Insights from combined virological and vaccine effectiveness surveillance

SARInet plus and REVELAC-i Regional Meeting
Panama City, Panama
March 24-26, 2026

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BC Centre for Disease Control
March 26, 2026 (virtual)

SPSN
Canadian Sentinel Practitioner Surveillance Network for Respiratory Pathogen and Vaccine Effectiveness Monitoring
Réseau sentinelles canadien de surveillance des pathogènes respiratoires et de l'efficacité des vaccins

BC Centre for Disease Control
Provincial Health Services Authority

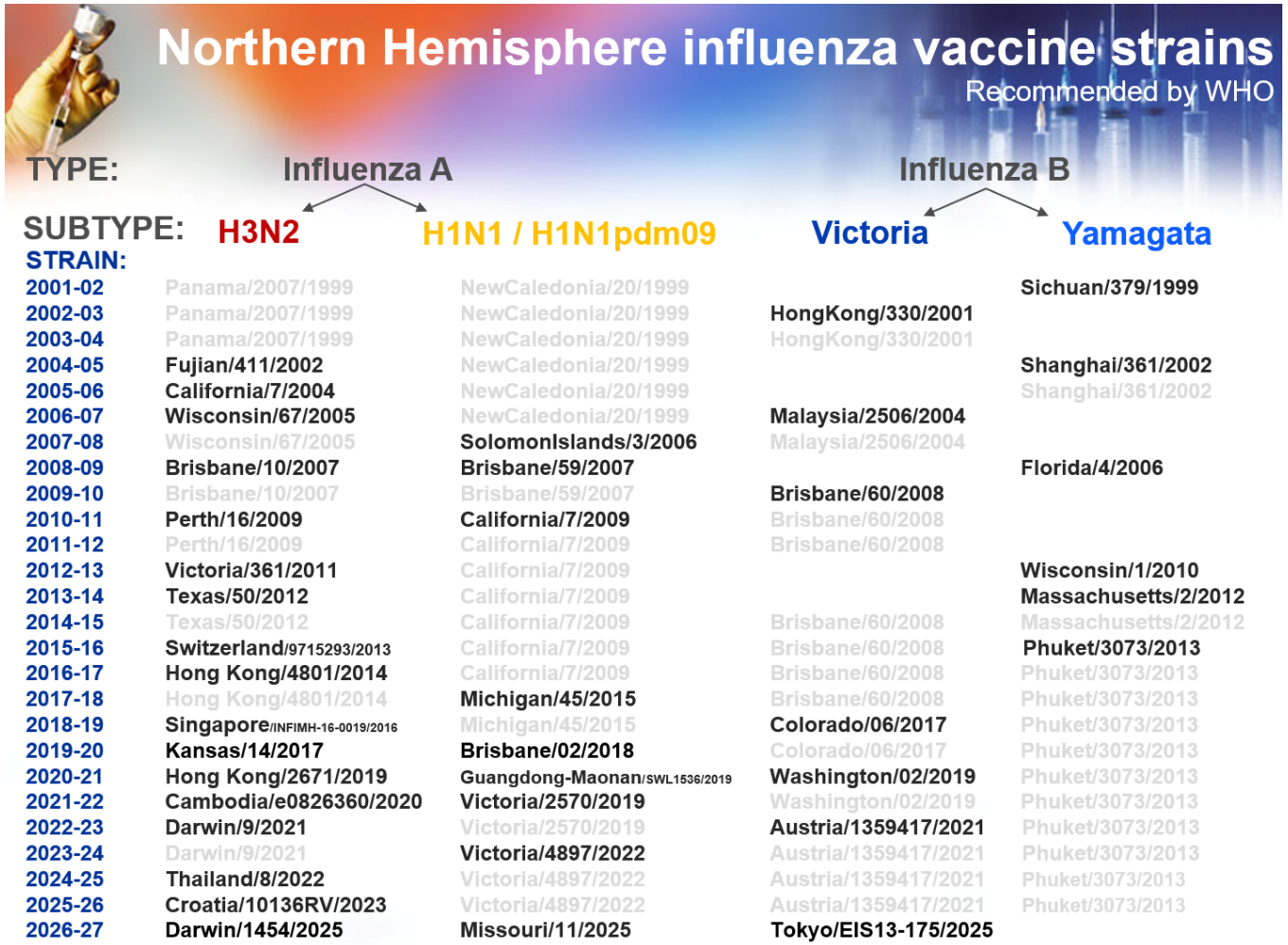
Provincial Health Services Authority

Annual vaccine strain selection is predicated upon the understanding that: Better vaccine match = Better vaccine protection

World Health Organization

The reason the WHO meets twice each year to review vaccine strains for the Northern (February) and Southern (September) hemispheres.

Extensive and expensive process: involving thousands of specimens collected by >150 institutions in >100 countries.



TYPE:	Influenza A		Influenza B	
SUBTYPE:	H3N2	H1N1 / H1N1pdm09	Victoria	Yamagata
STRAIN:				
2001-02	Panama/2007/1999	NewCaledonia/20/1999		Sichuan/379/1999
2002-03	Panama/2007/1999	NewCaledonia/20/1999	HongKong/330/2001	
2003-04	Panama/2007/1999	NewCaledonia/20/1999	HongKong/330/2001	
2004-05	Fujian/411/2002	NewCaledonia/20/1999		Shanghai/361/2002
2005-06	California/7/2004	NewCaledonia/20/1999		Shanghai/361/2002
2006-07	Wisconsin/67/2005	NewCaledonia/20/1999	Malaysia/2506/2004	
2007-08	Wisconsin/67/2005	SolomonIslands/3/2006	Malaysia/2506/2004	
2008-09	Brisbane/10/2007	Brisbane/59/2007		Florida/4/2006
2009-10	Brisbane/10/2007	Brisbane/59/2007	Brisbane/60/2008	
2010-11	Perth/16/2009	California/7/2009	Brisbane/60/2008	
2011-12	Perth/16/2009	California/7/2009	Brisbane/60/2008	
2012-13	Victoria/361/2011	California/7/2009		Wisconsin/1/2010
2013-14	Texas/50/2012	California/7/2009		Massachusetts/2/2012
2014-15	Texas/50/2012	California/7/2009	Brisbane/60/2008	Massachusetts/2/2012
2015-16	Switzerland/9715293/2013	California/7/2009	Brisbane/60/2008	Phuket/3073/2013
2016-17	Hong Kong/4801/2014	California/7/2009	Brisbane/60/2008	Phuket/3073/2013
2017-18	Hong Kong/4801/2014	Michigan/45/2015	Brisbane/60/2008	Phuket/3073/2013
2018-19	Singapore/INFIMH-16-0019/2016	Michigan/45/2015	Colorado/06/2017	Phuket/3073/2013
2019-20	Kansas/14/2017	Brisbane/02/2018	Colorado/06/2017	Phuket/3073/2013
2020-21	Hong Kong/2671/2019	Guangdong-Maonan/SWL1536/2019	Washington/02/2019	Phuket/3073/2013
2021-22	Cambodia/e0826360/2020	Victoria/2570/2019	Washington/02/2019	Phuket/3073/2013
2022-23	Darwin/9/2021	Victoria/2570/2019	Austria/1359417/2021	Phuket/3073/2013
2023-24	Darwin/9/2021	Victoria/4897/2022	Austria/1359417/2021	Phuket/3073/2013
2024-25	Thailand/8/2022	Victoria/4897/2022	Austria/1359417/2021	Phuket/3073/2013
2025-26	Croatia/10136RV/2023	Victoria/4897/2022	Austria/1359417/2021	Phuket/3073/2013
2026-27	Darwin/1454/2025	Missouri/11/2025	Tokyo/EIS13-175/2025	

Vaccine match or mismatch

- Based upon hemagglutination inhibition (HI) assay and first infection ferrets
  - HI antibody titre in ferret sera collected after first infection with a vaccine reference strain
    - Vaccine mis-match is defined by ≥8-fold HI titre reduction when the same ferret anti-sera are tested against circulating virus

- Can be translated into antigenic distance (AD) units, where:

x AD units = 2^x fold reduction in HI titre

  - No reduction (no antigenic distinction): AD = 0
  - 2-fold reduction: AD = 1
  - 4-fold reduction: AD = 2
  - **8-fold reduction: AD = 3**
  - 16-fold reduction: AD =4
  - 32-fold reduction: AD = 5

Fold difference
‹4 -fold
4-fold
8-fold
›8 -fold

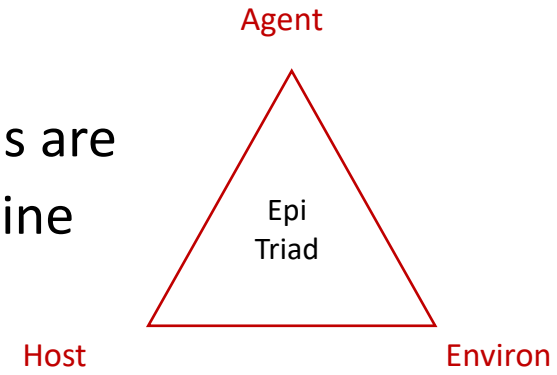
Vaccine reference strains	2025-26 NH Cell J.2	2025-26 NH Egg J.2	2025 SH Egg J.2.4	2025 SH Cell J.2.4	2025 SH Cell K	Subclade
A/Croatia/10136RV/2023c	320	320	40	40	40	J.2
A/Croatia/10136RV/2023e	1280	1280	160	80	40	J.2
A/Singapore/GP20238/2024e	80	320	5120	1280	640	J.2.4
A/Sydney/1359/2024c	80	160	2560	640	640	J.2.4
A/Darwin/1415/2025c	‹40	40	640	160	640	K
Circulating viruses						
A/Victoria/244/2025	320	640	40	40	‹40	J.2
A/Sydney/16/2025	320	320	2560	320	320	J.2
A/Victoria/699/2025	320	320	40	‹40	‹40	J.2
A/Victoria/257/2025	160	320	1280	320	160	J.2
A/Darwin/708/2025	160	160	40	‹40	‹40	J.2
A/South_Queensland/25/2025	320	320	40	‹40	‹40	J.2.1
A/Victoria/2226/2025	320	640	40	40	‹40	J.2.2
A/Singapore/NUH1188/2024	320	320	40	‹40	‹40	J.2.2
A/Victoria/701/2025	320	320	40	‹40	‹40	J.2.2
A/Victoria/869/2025	40	‹40	40	‹40	‹40	J.2.3
A/Perth/615/2025	40	160	640	80	80	J.2.4
A/Tasmania/807/2025	40	160	2560	320	320	J.2.4
A/Singapore/GP20238/2024	40	80	1280	160	160	J.2.4
A/Sydney/578/2025	40	80	2560	320	160	J.2.4
A/Victoria/211/2025	80	80	40	‹40	‹40	J.2.5
A/Darwin/1369/2025	‹40	40	640	160	640	K
A/Darwin/1415/2025	‹40	40	640	160	640	K
A/Darwin/1454/2025	‹40	40	2560	320	1280	K
A/Darwin/1497/2025	‹40	40	640	80	320	K
A/Darwin/1559/2025	‹40	‹40	640	80	320	K
A/Tasmania/787/2025	‹40	‹40	640	160	640	K

Adapted from: Dapat C. et al Eurosurveillance 2025;30(49):pii=2500894

Epidemiological monitoring of vaccine effectiveness (VE) is critical

- **Influenza vaccine strains are chosen 6-9 months before seasonal campaigns**
  - Ongoing viral evolution, egg-based manufacturing mutations, uncertain match

- **Unlike first infection ferrets, people accumulate influenza exposures/infections and have complex immunological histories vis-à-vis influenza virus**
  - Not just virological considerations, but agent-host interactions are relevant in understanding the epidemiological effects of vaccine



- **Annual immunization programs are costly**
  - Benefits, impact and value for money depend upon epidemiological considerations
    - Including vaccine effectiveness
  - VE surveillance is a basic due diligence requirement
    - Financial accountability, credibility and dispelling disinformation

Imprinting and pre-immunity

- **The first childhood influenza infection leaves a powerful immunological imprint**
  - Influences the immune response to subsequent influenza infections across the lifespan
    - Greater efficiency of memory over de novo responses
    - Preferential back-boosting of immunity against shared epitopes
    - Hierarchical effects at HA/NA group, subtype, strain levels

- **Imprinting is a kind of cohort effect**
  - Differential effects expressed by birth cohort
    - Point in time (period) effect (e.g., pandemic) that makes its immunological mark, then advances as cohorts sharing the same imprint advance in age

- **Pre-immunity also reflects age considerations**
  - Highest infection rates among school-aged children
  - Exposure and back-boosting effects accumulated with age

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

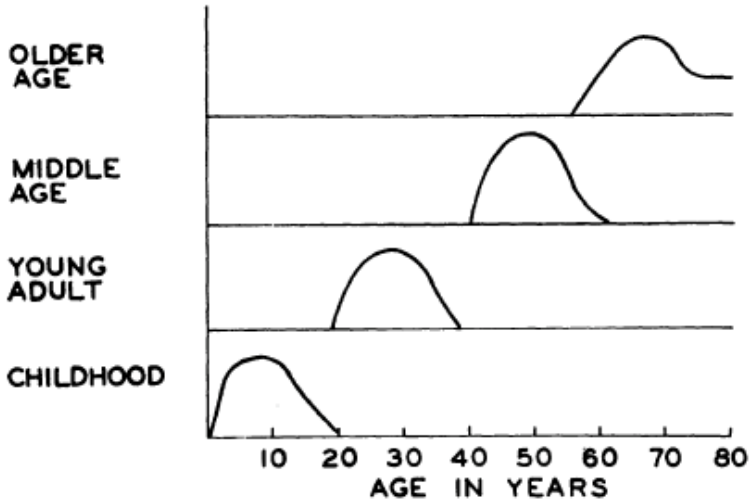
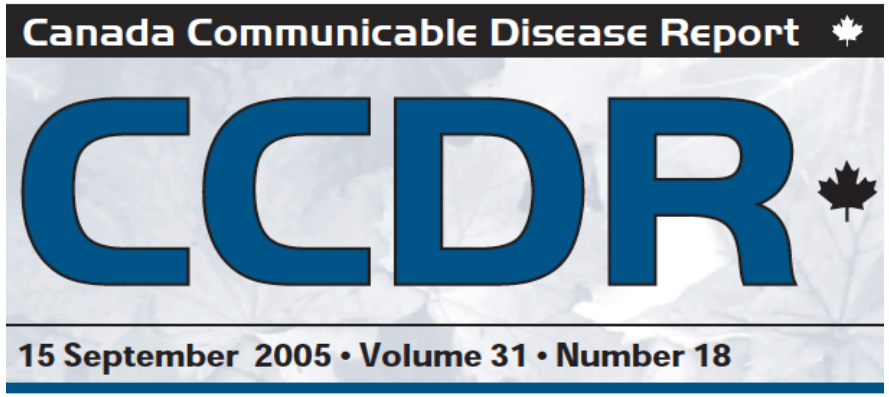


FIG. 10. The persistence of initial antibody throughout life.

2004-05: Canadian SPSN investigators were the first to publish influenza VE estimates based upon the test-negative design (TND)

SPSN

Canadian Sentinel Practitioner Surveillance Network for Respiratory Pathogen and Vaccine Effectiveness Monitoring

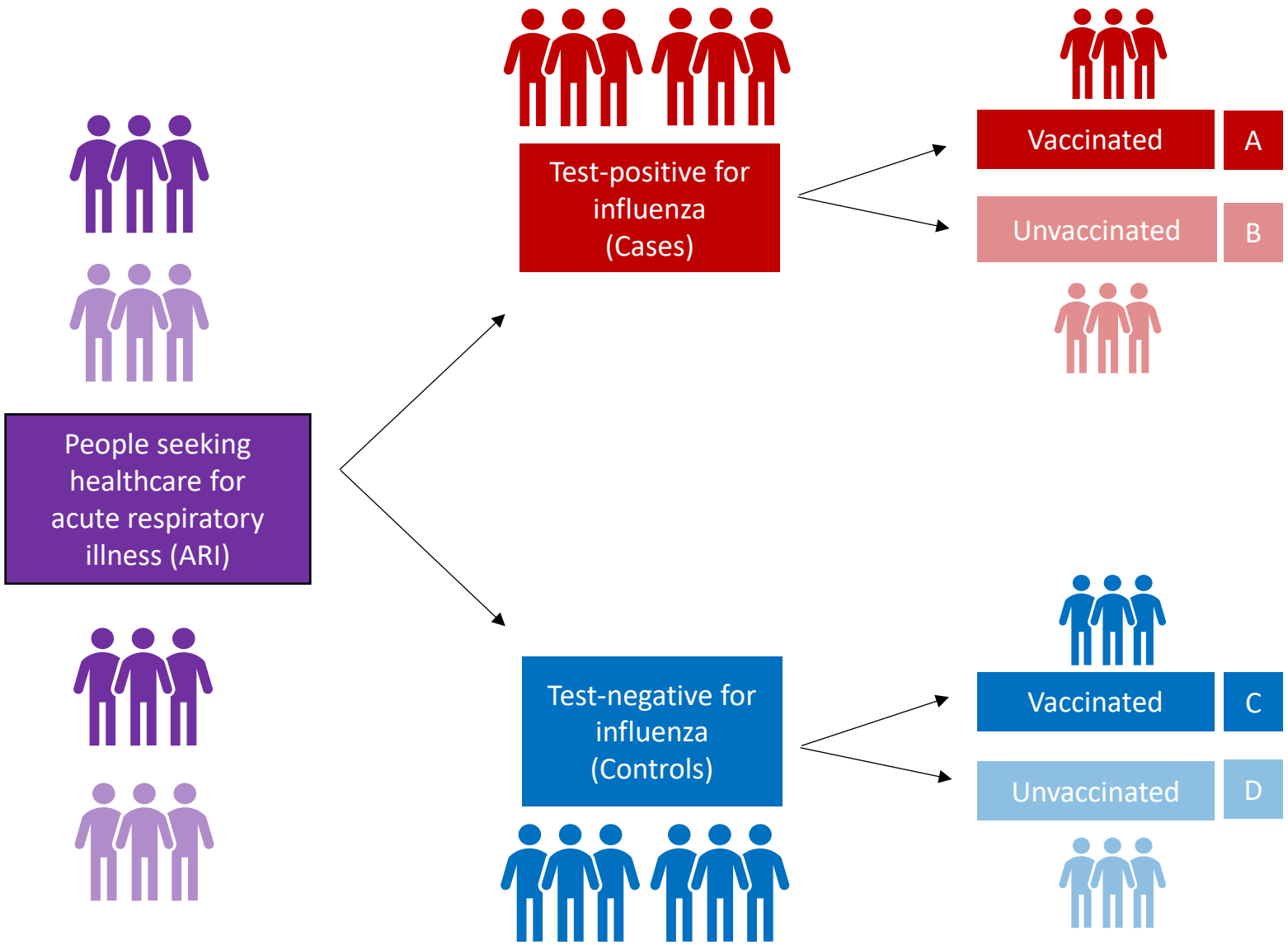


EFFECTIVENESS OF VACCINE AGAINST MEDICAL CONSULTATION DUE TO LABORATORY-CONFIRMED INFLUENZA: RESULTS FROM A SENTINEL PHYSICIAN PILOT PROJECT IN BRITISH COLUMBIA, 2004-2005

For the 2004-2005 season, the British Columbia Centre for Disease Control (BCCDC) piloted a novel approach for assessing influenza VE through its sentinel physician network. VE against medical consultation due to laboratory-confirmed influenza was undertaken using an observational case-control method. The purpose of the pilot study was to explore VE and to assess the feasibility of using a sentinel network for ongoing VE monitoring annually, as well as to identify key issues pertinent to that.

MADE IN CANADA
FABRIQUÉ AU CANADA

VE estimation by observational test-negative design



Odds Ratio (OR) =
odds of being vaccinated among cases vs controls

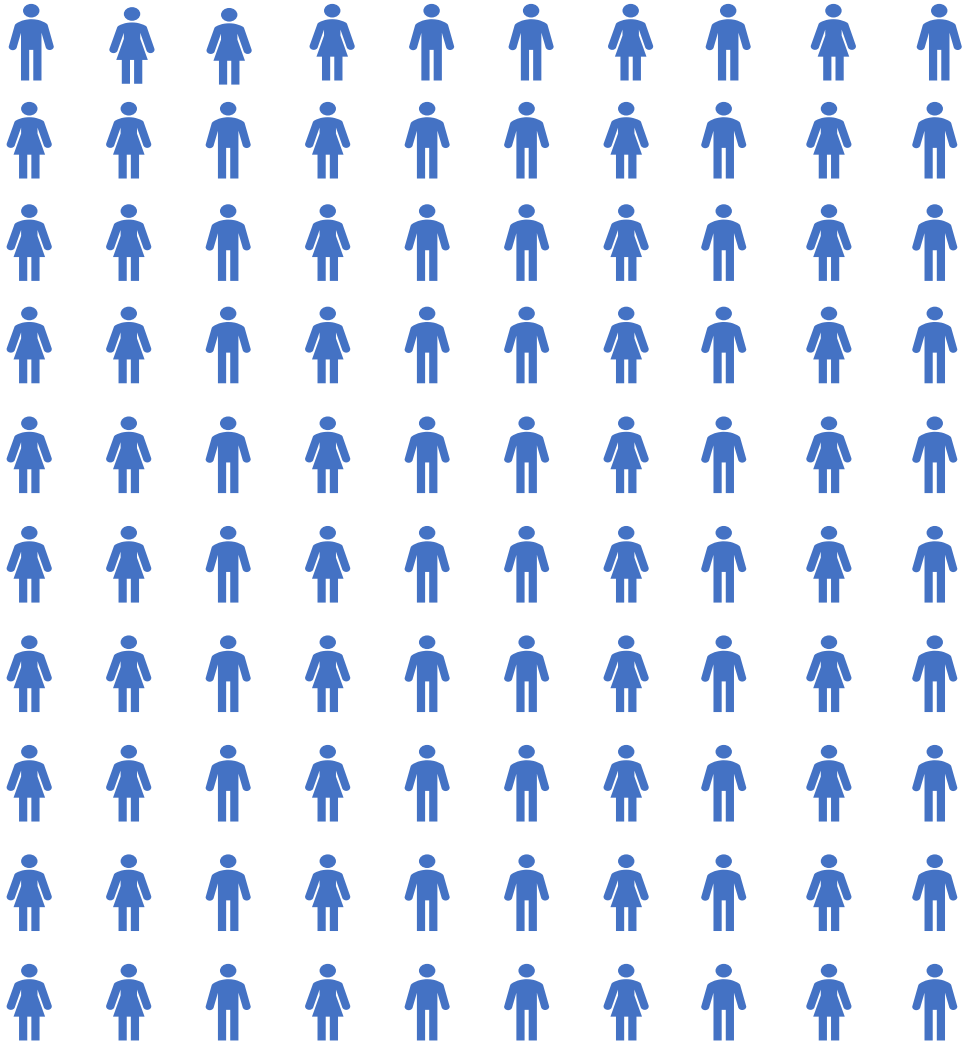
$$\frac{A/B}{C/D} = \frac{A}{C} \times \frac{D}{B}$$

VE = 1 – OR * 100

Odds (likelihood) of being an influenza case among vaccinated versus unvaccinated participants

What does a VE of 70% mean?

For every 100 influenza infections requiring a medical visit in unvaccinated people:



70 could have been prevented through vaccination

2005-06: importance of genetically characterizing case viruses

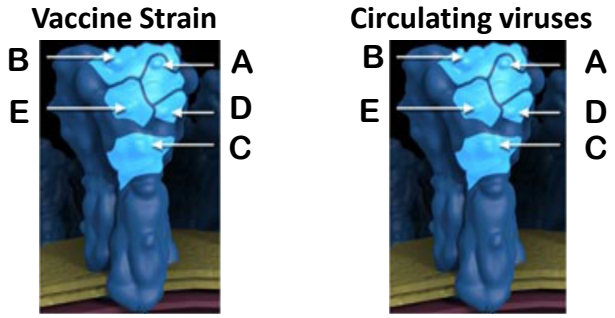
ELSEVIER

Available online at www.sciencedirect.com
ScienceDirect
Vaccine 25 (2007) 2842–2851

Vaccine
www.elsevier.com/locate/vaccine

Estimating vaccine effectiveness against laboratory-confirmed influenza using a sentinel physician network: Results from the 2005–2006 season of dual A and B vaccine mismatch in Canada

D.M. Skowronski [a,*], C. Masaro [a], T.L. Kwindt [a], A. Mak [b], M. Petric [b], Y. Li [c], R. Sebastian [a,d], M. Chong [a], T. Tam [e], G. De Serres [f]



- All H3N2 case viruses considered antigenically matched to the A/California/7/2004 vaccine strain
- **Vaccine effectiveness lower than expected for well-matched vaccine**
- Sequencing of H3N2 case viruses identified significant mutations in the hemagglutinin protein
- Subsequently confirmed antigenically using updated anti-sera
  - 80% of H3N2 case viruses recharacterized antigenically as being most like the emerging A/Wisconsin/67/2005 variant

MAJOR ARTICLE

2012;205:1858–68

Estimates of Influenza Vaccine Effectiveness for 2007–2008 From Canada's Sentinel Surveillance System: Cross-Protection Against Major and Minor Variants

Naveed Z. Janjua,[1,2] Danuta M. Skowronski,[1,2] Gaston De Serres,[3] Jim Dickinson,[4] Natasha S. Crowcroft,[5,6,7] Marsha Taylor,[1] Anne-Luise Winter,[5] Travis S. Hottes,[1] Kevin Fonseca,[8] Hugues Charest,[3] Steven J. Drews,[5,a] Suzana Sabaiduc,[1] Nathalie Bastien,[9] Yan Li,[9] Jennifer L. Gardy,[1,2] and Martin Petric[1,2]

Objectives. To estimate influenza vaccine effectiveness (VE) for the 2007–2008 season and assess the sentinel surveillance system in Canada for monitoring virus evolution and impact on VE.

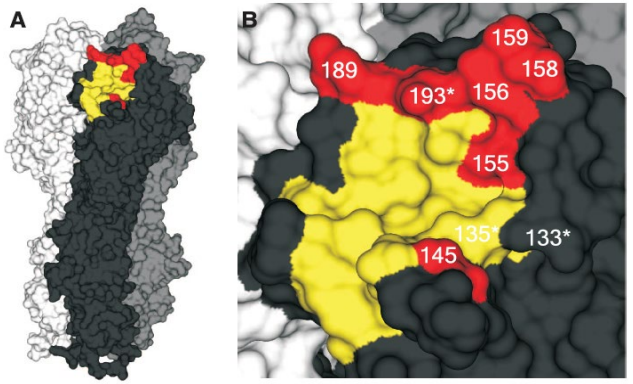
Methods. Nasal/nasopharyngeal swabs and epidemiologic details were collected from patients presenting to a sentinel physician within 7 days of influenza-like illness onset. Cases tested positive for influenza A/B virus by real-time polymerase chain reaction; controls tested negative. Hemagglutination inhibition (HI) and gene sequencing explored virus relatedness to vaccine. VE was calculated as 1 minus the odds ratio for influenza in vaccinated versus nonvaccinated participants, with adjustment for confounders.

Results. Of 1425 participants, 21% were vaccinated. Influenza virus was detected in 689 (48%), of which isolates from 663 were typed/subtyped: 189 (29%) were A/H1, 210 (32%) were A/H3, and 264 (40%) were B. Of A/H1N1 isolates, 6% showed minor HI antigenic mismatch to vaccine, with greater variation based on genetic identity. All A/H3N2 isolates showed moderate antigenic mismatch, and 98% of influenza B virus isolates showed major lineage-level mismatch to vaccine. Adjusted VE for A/H1N1, A/H3N2, and B components was 69% (95% confidence interval [CI], 44%–83%), 57% (95% CI, 32%–73%), and 55% (95% CI, 32%–70%), respectively, with an overall VE of 60% (95% CI, 45%–71%).

Conclusions. Detailed antigenic and genotypic analysis of influenza viruses was consistent with epidemiologic estimates of VE showing cross-protection. A routine sentinel surveillance system that combines detailed virus and VE monitoring annually, as modeled in Canada, may guide improved vaccine selection and protection.

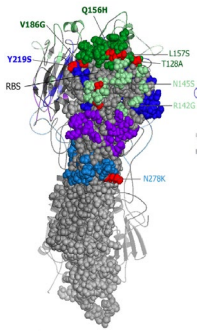
Science AAAS

Substitutions Near the Receptor Binding Site Determine Major Antigenic Change During Influenza Virus Evolution
Björn F. Koel *et al.*
Science **342**, 976 (2013);
DOI: 10.1126/science.1244730



Integrated genomics: examples of critical insights

Egg adaptation mutations in vaccine: effects shown epidemiologically for the first time



PLOS ONE

Low 2012–13 Influenza Vaccine Effectiveness Associated with Mutation in the Egg-Adapted H3N2 Vaccine Strain Not Antigenic Drift in Circulating Viruses

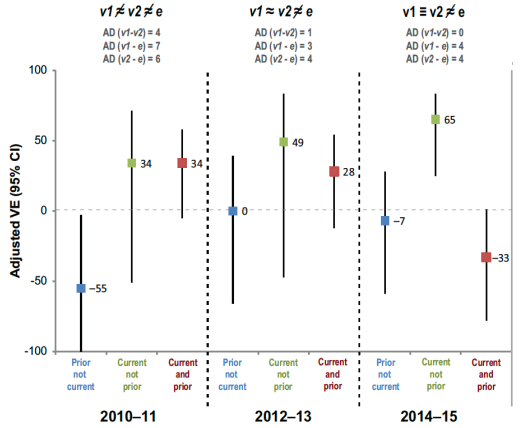
Danuta M. Skowronski[1,2*], Naveed Z. Janjua[2,3], Gaston De Serres[4,5], Suzana Sabaiduc[1], Alireza Eshaghi[6], James A. Dickinson[7], Kevin Fonseca[8,9], Anne-Luise Winter[10], Jonathan B. Gubbay[11,12,13], Mel Krajden[1,3], Martin Petric[1,3], Hugues Charest[14,15], Nathalie Bastien[16], Trijntje L. Kwindt[2], Salaheddin M. Mahmud[17], Paul Van Caeseele[18,19], Yan Li[16,19]

Repeat vaccination effects: determined by relatedness between V1 (prior season) and V2 (current season) vaccines and *e (*epidemic strain*)*

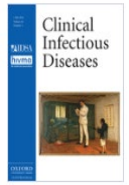
Volume 215, Issue 7
1 April 2017

Serial Vaccination and the Antigenic Distance Hypothesis: Effects on Influenza Vaccine Effectiveness During A(H3N2) Epidemics in Canada, 2010–2011 to 2014–2015

Danuta M. Skowronski,[1,2] Catharine Chambers,[1] Gaston De Serres,[3,4,5] Suzana Sabaiduc,[6] Anne-Luise Winter,[7] James A. Dickinson,[8] Jonathan B. Gubbay,[9,10] Kevin Fonseca,[11,12] Steven J. Drews,[13,14] Hugues Charest,[15,16] Christine Martineau,[15] Mel Krajden,[6,17] Martin Petric,[17] Nathalie Bastien,[18] Yan Li,[18] and Derek J. Smith[19]



Repeat vaccination effects (dose-response): exacerbated by successive use of similar vaccines, and a distinct epidemic strain

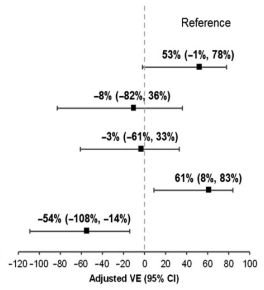


Volume 63, Issue 1
1 July 2016

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]

Vaccination History (2012–2013, 2013–2014, and 2014–2015)	Case n (%)	Control n (%)
Unvaccinated all 3 seasons	238 (46)	465 (49)
Current but neither prior (2012–2013 nor 2013–2014)	9 (2)	48 (5)
No current but 1 prior (2012–2013 or 2013–2014)	29 (6)	60 (6)
No current but both prior (2012–2013 and 2013–2014)	44 (8)	75 (8)
Current and 1 prior (2012–2013 or 2013–2014)	7 (1)	38 (4)
Current and both prior (2012–2013 and 2013–2014)	193 (37)	268 (28)

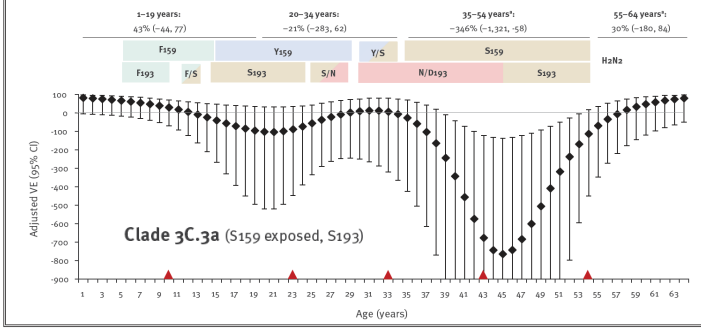


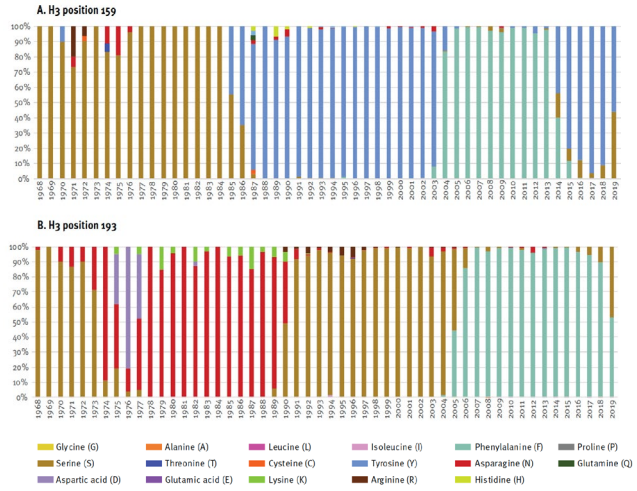
Imprint regulated effects of vaccine: cohort effects defined by distant viral circulation, differential childhood imprinting and pre-immunity influencing clade-specific VE by age

Eurosurveillance
Euro Surveill. 2019;24(46):pii=1900585

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]

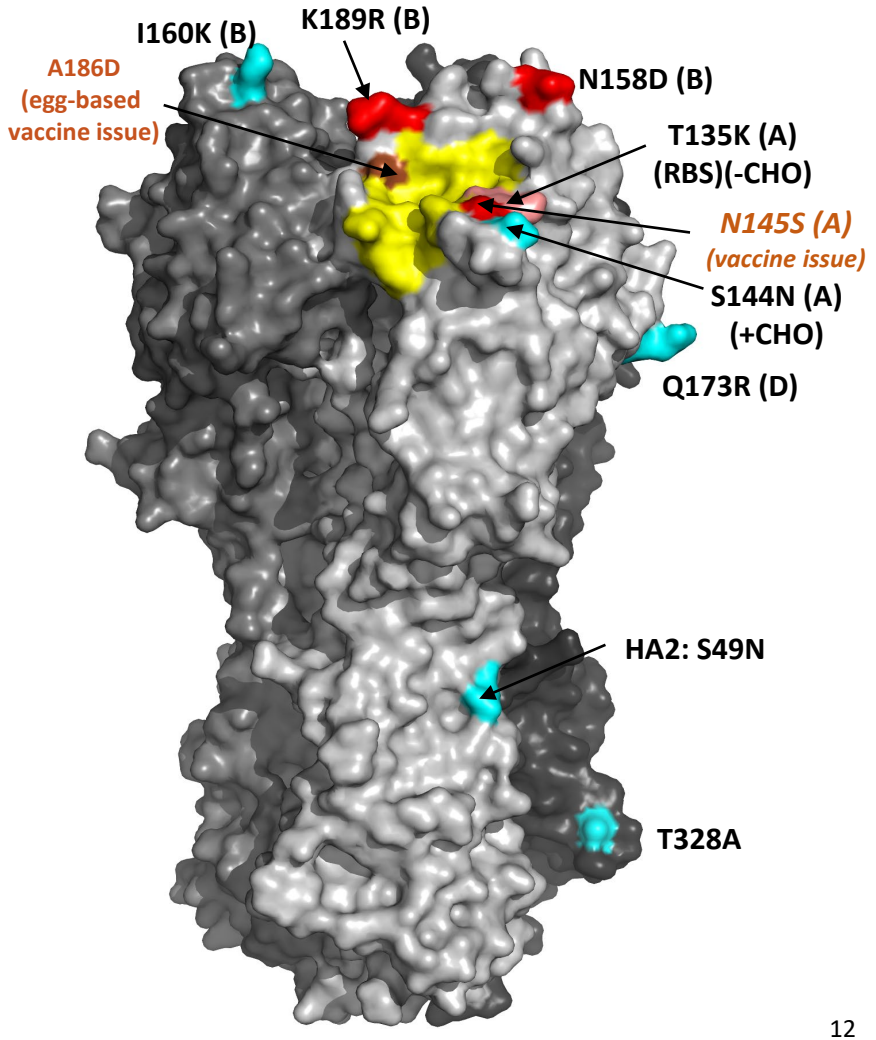




2025/26, subclade K: virological signals for concern

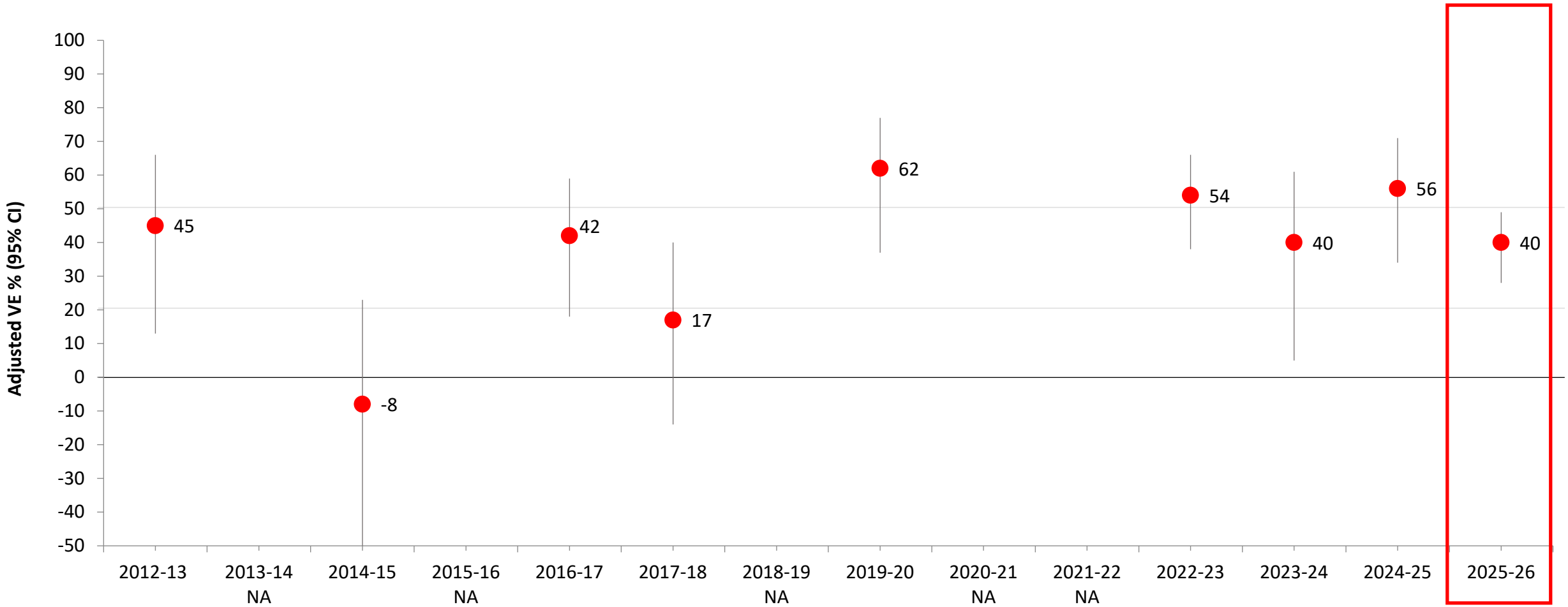
- **Genetic data:** viral evolution (drift) involving pivotal HA positions
  - **Site A: glycosylation changes** *(Sabaiduc, JAMMI, 2025) Separovic, EuroSurveillance, 2026)*
    - T135K (-CHO at N133)
    - S144N (+CHO at N144)
    - N145S (due to chosen J.2 vaccine strain)
  - **Site B: mutations at major antigenic cluster transition sites**
    - N158D
    - K189R
    - Additionally I160K, A186D (vaccine egg-adaptation mutation)
- **Antigenicity data:** substantial vaccine mismatch, AD = 4-5
- **Other surrogate laboratory information**
  - **Deep mutational scanning** *(Welsh et al, Cell Host & Microbe, 2024)*
    - Residue 189 very immuno-evasive, especially in children
    - Pre-existing N158 immunity in adults may cross-protect against D158 in subclade K
  - **High throughput sequencing-based neutralization** *(Kikawa et al, Virus Evolution, 2025 Kikawa et al, bioRxiv, Feb 19, 2026)*
    - Residue 158 and 189 mutated variants, notably including subclade K, react poorly with sera across age span
  - **Adult immunogenicity data** *(Liu et al, NEJM Evid, 2026)*
    - Low pre-existing antibody against subclade K, but cross-reactive J.2 vaccine responses

Subclade K mutations relative to 2025/26 egg-based J.2 vaccine



SPSN influenza A(H3N2) mid-season VE estimates: 2012-2025 (6/9 below 50%)

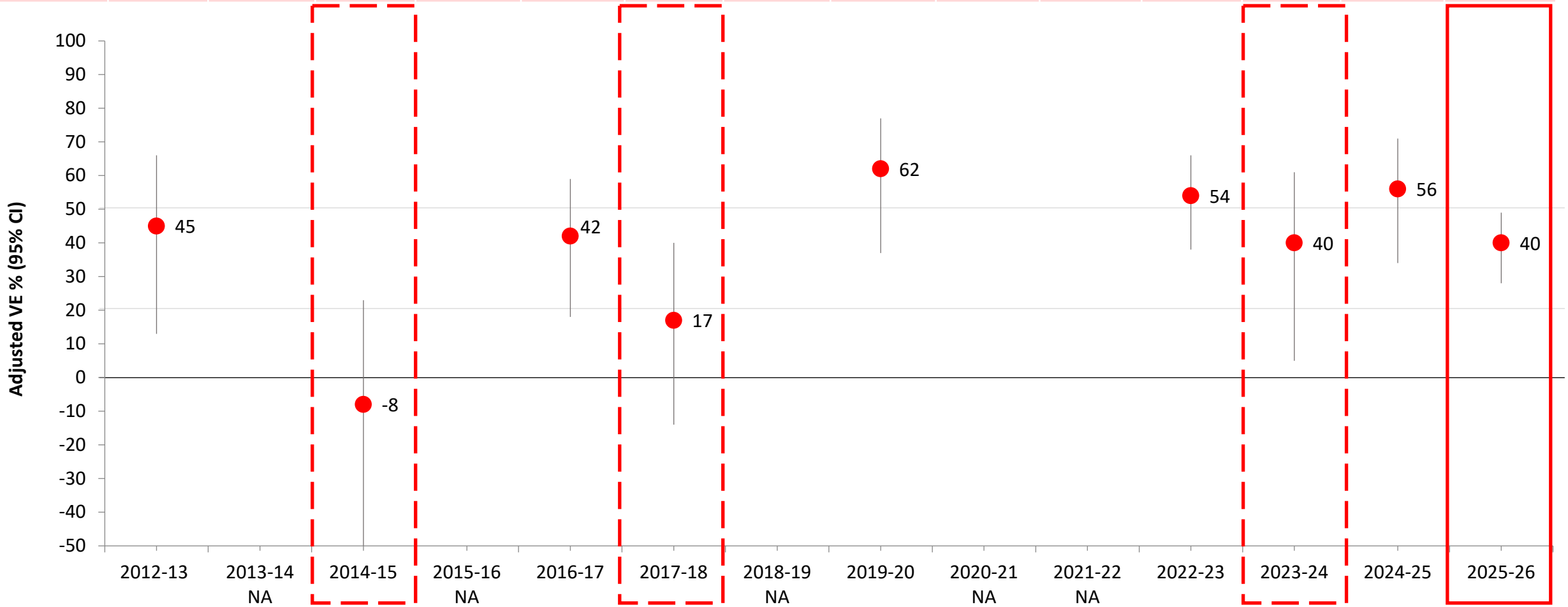
Despite subclade K concerns, 2025-26 mid-season VE against A(H3N2) mid-range



http://www.bccdc.ca/health-info/diseases-conditions/influenza/sentinel-network-spsn

SPSN influenza A(H3N2) mid-season VE estimates: 2012-2025 (6/9 below 50%)

Antigenic distance	4		4		≤2	≤2		4			≤3	≤2	2-4	4-5
Vaccine strain changed (✓)	✓	~	×	✓	✓	×	✓	✓	✓	✓	✓	×	✓	✓



http://www.bccdc.ca/health-info/diseases-conditions/influenza/sentinel-network-spsn

Pre-immunity effects?

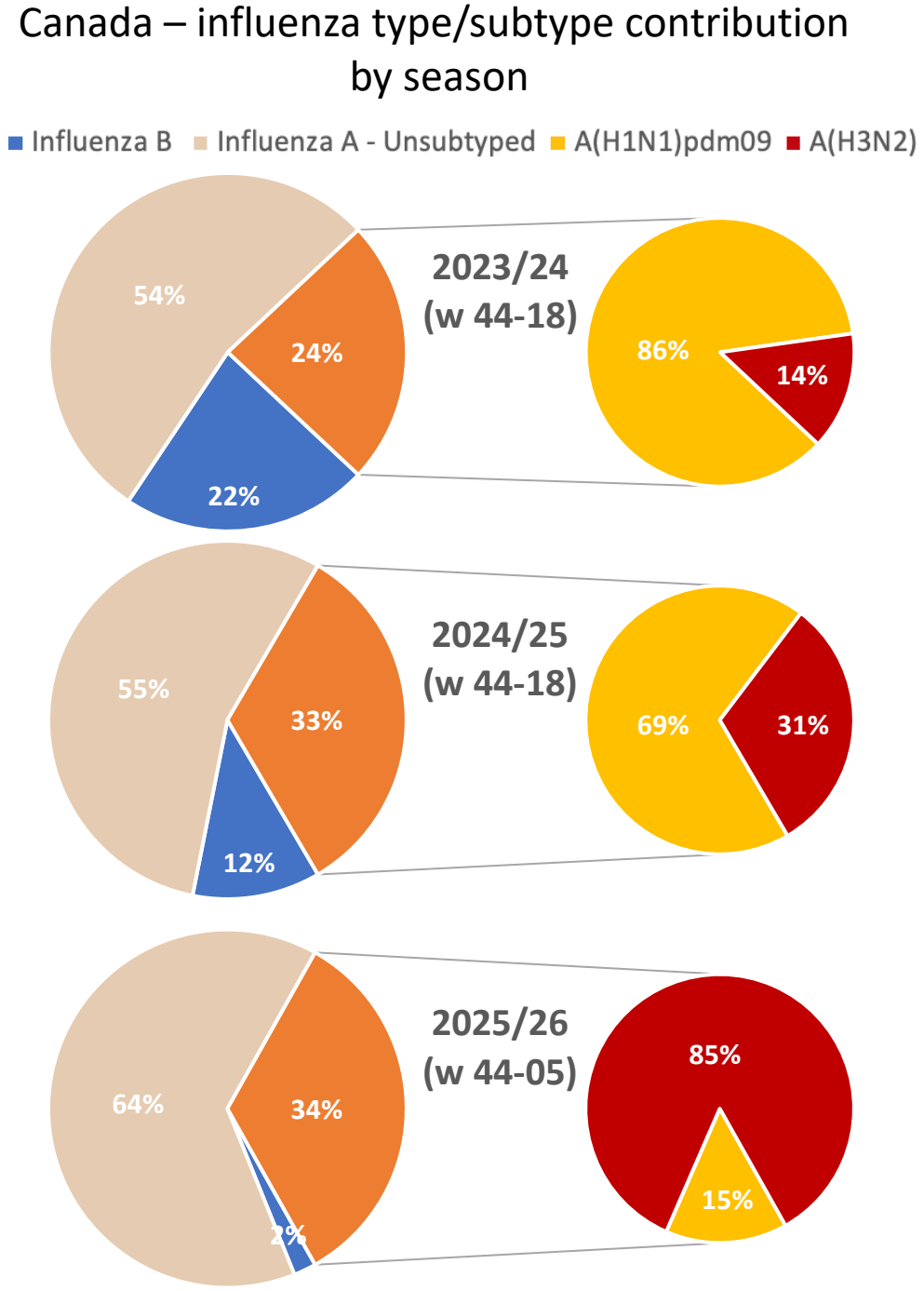
- **VE represents risk reduction relative to unvaccinated**
  - High levels of pre-existing immunity in the unvaccinated may be associated with lower VE estimates

(*Ioannidis, BMJ Evidence-Based Medicine, 2021*
Tsang et al, AJE, 2024)

- **Including prior infection and vaccination histories**
  - Imprinted, accumulated and recent

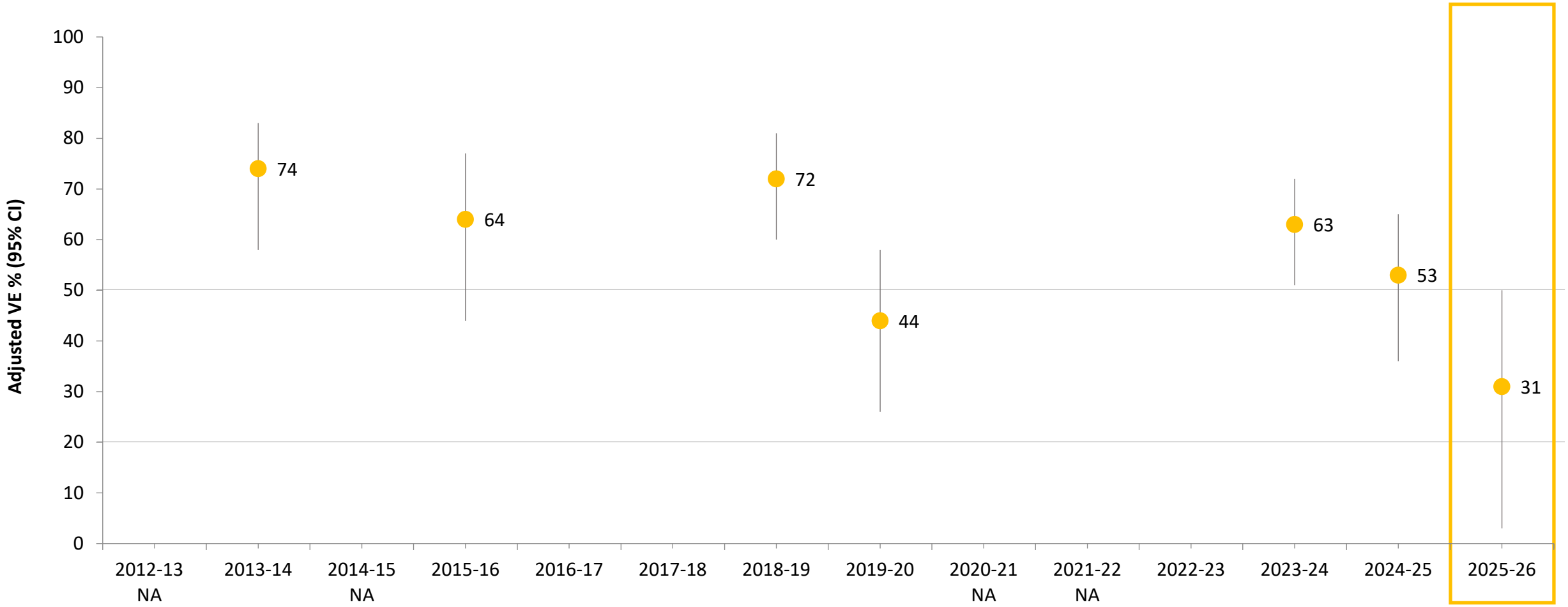
- **Not just antigenic sites of the HA head**
  - Other more conserved viral targets (e.g., HA stalk, NA)

- **Not just antibodies measured by serological assays**
  - Other immunological components (e.g., T-cell mediated)



SPSN influenza A(H1N1)pdm09 mid-season VE estimates: 2012-2025 (2/7 seasons, VE below 50%)

Antigenic distance		<2		<2			≤2	50% <3 50% ≥3				<3	<3	<3
Vaccine strain vaccine (✓)	×	×	×	×	×	✓	×	✓	✓	✓	×	✓	×	×



http://www.bccdc.ca/health-info/diseases-conditions/influenza/sentinel-network-spsn

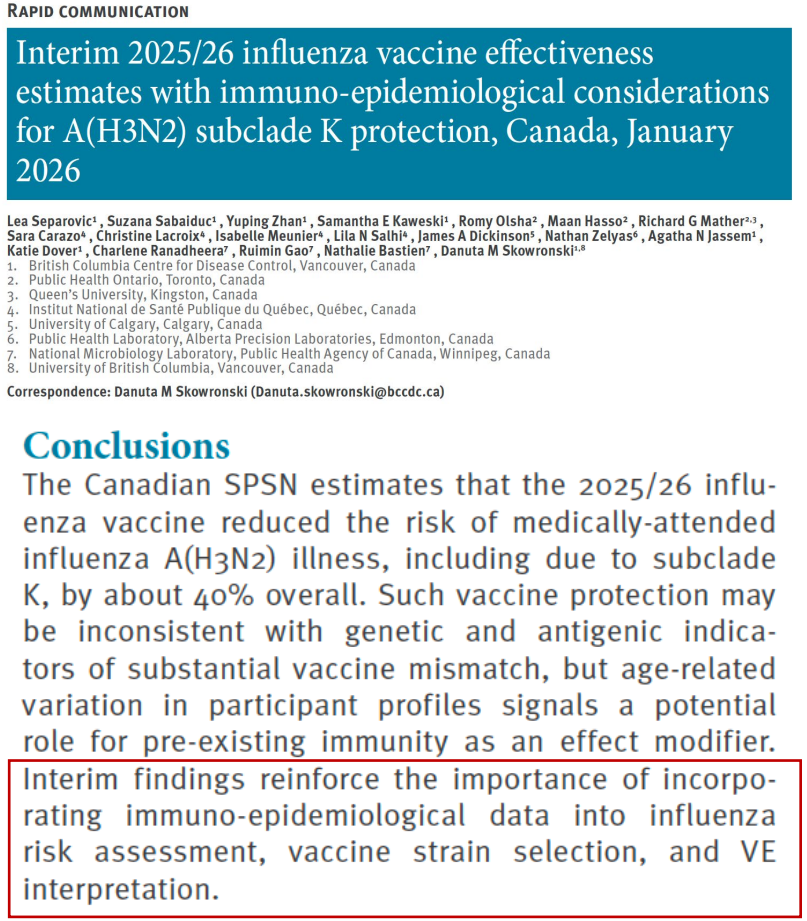
Conclusions

- Agent-host interactions underpin vaccine performance
  - Reinforces the importance of integrated virological & VE surveillance for highly changeable viruses like influenza
  - For influenza, surrogate lab indicators are necessary but insufficient and standalone VE estimates are of limited value – need both

- Assessments of influenza risk and predictions of vaccine protection must take into account complex immunological histories
  - Including imprinting and pre-immunity effects
  - Not adequately captured by first infection ferrets or serological / immunogenicity responses in small subsets of select cohorts

- Given the importance of the annually renewed influenza immunization program
  - Understanding the determinants of vaccine performance is critical
  - Much we have yet to learn
  - Requires routine integration of virological and immuno-epidemiological considerations into VE prediction, estimation and interpretation

For more in-depth discussion, see:



RAPID COMMUNICATION

Interim 2025/26 influenza vaccine effectiveness estimates with immuno-epidemiological considerations for A(H3N2) subclade K protection, Canada, January 2026

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Conclusions

The Canadian SPSN estimates that the 2025/26 influenza vaccine reduced the risk of medically-attended influenza A(H3N2) illness, including due to subclade K, by about 40% overall. Such vaccine protection may be inconsistent with genetic and antigenic indicators of substantial vaccine mismatch, but age-related variation in participant profiles signals a potential role for pre-existing immunity as an effect modifier. Interim findings reinforce the importance of incorporating immuno-epidemiological data into influenza risk assessment, vaccine strain selection, and VE interpretation.

See also link to this video recording, BCCDC Grand Rounds:

Subclade K, the sequel: 2025/26 influenza vaccine effectiveness findings from Canada, Feb 17, 2026