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To the editorial board,

Please consider the manuscript, "Childhood immune imprinting to influenza A shapes birth year-specific risk during seasonal H1N1 and H3N2 epidemics," for publication as a research article in PLoS Pathogens. This submission represents our original research and is not under consideration elsewhere.

Childhood influenza exposures leave an immunological imprint, which can have rippling, lifelong impacts on the strength and specificity of immune memory. Foundational studies on original antigenic sin and antigenic seniority (Lessler et al., *PLoS Pathogens*, 2012) first identified these patterns in serological data. Recently, we showed childhood immune imprinting can have dramatic epidemiological impacts, and strongly shapes birth year-specific risk from emerging, avian influenza subtypes. Here, we analyze a large epidemiological surveillance data set to test whether similar imprinting effects shape birth year-specific risk from the seasonal influenza A viruses that cause the greatest burden in humans.

Influenza A subtypes H1N1 and H3N2 both cause seasonal epidemics, but H3N2 causes a disproportionate number of cases and deaths in older adults. To our knowledge, this study is the first to analyze side-by-side several proposed drivers of these differences in age distribution. The data supported the hypothesis that immune memory imprinted in childhood does indeed shape birth year-specific risk from seasonal influenza, but that imprinted immune memory provides only narrow cross-protection against seasonal strains of the very same neuraminidase or hemagglutinin subtype as the first influenza virus encountered in childhood. The data did not support imprinting protection that acts broadly across subtypes, or impacts from differences in H1N1 and H3N2's rates of antigenic evolution.

Results confirm the hypothesis that birth year-specific differences in childhood immune history are indeed a strong driver of differences in H1N1 and H3N2's age-specific impacts. By ruling out alternative hypotheses, and identifying specific antigenic drivers of these patterns, our findings enable projections of how seasonal influenza risk profiles may shift in the future as differently imprinted cohorts become older. Our results also highlight the role of neuraminidase as a driver of immune protection, and the difficulty of inducing broadly protective immune responses against immunologically familiar seasonal influenza viruses.

This study ties in to a groundswell of interdisciplinary research, which aims to identify birth year-specific differences in epidemiological risk, and the underlying immunological drivers of these cohort effects. If published in PLoS Pathogens, we believe our study would reach its intended, interdisciplinary audience, which includes immunologists, virologists and vaccine researchers, as well as epidemiologists and infectious disease modelers.

The main text of our submission contains 5993 words (Abstract, Introduction, Results, Discussion and Methods), as well as 48 references, four figures, two tables and three supplementary figures. All data and code relevant to this study are provided as supplementary data files. Thank you for your consideration.

Sincerely,

Katelyn M. Gostic
On behalf of the authors