Vaccine Effectiveness and Seroconversion to 23 Valent Pneumococcal Polysaccharide Vaccination in Children With Type 1 Diabetes

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General Study Information

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Study Title: Vaccine effectiveness and seroconversion to 23 Valent Pneumococcal Polysaccharide Vaccination in Children with Type 1 Diabetes

Protocol version number and date: Version 4, 4/22/2022

Research Question and Aims

Hypothesis: Children with Type 1 Diabetes have reduced immunological response to 23 valent polysaccharide pneumococcal vaccination (PPSV23) as assessed by global IgG levels.

Aims, purpose, or objectives:
Specific Aim 1: To determine if children with type 1 diabetes have adequate immune response to PPSV23 vaccination and to assess factors affecting immune response.
Hypothesis 1: Children with type 1 diabetes (T1DM) will have a suboptimal immunological response to PPSV23 as assessed by global IgG assay. Lower age of the patient, longer duration of diabetes and poor glycemic control will be associated with impaired immunogenic response to the PPSV23.

Specific Aim 2: To assess if patients with T1DM have waning of immune response to PPSV23 six months following vaccination and associated factors that may be associated with the vaccine response.
Hypothesis 2: T1DM children will have higher waning of immunity as compared to general population without T1DM. Lower age of the patient, longer duration of diabetes and poor glycemic control will be associated with impaired immunogenic response to the PPSV23.

Background:
Diabetics are at risk for invasive pneumococcal infections and are more likely to have severe outcomes with infection compared to the general population.[1-3] Half of all school-age children with T1DM are colonized with Streptococcus pneumoniae, underscoring the need for pneumococcal vaccination.[4] While the CDC recommends all children > 2 years with type 1 diabetes receive PPSV23 to prevent invasive pneumococcal disease, literature suggests lack of compliance and missed opportunities for PPSV23 vaccination in diabetic children.[5,6] Furthermore, it is unknown if children with T1DM mount sufficient immunological response to PPSV23 vaccination.

PPSV23 immunological response relies upon the adaptive immune system including adequate T-cell activation by antigen presenting cells, T-cell proliferation, subsequent B-cells stimulation, and antibody production. While definitive data on the degree of global adaptive immune impairment in diabetics remains unclear, there are likely some T-cell interactions with antigen presenting cells that explain the decreased antibody response to vaccination. Adult studies indicate decreased antibody response to T-cell dependent antigens via altered antigen-presenting T-cell interactions.[7] Others describe functional immune impairments including abnormal CD4, CD8, and CD8 Treg proliferation as well as abnormalities in the antigen presenting cell including monocyte derived dendritic cells having reduced CD54 adhesion molecules and increased inhibitory cytokines (IL-10) in type 1 diabetics.[8,9] Mechanisms of poorer T-cell proliferation may be due to reduced antigen-induced interferon-γ and interleukin-13 release in type 1 diabetics compared to type 2 diabetics.[7] Limited data in children with type 1 diabetes also suggest reduced antibody response to T-cell dependent antigens such as the PPSV23.[10]

New techniques are available to assess antibody response to T-cell dependent antigens. Total IgG levels have traditionally been used to help assess serological response to vaccination though four separate IgG subclasses characterized by distinct immune properties exist. Assessing global IgG studies which include all subtypes may better inform clinicians of immune response. We hypothesize that serological response to PPSV23 as assessed by global IgG, IgM, and IgA response will be altered in T1DM. Better understanding the immune response to PPSV23 may lead to better timing of vaccination in relation to diabetes diagnosis, optimize diabetes care to prevent sustained and uncontrolled hyperglycemia around the time of infection, and perhaps even inform the need for further booster PPSV23 vaccinations. Optimizing PPSV23 vaccination may decrease invasive pneumococcal infections and related morbidity in young patients with T1DM.

Study Design and Methods

Methods: *Describe in lay terms, completely detailing the research activities that will be conducted by Mayo Clinic staff under this protocol.*

We aim to identify children with T1DM 3-18 years of age who have not received pneumococcal polysaccharide vaccination (Pneumovax 23). The diagnosis of T1DM will be confirmed clinically based upon a hemoglobin A1C > 6.5% and history consistent with T1DM. Children with other diseases known to significantly compromise immunity and vaccine response will be excluded. Target accrual will be 100 children.

Seroconversion assessment: Vaccine response as assessed by Global IgG will be drawn 6 months after immunization (+/- 4 months). Blood draws will be aligned when possible with the participant's quarterly clinical hemoglobin A1C checks, to minimize additional blood draws. Key clinical information will be abstracted including hemoglobin A1C history, years of diabetes, glucose variability, diabetes technology use, and anthropometric data.

Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual: 100

Subject population (children, adults, groups): children ages 3-18 years

Inclusion Criteria:
-Clinical diagnosis of Type 1 diabetes

Exclusion Criteria:
-Newly diagnosed with Type 1 diabetes with in the past month of study date
-Contraindications to receiving 23 valent pneumococcal vaccines
-Other conditions associated with compromised immunity and vaccine response
-Primary or Secondary Immune deficiency
-Previous receipt of PPSV-23 vaccination

Biospecimens

Collection of blood samples. When multiple groups are involved copy and paste the appropriate section below for example repeat section b when drawing blood from children and adults with cancer.

a. **From healthy, non-pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.
   Volume per blood draw: __up to 6___ml
   Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) ___twice: baseline 4-6 months post immunization

b. **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.
   Volume per blood draw: ____up to 6__ml
   Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) ____ baseline 4-6 months post immunization _____

Prospective collection of biological specimens other than blood: _____

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Review of medical records, images, specimens

Check all that apply (data includes medical records, images, specimens).

☐ Only data that exists before the IRB submission date will be collected.

Date Range for Specimens and/or Review of Medical Records:
Examples: *01/01/1999 through 12/31/2015*, or all records through *mm/dd/yyyy*.

Note: The Date Range must include the period for collection of baseline data, as well as follow-up data, if applicable.

X ☐ The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.
Examples

- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

Data Analysis

Power analyses may not be appropriate if this is a feasibility or pilot study, but end-point analysis plans are always appropriate even if only exploratory. Provide all information requested below, or provide justification if not including all of the information.

Data Analysis Plan: Clinical data will be summarized using descriptive statistics. The distribution of each serological laboratory parameter (Global IgG, will be assessed for normality. Transformations and/or nonparametric tests will be used if necessary to accurately assess the data. The relationship between serological

response parameters with each of the dependent variables (hemoglobin A1C, years of diabetes, glucose variability, body mass index, age at vaccination etc.) will be assessed with linear models and two-way interaction effects. All calculated p-values will be two-sided with a significance threshold alpha of < 0.05.

Endpoints
Primary: Serological response to polysaccharide pneumococcal vaccination as assessed by Global IgG,
Secondary: Serological response to polysaccharide pneumococcal vaccination by clinical diabetes control characteristics including but not limited to hemoglobin A1C, glucose variability, and diabetes technology use.

1. Schuetz P, Friedli N, Grolimund E, et al. Effect of hyperglycaemia on inflammatory and stress responses and clinical outcome of pneumonia in non-critical-care inpatients: results from an observational cohort study. Diabetologia 2014;57:275-84.
2. Yende S, van der Poll T, Lee M, et al. The influence of pre-existing diabetes mellitus on the host immune response and outcome of pneumonia: analysis of two multicentre cohort studies. Thorax 2010;65:870-7.
3. Kyaw MH, Rose CE, Jr., Fry AM, et al. The influence of chronic illnesses on the incidence of invasive pneumococcal disease in adults. J Infect Dis 2005;192:377-86.
4. Principi N, Iughetti L, Cappa M, et al. Streptococcus pneumoniae oropharyngeal colonization in school-age children and adolescents with type 1 diabetes mellitus: Impact of the heptavalent pneumococcal conjugate vaccine. Hum Vaccin Immunother 2016;12:293-300.
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6. Nuorti JP, Whitney CG, Centers for Disease C, Prevention. Prevention of pneumococcal disease among infants and children - use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine - recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2010;59:1-18.
7. Eibl N, Spatz M, Fischer GF, et al. Impaired primary immune response in type-1 diabetes: results from a controlled vaccination study. Clin Immunol 2002;103:249-59.
8. Pellegrino M, Crino A, Rosado MM, Fierabracci A. Identification and functional characterization of CD8+ T regulatory cells in type 1 diabetes patients. PLoS One 2019;14:e0210839.
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