Where we are going with vaccination of children against influenza

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Outline of my talk

- Global Burden of Influenza
  - *Morbidity and mortality in children*
- Influenza Vaccines
- Real life IIV and LAV effectiveness
- Immune responses and the Original Antigenic Sin
- Where we are with universal Influenza vaccination
- Next generation Influenza vaccines

Estimated Influenza Disease Burden, by Season 2010-11 through 2022-23

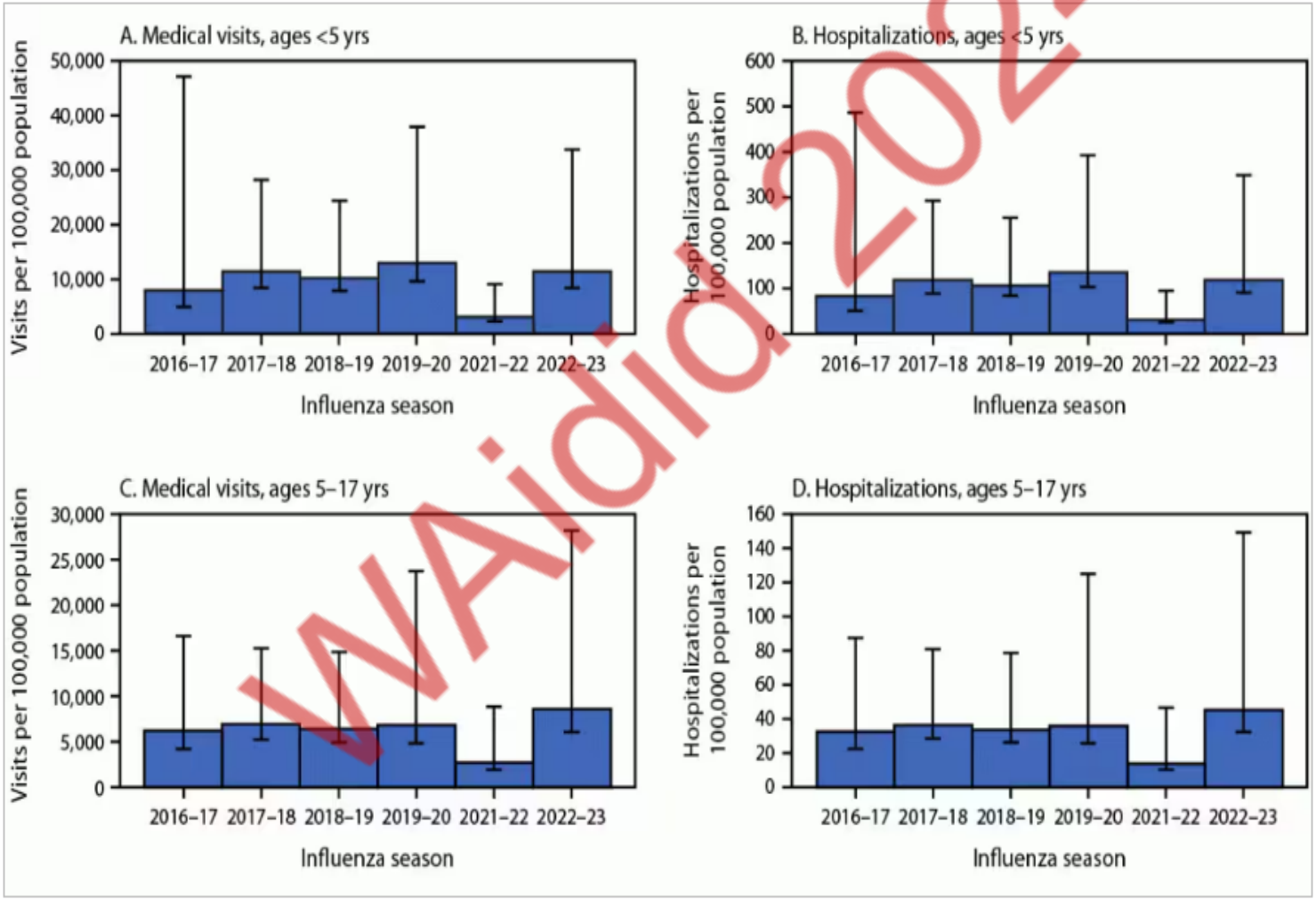
https://www.cdc.gov/flu/about/burden/index.html

Epidemiology of Influenza in paediatric populations

- 3–5 million cases of severe disease per year.
- 290–650 thousand deaths due to respiratory complications.
- 870,000 annual hospitalizations globally of children less than 5 years old.

Motaghi S. et al... Vaccine. 2024

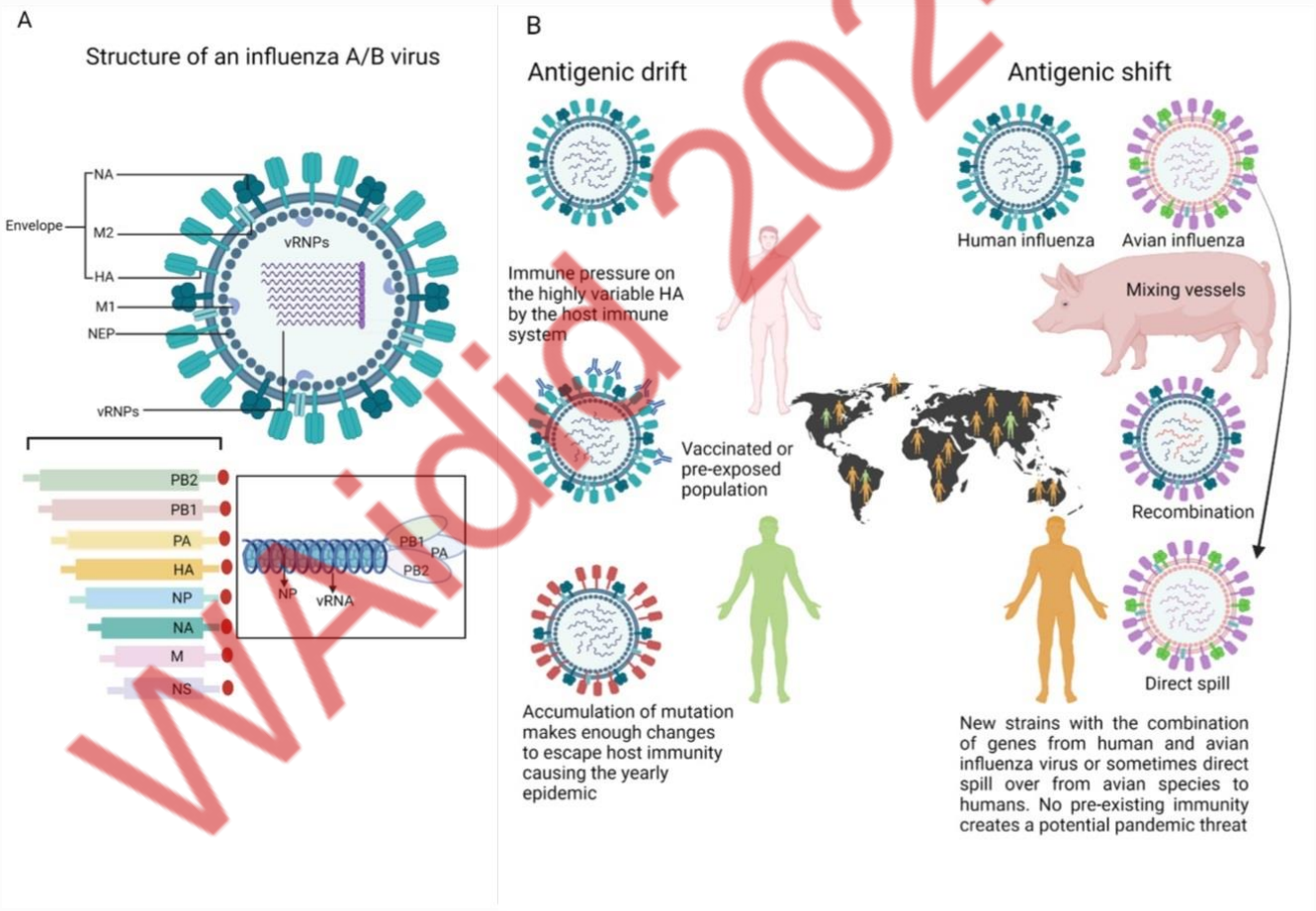
Disease burden 2016-–2023 in children and adolescents aged 5–17 years



https://www.cdc.gov/mmwr/volumes/72/wr/mm7241a2.htm?s_cid=mm7241a2_w

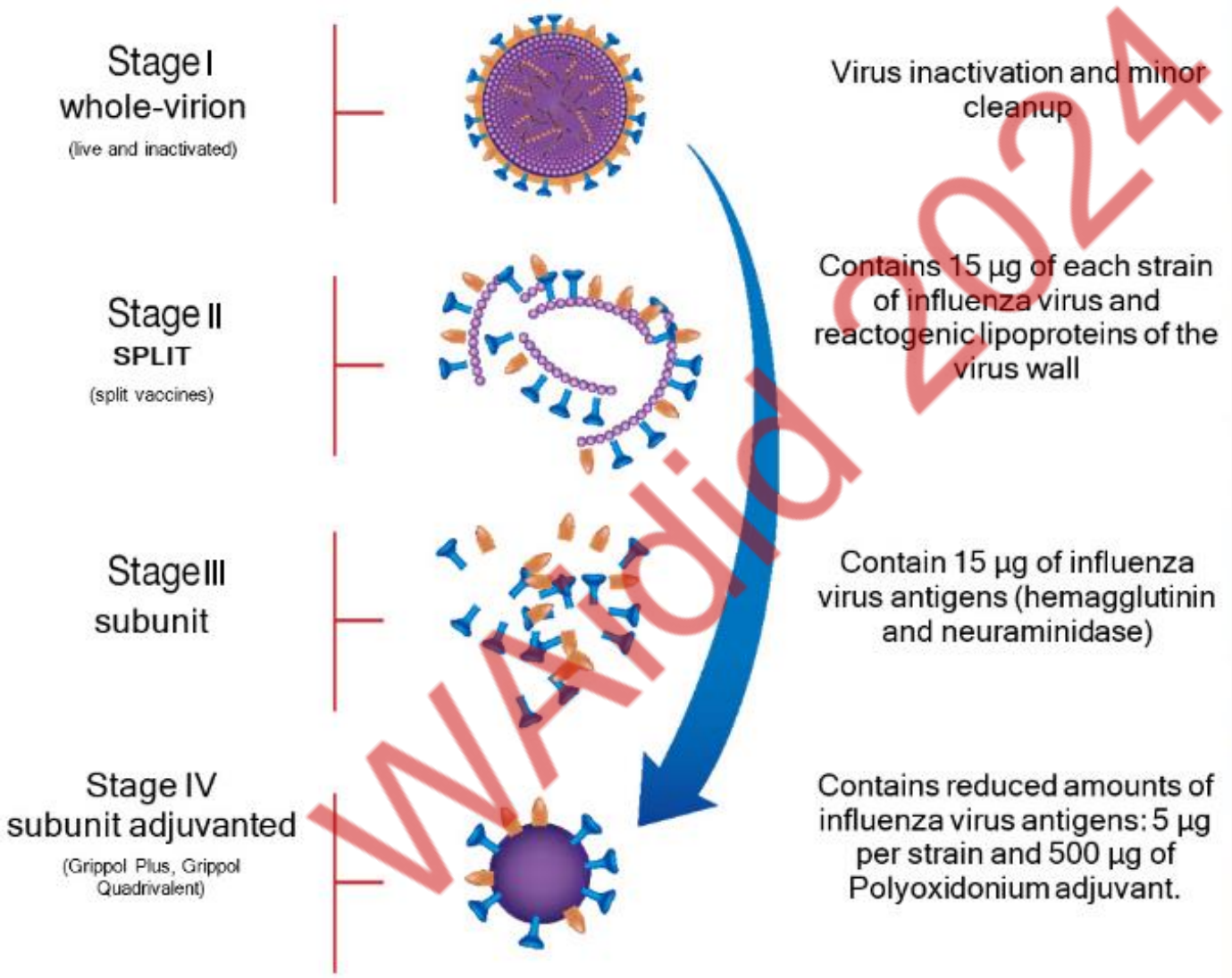
Influenza virus structure and antigenic drift and shift in influenza infections

(from Muraduzzaman HKM, et al. 2022)



Muraduzzaman, A. et al., Viruses. 2022.

Influenza vaccines



https://grippol.ru/en/vaccination/type/

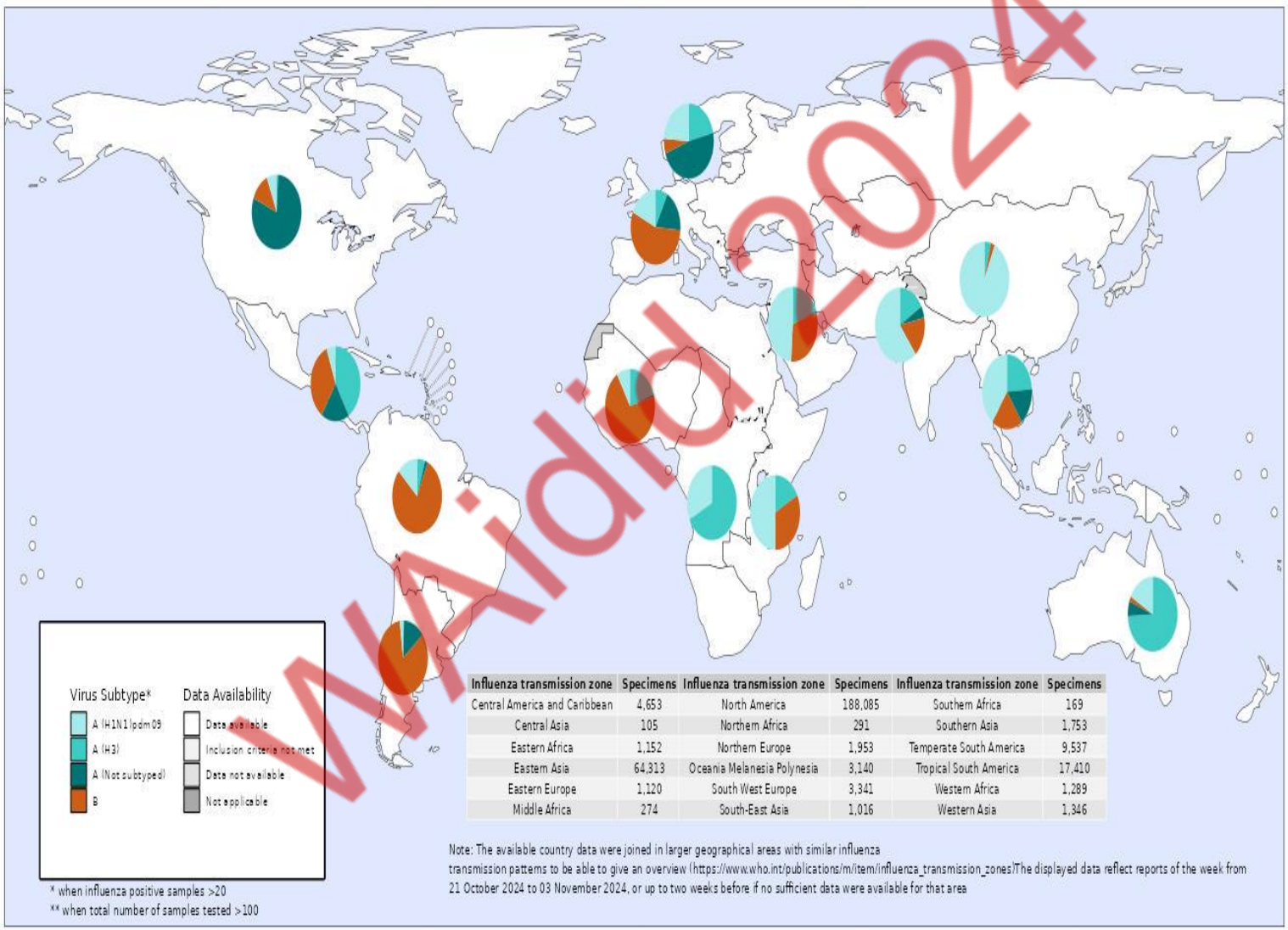
Types of influenza vaccine

	Quadrivalent vs trivalent*	Route	Approved age group	Comments
Inactivated	Quadrivalent or trivalent	Intramuscular	≥6 months	Contains 15 µg of each haemagglutinin
Inactivated: intradermal	Quadrivalent	Intradermal	18–64 years	Contains 9 µg of each haemagglutinin
Inactivated: derived from cell culture	Trivalent	Intramuscular	≥18 years	Contains 15 µg of each haemagglutinin; contains egg protein; manufacturing does not rely on eggs
Inactivated: high dose	Trivalent	Intramuscular	≥65 years	Contains 60 µg of each haemagglutinin
Live attenuated†	Quadrivalent	Intranasal	2–49 years	Cold adapted; uses a master donor virus plus the haemagglutinin and neuraminidase of the circulating viruses; generates a broader immune response (T-cell, mucosal); not approved for use in immunocompromised patients or pregnant women
Recombinant	Trivalent	Intramuscular	≥18 years	Made with recombinant DNA technology to produce full-length haemagglutinin; shorter manufacturing time than for egg-derived or cell-culture-derived vaccines; can be used in individuals with egg allergy

*Trivalent vaccines contain antigens from the circulating H1N1 and H3N2 influenza A viruses and the dominant influenza B virus circulating at the time of vaccine strain selection. Quadrivalent vaccines contain antigens from the circulating H1N1 and H3N2 influenza A viruses and both lineages of influenza B. †Live attenuated vaccine not recommended by the US Advisory Committee on Immunization Practices for the 2016–17 season; this table represents the 2015–16 influenza season.

Paules C, Subbarao K. Lancet. 2017

Global Influenza epidemiolgy , by virus type and subtype 2024



Influenza transmission zone	Specimens	Influenza transmission zone	Specimens	Influenza transmission zone	Specimens
Central America and Caribbean	4,653	North America	188,085	Southern Africa	169
Central Asia	105	Northern Africa	291	Southern Asia	1,753
Eastern Africa	1,152	Northern Europe	1,953	Temperate South America	9,537
Eastern Asia	64,313	Oceania Melanesia Polynesia	3,140	Tropical South America	17,410
Eastern Europe	1,120	South West Europe	3,341	Western Africa	1,289
Middle Africa	274	South-East Asia	1,016	Western Asia	1,346

Note: The available country data were joined in larger geographical areas with similar influenza transmission patterns to be able to give an overview (https://www.who.int/publications/m/item/influenza_transmission_zones)The displayed data reflect reports of the week from 21 October 2024 to 03 November 2024, or up to two weeks before if no sufficient data were available for that area

https://www.who.int/publications

VAXIGRIP TETRA & EFLUELDA TETRA Recommended Composition 2024-2025

- an A/Victoria/4897/2022 (H1N1)pdm09-like virus
- an A/Thailand/8/2022 (H3N2)-like virus
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus
- a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

https://www.who.int/publications/m/item/recommended-composition-of-influenza-virus-vaccines-for-use-in-the-2024-2025-northern-hemisphere-influenza-season

Influenza B Yamagata has disappeared

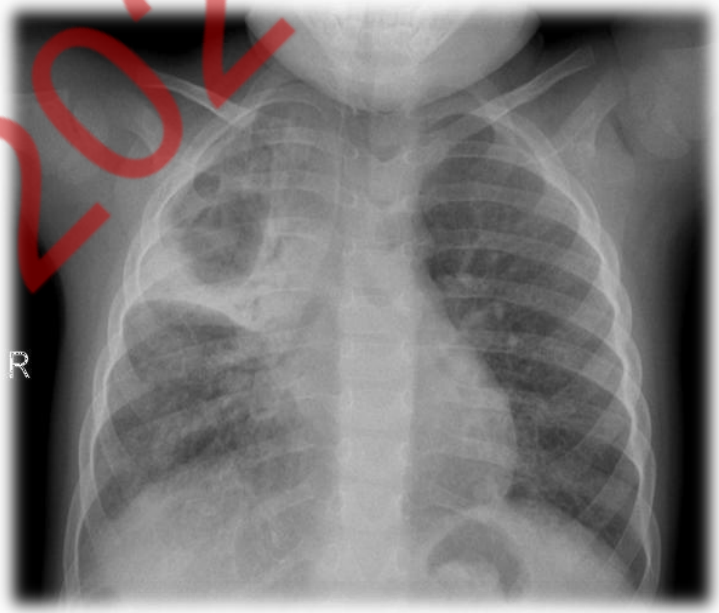
According to data from the Global Initiative on Sharing All Influenza Data (GISAID) and FluNet , **there has been no confirmed detection of the naturally occurring B/Yamagata virus since March 2020 .**

Live virus vaccines containing the B/Yamagata antigen **could pose a remote risk of the lineage being reintroduced into humans via reassortment of B/Yamagata vaccine strain with wild type B/Victoria strain.**

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

https://www.ema.europa.eu/en/documents

Flu Vaccine effectiveness (VE)



AMERICA - UNITED STATES

Interim Estimates of 2023–24 Seasonal Influenza Vaccine Effectiveness — United States

Aaron M. Frutos, PhD[1,2]; Ashley M. Price, MPH[1]; Elizabeth Harker, MPH[1]; Emily L. Reeves, MPH[1]; Haris M. Ahmad, MPH[1]; Vel Murugan, PhD[3]; Emily T. Martin, PhD[4]; Stacey House, MD, PhD[5]; Elie A. Saade, MD[6]; Richard K. Zimmerman, MD[7]; Manjusha Gaglani, MBBS[8,9,10]; Karen J. Wernli, PhD[11,12]; Emmanuel B. Walter, MD[13]; Marian G. Michaels, MD[7,14]; Mary A. Staat, MD[15,16]; Geoffrey A. Weinberg, MD[17]; Rangaraj Selvarangan, PhD[18,19]; Julie A. Boom, MD[20,21]; Eileen J. Klein, MD[22]; Natasha B. Halasa, MD[23]; Adit A. Ginde, MD[24]; Kevin W. Gibbs, MD[25]; Yuwei Zhu, MD[23]; Wesley H. Self, MD[23]; Sara Y. Tartof, PhD[12,26]; Nicola P. Klein, MD, PhD[27]; Kristin Dascomb, MD, PhD[28]; Malini B. DeSilva, MD[29]; Zachary A. Weber, PhD[30]; Duck-Hye Yang, PhD[30]; Sarah W. Ball, ScD[30]; Diya Surie, MD[31]; Jennifer DeCuir, MD, PhD[31]; Fatimah S. Dawood, MD[31]; Heidi L. Moline, MD[31]; Ariana P. Toepfer, MPH[31]; Benjamin R. Clopper, MPH[31]; Ruth Link-Gelles, PhD[31]; Amanda B. Payne, PhD[31]; Jessie R. Chung, MPH[1]; Brendan Flannery, PhD[1]; Nathaniel M. Lewis, PhD[1]; Samantha M. Olson, MPH[1]; Katherine Adams, MPH[1]; Mark W. Tenforde, MD, PhD[1]; Shikha Garg, MD[1]; Lisa A. Grohskopf, MD[1]; Carrie Reed, DSc[1]; Sascha Ellington, PhD[1]; CDC Influenza Vaccine Effectiveness Collaborators

Vaccine effectiveness against influenza-associated outpatient visits ranged from **59% to 67%** and against influenza-associated hospitalization ranged from **52% to 61%**

MMWR Morb Mortal Wkly Rep. 2024

Effects of Influenza Vaccination in the United States During the 2017–2018 Influenza Season

Melissa A. Rolfes,[1] Brendan Flannery,[1] Jessie R. Chung,[1] Alissa O'Halloran,[1] Shikha Garg,[1] Edward A. Belongia,[2] Manjusha Gaglani,[3] Richard K. Zimmerman,[4] Michael L. Jackson,[5] Arnold S. Monto,[6] Nisha B. Alden,[7] Evan Anderson,[8] Nancy M. Bennett,[9] Laurie Billing,[10] Seth Eckel,[11] Pam Daily Kirley,[12] Ruth Lynfield,[13] Maya L. Monroe,[14] Melanie Spencer,[15] Nancy Spina,[16] H. Keipp Talbot,[17] Ann Thomas,[18] Salina M. Torres,[19] Kimberly Yousey-Hindes,[20] James A. Singleton,[21] Manish Patel,[1] Carrie Reed,[1] and Alicia M. Fry[1]; for the US Influenza Vaccine Effectiveness (Flu VE) Network, the Influenza Hospitalization Surveillance Network, and the Assessment Branch, Immunization Services Division, Centers for Disease Control and Prevention

Vaccination prevented 10% of expected hospitalizations overall and 41% among young children (6 months–4 years)

Clin Infect Dis. 2019

Flu-Related VE by Age Group
(medical Visits, Hospitalizations, and Deaths)
2021-2022 Flu Season

	Influenza Vaccine		Symptomatic Illnesses		Medical Visits		Hospitalizations		Deaths	
Age group	Vaccine Coverage (%)	Adjusted VE (95% CI)	Estimate	95% UI	Estimate	95% UI	Estimate	95% UI	Estimate	95% UI
Influenza, all flu										
6 months-4 years	66.70%	77% (44, 91)	637,997	(240,883, 986,380)	427,458	(160,369, 660,943)	4,448	(1,679, 6,877)	0	(0, 0)
5-17 years	55.10%	32% (0, 53)	503,624	(835, 1,019,025)	261,884	(426, 532,732)	1,381	(2, 2,794)	0	(0, 0)
18-49 years	37.10%	32% (3, 52)	450,338	(24,603, 834,274)	166,625	(8,883, 309,046)	2,528	(138, 4,683)	12	(0, 37)
50-64 years	52.40%	8% (-86, 54)	58,873	(0, 525,764)	25,315	(0, 226,757)	624	(0, 5,576)	30	(0, 255)
65+ years	73.90%	32% (-79, 74)	152,716	(0, 573,968)	85,521	(0, 322,427)	13,883	(0, 52,179)	1,081	(0, 7,651)
All ages		36% (20, 49)	1,803,547	(1,052,143, 2,797,749)	966,803	(566,407, 1,472,052)	22,864	(6,544, 62,321)	1,122	(0, 7,790)

https://www.cdc.gov/flu-burden/php/data-vis-vac/2021-2022-prevented.html

Flu-Related VE by Age Group
(medical Visits, Hospitalizations, and Deaths)
2022-2023 Flu Season

			Symptomatic Illnesses		Medical Visits		Hospitalizations		Deaths	
Age group	Vaccine Coverage (%)	Adjusted VE (95% CI)	Estimate	95% UI	Estimate	95% UI	Estimate	95% UI	Estimate	95% UI
Influenza, all flu										
6 months-4 years	65.60%	53.6% (29.7, 70.7)	929,408	(381,274, 1,466,795)	622,704	(254,820, 982,169)	6,479	(2,658, 10,226)	63	(0, 108)
5-17 years	55.10%	45.2% (15.4, 63.4)	1,912,522	(561,523, 3,216,921)	994,512	(290,801, 1,673,209)	5,244	(1,540, 8,820)	53	(0, 151)
18-49 years	43.90%	50.2% (18, 66.1)	1,488,913	(505,456, 2,297,820)	550,898	(189,670, 856,078)	8,357	(2,837, 12,898)	134	(0, 309)
50-64 years	55.40%	47.3% (20.1, 65.2)	1,314,988	(480,874, 2,077,991)	565,445	(204,675, 899,908)	13,945	(5,100, 22,037)	947	(0, 1,839)
65+ years	69.70%	26.9% (9.54, 45.3)	340,168	(18,788, 664,899)	190,494	(10,509, 374,161)	30,924	(1,708, 60,445)	2,479	(0, 11,802)
All ages		46.1% (20.4, 63.6)	5,985,999	(4,051,721, 7,780,911)	2,924,052	(1,981,526, 3,831,442)	64,950	(34,744, 96,011)	3,676	(0, 12,942)

https://www.cdc.gov/flu-burden

Effectiveness against subtypes

Influenza season	Total Influenza cases	VE against A(H1N1) PDM09	VE against A(H3N2)	VE against Influenza B/Victoria
2022-2023	20,477 (six European studies, covering 16 countries)	All ages: 28-46% <18 yo: 49-77%	All ages: 2-44% <18 yo: 62-70%	All ages: >50% <18 yo:87-95%
2023-2024	1.885 (two European studies, covering 10 countries)	**Primary Care** All ages: 53% Among children: 85% **Hospital** All ages:44%	**Primary Care** All ages: 30% **Hospital** All ages:14%	

Kissling E, et al. Euro Surveill. 2023

Maurel M, er al.Euro Surveill.

LAIV4 effectiveness in primary care

2014/15 and 2018/19 seasons

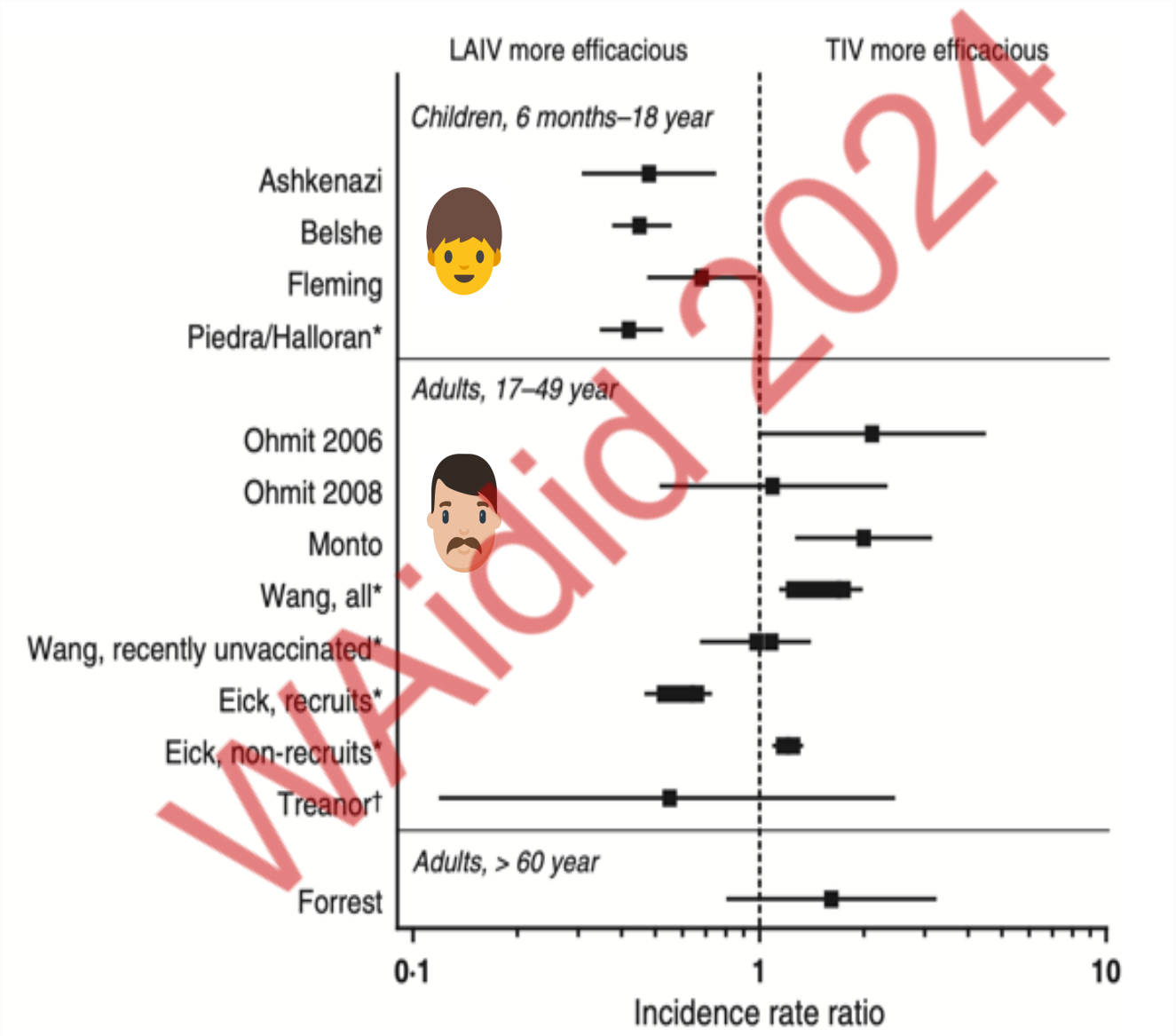
Year	A(H3N2)-adjusted VE (95% CI)	A(H1N1)pdm09-adjusted VE (95% CI)	B-adjusted VE (95% CI)	All-adjusted VE (95% CI)	Predominant circulating strain
2014/15 [70]	35.0 (−29.9 to 67.5)	Not available	100.0 (17.0–100.0)	Not available	A/H3N2
2015/16 [71]	Not available	41.5 (−8.5 to 68.5)	81.4 (39.6–94.3)	57.6 (25.1–76.0)	A/H1N1pdm09
2016/17 [72,73]	57.0 (7.7–80.0)	Not available	78.6 (−86.0 to 97.5)	65.8 (30.3–83.2)	A/H3N2
2017/18 [74,75]	−75.5 (−289.6 to 21.0)	90.3 (16.4–98.9)	60.8 (8.2–83.3)	26.9 (−32.6 to 59.7)	A/H3N2 and B
2018/19 [5]	27.1 (−130.5 to 77.0)	49.9 (−14.3 to 78.0)	Not available	48.6 (−4.4 to 74.7)[†]	A/H1N1pdm09

Interim 2023/2024 Season Influenza Vaccine Effectiveness in Primary and Secondary Care in the United Kingdom

Estimated vaccine effectiveness against all influenzas
63% to 65% (among children aged 2–17,
36% to 55% among adults 18–64
40% to 55% among adults aged 65 and over.

Kassianos G, et al . Vaccine. 2020 Aug
Influenza Other Respir Viruses 2024

The relative efficacy of trivalent live attenuated and inactivated influenza vaccines in children and adults



Ambrose CS *et al.* Influenza and Other Respir Viruses 2010

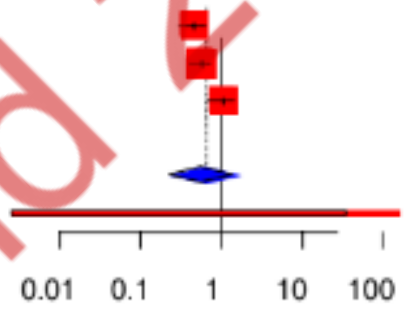
Comparing the incidence of confirmed influenza cases after influenza vaccination (all ages)

Garai., et al. Journal of Translational Medicine 2024

Comparing the incidence of confirmed influenza cases after influenza vaccination (children< 6 years)

Study	Nasal Events	Nasal Total	Injectable Events	Injectable Total	OR	OR	95%-CI	Weight
Ashkenazi et al. (2006)	29	1050	60	1035		0.46	[0.29; 0.73]	31.8%
Belshe et al. (2007)	53	4179	93	4172		0.56	[0.40; 0.79]	36.3%
Krishnan et al. (2021)	48	366	41	326		1.05	[0.67; 1.64]	32.0%
Random effects model		**5595**		**5533**		**0.65**	**[0.23; 1.83]**	**100.0%**
Prediction interval							**[0.00; 167.55]**	

Heterogeneity: I^2 = 72% [7%; 92%], τ^2 = 0.1325, p = 0.027
Test for overall effect: t_2 = -1.80 (p = 0.213)



Garai., et al. Journal of Translational Medicine 2024

Why current influenza vaccines do not have optimal effectiveness?

1. Mismatch of circulating and vaccine strains
2. Reduced immunogenicity of IIV
3. The potential effect of original antigenic sin (OAS)

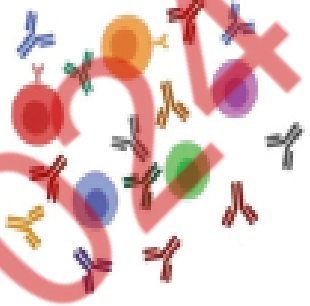
Influenza vaccine effectiveness, vaccine match, and strain prevalence by Northern Hemisphere influenza season and geographic region

Russell CA et al. Hum Vaccin Immunther 2024

Preexisting Immunity to influenza and response to infection and vaccination

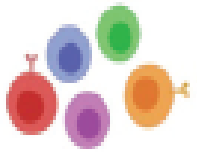
Influenza-naive infant

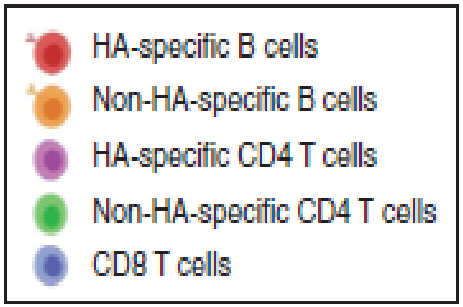
- Complex maternal antibody
- Naive CD4 and CD8 T-cell repertoire
- Developmentally immature immune system
- Circulating maternal Ab could impact immune response to infection



Influenza-naive toddler

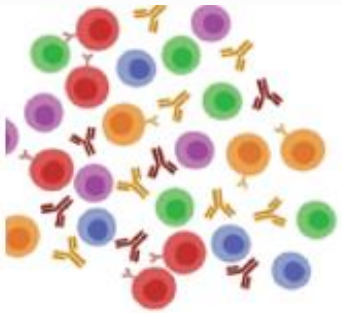
- Naive influenza-specific CD4, CD8, and B cells
- Little or no preexisting circulating antibody
- Prolonged duration of viral antigen





Postinfection

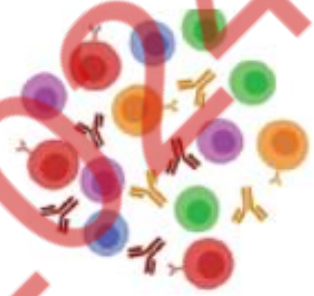
- Diverse CD4 and CD8 T-cell responses
- Diverse B-cell response and circulating Ab response, including stalk-reactive Ab



Nayak J.,et al. Cold Spring Harb Perspect Med. 2021

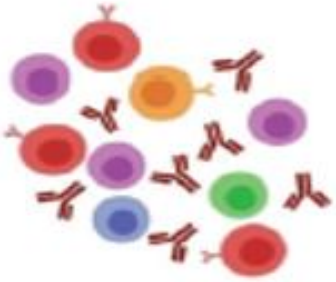
Toddler post-LAIV immunization

- Diverse memory CD4 and CD8 T-cell responses
- Diverse but limited abundance of B cells and circulating Ab



Infant/toddler post-IIV immunization

- HA-focused CD4 T-cell and B-cell response
- Circulating HA antibody
- Developmental status of the immune system depends on age at time of infection
- Preexisting HA-specific Ab may limit infection/duration of antigen presentation



Nayak J.,et al. Influenza in Children. Cold Spring Harb Perspect Med. 2021 4;11

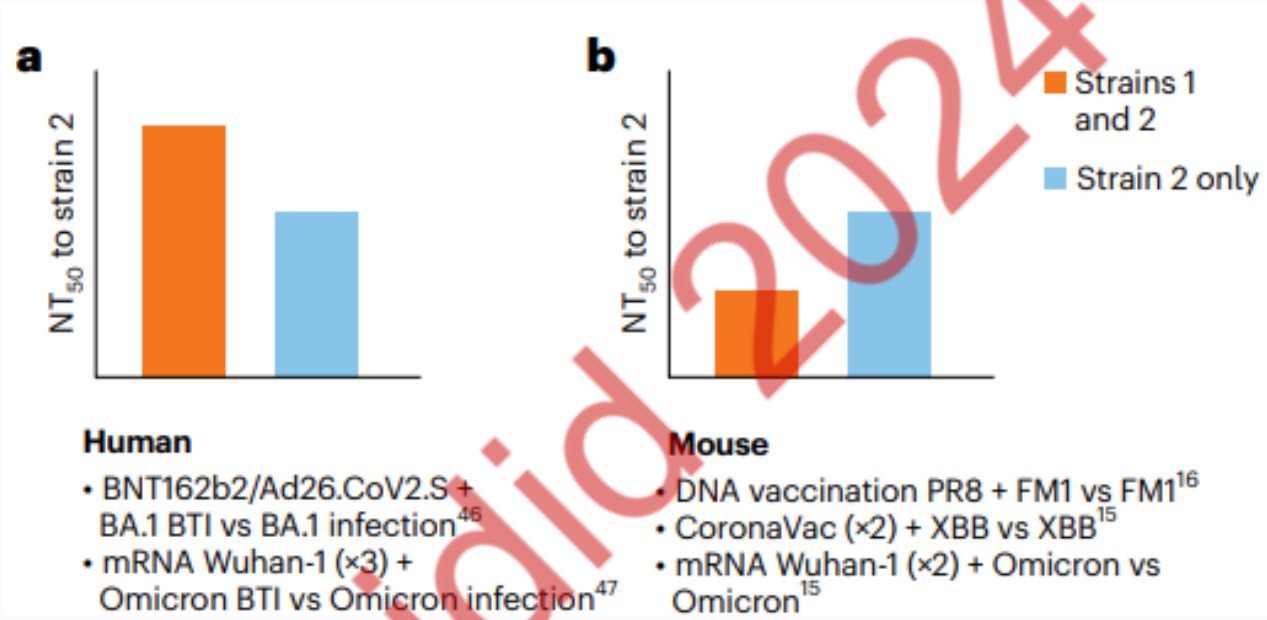
Original Antigenic Sin (OAS)

An immunological phenomenon where the immune system's response to a second encounter with a antigenically similar antigen is dominated by memory cells generated during the initial exposure, rather than generating a new response tailored to the new pathogen.

This effect can result in suboptimal immunity because the immune response is "biased" toward the original antigen and may not effectively neutralize the new variant of the pathogen.

OAS is often observed in infections with rapidly mutating viruses, such as influenza and COVID and can influence the effectiveness of vaccines targeting such pathogens.

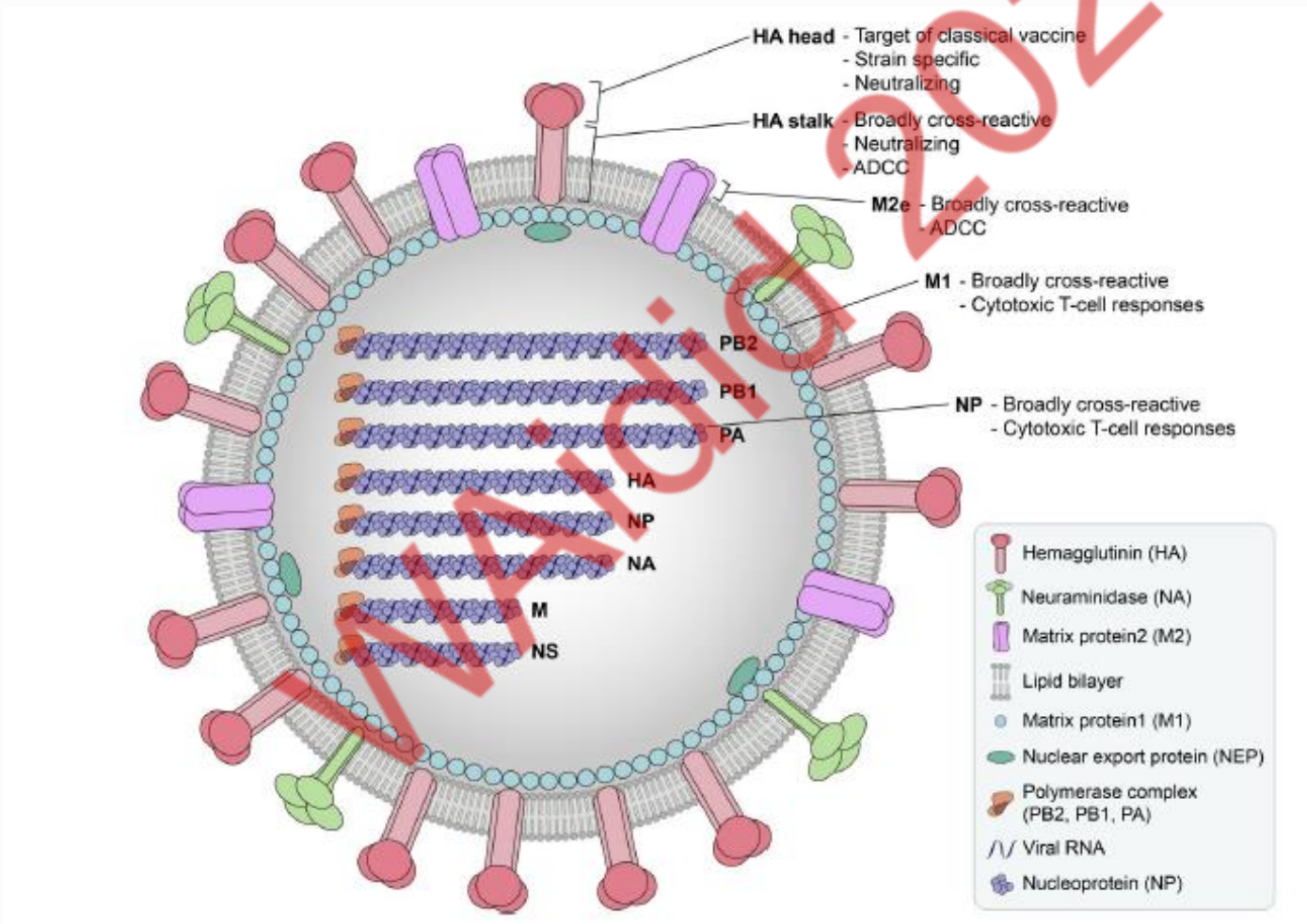
Prior exposures might increase or decrease total and/or neutralizing antibody responses after subsequent exposures



Cobey, S. *Nat Immunol* .2024

How to overcome OAS

Targeting Conserved Antigens



Kim YH, et al., Rev Med Virol. 2022

Strategies to develop new Influenza Vaccine

Next generation of non-egg-based influenza vaccines include:

- New manufacturing platforms
- Structure-based antigen design/computational biology
- Protein-based vaccines including recombinant technologie
- Nanoparticles
- Gene- and vector-based technologies
- Novel adjuvants
- New Epitopes for Rational Immunogen Design

The molecular definition of highly cross-reactive B cell epitopes can inform the design of vaccines for broad protection.

› Sci Rep. 2023 Sep 23;13(1):15911. doi: 10.1038/s41598-023-43003-2.

A computationally optimized broadly reactive hemagglutinin vaccine elicits neutralizing antibodies against influenza B viruses from both lineages

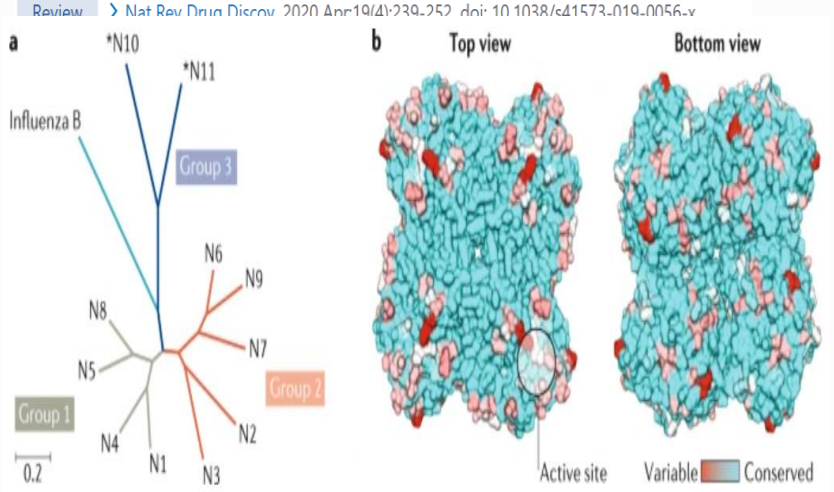
Michael A Carlock [1 2], Ted M Ross [3 4 5 6 7]

Review › Expert Rev Vaccines. 2019 Mar;18(3):269-280. doi: 10.1080/14760584.2019.1578216. Epub 2019 Feb 14.

Immunological basis for enhanced immunity of nanoparticle vaccines

Hannah G Kelly [1 2], Stephen J Kent [1 2 3], Adam K Wheatley [1 2]

Review › Nat Rev Drug Discov. 2020 Apr;19(4):239-252. doi: 10.1038/s41573-019-0056-x



Consensus criteria for a universal influenza vaccine

(Jang YH and Seong BL. Front Cell Infect Microbiol. 2019)

	NIAID	WHO	BMGF	Consensus
Breadth	All influenza A viruses (influenza B protection would be the second target)	All influenza A viruses	All influenza A and B viruses	All influenza A viruses
Efficacy	At least 75% effective against symptomatic influenza infection	Better than that of current seasonal influenza vaccine	At least 70% effective against symptomatic influenza infection	At least 70% effective
Target population	All age groups	>6 weeks, no upper age limit including high risk groups	>6 weeks, no upper age limit including high risk groups	>6 weeks, no upper age limit
Duration of protection	At least 1 year	At least 5 years	3–5 years	At least 1 year

Ideal universal Influenza vaccine would provide durable protection against circulating strains, seasonal and pre-pandemic

Immune responses to current vaccines focus on the haemagglutinin head domain, whereas next-generation vaccines target less variable virus structures, including the haemagglutinin stem

Country	Minimal age	Maximal age	Year of introduction
USA	6 months	18 years	
Finland	6 months	6 years	
Australia	6 months	5 years	
Austria	6 months	15 years	
UK	2 years	16 years	
Canada	6 months	5 years	2021
Irerand	2 years	12 years	2021
Spain	6 months	5 years	2021
Lettonia	6 months	17 years	2021 + 2022
Malta	6 months	5 years	2021
Estonia	6 months	7 years	2022
Greece	6 months	4 years	2024
Slovakia	6 months	3 years	-
Slovenia	6 months	2 years	-

Universal influenza vaccination

INFLUENZA VACCINATION COVERAGE

Country	Age group	Coverage
UK	2 years	55.2% (2022)
	3 years	57.8% (2022)
	4 – 11 years	61.9% (2021); 57.2% (2022); 48.0% (2023)
	12– 16 years	43.6% (2022)
Ireland	2 years – 4 years	59.7% (2017)
	2 years – 12 years	18.8% (2022)
	13 years – 17 years	11.6% (2022)
Finland	6 months – 3 years	42.9% (2021); 41.1% (2022)
	3 years – 6 years	34.7% (2021); 31.5% (2022)
USA	6 months – 4 years	75.2% (2020); 54.7% (2022); 60.6% (2023)
	5 months – 12 years	64.5% (2020); 50.3% (2022); 50.3% (2023)

Were we are now with vaccination of children against influenza

- Vaccinating children against influenza remains an essential public health measure
- Challenges persist, including the suboptimal effectiveness , the unresolved impact of original antigenic sin on vaccine performance.
- **The complexity of the immune response to influenza requires continued research for more broadly protective and durable vaccines**.

Where we are going..

- **Developing next-generation influenza vaccines**
- **Understanding the long-term effects of early immune priming,**
- **Enhancing public confidence and access** to vaccination to ensure the benefits of vaccination.