INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: *Vaxelis® in AI/AN Children*
-August 2024-

Background:
The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) conducted an overview of Vaxelis® immunization, with particular focus on findings from the HibVax Study which specifically enrolled American Indian/Alaska Native (AI/AN) children. All vaccines recommended by the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) are named to the IHS National Core Formulary (NCF). Following this clinical review, the NPTC made **no modifications** to the NCF.

Discussion:
Vaxelis® is a hexavalent pediatric immunization containing; (1) DTaP (diphtheria toxoid, tetanus toxoid, acellular pertussis), (2) Inactivated poliovirus (IPV), (3) *Haemophilus influenzae* type b (Hib, PRP-OMP), and (4) Hepatitis B recombinant vaccine (HepB).[1,2] It was licensed by the FDA in December 2018 for use in children 6 weeks to four years of age, as a 3-dose series ideally administered at 2, 4 and 6 months of age.[1] At that time, Vaxelis® did not receive a preferential recommendation for use in AI/AN children because of the lower dose of the PRP-OMP *Haemophilus influenza* type b component compared to the monovalent PedVaxHib®, which already carries this preferential recommendation.[1] On June 26, 2024, following review of data from the HibVax Study, the ACIP updated its recommendation which now states "DTaP-IPV-Hib-HepB (Vaxelis®) should be included with PRP-OMP (PedvaxHIB®) in the preferential recommendation for American Indian and Alaska Native infants based on the *Haemophilus influenzae* type b (Hib) component."[3]

History: *Haemophilus influenzae* type b (Hib) causes serious vaccine-preventable disease. Invasive Hib diseases include meningitis, bacteremia, epiglottitis, pneumonia +/-empyema, septic arthritis, cellulitis (orbital, periorbital and facial) and pericarditis.[4] Vaccination against Hib disease began in 1985.[4]

Epidemiology[6,7]	USA population	AI/AN population
Pre-Hib vaccine era: <5 years of age (3-6% fatality rate) Meningitis: (26.1% w/ significant sequelae)	24 per 100,000 children = ≈ 20,000 total children ≈ 12,000 w/ meningitis	280 per 100,000 children
Pre-Hib vaccine era: average age of onset of meningitis (Most common Hib invasive disease)	6-9 months of age	4-5 months of age
Post vaccine decrease of Hib invasive disease in children <5yo	>99% within 5 years	>99% within 5 years
Current post-Hib immunization era:	<0.03 per 100,000	2.5 per 100,000

Because of the higher rate of Hib invasive disease and early onset of meningitis in AI/AN infants, protective immunity after the first Hib vaccine dose is essential. Since 1999, the American Academy Pediatrics (AAP) has stated; "Because of the risk of invasive Hib disease at younger ages, the Indian Health Service (IHS) has recommended a preference for the PRP-OMP (PedvaxHIB®) 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." [5] Consistent with current ACIP recommendations, this preference of the PRP-OMP Hib conjugate vaccine is still recommended.[3]

Currently there are five Hib vaccines licensed in the United States.[7] The vaccines are Hib conjugate vaccines consisting of Hib polyribosyl ribitol phosphate (PRP) capsular material conjugated to either outer membrane protein of *Neisseria meningitidis* serogroup B (PRP-OMP) or tetanus toxoid (PRP-T). Two of the vaccines use the PRP-OMP conjugate which is preferred in AI/AN children, namely the monovalent PRP-OMP (PedvaxHIB®) and combination vaccine DTaP-IPV-Hib-HepB (Vaxelis®).[7] Vaxelis® had not previously received a preferential recommendation for AI/AN children as it has 60% less of the PRP-OMP component than in PedvaxHIB® and the post-dose 1 immunogenicity data was unknown.[7]

Conducted by the Johns Hopkins Center for Indigenous Health, the HibVax Study enrolled AI/AN infants from both the Navajo Nation and Alaska. The primary question addressed by the study was, "Do Hib antibody levels in AI/AN infants meet non-inferiority criteria 30 days after dose 1 of Vaxelis® compared to PedvaxHIB®?"[8]

The HibVax Study[8,9]	Phase 4, prospective, open label, randomized controlled clinic trial
Population	Healthy AI/AN infants born at >/= 35 weeks gestational age, 42-90 days of age at the time of first vaccination Locations: Anchorage AK, 4 Navajo sites (Chinle AZ, Fort Defiance AZ, Gallup NM, Shiprock, NM) Matched at location of study enrollment for: sex, gestational age, age at first vaccination
Intervention	Vaxelis® vaccine per current CDC immunization schedule = 2, 4, and 6 months of age
Comparator	PedvaxHIB® vaccine per current CDC immunization schedule = 2 and 4 months of age
Outcomes	Compare antibody levels: before vaccination vs. day 30, 120, and 150 days post-dose 1 Safety monitoring for serious adverse events: on day 0, 30, 60, 120 and 150
Length of Study	151 days (7 months)
Study Design	333 total infants: (Vaxelis®: 167) (PedVaxHib®: 166)

The HibVax Study[8,9]	Results
Invasive Hib disease	No invasive Hib disease in study population
Post dose 1 immunogenicity (30 days post-dose 1)	1. Anti-Hib IgG GMC ratio Vaxelis® vs. PedvaxHIB® by constrained longitudinal data analysis: 1.03 (95% CI: 0.75-1.41) which met the non-inferiority criteria 2. The % of infants with anti-Hib concentration above the putative correlate of short-term protection (≥0.15 µg/mL) was similar in the Vaxelis® group (75.7%) & the PedvaxHIB® group (71.2%, p=0.39)
Post series immunogenicity (150 days post-dose 1)	The % of infants with anti-Hib concentration above the putative correlate of long-term protection (≥1.0 µg/mL) was higher in the Vaxelis® group (83.6%) than PedvaxHIB® group (71.7%, p=0.03)
Severe adverse effects	Frequency of SAE was similar in Vaxelis® (5.4%) and PedvaxHIB® (7.2%, p=0.49) Most common: acute respiratory infection (21/25; 84%) No SAE deemed related to study participation; No invasive Hib disease in study participation

Combination Vaccines: Both the CDC and AAP state a general preference for combination vaccines over separate injections of equivalent component vaccines. Combination vaccines offer many advantages, including reduced number of injections and reduced confusion about childhood vaccines, as well as improved vaccine acceptance, timeliness of administration, and improved office visit efficiency.[9]

Use of Vaxelis® for prevention of invasive Hib disease[1]: Children should receive a primary series (2 or 3 doses, depending on the vaccine used) of a Hib conjugate vaccine and a booster dose of vaccine at age 12–15 months. Although PedvaxHIB® is licensed as a 2-dose primary series at ages 2 and 4 months, Vaxelis® is licensed as a 3-dose primary series. Therefore, if Vaxelis® is used, 3 doses are needed to complete the primary series if Vaxelis® is used for any doses. Vaxelis® should not be used for the booster dose (after completion of the 3-dose primary series). Any Hib conjugate vaccine licensed for a booster dose can be used.

Findings:

On June 26, 2024, the ACIP recommended DTaP-IPV-Hib-HepB (Vaxelis®) be included along with PedvaxHIB® in the preferential recommendation for AI/AN infants based on the *Haemophilus influenzae* type b (Hib) component.[3] This was based on non-inferiority post-dose 1 of the Hib component compared to the monovalent PedvaxHIB®. Additional advantages may include improved vaccine acceptance due to lower shot burden and possible better long-term protection based on post-series immunogenicity. Both Vaxelis® and PedVaxHib® offer a good option for protection from invasive Hib disease in AI/AN children.

References:

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8. Hammit L, et al. The HibVax Study: Immunogenicity of Hib type b PRP-OMP vaccines in AI/AN infants. (CDC slides). Feb 29, 2024.
9. U.S. Centers for Disease Control and Prevention. Evidence to Recommendations: Use of Vaxelis among AI/AN infants. June 26, 2024.