First impressions matter most: childhood influenza and birth cohort (immuno-epidemiological imprinting) effects

November 19, 2021
Birth cohort effects: age*period interactions

• Age effects
  • Developmental, behavioral or physiological changes associated with aging
    • E.g. Neonatal immune immaturity, social contacts in school children, immunosenescence with aging

• Period effects
  • Widespread/ubiquitous environmental exposures at a circumscribed point in time
    • E.g. Pandemic or widespread/prolonged epidemic (drift) influenza

• Cohort effects
  • Period effect experienced and expressed differentially by age
    • E.g. Period* age interaction
    • Short-lived or long term consequences
Influenza virus is highly changeable

- A constantly re-emerging and/or recycling RNA virus

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<thead>
<tr>
<th>H Subtype</th>
<th>Group 1</th>
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Image modified from: https://www.cdc.gov/flu/about/professionals/antigenic.htm
Periodic pandemics (shift), followed by seasonal epidemics (drift)
Virtually all have had a priming exposure by the age of five years

- Highest attack rates in children

**Estimating the annual attack rate of seasonal influenza among unvaccinated individuals: A systematic review and meta-analysis**

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Vaccine 36 (2018) 3199–3207

**Results:** We included 32 RCTs that had a total of 13,329 participants. The pooled estimates for symptomatic influenza were 12.7% (95% CI 8.5%, 18.6%) for children (<18 years), 4.4% (95% CI 3.0%, 6.3%) for adults, and 7.2% (95% CI 4.3%, 12.0%) for older people (65 years and above). The pooled estimates for symptomatic and asymptomatic influenza combined for all influenza were 22.5% (95% CI 9.0%, 46.0%) for children and 10.7% (95% CI 4.5%, 23.2%) for adults. Only one study was identified for symptomatic and asymptomatic combined in older people which had a rate of 8.8% (95% CI 7.0%, 10.8%). There was substantial heterogeneity between studies.

**Conclusion:** Overall, we found that approximately 1 in 5 unvaccinated children and 1 in 10 unvaccinated adults were estimated to be infected by seasonal influenza annually, with rates of symptomatic influenza roughly half of these estimates. Our findings help to establish the background risk of seasonal influenza infection in unvaccinated individuals.
• The first influenza infection is a significant lifetime event
  • Creates the largest background pool of long-lasting memory cells
    • Epitope specific immune B cell and T cell memory clones
  • Antibodies mostly targeting the immunodominant HA head
    • Other epitopes (stalk, NA) may also dominate in subsequent (heterologous) infections
  • CD8+ T cells – greater cross-reactivity between antigenically divergent viruses
    • Attenuating effects on severity
  • Subsequent influenza exposures preferentially recall or “back-boost” memory responses to the earliest priming epitopes
The antibody-forming mechanisms have been highly conditioned by the first stimulus, so that later infections with strains of the same type successively enhance the original antibody to maintain it at the highest level at all times in that age group. The imprint established by the original virus infection governs the antibody response thereafter. This we have called the doctrine of original antigenic sin.\textsuperscript{19}

Moreover, it seems probable that this broad antibody content and immunity tends to dampen the antibody response to dominant antigens of strains encountered in later years.
90% of 90 year olds were sero-protected pre-pandemic...

Attributed to lasting cross-reactivity due to exposure to related ancestral viruses in childhood.
But also potential untoward effects of immunological interactions

Association between the 2008–09 Seasonal Influenza Vaccine and Pandemic H1N1 Illness during Spring–Summer 2009: Four Observational Studies from Canada


<table>
<thead>
<tr>
<th>Study</th>
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2008-09 TIV protective seasonal viruses (OR<1)

2008-09 TIV associated with ~2-fold increased risk of 2009 pandemic H1N1 virus (OR>1)
Repeat vaccination with the same A(H3N2) vaccine strain in the context of big antigenic mismatch to circulating variant
We can conceive of two mechanisms whereby the childhood exposure of different age groups could have shaped the mortality patterns in 1918. First, a mechanism akin to original antigenic sin (OAS) (36) may have interfered with immune responses in some of those infected in 1918 (33, 37), peaking in those exposed to the 1889 virus. Although OAS has been traditionally considered a within-subtype phenomenon (36, 38–40), it is plausible that interactions between heterosubtypic viruses could also occur (41). Indeed, Masrel (42) reported that when immunized with an H3N2 vaccine, about 5% of individuals primed in childhood by H1N1 yielded strong HA inhibition antibody responses to H1N1, without any appearance of antibody responses to H3N2 virus. We also speculate that exposure to H1 HA stalk antigens could have resulted in unprotective (OAS-mediated) recall of antibodies to H3 HA stalk epitopes in some H3N8-primed individuals. Such misdirected immune responses could have had dire consequences in 1918 for those initially infected by H3N8.
First flu is forever

A change in the properties of influenza virus in 1968 has left a profound mark on population immunity

By Cécile Viboud\textsuperscript{1} and Suzanne L. Epstein\textsuperscript{2}

Population immunity to bird flu depends on birth year

In 1968, there was a change in a major protective antigen of influenza, hemagglutinin (HA). This altered the type of flu virus that new birth cohorts first encountered in life. Gostic \textit{et al.} show that resulting levels of broadly protective immunity differ by birth year and that these differences can predict the risk of severe infection with different types of bird flu.

- **Time line of influenza HA antigen circulation**
  - 1918
  - 1968
  - 1977

- **Level of immunity against group 1** (including bird flu H5)
  - Birth year
    - 1918
    - 1968
    - 1977

- **Level of immunity against group 2** (including bird flu H7)
  - Birth year
    - 1918
    - 1968
    - 1977

H5 cases

H7 cases
Children under 10 years of age were more affected by the 2018/19 influenza A(H1N1)pdm09 epidemic in Canada: possible cohort effect following the 2009 influenza pandemic.
Beyond Antigenic Match: Possible Agent-Host and Immuno-epidemiological Influences on Influenza Vaccine Effectiveness During the 2015–2016 Season in Canada

Danuta M. Skowronska, Catharine Chambers, Suzana Sahaiduc, Gaston Du Serres, Anne-Laure Winter, James A. Dickinson, Jonathan B. Gubhaju, Steven J. Dowse, Christine Martineau, Hughes Charest, Mel Kraje, Nathalie Bastien, and Yan Li
Paradoxical clade- and age-specific vaccine effectiveness during the 2018/19 influenza A(H3N2) epidemic in Canada: potential imprint-regulated effect of vaccine (I-REV)

• In 2018-19, two influenza A(H3N2) clades co-circulated: 3C.2a1 and 3C.3a

• The vaccine strain was clade 3C.2a1

• Clade 3C.2a1 circulating and vaccine strains are Y159
  • Circulating clade 3C.2a1 viruses are T160 glycosylated, shielding the Y159
  • Egg-adapted clade 3C.2a1 vaccine strains are K160 unglycosylated, exposing the Y159

• Clade 3C.3a wild-type viruses are S159
  • Circulating clade 3C.3a wild-type viruses are K160 unglycosylated, exposing the S159
Following the 1968 pandemic, H3 viruses were S159 for ~30 years

**Figure 3**
Percentage of worldwide influenza A(H3N2) viruses with specified amino acid residues at haemagglutinin (H3) positions 159 and 193, by year, GISAID, 1968–2019 (n=83,026)

*Global Initiative on Sharing All Influenza Data (www.gisaid.org)*
Differential effects of vaccine mismatch by age: imprinting effect?

**Figure 4**
Overall and clade-specific vaccine effectiveness against influenza A(H3N2), explored by age modelled by single year, Canadian Sentinel Practitioner Surveillance Network, 2018/19 (n = 1,735)
Influenza imprinting in childhood and the influence on vaccine response later in life

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B. Antibody responses to stable and changeable viruses

Panel B: At the second exposure of a stable virus such as measles virus, the antibody responses are boosted toward the original antigenic sites for a faster and larger response. In comparison, circulating influenza A (H3N2) viruses are constantly changing their antigenicity through antigenic drift. The viruses retain some antigenic similarity over time but changes also occur as a result. The secondary exposure of a person who has already been exposed to an influenza virus may lead to both back-boosting of originally acquired antibodies and also the development of antibodies to new epitopes.

Citation style for this article:
https://doi.org/10.2807/1560-7917.ES.2019.24.48.1900720
Concluding comments

• Influenza virus is a highly changeable virus
  • Constantly evolving, re-emerging and/or recycling to evade pre-existing immunity

• The first influenza infection is a significant lifetime event
  • Leaves a lasting immunological legacy or imprint

• On a population level, influenza epidemics/pandemics with high attack rates in children can induce signature cohort effects
  • Manifest as variation in age-related risk and vaccine response over time

• To date, annual influenza vaccination recommendations have largely ignored the complex role of pre-existing immunity
  • Assumes we are a blank slate, neutrally recalibrated before each annual dose
  • Complex conditions of antigenic relatedness between imprinting virus, consecutive vaccine doses and currently circulating virus

• Influenza vaccine performance has been suboptimal
  • Improvement requires consideration of these effects
Implications of immunological imprinting for other vaccine preventable diseases showing changeability, SARS-CoV-2 vaccination and variants

Reformulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines with variant strains is being pursued to combat the global surge in infections. We hypothesize that this may be suboptimal due to immune imprinting from earlier vaccination or infection with the original SARS-CoV-2 strain. New strategies may be needed to improve efficacy of SARS-CoV-2 variant vaccines.

Figure 1. Potential impact of repeated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike-based vaccine boosting on antibody responses. Human antibodies against SARS-CoV-2 epitopes that are conserved across ancestral (wild type WT) and variants of concern (VOC). Spike proteins (blue) are elicited by initial WT vaccination and are likely to be boosted in response to subsequent VOC-targeted vaccines. The preferential recall of conserved immune responses imprint to the WT strain may limit the generation of de novo responses against VOC receptor binding domain (RBD) epitopes (red and yellow) in response to booster vaccine doses. This figure was created using BioRender (https://biorender.com).