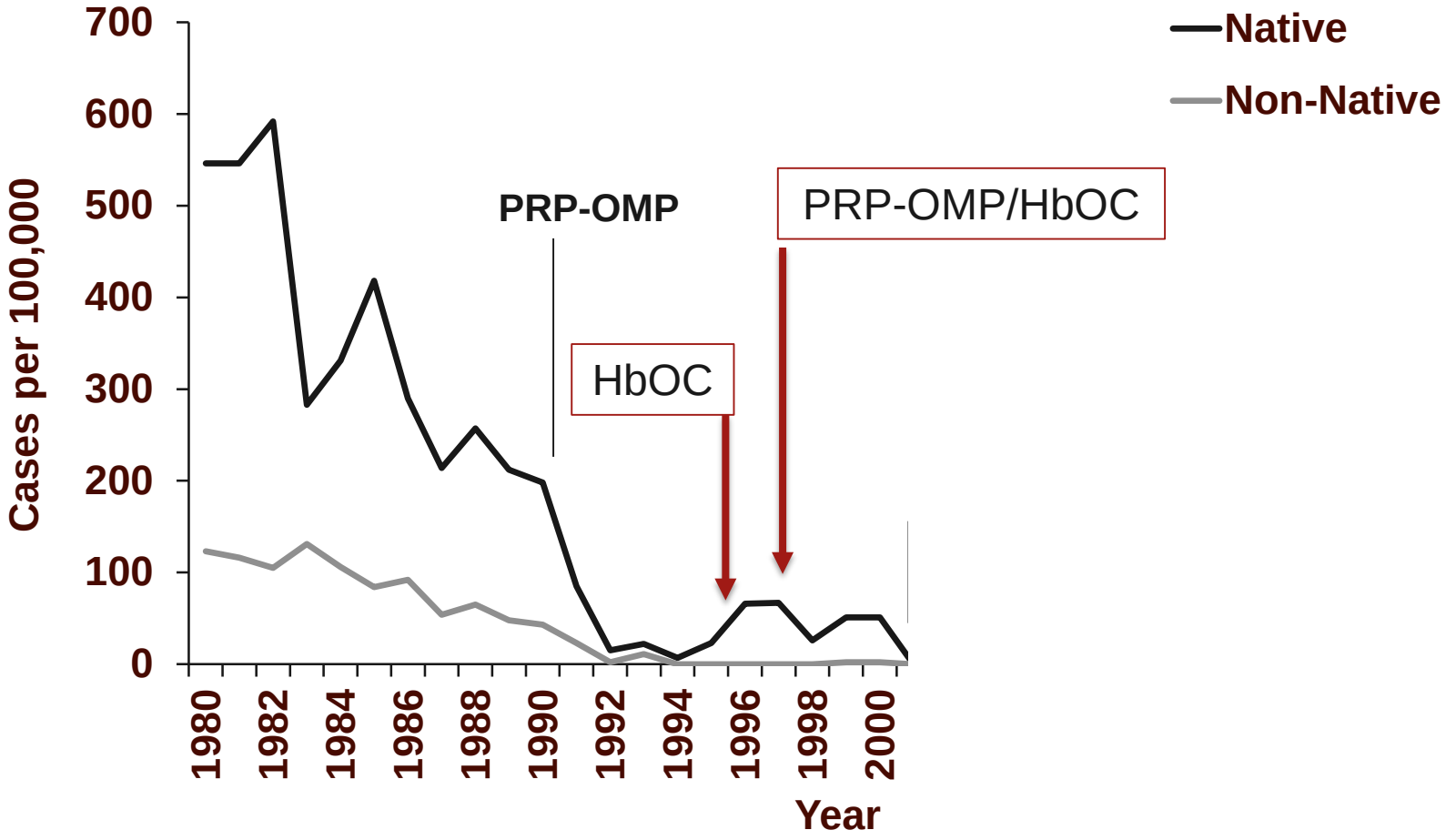


Hib disease declined but continues to occur in Navajo children <5 years



General US data available through 2016 only

Invasive Hib Disease, Children Aged <5 Years, Alaska, 1980 - 2018



Singleton, et al. J Pediatr 2000; 137:313-20 and CDC, unpublished

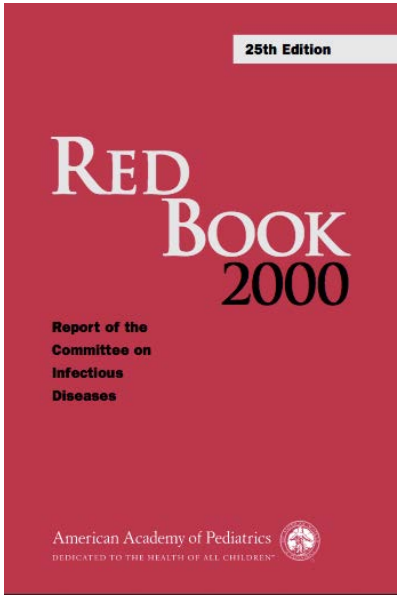
Preferential recommendation for PRP-OMP for Native American children

AMERICAN ACADEMY OF PEDIATRICS

Committee on Native American Child Health and Committee on Infectious Diseases

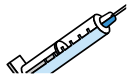
Immunizations for Native American Children

"Because of the risk of invasive Hib disease at younger ages, the Indian Health Service (IHS) has recommended a preference for the PRP-OMP (PEDVAX-HIB) Hib conjugate vaccine based on seroconversion rates of 60% after the first dose of PRP-OMP, compared with rates of only 20% for other Hib conjugate vaccines."



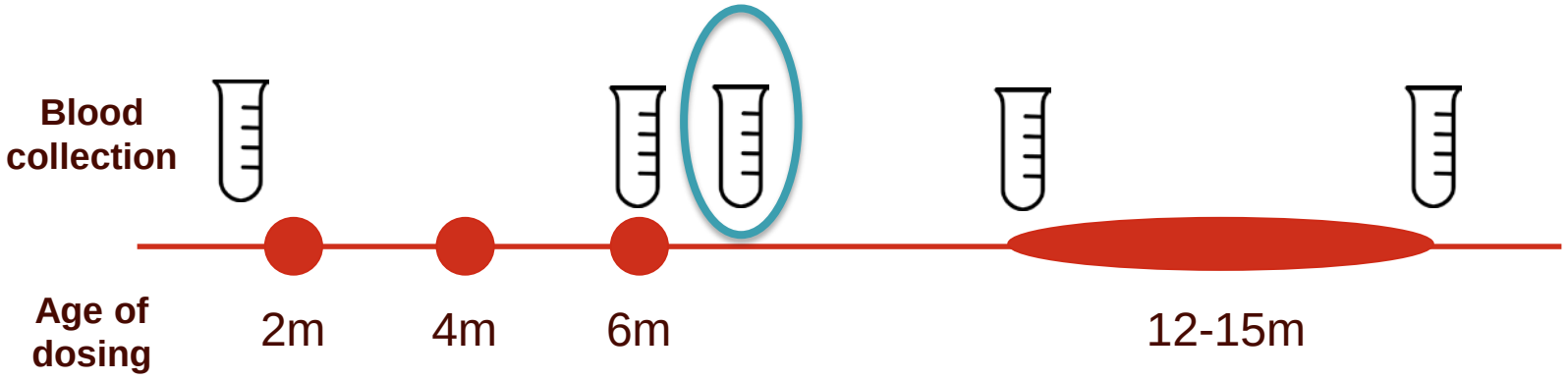
AAP Committee on Native American Child Health, *Pediatrics* 1999

Considerations around use of Hexavalent vaccine in Native American children

		 2m	 4m	 6m	 12-15m
PedvaxHIB (PRP-OMP)	PRP-OMP (7.5µg)	X	X		X
Hexavalent	PRP-OMP (3.0µg)	X	X	X	Other Hib vaccine

Immunogenicity post-dose 3 of Hib component for Hexavalent vaccine

- Hib component:
  - 3.0µg PRP-OMP vs. 6.0µg PRP-OMP vs. 12.0µg PRP-T
- Control vaccines: PENTACEL + RECOMBIVAX HB
- Immunogenicity: Post-dose 3 (at 7m)



Diaz-Mitoma, et al., *Vaccine* 2011; 29:1324-1331

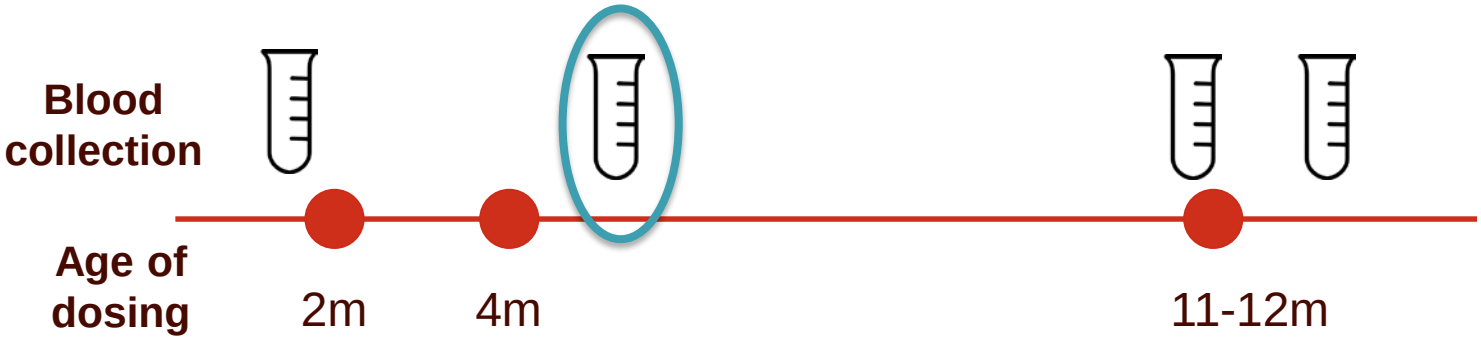
Post-dose 3 Hib component immunogenicity for Hexavalent vaccine

Post-dose 3 anti-PRP responses (95% CI)

	PRP-T (12µg) n=170	PRP-OMP (3µg) n=167	PRP-OMP (6µg) n=158	Control n=154
% ≥1.0 µg/mL	68.2 (60.7, 75.2)	95.8 (91.6, 98.3)	95.6 (91.1, 98.2)	80.5 (73.4, 86.5)
GMC µg/mL	1.9 (1.5, 2.5)	9.9 (8.1, 12.2)	11.9 (9.7, 14.6)	3.9 (3.1, 5.0)

PRP-T = Polyribosylribitol phosphate-tetanus toxoid conjugate, PRP-OMP = PRP-*Neisseria meningitidis* outer membrane protein complex conjugate, n = number of participants with results

Post-dose 2 immunogenicity of Hexavalent

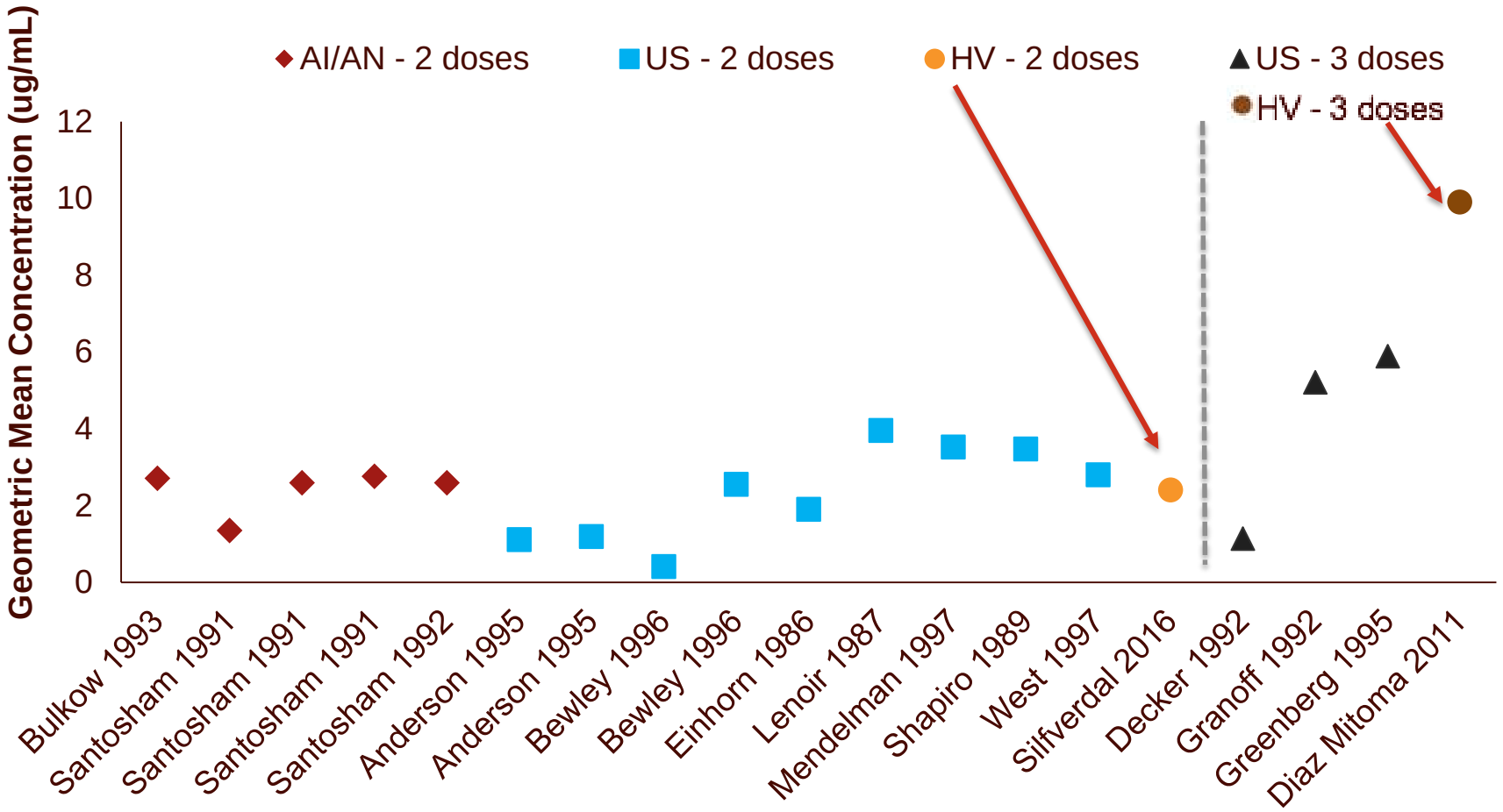


Time Point	Anti-PRP	Hexavalent (95% CI)	Control (95% CI)
Post-dose 2 (5 months)	% ≥0.15 µg/mL	96.6 (94.8, 97.9)	77.9 (74.3, 81.2)
	% ≥1.0 µg/mL	72.9 (69.2, 76.4)	26.7 (23.2, 30.5)
	GMT	2.4 (2.1, 2.7)	0.5 (0.4, 0.5)

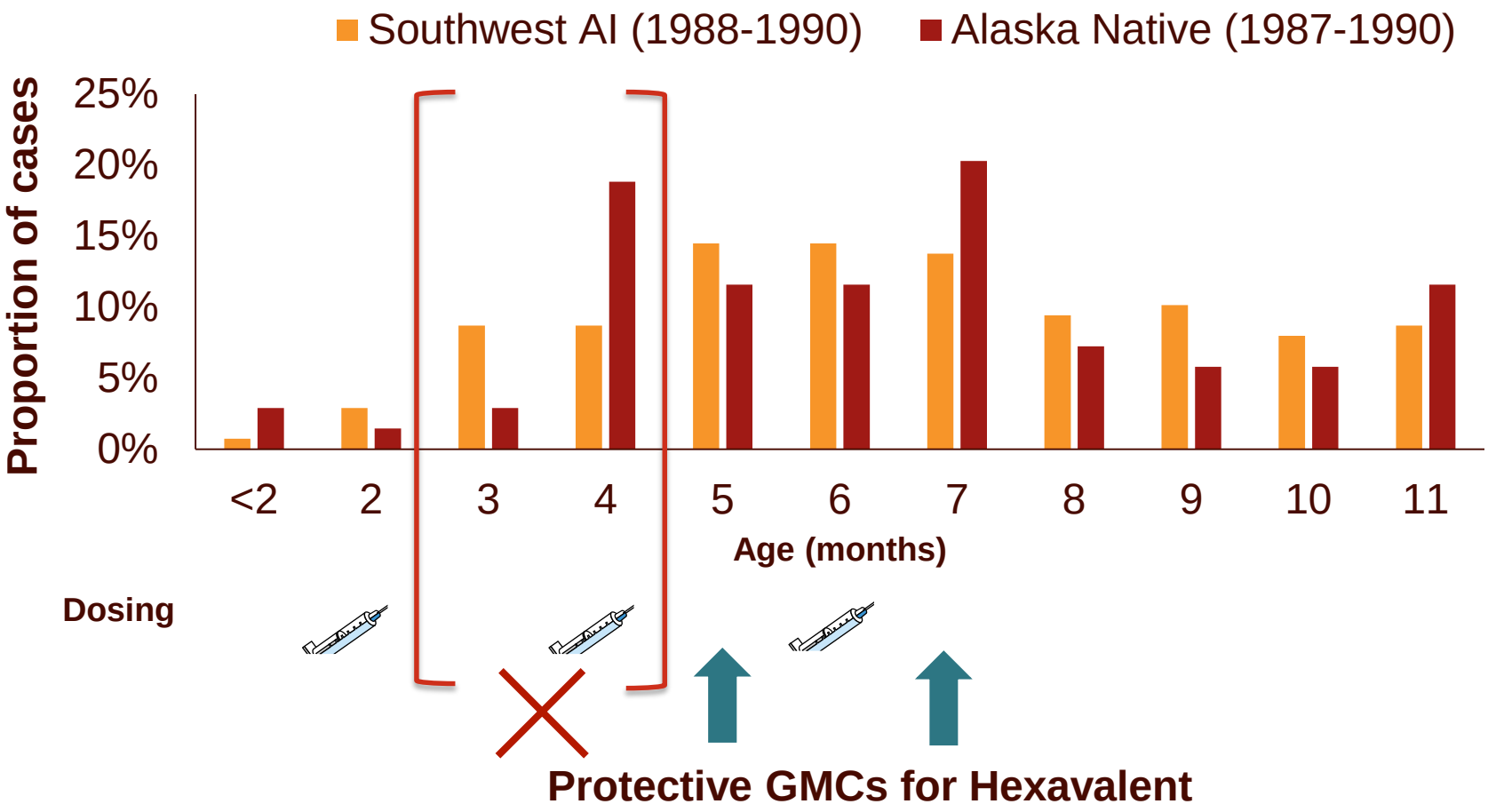
CI = 95% confidence interval, GMT = Geometric mean titer

Silfverdal et al., *Vaccine* 2016; 3810-3816.

Post-dose 2 immunogenicity of PRP-OMP and Hexavalent Vaccine (HV) are comparable



Post-dose 1 immunogenicity unknown for Hexavalent → window of vulnerability?



Conclusions

- Hib is still circulating in Native American rural and reservation-based communities
- Post-dose 1 immunogenicity is unknown for Hexavalent vaccine
  - There may be a window of vulnerability between dose 1 and 2
- Establishing immunogenicity post-dose 1 in high-burden Native American populations is important and could inform policy

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- CDC/AIP staff
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