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Seasonal Influenza Vaccines : Current Status and Opportunities for Improved Effectiveness

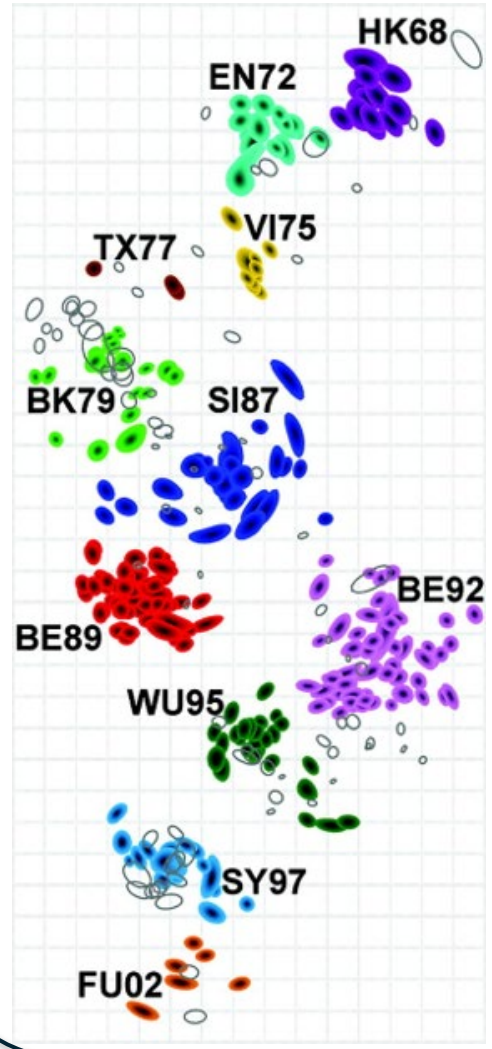
Richard Webby, PhD

outline

- Importance of vaccine match (to circuiting strains)
- Egg adaptive mutations
- Immune markers

match

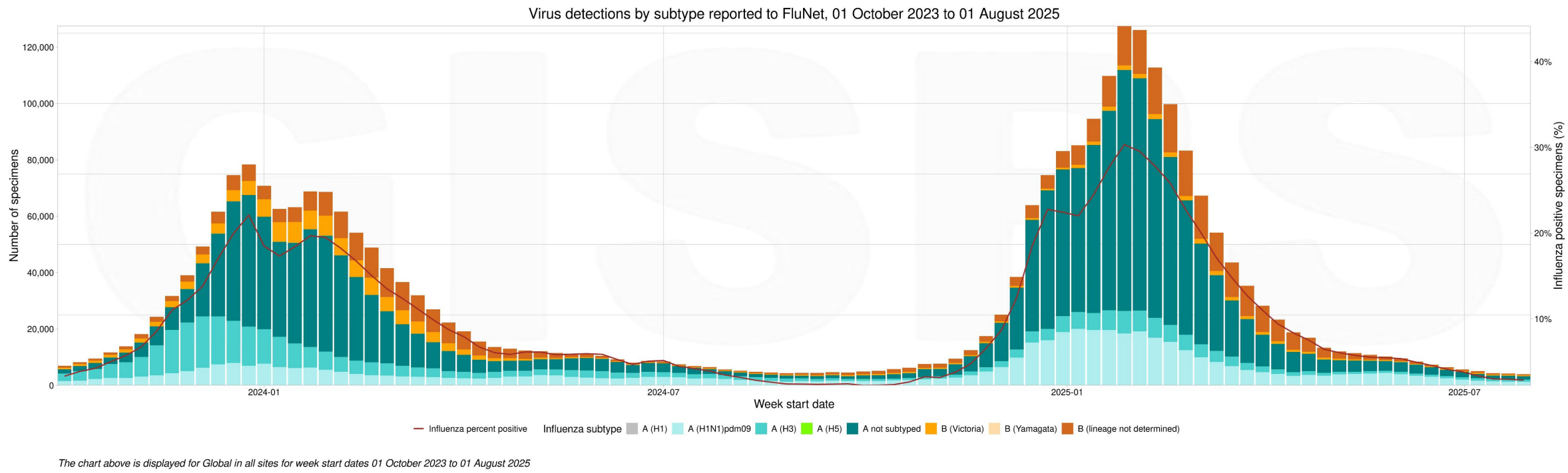
- Current influenza vaccine target viral hemagglutinin (HA)
- HA is characterized by flexible immunodominant loops
- Protective neutralizing antibodies target variable domains
- Global systems in place to monitor virus evolution



Antigenic evolution of A(H3N2) viruses

Smith et al. Science: 305, Issue: 5682, Pages: 371-376, DOI: (10.1126/science.1097211)

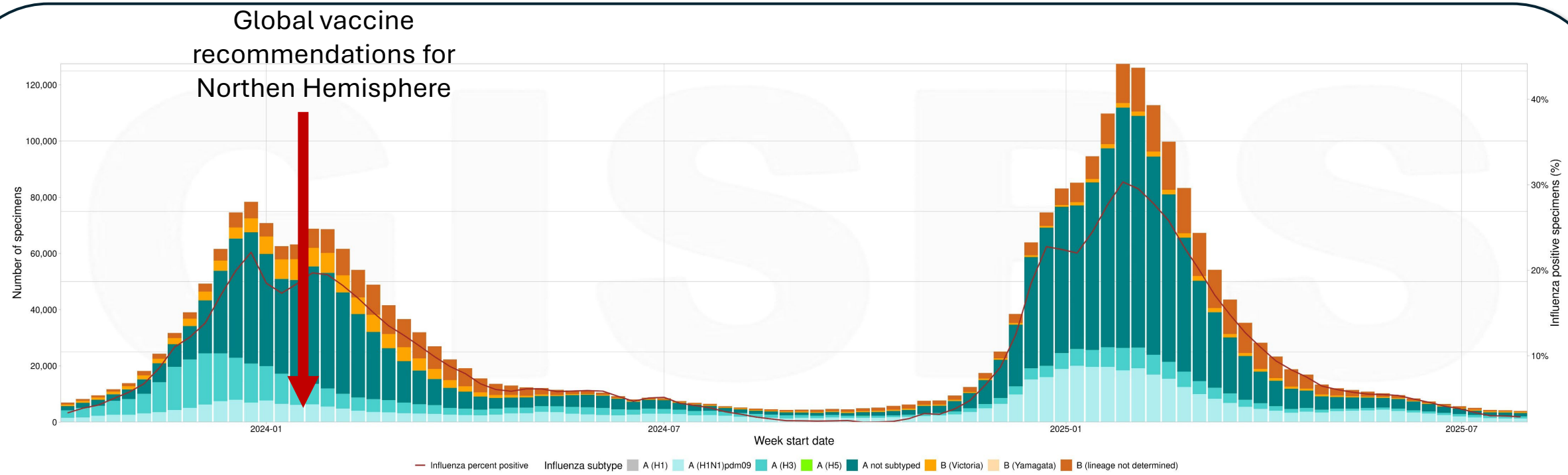
Many -not all- challenges in match driven by vaccine timelines



The chart above is displayed for Global in all sites for week start dates 01 October 2023 to 01 August 2025

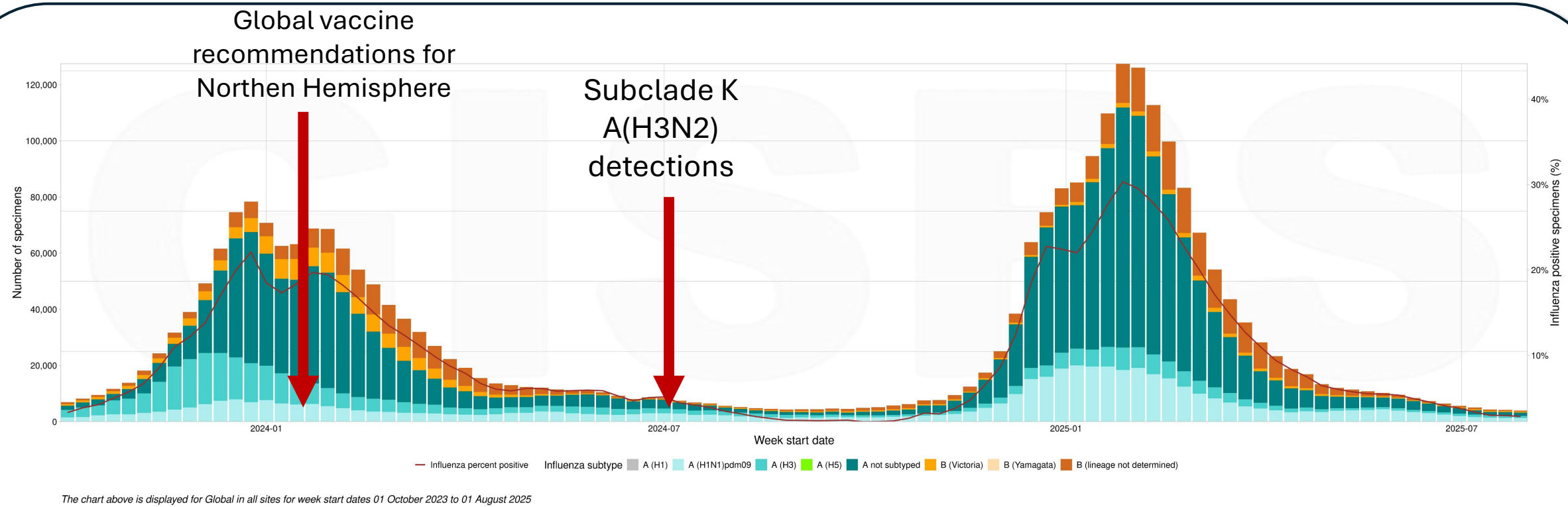
https://www.who.int/tools/flunet

Many -not all- challenges in match driven by vaccine timelines



https://www.who.int/tools/flunet

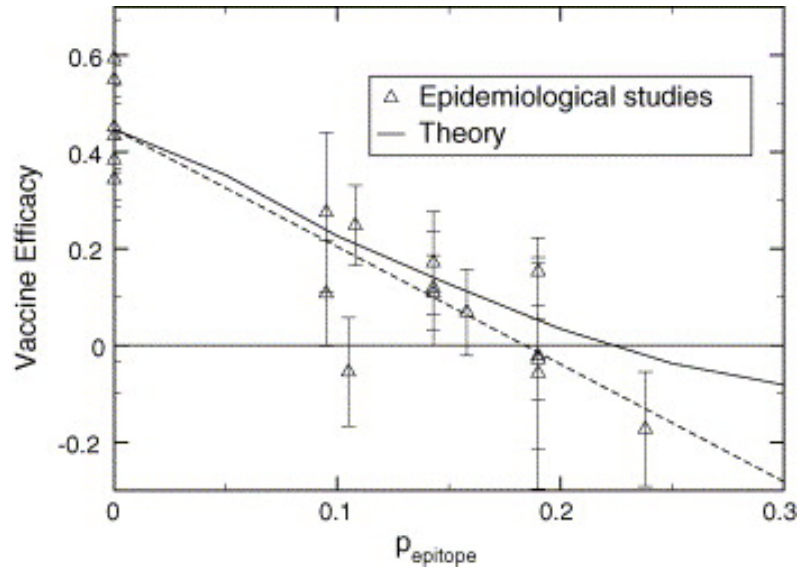
Influenza virus evolution doesn’t stop during NH summer



https://www.who.int/tools/flunet

Does match matter?

- Quantified similarities across antigenic regions
- Developed models to translate into vaccine effectiveness
- These estimates correlated well with epidemiologically determined estimates (in 18-64 yr olds)



Gupta et al. Vaccine. Volume 24, Issue 18, 1 May 2006, Pages 3881-3888

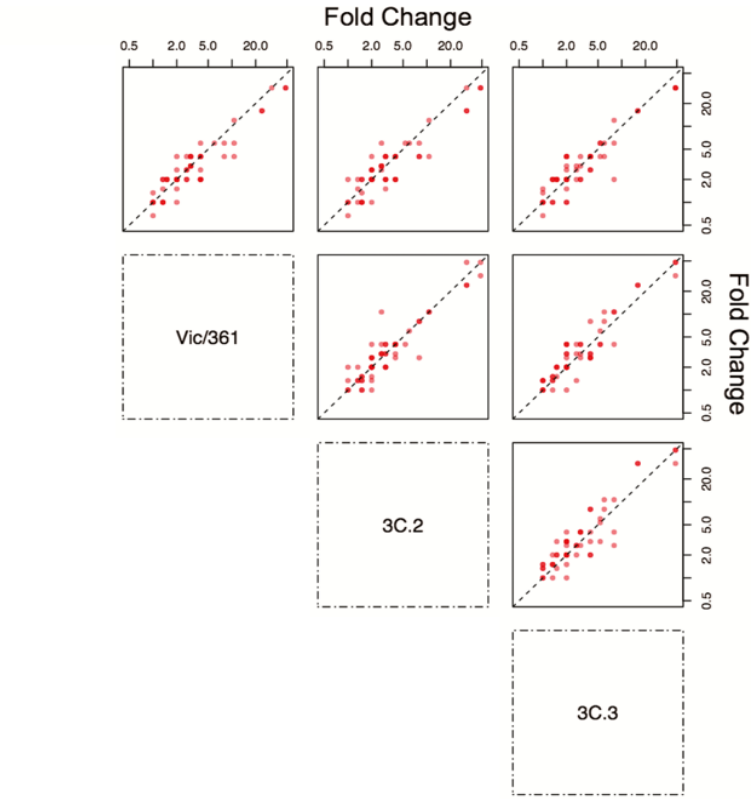
- Assessed VE in 2012-2013 mismatch season
- Mismatch was egg adaptation driven

VE estimates

A(H3N2): 41% (95%CI: 17–59%)
A(H1N1)pdm09: 59% (95%CI:16–80%)
B/Yamagata: 67% (95%CI: 30–85%)
B/Victoria: 75% (95%CI: 29–91%)

Skowronski et al. PLoS One. 2014 Mar 25;9(3):e92153.

Match may not necessarily be driver of lower VE



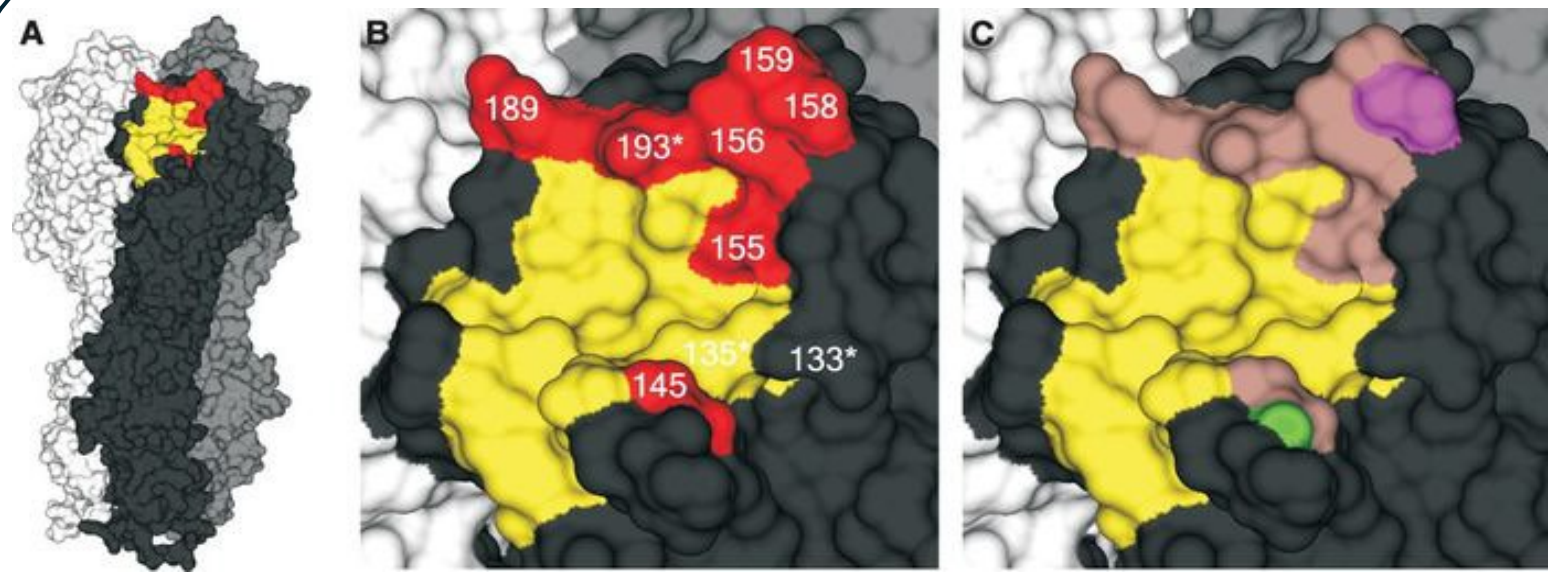
Cobey et al. Clin Infect Dis. 2018 Feb 20;67(3):327–333.

- Analysis of post vaccination serum showed similarly strong linear correlations between individuals ' antibody increases to IVR-165 and circulating clades.
- Viral changes not targeted by human response
- Suggested lower VE driven by lower immunogenicity, not mismatch

egg adaptation

"In many cases, the HA of virus cultivated in eggs was antigenically distinct from the HA of virus from the same individual grown in mammalian cells."

Katz et al. Virology. Volume 156, Issue 2, February 1987, Pages 386-395



Koel et al. Science. Volume: 342, Issue: 6161, Pages: 976-979

A recurring, but unpredictable property

HI antigenic analysis of B/Victoria lineage viruses

		REFERENCE ANTISERA			
		Cell B/Austria/ 1359417/2021	Cell B/Missouri/ 03/2024	Cell B/Texas/ 19/2024	Cell B/Pennsylvania/ 14/2025
	HA subclade	C	C.5.6	C.5.7	C.3.1
REFERENCE VIRUSES					
B/Austria/1359417/2021	C	320	1280	2560	40
B/Missouri/03/2024	C.5.6	320	2560	1280	40
B/Texas/19/2024	C.5.7	320	2560	2560	40
B/Pennsylvania/14/2025	C.3.1	20	80	80	80
TEST VIRUSES					
B/Shandong-Huancui/11058/2025	C.3	20	80	160	160
B/Colorado/65/2025	C.3	40	80	160	160
B/Pennsylvania/01/2026	C.3	40	80	160	160
B/Virginia/20/2025	C.3.1	40	80	320	320
B/Sao Paulo/358687134-IAL/2025	C.3.1	20	80	160	160
B/Hawaii/03/2026	C.3.1	40	80	160	160
B/Michigan/04/2026	C.3.1	40	80	160	160
B/Oklahoma/02/2026	C.3.1	40	80	160	160
B/New Hampshire/27/2025	C.3.1	20	40	80	80
B/Bangladesh/2898/2025	C.5.6	320	2560	5120	80
B/New York/43/2025	C.5.6	320	1280	2560	40
B/Kanagawa/Ac2504/2025	C.5.6	320	2560	2560	80
B/Tokyo/EIS13-776/2025	C.5.6.1	320	2560	2560	80
B/Bangladesh/2857/2025	C.5.6.1	320	2560	2560	80
B/North Dakota/02/2026	C.5.6.1	160	1280	1280	40
B/Vietnam/5315/2025	C.5.7	320	2560	5120	80
B/Cameroon/1888/2025	C.5.7	320	1280	5120	40
B/Missouri/36/2025	C.5.7	160	1280	1280	40

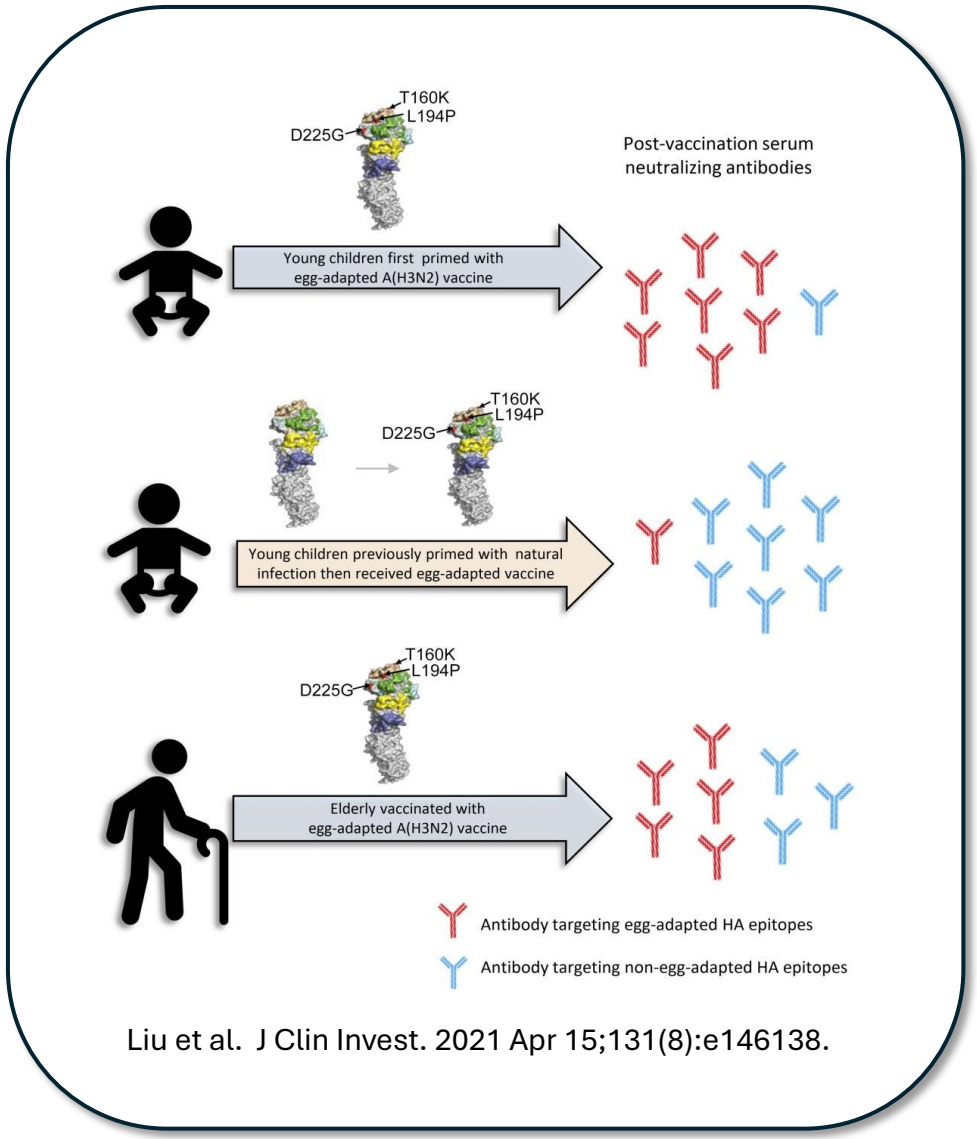
Source: CDC, USA

		REFERENCE ANTISERA	
		Egg B/Austria/ 1359417/2021	Egg B/Tokyo/ EIS13-175/2025
	HA subclade	C	C.3.1
REFERENCE VIRUSES			
B/Austria/1359417/2021	C	640	640
B/Austria/1359417/2021	C	640	320
B/Tokyo/EIS13-175/2025	C.3.1	160	1280
TEST VIRUSES			
B/Okinawa/491/2025	C.3	80	160
B/Tokyo/EIS14-299/2025	C.3	80	160
B/Kanagawa/AC2536/2026	C.3	80	160
B/Kanagawa/AC2542/2026	C.3	80	80
B/Sendai/1/2025	C.3	80	160
B/Yamaguchi/48/2025	C.3	80	160
B/Seoul/2678/2025	C.3	80	160
B/Kanagawa/AC2535/2026	C.3	80	160
B/Taiwan/C22327/2025	C.3.1	80	160
B/Tokyo/EIS13-175/2025	C.3.1	80	160
B/Tokyo/EIS13-011/2025	C.3.1	80	80
B/Pennsylvania/14/2025	C.3.1	80	160
B/Tokyo/EIS13-715/2025	C.5.7	640	1280
B/Taiwan/S27751/2025	C.5.7	640	640
B/Kanagawa/AC2504/2025	C.5.6	640	640
B/Taiwan/S28160/2025	C.5.6	640	640
B/Gifu-C/1/2025	C.5.6	320	640
B/Kanagawa/IC2536/2025	C.5.6.1	320	640

Source: WHO CC, Japan

VCM Information meeting: https://www.youtube.com/@whc

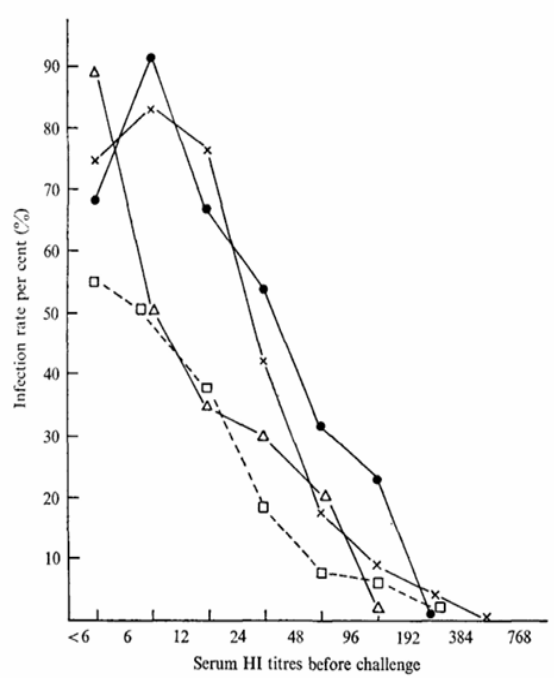
Egg adaptive mutation can be targeted by immune response



Liu et al. J Clin Invest. 2021 Apr 15;131(8):e146138.

- Analyzed post vaccination serum antibodies titers across 2016-2019 seasons when egg adaptations in AH3N2) viruses was abundant.
- Showed that targeting of egg adaptive mutations was common.
- Degree of targeting was age dependent and impacted by previous natural infection and vaccination history.

Immune markers



Hobson et al J. Hyg., Camb. (1972), 70, 767

- HI of ≥40 provides 50% protection
- Held up across natural infection and TIV studies
- Not formally demonstrated across all platforms, although expectations are that it would hold
- Likely more than ‘correlate” and an actual measure of protective mechanism

Unmet needs

- Platforms that offer more flexibility in timelines for manufacturing to distribution
- Platforms that are less prone to adaptive mutations (glycosylation patterns of HA and NA antigens depend on host system glycosylation machinery and may affect their immunogenicity)
- Platforms that can match or exceed current output of doses
- Vaccines that target multiple or more conserved antigens