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REVIEW



Immunofitness in the elderly: The role of vaccination in promoting healthy aging

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ABSTRACT

Aging reshapes immunity through immunosenescence and inflammaging, increasing susceptibility to infection, exacerbating chronic conditions, and blunting vaccine responses. This review frames “immunofitness” as a practical goal of healthy aging and examines how adult vaccination builds immune resilience. Vaccination strengthens adaptive memory, leverages adjuvants to optimize antigen presentation, and can reprogramme innate cells (trained immunity), yielding heterologous benefits beyond target pathogens. We integrate evidence in older adults for influenza, respiratory syncytial virus, pneumococcal, COVID-19, and recombinant zoster vaccines, including reductions in respiratory events, cardiovascular outcomes, hospitalization, and mortality. We highlight emerging platforms and precision vaccinology to tailor schedules by immune age, comorbidity, and frailty. Integrating routine, age-appropriate vaccination with lifestyle measures is a feasible, high-impact strategy to promote immunofitness.

PLAIN LANGUAGE SUMMARY

As we get older, our immune system becomes less efficient and more prone to chronic inflammation. Vaccines can help keep the immune system “fit” by preparing it to recognize germs and to bounce back faster after infections. Some vaccines do more than protect against a single disease: they can also improve general immune responses (sometimes called “trained immunity”). In older adults, vaccines against flu, RSV, pneumococcus, COVID-19 and shingles lower the chances of serious illness, hospitalization and even heart problems linked to infections. New vaccine technologies (like mRNA and advanced adjuvants) and personalized schedules may improve protection further. Making vaccination a routine part of healthy aging — together with good nutrition, exercise, sleep and managing chronic conditions — can meaningfully improve health and quality of life.

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Introduction

The immune system is a dynamic defense mechanism that changes with an individual’s health status and throughout their life. Aging affects the immune system itself and is exacerbated by lifestyle, chronic diseases and medications, which are more prevalent in older adults. Immunosenescence, the natural decline in immune function with age, is associated with longer recovery times and increased vulnerability to infection and diseases.¹

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However, improving or maintaining a resilient immune system, or immune fitness, could be achieved by improving overall health (maintaining healthy eating habits, positive social connections, avoiding smoking, moderating alcohol intake, getting a restful sleep, engaging in regular exercise, and regulating stress levels) but also specifically boosting the immune system with vaccinations.^{1,2} Vaccines can enhance immune fitness by stimulating both innate and adaptive immune responses, mitigating some effects of immunosenescence. In addition to pathogen-specific protection, some vaccines can induce heterologous (“off-target”) effects. In this context, immune activation by one vaccine may enhance responses to unrelated pathogens through trained immunity, potentially reducing infections and its related illnesses at the population level and partly offsetting age-related immune decline.^{3,4} These vaccine-induced effects can also support immune resilience, defined as the ability to return to homeostasis after immune activation. This may occur through epigenetic reprogramming of innate immune cells and by boosting preexisting immune memory established by prior vaccination.^{5,6}

Here, we explore the impact of adult vaccination on an aging immune system and its potential for improving immune fitness. Importantly, chronological age does not always reflect the true functional state of the immune system. The concept of ‘immune age’ – defined by immune biomarkers and functional capacity – has emerged as a more accurate predictor of health outcomes in older adults. This distinction reinforces the importance of interventions such as vaccination, which can actively modulate immune aging and promote resilience.

Immunosenescence, inflammaging and its impact on health

Immunosenescence, a term coined by Roy Walford, describes the progressive decline in immune system efficacy with aging.⁷ It is characterized by a dysregulated immune state that prevents proper immune responses and promotes a low-grade systemic inflammatory chronic state, a phenomenon described as inflammaging by Claudio Franceschi in 2000.⁸ The aged immune system exhibits functional deterioration, impacting innate and adaptive immunity and leading to poor vaccination outcomes, heightened infection susceptibility, and increased prevalence of age-related diseases including autoimmune diseases and malignancies.⁸

As we age, the immune system shows a reduced capacity to respond to new infections, vaccines, and antigens, accelerating a biological decline and as a result, the increase in incidence of chronic diseases.⁹ At the cellular and molecular levels, immunosenescence manifests as the remodeling and decay of immune organ structures, such as thymic involution, leading to a marked reduction in naïve T-cell output, which leads to diminishing the adaptive immune system’s ability to respond to novel antigens and underscoring the age-related decline in immune competence.¹⁰ This process is characterized by an imbalance in the naïve-to-memory T-cell ratio, an altered hematopoietic lineage, and a shift in immune cell phenotypes favoring a pro-inflammatory state.^{8,11} Such immune cell imbalances disrupt homeostasis, as senescent immune cells acquire a senescence-associated secretory phenotype (SASP), which drives the persistent inflammatory state observed in inflammaging.^{8,11,12} The accumulation of senescent T cells and changes in immune organ structures contribute further to immunosenescence. Aging immune cells, particularly T cells, undergo irreversible cell cycle arrest and exhibit decreased proliferative capacity, resistance to apoptosis, and morphological changes such as a more rigid membrane which decreases the formation of the immune synapse. These cells produce pro-inflammatory cytokines (e.g., IL-1, IL-6, TNF- α) and other factors, exacerbating tissue inflammation and fueling inflammaging.⁸ Also, at a cellular level, immune cells undergo significant epigenetic alterations and modulate gene expression patterns that hinder immune functionality.⁸

Furthermore, the innate immune system faces significant declines with age. Natural killer (NK) cells, macrophages, and dendritic cells (DCs) can develop functional impairments, including reduced cytotoxicity, diminished antigen presentation, and altered signaling pathways. For example, macrophages in the elderly often show decreased phagocytic activity and altered M1/M2 polarization, which can weaken pathogen clearance.⁸ These changes may also produce more proinflammatory mediators including free radicals and proinflammatory cytokines. At the same time, aged macrophages may respond less effectively to acute stimuli, resulting in impaired protective functions.⁸

Other processes related to aging may also contribute to inflammaging. These include: microbiome changes that increase the production of proinflammatory mediators; mitochondria alterations that increase

reactive oxygen species or release mitochondrial DNA into the cytosol; and cellular senescence in non-immune cell populations that amplifies inflammatory signaling.¹³ Indeed, recent studies suggest that age-associated gut dysbiosis, characterized by reduced microbial diversity and an altered Firmicutes/Bacteroidetes ratio, can accelerate inflammaging and impair vaccine responsiveness.¹⁴ This highlights the microbiome as a potential target for interventions aiming to restore immune balance in older adults.

The impact of these immune alterations on health is deep, leading to an increased burden of infectious diseases, autoimmune conditions, and chronic inflammatory disorders such as cardiovascular diseases, neurodegenerative conditions, and metabolic syndromes.^{15,16} Immunosenescence also compromises the body's ability to control latent infections, such as herpesviruses, which can reactivate and contribute to systemic inflammation.¹⁷ Additionally, the chronic inflammatory state associated with inflammaging is implicated in frailty, reduced physical function, and cognitive decline in elderly individuals, significantly affecting their quality of life and increasing healthcare needs.¹⁶

Chronic conditions prevalent in older adults are also accompanied by nonspecific immune deficiencies. In the case of chronic obstructive pulmonary disease (COPD), infectious exacerbations are associated with increased airway inflammation and, in parallel, a systemic inflammatory response. Systemic inflammation is reflected by elevated acute-phase markers such as interleukin IL-6 and plasma fibrinogen, whereas airway inflammation may be characterized by changes in inflammatory cell profiles, including eosinophils.^{18,19} Asthma presents an increased response to allergens post-infection, due to functional impairment of the respiratory epithelial barrier and a greater neutrophilic inflammation of the lower airways.^{20,21} In congestive heart failure (CHF), immune regulation mechanisms are impaired, with decreased interferon- γ signaling, which recruit cytotoxic T cells in response to viral pathogens.²² Diabetes, in addition to the known pro-inflammatory state, presents specific pulmonary alterations, where alveolar macrophages exhibit defective phagocytic function and may shift their phenotype toward pro-inflammatory M1 profiles with elevated IL-6, TNF- α , and IL-12 production.²³ Hyperglycemia-related immune dysfunctions include impaired chemotaxis, phagocytosis, and bactericidal capacity of innate immune cells, along with dysregulated Toll-like receptor 4 (TLR4) expression, which contributes to chronic inflammation.²³

Understanding the molecular pathways, changes in the immune cell pool, and the regulatory signaling linked to immunosenescence can help optimize health interventions to enhance outcomes in the aging population.^{8,24} Elderly individuals are at increased risk due to a combination of comorbidities and concurrent drug treatments that can exacerbate their susceptibility to infections,²⁵ making vaccination even more essential. Immunosenescence poses specific challenges for developing safe, immunogenic, and efficacious vaccines for older adults.

Vaccines as architects of immune resilience

Vaccines support immune resilience by priming the immune system to respond efficiently upon exposure and facilitating a faster return toward homeostasis after infectious challenges.²⁶ They promote adaptive immune memory through antigen-specific B- and T-cell responses and, in some cases, leverage adjuvants to enhance antigen uptake and presentation by innate immune cells such as dendritic cells.²⁷ Beyond pathogen-specific protection, certain vaccines can also induce *trained immunity*—epigenetic and functional reprogramming of innate immune cells – and thereby exert heterologous (“off-target”) effects that may contribute to broader reductions in morbidity and mortality.^{28,29} For instance, some studies have reported associations between childhood tuberculosis vaccination (BCG, Bacillus Calmette-Guérin) and lower lung cancer incidence in adulthood, and clinical benefits in bladder cancer when BCG is administered intravesically after tumor resection to reduce relapse risk.^{30,31} These complementary mechanisms underscore vaccination's potential benefits beyond preventing acute infection, supporting healthier aging and reducing downstream disease burden.^{32,33}

Immune fitness in the elderly

Immunosenescence in older adults is influenced by various factors that contribute to the gradual decline of the immune system (Figure 1). Key differences in immune responses between the elderly and younger populations when facing infectious diseases are significant and multifaceted. In the elderly, there is an

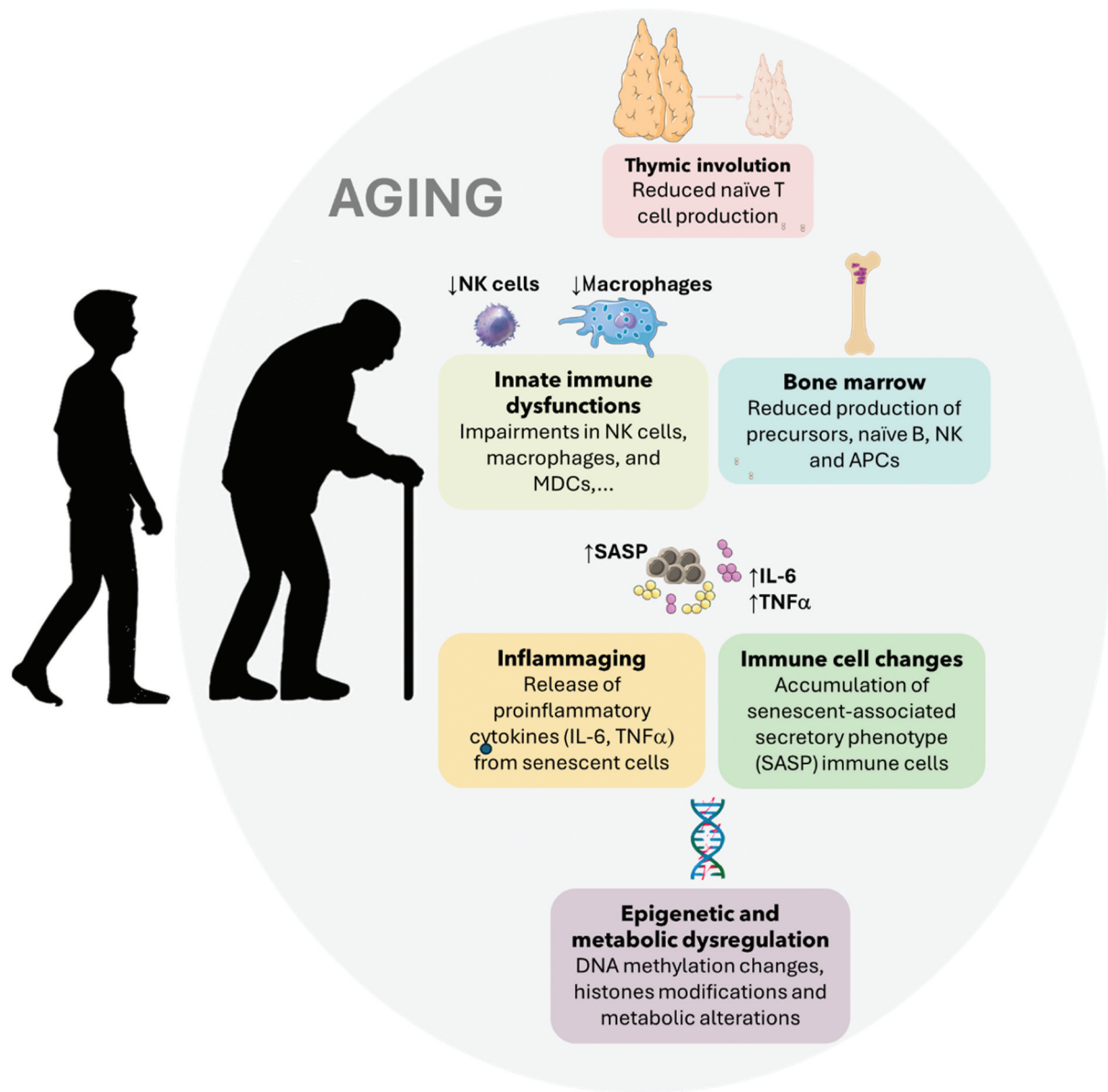


Figure 1. Impact of aging on immune system function.

imbalance between the effector memory response, which becomes diminished, and regulatory response, which is often overactive. Additionally, dendritic cells and NK cells exhibit reduced ability to present antigens and produce inflammatory cytokines, further compromising immune responses. Changes in adaptive immunity are also notable; the elderly experience a progressive loss of naïve T and B cells, a decline in switched memory B cells, and an increase in memory T cells. As a result, older adults face challenges in mounting effective immune responses, particularly to new pathogens.^{24,25} Moreover, elderly individuals are far from a homogeneous population: two patients of the same chronological age may exhibit very different immunological profiles depending on comorbidities, nutritional status, or polypharmacy. This heterogeneity underscores the need for tailored vaccination strategies in aging populations.

Vaccination programs are currently in place worldwide, and vaccines are thought to be among the safest, most efficient, and effective public health interventions for preventing disease and prolonging life. Regular immunizations can considerably lower morbidity and death linked to vaccine-preventable illnesses in older persons by maintaining or promoting immunological fitness.^{5,34–36} Vaccines stimulate the immune system by promoting the production of antibodies and activating T cells, which prepare the body to respond more effectively to actual pathogens. Vaccines can counteract the effects

of immunosenescence by improving the quality of immune responses, increasing the production of B and T cells, and optimizing antibody selection and maturation. Vaccines' adjuvants are particularly relevant in older adults because they can enhance antigen presentation, promote innate immune activation, and improve the magnitude and persistence of protective responses when baseline responsiveness is reduced by immunosenescence.³⁷ Different adjuvant systems act through complementary pathways (e.g., enhancing local innate activation, antigen uptake, and T-cell help), and they have been successfully incorporated into vaccines used in older populations, where improved effectiveness against clinically meaningful outcomes is a central goal.³⁸

Furthermore, vaccines not only protect against infections but also play a role in preventing chronic diseases, improving overall health and the immune system's ability to respond to new threats, and preventing infections that may trigger or exacerbate these conditions. For instance, vaccines like the hepatitis B vaccine can prevent chronic liver infections, which are linked to liver cancer. In contrast, the BCG vaccine has shown potential in reducing asthma risk and improving outcomes in immunocompromised patients. By preventing initial infections or modulating immune responses, vaccines can help mitigate the long-term health impact associated with chronic diseases.^{6,39}

From a safety perspective, vaccination is generally well tolerated in older adults. Across adult vaccines, older adults most commonly experience short-lived local reactions (pain, erythema, swelling) and systemic symptoms (fatigue, myalgia, headache, low-grade fever).⁴⁰ Reactogenicity tends to be more frequent with adjuvanted or mRNA based formulations, but events are generally mild-to-moderate and resolve within 1–3 days.⁴⁰ Serious adverse events are uncommon and are continuously monitored through clinical trials and post-marketing pharmacovigilance. In clinical decision-making, the benefits of preventing severe infection, hospitalization, and downstream complications in older adults typically outweigh transient reactogenicity.⁴¹

In addition to safety and tolerability, vaccine decision-making in older adults requires integrating baseline risk (age, comorbidities, living setting, and functional status) with standard contraindications and precautions.⁴² Older adults are heterogeneous; vaccine prioritization is particularly important in individuals with chronic cardiopulmonary disease, diabetes, chronic kidney disease, immunocompromise, or residence in long-term care facilities, as these factors increase the risk of severe outcomes.⁴² Frailty and functional status may also influence timing and co-administration strategies to optimize tolerability and adherence.⁴² As a general principle, the main contraindication to vaccination is a history of a severe allergic reaction (e.g., anaphylaxis) to a previous dose or a vaccine component⁴³; vaccination is commonly deferred during moderate-to-severe acute illness.⁴³ Vaccine choice should consider product-specific guidance (e.g., live vaccines in immunocompromised patients), local recommendations, and individualized risk – benefit assessment.⁴³

A holistic approach that integrates several lifestyle habits is recommended to improve immune fitness and counteract the effects of immunosenescence. Besides establishing effective vaccination schedules, core strategies include maintaining a balanced diet and nutrition and engaging in regular physical activity. Essential nutrients, such as vitamins A, D, C, and E, as well as zinc, play crucial roles in supporting immune function and modulating inflammatory responses.^{1,44} Physical exercise, especially moderate intensity, has proven benefits in reducing systemic inflammation, promoting anti-inflammatory cytokine release, and enhancing immune responses, all of which help manage immunosenescence-related decline.^{1,45} Furthermore, stress management and ensuring adequate sleep are also factors associated with immune resilience,⁴⁶ social connections, and psychological well-being, contributing further by reducing stress-induced immune suppression.⁴⁷

Harnessing immunofitness: broadening the scope of vaccination

In recent years, novel vaccination strategies have emerged to improve vaccine efficacy in older adults by counteracting the effects of immunosenescence. Some of these approaches include the use of advanced adjuvants such as AS01, AS03, Matrix-M, and MF59, which have been shown to enhance immunogenicity in this population, thereby improving vaccine effectiveness.⁴⁸ Also, the development of mRNA vaccines, exemplified by their success against COVID-19, offers a flexible platform that can be rapidly produced and updated for other infectious diseases prevalent in aging populations.⁴⁹

Nanoparticle-based vaccines also enhance the delivery of antigens and adjuvants to immune cells, ensuring a sustained release and a better immune response.⁵⁰ Also, viral vector vaccines represent a promising strategy, using modified viruses to deliver genetic material encoding antigens into cells, producing the target antigens and stimulating a robust immune response.⁵¹ Moreover, Generalized Modules for Membrane Antigens (GMMMA), a type of engineered bacterial outer membrane vesicle platform, has been proposed as a scalable approach for antigen presentation in vaccine design.⁵² While promising from a manufacturing and immunogenicity perspective, clinical experience in licensed products for older adults remains limited.⁵²

Lastly, personalized vaccination strategies, tailored to an individual's immunological profile and health status, can further optimize immune responses by adjusting vaccine types, doses, and schedules accordingly.⁵³ Such precision vaccinology approaches, integrating omics technologies, computational modeling, and immune profiling, are paving the way for a new era where vaccines can be personalized to maximize efficacy in the elderly.

Another approach to improving vaccine responsiveness in aged individuals involves regular booster vaccination every 10–20 years.⁵⁴ Healthy, aged adults who receive a booster of multivalent vaccine produce better humoral responses than younger individuals receiving a single dose.⁵⁵ Therefore, routine vaccine booster programs may be sufficient to induce humoral immunity and provide long-term protection in older populations.⁵⁶

To improve immune response and immune fitness in the elderly, some current research is focused on developing new vaccines or enhancing existing ones to address diseases prevalent in aging populations. Some vaccines show consistent results regarding efficacy and safety, significantly reducing morbidity and mortality associated with the target pathogen in older adults and their heterologous effect. A historically significant area, due to the intrinsic characteristics of the virus, is influenza vaccines, which are crucial for older adults due to their higher susceptibility to severe illness from the flu. Recent advancements include high-dose and adjuvanted influenza vaccines designed to elicit more robust immune responses in the elderly.^{57–59} Additionally, RSV vaccine targets an infection that can cause severe respiratory issues in older adults and the recombinant zoster vaccine is highly effective in preventing shingles and its complications in older adults, providing long-lasting protection.^{5,60}

Moreover, research is ongoing for vaccines against *Clostridioides difficile*, a Gram-positive spore-forming bacterium that causes severe gastrointestinal infections, particularly in healthcare settings. An effective *Clostridioides difficile* vaccine could greatly benefit older adults at increased risk of infection and complications.⁶¹ Also, cytomegalovirus (CMV) vaccine development remains an active and clinically relevant area, including strategies aimed at populations at higher risk of severe CMV-related complications, such as older adults.⁶² However, recent late-stage data underscore the scientific challenge: Moderna reported that its investigational CMV vaccine mRNA-1647 did not meet the primary efficacy endpoint in a Phase 3 trial designed to prevent CMV infection in CMV-seronegative women of childbearing age, leading the company to discontinue its congenital CMV vaccine development program.⁶³ Despite this setback, CMV vaccine research continues, and mRNA-1647 is still being explored in other high-risk clinical settings where CMV reactivation contributes substantially to morbidity. Overall, these efforts illustrate the ongoing commitment to improving prevention strategies for infections that can disproportionately impact vulnerable populations and contribute to healthy aging outcomes.⁶⁴

Clinical evidence: vaccine effects on health outcomes in older adults

The primary goal of vaccination is the prevention of infection by specific pathogens. Increasing evidence demonstrates the importance of vaccination not only for its direct effects on the target disease but also for its beneficial side effects, such as reducing mortality, morbidity, and hospitalization rates for other diseases.²⁴ The importance of vaccination extends beyond its direct action against pathogens, significantly impacting broader health outcomes. Recent studies have highlighted the heterologous effects of vaccines on the immune system, primarily focused on older adults (Table 1).

Table 1. Measures of the effect of vaccination in adults.

Category	Indicator	RSV	Influenza	SARS-CoV2	Pneumococcal Disease	RZV
Characteristics of the disease	Mortality	6,000–14,000 annual deaths (Tong et al. 2020) ⁶⁵	290,000–650,000 respiratory deaths globally; 15,000–70,000 in Europe ⁶⁸ 90% of deaths each year in the >65-year-old population are attributed to respiratory illnesses related to flu in Europe	>7 million globally since the pandemic began; >2 million in Europe (WHO) ⁶⁶	17.1% in adults > 65 in Europe (ECDC, 2022) ⁶⁷	
	Incidence	3% – 7% of healthy older adults and 4% – 10% of high-risk adults (Simon et al. 2023) ⁶⁸	Up to 50 million symptomatic cases annually in the EU/EEA (ECDC) ⁶⁹		5.1 cases per 100,000 persons (in 2022) (ECDC, 2022) ⁶⁷	
	Hospitalization	60,000–160,000 hospitalizations (Tong et al. 2020) ⁶⁵ 5.5 to 15.3 per 10,000 person/year <65 years	309 per 100,000; 151 per 100,000 person-years in >65 years (ECDC) ⁶⁹		NA	
Direct Effects on Disease	Vaccine efficacy/effectiveness	74.5% – 77.5% in adults aged ≥60 years (Meigar et al. 2023) ⁶⁰ 62.1% – 87.5% in infants (Beyfortus EMA) ⁷⁰	40% – 60% general (WHO); 17% – 53% in > 65 years (Grohskopf et al. 2024) ⁷¹	54% updated monovalent COVID-19 vaccine 23/24 (CDC) ⁷² ; 46% updated monovalent COVID-19 vaccine 23/24 >65 years old (CDC) ⁷²	Pneumococcal pneumonia or severe pneumococcal disease: PPV23: 10% – 11%; PCV13: 40% – 79%; sequential: 39% – 83% (Dunne et al. 2023) ⁷³ All cause: PPV23: 8% – 3%; PCV13: 9% – 12% (Dunne et al. 2023) ⁷³	97% (Simon et al. 2023) ⁶⁸
Other indirect effects	Reduction in cardiovascular events		Influenza vaccination shortly after a myocardial infarction or in high-risk coronary heart disease resulted in a lower risk of a composite of all-cause death, myocardial infarction or stent thrombosis, and a lower risk of all-cause death and cardiovascular death (Simon et al. 2023, Frobert et al. 2021) ^{68,74} ; Rates of all-cause death were 2.9% and 4.9% (hazard ratio, 0.59 [95% CI, 0.39–0.89]; P = .010), rates of cardiovascular death were 2.7% and 4.5% (hazard ratio, 0.59 [95% CI, 0.39–0.90]; P = .014), and rates of MI were 2.0% and 2.4% (hazard ratio, 0.86 [95% CI, 0.50–1.46]; P = .57) in the influenza vaccine and placebo groups, respectively (Frobert et al. 2021). ⁷⁴ the rate of coronary ischaemic events (MACE or hospitalisation for myocardial ischaemia) over 12 months was significantly lower in the vaccine group than in the placebo group (6.02% vs 9.97%, P value 0.047) influenza vaccination was found to be protective (HR 0.38, 95% CI 0.19 to 0.78, P value 0.009) (Clar et al. 2015) ⁷⁵	NA	NA	
	Reduction in COVID-19 severity		Reduction in COVID-19 severity (Yilmaz et al. 2023) ⁷⁶	NA		16% lower risk of COVID-19 diagnosis and 32% lower risk of COVID-19 hospitalization (Bruxvoort et al. 2022) ⁷⁷
	Reduction in all-cause respiratory infections		Reduction in respiratory infections among vaccinated individuals (Nichol et al. 2003; Yilmaz et al. 2023) ^{76,78}	NA	Lower incidence of all-cause respiratory infections (Dunne et al., Yilmaz et al.) ^{73,76}	

Influenza vaccines

Evidence supports several advantages of influenza vaccination in older adults other than preventing influenza itself (Figure 2). A Cochrane review shows that influenza vaccination significantly reduces cardiovascular mortality, with a risk ratio of 0.45 (95% CI 0.26 to 0.76, $p = 0.003$) and no significant heterogeneity among studies.⁷⁵ Additionally, studies have also shown that influenza vaccination reduces cardiovascular events and mortality, supporting international guidelines advocating immunization in older adults to protect against ischemic coronary events.^{57,79} Further strategies to mitigate cardiovascular risk from respiratory infections include enhancing the uptake of vaccines against other respiratory pathogens, developing more effective influenza vaccines, and promoting infection prevention practices like hand hygiene and social distancing.⁷⁹ Specifically, influenza vaccination soon after myocardial infarction or in individuals with high-risk coronary heart disease has been associated with a lower risk of all-cause death, myocardial infarction, stent thrombosis, and cardiovascular death.⁶⁸

According to the Advisory Committee on Immunization Practices (ACIP) from the CDC and WHO, adults over 65 should preferably receive higher-dose,⁵⁹ adjuvanted or recombinant influenza vaccines over standard inactivated vaccines because they provide better protection.^{68,71} Recent evidence has further strengthened the case for high-dose influenza vaccination in older adults. A 2024 meta-analysis of randomized trials confirmed superior effectiveness of high-dose versus standard-dose influenza vaccines against laboratory-confirmed influenza and severe outcomes in people aged ≥ 65 years.⁵⁹ In parallel, three large pragmatic trials – GALFLU⁸⁰ DANFLU⁸¹ and FLUNITY-HD⁸² demonstrated that high-dose influenza vaccination significantly reduces influenza-related hospitalizations and major cardiorespiratory events compared with standard-dose vaccines in real-world older adult populations, providing robust outcome-based evidence to support preferential use of enhanced influenza vaccines in this age group.^{59,82,83} Trivalent high-dose inactivated influenza vaccine (HD-IIV3), trivalent recombinant influenza vaccine (RIV3), or trivalent adjuvanted inactivated would be preferably used, if possible, according to ACIP.⁷¹ Still, any alternative age-appropriate influenza vaccine should be administered because all currently available inactivated and recombinant seasonal influenza vaccines have demonstrated benefits over no vaccination.⁸⁴

Moreover, new mRNA vaccines for influenza offer a promising advancement in flu vaccine development, especially for older adults at higher risk of severe flu complications. As older adults often have weakened

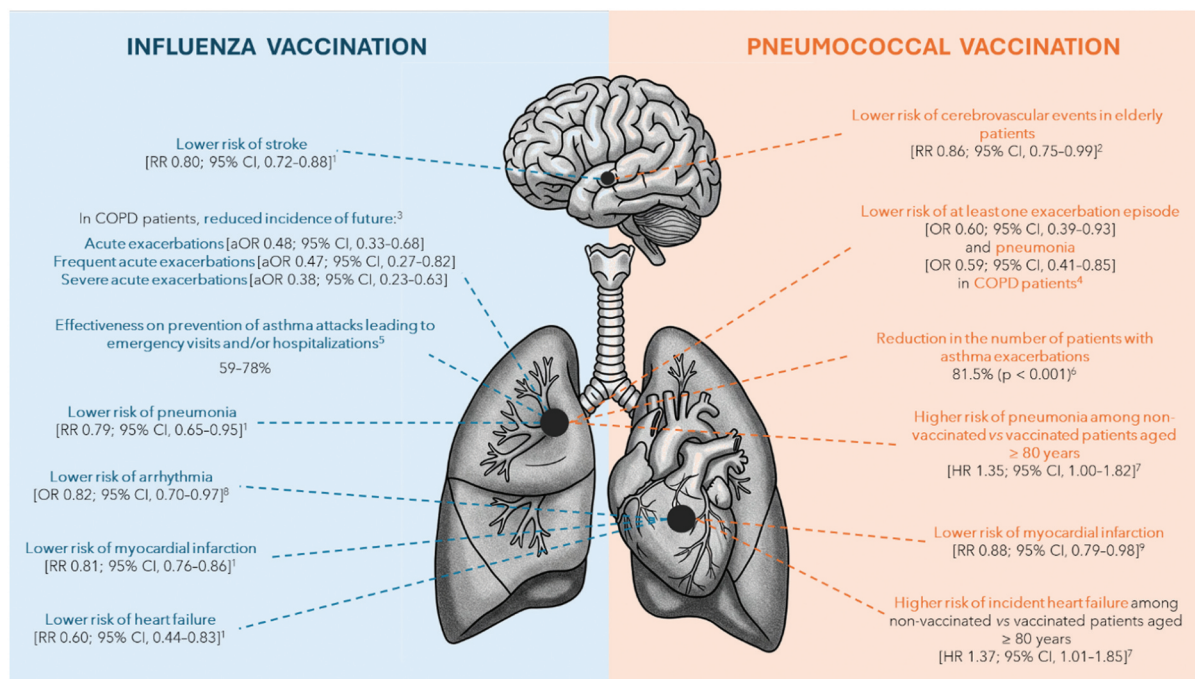


Figure 2. Reduction of cardiovascular and respiratory events associated with influenza and pneumococcal vaccination.¹¹⁹⁻¹²⁷ HR: hazard ratio; RR: relative risk.

immune systems, the enhanced effectiveness and adaptability of mRNA vaccines could provide superior protection against seasonal influenza and reduce the incidence of serious illness in this vulnerable population.

Respiratory syncytial virus (RSV) vaccines

RSV is increasingly recognized as a critical cause of morbidity and mortality and is known to exacerbate chronic respiratory diseases, particularly among the elderly and high-risk adults, such as those who are immunocompromised or have chronic cardiopulmonary conditions.⁶⁸ The infection rates for RSV in the elderly range from 3%-7%, rising to 4%-10% for high-risk adults, and 7% of RSV-associated infections in individuals over 50 years of age result in hospitalization.⁶⁵ Among several RSV complications the cardiovascular events such as chronic heart failure, ischemic heart disease, arrhythmia or ischemic stroke are well described.^{85,86} Epidemiological evidence suggests that individuals aged 60 years and older, especially those with chronic medical conditions or residing in long-term care facilities, are at the highest risk for severe RSV disease due to immunosenescence and could benefit the most from vaccination.⁶⁰ RSV vaccination has shown moderate to high efficacy in preventing RSV-associated lower respiratory tract diseases, potentially reducing substantial morbidity and short-, mid- and long-term mortality among older adults.⁶⁰ Beyond preventing RSV-associated lower respiratory tract disease in older adults, RSV immunization may also confer downstream cardiopulmonary benefits by reducing infection-triggered decompensation. In the pragmatic randomized DAN-RSV program, RSVpreF vaccination was associated with a significant reduction in all-cause cardiorespiratory hospitalizations versus no vaccination, whereas the effect on all-cause cardiovascular hospitalization was not statistically significant; prespecified analyses further suggested directionally favorable cardiovascular signals, including a lower incidence of stroke among participants with and without preexisting atherosclerotic cardiovascular disease.^{83,87} Importantly, early post-licensure data support real-world impact: during the first season after approval, RSV vaccines showed substantial effectiveness against RSV-associated emergency department visits, hospitalization, and critical illness in US test-negative evaluations, broadly consistent across age strata and vaccine types.⁸⁸ Additional U.S. observational analyses have reported vaccine effectiveness around ~75% against RSV-associated acute respiratory infection with urgent-care/ED visits or hospitalization, with ongoing monitoring of rare adverse events such as Guillain – Barré syndrome.^{89,90} Uptake has been meaningful but incomplete (~20%–25% of adults ≥60 years in the U.S. by spring 2024), and recommendations have evolved toward routine use in adults ≥75 years and in high-risk adults 60–74 years.⁹⁰ Newly licensed vaccines, including protein-based and mRNA formulations, offer innovative approaches to tackling this challenging virus. Data has been accumulating about the unequivocally important role of RSV in increasing the risk and severity of diseases caused by *S. pneumoniae* so -in addition to its intended action- RSV vaccination can potentially reduce its burden.⁹¹

COVID-19 vaccines

The first COVID-19 vaccinations were made available internationally by the end of 2020.⁹² There were, and still are, differences in the recommended number of booster shots between immunocompetent people and those who are immunocompromised or at risk. In older adults, COVID-19 vaccination has consistently been associated with clinically meaningful reductions in severe outcomes, including COVID-19-related hospitalization, critical illness, and death.⁹³ In parallel, during the COVID-19 pandemic period, hospital admissions for community respiratory viral infections decreased, and hospital admissions due to acute exacerbations of COPD were reduced by 50%, likely driven by the overall reduction in circulating respiratory viruses that trigger exacerbations.⁶⁸

Effectiveness against severe outcomes can wane over time, and recent evaluations show that updated doses provide additional protection against COVID-19-associated hospitalization in adults ≥65 years.^{54,56,94} Recent national registry data with updated vaccines also indicate sustained protection for several months against hospitalization and death in older adults.⁹⁵

Pneumococcal vaccines

A 23-valent polysaccharide vaccine against *Streptococcus pneumoniae* has been used for many years in the elderly population to prevent invasive disease. However, the introduction of the 13-valent conjugate vaccine (PCV13) marked a turning point. It has demonstrated clinical efficacy of 45.6% for confirmed vaccine-type community-acquired pneumonia and 75.0% for vaccine-type invasive disease in a large, randomized placebo-controlled study involving over 84,000 elderly individuals.^{96,97} This study supports the impact of age on vaccine efficacy, with a decrease in efficacy for vaccine-type community-acquired pneumonia and invasive disease from 65% in 65-year-old people to 40% in 75-year-old seniors.^{97,98}

Beyond pneumococcal infections, studies have shown that PCV13 also provided significant cross-protection against respiratory infections associated with human coronaviruses (HCoVs): 27.4% against HCoV-related pneumonia and 51.4% against non-pneumonia HCoV-related lower respiratory tract infections. It also showed protection against COVID-19 in older adults, reducing COVID-19 diagnosis by 35%, hospitalizations by 32%, and COVID-19-related mortality by 32%.⁷³ It might protect against RSV burden since biological, epidemiological, clinical and interventional data suggest a role for *S. pneumoniae* in the severity of RSV disease.⁹¹ Official organizations, such as the WHO, recommend pneumococcal vaccination for all adults over 65 to prevent invasive and noninvasive pneumococcal infections, which can be particularly severe in this age group. However, the ACIP in the United States has broadened this recommendation to include adults aged 50 and older,⁹⁹ recognizing the vulnerability of a wider age range to the complications of these infections. These guidelines emphasize the importance of tailoring vaccination strategies to each region's epidemiological characteristics and healthcare system capacities, which may involve using one or both pneumococcal vaccines, depending on public health priorities and available resources.

In response to the evolving landscape of pneumococcal disease, newer conjugate vaccines such as PCV15 and PCV20 have been introduced, offering broader serotype coverage and enhanced immunogenicity. Both vaccines have been recommended for use in adults, with PCV20 providing additional protection against serotypes not covered by previous formulations.¹⁰⁰ Furthermore, PCV21, which includes an expanded range of serotypes designed specifically for adults, has already been incorporated into some public health recommendations by the FDA and has recently received positive opinion from the Committee for Medicinal Products for Human Use (CMPH-EMA),¹⁰¹ reflecting the ongoing efforts to optimize protection across diverse populations.¹⁰²

Looking to the future, promising vaccine candidates such as PCV25 and VAX-31 are in development, aiming either to provide even broader serotype coverage or to employ novel conjugation methods for improved efficiency.¹⁰³ Additionally, novel vaccination approaches, such as Multiple Antigen Presenting System (MAPS) technology and vaccines developed by AFinivax, hold potential to revolutionize pneumococcal prevention by inducing stronger and more sustained immune responses.¹⁰⁴

The primary goal of pneumococcal vaccination in older adults remains the reduction of severe pneumococcal diseases, including pneumonia, bacteremia, and meningitis, which have higher mortality rates in this age group.^{35,105,106}

Herpes zoster vaccine (HZV)

Herpes zoster (shingles) vaccination is recommended for individuals aged 50 and above to prevent shingles and its complications.^{5,35} Recombinant zoster vaccine (RZV), against Varicella Zoster Virus, contains the AS01 adjuvant, which stimulates a potent innate immune response and robust cellular and humoral responses.⁷⁷ Avoiding several vasculopathies associated to herpes zoster as ischemic stroke, aneurysm, myocardial infarction or transient ischemic attack¹⁰⁷ are among the potential indirect benefits of its use as well as improving the associated loss in health-related quality of life.¹⁰⁸ One of the heterologous effects of RZV was detected during the first year of the COVID-19 pandemic, with evidence suggesting that RZV may have reduced the burden of COVID-19 in adults aged 50 years and older before the availability of the COVID-19 vaccine.⁷⁷ In a cohort analysis, adjusting for other vaccinations and potential confounders, RZV recipients (≥ 1 dose) had a 16% lower risk of COVID-19 diagnosis compared to unvaccinated individuals, with this association remaining consistent regardless of the time since the most recent RZV dose.⁷⁷ Additionally, the risk of

hospitalization due to COVID-19 was reduced by 32% among RZV recipients (≥ 1 dose) compared to unvaccinated individuals, underscoring the broader protective effects of the HZV vaccination.⁷⁷ Emerging real-world evidence suggests an association between herpes zoster vaccination – particularly RZV – and a lower subsequent risk of incident dementia. Large observational analyses report lower dementia incidence after RZV compared with live zoster vaccine and even other adult vaccines, with an estimated ~17% increase in dementia diagnosis – free time over 6 years in a natural-experiment setting.¹⁰⁹ A large claims-based cohort also found a lower hazard of dementia among RZV recipients (two doses HR ~ 0.68; one dose HR ~ 0.89 vs unvaccinated).¹¹⁰ In addition, a regression-discontinuity natural experiment in Wales found ~20% lower incident dementia over 7 years after live zoster vaccination.¹¹¹ However, these data are observational (or quasi-experimental) and do not establish causality; residual confounding, including healthy-vaccinee effects, cannot be fully excluded, and no randomized trial has evaluated zoster vaccination specifically for dementia prevention.^{109–111}

Tetanus, diphtheria and pertussis

Regular booster vaccinations against tetanus and diphtheria are recommended throughout life in many countries. However, elderly individuals often have insufficient levels of tetanus and diphtheria-specific antibodies considered protective. That may be related to the inefficacy of single booster shots in producing long-lasting antibody responses against some pathogens, such as diphtheria, in many elderly individuals.²⁴ Epidemiological data indicate that pertussis remains relevant in older age groups and is not limited to younger individuals. Consequently, some countries advise regular pertussis booster vaccinations in conjunction with tetanus/diphtheria vaccines or at least one booster shot during adulthood.²⁴

Hepatitis B and Human Papillomavirus (HPV)

The recommendations for Hepatitis B (HBV) vaccination emphasize its importance for adults at risk, including healthcare workers and individuals with chronic liver disease. Evidence from various studies demonstrates that the HBV vaccine is highly effective in preventing both acute and chronic infections, significantly reducing the incidence of liver-related complications, including cancer, and improving long-term health outcomes.¹¹² Similarly, the Human Papillomavirus (HPV) vaccination is recommended for adults up to age 45, particularly for those who are unvaccinated or under-vaccinated. Research has shown that HPV vaccination effectively decreases the risk of HPV-related cancers, such as cervical, urogenital and oropharyngeal cancers,¹¹³ as well as the incidence of genital warts¹¹⁴ or recurrent respiratory papillomatosis in some cases.¹¹⁵ Both vaccines are supported by robust clinical evidence, highlighting their critical role in enhancing public health and preventing serious diseases.¹¹²

Mumps, Rubella, and Measles (MMR)

The Mumps, Rubella, and Measles (MMR) vaccination recommendations advocate for two doses for adults born after 1970 who lack documentation of prior vaccination. This guidance is supported by robust evidence indicating that high vaccination coverage has effectively eliminated these diseases in many regions. Studies show that two doses of the MMR vaccine provide over 95% efficacy in preventing measles and rubella, significantly reducing the risk of outbreaks and associated complications.¹¹² However, live attenuated vaccines, such as MMR, are contraindicated in immunosuppressed.

Varicella (Chickenpox) and Poliomyelitis

For Varicella (Chickenpox) and Poliomyelitis, the recommendation is to vaccinate adults who have never had the disease or have not been previously vaccinated or are at risk (i.e., those traveling to areas where polio is still endemic should ensure proper protection). Clinical trials have demonstrated that the varicella vaccine is approximately 90% effective in preventing chickenpox. For those who do contract the disease, vaccination significantly reduces the severity and duration of symptoms and helps prevent more aggressive disease manifestations common in adults, such as a pneumonia, which

is associated with a mortality increase. This evidence underscores the vaccine's role in controlling varicella outbreaks and protecting public health.¹¹² Additionally, the inactivated poliovirus vaccine (IPV) has shown strong efficacy in providing immunity against poliomyelitis, with studies indicating that vaccination effectively prevents outbreaks and protects individuals from severe disease. This evidence highlights the importance of maintaining high vaccination coverage to prevent the reemergence of polio.¹¹²

Challenges and considerations of immunofitness enhancement through vaccination

Addressing vaccine hesitancy is crucial in tackling the global public health threat, as it undermines vaccination efforts and jeopardizes the achievement of widespread immunity needed to control and prevent infectious diseases. Even in countries where healthcare and vaccinations are fully reimbursed by the healthcare system and recommended by professionals and administrations, adult vaccine coverage remains significantly lower than that of children, indicating that non-economic and non-medical barriers, such as psychological and educational factors, play a critical role. Therefore, there are issues to consider when designing strategies to improve vaccine coverage that, in principle, are unrelated to access, affordability, reimbursement, and healthcare infrastructure.^{36,116} Our better understanding and knowledge about the value of vaccination and having the enough time and tools to be able to efficiently communicate it to population may be very useful to achieve it.

The importance of epidemiological surveillance should also be highlighted, not only after the implementation of new vaccines but also beforehand. This aspect has been notably missed in cases such as pneumococcal vaccination and almost in the case of RSV in the elderly population. Effective surveillance can provide crucial data to optimize vaccination strategies, ensuring timely responses to emerging health threats and improving public health planning.

Antibody responses are commonly used as a measure of vaccine efficacy. However, this approach may not fully capture the age-related changes in the immune system that impact vaccine effectiveness, especially in older adults.¹¹⁷ For this reason, clinical endpoints such as reduction in hospitalizations, prevention of functional decline, and improved quality of life should be prioritized as markers of vaccine effectiveness in the elderly, rather than antibody titers alone. Antibody measurements may not account for other crucial components of the immune system, such as cellular immunity, and may not always correlate with the actual clinical protection against infections.¹¹⁸ All vaccination strategies for older adults should be tailored to account for the aging immune system's response to vaccines, mainly emphasizing the importance of booster doses or the addition of adjuvants capable of stimulating the immune system properly.^{24,36} This underscores the need for an increased understanding of the regulation of the aging immune system and for developing vaccines specifically tailored to overcome or adapt to immunosenescence.²⁵ Additionally, to ensure proper vaccination rates, continuous evaluation and updates of vaccination guidelines are necessary to address the evolving landscape of infectious diseases and, concretely, the specific needs of the elderly population.^{5,33}

Immune training through increased adult vaccination has the potential to become a cornerstone of a healthy lifestyle. By boosting the immune system, we can enhance its resilience and mitigate the effects of immunosenescence and inflammaging. This approach can significantly reduce morbidity and mortality among older adults, offering a proactive strategy to improve health outcomes and quality of life in this vulnerable population.

Conclusion

Vaccination plays a pivotal role in maintaining immune fitness by providing a straightforward, effective, and easily implementable approach to enhancing immune health, particularly in aging. As the immune system naturally declines with age, vaccinations serve as a crucial tool for preserving immune function and protecting against infections that pose significant risks to older adults. Unlike other immune fitness measures, which may require complex lifestyle changes or prolonged interventions, vaccines offer

a rapid, simple, and well-defined method to strengthen the immune response. By stimulating the immune system to recognize and combat specific pathogens, vaccines help sustain immune resilience and reduce disease risk. This holistic approach to healthy aging integrates seamlessly into preventive care strategies, making vaccination a preferred and practical solution for supporting immune fitness throughout the aging process. Ultimately, vaccination should be regarded as a cornerstone of comprehensive healthy aging strategies, together with nutrition, physical activity, and management of chronic conditions. By embedding vaccines into a holistic model of immune fitness, we can better align preventive medicine with the challenges of an aging society.

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FM-T has acted as principal investigator in randomized controlled trials of Ablynx, Abbot, Seqirus, Sanofi Pasteur MSD, Sanofi Pasteur, Cubist, Wyeth, Merck, Pfizer, Roche, Regeneron, Jansen, Medimmune, Novavax, Novartis and GSK, with honoraria paid to his institution. FM-T reports a relationship with GSK Vaccines SRL that includes consulting or advisory. FM-T reports a relationship with Pfizer Inc. which provides for consulting or advisory. FM-T reports a relationship with Sanofi Pasteur Inc. that includes consulting or advisory. FM-T reports a relationship with Janssen Pharmaceuticals Inc. which provides consulting or advisory. FM-T reports a relationship with MSD that includes consulting or advisory. FM-T reports a relationship with Seqirus Pty Ltd that includes consulting or advisory. ER has participated in advisory boards, conferences, courses, and lectures organized by GlaxoSmithKline, Sanofi Pasteur, MSD, GSK, Seqirus, Pfizer, and AstraZeneca. IRC has participated in advisory boards organized by MSD, GSK, Sanofi, and Pfizer. IRC has been involved in clinical trials funded by Ablynx, Abbot, Seqirus, Sanofi Pasteur MSD, Cubist, Wyeth, Merck, Pfizer, Roche, Regeneron, Jansen, Medimmune, Novavax, Novartis and GSK, although the funds were paid to the institution. EM has participated in advisory boards by Astra-Zeneca, Boehringer Ingelheim, Esteve, GSK, MSD, Menarini, Mundifarma, Novartis, Orion, Pfizer, Roche, Rovi, Takeda and TEVA. DO has participated in advisory boards from Lilly, Boehringer Ingelheim, Novartis, Pfizer, Takeda, Esteve, Almirall, GlaxoSmithKline, Astra-Zeneca, Chiesi, Mundipharma, Teva, Solvay Pharma, Rovi, Gebro Pharma, Janssen, MSD, Novo Nordisk and Menarini. IJ has participated in advisory boards from Pfizer, Sanofi Pasteur, and conference attendance scholarships paid by Menarini, and Esteve. AG has participated in Pfizer, GlaxoSmithKline, Janssen, MSD, and Sanofi Pasteur advisory boards. ML has participated in advisory boards and research projects organized by Pfizer. FGR has participated in advisory boards, conferences, courses or lectures organized by GlaxoSmithKline, Sanofi Pasteur, MSD, Pfizer and Moderna. JY received grants from MSD-USA (Merck Investigator Studies Program), and Pfizer, outside of this work, and the funds were awarded to the Institution. JY participated in advisory boards organized by MSD and Pfizer. MAO has participated in advisory boards organized by Pfizer and MSD. JGR reports honoraria for lectures and scientific advisor for the following pharmaceutical companies: MSD, Pfizer, GSK, AstraZeneca, Seqirus, Moderna, Sanofi, Novavax. The remaining authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability statement

No new data were generated or analyzed in this study. This article is a narrative review; all information is derived from previously published sources cited in the reference list; therefore, data sharing is not applicable.

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