**Specific Aims**

Globally, rotavirus gastroenteritis is estimated to cause 146,000– 215,000 deaths annually among children under 5 years of age. While the introduction of two rotavirus vaccines, Rotarix (GlaxoSmithKline) and RotaTeq (Merck), has contributed to substantial reductions in the risk of rotavirus disease, rotavirus remains the leading cause of severe diarrheal disease worldwide among young children. Rotavirus vaccine efficacy ranges from 80-90% in areas of low child mortality but only 40-60% in regions with high child mortality. The reasons for this varied performance are not fully understood. There are two central impediments to further reducing the rotavirus burden. First, identifying factors at the individual-level that adversely impact vaccine immunogenicity and efficacy could inform strategies for modifying these factors for better performance. Second, identifying a correlate of protection could facilitate the development of new vaccine strategies and products, obviating the need for large-scale trials with clinical endpoints.

Rotavirus immunoglobulin A (IgA) antibodies play a critical role in the immune response to rotavirus infection and are possible markers of vaccine protection. IgA antibodies have been shown to be associated with vaccine efficacy on the aggregate level, when comparing countries by income level. Such data suggest that the individual-level IgA may be a useful correlate of protection.

This study aims to investigate host characteristics that contribute to vaccine immunogenicity. It also seeks to understand the value of IgA in predicting vaccine-related protection of rotavirus disease. I will conduct a pooled analysis of individual-level data available for more than 8,100 vaccinated infants from 34 countries/territories who participated in GlaxoSmithKline’s phase II and III Rotarix clinical trials. Combining data from multiple studies not only creates a dataset substantially larger than that of any other related study, but also enables investigation of a wider range of host, household and country-level factors that could contribute to immunogenicity.

**Aim 1: Identify host characteristics that contribute to rotavirus vaccine immunogenicity measured approximately 4 – 8 weeks after receipt of the last vaccine dose.** Infant characteristics including, but not limited to, gender, age at first dose, nutritional status, and breastfeeding status will be assessed as predictors of immune response to Rotarix immunization while using a hierarchical model to control for household and country factors as potential covariates and confounders. Immune response will be measured as 1) seroconversion defined as post-vaccine IgA antibody concentrations ≥ 20 U/mL in subjects initially seronegative; 2) seroconversion defined as a ≥ 3 fold-change in IgA antibody concentrations comparing pre- and post-vaccination levels; 3) post-vaccine IgA antibody titer. Logistic regression and linear regression of log-transformed data will be used to analyze IgA seroconversion and antibody titer, respectively.

**Aim 2: Quantify a threshold of post-vaccine IgA antibody units that serves as an individual-level immune correlate of protection against severe rotavirus disease.** I aim to identify a cutoff value of IgA antibody units, measured approximately 4 – 8 weeks after receipt of the last vaccine dose, which predicts protection against RVGE within 1 year of age and between 1 and 2 years of age. Potential threshold levels of IgA will be identified a priori through visualizing the IgA levels for all countries combined and separately by child mortality strata, calculating the median and identifying thresholds in related literature. The dichotomous outcomes of interest will be analyzed using logistic regression

I expect that identification of host factors that contribute to vaccine immunogenicity will inform strategies that could improve vaccine efficacy and vaccination programs. Identifying an individual-level correlate of protection will enable more rapid and efficient evaluation of new interventions to reduce the rotavirus disease burden.