Human Vaccines & Immunotherapeutics

ISSN: 2164-5515 (Print) 2164-554X (Online) Journal homepage: www.tandfonline.com/journals/khvi20

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

José Gomez Rial , Esther Redondo , Irene Rivero-Calle , Enrique Mascarós , Daniel Ocaña , Isabel Jimeno , Ángel Gil , Manuel Linares , María Ángeles Onieva-García , Fernando González-Romo , José Yuste & Federico Martinón-Torres

To cite this article: José Gomez Rial , Esther Redondo , Irene Rivero-Calle , Enrique Mascarós , Daniel Ocaña , Isabel Jimeno , Ángel Gil , Manuel Linares , María Ángeles Onieva-García , Fernando González-Romo , José Yuste & Federico Martinón-Torres (2026) Immunofitness in the elderly: The role of vaccination in promoting healthy aging, Human Vaccines & Immunotherapeutics, 22:1, 2624234, DOI: 10.1080/21645515.2026.2624234

To link to this article: https://doi.org/10.1080/21645515.2026.2624234

Published online: 10 Feb 2026.

HUMAN VACCINES & IMMUNOTHERAPEUTICS
2026, VOL. 22, NO. 1, 2624234
https://doi.org/10.1080/21645515.2026.2624234

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS Check for updates

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

José Gomez Rial[a], Esther Redondo[b], Irene Rivero-Calle[c,d,e], Enrique Mascarós[f], Daniel Ocaña[g], Isabel Jimeno[h], Ángel Gil[e,i], Manuel Linares[j], María Ángeles Onieva-García[k,l,m], Fernando González-Romo[n], José Yuste[e,o], and Federico Martinón-Torres[c,d,e]

[a]Immunology Department, Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela, Spain; [b]Infectious, Migrant, Vaccines, and Preventive Activities Group of SEMERGEN, International Healthcare Centre of the City Council of Madrid, Madrid, Spain; [c]Translational Paediatrics and Infectious Diseases Section, Paediatrics Department, Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela, Spain; [d]Genetics, Vaccines, and Infections Research Group (GENVIP), Healthcare Research Institute of Santiago de Compostela, University of Santiago de Compostela, Santiago de Compostela, Spain; [e]CIBER of Respiratory Diseases (CIBERES), Instituto de Salud Carlos III, Madrid, Spain; [f]Health Department, Hospital la Fe, Primary Care Centre Arquitecto Tolsá, Valencia, Spain; [g]Primary Care, Health Care Centre Algeciras, Algeciras, Spain; [h]Primary Care Health Centre Isla de Oza, Vaccine Responsible of SEMG, Madrid, Spain; [i]Preventive and Public Health, Rey Juan Carlos University, Madrid, Spain; [j]Specialist in Primary Care and Clinical Microbiology, Infectious Diseases Group SEMERGEN, Fundación Io, Madrid, Spain; [k]Preventive Medicine and Public Health Unit, Hospital Universitario Reina Sofia, Cordoba, Spain; [l]Preventive Medicine and Public Health Research Group, Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Cordoba, Spain; [m]Department of Medical and Surgical Sciences, University of Cordoba, Cordoba, Spain; [n]Clinical Microbiology Department, Hospital Universitario Clínico San Carlos, Madrid, Spain/Instituto de Investigación Sanitaria Hospital Clínico San Carlos (IdISSC), Madrid, Spain; [o]National Centre for Microbiology, Instituto de Salud Carlos III, Madrid, Spain

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.

ARTICLE HISTORY
Received 5 November 2025
Revised 14 January 2026
Accepted 26 January 2026

KEYWORDS
Immunofitness; immunosenescence; inflammaging; adult vaccination; older adults; trained immunity

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]

CONTACT Federico Martinón-Torres federico.martinon.torres@sergas.es Hospital Clínico Universitario de Santiago de Compostela, A Choupana S.N, Santiago de Compostela 15701, Spain.

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-ɣ 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

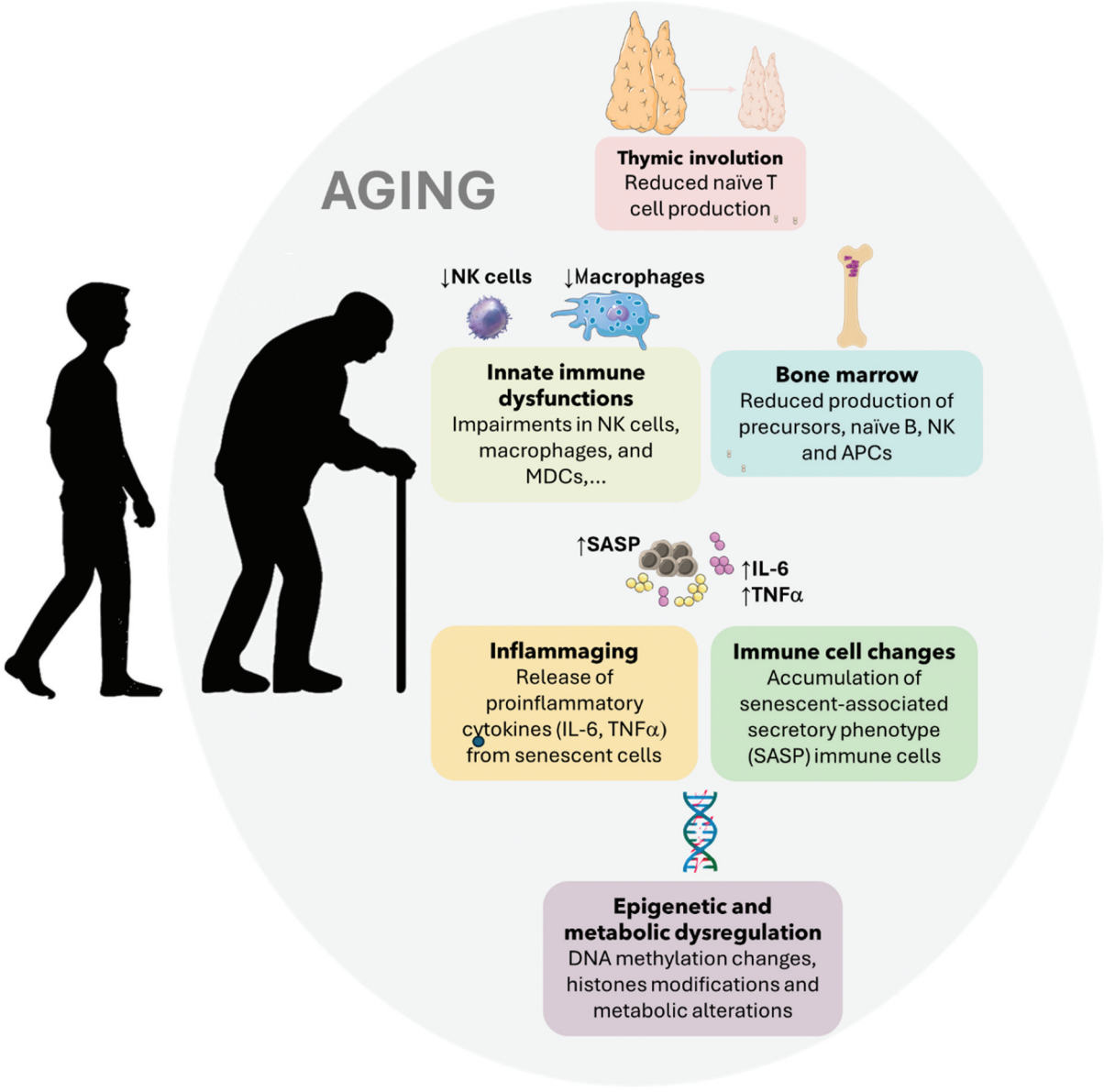

Figure 1. Impact of aging on immune system function.

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 naive 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 component[43]; 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 (GMMA), 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[58] 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 (Melgar 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 flu-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 – GALFLU[80] DANFLU[81] and FLUNITY-HD[82] 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

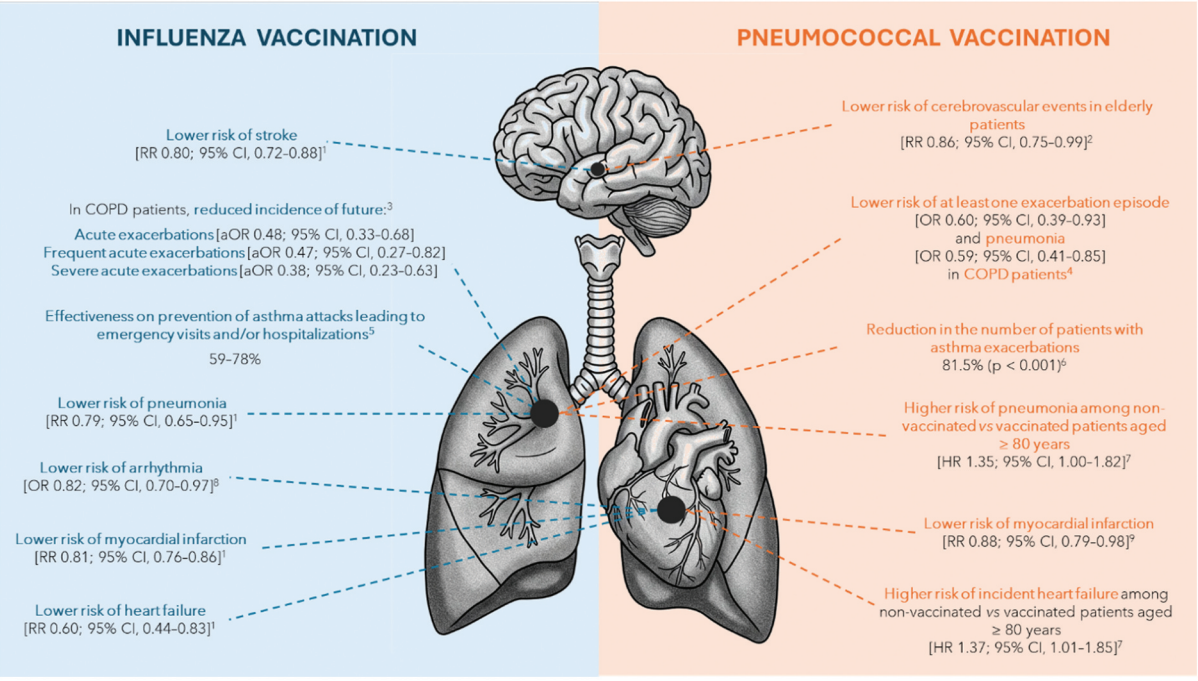

Figure 2. Reduction of cardiovascular and respiratory events associated with influenza and pneumococcal vaccination.[119–127] HR: hazard ratio; RR: relative risk.

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, arrythmia 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 attack[107] 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, diphteria 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 warts[114] 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.

Acknowledgments

Medical writing support under the guidance of the authors was provided by Maria Julia Lamborizio Melero, MD, Beatriz Albuixech Crespo, and Blanca Piedrafita, PhD, from Medical Statistics Consulting (MSC), Valencia, Spain, by Good Publication Practice guidelines (DeTora, L. M. et al. Ann Intern Med. 2022) and funded by Pharming.

Author contributions

CRediT: **José Gomez Rial:** Conceptualization, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing; **Esther Redondo:** Investigation, Resources, Writing – review & editing; **Irene Rivero-Calle:** Investigation, Resources, Writing – review & editing; **Enrique Mascarós:** Investigation, Project administration, Resources, Writing – review & editing; **Daniel Ocaña:** Investigation, Resources, Writing – review & editing; **Isabel Jimeno:** Investigation, Resources, Writing – review & editing; **Ángel Gil:** Investigation, Resources, Writing – review & editing; **Manuel Linares:** Investigation, Resources, Writing – review & editing; **María Ángeles Onieva-García:** Investigation, Resources, Writing – review & editing; **Fernando González-Romo:** Investigation, Resources, Writing – review & editing; **José Yuste:** Investigation, Resources, Writing – review & editing; **Federico Martinón-Torres:** Conceptualization, Funding acquisition, Investigation, Methodology, Resources, Supervision, Writing – original draft, Writing – review & editing.

Disclosure statement

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.

Funding

FMT research work is supported by Framework Partnership Agreement between the Consellería de Sanidad de la XUNTA de Galicia and GENVIP-IDIS-2021–2024 (SERGAS-IDIS March 2021; Spain); and consorcio Centro de Investigacion Biomédica en Red de Enfermedades Respiratorias (CB21/06/00103; F.M-T), Resvi-Omics (Instituto de Salud Carlos III (ISCIII)/PI19/01039/Co-funded FEDER), BI-BACVIR (PRIS-3; Agencia de Conocimiento en Salud (ACIS)—Servicio Gallego de Salud (SERGAS)—Xunta de Galicia; Spain), Programa Traslacional COVID-19 (ACIS—Servicio Gallego de Salud (SERGAS)—XUNTA de Galicia; Spain) and Axencia Galega de Innovacion (GAIN; IN607B 2020/08—XUNTA de Galicia; Spain); ReSVinext (Instituto de Salud Carlos III (ISCIII)/PI16/01569/Co-funded FEDER), Enterogen (ISCIII/PI19/01090/Co-funded FEDER), OMI-COVI-VAC (ISCIII PI22/00406/Co-funded FEDER, PNEUMOVAI (ISCIII PI25/01405/Co-funded FEDER), Grupos de Referencia Competitiva (IIN607A2021/05) and Axencia Galega de Innovación (GAIN; IN845D 2020/23—Xunta de Galicia; Spain).

Notes on contributors

José Gómez Rial, PhD is an Immunologist at the Hospital Clínico Universitario de Santiago de Compostela (Spain) and senior researcher at the GENVIP group (Genetics, Vaccines, and Infectious Diseases Research Group). His research focuses on immunopathogenesis and biomarker discovery in infectious and inflammatory diseases.

Esther Redondo, MD is a family physician at the International Healthcare Centre of Madrid City Council and responsible for the Vaccines Area of the SEMERGEN Group on Infectious, Migrant, Vaccines and Preventive Activities. She specializes in travel medicine, vaccination, and preventive healthcare in primary care.

Irene Rivero-Calle, MD, PhD is a Pediatric Infectious Diseases specialist at the Hospital Clínico Universitario de Santiago de Compostela and researcher at the GENVIP group (IDIS). Her work centers on respiratory viruses, pediatric vaccinology, and real-world evidence on vaccine impact.

Enrique Mascarós, MD is a family physician at Hospital La Fe–Primary Care Centre Arquitecto Tolsá (Valencia, Spain). His main interests include respiratory diseases, chronic patient management, and preventive medicine in primary care.

Daniel Ocaña, MD is a family physician at the Algeciras Primary Care Centre (Cádiz, Spain) and member of several national working groups on vaccines and chronic disease prevention.

Isabel Jimeno, MD is a family physician at the Isla de Oza Primary Care Health Centre in Madrid and Vaccination Lead for SEMG. She focuses on vaccine promotion and adult immunization programs in primary care.

Ángel Gil, MD, PhD is Professor of Preventive Medicine and Public Health at Rey Juan Carlos University (Madrid, Spain). He has coordinated multiple national and international vaccination programs and has published extensively on immunization and public health policy.

Manuel Linares, MD, PhD is a Primary Care and Clinical Microbiology specialist, and researcher at Fundación io (Madrid, Spain). He is an expert in emerging infections and diagnostic microbiology applied to community medicine.

María Ángeles Onieva-García, MD, PhD is a Preventive Medicine and Public Health specialist at Hospital Universitario Reina Sofía (Córdoba, Spain) and researcher at IMIBIC and the University of Córdoba. Her work focuses on vaccination programs, epidemiology, and population health.

Fernando González-Romo, MD, PhD is Senior Consultant at the Department of Clinical Microbiology, Hospital Clínico San Carlos (Madrid, Spain), and researcher at IdISSC. His expertise includes respiratory infections, antimicrobial resistance, and adult vaccination strategies.

José Yuste, PhD is a senior scientist at the National Centre for Microbiology (Instituto de Salud Carlos III, Madrid, Spain). His research focuses on pneumococcal pathogenesis, molecular epidemiology, and host-pathogen interactions.

Federico Martinón-Torres, MD, PhD is Head of Pediatrics at the Hospital Clínico Universitario de Santiago de Compostela, Principal Investigator of the GENVIP group (IDIS), and Director of the WHO Collaborating Centre for Vaccine Safety. His research spans infectious diseases, vaccine research, and implementation of evidence-based vaccination policies.

ORCID

Federico Martinón-Torres http://orcid.org/0000-0002-9023-581X

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.

References

1. Villar-Álvarez F, de la Rosa-Carrillo D, Fariñas-Guerrero F, Jiménez-Ruiz CA. Immunosenescence, immune fitness and vaccination schedule in the adult respiratory patient. Open Respir Arch. 2022;4(3):100181.
2. Kiani P, Balikji J, Kraneveld AD, Garssen J, Bruce G, Verster JC. Pandemic preparedness: The importance of adequate immune fitness. J Clin Med. 2022;11(9):2442. doi: 10.3390/jcm11092442.
3. Geckin B, Konstantin Föhse F, Domínguez-Andrés J, Netea MG. Trained immunity: implications for vaccination. Curr Opin Immunol. 2022;77:102190. doi: 10.1016/j.coi.2022.102190.
4. Martinon-Torres F. Expected and unexpected effects of vaccination. Pediatric vaccines and vaccinations. 2017;3–12.
5. Laupèze B, Del Giudice G, Doherty MT, Van der Most R. Vaccination as a preventative measure contributing to immune fitness. NPJ Vaccines. 2021;6(1):93. doi: 10.1038/s41541-021-00354-z.
6. Laupèze B, Doherty TM. Maintaining a 'fit' immune system: the role of vaccines. Expert Rev Vaccines. 2023;22 (1):256–266. doi: 10.1080/14760584.2023.2185223.
7. Walford RL. The immunologic theory of aging. Gerontologist. 1964;4(4):195–197. doi: 10.1093/geront/4.4.195.
8. Liu Z, Liang Q, Ren Y, Guo C, Ge X, Wang L, Cheng Q, Luo P, Zhang Y, Han X. Immunosenescence: molecular mechanisms and diseases. Sig Transduct Target Ther. 2023;8(1):200. doi: 10.1038/s41392-023-01451-2.
9. Ramasubramanian R, Meier HCS, Vivek S, Klopack E, Crimmins EM, Faul J, Nikolich-Žugich J, Thyagarajan B. Evaluation of T-cell aging-related immune phenotypes in the context of biological aging and multimorbidity in the health and retirement study. Immun Ageing. 2022;19(1):33. doi: 10.1186/s12979-022-00290-z.
10. Liang Z, Dong X, Zhang Z, Zhang Q, Zhao Y. Age-related thymic involution: mechanisms and functional impact. Aging Cell. 2022;21(8):e13671. doi: 10.1111/acel.13671.
11. Wrona MV, Ghosh R, Coll K, Chun C, Yousefzadeh MJ. The 3 i's of immunity and aging: immunosenescence, inflammaging, and immune resilience. Front Aging. 2024;5:1490302. doi: 10.3389/fragi.2024.1490302.
12. Franceschi C, Bonafè M, Valensin S, Olivieri F, De Luca M, Ottaviani E. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci. 2000;908:244–254.
13. Fulop T, Larbi A, Pawelec G, Khalil A, Cohen AA, Hirokawa K, Witkowski JM, Franceschi C. Immunology of aging: the birth of inflammaging. Clin Rev Allergy Immunol. 2023;64(2):109–122. doi: 10.1007/s12016-021-08899-6.
14. Lu Q, Feng Y, Wang H, Zhu K, Teng L, Yue M, Li Y. Gut microbiota as a regulator of vaccine efficacy: implications for personalized vaccination. Gut Microbes. 2025;17(1):2563709. doi: 10.1080/19490976.2025.2563709.
15. Goyani P, Christodoulou R, Vassiliou E. Immunosenescence: aging and immune system decline. Vaccines (Basel). 2024;12(12):1314. doi: 10.3390/vaccines12121314.
16. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol. 2018;15(9):505–522. doi: 10.1038/s41569-018-0064-2.
17. Muller L, Di Benedetto S. Immunosenescence and cytomegalovirus: exploring their connection in the context of aging, health, and disease. Int J Mol Sci. 2024;25(2):753. doi: 10.3390/ijms25020753.
18. Aghapour M, Raee P, Moghaddam SJ, Hiemstra PS, Heijink IH. Airway epithelial barrier dysfunction in chronic obstructive pulmonary disease: role of cigarette smoke exposure. Am J Respir Cell Mol Biol. 2018;58(2):157–169. doi: 10.1165/rcmb.2017-0200TR.
19. Papi A, Bellettato CM, Braccioni F, Romagnoli M, Casolari P, Caramori G, Fabbri LM, Johnston SL. Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. Am J Respir Crit Care Med. 2006;173(10):1114–1121. doi: 10.1164/rccm.200506-859OC.
20. Du X, Yang M. Unraveling the mechanisms of virus-induced asthma exacerbation: epithelial injury, immune dysregulation, and novel interventions. Chin Med J Pulm Crit Care Med. 2025;3(3):164–181. doi: 10.1016/j.pccm.2025.08.003.
21. Adeli M, El-Shareif T, Hendaus MA. Asthma exacerbation related to viral infections: an up to date summary. J Fam Med Prim Care. 2019;8(9):2753–2759. doi: 10.4103/jfmpc.jfmpc_86_19.
22. Mehta J, Walsh EE, Mahadevia PJ, Falsey AR. Risk factors for respiratory syncytial virus illness among patients with chronic obstructive pulmonary disease. COPD. 2013;10(3):293–299. doi: 10.3109/15412555.2012.744741.
23. Carvajal Castaño LM, Bastidas Rueda GD, Quisiguiña Cárdenas SB, Moreira Rojas RE, Romero Ortega MK, Jaramillo Palacios CL, Guerrón Tumipamba CA, Pico Arias CG, Robert Daniel OE, Mora Velasco CA, et al. Infecciones respiratorias y diabetes mellitus: situación actual. Rev Latinoam Hipertens. 2021;16(1):88–92.

24. Pinti M, Appay V, Campisi J, Frasca D, Fülöp T, Sauce D, Larbi A, Weinberger B, Cossarizza A. Aging of the immune system: Focus on inflammation and vaccination. Eur J Immunol. 2016;46(10):2286–2301. doi: 10.1002/eji.201546178.
25. Oviedo-Orta E, Li CK, Rappuoli R. Perspectives on vaccine development for the elderly. Curr Opin Immunol. 2013;25(4):529–534. doi: 10.1016/j.coi.2013.07.008.
26. Lam N, Lee Y, Farber DL. A guide to adaptive immune memory. Nat Rev Immunol. 2024;24(11):810–829. doi: 10.1038/s41577-024-01040-6.
27. Wang L, Nicols A, Turtle L, Richter A, Duncan CJ, Dunachie SJ, Klenerman P, Payne RP. T cell immune memory after COVID-19 and vaccination. BMJ Med. 2023;2(1):e000468. doi: 10.1136/bmjmed-2022-000468.
28. Netea MG, Joosten LAB. Trained innate immunity: concept, nomenclature, and future perspectives. J Allergy Clin Immunol. 2024;154(5):1079–1084. doi: 10.1016/j.jaci.2024.09.005.
29. Munkwase G. Implications of vaccine non-specific effects on licensure of new vaccines. Vaccine. 2024;42(5):1013–1021. doi: 10.1016/j.vaccine.2024.01.048.
30. Gupta S, Yadav S, Kumar P. Efficacy of Bacillus Calmette-Guérin in cancer prevention and its putative mechanisms. J Cancer Prev. 2024;29(1):6–15. doi: 10.15430/JCP.23.036.
31. Usher NT, Chang S, Howard RS, Martinez A, Harrison LH, Santosham M, Aronson NE. Association of BCG vaccination in childhood with subsequent cancer diagnoses: a 60-year follow-up of a clinical trial. JAMA Netw Open. 2019;2(9):e1912014. doi: 10.1001/jamanetworkopen.2019.12014.
32. Garnica M, Aiello A, Ligotti ME, Accardi G, Arasanz H, Bocanegra A, Blanco E, Calabrò A, Chocarro L, Echaide M, et al. How can we improve the vaccination response in older people? Part II: targeting immunosenescence of adaptive immunity cells. Int J Mol Sci. 2022;23(17):9797.
33. Goudsmit J, van den Biggelaar AHJ, Koudstaal W, Hofman A, Koff WC, Schenkelberg T, Alter G, Mina MJ, Wu JW. Immune age and biological age as determinants of vaccine responsiveness among elderly populations: the Human Immunomics initiative research program. Eur J Epidemiol. 2021;36(7):753–762. doi: 10.1007/s10654-021-00767-z.
34. Gyssens IC, Netea MG. Heterologous effects of vaccination and trained immunity. Clin Microbiol Infect. 2019;25(12):1457–1458. doi: 10.1016/j.cmi.2019.05.024.
35. Bloom DE, Pecetta S, Scorza FB, Carfi A, Carleton B, Cipriano M, Edwards K, Gasperini G, Malley R, Nandi A, et al. Vaccination for healthy aging. Sci Transl Med. 2024;16(745):eadm9183. doi: 10.1126/scitranslmed.adm9183.
36. Doherty TM, Del Giudice G, Maggi S. Adult vaccination as part of a healthy lifestyle: moving from medical intervention to health promotion. Ann Med. 2019;51(2):128–140. doi: 10.1080/07853890.2019.1588470.
37. Hou Y, Chen M, Bian Y, Hu Y, Chuan J, Zhong L, Zhu Y, Tong R. Insights into vaccines for elderly individuals: from the impacts of immunosenescence to delivery strategies. NPJ Vaccines. 2024;9(1):77. doi: 10.1038/s41541-024-00874-4.
38. Nanishi E, Angelidou A, Rotman C, Dowling DJ, Levy O, Ozonoff A. Precision vaccine adjuvants for older adults: a scoping review. Clin Infect Dis. 2022;75(Supplement_1):S72–S80. doi: 10.1093/cid/ciac302.
39. Rusek P, Wala M, Druszczyńska M, Fol M. Infectious agents as stimuli of trained innate immunity. Int J Mol Sci. 2018;19(2):456. doi: 10.3390/ijms19020456.
40. Schmader KE, Liu CK, Harrington T, Rountree W, Auerbach H, Walter EB, Barnett ED, Schlaudecker EP, Todd CA, Poniewierski M, et al. Safety, reactogenicity, and health-related quality of life after trivalent adjuvanted vs trivalent high-dose inactivated influenza vaccines in older adults: a randomized clinical trial. JAMA Netw Open. 2021;4(1):e2031266. doi: 10.1001/jamanetworkopen.2020.31266.
41. U.S Centers for Disease Control and Prevention (CDC). Chapter 4: Vaccine safety. 2024.
42. Veronese N, Barratt J, Coemans E, Dayananda P, Del Riccio M, Fulop T, Gabutti G, Gravenstein S, Hiligsmann M, Hummers E, et al. Infectious diseases, infection control, vaccines and long-term care: an European interdisciplinary council on ageing consensus document. Aging Clin Exp Res. 2025;38(1). doi: 10.1007/s40520-025-03271-6.
43. Opri R, Zanoni G, Caffarelli C, Bottau P, Caimmi S, Crisafulli G, Franceschini F, Liotti L, Saretta F, Vernich M, et al. True and false contraindications to vaccines. Allergologia et Immunopathologia. 2018;46(1):99–104. doi: 10.1016/j.aller.2017.02.003.
44. Balamurugan BS, Marimuthu MMC, Sundaram VA, Saravanan B, Chandrababu P, Chopra H, Malik T. Micro nutrients as immunomodulators in the ageing population: a focus on inflammation and autoimmunity. Immun Ageing. 2024;21(1):88. doi: 10.1186/s12979-024-00492-7.
45. Mathot E, Hemadeh A, Knoop V, Bautmans I, Lema-Arranz C, Lorenzo-Lopez L, Valdiglesias V, Laffon B. The effect of physical interventions in older adults on inflammatory markers (IL-6, IL-10, CRP, TNF-α): an umbrella review of systematic reviews and meta-analyses. Innov Aging. 2025;9(7):igaf072. doi: 10.1093/geroni/igaf072.
46. Ballesio A, Zagaria A, Violani C, Lombardo C. Psychosocial and behavioural predictors of immune response to influenza vaccination: a systematic review and meta-analysis. Health Phychol Rev. 2024;18(2):255–284. doi: 10.1080/17437199.2023.2208652.
47. Matthews T, Rasmussen LJH, Ambler A, Danese A, Eugen-Olsen J, Fancourt D, Fisher HL, Iversen KK, Schultz M, Sugden K, et al. Social isolation, loneliness, and inflammation: a multi-cohort investigation in early and mid-adulthood. Brain, Behav, Immun. 2024;115:727–736. doi: 10.1016/j.bbi.2023.11.022.

48. Garçon N, Di Pasquale A. From discovery to licensure, the adjuvant system story. Hum Vaccines Immunotherapeutics. 2017;13(1):19–33. doi: 10.1080/21645515.2016.1225635.
49. Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics — developing a new class of drugs. Nat Rev Drug Discov. 2014;13(10):759–780. doi: 10.1038/nrd4278.
50. Pati R, Shevtsov M, Sonawane A. Nanoparticle vaccines against infectious diseases. Front Immunol. 2018;9:2224. doi: 10.3389/fimmu.2018.02224.
51. McCann N, O'Connor D, Lambe T, Pollard AJ. Viral vector vaccines. Curr Opin Immunol. 2022;77:102210. doi: 10.1016/j.coi.2022.102210.
52. Piccioli D, Bartolini E, Micoli F. Gmma as a 'plug and play' technology to tackle infectious disease to improve global health: context and perspectives for the future. Expert Rev Vaccines. 2022;21(2):163–172. doi: 10.1080/14760584.2022.2009803.
53. Poland GA, Ovsyannikova IG, Kennedy RB. Personalized vaccinology: a review. Vaccine. 2018;36(36):5350–5357. doi: 10.1016/j.vaccine.2017.07.062.
54. Weinberger B. Adult vaccination against tetanus and diphtheria: the European perspective. Clin Exp Immunol. 2017;187(1):93–99. doi: 10.1111/cei.12822.
55. Allen JC, Toapanta FR, Chen W, Tennant SM. Understanding immunosenescence and its impact on vaccination of older adults. Vaccine. 2020;38(52):8264–8272. doi: 10.1016/j.vaccine.2020.11.002.
56. Kometani K, Yorimitsu T, Jo N, Yamaguchi E, Kikuchi O, Fukahori M, Sawada T, Tsujimoto Y, Sunami A, Li M, et al. Booster COVID-19 mRNA vaccination ameliorates impaired B-cell but not T-cell responses in older adults. Front Immunol. 2024;15:1455334. doi: 10.3389/fimmu.2024.1455334.
57. Grohskopf LA, Sokolow LZ, Broder KR, Olsen SJ, Karron RA, Jernigan DB, Bresee JS. Prevention and control of seasonal influenza with vaccines. MMWR Recomm Rep. 2016;65(5):1–54. doi: 10.15585/mmwr.rr6505a1.
58. WHO. Vaccines against influenza: WHO position paper – May 2022. Weekly epidemiological record. 2022;19:185–208.
59. Skaarup KG, Lassen MCH, Modin D, Johansen ND, Loiacono MM, Harris RC, Lee JKH, Dufournet M, Vardeny O, Peikert A, et al. The relative vaccine effectiveness of high-dose vs standard-dose influenza vaccines in preventing hospitalization and mortality: a meta-analysis of evidence from randomized trials. J Infect. 2024;89(1):106187. doi: 10.1016/j.jinf.2024.106187.
60. Melgar M, Britton A, Roper LE, Talbot HK, Long SS, Kotton CN, Havers FP. Use of respiratory syncytial virus vaccines in older adults: recommendations of the Advisory Committee on Immunization Practices — United States, 2023. MMWR Morb Mortal Wkly Rep. 2023;72(29):793–801. doi: 10.15585/mmwr.mm7229a4.
61. de Bruyn G, Saleh J, Workman D, Pollak R, Elinoff V, Fraser NJ, Lefebvre G, Martens M, Mills RE, Nathan R, et al. Defining the optimal formulation and schedule of a candidate toxoid vaccine against Clostridium difficile infection: a randomized phase 2 clinical trial. Vaccine. 2016;34(19):2170–2178. doi: 10.1016/j.vaccine.2016.03.028.
62. Plotkin SA, Wang D, Oualim A, Diamond DJ, Kotton CN, Mossman S, Carfi A, Anderson D, Dormitzer PR. The status of vaccine development against the human cytomegalovirus. J Infect Dis. 2020;221(Supplement_1):SS113–sS122. doi: 10.1093/infdis/jiz447.
63. PharmExec.com. Moderna ceases development of mRNA-1647 after failing to reach primary goal in clinical trial. 2025.
64. Permar SR, Schleiss MR, Plotkin SA. A vaccine against cytomegalovirus: how close are we? J Clin Investigation. 2025;135(1). doi: 10.1172/JCI182317.
65. Tong S, Amand C, Kieffer A, Kyaw MH. Incidence of respiratory syncytial virus related health care utilization in the United States. J Global Health. 2020;10(2):020422. doi: 10.7189/jogh.10.020422.
66. World Health Organization (WHO). Coronavirus disease (COVID-19) fact sheet. 2023.
67. European Centre for Disease Prevention and Control (ECDC). Invasive pneumococcal disease. Annual epidemiological report for 2022. 2022.
68. Simon S, Joean O, Welte T, Rademacher J. The role of vaccination in COPD: influenza, SARS-CoV-2, pneumococcus, pertussis, RSV and varicella zoster virus. Eur Respir Rev. 2023;32(169):230034. doi: 10.1183/16000617.0034-2023.
69. European Centre for Disease Prevention and Control (ECDC). Factsheet about seasonal influenza. 2024.
70. European Medicines Agency (EMA). Beyfortus. Nirsevimab. 2025.
71. Grohskopf L, Ferdinands J, Blanton L, Broder K, Loehr J. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices — United States, 2024–25 influenza season. MMWR Recomm Rep. 2024;73(5):1–25. doi: 10.15585/mmwr.rr7305a1.
72. Link-Gelles R, Ciesla AA, Mak J, Miller JD, Silk BJ, Lambrou AS, Paden CR, Shirk P, Britton A, Smith ZR, et al. Early estimates of updated 2023-2024 (monovalent XBB.1.5) COVID-19 vaccine effectiveness against symptomatic SARS-CoV-2 infection attributable to co-circulating omicron variants among immunocompetent adults - increasing community access to testing program, United States, September 2023-January 2024. MMWR Morb Mortal Wkly Rep. 2024;73(4):77–83. doi: 10.15585/mmwr.mm7304a2.

73. Dunne EM, Nunes MC, Slack MPE, Theilacker C, Gessner BD. Effects of pneumococcal conjugate vaccines on reducing the risk of respiratory disease associated with coronavirus infection. Pneumonia (Nathan). 2023;15 (1):10. doi: 10.1186/s41479-023-00112-w.
74. Frobert O, Gotberg M, Erlinge D, Akhtar Z, Christiansen EH, MacIntyre CR, Oldroyd KG, Motovska Z, Erglis A, Moer R, et al. Influenza vaccination after myocardial infarction: a randomized, double-blind, placebo-controlled, multicenter trial. Circulation. 2021;144(18):1476–1484. doi: 10.1161/CIRCULATIONAHA.121.057042.
75. Clar C, Oseni Z, Flowers N, Keshtkar-Jahromi M, Rees K. Influenza vaccines for preventing cardiovascular disease. Cochrane Database Systematic Rev. 2015;2015(5):Cd005050. doi: 10.1002/14651858.CD005050.pub3.
76. Yilmaz FK, Cakir M, Ikiisik H, Maral I. The effect of pneumococcal, influenza, and COVID-19 vaccinations on COVID-19 hospitalization and progression in people over 65 years old living in nursing homes. Vaccines (Basel). 2023;11(5):943. doi: 10.3390/vaccines11050943.
77. Bruxvoort KJ, Ackerson B, Sy LS, Bhavsar A, Tseng HF, Florea A, Luo Y, Tian Y, Solano Z, Widenmaier R, et al. Recombinant adjuvanted zoster vaccine and reduced risk of coronavirus disease 2019 diagnosis and hospitalization in older adults. J Infect Dis. 2022;225(11):1915–1922. doi: 10.1093/infdis/jiab633.
78. Nichol KL, Nordin J, Mullooly J, Lask R, Fillbrandt K, Iwane M. Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. N Engl J Med. 2003;348(14):1322–1332. doi: 10.1056/NEJMoa025028.
79. Kwong JC, Schwartz KL, Campitelli MA, Chung H, Crowcroft NS, Karnauchow T, Katz K, Ko DT, McGeer AJ, McNally D, et al. Acute myocardial infarction after laboratory-confirmed influenza infection. N Engl J Med. 2018;378(4):345–353. doi: 10.1056/NEJMoa1702090.
80. Pardo-Seco J, Rodriguez-Tenreiro-Sanchez C, Gine-Vazquez I, Mallah N, Miras-Carballal S, Pineiro-Sotelo M, Cribeiro-González M, Conde-Pájaro M, González-Pérez J-M, Rivero-Calle I, et al. High-dose influenza vaccine to reduce hospitalizations. N Engl J Med. 2025;393(23):2303–2312. doi: 10.1056/NEJMoa2509834.
81. Johansen ND, Modin D, Loiacono MM, Harris RC, Dufournet M, Larsen CS, Larsen L, Wiese L, Dalager-Pedersen M, Claggett BL, et al. High-dose influenza vaccine effectiveness against hospitalization in older adults. N Engl J Med. 2025;393(23):2291–2302. doi: 10.1056/NEJMoa2509907.
82. Johansen ND, Modin D, Pardo-Seco J, Rodriguez-Tenreiro-Sanchez C, Loiacono MM, Harris RC, Dufournet M, van Aalst R, Chit A, Larsen CS, et al. Effectiveness of high-dose influenza vaccine against hospitalisations in older adults (FLUNITY-HD): an individual-level pooled analysis. Lancet. 2025;406(10518):2425–2434. doi: 10.1016/S0140-6736(25)01742-8.
83. Pareek M, Lassen MCH, Johansen ND, Christensen SH, Aliabadi N, Skaarup KG, Modin D, Claggett BL, Larsen CS, Larsen L, et al. Effectiveness of bivalent respiratory syncytial virus prefusion F protein-based vaccine in individuals with or without atherosclerotic cardiovascular disease: the DAN-RSV trial. Eur Heart J. 2025;46 (41):4291–4298. doi: 10.1093/eurheartj/ehaf679.
84. CDC. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices — United States, 2023–24 influenza season. Recommendations and reports. 2023; 72.
85. Blackburn R, Zhao H, Pebody R, Hayward A, Warren-Gash C. Laboratory-confirmed respiratory infections as predictors of hospital admission for myocardial infarction and stroke: time-series analysis of English data for 2004–2015. Clin Infect Dis. 2018;67(1):8–17. doi: 10.1093/cid/cix1144.
86. Haeberer M, Bruyndonckx R, Polkowska-Kramek A, Torres A, Liang C, Nuttens C, Casas M, Lemme F, Ewnetu WB, Tran TMP, et al. Estimated respiratory syncytial virus-related hospitalizations and deaths among children and adults in Spain, 2016–2019. Infect Dis Ther. 2024;13(3):463–480. doi: 10.1007/s40121-024-00920-7.
87. Lassen MCH, Johansen ND, Christensen SH, Aliabadi N, Skaarup KG, Modin D, Claggett BL, Larsen CS, Larsen L, Wiese L, et al. Bivalent RSV prefusion F protein–based vaccine for preventing cardiovascular hospitalizations in older adults. JAMA. 2025;334(16):1431–1441. doi: 10.1001/jama.2025.15405.
88. Payne AB, Watts JA, Mitchell PK, Dascomb K, Irving SA, Klein NP, Grannis SJ, Ong TC, Ball SW, DeSilva MB, et al. Respiratory syncytial virus (RSV) vaccine effectiveness against RSV-associated hospitalisations and emergency department encounters among adults aged 60 years and older in the USA, October, 2023, to March, 2024: a test-negative design analysis. Lancet. 2024;404(10462):1547–1559. doi: 10.1016/S0140-6736(24)01738-0.
89. Fry SE, Terebuh P, Kaelber DC, Xu R, Davis PB. Effectiveness and safety of respiratory syncytial virus vaccine for US adults aged 60 years or older. JAMA Netw Open. 2025;8(5):e258322. doi: 10.1001/jamanetworkopen.2025.8322.
90. Britton A, Roper LE, Kotton CN, Hutton DW, Fleming-Dutra KE, Godfrey M, Ortega-Sanchez IR, Broder KR, Talbot HK, Long SS, et al. Use of respiratory syncytial virus vaccines in adults aged ≥60 years: updated recommendations of the Advisory Committee on Immunization Practices — United States, 2024. MMWR Morb Mortal Wkly Rep. 2024;73(32):696–702. doi: 10.15585/mmwr.mm7332e1.
91. Besteman SB, Bogaert D, Bont L, Mejias A, Ramilo O, Weinberger DM, Dagan R. Interactions between respiratory syncytial virus and Streptococcus pneumoniae in the pathogenesis of childhood respiratory infections: a systematic review. Lancet Respir Med. 2024;12(11):915–932. doi: 10.1016/S2213-2600(24)00148-6.
92. Europeans Medicine Agency (EMA). Ema recommends first COVID-19 vaccine for authorisation in the EU. 2020.

93. Ma KC, Webber A, Lauring AS, Bendall E, Papalambros LK, Safdar B. Effectiveness of 2024-2025 COVID-19 vaccination against COVID-19 hospitalization and severe in-hospital outcomes - ivy network, 26 hospitals, September 1, 2024-April 30, 2025. medRxiv. 2025.
94. Mallah N, Pardo-Seco J, Lopez-Perez LR, Gonzalez-Perez JM, Roson B, Otero-Barros MT, Durán-Parrondo C, Nartallo-Penas V, Mirás-Carballal S, Rodríguez-Tenreiro C, et al. Effectiveness of COVID-19 vaccine booster in the general population and in subjects with comorbidities. A population-based study in Spain. Environ Res. 2022;215:114252. doi: 10.1016/j.envres.2022.114252.
95. Hansen CH, Lassauniere R, Rasmussen M, Moustsen-Helms IR, Valentiner-Branth P. Effectiveness of the BNT162b2 and mRNA-1273 JN.1-adapted vaccines against COVID-19-associated hospitalisation and death: a Danish, nationwide, register-based, cohort study. Lancet Infect Dis. 2025;25(12):1293–1302. doi: 10.1016/S1473-3099(25)00380-9.
96. Melegaro A, Edmunds WJ. The 23-valent pneumococcal polysaccharide vaccine. Part I. Efficacy of PPV in the elderly: a comparison of meta-analyses. Eur J Epidemiol. 2004;19(4):353–363. doi: 10.1023/B:EJEP.0000024701.94769.98.
97. Bonten MJ, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Gault S, van Werkhoven CH, van Deursen AMM, Sanders EAM, Verheij TJM, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med. 2015;372(12):1114–1125. doi: 10.1056/NEJMoa1408544.
98. van Werkhoven CH, Huijts SM, Bolkenbaas M, Grobbee DE, Bonten MJ, van Werkhoven CH. The impact of age on the efficacy of 13-valent pneumococcal conjugate vaccine in elderly. Clin Infect Dis. 2015;61(12):1835–1838. doi: 10.1093/cid/civ686.
99. Kobayashi M, Leidner AJ, Gierke R, Xing W, Accorsi E, Moro P, Kamboj M, Kuchel GA, Schechter R, Loehr J, et al. Expanded recommendations for use of pneumococcal conjugate vaccines among adults aged ≥50 years: recommendations of the Advisory Committee on Immunization Practices — United States, 2024. MMWR Morb Mortal Wkly Rep. 2025;74(1):1–8. doi: 10.15585/mmwr.mm7401a1.
100. Essink B, Sabharwal C, Cannon K, Frenck R, Lal H, Xu X, Sundaraiyer V, Peng Y, Moyer L, Pride MW, et al. Pivotal phase 3 randomized clinical trial of the safety, tolerability, and immunogenicity of 20-valent pneumococcal conjugate vaccine in adults aged ≥18 years. Clin Infect Dis. 2022;75(3):390–398. doi: 10.1093/cid/ciab990.
101. European Medicines Agency (EMA). Capvaxive: ePAR - Product information. 2025.
102. Kobayashi M, Leidner AJ, Gierke R, Farrar JL, Morgan RL, Campos-Outcalt D, Schechter R, Poehling KA, Long SS, Loehr J, et al. Use of 21-valent pneumococcal conjugate vaccine among U.S. adults: recommendations of the Advisory Committee on Immunization Practices — United States, 2024. MMWR Morb Mortal Wkly Rep. 2024;73(36):793–798. doi: 10.15585/mmwr.mm7336a3.
103. ClinicalTrials.gov. Study to evaluate a 25-valent pneumococcal conjugate vaccine (IVT PCV-25). 2023.
104. Malley R, Lu Y-J, Sebastian S, Zhang F, Willer DO. Multiple antigen presenting system (MAPS): state of the art and potential applications. Expert Rev Vaccines. 2024;23(1):196–204. doi: 10.1080/14760584.2023.2299384.
105. Vila-Córcoles A, Ochoa-Gondar O. Pneumococcal disease in adults: risk levels and vaccine recommendations. Aten Primaria. 2017;49(2):111–117. doi: 10.1016/j.aprim.2016.06.007.
106. Rodrigues LP, Teixeira VR, Alencar-Silva T, Simonassi-Paiva B, Pereira RW, Pogue R, Carvalho JL. Hallmarks of aging and immunosenescence: connecting the dots. Cytokine Growth Factor Rev. 2021;59:9–21. doi: 10.1016/j.cytogfr.2021.01.006.
107. Yawn BP, Lindsay AC, Yousefi M, Wang C. Risk of, and risk factors for, vasculopathy associated with acute herpes zoster. J Stroke Cerebrovascular Dis. 2023;32(2):106891. doi: 10.1016/j.jstrokecerebrovasdis.2022.106891.
108. Van Oorschot D, McGirr A, Goulet P, Koochaki P, Pratiwadi R, Shah S, Curran D. A cross-sectional concept elicitation study to understand the impact of herpes zoster on patients' health-related quality of life. Infect Dis Ther. 2022;11(1):501–516. doi: 10.1007/s40121-021-00581-w.
109. Taquet M, Dercon Q, Todd JA, Harrison PJ. The recombinant shingles vaccine is associated with lower risk of dementia. Nat Med. 2024;30(10):2777–2781. doi: 10.1038/s41591-024-03201-5.
110. Tang E, Ray I, Arnold BF, Acharya NR. Recombinant zoster vaccine and the risk of dementia. Vaccine. 2025;46:126673.
111. Eyting M, Xie M, Michalik F, Hess S, Chung S, Geldsetzer P. A natural experiment on the effect of herpes zoster vaccination on dementia. Nature. 2025;641(8062):438–446. doi: 10.1038/s41586-025-08800-x.
112. Grupo de trabajo Vacunación en población adulta y grupos de riesgo (GT-GR). Vacunación en población adulta. 2018.
113. Cai X, Xu L. Human papillomavirus-related cancer vaccine strategies. Vaccines (Basel). 2024;12(11):1291. doi: 10.3390/vaccines12111291.
114. Blomberg M, Dehlendorff C, Munk C, Kjaer SK. Strongly decreased risk of genital warts after vaccination against human papillomavirus: Nationwide follow-up of vaccinated and unvaccinated girls in Denmark. Clin Infect Dis. 2013;57(7):929–934. doi: 10.1093/cid/cit436.
115. Mauz PS, Schafer FA, Iftner T, Gonser P. Hpv vaccination as preventive approach for recurrent respiratory papillomatosis - a 22-year retrospective clinical analysis. BMC Infect Dis. 2018;18(1):343. doi: 10.1186/s12879-018-3260-0.

116. Ciabattini A, Nardini C, Santoro F, Garagnani P, Franceschi C, Medaglini D. Vaccination in the elderly: the challenge of immune changes with aging. Semin Immunol. 2018;40:83–94. doi: 10.1016/j.smim.2018.10.010.
117. Pereira B, Xu XN, Akbar AN. Targeting inflammation and immunosenescence to improve vaccine responses in the elderly. Front Immunol. 2020;11:583019. doi: 10.3389/fimmu.2020.583019.
118. Pulendran B, Ahmed R. Immunological mechanisms of vaccination. Nat Immunol. 2011;12(6):509–517. doi: 10.1038/ni.2039.
119. Cheng Y, Cao X, Cao Z, Xu C, Sun L, Gao Y, Wang Y, Li S, Wu C, Li X, et al. Effects of influenza vaccination on the risk of cardiovascular and respiratory diseases and all-causemortality. Ageing Res Rev. 2020;62:101124. doi: 10.1016/j.arr.2020.101124.
120. Vlachopoulos CV, Terentes-Printzios DG, Aznaouridis KA, Pietri PG, Stefanadis CI. Association between pneumococcal vaccination and cardiovascular outcomes: a systematic review and meta-analysis of cohort studies. Eur J Prev Cardiol. 2015;22(9):1185–99. doi: 10.1177/2047487314549512.
121. Liu C, Song Q, Lin L, Li T, Zhang P, Zeng Y, Peng Y, Chen Y, Cai S, Chen P. Impact of intensive health education on influenza vaccination and acute exacerbations inoutpatients with chronic obstructive pulmonary disease: a real-world study. J Glob Health. 2025;15:04047. doi: 10.7189/jogh.15.04047.
122. Walters JA, Tang JNQ, Poole P, Wood-Baker R. Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2017;1(1):CD001390. doi: 10.1002/14651858.CD001390.pub4.
123. Vasileiou E, Sheikh A, Butler C, El Ferkh K, von Wissmann B, McMenamin J, Ritchie L, Schwarze J, Papadopoulos NG, Johnston SL, et al. Effectiveness ofInfluenza Vaccines in Asthma: A Systematic Review and Meta-Analysis. Clin Infect Dis. 2017;65(8):1388–95. doi: 10.1093/cid/cix524
124. Kostinov AM, Konishcheva AY, Protasov AD, Kostinov MP, Polishchuk VB, Zhestkov AV, Yastrebova NE, Kostinova AM, Musagulova ZS, Prutskova EV. Specific Features of Immune Response in Patients with DiffeAhmedrent Asthma Endotypes Following Immunization witha Conjugate Pneumococcal Vaccine. Vaccines (Basel). 2025;13(5). doi: 10.3390/vaccines13050459
125. Ahmed MB, Patel K, Fonarow GC, Morgan CJ, Butler J, Bittner V, Kulczycki A, Kheribek RE, Aronow WS, Fletcher RD, et al. Higher risk for incident heart failureand cardiovascular mortality among community-dwelling octogenarians without pneumococcal vaccination. ESC Heart Fail. 2016;3(1):11–7. doi: 10.1002/ehf2.12056.
126. Liu M, Lin W, Song T, Zhao Hm Ma J, Zhao Y, Yu P, Yan Z. Influenza vaccination is associated with a decreased risk of atrial fibrillation: A systematic review and meta-analysis. Front Cardiovasc Med. 2022;9:970533. doi: 10.3389/fcvm.2022.970533.
127. Marra F, Zhang A, Gillman E, Bessai K, Parhar K, Vadlamudi NK. The protective effect of pneumococcal vaccination on cardiovascular disease in adults: A systematic review and meta-analysis. Int J Infect Dis. 2020;99:204–13. doi: 10.1016/j.ijid.2020.07.038.