Effect of Obesity on Immune Response to Pneumovax 23 (ROVE)

NCT02471014

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Statistical Analysis Plan (SAP)
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Introduction:
Obesity has been correlated with higher mortality risk and is associated with a proinflammatory state. Obesity has also been associated with a lower immune response to various types of vaccination (e.g. influenza, hepatitis B, tetanus). As the prevalence of obesity increases, so does the need for a deeper mechanistic understanding of how obesity attenuates vaccination response. It is important to assess the effect of obesity on the immune response to vaccines. The pneumococcal polysaccharide vaccine (Pneumovax 23) is a safe method for stimulating an immune response and its effect on obesity has not been elucidated. As a growing population of obese individuals inevitably age and become susceptible to pneumococcal infections, it is important to consider how obesity may impact the efficacy of Pneumovax 23. We hypothesize that a chronically stressed immune system in obese individuals will be unable to respond as well to vaccination compared to individuals with a BMI between 22 and 25. We will utilize a prospective cohort design. We will also conduct various surveys to examine psychosocial factors that may influence the interaction between obesity and immune response to vaccination. We will also perform genotyping of STING to assess how it may influence the relationship between obesity and immune response to vaccination.

Study design:
This study is a prospective cohort study with two arms: (1) those with a body mass index (BMI) between 22 and 25 and (2) those with a BMI greater than or equal to 30 and a waist-to-hip ratio of at least 0.9 in males and 0.85 in females. Participants will have a baseline visit where they will receive a pneumococcal polysaccharide vaccine and a follow-up visit four-six weeks after.

Sample size calculation
The primary outcome measure for the power calculation was the number of positive pneumococcal titers using data from Wildes et al. (2019). This study included a range of BMIs under 30. By comparing the number of positive titers between those with a BMI < 25 and > 25, we expect that 23 evaluable obese participants and 23 evaluable normal weight participants will provide enough power for the study (see the distribution of positive titers below in Table 1) at a significance level of $\alpha = 0.05$ for a 2-sided t test at 80% power. We consider this estimation to be conservative, as we expect that having a greater separation of BMI values than Wildes et al. will provide greater power. The actual gain in power cannot be quantified.

Table 1. The distribution of positive titers amongst the 14 in Wildes et al. study was as follows:

BMI	5	6	7	8	9	10	11	12	Total
<25	1	2	0	2	2	1	4	2	14

>25	0	2	3	0	1	1	0	0	7

Aims and objectives

The aim of this project is to investigate the effect of obesity on the immune system's ability to mount a protective immune response against the pneumococcal polysaccharide vaccine (Pneumovax 23).

Outcomes

Primary outcome: Vaccine response as measured by serotype-specific IgG antibody responses against the 23 pneumococcal serotypes (i.e., 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F)

Statistics:

When comparing between populations (ie. baseline characteristics table), normality was first assessed by the Shapiro-Wilk test, then followed by either an unpaired 2-sided t test or a Wilcoxon's signed-rank test for parametric data or nonparametric data, respectively. Chi-square tests determined differences in categorical data (i.e. sex, ethnicity). For our primary analysis, we will use an ANCOVA to test for differences in fold change titer levels across groups (nonobese and obese), controlling for sex and age. All hypothesis tests were 2-sided where a P value < 0.05 was considered significant.

To assess the role of the STING genotype, a secondary analysis will be done using 2-way ANOVA of the fold change in titer levels between the wildtype, R232/R232, and HAQ carrier genotypes. Likewise, to assess the role of psychosocial variables, we will also be using an ANOVA or regression, as appropriate. For secondary analyses, we will not perform any multiple testing corrections for P values.

References

Wildes, T. J., Grippin, A., Fasanya, H., Dyson, K. A., & Brantly, M. (2019). Effect of atorvastatin on humoral immune response to 23-valent pneumococcal polysaccharide vaccination in healthy volunteers: The StatVax randomized clinical trial. *Vaccine*, *37*(10), 1313-1324.