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

November 19, 2021

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Birth cohort effects: age*period interactions

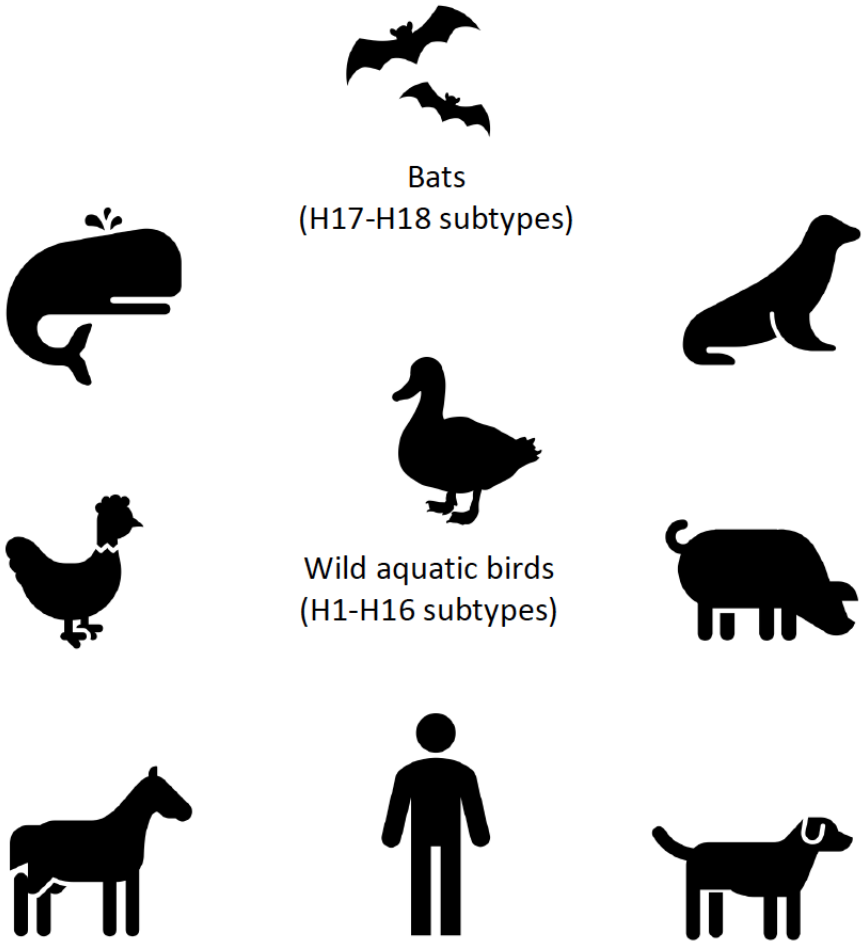
- Age effects
  - Developmental, behavioral or physiological changes associated with aging
    - E.g. Neonatal immune immaturity, social contacts in school children, immunosenescence with aging

- 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



H Subtype	
Group 1	Group 2
H1	H3
H2	H4
H5	H7
H6	H10
H8	H14
H9	H15
H11	
H12	
H13	
H16	
H17	
H18	

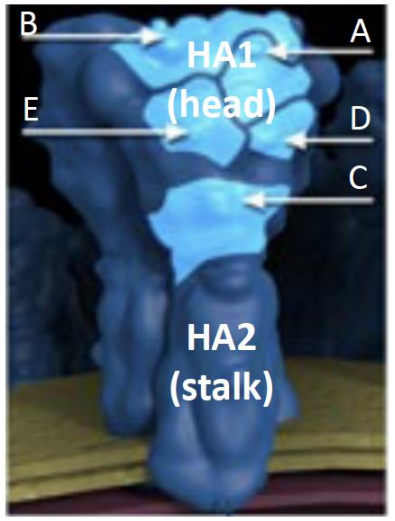
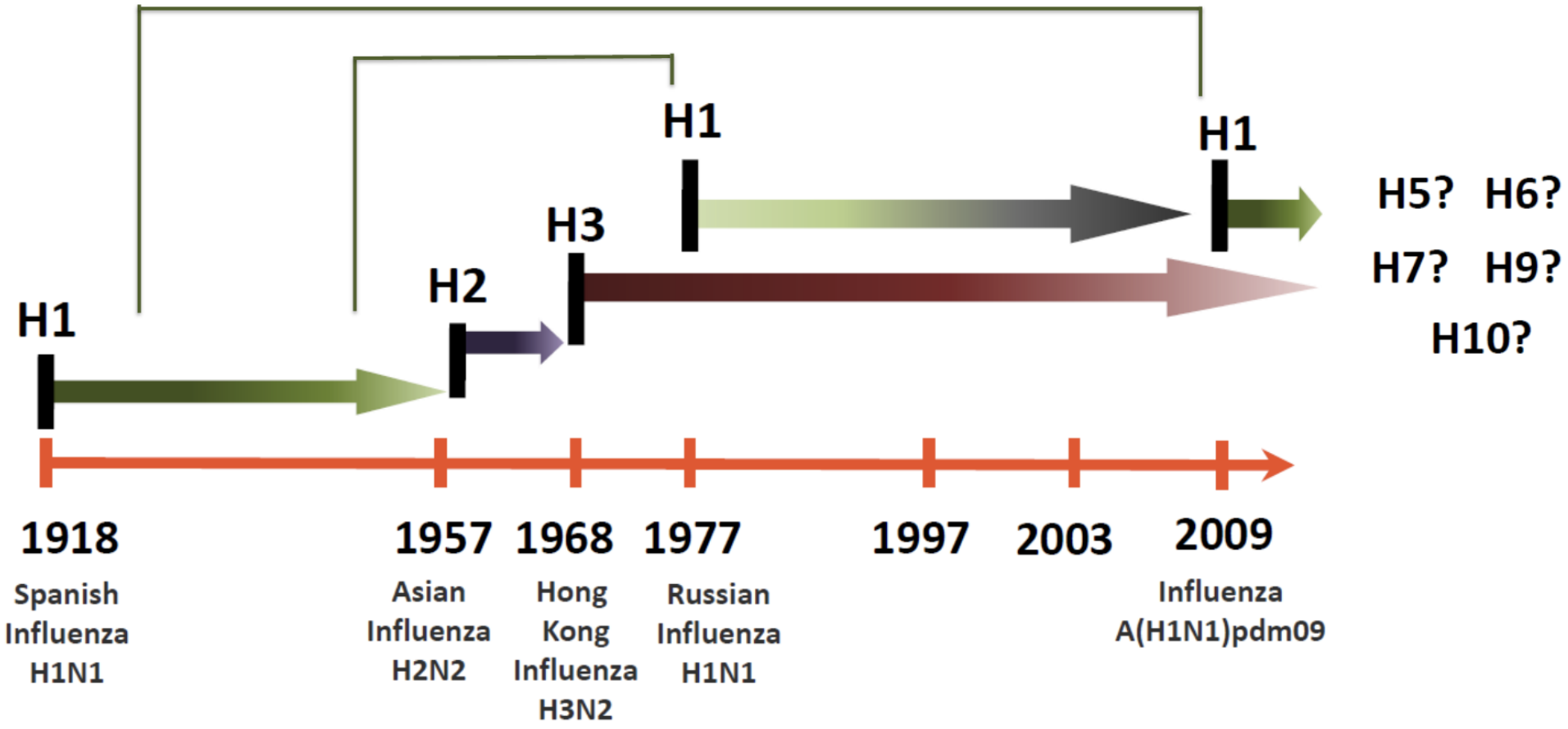


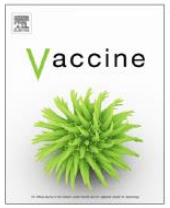
Image modified from: https://www.cdc.gov/flu/about/professionals/antigenic.htm

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

Mitchell P. Somes [a], Robin M. Turner [b], Liam J. Dwyer [a], Anthony T. Newall [a,*]

[a] *University of New South Wales, Sydney, NSW, Australia*
[b] *University of Otago, Dunedin, New Zealand*

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.

DOI:10.1111/irv.12074
www.influenzajournal.com

Original Article

Estimating age-specific cumulative incidence for the 2009 influenza pandemic: a meta-analysis of A(H1N1)pdm09 serological studies from 19 countries

Maria D. Van Kerkhove,[a,b,*] Siddhivinayak Hirve,[a,*] Artemis Koukounari,[b] Anthony W. Mounts,[a] for the H1N1pdm serology working group[†,‡]

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Correspondence: Anthony W. Mounts, Global Influenza Programme, World Health Organization, Geneva, Switzerland. E-mail: mountsa@who.int
*These authors contributed equally to this work.

Results

... Overall age-standardized H1N1pdm cumulative incidence was 24% (95%CI 20–27%) and varied significantly by age with the highest in children 5–19 (47% 95%CI 39–55%) and 0–4 years old (36% 95%CI 30–43%).

Please cite this paper as: Van Kerkhove *et al.* (2013) Estimating age-specific cumulative incidence for the 2009 influenza pandemic: a meta-analysis of A(H1N1) pdm09 serological studies from 19 countries. Influenza and Other Respiratory Viruses DOI: 10.1111/irv.12074.

viruses

MDPI

Published: 30 January 2019

Review

Back to the Future for Influenza Preimmunity—Looking Back at Influenza Virus History to Infer the Outcome of Future Infections

Magen Ellen Francis [1], Morgan Leslie King [1] and Alyson Ann Kelvin [1,2,3,*]

- 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

On the Doctrine of Original Antigenic Sin
Author(s): Thomas Francis, Jr.
Source: *Proceedings of the American Philosophical Society*, Vol. 104, No. 6 (Dec. 15, 1960), pp. 572-578
Published by: American Philosophical Society

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.[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.

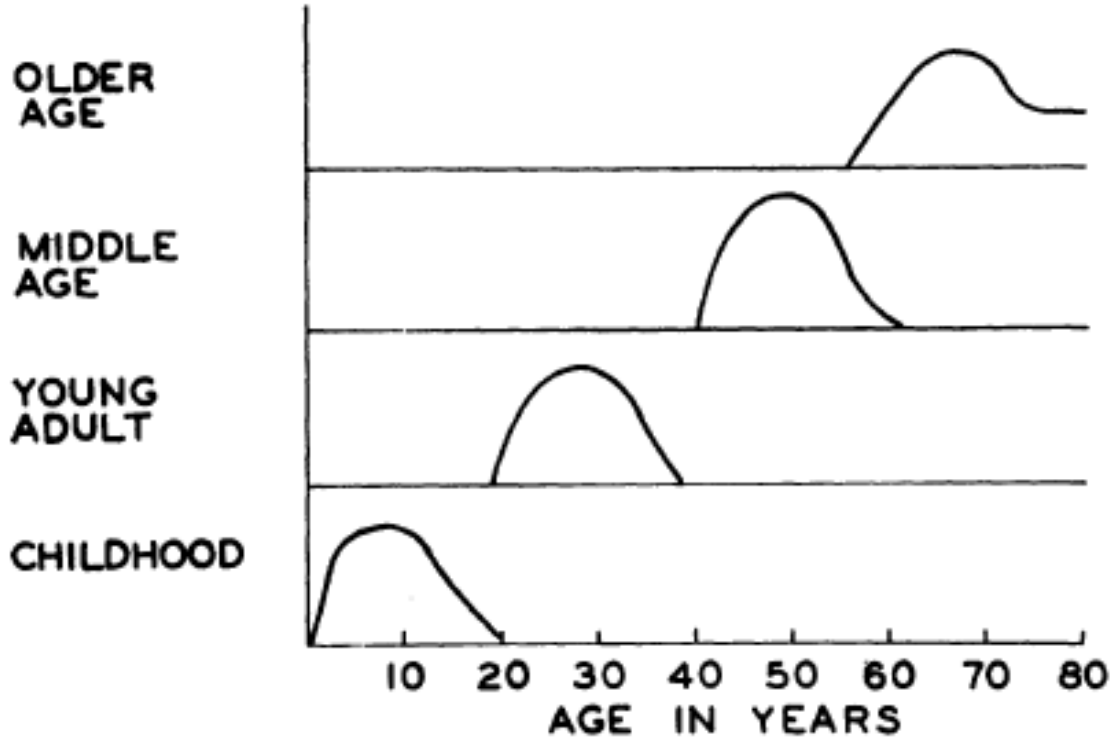


FIG. 10. The persistence of initial antibody throughout life.

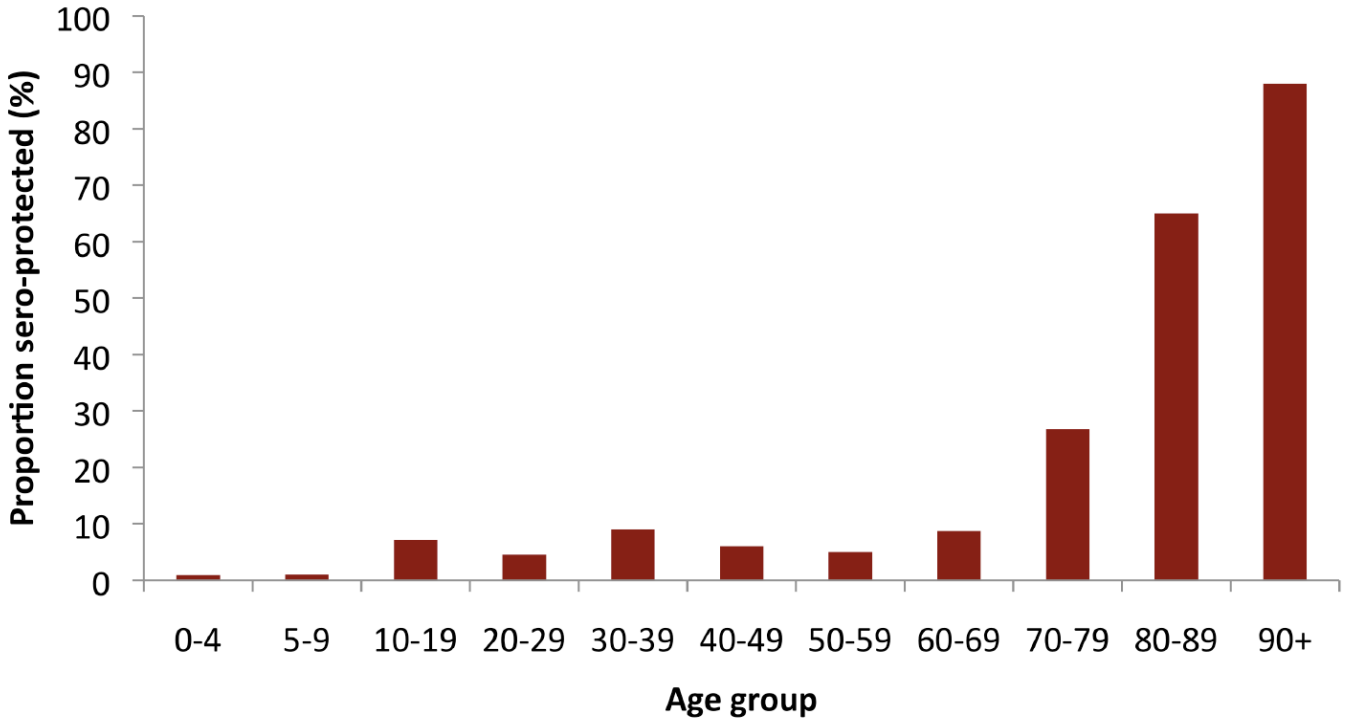
2009 pandemic reinforced the potential long-term benefits of imprinting

MAJOR ARTICLE

Volume 203, Issue 2
15 January 2011

Immuno-epidemiologic Correlates of Pandemic H1N1 Surveillance Observations: Higher Antibody and Lower Cell-Mediated Immune Responses with Advanced Age

Danuta M. Skowronski,[1,2] Travis S. Hottes,[1] Janet E. McElhaney,[3,6] Naveed Z. Janjua,[1,2] Suzana Sabaiduc,[1] Tracy Chan,[1] Beth Gentleman,[3,6] Dale Purych,[7] Jennifer Gardy,[1,4] David M. Patrick,[1,2] Robert C. Brunham,[1,3] Gaston De Serres,[8,9] and Martin Petric[1,5]



90% of 90 year olds
were sero-protected pre-pandemic…

Attributed to lasting cross-reactivity due to exposure to related ancestral viruses in childhood

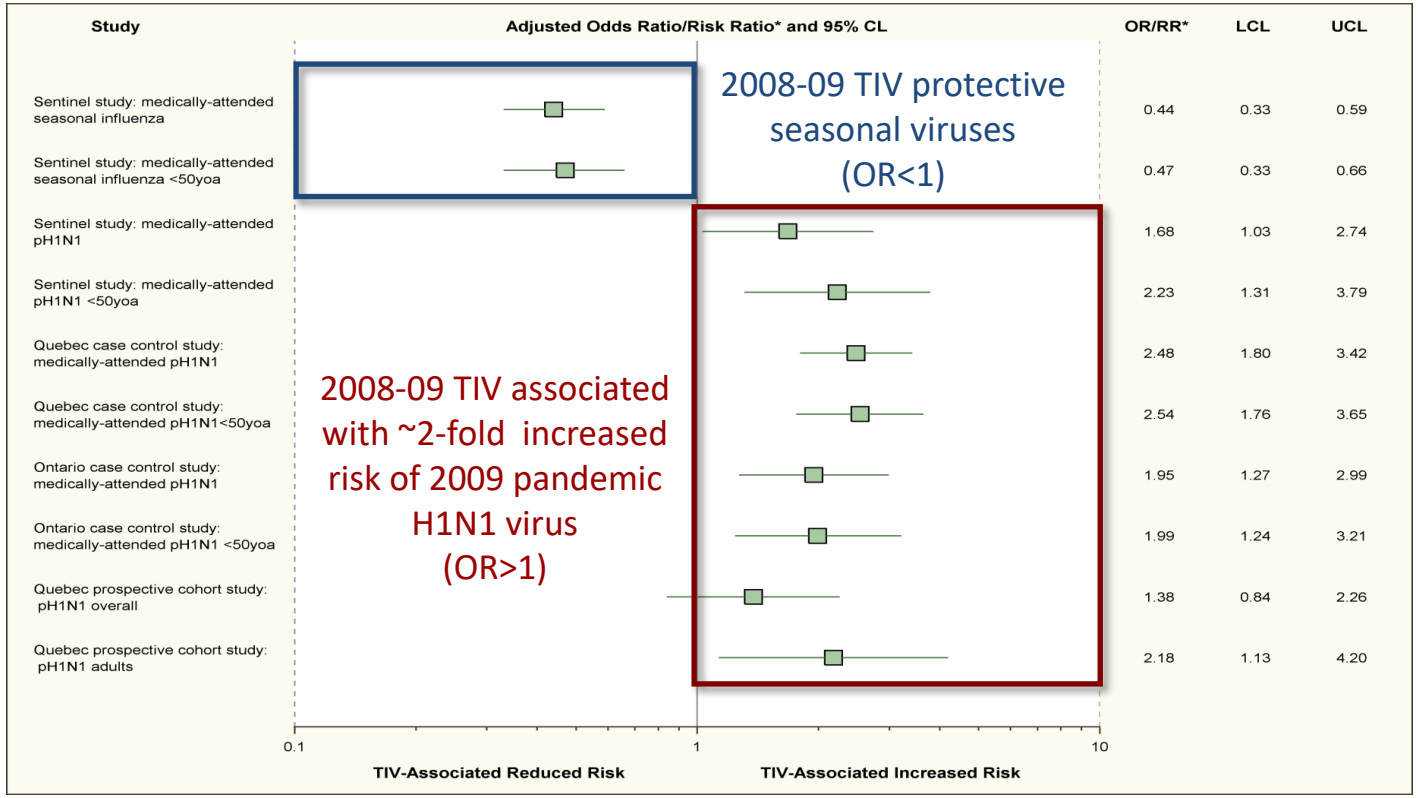
But also potential untoward effects of immunological interactions

OPEN ACCESS Freely available online

PLoS MEDICINE

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

Citation: Skowronski DM, De Serres G, Crowcroft NS, Janjua NZ, Boulianne N, et al. (2010) Association between the 2008–09 Seasonal Influenza Vaccine and Pandemic H1N1 Illness during Spring–Summer 2009: Four Observational Studies from Canada. PLoS Med 7(4): e1000258. doi:10.1371/journal.pmed.1000258

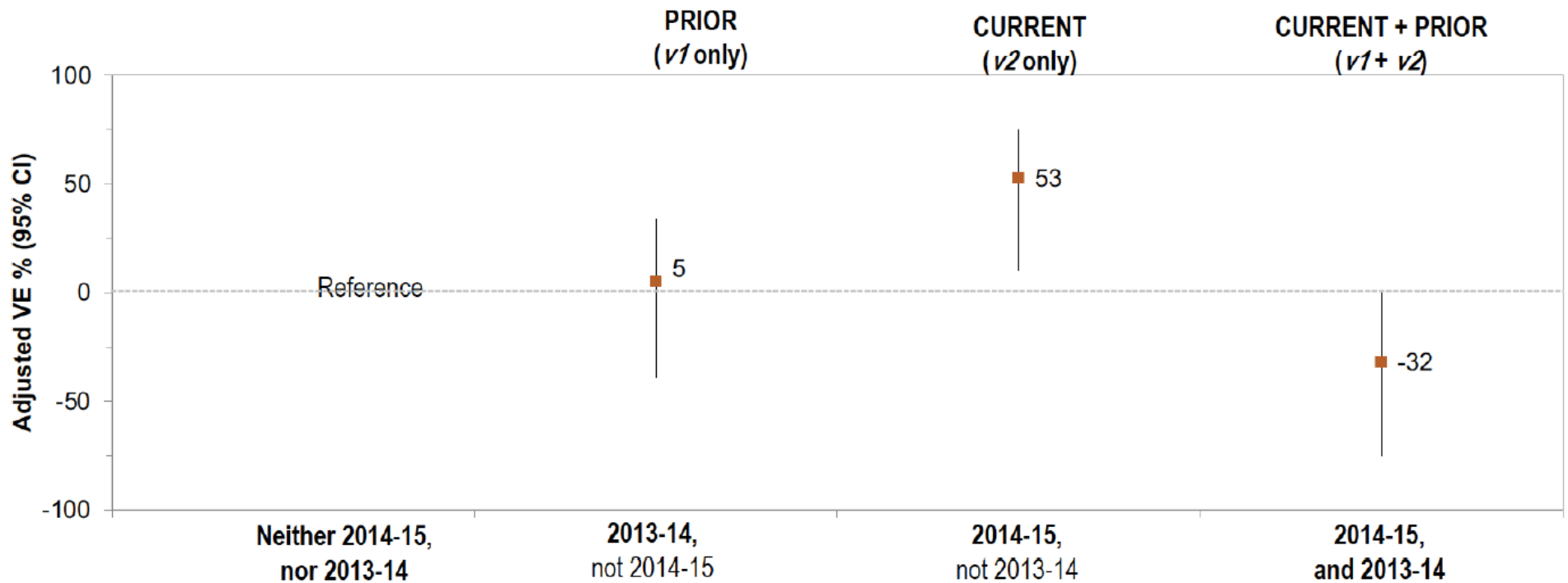


Volume 63, Issue 1
1 July 2016

A Perfect Storm: Impact of Genomic Variation and Serial Vaccination on Low Influenza Vaccine Effectiveness During the 2014–2015 Season

Danuta M. Skowronski,[1,2] Catharine Chambers,[1] Suzana Sabaiduc,[1] Gaston De Serres,[3,4,5] Anne-Luise Winter,[6] James A. Dickinson,[7] Mel Krajden,[1,2] Jonathan B. Gubbay,[6,8] Steven J. Drews,[9,10] Christine Martineau,[3] Alireza Eshaghi,[6] Trijntje L. Kwindt,[1] Nathalie Bastien,[11] and Yan Li[11]

Repeat vaccination with the same A(H3N2) vaccine strain in the context of big antigenic mismatch to circulating variant

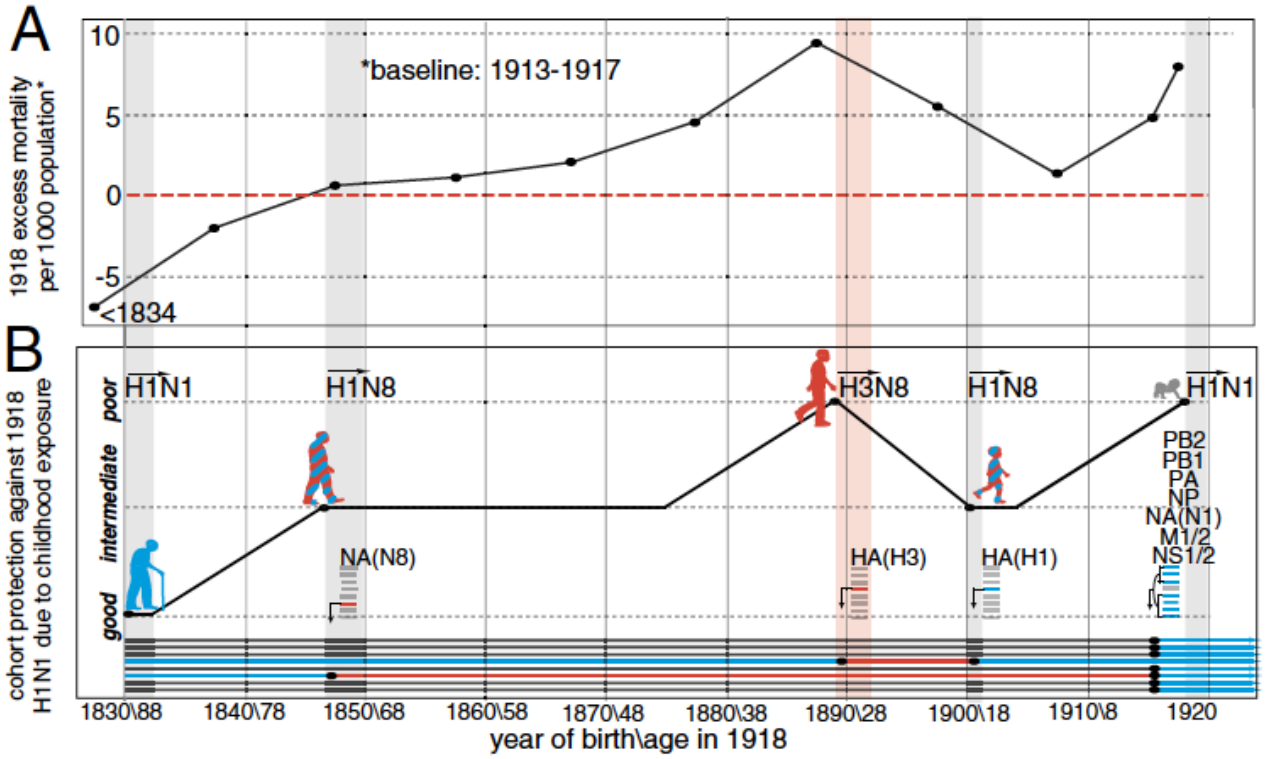


PNAS

Genesis and pathogenesis of the 1918 pandemic H1N1 influenza A virus

PNAS | June 3, 2014 | vol. 111 | no. 22 | 8107–8112

Michael Worobey[a,1], Guan-Zhu Han[a], and Andrew Rambaut[b,c,d]



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, Masurel (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

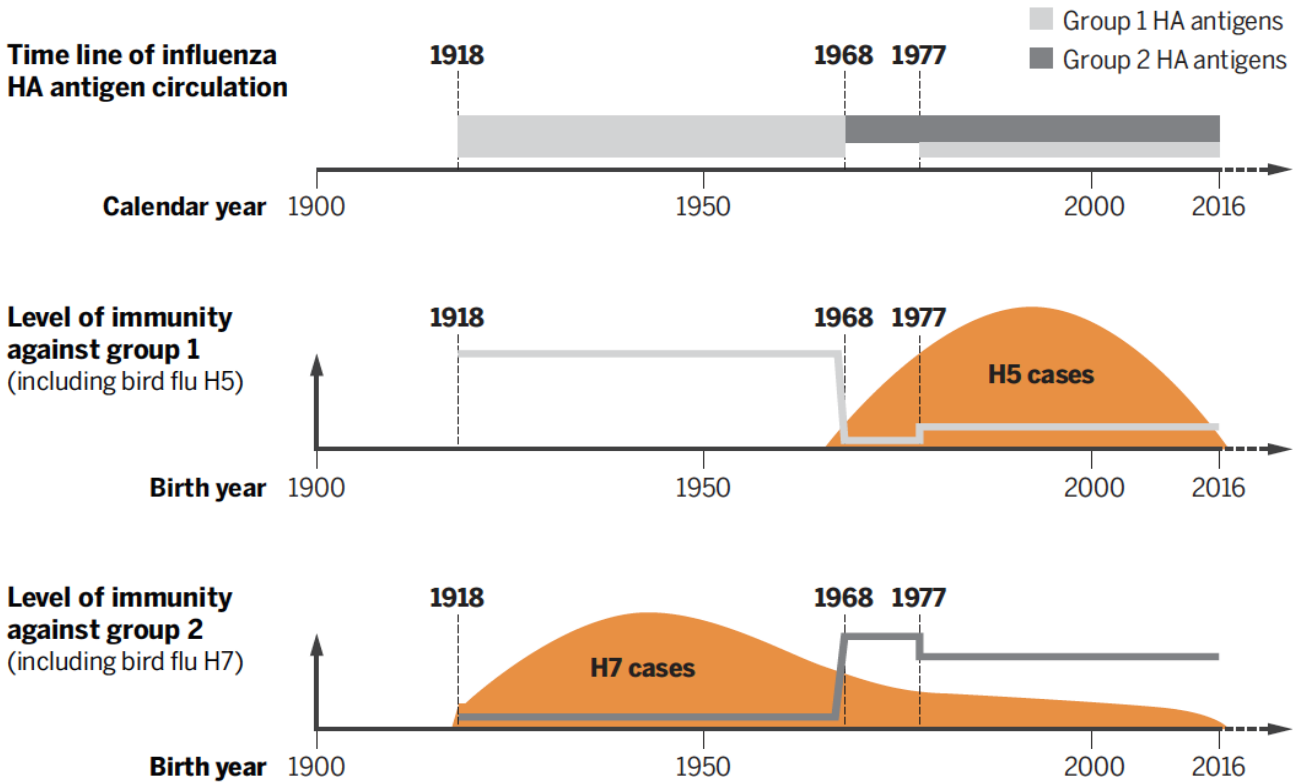
sciencemag.org SCIENCE
11 NOVEMBER 2016 • VOL 354 ISSUE 6313

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

By **Cécile Viboud**[1] *and* **Suzanne L. Epstein**[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 *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.



RESEARCH

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

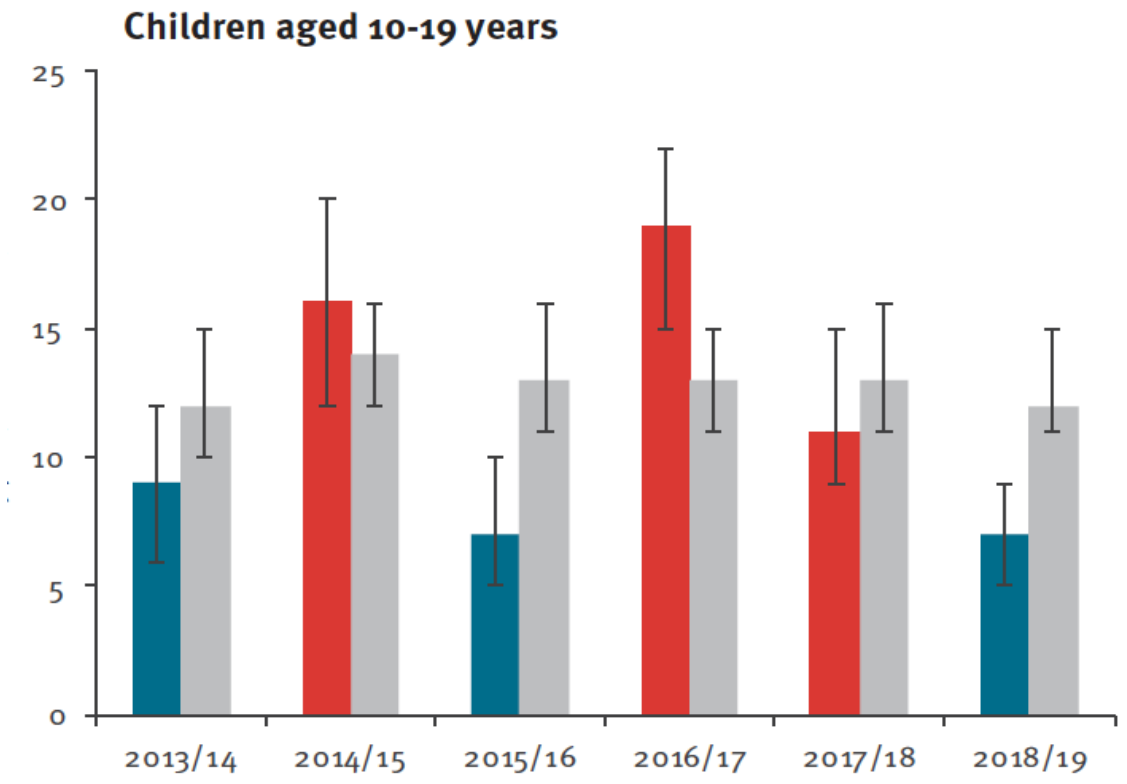
Danuta M Skowronski[1,2], Siobhan Leir[1], Gaston De Serres[3,4,5], Michelle Murti[6,7], James A Dickinson[8], Anne-Luise Winter[6], Romy Olsha[6], Matthew A Croxen[9,10], Steven J Drews[9,10], Hugues Charest[3], Christine Martineau[3], Suzana Sabaiduc[1], Nathalie Bastien[11], Yan Li[11], Martin Petric[2], Agatha Jassem[1,2], Mel Krajden[1,2], Jonathan B Gubbay[6,7]

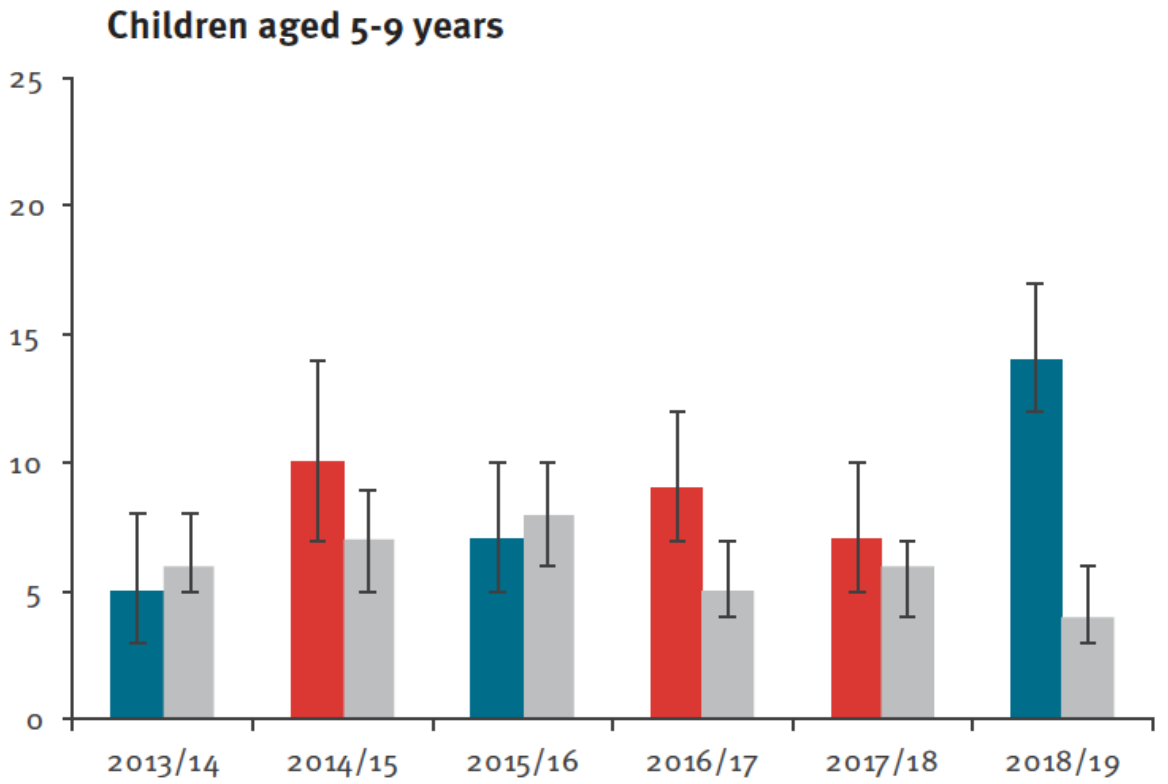
Eurosurveillance

Unvaccinated H1N1pdm09 cases

Unvaccinated H3N2 cases

Unvaccinated test negative controls





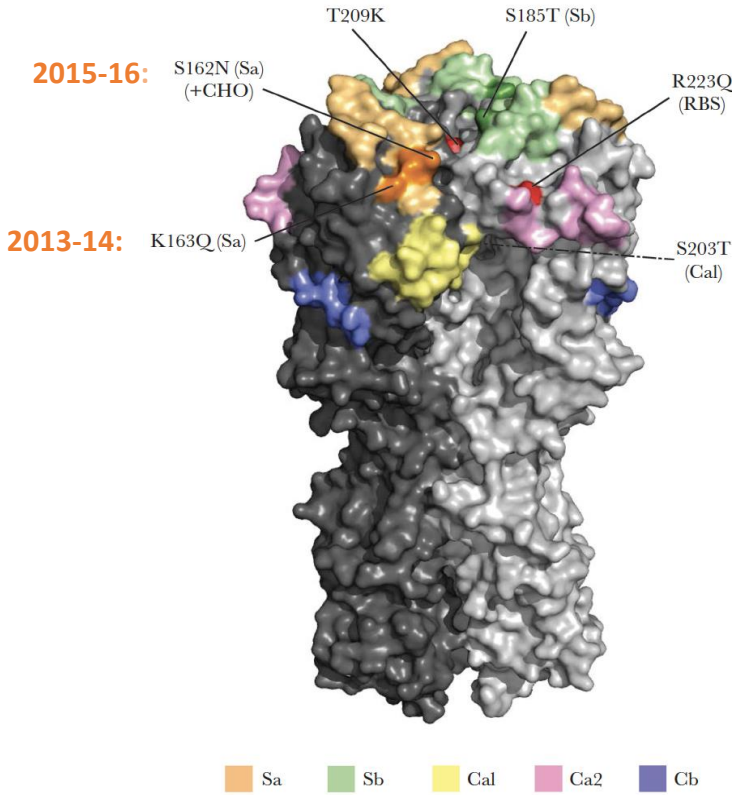
The Journal of Infectious Diseases

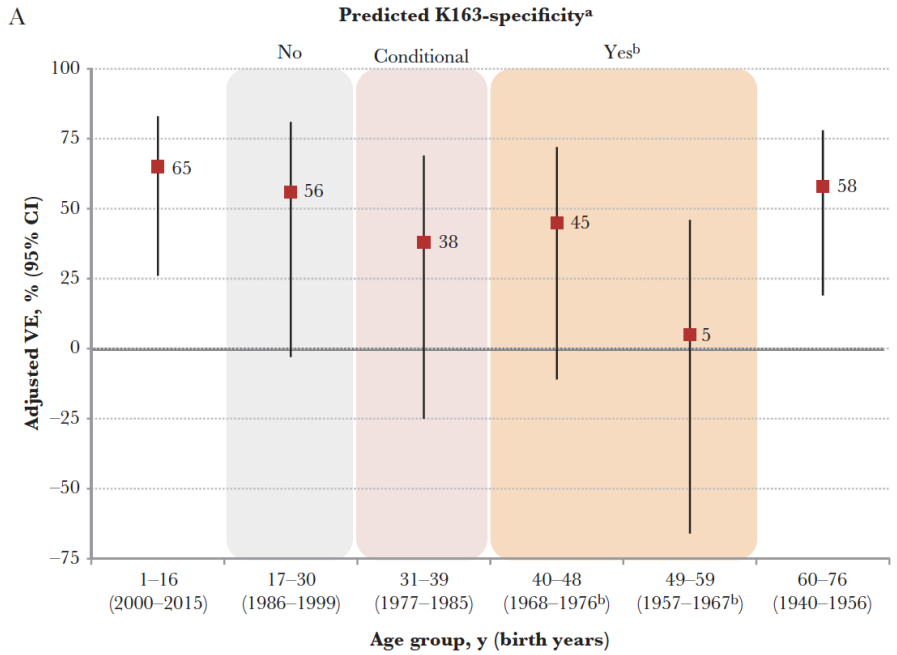
Volume 216, Issue 12
15 December 2017

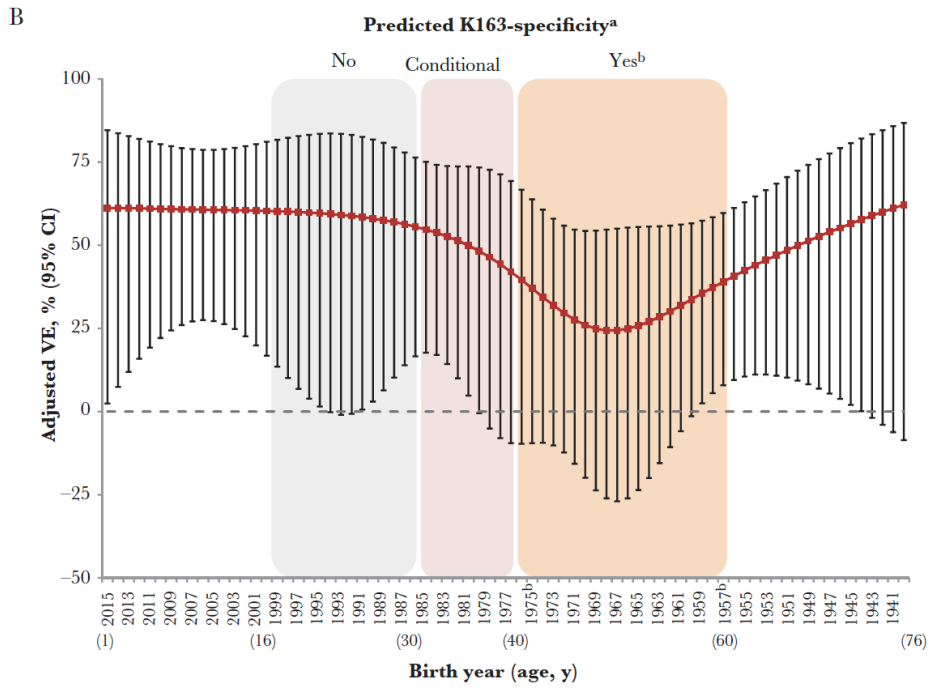
MAJOR ARTICLE

Beyond Antigenic Match: Possible Agent-Host and Immuno-epidemiological Influences on Influenza Vaccine Effectiveness During the 2015–2016 Season in Canada

Danuta M. Skowronski,[1,2] Catharine Chambers,[1] Suzana Sabaiduc,[1] Gaston De Serres,[3,4,5] Anne-Luise Winter,[6] James A. Dickinson,[7] Jonathan B. Gubbay,[6,8] Steven J. Drews,[9,10] Christine Martineau,[3] Hugues Charest,[3] Mel Krajden,[1,2] Nathalie Bastien,[11] and Yan Li[11]







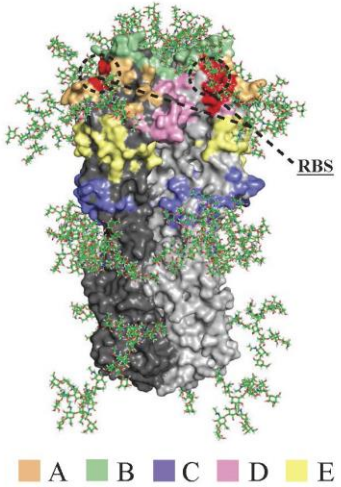
Paradoxical clade- and age-specific vaccine effectiveness during the 2018/19 influenza A(H3N2) epidemic in Canada: potential imprint-regulated effect of vaccine (I-REV)

Danuta M Skowronski[1,2], Suzana Sabaiduc[1], Siobhan Leir[1], Caren Rose[1,2], Macy Zou[1], Michelle Murti[3,4], James A Dickinson[5], Romy Olsha[3], Jonathan B Gubbay[3,4], Matthew A Croxen[6,7], Hugues Charest[8], Nathalie Bastien[9], Yan Li[9], Agatha Jassem[1,2], Mel Krajden[1,2], Gaston De Serres[8,10,11]

Eurosurveillance

2a1: Y159

3a: S159



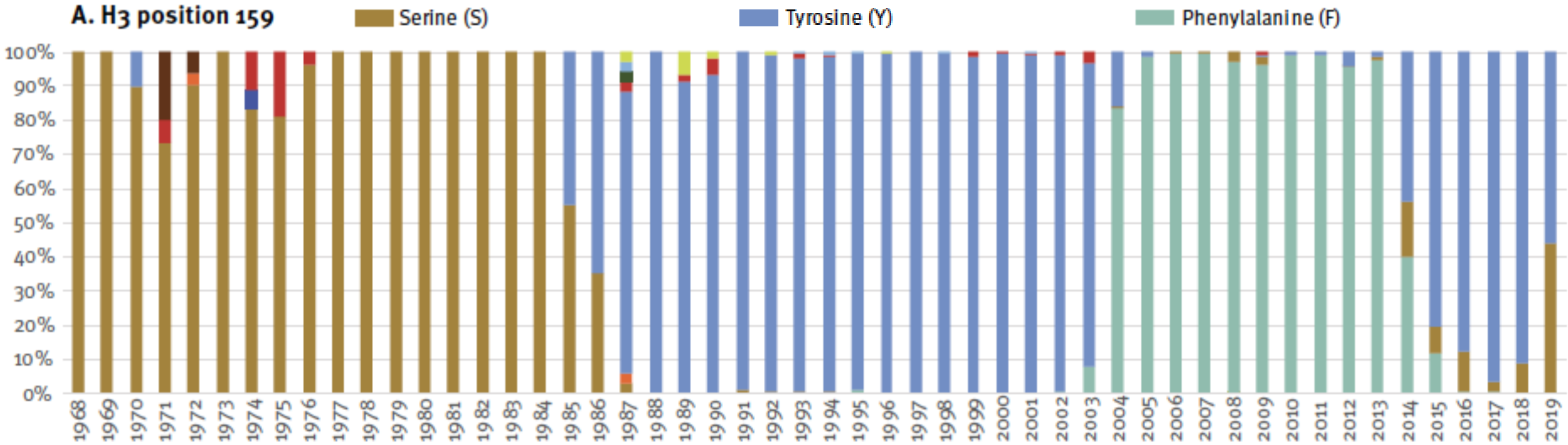
- In 2018-19, two influenza A(H3N2) clades co-circulated: 3C.2a1 and 3C.3a
- The vaccine strain was clade 3C.2a1
- Clade 3C.2a1 circulating and vaccine strains are Y159
  - Circulating clade 3C.2a1 viruses are T160 glycosylated, shielding the Y159
  - Egg-adapted clade 3C.2a1 vaccine strains are K160 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

Citation style for this article:
Skowronski Danuta M, Sabaiduc Suzana, Leir Siobhan, Rose Caren, Zou Macy, Murti Michelle, Dickinson James A, Olsha Romy, Gubbay Jonathan B, Croxen Matthew A, Charest Hugues, Bastien Nathalie, Li Yan, Jassem Agatha, Krajden Mel, De Serres Gaston. 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). Euro Surveill. 2019;24(46):pii=1900585. https://doi.org/10.2807/1560-7917.ES.2019.24.46.1900585

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)

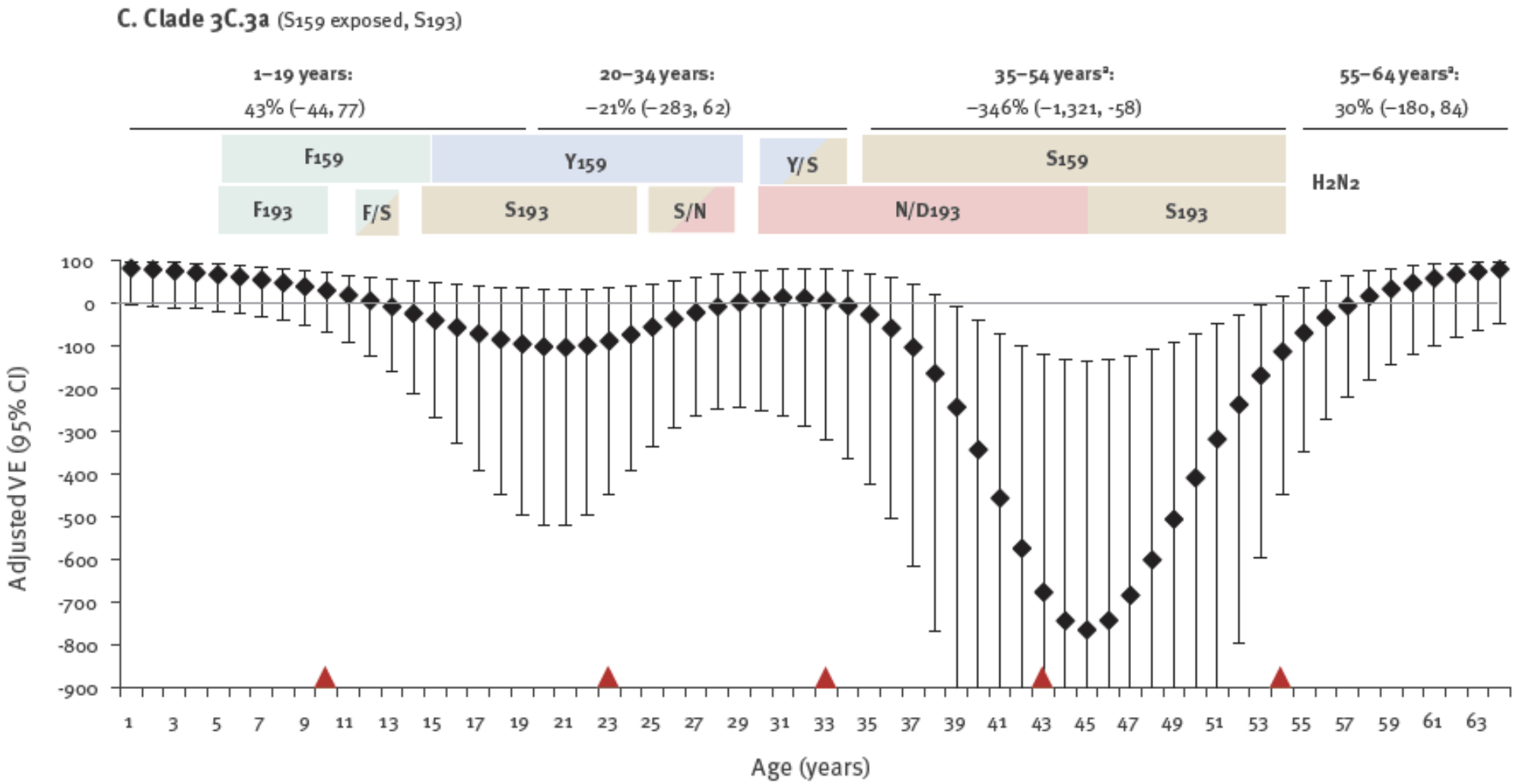


*Global Initiative on Sharing All Influenza Data (www.gisaid.org)

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)

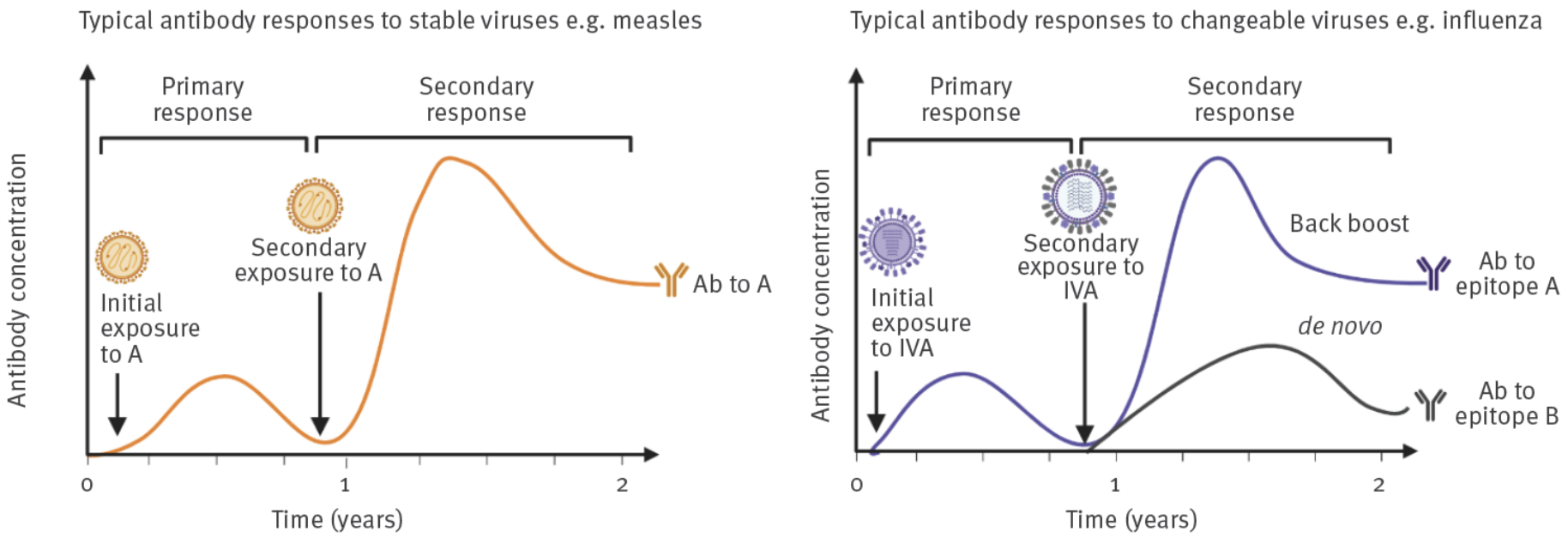


Influenza imprinting in childhood and the influence on vaccine response later in life

Eurosurveillance

Alyson A Kelvin[1,2], Maria Zambon[3]
1. Department of Pediatrics, Division of Infectious Disease, Faculty of Medicine, Dalhousie University, Halifax, Canada
2. Canadian Centre for Vaccinology, IWK Health Centre, Halifax, Canada
3. National Infection Service, Public Health England, London, United Kingdom

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(H_3N_2) 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:
Kelvin Alyson A, Zambon Maria. Influenza imprinting in childhood and the influence on vaccine response later in life . Euro Surveill. 2019;24(48):pii=1900720.
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

CellPress

Trends in Immunology

Forum

Immune imprinting and SARS-CoV-2 vaccine design

Adam K. Wheatley,[1] Annette Fox,[2] Hyon-Xhi Tan,[1] Jennifer A. Juno,[1] Miles P. Davenport,[3] Kanta Subbarao,[1,2] and Stephen J. Kent[1,*,@]

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.

Risks of immune imprinting undermining SARS-CoV-2 vaccine efficacy

Similar to antigenically drifted IAV, SARS-CoV-2 neutralization escape variants have only a few key mutations at neutralization epitopes compared with the ancestral strain [4]. Most antibody responses to Spike are directed against conserved, nonneutralizing epitopes [3]. Reduced effectiveness is observed against neutralization escape strains relative to ancestral strains for all SARS-CoV-2 vaccines studied to date [9], suggesting that nonneutralizing responses might only elicit modest protective value against such new strains.

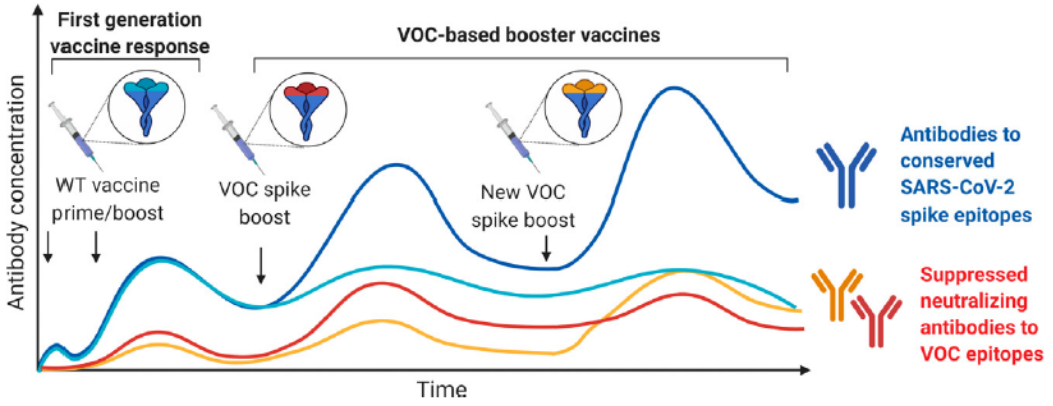


Figure 1. Potential impact of repeated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike-based vaccine boosting on antibody responses. Human antibodies against SARS-CoV-2 epitopes that are conserved across ancestral [wild type (WT)] and variants of concern (VOC) Spike proteins (blue) 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 imprinted 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/).

Trends in Immunology, November 2021, Vol. 42, No. 11