Immunogenicity of H. Influenzae Type b PRP-OMP Vaccines in American Indian and Alaska Native Children (the HibVax Study)

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JHSPH IRB Research Plan for New Data Collection

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Study Title: **Immunogenicity of *H. influenzae* type b PRP-OMP vaccines in American Indian and Alaska Native children (the "HibVax Study")**

I. Aims of the Study:

The main goal of this study is to compare the *Haemophilus influenzae* type b antibody response in American Indian / Alaska Native (AI/AN) infants to two licensed vaccines: Vaxelis and PedvaxHIB.

Primary Hypothesis:

The anti-PRP IgG GMC in infants 30 days after dose 1 of Vaxelis will meet non-inferiority criteria compared to that 30 days after dose 1 in infants given PedvaxHIB

Secondary Hypotheses:

1) The proportion of infants with anti-PRP IgG levels ≥0.15 µg/mL, 30 days after dose 1 of Vaxelis or PedvaxHIB, will be similar.
2) The proportion of infants with anti-PRP IgG levels ≥0.15 µg/mL and ≥1.0 µg/mL on Day 121 after initiation of the primary series, i.e., 60 days after dose 2 of Vaxelis and 60 days after dose 2 of PedvaxHIB, will be similar.
3) The proportion of infants with anti-PRP IgG levels ≥0.15 µg/mL and ≥1.0 µg/mL on Day 151 after initiation of the primary series, i.e., 30 days after dose 3 of Vaxelis and 90 days after dose 2 of PedvaxHIB, will be similar.
4) The nutritional status of infants, may be related to the magnitude, duration and nature of the infants' immune response to vaccination.

The primary objective of the proposed research is to assess, among AI/AN children:

(1) The non-inferiority of the anti-PRP IgG Geometric Mean Concentration (GMC) 30 days after dose 1 of Vaxelis administered at 2 months of age, compared to PedvaxHIB.

The secondary objectives are to:

(2) Describe the proportion of infants with anti-PRP IgG ≥0.15 µg/mL 30 days after dose 1 of Vaxelis or PedvaxHIB.
(3) Describe the proportion of infants with anti-PRP IgG ≥0.15 µg/mL and ≥1.0 µg/mL on Day 121 after initiation of the primary series, i.e., 60 days after dose 2 of Vaxelis and dose 2 of PedvaxHIB.
(4) Describe the proportion of infants with anti-PRP IgG ≥0.15 µg/mL and ≥1.0 µg/mL on Day 151 after initiation of the primary series, i.e., 30 days after dose 3 of Vaxelis and 90 days after dose 2 of PedvaxHIB.
(5) Describe nutrition-related behaviors, practices and food-related resources among care-givers of AI/AN infants presenting for routine vaccination, and explore the nature of the infants' immune response in relation to these factors.

II. Background and Rationale:

Historically, American Indian and Alaska Native (AI/AN) children aged <5 years have experienced invasive *H. influenzae* type b (Hib) disease at a rate that is at least 5 times higher than the general U.S. population. In the pre-vaccine era, the incidence of Hib disease peaked earlier for AI/AN children at 4-5 months than general US children at 6-9 months (Ward JI et al., *Lancet*, 1981). Therefore, prevention efforts for AI/AN populations focused on identifying a vaccine that would protect against disease in early infancy. Studies in AI/AN children revealed that the Hib conjugate vaccine with the capsular polysaccharide (polyribosylribitol phosphate polysaccharide [PRP]) coupled to the outer membrane protein complex of *Neisseria meningitidis* (OMP) induced anti-PRP IgG titers that correlated with protection (GMC ≥0.15 µg/mL) and demonstrated high efficacy after a single dose in infancy (Bulkow et al., *Pediatr Infect Dis J,* 1993; Santosham et al., *N Engl J Med,* 1991). Hib PRP-OMP was licensed in 1991 as PedvaxHIB; following introduction of a two-dose primary series and a booster dose, the rate of Hib disease decreased substantially among AI/AN children. The importance of PRP-OMP vaccine to disease control was highlighted in the 1990s in Alaska when use of a non-PRP OMP Hib vaccine was associated with an increase in disease incidence in AN children (Singleton et al, *J Pediatr,* 2000). In 1999, the American Academy of Pediatrics Committee for Native American Child Health released its official preference for Hib PRP-OMP for use in AI/AN populations.

In spite of Hib vaccine coverage similar to or greater than the national average, AI/AN populations periodically experience pediatric cases of invasive Hib disease. In contrast to the pre-Hib vaccine era, a majority of these cases occur in fully vaccinated children beyond the first year of life (Singleton et al., *Pediatrics*, 2006) (*State of Alaska Epi Bulletin*; Aug 11, 2009). This epidemiologic shift in the age at which disease occurs may indicate ongoing transmission in the presence of waning immunity following vaccination. It is important to provide additional data to demonstrate that infants will be protected early in life, given the historic early peak of Hib disease, and evidence that Hib is still circulating in village-based and reservation-based AI/AN communities.

Nutrition plays an important role in determining the strength and competence of the immune system (Maggini et al., *Nutrients*, 2018). However, the literature presents a complex, mixed picture on whether, and how, an infant's micronutrient status affects susceptibility to infection, and immunity – in our context, the antibody response to vaccination, and/or the durability of the antibody response (Cunningham-Rundles, *J Allergy and Clinical Immunology*, 2005). In order to understand common behaviors, practices and food security resources in the AI/AN community, it will be helpful to assess the dietary history for the caregiver (and/or) mother, including diet in pregnancy and whether or not the mother took prenatal vitamins (Obanewa & Newell, *Future Virology,* 2017).

Vaxelis is a licensed hexavalent combination vaccine that contains Hib PRP-OMP and antigens (Hepatitis B surface antigen, Diphtheria Toxoid, Tetanus Toxoid, Acellular Pertussis [DTaP], and Inactivated Polio Virus [IPV]) to protect against diseases caused by 5 other organisms. Vaxelis contains 3.0 µg/mL of PRP-OMP antigen, compared to 7.5 µg/mL in PedvaxHIB. This lower concentration of PRP-OMP has been shown to be less reactogenic and similarly immunogenic to higher doses (Diaz-Mitoma et al., *Vaccine*, 2011). Vaxelis is approved for administration as a 3-dose primary series at 2, 4, and 6 months of age. A booster dose with a different licensed Hib vaccine (e.g., PedvaxHIB, ActHib) is required at 12-15 months. Vaxelis Hib PRP-OMP was found to be highly immunogenic post-dose 2 at 4 months (Silfverdal et al., *Vaccine*, 2016) and post-dose 3 at 6 months (Vesikari et al., *Pediatr Infect Dis J*, 2017). However, immunogenicity data post-dose 1 were not measured in the phase 3 clinical trials of this vaccine.

In June 2019, the ACIP passed a resolution supporting inclusion of Vaxelis in the Vaccines For Children Program for the general U.S. population. It is expected that this vaccine will be made available for routine use in the U.S. in 2021. A preferential recommendation for use of this vaccine in AI/AN children was not given

because post-dose 1 immunogenicity data were not yet available. To support policy recommendations to protect the health of the AI/AN community, the ACIP recommended a study to demonstrate non-inferiority of the post-dose 1 immune response to Vaxelis compared to the current recommended product (PedvaxHIB). It is important to demonstrate that infants will be protected early in life, given the historic early peak of Hib disease.

If this study finds that Vaxelis and PedvaxHIB provide comparable protection after one dose, this would support the CDC making a preferential recommendation for Vaxelis for AI/AN infants. This would expand the options of preferred vaccines for AI/AN infants and potentially provide more long-lasting protection.

III. Study Design:

This study will be a prospective, randomized, unblinded, phase IV study of the immunogenicity of two licensed Hib vaccines among AI/AN infants. The study will enroll approximately 330 AI/AN infants on Navajo Nation and in Anchorage, Alaska who are 6-12 weeks of age and due to receive their first set of routine infant immunizations. After their parents have provided informed consent, eligible infants will be randomized to one of two study arms – either Vaxelis or PedvaxHIB. Participants will make 5 study visits over the course of approximately 5 months.

Four blood samples will be collected: before and after the first dose of Hib vaccine, 60 days after the second dose of Hib vaccine, and after the final dose; these specimens will be tested with ELISA to assess levels of IgG antibody against Hib. IgG antibody levels will be compared between infants receiving Vaxelis and those receiving PedvaxHIB, using a non-inferiority analysis.

We propose to enroll 330 children. For the primary series, 165 will receive Vaxelis at 2, 4, and 6 months of age (regimen 1) and 165 will receive PedvaxHIB at 2 and 4 months of age (regimen 2). We anticipate a retention rate of approximately 90% (n=300) through the post-dose 1 blood draw, associated with our primary hypothesis.

Among infants vaccinated at 2 months of age, the anti-PRP IgG GMC 30 days post dose 1 of Vaxelis will be considered non-inferior if the ratio of the GMC in the Vaxelis group relative to the PedvaxHIB group is >0.67. The statistical criterion we are using to define non-inferiority corresponds to the lower bound of the two-sided 95% confidence interval (CI) on the anti-PRP IgG GMC ratio [Vaxelis / PedvaxHIB] being >0.67. A sample size of 150 evaluable children per group will provide at least 80% power to detect non-inferiority using a one-sided two-sample t-test.

The table below summarizes the visit schedule for the study.

Visit Number:	**Visit1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Study Day:	Day 1	Day 31	Day 61	Day 121	Day 151
Approximate Child's Age:	2 months	3 months	4 months	6 months	7 months
Visit interval		30 to 48 days since Visit 1	42 to 90 days since Visit 1	56 to 90 days since Visit 3	30 to 48 days since Visit 4
Verify eligibility	x				
Medical history, baseline characteristics	x				
Randomization	x				

Medical history update and nutrition assessment		x	x	x	x
Physical exam	x		x	x	
Blood draw	x	x		x	x
Receive Hib vaccine, if in Vaxelis arm	x		x	x	
Receive Hib vaccine, if in PedvaxHIB arm	x		x		
Receive Other routine immunizations	x		x	x	

IV. Participants:

A. Inclusion Criteria:

Subjects must meet all of the following:

- Born at gestational age of ≥35 weeks
- AI/AN infant between 6 to 12 weeks of age (42-90 days) at the time of the first vaccination (i.e., Study Day 1)
- Written informed consent provided by parent(s)/Legally Authorized Representative(s) (LARs)
- Investigators believe that the parent(s)/LARs can and will comply with the requirements of the protocol (i.e., return for follow-up visits, recall of adverse events)
- Infant is available to complete the follow-up period of 5 months
- Healthy infant, as established by medical history and clinical examination before entering the study

B. Exclusion Criteria:

Subjects may meet any of the following:

- History of receipt of blood, blood products, or immunoglobulin products since birth or expected receipt through the duration of the study
- Chronic seizure or evolving or unstable neurologic disorder
- Congenital Heart Disease, except for uncomplicated CHD (e.g., PDA, small septal defect)
- Infant of mother with HIV infection
- History of reaction or hypersensitivity likely to be exacerbated by any vaccine component, or to latex
- Infant with confirmed or suspected immunocompromising medical condition, based on medical history, including chronic administration (more than 14 days in the lifetime) of immunosuppressants or other immune-modifying drugs since birth
- Administration of infant vaccines other than birth dose Hepatitis B, prior to the time of enrollment
- Any condition which might interfere with the evaluation of the investigational product, or interpretation of subject safety or study results, in the opinion of the investigator
- Child of an employee of the sponsor, clinical study site, or any other individual involved with the conduct of the study, or an immediate family member of such individuals
- Acute illness and/or fever (temperature ≥100.4 F or ≥38.0 C) at time of enrollment (Note: Participant with fever may be enrolled at later date if symptoms have resolved and all other criteria for inclusion are met at that time)
- Current (or within the past 7 days) or expected receipt of immunosuppressive agents, including steroids, except topical or inhaled steroids (Note: For oral corticosteroids, this will mean prednisone (≥ 0.5 mg/kg/day, or equivalent; participant may be enrolled at a later date if medication use ends and all other criteria for inclusion are met at that time)

V. Study Procedures:

A. Recruitment Process:

Study staff will identify potentially eligible infants through pediatric and family practice clinics, referrals from healthcare providers, and self-referral. Study staff will then request permission to discuss the consent form. Study staff will be available to meet parents in clinic at regularly scheduled primary care appointments, to discuss the study and to administer informed consent.

B. Consent Process:

During the consent process, the study staff will explain the study to the parent/LAR, including study procedures, risks and benefits associated with participating in the study, and the rights and responsibilities of study participants. The parent/LAR will be encouraged to ask questions. The study staff will also ask the parent/LAR to explain the study in their own words to ensure they understand the purpose of the study, their child's participation, and the risks and benefits.

If the parent/LAR is interested in their child participating in the study, the RPA will have the parent/LAR sign and date the consent form. After that, the study staff will sign and date the consent form. The parent/LAR will be given a copy of the consent form.

The consent discussion will occur in a private location, e.g. at home, in a study clinic, or in office space maintained by the JHU CAIH.

C. Study Procedures:

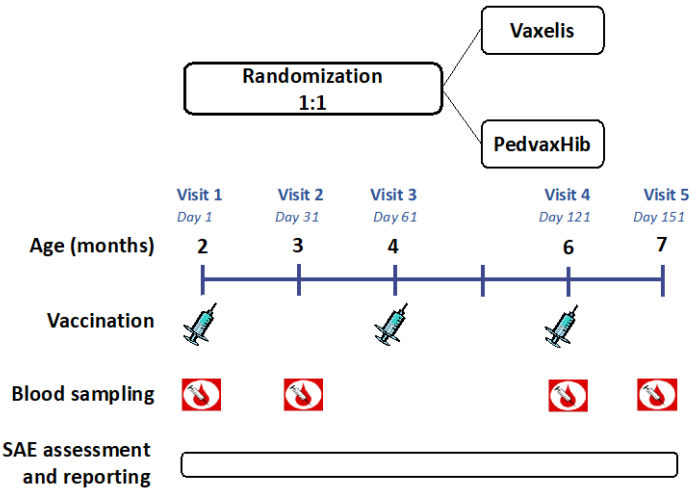
Vaccine Regimens

165 infants will be randomized to the Vaxelis group, which is licensed for primary vaccination at 2, 4 and 6 months of age.
165 infants will be randomized to the PedvaxHIB group, which is licensed for primary vaccination at 2 and 4 months of age.

Each participant will also be given other routine pediatric immunizations that are not part of the study regimen, per ACIP schedule and recommendations, (e.g., DTaP and IPV at 2, 4 and 6 months, and hepatitis B vaccine at 2 and 6 months, for participants randomized to PedvaxHIB; Prevnar13 at 2, 4 and 6 months, and the rotavirus vaccine series at either 2, 4 and 6 months (if given RotaTeq) or 2 and 4 months (if given Rotarix). Inactivated influenza vaccine will be offered at 6 months of age, as appropriate based on season.

Vaxelis (3.0μg/mL Hib PRP-OMP, HBsAg, DTaP, and IPV), Prevnar13, Pediarix, PedvaxHIB, and inactivated influenza vaccine are injectable vaccines that are administered intramuscularly. RotaTeq and Rotarix are orally-administered vaccines.

Study design graphic



Participants will participate in up to six in-person study visits: screening (if done in advance of visit 1) followed by five visits as listed above. Study visits will occur in a private location, at the participant's home, in a study clinic, at the study office, or over the phone. In-person visits will be conducted using appropriate personal protective equipment. All vaccination visits will occur in the clinic. If it is not possible to conduct non-vaccination visits in-person, study procedures that do not required in-person participant contact may be performed by telehealth. Screening (e.g., COVID-19 health checks) prior to in-person visits will be conducted per local institutional requirements. Each study visit after randomization will last approximately one hour.

This study will collect blood biospecimens at four visits. These will be collected by trained research or clinical staff, using appropriate personal protective equipment. Samples will be labeled with the participant's study ID. No personally identifying information will be included. Samples will be stored in refrigerators/freezers at the study sites prior to testing. Samples will be stored securely and only accessible to authorized staff, at all times. Once testing is complete, any remaining sample will be discarded.

Participants will remain in the study for approximately 5 months (150 days after randomization).

VI. Statistical Analysis Plan:

Immunogenicity laboratory values will be reported as anti-PRP IgG geometric mean concentrations (GMC), in µg/mL. The proportion of children with anti-PRP antibody concentrations above the established protective concentration thresholds of 0.15 mcg/mL for short-term protection and 1.0 mcg/mL for long-term protection will be calculated at each timepoint.

Analysis for Primary Hypothesis

(1): Non-inferiority

The GMC ratio of anti-PRP IgG 30 days following a single dose of Vaxelis and PedvaxHIB will be assessed for non-inferiority, using a constrained longitudinal analysis (cDLA) model, which regresses the log anti-PRP IgG concentration on whether the measure is pre-, or post-vaccination and whether the interaction of this indicator with vaccination group. The main effect of vaccination group is omitted from the model because GMC is assumed to be equal at baseline. For the primary analysis, the cLDA will be restricted to the data from the first and second study visits.

The coefficient of the interaction term (effect of vaccination group at 30 days post vaccination) will be reported, along with 95% confidence intervals for the GMC ratio. The anti-PRP IgG GMC for children receiving dose 1 of Vaxelis will be considered non-inferior if it is within a 1.5-fold margin of the GMC for children receiving dose 1 of PedvaxHIB. The associated statistical criterion corresponds to the lower bound of the two-sided 95% confidence interval (CI) around the anti-PRP IgG GMC ratio [Vaxelis / PedvaxHIB] being > 0.67.

Additional secondary analysis:

(1) The proportion of children with anti-PRP IgG at short-term protective levels (≥0.15 µg/mL) 31 days after dose 1 of Vaxelis, compared to 31 days after dose 1 of PedvaxHIB, will be compared using the Chi-square test.

(2) The proportion of children with anti-PRP IgG at short-term protective levels (≥0.15 µg/mL) and long-term protective levels (≥1.0 µg/mL) 61 days after dose 2 of Vaxelis and dose 2 of PedvaxHIB, will be compared using the Chi-square test.

(3) The proportion of children with anti-PRP IgG at short-term protective levels (≥0.15 µg/mL) and long-term protective levels (≥1.0 µg/mL) 31 days after dose 3 of Vaxelis and 91 days after dose 2 of PedvaxHIB, will be compared using the Chi-square test.

(4) The proportion of children with at least a 4-fold rise in anti-PRP IgG from baseline to day 31 after dose 1 of Vaxelis, compared to from baseline to day 31 after dose 1 of PedvaxHIB, will be compared using the Chi-square test.

(5) The proportion of children with at least a 4-fold rise in anti-PRP IgG from baseline to day 61 after dose 2 of Vaxelis, compared to from baseline to day 61 after dose 2 of PedvaxHIB, will be compared using the Chi-square test.

(6) The proportion of children with at least a 4-fold rise in anti-PRP IgG from baseline to 31 days after dose 3 of Vaxelis, compared to from day 1 to day 61 after dose 2 of PedvaxHIB, will be compared using the Chi-square test.

VII. Safety Monitoring:

All serious adverse events (SAEs) will be recorded and reported throughout the entire study period. SAEs will be assessed by querying parents/LARs at each study visit and through chart review throughout the course of participation in the study. In addition to the scheduled visits, parents/LARs will be encouraged to bring the infant participant to the clinic or notify the investigator if an SAE occurs at any time following enrolment. Parents/LARs will also be encouraged to report, or ask the infant's primary healthcare provider/pediatrician to report at any time, any SAE.

Surveillance at the local hospital facility associated with study sites will be conducted to identify participants who have been seen for medically attended visits.

SAEs will be assessed for severity and causality by the PIs or JHU Study Physician who have been trained and delegated to do this. Any SAE occurring at any study site (i.e., CAIH site or Alaska site) will be reported to the sponsor and the IRBs.