Superior
Health Council

Vaccination against Seasonal Influenza 2026 - 2027

February 2026
No. 9897

.be

Copyright

Superior Health Council
Avenue Galilée, 5 bte 2
B-1210 Brussels

Tel.: +32 2 524 97 97
E-mail: info.hgr-css@health.fgov.be

Please cite this document as follows:
Superior Health Council (of Belgium). Vaccination against Seasonal Influenza 2026 - 2027. Brussels: SHC; 2026. Report No. 9897.

Public advisory reports as well as booklets may be consulted in full on the Superior Health Council website:
http://www.superiorhealthcouncil.be

With the support of:
Federal Public Service Health, Food Chain Safety and Environment.

Superior Health Council

ADVISORY REPORT OF THE SUPERIOR HEALTH COUNCIL no. 9897

Vaccination against Seasonal Influenza 2026 - 2027

In this scientific advisory report, which offers guidance to public health policy-makers, the Superior Health Council of Belgium **provides recommendations for vaccination against influenza for the season 2026 - 2027**.

This version was validated[1] by the Board on
4 February 2026

Disclaimer

These influenza guidelines have been developed prior to the finalization of the seasonal vaccine composition for the 2026-2027 influenza season. This early publication is essential to enable health authorities to initiate vaccine procurement procedures and to ensure adequate vaccine availability throughout the healthcare system. Regional authorities, pharmacies, and healthcare facilities require this advanced notice to prepare their vaccine supply chains and immunization programs effectively.

Should significant new epidemiological data emerge or substantial changes in influenza virus circulation patterns occur, the Superior Health Council may issue an updated version of these guidelines during the course of 2026. Healthcare providers are advised to consult the Superior Health Council's official channels for any amendments or supplementary guidance.

I INTRODUCTION

The Winter Plan, a coordinated effort of Belgian federal and regional health authorities, positions vaccination against respiratory pathogens as a cornerstone of seasonal preparedness. Within this framework, seasonal influenza causes 280,000 – 470,000 annual cases in Belgium, with burden highest among adults aged ≥ 65 years (defined here as older adults). European vaccination coverage remains below the 75% European Union (EU) Council target, with Belgian coverage at approximately 56% in older adults. Post-pandemic declines in healthcare worker vaccination and persistent gaps in high-risk population underscore the need for updated, evidence-based recommendations aligned with evolving scientific understanding.

These recommendations were developed by a NITAG working group comprising experts in infectious diseases, vaccinology, epidemiology, health economics, and paediatrics. The evidence reviews synthesized data from systematic literature searches, European surveillance reports, and manufacturer consultations.

[1] The Council reserves the right to make minor typographical amendments to this document at any time. On the other hand, amendments that alter its content are automatically included in an erratum. In this case, a new version of the advisory report is issued.

The target groups for influenza vaccination remain unchanged since last season: adults aged 65 years and older, individuals with chronic medical conditions, pregnant women, residents of long-term care facilities, healthcare workers, and household contacts of high-risk individuals. The Superior Health Council recommends preferential use of enhanced influenza vaccine (high-dose or MF59-adjuvanted formulations) for adults aged 65 years and older.

II CONCLUSIONS AND RECOMMENDATIONS

Recommendations by Age Group and Risk Profile

Target group	Priority	Recommended Vaccine	Enhanced vaccine?	Rationale
CHILDREN & ADOLESCENTS				
6 mo – 17 y (at-risk)	High	IIV3	No	Chronic pulmonary, cardiac, renal, hepatic, neurological, metabolic disease; immunocompromised
Children on long-term aspirin	High	IIV3	No	Reye syndrome risk; includes children with Kawasaki disease
BMI ≥40 (children)	High	IIV3	No	Increased risk of severe influenza and complications
6 mo – 17 y (healthy)	Not routine	Not routinely recommended	No	Risk-based strategy; Belgium does not recommend universal childhood vaccination
ADULTS 18–49 YEARS				
18–49 y (at-risk)	High	IIV3	No	Same chronic conditions; also pregnant women, HCWs
18–49 y (healthy)	Not routine	Not routinely recommended	No	Unless occupational exposure (HCW, poultry/pig workers)
ADULTS 50–64 YEARS				
50–64 y (at-risk)	High	IIV3 or aIIV3	Consider	aIIV3 (Fluad) approved ≥50
50–64 y with CKD	High	IIV3; consider HD-IIV3	Consider	Extrapolation from DANFLU-2 CKD subgroup (rVE 68.6%); individual decision
50–64 y (healthy)	Moderate	IIV3	No	–
ADULTS ≥65 YEARS				
65–74 y	High	HD-IIV3 preferred; aIIV3 acceptable	Yes (conditional)	HD-IIV3 has more extensive RCT evidence; aIIV3 based on observational data; individual factors may guide choice
≥75 y	Very High	HD-IIV3 preferred; aIIV3 acceptable	Yes (strong)	Strong recommendation for enhanced vaccines; maximum benefit in this group; HD-IIV3 has more extensive RCT evidence; aIIV3 based on observational data;
LTCF residents (≥65)	Very High	HD-IIV3 preferred; aIIV3 acceptable	Yes (strong)	Highest risk; frailty, comorbidity, congregate setting; HD-IIV3 has more extensive RCT evidence; aIIV3 based on observational data;
SPECIAL POPULATIONS				

Target group	Priority	Recommended Vaccine	Enhanced vaccine?	Rationale
Pregnant women (any trimester)	High	IIV3	No	Protect mother and infant; safe all trimesters
HCW (healthy)	High	IIV3	No	Protect patients; maintain healthcare capacity
Poultry/pig workers (healthy)	High	IIV3	No	Reduce reassortment risk; occupational exposure
Immunocompromised (18–64)	High	IIV3; consider aIIV3	Consider	Suboptimal responses; aIIV3 may partially improve immunogenicity (observational evidence)
CKD (≥65)	High	HD-IIV3 preferred	Yes	DANFLU-2: rVE 68.6% vs 30.6% in non-CKD; NNT 561 vs 3953
BMI ≥40 (adults)	High	IIV3	No	Increased risk of severe disease; no enhanced vaccine data
Household contacts of high-risk	Moderate	IIV3	No	Cocooning strategy; indirect protection
Household contacts of infants <6 mo	Moderate	IIV3	No	Cocooning strategy; infants cannot be vaccinated
EGG ALLERGY				
Most egg-allergic individuals	Per indication	Any age-appropriate IIV3; consider Flucelvax (cell-based)	Per indication	Standard vaccination setting; 15-min observation
History of severe anaphylaxis to egg	Per indication	Flucelvax; if unavailable, hospital setting	Per indication	Allergist consultation recommended; anaphylaxis management must be available in case of egg-based vaccine administration

Abbreviations: aIIV3 = MF59-adjuvanted IIV3 (Fluad); CKD = chronic kidney disease; Flucelvax = cell-based IIV; HCW = healthcare worker; HD-IIV3 = high-dose IIV3 (Efluelda); IIV3 = trivalent inactivated influenza vaccine; LTCF = long-term care facility; NNT = number needed to treat; rVE = relative vaccine effectiveness

Vaccine Formulations Available in Belgium

Vaccine Type	Trade Name	Age Indication	Key Feature
Egg-based Standard-dose IIV3	Influvac, α-Rix, Vaxigrip	≥6 months	15 µg HA per strain
Egg-based High-dose IIV3 (HD-IIV3)	Efluelda	≥60 years	60 µg HA per strain (4× antigen)
Egg-based Adjuvanted IIV3 (aIIV3)	Fluad	≥50 years	15 µg HA per strain, MF59 adjuvant
Cell-based vaccine Standard-dose	Flucelvax	≥6 months	15 µg HA per strain

Key Messages

- Group 1 (high-risk individuals)

    - **HD-IIV3 preferred and aIIV3 as an acceptable alternative for ≥65 years.**
      Both high-dose and adjuvanted vaccines reduce influenza-related hospitalization compared to standard-dose vaccines. The evidence differs in methodology (RCTs for high-dose; observational studies for adjuvanted) but not in direction of effect. Immunogenicity comparisons show equivalence for influenza A strains; high-dose achieves modestly higher seroconversion, adjuvanted vaccines broader heterologous responses. These differences do not translate into demonstrable clinical superiority.

    - **Standard IIV3 for <65 years with chronic conditions; consider HD-IIV3 for patients with chronic kidney diseases.**
      For adults aged 50–64 years with CKD, clinicians may consider preferential use of HD-IIV on an individual basis. This recommendation reflects extrapolation from the ≥65 trial population, supported by the observed effect modification by CKD status and the biological plausibility of enhanced benefit in patients with impaired vaccine immunogenicity. This consideration does not extend to other chronic conditions in younger adults, where evidence for differential HD-IIV benefit is lacking.

    - **Consider aIIV3 for immunocompromised.**

    - **Standard IIV3 for BMI ≥ 40**

    - **Standard IIV3 for children on long-term aspirin**

    - **Standard IIV3 for pregnant women (at any trimester)**

- Group 2 (Healthcare workers)

    - **Standard IIV3**

- Group 3 (Children and household contacts)

    - **Standard IIV3 – cocooning strategy; protects those who cannot be vaccinated (e.g. infants <6 months)**

- **If enhanced vaccines unavailable**: Do not delay; standard-dose IIV3 remains effective.

- **In case of history of severe anaphylaxis to egg**: use egg-free vaccines.

Keywords and MeSH *descriptor terms*[2]

MeSH terms*	Keywords	Sleutelwoorden	Mots clés	Schlüsselwörter
Influenza, Human	Flu	Griep	Grippe	Grippe
	Seasonal influenza	Seizoensgriep	Grippe saisonnière	Saisonale Grippe
	Vaccination	Vaccinatie	Vaccination	Impfung
Vaccination	High-dose vaccine	Hooggedoseerd vaccin	Vaccin à haute dose	Hochdosis-Impfstoff
Pregnancy	Adjuvanted vaccine	Geadjuveerd vaccin	Vaccin adjuvanté	Adjuvantierter Impfstoff
	Older adults	Ouderen	Personnes âgées	Ältere Personen
Health Personnel	At-risk population	Risicogroepen	Groupes à risque	Risikogruppen
Risk factors	Pregnancy	Zwangerschap	Grossesse	Schwangerschaft
Poultry and swine workers	Healthcare workers	Zorgverleners	Personnel soignant	Gesundheitspersonal
Immunocompromised host	Children	Kinderen	Enfants	Kinder

MeSH (Medical Subject Headings) is the NLM (National Library of Medicine) controlled vocabulary thesaurus used for indexing articles for PubMed http://www.ncbi.nlm.nih.gov/mesh.

[2] The Council wishes to clarify that the MeSH terms and keywords are used for referencing purposes as well as to provide an easy definition of the scope of the advisory report. For more information, see the section entitled "methodology".

III TABLE OF CONTENTS

IV METHODOLOGY

After analysing the request, the Board and the co-presidents of the NITAG identified the necessary fields of expertise. An *ad hoc* working group was then set up which included experts in internal medicine, infectious diseases, paediatrics, geriatrics, vaccinology, epidemiology, general practice, clinical microbiology, pharmacology, pharmacovigilance, and public health. The experts of this working group provided a general and an *ad hoc* declaration of interests and the Committee on Deontology assessed the potential risk of conflicts of interest.
Three working meetings were held for the development of these recommendations: (1) a meeting to address the scope of the present advisory report; (2) a meeting with epidemiological modelers to discuss Belgian-specific transmission dynamics and cost-effectiveness parameters; (3) and a plenary meeting with the complete working group to integrate findings. In addition, a pharma industry consultation process through formal hearings with vaccine manufacturers (AstraZeneca, CSL Seqirus, GSK, Viatris, Sanofi) was held on December 19, 2025.
Belgian-specific epidemiological data, including surveillance data, vaccination coverage, and hospitalization statistics, were supplied by Sciensano. The chair of the working group compiled these inputs and redacted a first draft for circulation to members.
The evidence synthesis and document preparation employed artificial intelligence tools as research assistants under direct expert supervision. Claude (Anthropic, versions 3.5 Sonnet and Opus 4.5) and Gemini 2.5 Pro (Google) were used for systematic literature verification, reference checking, full-text data extraction, and draft text generation. Each paragraph containing quantitative claims underwent structured verification against primary sources. Full-text articles were retrieved and processed by the Artificial Intelligence (AI) systems for cross-verification of statistical values, confidence intervals, and study conclusions. Mendeley reference manager (version 2.142.0) was used for bibliography organization and citation formatting; final scientific judgments regarding evidence quality, recommendations strength, and clinical interpretation remained exclusively with the human expert.
This advisory report is based on a review of the scientific literature published in both scientific journals and reports from national and international organisations competent in this field (peer-reviewed), as well as on the opinion of the experts.
Once the advisory report was endorsed by the working group and NITAG it was ultimately validated by the Board.

List of abbreviations used

ACM	All-Cause Mortality
ADEM	Acute Disseminated Encephalomyelitis
AE	Adverse Event
AF	Atrial Fibrillation
AI	Artificial Intelligence
aIIV	Adjuvanted Inactivated Influenza Vaccine
aIIV3	Adjuvanted Trivalent Inactivated Influenza Vaccine
aIIV4	Adjuvanted Quadrivalent Inactivated Influenza Vaccine
IIV4c	Cell-based Quadrivalent Influenza Vaccine
ASCVD	Atherosclerotic Cardiovascular Disease
aVE	Absolute Vaccine Effectiveness
BMI	Body Mass Index
cbIIV	Cell-Based Inactivated Influenza Vaccine
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CKD	Chronic Kidney Disease
cRNA	complementary ribonucleic acid
CSMI	Conseil Supérieur des Maladies Infectieuses
CVD	Cardiovascular Disease
DTaP	Diphtheria, Tetanus acellular Pertussis
ebIIV	Egg-Based Inactivated Influenza Vaccine
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GBS	Guillain-Barré Syndrome
GMT	Geometric Mean Titre
GP	General Practitioner
HA	Hemagglutinin
HAS	Haute Autorité de la Santé
HCW	Healthcare Worker
HD-IIV4	High-Dose Quadrivalent Inactivated Influenza Vaccine
HD-IIV3	High-Dose Trivalent Inactivated Influenza Vaccine
HF	Heart Failure
HLA	Human Leukocyte Antigen
HTA	Health Technology Assessment
ICU	Intensive Care Unit
IFN	Interferon
Ig	Immunoglobulin
IHD	Ischemic Heart Disease
IIV	Inactivated Influenza Vaccine
IIV3	Trivalent Inactivated Influenza Vaccine
IIV4	Quadrivalent Inactivated Influenza Vaccine
ILI	Influenza-Like Illness
IRH	Influenza-Related Hospitalization
IRME	influenza-related medical encounters

IRR	Incidence Rate Ratio
JCVI	Joint Committee on Vaccination and Immunisation
LAIV	Live Attenuated Influenza Vaccine
LCI	Laboratory-Confirmed Influenza
LTCF	Long-Term Care Facility
MACE	Major Adverse Cardiovascular Event
MF59	MF59 adjuvant (squalene-based oil-in-water emulsion)
MI	Myocardial Infarction
MOVE	Monitoring Vaccine Effectiveness
NA	Neuraminidase
NHS	National Health Service
NITAG	National Immunization Technical Advisory Group
NNT	Number Needed to Treat
NP	Nucleoprotein
NR	Not Reported
NS	Not Significant
PA-X	Polymerase Acidic Protein X
PB	Polymerase Basic protein
PCV	Pneumococcal Conjugate Vaccine
PCV20	20-valent Pneumococcal Conjugate Vaccine
PCV21	21-valent Pneumococcal Conjugate Vaccine
PRR	Pattern Recognition Receptors
RCT	Randomised controlled trial
RIV	Recombinant Influenza Vaccine
RR	Relative Risk
RSV	Respiratory Syncytial Virus
RSVPreF3 OA	RSV Prefusion F Protein Vaccine for Older Adults
RT-PCR	Reverse Transcription Polymerase Chain Reaction
rVE	Relative Vaccine Effectiveness
RZV	Recombinant Zoster Vaccine
SAE	Serious Adverse Event
SARI	Severe Acute Respiratory Infection
SCR	Seroconversion rate
SD-IIV	Standard-Dose Inactivated Influenza Vaccine
SD-IIV3	Standard-Dose Trivalent Inactivated Influenza Vaccine
SD-IIV4	Standard-Dose Quadrivalent Inactivated Influenza Vaccine
SHC	Superior Health Council
SPC	Summary of Product Characteristics
STIKO	Ständige Impfkommission
US	United States
VCR	Vaccination Coverage Rate
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Effectiveness
VEBIS	Vaccine Effectiveness, Burden and Impact Studies
VSD	Vaccine Safety Datalink
WHO	World Health Organisation

V ELABORATION AND ARGUMENTATION

1 Influenza

1.1 Viral Characteristics and Structure

1.1.1 Viral Classification and Structure

Influenza viruses belong to the family Orthomyxoviridae, with types A, B, and C causing human infections [1]. Influenza D virus, identified in 2011, primarily infects cattle and swine. Serological studies demonstrate human exposure, particularly among individuals with occupational cattle contact, though confirmed human disease has not been reported [2]. The genome consists of eight single-stranded negative-sense RNA segments in influenza A and B viruses [1,3–5]. Each segment contains conserved partially complementary 5' and 3' termini, segment-specific untranslated regions, and one or more open reading frames [3]. These eight segments encode ten major proteins for viral replication: Polymerase Basic protein (PB)-2, -1, PA (polymerase subunits), hemagglutinin (HA), nucleoprotein (NP), neuraminidase (NA), matrix proteins M1 and M2, non-structural protein NS1, and nuclear export protein [3]. The genome also encodes up to eleven non-essential accessory proteins including PB1-F2 and Polymerase Acidic protein X (PA-X) [3].

1.1.2 Viral Envelope and Surface Glycoproteins

Each RNA segment is assembled into a viral ribonucleoprotein complex (vRNP) where the vRNA associates with oligomerized nucleoprotein at inter-protomer interfaces, forming a helical scaffold with the heterotrimeric polymerase (PB1, PB2, PA) bound to the conserved 5′ and 3′ termini [1,6]. The viral particle is enclosed by a host-derived lipid envelope containing three integral membrane proteins: the glycoproteins hemagglutinin and neuraminidase, and the M2 ion channel [3].

1.1.3 Virus Subtypes and Lineages

Eighteen hemagglutinin subtypes (H1-H18) and eleven neuraminidase subtypes (N1-N11) have been identified across different species [7,8]. The combinations of these glycoproteins define influenza A virus subtypes (H1N1, H3N2, H5N1, etc.). Influenza A viruses are zoonotic, with wild aquatic birds serving as natural reservoirs for subtypes H1-H16 and N1-N9, while H17, H18, N10, and N11 have been identified exclusively in bats [7,8]. Swine play a distinct epidemiological role as potential "mixing vessels" for influenza reassortment. Porcine respiratory epithelium expresses both α2,3-linked sialic acid receptors (preferred by avian viruses) and α2,6-linked receptors (preferred by human viruses), permitting co-infection with viruses from multiple host species. This dual receptor expression facilitates generation of reassortant strains with novel gene constellations and pandemic potential, as occurred with the 2009 A(H1N1)pdm09 virus [9]. Influenza B viruses circulate almost exclusively in humans and comprise two phylogenetically distinct lineages: Victoria and Yamagata. However, B/Yamagata has not been detected in natural circulation since March 2020 and is considered probably extinct [10–12]. Currently circulating human strains include A(H1N1)pdm09, A(H3N2), and B/Victoria lineage only [11,12].

1.1.4 Viral Replication Machinery

The heterotrimeric RNA-dependent RNA polymerase catalyses both transcription and replication of the viral genome in the nucleus of infected cells [1,13]. Transcription produces capped and polyadenylated viral mRNAs through a cap-snatching mechanism, whereby the PB2 subunit binds host capped RNAs and the PA endonuclease cleaves them to use as

primers [1,13]. Replication proceeds through a positive-sense complementary RNA (cRNA) intermediate to generate progeny viral RNA segments [1,13].

1.1.5 Mechanisms of Viral Evolution

Antigenic drift: Continuous accumulation of point mutations in the HA and NA genes results in gradual antigenic changes [14]. This evolution allows viruses to escape pre-existing population immunity, driving annual seasonal epidemics and necessitating regular vaccine updates [14,15].
Antigenic shift (reassortment): The segmented nature of the influenza genome allows reassortment when different viruses co-infect a single cell [14]. Segments can be exchanged between viruses, potentially creating novel viral strains with pandemic potential when human population lack immunity to the new antigenic combinations [14,16]. Reassortment occurs exclusively within influenza types; segment exchange between influenza A and B viruses has not been documented despite their cocirculation in humans. Experimental studies demonstrate this barrier results from divergent packaging signals rather than polymerase incompatibility, as influenza A and B polymerases can transcribe heterotypic segments and influenza B glycoproteins can functionally complement influenza A viruses. Artificial rescue of influenza A/B chimeric viruses becomes possible only when influenza A packaging signals are appended to influenza B segments, confirming that type-specific packaging signal evolution maintains the speciation boundary [17,18].
Host factor ANP32A/B plays a key role in viral genome replication, and species-specific difference in ANP32 proteins restrict avian influenza virus polymerase activity in mammalian cells [19,20], constituting one of the major barriers to cross-species transmission.

1.2 Pathophysiology and Viral Transmission

1.2.1 Cellular Tropism and Receptor Binding

Influenza virus infects respiratory epithelial cells throughout the upper and lower respiratory tract [21]. For viruses with monobasic hemagglutinin cleavage sites, proteolytic activation occurs predominantly in respiratory epithelium via TMPRSS2 and related trypsin-like proteases, restricting productive infection to the airways [22]. Human respiratory epithelial cells express predominantly α2,6-linked sialic acid receptors, while α2,3-linked receptors are sparse in the upper tract but present on alveolar type II pneumocytes [23,24]. Avian influenza viruses typically bind α2,3-linked sialic acids, whereas human viruses preferentially recognize α2,6-linked receptors; only a few amino acid changes in HA can switch receptor specificity [25,26].

1.2.2 Pathophysiological Mechanisms

Disease severity correlates with the extent of lower respiratory tract involvement, with infection of alveolar epithelial cells directly compromising gas exchange and driving acute respiratory distress syndrome [27]. The primary mechanism of influenza pathophysiology results from lung inflammation caused by direct viral infection of respiratory epithelium combined with immune responses recruited to control viral spread [27,28]. Impaired gas exchange results from airway obstruction, loss of alveolar structure, epithelial cell death, and extracellular matrix degradation [29]. Infected epithelial cells initiate regulated responses involving pattern recognition receptors (PRR) and inflammatory mediators including type I/III interferons (IFN), tumour necrosis factor, interleukin-6, and chemokines [30]. Fatal influenza cases typically result from dysregulated inflammatory responses that exacerbate lung injury independently of viral replication [31,32]. Neutrophils contribute substantially to immunopathology during severe influenza. Within hours of infection, neutrophils may comprise up to 50% of bronchoalveolar lavage cellularity. Neutrophil-derived proteases, reactive oxygen species,

and neutrophil extracellular traps (NETs) directly damage respiratory epithelium and contribute to airway obstruction, independent of their antimicrobial function [33].

1.2.3 Immune Response and Immune Evasion

Immunity through natural infection

Influenza virus triggers innate immunity through PRR detecting viral RNA, leading to interferon and pro-inflammatory cytokine production. The virus counters these defences through NS1, which inhibits IFN signalling and host mRNA processing, and PA-X, an endonuclease that degrades host transcripts while sparing viral mRNAs. Together, NS1 and PA-X antagonize host innate immune responses, enabling efficient viral replication before adaptive immunity is mobilized [34].
Viral clearance is mediated by neutralizing antibodies and cytotoxic CD8+ T cells that lyse infected cells and secrete IFN-γ [35]. Natural infection generates broader immunity than standard inactivated vaccination, including mucosal Immunoglobulin (Ig)A, robust stalk-directed antibodies, and cross-reactive memory B cells capable of recognizing antigenically drifted variants [36,37]. Antibodies targeting the conserved HA stalk domain provide heterosubtypic protection through Fc-mediated effector functions including antibody-dependent cellular cytotoxicity [38].
The adaptive immune response follows a defined temporal sequence. CD8+ cytotoxic T lymphocytes capable of lysing infected cells differentiate by days 7-10 post-infection. Humoral immunity emerges in parallel: IgM antibodies appear around day 7, followed by class switching to high-affinity IgG and IgA antibodies by days 10-14. Following viral clearance at approximately two weeks, most effector cells undergo apoptosis, while memory T cells, memory B cells, and long-lived plasma cells persist in lymphoid tissue, providing durable protection against homologous and antigenically similar strains [39].
Influenza evades pre-existing immunity through antigenic drift (point mutations at antibody-binding sites) and antigenic shift (reassortment generating novel HA/NA combinations). N-linked glycosylation near antigenic sites provides additional epitope shielding [40].
Immune imprinting from childhood HA exposure may provide lifelong protection against severe infection, with immunity to seasonal A(H1N1) potentially reducing disease severity from H5N1 due to shared group 1 HA stalk domains [41]. This cross-protection involves memory B cells recognizing conserved stalk epitopes and cross-reactive anti-N1 neuraminidase antibodies [42].

Natural immunity versus vaccine induced immunity

Natural infection elicits qualitatively and quantitatively different immune responses compared to standard inactivated vaccination. Natural infection induces long-lived and relatively broad immune responses characterized by robust mucosal immunity, including secretory IgA at respiratory surfaces that provides first-line defence against subsequent exposures [43]. Infection may generate stronger HA stalk-directed antibody responses compared to intramuscular vaccination, likely due to prolonged antigen exposure during active viral replication and the inflammatory milieu accompanying infection, though cumulative exposures via any route contribute to stalk antibody breadth [44]. Studies using influenza virus protein microarrays demonstrated that adults infected with A(H1N1) develop a broad recall response boosting antibodies against multiple group 1 HA, whereas children respond more narrowly to the infecting strain [36].
Standard inactivated influenza vaccine administered intramuscularly induce primarily systemic IgG responses with limited mucosal immunity (IgA) [45]. The antibody response is predominantly directed against the immunodominant HA head domain with minimal stalk-directed antibodies generated. Vaccine-induced antibody responses show substantial inter-individuals heterogeneity: over half of recipients demonstrated weak responses (<4× fold-

change), while durable responders maintain protective titres for 12 months [46]. However, vaccines avoid the morbidity associated with infection.
Live attenuated influenza vaccine administered intranasally more closely mimic natural infection, inducing mucosal IgA and broader cellular responses [47]. Effectiveness data have shown temporal and strain-specific variation: a 2003-2023 network meta-analysis found comparable overall effectiveness between live attenuated influenza vaccine (LAIV) and inactivated influenza vaccine (IIV) in children (~50%), though IIV performed better against A(H1N1)pdm09 during 2010-2017 while LAIV showed superior effectiveness against influenza B after 2017 [48].

1.2.4 Transmission Routes

Influenza viruses transmit through aerosols, large droplets, and direct contact with secretions; these modes operate concurrently rather than exclusively [49,50]. Mathematical modelling of household transmission data indicates aerosol transmission accounts for approximately half of all transmission events [51]. Larger droplets settle within 1-2 meters, while particles below 5 µm remain airborne for extended periods [49,50].
Viral shedding follows a predictable temporal pattern in immunocompetent adults: nasal virus excretion begins approximately one day post-infection, peaks at days 2-3 coinciding with symptom onset, and typically becomes undetectable by day 7. The incubation period ranges from 1 to 4 days, with illness duration averaging 7 days in uncomplicated cases [52]. Viral shedding often starts in the 24 hours preceding symptom onset, though the exact timing and magnitude vary between individuals [53].
Dose-response modelling of human challenge studies demonstrated that aerosol delivery results in approximately 20-fold higher infectivity compared to intranasal inoculation, with aerosol-acquired infections more frequently producing typical influenza-like illness with fever and cough [51,54]. Preferential binding to α2,6-linked sialic acid receptors in the upper respiratory tract remains a key determinant of airborne transmissibility between mammals [55]. Recent experimental data demonstrated that commensal respiratory bacteria stabilize influenza viruses in droplets and aerosols, with 10 to 100-fold more infectious virus remaining after one hour in the presence of bacteria [56]. Children lacking prior immunity and immunocompromised individuals shedding virus at high titres for prolonged periods serve as particularly efficient transmitters [55].

2 Clinical presentation

2.1 Clinical Presentation of Influenza in Adults: Focus on High-Risk Population and Complications

2.1.1 Clinical Features and High-Risk Population

Seasonal influenza presents characteristically with abrupt onset of fever, nonproductive cough, and myalgia, though clinical manifestations vary considerably across population [57,58]. Adults aged ≥ 65 years (defined as “older adults” in the present document), individuals with chronic medical conditions including cardiovascular disease (CVD), diabetes, chronic obstructive pulmonary disease, and immunocompromised patients constitute high-risk groups for severe disease and complications [58,59]. Advanced age, presence of multiple chronic conditions, and delayed treatment initiation are associated with prolonged hospitalization and progression to respiratory failure [59–61]. Older adults and immunocompromised patients may present atypically, with subtle findings including absence of fever or myalgias [57,59,62]. In these population, generalized symptoms such as anorexia, malaise, weakness, and altered mental status may predominate over classic respiratory manifestations, potentially delaying diagnosis and appropriate management [59,62].

2.1.2 Respiratory Complications

Pneumonia remains the most common and severe complications of influenza, with incidence varying substantially by age: approximately 0.5% among healthy adults aged 18-64 years but rising progressively in older population to 1.6% in those 65-74 years, 5.3% in those 75-84 years, and exceeding 9% in individuals ≥85 years [63]. Three distinct forms exist: secondary bacterial pneumonia, mixed viral-bacterial pneumonia, and primary influenza pneumonia. Secondary bacterial pneumonia typically develops within days of influenza onset, with *Streptococcus pneumoniae* and *Staphylococcus aureus* representing the most common pathogens, accounting for approximately 60% of cases, followed by *Haemophilus influenzae* [64]. Clinical differentiation remains important: patients with secondary bacterial pneumonia often demonstrated initial improvement followed by fever recrudescence and productive cough, whereas those with primary influenza pneumonia exhibit persistent high fever and dyspnoea three to five days after symptom onset [65].

2.1.3 Cardiovascular Complications

Influenza infection carries substantial cardiovascular morbidity. Self-controlled case series demonstrated that laboratory-confirmed influenza (LCI) increases acute myocardial infarction (MI) risk approximately 6-fold during the first week post-infection [66]. A United States (US) surveillance study of over 80,000 hospitalized adults with influenza found nearly 12% experienced acute cardiovascular events, predominantly acute heart failure (HF) (6.2%) and acute ischemic heart disease (IHD) (5.7%) [67]. Randomized trial evidence now confirms vaccination's cardioprotective effects: the Influenza-Associated Myocardial Infarction trial demonstrated 28% reduction in major adverse cardiovascular events and 41% reduction in cardiovascular mortality when influenza vaccine was administered early after MI [68]. Less common complications include myocarditis, pericarditis, and arrhythmias, including atrial fibrillation and ventricular arrhythmias [69,70].

2.1.4 Morbidity and Mortality

Worldwide, the number of yearly episodes of lower respiratory tract infections due to influenza across all ages is estimated at 36 million (pre-pandemic), with substantial variation between seasons [71]. Global mortality is estimated at 291,000-646,000 annual influenza-associated respiratory deaths [72]. Limited influenza testing can underestimate both mild and severe influenza-associated illnesses. Worldwide, hospitalization rates for influenza are highest among people aged 65 years and older. In high-income countries, hospitalization rates are typically highest among people aged 65 years and older, children younger than 5 years, and people aged 50-64 years. Mortality is highest in people aged 65 years and older, with about two-thirds of deaths in that age group [71]. In Belgian data, the hospitalization burden is highest in the ≥65 age group but not the incidence rate, which is highest in small children. In Denmark, annual influenza mortality rates in adults ≥65 years reach 42.9 per 100,000, with hospitalization rates of 164.6 per 100,000 [73]. These rates are substantially lower than COVID-19 (mortality 88.5, hospitalization 398.7 per 100,000 for the period 2015-2024) but differ from Respiratory Syncytial Virus (RSV) in a discordant pattern: RSV causes lower mortality (31.2 per 100,000) yet slightly higher hospitalization (177.4 per 100,000) [73]. The cumulative burden encompasses not only direct mortality but also prolonged hospitalization, functional disability in 8-10% of hospitalized older adults [74], and exacerbation of underlying chronic conditions including a 6-fold increased risk of MI in the week following infection [66].

2.1.5 Diagnosis

Molecular assays, particularly reverse transcription polymerase chain reaction (RT-PCR), remain the preferred diagnostic approach given their high sensitivity (approximately 91%) and specificity (exceeding 96%) [75]. Clinical diagnosis during influenza season may suffice for

low-risk outpatients when antiviral therapy is not indicated. For hospitalized and high-risk patients, confirmatory molecular testing is recommended to inform treatment decisions and infection control measures [58].

2.2 Clinical Presentation of Influenza in Children

Certain groups of children are at substantially increased risk for severe or complicated influenza infection. High-risk groups include infants under 6 months (who cannot be vaccinated and require protection through maternal immunization and cocooning), children aged 6 months to 2 years, and those with chronic medical conditions such as asthma, neurologic disorders, heart disease, immunocompromising conditions, and metabolic disorders [76]. Children with obesity (body mass index (BMI) ≥140% of the 95th percentile) face elevated risk, with meta-analysis demonstrating nearly twofold increased odds of hospitalization [77]. Despite these risk factors, approximately 50-65% of young children hospitalized with influenza have no underlying medical conditions [76], and a substantial proportion of paediatric influenza deaths occur in previously healthy children [78].

2.2.1 Clinical Presentation

The classic presentation of influenza includes abrupt onset of fever, headache, myalgia, malaise, and respiratory symptoms including cough, sore throat, and rhinitis. In children, clinical presentation varies by age and developmental stage. Fever and cough are predominant symptoms across all paediatric age groups, present in 77-95% of laboratory-confirmed cases [79,80]. Young children under 3 years present with high fever (including 20% with fever ≥40°C), cough, and rhinitis, with clinical presentation often being most severe in this age group [79]. Gastrointestinal symptoms such as vomiting and diarrhoea occur in approximately 16-23% of paediatric cases [81]. Headache and myalgia are reported primarily in older children who can verbalize these symptoms [79].

2.2.2 Respiratory Complications

As in adults, pneumonia is a major complication of influenza, particularly in high-risk patients and children under 2 years of age. In population-based surveillance, 17-28% of children hospitalized with influenza develop pneumonia, with rates varying by season and population studied [82,83]. Influenza pneumonia is usually mild but increases the risk of severe clinical outcomes. The radiographic pattern is variable. In a Finnish series of 134 children <4 years with influenza pneumonia, infiltrates were interstitial in approximately half of cases and alveolar in one quarter; however, interrater reliability for distinguishing interstitial from alveolar patterns is poor [84,85].
Secondary bacterial coinfection may be particularly severe and rapidly fatal. *S. pneumoniae* and *S. aureus* are the most common causative pathogens, together accounting for approximately 60% of bacterial coinfections; *S. pyogenes* occurs less frequently but is associated with toxic shock syndrome [29].
Necrotizing tracheobronchitis has emerged as a severe complication of influenza A with *S. aureus* coinfection, characterized by extensive mucosal necrosis and purulent haemorrhagic exudates requiring bronchoscopic intervention [86]. Other respiratory complications include asthma exacerbations (occurring in 22% of hospitalized children over 2 years), respiratory failure (5%), and croup [82,87].

2.2.3 Paediatric-Specific Complications

Central nervous system complications occur in approximately 7-11% of hospitalized children with influenza, including febrile seizures (5%), encephalopathy (1.7%), and non-febrile seizures (1.2%) [88]. During the 2024-2025 season, influenza-associated encephalopathy was identified in 13% of paediatric influenza deaths in the US (United States), though whether

this represents an increase above expected levels remains undetermined due to absence of dedicated surveillance [89]. These complications are associated with increased severity of illness, prolonged hospitalization, and higher mortality rates [88]. In Europe, neurological features were documented in 10.3% of hospitalized children during 2018-2023, with severe encephalopathy outbreaks reported in Italy during the 2023-2024 season [90,91].
Acute myositis, characterized by extreme tenderness of the calf muscles and markedly elevated creatine phosphokinase levels, is a rare but recognized complications more frequently observed with influenza B infections [92]. In severe cases, rhabdomyolysis with myoglobinuria and acute kidney injury may occur, though outcomes are typically favourable with supportive care [93].

2.2.4 Morbidity and Mortality

The number of yearly episodes of lower respiratory tract infections due to influenza in children younger than 5 years, worldwide, is estimated at 109.5 million influenza illnesses, 870,000 hospitalization, more than 15,000 in-hospital deaths and up to 35,000 deaths [94]. In the US, annual incidence of symptomatic influenza was estimated at approximately 9% in children 0-17 years, with higher attack rates (12.7%) documented in unvaccinated children [95,96]. Adjusted influenza-associated hospitalization incidence rates in children 0-17 years during 2010-2019 ranged from 10 to 375 per 100,000 persons each season and were highest among infants <6 months old [97]. Rates decreased with increasing age. The highest in-hospital mortality rates were observed in children <6 months old (0.73 per 100,000 persons). Among hospitalized children, 20% were admitted to the intensive care unit (ICU), 17% had pneumonia, 5% required mechanical ventilation, and 0.5% died during hospitalization. The 2024-2025 season was classified as high severity across all age groups in the US, the first such designation since 2017-18, with the cumulative hospitalization rate reaching 127.1 per 100,000, the highest since 2010-11 [76]. Paediatric influenza-associated deaths in the United States reached 279 during the 2024-2025 season, the highest number since paediatric mortality surveillance began in 2004, compared with the previous high of 207 deaths in 2023-2024 [98]. Among paediatric decedents eligible for vaccination with known status, 89% were not fully vaccinated. Factors associated with increased mortality include age under 2 years (particularly under 6 months), underlying medical conditions, and bacterial coinfection [99].

3 Influenza Epidemiology in the Post-Pandemic Era: European and Belgian Perspectives

3.1 European Context

The COVID-19 pandemic fundamentally disrupted influenza circulation across Europe. During the 2020-2021 season, the World Health Organisation (WHO) European Region documented a 99.8% reduction in sentinel influenza detections (33/25,606 tested; 0.1%, Table 1) compared to a six-season average of 38.0% positivity [100]. This suppression, attributable to widespread masking, social distancing, and mobility restrictions, effectively extinguished seasonal transmission. The B/Yamagata lineage disappeared entirely after March 2020, prompting WHO to recommend exclusion of B/Yamagata antigens from vaccine formulations in September 2023 [101].

Table 1: European Influenza Season Characteristics, Pre- and Post-Pandemic [102–107]

Season	Start Week	Duration (weeks >10%)	Peak Positivity	Mean Positivity	Dominant Type/Subtype
2016-2017	46	19	48%	25.6%	A(H3N2)
2017-2018	48	18	58%	32.7%	B/Yamagata
2018-2019	49	19	47%	25.2%	A(H3N2)/A(H1N1)pdm09
2019-2020	47	19	≥50%	23.9%	A(H1N1)pdm09/B/Victoria co-circulation
2020-2021	—	0	0.1%	<1%	Absent

2021-2022	08 (2022)	25	31%	14.5%	A(H3N2)
2022-2023	45	25	42%	20.3%	A(H3N2)
2023-2024	49	15	39%	13.8%	A(H1N1)pdm09

Influenza circulation resumed in 2021-2022 with altered patterns: a late onset, shorter duration, and different age distribution compared to pre-pandemic seasons [104]. The 2022-2023 season marked return to near pre-pandemic activity levels, characterized by earlier onset and A(H3N2) dominance with subsequent A(H1N1)pdm09 and B/Victoria circulation. The 2023-2024 season was shorter (15 weeks above the 10% threshold versus 25 weeks in 2022-2023), with A(H1N1)pdm09 predominating [105] (Table 1).
During 2023-2024, seven European Union / European Economic Area (EU/EEA) countries reported 8,209 laboratory-confirmed hospitalized influenza cases and 1,604 ICU admissions (Table 2). The most affected age groups for ICU admission were adults 65-79 years (25%), 30-64 years (25%), those 80 years and older (17%), and children 0-4 years (16%). Among 505 in-hospital deaths, 71% occurred in individuals aged 60 years and older, with 73% associated with influenza A (unsubtyped) [102].

Table 2: Influenza Hospitalizations and Deaths by Age Group, EU/EEA 2023-2024 [102]

Age Group	ICU Cases (%) (n=1604)	Non-ICU Cases (%) (n=6100)	Deaths (%) (n=8214)
0-4 years	16%	19%	1.4%
5-14 years	12%	14%	0.9%
15-29 years	5%	5%	0.8%
30-64 years	25%	20%	26%
65-79 years	25%	22%	39%
≥80 years	17%	19%	32%

Percentages do not sum to 100% due to rounding.
Abbreviations: ICU: Intensive Care Unit

3.2 Belgian Surveillance

Belgian influenza surveillance, coordinated by Sciensano, comprises sentinel networks of general practitioners (GP), laboratories, hospitals, and nursing homes, complemented by wastewater surveillance from January 2024 [108]. The 2020-2021 season demonstrated near-complete absence of influenza coinciding with COVID-19 pandemic control measures, a pattern observed across the WHO European Region with 99.8% reduction in detections [100]. Influenza returned in 2021-2022 with a late, short epidemic (February-April 2022) mirroring European observations [109] (Table 3).

Table 3: Belgian Influenza and Respiratory Virus Circulation Patterns, 2020-2025 [108,110,111]

Season	Influenza Activity	Start – End dates (flu epidemic)	RSV Activity	SARS-CoV-2 Activity	Other Respiratory Viruses
2020-2021	Absent	–	Out-of-season surge	High (Alpha dominant)	Markedly reduced
2021-2022	Return of circulation; late and short epidemic	7/03 – 17/04	Irregularly long but with low intensity	Continued high circulation (Delta, Omicron)	Gradual return
2022-2023	Long epidemic with two peaks	12/12 – 26/03	Normal seasonal pattern	Consecutive waves, reduction in intensity	PIV and ADV
2023-2024	Return to pre-pandemic timing	11/12 – 25/02	Early onset	Continued low-level	M. pneumoniae wave
2024-2025	Pre-pandemic timing, but intense and long	9/12 – 9/03	Normal seasonal pattern; reduced incidence in 0-6 months	Low activity	Normal pre-pandemic patterns

Abbreviations: RSV: Respiratory Syncytial Virus; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

The 2024-2025 season was marked by a prolonged (13 weeks) and intense influenza epidemic (Table 3). Type A viruses predominated, with B appearing later. RSV and influenza co-circulation in older adult population created substantial healthcare burden, while younger

infants (0-5 months) showed reduced RSV impact during the first season of Nirsevimab availability [110].
Estimates derived from the national surveillance data collected by Sciensano are presented in Table 4.

Table 4: Belgian Influenza Disease Burden and Healthcare Impact

Parameter	Estimate	Details
Annual influenza consultations	300,000 (240,000 – 655,000)	~3% of population
Hospitalizations	10.000 (7,500-12,000)	~0.1% of population; 3% of influenza consultations
Complicated hospitalizations*	17%	Of hospitalized cases
ICU admission	12%	Of hospitalized cases
In-hospital mortality	6%	Of hospitalized cases
Deaths >65 years	>80%	Age distribution of deaths
Median hospital stay	5 days	From 2 days in 0-4 years to 7 days in 65+

** A hospitalization is considered complicated when it involves ARDS, admission to intensive care, treatment with ECMO, invasive ventilation, or death.*

Belgian Severe Acute Respiratory Infection (SARI) surveillance demonstrated that hospitalization incidence is highest among children 0-4 years and adults 65 years and older, though absolute hospitalization numbers remain greatest in the older adult population due to its size [109] (Figures 1 & 2). For example, during the 2024–2025 season, the annual incidence was 456 per 100,000 in children aged 0–4 years, compared with 254 per 100,000 in adults aged ≥65 years, which corresponds to a total number of influenza-related hospitalizations of 2,634 in children aged 0–4 years versus 6,228 in adults aged ≥65 years. Analysis of paediatric SARI admissions (2011-2020) showed complications in 23.4% of influenza cases, primarily pneumonia, with children having underlying risk factors (particularly asthma) at approximately two-fold higher risk (aRR 1.87; 95% CI 1.46-2.30) [83]. Adult SARI data confirm that comorbidity prevalence among influenza patients increases with age, with 94.6 % of older adults having at least one comorbidity [112].

Figure 1: Weekly incidence of hospital admissions for influenza, by age group, 2024-2025 (SARI surveillance)

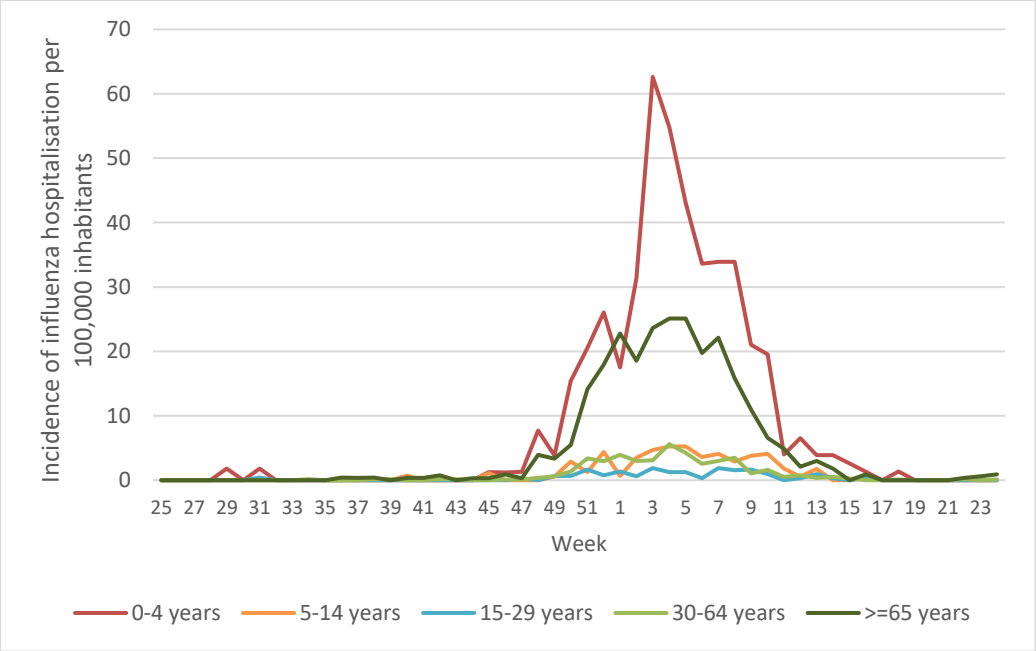
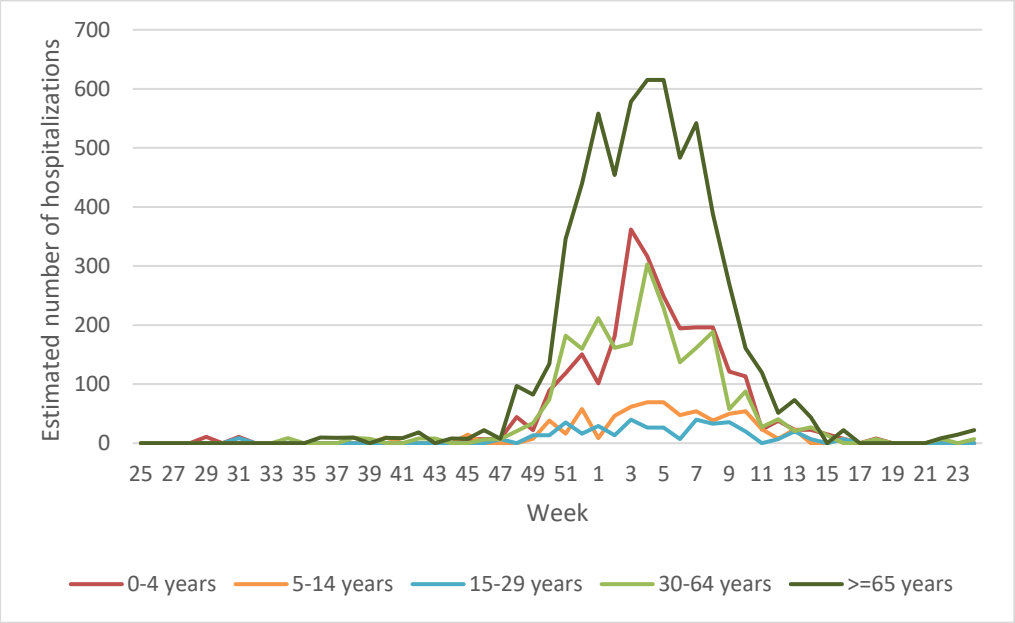


Figure 2: Estimated weekly number of hospital admissions for influenza, by age group, 2024-2025 (SARI surveillance)



4 Vaccine effectiveness

4.1 European Vaccine Effectiveness

Influenza vaccine effectiveness (VE) across Europe has varied considerably by season, reflecting viral circulation patterns, vaccine-virus antigenic match, and population characteristics (Table 5) but generally lies between 40-60% against hospitalization. Danish data for 2021-22 season indicated VE of 63% in vaccinated children aged 2-6 years, with lower effectiveness in older age groups [113]. The 2022-23 season interim estimates from six European studies encompassing 16 countries demonstrated VE against influenza A ranging from 27% to 44% across settings, with subtype-specific VE of 28-46% against A(H1N1)pdm09 and 2-44% against A(H3N2) reflecting variable antigenic match [114]. VE against influenza B/Victoria exceeded 50% in all studies, reaching 87-95% in children [114,115]. The 2023-24 interim Vaccine Effectiveness, Burden and Impact Studies (VEBIS) data from 10 European countries showed primary care VE of 53% against A(H1N1)pdm09 and 30% against A(H3N2), with hospital VE of 44% and 14% respectively [116]. The most recent 2024-25 interim data from eight European studies covering 17 countries indicates all-age influenza A VE of 32-53% in primary care and 33-56% in hospital settings, with A(H1N1)pdm09 predominating and VE against influenza B remaining high at ≥58% across settings [117]. Early surveillance from the 2025-26 season showed interim VE remaining within expected ranges: 72-75% against emergency department attendance and hospitalization in children and adolescents, and 32-39% in adults aged 18-64 years [118]. These findings support continued vaccination despite anticipated antigenic drift.

Table 5 European Influenza Vaccine Effectiveness by Season

Season	Dominant Strain	Overall VE Influenza A	Subtype-Specific VE	VE Influenza B	Key Reference
2020-21	*Minimal circulation*	*Not estimable*	—	—	[104]
2021-22	A(H3N2)	25-63% *(age-dependent)*	Children 2-6y: 63% Adults 7-44y: 25%	*Limited data*	[113]
2022-23	A(H3N2) + B	27-44% *(6 studies, 16 countries)*	A(H1N1)pdm09: 28-46% A(H3N2): 2-44%	>50% Children: 87-95%	[114,115]
2023-24	A(H1N1)pdm09	PC: 30-53% Hosp: 14-44%	A(H1N1)pdm09: PC 53% / Hosp 44%	*Limited circulation*	[116]

			A(H3N2): PC 30% / Hosp 14%		
2024-25	A(H1N1)pdm09	PC: 32-53% Hosp: 33-56% *(8 studies, 17 countries)*	A(H1N1)pdm09: 32-56% *A(H3N2): limited data*	≥58%	[117]
2024-25 *(≥65 years)*	Denmark	Standard IIV4: 33% Adjuvanted: 48%	Enhanced vs standard: +15 percentage points	—	[119]

Abbreviations: Hosp = hospital; IIV4 = quadrivalent influenza inactivated vaccine; PC = primary care; VE = vaccine effectiveness

4.2 Subtype-Specific and Age-Stratified Effectiveness

Influenza VE demonstrated substantial heterogeneity across viral subtypes and age groups (Table 5). A(H3N2) viruses consistently show lower VE compared to A(H1N1)pdm09 and B viruses, primarily due to egg adaptation mutations during vaccine production and rapid antigenic drift [117]. During the 2022-23 season, VE against A(H3N2) ranged from 2-44% in European studies, while VE against A(H1N1)pdm09 was higher at 28-46% [114]. The 2023-24 season showed continued subtype-specific variation, with A(H3N2) VE of 14-30% depending on setting [116]. The 2024-25 data indicate overall influenza A VE of 32-56%, with signals of lower effectiveness against A(H3N2) [117]. Influenza B/Victoria lineage demonstrated consistently high VE (≥58% in 2024-25, with estimates of 76-95% in previous seasons), reflecting greater antigenic stability [114,120].

Age-stratified analyses reveal higher VE in paediatric population (49-95% depending on subtype) compared to older adults (null to 45%) [114]. This age-related decline reflects immunosenescence, reducing both antibody responses and cell-mediated immunity. Danish 2024-25 season data comparing enhanced vaccines formulations demonstrated the clinical relevance: standard-dose Quadrivalent Inactivated Influenza Vaccine (IIV4) showed VE of 33% in adults aged 65 and older, while adjuvanted IIV4 achieved 48% [119]. The pooled FLUNITY-HD analysis of randomized trials demonstrated high-dose IIV relative VE of 31.9% against LCI hospitalization versus standard-dose vaccines [121]. More details are provided in Section 8.

4.3 Belgian-Specific Vaccine Effectiveness

Sciensano conducts annual vaccine effectiveness estimation through a test-negative design case-control study, utilizing data from both Influenza-Like Illness (ILI) surveillance in primary care and Severe Acute Respiratory Infections (SARI) surveillance in hospital settings. The methodology accounts for critical confounders including age, gender, sampling month, underlying medical conditions, and surveillance program type, providing robust estimates of real-world vaccine performance in the Belgian population. Historical Belgian data from the decade 2009-2019 showed that 49.6% (±8.5%) of all ILI samples tested positive for influenza, with significant seasonal variation reflecting epidemic intensity and dominant circulating strains [Ref]. Belgium participates in the European VEBIS network and contributes data to multicentre studies, ensuring that Belgian-specific estimates align with broader European methodological standards while capturing local epidemiological patterns.

Belgian surveillance data from 2014-2023 demonstrated the substantial burden of influenza despite moderate vaccination coverage as the minimal hospital data reported yearly 2500–10000 hospitals admissions for influenza [122,123]. Annual influenza cases in Belgium vary by season, ranging from approximately 280,000 to 470,000 laboratory-confirmed infections based on sentinel surveillance data [122]. Approximately 0.1-1 in 1,000 cases develops complications requiring hospitalization, with over 90% of influenza-related deaths occurring in individuals aged 65 years and older [122,124].

For the 2024–2025 season, the effectiveness of seasonal influenza vaccines in Belgium provided low to moderate protection, estimated at 44% (95% CI: -53, +79) for the prevention

of GP consultations and 17.4% (95% CI: -3.7, +34.2) for the prevention of hospitalization, across all age groups combined [125].

4.4 Modelled Vaccination Impact on Hospitalization Burden

Beyond individuals-level VE, population-level impact depends on coverage rates and implementation. The European Centre for Disease Prevention and Control (ECDC) published a multi-model analysis in November 2025 quantifying the averted hospitalization burden attributable to influenza and COVID-19 vaccination programs across the EU/EEA during the 2024/25 season [126]. This analysis, coordinated through the RespiCompass scenario modelling hub, aggregated projections from six independent transmission models to generate ensemble estimates under standardized scenarios varying coverage levels and transmission assumptions.

For adults aged 65 years and older, influenza vaccination prevented an estimated 26% to 41% of influenza-related hospitalization (IRH, a composite of influenza, pneumonia, respiratory, and cardiovascular causes) across EU/EEA countries during the 2024/25 epidemiological season, with the range reflecting difference in assumed vaccine coverage and viral transmissibility [126]. The models assumed 40% VE against symptomatic infection and 60% effectiveness against hospitalization, consistent with contemporary European estimates. Country-specific impact varied markedly with coverage: nations exceeding 68% coverage among older adults achieved 45% to 67% hospitalization reductions, while those below 32% coverage showed reductions of only 12% to 20% [126].

Belgium, with reported coverage of 56% among adults 65 years and older in the reference season, achieved estimated hospitalization reductions of 33% to 52% depending on the scenario (Table 6) [126]. Under optimistic coverage assumptions (15% above baseline), averted hospitalization reached 46-52%; under pessimistic assumptions (15% below baseline), this declined to 33-38%. These estimates position Belgium in the moderate-impact tier, substantially below high-coverage countries but above the lowest performers.

The analysis revealed a 48 to 70 percentage point gap in averted hospitalization between the highest-performing countries (Denmark, Portugal, Ireland with coverage exceeding 75%) and the lowest performers (Slovakia, Poland, Bulgaria with coverage below 10%) [126] (Table 6). This heterogeneity represents, in ECDC's assessment, "untapped potential to reduce hospital burden in the EU/EEA through established programs."

Table 6: Modelled Reductions in Influenza Hospitalizations, Adults ≥65 Years, EU/EEA 2024/25 [126]

Country	Coverage (%)	Scenario A (%)	Scenario B (%)	Scenario C (%)	Scenario D (%)
Denmark	78	71	73	58	51
Portugal	76	74	69	64	53
Ireland	75	68	75	50	44
Belgium	56	52	46	38	33
EU/EEA average	47	41	36	32	26
Germany	43	41	30	34	24
Slovakia	6	7	5	5	4

Scenario definitions:
Scenario A: Optimistic coverage (+15% above baseline), typical transmission potential
Scenario B: Optimistic coverage (+15% above baseline), higher transmission potential (+10%)
Scenario C: Pessimistic coverage (-15% below baseline), typical transmission potential
Scenario D: Pessimistic coverage (-15% below baseline), higher transmission potential (+10%)
All scenarios assume 40% vaccine effectiveness against symptomatic infection and 60% against hospitalization. Values represent mean percentage of hospitalization averted compared with counterfactual scenarios assuming no vaccination.
Note:
Coverage data in Table 6 derive from Eurostat figures for the 2021/22 season, used as baseline inputs for the ECDC multi-model scenario analysis [126]. These differ from the 2024/25 survey data presented in Table 7 [127]. Notable shifts between reference periods include Slovakia (6% → 18%) and Germany (43% → 38.2%), reflecting ongoing coverage dynamics across EU/EEA countries. For Belgium, which does not report coverage data to ECDC surveys, the 56% baseline used in modelling likely reflects historical Flemish coverage estimates; current national coverage is estimated at 40-50% based on regional variation. Direct comparison of Belgium's relative position across tables should account for these methodological differences.

5 Vaccination coverage

5.1 Vaccine coverage in Europe

Influenza vaccination coverage across the EU/EEA remains substantially below recommended targets. The median vaccination coverage rate (VCR) for adults aged 65 years and older during the 2024-25 season was 47%, showing minimal recovery from the 45.7% recorded in 2023-24 and representing a sustained decline from the 59% peak during the 2020-21 season [128]. This persistent shortfall is concerning as the 2009 Council of the EU established a target of 75% vaccination coverage for older adults [129]. The 2024-25 season data reveal substantial heterogeneity across member states, with coverage rates ranging from 5% to 76%; only Denmark (76%) exceeded the 75% threshold, while Ireland (74.7%), Portugal (70.5%), and Sweden (68%) approached but did not reach the target (Table 7) [128]. Coverage levels continue to remain suboptimal in most EU countries without overall progress since prior influenza season, suggesting that the elevated uptake observed during 2020-21 reflected transient pandemic-related effects rather than sustainable programmatic gains [128]. The post-pandemic period has witnessed declines in vaccination uptake across multiple target groups. Healthcare worker (HCW) vaccination rates decreased from a median of 52% during 2020-21 to 22.1% in 2023-24, with modest recovery to 32% in 2024-25 among nine reporting countries (range: 13.5-62.8%) [128]. Pregnancy vaccination coverage remains suboptimal, with eight countries reporting rates ranging from <2% to 60.9% during 2024-25 (median 22%) [128]. While vaccination programs have expanded considerably (all 30 EU/EEA countries now have recommendations for children and adolescents in 2024-25, compared with only five countries with age-based recommendations during 2017-18), vaccination coverage remains well below targets across key target groups [127,128]. This pattern indicates that expanding policy recommendations alone is insufficient without concurrent strategies to address implementation barriers and vaccine hesitancy.

Table 7: Influenza Vaccination Coverage Among Older Adults, Selected Countries

Country	Coverage (%)	Age Threshold	Season	Data Source
Denmark	76.0	≥65 years	2024/25	[128]
Ireland	74.7	≥65 years	2024/25	[128]
Spain	66.0	≥65 years	2024/25	[128]
Netherlands	55.2	≥60 years	2023/24	[130]
EU/EEA Median	47.0	≥65 years	2024/25	[128]
Germany	38.2	≥60 years	2023/24	[131]
Slovakia	18.0	≥65 years	2024/25	[128]
Belgium (nat. est.)	40-50	≥65 years	—	Sciensano

Belgium does not report VCR data to ECDC surveys. Historical estimates (2015-2019) suggest coverage of approximately 60% in Flanders; national coverage estimated at 40-50% based on regional variation.
Denmark figure excludes long-term care facility residents (85% coverage reported separately).
EU Council target: 75% coverage for adults ≥65 years.

Belgium's estimated 40-50% national coverage translates to approximately 33-52% of hospitalization averted, leaving substantial room for improvement through coverage intensification alone. Each 10-percentage point increase in coverage among older adults corresponds to approximately 8-12 percentage points of additional hospitalization prevented [126]. For Belgium, achieving the 75% EU target from current levels would require vaccinating an additional 250,000-300,000 older individuals annually but could prevent an estimated 2,000-4,000 additional hospitalization per season based on historical burden data [122,123]. The ECDC analysis supports prioritizing coverage optimization within existing target groups as a high-yield intervention before expanding recommendations to new population.

5.2 Coverage in High-Risk Population and health care workers

All EU/EEA countries maintain specific recommendations for high-risk population. Universal recommendations exist for adults with chronic medical conditions, including chronic pulmonary, cardiovascular, renal, hepatic, and metabolic diseases, haematological and

neurological conditions, as well as immunosuppression. All 30 EU/EEA countries recommended vaccination for pregnant women in the 2024/25 season; eight countries reported coverage rates ranging from 1% to 60.9%, with a median of 22% (up from 16% in 2023/24) [128]. HCW receive recommendations in 29 member states, with 23 countries offering universal HCW vaccination and six countries targeting specific staff in close patient contact; nine countries reported HCW coverage rates of 16.6% to 62.8%, with a median of 32% (up from 22.1% in 2023/24) [128]. Despite this improvement, coverage remains far below the 52% median observed during 2020/21, reflecting persistent post-pandemic decline in this target group.
Vaccination coverage data for patients with chronic medical conditions remains largely unavailable across most member states, with only two countries reporting data for the 2024/25 season.
All 30 EU/EEA countries now have recommendations for children and adolescents, with 19 countries implementing age-based recommendations and 11 countries targeting risk groups only during 2024/25. This represents a substantial increase from 18 countries in 2023/24, 14 countries in 2020/21, and only five in 2017/18. Greece expanded from risk-based to age-based recommendations (6 months to 5 years) in 2024/25, while Denmark shifted from universal to risk-group targeting [128]. Both LAIV and Trivalent Inactivated Influenza Vaccine (IIV3) are recommended, often in parallel, across member states. However, vaccination coverage among children remains suboptimal. Of the 13 countries reporting data for 2024/25, coverage ranged from 1% to 48.1%, with Spain (48.1%), Finland (32.9%), and Iceland (22.2%) achieving the highest rates. The median paediatric coverage was 6.9%, slightly lower than 7.2% in 2023/24 [128].

5.3 Vaccine coverage in Belgium

Historical data from Sciensano indicates that Belgian vaccination coverage has fluctuated considerably over time. Survey data from Sciensano showed that 45.2% of the participants ≥ 15 years received at least one influenza vaccination in their lifetime. Among the population at risk (defined as 65+ and people with comorbidities), the vaccination coverage remained stable between 2001 and 2018. From 2018 (56.8%) and 2023-2024 (64.2%) an increase is observed [122].
More recent data indicates that Belgium also experienced the characteristic post-pandemic surge and subsequent decline observed across Europe. The latest Sciensano health survey showed that vaccination coverage reached 50.6% (60.0% in Flanders, 41.8% in Brussels and 36.8% in Wallonia) among the population at risk (defined as 65+ and people with comorbidities) in 2023. This number was higher than in any previous survey.[127]. Regional variation exists within Belgium, with Flanders demonstrating better reporting and generally higher coverage rates compared to Wallonia and Brussels. The Belgian healthcare system's structure, with vaccination campaigns coordinated through mutualités/ziekenfondsen (health insurance funds) and GP, creates both opportunities for targeted outreach and challenges in achieving uniform national coverage. Current estimates indicate Belgium falls below the European median of 45.7%, with coverage rates among older adults substantially below the 75% target; only adults aged 85+ in Flanders achieved this threshold [127].

5.4 Belgian High-Risk Population Coverage

Age-stratified data from Belgian administrative databases reveal that older adults constitute the primary recipients of influenza vaccination. According to the latest Sciensano health survey, among the population at risk (defined as 65+ and people with comorbidities), vaccination coverage in Belgium increases systematically with age: 4.0% for ages 15-24, 20.6% for 25-34, 13.6% for 35-44, 28.7% for 45-54, 38.0% for 55-64, 58.4% for 65-74 and 71.7% for those aged 75 and older. Notably, only the 85+ age group reached the 75% target established by the 2009 EU Council Recommendations [129]. Data for Flanders are presented in Table 8.

Table 8: Adults ≥65 years (Flanders 2019, intermutualistisch agentschap / Sciensano EPS)

Age Group	Coverage (%)	Notes
65+ overall	61.0	
65-69 years	46.9	Youngest older adult subgroup
70-74 years	58.9	
75-79 years	67.3	
80-84 years	72.2	
85+ years	75.0	Only group reaching WHO/EU target
With comorbidities	70-80	Higher than general older adults
2020 COVID surge	>70	Temporary increase

6 Available vaccines and their composition (based on SPC)

Table 9 Available vaccines and their composition

Vaccine	Standard-Dose, adjuvanted or High-Dose	Age Indication	Composition*	Immunogenicity Highlights	Safety Profile	Key Clinical Points
Influvac	Standard-Dose, 15 µg, Egg-based	≥6 months	A(H1N1), A(H3N2), B/Austria (Victoria)	Adults 18–60y: A(H3N2) GMT 442.4; Older adults: lower GMTs, esp. for A(H1N1) & B	Mild/moderate reactions: injection site pain, fatigue, headache, myalgia; rare serious events include anaphylaxis, GBS	
Vaxigrip	Standard-Dose, 15 µg, Egg-based	≥6 months	A(H1N1), A(H3N2), B/Austria (Victoria)	Adults 18–60y: A(H1N1) GMT 685; Children 6–35mo: A(H3N2) GMT 1021, B GMT 835	Mild/moderate reactions: injection site pain, headache, myalgia; malaise; rare serious events include anaphylaxis, GBS	
Alpharix	Standard-Dose, 15 µg, Egg-based	≥6 months	A(H1N1), A(H3N2), B/Austria (Victoria)	Adults: A(H3N2) GMT 298.2; Children 6–35mo: A(H1N1) GMT 165.3	Mild/moderate reactions: injection site pain, fatigue, headache; myalgia; rare serious events include anaphylaxis, GBS	
Fluad	Adjuvanted (MF59C.1), Standard-Dose, Egg-based	≥50 years	Trivalent: 15 µg HA/strain (H1N1, A(H3N2), B); egg-based; MF59C.1 adjuvant	GMT ratios vs non-adjuvanted: A(H3N2): 1.61, A(H1N1): 1.40, B: 1.15 in ≥65y; enhanced response in at-risk population	Mild/moderate reactions: injection site pain, fatigue, headache; myalgia; rare serious events include anaphylaxis, GBS	Preferred for ≥65 years or comorbidities
Efluelda	High-Dose (60 µg HA/strain), Egg-based	≥60 years	Trivalent: 60 µg HA/strain (H1N1, A(H3N2), B); egg-based; no adjuvant	GMTs in 60–64y: A(H1N1): 471, A(H3N2): 303, B: 497; higher than ≥65y group; seroconversion	Mild/moderate reactions: injection site pain, myalgia, headache; malaise; rare serious events	Superior efficacy in ≥65 years or comorbidities

				rates (SCR) up to 89.4%	include anaphylaxis, GBS	
Flucelvax	Standard-Dose (15 µg HA/strain); no adjuvant; cell-based	≥6 months	Trivalent: A(H1N1)pdm09 (A/Wisconsin/67/2022-like), A(H3N2) (A/District of Columbia/27/2023-like), B/Austria/1359417/2021 (Victoria lineage); MDCK cell culture; egg-free	Adults ≥18y: A(H1N1) GMT 303, A(H3N2) GMT 372, B GMT 133–177; SCR 36–49%. Children 4–17y: A(H1N1) GMT 1090, A(H3N2) GMT 738, B GMT 155–185; SCR 47–73%	Mild/moderate reactions: injection site pain, fatigue, headache, erythema, myalgia; rare serious events include anaphylaxis, GBS	Egg-free alternative for egg-allergic patients; safe in pregnancy (any trimester); preferred when egg allergy precludes other options

**Note: conditional to WHO recommendation (https://www.who.int/teams/global-influenza-programme/vaccines/who-recommendations*
Abbreviations: HA: Hemagglutinin; GBS: Guillain-Barré Syndrome; GMT: Geometric Mean Titre; MDCK: Madin-Darby Canine Kidney; SCR: Seroconversion rate

7 Safety Profile of Standard-Dose Inactivated Influenza Vaccine

7.1 Introduction

Multiple clinical and post-marketing surveillance studies have shown a favourable safety profile for inactivated influenza vaccines (IIV) [132]. European and other regulatory systems continuously monitor the safety of influenza vaccines to ensure any possible risks are detected and managed as early as possible. EMA (European Medicines Agency) continuously checks new information on the safety of all vaccines available in Europe from many data sources (EMA). These include:

- Reports of suspected side effects from patients and healthcare professionals
- Post-authorisation studies
- Medical literature
- Non-clinical studies
- Real-world evidence

The vast majority of known side effects following IIV are mild and short-lived. Serious side effects may occur, but they are very rare. The full list of known side effects can be found in the product information for each influenza vaccine, available in all languages: https://medicinesdatabase.be/human-use/medicines

Reporting of adverse events

Patients and healthcare providers are encouraged to declare possible adverse effects following vaccination to the health authority in charge of post-marketing surveillance. Reporting of adverse reactions can be done directly to:
www.notifieruneffetindesirable.be or **www.eenbijwerkingmelden.be** .

7.2 Reactogenicity

Clinical trial data and post-marketing surveillance establish consistent reactogenicity patterns across populations. IIV are generally well-tolerated within their indicated age ranges, including older adults, pregnant women, and individuals with underlying conditions.

The most frequent adverse reactions observed with influenza vaccines in adults and paediatrics are (see summary of product characteristics (SPC) for product specific information):

- Injection-site adverse reactions (all ages): pain, swelling, redness, erythema, induration, ecchymosis (bruising).
- General symptoms (all ages): fatigue, headache, malaise, shivering, myalgia, arthralgia and fever.
- Paediatric-specific symptoms (particularly <2 years): Irritability/fussiness, abnormal crying, drowsiness, decreased appetite, vomiting.

These reactions are typically mild to moderate and usually resolve without treatment [133].
Meta-analysis comparing IIV4 to trivalent vaccines in children aged 6-35 months found slightly higher injection site reactions with IIV4 (RR 1.12, 95% CI: 1.01-1.25) but no significant difference in solicited systemic reactions, unsolicited adverse events (AE), or serious adverse events (SAE) [134]. Older vaccinees often show lower reactogenicity than younger adults [133].

7.3 Syncope

Anxiety-related reactions (e.g., syncope, hyperventilation, dizziness) may occur before or after vaccination, particularly in adolescents. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia, and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from fainting, such as ensuring the patient is seated and observed after vaccination.

7.4 Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) has been reported very rarely after immunisation with influenza vaccine. Multiple studies over a number of influenza seasons have shown variable incidence; some have demonstrated a vaccine-attributable risk of 1–2 cases of GBS per million persons vaccinated. The data also show that a person is more likely to get GBS after influenza disease than after getting an influenza vaccine [132].
The 1976 swine flu vaccine demonstrated an elevated Guillain-Barré syndrome (GBS) risk of approximately 1 per 100,000 vaccinations, an anomaly attributed to that specific vaccine formulations [135]. Current seasonal vaccines carry a substantially lower risk. A meta-analysis documented a pooled GBS incidence of 2.77 per million persons (95% CI: 2.47-3.07) within 6 weeks of influenza vaccination [136]. A separate meta-analysis of 22 studies found a pooled effect size of 1.15 (95% CI: 0.97-1.35), indicating no statistically significant increased risk [137]. Large European cohort studies provide reassuring data: a French nationwide study (2010-2014) found no significant association between seasonal influenza vaccination and GBS (IRR 1.02, 95% CI: 0.83-1.25) [138], while a Danish 15-year nationwide study (2002-2016) found that only 1.5% of GBS cases were associated with influenza vaccination [139]. GBS risk from influenza infection exceeds vaccination risk by approximately 17-fold; Canadian data show 17 GBS admissions per million influenza-coded encounters versus 1 per million vaccinations [140]. GBS remains a precaution (not contraindication) for vaccination only in individuals with GBS history within 6 weeks of a prior influenza vaccine if no other cause was found for GBS.

7.5 Hypersensitivity and Anaphylaxis

Hypersensitivity reactions (such as urticaria, pruritus, or rash) occur rarely, while anaphylaxis has been reported only as a very rare event in post-marketing experience. Vaccine Safety Datalink (VSD) analysis documented an anaphylaxis rate of 1.35 per million doses (95% CI: 0.65–2.47) for 7 million doses given for inactivated trivalent influenza vaccine, comparable to the all-vaccine rate of 1.31 per million [141]. Contrary to earlier assumptions, Vaccine Adverse Event Reporting System (VAERS) surveillance (1990–2016) found that 41% of anaphylaxis cases after vaccination occurred in persons with no documented history of hypersensitivity [142]. A recent European systematic review and meta-analysis confirmed anaphylaxis following influenza vaccination remains rare in adults [143].
As of the 2023–2024 season, Centers for Disease Control and Prevention (CDC) / Advisory Committee on Immunization Practices eliminated recommendations for additional safety measures when vaccinating egg-allergic individuals, regardless of reaction severity [144]. This shift reflects accumulated safety evidence demonstrating that influenza vaccines with low ovalbumin content (< 0.12 µg/mL, equivalent to < 0.06 µg per 0.5 mL dose) can be administered safely to individuals with egg allergy [145].
The Superior Health Council (SHC) recommends a risk-stratified approach aligned with current UK guidance [146]:

- **Most egg-allergic individuals**: may receive any age-appropriate influenza vaccine in any vaccination setting where anaphylaxis management is available. Egg-free vaccines should be considered when readily available.

- **Individuals with history of severe anaphylaxis to egg**: should receive egg-free vaccine. If unavailable, vaccination should occur in a hospital setting with specialist assessment. A severe anaphylaxis is defined as a reaction which are fatal, life threatening, cause hospitalisation, result in persistent or significant disability or incapacity, require intervention to prevent permanent damage (IGGI (Infectiologiegids/Guide d'Infectiologie)).

Standard post-vaccination observation (15 minutes) and anaphylaxis management capacity apply to all vaccination settings.

7.6 Pregnancy

Regarding pregnancy, systematic reviews confirm that standard-dose inactivated influenza vaccination is safe and not associated with adverse outcomes. A SR (2023) analysing studies that controlled for immortal time bias found no significant association with preterm birth (aHR 1.08, 95% CI: 0.89-1.30) [147]. Meta-analyses from this review demonstrated no increased risk for stillbirth, small-for-gestational-age birth (aRR 0.99, 95% CI: 0.95-1.04), or congenital anomalies, though all evidence was graded as very low certainty [147]. A US claims-based cohort study of 117,626 pregnancies (2009-2018) found no increased foetal loss risk; miscarriage risk was actually 39% lower among vaccinated women (aHR 0.61, 95% CI: 0.50-0.74) [148]. The Canadian National Advisory Committee on Immunization (2024) confirms these safety findings, strongly recommending that inactivated influenza vaccination during any trimester is not associated with adverse pregnancy or neonatal outcomes [149]. An overview of systematic reviews from the Norwegian Institute of Public Health (2021) concluded that maternal influenza vaccination with the H1N1pdm09 vaccine in any trimester was not associated with preterm birth, small-for-gestational-age, congenital malformations, or foetal death [150].

7.7 Febrile seizures

Standard-dose IIV alone does not independently increase febrile seizure risk in young children, with VSD data showing no significant association (IRR 0.46; 95% CI: 0.21–1.02) [151]. Coadministration with Pneumococcal Conjugate Vaccine (PCV) in children 6–23 months increased risk (IRR 3.50; 95% CI: 1.13–10.85), as did coadministration with Diphtheria, Tetanus acellular Pertussis (DTaP; IRR 3.50; 95% CI: 1.52–8.07) [151]. The maximum estimated absolute excess risk from concomitant IIV, PCV, and DTaP administration reaches 30 febrile seizures per 100,000 vaccinees compared with separate-day administration. Analysis from claims databases (2023–2024) confirms minimal independent febrile seizure risk with influenza vaccination [152].

7.8 Cardiovascular risk

Food and Drug Administration (FDA) post-marketing surveillance of the 2023-2024 season analysed 20.3 million Medicare beneficiaries ≥65 years using self-controlled case series methodology [153]. No statistically significant elevation was found for anaphylaxis, encephalitis/ADEM, GBS, transverse myelitis, or haemorrhagic stroke. A small but statistically significant signal for non-haemorrhagic stroke / Transient Ischemic Attack emerged in the 22–42-day risk window among high-dose vaccines recipients (IRR 1.07–1.10) and Medicare Advantage beneficiaries receiving any vaccine (IRR 1.11); FDA concluded that established benefits likely outweigh these risks [153]. European data provide contrasting evidence: the UK Clinical Practice Research Datalink shows 28% reduced acute cardiovascular event risk 15-28 days post-vaccination [154].

7.9 Contraindications

Hypersensitivity to any of the active substances, excipients or trace components such as ovalbumin, chicken proteins, formaldehyde, or antibiotics (e.g., gentamicin or neomycin), which may be present due to egg-based production, is a contraindication to the influenza vaccine. As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of rare anaphylactic reactions following administration.

7.10 Position of regulatory bodies

The Vaccine Safety Datalink (VSD) conducts weekly near-real-time surveillance using Maximum Sequential Probability Ratio Testing methodology across approximately 10 million members. Routine safety monitoring during 2023-2024 has not identified concerning safety signals, though occasional statistical signals (e.g., stroke outcomes in high-dose recipients) have been contextualized within the favourable benefit-risk profile [153]. Regulatory bodies maintain consistent positions on influenza vaccine safety. The ECDC states that risks of AE following influenza vaccination are far less common than complications related to influenza itself, and that benefits of vaccination substantially outweigh the risks [155]. The CDC affirms that hundreds of millions of Americans have safely received influenza vaccine over more than 50 years, and the body of scientific evidence strongly supports their safety [156].
Inactivated influenza vaccines have been manufactured and used since 1945 with a well-documented safety profile [132,157,158].The WHO 2022 position paper confirms that these vaccines remain the most widely used globally [132]. As inactivated vaccines contain non-infectious viral components, they cannot cause influenza infection.

The table 10 presents AE following SD-IIV vaccination.

Table 10: Adverse Events Following Standard Dose Inactivated Influenza Vaccination (see the product information for product specific information)

Category	AE	Incidence	Evidence Quality / Notes
Very common (≥10%)	Injection site pain	20-25%	High. Mild intensity, resolves <48h. [133]
Common (1-10%)	Headache	7-12%	High. Self-limiting, 1-2 days. [133,159]
Common (1-10%)	Myalgia	6-15%	High. More common in children/naive. [133]
Common (1-10%)	Fatigue/malaise	6-18%	High. Short duration (1-2 days). [133,159]
Common (1-10%)	Injection site swelling	4-8%	High. Rarely interferes with activities. [133]
Common (1-10%)	Injection site erythema	5-8%	High. Typically, <5 cm diameter. [133]
Uncommon (0.1-1%)	Fever (≥38°C)	1-2% adults	High. Higher in children (up to 10%). [133]
Very rare (<0.01%)	Guillain-Barré syndrome	0-1 per million*	High. MA: OR 1.15 (95% CI 0.97-1.35). [137]
Very rare (<0.01%)	Anaphylaxis	1.31-1.35 per million	High. VSD data: 1.35/million doses IIV3. Brighton criteria. [141]
Very rare (<0.01%)	Febrile seizures (children)	1.1-12.5 per 100,000**	Moderate. Age-dependent; higher with PCV13 co-admin. [160]

**Additional risk above background (10-20/million annually). 1976 swine flu vaccine: ~10/million; subsequent seasonal vaccines show no significant increase.*
***Risk varies by age: 12.5/100,000 at 16 months vs 1.1/100,000 at 59 months (IIV alone without PCV13 co-administration).*
Abbreviations: CI: Confidence Interval MA: Meta-Analysis; OR: Odds-Ratio; VSD: Vaccine Safety Datalink

8 Enhanced Vaccines: High-dose and Adjuvanted.

8.1 Introduction

Immunosenescence reduces influenza VE in older adults. Two strategies address this limitation: high-dose inactivated influenza vaccine (HD-IIV, containing 60µg HA per strain) increases antigen content fourfold, while MF59-adjuvanted inactivated influenza vaccine (aIIV) enhances immune responses through adjuvant-mediated stimulation of antigen-presenting cells.

High-dose vaccine. Two European randomized controlled trials published in 2025 (DANFLU-2 in Denmark [161] and GALFLU in Spain [162]), together with their prespecified pooled analysis FLUNITY-HD encompassing 466,320 participants [121], provide evidence for preferential use of HD-IIV in adults aged 65 years and older. The pooled analysis demonstrated relative VE of 8.8% (95% CI 1.7–15.5) against hospitalization for influenza or pneumonia, with more pronounced benefits for laboratory-confirmed influenza hospitalization (rVE 31.9%, 95% CI 19.7–42.2) [115]. Meta-analyses of prior observational studies indicated relative VE improvements of 15–25% [163].
Adjuvanted vaccine. Evidence for aIIV derives primarily from observational studies and meta-analyses. Pooled analysis of observational data demonstrated 51% absolute VE against hospitalization for pneumonia/influenza among community-dwelling seniors, with 25% relative VE compared to standard-dose vaccines [164]. The United Kingdom has used aIIV preferentially for adults aged 65 years and older since 2018, with programmatic feasibility confirmed at coverage rates of 70–75%. Head-to-head comparisons between HD-IIV and aIIV, including US Medicare data analyses and network meta-analyses [165], show comparable effectiveness with overlapping confidence intervals; no consistent pattern favours either formulation.

8.2 High-dose vaccines

8.2.1 Summary

High-dose inactivated influenza vaccine (HD-IIV, containing 60 µg hemagglutinin per strain vs 15 µg in standard-dose) provides superior protection against IRH in adults aged 65 years and older. Two large European pragmatic randomised controlled trials (RCT) (DANFLU-2 in Denmark and GALFLU in Spain) with a prespecified pooled analysis (FLUNITY-HD) enrolling 466,320 participants, combined with systematic reviews encompassing a total of >45 million individuals, establish the evidence base for preferential recommendations [121,162,163,166]. The pooled RCT analysis demonstrated relative vaccine effectiveness (rVE) of 31.9% (95% CI 19.7–42.2) against LCI hospitalization and 6.3% (95% CI 2.5–10.0) against cardiorespiratory hospitalization [121]. Observational meta-analyses report higher cardiorespiratory relative vaccine effectiveness (rVE) of 17.9% (95% CI 15.0–20.8), likely reflecting residual confounding [163]. Meta-analytic data confirm consistent protection across age strata including those ≥85 years, with benefits observed regardless of circulating strain or antigenic match [163,167].

8.2.2 Randomized Controlled Trial Evidence

<u>FDA Pivotal Trial: [168]</u>

DiazGranados and colleagues conducted a multicentre, double-blind RCT randomizing 31,989 adults aged 65 years or older to High-Dose Trivalent Inactivated Influenza Vaccine (HD-IIV3) or Standard-Dose Trivalent Inactivated Influenza Vaccine (SD-IIV3) across two seasons (2011–2013). The FDA approved the high-dose vaccines based on this trial meeting the pre-specified superiority threshold. The primary endpoint of LCI with influenza-like illness showed rVE of 24.2% (95% CI 9.7–36.5). SAE were lower in the high-dose group compared with standard dose (8.3% vs 9.0%; RR 0.92, 95% CI 0.85–0.99).

<u>Secondary Analysis: [169]</u>

A post-hoc analysis examined SAE possibly related to influenza from the pivotal trial. HD-IIV3 reduced SAEs possibly influenza-related by 17.7% (95% CI 6.6–27.4) and severe pneumonia by 39.8% (95% CI 19.3–55.1) compared with SD-IIV3. The reduction in all-cause hospitalization reached borderline significance at 6.9% (95% CI 0.5–12.8).

DANFLU-2 Trial [166]

Pragmatic, open-label, individually randomized trial across three influenza seasons (2022–2025). Enrolled 332,438 community-dwelling adults ≥65 years randomized 1:1 to High-Dose Quadrivalent Inactivated Influenza Vaccine (HD-IIV4; Efluelda, 60 µg HA/strain) or Standard-Dose Quadrivalent Inactivated Influenza Vaccine (SD-IIV4, VaxigripTetra, 15 µg HA/strain). Mean age 73.7±5.8 years; 48.6% women. Follow-up extended from 14 days post-vaccination through May 31 annually. Primary endpoint (influenza or pneumonia hospitalization): rVE 5.9% (95.2% CI −2.1 to 13.4, p=0.14). The non-significant result was inconsistent with the rVE of 35.9% observed for LCI hospitalization. rVE for secondary endpoints are presented in Table 11.

Table 11. DANFLU-2 Secondary Endpoints

Endpoint	rVE (95.2% CI)
influenza hospitalization	43.6% (27.5–56.3)
Pneumonia hospitalization	0.5% (−8.6 to 8.8)
Cardiorespiratory hospitalization	5.7% (1.4–9.9)
All-cause hospitalization	2.1% (−0.1 to 4.3)
ACM	−2.5% (−11.6 to 5.9)

Note: CIs are 95.2% due to alpha spending.
Abbreviations: ACM: all-cause mortality; rVE: relative Vaccine Effectiveness

GALFLU Trial [162]

Pragmatic, registry-based, individually randomized trial conducted across two influenza seasons (2023–2025) in Galicia, Spain. Enrolled 103,169 community-dwelling adults aged 65–79 years with mean age 72.3±4.3 years. By excluding those aged ≥80 years and nursing home residents, the study selected a population with lower comorbidity burden than DANFLU-2 (chronic CVD 12.5% vs 27.5%). Primary endpoint of influenza or pneumonia hospitalization showed rVE of 23.7% (95% CI 6.6–37.7), and rVE of 31.8% (95% CI 5.0–51.3) against influenza hospitalization alone. The intention-to-treat analysis showed rVEs of 8.4% (95% CI 0.1–16.1) for cardiorespiratory hospitalization and 2.5% (95% CI −1.7 to 6.5) for all-cause hospitalization.

FLUNITY-HD Pooled Analysis [121]

Prespecified individuals-level pooled analysis of DANFLU-2 and GALFLU: 466,320 participants (233,311 HD-IIV; 233,009 SD-IIV). Mean age 73.3 years; 48% female; 48.9% with ≥1 chronic condition. Data are presented in Table 12.

Table 12. FLUNITY-HD Pooled Analysis Results

Endpoint	rVE (95% CI)	P-Value
Influenza/pneumonia hospitalization (primary)	8.8% (1.7–15.5)	0.008
LCI hospitalization	31.9% (19.7–42.2)	<0.0001
ICD-10 influenza hospitalization	39.6% (26.4–50.5)	<0.0001
Pneumonia hospitalization	2.3% (−6.0 to 10.0)	NS
Cardiorespiratory hospitalization	6.3% (2.5–10.0)	0.0006
All-cause hospitalization	2.2% (0.3–4.1)	0.012
ACM	1.2% (−6.3 to 8.3)	NS

Abbreviations: ACM: all-cause mortality; LCI: Laboratory-Confirmed Influenza

Explaining Heterogeneity Between DANFLU-2 and GALFLU

The discrepancy in primary endpoint results (DANFLU-2: rVE 5.9% NS; GALFLU: rVE 23.7% significant) may reflect endpoint composition and population difference. In DANFLU-2, pneumonia hospitalizations were significantly more frequent than influenza hospitalizations (0.63% vs 0.11% in standard dose group), potentially diluting the influenza-specific effect. In GALFLU, the incidences were more comparable (0.21% vs 0.14%). Additionally, GALFLU excluded those ≥80 years and nursing home residents. Lastly there was seasonal variation: higher baseline influenza activity in Galicia created greater opportunity for vaccine-preventable events.

8.2.3 Systematic reviews and meta-analyses

Table 13. Systematic reviews and meta-analyses of HD-IIV vs SD-IIV [163,167,170]

Characteristic	Lee et al. (2021)	Lee et al. (2023)	Skaarup et al. (2024)
Study Design	SR/MA	SR/MA (update)	MA of RCTs only
Data Sources	RCTs + Observational	RCTs + Observational	RCTs exclusively
Seasons Analysed	10 (2009/10–2018/19)	12 (2009/10–2021/22)	Variable by trial
Population	>34 million (>22 million HD-IIV)	>45 million	105,685
Outcomes: rVE % (95% CI)			
Influenza-like illness	15.9 (4.1–26.3)	14.3 (4.2–23.3)	NR
influenza hospitalization	11.7 (7.0–16.1)	11.2 (7.4–14.8)	NR
Pneumonia hospitalization	27.3 (15.3–37.6)	27.8 (12.5–40.5)	NR
Pneumonia/influenza hospitalization	13.4 (7.3–19.2)	14.4 (6.8–20.6)	23.5 (12.3–33.2)
Respiratory hospitalization	NR	14.7 (8.5–20.4)	NR
Cardiovascular hospitalization	NR	12.8 (10.2–15.3)	NR
Cardiorespiratory hospitalization	17.9 (15.0–20.8)	16.7 (13.8–19.5)	NR
All-cause hospitalization	8.4 (5.7–11.0)	8.2 (5.5–10.8)	7.3 (4.5–10.0)
Pneumonia/influenza mortality	39.9 (18.6–55.6)	NR	NR
Cardiorespiratory mortality	27.7 (13.2–32.0)*	NR	NR
ACM	2.5 (−5.2 to 9.5) NS	NR	1.6 (−2.0 to 5.0) NS
Age Subgroup rVE: Influenza Hospitalization			
65–74 years	NR	8.7 (1.5–15.2)	NR
≥75 years	NR	12.2 (7.3–16.9)	NR
≥85 years	NR	16.0 (9.8–21.8)	NR

**Lee 2021 abstract reports cardiorespiratory mortality 95% CI as 13.2–32.0%, which appears to be a typographical error (should likely be 13.2–40.0% based on point estimate of 27.7%).*

Abbreviations: ACM: all-cause mortality; HD-IIV: High-Dose Inactivated Influenza Vaccine; MA: Meta-Analysis; NR: Not Reported; NS: Not Significant; RCT: Randomized Controlled Trial; rVE: relative Vaccine Effectiveness; SD-IIV: Standard-Dose Inactivated Influenza Vaccine

Three systematic reviews provide complementary evidence for HD-IIV superiority over standard-dose inactivated influenza vaccine (SD-IIV) in older adults. Lee et al. (2021) [163]analysed 10 consecutive influenza seasons encompassing >34 million individuals, demonstrating consistent benefits regardless of circulating strain (A(H3N2) vs A(H1N1)) or antigenic match. Lee et al. (2023) [167] extended the analysis through 2021–2022 with >45 million individuals and added age-stratified estimates showing increasing rVE with advancing age (8.7% at 65–74 years to 16.0% at ≥85 years against influenza hospitalization). Skaarup et al. (2024) [170] restricted analysis to five RCTs (n=105,685), providing higher-quality causal evidence: HD-IIV reduced pneumonia/influenza hospitalization by 23.5% and all-cause hospitalization by 7.3%, though no significant mortality reduction was observed.

8.2.4 Observational Evidence

US Medicare Studies The FDA/Medicare collaboration has conducted serial retrospective cohort analyses. The initial single-season analysis (2012-2013) of >2.5 million community pharmacy recipients demonstrated rVE of 22.6% (95% CI 15.7-29.0) for influenza-related office visits and 20.6% (95% CI 14.9-24.8) for IRH [171]. A subsequent 6-season analysis (2012-2018) encompassing >19 million beneficiaries demonstrated that rVE increases with age, with consistent HD-IIV superiority in those ≥85 years across all seasons [172].

Veterans Health Administration Studies Young-Xu et al. conducted complementary analyses. A single-season (2015-2016) retrospective cohort using difference-in-difference design demonstrated rVE of 25% (95% CI 2-43) against influenza/pneumonia hospitalization [173,174]. A 5-season instrumental variable analysis (~1.7 million Veterans, 2010-2015) addressing unmeasured confounding showed rVE of 10% (95% CI 8-12) for all-cause hospitalization, 18% (95% CI 15-21) for cardiorespiratory hospitalization, and 14% (95% CI 6-22) for influenza/pneumonia hospitalization [174].

European Observational Evidence Italian test-negative studies in Liguria (2022/2023-2024/2025 seasons) address a data gap for laboratory-confirmed outcomes in European population. Among adults ≥80 years, for whom HD-IIV was preferentially recommended, rVE reached 54% (95% CI 10-76%) against LCI [175].

Nordic Brand-Specific Effectiveness Study The Faksova et al. (2025) target trial emulation study provides complementary data on absolute vaccine effectiveness (aVE) by brand. This EMA-funded analysis linked national health registries in Denmark, Finland, and Sweden during the 2024/2025 season, matching 1,164,686 vaccinated individuals aged ≥65 years to unvaccinated controls [176]. Against LCI hospitalization at 18 weeks post-vaccination, brand-specific VE was 63.4% (95% CI 38.1–88.7) for high-dose Efluelda Tetra, 48.2% (40.8–55.6) for adjuvanted Fluad Tetra, 43.6% (23.7–63.6) for standard-dose Vaxigrip Tetra, and 30.6% (−7.8 to 69.1) for standard-dose Influvac Tetra. The study documented VE waning of −6.5 percentage points (−10.5 to −2.5) per three weeks, supporting timely vaccination before seasonal circulation peaks.

RCT vs Observational Discrepancies

Observational studies consistently report larger rVE estimates than RCTs. Cardiorespiratory hospitalization shows rVE of 17-18% in observational studies versus 5.7-6.3% in European pragmatic RCTs (FLUNITY-HD pooled analysis). This pattern suggests residual confounding despite propensity scoring, instrumental variable methods, and matching. Authors consistently acknowledge that unmeasured confounders related to health-seeking behaviour and physician prescribing preferences may bias results. RCT estimates, while smaller, should be considered more reliable indicators of true vaccine effectiveness.

8.2.5 Effectiveness by Subgroup

Age-Dependent Benefit

Relative effectiveness has historically been shown to increase with advancing age. A 6-season Medicare analysis demonstrated consistent HD-IIV superiority in those ≥85 years across all seasons studied, with the trend toward increasing rVE with age reaching statistical significance [172]. The updated meta-analysis confirmed this pattern across age strata (65+, 75+, ≥85 years), with subgroup consistency regardless of study design [167]. Italian observational data found rVE of 54% (95% CI 10-76%) against LCI in adults ≥80 years [175]. There is biological plausibility: immunosenescence is more pronounced in older adults, making the quadrupled antigen content (60 µg vs 15 µg per strain) more impactful for achieving protective immune responses.
However, recent data from the large-scale, pragmatic randomized DANFLU-2 trial suggests that clinical risk profiles may be as significant as chronological age in determining benefit. In subgroup analyses of the trial, rVE against clinical endpoints was generally consistent across age stratifications (e.g., participants above vs. below the median age of 74 years) [121]. This indicates that while HD-IIV is effective in the oldest adults, high-risk underlying conditions may drive heterogeneity in vaccine response more than age alone.

By Influenza Strain and Antigenic Match

The Lee et al. 2021 meta-analysis found that HD-IIV3 consistently demonstrated superior effectiveness compared to SD-IIV regardless of predominantly circulating strain (A(H3N2) vs A(H1N1)) and vaccine-strain antigenic match or mismatch, though some subgroup analyses did not reach statistical significance [163]. The 2023 update confirmed these findings through the 2021–2022 season, concluding that HD-IIV provided better protection across age ranges and seasonal characteristics [167].

High-Risk Population

In the FLUNITY-HD pooled analysis, 48.9% of the 466,320 participants had at least one chronic condition [121]. The FLUNITY-HD cardiovascular secondary analysis demonstrated that rVE against cardiorespiratory hospitalization (6.3%, 95% CI 2.5-10.0%) did not differ by baseline CVD history, indicating consistent benefit across risk strata [177]. HF hospitalization showed a 21.3% reduction (95% CI 7.6-33.0%) with HD-IIV [177].

Chronic Kidney Disease

In the DANFLU-2 trial, chronic kidney disease (CKD) was identified in 14.1% (46,788) of 332,438 participants, representing the largest CKD population ever studied in an individually randomized vaccine trial [178]. Individuals with CKD had a higher burden of comorbidities compared to those without, including higher prevalence of diabetes (34.7% vs 9.7%) and CVD (47.6% vs 24.1%). The effectiveness of the high-dose inactivated influenza vaccine (HD-IIV) compared to SD-IIV was modified by CKD status. While the overall rVE for hospitalization for influenza or pneumonia was 0.6% in the non-CKD group, it rose to 16.9% in the CKD group (P_interaction = 0.046). For the specific outcome of influenza hospitalization, the benefit was substantially greater in participants with CKD (rVE 68.6%) compared to those without (rVE 30.6%), resulting in a number needed to treat (NNT) of 561 in the CKD population versus 3,953 in the non-CKD population.

Atherosclerotic CVD

A prespecified analysis of the DANFLU-2 trial characterized the burden of atherosclerotic CVD (ASCVD), present in 14.1% (46,825) of participants [179]. Among those with ASCVD, 9.4% had IHD, 4.9% had cerebrovascular disease, and 0.9% had peripheral artery disease. These individuals experienced higher incidence rates of all primary and secondary outcomes compared to those without ASCVD. Unlike the CKD subgroup, the relative effectiveness of HD-IIV versus SD-IIV was consistent across participants with and without ASCVD for respiratory and cardiovascular outcomes (P_interaction ≥ 0.05). The rVE for major adverse cardiovascular events (MACE) was 0.30% in participants with ASCVD and 4.29% in those without.

Atrial Fibrillation

Atrial fibrillation (AF) was identified in 10.3% (34,085) of the DANFLU-2 study population [180]. These patients were older (mean age 76.1 years) and had a higher prevalence of comorbidities compared to non-AF participants. Individuals with AF had higher absolute risks for all hospitalization endpoints, including influenza, pneumonia, and cardiovascular events. The relative effectiveness of HD-IIV versus SD-IIV was consistent regardless of AF history; however, the higher absolute risk in the AF population translated to greater absolute benefit. The NNT to prevent one cardiorespiratory hospitalization was 243 in the AF group compared to 933 in the non-AF group.

Acute Cardiac Dysfunction during Influenza Infection

The prospective FluHeart study provided data on cardiac function during acute influenza infection [181]. In hospitalized patients with LCI, 75% exhibited left ventricular dysfunction and 20% exhibited right ventricular dysfunction. Biochemical evidence of cardiac stress was prevalent, with 62% of influenza patients showing elevated N-terminal pro-B-type Natriuretic Peptide levels ≥300 pg/mL, and 19% showing myocardial injury via elevated high-sensitivity troponin I levels. Compared to matched controls, influenza patients had significantly worse left ventricular diastolic function and right ventricular tricuspid annular plane systolic excursion.

Myocarditis and Pericarditis

In an analysis addressing safety concerns regarding inflammatory heart conditions, the incidence of myocarditis or pericarditis was extremely low in the older adult population of the

DANFLU-2 trial [182]. Among 332,438 participants, the risk was significantly lower in the HD-IIV group compared to the SD-IIV group (19 vs 35 events), translating to a rVE of 45.71% against these conditions. High-dose vaccination does not increase the risk of myocarditis or pericarditis and may offer a protective benefit, potentially by reducing influenza infection, which is a known trigger for these cardiac complications.

8.2.6 Safety Profile

Reactogenicity

HD-IIV produces modestly higher rates of local and systemic reactions compared with SD-IIV. The DiazGranados pivotal trial demonstrated injection site pain in approximately 36% versus 24% of recipients, with myalgia (21% vs 18%) and malaise (18% vs 15%) also slightly elevated [168]. These reactions are self-limiting, resolving within 72 hours, and predominantly mild in intensity.

Serious adverse events

SAE incidence was similar or lower with HD-IIV across all studies. The pivotal trial showed SAEs in 8.3% of HD-IIV versus 9.0% of SD-IIV recipients (RR 0.92, 95% CI 0.85-0.99) [168]. The FLUNITY-HD European pooled analysis confirmed safety balance: 16,032 SAEs in the HD-IIV group versus 15,857 in the SD-IIV group among 466,320 randomized participants [121].

Cardiovascular Safety

The DANFLU-2 cardiovascular secondary analysis of 332,438 older adults found HD-IIV reduced cardiovascular hospitalization (rVE 7.5%, 95% CI 1.5-12.5%) and HF hospitalization (rVE 19.5%, 95% CI 3.3-33.1%) compared with SD-IIV, with no difference by baseline CVD history [183]. These findings indicate HD-IIV poses no cardiovascular safety concerns and may confer cardiovascular benefit.

8.2.7 Conclusions and Guideline Implications

Evidence Quality

Two large European pragmatic RCTs pooled in FLUNITY-HD (466,320 participants from Denmark and Spain) provide definitive effectiveness data against hospitalization outcomes [121]. Multiple systematic reviews encompassing >45 million individuals confirm consistency across settings, seasons, and population [167].

Clinical Significance

HD-IIV reduces LCI hospitalization by 32% versus SD-IIV (rVE 31.9%, 95% CI 19.7-42.2). Cardiorespiratory hospitalisations are reduced by 6% in RCTs and up to 18% in observational studies. Benefit increases with advancing age, with consistent superiority demonstrated in those ≥85 years across all seasons studied [172]. RCTs were not powered to detect mortality benefit; observational data suggest reductions in influenza-related deaths.

Recommendations Implications

The evidence supports preferential use of high-dose influenza vaccine for adults aged ≥65 years in Belgium. Within this population, prespecified subgroup analyses from DANFLU-2 demonstrate that patients with CKD derive enhanced relative benefit compared to those without CKD, with a substantially more favourable number needed to treat (561 vs 3,953). The relative effectiveness of HD-IIV was consistent across participants with and without atherosclerotic cardiovascular disease, atrial fibrillation, or heart failure, though these groups' elevated baseline risk translates to greater absolute benefit.

For adults aged 50–64 years with CKD, clinicians may consider preferential use of HD-IIV on an individual basis. This recommendation reflects extrapolation from the ≥65 trial population, supported by the observed effect modification by CKD status and the biological plausibility of enhanced benefit in patients with impaired vaccine immunogenicity. This consideration does not extend to other chronic conditions in younger adults, where evidence for differential HD-IIV benefit is lacking.
Implementation considerations include vaccine availability, procurement timelines, and insurance coverage arrangements. Vaccination should not be delayed if HD-IIV is unavailable; standard-dose vaccine remains preferable to non-vaccination.

8.3 Adjuvanted vaccine

MF59-adjuvanted vaccine show 51% effectiveness against pneumonia/influenza hospitalization in community-dwelling older adults [164] and 25% reduced hospitalization risk compared with nonadjuvanted vaccines [184]. In head-to-head comparisons with high-dose vaccines, adjuvanted and high-dose formulations demonstrated similar effectiveness across most clinical endpoints in the general older adult population, though adjuvanted vaccine show improved relative effectiveness (12.5–18.4%) in adults with multiple comorbidities [185,186]. Among kidney transplant recipients aged 18–64, adjuvanted vaccine showed enhanced seroconversion (OR 6.10, 95% CI: 1.25–28.6) without inducing human leukocyte antigen (HLA) alloantibodies [187]. Safety profiles show increased local reactogenicity but equivalent SAE (RR 1.02, 95% CI: 0.64–1.63) in meta-analysis of younger adults [188].

8.3.1 Influenza-related hospitalisation (IRH)

MF59-adjuvanted vaccine consistently reduce IRH in older adults (Table 14). A 2024 network meta-analysis confirmed enhanced vaccines provide approximately 18% relative benefit over standard-dose formulations for hospitalization prevention, with no significant difference between adjuvanted, high-dose, and recombinant vaccines [165].
Two independent meta-analyses arrived at nearly identical pooled estimates of approximately 51% aVE against pneumonia/influenza hospitalization [164,189]. Protection varies by circulating strain: while one study reported 48.3% aVR in a season with co-circulating strains [189,190], specific aVE against A(H1N1)pdm09 was estimated at 34.4% in Valencia [191]. Conversely, A(H3N2)-dominant seasons can yield negligible protection; Valencia data showed 10.0% overall aVE driven by poor A(H3N2) match [191]. Adjuvanted vaccines maintained partial protection (30.1%) against mismatched B-lineage strains in that same season [191]. Protection appears highest in institutionalized older adults (94% against ILI), though this estimate was unadjusted [164].

Table 14. Vaccine effectiveness of adjuvanted influenza vaccines: Influenza-related hospitalisation

Study	Population	Outcome	VE (95% CI)	Notes
[164]	≥65y	Pneumonia/influenza hospitalization	51% (39 to 61%)	Pooled adjusted estimate (4 case-control studies).
[189]	≥65y	Influenza/pneumonia hospitalization	51.3% (39.1 to 61.1%)	MA (case-control).
[189]	≥65y	Hospitalized patients (Lab-confirmed)	58.5% (40.7 to 70.9%)	MA (TND).
[190]	≥65y	All influenza hospitalization	48.3% (18.7 to 67.2%)	
[191]	≥60y	Overall (hospitalized)	10.0% (-24.4 to 34.9%)	Low VE season
[191]	≥60y	A(H1N1)pdm09	34.4% (-34.6 to 68.0%)	
[191]	≥60y	A(H3N2)	-23.9% (-87.9 to 18.3%)	Mismatch season.
[194]	≥60y	B/Yamagata	30.1% (-15.9 to 57.8%)	Lineage mismatched to vaccine.
[164]	Institutionalized	ILI	94% (47 to 100%)	Unadjusted estimate; outcome is Influenza-Like Illness (not lab-confirmed).

Abbreviations: CI: confidence interval; ILI: influenza-like illness; MA: meta-analysis; TND: test-negative design; VE: vaccine effectiveness; y: years

8.3.2 All-Cause and Influenza-Related Mortality

Vaccination with MF59-adjuvanted influenza vaccine was associated with a 37% reduction in all-cause mortality (ACM) during influenza season in Italian adults aged 65 years and older [192] (Table 15). This effect size exceeds what would be expected from influenza prevention alone and likely reflects both direct protection against influenza-attributable deaths and prevention of influenza-triggered cardiovascular and respiratory decompensation. The 14% reduction in IRH in the same cohort provides a more conservative estimate of overall protection, while influenza-specific hospitalization showed a 34% reduction [192]. These data derive from a large retrospective cohort with robust statistical adjustment, though residual confounding by health-seeking behaviour remains a consideration in observational mortality studies. The magnitude of mortality reduction aligns with earlier findings suggesting substantial benefits of influenza vaccination in older adult population.

Table 15. Vaccine Effectiveness of adjuvanted influenza vaccines: All-Cause and Influenza-Related Mortality

Study	Population	Outcome	Effect Estimate	95% CI	Notes
[192]	≥65y, Italy	All-cause mortality	IRR 0.63	0.58–0.69	p<0.001, during influenza season
[192]	≥65y, Italy	Influenza-related hospitalization	IRR 0.86	0.81–0.91	p<0.001, composite endpoint
[192]	≥65y, Italy	Influenza-specific hospitalization	IRR 0.66	0.52–0.83	p<0.001

8.3.3 Cardiovascular Outcomes

The cardiovascular protection observed with MF59-adjuvanted influenza vaccination is notable, though estimates derive from observational studies requiring cautious interpretation (Table 16). During the 2004-2005 influenza season in Valencia, Spain, vaccination was associated with an 87% reduction in hospitalization for acute coronary syndrome (95% CI: 35-97%) and 93% for cerebrovascular accident (95% CI: 52-99%) during peak virus circulation REF. Protection appeared only during the epidemic period; no effect was observed pre-season, strengthening causal inference. These findings receive support from an Italian nested case-control study spanning 15 influenza seasons (n=43,000 older adults), where MF59-adjuvanted vaccine showed 39% rVE (95% CI: 4-61%) versus non-adjuvanted vaccines in preventing combined pneumonia and cerebro/cardiovascular hospitalization [193].

Table 16. aVE: Cardiovascular Outcomes

Study	Season	Population	Outcome	aVE/rVE	95% CI	Design	Adjustment
Puig-Barberà et al., 2007	2004-05	≥65y, Spain	Acute coronary syndrome	87% aVE	35-97%	Case-control	Propensity score, CV risk factors
Puig-Barberà et al., 2007	2004-05	≥65y, Spain	Cerebrovascular accident	93% aVE	52-99%	Case-control	Age, smoking, COPD, BP, TIA, lipid Rx, Barthel
Lapi et al., 2019	1999-2014 (15 seasons)	≥65y, Italy	Pneumonia + cerebro/CV hospitalization	39% rVE	4-61%	Nested case-control	Matched; MF59 vs non-adjuvanted

Abbreviations: aVE: absolute Vaccine Effectiveness; CI: Confidence Interval; COPD: Chronic obstructive pulmonary disease; CV: Cardiovascular; rVE: relative Vaccine Effectiveness; TIA: Transient Ischemic Attack

8.3.4 Outpatient and Mild Illness

Protection against medically-attended outpatient influenza is more modest than hospitalization outcomes, as expected given the threshold for healthcare seeking and the spectrum of illness severity (Table 17). The 40.7% effectiveness against non-emergency outpatient visits represents prevention of symptomatic illness sufficient to prompt medical consultation but not severe enough to require hospitalization [189]. The wide confidence interval for LCI (ranging

from no effect to 84% protection) reflects the small sample sizes in the studies contributing to the pooled estimate rather than between-study heterogeneity [164]. Recent observational data confirm that MF59-adjuvanted vaccine provide approximately 23% relative effectiveness advantage over standard-dose vaccines for preventing outpatient influenza-related medical encounters (IRME) in older adults with comorbidities [194]. Most adjuvanted vaccine studies have focused on severe outcomes in older adult population, where the public health impact is greatest.

Table 17. Outpatient and Mild Illness

Study	Population	Outcome	VE	95% CI	Notes
[189]	≥65 years	Non-emergency outpatient visits	40.7%	21.9-54.9%	MA, I^2=0%
[164]	≥65 years	Laboratory-confirmed influenza	60.1%	-1.3 to 84.3%	Wide CI due to small sample sizes

Abbreviations: CI: Confidence Interval; MA: Meta-Analysis; VE: Vaccine Effectiveness

8.3.5 Relative Vaccine Effectiveness Compared to Standard-Dose Vaccines

Compared to standard-dose non-adjuvanted vaccine, MF59-adjuvanted vaccine consistently demonstrated superior effectiveness (Table 18). A network meta-analysis of over 71 million participants found adjuvanted vaccine provided a 10% (95% CI 6–15%) reduction in hospitalization risk compared to standard vaccines [165]. A foundational Italian cohort study demonstrated a 25% lower risk of hospitalization for influenza or pneumonia (RR 0.75, 95% CI 0.57–0.98) with adjuvanted versus non-adjuvanted vaccine [184]. US claims analyses across three seasons showed relative effectiveness ranging from 20.8% to 27.5% for IRME [195]. Meta-analytic pooling suggests adjuvanted vaccine provide approximately 14% greater protection than both trivalent and quadrivalent standard-dose comparators [189]. In high-risk older adults with comorbidities, MF59-adjuvanted vaccine demonstrated 23.6% (95% CI 20.9–26.1%) rVE against any influenza-related medical encounter (IRME) and 19.0% (95% CI 16.3–21.6%) against influenza/pneumonia hospitalization [194]. An Italian health technology assessment (HTA) reported a pooled relative effectiveness of 34.6% (95% CI 2.0–66.0%) against LCI [196].

Table 18. Relative Vaccine Effectiveness: MF59-Adjuvanted vs Standard-Dose Vaccines

Study	Comparison	Outcome	rVE (Estimate)	95% CI / Statistics
[184]	aIIV3 vs IIV3	Influenza/pneumonia hospitalization	25%	RR 0.75 (0.57–0.98)
[195]	aIIV3 vs IIV4e	IRMEs (2017–18)	20.8%	18.4–23.2%
[195]	aIIV3 vs IIV4e	IRMEs (2018–19)	26.0%	23.4–28.6%
[195]	aIIV3 vs IIV4e	Outpatient visits (2019–20)	31.3%	27.8–34.6%
[195]	aIIV3 vs IIV4e	Inpatient IRMEs (2019–20)	17.1%	10.8–23.2%
[189]	aIIV3 vs IIV3	Various medical encounters	13.9%	4.2–23.5%
[189]	aIIV3 vs IIV4	Various medical encounters	13.7%	3.1–24.2%
[196]	aIIV3 vs IIV4e	Lab-confirmed influenza	34.6%	2.0–66.0%
[165]	ADJ vs SD	Influenza Hospitalization	10%	6–15%
[197]	aIIV3 vs conventional	Influenza-associated endpoints	6.5–33%	*Range across 9 analyses*
[194]	aIIV3 vs IIV4e	Any IRME (high-risk ≥65y)	23.6%	20.9–26.1%
[194]	aIIV3 vs IIV4e	Outpatient IRME (high-risk)	23.3%	20.4–26.1%
[194]	aIIV3 vs IIV4e	Flu/pneumonia hosp (high-risk)	19.0%	16.3–21.6%
[185]	aIIV3 vs HD-IIV3	Any IRME (≥1 risk factors)	12.5%	10.0–15.0%
[185]	aIIV3 vs HD-IIV3	Any IRME (≥3 risk factors)	10.4%	7.4–13.3%
[198]	aIIV3 vs HD-IIV3	Test-confirmed flu ED/IP	−2.5%*	−19.6 to 12.2%

Abbreviations: ADJ: Adujvanted; aIIV3: Adjuvanted Trivalent Inactivated Influenza Vaccine; ED: Emergency Department; hosp: hospitalised; IIV3: Trivalent Inactivated Influenza Vaccine (Standard-Dose); IIV4e: Quadrivalent Inactivated Influenza Vaccine (Egg-based, Standard-Dose); IRMEs: Influenza related Medical Encounter; rVE: Relative Vaccine Effectiveness

8.3.6 Effectiveness of MF59-Adjuvanted Vaccines in Special Population

The evidence for MF59-adjuvanted vaccines in immunocompromised population remains limited but implies benefit (Table 19). In kidney transplant recipients, a randomized trial found seroconversion rate (SCR) of 71.0% with adjuvanted vaccine versus 55.2% with non-adjuvanted vaccine (P=0.21) [187]. Among transplant recipients aged 18–64 years, adjuvanted vaccine demonstrated significantly greater immunogenicity (OR 6.10, 95% CI: 1.25–28.6), whereas no significant difference was observed in those aged 65 years and older,

where immunogenicity was particularly poor [187]. No vaccine-induced alloimmunization was observed [187]. High-dose mycophenolate mofetil (≥2g daily) was associated with significantly reduced seroconversion (44.4% vs 71.4%, P=0.047) [187].
In younger adults (Table 19), meta-analysis indicates adjuvanted vaccine elicit 8.8%–13.1% higher seroconversion rates against vaccine-like strains compared to non-adjuvanted vaccine, with advantages noted in immunocompromised subgroups [188]. Among older patients with multiple comorbidities (≥3 risk factors), adjuvanted vaccine demonstrated 10.4% relative effectiveness against IRME compared to high-dose vaccines [185]. In community-dwelling older adults, who generally exhibited low baseline antibody titres, adjuvanted vaccine improved humoral and cell-mediated immune responses compared to standard-dose vaccines [199].

Table 19. Effectiveness of MF59-Adjuvanted Vaccines in Special Population

Study	Population	Outcome	Effect Measure	Result
Transplant Recipients				
[187]	Kidney transplant (18–64y)	Seroconversion	OR	6.10 (95% CI: 1.25–28.6)
[187]	Kidney transplant (overall)	Seroconversion	Rate	71.0% (aIIV3) vs 55.2% (IIV3)
[187]	Kidney transplant (≥65y)	Seroconversion	Rate	20% (aIIV3) vs 20% (IIV3); P = NS
[187]	Kidney transplant	Alloimmunization	DSA development	No increase vs non-adjuvanted
[187]	High-dose MMF (≥2g/day)	Seroconversion	Rate	44.4% vs 71.4% (low dose); P = 0.047
Older Adults & Comorbidities				
[185]	Older adults with ≥3 risk factors	Any IRME	rVE vs HD-IIV3	10.4% (95% CI: 7.4%–13.3%)
[192]	Adults ≥75 years	Hospitalization (flu-related)	IRR	0.85 (75-84y) and 0.79 (≥85y) vs 1.00 (≤74y)
[188]	Younger adults	Seroconversion	Rate Difference	8.8% (H1N1), 13.1% (H3N2), 11.7% (B)*
[199]	Community-dwelling older adults	Humoral/Cellular Response	MFR / GMT	Enhanced vaccines superior to SD vaccine

**Note: Domnich et al. (2024) note that the immunogenicity advantage was more pronounced in immunocompromised adults (e.g., ΔSCR for A(H1N1) was 13.1% in immunocompromised vs 5.4% in non-immunocompromised).*
Abbreviations: aIIV3: Adjuvanted Trivalent Inactivated Influenza Vaccine; DSA: Donor-Specific Antibody; GMT: Geometric Mean Titre; HD-IIV3: High-Dose Trivalent Inactivated Influenza Vaccine; IIV3: Trivalent Inactivated Influenza Vaccine; IRME: Influenza-Related Medical Encounter; IRR: Incidence Rate Ratio; MMF: Mycophenolate Mofetil; MFR: Mean Fold Rise; rVE: Relative Vaccine Effectiveness; SD: Standard-Dose

8.3.7 Safety Profile of MF59-Adjuvanted Influenza Vaccine

MF59-adjuvanted vaccine are associated with increased local reactogenicity compared to non-adjuvanted vaccine, though reactions are generally mild and transient [188,200]. The most common local reaction is injection site pain, with reported frequencies ranging from 16.3% in a large efficacy trial of adults aged 65 years and older [201], 30-50% in adult and older subjects in one trial [202] and 58-65% in trials covering adults aged 50 years and older with either egg- or cell-based adjuvanted formulations [203,204]. Induration is reported more frequently with adjuvanted vaccine (16% vs 4%) [200].
Systemic reactions are modestly increased; a cell-based adjuvanted vaccine trial reported fatigue in 43.5% of recipients compared to 24.8% for non-adjuvanted [204] and higher relative risks for myalgia (RR=1.39) and chills (RR=1.48) [196], although these events remain self-limiting. Post-marketing enhanced passive surveillance indicates that fever is rare, with pyrexia reported in only 0.09% of recipients [205].
SAE rates do not differ significantly between adjuvanted and non-adjuvanted vaccine. A meta-analysis of randomized trials demonstrated an SAE risk ratio of 1.02 (95% CI: 0.64-1.63) [188], while a Phase 3 efficacy trial found balanced SAE rates between adjuvanted vaccine (7.0%) and non-influenza comparator (Tdap; specifically, Boostrix) (6.9%) [201]**.** A large-scale observational study evaluating 170,988 vaccine doses found that risks of AE of special interest (AESIs) requiring hospitalization were similar in both vaccination groups [206].
In kidney transplant recipients, safety was confirmed in a randomized trial which found significantly greater local tenderness with adjuvanted vaccine (77.4% vs 51.6%) but no significant difference in systemic side effects [187]. Crucially, there was no evidence of de

novo or nonspecific HLA alloantibody formation following adjuvanted vaccination, and no episodes of acute rejection occurred in the adjuvanted arm [187].
The summary of evidence regarding the safety profile of MF59-adjuvanted influenza vaccine is presented in Table 20.

Table 20. Safety Profile of MF59-Adjuvanted Influenza Vaccine

Study	Design	Population	Local Reactions	Systemic Reactions	SAEs
[200]	RCT	Older adults	Pain reported more frequently; Induration 16% vs 4%	Headache ~10% vs ~3%	No vaccine-related
[196]	HTA	Older adult	Pain 89%, erythema 54%, induration 58%	Chills RR=1.48, myalgia RR=1.39	Not reported
[187]	RCT	Transplant	Tenderness 77.4% vs 51.6%	No significant difference	None in adjuvant arm
[206]	Cohort	Older adult	Not detailed	Not detailed	Risks of AESI similar
[202]	RCT	Adults/Older adult	Pain 30-50% (1st dose)	Myalgia 19-26%	Rare
[188]	MA	Younger adults	Pain 51.0%, induration 13.1%	Malaise 19.9%, headache 19.4%	RR 1.02 (0.64-1.63)
[203]	RCT	Adults	Pain 65% vs 39%	Muscle aches 40%	None
[205]	Surveillance	Older adult	Not reported	Pyrexia 0.09%	None
[201]	RCT (Phase 3)	Older adult (≥65)	Pain 16.3% vs 11.2% (comparator)	Fatigue 10.5%; Headache 10.8%	7.0% vs 6.9% (balanced)
[204]	RCT (Phase 2)	Adults (>=50)	Pain 60.9% (cell-based); 57.9% (egg-based)	Fatigue 43.5% vs 24.8% (non-ADJ)	No vaccine-related

Abbreviations: ADJ: adjuvanted; AESI: adverse events of special interest; HTA: health technology assessment; MA: meta-analysis; RCT: randomized controlled trial; RR: risk ratio; SAEs: serious adverse events

8.3.8 Reconciling Effectiveness Estimates Across Studies

The heterogeneity in vaccine effectiveness estimates across studies can be explained by several key factors. Regarding population and risk factors stratification, a US cohort study (n=3.67 million) found adjuvanted vaccine provided 12.5% (95% CI: 10.0–15.0%) greater effectiveness against any IRME and 10.8% (8.3–13.2%) against influenza- or pneumonia-related hospitalization among adults ≥65 years with ≥1 risk factors [185]. While absolute effectiveness was comparable in those with 0 risk factors, the relative benefit of adjuvanted vaccine was observed across groups with 1–2 or ≥3 risk factors [185]. Immunogenicity trials demonstrated non-inferiority against homologous strains regardless of comorbidity scores [207], supporting European expert recommendations for enhanced vaccines in this population [208]. Effectiveness varies substantially by season; against A(H1N1)pdm09, adjuvanted vaccine effectiveness was 48.3% (95% CI: 13.5–69.1%) in a Spanish cohort, whereas effectiveness against A(H3N2) was -29.9% (95% CI: -79.1% to 5.8%) [191], reflecting known challenges with A(H3N2) antigenic drift. However, adjuvanted vaccine demonstrated higher immunogenicity to drifted A(H3N2) strains (+35% advantage) compared to standard egg-based trivalent vaccines [196] and confer superior immunogenicity against mismatched B strains [207]. Regarding study design, a network meta-analysis of five randomized trials found enhanced vaccines reduced hospitalization risk by 18% (95% CI: 3–32%) versus standard-dose [165]. Conversely, a meta-analysis of observational studies by Domnich and de Waure found that "when only estimates from the publicly funded studies were pooled, no significant difference was usually found" [186]. Finally, regarding outcomes, an earlier meta-analysis found adjusted effectiveness against LCI was 60.1% (95% CI: -1.3% to 84.3%) [164]. In a review where no study used laboratory-confirmed endpoints, adjuvanted vaccine was associated with better protection for IRME (rVE 9.7%; 95% CI: 5.0-14.2%), while high-dose vaccines was more effective for hospitalization for any respiratory condition (rVE -13.9%; 95% CI: -25.4% to -3.4%) [186].

8.4 Comparative Effectiveness of Adjuvanted versus High-Dose Influenza Vaccine in Older Adults

8.4.1 Enhanced vaccines outperform standard-dose vaccines

Both formulations consistently demonstrated superiority over standard-dose vaccines. The Cowling RCT documented mean fold rises in microneutralization titres at day 30: HD-IIV3 3.4-fold, Adjuvanted Trivalent Inactivated Influenza Vaccine (aIIV3) 2.9-fold, versus lower responses with SD-IIV4 [199]. Real-world effectiveness data from the Frühwein review (53 million older adults, 12 seasons) found relative vaccine effectiveness of 6.5% to 33% for adjuvanted vaccine over conventional vaccines [197].

8.4.2 Limited direct comparative evidence between adjuvanted and high-dose formulations

No head-to-head randomized trials compare aIIV3 with HD-IIV. The available evidence derives entirely from retrospective observational studies, predominantly from US administrative databases before 2020. The Domnich systematic review identified 52 relative effectiveness estimates: most showed no statistically significant difference, though effect directions were inconsistent and estimates were imprecise [186]. The authors appropriately concluded that current data do not permit preference of one formulation over another.
This uncertainty does not imply equivalence. The evidence base for HD-IIV is more extensive and includes the pivotal FIM12 RCT demonstrating superiority over standard-dose vaccine. For aIIV3, clinical effectiveness data rely more heavily on observational studies. When selecting between enhanced vaccines for older populations, this asymmetry in evidence quality warrants consideration.

Table 21. Head-to-Head Comparative Effectiveness: aIIV3 versus HD-IIV3

Source	Outcome	rVE (95% CI)	Direction	Significance
[186]	Pooled (52 estimates)	Variable	59.6% null, 25% favour aIIV, 15.4% favour HD	Most non-significant
[186]	influenza hospitalization (2017-18)	-1.2% (-9.5 to 6.4)	No difference	NS
[186]	Pneumonia hospitalization (2017-18)	0.5% (-2.0 to 2.9)	No difference	NS
[185]	Any IRME (0 risk factors)	5.2% (-5.9 to 15.1)	No difference	NS
[185]	Any IRME (≥1 risk factors)	12.5% (10.0 to 15.0)	Favors aIIV3	p<0.05
[185]	Any IRME (1-2 risk factors)	18.4% (13.7 to 22.9)	Favors aIIV3	p<0.05
[185]	Influenza/pneumonia hospitalization (≥1 RF)	10.8% (8.3 to 13.2)	Favors aIIV3	p<0.05

Abbreviations: aIIV3: Adjuvanted Trivalent Inactivated Influenza Vaccine; HD-IIV3: High-Dose Trivalent Inactivated Influenza Vaccine; IRME = influenza-related medical encounter; NS = not significant; RF = risk factors; rVE = relative vaccine effectiveness

8.4.3 Potential superiority of aIIV in high-risk subgroups

The Imran 2024 cohort study found that among patients with ≥1 comorbidity, adjuvanted vaccine showed higher effectiveness than high-dose (rVE 12.5%, 95% CI: 10.0-15.0%) [185] (Table 21). This effect was most pronounced in patients with 1-2 risk factors (rVE 18.4%). Among patients without identified risk factors, no difference was observed [185]. This represents hypothesis-generating data from a single season; replication across multiple seasons would be needed before considering differential recommendations by comorbidity status.

8.4.4 Limitations

Several key limitations constrain the interpretation of the current evidence. First, the absence of head-to-head randomized controlled trials utilizing clinical endpoints prevents the establishment of definitive causal superiority between the vaccine formulations. Second, the available evidence relies on observational data characterized by a moderate risk of bias, suggesting that residual confounding may influence the results. Additionally, the use of non-laboratory-confirmed outcomes in these studies introduces the potential for outcome misclassification. External validity is also a concern; because the comparative effectiveness data is derived exclusively from the US, its generalizability to other specific contexts, such as the Belgian healthcare setting, remains uncertain. Finally, the potential for reporting bias must be considered, as 60% of the studies included in the meta-analysis were industry-sponsored [186].

8.4.5 Recommendations

Primary statement: Adults aged ≥65 years should preferentially receive an enhanced influenza vaccine (high-dose or MF59-adjuvanted formulation) rather than standard-dose vaccine.
Comparative statement: The evidence base supporting high-dose vaccine is more extensive, including multiple randomized controlled trials demonstrating clinical endpoint superiority over standard-dose vaccine. For adjuvanted vaccine, effectiveness evidence derives primarily from observational studies. Head-to-head comparisons between these formulations show no statistically significant differences but are limited to retrospective observational data and may be underpowered to detect clinically meaningful differences. When both formulations are available, selection may be guided by procurement considerations, but this should not be interpreted as evidence of equivalence.

8.5 Overview neighbouring country recommendations on enhanced vs standard-dose vaccines

Several European NITAGs have recently evaluated the comparative effectiveness of enhanced influenza vaccine (high-dose and adjuvanted formulations) versus standard-dose vaccines for older adults.
The shift toward preferential enhanced vaccines recommendations in multiple countries follows accumulating evidence demonstrating 10-30% relative improvements in VE against hospitalization in adults aged 65 years and older, alongside favourable cost-effectiveness profiles within European healthcare systems (Table 22).

8.5.1 France – HAS [209]

> « La HAS recommande que les vaccins Efluelda et Fluad soient utilisés préférentiellement chez les personnes de 65 ans et plus par rapport aux vaccins à dose standard disponibles dans cette population, dans le cadre de la stratégie vaccinale française vis-à-vis de la grippe saisonnière. La HAS positionne de manière équivalente les vaccins adjuvantés et hautement dosés. La HAS précise que cette recommandation préférentielle n'exclut pas les vaccins à dose standard de la stratégie vaccinale antigrippale des personnes âgées de 65 ans et plus »

Haute Autorité de la Santé (HAS) recommends preferential use of high-dose (Efluelda) and adjuvanted (Fluad) vaccines for persons aged 65 years and older. Both enhanced formulations are positioned as equivalent, with no preference between them. Standard-dose vaccines remain acceptable alternatives when enhanced vaccines are unavailable. The recommendation follows the severe 2024-25 influenza season, which caused approximately 20,000 hospitalization and contributed to excess mortality of 14,000 deaths predominantly

among persons aged 65 and older. Reimbursement was confirmed in July 2025 for the 2025-26 campaign.

8.5.2 Netherlands – Gezondheidsraad [210]

> « Het doel van vaccinatie is om ernstige ziekte door griep te voorkomen, waarbij ziekenhuisopname en sterfte als indicator dienen. Het geadjuveerd vaccin, vaccin met een verhoogde dosis antigeen en het recombinant vaccin voldoen volgens de commissie aan de criteria van het beoordelingskader voor vaccinaties. Voor ouderen is er de voorkeur voor een geadjuveerd vaccin of een vaccin met een verhoogde dosis antigeen, omdat deze vaccins ongeveer 10 tot 30% effectiever zijn tegen ziekenhuisopname dan het huidige vaccin, voor risicogroepen van 50 tot 60 jaar geldt dat voor het geadjuveerde vaccin. Voor risicogroepen van 18 tot 50 jaar zou het recombinante vaccin beter griep en griepgerelateerde ziekenhuisopname kunnen voorkomen dan het huidige vaccin, maar niet zoveel beter dat een duidelijke voorkeur kan worden uitgesproken. »

The Dutch Health Council provides nuanced, age-stratified recommendations. For older adults, the Council expresses preference for adjuvanted or high-dose vaccines based on 10-30% improved effectiveness against hospitalization. For risk groups aged 50-60 years, preference extends to adjuvanted vaccine specifically. For risk groups aged 18-50 years, recombinant vaccine shows potential advantages but insufficient evidence for preferential recommendations. This represents one of the most granular European NITAG (National Immunization Technical Advisory Group) positions on enhanced vaccines.

8.5.3 Germany – STIKO [211]

> « Influenza: For protection against seasonal influenza, STIKO recommends the MF-59-adjuvanted influenza vaccine for persons aged 60 years and older, in addition to the high-dose influenza vaccine, each with the current antigen combination recommended by the WHO. »

Ständige Impfkommission (STIKO) recommends both MF59-adjuvanted vaccine and high-dose vaccines for adults aged 60 years and older, with no stated preference between these formulations. The German age threshold (60 years) is lower than most other European NITAGs (typically 65 years), reflecting STIKO's assessment of influenza burden and immunosenescence onset. Both vaccines are available within the German healthcare system, with choice typically based on availability and provider preference.

8.5.4 Luxembourg – CSMI [212]

> « Le CSMI recommande l'utilisation préférentielle des vaccins contre la grippe hautement dosés ou adjuvantés chez les personnes âgées de 65 ans et plus, dans le cadre de la campagne vaccinale saisonnière. En cas d'indisponibilité de ces vaccins, l'administration d'un vaccin à dose standard reste une alternative acceptable. Il souligne l'importance de renforcer la vaccination antigrippale chez les personnes 65 ans et plus ainsi que celles des professionnels de santé. Une meilleure couverture permettrait de réduire la pression sur le système de soins en cas de co-circulation grippe/SARS-CoV-2/RSV. Le maintien des gestes barrières et des mesures d'hygiène en période épidémique reste important dans la lutte des infections respiratoires. »

Luxembourg's Conseil Supérieur des Maladies Infectieuses (CSMI) recommends preferential use of high-dose or adjuvanted vaccine for adults aged 65 years and older, with standard-dose remaining acceptable when enhanced vaccines are unavailable. The recommendation explicitly addresses the context of potential co-circulation of influenza, SARS-CoV-2, and

RSV, emphasizing healthcare system protection. The CSMI also highlights the importance of HCW vaccination and maintenance of infection prevention measures during epidemic periods.

8.5.5 United Kingdom (JCVI) [213]

> « For vaccination of those aged 65 years and over, Joint Committee on Vaccination and Immunisation (JCVI) advises the use of the following vaccines: aIIV; HD-IIV-HD; RIV.
> The inactivated influenza cell-culture vaccine (IIVc) can also be considered for use in this age group if all other options are unavailable, subject to the considerations below.
> (…)
> When considering a preference between IIV-HD and aIIV, there is little available data comparing these. The available data is somewhat inconsistent, not available over multiple seasons, at risk of bias and limited by the use of non-laboratory confirmed influenza endpoints. The level of uncertainty in the available evidence is considered too great to allow for a preferential recommendation between the vaccines at the current time.
> JCVI is also of the view that there is enough supporting evidence for IIVr to be considered as equivalent to aIIV and IIV-HD for use in those aged 65 years and older.»

The UK has used aIIV preferentially for all adults aged 65 years and older since 2018, representing the longest implementation experience in Europe. The JCVI recommendations is based on demonstrated superiority of aIIV over standard-dose vaccines in this age group, with cost-effectiveness confirmed in the National Health Service (NHS) context. The UK also permits HD-IIV Recombinant Influenza Vaccine (RIV) for certain age bands when appropriate. Centralized NHS procurement ensures consistent implementation across the country.

Table 22 Comparative Summary of Country Recommendations

Country	Age Threshold	Recommendations	Enhanced Vaccines
France (HAS)	≥65 years	Preferential; equivalent positioning of HD-IIV and aIIV; SD acceptable if unavailable	Efluelda (HD), Fluad (ADJ)
Netherlands (GR)	≥60 years*	Preferential for older adults; aIIV for risk 50-60y; RIV potential for 18-50y risk groups	HD-IIV, aIIV, RIV (age-stratified)
Germany (STIKO)	≥60 years	Recommended (both HD-IIV and aIIV); no stated preference between formulations	HD-IIV, MF59-aIIV
Luxembourg (CSMI)	≥65 years	Preferential; SD acceptable if unavailable; emphasis on HCW vaccination	HD-IIV, aIIV
United Kingdom (JCVI)	≥65 years	Preferential since 2018; aIIV primary; HD-IIV/RIV alternatives for specific situations	aIIV (primary), HD-IIV, RIV

Netherlands: Nuanced age-stratified approach across risk categories.
Abbreviations: ADJ: Adjuvanted; aIIV: adjuvanted inactivated influenza vaccine; GR: Gezondheidsraad; HCW: Healthcare Workers; HD-IIV: high-dose inactivated influenza vaccine; RIV: recombinant influenza vaccine; SD: Standard-Dose

8.5.6 Key observations

All reviewed neighbouring NITAGs have adopted preferential recommendations for enhanced vaccines in older adults, typically aged 65 years and older (60 years in Germany), positioning Belgium as an outlier among its immediate neighbours despite enhanced vaccines availability. Most countries position high-dose and adjuvanted vaccine as equivalent alternatives, reflecting comparable clinical effectiveness and the absence of head-to-head superiority data; the Netherlands provides more granular age-stratified guidance with specific recommendations for adjuvanted vaccines in certain risk-age combinations. All NITAGs explicitly maintain standard-dose vaccines as acceptable alternatives when enhanced vaccines are unavailable, ensuring vaccination is not delayed for vaccine-type preference while acknowledging supply chain realities.
The consistent 10-30% relative effectiveness improvement against hospitalization cited across NITAGs represents the evidence threshold at which preferential recommendations become justified, aligning with meta-analytic estimates applicable to the Belgian context. The UK's

seven-year experience with universal adjuvanted vaccine use in adults aged 65 and older demonstrated programmatic feasibility, with coverage maintained at 70-75% and cost-effectiveness confirmed in real-world use.
An alternative perspective warrants acknowledgment. German modelling by Pahmeier et al. calculated that achieving the WHO 75% coverage target with standard-dose vaccines in persons aged 60 years and older would result in lower costs (€673M versus €782M) and prevent more influenza infections than current vaccination rates with high-dose vaccines [214]. This analysis suggests that coverage optimization may yield greater population-level benefit than vaccine type switching when baseline coverage remains suboptimal. For Belgium, where coverage in adults aged 65 years and older ranges from 47% to 75% depending on age stratum, a dual strategy that prioritizes both enhanced vaccines use and coverage improvement addresses this concern. The recommendations below therefore emphasize that vaccination with any available vaccine should not be delayed to obtain a specific formulation, and that coverage gains in target population remain the primary objective alongside vaccine optimization.

8.6 Cell-based influenza vaccine

8.6.1 Introduction

Observational studies demonstrated cell-based quadrivalent influenza vaccine provide modest relative effectiveness advantages over egg-based vaccines (ebIIV), with pooled estimates of 8.4% (95% CI 6.5%–10.2%) [215]. For adults aged 18–64 years, season-specific estimates ranged from 6.1% to 16.2% across 2017–2020 [215], with the most recent US data showing 18.5% (95% CI 12.1%–24.5%) in 2023–2024 [216]. Age-stratified analysis of the 2023-24 US data demonstrated consistent cell-based vaccine (cbIIV) advantages across paediatric and adult population. Among children aged 6 months to 17 years (n=60,990), rVE was 20.1% (95% CI 13.8%-25.9%) favouring cell-based IIV4 (IIV4c) over egg-based IIV4 (IIV4e), representing the first large-scale paediatric-specific estimate for cbIIV. Adults aged 18-64 years showed comparable benefit (rVE 18.5%, 95% CI 12.1%-24.5%). High-risk subgroups defined by CDC criteria showed rVE of 18.2% (95% CI 12.4%-23.6%), indicating preserved relative effectiveness in population at increased risk of influenza complications [216]. The largest benefits occurred during seasons with substantial egg adaptation, notably 2017–2018 when A(H3N2) mismatch yielded rVE exceeding 25% [217,218]. Immunogenicity studies showed significantly higher seroconversion against A(H3N2) specifically (44.0% vs 30.4%, $p<0.001$) for cbIIV [219]. The relative advantage attenuates in older adults, where high-dose and adjuvanted formulations demonstrated superior benefit compared to standard-dose cbIIV [220]. A European systematic review rated the certainty of evidence as "low" due to risk of bias and inconsistency, with UK data showing no significant difference by vaccine type against hospitalization [221,222].

8.6.2 Relative Vaccine effectiveness

The rVE of IIV4c compared to IIV4e has been assessed across multiple observational studies and one randomized trial (Table 23]. The highest rVE was observed during the 2017–2018 season, reaching 36.2% for ILI prevention [218], which coincided with substantial egg adaptation in the A(H3N2) vaccine component. More recent US data from the 2023–2024 season showed an rVE of 19.8% [216]. However, conflicting evidence exists: one pragmatic randomized trial among US military beneficiaries found no significant difference between vaccine types (rVE -27%; 95% CI -73% to 8%) [219], a US Flu VE Network analysis similarly found no significant difference [223] and UK data from 2022–2024 showed no significant effectiveness difference by vaccine type [222]. The ECDC systematic review rated certainty of evidence as "low" [221].

Table 23 Relative Vaccine Effectiveness of Cell-Based vs Egg-Based Influenza Vaccine

Study	Outcome	rVE (95% CI)	Population	Season
[224]	Cardiorespiratory hospitalization	2.5% (0.9%-4.1%)	Adults 18-64	2019-2020
[224]	Respiratory hospitalization	3.7% (1.5%-5.8%)	Adults 18-64	2019-2020
[224]	influenza hospitalization	9.3% (0.4%-17.3%)	Adults 18-64	2019-2020
[215]	IRME (pooled)	8.4% (6.5%-10.2%)	All ages	2017-2020
[215]	Influenza-related medical encounters	16.2% (7.6%-24.8%)	4-64 years	2017-2018
[215]	Influenza-related medical encounters	6.1% (4.9%-7.3%)	4-64 years	2018-2019
[215]	Influenza-related medical encounters	10.1% (6.3%-14.0%)	4-64 years	2019-2020
[217]	Test-confirmed influenza	14.8% (7.0%-22.0%)	4-64 years	2017-2018
[217]	Test-confirmed influenza	12.5% (4.7%-19.6%)	4-64 years	2018-2019
[217]	Test-confirmed influenza	10.0% (2.7%-16.7%)	4-64 years	2019-2020
[218]	Influenza-like illness	36.2% (26.1%-44.9%)	≥4 years	2017-2018
[218]	Medical encounters	7.6% (6.5%-8.6%)	≥4 years	2018-2019
[218]	Medical encounters	9.5% (7.9%-11.1%)	≥18 years	2019-2020
[216]	Test-confirmed influenza	19.8% (15.7%-23.8%)	6mo-64y	2023-2024
[219]	Laboratory-confirmed influenza	-27% (-73% to 8%)	Military adults	2018-2021
[223]	Symptomatic influenza	NS	≥4 years	2017-2019
[221]	Laboratory-confirmed influenza	-5.8% to 21.4%	Adults ≥18y	2015-2020
[222]	influenza hospitalization	NS	All ages	2022-2024

Abbreviation: rVE: relative Vaccine Effectiveness

8.6.3 Absolute Vaccine Effectiveness

cbIIV demonstrated 70% efficacy against any influenza in placebo-controlled RCTs conducted in adults aged 18-49 years [225]. In observational settings, aVE difference between cell-based and egg-based products were modest, with both vaccine types showing approximately 30-37% effectiveness against symptomatic influenza [226]. European multicentre hospital data spanning 2015-2024 demonstrated pooled VE of 37% against A(H1N1)pdm09 but only 17% against A(H3N2) in older adults, highlighting subtype-specific variation [120]. Contemporary UK data confirmed VE of 34-38% against influenza hospitalization in working-age adults [222].

8.6.4 Subgroup Analyses by Age

Several studies examined differential effectiveness across age subgroups within the adult population. Among adults aged 18-64 years, cbIIV consistently demonstrated statistically significant benefits over ebIIV, with meta-analysis showing pooled rVE of 9.9% (95% CI 5.3%-14.5%) [215]. For adults aged 18-49 years, one study found higher effect sizes for respiratory and influenza hospitalization compared to the overall population [224], while those aged 50-64 years showed additional benefit against MI [224].
For older adults (≥65 years), the relative effectiveness was attenuated and not statistically significant, with pooled rVE of only 0.5% (95% CI -5.7% to +6.8%) [215]. European multicentre data spanning 2015-2024 similarly demonstrated low-to-moderate aVE in older adults (≥65 years), ranging from 17% to 37% depending on the strain [120].
Interestingly, immunological studies showed the opposite pattern: adjuvanted cbIIV produced more pronounced immune responses in participants aged ≥65 years compared to those aged 50-64 years [204]. In younger adults (28-60 years), cell-based Flucelvax induced superior cellular immunity compared to standard-dose ebIIV, correlating with enhanced antibody production [227].

8.6.5 Health Condition-Specific Results

A meta-analysis of four observational studies evaluated vaccine effectiveness in higher-risk population (defined by chronic pulmonary, cardiac, renal, hepatic disease, diabetes, malignancy, or immunosuppression), finding the rVE favouring cbIIV was 10.3% (95% CI 5.7%-15.0%), compared to 8.2% in general population [215].
Contemporary European data from the I-MOVE/VEBIS hospital network, analysing six seasons between 2015-2024, now provides stratified effectiveness estimates by specific condition [120]. Among adults ≥65 years, VE was similar across most chronic conditions

(diabetes, heart disease, lung disease), but markedly reduced in immunocompromised patients (VE -7% to +5%) and those with kidney disease (VE 6%-17%), with significant interaction terms for both conditions against A(H1N1)pdm09 [120]. The PAIVED randomized pragmatic trial among a younger, healthier military population found no significant difference between vaccine types, possibly reflecting the younger, healthier study population with lower comorbidity burden [219].

8.6.6 Safety Outcomes

cbIIV demonstrated safety profiles comparable to traditional ebIIV [225]. Local AE are generally similar, though one systematic review noted higher rates of ecchymosis with cbIIV (RR 1.27, low-certainty evidence) [225]. The adjuvanted cbIIV is associated with higher rates of systemic AE compared to non-adjuvanted formulations, but these are predominantly mild-to-moderate and no safety concerns were identified [204]. Pooled analysis from 6 RCTs found no increased risk of SAE for cbIIV compared to standard vaccines (RR 0.39, 95% CI 0.02-9.49) [221]. SAE were rare and not causally related to vaccination across all cbIIV types [221].

8.6.7 Certainty of Evidence

The systematic review by Askar et al. rated the certainty of evidence for cbIIV effectiveness as "low" due to risk of bias and inconsistency across studies [221]. While multiple observational studies show a consistent direction of effect, the first randomized pragmatic trial (PAIVED) found no significant difference between cell-based and ebIIV (rVE -27%, 95% CI -73% to 8%), though low influenza case numbers limited precision [219]. The observed effectiveness difference in meta-analysis approximate 6-16% across seasons for persons aged 4-64 years [215], with benefit most apparent during seasons with documented egg adaptation in A(H3N2) strains.

8.6.8 Conclusion

In summary, cbIIV demonstrated modest relative effectiveness advantages over ebIIV in some observational studies, but confirmatory RCT evidence is lacking. The magnitude of benefit varies by influenza season and the degree of egg adaptation in vaccine strains. Given the low certainty of evidence and heterogeneous observational findings (whereas RCTs against placebo were consistent), firm preferential recommendations are not supported by current data, and both vaccine types provide meaningful protection against influenza compared to no vaccination [225].

8.7 Immunological Outcomes across platforms

Immunological responses were assessed in several randomized trials comparing cbIIV and ebIIV (Table 24). The immunological data revealed important distinctions between vaccine platforms. RIV consistently demonstrated superior antibody responses compared to both cell-based and ebIIV, particularly against A(H3N2), with Geometric Mean Titre (GMT) ratios of 3.0 favouring RIV4 over ebIIV4 [228]. cbIIV showed responses largely similar to ebIIV in head-to-head immunogenicity trials [228], though one study found significantly higher SCR against A(H3N2) for cbIIV (44.0% vs 30.4%) [219].
Among cellular immune response assessments, the cell-based Flucelvax induced early and cytokine-secreting HA-specific CD4+ T cell responses in younger adults, which correlated with early B cell proliferation and enhanced antibody production [227]. This finding suggests that the quality of antigen in cbIIV may provide immunological advantages beyond what is captured by standard hemagglutination inhibition assays.
The MF59-adjuvanted cbIIV (Cell-based Quadrivalent Influenza Vaccine, aIIV4c) elicited higher immune responses than non-adjuvanted cell-based and ebIIV against all four influenza

strains, with GMT ratios ranging from 1.18 to 1.85 [204]. However, responses against A strains were lower than those achieved with high-dose recombinant vaccines [204].

Table 24 Immunological outcomes.

Study	Vaccine Comparison	Strain	Outcome	Finding
[228]	RIV4 vs IIV4	A(H1N1)	GMT ratio	1.5 (95% CI 1.2-1.9)
[228]	RIV4 vs IIV4	A(H3N2)	GMT ratio	3.0 (95% CI 2.4-3.7)
[228]	cbIIV4 vs IIV4	All strains	GMT/SCR	Similar responses
[219]	RIV vs eIIV	A(H1N1)	Seroconversion	49.1% vs 29.0% (p<0.001)
[219]	RIV vs eIIV	A(H3N2)	Seroconversion	71.2% vs 30.4% (p<0.001)
[219]	cbIIV vs eIIV	A(H3N2)	Seroconversion	44.0% vs 30.4% (p<0.001)
[229]	RIV vs IIV	A(H3N2)	GMT	RIV higher (p=0.001)
[229]	RIV vs cbIIV	A(H3N2)	GMT	RIV higher (p=0.001)
[227]	FCEL vs FSD	A(H1N1)	Positivity rate	62% vs lower (younger adults)
[227]	FCEL vs FSD	A(H3N2)	Positivity rate	69% vs lower (younger adults)
[204]	aIIV4c vs IIV4c	All strains	GMT ratio	1.18-1.85
[230]	cbIIV4	All strains	Seroprotection	Best results for most strains

Abbreviations: cbIIV: Cell-Based Inactivated Influenza Vaccine; eIIV: Egg-Based Inactivated Influenza Vaccine; GMT: Geometric Mean Tire; IIV4: Quadrivalent Inactivated Influenza Vaccine; RIV: Recombinant Influenza Vaccine; SCR: Seroconversion rate

9 Health Economic Evidence

This chapter summarizes the available health economic evidence for enhanced influenza vaccines in older adults. The Working Group presents this information to support informed decision-making by healthcare authorities and procurement bodies, not to derive specific cost-effectiveness-based recommendations. Most published economic evaluations are manufacturer-sponsored, and their conclusions depend on pricing assumptions, analytical perspectives, and country-specific parameters that may not apply to the Belgian context. Belgium does not apply a formal willingness-to-pay threshold for vaccine reimbursement decisions, which limits direct interpretation of incremental cost-effectiveness ratios from other jurisdictions. Nevertheless, in view of the size of the groups to be vaccinated annually, economical aspects deserve due consideration by policy makers.

9.1 National Health Technology Assessments

9.1.1 Ireland (HIQA 2024)

Given the Irish guidelines for economic evaluation and the national decision context, the Health Information and Quality Authority concluded that the adjuvanted influenza vaccine represents good value for money compared with standard-dose vaccination in adults aged ≥65 years [231]. While the high-dose vaccine was found to provide additional health benefits relative to the adjuvanted option, these gains were not considered sufficient to justify its higher cost within Ireland's accepted willingness-to-pay framework. As a result, HIQA recommended the adjuvanted vaccine for public funding under the national programme, whereas the high-dose vaccine was not adopted following unsuccessful price negotiations [231]. The assessment emphasized that conclusions were highly sensitive to assumptions about the relative prices of the available vaccines.

9.2 Netherlands (Gezondheidsraad 2024)

In line with Dutch health-economic reference values and advisory practice, the Health Council of the Netherlands concluded that both adjuvanted and high-dose influenza vaccines could be appropriate options for adults aged ≥60 years, provided that procurement prices allow them to meet national cost-effectiveness benchmarks [210]. The Council highlighted that much of the available economic evidence is derived from industry-sponsored studies and explicitly called for independent confirmation. No preferential recommendation was made between the two enhanced vaccines, with the final choice intentionally left to price negotiations and implementation considerations.

9.3 United Kingdom (JCVI / NICE)

Within the UK decision framework for immunisation, an independent economic assessment supported the use of adjuvanted influenza vaccine for adults aged ≥65 years as representing good value for money for the National Health Service [232]. On this basis, adjuvanted vaccine has been preferentially recommended and used in the national programme since 2018 [213]. High-dose influenza vaccine has not been formally assessed for inclusion in the UK programme and therefore has not been considered for routine use.

9.4 Industry-Sponsored Cost-Effectiveness Analyses

Virtually all published economic evaluations of high-dose (HD-IIV), adjuvanted (aIIV), and cell-based (cbIIV) influenza vaccines are manufacturer-sponsored. Their conclusions should therefore be interpreted cautiously and in light of national economic-evaluation guidelines, pricing assumptions, the chosen comparator (SD-IIV or another enhanced vaccine) and procurement realities.

9.4.1 High-dose vaccine (HD-IIV)

Industry-sponsored analyses generally conclude that HD-IIV could represent acceptable value compared with standard-dose vaccines in older adults under national decision frameworks, particularly when broader clinical benefits such as reduced cardiorespiratory hospitalisations are assumed [233,234]. However, the applicability of these findings varies across countries due to reliance on non-local data sources, expanded outcome definitions, and assumptions about vaccine prices. As a result, conclusions regarding value for money remain highly sensitive to context and cost inputs.

9.4.2 Adjuvanted vaccine (aIIV)

Manufacturer-funded studies consistently indicate that aIIV represents good value compared with standard-dose vaccines within national evaluation frameworks [196,235,236]. Some analyses further suggest that aIIV may be economically preferable to HD-IIV, largely due to lower assumed acquisition costs combined with comparable effectiveness [235]. These findings, however, depend on list-price assumptions that may not reflect confidential procurement arrangements. Note that in Belgium also current list prices are substantially higher for HD-IIV than for aIIV.

9.4.3 Cell-based vaccine (cbIIV)

There are also pharmacoeconomic studies for cbIIV. These industry-funded studies suggest that cbIIV could be acceptable under certain pricing and effectiveness assumptions [215,237,238], but its value proposition—primarily improved antigenic match rather than demonstrable reductions in severe outcomes—complicates direct comparison with HD-IIV and aIIV.

9.4.4 Head-to-head comparisons

There are aware of a few pharmacoeconomic analyses comparing HD-IIV and aIIV directly. While an HD-IIV manufacturer-funded analysis for Italy favoured HD-IIV under specific assumptions [239], an aIIV manufacturer-sponsored analysis for three Scandinavian countries found aIIV to be cost saving versus HD-IIV [235] (Jacob et al., 2023). An independent HTA assessment for Ireland also found relatively unfavourable cost-effectiveness results for HD-IIV versus aIIV, despite higher assumed effectiveness for HD-IIV [231].

10 Belgian recommendations for the 26/27 season

10.1 Target groups at increased risk of severe disease or transmission

Group 1 (High-risk individuals):
Persons ≥65 years; residents of long-term care facilities; individuals with chronic pulmonary, cardiac, hepatic, renal, neurological, or metabolic conditions; immunocompromised persons; those with BMI ≥40; children on long-term aspirin therapy; pregnant women at any trimester [128,144]. Influenza vaccination in patients with established CVD reduces major adverse cardiovascular events by 34% (RR 0.66, 95% CI 0.53-0.83); in those with recent acute coronary syndrome, MACE reduction reaches 45% (RR 0.55, 95% CI 0.41-0.75) with cardiovascular mortality reduced by 56% (RR 0.44, 95% CI 0.23-0.85) [240]. A 2024 meta-analysis of five RCTs in IHD confirmed reduced ACM (RR 0.58, 95% CI 0.40-0.84; NNT 41) with high certainty evidence [241].
Group 2 (HCW):
All professional categories in healthcare settings with patient contact, including preventive services and community health workers. Consider enhanced vaccine in case of at-risk profile. HCW vaccination reduces ACM among older patients (pooled RR 0.71, 95% CI 0.59-0.85) and ILI (RR 0.58, 95% CI 0.46-0.73) with moderate quality evidence [241].
Group 3 (Children and household contacts):
Healthy children aged 6 months to 17 years; household contacts of high-risk individuals and infants <6 months ineligible for vaccination [128,144,242]. Vaccine efficacy in healthy children ranges 26-74% depending on season and match, with comparable effectiveness for inactivated and live-attenuated formulations [243,244].
Group definitions are presented in Table S1 (Appendix).

10.2 Occupational Indications Beyond Healthcare

Workers with professional contact with poultry or pigs are recommended for seasonal influenza vaccination [245,246]. The rationale is pandemic preparedness: reducing the theoretical risk of coinfection with both seasonal and zoonotic influenza viruses that could enable reassortment [245]. Direct evidence supporting effectiveness of this intervention is lacking; the recommendations is precautionary. In case of an at-risk profile, consider/recommend enhanced vaccine.

10.3 Recommendations by age group and risk profile

Table 25 Recommendations by Age Group and Risk Profile

Target group	Priority	Recommended Vaccine	Enhanced vaccine?	Rationale
CHILDREN & ADOLESCENTS				
6 mo – 17 y (at-risk)	High	IIV3	No	Chronic pulmonary, cardiac, renal, hepatic, neurological, metabolic disease; immunocompromised
Children on long-term aspirin	High	IIV3	No	Reye syndrome risk; includes children with Kawasaki disease
BMI ≥40 (children)	High	IIV3	No	Increased risk of severe influenza and complications
6 mo – 17 y (healthy)	Not routine	Not routinely recommended	No	Risk-based strategy; Belgium does not recommend universal childhood vaccination

Target group	Priority	Recommended Vaccine	Enhanced vaccine?	Rationale
ADULTS 18–49 YEARS				
18–49 y (at-risk)	High	IIV3	No	Same chronic conditions; also pregnant women, HCWs
18–49 y (healthy)	Not routine	Not routinely recommended	No	Unless occupational exposure (HCW, poultry/pig workers)
ADULTS 50–64 YEARS				
50–64 y (at-risk)	High	IIV3 or aIIV3	Consider	aIIV3 (Fluad) approved ≥50
50–64 y with CKD	High	IIV3; consider HD-IIV3	Consider	Extrapolation from DANFLU-2 CKD subgroup (rVE 68.6%); individual decision
50–64 y (healthy)	Moderate	IIV3	No	–
ADULTS ≥65 YEARS				
65–74 y	High	HD-IIV3 preferred; aIIV3 acceptable	Yes (conditional)	HD-IIV3 has more extensive RCT evidence; aIIV3 based on observational data; individual factors may guide choice
≥75 y	Very High	HD-IIV3 preferred; aIIV3 acceptable	Yes (strong)	Strong recommendation for enhanced vaccines; maximum benefit in this group; HD-IIV3 has more extensive RCT evidence; aIIV3 based on observational data;
LTCF residents (≥65)	Very High	HD-IIV3 preferred; aIIV3 acceptable	Yes (strong)	Highest risk; frailty, comorbidity, congregate setting; HD-IIV3 has more extensive RCT evidence; aIIV3 based on observational data;
SPECIAL POPULATIONS				
Pregnant women (any trimester)	High	IIV3	No	Protect mother and infant; safe all trimesters
HCW (healthy)	High	IIV3	No	Protect patients; maintain healthcare capacity
Poultry/pig workers (healthy)	High	IIV3	No	Reduce reassortment risk; occupational exposure
Immunocompromised (18–64)	High	IIV3; consider aIIV3	Consider	Suboptimal responses; aIIV3 may partially improve immunogenicity (observational evidence)
CKD (≥65)	High	HD-IIV3 preferred	Yes	DANFLU-2: rVE 68.6% vs 30.6% in non-CKD; NNT 561 vs 3953
BMI ≥40 (adults)	High	IIV3	No	Increased risk of severe disease; no enhanced vaccine data
Household contacts of high-risk	Moderate	IIV3	No	Cocooning strategy; indirect protection
Household contacts of infants <6 mo	Moderate	IIV3	No	Cocooning strategy; infants cannot be vaccinated

Target group	Priority	Recommended Vaccine	Enhanced vaccine?	Rationale
EGG ALLERGY				
Most egg-allergic individuals	Per indication	Any age-appropriate IIV3; consider Flucelvax (cell-based)	Per indication	Standard vaccination setting; 15-min observation
History of severe anaphylaxis to egg	Per indication	Flucelvax; if unavailable, hospital setting	Per indication	Allergist consultation recommended; anaphylaxis management must be available in case of egg-based vaccine administration

Abbreviations: aIIV3: MF59-adjuvanted IIV3 (Fluad); BMI: Body mass index; CKD: Chronic kidney disease; HCW: Healthcare workers; HD-IIV3: high-dose IIV3 (Efluelda); IIV3: trivalent inactivated influenza vaccine; LTCF: long-term care facility; mo: months; NNT: number needed to treat; rVE: relative vaccine effectiveness; y: years

11 Co-administration with other vaccines

11.1 Background

Adults aged 65 years and older face overlapping disease burden from influenza, respiratory syncytial virus (RSV), Streptococcus pneumoniae, and SARS-CoV-2. These pathogens share seasonal peaks and co-administration offers a strategy to maximize protection while reducing healthcare visits and missed vaccination opportunities.

11.2 Evidence Summary

A 2025 systematic review synthesizing data from randomized controlled trials and surveillance systems confirms that co-administration of respiratory vaccines in adults is safe, immunogenic, and well-tolerated [247].
Safety: No serious safety signals have been identified across any assessed vaccine combination. VAERS surveillance data from 2021-2022 revealed no unusual or unexpected AE patterns with co-administration [247].
Reactogenicity: AE are predominantly mild to moderate and self-limiting. Injection site pain, fatigue, headache, and myalgia occur most frequently. Some studies document modestly increased systemic reactogenicity with co-administration compared to single-vaccine administration, but these differences lack clinical significance. Vaccine Safety Active Surveillance showed co-administration increased systemic reaction reports by 8-11% compared with COVID-19 vaccine alone [247].
Immunogenicity: Nearly all studies demonstrated that co-administration does not result in clinically meaningful interference with immune response. Minor reductions in antibody titres observed in some studies have unknown clinical significance [247].

11.3 Specific Vaccine Combinations

11.3.1 Influenza + RSV vaccines (adults ≥65 years)

Phase 3 trials demonstrated non-inferior immune responses when RSV Prefusion F Protein Vaccine for Older Adults (RSVPreF3 OA) is co-administered with high-dose or adjuvanted influenza vaccine compared to sequential administration [248–251]. One combination (GSK RSVPreF3 + adjuvanted IIV4) showed lower titres against influenza A/Darwin A(H3N2) that narrowly missed non-inferiority criteria; the clinical relevance remains uncertain [248]. The mRNA-1345 RSV vaccine demonstrated acceptable safety and mostly non-inferior immune responses when co-administered with seasonal influenza vaccines in adults ≥50 years

[252,253]. Lot-to-lot consistency studies confirm preserved immunogenicity when RSVPreF3 OA is co-administered with quadrivalent influenza vaccine [253].

11.3.2 Influenza + Pneumococcal Conjugate vaccines (adults ≥50 years)

PCV20 (20-valent pneumococcal conjugate vaccine): A Phase 3 randomized trial in 1796 adults ≥65 years demonstrated non-inferior immune responses for all 20 pneumococcal serotypes and all 4 influenza vaccine strains when PCV20 was co-administered with adjuvanted quadrivalent influenza vaccine compared to sequential administration [254]. Mild and moderate fatigue occurred more frequently after co-administration (32.3% vs 19.2-22.2%) but was not considered clinically significant. No SAE were vaccination-related [254].
PCV21 (21-valent pneumococcal conjugate vaccine): The 21-valent pneumococcal conjugate vaccine (V116) meets non-inferiority criteria for 20 of 21 serotypes when co-administered with quadrivalent influenza vaccines in adults ≥50 years. Safety profiles are comparable between concomitant and sequential administration. Serotype 23B and influenza A(H3N2) narrowly missed non-inferiority criteria [255].

11.3.3 Influenza + COVID-19 vaccines

Multiple RCTs and observational studies confirm acceptable safety and preserved immunogenicity with co-administration [247]. A comparative effectiveness study of over 3 million US adults found similar real-world effectiveness for co-administration compared with single-vaccine groups [247].

11.3.4 Pneumococcal + COVID-19 vaccines (adults ≥60 years)

PCV20 + COVID-19 mRNA vaccines: A Phase 3 trial in 570 adults ≥65 years demonstrated that co-administration of PCV20 with BNT162b2 booster elicited robust immune responses comparable to either vaccine alone [256]. Geometric mean fold rises for opsonophagocytic activity ranged from 2.5-24.5 across PCV20 serotypes in the co-administration group. Safety profiles were similar across groups [256].
PCV20 + Novavax COVID-19 vaccine: A randomized, double-blind trial in 256 adults ≥60 years demonstrated non-inferior immunogenicity when NVX-CoV2601 (Omicron XBB.1.5-adapted) was co-administered with PCV20 compared to NVX-CoV2601 alone (GMT ratio 0.96; 95% CI 0.73-1.27). Local and systemic reactogenicity was similar across active treatment groups [252,257].

11.3.5 RSV + COVID-19 vaccines (adults ≥50 years)

The mRNA-1345 RSV vaccine demonstrated acceptable safety and mostly non-inferior immune responses when co-administered with COVID-19 mRNA vaccines [252].

11.3.6 Considerations for Adjuvanted Vaccines

Concerns have been raised about the theoretical potential for increased reactogenicity when co-administering multiple vaccines containing novel adjuvants. The Adjuvanted Quadrivalent Inactivated Influenza Vaccine (aIIV4, Fluad) contains MF59, while the recombinant zoster vaccine (RZV; Shingrix) contains AS01B. A randomized clinical trial in 267 adults ≥65 years demonstrated that simultaneous administration of RZV with aIIV4 was noninferior in safety to RZV with high-dose non-adjuvanted influenza vaccine, with severe reactions occurring in 11.5% vs 12.5% respectively (absolute difference −1.0%; 95% CI −8.9% to 7.1%) [258]. Post-marketing surveillance of RZV co-administered with adjuvanted, high-dose, or recombinant influenza vaccines in adults ≥65 years detected no new safety signals [259].

11.4 Recommendations

Simultaneous administration of influenza vaccine with RSV, pneumococcal conjugate (PCV20 or PCV21), COVID-19, or Tdap vaccines is acceptable for adults in recommended age groups. Co-administration should be offered to optimize vaccine uptake, particularly for individuals unlikely to return for subsequent visits.
When using adjuvanted influenza vaccine (aIIV3) together with adjuvanted RSV vaccines in adults ≥65 years, clinicians should be aware of slightly lower A(H3N2) antibody titres observed in one study, though clinical significance is uncertain [248].
Patient-centred considerations should inform the decision to co-administer, including patient preference, vaccination history, and feasibility of return visits [260].
Vaccines should be administered at different injection sites when given concomitantly

11.5 Optimal vaccination timing

Influenza circulation typically peaks between December and February, though onset and intensity vary by season. Vaccine-induced antibody titres reach maximum levels approximately 2–4 weeks after vaccination and decline over the following months.
Balancing these considerations, vaccination from mid-October through November positions most recipients to maintain adequate protection through the period of highest transmission risk. September vaccination is acceptable, particularly for organized campaigns or high-risk individuals, but may result in suboptimal protection during late-season circulation. Conversely, delaying vaccination beyond November increases the risk of infection before immunity develops.
Recommendation: Administer influenza vaccine from mid-October, with the primary campaign targeting completion by late November. Do not withhold vaccination in December or later if an individual has not yet been vaccinated; late vaccination confers benefit throughout the season.

12 REFERENCES

[1] Fodor E, Velthuis AJWT. Structure and Function of the Influenza Virus Transcription and Replication Machinery. Cold Spring Harb Perspect Med 2020;10:1–14. https://doi.org/10.1101/CSHPERSPECT.A038398.

[2] Liu R, Sheng Z, Huang C, Wang D, Li F. Influenza D virus. Curr Opin Virol 2020;44:154–61. https://doi.org/10.1016/j.coviro.2020.08.004.

[3] Carter T, Iqbal M. The Influenza A Virus Replication Cycle: A Comprehensive Review. Viruses 2024;16:316. https://doi.org/10.3390/v16020316.

[4] Bonazza S, Courtney DG. Influenza A virus RNA localisation and the interceding trafficking pathways of the host cell. PLoS Pathog 2025;21:e1013090. https://doi.org/10.1371/journal.ppat.1013090.

[5] Deng T, Zhang L, Shi Y, Gao GF. In Transition: How Influenza Virus Switches from Transcription to Genome Replication. Annu Rev Virol 2025;12:239–58. https://doi.org/10.1146/ANNUREV-VIROLOGY-092623-095030.

[6] Chenavier F, Estrozi LF, Teulon JM, Zarkadas E, Freslon LL, Pellequer JL, et al. Cryo-EM structure of influenza helical nucleocapsid reveals NP-NP and NP-RNA interactions as a model for the genome encapsidation. Sci Adv 2023;9. https://doi.org/10.1126/SCIADV.ADJ9974.

[7] Cdc C for DC and P. About Influenza A in Animals | Influenza in Animals | CDC n.d. https://www.cdc.gov/flu-in-animals/about/index.html (accessed December 16, 2025).

[8] Osman MK, Robert J, Broich L, Frank D, Grosse R, Schwemmle M, et al. The bat influenza A virus subtype H18N11 induces nanoscale MHCII clustering upon host cell attachment. Nature Communications 2025 16:1 2025;16:3847-. https://doi.org/10.1038/s41467-025-58834-y.

[9] Webster RG, Sharp GB, Claas ECJ. Interspecies Transmission of Influenza Viruses. Am J Respir Crit Care Med 1995;152:S25–30. https://doi.org/10.1164/ajrccm/152.4_Pt_2.S25.

[10] Caini S, Meijer A, Nunes MC, Henaff L, Zounon M, Boudewijns B, et al. Probable extinction of influenza B/Yamagata and its public health implications: a systematic literature review and assessment of global surveillance databases. Lancet Microbe 2024;5:100851. https://doi.org/10.1016/S2666-5247(24)00066-1.

[11] Monto AS, Zambon M, Weir JP. The End of B/Yamagata Influenza Transmission — Transitioning from Quadrivalent Vaccines. New England Journal of Medicine 2024;390:1256–8. https://doi.org/10.1056/NEJMP2314801;WGROUP:STRING:MMS.

[12] Chen Z, Tsui JL-H, Gutierrez B, Busch Moreno S, du Plessis L, Deng X, et al. COVID-19 pandemic interventions reshaped the global dispersal of seasonal influenza viruses. Science (1979) 2024;386. https://doi.org/10.1126/science.adq3003.

[13] Pflug A, Lukarska M, Resa-Infante P, Reich S, Cusack S. Structural insights into RNA synthesis by the influenza virus transcription-replication machine. Virus Res 2017;234:103–17. https://doi.org/10.1016/J.VIRUSRES.2017.01.013.

[14] Liang Y. Pathogenicity and virulence of influenza. Virulence 2023;14. https://doi.org/10.1080/21505594.2023.2223057;ISSUE:ISSUE:DOI.

[15] Kosik I, Yewdell JW, Kosik I, Yewdell JW. Influenza Hemagglutinin and Neuraminidase: Yin–Yang Proteins Coevolving to Thwart Immunity. Viruses 2019, Vol 11, 2019;11. https://doi.org/10.3390/V11040346.

[16] Taylor KY, Agu I, José I, Mäntynen S, Campbell AJ, Mattson C, et al. Influenza A virus reassortment is strain dependent. PLoS Pathog 2023;19:e1011155. https://doi.org/10.1371/JOURNAL.PPAT.1011155.

[17] Baker SF, Nogales A, Finch C, Tuffy KM, Domm W, Perez DR, et al. Influenza A and B Virus Intertypic Reassortment through Compatible Viral Packaging Signals. J Virol 2014;88:10778–91. https://doi.org/10.1128/JVI.01440-14.

[18] Jakob C, Paul-Stansilaus R, Schwemmle M, Marquet R, Bolte H. The influenza A virus genome packaging network — complex, flexible and yet unsolved. Nucleic Acids Res 2022;50:9023–38. https://doi.org/10.1093/nar/gkac688.

[19] Long JS, Idoko-Akoh A, Mistry B, Goldhill D, Staller E, Schreyer J, et al. Species specific differences in use of ANP32 proteins by influenza A virus. Elife 2019;8:696–7. https://doi.org/10.7554/ELIFE.45066.001.
[20] Peacock TP, Swann OC, Salvesen HA, Staller E, Leung PB, Goldhill DH, et al. Swine ANP32A Supports Avian Influenza Virus Polymerase. J Virol 2020;94. https://doi.org/10.1128/JVI.00132-20.
[21] Thompson CI, Barclay WS, Zambon MC, Pickles RJ. Infection of human airway epithelium by human and avian strains of influenza a virus. J Virol 2006;80:8060–8. https://doi.org/10.1128/JVI.00384-06.
[22] Bestle D, Limburg H, Kruhl D, Harbig A, Stein DA, Moulton H, et al. Hemagglutinins of Avian Influenza Viruses Are Proteolytically Activated by TMPRSS2 in Human and Murine Airway Cells. J Virol 2021;95. https://doi.org/10.1128/JVI.00906-21.
[23] Trebbien R, Larsen LE, Viuff BM. Distribution of sialic acid receptors and influenza A virus of avian and swine origin in experimentally infected pigs. Virology Journal 2011 8:1 2011;8:434-. https://doi.org/10.1186/1743-422X-8-434.
[24] Yao L, Korteweg C, Hsueh W, Gu J. Avian influenza receptor expression in H5N1-infected and noninfected human tissues. FASEB J 2008;22:733–40. https://doi.org/10.1096/fj.06-7880com.
[25] Lin T-H, Zhu X, Wang S, Zhang D, McBride R, Yu W, et al. A single mutation in bovine influenza H5N1 hemagglutinin switches specificity to human receptors. Science 2024;386:1128–34. https://doi.org/10.1126/science.adt0180.
[26] Song H, Hao T, Han P, Wang H, Zhang X, Li X, et al. Receptor binding, structure, and tissue tropism of cattle-infecting H5N1 avian influenza virus hemagglutinin. Cell 2025;188:919-929.e9. https://doi.org/10.1016/j.cell.2025.01.019.
[27] Herold S, Becker C, Ridge KM, Budinger GRS. Influenza virus-induced lung injury: pathogenesis and implications for treatment. Eur Respir J 2015;45:1463–78. https://doi.org/10.1183/09031936.00186214.
[28] Klomp M, Ghosh S, Mohammed S, Nadeem Khan M. From virus to inflammation, how influenza promotes lung damage. J Leukoc Biol 2021;110:115–22. https://doi.org/10.1002/JLB.4RU0820-232R.
[29] Kalil AC, Thomas PG. Influenza virus-related critical illness: pathophysiology and epidemiology. Crit Care 2019;23:258. https://doi.org/10.1186/s13054-019-2539-x.
[30] Galani IE, Rovina N, Lampropoulou V, Triantafyllia V, Manioudaki M, Pavlos E, et al. Untuned antiviral immunity in COVID-19 revealed by temporal type I/III interferon patterns and flu comparison. Nature Immunology 2020 22:1 2020;22:32–40. https://doi.org/10.1038/s41590-020-00840-x.
[31] Hartshorn KL. Innate Immunity and Influenza A Virus Pathogenesis: Lessons for COVID-19. Front Cell Infect Microbiol 2020;10. https://doi.org/10.3389/FCIMB.2020.563850.
[32] Li X, Huang C, Rai KR, Xu Q. Innate immune role of IL-6 in influenza a virus pathogenesis. Front Cell Infect Microbiol 2025;15:1605446. https://doi.org/10.3389/FCIMB.2025.1605446/FULL.
[33] Narasaraju T, Yang E, Samy RP, Ng HH, Poh WP, Liew A-A, et al. Excessive Neutrophils and Neutrophil Extracellular Traps Contribute to Acute Lung Injury of Influenza Pneumonitis. Am J Pathol 2011;179:199–210. https://doi.org/10.1016/j.ajpath.2011.03.013.
[34] An W, Lakhina S, Leong J, Rawat K, Husain M, An W, et al. Host Innate Antiviral Response to Influenza A Virus Infection: From Viral Sensing to Antagonism and Escape. Pathogens 2024, Vol 13, 2024;13. https://doi.org/10.3390/PATHOGENS13070561.
[35] Su G, Chen Y, Li X, Shao J-W. Virus versus host: influenza A virus circumvents the immune responses. Front Microbiol 2024;15:1394510. https://doi.org/10.3389/fmicb.2024.1394510.
[36] Meade P, Kuan G, Strohmeier S, Maier HE, Amanat F, Balmaseda A, et al. Influenza Virus Infection Induces a Narrow Antibody Response in Children but a Broad Recall Response in Adults. MBio 2020;11. https://doi.org/10.1128/mBio.03243-19.

[37] Kasten-Jolly J, Lawrence DA, Kasten-Jolly J, Lawrence DA. Cellular and Molecular Immunity to Influenza Viruses and Vaccines. Vaccines 2024, Vol 12, 2024;12. https://doi.org/10.3390/VACCINES12040389.
[38] Guthmiller JJ, Han J, Utset HA, Li L, Lan LYL, Henry C, et al. Broadly neutralizing antibodies target a haemagglutinin anchor epitope. Nature 2021 602:7896 2021;602:314–20. https://doi.org/10.1038/s41586-021-04356-8.
[39] Van de Sandt CE, Kreijtz JHCM, Rimmelzwaan GF. Evasion of Influenza A Viruses from Innate and Adaptive Immune Responses. Viruses 2012;4:1438–76. https://doi.org/10.3390/v4091438.
[40] Galeone V, Lee C, Monaghan MT, Bauer DC, Wilson LOW. Evolutionary Insights from Association Rule Mining of Co-Occurring Mutations in Influenza Hemagglutinin and Neuraminidase. Viruses 2024;16. https://doi.org/10.3390/V16101515/S1.
[41] Le Sage V, Werner BD, Merrbach GA, Petnuch SE, O'Connell AK, Simmons HC, et al. Influenza A(H5N1) Immune Response among Ferrets with Influenza A(H1N1)pdm09 Immunity - Volume 31, Number 3—March 2025 - Emerging Infectious Diseases journal - CDC. Emerg Infect Dis 2025;31:477–87. https://doi.org/10.3201/EID3103.241485.
[42] Sun X, Belser JA, Li Z-N, Brock N, Pulit-Penaloza JA, Kieran TJ, et al. Effect of Prior Influenza A(H1N1)pdm09 Virus Infection on Pathogenesis and Transmission of Human Influenza A(H5N1) Clade 2.3.4.4b Virus in Ferret Model. Emerg Infect Dis 2025;31:458–66. https://doi.org/10.3201/eid3103.241489.
[43] Oh JE, Song E, Moriyama M, Wong P, Zhang S, Jiang R, et al. Intranasal priming induces local lung-resident B cell populations that secrete protective mucosal antiviral IgA. Sci Immunol 2021;6:eabj5129. https://doi.org/10.1126/sciimmunol.abj5129.
[44] Zhang A, Chaudhari H, Agung Y, D'Agostino MR, Ang JC, Tugg Y, et al. Hemagglutinin stalk-binding antibodies enhance effectiveness of neuraminidase inhibitors against influenza via Fc-dependent effector functions. Cell Rep Med 2022;3:100718. https://doi.org/10.1016/J.XCRM.2022.100718.
[45] Thwaites RS, Uruchurtu ASS, Negri VA, Cole ME, Singh N, Poshai N, et al. Early mucosal events promote distinct mucosal and systemic antibody responses to live attenuated influenza vaccine. Nature Communications 2023 14:1 2023;14:8053-. https://doi.org/10.1038/s41467-023-43842-7.
[46] Lane A, Quach HQ, Ovsyannikova IG, Kennedy RB, Ross TM, Einav T. High-resolution antibody dynamics following influenza vaccination reveal predominantly weak responses as well as infrequent but durable immunity across the 2014–2022 seasons. Vaccine 2025;64:127677. https://doi.org/10.1016/J.VACCINE.2025.127677.
[47] Carniel BF, Marcon F, Rylance J, German EL, Zaidi S, Reiné J, et al. Pneumococcal colonization impairs mucosal immune responses to live attenuated influenza vaccine. JCI Insight 2021;6. https://doi.org/10.1172/JCI.INSIGHT.141088.
[48] Stuurman AL, Enxing J, Gutiérrez A V., Gray CM, Sepúlveda-Pachón IT, Ubamadu E, et al. Real-world effectiveness of live attenuated influenza vaccines (LAIV) and inactivated influenza vaccines (IIV) in children from 2003 to 2023: a systematic literature review and network meta-analysis. Expert Rev Vaccines 2025;24:703–25. https://doi.org/10.1080/14760584.2025.2536087.
[49] Tellier R. Review of aerosol transmission of influenza A virus. Emerg Infect Dis 2006;12:1657–62. https://doi.org/10.3201/eid1211.060426.
[50] Leung NHL. Transmissibility and transmission of respiratory viruses. Nature Reviews Microbiology 2021 19:8 2021;19:528–45. https://doi.org/10.1038/s41579-021-00535-6.
[51] Cowling BJ, Ip DKM, Fang VJ, Suntarattiwong P, Olsen SJ, Levy J, et al. Aerosol transmission is an important mode of influenza A virus spread. Nat Commun 2013;4:1935. https://doi.org/10.1038/ncomms2922.

[52] Carrat F, Vergu E, Ferguson NM, Lemaitre M, Cauchemez S, Leach S, et al. Time Lines of Infection and Disease in Human Influenza: A Review of Volunteer Challenge Studies. Am J Epidemiol 2008;167:775–85. https://doi.org/10.1093/aje/kwm375.
[53] Morris SE, Nguyen HQ, Grijalva CG, Hanson KE, Zhu Y, Biddle JE, et al. Influenza virus shedding and symptoms: Dynamics and implications from a multiseason household transmission study. PNAS Nexus 2024;3. https://doi.org/10.1093/pnasnexus/pgae338.
[54] Teunis PFM, Brienen N, Kretzschmar MEE. High infectivity and pathogenicity of influenza A virus via aerosol and droplet transmission. Epidemics 2010;2:215–22. https://doi.org/10.1016/j.epidem.2010.10.001.
[55] Richard M, Fouchier RAM. Influenza A virus transmission via respiratory aerosols or droplets as it relates to pandemic potential. FEMS Microbiol Rev 2016;40:68–85. https://doi.org/10.1093/femsre/fuv039.
[56] David SC, Schaub A, Terrettaz C, Motos G, Costa LJ, Nolan DS, et al. Stability of influenza A virus in droplets and aerosols is heightened by the presence of commensal respiratory bacteria. J Virol 2024;98:e0040924. https://doi.org/10.1128/jvi.00409-24.
[57] Uyeki TM. Influenza. Ann Intern Med 2021;174:ITC161–76. https://doi.org/10.7326/AITC202111160.
[58] Uyeki TM, Bernstein HH, Bradley JS, Englund JA, File TM, Fry AM, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenzaa. Clinical Infectious Diseases 2019;68:e1–47. https://doi.org/10.1093/cid/ciy866.
[59] Watson A, Wilkinson TMA. Respiratory viral infections in the elderly. Ther Adv Respir Dis 2021;15:1753466621995050. https://doi.org/10.1177/1753466621995050.
[60] Wong PL, Sii HL, P'ng CK, Ee SS, Yong Oong X, Ng KT, et al. The effects of age on clinical characteristics, hospitalization and mortality of patients with influenza-related illness at a tertiary care centre in Malaysia. Influenza Other Respir Viruses 2020;14:286–93. https://doi.org/10.1111/irv.12691.
[61] Gao Y, Guyatt G, Uyeki TM, Liu M, Chen Y, Zhao Y, et al. Antivirals for treatment of severe influenza: a systematic review and network meta-analysis of randomised controlled trials. The Lancet 2024;404:753–63. https://doi.org/10.1016/S0140-6736(24)01307-2.
[62] Putot A, Garin N, Rello J, Prendki V. Comprehensive management of pneumonia in older patients. Eur J Intern Med 2025;135:14–24. https://doi.org/10.1016/J.EJIM.2025.02.025.
[63] Miyashita K, Nakatani E, Hozumi H, Sato Y, Miyachi Y, Suda T. Risk Factors for Pneumonia and Death in Adult Patients With Seasonal Influenza and Establishment of Prediction Scores: A Population-Based Study. Open Forum Infect Dis 2021;8. https://doi.org/10.1093/ofid/ofab068.
[64] Arranz-Herrero J, Presa J, Rius-Rocabert S, Utrero-Rico A, Arranz-Arija JÁ, Lalueza A, et al. Determinants of poor clinical outcome in patients with influenza pneumonia: A systematic review and meta-analysis. International Journal of Infectious Diseases 2023;131:173–9. https://doi.org/10.1016/j.ijid.2023.04.003.
[65] Boattini M, Charrier L, Almeida A, Christaki E, Moreira Marques T, Tosatto V, et al. Burden of primary influenza and respiratory syncytial virus pneumonia in hospitalised adults: insights from a 2-year multi-centre cohort study (2017–2018). Intern Med J 2023;53:404–8. https://doi.org/10.1111/imj.15583.
[66] Kwong JC, Schwartz KL, Campitelli MA, Chung H, Crowcroft NS, Karnauchow T, et al. Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection. New England Journal of Medicine 2018;378:345–53. https://doi.org/10.1056/NEJMOA1702090;WGROUP:STRING:MMS.
[67] Chow EJ, Rolfes MA, O'Halloran A, Anderson EJ, Bennett NM, Billing L, et al. Acute Cardiovascular Events Associated With Influenza in Hospitalized Adults. Ann Intern Med 2020;173:605–13. https://doi.org/10.7326/M20-1509.

[68] Fröbert O, Götberg M, Erlinge D, Akhtar Z, Christiansen EH, MacIntyre CR, et al. Influenza Vaccination After Myocardial Infarction: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial. Circulation 2021;144:1476–84. https://doi.org/10.1161/CIRCULATIONAHA.121.057042.
[69] Radovanovic M, Petrovic M, Barsoum MK, Nordstrom CW, Calvin AD, Dumic I, et al. Influenza Myopericarditis and Pericarditis: A Literature Review. J Clin Med 2022;11:4123. https://doi.org/10.3390/jcm11144123.
[70] Ouranos K, Vassilopoulos S, Vassilopoulos A, Shehadeh F, Mylonakis E. Cumulative incidence and mortality rate of cardiovascular complications due to laboratory-confirmed influenza virus infection: A systematic review and meta-analysis. Rev Med Virol 2024;34. https://doi.org/10.1002/rmv.2497.
[71] Bender RG, Sirota SB, Swetschinski LR, Dominguez RMV, Novotney A, Wool EE, et al. Global, regional, and national incidence and mortality burden of non-COVID-19 lower respiratory infections and aetiologies, 1990–2021: a systematic analysis from the Global Burden of Disease Study 2021. Lancet Infect Dis 2024;24:974–1002. https://doi.org/10.1016/S1473-3099(24)00176-2.
[72] Iuliano AD, Roguski KM, Chang HH, Muscatello DJ, Palekar R, Tempia S, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. The Lancet 2018;391:1285–300. https://doi.org/10.1016/S0140-6736(17)33293-2.
[73] Egeskov-Cavling AM, Hansen CL, Johannesen CK, Lindegaard B, Bhatt S, Viboud C, et al. Excess mortality and hospitalisations associated with respiratory syncytial virus, influenza, and COVID-19 among adults in Denmark (2015–2024): a modelling study. The Lancet Regional Health - Europe 2025;55:101396. https://doi.org/10.1016/j.lanepe.2025.101396.
[74] Andrew MK, MacDonald S, Godin J, McElhaney JE, LeBlanc J, Hatchette TF, et al. Persistent Functional Decline Following Hospitalization with Influenza or Acute Respiratory Illness. J Am Geriatr Soc 2021;69:696–703. https://doi.org/10.1111/jgs.16950.
[75] Vos LM, Bruning AHL, Reitsma JB, Schuurman R, Riezebos-Brilman A, Hoepelman AIM, et al. Rapid Molecular Tests for Influenza, Respiratory Syncytial Virus, and Other Respiratory Viruses: A Systematic Review of Diagnostic Accuracy and Clinical Impact Studies. Clin Infect Dis 2019;69:1243–53. https://doi.org/10.1093/CID/CIZ056.
[76] Naquin A, O'Halloran A, Ujamaa D, Sundaresan D, Masalovich S, Cummings CN, et al. Laboratory-Confirmed Influenza-Associated Hospitalizations Among Children and Adults — Influenza Hospitalization Surveillance Network, United States, 2010–2023. MMWR Surveillance Summaries 2024;73:1–19. https://doi.org/10.15585/MMWR.SS7706A1.
[77] Vitoratou DI, Milas GP, Korovessi P, Kostaridou S, Koletsi P. Obesity as a risk factor for severe influenza infection in children and adolescents: a systematic review and meta-analysis. European Journal of Pediatrics 2022 182:1 2022;182:363–74. https://doi.org/10.1007/S00431-022-04689-0.
[78] Al-Rashdi J, BaAlawi F, Al Maamari K, Al-Ajmi E, Al Yazidi L, Elsidig N, et al. Influenza-associated Neurologic Complications in Children: Insights From a Single-center Study in Oman. Pediatric Infectious Disease Journal 2025. https://doi.org/10.1097/INF.0000000000005046.
[79] Silvennoinen H, Peltola V, Lehtinen P, Vainionpää R, Heikkinen T. Clinical presentation of influenza in unselected children treated as outpatients. Pediatric Infectious Disease Journal 2009;28:372–5. https://doi.org/10.1097/INF.0B013E318191EEF7.
[80] Ma X, Conrad T, Alchikh M, Reiche J, Schweiger B, Rath B. Can we distinguish respiratory viral infections based on clinical features? A prospective pediatric cohort compared to systematic literature review. Rev Med Virol 2018;28:e1997. https://doi.org/10.1002/rmv.1997.
[81] Bryant PA, Tebruegge M, Papadakis G, Clarke C, Barnett P, Daley AJ, et al. Clinical and microbiologic features associated with novel swine-origin influenza A pandemic 2009 (H1N1) virus in children: A prospective cohort study. Pediatric Infectious Disease Journal 2010;29:694–8. https://doi.org/10.1097/INF.0B013E3181DE4B9C.

[82] Dimopoulou D, Maltezou HC, Neofytou A, Giannouchos T, Pantelia E, Dimitroglou M, et al. Characteristics of children with influenza admitted to a pediatric hospital in Greece during the 2022/2023 and 2023/2024 seasons. European Journal of Pediatrics 2025 184:8 2025;184:530-. https://doi.org/10.1007/S00431-025-06338-8.

[83] Fischer N, Moreels S, Dauby N, Reynders M, Petit E, Gerard M, et al. Influenza versus other respiratory viruses - assessing severity among hospitalised children, Belgium, 2011 to 2020. Eurosurveillance 2023;28:2300056. https://doi.org/10.2807/1560-7917.ES.2023.28.29.2300056/CITE/REFWORKS.

[84] Lahti E, Peltola V, Virkki R, Ruuskanen O. Influenza pneumonia. Pediatr Infect Dis J 2006;25:160–4. https://doi.org/10.1097/01.INF.0000199265.90299.26.

[85] Voigt GM, Thiele D, Wetzke M, Weidemann J, Parpatt P, Welte T, et al. Interobserver agreement in interpretation of chest radiographs for pediatric community acquired pneumonia: Findings of the pedCAPNETZ-cohort. Pediatr Pulmonol 2021;56:2676–85. https://doi.org/10.1002/ppul.25528.

[86] Hu C, Zhang N, Xu D, Chen Z, Yu J, Yang Z, et al. Clinical presentations and diagnostic approaches of pediatric necrotizing tracheobronchitis with influenza A virus and Staphylococcus aureus co-infections. Scientific Reports 2024 14:1 2024;14:20880-. https://doi.org/10.1038/s41598-024-71867-5.

[87] Bosch Castells V, Mira-Iglesias A, López-Labrador FX, Mengual-Chuliá B, Carballido-Fernández M, Tortajada-Girbés M, et al. Pediatric Respiratory Hospitalizations in the Pre-COVID-19 Era: The Contribution of Viral Pathogens and Comorbidities to Clinical Outcomes, Valencia, Spain. Viruses 2024;16. https://doi.org/10.3390/V16101519.

[88] Antoon JW, Hall M, Herndon A, Johnson DP, Brown CM, Browning WL, et al. Prevalence, Risk Factors, and Outcomes of Influenza-Associated Neurologic Complications in Children. Journal of Pediatrics 2021;239:32-38.e5. https://doi.org/10.1016/j.jpeds.2021.06.075.

[89] Fazal A, Reinhart K, Huang S, Kniss K, Olson SM, Dugan VG, et al. Reports of Encephalopathy Among Children with Influenza-Associated Mortality — United States, 2010–11 Through 2024–25 Influenza Seasons. MMWR Morb Mortal Wkly Rep 2025;74:91–5. https://doi.org/10.15585/MMWR.MM7406A3.

[90] Savagner J, Trémeaux P, Baudou E, Mansuy JM, Cheuret E. Neurological involvement related to the influenza virus in children: A 5-year single-centre retrospective study. European Journal of Paediatric Neurology 2024;51:100–9. https://doi.org/10.1016/j.ejpn.2024.05.012.

[91] Bartolini L, Ricci S, Azzari C, Moriondo M, Nieddu F, Erario ML, et al. Severe A(H1N1)pdm09 influenza acute encephalopathy outbreak in children in Tuscany, Italy, December 2023 to January 2024. Eurosurveillance 2024;29:2400199. https://doi.org/10.2807/1560-7917.ES.2024.29.17.2400199/CITE/REFWORKS.

[92] Brisca G, Mariani M, Bellini T, Cervello C, Di Jorgi M, Mesini A, et al. Increase in benign acute childhood myositis in the post-COVID era: a retrospective study from a tertiary pediatric center. European Journal of Pediatrics 2025 184:9 2025;184:599-. https://doi.org/10.1007/S00431-025-06450-9.

[93] Kosmeri C, Papasavva ME, Kyrkou A, Gketsi V, Siomou E, Ladomenou F, et al. Influenza-Associated Benign Acute Childhood Myositis During the 2024–2025 Season: A Retrospective Multicenter Study. Children 2025, Vol 12, 2025;12. https://doi.org/10.3390/CHILDREN12101333.

[94] Wang X, Li Y, O'Brien KL, Madhi SA, Widdowson MA, Byass P, et al. Global burden of respiratory infections associated with seasonal influenza in children under 5 years in 2018: a systematic review and modelling study. Lancet Glob Health 2020;8:e497–510. https://doi.org/10.1016/S2214-109X(19)30545-5.

[95] Tokars JI, Olsen SJ, Reed C. Seasonal Incidence of Symptomatic Influenza in the United States. Clinical Infectious Diseases 2018;66:1511–8. https://doi.org/10.1093/cid/cix1060.

[96] Somes MP, Turner RM, Dwyer LJ, Newall AT. Estimating the annual attack rate of seasonal influenza among unvaccinated individuals: A systematic review and meta-analysis. Vaccine 2018;36:3199–207. https://doi.org/10.1016/J.VACCINE.2018.04.063.
[97] Kamidani S, Garg S, Rolfes MA, Campbell AP, Cummings CN, Haston JC, et al. Epidemiology, Clinical Characteristics, and Outcomes of Influenza-Associated Hospitalizations in US Children Over 9 Seasons Following the 2009 H1N1 Pandemic. Clinical Infectious Diseases 2022;75:1930–9. https://doi.org/10.1093/cid/ciac296.
[98] Reinhart K, Huang S, Kniss K, Reed C, Budd A. Influenza-Associated Pediatric Deaths — United States, 2024–25 Influenza Season. MMWR Morb Mortal Wkly Rep 2025;74:565–9. https://doi.org/10.15585/MMWR.MM7436A2.
[99] Trusinska D, Zin ST, Sandoval E, Homaira N, Shi T. Risk Factors for Poor Outcomes in Children Hospitalized with Virus-associated Acute Lower Respiratory Infections: A Systematic Review and Meta-analysis. Pediatric Infectious Disease Journal 2024;43:467–76. https://doi.org/10.1097/INF.0000000000004258.
[100] Adlhoch C, Mook P, Lamb F, Ferland L, Melidou A, Amato-Gauci AJ, et al. Very little influenza in the WHO European Region during the 2020/21 season, weeks 40 2020 to 8 2021. Eurosurveillance 2021;26:1–8. https://doi.org/10.2807/1560-7917.ES.2021.26.11.2100221.
[101] Riccio M Del, Nunes MC, Cowling BJ, Lina B, McCauley JW, Meijer A, et al. Post-disappearance scenarios: policy implications following the potential disappearance of B/Yamagata lineage influenza viruses. Eurosurveillance 2024;29:2400196. https://doi.org/10.2807/1560-7917.ES.2024.29.45.2400196/CITE/REFWORKS.
[102] (ECDC) EC for DP and C. Seasonal influenza - Annual Epidemiological Report for 2023/2024. n.d.
[103] Adlhoch C, Sneiderman M, Martinuka O, Melidou A, Bundle N, Fielding J, et al. Spotlight influenza: The 2019/20 influenza season and the impact of COVID-19 on influenza surveillance in the WHO European Region. Eurosurveillance 2021;26:2100077. https://doi.org/10.2807/1560-7917.ES.2021.26.40.2100077.
[104] (ECDC) EC for DP and C. Seasonal influenza - Annual Epidemiological Report for 2021−2022. n.d.
[105] (ECDC) EC for DP and C. Seasonal influenza - Annual Epidemiological Report for 2022/2023. n.d.
[106] (ECDC) EC for DP and C. Seasonal influenza - Annual Epidemiological Report for 2020-2021. n.d.
[107] Nørgaard SK, Nielsen J, Nordholm AC, Richter L, Chalupka A, Sierra NB, et al. Excess mortality in Europe coincides with peaks of COVID-19, influenza and respiratory syncytial virus (RSV), November 2023 to February 2024. Euro Surveill 2024;29:2400178. https://doi.org/10.2807/1560-7917.ES.2024.29.15.2400178.
[108] Sciensano. Surveillance des infections respiratoires aiguës : rapport épidémiologique saisons 2022-2023 et 2023-2024 | sciensano.be. n.d.
[109] Sciensano. Surveillance des infections respiratoires aiguës. Rapport épidémiologique des saisons 2020-2022 | sciensano.be. n.d.
[110] De Muylder G, Couvreur S, Stefani G, Brugerolles C, Dockx Y, Callies M, et al. Respi-Radar: a tool to monitor respiratory infections, Belgium, winter season 2023/24. Eurosurveillance 2025;30. https://doi.org/10.2807/1560-7917.ES.2025.30.35.2400756.
[111] Sciensano. Profil de risque et gravité de la maladie chez les patients adultes atteints d'une infection sévère à VRS, grippe ou COVID-19 | sciensano.be n.d. https://www.sciensano.be/en/biblio/profil-de-risque-et-gravite-de-la-maladie-chez-les-patients-adultes-atteints-dune-infection-severe-a (accessed December 16, 2025).
[112] Risicoprofiel en ziektegraad van volwassen RSV, influenza en COVID-19 patiënten met een ernstige infectie | sciensano.be n.d. https://www.sciensano.be/en/biblio/risicoprofiel-en-ziektegraad-van-volwassen-rsv-influenza-en-covid-19-patienten-met-een-ernstige (accessed January 25, 2026).
[113] Emborg HD, Vestergaard LS, Botnen AB, Nielsen J, Krause TG, Trebbien R. A late sharp increase in influenza detections and low interim vaccine effectiveness against the circulating A(H3N2)

strain, Denmark, 2021/22 influenza season up to 25 March 2022. Eurosurveillance 2022;27:2200278. https://doi.org/10.2807/1560-7917.ES.2022.27.15.2200278/CITE/REFWORKS.
[114] Kissling E, Maurel M, Emborg HD, Whitaker H, McMenamin J, Howard J, et al. Interim 2022/23 influenza vaccine effectiveness: six European studies, October 2022 to January 2023. Eurosurveillance 2023;28:2300116. https://doi.org/10.2807/1560-7917.ES.2023.28.21.2300116/CITE/REFWORKS.
[115] Maurel M, Pozo F, Pérez-Gimeno G, Buda S, Sève N, Oroszi B, et al. Influenza vaccine effectiveness in Europe: Results from the 2022–2023 VEBIS (Vaccine Effectiveness, Burden and Impact Studies) primary care multicentre study. Influenza Other Respir Viruses 2024;18:e13243. https://doi.org/10.1111/irv.13243.
[116] Maurel M, Howard J, Kissling E, Pozo F, Pérez-Gimeno G, Buda S, et al. Interim 2023/24 influenza A vaccine effectiveness: VEBIS European primary care and hospital multicentre studies, September 2023 to January 2024. Eurosurveillance 2024;29:2400089. https://doi.org/10.2807/1560-7917.ES.2024.29.8.2400089/CITE/REFWORKS.
[117] Rose AMC, Lucaccioni H, Marsh K, Kirsebom F, Whitaker H, Emborg HD, et al. Interim 2024/25 influenza vaccine effectiveness: eight European studies, September 2024 to January 2025. Eurosurveillance 2025;30:9–19. https://doi.org/10.2807/1560-7917.ES.2025.30.7.2500102/CITE/REFWORKS.
[118] Kirsebom FC, Thompson C, Talts T, Kele B, Whitaker HJ, Andrews N, et al. Early influenza virus characterisation and vaccine effectiveness in England in autumn 2025, a period dominated by influenza A(H3N2) subclade K. Eurosurveillance 2025;30. https://doi.org/10.2807/1560-7917.ES.2025.30.46.2500854.
[119] Emborg HD, Valentiner-Branth P. Enhanced influenza vaccines impact effectiveness in individuals aged 65 years and older, Denmark, 2024/25 influenza season up to 4 March 2025. Euro Surveill 2024;30:2500174. https://doi.org/10.2807/1560-7917.ES.2025.30.12.2500174.
[120] Rose AMC, Nicolay N, Mazagatos C, Martínez-Baz I, Launay O, De Mot L, et al. Vaccine effectiveness against influenza A in older adults and the effect of chronic conditions: results from the I-MOVE and VEBIS multicentre European hospital case–control studies, 2015/16–2023/24. BMC Medicine 2025 23:1 2025;23:602-. https://doi.org/10.1186/S12916-025-04426-Y.
[121] Johansen ND, Modin D, Pardo-Seco J, Rodriguez-Tenreiro-Sánchez C, Loiacono MM, Harris RC, et al. Effectiveness of high-dose influenza vaccine against hospitalisations in older adults (FLUNITY-HD): an individual-level pooled analysis. Lancet 2025;406:2425–34. https://doi.org/10.1016/S0140-6736(25)01742-8.
[122] Prezzi A, Saelens X, Vandijck D. Epidemiology of influenza over a ten-year period in Belgium: overview of the historical and current evidence. Virology Journal 2023 20:1 2023;20:271-. https://doi.org/10.1186/S12985-023-02238-1.
[123] Manansala R, Bilcke J, Willem L, Hens N, Beutels P. Optimizing influenza vaccine allocation by age using cost-effectiveness analysis: A comparison of 6720 vaccination program scenarios in children and adults in Belgium. Epidemics 2025;51:100826. https://doi.org/10.1016/J.EPIDEM.2025.100826.
[124] Sciensano. Surveillance van griepinfecties. Epidemiologisch rapport seizoen 2018-2019 | sciensano.be. n.d.
[125] Sciensano. Cijfers | sciensano.be n.d. https://www.sciensano.be/nl/gezondheidsonderwerpen/influenza/cijfers (accessed December 18, 2025).
[126] (ECDC) EC for DP and C. Multi-model analysis to quantify the impact of vaccination on COVID-19 and influenza hospitalisation burden among older adults in the EU/EEA, 2024/25. n.d. https://doi.org/10.2900/3212996.

[127] (ECDC) EC for DP and C. Survey report on national seasonal influenza vaccination recommendations and coverage rates in EU/EEA countries. n.d.
[128] (ECDC) EC for DP and C. Survey report on national seasonal influenza vaccination recommendations and coverage rates in EU/EEA countries, 2024/25. n.d.
[129] European Union. EUR-Lex - 32009H1019 - EN - EUR-Lex n.d. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32009H1019 (accessed December 18, 2025).
[130] Nivel. Vaccine Coverage Dutch National Influenza Prevention Program 2023: brief monitor. | Nivel n.d. https://www.nivel.nl/en/publicatie/vaccine-coverage-dutch-national-influenza-prevention-program-2023-brief-monitor (accessed December 20, 2025).
[131] Robert Koch Institute. GBE - Influenza: vaccination coverage (from 60 years) n.d. https://www.gbe.rki.de/EN/Topics/HealthPromotionPreventionAndCare/HealthPromotionAndPrevention/PreventiveHealthCareAndEarlyDetection/InfluenzaVaccination/InfluenzaVaccination_node.html?darstellung=0&kennzahl=1&zeit=2024&geschlecht=0&standardisierung=0 (accessed December 20, 2025).
[132] (WHO) WHO. Vaccines against influenza: WHO position paper – May 2022. 2022.
[133] Trombetta CM, Gianchecchi E, Montomoli E. Influenza vaccines: Evaluation of the safety profile. Hum Vaccin Immunother 2018;14:657–70. https://doi.org/10.1080/21645515.2017.1423153.
[134] Wei X, Tan X, Guan Q, Zhang R, Lei S, Wei S. Immunogenicity and safety of quadrivalent inactivated influenza vaccine in children aged 6 to 35 months: A systematic review and meta-analysis. Hum Vaccin Immunother 2023;19. https://doi.org/10.1080/21645515.2023.2256510.
[135] Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, Keenlyside RA, Ziegler DW, Retailliau HF, et al. Guillain-Barre syndrome following vaccination in the National Influenza Immunization Program, United States, 1976--1977. Am J Epidemiol 1979;110:105–23. https://doi.org/10.1093/oxfordjournals.aje.a112795.
[136] Wang F, Wang D, Wang Y, Li C, Zheng Y, Guo Z, et al. Population-Based Incidence of Guillain-Barré Syndrome During Mass Immunization With Viral Vaccines: A Pooled Analysis. Front Immunol 2022;13. https://doi.org/10.3389/FIMMU.2022.782198/PDF.
[137] Petráš M, Lesná IK, Dáňová J, Čelko AM. Is an Increased Risk of Developing Guillain-Barré Syndrome Associated with Seasonal Influenza Vaccination? A Systematic Review and Meta-Analysis. Vaccines (Basel) 2020;8. https://doi.org/10.3390/VACCINES8020150.
[138] Grave C, Boucheron P, Rudant J, Mikaeloff Y, Tubert-Bitter P, Escolano S, et al. Seasonal influenza vaccine and Guillain-Barré syndrome: A self-controlled case series study. Neurology 2020;94:E2168–79. https://doi.org/10.1212/WNL.0000000000009180.
[139] Levison LS, Thomsen RW, Andersen H. Guillain-Barré syndrome following influenza vaccination: A 15-year nationwide population-based case-control study. Eur J Neurol 2022;29:3389–94. https://doi.org/10.1111/ENE.15516.
[140] Kwong JC, Vasa PP, Campitelli MA, Hawken S, Wilson K, Rosella LC, et al. Risk of Guillain-Barré syndrome after seasonal influenza vaccination and influenza health-care encounters: A self-controlled study. Lancet Infect Dis 2013;13:769–76. https://doi.org/10.1016/S1473-3099(13)70104-X.
[141] McNeil MM, Weintraub ES, Duffy J, Sukumaran L, Jacobsen SJ, Klein NP, et al. Risk of anaphylaxis after vaccination in children and adults. Journal of Allergy and Clinical Immunology 2016;137:868–78. https://doi.org/10.1016/j.jaci.2015.07.048.
[142] Su JR, Moro PL, Ng CS, Lewis PW, Said MA, Cano M V. Anaphylaxis after vaccination reported to the Vaccine Adverse Event Reporting System, 1990-2016. Journal of Allergy and Clinical Immunology 2019;143:1465–73. https://doi.org/10.1016/j.jaci.2018.12.1003.
[143] Pennisi F, D'Amelio AC, Cuciniello R, Borlini S, Mirzaian L, Ricciardi GE, et al. Post-Vaccination Anaphylaxis in Adults: A Systematic Review and Meta-Analysis. Vaccines (Basel) 2025;13. https://doi.org/10.3390/VACCINES13010037.

[144] Grohskopf LA, Blanton LH, Ferdinands JM, Reed C, Dugan VG, Daskalakis DC. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2025–26 Influenza Season. MMWR Morb Mortal Wkly Rep 2025;74:500–7. https://doi.org/10.15585/mmwr.mm7432a2.
[145] Des Roches A, Paradis L, Gagnon R, Lemire C, Bégin P, Carr S, et al. Egg-allergic patients can be safely vaccinated against influenza. Journal of Allergy and Clinical Immunology 2012;130:1213-1216.e1. https://doi.org/10.1016/j.jaci.2012.07.046.
[146] https://www.gov.uk/government/publications/influenza-the-green-book-chapter-19 n.d.
[147] Wolfe DM, Fell D, Garritty C, Hamel C, Butler C, Hersi M, et al. Safety of influenza vaccination during pregnancy: a systematic review. BMJ Open 2023;13:e066182. https://doi.org/10.1136/bmjopen-2022-066182.
[148] Regan AK, Sullivan SG, Arah OA. Maternal influenza vaccination and associated risk of fetal loss: A claims-based prospective cohort study. Vaccine 2024;42. https://doi.org/10.1016/j.vaccine.2024.126256.
[149] Siu W, Sinilaite A, Papenburg J. Summary of the National Advisory Committee on Immunization (NACI) Updated Guidance on Influenza Vaccination During Pregnancy. Canada Communicable Disease Report 2024;50:86–92. https://doi.org/10.14745/ccdr.v50i34a01.
[150] Juvet LK, Robertson AH, Laake I, Mjaaland S, Trogstad L. Safety of Influenza A H1N1pdm09 Vaccines: An Overview of Systematic Reviews. Front Immunol 2021;12. https://doi.org/10.3389/FIMMU.2021.740048/PDF.
[151] Duffy J, Weintraub E, Hambidge SJ, Jackson LA, Kharbanda EO, Klein NP, et al. Febrile Seizure Risk After Vaccination in Children 6 to 23 Months. Pediatrics 2016;138. https://doi.org/10.1542/peds.2016-0320.
[152] Lloyd PC, Acharya G, Zhao H, Chen B, Beachler DC, Secora A, et al. Safety monitoring of health outcomes following influenza vaccination during the 2023–2024 season among U.S. Commercially-insured individuals aged 6 months through 64 years: Self-controlled case series analyses. Vaccine 2025;63. https://doi.org/10.1016/j.vaccine.2025.127614.
[153] Lloyd PC, Acharya G, Zhao H, Shah N, Anguzu G, Ambarsoomzadeh D, et al. Safety monitoring of health outcomes following influenza vaccination during the 2023–2024 season among U.S. Medicare beneficiaries aged 65 years and older. Vaccine 2025;53:127069. https://doi.org/10.1016/j.vaccine.2025.127069.
[154] Davidson JA, Banerjee A, Douglas I, Leyrat C, Pebody R, McDonald HI, et al. Primary prevention of acute cardiovascular events by influenza vaccination: an observational study. Eur Heart J 2023;44:610–20. https://doi.org/10.1093/eurheartj/ehac737.
[155] (ECDC) EC for DP and C. Influenza vaccine safety n.d. https://www.ecdc.europa.eu/en/seasonal-influenza/prevention-and-control/vaccine-safety (accessed December 20, 2025).
[156] Cdc C for DC and P. Influenza (Flu) Vaccine Safety | Vaccine Safety | CDC n.d. https://www.cdc.gov/vaccine-safety/vaccines/flu.html (accessed December 20, 2025).
[157] Barberis I, Myles P, Ault SK, Bragazzi NL, Martini M. History and evolution of influenza control through vaccination: from the first monovalent vaccine to universal vaccines. J Prev Med Hyg 2016;57:E115–20.
[158] Dos Santos G, Nguyen B-Y, Damaso S, Godderis L, Martínez-Gómez X, Eckermann T, et al. Brand-Specific Enhanced Safety Surveillance of GSK's Quadrivalent Seasonal Influenza Vaccine in Belgium, Germany and Spain for the 2018/2019 Season. Drug Saf 2020;43:265–79. https://doi.org/10.1007/s40264-019-00893-4.
[159] Haber P, Moro PL, Lewis P, Woo EJ, Jankosky C, Cano M. Post-licensure surveillance of quadrivalent inactivated influenza (IIV4) vaccine in the United States, Vaccine Adverse Event Reporting System (VAERS), July 1, 2013−May 31, 2015. Vaccine 2016;34:2507–12. https://doi.org/10.1016/j.vaccine.2016.03.048.

[160] Tse A, Tseng HF, Greene SK, Vellozzi C, Lee GM, VSD Rapid Cycle Analysis Influenza Working Group. Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010-2011. Vaccine 2012;30:2024–31. https://doi.org/10.1016/j.vaccine.2012.01.027.
[161] Skaarup KG, Johansen ND, Modin D, Loiacono MM, Harris RC, Dufournet M, et al. High-Dose Versus Standard-Dose Influenza Vaccine in Heart Failure: A Prespecified Analysis of the DANFLU-2 Trial. Circ Heart Fail 2025;18:e013678. https://doi.org/10.1161/CIRCHEARTFAILURE.125.013678.
[162] Pardo-Seco J, Rodríguez-Tenreiro-Sánchez C, Giné-Vázquez I, Mallah N, Mirás-Carballal S, Piñeiro-Sotelo M, et al. High-Dose Influenza Vaccine to Reduce Hospitalizations. New England Journal of Medicine 2025;393:2303–12. https://doi.org/10.1056/NEJMoa2509834.
[163] Lee JKH, Lam GKL, Shin T, Samson SI, Greenberg DP, Chit A. Efficacy and effectiveness of high-dose influenza vaccine in older adults by circulating strain and antigenic match: An updated systematic review and meta-analysis. Vaccine 2021;39:A24–35. https://doi.org/10.1016/J.VACCINE.2020.09.004.
[164] Domnich A, Arata L, Amicizia D, Puig-Barberà J, Gasparini R, Panatto D. Effectiveness of MF59-adjuvanted seasonal influenza vaccine in the elderly: A systematic review and meta-analysis. Vaccine 2017;35:513–20. https://doi.org/10.1016/j.vaccine.2016.12.011.
[165] Ferdinands JM, Blanton LH, Alyanak E, Chung JR, Trujillo L, Taliano J, et al. Protection against influenza hospitalizations from enhanced influenza vaccines among older adults: A systematic review and network meta-analysis. J Am Geriatr Soc 2024;72:3875–89. https://doi.org/10.1111/jgs.19176.
[166] Johansen ND, Modin D, Loiacono MM, Harris RC, Dufournet M, Larsen CS, et al. High-Dose Influenza Vaccine Effectiveness against Hospitalization in Older Adults. New England Journal of Medicine 2025;393:2291–302. https://doi.org/10.1056/NEJMoa2509907.
[167] Lee JKH, Lam GKL, Yin JK, Loiacono MM, Samson SI. High-dose influenza vaccine in older adults by age and seasonal characteristics: Systematic review and meta-analysis update. Vaccine X 2023;14:100327. https://doi.org/10.1016/j.jvacx.2023.100327.
[168] DiazGranados CA, Dunning AJ, Kimmel M, Kirby D, Treanor J, Collins A, et al. Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults. New England Journal of Medicine 2014;371:635–45. https://doi.org/10.1056/NEJMoa1315727.
[169] DiazGranados CA, Robertson CA, Talbot HK, Landolfi V, Dunning AJ, Greenberg DP. Prevention of serious events in adults 65 years of age or older: A comparison between high-dose and standard-dose inactivated influenza vaccines. Vaccine 2015;33:4988–93. https://doi.org/10.1016/j.vaccine.2015.07.006.
[170] Skaarup KG, Lassen MCH, Modin D, Johansen ND, Loiacono MM, Harris RC, 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. Journal of Infection 2024;89:106187. https://doi.org/10.1016/j.jinf.2024.106187.
[171] Izurieta HS, Thadani N, Shay DK, Lu Y, Maurer A, Foppa IM, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: A retrospective cohort analysis. Lancet Infect Dis 2015;15:293–300. https://doi.org/10.1016/S1473-3099(14)71087-4.
[172] Lu Y, Chillarige Y, Izurieta HS, Wei Y, Xu W, Lu M, et al. Effect of Age on Relative Effectiveness of High-Dose Versus Standard-Dose Influenza Vaccines Among US Medicare Beneficiaries Aged ≥65 Years. J Infect Dis 2019;220:1511–20. https://doi.org/10.1093/infdis/jiz360.
[173] Young-Xu Y, Van Aalst R, Mahmud SM, Rothman KJ, Snider JT, Westreich D, et al. Relative Vaccine Effectiveness of High-Dose Versus Standard-Dose Influenza Vaccines Among Veterans Health Administration Patients. J Infect Dis 2018;217:1718–27. https://doi.org/10.1093/infdis/jiy088.

[174] Young-Xu Y, Snider JT, van Aalst R, Mahmud SM, Thommes EW, Lee JKH, et al. Analysis of relative effectiveness of high-dose versus standard-dose influenza vaccines using an instrumental variable method. Vaccine 2019;37:1484–90. https://doi.org/10.1016/J.VACCINE.2019.01.063.
[175] Domnich A, Orsi A, Signori A, Panatto D, Icardi G. Relative effectiveness of the high-dose versus standard-dose influenza vaccines for the prevention of laboratory-confirmed influenza among Italian older adults during three recent seasons. International Journal of Infectious Diseases 2025;161:108100. https://doi.org/10.1016/j.ijid.2025.108100.
[176] Faksova K, Thiesson EM, Pihlström N, Baum U, Biering-Sørensen T, Poukka E, et al. Brand-specific influenza vaccine effectiveness in three Nordic countries during the 2024-2025 season: a target trial emulation study based on registry data. 2025.
[177] Johansen ND, Modin D, Pardo-Seco J, Rodriguez-Tenreiro-Sánchez C, Loiacono MM, Harris RC, et al. High-Dose vs. Standard-Dose Influenza Vaccine and Cardiovascular Outcomes in Older Adults: The FLUNITY-HD Prespecified Pooled Analysis. Circulation 2025. https://doi.org/10.1161/CIRCULATIONAHA.125.077801.
[178] Bartholdy KV, Johansen ND, Modin D, Loiacono MM, Harris RC, Dufournet M, et al. High-Dose vs Standard-Dose Influenza Vaccine in Chronic Kidney Disease. JACC 2025. https://doi.org/10.1016/j.jacc.2025.10.005.
[179] Pareek M, Johansen ND, Modin D, Loiacono MM, Harris RC, Dufournet M, et al. High-dose vs. standard-dose inactivated influenza vaccine and cardiovascular outcomes in persons with or without pre-existing atherosclerotic cardiovascular disease: the DANFLU-2 trial. Eur Heart J 2025;46:4282–90. https://doi.org/10.1093/eurheartj/ehaf678.
[180] Espersen C, Johansen ND, Modin D, Loiacono MM, Harris RC, Dufournet M, et al. High-Dose vs Standard-Dose Influenza Vaccine in Older Adults With Atrial Fibrillation. JACC 2025. https://doi.org/10.1016/j.jacc.2025.09.1578.
[181] Skaarup KG, Davidovski FS, Durukan E, Modin D, Lassen MCH, Dons M, et al. Cardiac Characteristics of Hospitalized Influenza Patients: An Interim Analysis From the FluHeart Study. Influenza Other Respir Viruses 2025;19:e70067. https://doi.org/10.1111/irv.70067.
[182] Pareek M, Johansen ND, Modin D, Loiacono MM, Harris RC, Dufournet M, et al. Risk of Myocarditis or Pericarditis With High-Dose vs Standard-Dose Influenza Vaccine: A Prespecified Secondary Analysis of the Randomized DANFLU-2 Trial. JAMA Netw Open 2025;8:e2536889. https://doi.org/10.1001/jamanetworkopen.2025.36889.
[183] Johansen ND, Modin D, Loiacono MM, Harris RC, Dufournet M, Larsen CS, et al. High-Dose vs Standard-Dose Influenza Vaccine and Cardiovascular Outcomes in Older Adults: A Prespecified Secondary Analysis of the DANFLU-2 Randomized Clinical Trial. JAMA Cardiol 2025;10:1186–94. https://doi.org/10.1001/JAMACARDIO.2025.3460.
[184] Mannino S, Villa M, Apolone G, Weiss NS, Groth N, Aquino I, et al. Effectiveness of Adjuvanted Influenza Vaccination in Elderly Subjects in Northern Italy. Am J Epidemiol 2012;176:527–33. https://doi.org/10.1093/aje/kws313.
[185] Imran M, Mills CW, McDermott KW, Dean A, Bogdanov A, McGovern I, et al. Relative Effectiveness of the MF59-Adjuvanted Influenza Vaccine Versus High-Dose Influenza Vaccine in Older Adults With Influenza Risk Factors During the 2019–2020 US Influenza Season. Open Forum Infect Dis 2024;11:ofae459. https://doi.org/10.1093/ofid/ofae459.
[186] Domnich A, de Waure C. Comparative effectiveness of adjuvanted versus high-dose seasonal influenza vaccines for older adults: a systematic review and meta-analysis. International Journal of Infectious Diseases 2022;122:855–63. https://doi.org/10.1016/j.ijid.2022.07.048.
[187] Kumar D, Campbell P, Hoschler K, Hidalgo L, Al-Dabbagh M, Wilson L, et al. Randomized Controlled Trial of Adjuvanted Versus Nonadjuvanted Influenza Vaccine in Kidney Transplant Recipients. Transplantation 2016;100:662–9. https://doi.org/10.1097/TP.0000000000000861.

[188] Domnich A, Trombetta CS, Fallani E, Salvatore M. Immunogenicity and safety of the MF59-adjuvanted seasonal influenza vaccine in non-elderly adults: A systematic review and meta-analysis. PLoS One 2024;19:e0310677. https://doi.org/10.1371/JOURNAL.PONE.0310677.
[189] Coleman BL, Sanderson R, Haag MDM, McGovern I. Effectiveness of the MF59-adjuvanted trivalent or quadrivalent seasonal influenza vaccine among adults 65 years of age or older, a systematic review and meta-analysis. Influenza Other Respir Viruses 2021;15:813–23. https://doi.org/10.1111/irv.12871.
[190] Bella A, Gesualdo F, Orsi A, Arcuri C, Chironna M, Loconsole D, et al. Effectiveness of the trivalent MF59 adjuvated influenza vaccine in preventing hospitalization due to influenza B and A(H1N1)pdm09 viruses in the elderly in Italy, 2017 – 2018 season. Expert Rev Vaccines 2019;18:671–9. https://doi.org/10.1080/14760584.2019.1627206.
[191] Mira-Iglesias A, López-Labrador FX, Baselga-Moreno V, Tortajada-Girbés M, Mollar-Maseres J, Carballido-Fernández M, et al. Influenza vaccine effectiveness against laboratory-confirmed influenza in hospitalised adults aged 60 years or older, Valencia Region, Spain, 2017/18 influenza season. Eurosurveillance 2019;24. https://doi.org/10.2807/1560-7917.ES.2019.24.31.1800461.
[192] Bellino S, Piovesan C, Bella A, Rizzo C, Pezzotti P, Ramigni M. Determinants of vaccination uptake, and influenza vaccine effectiveness in preventing deaths and hospital admissions in the elderly population; Treviso, Italy, 2014/2015-2016/2017 seasons. Hum Vaccin Immunother 2020;16:301–12. https://doi.org/10.1080/21645515.2019.1661754.
[193] Lapi F, Marconi E, Simonetti M, Baldo V, Rossi A, Sessa A, et al. Adjuvanted versus nonadjuvanted influenza vaccines and risk of hospitalizations for pneumonia and cerebro/cardiovascular events in the elderly. Expert Rev Vaccines 2019;18:663–70. https://doi.org/10.1080/14760584.2019.1622418.
[194] Imran M, Mills C, McDermott KW, Dean A, Bogdanov A, McGovern I, et al. Relative effectiveness of adjuvanted versus non-adjuvanted influenza vaccines in older adults with risk factors for influenza complications during the 2019–2020 U.S. influenza season. Vaccine 2024;42. https://doi.org/10.1016/j.vaccine.2024.126316.
[195] Boikos C, McGovern I, Ortiz JR, Puig-Barberà J, Versage E, Haag M. Relative Vaccine Effectiveness of Adjuvanted Trivalent Influenza Vaccine over Three Consecutive Influenza Seasons in the United States. Vaccines (Basel) 2022;10:1456. https://doi.org/10.3390/vaccines10091456.
[196] Calabrò GE, Boccalini S, Panatto D, Rizzo C, Di Pietro ML, Abreha FM, et al. The New Quadrivalent Adjuvanted Influenza Vaccine for the Italian Elderly: A Health Technology Assessment. Int J Environ Res Public Health 2022;19:4166. https://doi.org/10.3390/ijerph19074166.
[197] Frühwein M, Schelling J, Wahle K, Beier D, Kwetkat A, Schwarz TF. Enhanced targeted influenza vaccines - New evidence shows higher effectiveness in older adults. Deutsche Medizinische Wochenschrift 2023;148:556–62. https://doi.org/10.1055/A-2032-1368.
[198] McGovern I, Chastek B, Bancroft T, Webb N, Imran M, Pelton SI, et al. Relative vaccine effectiveness of MF59-adjuvanted vs high-dose trivalent inactivated influenza vaccines for prevention of test-confirmed influenza hospitalizations during the 2017–2020 influenza seasons. International Journal of Infectious Diseases 2024;146. https://doi.org/10.1016/j.ijid.2024.107160.
[199] Cowling BJ, Perera RAPM, Valkenburg SA, Leung NHL, Iuliano AD, Tam YH, et al. Comparative Immunogenicity of Several Enhanced Influenza Vaccine Options for Older Adults: A Randomized, Controlled Trial. Clinical Infectious Diseases 2020;71:1704–14. https://doi.org/10.1093/cid/ciz1034.
[200] De Donato S, Granoff D, Minutello M, Lecchi G, Faccini M, Agnello M, et al. Safety and immunogenicity of MF59-adjuvanted influenza vaccine in the elderly. Vaccine 1999;17:3094–101. https://doi.org/10.1016/S0264-410X(99)00138-3.

[201] Beran J, Reynales H, Poder A, Yu CY, Pitisuttithum P, Yuan LL, et al. Prevention of influenza during mismatched seasons in older adults with an MF59-adjuvanted quadrivalent influenza vaccine: a randomised, controlled, multicentre, phase 3 efficacy study. Lancet Infect Dis 2021;21:1027–37. https://doi.org/10.1016/S1473-3099(20)30694-0.
[202] Vesikari T, Forstén A, Herbinger K-H, Cioppa G Della, Beygo J, Borkowski A, et al. Safety and immunogenicity of an MF59®-adjuvanted A/H5N1 pre-pandemic influenza vaccine in adults and the elderly. Vaccine 2012;30:1388–96. https://doi.org/10.1016/j.vaccine.2011.12.009.
[203] Clark TW, Pareek M, Hoschler K, Dillon H, Nicholson KG, Groth N, et al. Trial of 2009 Influenza A (H1N1) Monovalent MF59-Adjuvanted Vaccine. New England Journal of Medicine 2009;361:2424–35. https://doi.org/10.1056/NEJMoa0907650.
[204] Essink BJ, Vermeulen W, Andrade C, de Rooij R, Isakov L, Casula D, et al. A randomised phase 2 immunogenicity and safety study of a MF59-adjuvanted quadrivalent subunit inactivated cell-derived influenza vaccine (aQIVc) in adults aged 50 years and older. Vaccine 2025;51:126791. https://doi.org/10.1016/j.vaccine.2025.126791.
[205] Amicizia D, Domnich A, Lai PL, Orsi A, Icardi G, Tkach-Motulyak O, et al. Enhanced passive safety surveillance of the MF59-adjuvanted quadrivalent influenza vaccine in the elderly during the 2021/22 influenza season. Hum Vaccin Immunother 2023;19:2190279. https://doi.org/10.1080/21645515.2023.2190279.
[206] Villa M, Black S, Groth N, Rothman KJ, Apolone G, Weiss NS, et al. Safety of MF59-Adjuvanted Influenza Vaccination in the Elderly: Results of a Comparative Study of MF59-Adjuvanted Vaccine Versus Nonadjuvanted Influenza Vaccine in Northern Italy. Am J Epidemiol 2013;178:1139–45. https://doi.org/10.1093/aje/kwt078.
[207] Essink B, Fierro C, Rosen J, Figueroa AL, Zhang B, Verhoeven C, et al. Immunogenicity and safety of MF59-adjuvanted quadrivalent influenza vaccine versus standard and alternate B strain MF59-adjuvanted trivalent influenza vaccines in older adults. Vaccine 2020;38:242–50. https://doi.org/10.1016/j.vaccine.2019.10.021.
[208] Gavazzi G, Fougère B, Hanon O, Leroux-Roels I, Brochot E, Blanchard E, et al. Enhanced influenza vaccination for older adults in Europe: a review of the current situation and expert recommendations for the future. Expert Rev Vaccines 2025;24:350–64. https://doi.org/10.1080/14760584.2025.2499728.
[209] HAS France. HAS • Vaccination contre la grippe saisonnière des personnes de 65 ans et plus • avril 2025 2 Descriptif de la publication Titre Vaccination contre la grippe saisonnière des personnes de 65 ans et plus Place des vaccins Efluelda et Fluad n.d. www.has-sante.fr (accessed December 19, 2025).
[210] Gezondheidsraad Nederland. Inzet van vernieuwde typen griepvaccins in het Nationaal Programma Grieppreventie. n.d.
[211] Robert Koch Institute. Epidemiologisches Bulletin Recommendations by the Standing Committee on Vaccination (STIKO) at the Robert Koch Institute. 2025.
[212] Santé Sécu Luxembourg. Grippe saisonnière - Portail Santé - Luxembourg n.d. https://santesecu.public.lu/fr/espace-professionnel/recommandations/conseil-maladies-infectieuses/grippe-saisonniere.html (accessed December 19, 2025).
[213] GOV.UK. JCVI statement on influenza vaccines for 2025 to 2026 - GOV.UK n.d. https://www.gov.uk/government/publications/flu-vaccines-2025-to-2026-jcvi-advice/jcvi-statement-on-influenza-vaccines-for-2025-to-2026 (accessed December 19, 2025).
[214] Pahmeier K, Speckemeier C, Neusser S, Wasem J, Biermann-Stallwitz J. Vaccinating the German Population Aged 60 Years and Over with a Quadrivalent High-Dose Inactivated Influenza Vaccine Compared to Standard-Dose Vaccines: A Transmission and Budget Impact Model. PharmacoEconomics 2023 41:11 2023;41:1539–50. https://doi.org/10.1007/S40273-023-01299-Y.

[215] Coleman BL, Gutmanis I, McGovern I, Haag M. Effectiveness of Cell-Based Quadrivalent Seasonal Influenza Vaccine: A Systematic Review and Meta-Analysis. Vaccines (Basel) 2023;11:1607. https://doi.org/10.3390/vaccines11101607.
[216] Stein AN, Thanataveerat A, McDermott K, Dean A, Wall S, Pack C, et al. Superior Effectiveness and Estimated Public Health Impact of Cell- Versus Egg-Based Influenza Vaccines in Children and Adults During the US 2023–2024 Season. Infectious Diseases and Therapy 2025 14:12 2025;14:2693–718. https://doi.org/10.1007/S40121-025-01230-2.
[217] Stein AN, Mills CW, McGovern I, McDermott KW, Dean A, Bogdanov AN, et al. Relative Vaccine Effectiveness of Cell- vs Egg-Based Quadrivalent Influenza Vaccine Against Test-Confirmed Influenza Over 3 Seasons Between 2017 and 2020 in the United States. Open Forum Infect Dis 2024;11:398. https://doi.org/10.1093/ofid/ofae175.
[218] Gärtner BC, Beier D, Gosch G, Wahle K, Wendt L, Förster L-C, et al. Cell-based influenza vaccines: An effective vaccine option for under 60-year-olds. GMS Hyg Infect Control 2024;19:Doc21. https://doi.org/10.3205/dgkh000476.
[219] Colombo RE, Richard SA, Schmidt K, Schofield C, Ganesan A, Campbell W, et al. Randomized Pragmatic Trial of the Comparative Effectiveness of Chicken Egg-Based Inactivated, Mammalian Cell Culture-Based Inactivated, and Recombinant Protein Quadrivalent Seasonal Influenza Vaccines in United States Military Health System Beneficiaries. Clinical Infectious Diseases 2025;15. https://doi.org/10.1093/cid/ciaf503.
[220] Ku JH, Rayens E, Sy LS, Qian L, Ackerson BK, Luo Y, et al. Comparative Effectiveness of Licensed Influenza Vaccines in Preventing Influenza-related Medical Encounters and Hospitalizations in the 2022–2023 Influenza Season Among Adults ≥65 Years of Age. Clinical Infectious Diseases 2024;79:1283–92. https://doi.org/10.1093/cid/ciae375.
[221] Askar M, Ali KA, Batke M, Brugger T, Falman A, Robertson AH, et al. Relative Efficacy, Effectiveness and Safety of Newer and/or Enhanced Seasonal Influenza Vaccines for the Prevention of Laboratory-Confirmed Influenza in Individuals Aged 18 years and Over: Update of a Systematic Review. Rev Med Virol 2025;35. https://doi.org/10.1002/rmv.70020.
[222] Whitaker HJ, Kirsebom FCM, Hassell K, Quinot C, Stowe J, Hoschler K, et al. Effectiveness of Influenza Vaccines and Duration of Protection Against Hospitalisation in England: 2022/2023 and 2023/2024 Seasons. Influenza Other Respir Viruses 2025;19:e70194. https://doi.org/10.1111/irv.70194.
[223] Gaglani M, Raiyani C, Murthy K, Smith M, da Graca B, Dubrocq G, et al. Absolute and Relative Effectiveness of Cell Culture–Based and Egg–Based Quadrivalent Inactivated Influenza (Flu) Vaccine Products From the 2014–2015 to 2018–2019 Seasons, US Flu VE Network. Clinical Infectious Diseases 2025. https://doi.org/10.1093/cid/ciaf579.
[224] Imran M, Puig-Barbera J, Ortiz JR, Lopez-Gonzalez L, Dean A, Bonafede M, et al. Relative Effectiveness of the Cell-Based Quadrivalent Influenza Vaccine in Preventing Cardiorespiratory Hospitalizations in Adults Aged 18-64 Years During the 2019-2020 US Influenza Season. Open Forum Infect Dis 2023;10. https://doi.org/10.1093/ofid/ofad304.
[225] Jordan K, Murchu EO, Comber L, Hawkshaw S, Marshall L, O'Neill M, et al. Systematic review of the efficacy, effectiveness and safety of cell-based seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in individuals ≥18 years of age. Rev Med Virol 2023;33. https://doi.org/10.1002/rmv.2332.
[226] Gaglani M, Raiyani C, Murthy K, Smith M, da Graca B, Dubrocq G, et al. Absolute and Relative Effectiveness of Cell Culture–Based and Egg–Based Quadrivalent Inactivated Influenza (Flu) Vaccine Products From the 2014–2015 to 2018–2019 Seasons, US Flu VE Network. Clinical Infectious Diseases 2025. https://doi.org/10.1093/cid/ciaf579.
[227] Silva-Moraes V, Reis LR, Ross TM. Comparative analysis of cellular immune responses to four seasonal inactivated influenza vaccines in younger and older adults. The Journal of Immunology 2025. https://doi.org/10.1093/jimmun/vkaf286.

[228] Dawood FS, Naleway AL, Flannery B, Levine MZ, Murthy K, Sambhara S, et al. Comparison of the Immunogenicity of Cell Culture-Based and Recombinant Quadrivalent Influenza Vaccines to Conventional Egg-Based Quadrivalent Influenza Vaccines Among Healthcare Personnel Aged 18–64 Years: A Randomized Open-Label Trial. Clinical Infectious Diseases 2021;73:1973–81. https://doi.org/10.1093/cid/ciab566.
[229] Boyce TG, Levine MZ, McClure DL, King JP, Flannery B, Nguyen HQ, et al. Antibody response to sequential vaccination with cell culture, recombinant, or egg-based influenza vaccines among U.S. adults. Hum Vaccin Immunother 2024;20. https://doi.org/10.1080/21645515.2024.2370087.
[230] Mannocci A, Pellacchia A, Millevolte R, Chiavarini M, de Waure C. Quadrivalent Vaccines for the Immunization of Adults against Influenza: A Systematic Review of Randomized Controlled Trials. Int J Environ Res Public Health 2022;19:9425. https://doi.org/10.3390/ijerph19159425.
[231] Hiqa. Health technology assessment of use of an enhanced inactivated influenza vaccine for those aged 65 years and older in the HSE Seasonal Influenza Vaccination Programme n.d.
[232] Thorrington D, van Leeuwen E, Ramsay M, Pebody R, Baguelin M. Assessing optimal use of the standard dose adjuvanted trivalent seasonal influenza vaccine in the elderly. Vaccine 2019;37:2051–6. https://doi.org/10.1016/j.vaccine.2019.03.002.
[233] Alvarez FP, Chevalier P, Borms M, Bricout H, Marques C, Soininen A, et al. Cost-effectiveness of influenza vaccination with a high dose quadrivalent vaccine of the elderly population in Belgium, Finland, and Portugal. J Med Econ 2023;26:710–9. https://doi.org/10.1080/13696998.2023.2194193;WGROUP:STRING:PUBLICATION.
[234] van der Pol S, Zeevat F, Postma MJ, Boersma C. Cost-effectiveness of high-dose influenza vaccination in the Netherlands: Incorporating the impact on both respiratory and cardiovascular hospitalizations. Vaccine 2024;42:3429–36. https://doi.org/10.1016/J.VACCINE.2024.04.040.
[235] Jacob J, Biering-Sørensen T, Holger Ehlers L, Edwards CH, Mohn KG-I, Nilsson A, et al. Cost-Effectiveness of Vaccination of Older Adults with an MF59®-Adjuvanted Quadrivalent Influenza Vaccine Compared to Standard-Dose and High-Dose Vaccines in Denmark, Norway, and Sweden. Vaccines (Basel) 2023;11:753. https://doi.org/10.3390/vaccines11040753.
[236] Marbaix S, Dauby N, Mould-Quevedo J. Cost-effectiveness of the adjuvanted quadrivalent influenza vaccine in the elderly Belgian population. Expert Rev Vaccines 2023;22:608–19. https://doi.org/10.1080/14760584.2023.2229917.
[237] Gavazzi G, Paccalin M, Berkovitch Q, Leleu H, Moreau R, Ciglia E, et al. Cost-effectiveness of cell-based influenza vaccine in France. Expert Rev Vaccines 2024;23:1020–8. https://doi.org/10.1080/14760584.2024.2417854.
[238] Cai R, Gerlier L, Eichner M, Schwehm M, Rajaram S, Mould-Quevedo J, et al. Cost-effectiveness of the cell-based quadrivalent versus the standard egg-based quadrivalent influenza vaccine in Germany. J Med Econ 2021;24:490–501. https://doi.org/10.1080/13696998.2021.1908000.
[239] Rumi F, Basile M, Cicchetti A, Alvarez FP, Azzi MV, Muzii B. Cost-effectiveness for high dose quadrivalent versus the adjuvanted quadrivalent influenza vaccine in the Italian older adult population. Front Public Health 2023;11. https://doi.org/10.3389/fpubh.2023.1200116.
[240] Behrouzi B, Bhatt DL, Cannon CP, Vardeny O, Lee DS, Solomon SD, et al. Association of Influenza Vaccination With Cardiovascular Risk: A Meta-analysis. JAMA Netw Open 2022;5:e228873–e228873. https://doi.org/10.1001/JAMANETWORKOPEN.2022.8873.
[241] Ahmed F, Lindley MC, Allred N, Weinbaum CM, Grohskopf L. Effect of influenza vaccination of healthcare personnel on morbidity and mortality among patients: systematic review and grading of evidence. Clin Infect Dis 2014;58:50–7. https://doi.org/10.1093/CID/CIT580.
[242] Oguz MM, Senel S. Effectiveness of cocoon strategy vaccination on prevention of influenza-like illness in young infants. Hum Vaccin Immunother 2024;20. https://doi.org/10.1080/21645515.2024.2350090.

[243] Orrico-Sánchez A, Valls-Arévalo Á, Garcés-Sánchez M, Álvarez Aldeán J, Ortiz de Lejarazu Leonardo R. Efficacy and effectiveness of influenza vaccination in healthy children. A review of current evidence. Enfermedades Infecciosas y Microbiologia Clinica (English Ed) 2023;41:396–406. https://doi.org/10.1016/j.eimce.2022.02.016.
[244] Garai R, Jánosi Á, Krivácsy P, Herczeg V, Kói T, Nagy R, et al. Head-to-head comparison of influenza vaccines in children: a systematic review and meta-analysis. J Transl Med 2024;22:903. https://doi.org/10.1186/s12967-024-05676-9.
[245] Melidou A, Enkirch T, Willgert K, Adlhoch C, Alm E, Lamb F, et al. Drivers for a pandemic due to avian influenza and options for One Health mitigation measures. EFSA Journal 2024;22:e8735. https://doi.org/10.2903/j.efsa.2024.8735.
[246] (ECDC) EC for DP and C. Scenarios for pre-pandemic zoonotic influenza preparedness and response n.d. https://www.ecdc.europa.eu/en/publications-data/scenarios-pre-pandemic-zoonotic-influenza-preparedness-and-response (accessed December 20, 2025).
[247] Tan LJ, Trevas D, Falsey AR. Adult vaccine coadministration is safe, effective, and acceptable: results of a survey of the literature. Influenza Other Respir Viruses 2025;19:e70090. https://doi.org/10.1111/irv.70090.
[248] Clark R, Davies S, Labrador J, Loubet P, Natalini Martínez S, Moríñigo HM, et al. Safety and Immunogenicity of Respiratory Syncytial Virus Prefusion F Protein Vaccine when Co-administered with Adjuvanted Seasonal Quadrivalent Influenza Vaccine in Older Adults: A Phase 3 Randomized Trial. Clinical Infectious Diseases 2024;79:1088–98. https://doi.org/10.1093/cid/ciae365.
[249] Buynak R, Cannon K, DeAtkine D, Kirby J, Usdan L, Bhavsar A, et al. Randomized, Open-Label Phase 3 Study Evaluating Immunogenicity, Safety, and Reactogenicity of RSVPreF3 OA Coadministered with FLU-QIV-HD in Adults Aged ≥ 65. Infect Dis Ther 2024;13:1789–805. https://doi.org/10.1007/s40121-024-00985-4.
[250] Goswami J, Cardona JF, Hsu DC, Simorellis AK, Wilson L, Dhar R, et al. Safety and immunogenicity of mRNA-1345 RSV vaccine coadministered with an influenza or COVID-19 vaccine in adults aged 50 years or older: an observer-blinded, placebo-controlled, randomised, phase 3 trial. Lancet Infect Dis 2025;25:411–23. https://doi.org/10.1016/S1473-3099(24)00589-9.
[251] Omole T, Weinberg AS, Azizad M, Greenberg D, Grijalva CG, Orenstein WA, et al. A phase 3 randomized, double-blind clinical study to evaluate the safety and immunogenicity of V116 when administered concomitantly with influenza vaccine in adults 50 years of age or older. Vaccine 2025;62:127514. https://doi.org/10.1016/j.vaccine.2025.127514.
[252] Bai S, Zhou S, Zhang J, Chen W, Lv M, Wang J, et al. Immunogenicity and safety of different combinations involving a third booster dose of SARS-CoV-2 inactivated vaccine, inactivated quadrivalent influenza vaccine, and 23-valent pneumococcal polysaccharide vaccine in adults aged ≥60 years: a phase 4, randomized, open-label study. Front Immunol 2024;15. https://doi.org/10.3389/fimmu.2024.1437267.
[253] Chandler R, Montenegro N, Llorach C, Aguirre LN, Germain S, Kuriyakose SO, et al. Immunogenicity, Reactogenicity, and Safety of AS01E-adjuvanted Respiratory Syncytial Virus (RSV) Prefusion F Protein-based Candidate Vaccine (RSVPreF3 OA) When Co-administered With a Seasonal Quadrivalent Influenza Vaccine in Older Adults: Results of a Phase 3, Open-Label, Randomized Controlled Trial. Clinical Infectious Diseases 2024;78:1360–8. https://doi.org/10.1093/cid/ciad786.
[254] Widagdo W, Bastian AR, Jastorff AM, Scheys I, De Paepe E, Comeaux CA, et al. Concomitant administration of Ad26.RSV.preF/RSV preF protein vaccine and high-dose influenza vaccine in adults 65 years and older: a noninferiority trial. J Infect Dis 2024;230:e374–83. https://doi.org/10.1093/infdis/jiad594.
[255] Chime N, Anspach B, Jain V, Laajalahti O, Ollinger T, Yaplee D, et al. Phase 3 Study Assessing Lot-to-Lot Consistency of Respiratory Syncytial Virus Prefusion Protein F3 Vaccine and Its

Immune Response, Safety, and Reactogenicity When Co-administered With Quadrivalent Influenza Vaccine. J Infect Dis 2025;231:e144–53. https://doi.org/10.1093/infdis/jiae342.
[256] Zhu Z, Sun J, Xie Y, Lu X, Tang W, Zhao Y, et al. Immunogenicity and Safety of an Inactivated Quadrivalent Influenza Vaccine Administered Concomitantly with a 23-Valent Pneumococcal Polysaccharide Vaccine in Adults Aged 60 Years and Older. Vaccines (Basel) 2024;12. https://doi.org/10.3390/VACCINES12080935/S1.
[257] Hermida N, Ferguson M, Leroux-Roels I, Pagnussat S, Yaplee D, Hua N, et al. Safety and Immunogenicity of Respiratory Syncytial Virus Prefusion Maternal Vaccine Coadministered With Diphtheria-Tetanus-Pertussis Vaccine: A Phase 2 Study. J Infect Dis 2024;230:e353–62. https://doi.org/10.1093/infdis/jiad560.
[258] Schmader KE, Walter EB, Talaat KR, Rountree W, Poniewierski M, Randolph E, et al. Safety of Simultaneous Vaccination With Adjuvanted Zoster Vaccine and Adjuvanted Influenza Vaccine: A Randomized Clinical Trial. JAMA Netw Open 2024;7:e2440817. https://doi.org/10.1001/JAMANETWORKOPEN.2024.40817.
[259] Li Y, Xia H, Zhang H, Lu Y, Zhou H, Yu R, et al. The safety of co-administration of recombinant zoster vaccine (Shingrix) and influenza vaccines in the elderly in VAERS during 2018-2024. Hum Vaccin Immunother 2025;21. https://doi.org/10.1080/21645515.2025.2525603.
[260] Melgar M, Britton A, Roper LE, Talbot HK, Long SS, Kotton CN, et al. 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;72:793–801. https://doi.org/10.15585/mmwr.mm7229a4.

VI APPENDIX

Table S1. Group Definitions

Group	Definition	Rationale
Group 1	Persons at increased risk of severe influenza disease	Direct protection against complications, hospitalization, death
Group 2	Healthcare workers and occupational risk	Protect vulnerable patients; maintain healthcare capacity; reduce zoonotic reassortment risk
Group 3	Children and household contacts of high-risk persons	Indirect protection (cocooning); reduce transmission to vulnerable individuals

VII COMPOSITION OF THE WORKING GROUP

The composition of the Committee and that of the Board as well as the list of experts appointed by Royal Decree are available on the following website: About us.

All experts joined the working group ***in a private capacity***. Their general declarations of interests as well as those of the members of the Committee and the Board can be viewed on the SHC website (site: conflicts of interest).

For this specific document, Anna PARYS declared a political mandate at the local level.

The following experts were involved in drawing up and endorsing this advisory report. The working group was chaired by **Steven CALLENS**; the scientific secretaries were Veerle MERTENS and Michael PEETERS.

BEUTELS Philippe	Social Sciences, Health Care Economics and Organizations, Infectious Disease Medicine.	UAntwerpen, CHERMID, SIMID
BLUMENTAL Sophie	Pediatrics, Infectious Disease Medicine, Vaccinology, Primary Immunodeficiency Diseases, Pneumococcal Infections, Tuberculosis.	ULB, CHIREC
CALLENS Steven	Internal Medicine, Infectious Disease Medicine, Emerging Communicable Diseases, Travel Medicine, Vaccinology, Tuberculosis, AIDS-HIV, Ebola, COVID-19.	UGent, UZ Gent
DE MOT Laurane	Epidemiology	Sciensano
DESMAELE Sara	Pharmacology	CBIP/BCFI
FRERE Julie	Pediatrics and infectiology	CHR Citadelle
HENS Niel	Modelling, Biostatistics, Epidemiology, Infectious Diseases	U Hasselt
LAFORT Yves	Epidemiology	Sciensano
LAURENT Michaël	Geriatrics	Imelda
MAERTENS Kirsten	Vaccinology and maternal immunization	U Antwerpen
PARYS Anna	Virology, Public Health	Sciensano
ROBERTFROID Dominique	Epidemiology, anthropology and health sciences	KCE, U Namur
SABBE Martine	Vaccinovigilance and safety of vaccines	AFMPS-FAGG
SCHOEVAERDTS Didier	Geriatrics, infectiology	UC Louvain, CHU Namur
TUERLINCKX David	Pediatrics and vaccinology	CHU UCL Namur
VAN DAMME Pierre	Epidemiology, vaccinology, infectiology, public health	U Antwerpen
VAN LAETHEM Yves	Infectiology, vaccinology and travel medicine	ex-CHU Saint-Pierre, ULB

The standing working group NITAG has endorsed the advisory report. The standing working group was chaired by **Steven CALLENS** and **David TUERLINCKX**; the scientific secretaries were Laura KOSTOV, Veerle MERTENS and Michael PEETERS. This document was approved at the meeting held on 29 January 2026.
Were present during the meeting:

ALDERS Nele	Paediatrics, Infectiology, Travel and Tropical Medicine	ITG
BEUTELS Philippe	Social Sciences, Health Care Economics and Organizations, Infectious Disease Medicine.	UAntwerpen, CHERMID, SIMID
BLUMENTAL Sophie	Paediatrics, Infectious Disease Medicine, Vaccinology, Primary Immunodeficiency Diseases, Pneumococcal Infections, Tuberculosis.	ULB, CHIREC
BOIY Tine	Paediatrics, Rare Diseases, Congenital Hereditary and Neonatal Diseases and Abnormalities, Down Syndrome.	UAntwerpen, UZA
CALLENS Steven	Internal Medicine, Infectious Disease Medicine, Emerging Communicable Diseases, Travel Medicine, Vaccinology, Tuberculosis, AIDS-HIV, Ebola, COVID-19.	UGent, UZ Gent
CARRILLO SANTISTEVE Paloma	General Practice, Infectious Disease Medicine, Vaccinology, Preventive Medicine, Public Health.	ONE
CHATZIS Olga	Paediatrics, Infectious Disease Medicine, Congenital Hereditary and Neonatal Diseases and Abnormalities, Vaccinology.	UCLouvain, Cliniques universitaires Saint-Luc
CHRISTIAENS Thierry	Pharmacology.	CBIP/BCFI, UGent
CORNELISSEN Laura	Obstetrics, Gynaecology, Epidemiology, Infectious Disease Medicine, Maternal Health, Public Health.	Sciensano
DE COSTER Ilse	Head of the Ambulatory Trial Unit	UAntwerpen
DE SCHEERDER Marie-Angélique	Internal Medicine, Infectious Disease Medicine, Travel Medicine, AIDS-HIV, Anti-Bacterial Agents.	UGent, UZ Gent
DE SCHRYVER Antoon	Occupational and environmental medicine	U Antwerpen
DESMET Stefanie	Clinical microbiology, epidemiology	UZ Leuven, NRC for Pneumococci
DOGNE Jean-Michel	Pharmacy and pharmacovigilance	U Namur, AFMPS, EMA
FRERE Julie	Paediatrics and infectiology	CHU Liège
HERCOT David		
MAERTENS Kirsten	Vaccinology and maternal immunization	U Antwerpen
MANIEWSKI-KELNER Ula	Vaccinology and maternal immunization	U Antwerpen
ROBERFROID Dominique	Epidemiology, anthropology and health sciences	KCE, UNamur
SOENTJENS Patrick	Travel medicine, vaccinology, zoonotic diseases, HIV	ITG-IMT-ITM, Defense
SWENNEN Béatrice	Epidemiology and vaccinology	ULB
TUERLINCKX David	Paediatrics and vaccinology	CHU UCL Namur

VAN DAMME Pierre	Epidemiology, vaccinology, infectiology, public health	U Antwerpen
VANDEN DRIESSCHE Koen	Paediatrics, infectiology, oncology	UZA
VAN LAETHEM Yves	Infectiology, vaccinology and travel medicine	ex-CHU Saint-Pierre, ULB
WAETERLOOS Geneviève	Quality of vaccines and blood products	Sciensano

The following experts were heard but did not take part in endorsing the advisory report:

MAMBOURG Francoise	Medical Doctor Société Scientifique de Médecine Générale, Vaccinology	SSMG
TEUGHELS Stefan	Medical Director Domus Medica General medicine, public health, EBM	Domus Medica

The following administrations and/or ministerial cabinets were heard:

CORNELISSEN Tine	Vaccinology	Opgroeien (Kind en Gezin)
DAEMS Joel	Directorate Drugs	RIZIV-INAMI
THEETEN Heidi	Vaccinology	VAZG
VIGNERON Laurence	Coordinator of the Spearhead Domain Vaccines	AFMPS-FAGG

The following pharmaceutical companies were heard on 19 December 2025:

AstraZeneca	DILLON Susan	Head of Commercial
	EVANS David	Global Healthcare
	HARDY Xavier	Market Access, Vaccines
	JAH Fungwe	Medical Affairs, Vaccines
	ZHOU Amy	Global Pricing and Market Access
CSL Seqirus	BAHRA Ranbir	Medical Affairs, Vaccines
	HAAG Mendel	Global Medical Affairs
	MERCE MALDONADO Eva	Emerging Markets
GSK	DEKEYE Jeroen	Medical Affairs, Vaccines
	AKKAYNAK Diyar	Medical Director, Vaccines
Sanofi	DHONT Patrick	Medical Head, Vaccines
	VERCAMMEN Linda	Medical Lead, Vaccines
	NEIRINCK Koen	General Manager, Vaccines
Viatris	PEETROONS Ine Geert Ans	Medical Advisor
	IRDA Nora	
	SCHUER Jasperina	Head of Marketing
	BUCZEK Tomasz	Country Manager
	VANMERBERGHE Tineke	Medical Director
	DAUGINET Adrianne	Product Manager

About the Superior Health Council (SHC)

The Superior Health Council is a federal advisory body. Its secretariat is provided by the Federal Public Service Health, Food Chain Safety and Environment. It was founded in 1849 and provides scientific advisory reports on public health issues to the Ministers of Public Health and the Environment, their administration, and a few agencies. These advisory reports are drawn up on request or on the SHC's own initiative. The SHC aims at giving guidance to political decision-makers on public health matters. It does this on the basis of the most recent scientific knowledge.

Apart from its 25-member internal secretariat, the Council draws upon a vast network of over 500 experts (university professors, staff members of scientific institutions, stakeholders in the field, etc.), 300 of whom are appointed experts of the Council by Royal Decree. These experts meet in multidisciplinary working groups in order to write the advisory reports.

As an official body, the Superior Health Council takes the view that it is of key importance to guarantee that the scientific advisory reports it issues are neutral and impartial. In order to do so, it has provided itself with a structure, rules and procedures with which these requirements can be met efficiently at each stage of the coming into being of the advisory reports. The key stages in the latter process are: 1) the preliminary analysis of the request, 2) the appointing of the experts within the working groups, 3) the implementation of the procedures for managing potential conflicts of interest (based on the declaration of interest, the analysis of possible conflicts of interest, and a Committee on Professional Conduct) as well as the final endorsement of the advisory reports by the Board (ultimate decision-making body of the SHC, which consists of 30 members from the pool of appointed experts). This coherent set of procedures aims at allowing the SHC to issue advisory reports that are based on the highest level of scientific expertise available whilst maintaining all possible impartiality.

Once they have been endorsed by the Board, the advisory reports are sent to those who requested them as well as to the Minister of Public Health and are subsequently published on the SHC website (www.hgr-css.be). Some of them are also communicated to the press and to specific target groups (healthcare professionals, universities, politicians, consumer organisations, etc.).

In order to receive notification about the activities and publications of the SHC, please contact: info.hgr-css@health.belgium.be.

www.superiorhealthcouncil.be

With the administrative support of FPS
Health
Food Chain Safety
Environment