# 1. Specific Aims

Recent concerns about H5N1 influenza spillover events acutely highlight the need for a universal influenza vaccine with the ability to mitigate future pandemic events. However, a combination of rapid antigenic evolution and heterogeneity in individual host responds makes developing such a universal vaccine difficult. Previous literature has characterized the importance of prior immunity in a path-dependent context, vaccine design (including dose and route of administration), and antigenic distance between the vaccine and host strain, but robust quantitative predictions of these effects are lacking. Our *long-term goal* is to determine how pre-existing immunity affects individual response to the seasonal influenza vaccine, and how this effect differs by host factors, vaccine types, and characteristics of the virus strain used for vaccination.

The objective of our proposal is to focus on antigenic distance between the vaccine strain and circulating strains, vaccine dose, and prior immunity. We will utilize state-of-the-art Bayesian hierarchical modeling techniques in conjunction with causal inference and machine learning methodologies to quantify these effects on the individual immune response to influenza, while taking complex interaction effects into account. We also propose to develop metrics for the quantification of the immune response to a panel of antigenically distinct viruses, an area which has been previously underdeveloped. Our work will leverage longitudinal influenza vaccination data collected by Ted Ross, Ben Cowling, and other investigators involved with the DIVERsity study (NIH project number 1R01AI170116-01).

**Aim 1. Develop metrics for the quantification of the total immune response to an influenza vaccine, incorporating both strength and breadth.** We hypothesize that by fitting a curve to the relationship between total immune response and antigenic distance from the vaccine data for a study sample tested against multiple potentially cross-protective ciruses will allow us to extract information about the fitted curve which quantifies the overall effect of vaccination.

**Aim 2. Quantify the effect of vaccine dose on the effect of the vaccine after accounting for pre-existing immunity and antigenic distance.** We hypothesize that a higher vaccine dose will be able to overcome the previously observed antigenic ceiling effect induced by pre-existing immunity, and that this relationship will be modulated by the antigenic distance between the vaccine and the strain of interest.

**Aim 3. Determine whether antigenic distance is a sufficient single measurement of difference between viral strains in the context of vaccination.** We hypothesize that the antigenic distance between a vaccine strain and another viral strain provides enough information to predict how an individual will respond to that strain following vaccination.

Our work will leverage previously collected data and powerful statistical models in order to elucidate patterns in host response and viral evolution which drive individual immune responses to influenza vaccination. By understanding the complex network of factors which modulate the response, we can delineate key factors for consideration in the development of novel vaccines, and inform vaccination strategies at relatively low cost. Understanding these complex factors is essential for strategic planning to curtail future influenza pandemics.