An update to this article is included at the end

Vaccine: X 24 (2025) 100662

Contents lists available at ScienceDirect

Vaccine: X

journal homepage: www.elsevier.com/locate/jvacx

Seasonal influenza vaccination: Overcoming immunosenescence with enhanced vaccines

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ARTICLE INFO

Keywords:
Older adults
Immunosenescence
Inflammaging
Adjuvanted influenza vaccine
High-dose influenza vaccine
Recombinant influenza vaccine
Enhanced influenza vaccines

ABSTRACT

Influenza causes substantial morbidity and mortality worldwide. Risks are increased in older adults aged 50–64 and ≥ 65 years. They are further exacerbated in those with age-related comorbidities. Immunosenescence (strictly defined here as detrimental age-related decline in the function of some or all parts of the immune system) is associated with increased susceptibility to influenza infection and more severe disease, a process that begins at approximately 50 years of age. Age-associated chronic low-level inflammation (inflammaging) may also increase influenza risk and is associated with more serious disease but may also enhance responses to high-dose vaccines in older adults. The frequency of comorbidities also increases with age. Frail older adults are at highest risk of influenza complications, but adults with high-risk comorbidities also show improved immune responses to enhanced influenza vaccines (high-dose, adjuvanted, recombinant). Moreover, clinical studies with some enhanced influenza vaccines show improved immunogenicity and greater efficacy or effectiveness, not only for persons aged ≥65 years but also in those aged 50–64 years. Reduced immunogenicity in persons aged 50–64 years may be even greater in those with comorbidities who would specifically benefit from receiving enhanced vaccines. Thus, accelerated immunosenescence, inflammaging, and chronic disease may place some adults aged 50–64 years at high risk of influenza, justifying meeting an unmet need in vaccination with enhanced vaccines normally used in persons ≥65 years of age.

The global population is rapidly ageing, with adults aged ≥60 years now outnumbering children ≤5 years worldwide. By 2030, 17 % of the population is expected to be 60 years or older, and the number of older adults is expected to double by 2050. Although populations began to age first in high-income regions, the proportion of adults in low- and middle-income nations are now growing fastest in low- and middle-income countries [1].

Influenza causes significant morbidity and mortality across the globe, regardless of national wealth [2]. Prior to the coronavirus disease 2019 (COVID-19) pandemic, influenza accounted for 13 % of all respiratory disease deaths worldwide per year [3,4], and since the pandemic, influenza has resurged as a leading cause of hospitalizations and deaths worldwide [5,6]. It is also costly, with direct expenditures totaling $3.2 billion in the US and 6 billion Euros in the EU and indirect costs of $8 billion and 14 billion Euros, respectively [7–9]. Although direct costs are highest in adults aged ≥65 years, on a per-case level, hospitalization costs tend to be higher in the 50–64 year age group, perhaps due to greater illness severity in persons in this age group who require hospitalization. In addition, indirect costs associated with influenza (absenteeism due to infection or caring for infected family

Abbreviations: AID, activation-induced cytidine deaminase; aQIV, adjuvanted quadrivalent influenza vaccine; aTIV, adjuvanted trivalent influenza vaccine; aTIVc, adjuvanted cell-based trivalent influenza vaccine; BMI, body mass index; COVID-19, coronavirus disease 2019; CSR, class-switch recombination; HA, hemagglutinin; HD, high dose; HI, hemagglutination inhibition; MDCK, Madin-Darby canine kidney; NA, neuraminidase; PCR, polymerase chain reaction; QIV, quadrivalent influenza vaccine; RdRP, RNA-dependent RNA polymerase; RIV4, recombinant influenza vaccine; sa-mRNA, self-amplifying mRNA; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard dose; SHM, somatic hypermutation; TCR, T cell receptor; TIV, trivalent influenza vaccine; WHO, World Health Organization.

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https://doi.org/10.1016/j.jvacx.2025.100662
Received 22 December 2024; Received in revised form 20 April 2025; Accepted 19 May 2025
Available online 20 May 2025
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members or lost productivity due to death) are higher in the group aged 50–64 years than in younger adults [7].

Influenza also disproportionately affects adults aged ≥50 years. US data suggest rates of seasonal influenza infection tend to be higher among adults aged 50–64 years than in younger adults or those aged ≥65 years—between 2010 and 2016, the median incidence of influenza was 12.0 % in the 50–64-year age group compared with 7.4 % among those aged 18–49 years and 3.9 % in the ≥65-year population in the US [10]. Other studies have found a similar burden of influenza infection in the 50–64 year age group and suggest that while the overall susceptibility to influenza infection is greatest in the ≥65 year age group, adults aged 50–64 years may be more likely to be exposed to influenza through workplace or household contacts and are also less likely than those aged ≥65 years to be vaccinated against influenza [11]. The risk of influenza-related hospitalizations and death is also increased among persons aged 50–64 years compared with those ≤49 years, while adults aged ≥65 years have the highest influenza-related morbidity and mortality [12,13]. However, the presence of multiple high-risk medical conditions skews the relationship between age and increased risk of influenza complications such that persons aged 50–64 years may be at even greater risk of influenza hospitalization than those aged ≥65 years with the same number of comorbidities [14].

Medical conditions acknowledged by health authorities to increase influenza risk include pre-existing respiratory conditions, neurological conditions, kidney disease, liver disease, diabetes, obesity, cardiovascular disease, and hematologic diseases, as well as immunocompromising conditions and residence in a nursing home (Fig. 1) [15–18]. Most of these conditions are related to advancing age, with an incidence that increases dramatically after age 50 years [13,19]. In a recent review of electronic medical records from a US database, 38 % of persons aged 18–49 years had ≥1 high-risk comorbidity, compared with 62 % among those aged 50–64 years and 80 % of persons ≥65 years [14]. The presence of these conditions further increases the risk of influenza-related hospitalization and death in persons aged ≥50 years [14,20,21]. Influenza itself increases the risk of pneumonia, other respiratory infections, and cardiovascular complications, including stroke and myocardial infarction, further contributing to high morbidity and mortality in infected patients. It may also worsen neurological disorders, diabetes, kidney disease, and overall wellbeing [22,23].

Various factors are associated with the increased susceptibility of adults 50 years and older to influenza infection and complications, including waning of antibody and cell-mediated responses to influenza vaccines [24,25]. Alterations in immune function are frequently discussed in the context of adults aged ≥65 years, but evidence points to these changes occurring earlier, in persons aged 50–60 years or younger, with age-related immune changes that continually progress toward "immunosenescence" in a majority by 60 years of age [26,27]. Chronic low-level inflammation increases with age ("inflammaging") and is associated with multiple cardiometabolic conditions that increase influenza risk, but at the same time may also positively influence the immune response to vaccines [28].

In this review, we examine key factors related to age and/or comorbidities that contribute to vulnerability to influenza complications as well as alterations in the immune response to both influenza infection and vaccination. We summarize findings for persons aged ≥65 years, while highlighting available data for the group aged 50–64 years. Like their older counterparts, middle-aged adults—particularly those with multiple comorbidities—are at high risk of influenza complications and may have impaired immune responses to standard influenza vaccines. Here, we explore the potential for enhanced vaccines to improve immune responses and reduce influenza infections and complications in adults aged ≥50 years.

1. Age-related immune changes

With advancing age comes a diminished ability to resist infection or mount an optimal immune response following vaccination. "Immunosenescence" is a multifaceted and dynamic process that is characterized by dysregulation of both innate and adaptive immune functions as individuals age. Additionally, ageing is commonly accompanied by a state of chronic, low-grade inflammation termed "inflammaging," which contributes to the pathogenesis of various chronic conditions and may be accompanied by further decline in immune function [29–31].

To avoid confusion, immunosenescence should be strictly described as "a state defined by robust measures of immune parameters that are different in younger and older individuals and which have been associated with a clearly detrimental clinical outcome" [32]. The term immunosenescence should therefore be used exclusively to mean an impairment of immune function, rather than the adaptive remodeling of the way the immune system responds to infection, which is a hallmark of adaptive immunity [32–34]. Inflammaging is centered in the innate immune system, which may have both negative and positive effects on

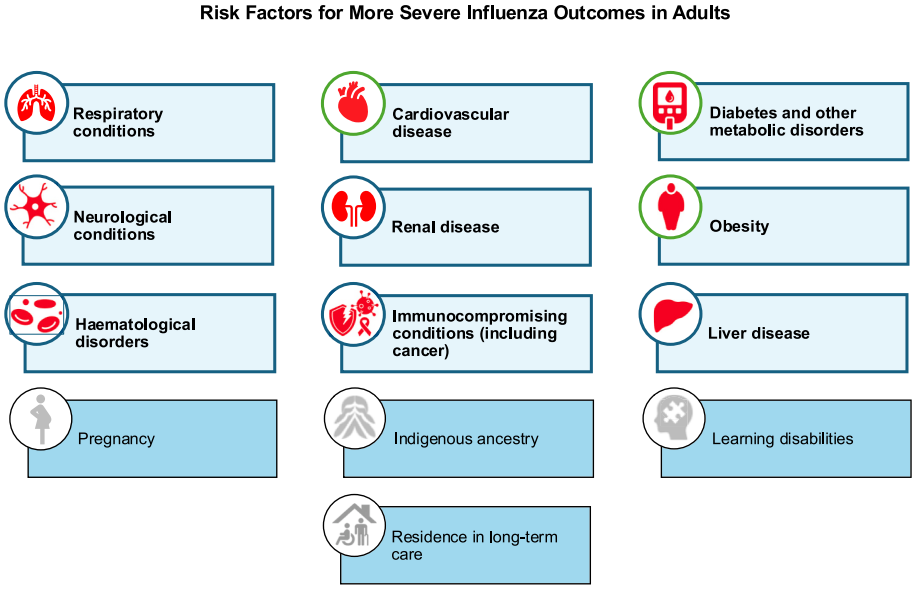


Fig. 1. Medical comorbidities (*red icons*) and other conditions (*gray icons*) associated with a high risk of influenza complications in adults. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

immune function [28,33,35,36]. On the positive side, a background state of heightened inflammation can initially enhance immune surveillance, helping to detect and respond to pathogens and abnormal cells more effectively. This heightened state of alert can be beneficial in preventing infections and, potentially, early-stage cancers [37]. However, inflammaging may also result in a reduced ability to clear infections and an increased susceptibility to chronic diseases [38]. The overall impact of inflammaging is a significant decline in immune function, contributing to the increased morbidity and mortality observed in the elderly population [39].

Age-related dysregulation of immunity paradoxically includes decreased responses of adaptive immunity (immunosenescence) and over-exuberant innate immunity (inflammaging), both of which can be associated with impaired immune responses to vaccines [33,36,40,41]. Studies have shown that significant immune alterations begin very early in life, including reductions in naïve T cell populations, decreased B cell diversity, and altered cytokine production profiles [29,42–44]. In addition to age, these changes depend on the individual's history of exposure to pathogens, among many other factors, and to a great extent are a result of the adaptive functionality of immunity (immune memory). Differences manifested in individuals 50 years of age, while not usually as pronounced as those in individuals aged ≥65 years, may still impact vaccine responses and susceptibility to influenza.

Paralleling age-related decline in immune function, ageing is also associated with an increased susceptibility to cancer, autoimmune diseases, chronic kidney disease, cardiovascular and cerebrovascular diseases, and diabetes [19–21,30,31,36]. As a result of the accumulation of chronic comorbidities, many individuals aged ≥50 years have an increased biological age (also known as functional or physiologic age) relative to their chronological age. Such persons have biomarkers that fall outside the average range for their age group, and which typically signal diminished physiological function [45]. Many different measures have been used to estimate biological age, including physiologic biomarkers, cognitive function assessment, body mass index (BMI), frailty indices, and estimators of DNA methylation, and increases in these measures are associated with increased mortality risk [46].

Comorbidity burden may be a better predictor of immune response than chronological age [47], although the inter-relationships between biological age, chronological age, number of comorbidities, and the various frailty assessment indices are unclear. The risk of severe influenza outcomes is exacerbated by underlying diseases, and influenza complications leading to serious illness and death become increasingly common in middle-aged persons and those with high-risk conditions [14,20,21,48]. In addition, the risk of severe influenza increases with accumulation of high-risk comorbidities, particularly in persons aged 50–64 years. In a retrospective analysis of electronic medical records of US adults over five consecutive influenza seasons (2015–2020), 62 % of those aged 50–64 and 80 % of those aged ≥65 years had at least one high-risk comorbidity. Across all adults, each additional comorbidity increased the odds of influenza-related outpatient and emergency department (ED) visits and hospital admissions. Although more adults aged ≥65 (20 %) than 50–64 years (10 %) had four or more comorbidities, the 50–64 year group was more likely to receive ED care or be admitted to the hospital than all other age groups (Fig. 2) [14].

2. Effect of immune changes on the influenza vaccination response in persons aged ≥ 50 years

Age-related changes in the immune system that can be distinguished from adaptive immunity include altered B cell and T cell responses and shifts in inflammatory markers that mediate maturation and proliferation of dendritic and other immune system cells [42–44]. B cell defects include decreased expression of activation-induced cytidine deaminase (AID), E47, and PAX5, which together regulate class-switch recombination (CSR) and somatic hypermutation (SHM) of immunoglobulin genes. Defects in CSR and SHM retard generation of secondary class-switched high-affinity antibodies, contributing to reduced influenza vaccine responses. Additional B cell impairments involve reduced binding specificity and neutralization capacity of secreted antibodies, increases in inflammatory B cell subsets, and shorter telomeres on B cell DNA [44]. T cells may exhibit altered sensitivity of T cell receptors (TCR) and diminished T cell and helper T cell activation, signaling, and functionality, with consequent negative impacts on memory B cells [43]. The impacts of these age-related cellular changes are highlighted in Fig. 3.

Infection with influenza induces immunological memory and

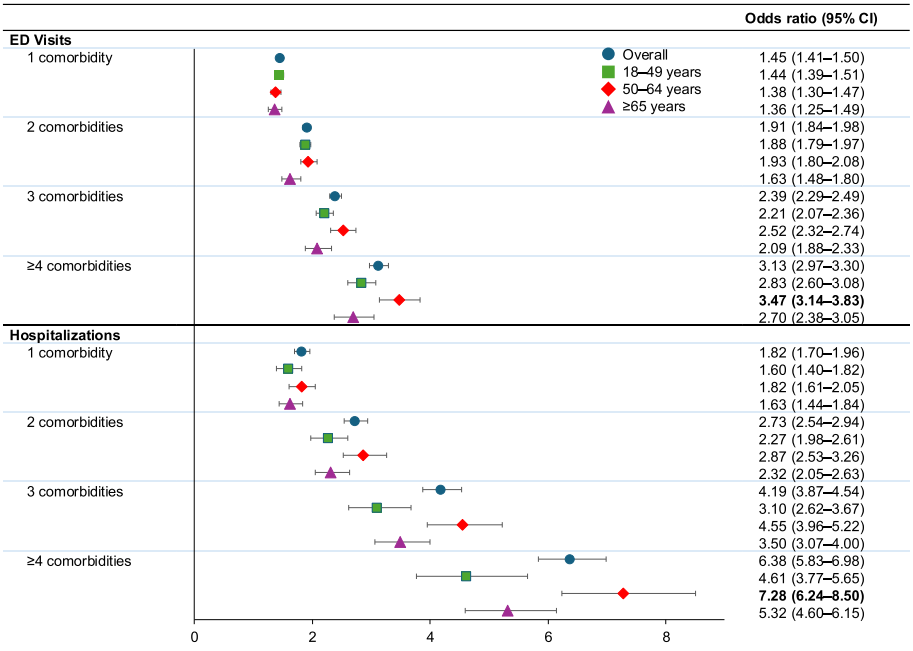


Fig. 2. Association between number of comorbidities and likelihood of an emergency department (ED) or hospitalization for influenza complications. Boldface indicates statistically significant differences for age 50–64 years vs. other age groups. Adapted from McGovern et al. 2024 [14].

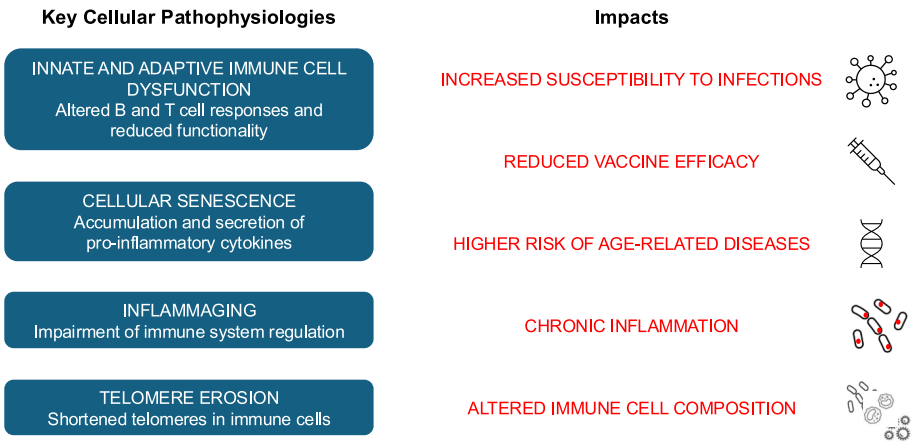


Fig. 3. Immunosenescence: an age-associated dysregulation and dysfunction of the immune system.

improves responses in older adults once they have recovered, suggesting that poor immune stimulation observed in vaccinated older adults reflects a limitation of current standard seasonal influenza vaccines rather than a limitation of the ageing immune system per se [49,50]. The disparate findings in groups given standard vs. enhanced influenza vaccines suggest that appropriate vaccine strategies may help overcome detriments in immune function associated with immunosenescence, inflammaging, and frailty. With the appropriate formulation (including strategies involving adjuvants or high doses of antigen), protection after vaccination can exceed that from natural infection, as has been seen with vaccines against human papillomavirus, varicella zoster, and SARS-CoV-2 (mRNA) [51–54].

3. Enhanced vaccine approaches to improve immune responses to influenza vaccines in adults aged ≥ 50 years

In most regions, adults in their fifties typically receive standard influenza vaccines containing 15 µg of antigen per influenza strain. Enhanced vaccines containing either 60 µg of antigen per strain or an immune response–boosting adjuvant are usually indicated for older adults aged ≥60 or ≥ 65 years, based on regional guidance. However, as more research becomes available, indications for enhanced vaccines are expanding to younger individuals (and one enhanced vaccine containing 45 µg of antigen per strain is indicated for ages ≥18 years). Here, we review available evidence for enhanced seasonal influenza vaccines in populations aged ≥50 years and also describe enhancements to pandemic influenza vaccines and new and emerging vaccine formulations based on cell culture, recombinant, and mRNA techniques.

3.1. *Seasonal influenza vaccines*

Annual vaccination is a critical measure in the prevention of influenza and its cardiorespiratory complications, especially among high-risk groups, including adults aged ≥50 years with and without comorbidities [23,48,55].

The antigenic composition of all seasonal influenza vaccines matches the World Health Organization (WHO) recommendations for the A (H1N1), A(H3N2), and B/Victoria strains (trivalent vaccines) and A (H1N1), A(H3N2), B/Yamagata, and B/Victoria strains (quadrivalent vaccines) that are predicted to circulate each influenza season. Due to recent declines in circulation of B/Yamagata, trivalent influenza vaccines are currently the global standard. Although all seasonal influenza vaccines contain the same antigenic strains, the three currently available enhanced vaccines differ in terms of their formulation, antigen dosage, and mechanistic effects.

3.2. *Adjuvanted inactivated influenza vaccines*

Adjuvanted inactivated influenza vaccines contain a standard antigen dose (15 µg per strain) but are formulated with the MF59 adjuvant, a squalene-based, oil-in-water emulsion that has been shown to boost hemagglutination inhibition (HI) titers against both homologous and heterologous strains [56–60]. The adjuvant promotes T cell activation and B cell expansion and enhances macrophage recruitment and lymph node migration. These actions increase the magnitude, breadth, and duration of immune response [61–64]. Adjuvanted trivalent and quadrivalent influenza vaccines (aTIV and aQIV, respectively) have a well-established safety profile in adults aged ≥65 years, with several million doses administered in the US, UK, Canada, Europe, Australia, and elsewhere worldwide [56,65–69]. A recent review of the immunogenicity of aTIV against mismatched strains in older adults reported that, in six studies, aTIV consistently increased heterologous antibody titers relative to standard influenza vaccine, with evidence of a broad heterologous immune response across multiple genetic clades and enhanced efficacy [70]. Additionally, a systematic review of 21 pooled studies of MF59-adjuvanted influenza vaccine among adults ≥65 years found that aTIV significantly improved vaccine effectiveness compared to non-adjuvanted standard-dose (SD)–TIV or SD-QIV and had comparable effectiveness as high-dose (HD)–TIV [71].

The immunogenicity and safety of MF59-adjuvanted influenza vaccines have also been established in adults younger than 65 years [72–76]. In a study of healthy adults aged <65 years, aTIV elicited higher HI titers against A(H3N2) than SD-TIV [75]. In adults aged 50–64 years with and without chronic conditions, aQIV demonstrated significantly higher antibody titers against A(H1N1) and A(H3N2) strains compared to standard-dose QIV. The effects were even more pronounced in the subgroup with chronic conditions [76]. Other studies have highlighted benefits in adults with high-risk comorbidities. In a population aged 18–60 years with cardiovascular disease; lung, liver or renal insufficiency; and/or diabetes, significantly higher HI titers against A(H3N2) and B strains and significantly higher seroprotection rate against A(H3N2) were seen with aTIV vs. SD-TIV [72]. The same investigators observed significantly higher HI titers against all three strains in another trial that involved adults aged 18–60 years with arteriosclerotic disease; insulin-dependent diabetes; or moderate to severe forms of hypertension, heart failure, chronic obstructive pulmonary disease (COPD), asthma, or hepatic or renal insufficiency [73]. In patients aged ≥19 years on dialysis, seroconversion rates and HI titers were significantly greater against all three vaccine strains in aTIV recipients compared with SD-TIV recipients [74].

3.3. High-dose inactivated influenza vaccines

HD-TIV and HD-QIV contain 60 μg per strain (180 μg and 240 μg of influenza antigens per dose, respectively), four times more antigen than standard-dose influenza vaccines. In adults given a high-dose influenza vaccine, the magnitude of the immune response increases in a dose-proportional manner [77,78]. Multiple studies have demonstrated significant increases in antibody titers with HD-TIV/QIV vaccines relative to standard doses, and HD-TIV has been shown to have superior efficacy to SD-TIV in 65 years and older [77,79–81].

High-dose inactivated influenza vaccines have not been studied in populations younger than 65 years, so we are unable to draw conclusions for this vaccine in the 50–64 age group. Nevertheless, although increased biological age is associated with diminished responses to standard influenza vaccines, antibody responses to high-dose influenza vaccines have been shown to be improved in people with higher vs. lower biological age [24,49,82,83]. With regards to comorbidities, biomarkers, and frailty, findings from an analysis of data from a 4-year trial showed improved immunogenicity in participants with higher frailty scores who received HD-TIV but not those receiving SD-TIV [24]. To further investigate this finding, the authors conducted a nested analysis of trial data in which biological age was quantified based on 10 serological biomarkers associated with inflammation and/or chronic cardiorenal or metabolic conditions. Increased biological age was associated with improved post-vaccination antibody titers in trial participants receiving HD-TIV but not SD-TIV [82].

Another analysis of data from the 4-year trial of HD-TIV confirmed that the protection conferred by high-dose influenza vaccines is mediated by increased antibody responses. HD-TIV also amplified IL-10, resulting in significantly lower IFNγ:IL-10 ratios in older adults receiving HD-TIV compared with those receiving SD-TIV as well as younger adults receiving SD-TIV [81].

3.4. Recombinant influenza vaccine

Quadrivalent recombinant influenza vaccine (RIV4) contains three times the amount of antigen as standard-dose vaccines (45 μg per strain; 180 μg antigen per dose) and is authorized for adults aged ≥18 years. Whereas other influenza viruses are produced in either hens' eggs or in Madin-Darby canine kidney (MDCK) cell lines and contain both hemagglutinin (HA) and neuraminidase (NA), RIV4 contains only a recombinant HA synthesized via a baculovirus vector in an insect cell line, resulting in HA antigens that are not subject to adaptive changes seen with egg-grown vaccine strains [84,85].

In clinical trials, RIV4 has demonstrated greater immunogenicity and better protection against influenza illness, with similar tolerability, in adults aged ≥50 years [86–88]. In a study of adults aged 50–64 years of age, HI titers against A(H1N1) and A(H3N2) and seroconversion against A(H3N2) were significantly higher in RIV4 recipients than in SD-TIV recipients [88]. Another study involving adults aged ≥50 years showed significantly higher HI titers against A(H3N2). The relative vaccine efficacy of RIV4 vs. SD-QIV against polymerase chain reaction (PCR)–confirmed influenza was 30 % (95 % CI, 10 % to 47 %) [86]. A recent observational study comparing RIV4 to SD-QIV in 675,252 persons aged 50–64 years showed a relative vaccine effectiveness against PCR-confirmed influenza of 15.7 % (95 % CI, 6.0 % to 24.5 %), driven by effectiveness against influenza A strain. RIV4 was not more effective than SD-QIV against influenza B or against any hospitalization outcome [89].

3.5. Pandemic influenza vaccines

Pandemic influenza is usually caused by zoonotic influenza viruses that mutate and become infectious to humans, leading to substantial global morbidity and mortality [90,91]. Infection with avian-origin H5N1 (the causative agent of "bird flu") is rare in humans, but 52 % of those who were infected over the past 20 years have died [92]. Because development of antigenically matched pandemic vaccines may take 6 months or more, health authorities rely on pre-pandemic vaccines containing likely pandemic influenza candidate strains and an immune response–boosting adjuvant for vaccination of essential workers and vulnerable populations before antigenically matched vaccines are available [93,94].

Pandemic influenza vaccines have not been studied in the 50–64 year age group. In adults ≥60 years, a meta-analysis of H5N1 vaccines adjuvanted with MF59, AS03, or alum demonstrated that two doses of adjuvanted vaccine elicited strong immune responses, although responses in younger adults were greater [95]. A recent study of an MF59-adjuvanted H5N1 vaccine in separate groups of adults younger and older than ≥61 years who were healthy or had high-risk medical conditions demonstrated that immune responses to the adjuvanted vaccine were robust in both groups, although slightly lower in the older age group. Within age groups, immune responses were similar between those with and without high-risk health conditions [96].

3.6. Influenza vaccines in development

Investigational influenza vaccines that might improve protection for middle-aged and older adults include a universal influenza vaccine; a cell-based, adjuvanted, higher dose vaccine; and mRNA influenza vaccines, which may potentially be used for either pandemic or seasonal influenza. A universal influenza vaccine that would provide broad and durable protection from influenza, without the need for annual immunizations, is a long-sought goal of influenza research. Recent strategies have focused on the HA stalk domain, which has broad sequence conservation between influenza subtypes and the potential to confer cross-reactive protection [97–100]. However, in studies to date, protection has been short-lived and resistant to boosting [101–103].

Cell-based vaccines for influenza continue to be developed and offer several significant benefits over traditional egg-based vaccines. Notably, they eliminate the risk of egg-adapted changes, which can occur when viruses adapt to grow in eggs, potentially leading to a mismatch between the vaccine strain and circulating viruses, thereby improving vaccine effectiveness [104,105]. Evidence from observational studies suggests cell-based vaccines provide greater protection against influenza-related medical encounters, hospitalizations, and outpatient visits compared to egg-based vaccines [104,106], and in the 50–64 year population, cell-based vaccines prevented significantly more influenza-related medical encounters than egg-based vaccines [107]. Additionally, cell-based vaccine production is not dependent on the supply of eggs, which can be advantageous in the event of supply disruptions and allows for a faster start-up of the manufacturing process during pandemics [105,106]. This technology also ensures a more consistent and scalable production process, enhancing overall vaccine availability and reliability [106]. Adjuvants such as MF59 and high-dose antigen formulations are proven to elicit higher antibody responses and safely improve vaccine effectiveness compared to standard vaccines against influenza [56,71,76,108,109]. Currently, a Phase 2/3 clinical program is evaluating the benefits of combining cell-based vaccine technology with MF59-adjuvant and high-dose antigen in a novel influenza vaccine tested in persons aged 50–64 and ≥ 65 years (adjuvanted cell-based trivalent influenza vaccine [aTIVc]) (Seqirus, data on file). Integrating MF59-adjuvant, cell-based technology, and a higher antigen dose may offer enhanced immunogenicity and protection against influenza beyond standard vaccines.

mRNA vaccines played an integral role in bringing the SARS-CoV-2 pandemic under control, and several mRNA influenza vaccines are under development. Rather than carrying HA and/or NA proteins, mRNA vaccines contain the mRNA constructs that carry the genetic code for the antigen(s) of interest. These vaccines can be rapidly synthesized and manufactured, making them ideal for use against either pandemic or seasonal influenza viruses. When brought into host cells, mRNA co-opts

host cell protein synthesis machinery to produce antigens that are exact matches of the reference antigen (thus avoiding adaptive mutations seen with conventional egg-based influenza vaccines); in turn, expression of the vaccine antigens stimulates robust responses from both the innate and adaptive immune systems, including broad T and B cell responses and increased inflammatory cytokines, which may have an adjuvant-like effect on immunogenicity [110–112]. The lipid carriers in mRNA vaccines may also contribute an adjuvant-like effect. While age-group data are limited for these vaccines, these adjuvant-like effects may prove beneficial in middle-aged and older adults. Drawbacks of conventional mRNA vaccines (such as those approved for SARS-CoV-2) include higher reactogenicity and that the duration of the immune response appears to be short-lived, with little cross-reactivity [113,114]. Self-amplifying mRNA (sa-mRNA) vaccines may overcome this limitation. These modified mRNA vaccines include an RNA-dependent RNA polymerase (RdRP) complex, or replicon, which amplifies transcription of the RNA sequences within the host cell, thereby dramatically increasing antigen production and the immunogenic response relative to that produced by conventional mRNA vaccines [110,115]. Relative to a conventional mRNA SAR-CoV-2 vaccine, an sa-mRNA vaccine raised higher titers against both the original Wuhan and the heterologous omicron strain of SARS-CoV-2, and the duration of the immune response to the sa-mRNA vaccine was also longer, with twice as many antibody titers as the mRNA at 6 months post-vaccination [116,117]. Recent clinical trials have demonstrated the feasibility and immunogenicity of combined mRNA vaccines targeting SARS-CoV-2 and influenza viruses. Additionally, concurrent administration of separate COVID-19 and influenza vaccines has been associated with enhanced spike-specific antibody responses, suggesting potential immunological benefits to simultaneous vaccination [118]. Protein-based combination vaccines for COVID-19 influenza are also in development and may provide an improved reactogenicity profile. While both mRNA vaccine combination approaches show promise, mRNA vaccines may offer advantages in manufacturing speed and adaptability [119,120].

4. Conclusions

Influenza burden of disease increases with advancing age and number of comorbidities. Immunosenescence, inflammation, frailty, and comorbidities associated with ageing can impact disease severity and immune responses. These factors affect not only persons aged ≥65 years but also those aged 50–64 years, in whom the processes contributing to immunosenescence have begun. In addition, multimorbidity increases with age. In middle-aged and older persons, inflammation-related comorbidities contribute to changes in the immune system that may increase susceptibility to infection and severe disease but paradoxically may also enable a more robust response to enhanced influenza vaccines. Data from clinical studies with several enhanced influenza vaccines show improved outcomes in persons aged 50–64 years, and the depressed immunogenicity responses in this age group may be even greater in persons with high-risk comorbidities. These findings suggest that enhanced influenza vaccination may be important for some younger as well as older persons and that the use of enhanced vaccines for at-risk adults may be warranted.

Future research should be directed at defining the adult population most likely to benefit from enhanced vaccines. Frailty—regardless of chronological age—appears to be associated with improved responses to enhanced vaccines. However, specific biomarkers of frailty need to be better defined. Although some reports have highlighted potential inflammatory biomarkers, other research has shown that these do not consistently correlate with frailty indicators [121,122]. Additional efforts should be made to identify biomarkers predictive of poor responses to standard or enhanced influenza vaccines and to gather data on how these biomarkers reflect age and/or comorbidities. Such biomarkers might involve changes in the number or dynamics of both naïve and memory T and B cells, innate immune cells, transcriptomic profiles, and epigenetic profiles.

CRediT authorship contribution statement

Wendy Boivin: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Mark Loeb:** Writing – review & editing. **Peter Openshaw:** Writing – review & editing, Conceptualization. **Mansoor Ashraf:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Graham Pawelec:** Writing – review & editing, Conceptualization.

Funding

This work was supported by CSL Seqirus.

Declaration of competing interest

The 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.

Acknowledgements

Consultant C. Gordon Beck and Amanda M. Justice provided medical writing and editorial support in the preparation of this article, which was funded by CSL Seqirus.

Data availability

No data was used for the research described in the article.

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DOI: https://doi.org/10.1016/j.jvacx.2025.100680

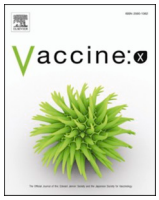
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Corrigendum



Corrigendum to "Seasonal influenza vaccination: Overcoming immunosenescence with enhanced vaccines" [Vaccine: X 24 (2025) 100662]

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The authors regret an error of omission in Section 3.3 of the above referenced article. The second sentence of the first paragraph of that section ("In adults given a high-dose influenza vaccine, the magnitude of the immune response increases in a dose-proportional manner [77,78].") should have also cited a third reference: Pepin S, Nicolas JF, Szymanski H, Leroux-Roels I, Schaum T, Bonten M, et al.; QHD00011 study team. Immunogenicity and safety of a quadrivalent high-dose inactivated influenza vaccine compared with a standard-dose quadrivalent influenza vaccine in healthy people aged 60 years or older: a randomized Phase III trial. Hum Vaccin Immunother. 2021;17:5475–5486. https://www.tandfonline.com/doi/full/10.1080/21645515.2021.1983387.

In addition, the first sentence of the second paragraph of Section 3.3 should have read: "High-dose inactivated influenza vaccines have not been studied in populations younger than 60 years, so we are unable to draw conclusions for this vaccine in the 50–59 age group."

The authors apologise for any inconvenience caused.

DOI of original article: https://doi.org/10.1016/j.jvacx.2025.100662.
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https://doi.org/10.1016/j.jvacx.2025.100680

Available online 25 June 2025
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