

# I Vaccini nell'anziano

Raffaele Antonelli Incalzi

Università Campus Bio-Medico

Roma

# Outline

- Age as a risk factor and a severity factor for infectious diseases
- Biological aging and immunosenescence
- The burden of vaccine preventable diseases (VPDs) at older ages
- Vaccines: direct and indirect effects
- The obstacles to vaccines

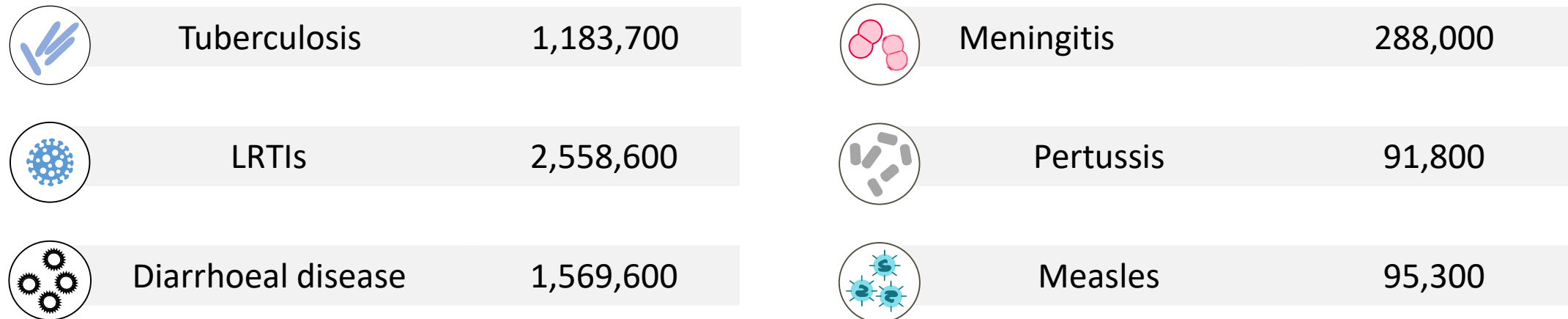
Age as a risk factor and a severity factor for infectious diseases

# Despite the success of vaccines, communicable diseases remain a global burden<sup>1</sup>

Vaccines prevent an estimated **2.5 million deaths** each year, making them one of the most successful healthcare interventions<sup>1</sup>

Despite this success, communicable diseases still occur globally<sup>1</sup>

## Number of deaths due to communicable diseases worldwide, 2017<sup>2</sup>



LRTI, lower respiratory tract infection

1. World Health Organization (WHO), 2013. Global vaccines action plan 2011–20. [http://www.who.int/immunization/global\\_vaccine\\_action\\_plan/GVAP\\_doc\\_2011\\_2020/en/](http://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/) (accessed November 2019); 2. Global Burden of Disease 2017 Causes of Death Collaborators. *Lancet* 2018;392:1736–1788

# Older adults are known to be at higher risk of severe outcomes from infectious diseases than younger individuals



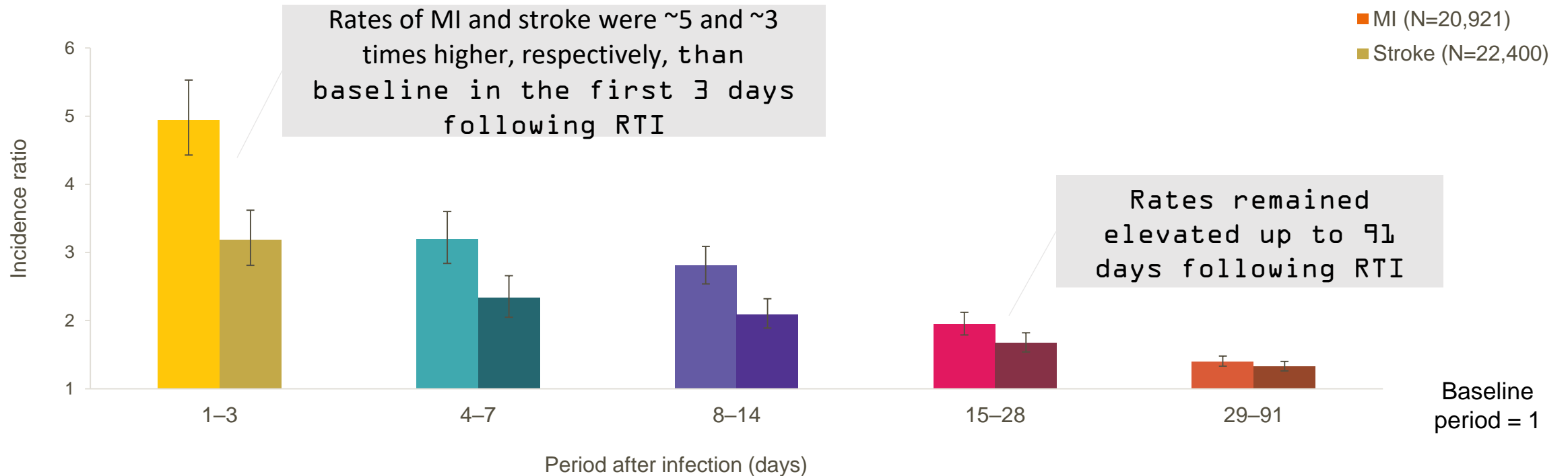
Almost **75% of deaths** due to influenza and pneumococcal disease occur in adults aged ≥65 years<sup>1,2</sup>

EU, European Union

1. European Centre for Disease Prevention and Control (ECDC), 2020. Surveillance atlas of infectious diseases. <https://atlas.ecdc.europa.eu/public/index.aspx>; 2. Centers for Disease Control and Prevention (CDC), 2020. Estimated influenza illnesses, medical visits, hospitalizations, and deaths in the United States — 2018–2019 influenza season. <https://www.cdc.gov/flu/about/burden/2018-2019.html> (URLs accessed June 2022)

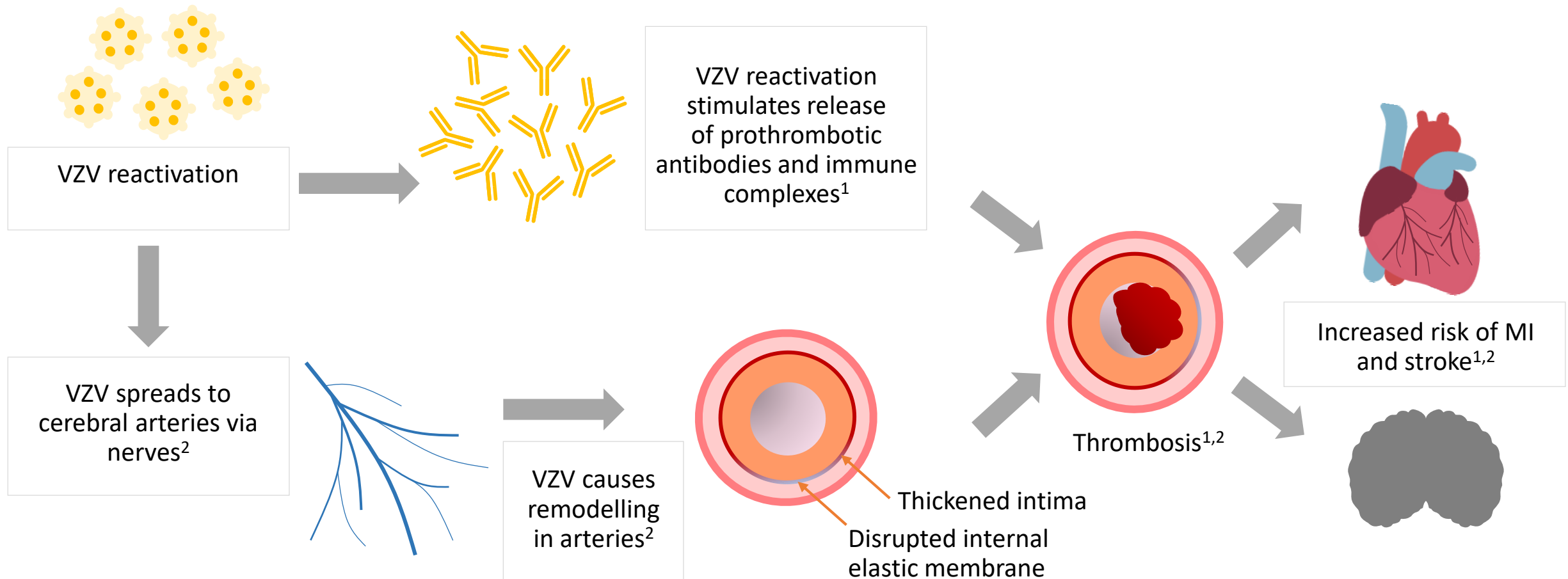
# Respiratory tract infections such as influenza increase the risk of myocardial infarction and stroke in adults

Age-adjusted incidence ratios of a first myocardial infarction or stroke after respiratory tract infection, in adults aged  $\geq 18$  years



MI, myocardial infarction; RTI, respiratory tract infection

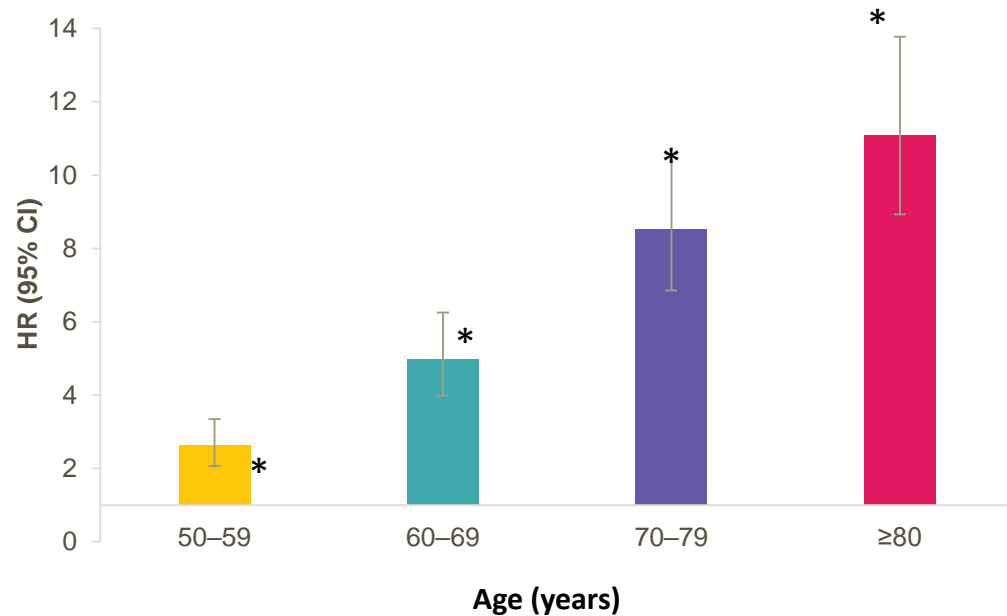
# Varicella zoster virus reactivation may lead to cardiovascular events by inflaming and remodelling cerebral arteries



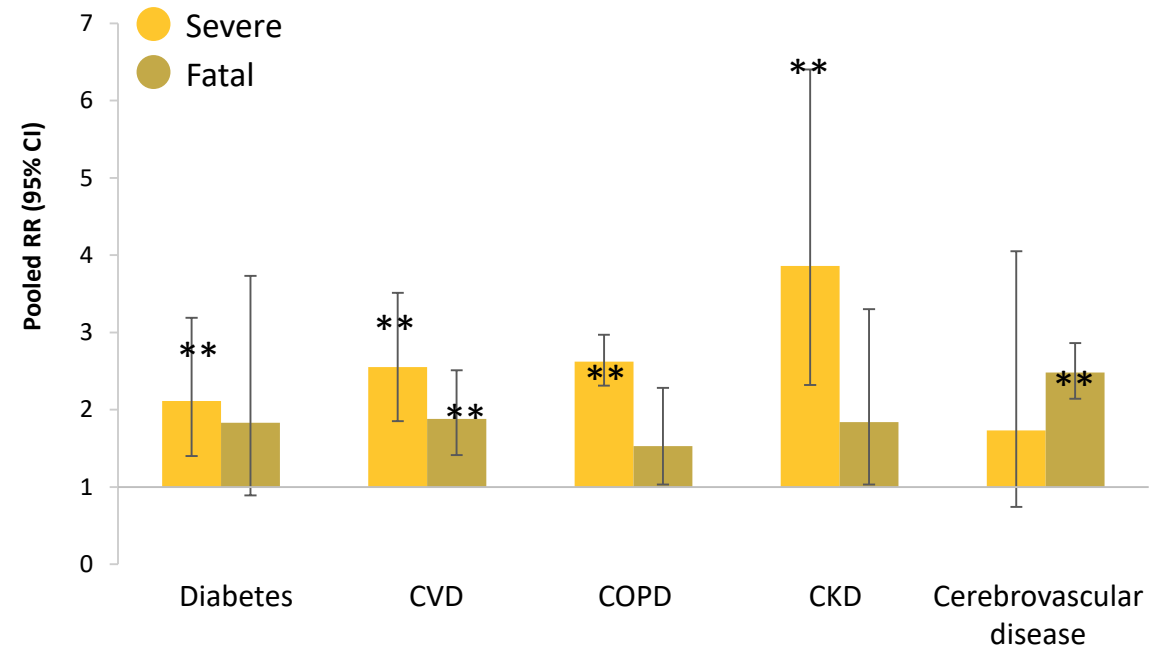
# During the COVID-19 pandemic, older adults and those with comorbidities have experienced higher rates of severe or fatal infection



Risk of death due to COVID-19 infection in adults aged  $\geq 50$  years compared with those aged  $< 50$  years (N = 20,133)<sup>1</sup>



Risk of suffering severe or fatal COVID-19 infection in individuals with comorbidities compared with those without (N = 14,558)<sup>2</sup>



\* $P < 0.001$ ; \*\* $P < 0.001$ . CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HR, hazard ratio; RR, risk ratio

1. Docherty AB et al. BMJ 2020;369:m1985; 2. Singh AK et al. Diabetes Obes Metab 2020;10.1111/dom.14124



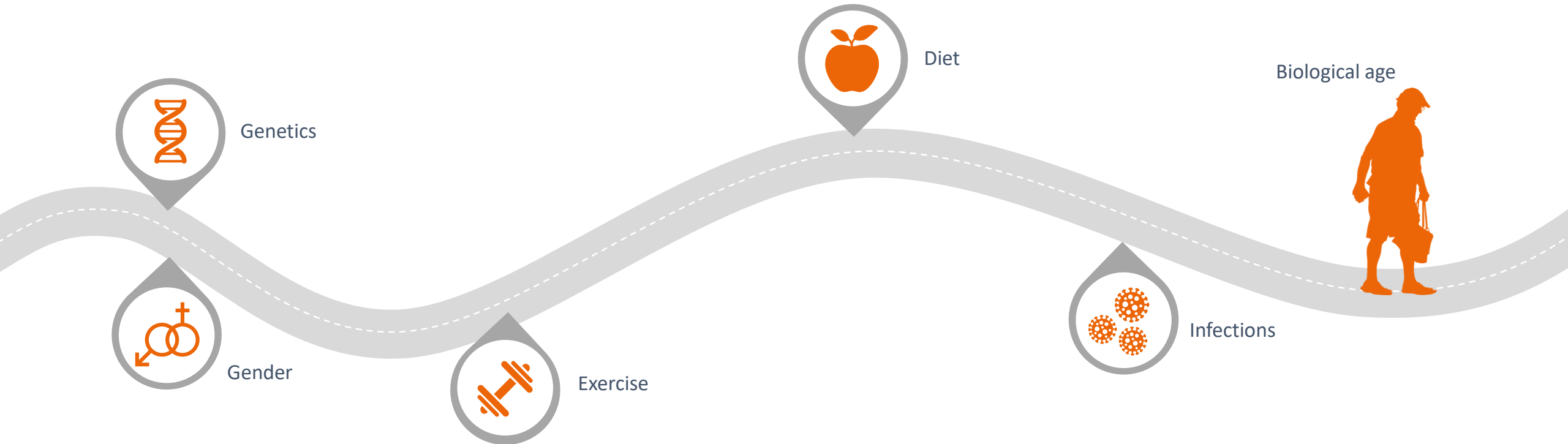
# Biological aging and immunosenescence

# Individuals age at different rates, determined by both biological factors and external influences

Figure is for illustrative purposes only

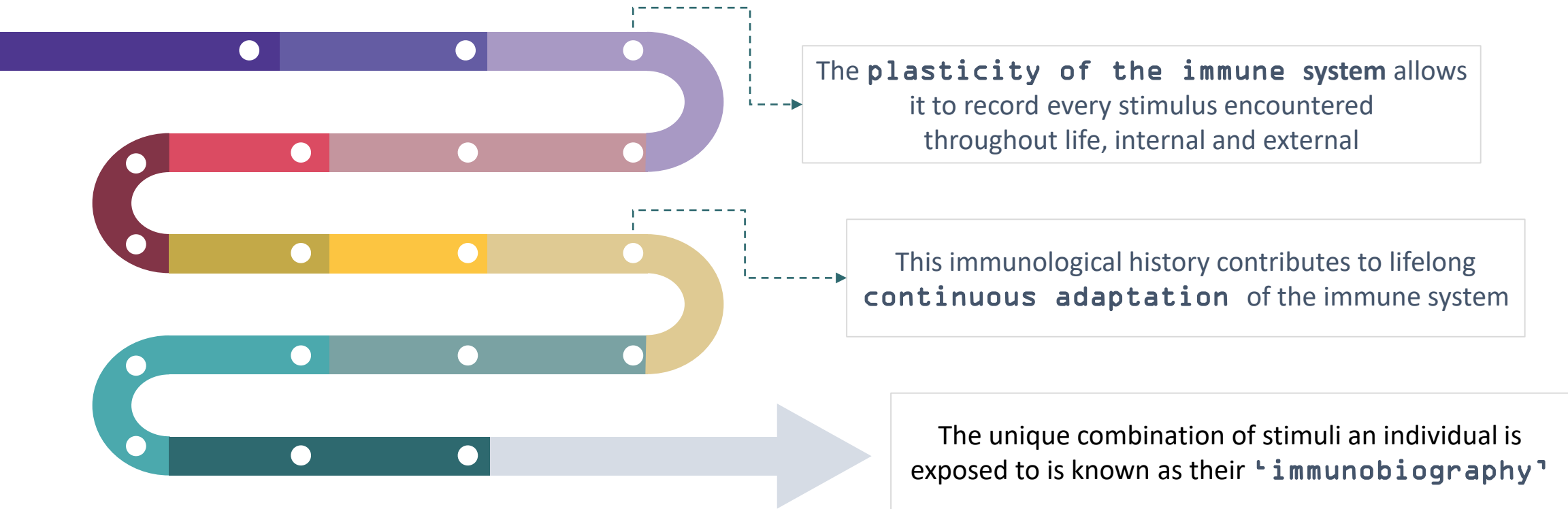
Both intrinsic factors, such as genetics, and extrinsic factors, such as lifestyle choices, impact the rate at which an individual ages

Biological age accounts for the impact of these factors in an individual's ageing process



# The immune system changes over time as it encounters immunological stimuli

Throughout life, individuals are continuously exposed to a wide variety of stressors, both potentially harmful and beneficial, though diet, injuries, infections, vaccinations, etc.

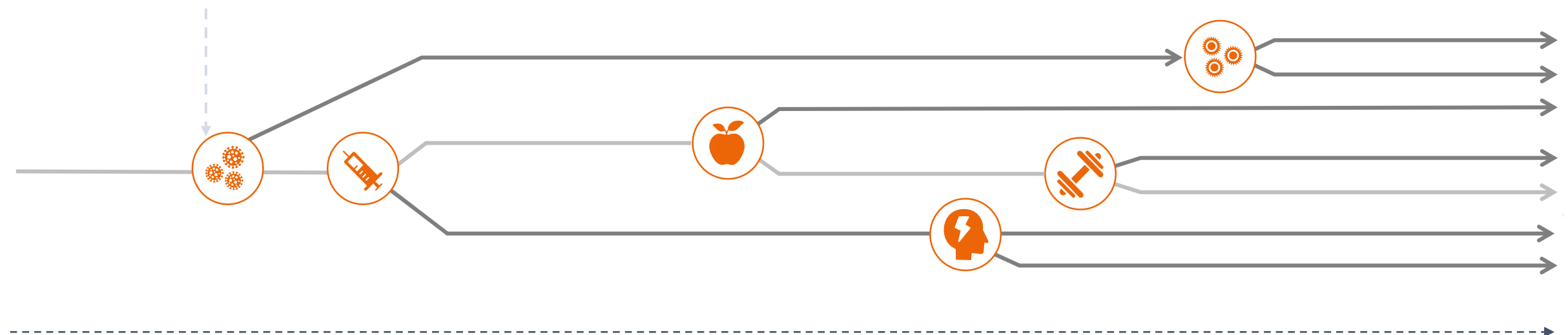


# Immune system health can be optimised by taking into account environmental exposures

Figure is for illustrative purposes only and is not intended to represent favourable or unfavourable exposures

Different **environmental exposures** occur during different life periods, and each play a role in immune programming

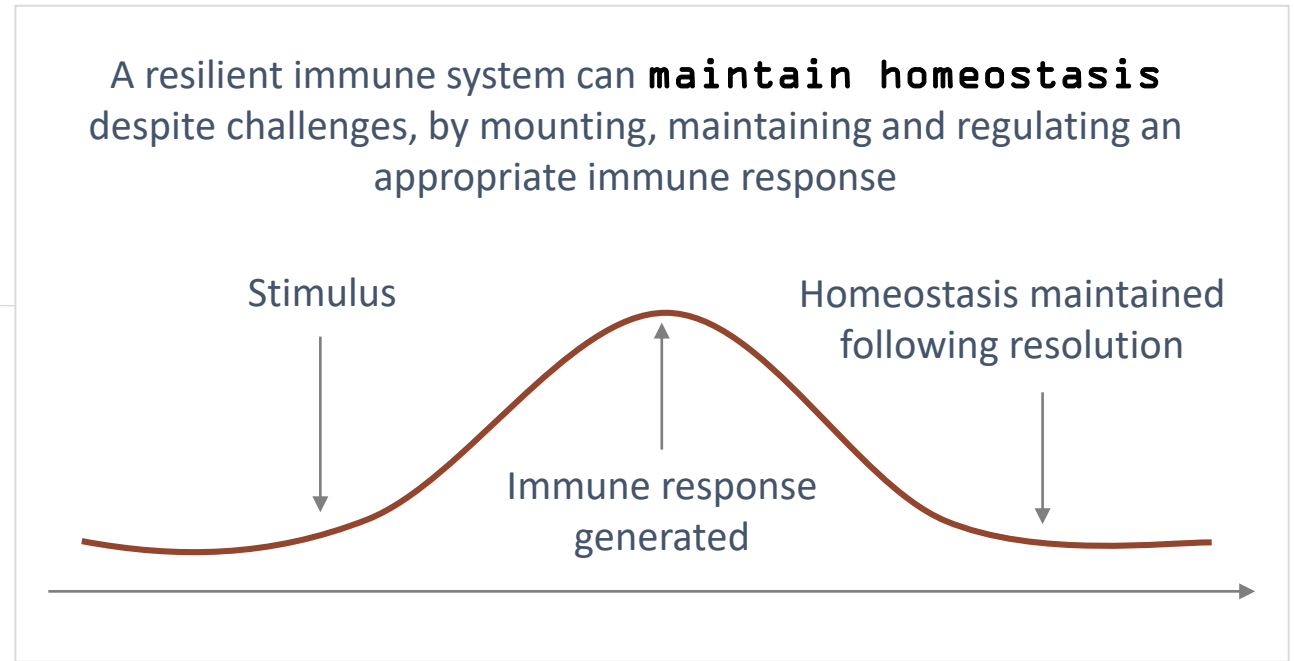
Some may have more favourable effects than others, both immediate and long term



Age

By considering these, immune development may be able to be **directed** towards **better outcomes**

Immune fitness is a state in which the immune system is resilient and capable of adapting to challenges appropriately



**Immune resilience can be built throughout life, by controlling the environmental factors that the immune system encounters**

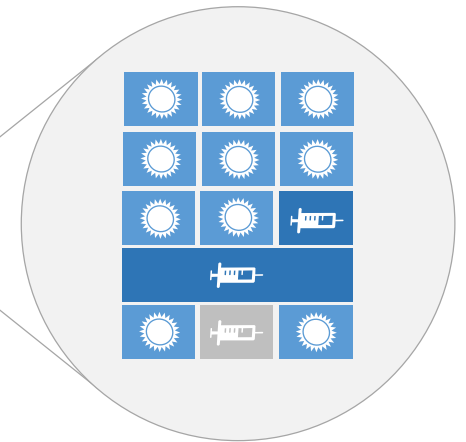
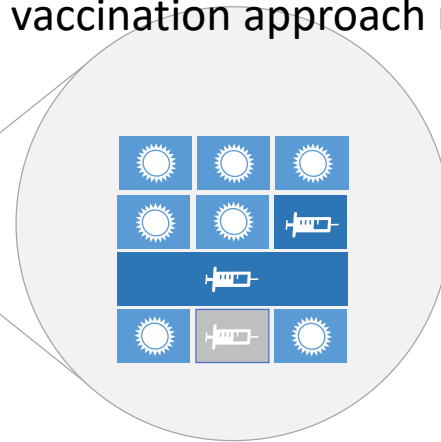
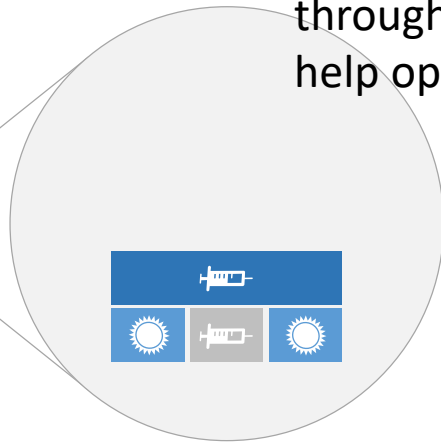
# The bases for immune system resilience

Each new infection or vaccine an individual is exposed to during a lifetime may **educate** and **alter** their immune system dynamics

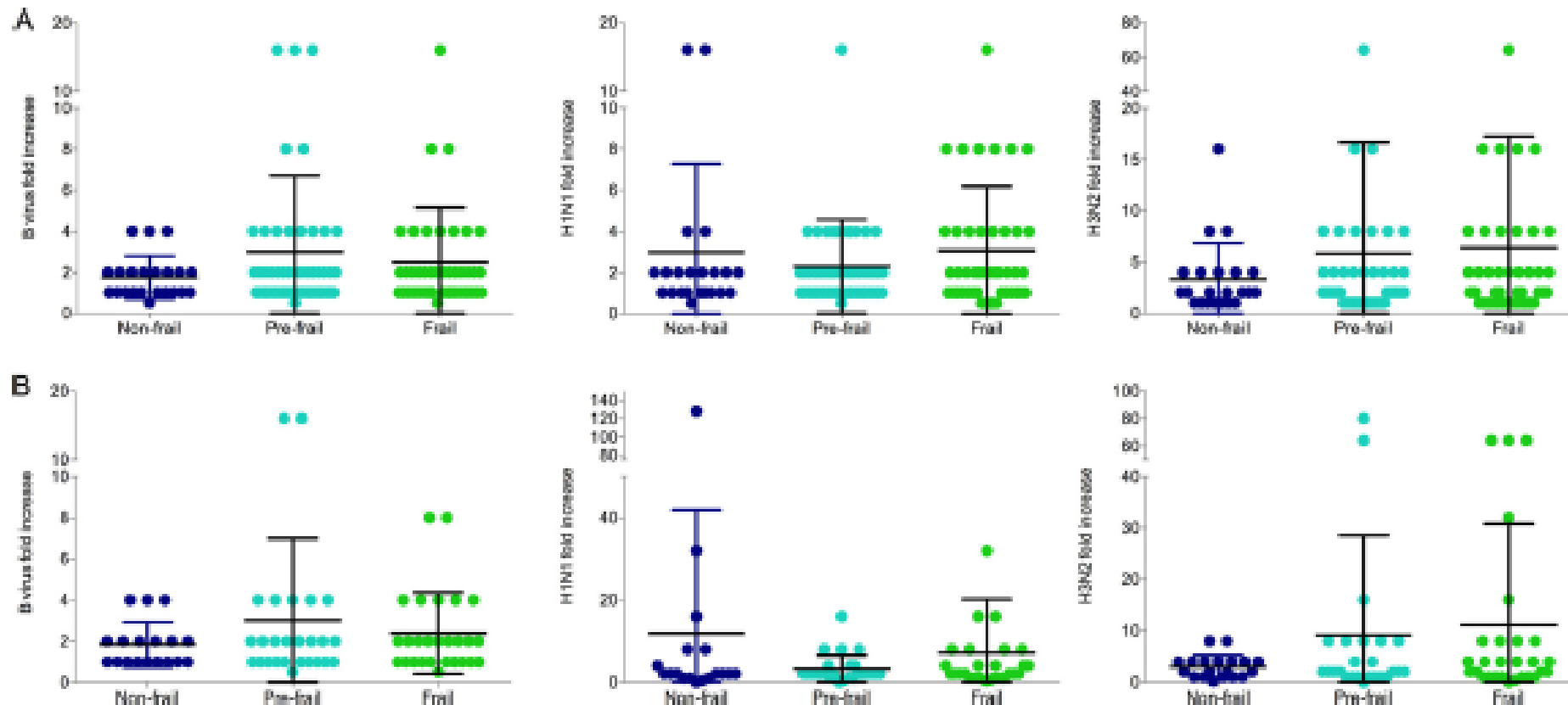
This lays down the foundation for all subsequent responses

This may suggest some vaccination strategies are **more optimal than others** in educating a resilient immune system

Infections and vaccinations can affect immune function throughout life - a tailored vaccination approach may help optimise immune



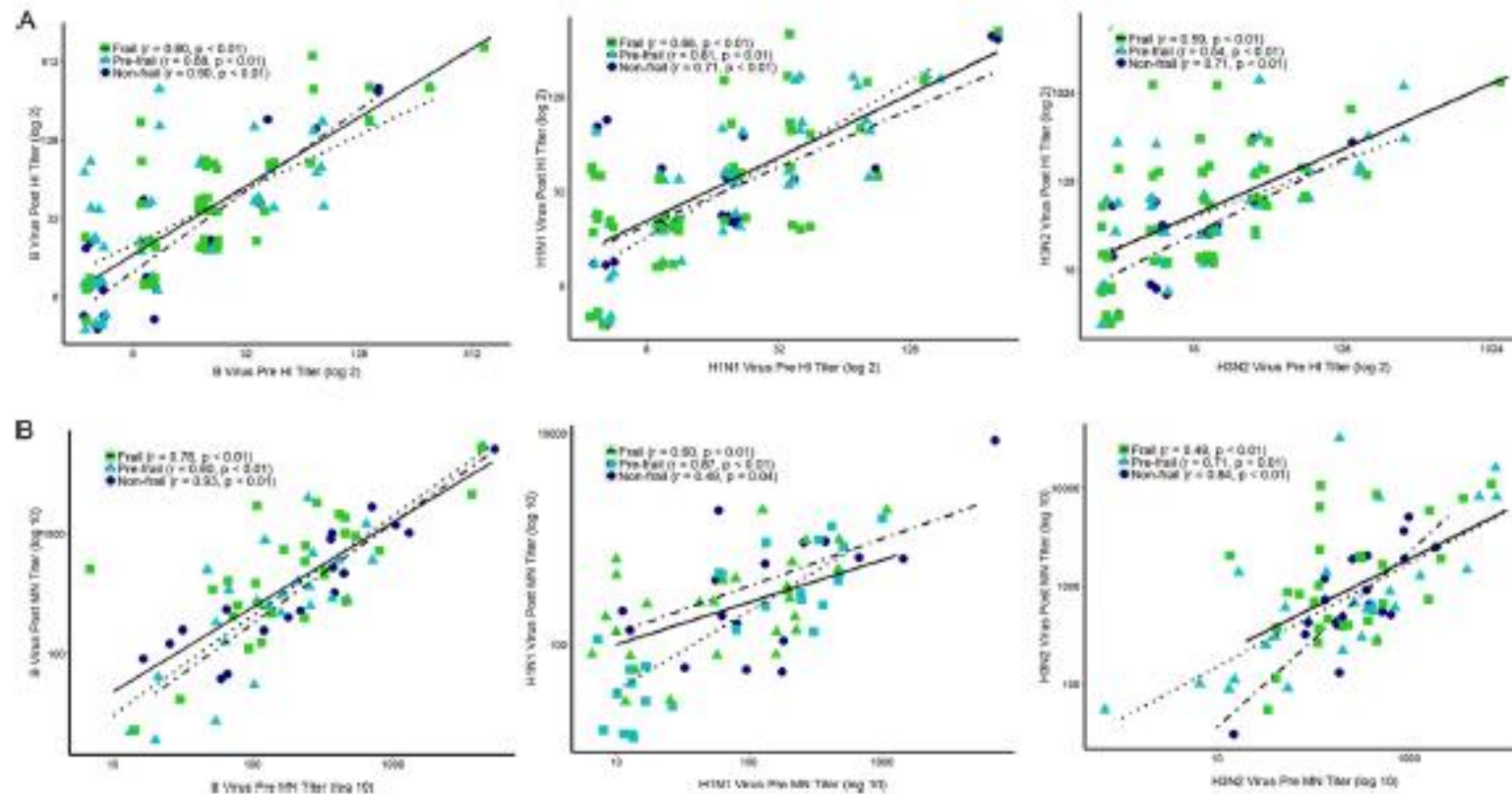
# Frailty does not weaken the Antibody response to influenza vaccine...



**FIG 1** Comparison of hemagglutination inhibition (HI) (A) and microneutralization (MN) (B) postvaccination/prevaccination geometric mean titer (GMT) ratios within frailty groups. No statistically significant differences, as measured by one-way ANOVA, were found between frailty groups. Horizontal black lines represent the mean, and the vertical lines represent 1 standard deviation (SD).

- Frailty does not weaken the Antibody response to influenza vaccine (Van Epps P et al. March 2017 Volume 24 Issue 3 e00498-16 Clinical and Vaccine Immunology)

..., while previous immunization does (Van Epps P et al. March 2017 Volume 24 Issue 3 e00498-16 Clinical and Vaccine Immunology)



**FIG 2** Correlation of preexisting immunity with postvaccination responses, as measured by hemagglutination inhibition (HI) (A) and microneutralization (MN) (B) assays. Antibody levels were plotted within frailty groups, and correlations were calculated to determine the effect of preexisting immunity on postvaccination antibody titers. The Spearman correlation coefficient and *P* value are presented for each frailty group.



# Even the old old has a satisfactory response to Covid-19 vaccine (Fedele G et al. JAMDA 2022... )

**Table 1**  
Geometric Means (GMs) and SEs of SARS-CoV-2 TrimericS IgG Serum Concentration at Baseline Assessment (Prior to Vaccination, T0), 2 and 6 Months After First Dose (T1 and T2), and 2 Months After Third Dose (T3) in Nursing Home Residents

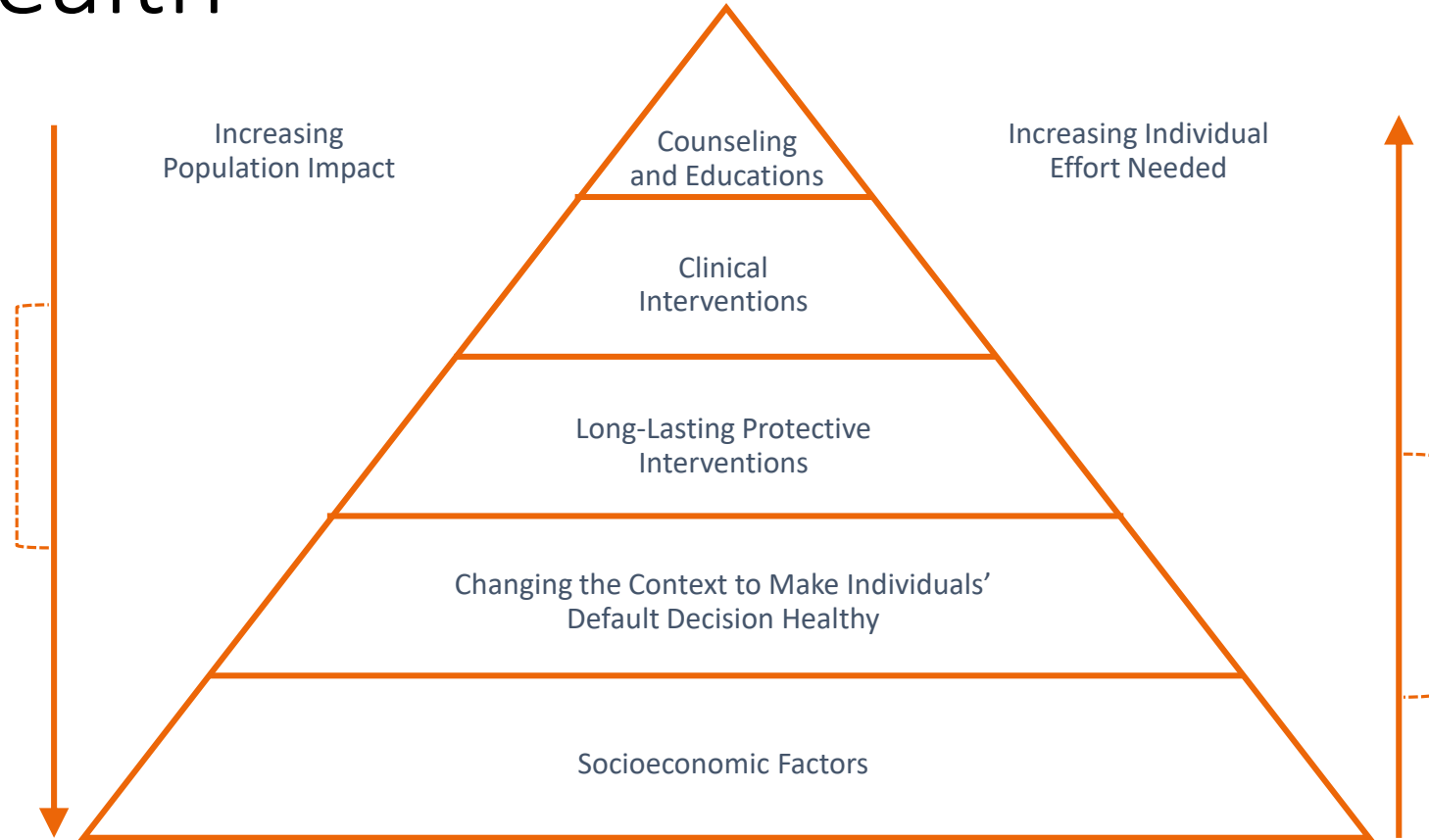
	SARS-CoV-2 TrimericS IgG Serum Concentration, BAU/mL											
	T0: Prior to Vaccination			T1: 2 mo After First Dose			T2: 6 mo After First Dose			T3: 2 mo After Third Dose		
	GM	SE	<i>P</i> Value	GM	SE	<i>P</i> Value	GM	SE	<i>P</i> Value	GM	SE	<i>P</i> Value
Whole sample (n=144)	4.9	0.1	<.001	833.7	89.8	Ref.	92.0	8.7	<.001	3597.9	339.5	<.001
Sex												
Women (n=104)	5.0	0.1	<.001	812.0	103.3	Ref.	98.3	11.9	<.001	3690.6	663.9	<.001
Men (n=40)	4.8	0.1	<.001	892.7	183.0	Ref.	95.3	18.5	<.001	3562.9	397.5	<.001
Age group												
<80 y (n=35)	4.8	0.14	<.001	1176.1	255.0	Ref.	124.8	23.9	<.001	4832.0	919.1	<.001
≥80 y (n=109)	5.0	0.08	<.001	746.4	91.7	Ref.	83.4	9.0	<.001	3272.8	352.7	<.001

Ref., reference.

All participants received 2 doses of BNT162b2 vaccine 3 weeks apart and a third dose of an mRNA vaccine (mRNA-1273 or BNT162b2) between 6 and 9 months from the first vaccine dose. GMs were compared across the 4 time points (T1 is the reference).

# The burden of vaccine preventable diseases (VPDs) at older ages

# Place and role of different interventions to preserve health



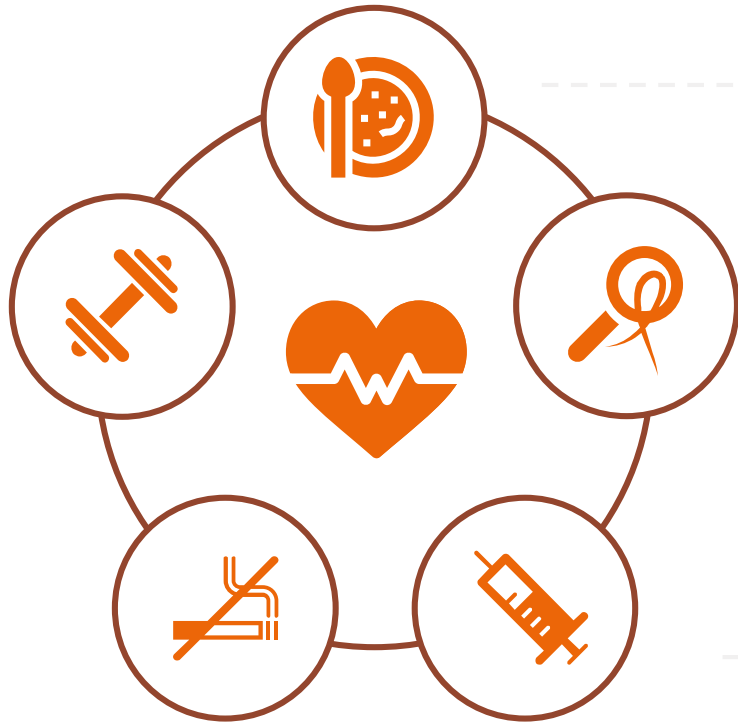
# To maximise immune benefits throughout life, the focus of vaccination must move from just childhood to the life-course

Immunization programmes have traditionally focused almost entirely on childhood vaccinations<sup>1,2</sup>

In order to protect the increasingly ageing population throughout life, programmes must evolve to focus on the **entire life-course**<sup>1,2</sup>



# Promoting life-course vaccination to improve immune resilience as part of a wellness package may help encourage behavioural change



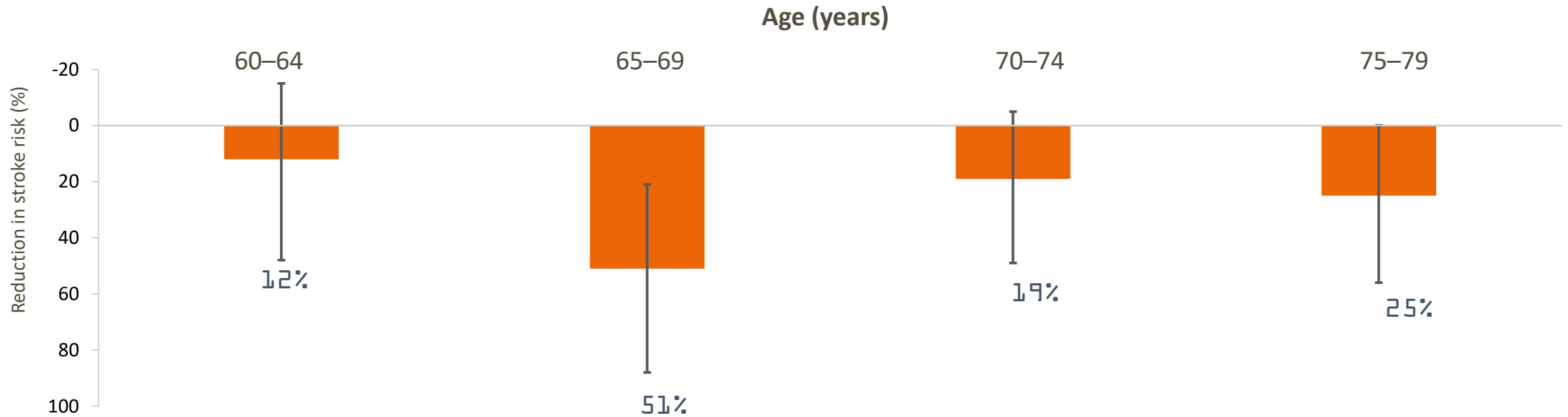
Active participation in self-care and healthy lifestyle behaviours, such as physical activity, healthy eating and not smoking, are important **throughout the life-course**<sup>1</sup>

Even in older age, positive health behaviours continue to have significant impact, extending longevity and **enhancing quality of life**<sup>1</sup>

Promoting life-course vaccination as part of an informed **health and wellbeing package** alongside such behaviours may help generate a change in focus and improved uptake<sup>2,3</sup>

# Vaccination against herpes zoster was associated with a reduced stroke risk in some older populations

Stroke risk in US subjects after vaccination against herpes zoster vs unvaccinated subjects; results from a nationwide survey (N = 172,770)



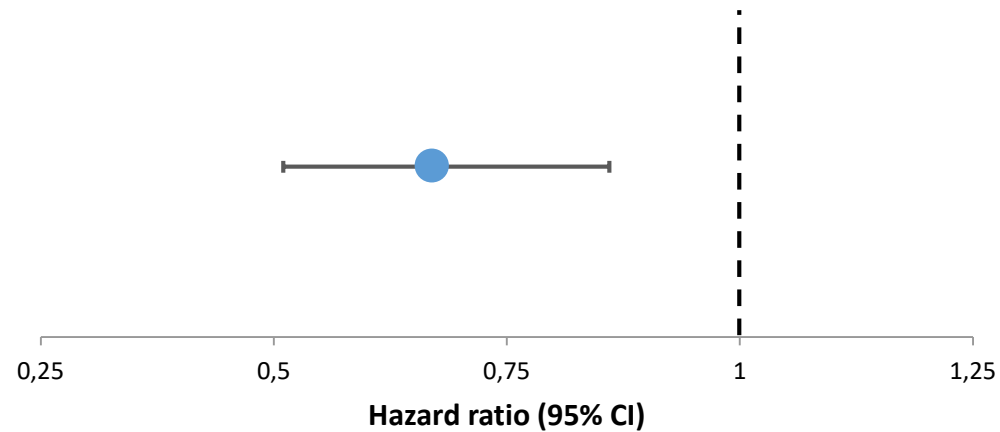
Vaccination against herpes zoster significantly reduced the risk of stroke **by 51%** in older adults aged 65-69 years

OR, odds ratio

Klaric JS et al. Mil Med. 2019;184:126-132

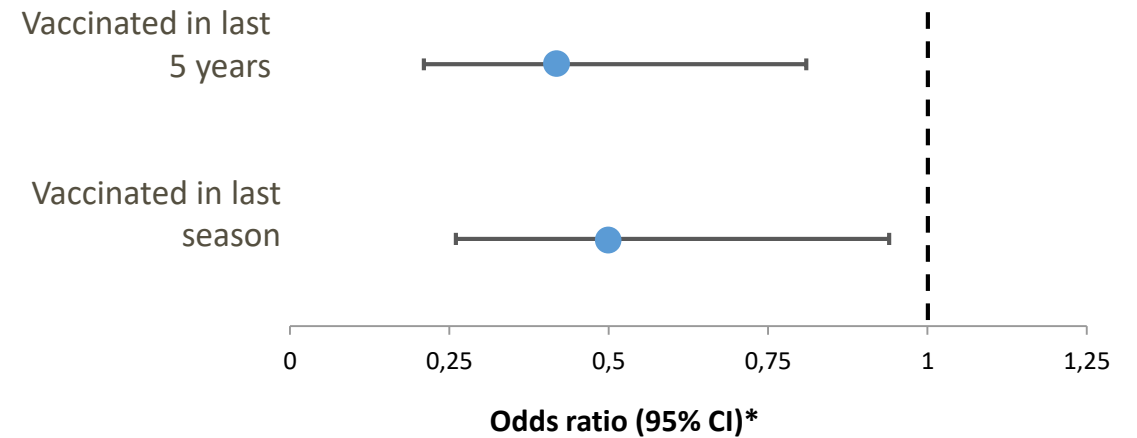
# The risk of major cardiovascular and cerebrovascular events was significantly reduced following influenza vaccination

Risk of major adverse CV event in influenza-vaccinated subjects with ACS aged >50 years (n = 221) vs unvaccinated (n = 218)<sup>1</sup>



Influenza vaccination significantly reduced the risk of major adverse cardiovascular events **by 33%**

Risk of brain infarction in influenza-vaccinated subjects aged ≥60 years vs unvaccinated<sup>2</sup>



Influenza vaccination **significantly reduced** the risk of brain infarction regardless of time since vaccination

ACS, acute coronary syndrome; CI, confidence interval; CV, cardiovascular; \*adjusted for age, sex, diabetes, hypertension, body mass index, current smoking, cholesterol and use of antibiotics in the last 3 months.

1. Phrommintikul A *et al.* *Eur Heart J* 2011;32:1730–1735; 2. Lavalley *et al.* *Stroke* 2002;33:513–518

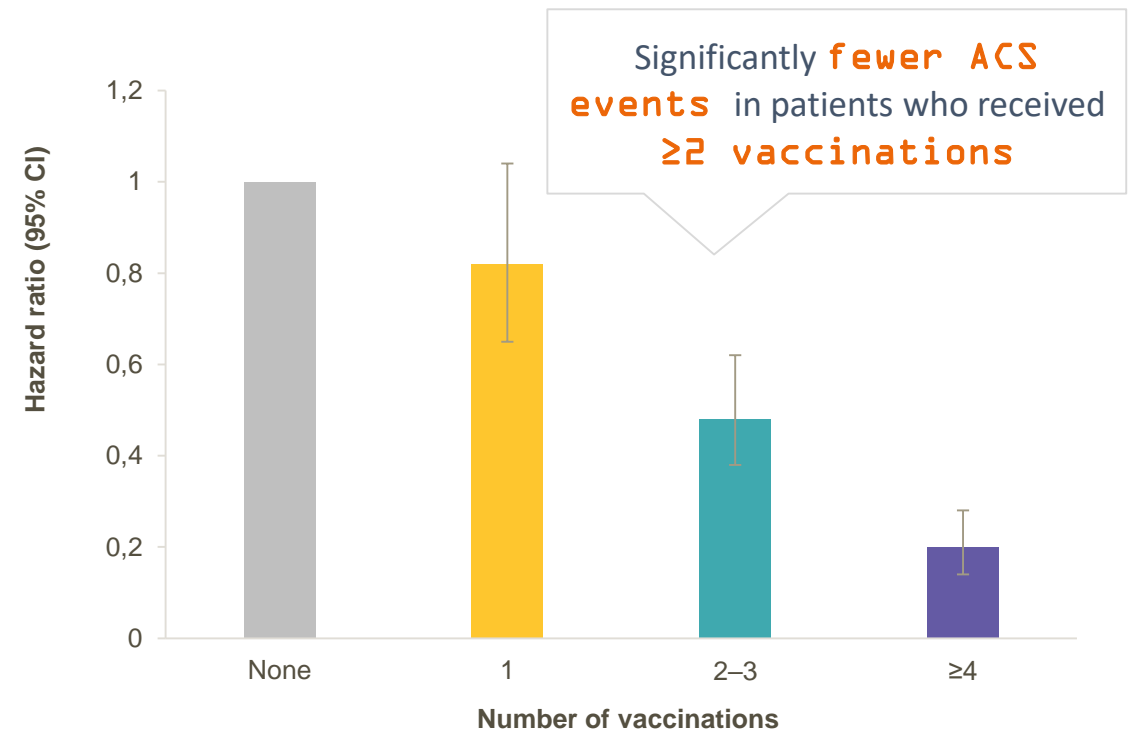
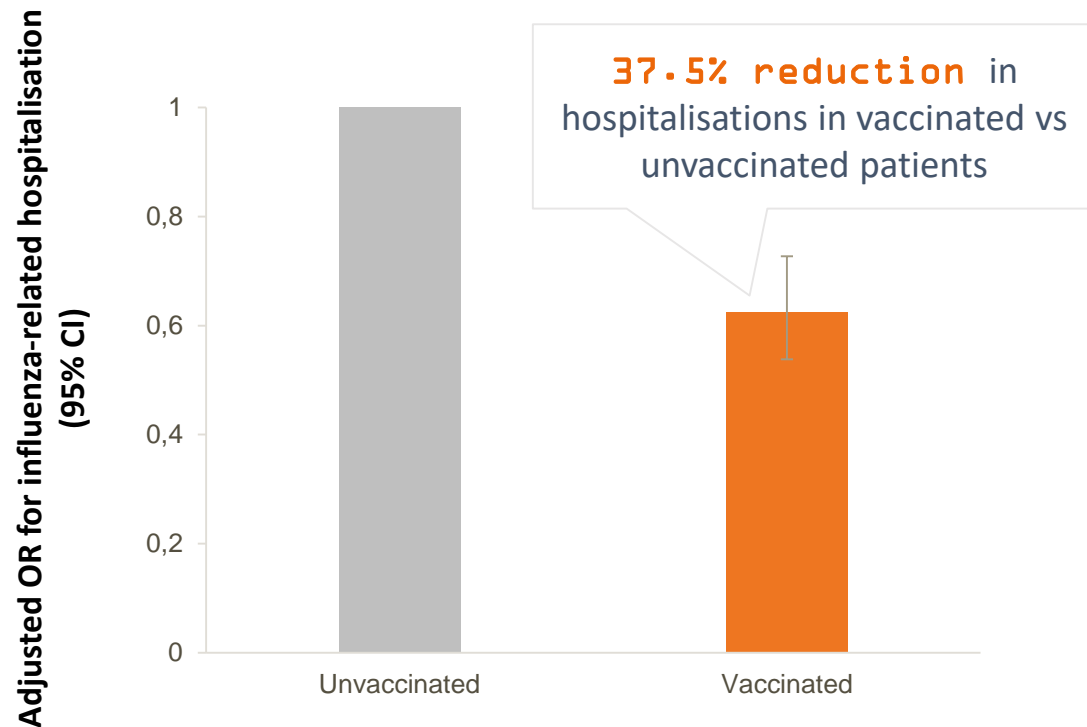
# Vaccination against influenza reduces the risk of hospitalisation in individuals with underlying disease such as COPD



Influenza-related hospitalisations in patients with COPD, 2011-2015 (N = 4198)<sup>1</sup>



Risk of ACS in patients with COPD aged  $\geq 55$  years receiving influenza vaccination compared with unvaccinated patients; Taiwan, 2000-2007 (N = 7722; 3027 vaccinated)<sup>2</sup>



ACS, acute coronary syndrome; CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio

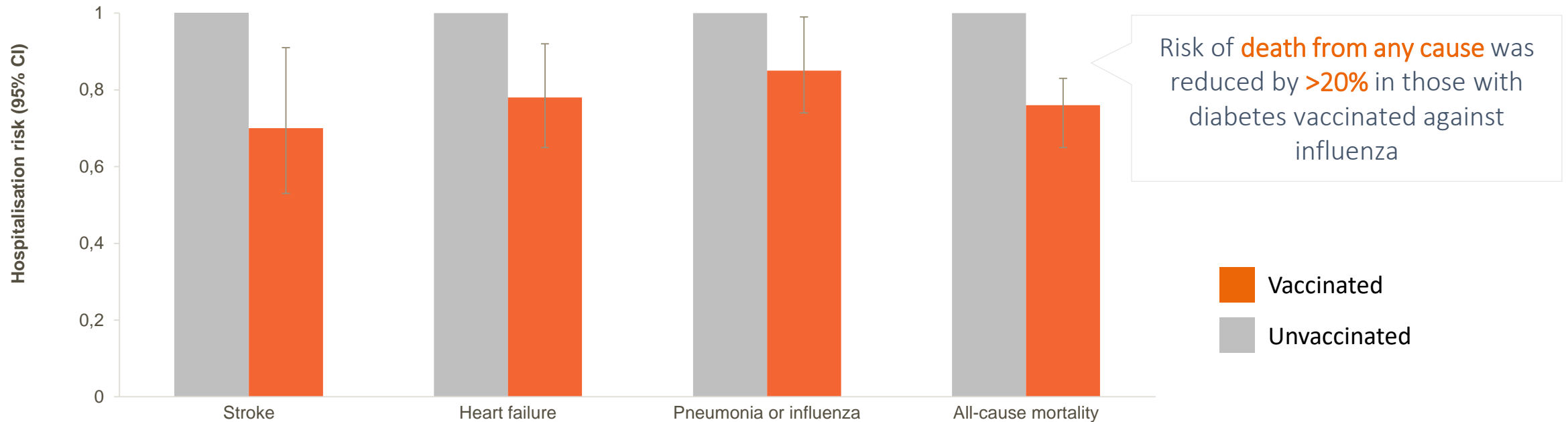
1. Mulpuru S *et al.* *Chest* 2019;155:69–78; 2. Sung LC *et al.* *Vaccine* 2014;32:3843–3849



# In those with diabetes, influenza vaccination reduces the risk of not only hospitalisation, but also cardiovascular events and death



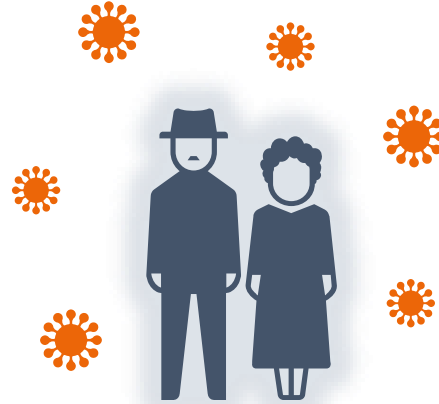
Risk of hospitalisation for acute CV and respiratory conditions and all-cause death in adults aged  $\geq 18$  years with T2DM vaccinated against influenza compared with unvaccinated, 2003/04 to 2009/10 (N = 124,503)



# While vaccination against influenza does not prevent COVID-19 infection, there are many important benefits



Flu vaccination can reduce the risk of  
**flu-associated  
hospitalisation**  
for all ages



Getting vaccinated can help to  
**protect more vulnerable  
people** around you



Getting a flu vaccine helps  
**save healthcare resources**  
for the care of patients with COVID-19



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# Vaccine

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## Commentary

### Are vaccines against COVID-19 tailored to the most vulnerable people?

Raffaele Antonelli Incalzi <sup>a</sup>, Caterina Trevisan <sup>b,\*</sup>,<sup>1</sup>, Susanna Del Signore <sup>c,1</sup>, Stefano Volpato <sup>d</sup>,  
Stefano Fumagalli <sup>e</sup>, Fabio Monzani <sup>f</sup>, Giuseppe Bellelli <sup>g</sup>, Pietro Gareri <sup>h</sup>, Enrico Mossello <sup>e</sup>, Alba Malarica  
Alessandra Coin <sup>b</sup>, Gianluca Zia <sup>c</sup>, Anette Hylén Ranhoff <sup>j</sup>

<sup>a</sup> Unit of Geriatrics, Department of Medicine, Campus Bio-Medico University and Teaching Hospital, Rome, Italy

<sup>b</sup> Geriatrics Division, Department of Medicine (DIMED), University of Padua, Italy

<sup>c</sup> Bluecompanion Ltd, London, UK

<sup>d</sup> Department of Medical Science, University of Ferrara, Ferrara, Italy

<sup>e</sup> Geriatric Intensive Care Unit, Department of Experimental and Clinical Medicine, University of Florence, Italy

<sup>f</sup> Geriatrics Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

<sup>g</sup> School of Medicine and Surgery, University of Milano-Bicocca and Acute Geriatric Unit, San Gerardo Hospital, Monza, Italy

<sup>h</sup> Center for Cognitive Disorders and Dementia - Catanzaro Lido, ASP Catanzaro, Italy

<sup>i</sup> Scientific Committee of National Association of Third Age Residences (ANASTE) Calabria, Lamezia Terme (Catanzaro), Italy

<sup>j</sup> Department of Clinical Science, University of Bergen, Norway and Diakonhjemmet Hospital, Oslo, Norway



# Older, frail and multimorbid people were dramatically underrepresented in the populations testing Covid-19 vaccines

**Table 1**  
Health-related eligibility criteria influencing geriatric representation in the clinical trials for vaccines against COVID-19.

	Pfizer/BionTech [4]	Moderna [5]	Oxford-AstraZeneca [7]
Age classes	42.2% with age > 55 years	24.8% with age $\geq$ 65 years	15.9% with age >55 year (10.9% from 56 to 70 years, and 5% >70 years)
Inclusion criteria	<ul style="list-style-type: none"> <li>- Healthy participants who, through medical history, physical examination, and clinical judgment of the investigator are eligible for inclusion in the study.</li> <li>- Individuals with preexisting stable disease (i.e. disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment).</li> </ul>	<p>Healthy adults or adults with pre-existing medical conditions who are in stable condition (i.e. not requiring significant change in therapy or hospitalization for worsening disease during the 3 months before enrollment).</p>	<p>Healthy adults or adults with comorbidities assessed as mild or moderate and well controlled by the Investigator.</p>
Exclusion criteria	<ul style="list-style-type: none"> <li>- Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.</li> <li>- Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.</li> </ul>	<ul style="list-style-type: none"> <li>- Acute illness or fever 72 h prior to or at screening.</li> <li>- Immunosuppressive or immunodeficient state.</li> </ul>	<ul style="list-style-type: none"> <li>- Severe or uncontrolled conditions, e.g. cardiovascular, respiratory, gastrointestinal, liver, renal diseases, endocrine, autoimmune/ rheumatological disorders, neurological illness, immunosuppression, and cancer.</li> <li>- Chronic use of anticoagulants.</li> <li>- Psychiatric conditions (including dementia or cognitive impairment), or psychiatric history.</li> <li>- Any other comorbidities deemed severe or uncontrolled as determined by the clinical judgement of the Investigator. In case of uncertainty regarding the nature or severity of the comorbidity (e.g. new medical diagnosis; new symptom, disorder or finding that are currently under investigation; recent change or deterioration in a symptom, disorder or finding) the participant may be excluded, at the discretion of the investigator.</li> <li>- Clinical Frailty Scale <math>\geq</math>4 (vulnerable and frail), only for participants aged <math>\geq</math>65 years.</li> </ul>

Diffusion of and shared indication to a given vaccine are directly related to its age

Country	Influenza Age	Pneumococcal Age, type of vaccine	Herpes zoster Age, type of vaccine
Australia	≥65	≥65; PPV	70–79; ZVL <sup>o</sup>
Austria	All adults	≥50; PCV+PPV*	≥50; RZV <sup>o</sup>
Belgium	≥65	≥65; PCV+PPV*	≥65; catch up 79
Bulgaria	≥65	–	–
Canada	All adults(a)	≥65; PPV(b)	≥50; RZV(c)
Croatia	≥65	–	–
Cyprus	≥65	≥65; PPV	–
Czech Republic	All adults	≥65; PCV+PPV*	≥50; ZVL
Denmark	≥65	≥65; PCV or PPV	–
Estonia	≥65	–	–
Finland	≥65	≥65; PCV or PPV	–
France	≥65	–	65–74; catch-up 75–79; ZVL
Germany	≥60	≥60; PPV	≥60; RZV
Greece	≥60	≥65; PCV	≥60; ZVL
Hungary	≥60	≥50; PPV	–
Island	≥60	≥60; PPV	–
Ireland	≥65	≥65; PPV	–
Italy	≥65	≥65; PCV+PPV*	≥65; ZVL

- ZVL = Zoster vaccine live attenuated; RZV = recombinant zoster vaccine
- The United States Advisory Committee on Immunization Practices (ACIP) recommends one dose of PPSV23 for adults 65 years of age
- Antonelli Incalzi R et al. ACER 2020; 32:1405-1415

## Indicazioni e loro basi 1

Vaccino	Tipo	Indicazione	Età
Influenza	Vari tipi, inattivati	Popolazione generale Categorie a rischio	>65 Nessuna soglia
Pneumococco	PPSV23*	Popolazione generale Categorie a rischio§	>65 Nessuna soglia
HVZ	ZVL: vivo RZV: liofilizzato, ricombinante	Pazienti immunocompetenti Anche pazienti immunocompromessi	>50 (In Italia: >65) Nessuna soglia
Tetano		Popolazione generale	Adulta
Pertosse		Popolazione generale	Adulta

- PCV13: il vaccino coniugato non è più considerato propedeutico al polisaccaridico PPS23
- §: anche portatori di impianto cocleare

## Indicazioni e loro basi 2

Vaccino	Tipo	Efficacia	Copertura attesa
Influenza	Vari tipi, inattivati (Tetraivalente ad alta carica nell'anziano)	Riduce mortalità e ricoveri sia nell'anziano che nel paziente a rischio	75% 95% in categorie a maggiore rischio
Pneumococco	PPSV23*	Particolarmente efficace nei soggetti a maggiore rischio	75%
HVZ	ZVL: vivo RZV: liofilizzato, ricombinante	Previene sia la malattia, primaria o recidiva, che la nevralgia postherpetica RZV pare più efficace del pur efficace ZVL RZV può essere somministrato in chi abbia già ricevuto ZVL	50%

# High dose influenza vaccine is highly effective in the elderly (Van Aalst R et al.

Vaccine 2020; 38: 372–379)

## Table 4

Relative vaccine effectiveness (rVE) with 95% confidence intervals of high dose (HD-IIV3) versus adjuvanted influenza vaccine (aIIV3) for respiratory seasons 2016–17, 2017–18 and the two seasons combined (summary rVE), adjusted for baseline characteristics.

Hospitalizations	2016–17 season	2017–18 season	Summary rVE
Respiratory disease	13% (–6.3%, 32%)	12% (2.1%, 21%)	12% (3.3%, 20%)
Cardio-respiratory disease	13% (2.3%, 23%)	6% (0.6%, 11%)	7.0% (2.3%, 12%)
Urinary Tract Infection	–20% (–59%, 19%)	2.5% (–12%, 17%)	–0.7% (–14%, 13%)

Confidence intervals were calculated using a robust variance estimator. We applied the Previous Event Rate Ratio (PERR) to address unmeasured confounders by including an interaction term of Period (observation versus baseline period) and treatment (HD-IIV3 versus aIIV3). The PERR was adjusted for observed confounding factors by including all the baseline characteristics of [Table 1](#) as covariates, except for Age Groups and the Deyo-Charlson Score, to prevent collinearity with Age and individual comorbid conditions. Hospitalizations were classified using the principal discharge diagnosis.

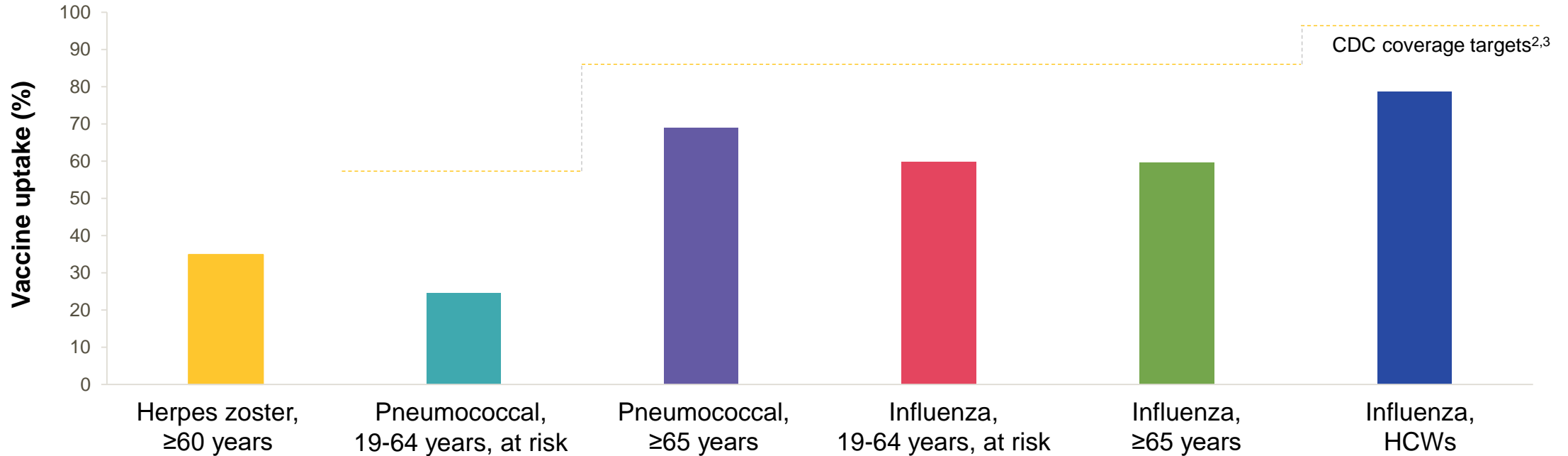


# The obstacles to vaccines

# Despite the importance of vaccination, coverage in adults remains below recommended levels



Vaccine uptake in older adults, adults aged <65 years with high-risk conditions and HCWs, 2017\*<sup>1,2</sup>



Vaccine uptake remains **below target**, both for HCWs and vulnerable individuals

\*'High-risk' defined as medical conditions such as asthma, heart disease and diabetes. HCW, healthcare worker; CDC, Centers for Disease Control and Prevention

1. Centers for Disease Control and Prevention (CDC), 2018. Vaccination coverage among adults in the United States, National Health Interview Survey, 2017. <https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/pubs-resources/NHIS-2017.html>; 2. Black CL *et al.* *MMWR Morb Mortal Wkly Rep* 2017;66:1009–1015; 3. HealthyPeople.gov. Immunization and infectious diseases. <https://www.healthypeople.gov/2020/topics-objectives/topic/immunization-and-infectious-diseases/objectives> (URLs accessed June 2022)

# The obstacles to vaccines

Obstacles	Note	Suggested intervention
Heterogeneity between countries	Poor attitude to co-operation	Organisms like WHO should promote international coordination
Available professional resources are frequently underpowered	Differences in the role of general practitioners and in the quality of ambulatory and home care services	To value the role of the general practitioner and selected other health professionals, as available and as needed
Poor information about vaccines	The information strategy differs among countries	Suggested multimodal strategy: «convenient» approach, ie, tailored to the target population
No universal informative system on vaccinated people is available	This prevents a careful assessment of the health effects of vaccines	Immunization registers should be the rule
The education of health professionals is frequently defective in vaccinology	This limits the role of health professionals as vaccine promoters	Vaccines should be a key didactic topic either in the degree course or in many post-doctoral courses
Disinformation and mystification of the reality	Multiple causes	Communication campaigns involving influencers

**Table 2** Qualitative initiatives to promote vaccinations of older populations, and monitoring of vaccination campaigns: selected proposals

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To promote vaccination

Provide physicians and specialists with information tools for informing patients. A basic guide about useful vaccines for older persons, including answers to the most frequently asked questions, would be a helpful support for both patients and physicians

Support pilot projects, such as “vaccination days” in healthcare establishments

Hold lectures on vaccines for elders in major professional congresses and events, to promote best practice within the medical and scientific community

Adopt a multitarget approach to increase awareness among all health professionals likely to be in direct contact with patients. Social services and groups and associations providing activities for over 65 s should also be involved

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To monitor vaccination campaigns

Develop and put into use a central vaccine registry. This would enable accurate monitoring of vaccine administrations and timely evaluation of vaccine coverage by facilitating the flow of real-time vaccination data

Use feedback to modify strategy: systematic monitoring of coverage rates could identify areas that could be targeted for improvement and respond to specific challenges

Share access to the vaccine registry with all stakeholders. GPs should be able to access the vaccine registry, with special programmes online to record vaccines administered to elderly and high-risk subjects

Analyse procedures and strategies used in the areas achieving the highest coverage rates to implement them in low coverage areas

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# The obstacles to vaccines: the view of the diabetic patient

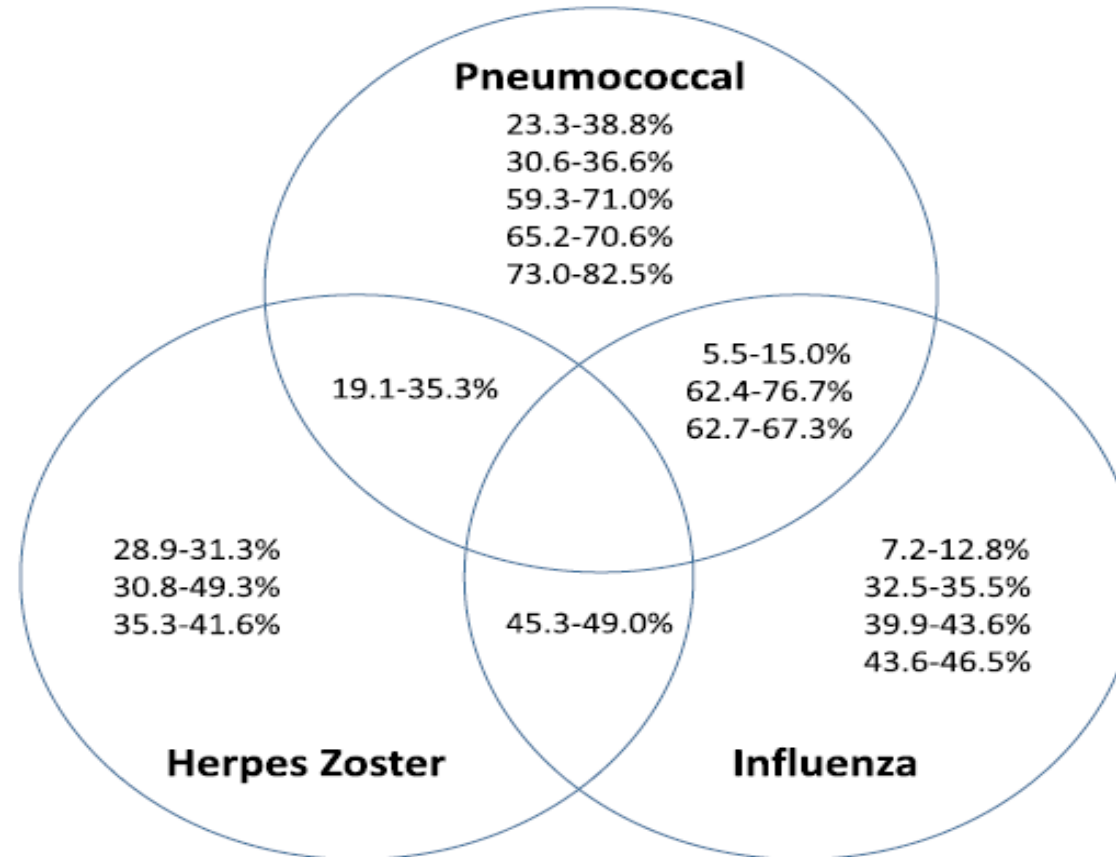
**Table 2 – Reasons for being or not being vaccinated.**

Variables	Age		p
	<65 (n = 373)	≥65 (n = 206)	
Reasons for not being vaccinated [n (%)]			
I do not need	366 (98.1)	189 (91.7)	<b>&lt;0.001</b>
Disease gives	0	2 (1.0)	0.126
Forgot	1 (0.3)	0	0.995
Side effects	0	5 (2.4)	<b>0.006</b>
I did not think would protect	4 (1.1)	6 (2.9)	0.178
The doctor did not mention vaccines	275 (73.7)	148 (71.8)	0.626
I did not have the opportunity to reach	0	3 (1.5)	0.076
I do not trust	1 (0.3)	5 (2.4)	<b>0.023</b>

The categorical variables are showed as n (%).

Bold values were considered statistically significant.


# I limiti delle conoscenze tra specialisti e specializzandi in Geriatria: quadro sinottico



**Fig. 1.** Range (minimum and maximum) of correct response rates achieved on each question by qualified specialists and residents, according to the vaccine mentioned in the question. (Note: the single question about measles is not included).



# Vaccines in older age: moving from current practice to optimal coverage—a multidisciplinary consensus conference

Raffaele Antonelli Incalzi<sup>1,2</sup> · Roberto Bernabei<sup>3</sup> · Paolo Bonanni<sup>4</sup> · Michele Conversano<sup>5</sup> · Fiona Ecartot<sup>6,7</sup>  · Giovanni Gabutti<sup>8</sup> · Stefania Maggi<sup>9,10</sup> · Diana Paolini<sup>4</sup> · Federica Sandri<sup>8</sup>

Received: 21 April 2020 / Accepted: 3 June 2020

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To be updated upon vaccines

[Recommended Vaccines by Age | CDC](#)

[https://www.cdc.gov › vpd › vacc.](https://www.cdc.gov/vpd/vacc.)

[CDC Resources: Immunization schedules](#)

[https://www.immunize.org › cdc](https://www.immunize.org/cdc)