Two influenza A virus (IAV) subtypes, H1N1 and H3N2, circulate seasonally in humans, and show consistent differences in epidemiological age distribution. Proportionally, H1N1 causes more cases in young cohorts, whereas H3N2 causes more cases in older cohorts. Viral differences in evolutionary rate (CITE Bedford eLife, Nature), or host differences in childhood immune imprinting (CITE) may contribute to observed differences in H1N1 and H3N2’s age-specific impacts. But to date, no study has compared these hypotheses side by side, making it difficult to determine which is the dominant driver of observed differences in age distribution.

H3N2 has a slightly faster rate of antigenic evolution than H1N1, an as a result, H3N2 enjoys slightly higher rates of immune escape (Bedford eLife). Models that jointly simulate influenza’s epidemic and evolutionary dynamics show that the proportion of adult cases increases with the evolutionary rate parameter (Bedford, Nature, 2015). These simulated patterns are qualitatively consistent with observed patterns, in which H3N2 causes a greater proportion of cases in older cohorts than H1N1.

Childhood imprinting patterns are also qualitatively consistent with a greater impact of H3N2 in older cohorts, and thus, provide an alternative hypothesis. EXPLAIN IMPORTANCE OF CHILDHOOD EXPOSURES. Older adults would have imprinted to H1N1 in childhood, and may now be preferentially protected against modern, seasonal variants of the same subtype. Younger cohorts are much more likely to have imprinted in childhood to H3N2. Our first objective is to test

A tradition of reporting and analyzing seasonal influenza epidemiological data in terms of broad age categories, rather than by single year of age, has made it difficult to tease apart the impacts of age-specific risk from birth year-specific risk, and has obfuscated the signals necessary to compare hypothetical drivers.