Exposures to influenza in childhood play a particularly strong role in shaping an individual’s lifelong immune memory. Foundational work on original antigenic sin [CITE] and antigenic seniority [CITE] [ONLY LOOKED FOR PATTERNS OF NARROW IMMUNITY]. showed individuals maintain the highest serological titers against the influenza strains encountered in childhood, and not necessarily against contemporary strains of the same subtype, which pose an actual risk of infection. Although Francis [cite] originally argued that strong immune imprinting from childhood would not interfere with subsequent immune responses, the phase “antigenic sin” has now become synonymous with the potential for obsolete antibody clones primed in childhood to re-emerge and compete against more effective, *de-novo* responses.

In contrast to potential negative impacts from antigenic sin, a recent wave of studies has highlighted imprinting’s potential to provide lifelong immunological benefits, and its ability to shape multiple layers of influenza immune memory, both broad and narrow. We now know immune imprinting in childhood can drive broad, heterologous (cross-subtype) protection against novel avian [CITE] or pandemic [CITE] influenza viruses.

But until recently, research on the importance of childhood immune imprinting has primarily existed within the paradigm of narrow, within-subtype (homologous) immunity. Narrow immunity against influenza is common because immunodominant hemagglutinin (HA) and neuraminidase (NA) epitopes, which are the primary target of most antibody responses, are genetically and antigenically variable. Because these epitopes experience rapid antigenic drift, most antibodies against seasonal influenza provide narrow cross protection against closely related strains of the same subtype, and immune memory’s effectiveness decays rapidly over time.

[BROAD VS. NARROW]. Although these viruses would not previously have been expected to face any pre-existing immunity as they emerged into humans, birth cohorts who imprinted in childhood to strains with shared antigenic properties can show strong protection [CITE]. In particular, childhood imprinting to subtypes from a specific HA group can provide lifelong protection against all other subtypes in the same group. In the past 100 years, only three HA subtypes have circulated seasonally in humans. H1 and H2 fall in group 1, while H3 falls in group 2 (REF, Fig. ##).

Childhood imprinting may also have beneficial impacts on seasonal influenza immunity. Since 1977, two distinct subtypes of influenza A, H1N1 and H3N2, have circulated seasonally in humans, and these subtypes show consistent differences in age distribtuion. H3N2 causes the vast majority of cases in adults over age 65, while H1N1 causes a greater proportion of cases in younger cohorts [CITE CITE CITE]. These differences in age distribution are qualitatively consistent with childhood imprinting patterns, in that older cohorts were almost certainly exposed to historical variants of H1N1 in childhood, and may now be preferentially protected against modern, seasonal H1N1 by virtue of their childhood imprinting [CITE CITE CITE]. Likewise, younger cohorts have the highest probabilities of childhood imprinting to H3N2, which is consistent with greater incidence of the opposite seasonal subtype, H1N1.

However, it remains unclear whether these ostensible cohort effects (i.e. birth year-specific differences in risk) arise due to immune memory imprinted at the narrow, within-subtype level, or at the broader group level. The well established impacts of narrow, within-subtype seasonal influenza immunity intuitively suggest that narrow, subtype-level imprinting may also drive cohort effects. If HA subtype-level imprinting is the key driver, then childhood imprinting to H1, or to H3 might provide preferential lifelong protection against seasonal variants of the same HA subtype. Similarly, childhood imprinting might act strongly at the NA subtype level, providing lifelong protection specific to N1 or to N2 (Fig. ##).

Alternatively, broad, HA group-level imprinting might drive seasonal influenza cohort effects. Although the antibodies involved in group-level protection usually play a minimal role in immunity against familiar, seasonal influenza viruses [CITE], these antibodies can rise in frequency and play a strong role in immunity if the host lacks effective immune memory of variable, immunodominant epitopes [CITE]. Thus, in theory, HA group-level immune memory may serve as a second line of defense against drifted seasonal strains, called in as backup to target conserved epitopes only when first-line antibodies are no longer able to recognize their drifted, variable targets. If HA group level imprinting is a strong driver of seasonal influenza cohort effects, then cohorts imprinted to H1 or H2 (both group 1) should be protected against modern, seasonal H1N1, while only cohorts imprinted to H3 (group 2) would be protected against modern, seasonal H3N2 (Fig. ##).

An orthogonal hypothesis is that observed differences in the age distribution of H1N1 and H3N2 cases arise not because of cohort effects, but because of differences in H1N1 and H3N2’s rate of antigenic drift. Subtype H1N1 drifts more slowly than H3N2, and as a result, H3N2 may be more able to cause repeated infections in older cohorts, whereas H1N1 may cause a disproportionate number of cases in immunologically naïve children [CITE].

METHODS.

Although the subtype-level hypothesis is intuitive, narrow immunity provides only ephemeral protection, which decays rapidly with antigenic drift. Thus, it is not clear that narrow, within-subtype responses primed in childhood should provide lifelong imprinting protection against drifted, homologous strains circulating decades later.

A third possibility is that differences in H1N1 and H3N2’s rate of genetic and antigenic advance are responsible for observed differences in their age-specific impact.

For decades, influenza biologists have known that childhood exposures shape lifelong immunological trajectories. In a phenomenon alternatively referred to as original antigenic sin, antigenic seniority or immune imprinting, individuals maintain the highest serological titers against strains encountered in childhood, and not necessarily against the homologous (same-subtype), contemporary strains that currently circulate and cause disease. Until recently, most research on childhood immune imprinting focused on the potential for mis-targeted homologous responses.

In contrast to potential negative impacts from antigenic sin, recent studies have highlighted imprinting’s potential to provide lifelong immunological benefits. We now know immune imprinting can provide broad, heterologous (cross-subtype) protection against novel avian [CITE] or pandemic [CITE] influenza viruses, which would not previously have been expected to face any pre-existing immunity as they emerged into humans. This new wave of studies has highlighted imprinting’s ability to shape multiple layers of influenza immune memory, both broad and narrow.

One potential, but poorly understood benefit of imprinting is its impact on subtype-specific risk from seasonal influenza viruses. Since 1977, two distinct subtypes of influenza A, H1N1 and H3N2, have circulated seasonally in humans, and these subtypes show consistent differences in age-specific impact. H3N2 causes the vast majority of cases in adults over age 65, while H1N1 causes a greater proportion of cases in younger cohorts [CITE CITE CITE]. These differences in age distribution are qualitatively consistent with childhood imprinting patterns, in that older cohorts were almost certainly exposed to historical variants of H1N1 in childhood, and may now be preferentially protected against modern, seasonal H1N1 by virtue of their childhood imprinting [CITE CITE CITE]. Likewise, younger cohorts have the highest probabilities of childhood imprinting to H3N2, which is consistent with greater incidence of the opposite seasonal subtype, H1N1, in these cohorts.

Many existing studies have speculated that generational differences in childhood imprinting are at least partially responsible for observed, age-specific differences in risk from seasonal circulation of H1N1 or H3N2 [CITE]. However, it remains unclear whether these ostensible cohort effects (defined as birth year-specific differences in risk) arise due to immune memory imprinted at the narrow, within-subtype level, or due to broader, cross-subtype imprinting.

In addition to the potential benefits of imprinting, a Most seasonal influenza immunity is narrow, providing cross-protection across a limited breadth of closely related homologous strains. Narrow immunity arises due to the immunodominance of genetically variable epitopes, especially those found on the head of the HA or NA antigens. Antibodies against these variable epitopes typically dominate the immune response, and often competitively exclude clones that recognize more conserved influenza epitopes. Recent work on

In turn, these narrow antibody responses drive epidemiological patterns like antigenic drift and vaccine escape.

Given the well-established impacts of narrow, within-subtype immunity on seasonal influenza, an obvious hypothesis is that narrow within-subtype childhood imprinting is the strongest driver of birth year-specific differences in H1N1 and H3N2 risk. If childhood imprinting against seasonal influenza acts strongly at the HA subtype level, then imprinting to H1 subtype, or to H3 subtype might provide preferential lifelong protection against seasonal variants of the same HA subtype. Similarly, childhood imprinting might act strongly at the NA subtype level, providing lifelong protection specific to N1 or to N2 (Fig. ##).

But on the other hand, foundational work on original antigenic sin and antigenic seniority emphasizes that within-subtype responses primed in childhood are too narrow to provide effective cross-protection against all strains of a given subtype [CITE]. Furthermore, narrow, within-subtype immunity is known to be ephemeral. Influenza viruses drift at an estimated rate of approximately one antigenic unit per year, which means that cross-protective titers from past exposures have, on average, no more than a one-year half-life. Cross-protective titers are rarely detectable between strains that circulated more than 15 years apart. Thus, it is unclear how narrow, immune responses primed in childhood could provide effective cross-protection against strains of the same subtype circulating decades later.

. We now know that imprinting not only shapes homologous immune memory, but also broader, heterologous responses [CITE]. Thus, childhood imprinting has the potential to prime l

risk from avian [CITE GOSTIC] or pandemic [CITE ANDREWS, GANGON, WOROBEY, DUSHOFF] influenza viruses

. During the 2009 pandemic, a new, swine-origin H1N1 variant emerged into humans, and replaced the older H1N1 lineage that had circulated continuously from 1977 to 2009. The current lineage of H3N2 has circulated continuously since 1968.

Subtypes H1N1 and H3N2

Individuals develop particularly strong, lifelong immunity against influenza viruses

2

antigenically similar to those encountered in childhood, a phenomenon alternatively

3

referred to as original antigenic sin [4], antigenic seniority [10], or antigenic

4

imprinting [6, 11].

and universal vaccine work is showing more about conserved epitopes and potential heterosubtypic protection.

- seasonal flu epi has tradition of considering OAS/seniority, but the focus has been more on mis-targeted responses within a subtype.  Little or no research on childhood imprinting and its possible benefits for lifelong protection.

- motivated by recent discovery of significant heterosubtypic protection within HA groups for zoonotic flus, we evaluate two big seasonal flu datasets for evidence of childhood imprinting, considering both within-subtype HA, within-group HA, and within-subtype NA.

[re novelty: definitely nobody has looked at HA group before.  has anyone formally looked at the others?  (excluding the pending Cobey paper of course)]