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Country: Netherlands

Affiliation: Amsterdam UMC

Function: Professor

Main expertise: Virus Evolution

Influenza: high-dose and adjuvanted vaccines

Disclosures

I have received advisory, consulting, and/or speaking fees from BioNTech, CSL Seqirus, GSK, Moderna, Pfizer, Roche, & Sanofi

Inzet van vernieuwde typen griepvaccins in het Nationaal Programma Griepppreventie

Aan: de staatssecretaris Jeugd, Preventie en Sport (VWS)
Nr. 2024/18, Den Haag, 17 december 2024

Tabel 1 Geadviseerde vaccins per doelgroep

Doelgroep	Vaccin
Risicogroepen van 6 maanden tot 18 jaar	Standaardvaccin
Zwangere vrouwen	Standaardvaccin
Risicogroepen van 18-50 jaar	Standaardvaccin of recombinant vaccin
Risicogroepen van 50-60 jaar	Vaccin met adjuvans
Mensen van ≥60 jaar	Vaccin met adjuvans of vaccin met verhoogde dosis antigeen

Many factors impact standard vaccine effectiveness

Patient Factors

Reduced immune response to the vaccine[1]

e.g. immunosenescence (declining immune function in the elderly)

Viral Factors

Potential for vaccine-virus mismatch[2]

e.g. antigenic drift (natural mutation in circulating flu strains)

Vaccine Factors

Potential for vaccine-virus mismatch[3]

e.g. egg-adaptation (changes introduced during egg-based manufacturing)

Utilisation Factors

e.g. lack of patient demand and/or provider recommendation leading to under-vaccination[4,5]

1. McElhaney JE. Aging Health. 2008;4(6):603-13. **2.** Ansaldi et al. Vaccine. 2010;s8:4123-29 **3.** Skowronski DM et al. PLoS One. 2014;9(3):e92153. **4.** Menzies RI et al. Med J Aust. 2017;206(6):238-239. **5.** Rao S et al. Hosp Pediatr. 2016;6(9):513-519.

There are a variety of avenues for improving influenza vaccine effectiveness

CURRENT	EMERGING		
			
Differentiated vaccines Adjuvanted, higher antigen dose, cell-based	**New platforms** mRNA, sa-mRNA, other protein-based vaccines	**Alternate routes** nasal, oral, skin	**Broader protection** viral vector universal, supraseasonal

Age-related changes in immune response can impact VE

Immunosenescence

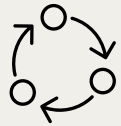
Innate immune cell† function
- Phagocytosis / antigen-processing & presentation

Adaptive immune cell function
- Naïve B & T cells
- Antibody production, diversity and affinity

- Memory T cells

Inflammaging

- Impairment of immune system regulation



- Pro-inflammatory cytokines

- Chronic inflammation / Metainflammation

Poor vaccination outcomes & increased susceptibility to infection[1,2]

Figure adapted from Santoro A, et al. *Ageing Res Rev.* 2021;71:101422. †Cells include neutrophils, natural killer cells, macrophages and dendritic cells.

1. Santoro A, et al. *Ageing Res Rev.* 2021;71:101422. **2.** Crooke SN, et al. Immun Ageing. 2019;16:25;

Adjuvanted and higher dose vaccines have been designed to boost immune response

Challenge: Lower immune response to standard dose influenza vaccine

Strategy 1: Enhance the immune response to a vaccine by adding an adjuvant

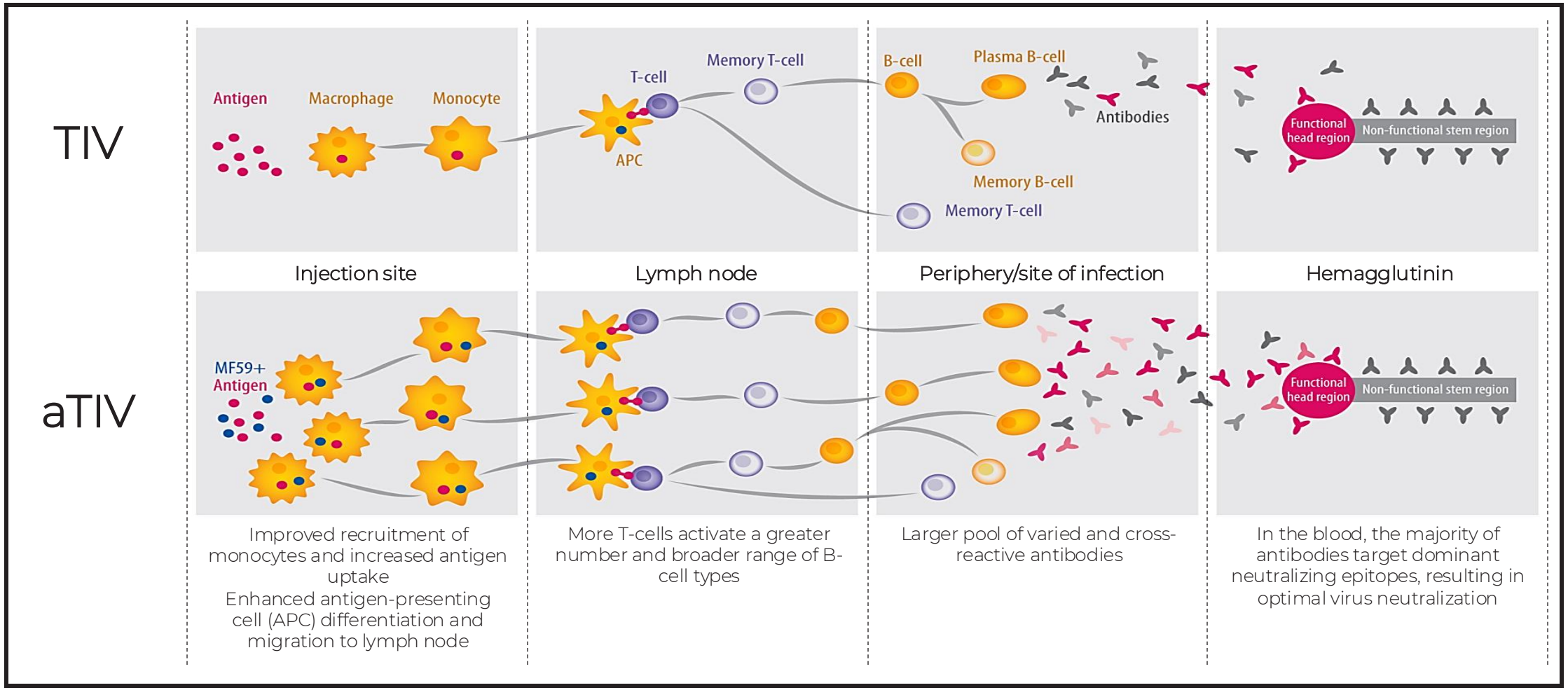
Adjuvanted vaccine
- Contain 15 µg of haemagglutinin per strain per dose PLUS an MF59 adjuvant

Strategy 2: Increasing the amount of antigen in a vaccine

Higher antigen dose vaccine
- Contain 60 µg of haemagglutinin per strain per dose with no adjuvant

MF59-adjuvanted vaccines are designed to improve the magnitude, persistence, and breadth of the immune response[1-7]

MOA for MF59 Adjuvant (Compared to TIV)



1. Siegrist CA in Plotkin SA *et al.* Vaccines. 5th Edition. 2008. 2. O'Hagan DT. *Expert Rev Vaccines* 2007; 6:699–710. 3. Mosca F, *et al. Proc Natl Acad Sci U S A* 2008; 105:10501–10506. 4. Calabro S, *et al. Vaccine* 2011; 29:1812–1823. 5. Khurana S, *et al. Sci Transl Med* 2011; 3:85ra48. 6. O'Hagan DT. *Expert Rev Vaccines* 2011; 10:447–462. 7. Seubert A, *et al. J Immumol* 2008; 180:5402–5412.

Advantages of adjuvant and high-dose vaccines

Strengthen
Improve the magnitude of antibody response[1-3]

Broaden
Adjuvanted vaccines induce higher antibody response against heterologous strains, especially A/H3N2[4]

Lengthen
Provides protection throughout the season[1-3]

1. Tregoning JS *et al.* Ajuvanted influenza vaccines *Hum Vaccine* Immunother 2018; 14(3):550-564. 2. Australian Technical Advisory Group on Immunisation (ATAGI). Australian Immunisation Handbook, Australian Government Department of Health and Aged Care, Canberra, 2022, immunisationhandbook.health.gov.au.[Accessed August 2024]. 3. Centres for Disease Control and Prevention. Fluzone High-Dose Seasonal Influenza Vaccine. Available at: https://www.cdc.gov/flu/prevent/qa_fluzone.htm [Accessed August 2024]. 4. Youhanna J *et al. Influenza and other respiratory viruses* 2024; 18:e13286.

RCT study of high-dose vs standard-dose vaccines

Variable	Laboratory-Confirmed Influenza†		
	IIV3-HD (N=15,990)	IIV3-SD (N=15,993)	Relative Efficacy (95% CI)
	no. (%)		%
Protocol-defined influenza-like illness	228 (1.4)	301 (1.9)	24.2 (9.7 to 36.5)‡
Influenza A	190 (1.2)	250 (1.6)	24.0 (7.8 to 37.4)
A/H1N1	8 (<0.1)	9 (0.1)	11.1 (–159.6 to 70.2)
A/H3N2	171 (1.1)	223 (1.4)	23.3 (6.0 to 37.5)
Influenza B	38 (0.2)	51 (0.3)	25.5 (–15.7 to 52.4)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults

Carlos A. DiazGranados, M.D., Andrew J. Dunning, Ph.D., Murray Kimmel, D.O., Daniel Kirby, B.Sc., John Treanor, M.D., Avi Collins, B.Sc.N., Richard Pollak, D.P.M., Janet Christoff, R.N., John Earl, M.D., Victoria Landolfi, M.Sc., M.B.A., Earl Martin, D.O., Sanjay Gurunathan, M.D., Richard Nathan, D.O., David P. Greenberg, M.D., Nadia G. Tornieporth, M.D., Michael D. Decker, M.D., M.P.H., and H. Keipp Talbot, M.D., M.P.H.

N=~30,000

Retrospective cohort study of high-dose vs standard-dose vaccines

Table 2
Relative vaccine effectiveness and sensitivity analysis against influenza hospitalizations

Vaccine group	Hospitalization rate per 100 000 person years (95% CI)	IRR HD-QIV vs. SD-QIV (95% CI)	rVE (95% CI)	p value
HD-QIV	69.47 (59.64–80.92)	0.77 [0.64–0.92]	23.29 [8.38–35.77]	0.003
SD-QIV	90.53 (84.68–96.78)			
Sensitivity analysis including influenza hospitalizations with a COVID-19 code				
HD-QIV	70.31 (60.42–81.83)	0.76 [0.64–0.91]	23.61 [8.88–35.96]	0.003
SD-QIV	92.00 (86.10–98.29)			
Sensitivity analysis during the peak of the season				
HD-QIV	52.63 (44.17–62.71)	0.73 [0.59–0.89]	27.38 [11.05–40.70]	0.002
SD-QIV	72.36 (67.15–77.97)			

HD, high-dose; QIV, quadrivalent influenza vaccine; rVE, relative vaccine effectiveness; SD, standard dose.

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

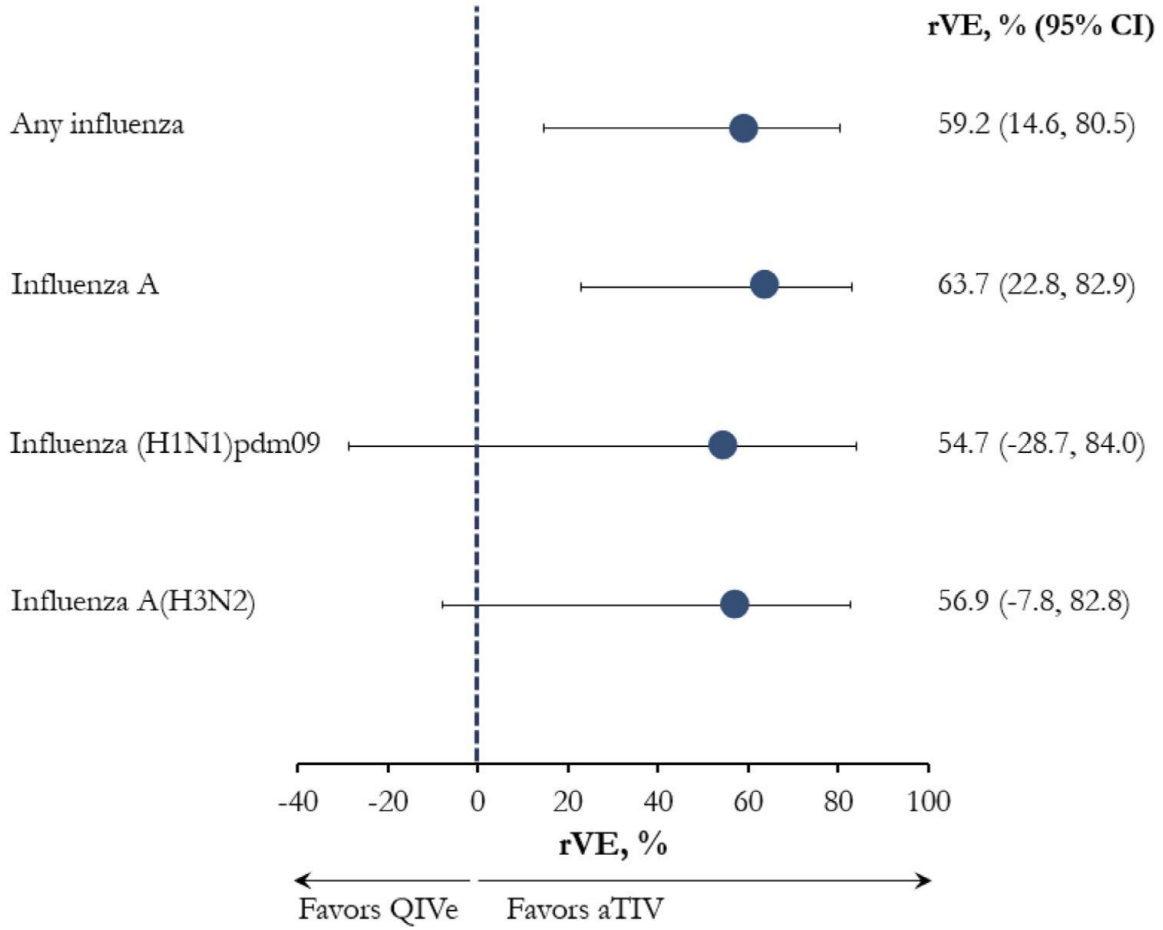
Original article

The relative effectiveness of a high-dose quadrivalent influenza vaccine versus standard-dose quadrivalent influenza vaccines in older adults in France: a retrospective cohort study during the 2021–2022 influenza season

Hélène Bricout [1,*], Marie-Cécile Levant [1], Nada Assi [2], Pascal Crépey [3], Alexandre Descamps [4], Karine Mari [5], Jacques Gaillat [6], Gaétan Gavazzi [7,8], Benjamin Grenier [2], Odile Launay [4], Anne Mosnier [9], Fanny Raguideau [2], Laurence Watier [10], Rebecca C. Harris [11], Ayman Chit [1,12]

N=~2,000,000

Test negative case control study of adjuvanted vs standard-dose vaccines



Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Relative effectiveness of the adjuvanted vs non-adjuvanted seasonal influenza vaccines against severe laboratory-confirmed influenza among hospitalized Italian older adults

Alexander Domnich[1,*], Donatella Panatto[2,3], Elena Pariani[3,4], Christian Napoli[5], Maria Chironna[6], Ilaria Manini[3,7], Caterina Rizzo[8], Andrea Orsi[1,2,3], Giancarlo Icardi[1,2,3], on behalf of the IT-BIVE-HOSP Network Study Group

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[7] Department of Molecular and Developmental Medicine, University of Siena, Siena, Italy
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N=512

Systematic review of VE in older adults

Received: 10 June 2024 | Accepted: 3 July 2024
DOI: 10.1111/jgs.19176

REVIEW ARTICLE

Journal of the American Geriatrics Society

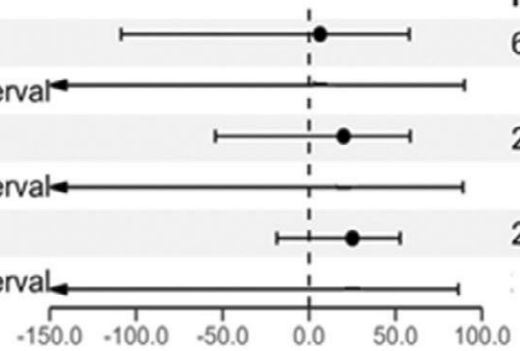
Protection against influenza hospitalizations from enhanced influenza vaccines among older adults: A systematic review and network meta-analysis

J. M. Ferdinands PhD, MSc[1] | L. H. Blanton MPH[1] | E. Alyanak MPH[1] | J. R. Chung MPH[1] | L. Trujillo MPH[1] | J. Taliano MA, MLS[2] | R. L. Morgan PhD, MPH[3,4] | A. M. Fry MD, MPH[1] | L. A. Grohskopf MD, MPH[1]

RCT

(A)

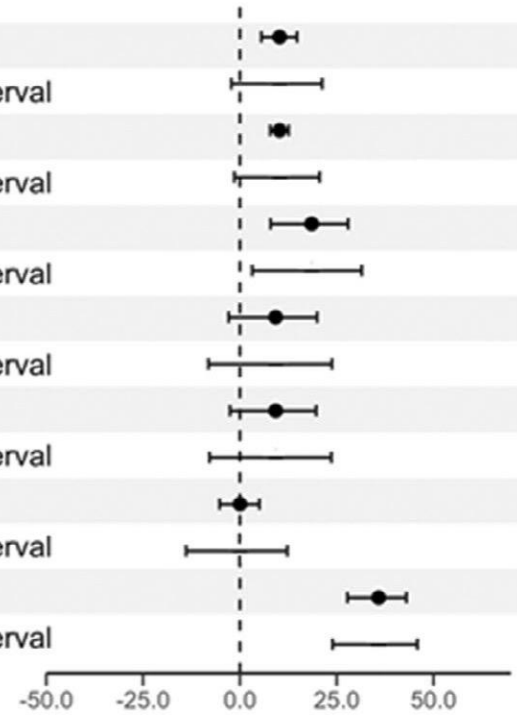
Vaccine	Comparator	Estimate	Relative VE (95% CI)
HD	ADJ	mean	6.3 (-108.7 to 58.0)
		prediction interval	(-772.7 to 89.9)
ADJ	SD	mean	20.0 (-54.2 to 58.5)
		prediction interval	(-485.9 to 89.1)
HD	SD	mean	25.1 (-18.6 to 52.7)
		prediction interval	(-312.0 to 86.4)



RWE

(B)

Vaccine	Comparator	Estimate	Relative VE (95% CI)
ADJ	SD	mean	10.3 (5.5 to 14.7)
		prediction interval	(-2.2 to 21.2)
HD	SD	mean	10.2 (7.8 to 12.6)
		prediction interval	(-1.4 to 20.6)
RIV	SD	mean	18.5 (7.9 to 27.9)
		prediction interval	(3.2 to 31.5)
RIV	ADJ	mean	9.2 (-2.9 to 19.9)
		prediction interval	(-8.1 to 23.8)
RIV	HD	mean	9.2 (-2.6 to 19.7)
		prediction interval	(-7.9 to 23.6)
ADJ	HD	mean	0.0 (-5.3 to 5.0)
		prediction interval	(-13.9 to 12.2)
SD	No vaccine	mean	35.8 (27.8 to 43.0)
		prediction interval	(24.0 to 45.8)



Reactogenicity of high-dose, adjuvanted, and standard-dose vaccines

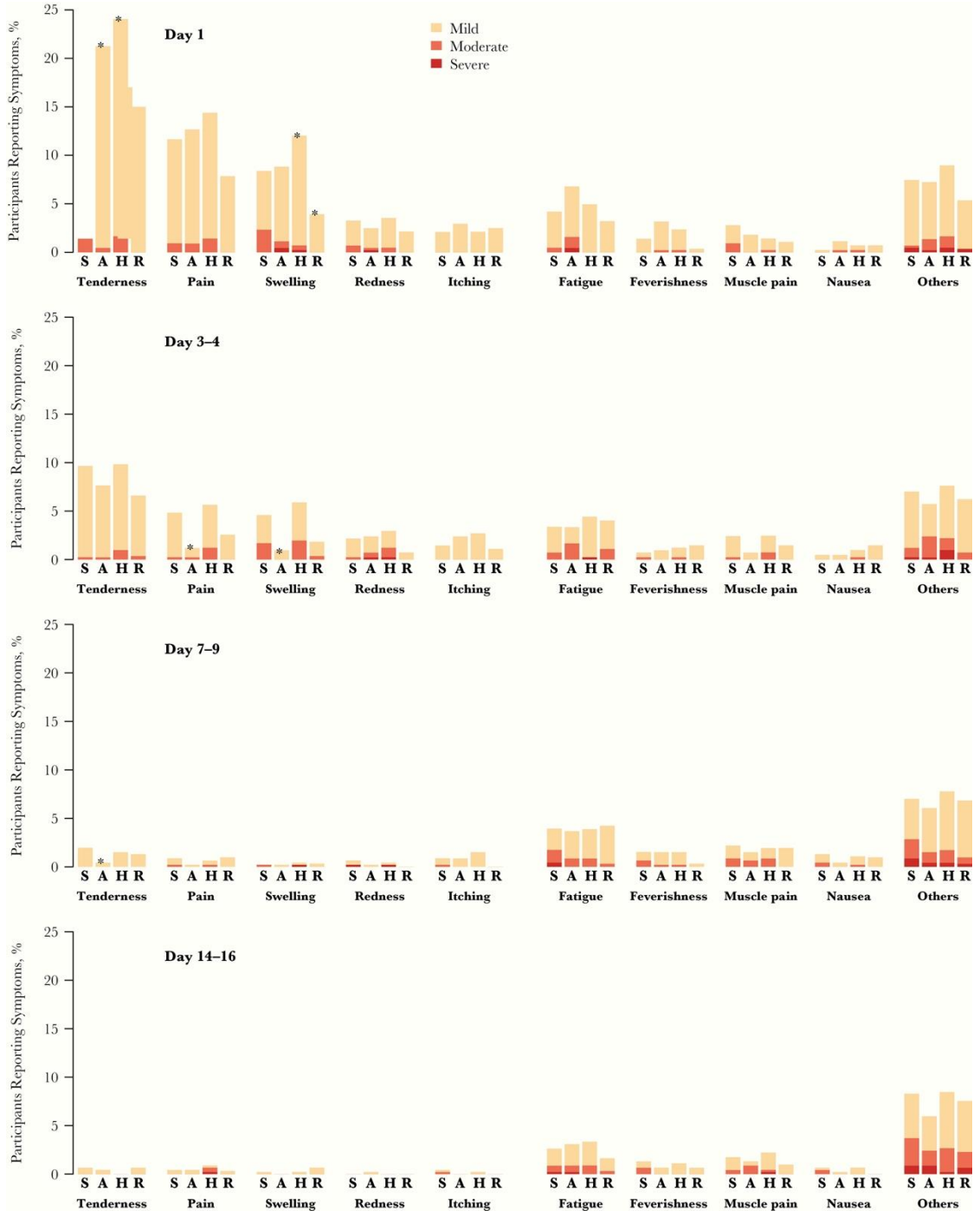
The Journal of Infectious Diseases

MAJOR ARTICLE

Comparative Reactogenicity of Enhanced Influenza Vaccines in Older Adults

Benjamin J. Cowling,[1] Mark G. Thompson,[2] Tiffany W. Y. Ng,[1] Vicky J. Fang,[1] Ranawaka A. P. M. Perera,[1] Nancy H. L. Leung,[1] Yuyun Chen,[1] Hau Chi So,[1] Dennis K. M. Ip,[1] and A. Danielle Iuliano[2]

[1]World Health Organization Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, The University of Hong Kong, Hong Kong Special Administrative Region, China; [2]Influenza Division, Centers for Disease Control and Prevention, Atlanta, Georgia, USA



Benefits of vaccinations

DECEMBER 13, 2023

Flu Burden Prevented from Vaccination 2022-2023 Flu Season

WHAT TO KNOW

This web page provides estimates on the burden of influenza (flu) and the effects of annual flu vaccination in the United States for the 2022–2023 season.

CDC estimates that during the 2022-2023 season, flu vaccination prevented **6.0 million** flu-related illnesses, **2.9 million** medical visits, **65,000** hospitalizations, and **3,700** deaths.

https://www.cdc.gov/flu-burden/php/data-vis-vac/2022-2023-prevented.html