# Background on invasive Hib disease and vaccination among American Indian and Alaska Native populations

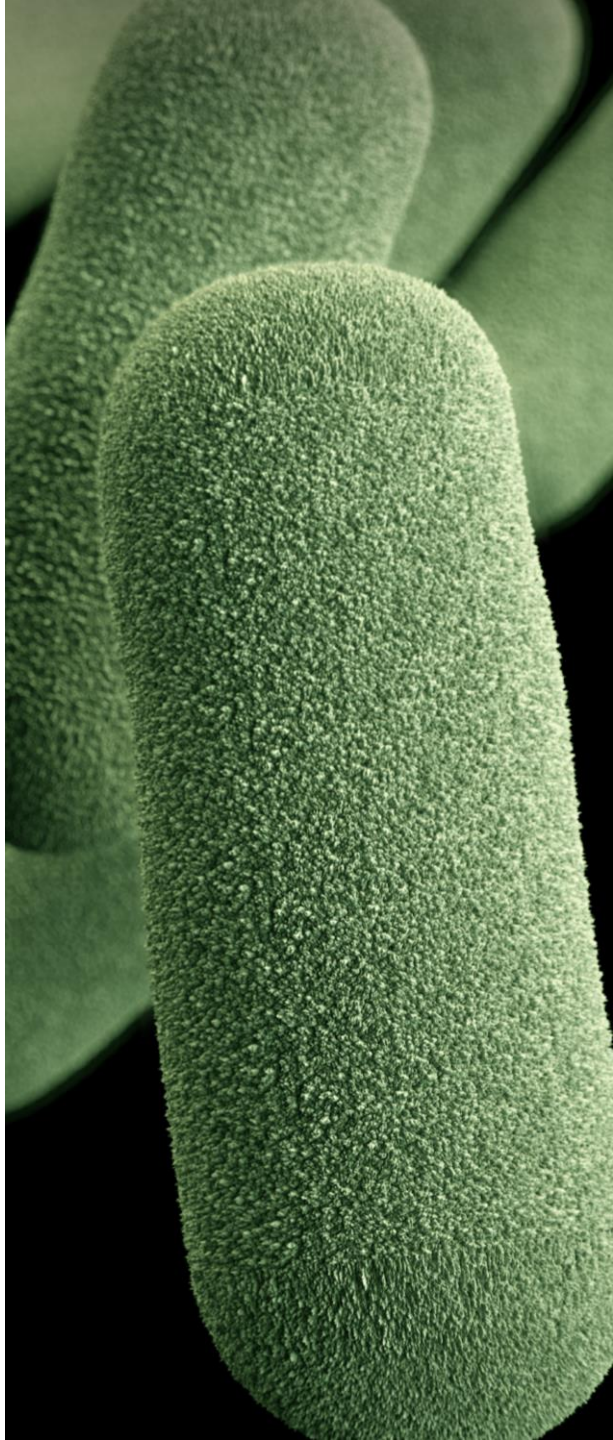
Jennifer Collins MD, MSc
Co-Lead, ACIP Hib/Meningococcal Vaccines Work Group

February 29, 2024

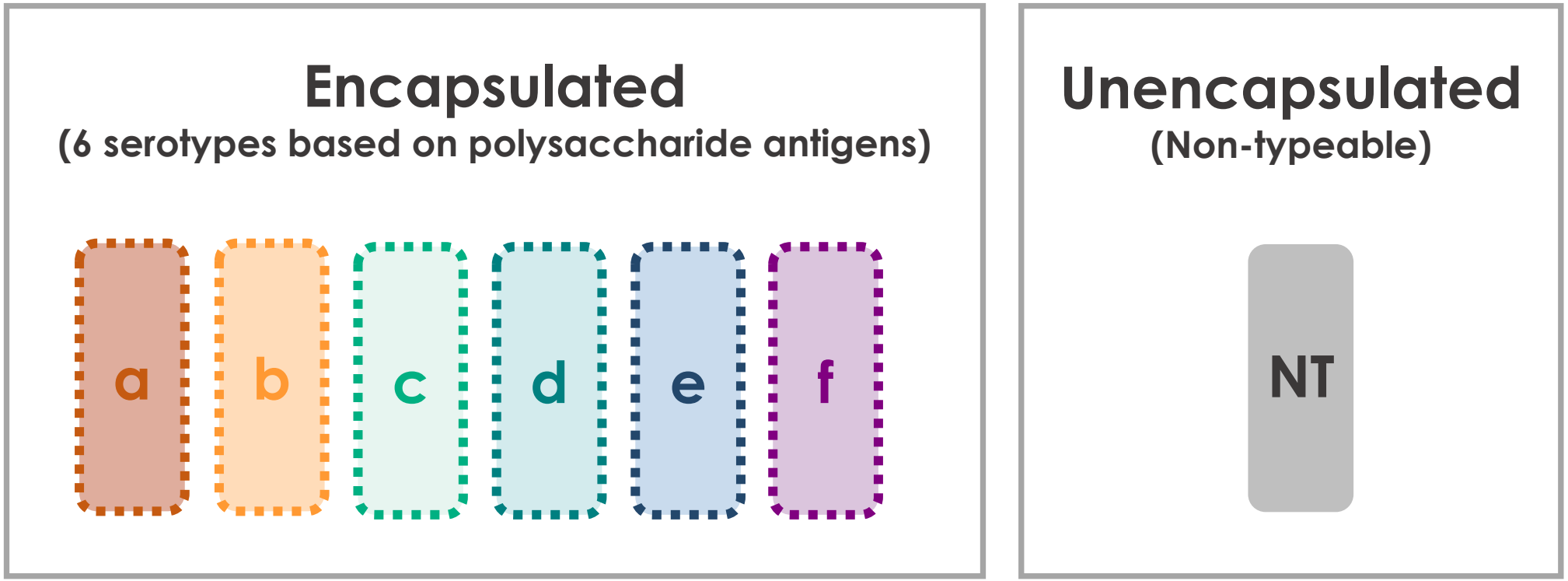
# Background

# *Haemophilus influenzae*

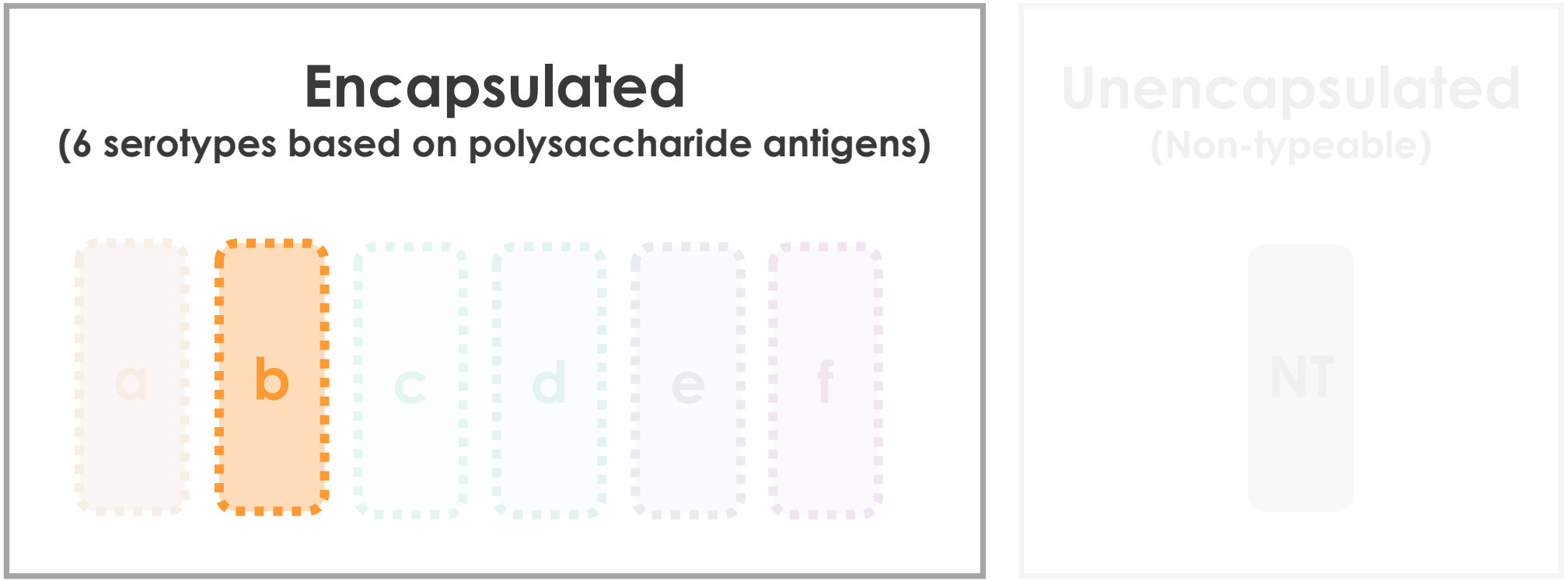
- Gram-negative bacilli
- Originally thought to be the cause of influenza
- Abbreviated "*H. flu*" or Hi
- Infections range from mild to severe invasive disease



# Classification of *H. influenzae*



# *H. influenzae* serotype b (Hib) is most virulent and is the only type preventable through vaccination




- Before the introduction of effective vaccines, Hib was the leading cause of bacterial meningitis and other invasive bacterial disease in the United States, primarily among children aged <5 years

# Risk factors for invasive Hib disease in the pre-vaccine era

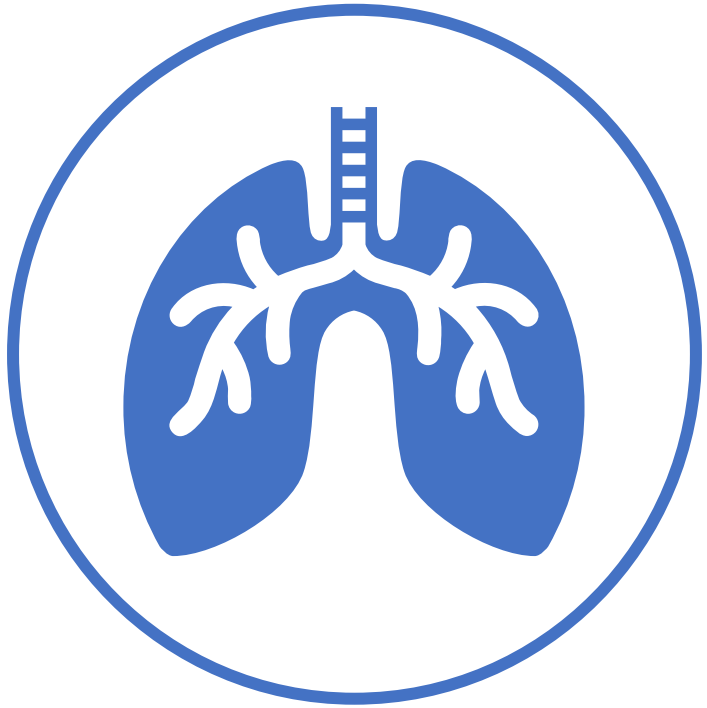
**Demographic factors**

- Male sex
- Race/Ethnicity
  - American Indian
  - Alaska Native
  - Black
- Social factors
  - Household crowding
  - Large household size
  - Low SES
  - School-aged siblings
  - Daycare attendance

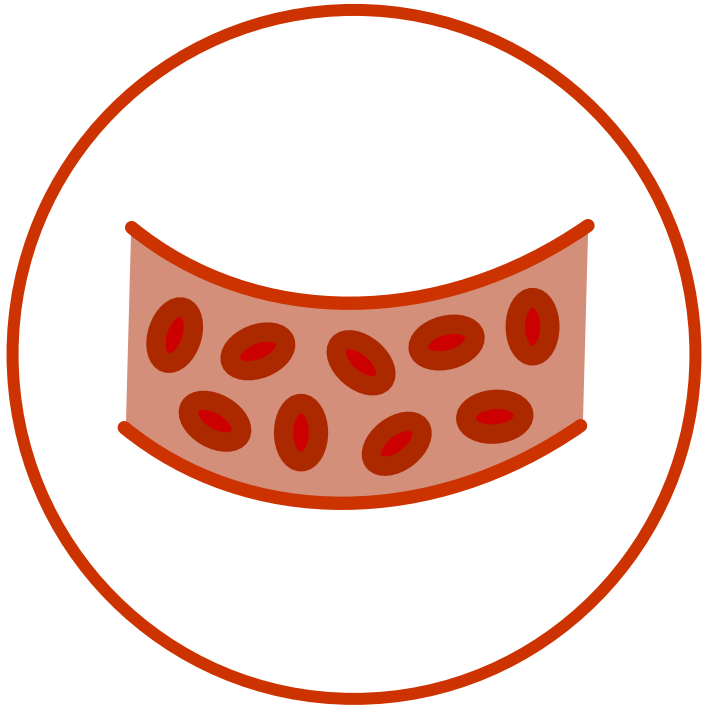
**Immunocompromising conditions**

- HIV infection
- Asplenia / Sickle cell disease
- IgG deficiency
- Early component complement deficiency
- Hematopoietic stem cell transplantation
- Chemotherapy

# Most common clinical syndromes of invasive Hib disease in the post-vaccine era



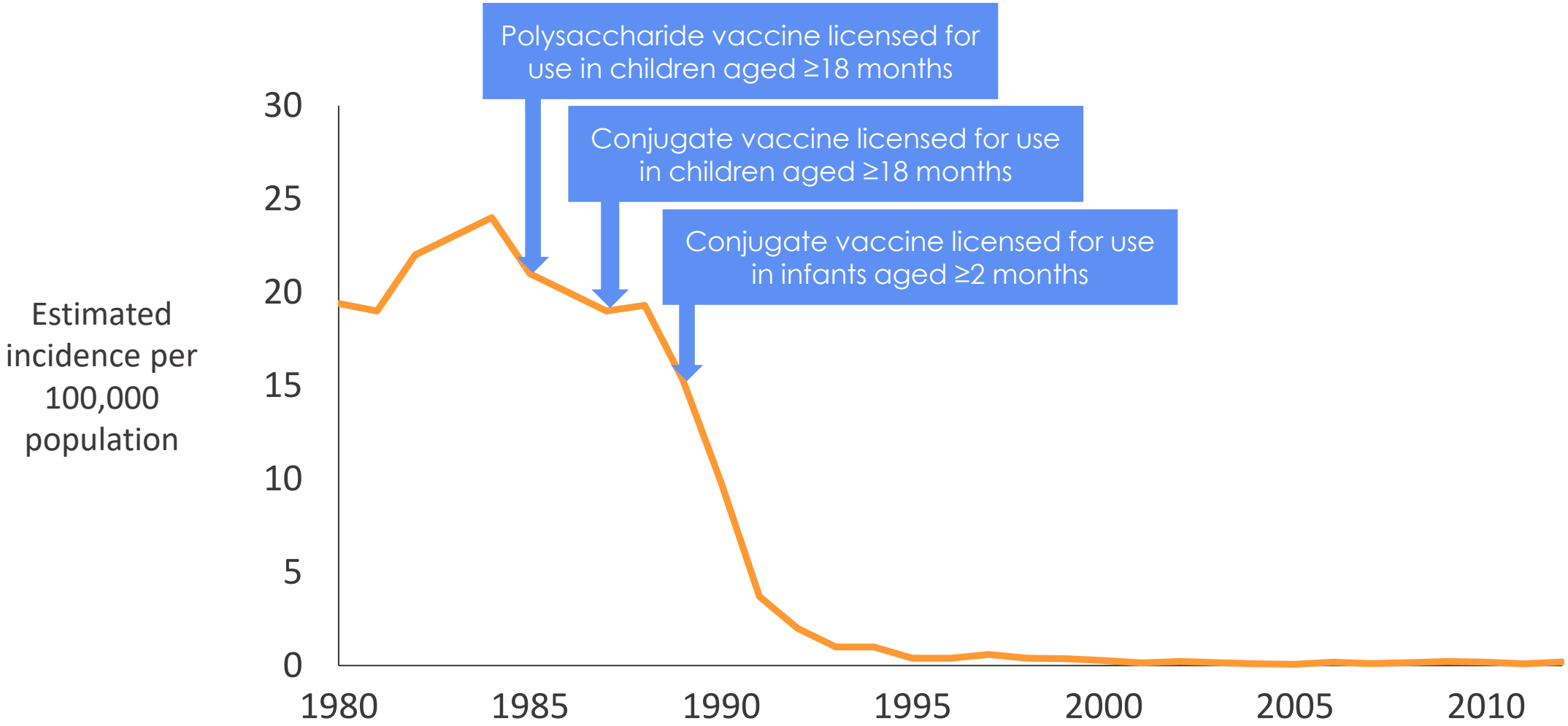
Bacteremic pneumonia



Bacteremia without a focus

Meningitis

# Estimated incidence of invasive Hib disease in children aged <5 years decreased dramatically after introduction of Hib vaccines



# Hib polysaccharide conjugate vaccines remain the primary prevention strategy for Hib

- Capsular polysaccharide (PRP) conjugated to carrier proteins
  - Tetanus toxoid (PRP-T)
  - Outer membrane protein of meningococcal serogroup B (PRP-OMP)
- Highly immunogenic via activation of T-cell dependent immunity
  - 95% of infants develop protective antibody levels after a primary series
  - No cross protection against non-b serotypes/NTHi
- Estimated clinical efficacy 95%–100%
- Invasive Hib disease is uncommon in children who are fully vaccinated

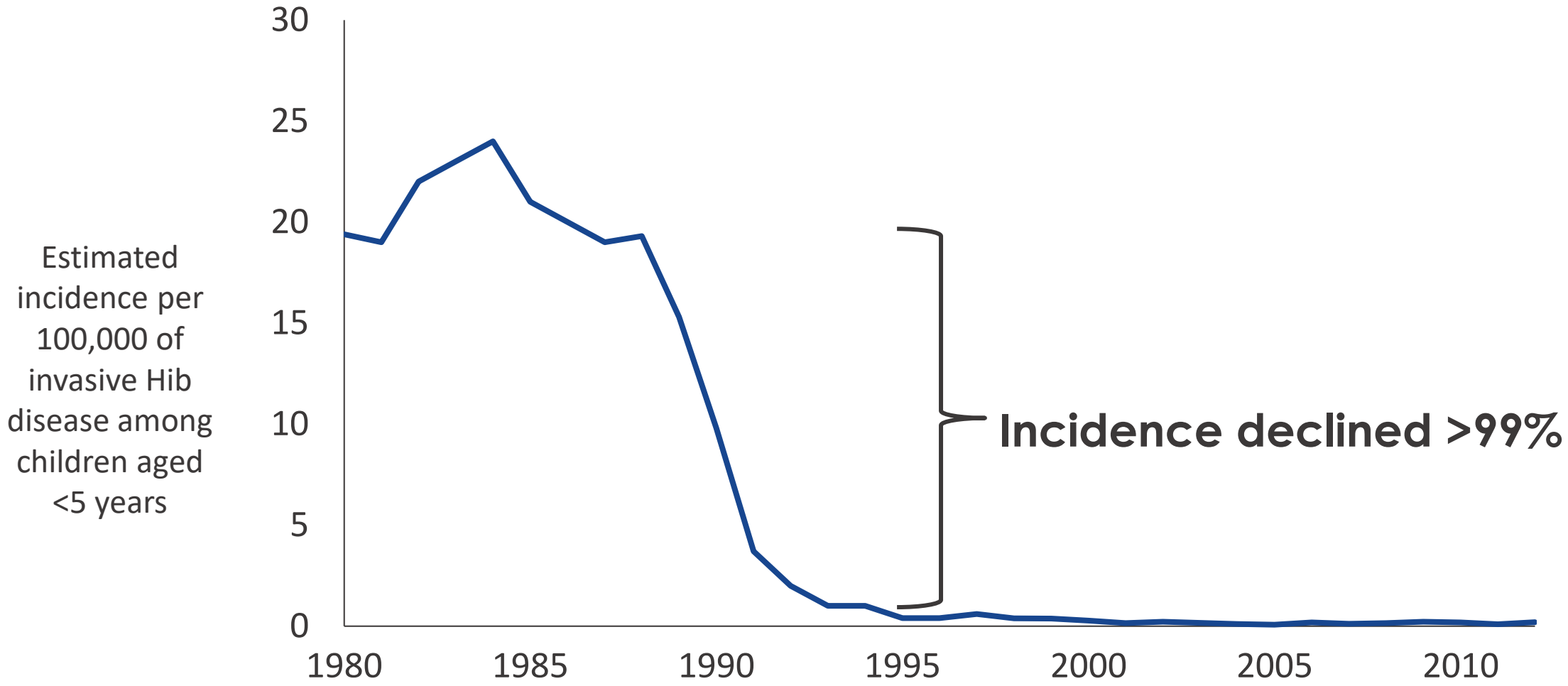
# Current Hib vaccines in the United States

| Vaccine Product | Trade Name | Primary series | Booster dose |
|---|---|---|---|
| **Monovalent vaccines** | | | |
| PRP-OMP | PedvaxHIB* | 2, 4 months | 12–15 months |
| PRP-T | ActHIB | 2, 4, 6 months | 12–15 months |
| PRP-T | Hiberix | 2, 4, 6 months | 12–15 months |
| **Combination vaccines**** | | | |
| DTaP-IPV/Hib | Pentacel | 2, 4, 6 months | 12–15 months |
| DTaP-IPV-Hib-HepB | Vaxelis | 2, 4, 6 months | *** |

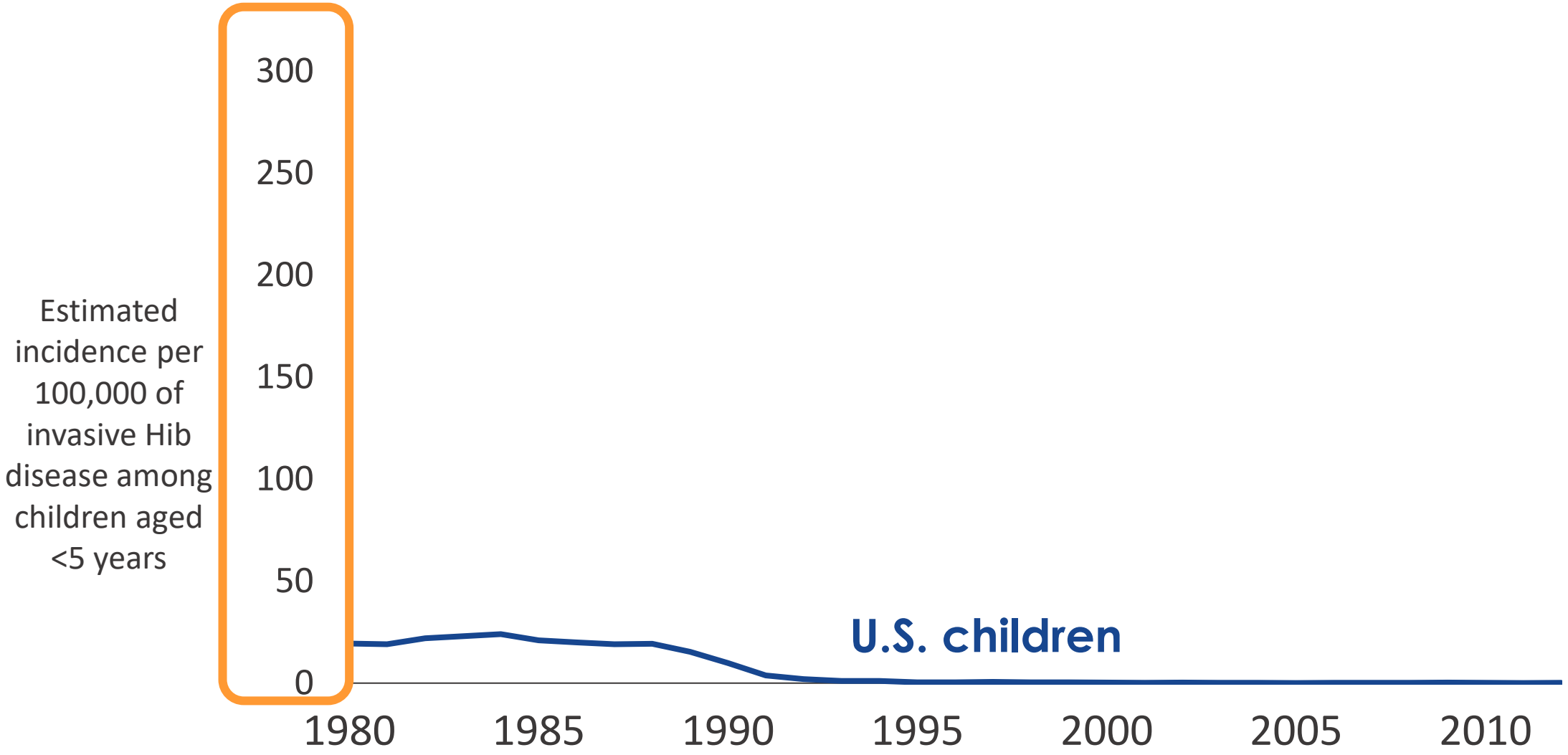
*Recommended vaccine for American Indian/Alaska Native children
**Hib component of Pentacel is PRP-T. Hib component of Vaxelis is PRP-OMP.
***Vaxelis is not recommended for the booster dose. A different Hib-containing vaccine should be administered as a booster at 12–15 months.

# Invasive Hib disease disproportionately affects American Indian and Alaska Native populations

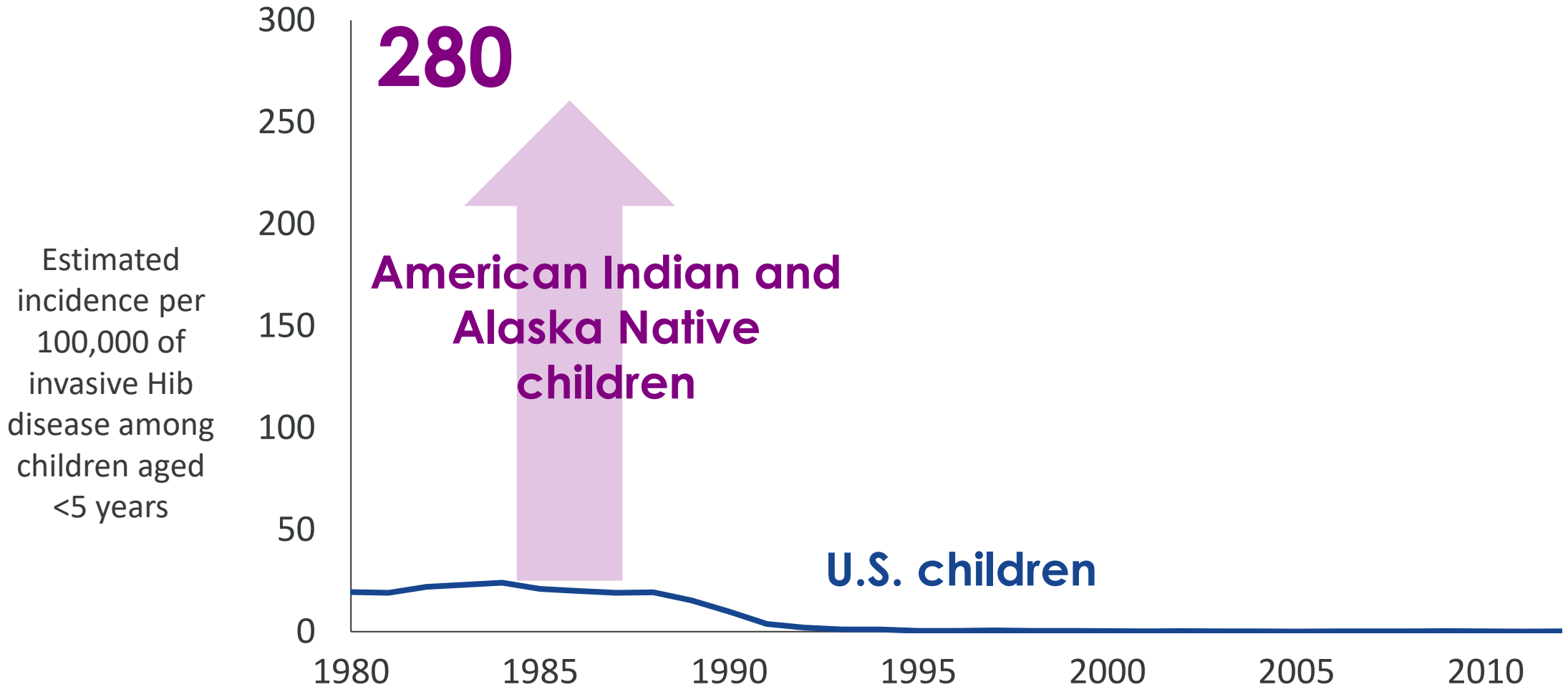
# Incidence of invasive Hib disease among children aged <5 years declined >99% with introduction of Hib vaccines



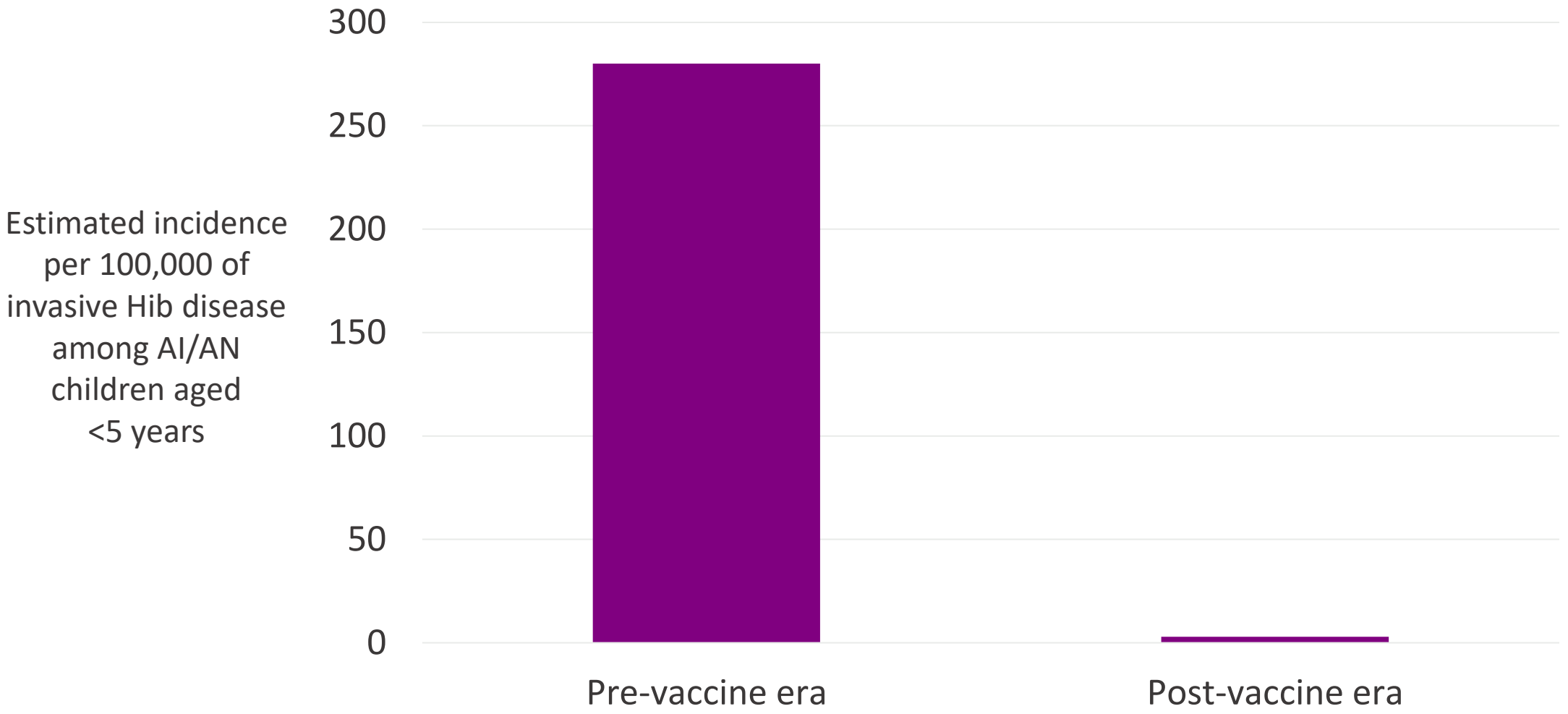
# Expanding the y-axis…



# Incidence among AI/AN children aged <5 years was >10x the incidence among U.S. children aged <5 years overall

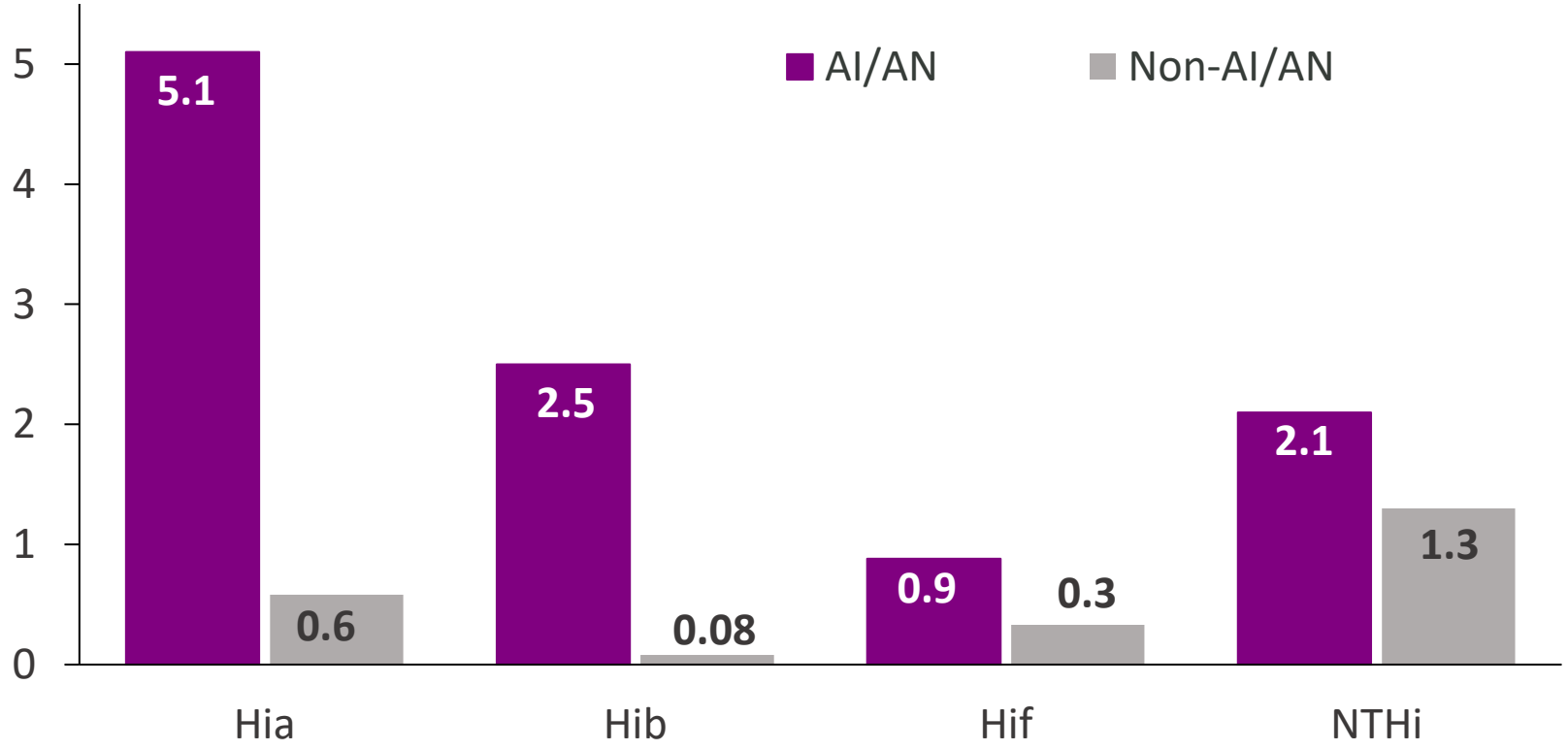


# Incidence of Hib disease among AI/AN children aged <5 years declined >98% with Hib vaccination



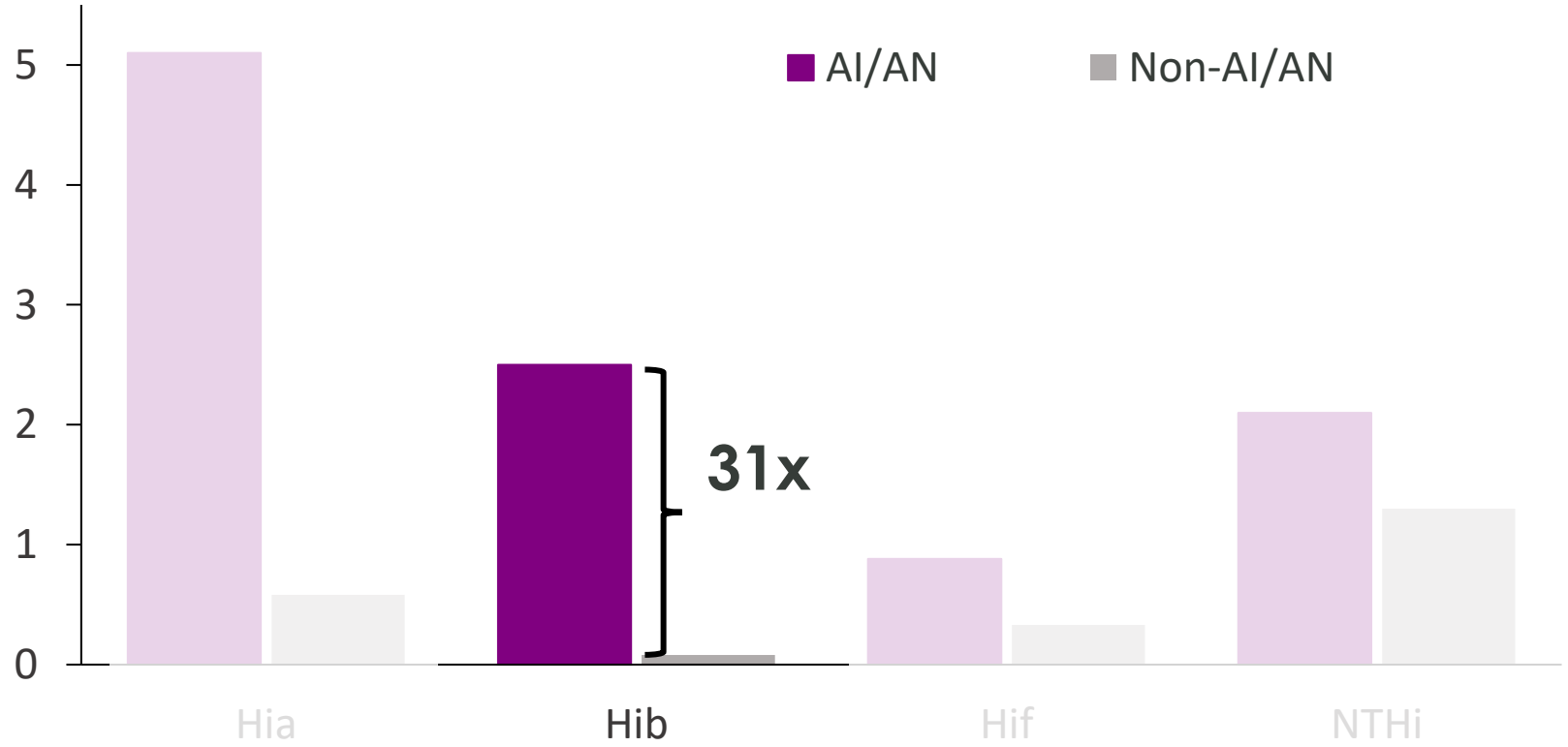
# Incidence of invasive *H. influenzae* disease remains substantially higher among American Indian and Alaska Native children compared with non-Native children

Incidence per 100,000 of invasive *H. influenzae* disease by type among children aged <5 years, 2011–2020

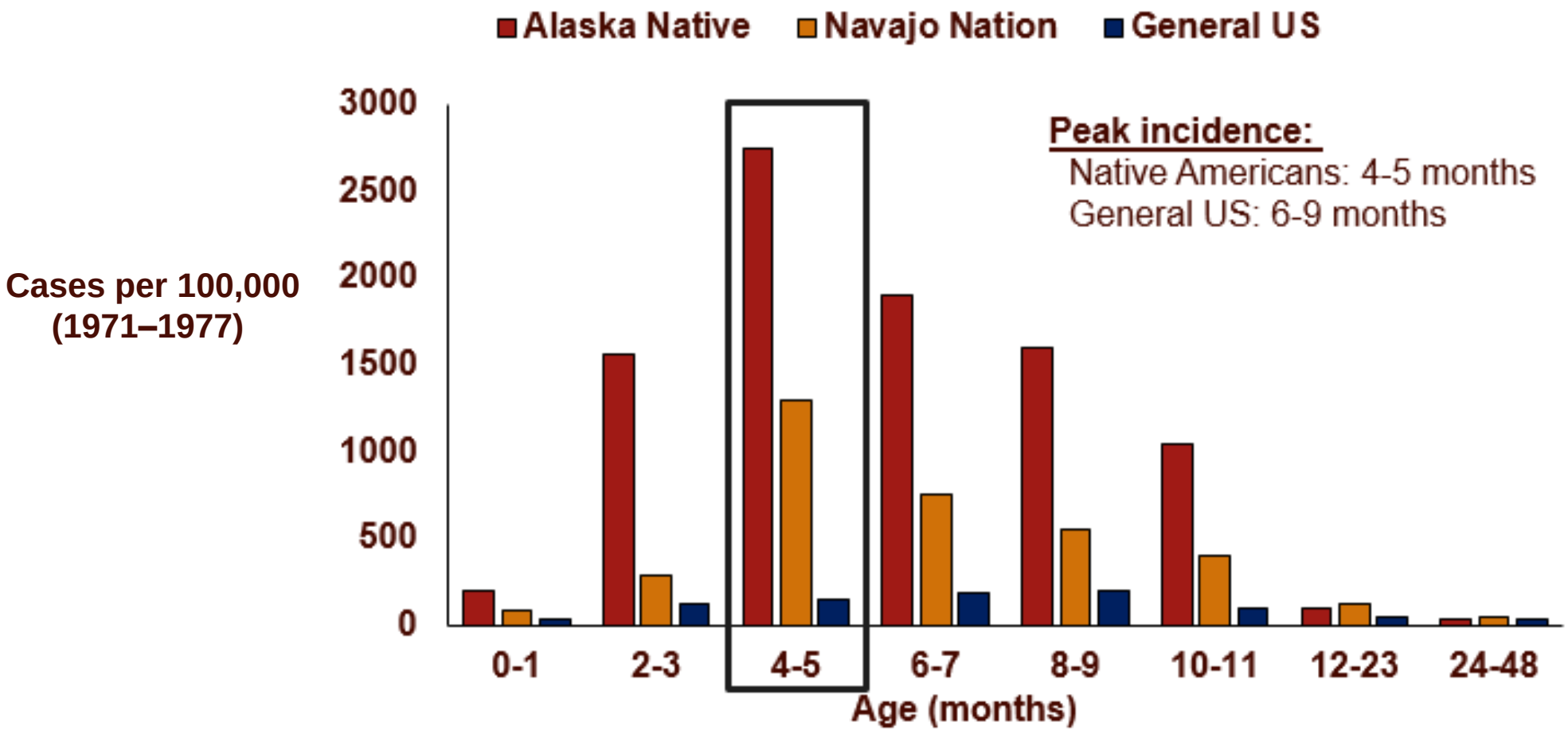


# AI/AN children have 31-fold higher incidence of invasive Hib disease than non-Native children

Incidence per 100,000 of invasive *H. influenzae* disease by type among children aged <5 years, 2011–2020



# In the pre-vaccine era, the incidence of Hib meningitis peaked at a younger age among AI/AN populations than the general U.S. population




Data from Ward JI, et al. *Lancet*. 1981. 1(8233); 1281–5. Graph credit: Laura Hammitt's February 2019 ACIP Meeting presentation

# Invasive Hib disease among AI/AN children aged <5 years—Active Bacterial Core surveillance, 2003–2023*

| Characteristic | N=28 |
|---|---|
| **Patient age, months** | |
| Median | 12 |
| IQR | 5–31 |
| Range | 0–56 |
| **Unvaccinated, n (%)** | 9 (31) |
| **Syndrome** | |
| Meningitis | 13 (45) |
| Pneumonia | 12 (41) |
| Cellulitis | 3 (10) |
| Bacteremia without a focus | 1 (3) |

*2022 and 2023 data are preliminary

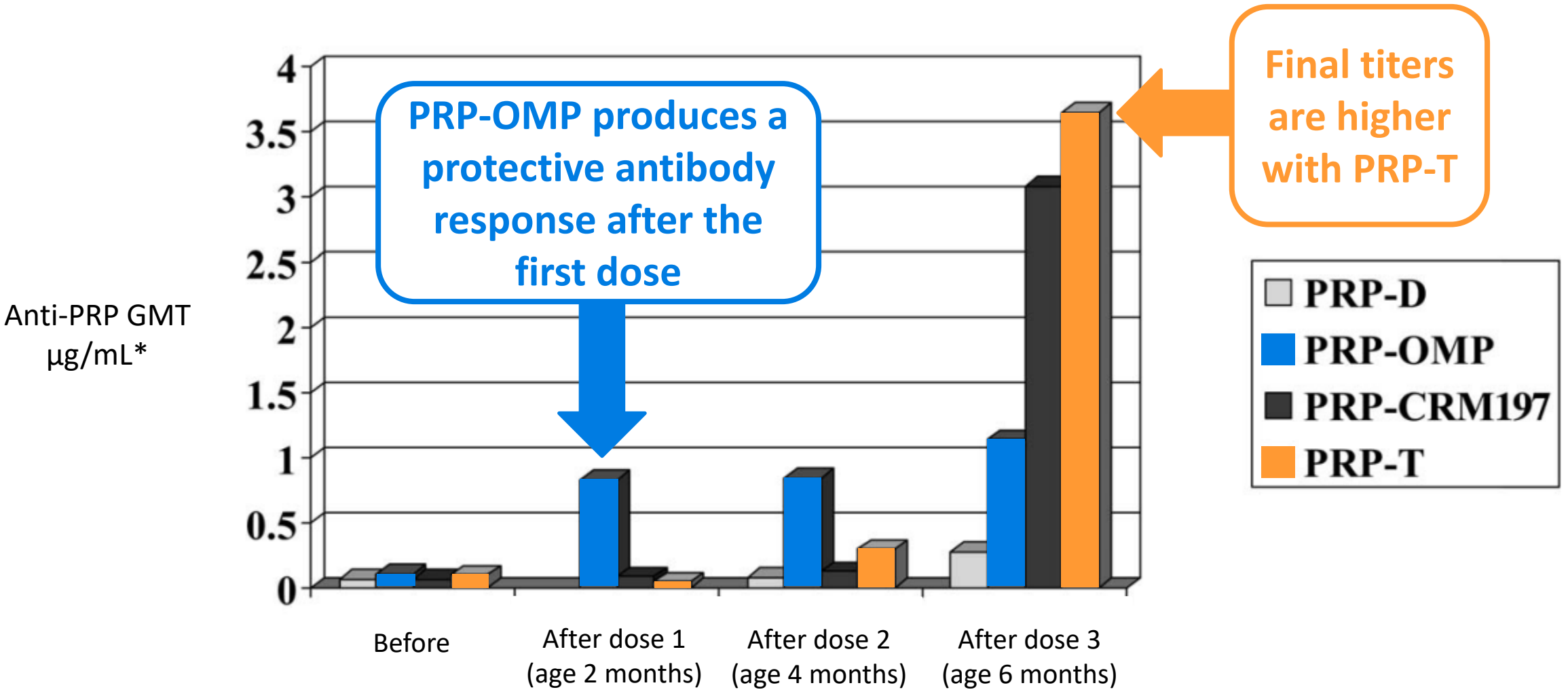
# Hib vaccination among American Indian and Alaska Native infants

# PedvaxHIB (PRP-OMP) is preferentially recommended for AI/AN infants

- Vaccination with a 2 dose primary series of a Hib vaccine that contains PRP-OMP (PedvaxHIB) is preferred for AI/AN infants to provide early protection because this vaccine produce a protective antibody response after the first dose
- A booster dose (dose 3) of Hib vaccine is recommended at age 12 through 15 months; for the booster dose, there is no preferred vaccine formulation

Briere EC, et al. Prevention and Control of *Haemophilus influenzae* Type b Disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recommendations and Reports*. 63(RR01);1-14

# PRP-OMP provides earlier protection

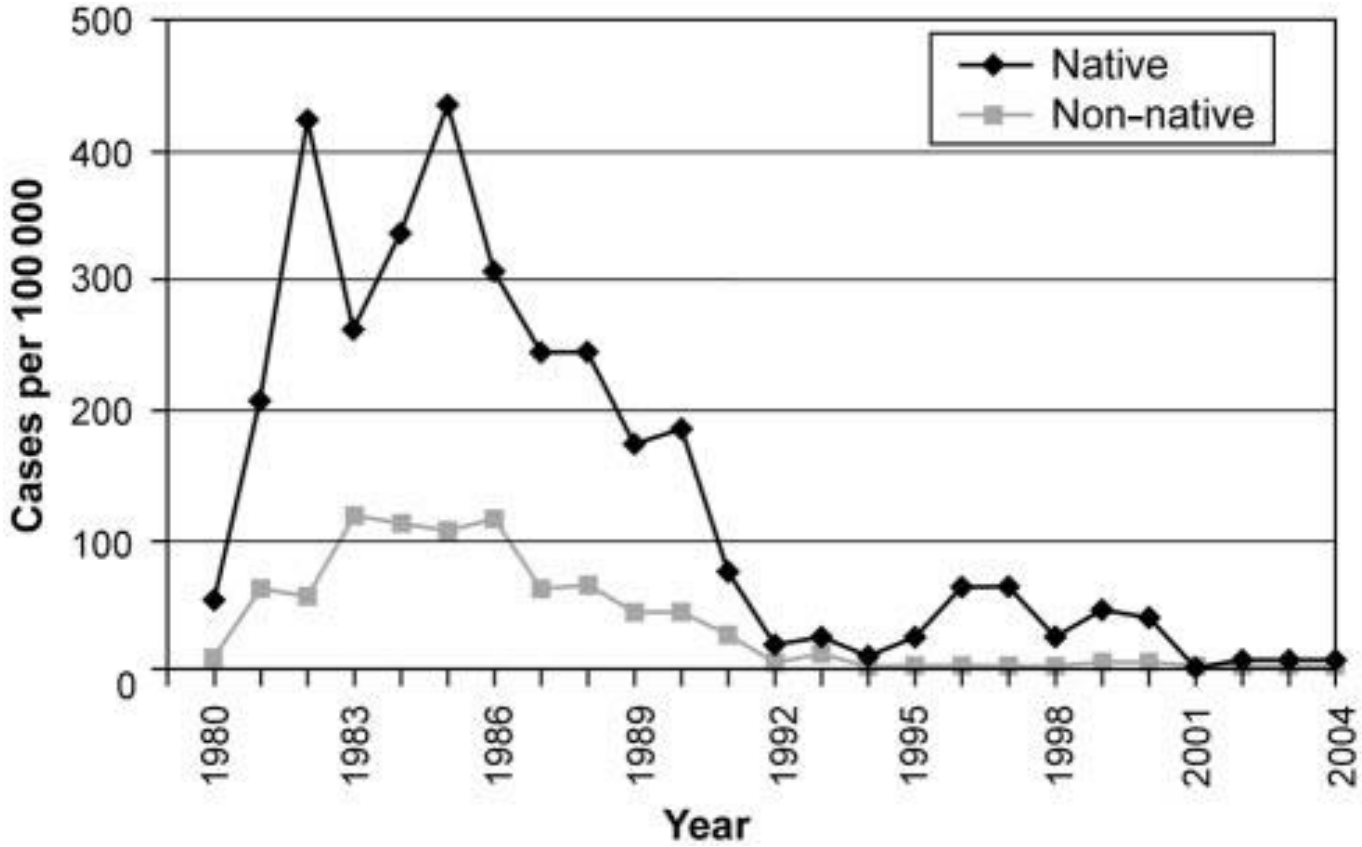



*PRP ≥0.15 ug/ml and ≥1.0 ug/ml are correlates of short-term, and long-term protection, respectively.

Watt JP, et al. Global reduction of Hib disease: what are the next steps? The Journal of Pediatrics 2003.

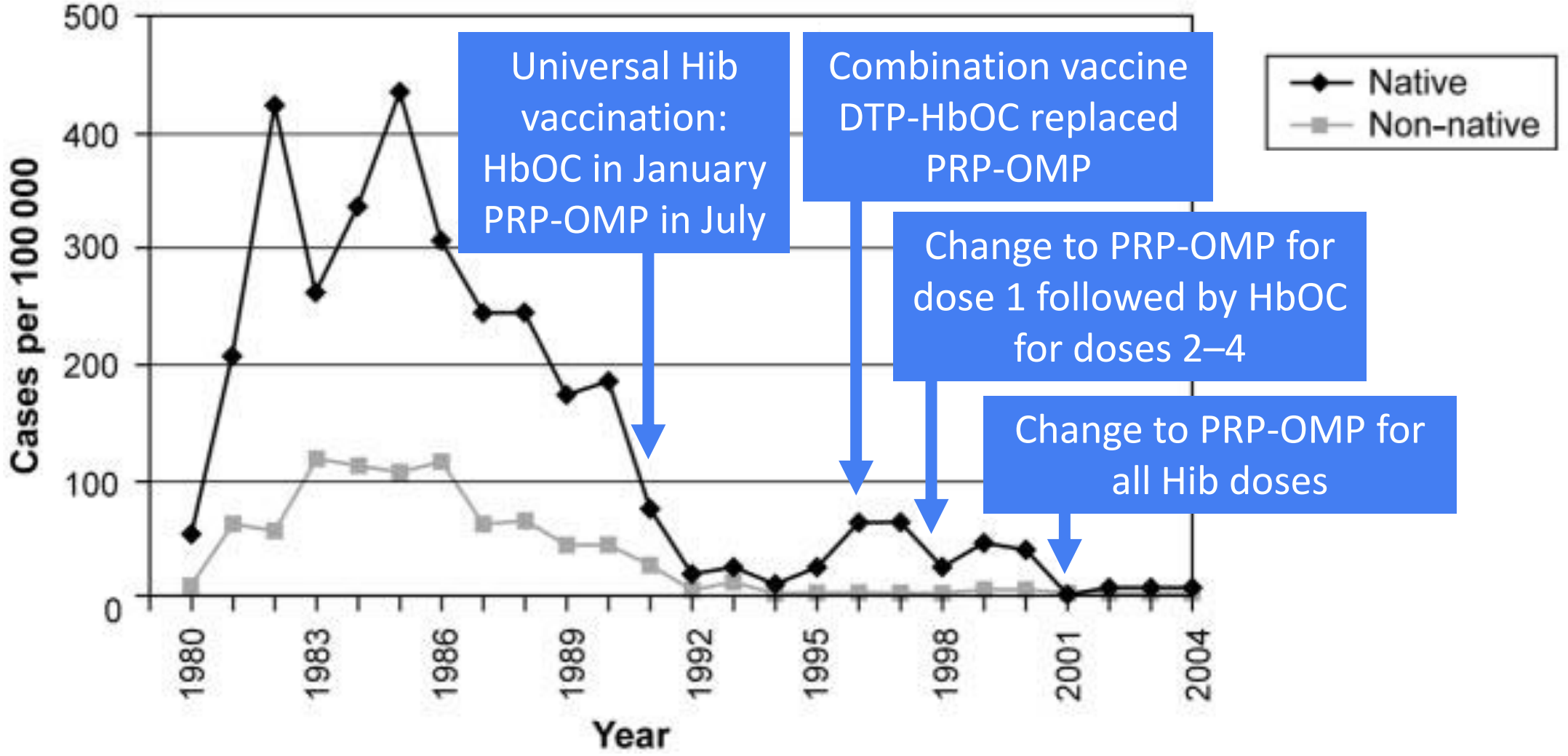
# The incidence of invasive Hib disease in Alaska Native populations increased in late 1990s amid vaccine policy changes

Invasive Hib disease rates per 100 000 in Alaska Native and non-Native children aged 5 years, 1980–2004




Singleton R et al. The Alaska *Haemophilus influenzae* Type b Experience: Lessons in Controlling a Vaccine-Preventable Disease. Pediatrics. 2006 Aug;118(2):e421-9

# Timeline of Hib vaccine policy changes in Alaska

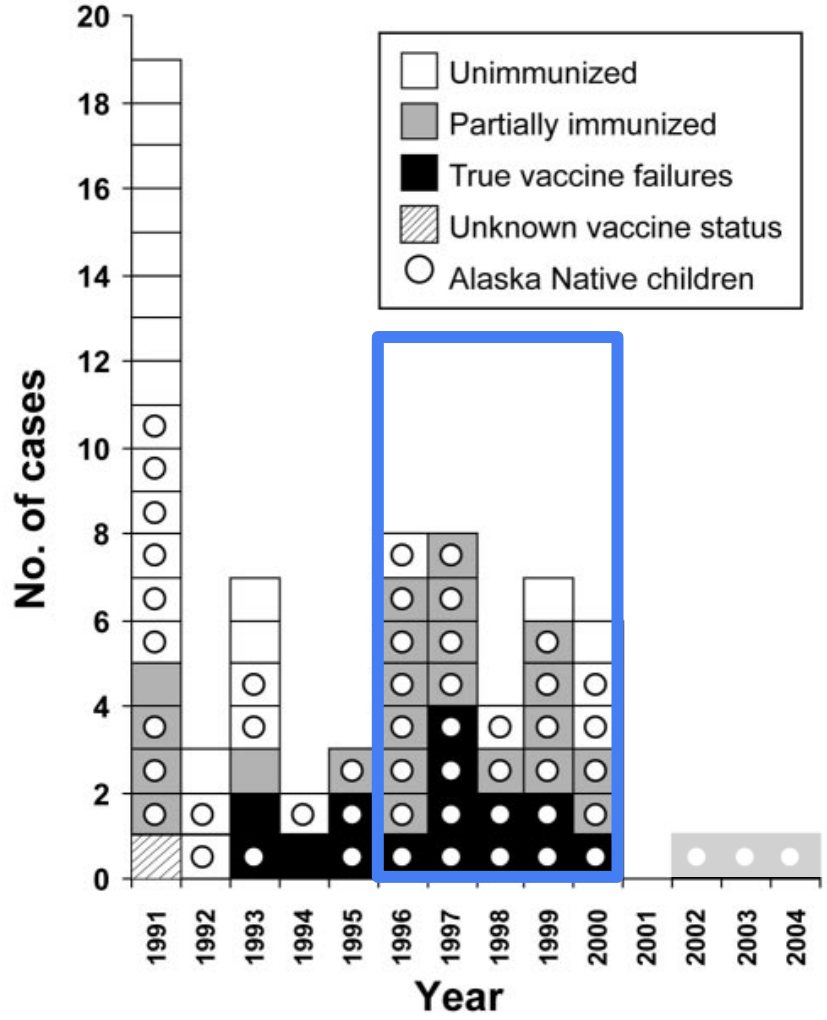



HbOC = Hib oligosaccharide CRM 197 vaccine

DTP = Diphtheria, tetanus toxoids, pertussis

Singleton R et al. The Alaska *Haemophilus influenzae* Type b Experience: Lessons in Controlling a Vaccine-Preventable Disease. Pediatrics. 2006 Aug;118(2):e421-9

# Vaccine status among children aged <10 years with invasive Hib disease in Alaska, 1991–2004




- During **1996–2000**, a greater proportion of cases
  - Occurred among Alaska Native children
  - Occurred among partially immunized children
  - Were considered true vaccine failures

Singleton R et al. The Alaska *Haemophilus influenzae* Type b Experience: Lessons in Controlling a Vaccine-Preventable Disease. Pediatrics. 2006 Aug;118(2):e421-9

# Vaccine administration errors may have contributed to some cases when both PRP-OMP and HbOC were used

- October 1997–December 2000
  - 14 cases occurred in Alaska Native children aged <5 years
  - 3 children (21%) had inadvertently received HbOC for their first and only dose

Singleton R et al. The Alaska *Haemophilus influenzae* Type b Experience: Lessons in Controlling a Vaccine-Preventable Disease. Pediatrics. 2006 Aug;118(2):e421-9

# Increases in Hib disease in Alaska during 1996–2000 were attributed to

- Use of HbOC, which did not achieve short-term protective antibody concentrations (0.15 µg/mL) until the third dose
- Low rates of on-time immunization

Singleton R et al. The Alaska *Haemophilus influenzae* Type b Experience: Lessons in Controlling a Vaccine-Preventable Disease. Pediatrics. 2006 Aug;118(2):e421-9

# National Immunization Survey–Child

## Estimated vaccination coverage with Hib full series* by age 24 months among American Indian or Alaska Native children by birth year

| Birth year† | % | 95% CI |
|---|---|---|
| 2016 | 77.0 | 64.8–87.4 |
| 2017 | 69.6 | 55.1–83.0 |
| 2018 | 76.3 | 66.0–85.4 |
| 2019 | 69.9 | 59.5–79.7 |
| 2020 | 67.5 | 54.6–79.7 |

* Hib Full Series: primary series and booster dose, which includes receipt of ≥3 or ≥4 doses, depending on product type received.

† Data for the 2016 birth year are from survey years 2017, 2018, and 2019; data for the 2017 birth year are from survey years 2018, 2019, and 2020; data for the 2018 birth year are from survey years 2019, 2020, and 2021; data for the 2019 birth year are from survey years 2020, 2021, and 2022; data for the 2020 birth year are considered preliminary and are from survey years 2021 and 2022 (2023 data are not yet available).

Hill HA et al. Vaccination Coverage by Age 24 Months Among Children Born in 2019 and 2020 — National Immunization Survey-Child, United States, 2020–2022. *MMWR Weekly* / November 3, 2023 / 72(44);1190–1196.

# National Immunization Survey–Child:
## In 2019–2020, American Indian/Alaska Native children were less likely than White children to have received the Hib full series* by age 24 months

| Race, Ethnicity | 2019–2020 (prelim)† %, 95% CI | Difference (White–AI/AN) 2019–2020 (prelim)† | | |
|---|---|---|---|---|
| | | % | 95% CI | p-value |
| White, non-Hispanic | 80.8 (79.4–82.1) | REF | REF | REF |
| American Indian or Alaska Native, non-Hispanic | 68.7 (60.3–76.8) | 12.1 | (3.6–20.5) | 0.01 |

*Hib full series: primary series and booster dose, which includes receipt of ≥3 or ≥4 doses, depending on product type received.
†Data for the 2019 birth year are from survey years 2020, 2021, and 2022; data for the 2020 birth year are considered preliminary and are from survey years 2021 and 2022 (2023 data are not yet available).

Hill HA et al. Vaccination Coverage by Age 24 Months Among Children Born in 2019 and 2020 — National Immunization Survey-Child, United States, 2020–2022. *MMWR Weekly* / November 3, 2023 / 72(44);1190–1196.

# Vaxelis (DTaP-IPV-Hib-HepB)

# Vaxelis (DTaP-IPV-Hib-HepB) is newer

- Licensed in December 2018
- ACIP voted to include in VFC in June 2019
- More than 6.2 million doses distributed in the United States as of Q4 2023

*Data provided by the manufacturer.

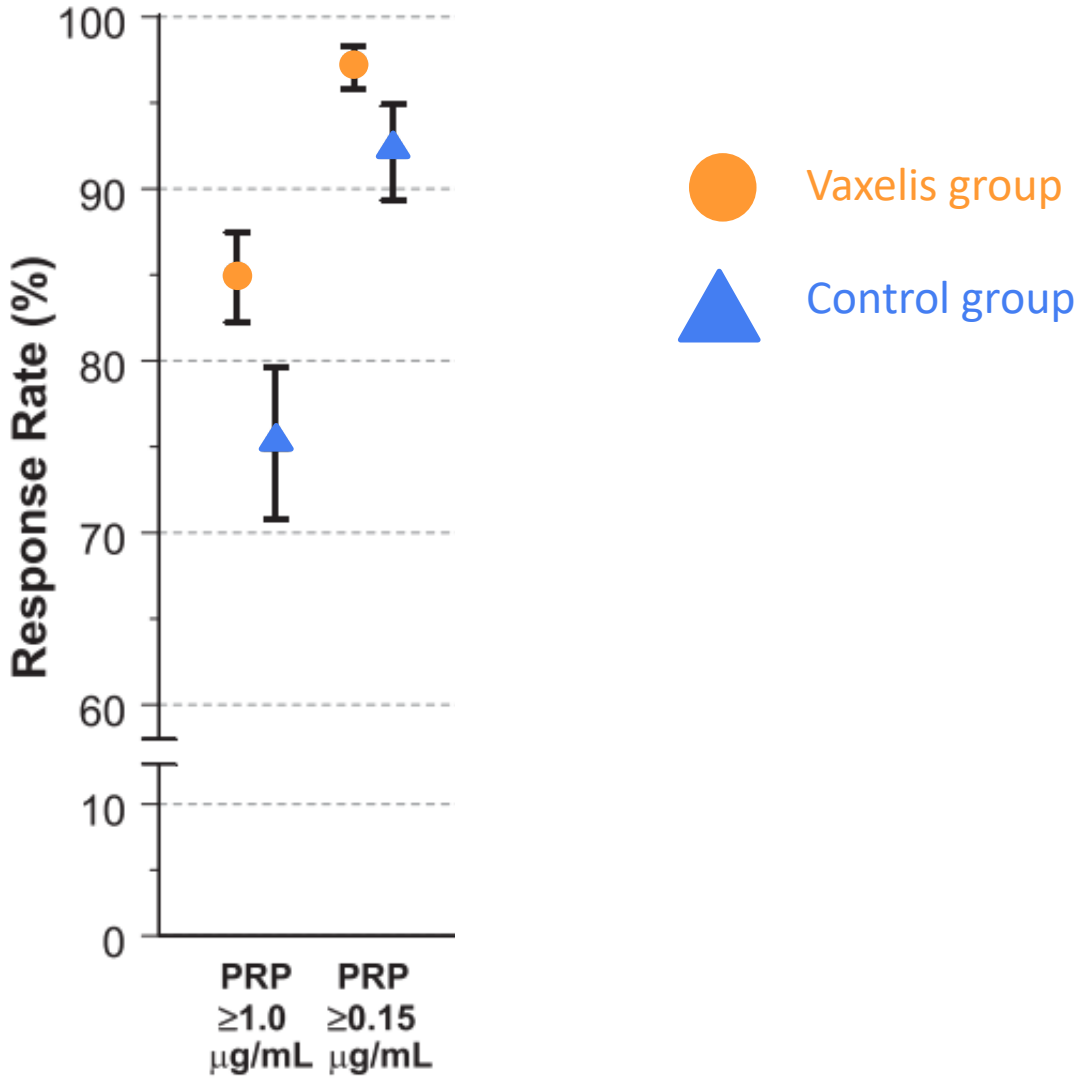
# Vaxelis (DTaP-IPV-Hib-HepB) does not currently have a preferential recommendation for AI/AN infants

- Post-dose 1 immunogenicity data not previously available
- Lower dose of PRP-OMP than PedvaxHIB

| Vaccine Product | Trade Name | PRP | OMP |
|---|---|---|---|
| PRP-OMP | PedvaxHIB | 7.5 mcg | 125 mcg |
| DTaP-IPV-Hib-HepB | Vaxelis | 3 mcg | 50 mcg |

The use of trade names is for identification purposes only and does not imply endorsement by CDC.

# In Phase III clinical trials, Hib antibody responses after the 3-dose primary series were non-inferior to licensed comparator vaccines

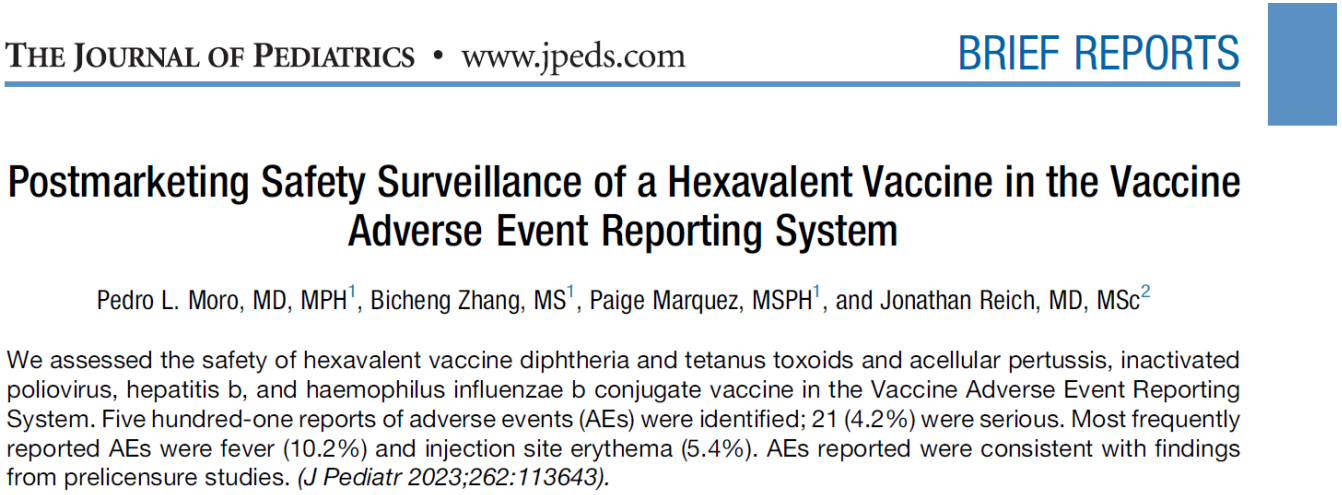



- Vaxelis group received DTaP5-IPV-Hib-HepB, PCV13, and RV5 at 2, 4, and 6 months of age followed by DTaP5, Hib-OMP, and PCV13 at 15 months of age.
- Control group received DTaP5-IPV/Hib,PCV13, and RV5 at 2, 4, and 6 months of age, with HepB at 2 and 6 months of age, followed by DTaP5, Hib-TT, and PCV13 at 15 months of age.
- PRP ≥0.15 ug/ml and ≥1.0 ug/ml are correlates of short-term, and long-term protection, respectively.
- The use of trade names is for identification purposes only and does not imply endorsement by CDC.

Marshall GS, et al. Immunogenicity, safety and tolerability of a hexavalent vaccine in infants. *Pediatrics* 2015;136:e323–32.

# Safety of Vaxelis (DTaP-IPV-Hib-HepB)

- In clinical trials, the safety profile was consistent with that of licensed comparator vaccines except higher rate of fever than with DTaP-IPV/Hib (47.1%–47.4% vs. 33.2%–34.4%)[1,2]; rates of fever-related medical events were similar between groups
- Post-licensure analysis of VAERS data from June 26, 2019 – June 16, 2023 did not identify new or unexpected safety issues



THE JOURNAL OF PEDIATRICS • www.jpeds.com BRIEF REPORTS

**Postmarketing Safety Surveillance of a Hexavalent Vaccine in the Vaccine Adverse Event Reporting System**

Pedro L. Moro, MD, MPH[1], Bicheng Zhang, MS[1], Paige Marquez, MSPH[1], and Jonathan Reich, MD, MSc[2]

We assessed the safety of hexavalent vaccine diphtheria and tetanus toxoids and acellular pertussis, inactivated poliovirus, hepatitis b, and haemophilus influenzae b conjugate vaccine in the Vaccine Adverse Event Reporting System. Five hundred-one reports of adverse events (AEs) were identified; 21 (4.2%) were serious. Most frequently reported AEs were fever (10.2%) and injection site erythema (5.4%). AEs reported were consistent with findings from prelicensure studies. *(J Pediatr 2023;262:113643).*

[1]Marshall GS, et al. Immunogenicity, safety and tolerability of a hexavalent vaccine in infants. *Pediatrics* 2015;136:e323–32.

[2]Block SL, et al. Lot-to-lot consistency, safety, tolerability and immunogenicity of an investigational hexavalent vaccine in U.S. infants. *Pediatr Infect Dis J* 2017;36:202–8.

# Vaxelis protects against 6 infections with fewer injections

| Option | 2 months | 4 months | 6 months | 12–15 months | Total shots |
|---|---|---|---|---|---|
| 1 | **Vaxelis** | **Vaxelis** | **Vaxelis** | PedvaxHIB<br>DTaP | 5 |
| 2 | PedvaxHIB<br>Pediarix | PedvaxHIB<br>Pediarix | Pediarix | PedvaxHIB<br>DTaP | 7 |
| 3 | PedvaxHIB<br>DTaP<br>IPV<br>HepB | PedvaxHIB<br>DTaP<br>IPV | DTaP<br>IPV<br>HepB | PedvaxHIB<br>DTaP | 12 |

Pediarix is a combination vaccine that protects against diphtheria, tetanus, pertussis, polio, and hepatitis B.
DTaP is a vaccine that protects against diphtheria, tetanus, and pertussis. The 4$^{th}$ dose of DTaP is recommended at age 15–18 months.
IPV is inactivated polio vaccine.

# Policy question

- Should Vaxelis (DTaP-IPV-Hib-HepB) be included with PedvaxHIB in the preferential recommendation for American Indian and Alaska Native infants?

# Acknowledgments


- ACIP Members on the WG
  - Jamie Loehr (Interim Chair)
  - Wilbur Chen
- Ex Officio WG Members
  - Margaret Bash (FDA)
  - Matthew Clark (IHS)
  - Mark Connelly (FDA)
  - Francisco Leyva (NIH)
- WG Liaisons and Consultants
  - Amra Resic (AAFP)
  - Samir Shah (AAP)
  - Barb Fluty (ACHA)
  - Karyn Lyons (AIM)
  - Paul Cieslak (CSTE)
  - Kathy Hsu (IDSA)
  - Joseline Zafack (NACI)
  - Jeff Goad (NFID)
  - Jessica Cataldi (PIDS)
  - Amy Middleman (SAHM)
  - Kathy Poehling (Wake Forest)
  - Lynn Bahta (Minnesota Department of Health)
  - David Stephens (Emory)
- CDC Contributors
  - Lucy McNamara (DBD/NCIRD)
  - Sarah Schillie (DBD/NCIRD)
  - LeAnne Fox (DBD/NCIRD)
  - Susan Hariri (DBD/NCIRD)
  - Amy Rubis (DBD/NCIRD)
  - Noele Nelson (DBD/NCIRD)
  - Alison Albert (DBD/NCIRD)
  - Angela Jiles (DBD/NCIRD)
  - Marc Fischer (DIDRI/NCEZID)
  - Jonathan Duffy (DHQP/NCEZID)
  - Pedro Moro (DHQP/NCEZID)
  - Tanya Myers (DHQP/NCEZID)
  - Liz Velazquez (ISD/NCIRD)
  - Jessica MacNeil (ACIP Secretariat)
  - Hannah Rosenblum (ACIP Secretariat)
  - Melinda Wharton (ACIP Secretariat)
- GRADE/EtR Support
  - Doug Campos-Outcalt (Arizona)
  - Rebecca Morgan (Case Western Reserve)

# Thank you!
# Questions?