

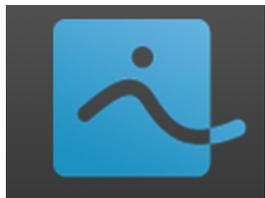
The value of adult vaccinations and their impact on public health

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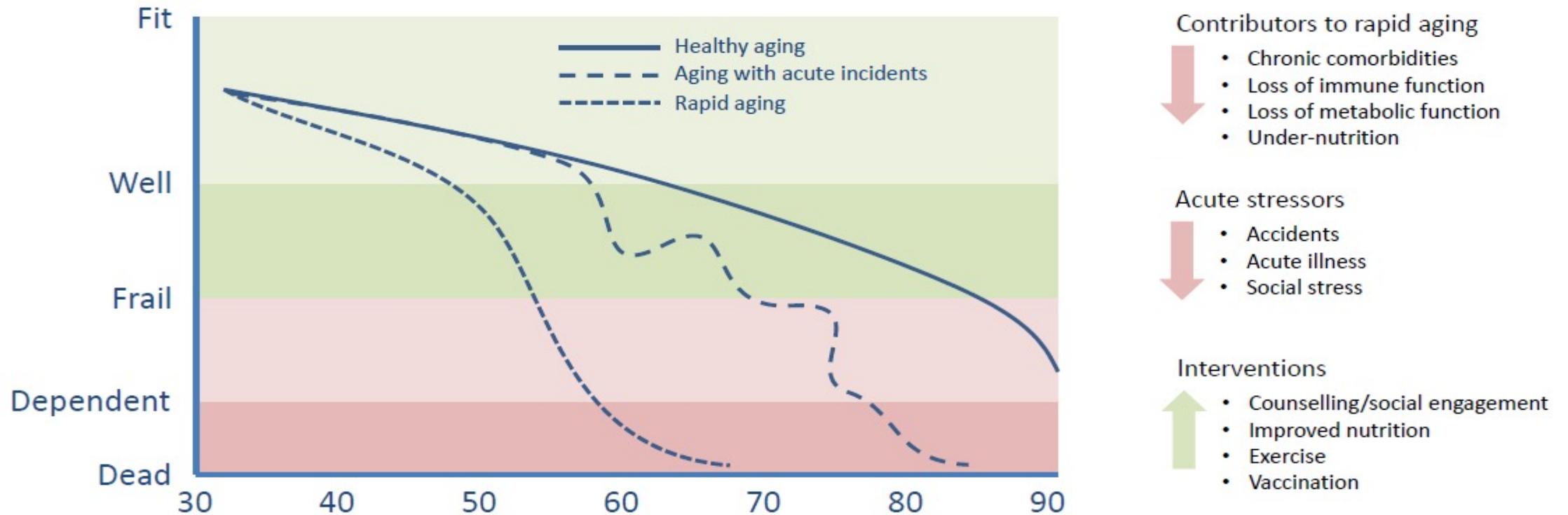
Consiglio Nazionale delle Ricerche



Outline

- Concepts of healthy ageing and frailty
- Impact of vaccine-preventable diseases (VPDs)
- Vaccination as a tool for healthy ageing and as a cost-effective preventive measure

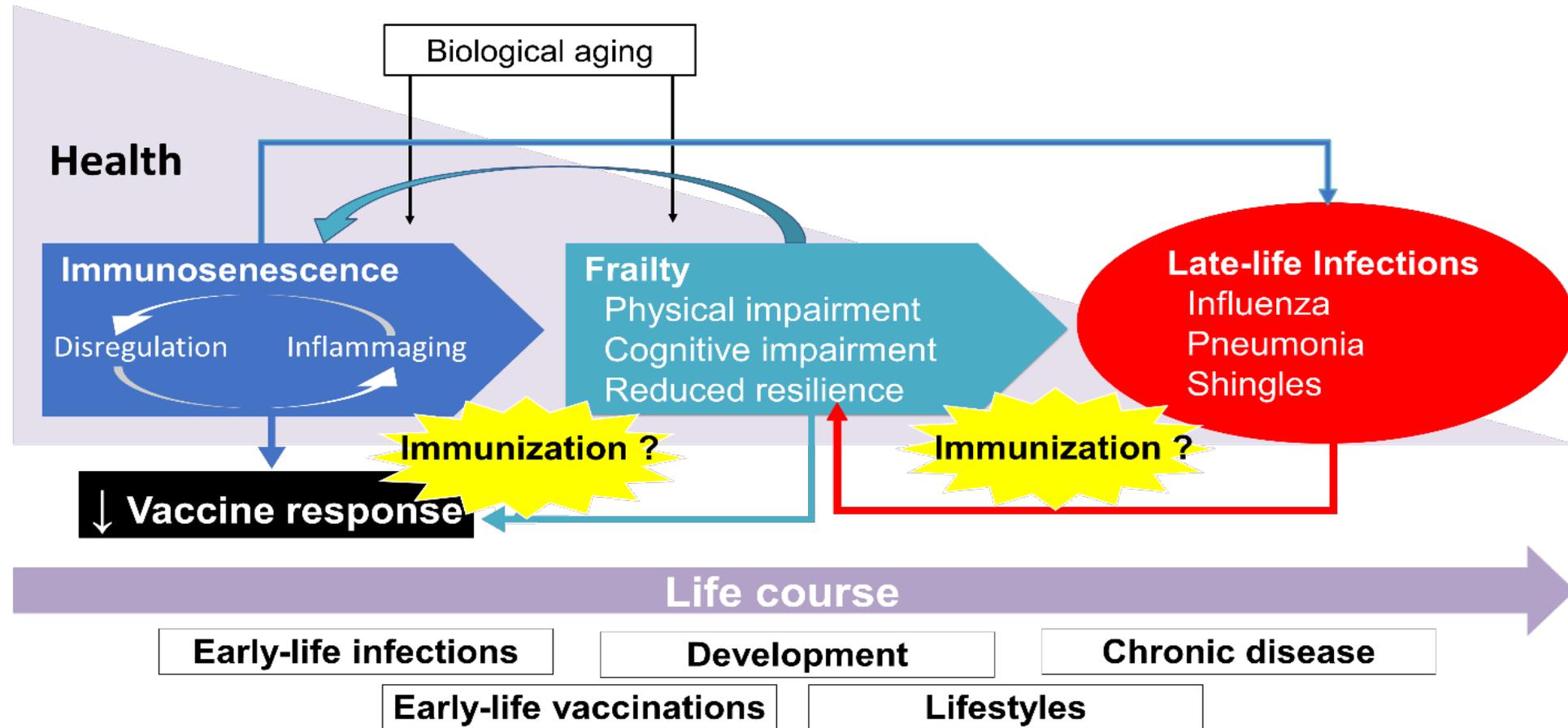
Ageing trajectories: focus on function



Factors contributing to increased risk of infections

- Anatomical and physiological changes:
 - difficulties swallowing/cough reflex
 - decreased mucociliary clearance in the lung
 - anatomical changes in the urinary tract (bladder capacity, urinary flow rate)
 - decreased gastric acidity and intestinal motility
 - structural alterations of the skin and other epithelia
- Hospitalisation
- Invasive procedures
- Use of antibiotics
- Polypharmacy
- Comorbidities
- Immunosenescence

A Unifying Framework of the Relationship Between Immunosenescence, Frailty, and Late-Life Infections



Ageing, infectious diseases and vaccination

Ageing is associated with:

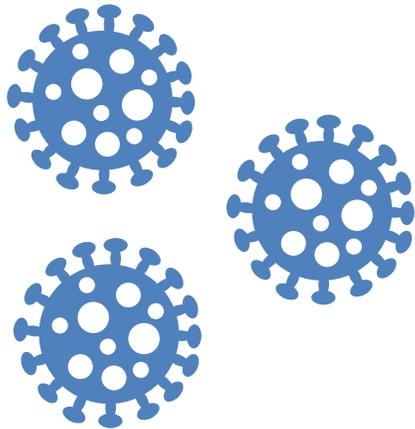
- increased incidence and severity of infectious diseases
 - influenza
 - *Streptococcus pneumoniae*
 - varicella zoster virus
 - Covid-19
 - RSV
 -
- decreased efficacy of vaccination
 - reduced antibody titres
 - reduced clinical efficacy

Outline

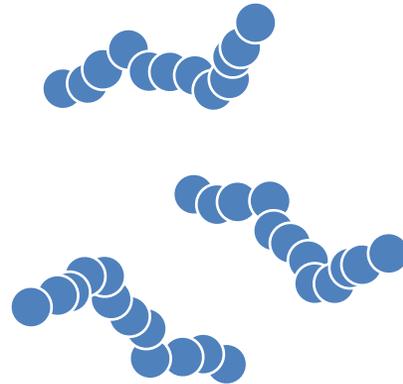
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‘The cursed triad’ among the vaccine-preventable diseases in older adults

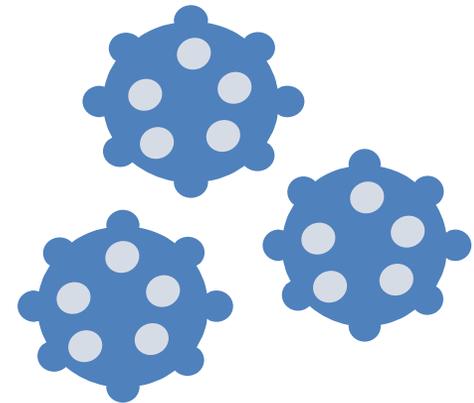
Influenza



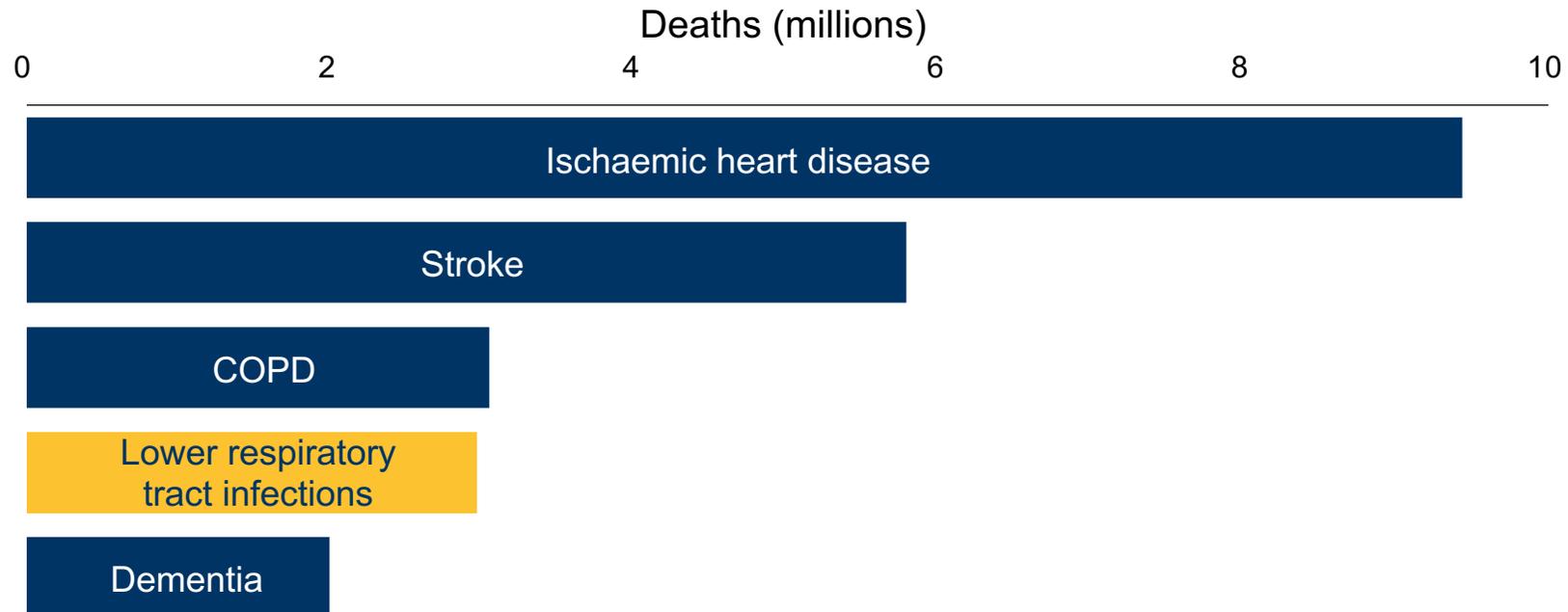
Pneumococcal pneumonia



Herpes zoster



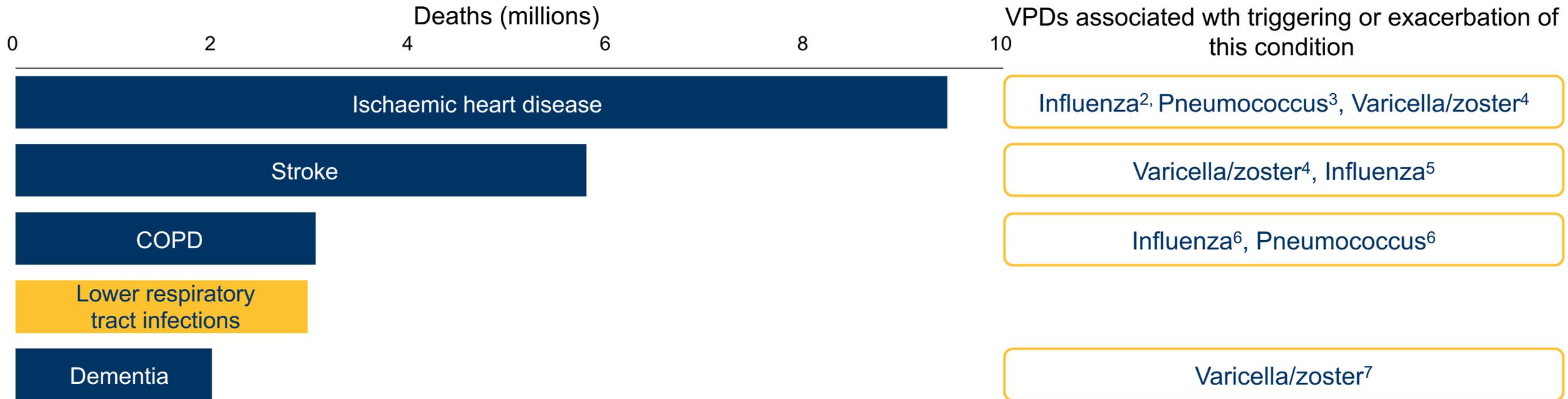
Globally, most leading causes of death are non-communicable diseases¹



1. WHO. The top 10 causes of death. 2018. <https://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death> [last accessed 29-Jul 2019].

Globally, most leading causes of death are non-communicable diseases¹

... but vaccine preventable diseases may play a role

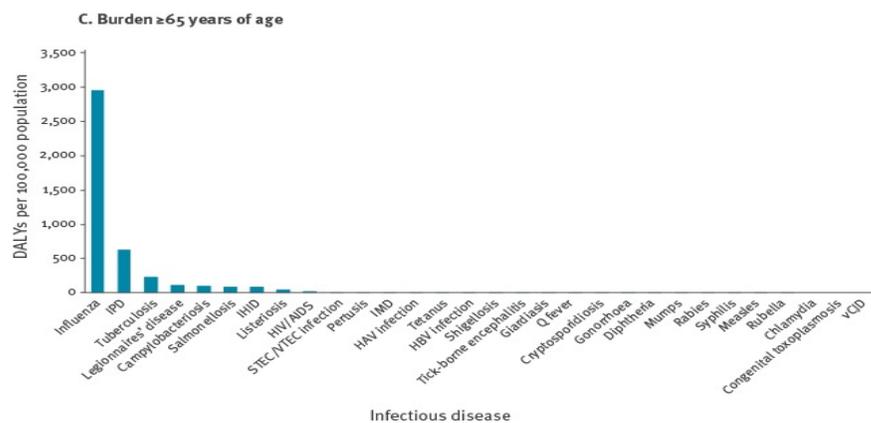
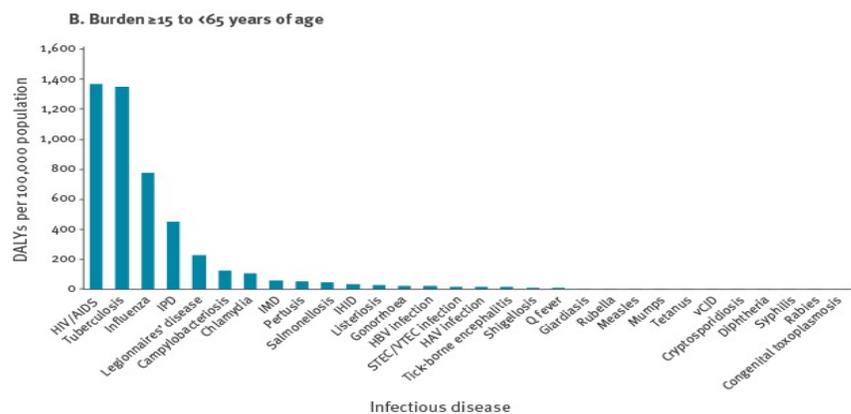
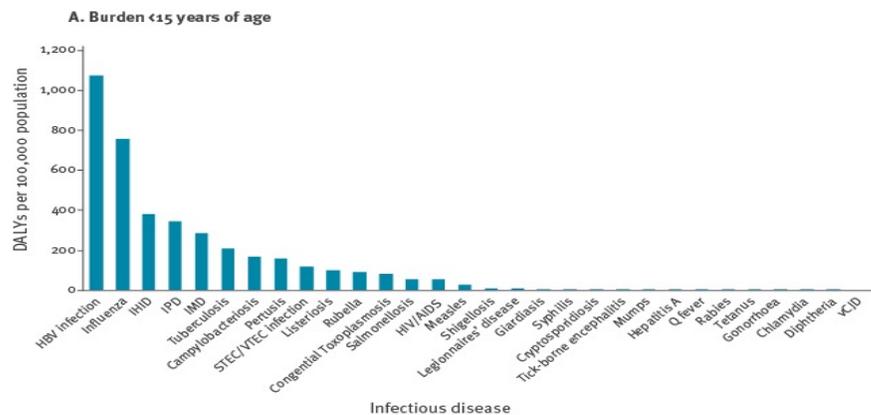


1. WHO. The top 10 causes of death. 2018. <https://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death> [last accessed 29-Jul 2019]; 2. Fischer WA 2nd et al. *Glob Heart* 2014;**9**:325–36; 3. Corrales-Medina VF et al. *PLoS Med* 2011;**8**:e1001048; 4. Zhang Y et al. *J Stroke Cerebrovasc Dis* 2017;**26**:1807–16; 5. Lee KR et al. *Neuroepidemiology* 2017;**48**:103–10; 6. Froes F et al. *Int J Chron Obstruct Pulmon Dis* 2017;**12**:3457–68. 7. Chen VC et al. *J Clin Psychiatry* 2018;**79**:pii:16m11312.

Number of influenza cases in Europe

- 5–15% of the population each year¹
- 4–50 million symptomatic cases in EU/EEA each year²
- 15,000–70,000 influenza-associated deaths in Europe every year²
- Influenza-associated hospitalisations are more common in adults ≥ 65 years of age (309/100,000 persons-years)²

Annual age group-specific burden of selected infectious diseases by age groups < 15 years of age, 15–64 years of age and ≥ 65 years of age, EU/EEA countries, 2009–2013



J. Paget, A. Danielle Iuliano, R.J. Taylor et al.

Vaccine 40 (2022) 1361–1369

Table 3
EU seasonal excess influenza mortality estimates by three different research groups: GLaMOR, US CDC and EuroMOMO.

Research group	Methodology	Total number of influenza-associated deaths in the EU (range)	All age rate (range)	Age 65+ rate (range)	Percentage over 65
GLaMOR	- Respiratory mortality - Years: 2002-2011 - Extrapolation of national estimates using multiple imputation method [3]	26,200 (13,700-40,800)	5.3 per 100,000 (3.8-6.7 per 100,000)	29.0 per 100,000 (16.6-41.2 per 100,000)	87%
US Centers for Disease Control and Prevention	- Respiratory mortality - Years: 1999-2015 - Extrapolation of national estimates based on WHO respiratory mortality data [4]	28,200	5.6 per 100,000	30.3 per 100,000	92%
EuroMOMO	- All-cause mortality - Years: 2012-2018 - Excess mortality estimate based on multiple European countries [8]*	81,600 (1,600-145,000)	16.1 per 100,000 (0.3-28.6 per 100,000)	79.4 per 100,000 (range 0.6-147.4 per 100,000)	94%

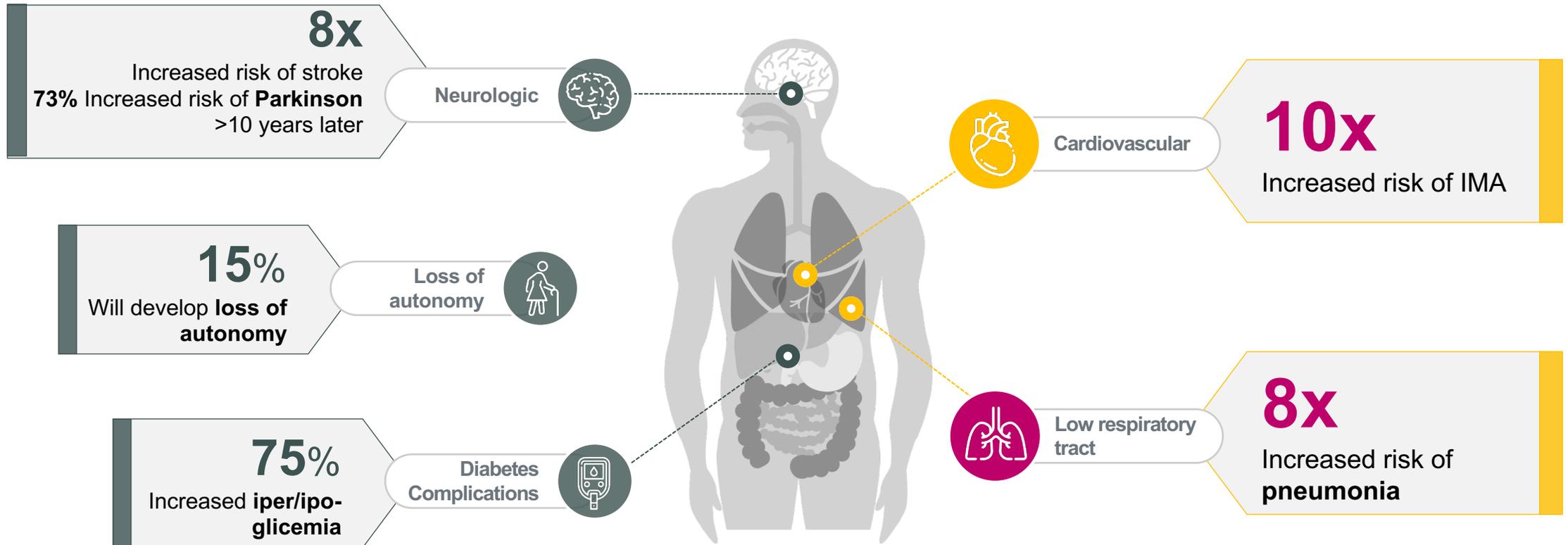
Note: The Global Burden of Disease (GBD) estimates prepared by IHME have been excluded from the Table as they define influenza-associated deaths in a different manner (GBD estimates only include deaths from lower respiratory tract infections that are directly caused by influenza) [14].

* We present the mean rates so that they are comparable to the GLaMOR estimates.

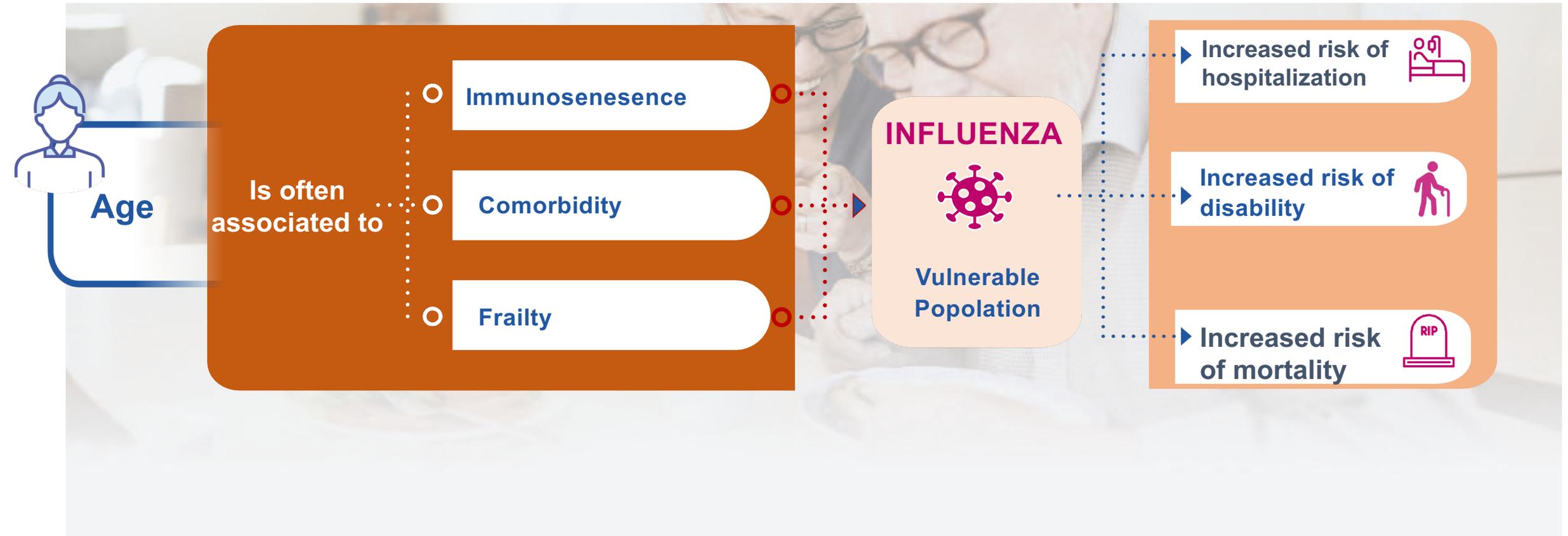
Paget J, et al. Vaccine. 2022 Feb 23;40(9):1361-1369

Influenza is associated with severe outcomes, not only limited to the respiratory system

A heavy, multidimensional impact



Older adults are more vulnerable to influenza



- In population 65+ we have the largest proportion of **hospitalizations (>60%)** and **deaths (90%)**
- The cost of hospitalization for flu complications is about twofold **compared to younger adults**

Disability and influenza

Catastrophic Disability:

Defined as a loss of independence in ≥ 3 basic activities of daily living²

- 14.6% of older adults hospitalized with influenza experience catastrophic disability³
- Dysregulated immune response is the 'sleeping giant' of chronic diseases. Flu wakes the giant, **increasing the risk of catastrophic disability** with:
 - Stroke, heart failure
 - Pneumonia⁴
 - Ischemic heart disease
 - hip fracture



Incidence (per 1000 person-years) of community-acquired pneumonia (CAP) in Europe in the adult population and by risk group

CAP incidence in
men aged >15 years
1.22 (1.18–1.26)¹

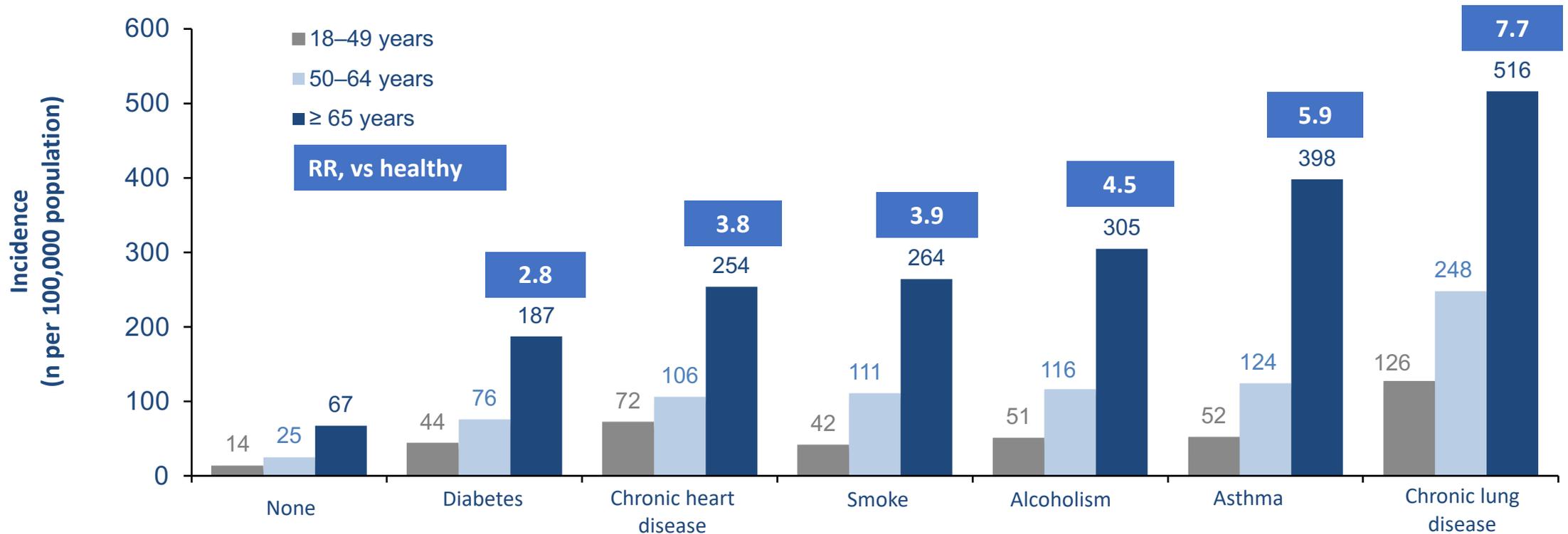
CAP incidence in
women aged >15 years
0.93 (0.89–0.96)¹



Incidence in adults aged >65 years
14.0 (12.7–15.3)^{1,2}

Common medical conditions increase pneumococcal pneumonia risk in adults

Data from a retrospective cohort study from three large, longitudinal, US healthcare databases of medical and outpatient pharmacy claims from 2006 to 2010*



Comorbidity risk group

*Persons aged 18–49 years, 50–64 years, and ≥65 years contributed a total of 49.3 million, 30.6 million and 11.7 million person-years of observation, respectively; RR, risk ratio

The same results were first published in Shea KM et al. *et al. Open Forum Infect Dis* 2014;1:[Epub] 2014. The graph has been

Long-term survival following pneumococcal pneumonia

Kaplan–Meier plots show the cumulative 10-year survival of 344 patients who survived pneumococcal pneumonia, stratified by severity (PSI) compared with the expected 10-year survival of an average 63-year-old American male

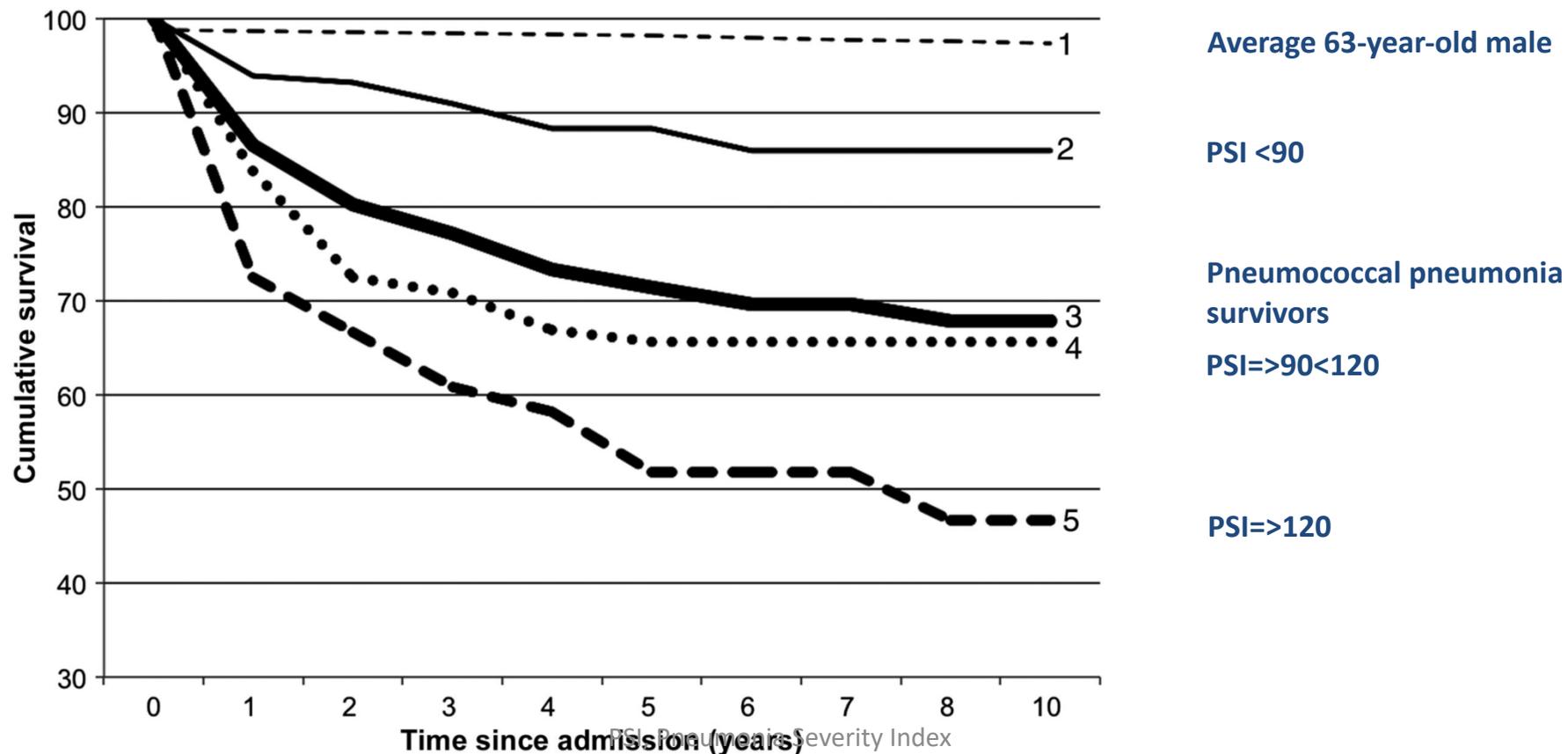


Figure reproduced from Long-term survival following pneumococcal pneumonia. Sandvall B *et al. Clin Infect Dis* 2013; 56:1145–1146

Shingles: a case study of a vaccine-preventable disease in older adults

≥99.5% of adults ≥50 years have anti-varicella zoster virus (VZV) antibodies and are at risk for shingles¹



Image source Shutterstock

Shingles presentation²

- VZV can reactivate years after primary infection, causing:
 - a unilateral, vesicular rash distributed across nearby dermatomes
 - neurological pain symptoms

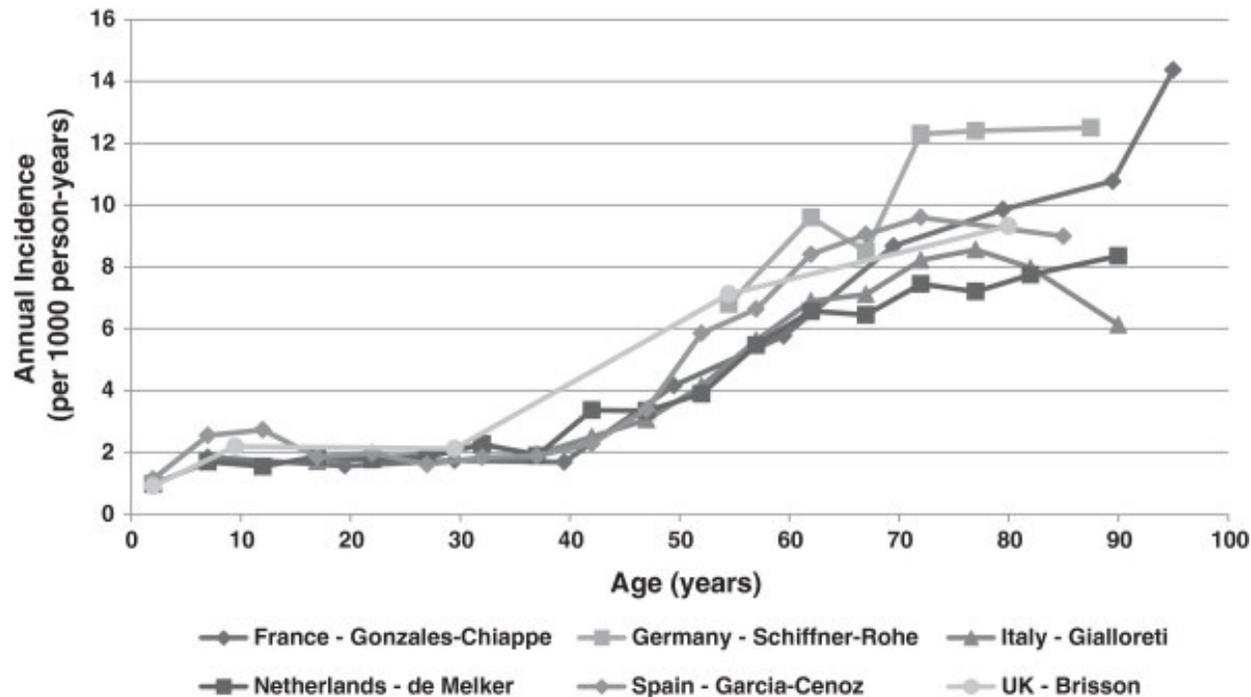


Courtesy of MN Oxman, UCSD

Complications of shingles²⁻⁴

- Postherpetic neuralgia (PHN): debilitating nerve pain affecting up to 30% of people with shingles; sometimes lasting months to years after rash onset
- Herpes zoster ophthalmicus (HZO): herpes zoster (HZ) of the eye, which can affect up to 25% of patients with shingles

The incidence rates of herpes zoster and PHN increase with age *2/3 of cases occur in >50-years-olds*



Euro estimates

(new cases x 1000 person-years)

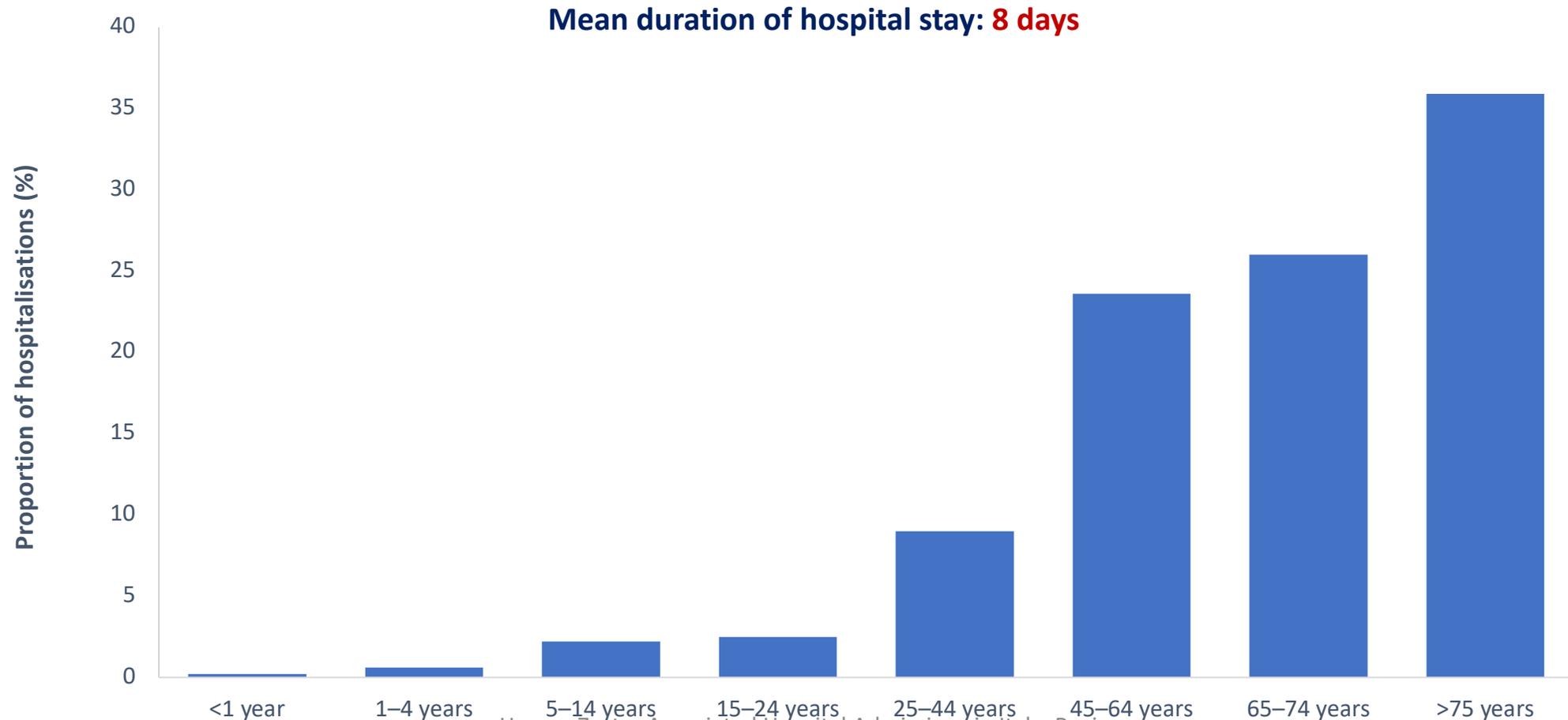
- 2.0–4.6 overall
- 7–8 in ≥50-year-olds
- 10 in ≥80-year-olds
- 20–50% of patients affected by PHN

Pinchinat 2013: In the case of several publications per country, the studies with the most recent data and the highest herpes zoster case sample size is presented

PHN, post-herpetic neuralgia

Similar herpes zoster incidence across Europe: results from a systematic literature review. Pinchinat S *et al.* *BMC Infect Dis*

Herpes zoster: hospitalisations and day-hospital admissions stratified by age classes, Italy (1999–2005)



Herpes Zoster Associated Hospital Admissions in Italy: Review of the Hospital Discharge Forms. Gabutti G *et al.* *Int J Environ Res Public Health* 2009;6:2344–2353, under Creative Commons Attribution 4.0 International License

Why vaccinate for shingles?¹

Treatment of acute HZ²

- Antivirals started within 72 hours of rash onset
- However, treatment within this timeframe is often not achievable

Management of HZ pain²

- Simple analgesics
- Drugs for neuropathic pain
- Combination therapy³

Prevention of HZ¹

- Current treatment options for PHN are suboptimal and often accompanied by intolerable side-effects
- Preventative public health options are limited because the disease is caused by a latent infection^{4,5}
 - **Effective preventative strategies (vaccination) are required**

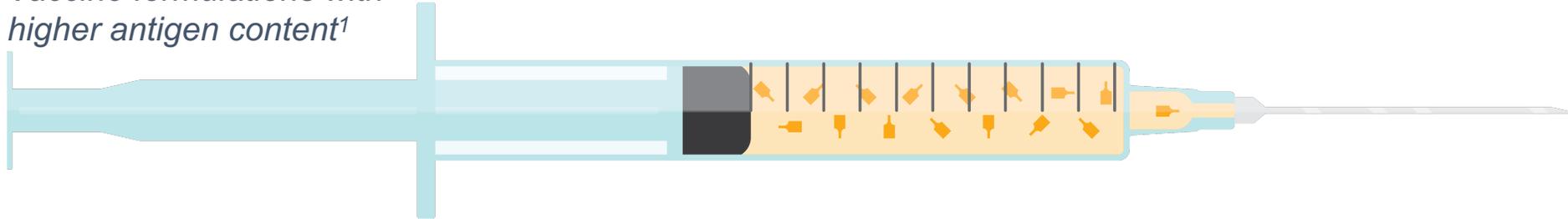
Outline

- Concepts of healthy ageing and frailty
- Human and economic cost of vaccine-preventable diseases (VPDs)
- Vaccination as a tool for healthy ageing and as a cost-effective preventive measure

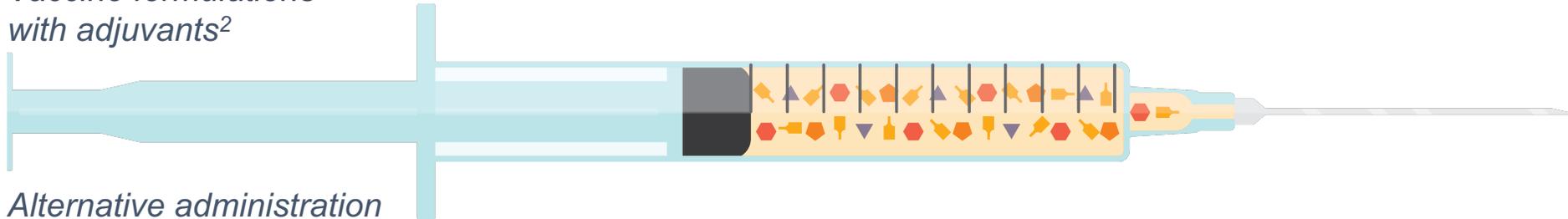
REDUCED RESPONSIVENESS TO VACCINATION IN OLDER ADULTS REQUIRES NOVEL STRATEGIES

These include different vaccine formulations, eg higher antigen content or the use of adjuvants, and alternative delivery routes¹⁻³

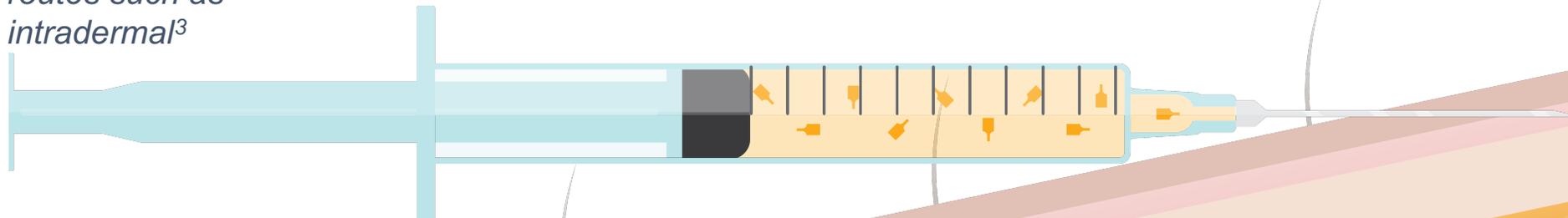
Vaccine formulations with higher antigen content¹



Vaccine formulations with adjuvants²



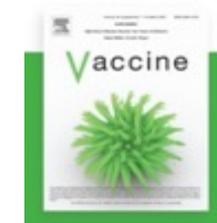
Alternative administration routes such as intradermal³



1. Robertson CA et al. *Expert Rev Vaccines* 2016;15:1495–1505; 2. Lal H et al. *N Engl J Med* 2015;372:2087–2096; 3. Arakane R et al. *Vaccine* 2015;33:6650–6658

Efficacy and effectiveness of high-dose influenza vaccine in older adults by circulating strain and antigenic match: An updated systematic review and meta-analysis [☆]

Jason K.H. Lee ^{a,b,*}, Gary K.L. Lam ^{a,b}, Thomas Shin ^{b,c}, Sandrine I. Samson ^d, David P. Greenberg ^d, Ayman Chit ^{a,d}



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							
	n	rVE ^c (95%CI)	p-value	A/H3N2-predominant Seasons		A/H1N1-predominant Seasons		Matched Seasons		Mismatched Seasons					
				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%	<0.001	6	17.7%	<0.001	1	–	–	4	17.4%	<0.001	3	18.6%	<0.001

Data on 34 Million individuals (22 M > 65 a.) over 10 seasons suggest that HD vaccine has significant higher efficacy/effectiveness compared to standard vaccine in multiple outcomes, independently from the circulating strain and antigenic match

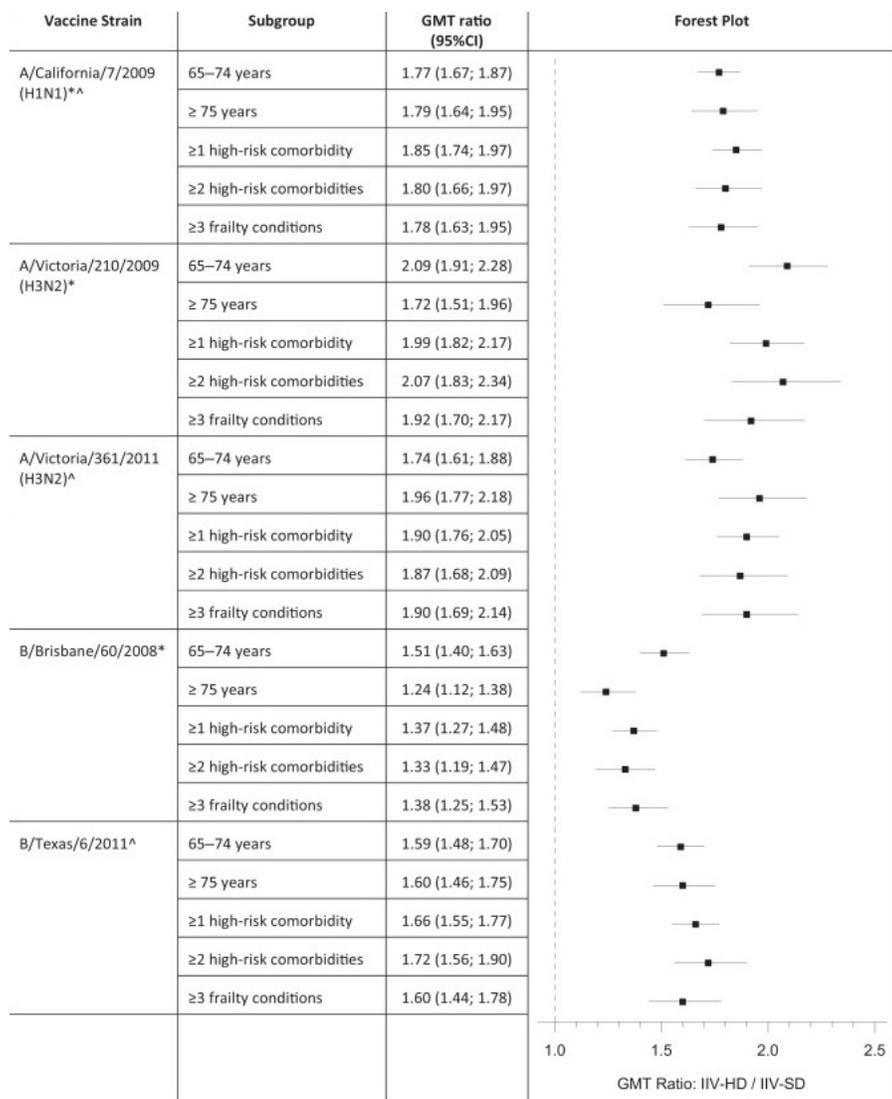


Fig. 1. HAI antibody GMT ratios (IIV-HD to IIV-SD) for vaccine strains.

(*) Corresponds to a year 1 vaccine strain; (^) corresponds to a year 2 vaccine strain. As the H1N1 vaccine strain was the same for year 1 and year 2, the data were pooled. The plot on the right depicts GMT ratios for each subgroup of interest; horizontal lines represent the 95% confidence intervals and solid squares represent the point estimates. All estimates to the right of the null value of 1 favor IIV-HD over IIV-SD. Estimates that do not intersect with the null value are statistically significant.

Received: 18 November 2021 | Revised: 16 January 2022 | Accepted: 18 January 2022

DOI: 10.1002/rmv.2330

WILEY

REVIEW

Systematic review of the efficacy, effectiveness and safety of high-dose seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in individuals ≥ 18 years of age

Laura Comber¹ | Eamon O Murchu^{1,2} | Karen Jordan¹ | Sarah Hawkshaw¹ | Liam Marshall¹ | Michelle O'Neill¹ | Conor Teljeur¹ | Máirín Ryan^{1,3} | AnnaSara Carnahan^{4,5} | Jaime Jesús Pérez Martín^{4,6} | Anna Hayman Robertson^{4,7} | Kari Johansen^{4,8} | Jorgen de Jonge^{4,9} | Tyra Krause^{4,10} | Nathalie Nicolay^{4,8} | Hanna Nohynek^{4,11} | Ioanna Pavlopoulou^{4,12,13} | Richard Pebody^{4,14} | Pasi Penttinen^{4,8} | Marta Soler-Soneira^{4,15} | Ole Wichmann^{4,16} | Patricia Harrington¹

Overall, high-dose influenza vaccines may provide better protection against laboratory-confirmed influenza and proxy outcome measures compared with SD-IIV3 in older adults. However, the evidence base is limited and largely restricted to cohort studies, so caution should be used when interpreting these results. A large body of evidence indicates that high-dose vaccines elicit more reactions overall compared with standard-dose equivalents, which is not surprising given dosage differences, however these seem relatively minor in the context.

ADJUVANTS ARE USED TO ENHANCE AND MODULATE THE IMMUNE RESPONSE TO VACCINE ANTIGENS

Adjuvants work together with antigens to produce an appropriate immune response in vaccinated individuals

*In **non-adjuvanted vaccines**, such as those containing live but weakened pathogens, antigens have sufficient pathogen immune defence triggers to activate an innate immune response*



Key



Macrophage



Dendritic cell



Antigen

ADJUVANTS ARE USED TO ENHANCE AND MODULATE THE IMMUNE RESPONSE TO VACCINE ANTIGENS

Adjuvants work together with antigens to produce an appropriate immune response in vaccinated individuals

*In **adjuvanted vaccines**, such as purified recombinant subunit vaccines, adjuvants are needed to enhance the immune response, for example, by mimicking some of the components of the pathogen*



Key



Macrophage



Dendritic cell

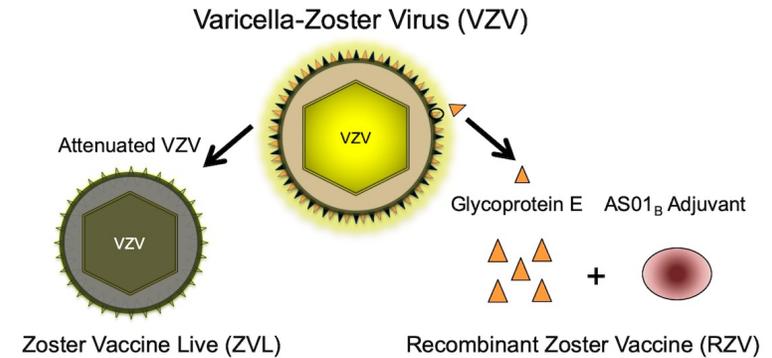
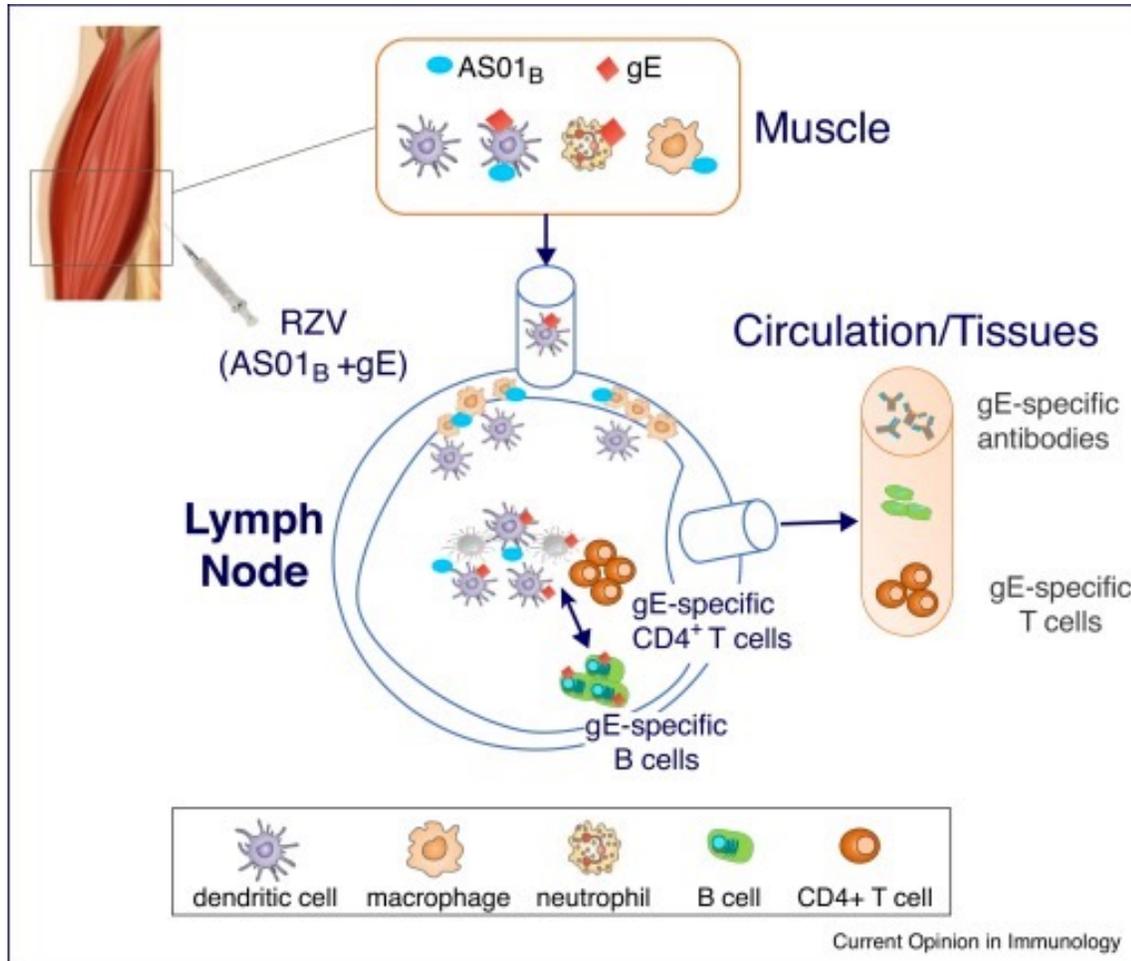


Antigen



Adjuvants

Case Example- Zoster vaccine: RZV elicits robust immunity in elderly population



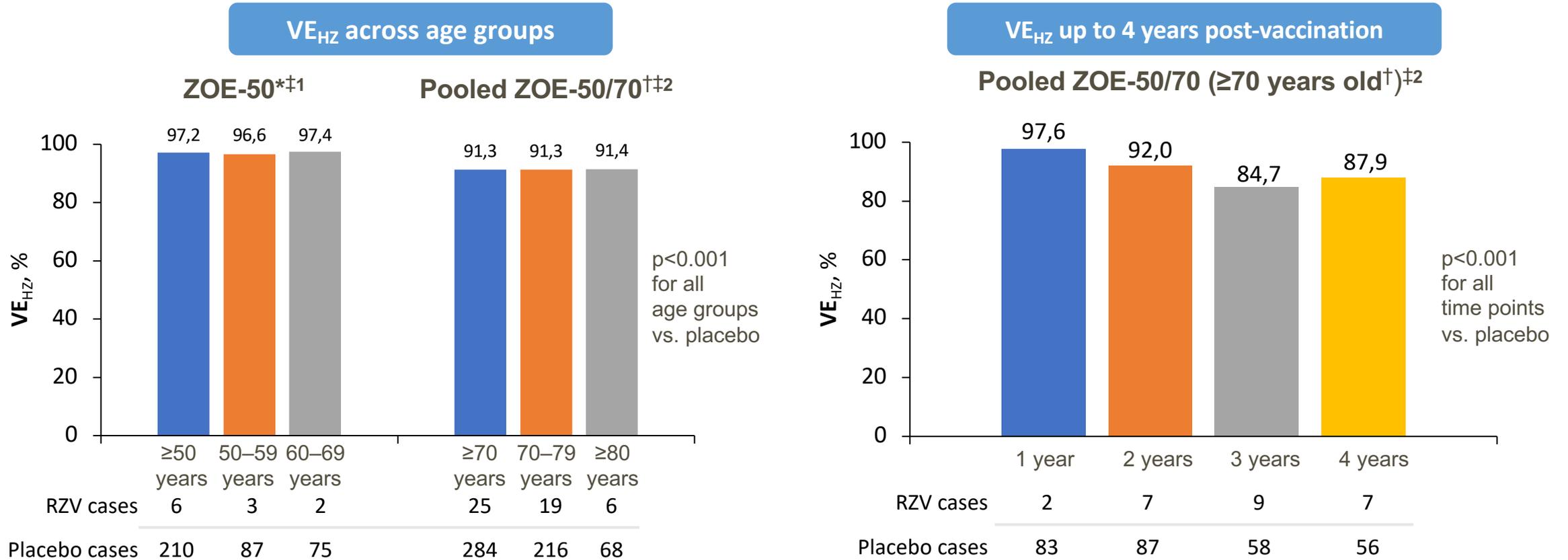
Spach DH ; National HIV Curriculum, April 2021

RZV stimulates broad, robust and persistent immune responses that include polyfunctional effector and memory T cells.

•RZV can overcome immune compromise resulting from age, disease or medication to stimulate protective immune responses.

Recombinant Zoster vaccine (RZV) Efficacy by age and duration

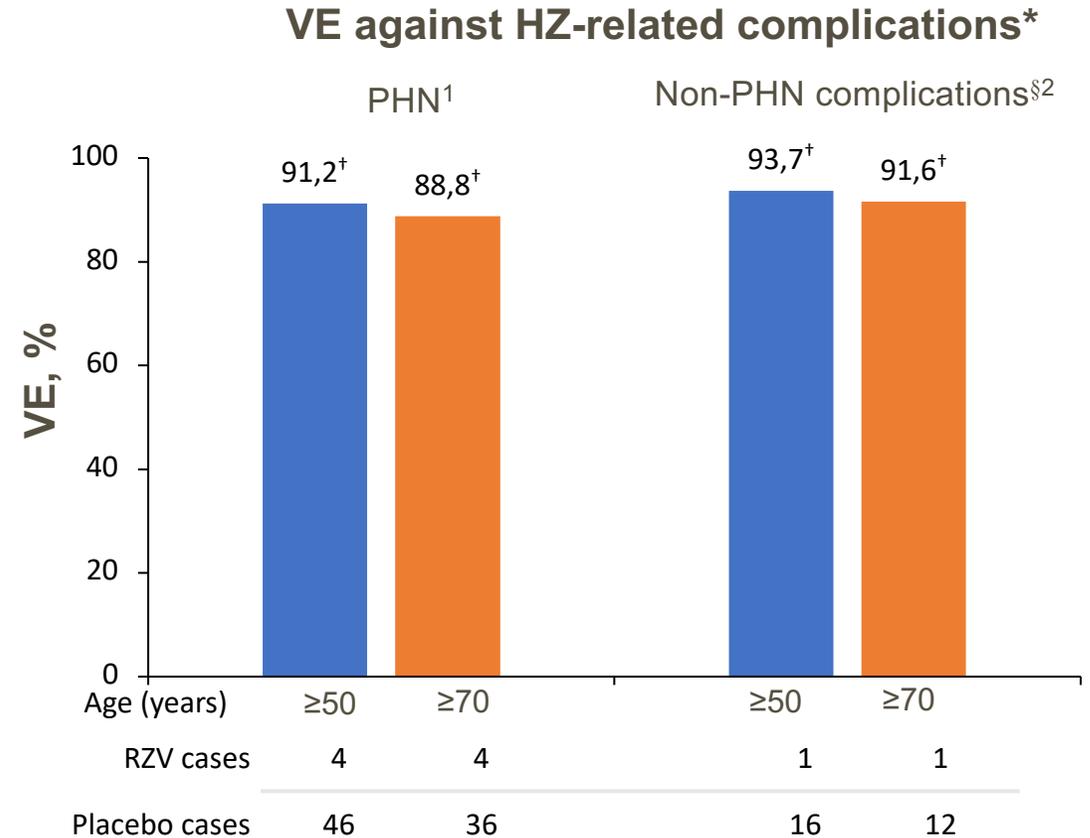
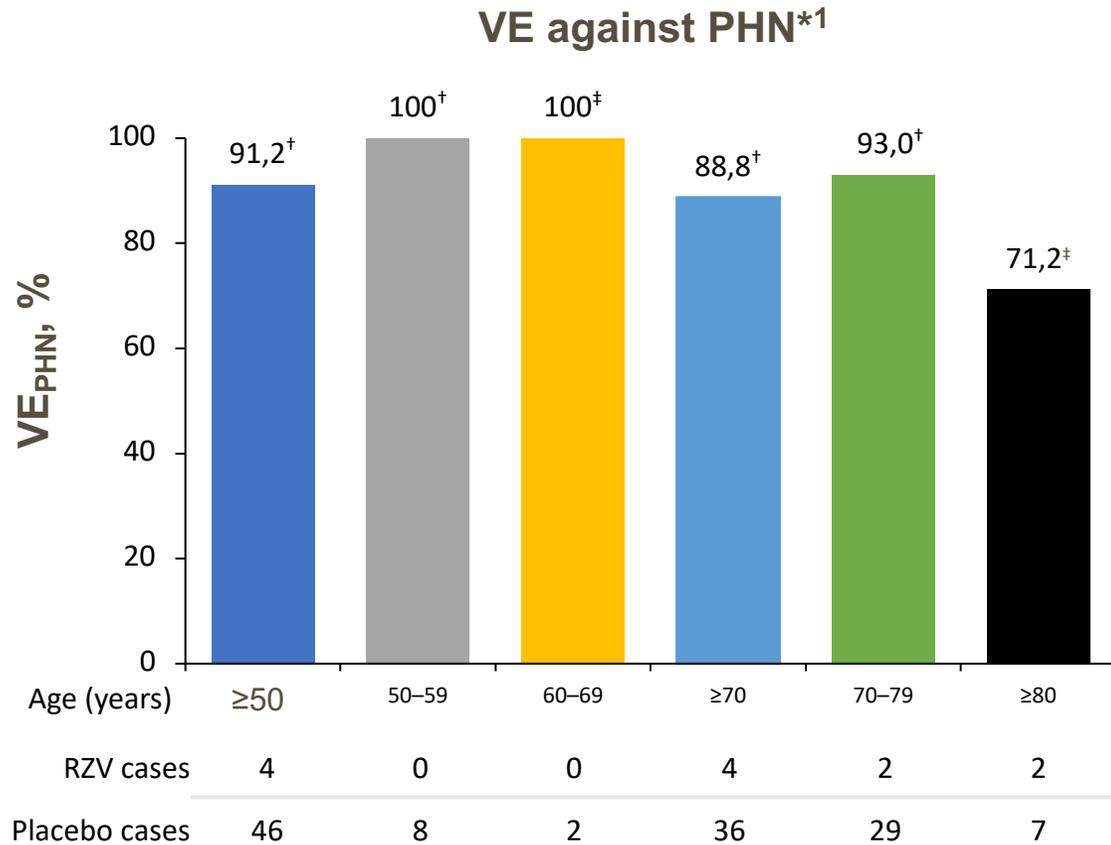
VE similar in all age groups and was 87.9% 4 years post-vaccination in patients ≥ 70 years old^{†1,2}



*Mean follow-up 3.2 years (ZOE-50)¹; [†]Mean follow-up 3.7 years (pooled ZOE-50/70 data for subjects ≥ 70 years old)²; [‡]Modified vaccinated cohort (excludes subjects not receiving dose 2 or who developed HZ within 1 month after dose 2); HZ, herpes zoster; VE_{HZ}, vaccine efficacy against HZ

PHN and non-PHN complications across age groups

Among patient groups ≥ 50 years of age in pooled analysis (ZOE-50 and ZOE-70)



*Mean follow-up periods: overall, 3.8 years¹; ZOE-50, 3.9 years²; and ZOE-70, 3.7 years²; [†]p<0.01 vs placebo (not shown); [†]Numbers of cases in the placebo group were not sufficient to obtain a significant result;

[§]HZ vasculitis, disseminated, ophthalmic, and neurological disease; HZ, herpes zoster; PHN, postherpetic neuralgia. PHN defined as zoster-associated pain rated as ≥ 3 (on a 0–10 scale), persisting or appearing more than 90 days after onset of zoster rash using Zoster Brief Pain Inventory (ZBPI); RZV, recombinant zoster vaccine; VE, vaccine efficacy

1. Cunningham AL, et al. *N Engl J Med* 2016;75:1019–32; 2. Kovac M, et al. *Vaccine* 2018; 36:1537–41

THE MOST FREQUENTLY REPORTED SOLICITED* ADVERSE EVENTS WERE INJECTION SITE PAIN, MYALGIA, AND FATIGUE

			RZV % (95% CI)†	Placebo % (95% CI)†
Injection site pain		Overall	68.1 (67.1–69.0)	6.9 (6.4–7.4)
		Grade 3	3.8 (3.5–4.3)	0.2 (0.1–0.3)
Myalgia		Overall	32.9 (31.9–33.8)	7.3 (6.8–7.8)
		Grade 3	2.9 (2.6–3.3)	0.4 (0.3–0.5)
Fatigue		Overall	32.2 (31.3–33.2)	10.5 (9.9–11.1)
		Grade 3	3.0 (2.6–3.3)	0.5 (0.4–0.7)

Mean duration of adverse events: Local solicited ≤3 days; General solicited ≤2 days; Any Grade 3 solicited ≤2 days

Rates of serious adverse events were similar between the RZV and placebo groups

Other solicited events included: redness, swelling, fever, headache, gastrointestinal symptoms and shivering

*Solicited adverse events were collected for 7 days after each vaccination in the reactogenicity sub-cohort, consisting of participants (≥50 years of age) who completed diary cards;

†Percentage of documented doses (RZV: N=9,560 for local symptoms, N=9,544 for general symptoms; Placebo: N=9,580 for local symptoms, N=9,576 for general symptoms)

CI, confidence interval; RZV, recombinant zoster virus

López-Fauqued M *et al. Vaccine* 2019;37:2482–93 (Supplementary appendix)

Benefits from vaccinations:

not only prevention of infectious diseases, BUT also of FRAILTY

- **Avoid mortality and costs linked to VPD**

E.g. Influenza vaccination coverage of 75% among individuals >65 years in Europe would result in 1.6–2.1 million cases prevented, and 25,000–37,000 related deaths avoided^{1,2}

- **Reduce complications and hospitalisation for chronic diseases**

E.g. **CVD, T2D, COPD, renal and hepatic diseases are more often associated with negative outcomes** in cases of infectious diseases^{1,3}

- **Decrease antibiotic use/polypharmacy**

E.g. **Antibiotic prescription was reduced by 64%** following influenza vaccination in Ontario, Canada⁴

- **Decrease antibiotic-resistant infections**

E.g. Pneumococcal vaccines reduce the incidence of **penicillin-resistant *Streptococcus pneumoniae***⁵

- **Improve quality of life and reduction of noncommunicable diseases**

E.g. Herpes zoster vaccine increases quality-adjusted life years in older adults by decreasing the burden of disease, including **decreased risk of stroke**^{1,6}

Influenza and pneumococcal vaccination may reduce the incidence of MI up to 50%^{1,7}

COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; MI, myocardial infarction; T2D, type 2 diabetes
1. Doherty TM et al. Eur Geriatr Med 2018;9:289–300; 2. Freaud E et al. BMC Public Health 2014;14 [Epub]; 3. Andre FE et al. Bull World Health Organ 2009;85:140–146; 4. Kwong N et al. Clin Infect Dis 2009;49:750–756; 5. Dagan B. Clin

A public health MUST

- The population in the EU is rapidly ageing^{1,2}
- Older adults constitute the largest risk group for VPDs^{1,2}
- VPDs in older adults place a substantial burden on individuals and on the health system²
- In spite of the availability of effective vaccines, some VPDs affect million of Europeans annually, with the greatest burden in older adults^{1,2}

Infections in Elderly Adults

Traditional parameters

- Clinical features
- Changes in laboratory values
- Clinical response
- Microbiological response
- Cause-specific mortality

Geriatric parameters

Physical and Cognitive functions
Complications
Health care aspects

Geriatric Parameters

Physical & Cognitive functions

Does the patient return to the same level of physical function?

Did the cognitive function of the patient change during and after the infection?

Has depression become clinically apparent and has it affected the recovery of function?

Complications

What are the infectious and not infectious complications?

Do they differ from those seen in the younger patients with the same infection?

Healthcare aspects

Is the length of hospitalization and the cost care higher for older than for younger patients with the same infectious disease?

Is the discharge to a place other than home required?

Conclusions

As individuals grow older, an age-related decline in immunity occurs and vaccine-preventable diseases increase morbidity and mortality, both directly, and by triggering or exacerbating non-communicable diseases

Vaccinations can improve adult health to a greater extent than that attributable to prevention of acute cases of infectious diseases

Vaccinations can play a key role in improving healthy life expectancy – and **adjuvants** can play a major role in improving their efficacy