Optimizing Influenza Protection in Older Adult: Evidence and Clinical Impact of High-Dose Influenza Vaccine

ศ. นพ.ธีระพงษ์ ตัณฑวิเชียร MD., FRCP(Edin)
ผู้อำนวยการศูนย์วิจัยโรคเอดส์และโรคติดเชื้อ (AIDSID) สภากาชาดไทย
ผู้ช่วยผู้อำนวยการ สถานเสาวภา สภากาชาดไทย
Committee, Board of Directors, Asia Pacific Alliance for the Control of Influenza (APACI)

MAT-TH-2500687-V1.0-10/2025

Disclosure (2019 – 2026)

Prof. Terapong Tantawichien: has received support for

- Travel for International Conference (Bionet, Siam Pharm)
- Lectureships (GlaxoSmithKline, Pfizer, MSD, Roche, Thai Meiji, Siam Pharm, Sanofi , Biovalys, Biogenetec……).
- Advisory board for zoster vaccine/pneumococcal vaccine (MSD),rabies vaccine (GSK), dengue vaccines (Sanofi, MSD, Takeda), influenza vaccine(Sanofi)

Prof. Terapong Tantawichien: has received research funds from

- MPH, Thailand (shorten rabies PET) 2019-2020
- NSTDA Thailand/Bionet (Asia)-Spearhead project (Tdap: recombinant pertussis toxin)-2019-2024)
- Sanofi (Rabies vaccine:VRV-12) 2020-2021
- Sanofi (Rabies vaccine: VRV-14) 2020-2021
- Baiya /NVI Thailand (Covid-19 vaccine phase I) 2021-2023
- Sanofi (Yellow fever vaccine) 2021-2025
- Jansen (RSV vaccine) 2021-2023
- Baiya/National Vaccine Institute Thailand (Covid-19 vaccine phase IIa) 2023-2024
- Chulalongkorn University (Covid-19 mRNA vaccine phase II) 2023-2024
- Jansen (*E.coli* vaccine phase III) 2023-2025
- Bionet Asia (Pertussis vaccine safety) 2025

Optimizing Influenza Protection in Older Adult: Evidence and Clinical Impact of High-Dose Influenza Vaccine

Outlines

- Better Vaccine for Elderly Population
- Update on Clinical Evidence Supporting High-Dose Influenza Vaccines for Older Adults- Flunity HD Study
- Current HD Influenza Vaccination Recommendations for Elderly

Immunosenescence and Inflammaging in Ageing population

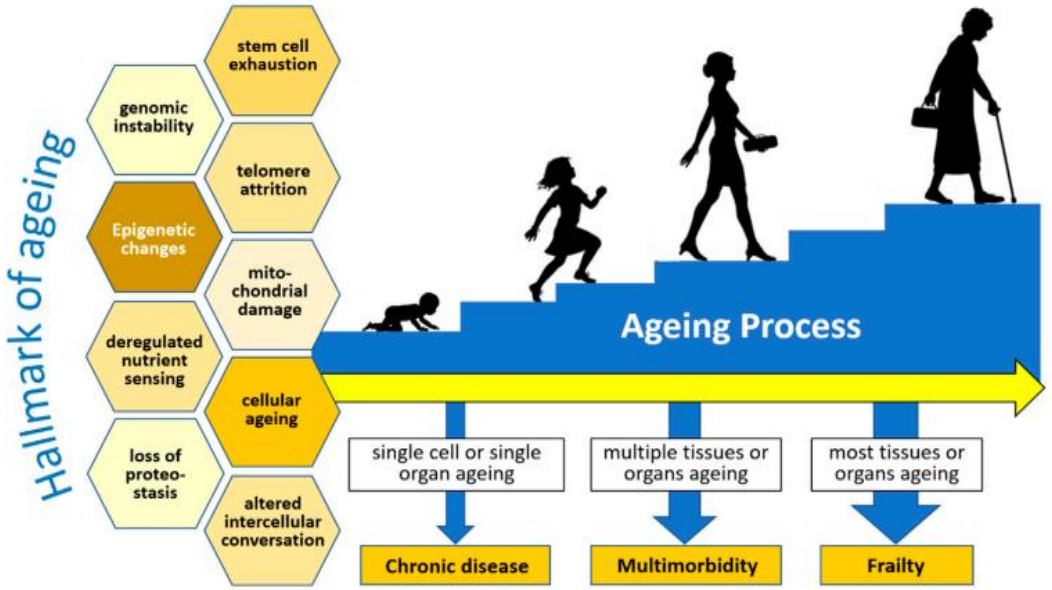


Figure 1. The multisystem aging process and frailty. Redrawn and adapted from Thillainadesan, J., et al

Gatot Soegiarto; Pathophysiology 2023, 30, 155–173.

Cell-mediated response/changes in lymphocyte subpopulation,senescencs T cell – reduced functional capacity

Misplaced and misfolded (apoptosis) self-molecules from damaged cells

Chronic activation of innate immune system

Inflam-aging or low-grade pro-inflammatory status

Older adults are the most vulnerable to severe outcomes from influenza infection

Aging ***Leads to…***

- **Immunosenescence**
- **Underlying conditions**
- **Frailty**

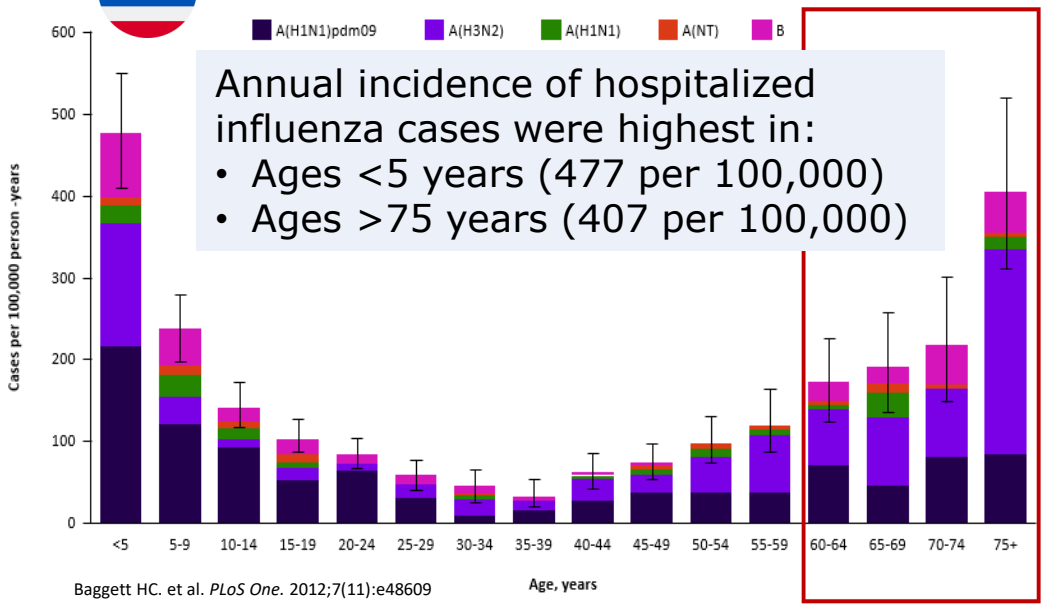
→ **Vulnerable population**

- **Increased Hospitalization** **10X** greater among aged ≥65[7,8]
- **Reduced autonomy** **23%** experience **loss of independence**[9]
- **Increased Mortality** **6x** greater among those aged ≥65[6]

Gatot Soegiarto; Pathophysiology 2023, 30, 155–173.

Gomez Rial J at el., Hum Vaccin Immunother. 2026 Dec;22(1):2624234

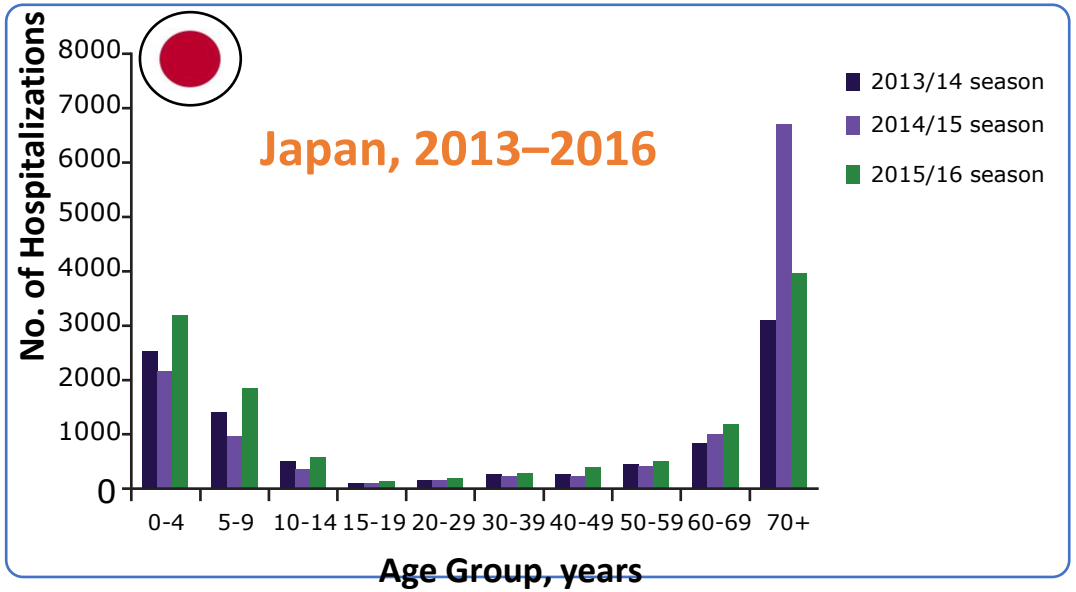
Influenza Associated Hospitalization



Annual incidence of hospitalized influenza cases were highest in:

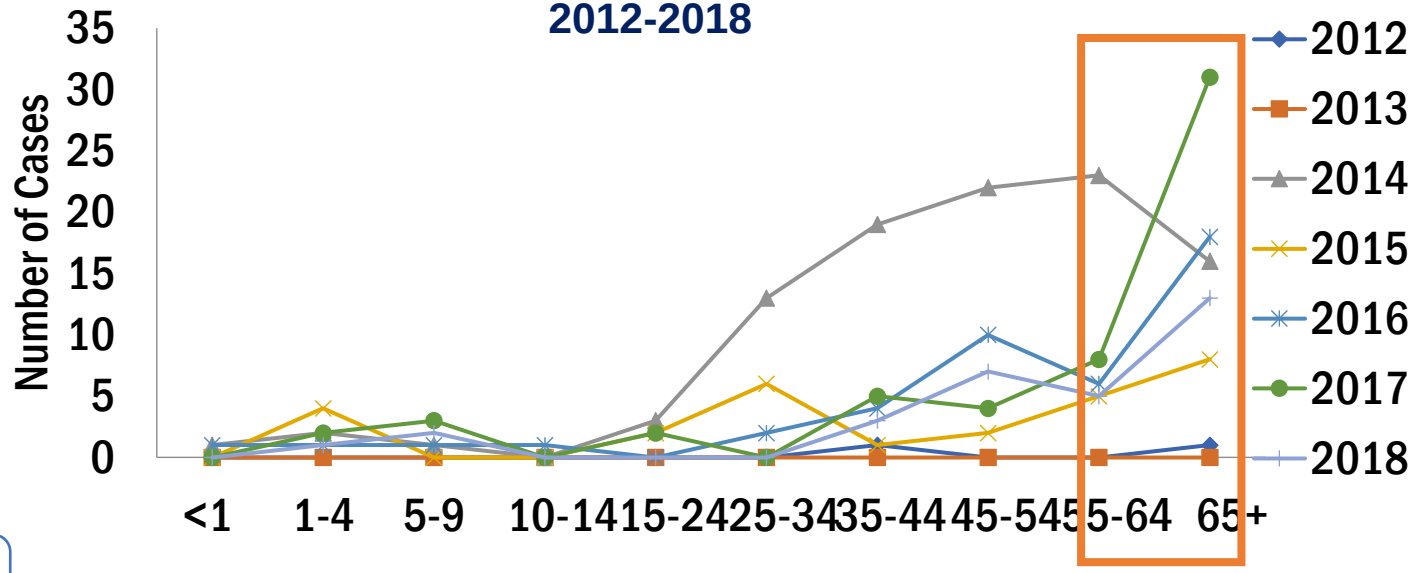
- Ages <5 years (477 per 100,000)
- Ages >75 years (407 per 100,000)

Baggett HC. et al. *PLoS One.* 2012;7(11):e48609



Cooper BS. et al. *Am J Epidemiol.* 2015;181(11):898-907

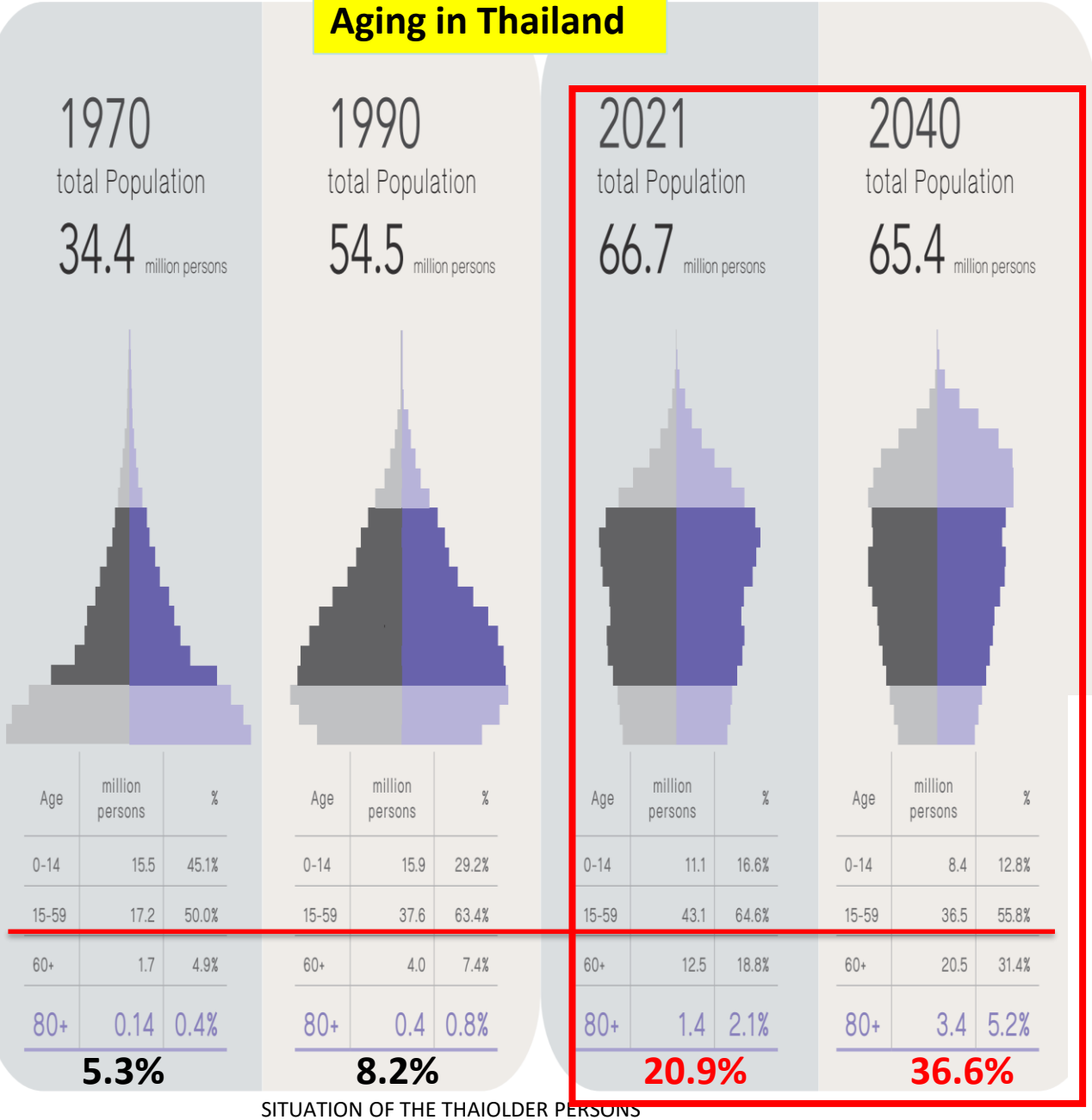
Mortality rate of influenza by age group, 2012-2018



An estimated 6.1 (95% CrI: 0.5, 12.4) annual deaths per 100,000 population were attributable to influenza A and B, predominantly in those aged ≥60 years[1]

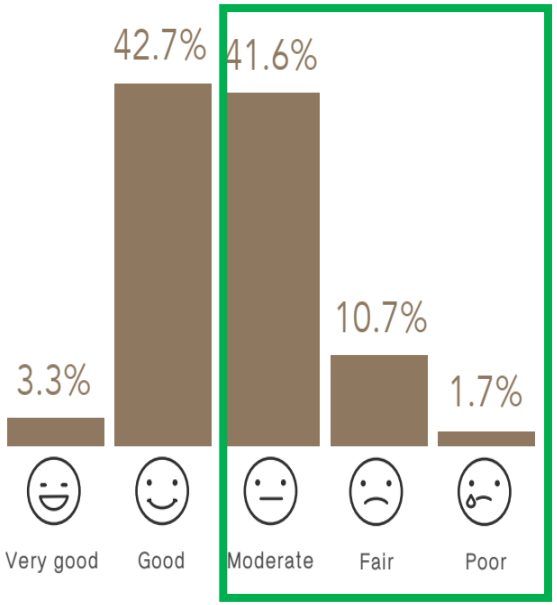
Reference: **1**. NIID and MHLW. Influenza 2015/16 season. http://www.nih.go.jp/niid/images/idsc/disease/influ/fludoco1516.pdf. Accessed October 21, 2022 **2**. Ng Y et al. Influenza Other Respir Viruses. 2019;13(6):574-581. DOI: 10.1111/irv.12676

Aging in Thailand



SITUATION OF THE THAIOLDER PERSONS
2021Foundation of Thai Gerontology Research and Development Institute (TGRI)
Source: NESDC (2019)[9]

46% of older persons assessed their health as good to very good.



2 Decreased dependency ratio

(1 older person : per number of working-age persons)

Influenza and Complications

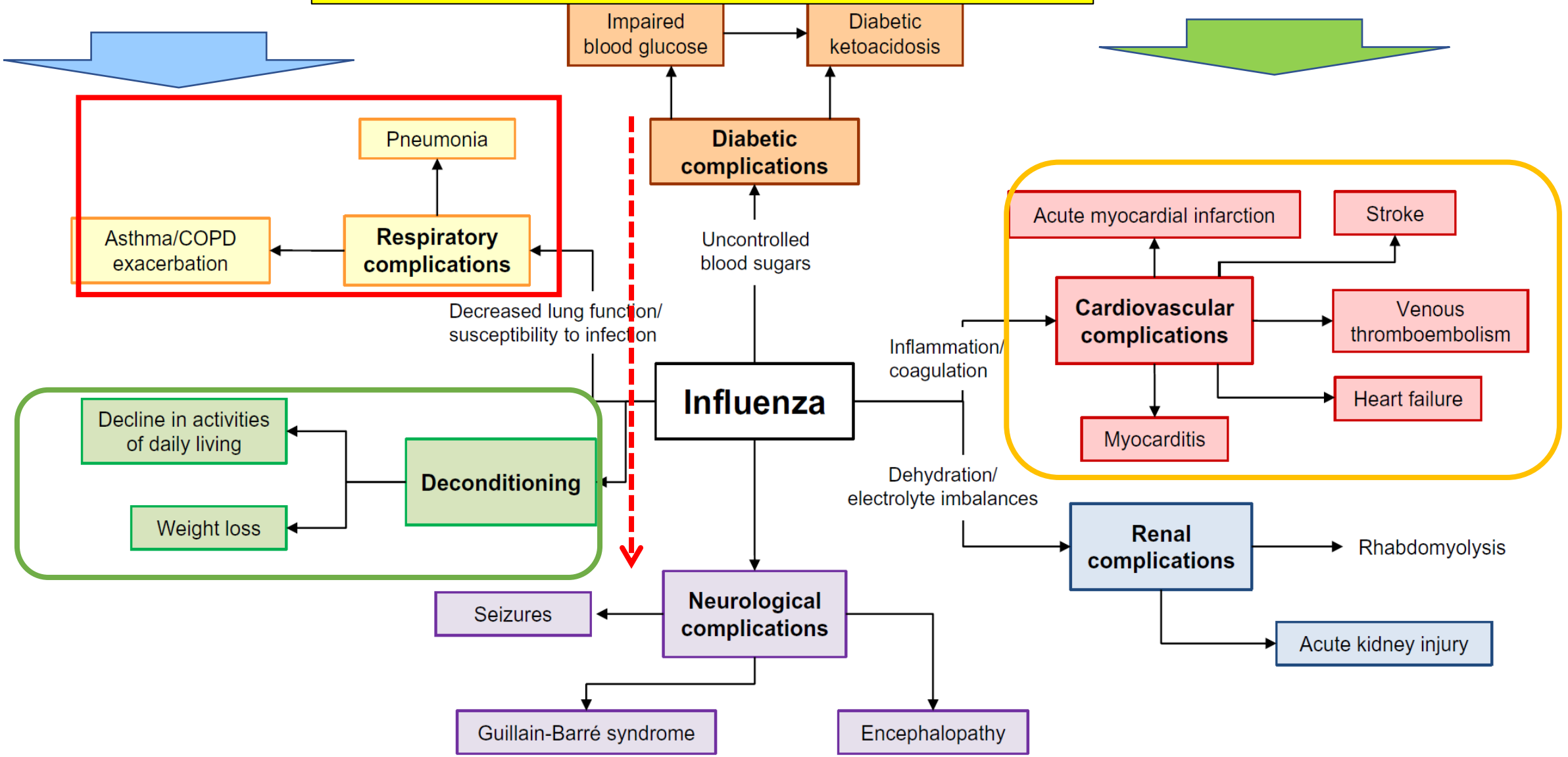
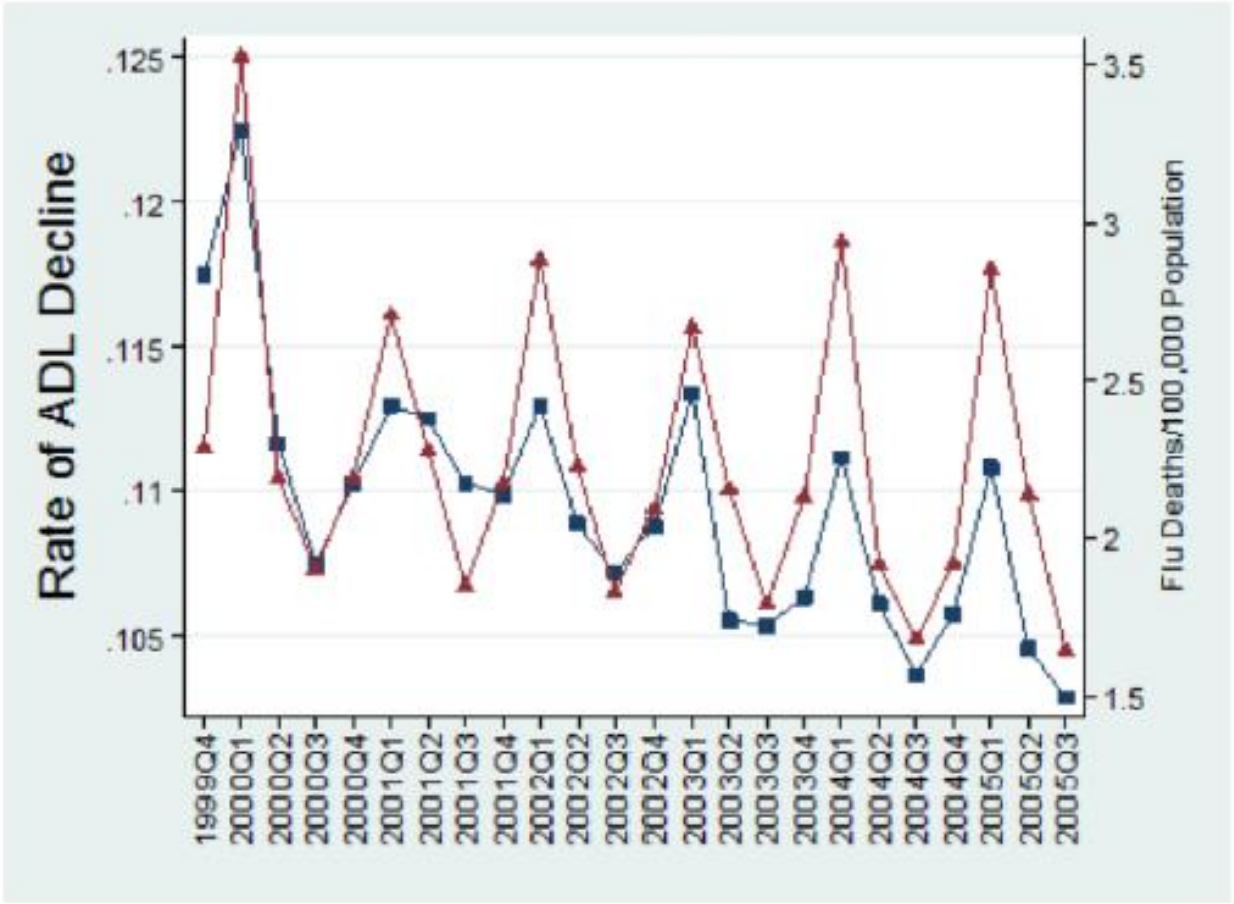


Fig. 1. Domino effect of influenza. The influenza virus infection triggers various effects that can exacerbate underlying chronic medical conditions, leading to an increased risk for hospitalization and death [15,34,36,57,65,74,77,91,92,109–113].

The Impact Of Influenza On Functional Status, US Nursing Home Residents

Quarterly Patterns of ADL Decline versus Influenza City-Level Mortality for long-stay (>90 days) nursing home residents in 122 CDC-monitored cities in the USA



ADL Decline (>3 points in the 0-28 ADL scale)

Influenza Mortality

influenza mortality was strongly associated with high (≥4 points) ADL decline

GOZALO PL, ET AL. J AM GERIATR SOC 2012; 60(7): 1260-1267

Associations between influenza, respiratory infections and cardiovascular outcomes have been apparent for many years

Myocardial Infarction

6–17x elevated risk of MI within 1 week of infection[1,2]

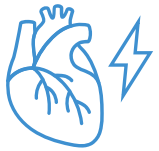
A significantly elevated incidence ratio(IR) for first AMI event occurring following influenza infection[3]

Stroke

3–10x elevated risk of stroke; longer risk window[2,4]

A significantly elevated IR for first stroke occurring following influenza infection[3]

Heart Failure



24% elevated risk in HF hospitalisation rates associated with **5%** increase in ILI activity[5]

CV complications

Results from SCCS studies have generally estimated a **2- to 6-fold increase in the risk of cardiovascular complications** after ARIs – particularly MI and stroke

Diabetes complications

3x more risk of hospitalizations
6x more risk of deaths compared to non-diabetics population

ARI, acute respiratory infection; CV, cardiovascular; MI, myocardial infarction; SCCS, self-controlled case series
HF, heart failure; ILI, influenza-like illness; MI, myocardial infarction; RCT, randomized clinical trial

1. Kwong JS, *et al. N Engl J Med*. 2018;378(4):345–53 2. Warren-Gash C, *et al. Eur Respir J*. 2018;29:51(3) 3. Ohland J, *et al. Euro Surveill*. 2020;25(17):pii=1900199 4. Boehme AK, *et al. Ann Clin Transl Neurol*. 2018;5(4):456–63 5. Kytömaa S, *et al. JAMA Cardiol*. 2019;4(4):363–9

Economic Burden of Influenza in Thailand: A Systematic Review

S. Kiertiburanakul; INQUIRY: The Journal of Health Care Organization, Provision, and Financing, 2020; Volume 57: 1–14

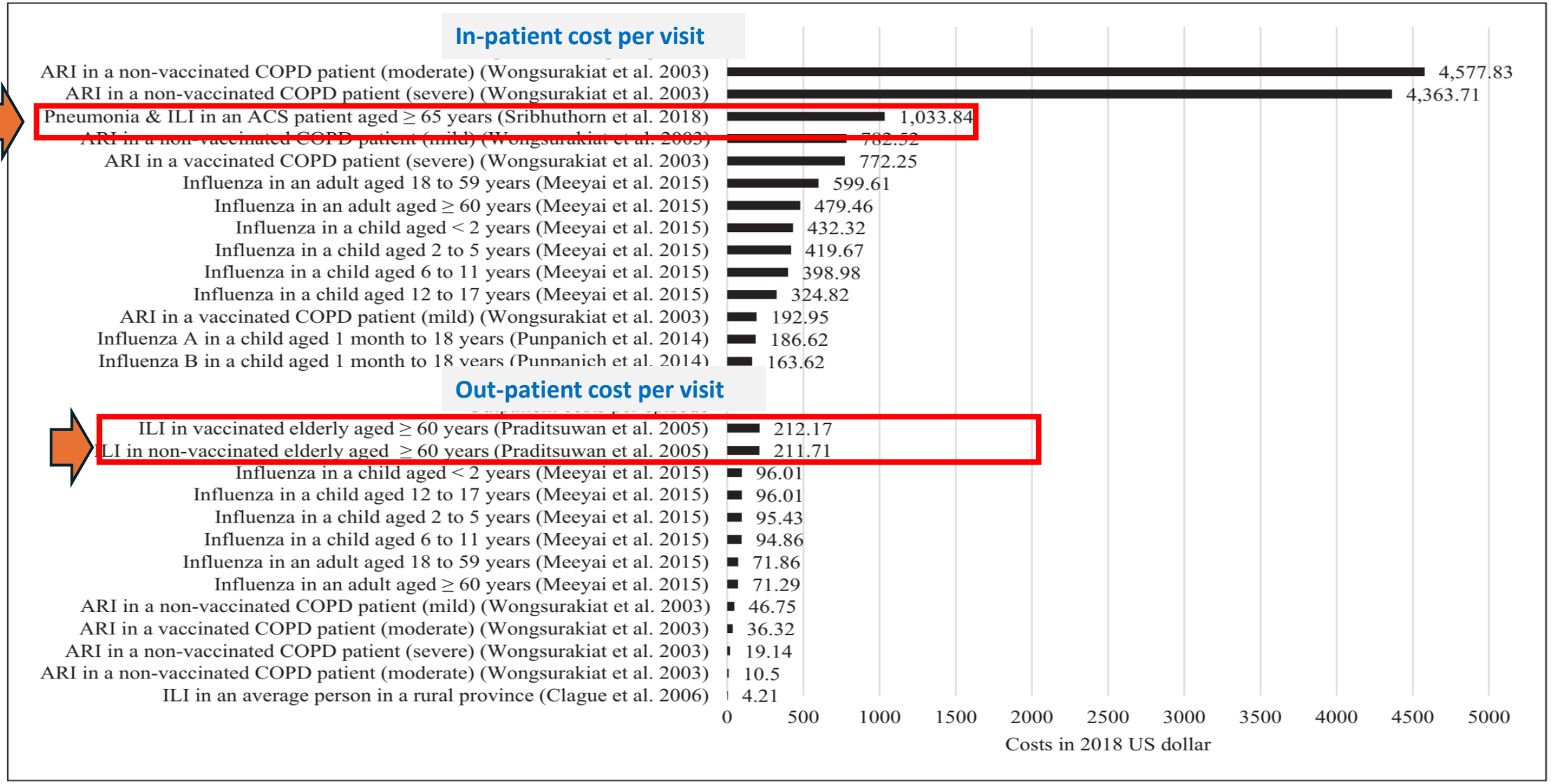
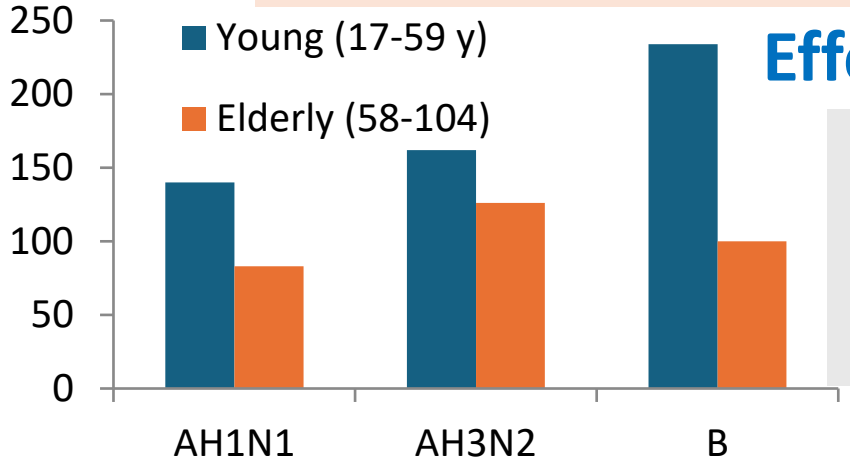


Figure 2. Direct medical costs in 2018 US dollar value for outpatients and inpatients across influenza illnesses from different studies.

Immunosenescence
Decreased Response to Vaccines Among Elderly/Immunocompromised

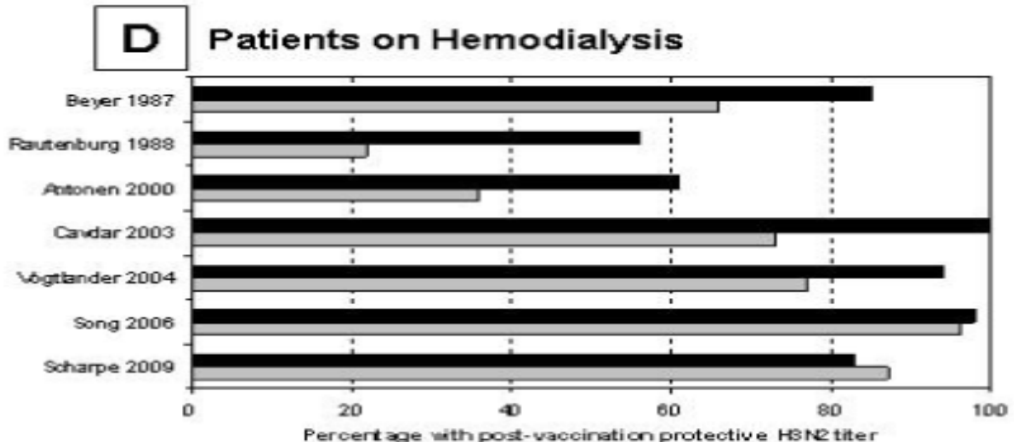
Gradual deterioration of the immune system associated with aging and leading to[1]

- **Reduced response to vaccination**
- **The need for more immunogenic vaccine formulations for the elderly**



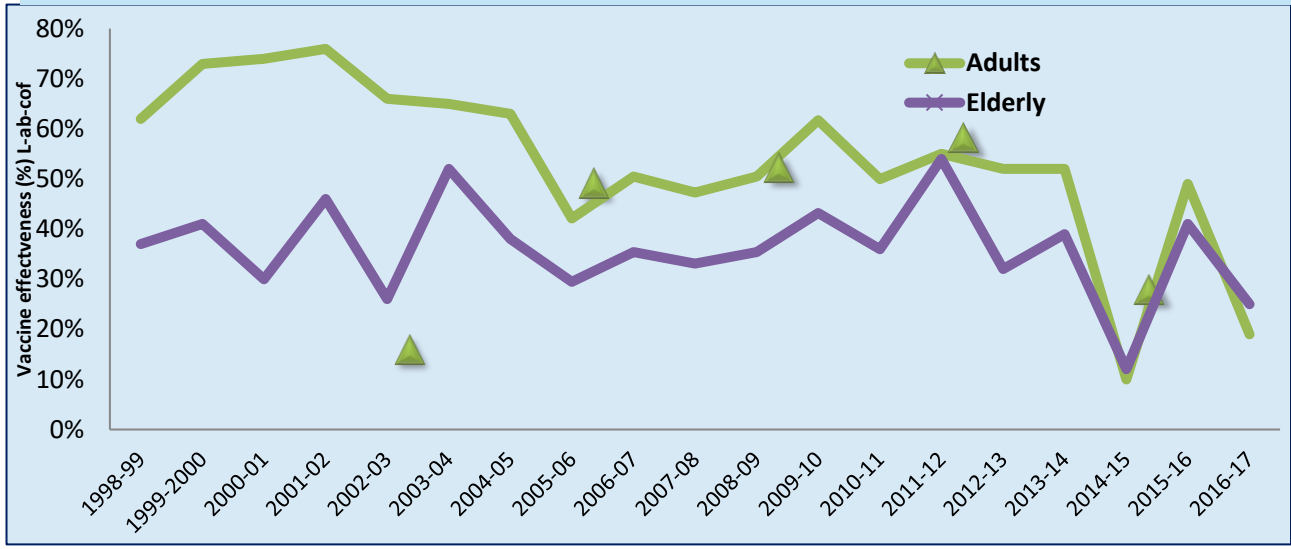
Effect of age on antibody response to flu vaccine

- Review of 31 vaccine antibody response studies (1986 – 2002)
- Adjusted antibody response was 2-4 lower in older adults
- **The results "highlight the need for more immunogenic vaccine formulations for the elderly"**



Ab response in Patients on Hemodialysis

Vaccine Effectiveness Against Influenza-Like Illness Is Lower in Older vs younger Adults



1. Goodwin K, et al. Vaccine 2006;24(8):1159-1169.

Goodwin K, et al. Vaccine. 2006;24(8):1159-1169.

Lower protection among elderly against influenza hospitalizations

A systematic review and meta-analysis in 2017 (CDC & WHO) assess vaccine effectiveness (VE) in adult

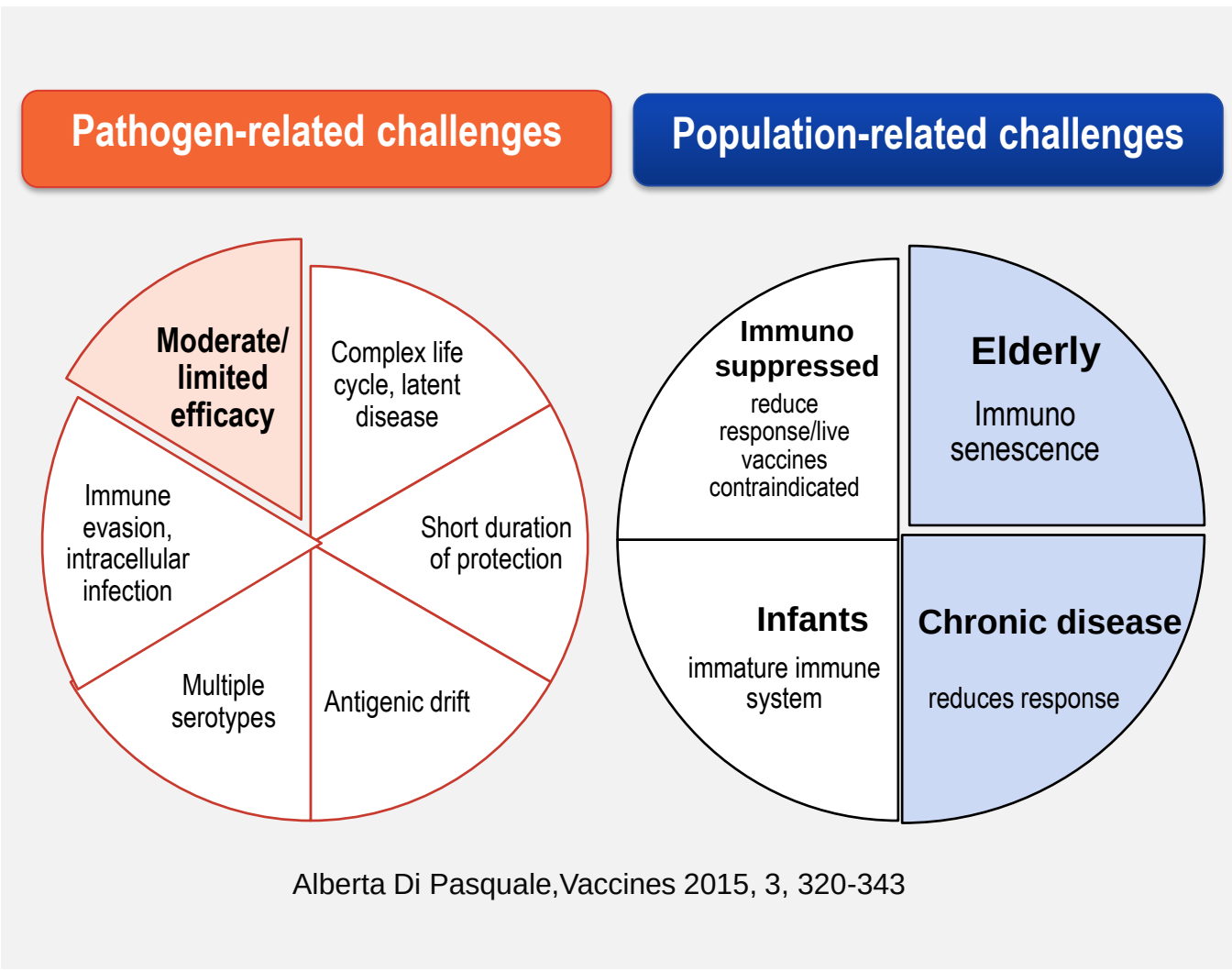
Pooled seasonal vaccine effectiveness (VE) against influenza hospitalizations by type and subtype of influenza virus and by age group

	Pooled VE (%)	95%CI	Number of VE estimates	p-value for heterogeneity	I^2
Any influenza					
All adults	41	34;48	24	0,005	48
Under 65 years	51	44;58	14	0,762	0
65 years and above	37	30;44	21	0,137	26
A(H1N1)pdm09					
All adults	48	37;59	7	0,212	28
Under 65 years	55	34;76	3	0,948	0
65 years and above	54	26;82	5	0,026	64
A(H3N2)					
All adults	37	24;50	9	0,021	56
Under 65 years	50	38;62	7	0,775	0
65 years and above	33	21;45	11	0,137	33
B					
All adults	38	23;53	5	0,640	0
Under 65 years	45	8;81	2	0,907	0
65 years and above	31	11;51	4	0,812	0

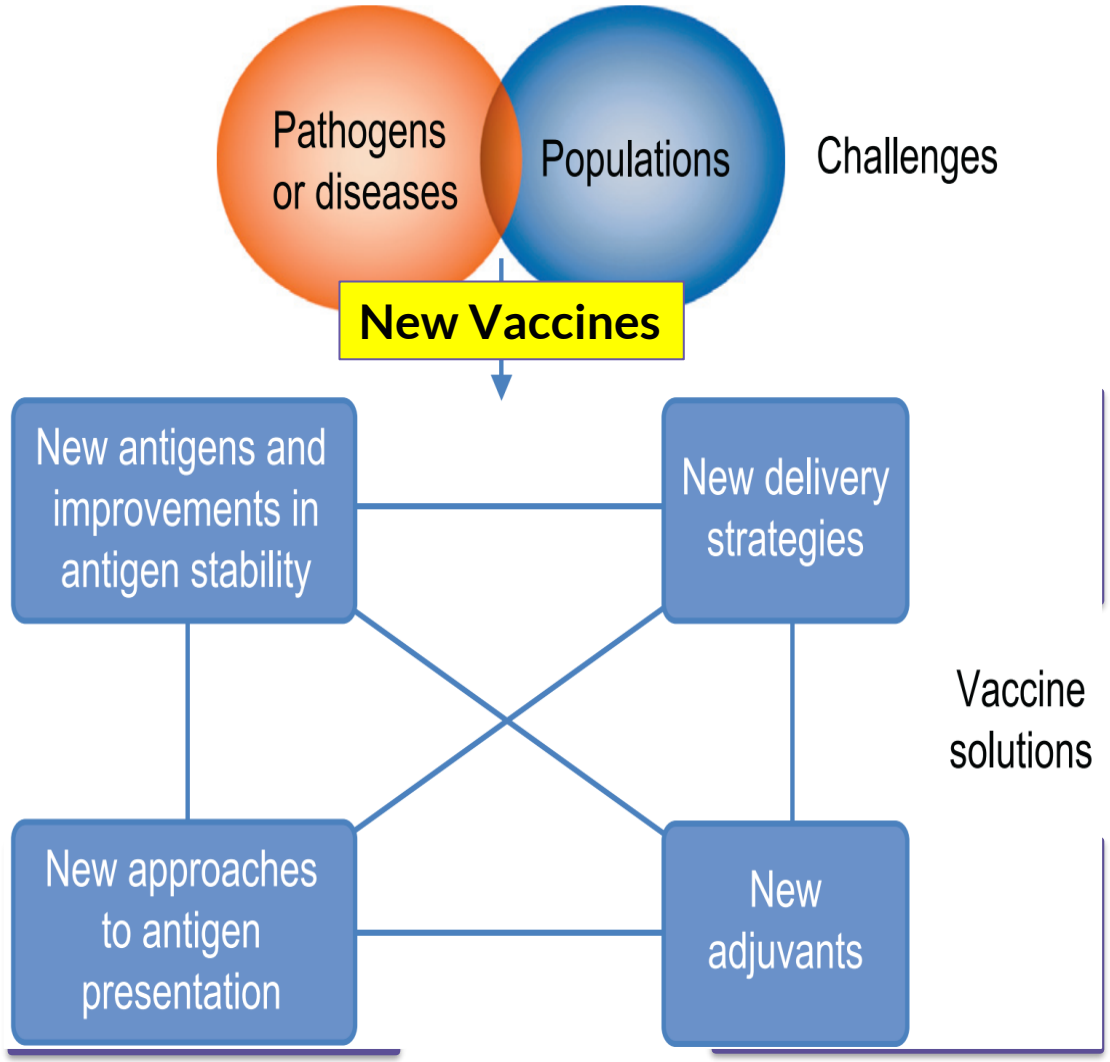
- **For adults younger than 65 years of age, pooled IVE estimate was 51% (95%CI: 44-58)**
- **For adults aged ≥65 years, the pooled IVE estimate was statistically lower at 37% (95%CI: 30-44)**

Rondy M et al, Effectiveness of influenza vaccines in preventing severe influenza illness among adults: J Infect. 2017 Nov;75(5):381-394. doi: 10.1016/j.jinf.2017.09.010.

Challenges for Modern Vaccine Development: Zoster, RSV



Alberta Di Pasquale,Vaccines 2015, 3, 320-343



DM patients have impaired cell-mediated immunity (CMI) against VZV, increasing their HZ risk.

Stanberry LR;Understanding Modern Vaccines;Chapter 6; 2011;1;151-199

Type of Influenza Vaccines in Thailand

Egg-based platform

Egg-based TIV, QIV (15 µg/0.5 ml) ≥6 months

Influvac, Vaxigrip, Fluquadri

Live attenuated 0.2 ml Intranasal (2-49 years)

Flumist

Egg-based-High dose (60 µg/0.7 ml), ≥60 years

Influenza for elderly

Efluelda

Egg-based with Adjuvant

Non-Egg platform

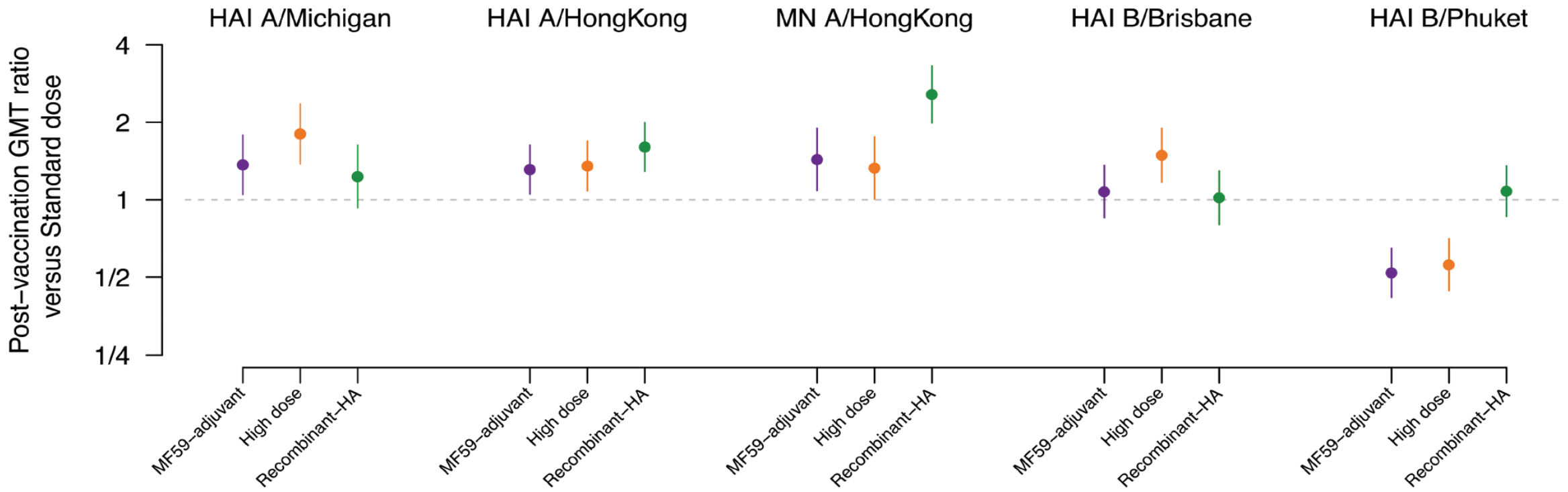
Cell-based (15 µg/0.5 ml) ≥6 months

Skycellflu

Recombinant vaccine (45 µg/0.5 ml) ≥18 years

Comparative Immunogenicity of Several Enhanced Influenza Vaccine Options for Older Adults: A Randomized, Controlled Trial

Benjamin J. Cowling; Clinical Infectious Diseases 2020;71(7):1704–14

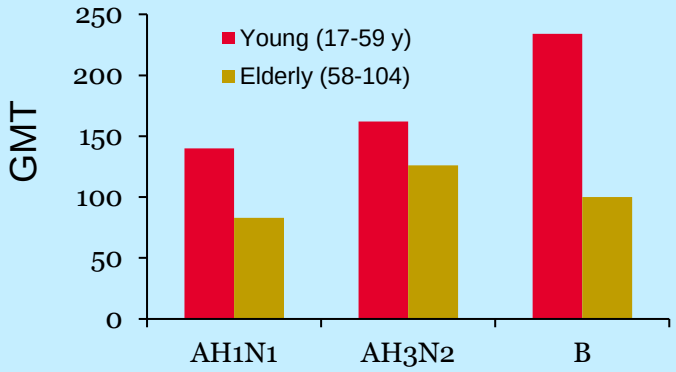


	HAI A/Michigan GMTR	(95% CI)	HAI A/HongKong GMTR	(95% CI)	MN A/HongKong GMTR	(95% CI)	HAI B/Brisbane GMTR	(95% CI)	HAI B/Phuket GMTR	(95% CI)
Standard dose	1.00		1.00		1.00		1.00		1.00	
MF59–adjuvant	**1.37**	**(1.05 – 1.78)**	**1.31**	**(1.05 – 1.63)**	**1.43**	**(1.09 – 1.89)**	1.08	(0.85 – 1.36)	**0.52**	**(0.42 – 0.65)**
High dose	**1.80**	**(1.38 – 2.36)**	**1.35**	**(1.08 – 1.69)**	**1.33**	**(1.01 – 1.75)**	**1.49**	**(1.17 – 1.89)**	**0.56**	**(0.44 – 0.70)**
Recombinant–HA	1.23	(0.93 – 1.63)	**1.60**	**(1.29 – 1.99)**	**2.57**	**(1.99 – 3.31)**	1.02	(0.80 – 1.29)	1.08	(0.86 – 1.35)

Why Do We Need Influenza High-dose Vaccine

Why elderly need better protection?

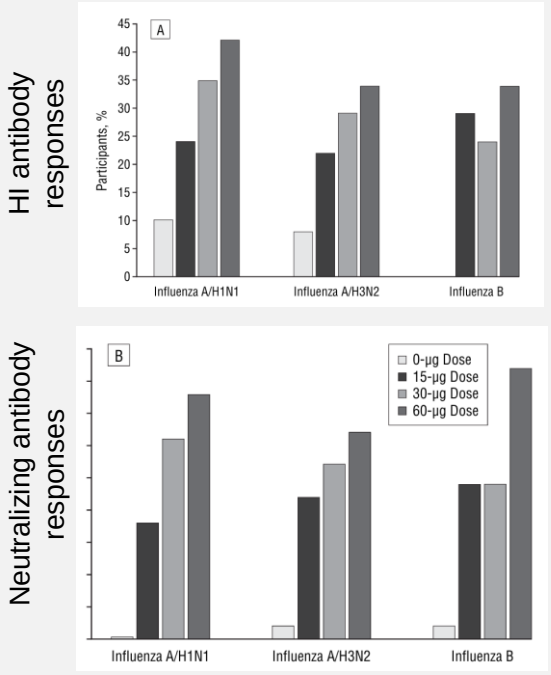
Aging is associated to a decline in the immune response including decreased T cell help that limits B and T cell responses to pathogens and consequently contributes to the increased susceptibility of the elderly to infectious diseases[1]



For all 3 antigens (H1, H3, and B) and both measures studied (seroconversion and seroprotection), adjusted antibody response to vaccine ***were 2- to 4-fold lower among older adults***[2]

Increased dose to improve immune response in elderly

Study to evaluate safety and immunogenicity of 2001-2002 formulation of trivalent inactivated influenza vaccine **containing 15, 30, or 60 µg of hemagglutinin per strain (up to 180 µg total per dose) or placebo**[3]

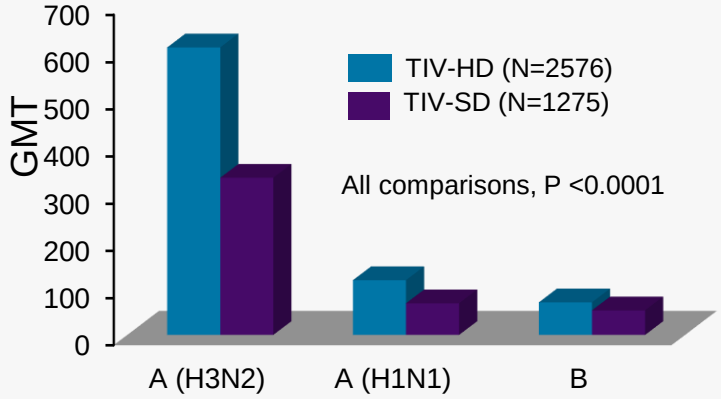


RCT phase 3: immunogenicity and safety of HD vs SD influenza vaccine in adults ≥65 years[4]

Superiority of immune responses achieved for A (H1N1) and A (H3N2); non-inferiority for B

Seroprotection rates were also higher for those who received HD vaccine, for all strains

Local reactions were more frequent in individuals who received HD vaccine, but were mild to moderate



1. Pera A, et al. Maturitas 2015;82:50-5. 2. Goodwin K, et al. Vaccine 2006;24:1159-69. 3. Keitel WA, et al, Arch Intern Med 2006;166:1121-7.
4. Falsey A, et al. J Infect Dis 2009;200:172-80.

Optimizing Influenza Protection in Older Adult: Evidence and Clinical Impact of High-Dose Influenza Vaccine

Outlines

- Better Vaccine for Elderly Population
- Current HD Influenza Vaccination Recommendations for Elderly
- Update on Clinical Evidence Supporting High-Dose Influenza Vaccines for Older Adults- Flunity HD Study

Table 1 Recommended Adult Immunization Schedule by Age Group, United States, 2025

Vaccine	19–26 years	27–49 years	50–64 years	≥65 years
COVID–19	1 or more doses of 2024–2025 vaccine (See Notes)			2 or more doses of 2024-2025 vaccine (See Notes)
Influenza inactivated (IIV3, ccIIV3) **Influenza recombinant** (RIV3)	1 dose annually			1 dose annually (HD–IIV3, RIV3, or aIIV3 preferred)
Influenza inactivated (aIIV3; HD–IIV3) **Influenza recombinant** (RIV3)	Solid organ transplant (See Notes)			
Influenza live, attenuated (LAIV3)	1 dose annually			
Respiratory syncytial virus (RSV)				
Tetanus, diphtheria, pertussis (Tdap or Td)				
Measles, mumps, rubella (MMR)				
Varicella (VAR)				
Zoster recombinant (RZV)				
Human papillomavirus (HPV)				
Pneumococcal (PCV15, PCV20, PCV21, PPSV23)				
Hepatitis A (HepA)				
Hepatitis B (HepB)				
Meningococcal A, C, W, Y (MenACWY)				
Meningococcal B (MenB)				
***Haemophilus influenzae* type b** (Hib)				
Mpox				
Inactivated poliovirus (IPV)				

Influenza vaccination

Routine vaccination

- **Age 19 years or older:** 1 dose any influenza vaccine appropriate for age and health status annually
  - **Solid organ transplant recipients aged 19 through 64 years receiving immunosuppressive medications:** HD–IIV3 and aIIV3 are acceptable options. No preference over other age–appropriate IIV3 or RIV3.
  - **Age 65 years or older:** Any one of HD-IIV3, RIV3, or aIIV3 is preferred. If none of these three vaccines is available, then any other age–appropriate influenza vaccine should be used.
- For the 2024–25 season, see www.cdc.gov/mmwr/volumes/73/rr/rr7305a1.htm
- For the 2025–26 season, see the 2025–26 ACIP influenza vaccine recommendations.

~284 M doses of HD vaccine (139 M of TIV-HD and 145 M doses of QIV-HD) have been distributed, as of 2023-2024 season

Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of immunity

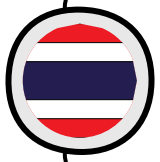
Recommended vaccination for adults with an additional risk factor or another indication

Recommended vaccination based on shared clinical decision–making

No Guidance/ Not Applicable

https://www.cdc.gov/vaccines/hcp/imz-schedules/downloads/adult/adult-combined-schedule.pdf Access online 12/03/2025

High-Dose influenza vaccine is recommended over conventional Standard-Dose influenza vaccines by scientific societies worldwide



Thailand[1]

- Collaboration between 7 medical associations and 1 royal college

June 2023

Malaysia[2,3]

- Malaysian Society of Infectious Diseases and Chemotherapy, and Malaysian Society of Geriatric Medicine: HD influenza vaccine is preferentially recommended for older persons

December 2022

South Korea[4]

- Society of Infectious Disease (KSID)

August 2023

Brazil[9-13]

- Immunization scientific society (SBIM), Cardiology society (DEIC), Society of Pulmonology and Tisiology (SBPT), Society of Clinical Oncology (SBOC): recommend to use HD as the vaccine of choice for older adults aged ≥60 years
- Society of Geriatry & Gerontology (SBGG): recommend to use HD as the vaccine of choice for most vulnerable population

March-June 2023

June 2024

Argentina[5,6]

- Argentine Association of Respiratory Medicine (AAMR)

December 2023

- Society of Infectious Disease (SADI)

April 2024

US[7]

- American College of Cardiology (ACC): "Not all flu vaccines are the same for people 65 and older. HD vaccines are better"

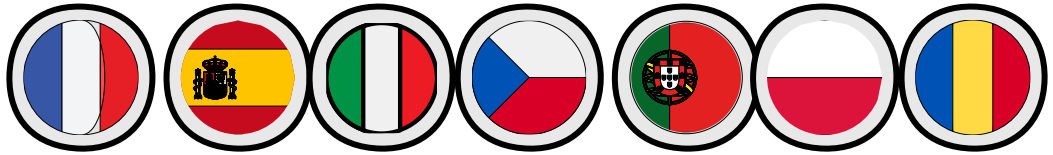
October 2024

Canada[8]

- Quebec Society of Geriatrics: strongly recommends that the CIQ (Quebec Immunization Committee) endorse the free use of the HD influenza vaccine for people aged ≥75 years

October 2022

+ more European societies



Cut of date: February 2025

AAMR: Argentine Association of Respiratory Medicine; ACC, American College of Cardiology; CIQ: Quebec Immunization Committee; HD: high-dose; KSID: Korean Society of Infectious Diseases; SBIM: Sociedade Brasileira de Imunizações; SD: standard-dose References in slide notes.

ตารางที่ 1 คำแนะนำการให้วัคซีนป้องกันโรคสำหรับผู้ใหญ่และผู้สูงอายุ จำแนกตามอายุ

สมาคมโรคติดเชื้อแห่งประเทศไทย

Vaccines	Age groups		
	18-26 years	27-64 years	≥65 years
Tetanus, diphtheria, and pertussis	Boost with 1 dose of Td every 10 years Substitute one-time of Td with Tdap or TdaP		
Influenza	1 dose annually		1 dose annually (see text)
COVID-19	1 dose annually (see text)		1 dose annually (age ≥60 years)
Measles, mumps, and rubella	2 doses (see text)		
Varicella	2 doses (see text)		
Hepatitis A virus	2 doses (see text)		
Hepatitis B virus	See text	3 doses (see text)	
Human papillomavirus	3 doses for female 3 doses for male	Age 27–45 years	
Pneumococcal	PCV20 1 dose or PCV13/PCV15 1 dose; consider followed by PPSV23 1 dose (see text) PCV20 1 dose or PCV13/PCV15 1 dose followed by PPSV23 1–2 dose(s) for persons with immunocompromising conditions including cerebrospinal fluid leak and cochlear implant (see text)		PCV20 1 dose or PCV13/PCV15 1 dose; consider followed by PPSV23 1 dose (see text)
Respiratory syncytial virus	1 dose in pregnancy (see text)	1 dose (age 60–74 years) (see text)	1 dose (age ≥75 years)
Live-attenuated zoster		1 dose (age ≥60 years)	
Recombinant zoster	2 doses for persons with immunocompromising conditions	2 doses (age ≥50 years)	

คำแนะนำเพิ่มเติม

60 ปีขึ้นไป

- พิจารณาให้วัคซีนไข้หวัดใหญ่ขนาดสูง ในผู้ที่อายุตั้งแต่ 65 ปีขึ้นไป เนื่องจากมีประสิทธิภาพลดการติดเชื้อแบบมีอาการได้ร้อยละ 24 ลดการนอนโรงพยาบาลได้ร้อยละ 64 และลดอัตราการเสียชีวิตได้ร้อยละ 49 เมื่อเทียบกับวัคซีนไข้หวัดใหญ่ขนาดมาตรฐาน
- พิจารณาให้วัคซีนไข้หวัดใหญ่ชนิดพ่นเข้าจมูกแทนวัคซีนชนิดฉีดเข้ากล้ามเนื้อ ในผู้ที่มีอายุ 2–49 ปี ที่ไม่ใช่หญิงตั้งครรภ์ ผู้ป่วยที่มีภาวะภูมิคุ้มกันบกพร่อง หรือผู้ที่ใกล้ชิดผู้ที่มีภาวะภูมิคุ้มกันบกพร่องรุนแรง
- การให้วัคซีนไข้หวัดใหญ่ประจำปีทั้งชนิดฉีดเข้ากล้ามเนื้อและชนิดพ่นเข้าจมูก ไม่จำเป็นต้องรอให้ครบ 1 ปี สามารถให้ได้โดยมีระยะห่างจากโดสก่อนมากกว่า 6 เดือน

IDAT. Recommended Adult and Elderly Immunization Schedule 2025.

Optimizing Influenza Protection in Older Adult: Evidence and Clinical Impact of High-Dose Influenza Vaccine

Outlines

- Better Vaccine for Elderly Population
- Current HD Influenza Vaccination Recommendations for Elderly
- Update on Clinical Evidence Supporting High-Dose Influenza Vaccines for Older Adults- Flunity HD Study

HD influenza vaccine is tailored for older adults, addressing a significant health burden in this population

HD vaccine is a split inactivated influenza vaccine containing *4x the active component dosage of hemagglutinin (HA) per strain* = **TAILORED DOSE**[1]

Standard dose
influenza vaccine

High dose
influenza vaccine

HD vaccine is indicated for ***people 60[1] or 65[2] years of age*** and older depending on the country immunization programs

HD influenza vaccine is the only licensed influenza vaccine with a proven superior protection against LCI infection versus a standard dose influenza vaccine in a randomized controlled trial in adults aged 65 years and older[3]

1:1
randomization

32K
older adults

Relative Vaccine Effectiveness
+24.2%
95%CI, 9.7–36.5

US, Canada
2 seasons
126 sites

LCI cases

EU, European Union; HA, hemagglutinin; HD, high-dose; LCI, laboratory-confirmed influenza; NA, neuraminidase; rVE, relative vaccine effectiveness; SD, standard-dose; US, United States

References: 1. SmPC Efluelda. 2024. Available at: https://www.hpra.ie/find-a-medicine/for-human-use/authorised-medicines/details/42192 (Accessed 20 June 2025); 2. Package inset Fluzone high-dose. 2025. Available at: Package-Insert-Fluzone-High-Dose.pdf (Accessed 05 August 2025); 3. DiazGranados CA, et al. *N Engl J Med.* 2014;371(7):635–45

Efficacy and effectiveness of high-dose influenza vaccine in older adults by circulating strain and antigenic match: An updated systematic review and meta-analysis *Lee JK;Vaccine 39 (2021) A24–A35*

15 publications were meta-analyzed after screening 1,293 studies, providing data on **10 consecutive influenza seasons and over 22 million individuals receiving HD-IIV3 in randomized and observational settings**.

Across all influenza seasons,

HD-IIV3 protection against ILI compared to SD-IIV (rVE = 15.9%, 95% CI: 4.1–26.3%).

HD-IIV3 prevent:

Hospital admissions from all-causes (rVE = 8.4%)
Influenza (rVE = 11.7%),
Pneumonia (rVE = 27.3%),
Combined pneumonia/influenza (rVE = 13.4%)
Cardiorespiratory events (rVE = 17.9%).

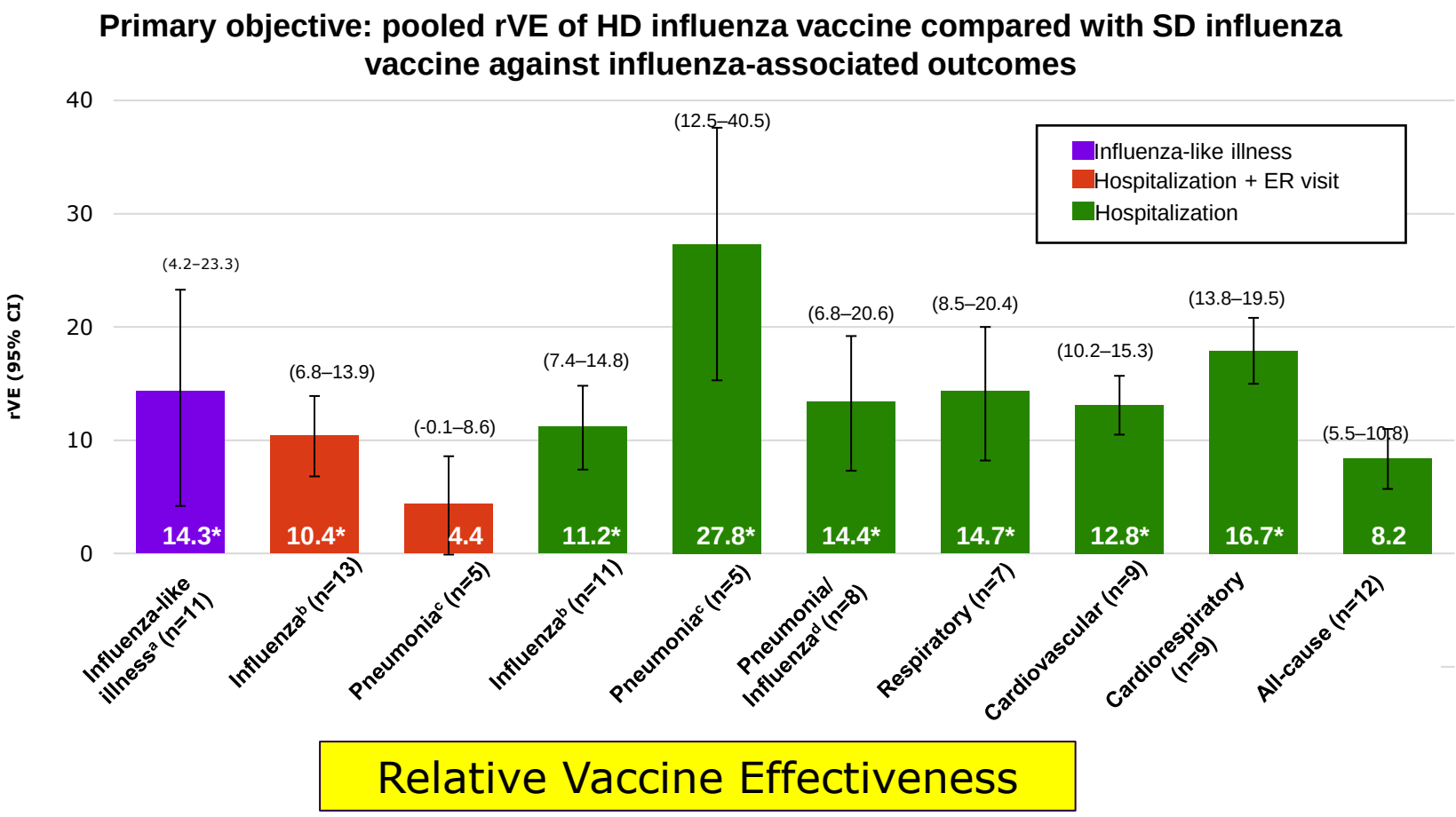
Reductions in mortality due to pneumonia/influenza (rVE = 39.9%) and cardiorespiratory causes (rVE = 27.7%)

Table 3
Pooled relative vaccine efficacy/effectiveness of HD-IIV3 vs. SD-IIV against influenza-related outcomes.

Outcome	All Seasons			Predominant Circulating Strain[a]						Antigenic Similarity with Predominant Circulating Strain[b]					
				A/H3N2-predominant Seasons			A/H1N1-predominant Seasons			Matched Seasons			Mismatched Seasons		
	n	*rVE*[c] *(95%CI)*	*p-value*	*n*	*rVE (95%CI)*	*p-value*	*n*	*rVE (95%CI)*	*p-value*	*n*	*rVE (95%CI)*	*p-value*	*n*	*rVE (95%CI)*	*p-value*
Influenza-like Illness[d]	7	**15.9%** (4.1–26.3%)	0.01	4	**18.3%** (0.8–32.7%)	0.041	3	10.7% (-6.1–24.8%)	0.199	3	27.0% (-6.8–50.1%)	0.105	4	14.3% (-3.4–29.0%)	0.107
Influenza Hospitalization[e]	10	**11.7%** (7.0 – 16.1%)	<0.001	7	**12.1%** (6.3 – 17.6%)	<0.001	3	**9.6%** (2.1–18.9%)	<0.001	3	**10.9%** (2.1–18.9%)	0.016	7	**12.1%** (6.3 – 17.6%)	<0.001
Pneumonia Hospitalization[f]	4	**27.3%** (15.3–37.6%)	<0.001	2	**39.9%** (19.3–55.3%)	<0.001	2	**22.0%** (6.7–34.8%)	<0.001	3	**28.9%** (10.1–43.8%)	0.004	1	–	–
Pneumonia/Influenza Hospitalization[g]	7	**13.4%** (7.3–19.2%)	<0.001	5	**12.4%** (5.7–18.7%)	<0.001	2	**19.6%** (3.0–33.4%)	0.023	5	**13.5%** (5.0–21.3%)	0.002	2	**13.3%** (4.1–21.6%)	0.005
Cardiorespiratory Hospitalization	7	**17.9%** (15.0–20.8%)	<0.001	6	**17.7%** (14.5–20.8%)	<0.001	1	–	–	4	**17.4%** (13.5–21.1%)	<0.001	3	**18.6%** (14.1–22.9%)	<0.001
All-cause Hospitalization	11	**8.4%** (5.7–11.0%)	<0.001	8	**8.3%** (4.5–12.0%)	<0.001	3	**8.9%** (5.4–12.2%)	<0.001	7	**6.4%** (4.1–8.6%)	<0.001	4	**12.6%** (7.8–17.2%)	<0.001
Post-influenza Mortality	2	22.2% (-18.2–48.8%)	0.240	1	–	–	1	–	–	1	–	–	1	–	–
Pneumonia/Influenza Mortality	3	**39.9%** (18.6–55.6%)	<0.001	2	**43.2%** (18.1 – 60.6%)	0.002	1	–	–	1	–	–	2	**43.2%** (18.1 – 60.6%)	0.002
Cardiorespiratory Mortality	3	**27.7%** (13.2–32.0%)	<0.001	2	**27.3%** (20.3 – 33.6%)	<0.001	1	–	–	1	–	–	2	**27.3%** (20.3 – 33.6%)	<0.001
All-cause Mortality	5	2.5% (-5.1–9.5%)	0.514	4	4.6% (-12.6–19.3%)	0.575	1	–	–	3	0.7% (-4.3–5.6%)	0.768	2	**17.3%** (0.2–31.5%)	0.048

HD vaccine is consistently more effective than SD influenza vaccines

at reducing the clinical outcomes associated with influenza infection in older adults



- **Literature search up to April 2023**
- **21 publications meta-analyzed**
  - 6 from randomized studies
  - 15 from observational studies
- **12 seasons, >45M people**

HD vaccine is **consistently** more effective than SD influenza vaccines at reducing the clinical outcomes associated with influenza infection in older adults **irrespective of outcome, season, circulating strain, antigenic match, study type, study setting and age subgroup.**

Reference: Lee J, et al. Vaccine: X. 2023 doi:10.1016/j.jvacx.2023.100327.

*p<0.05; [a]Probable/laboratory confirmed influenza like illness; [b]ICD-9-CM 487 coded hospitalizations; [c]ICD-9-CM 480–486 coded hospitalizations; [d]ICD-9-CM 480–488 coded hospitalizations
CI: confidence interval; ER: emergency room; HD: high-dose; rVE: relative vaccine efficacy/effectiveness; RCT: randomized controlled trial; SD: standard-dose.

Estimating public health and economic benefits along 10 years of Fluzone® High Dose in the United States ☆

Vaccine 39 (2021) A56–A69

Pierre Net [a], Florian Colrat [b], Mafalda Nascimento Costa [c], Florence Bianic [a], Edward Thommes [d], Fabián P. Alvarez [b,*]

Over 10 years, it is estimated that HD TIV resulted in an averted 1,333,479 influenza cases, 769,476 medical visits, 40,004 ED presentations, 520,342 cardiorespiratory hospitalizations and 73,689 deaths and generated an absolute $4.6 billion in savings, **translating into a return on investment of 214.4%.**

Hospitalizations and HD TIV relative vaccine efficacy vs SD TIV as a major cost driver were further confirmed in scenario analysis and DSA. HD TIV remained cost saving under all the scenarios.

DANFLU 2: Denmark

ORIGINAL ARTICLE

Pragmatic, open-label, randomized, controlled trial

High-Dose Influenza Vaccine Effectiveness against Hospitalization in Older Adults

Niklas Dyrby Johansen; N Eng J Med Aug30; 2025

GALFLU: Spain

ORIGINAL ARTICLE

High-Dose Influenza Vaccine to Reduce Hospitalizations

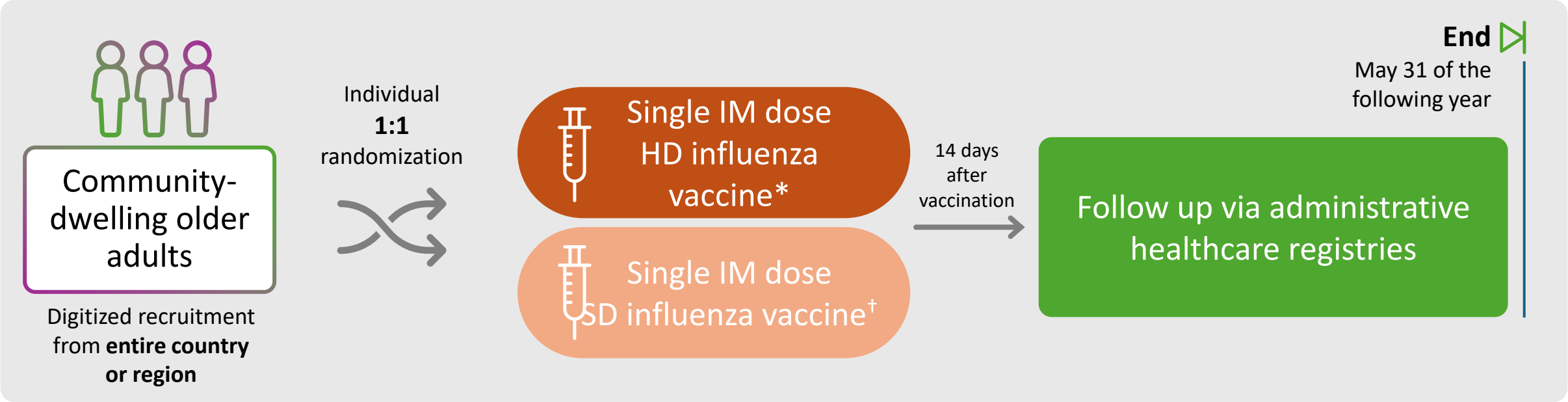
J. Pardo-Seco; N Eng J Med Aug 30 ;2025

FLUNITY-HD (DANFLU2 + GALFLU)

Effectiveness of high-dose influenza vaccine against hospitalisations in older adults (FLUNITY-HD): an individual-level pooled analysis

Niklas Dyrby Johansen; Lancet Oct 17;2025

Participants in both trials received a single dose of either HD or SD vaccine



- Co-administration with other seasonal vaccines, including COVID-19 vaccines, permitted in accordance with local guidelines
- HD vaccine was not available outside of the trial for the target populations in both trials across all seasons

Trials required participants to appear at **only one physical visit** for randomization and vaccination

- *Quadrivalent HD-IIV (Fluzone® High-Dose Quadrivalent/Efluelda®/Efluelda Tetra®; [Sanofi]). †Quadrivalent SD-IIV (VaxigripTetra [Sanofi] in DANFLU-2; InfluvacTetra [Viatris] in GALFLU).
- HD, high-dose; IIV, inactivated influenza vaccine; IM, intramuscular; SD, standard-dose.
- Johansen ND, et al. *Lancet.* 2025.

FLUNITY-HD is an individually randomized study powered to assess superior effectiveness of High-Dose over Standard-Dose influenza vaccine against severe outcomes in older adults[1-3]

466K

Older adults in **FLUNITY-HD**: uniting the harmonized **DANFLU-2 332K** + **GALFLU 134K** trials

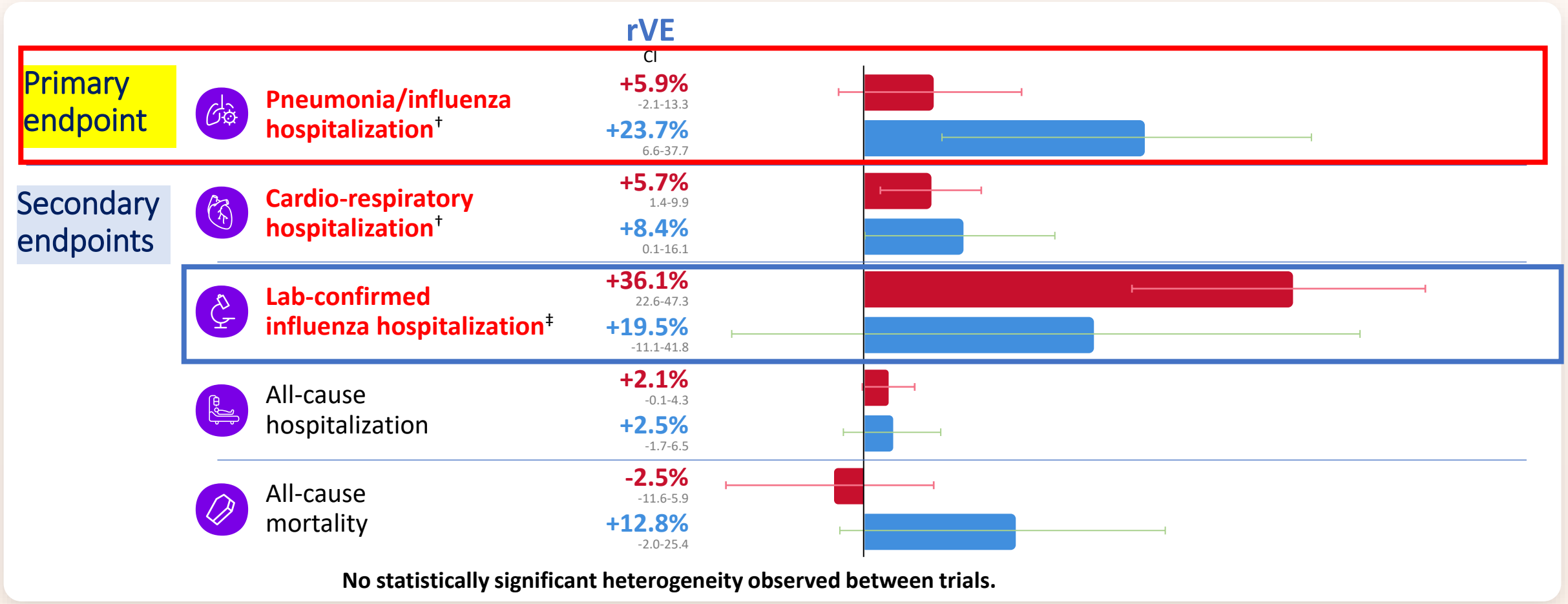
FLUNITY-HD

	DANFLU-2[2]	GALFLU[3]
Design	Methodologically harmonized, pragmatic, registry-based, externally-sponsored, open-label, active-controlled, individually randomized (1:1) trial	
Intervention	**HD vs SD influenza vaccine**	
Location	**Denmark***	**Galicia, Spain†**
Seasons	2022/23, 2023/24, 2024/25	2023/24, 2024/25
Vaccination campaign start (3-4-week campaigns)	Early October (End 31 May following year)	Late October (End 31 May following year)
Inclusion Criteria	**Any adults ≥65 years (Mean 73yrs)**	**Community-dwelling older adults aged 65-79 years (mean 72 yrs)**
Exclusion Criteria	**No formal exclusion criteria**	**Those residing in nursing homes‡**

Methodological alignment: DANFLU-2 and GALFLU's harmonized approach[1]

*Sponsor: Academic research group at CTCPR at the Department of Cardiology, Copenhagen University Hospital. Collaborators: Private vaccination provider Danske Lægers Vaccinations Service/ELCG. †Sponsor: Dr. Federico Martinón-Torres. Collaborator: Galician Health Service (SERGAS) through the General Public Health Directorate and the Regional Vaccination Program of Galicia. ‡Individuals ≥80 years or >60 years in nursing homes were already eligible to receive the HD influenza vaccine via the Galician public vaccination program.
CTCPR, Center for Translational Cardiology and Pragmatic Randomized Trials; ELCG, European LifeCare Group; HD, high-dose; SD, standard-dose.
1. Johansen ND, et al. *Lancet*. 2025. 2. Johansen ND, et al. *N Engl J Med*. 2025. 3. Pardo Seco J, et al. *N Engl J Med*. 2025.

Results by DANFLU-2 and GALFLU*



- *Per the hierarchical testing sequence, if the null hypothesis for the primary endpoint was not rejected, no formal hypothesis testing was conducted for the secondary endpoints, and these endpoints are assessed descriptively only. †Endpoint defined by ICD-10 code. ‡Originally exploratory in DANFLU-2, but promoted to the 2nd secondary endpoint based on updated ECDC recommendations.
- CI, confidence interval; ECDC, European Centre for Disease Prevention and Control; ICD, International Classification of Diseases; rVE, relative vaccine efficacy.
- Johansen ND, et al. *Lancet*. 2025. doi: 10.1016/S0140-6736(25)01742-8.

Groups assigned HD vs SD vaccines were well-balanced in *FLUNITY-HD (DANFLU-2 and GALFLU)*

FLUNITY-HD

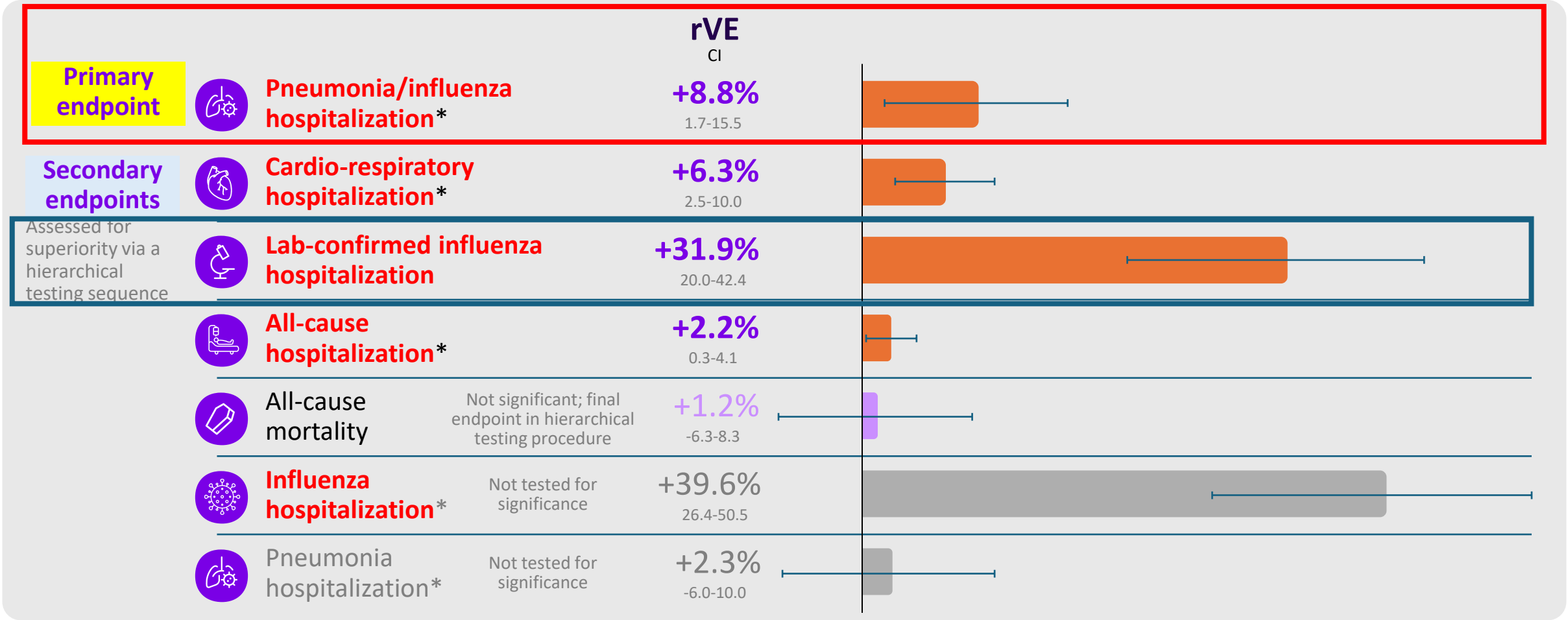
Characteristics	HD n=233,311*	SD n=233,009*
Age, years, mean ± SD	**73.3 ± 5.4**	**73.3 ± 5.4**
Female	**111,809 (47.9)**	**111,872 (48.0)**
Presence of ≥1 chronic disease:	**114,073 (48.9)**	**114,052 (48.9)**
Diabetes	32,489 (13.9)	32,492 (13.9)
Cardiovascular disease	54,061 (23.2)	53,639 (23.0)
Ischemic heart disease	19,033 (8.2)	18,809 (8.1)
Atrial fibrillation	19,179 (8.2)	19,043 (8.2)
Heart failure	6,497 (2.8)	6,536 (2.8)
Cancer	28,548 (12.2)	28,455 (12.2)
Chronic lung disease	16,022 (6.9)	15,954 (6.8)
COPD	8,252 (3.5)	8,100 (3.5)
Chronic kidney disease	24,062 (10.3)	24,195 (10.4)
Immunosuppression	12,308 (5.3)	12,308 (5.2)

FLUNITY-HD (cont'd)

Vaccination status	HD n=233,311*	SD n=233,009*
Co-administration with COVID-19 vaccine	70.9%	71.0%
COVID-19 vaccine during same season	96.2%	96.2%
Pneumococcal vaccination after age 65 years	**79.3%**	**79.5%**

- Baseline characteristics were sourced from nationwide administrative health registries using prespecified definitions. *Values are n (%) unless otherwise specified.
- COPD, chronic obstructive pulmonary disease; HD, high-dose; SD, standard-dose.
- Johansen ND, et al. *Lancet.* 2025.

In *FLUNITY-HD,* the HD vaccine significantly reduced the incidence of many severe outcomes relative to SD



*Endpoint defined by ICD-10 code.

CI, confidence interval; HD, high-dose; ICD, International Classification of Diseases; rVE, relative vaccine effectiveness; SD, standard-dose.

Reference: Johansen ND, et al. *Lancet.* 2025.

Safety of HD Influenza Vaccine: Surveillance during 2011-2019 in Person Aged ≥65 Years

Moro PL, et al. Vaccine 2020;38:5923-6.

Causes of death after administration of TIV-HD

Body system	N (%)
Diseases of the circulatory system	23 (41.8)
Coronary artery disease/myocardial infarction	15 (27.3)
Hypertension/hypotension	3 (5.4)
Rhythm alterations (e.g arrythmias)	2 (3.6)
Cerebrovascular accidents	2 (3.6)
Cardiovascular disease	1 (1.8)
Diseases of the respiratory system	8 (14.5)
Chronic obstructive pulmonary disease	4 (7.3)
Pneumonia	2 (3.6)
Acute respiratory distress syndrome	1 (1.8)
Pulmonary fibrosis	1 (1.8)
Infectious diseases	5 (9.1)
Sepsis/septic shock	5 (9.1)
Neoplasms	5 (9.1)
Diseases of the nervous system	3 (5.4)
Guillain-Barré Syndrome	3 (5.4)
Injury, poisoning and certain other consequences of external causes	2 (3.6)
Aspiration	2 (3.6)
Endocrine, nutritional and metabolic diseases	1 (1.8)
Diseases of the genitourinary system	1 (1.8)
Immune system disorders	1 (1.8)
Unevaluable/no information	6 (10.9)
Total	55

55 reports of death

- Most common causes of death were diseases of the circulatory system (42%)

61 reports of GBS

- **0.54 per 1,000,000 doses**
- 52 cases within 42 days of vaccine administration

13 reports of anaphylaxis,no deaths

The Journal of Infectious Diseases

MAJOR ARTICLE

Guillain-Barré Syndrome After High-Dose Influenza Vaccine Administration in the United States, 2018–2019 Season

Silvia Perez-Vilar,[1,a] Mao Hu,[2] Eric Weintraub,[3] Deepa Arya,[1,a] Bradley Lufkin,[2] Tanya Myers,[3] Emily Jane Woo,[1] An-Chi Lo,[2] Steve Chu,[4] Madeline Swarr,[2] Jiemin Liao,[2] Michael Wernecke,[2] Tom MaCurdy,[2,5] Jeffrey Kelman,[4] Steven Anderson,[1] Jonathan Duffy,[3] and Richard A. Forshee[1]

[1]Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA, [2]Acumen LLC, Burlingame, California, USA, [3]Immunization Safety Office, Centers for Disease Control and Prevention, Atlanta, Georgia, USA, [4]Centers for Medicare & Medicaid Services, Washington, DC, USA, [5]Department of Economics, Stanford University, Stanford, California, USA

HD-IIV is the ONLY vaccine to provide SUPERIOR protection against both INFLUENZA infection and its SEVERE OUTCOMES

INFLUENZA INFECTION DATA

Individually Randomized Studies

EFFICACY DATA[1]

Randomized Controlled Trial (1:1) vs standard dose (SD-IIV)

Superiority objective

32,000 subjects aged 65+ years
USA, Canada
2 seasons

Lab-confirmed influenza infection

+24.2%

(95% CI: 9.7–36.5)

relative efficacy against lab-confirmed influenza infection

HOSPITALISATIONS DATA

FLUNITY-HD STUDY[2]

Prespecified pooled analysis of DANFLU-2 and GALFLU[2]

2 harmonized pragmatic RCTs with superiority objective

>466K adults aged 65+ years
Denmark, Spain (Galicia)
3 seasons

Severe outcomes

Reduction in hospitalizations vs SD (rVE)

LCI	P/I*
+31.9% (95% CI: 19.7-42.2)	*+8.8%* (95% CI: 1.7-15.5)

CARDIO-RESPIRATORY	ALL-CAUSE
+6.3% (95% CI: 2.5-10.0)	*+2.2%* (95% CI: 0.3-4.1)

15 years (seasons) of evidence (real-world + clinical studies) in more than 45M older adults[2,3]

~328M

Doses of HD-IIV have been distributed since first use (as of March 2025)

No safety concerns identified during clinical development nor post-marketing surveillance[4,5]

Reactogenicity of HD-IIV was slightly increased as compared to SD-IIV, but no major difference in intensity was observed[6]

*Primary endpoint

CI: confidence interval; M: million; HD-IIV: high-dose inactivated influenza vaccine; SD-IIV: standard-dose inactivated influenza vaccine

References: 1. DiazGranados CA, et al. *N Engl J Med*. 2014;371:635-45; 2. Johansen ND, et al. *LANCET*. 2025 (Accepted for Publication, In Press); 3. Lee J, et al. *Vaccine: X*. 2023;14:100327; 4. Falsey A, et al. J Infect Dis. 2009 200:172-80; 5. Kaka et al. Open Forum Infect Dis. 2017;4:ofx001; 6. HD SmPC

Rachadamri Clinic
TRCS
Empowering Health Equity

Thank you

Fast tract Vaccination:
iRedcross website