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**Proposal**

**Working Title [Limit approximately 30 words]:**

Using INSIGHT data to assess the impact of heterosubtypic immunity from childhood imprinting on the age-specific incidence and severity of seasonal influenza.

**Short Title [Limit approximately 15 words]:**

Using INSIGHT data to assess whether broadly protective immunity from childhood shapes seasonal flu risk.

**Scientific Rationale/Background [Limit approximately 200 words]:**

Recently, we analyzed data on H5N1 and H7N9, two avian influenza A viruses (IAVs) of concern for pandemic emergence, and showed **individuals gain lifelong immune protection against novel HA subtypes in the same genetic group as the first IAV encountered during childhood** (*1*)(See appendix Fig. 1)**.** These findings extend the concept of antigenic seniority (*2*) to heterosubtypic protection at the level of HA groups. Thus, heterosubtypic immunity has predictable, but previously unrecognized impacts in human populations, and strongly shapes age distributions of infection with novel, emerging IAVs.

There is now a need to determine whether these same effects carry over to influence the epidemiology of seasonal influenza (subtypes H3N2 and H1N1). Another open question is whether heterosubtypic immunity from childhood imprinting prevents infection entirely (sterilizing immunity), or reduces the severity, and possibly the transmissibility, of infections in protected individuals (partial protection). In addition to its relevance to seasonal influenza epidemiology and control, this research has the potential to shed light on the mechanistic underpinnings of heterosubtypic childhood imprinting protection, and thus, to inform ongoing efforts to develop a universal influenza vaccine.

**Hypothesis [150 words]:**

**Null –** Heterosubtypic immunity from childhood imprinting does not impact seasonal influenza epidemiology.

This is consistent with evidence that hosts are more likely to express broadly protective antibodies upon challenge with novel or highly drifted influenza variants, than with familiar seasonal variants (*3*).

**Alternative –** Childhood exposures to HA subtypes in genetic group 1 or group 2 confer some lifelong immune protection against seasonal subtypes in the same group. Reduced incidence of H1N1 or H3N2 in protected birth years would indicate this protection provides sterilizing immunity, while reduced case severity in protected birth years would indicate partial protection.

This is consistent with the fact that older individuals, who imprinted to group 1 as children, are 4.5 times as likely to become infected with[[1]](#footnote-1), and 20 times as likely to die (*4*) from the group 2 seasonal subtype H3N2.

**Aims [100 words]:**

1. Assess whether childhood imprinting to the same HA group or to the same HA subtype is negatively associated with H1N1 and H3N2 influenza incidence in specific birth years, using data from protocol 002. A positive result would imply that heterosubtypic protection from childhood imprinting prevents some seasonal infections entirely.
2. Assess whether childhood imprinting to the same HA group or to the same HA subtype is negatively associated with H1N1 and H3N2 severity in specific birth years, using data from protocols 002 and 003. A positive result would imply that heterosubtypic protection from childhood imprinting provides partial protection.

**Study Design [250 words]:**

* Based on the birth year of each case in the data (protocol 002 and 003), assign probabilities of having imprinted in childhood to subtype H1, H2 or H3. These probabilities can be estimated using an existing model, as in our previous study (*1*).

**Aim 1**

* Fit multinomial models to describe the proportion of cases occurring in each age group.
  + The baseline model will consider age-specific risk, vaccination history, antiviral use and underlying conditions.
  + More complex models will include subtype-specific childhood imprinting protection or group-specific childhood imprinting protection.
  + Model comparison (AICc) will be used to determine which model best fits the observed data.

**Aim 2**

* Use generalized additive models (GAMs) to test for associations between childhood imprinting history and the following measures of severity:
  + Probability of hospitalization (Data from protocol 002)
  + Probability of ICU admission (002 and 003)
  + Probability of death (002 and 003)
  + Duration of symptoms (002 and 003)
* All models will include age, vaccination history, antiviral use and underlying conditions as baseline factors.
* Model comparison (AICc) will be used to determine whether models with an additional factor representing subtype-specific childhood imprinting protection or group-specific childhood imprinting are the best fit to data.

**Potential Funding Sources [100 words]:**

No additional funds are required. This project consists solely of analysis of existing data in the INSIGHT database, and thus no additional data collection is necessary. Applicant Katelyn Gostic is supported by a Ruth L. Kirschstein NRSA Predoctoral Fellowship awarded by NIAID for the duration of her PhD.

**Imprinting_diagram.pdf**

**Appendix Fig 1:** **Explanation of HA imprinting.**

**(A)** Conserved epitopes facilitate broadly protective immune responses against HA subtypes in the same genetic group (*5*–*10*). HA phylogeny modified from (*11*).

🡪 Individuals gain lifelong protection against novel subtypes in the same HA group first encountered in childhood.

**(B)** Timeline of influenza A circulation in humans, and HA imprinting consequences

🡪 Birth years with mismatched childhood exposures are at high risk of infection by emerging, avian influenza subtypes H5N1 and H7N9 [8].

**(C)** We can predict an individual’s imprinting status based on birth year.

**References:**

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4. W. W. Thompson *et al.*, Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA*. **289**, 179–186 (2003).

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7. G.-M. Li *et al.*, Pandemic H1N1 influenza vaccine induces a recall response in humans that favors broadly cross-reactive memory B cells. *Proc. Natl. Acad. Sci.* . **109**, 9047–9052 (2012).

8. M. S. Miller *et al.*, *Sci. Transl. Med.*, in press, doi:10.1126/scitranslmed.3006637.

9. F. Krammer *et al.*, H3 Stalk-Based Chimeric Hemagglutinin Influenza Virus Constructs Protect Mice from H7N9 Challenge. *J. Virol.* **88**, 2340–2343 (2014).

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11. R. J. Russell *et al.*, Structure of influenza hemagglutinin in complex with an inhibitor of membrane fusion. *Proc. Natl. Acad. Sci.* **105**, 17736–17741 (2008).

1. From unpublished analyses of surveillance data on 14,835 cases of H1N1 and 10,563 cases of H3N2 occurring from 1990-2014. Data was obtained from the Arizona Dept. of Health Services, and from the publicly available NCBI Influenza Virus Database. [↑](#footnote-ref-1)