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A Narrative Review of Influenza Vaccine Evaluation Criteria and Recommendations by National Immunization Technical Advisory Groups for Older Adults: Insights from Canada, Germany, the United States, and Australia

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I would like to close with a quote from the renowned French-Lebanese author and perpetual secretary of the Académie française, Amin Maalouf—a sentiment I have personally embraced, and will continue to live by:

« N'hésitez jamais à partir loin, au-delà de toutes les mers, toutes les frontières, tous les pays, toutes les croyances »

"Never hesitate to go far away, beyond all seas, all frontiers, all countries, all beliefs"

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List of Acronyms

ACIP	Advisory Committee on Immunization Practices
Adj-IIV	Adjuvanted Inactivated Influenza Vaccine
Adj-IIV3	Adjuvanted Trivalent Inactivated Influenza Vaccine
Adj-IIV4	Adjuvanted Quadrivalent Inactivated Influenza Vaccine
AE	Adverse Event
AGI	Arbeitsgemeinschaft Influenza (Influenza Working Group, Germany)
AESI	Adverse Event of Special Interest
CI	Confidence Interval
CIQ	Comité sur l'immunisation du Québec
CINeMA	Confidence in Network Meta-Analysis
DSEN	Drug Safety and Effectiveness Network
ECDC	European Centre for Disease Prevention and Control
EBM	Evidence-Based Medicine
ED	Emergency Department
EEFA	Ethics, Equity, Feasibility, and Acceptability
EtD	Evidence-to-Decision
EtR	Evidence-to-Recommendations
GAVI	Global Alliance for Vaccines and Immunization
GBS	Guillain-Barré Syndrome
GNN	Global NITAG Network
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
GVAP	Global Vaccine Action Plan
HA	Hemagglutinin
HD-IIV	High-Dose Inactivated Influenza Vaccine
HD-IIV3	High-Dose Trivalent Inactivated Influenza Vaccine
HD-IIV4	High-Dose Quadrivalent Inactivated Influenza Vaccine
HIQA	Health Information and Quality Authority
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
IfSG	Infection Protection Act
IIV	Inactivated Influenza Vaccine
HD-IIV	High-Dose Inactivated Influenza Vaccine
IIV3	Trivalent Inactivated Influenza Vaccine
Adj-IIV3	Adjuvanted Trivalent Inactivated Influenza Vaccine
SD-IIV4	Standard-Dose Quadrivalent Inactivated Influenza Vaccine
ILI	Influenza-Like Illness
ILI-related	Influenza-Like Illness Related
LCI	Laboratory-Confirmed Influenza
MAGIC	Methods and Applications Group for Indirect Comparisons
MMWR	Morbidity and Mortality Weekly Report
NACI	National Advisory Committee on Immunization
NH	Northern Hemisphere
NIP	National Immunisation Program
NITAG(s)	National Immunization Technical Advisory Group(s)
NPIs	Nonpharmacological Interventions
OR	Odds Ratio
PBAC	Pharmaceutical Benefits Advisory Committee
PCR	Polymerase Chain Reaction
PHAC	Public Health Agency of Canada
PICO	Patient (or Population), Intervention, Comparator, Outcome
QALY	Quality-Adjusted Life Year
RCT	Randomized Controlled Trial
rVE	Relative Vaccine Effectiveness
RIV	Recombinant Influenza Vaccine
RIV3	Recombinant Trivalent Influenza Vaccine

RIV4	Recombinant Quadrivalent Influenza Vaccine
ROBINS-I	Risk Of Bias In Non-randomized Studies of Interventions
RR	Risk Ratio
RKI	Robert Koch Institute
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts (on Immunization)
SD	Standard Dose
SD-IIV	Standard-Dose Inactivated Influenza Vaccine
SD-IIV4	Standard-Dose Quadrivalent Inactivated Influenza Vaccine
SOP	Standard Operating Procedure
STIKO	Ständige Impfkommission (Standing Committee on Vaccination, Germany)
WHA	World Health Assembly
WHO	World Health Organization
WG	Working Group

Abstract

Context

Seasonal influenza causes high rates of illness and death worldwide, especially in adults aged 65 years and older. Older adults are more vulnerable due to weaker immune system. To better protect this group, many countries recommend enhanced influenza vaccines—such as high-dose, adjuvanted, and recombinant formulations. This project aimed to compare how four high-income countries—Canada, Germany, the United States, and Australia—evaluated and recommended these vaccines for the 2024–2025 influenza season in older adults.

Methods

A narrative review was conducted to collect data from the official websites of national public health authorities, to better understand and compare how countries formulate influenza vaccine recommendations for older adults. Sources included recommendation statements, technical reports, and evidence assessment documents. The review focused on how National Immunization Technical Advisory Groups (NITAGs) in each country used scientific evidence—particularly GRADE-based frameworks—to guide their decisions.

Results

All four countries recommended enhanced influenza vaccines for older adults, but their preferences and justifications varied. Germany exclusively recommended the high-dose vaccine. The United States gave equal preference to high-dose, adjuvanted, and recombinant vaccines. Australia recommended the high-dose and adjuvanted vaccines, while Canada endorsed all three options. Some countries incorporated considerations such as equity, feasibility, and acceptability into their decision-making frameworks, whereas others focused more narrowly on clinical data or supplemented their decisions with more explicit cost-effectiveness evaluations. Even when drawing on largely the same body of evidence, countries reported different results or interpreted findings differently.

Conclusion

This study shows that national context strongly shapes vaccine recommendations, even when the scientific evidence is similar. Greater international collaboration, standardized tools, and transparent processes could support more consistent and equitable vaccine policies. Future research should explore how NITAGs make decisions beyond public documentation and how low- and middle-income countries rely on evidence from higher-income nations.

Keywords: Influenza, Older adults, Vaccine policy, GRADE framework, NITAG

1. Introduction

1.1. Epidemiology and Global Impact of Influenza

Seasonal Influenza is a contagious, acute respiratory illness with global prevalence, affecting people of all ages and causing an estimated 1 billion cases each year [1,2]. Annually, it leads to approximately 290,000–650,000 respiratory-related deaths, excluding deaths from other influenza-related complications [3]. In temperate climates, influenza mainly occurs during the winter—typically from January to March in the Northern Hemisphere and June to September in the Southern Hemisphere. In contrast, tropical and subtropical regions experience year-round circulation of the virus, often with multiple seasonal peaks [4]. In addition, the severity of influenza varies significantly from one season to another and across different regions, and in some cases, this variability can lead to localized epidemics when transmission levels exceed expected seasonal norms [5,6].

1.2. Influenza Virus Types and Strains

Influenza viruses are negative-sense, single-stranded RNA viruses that belong to the Orthomyxoviridae family. Among the four known types, only types A, B, and C infect humans—types A and B cause seasonal flu epidemics, while type C is rare and typically affects children. Type D is known to infect cattle but not humans [7]. The virus is characterized by two surface proteins—hemagglutinin (HA) and neuraminidase (NA)—which are key for classification and immune recognition [1].

1.3. Pathophysiology of Influenza Virus

Influenza virus primarily replicates in the respiratory epithelium, though other cells, including immune cells, can initiate viral protein production. However, efficient viral replication is largely restricted to the respiratory tract, where the hemagglutinin (HA) protein is properly cleaved to produce infectious particles. Transmission occurs through aerosols or contaminated respiratory droplets. The disease's pathophysiology is mainly driven by lung inflammation resulting from both direct viral damage and immune responses. In severe cases, this inflammation can extend beyond the lungs, potentially leading to multiorgan failure. Additionally, influenza infection has been linked to cardiac complications, such as an increased risk of myocardial disease shortly after infection, though the exact mechanisms remain unclear.

1.4. Risk Groups and Factors Associated with Severe Outcomes

Individuals at higher risk of severe influenza outcomes include adults over 65, infants under 6 months, pregnant and postpartum women, nursing home residents, people with chronic cardiovascular or respiratory conditions, and immunocompromised individuals [8–10]. Among hospitalized adults, increased mortality risk is associated with older age (particularly those over 65 or aged 50–64 compared to 18–49), male sex, recent chemotherapy, and higher Sequential Organ Failure Assessment (SOFA) scores [8–10].

More than 90% of influenza-related deaths occur among older adults, partly due to age-related changes in the immune system known as immunosenescence [11]. This decline impairs the body's ability to fight infections and reduces the effectiveness of vaccines, in comparison to their effect in younger adults [11].

1.5. Prevention of Influenza: Focus on Vaccination

Influenza prevention relies primarily on two strategies: nonpharmacological interventions (NPIs) and vaccination [12]. NPIs—such as mask-wearing, social distancing, and hand hygiene—have been effective in reducing the spread of influenza and other respiratory viruses. Their continued use, particularly among high-risk populations, can offer protection during future outbreaks [13]. However, vaccination remains the cornerstone of influenza prevention and continues to be the most effective way to reduce influenza complications [14].

To protect those most at risk, both the World Health Assembly resolution WHA56.19 and a European Council recommendation have set a target of 75% influenza vaccination coverage among high-risk groups, particularly older adults [15]. While SD influenza vaccines have been in use for decades [16], their effectiveness in older populations is limited due to immunosenescence. To overcome this reduced immune responsiveness, enhanced vaccine formulations—such as high-dose vaccines with increased antigen content, adjuvanted vaccines, and recombinant vaccines—have been developed to improve immunogenicity and efficacy in older adults[1] [17–20].

1.6. Evolution of Influenza Vaccine Formulations

Since 1977, four influenza strains have circulated globally: two type A subtypes (H1N1 and H3N2) and two type B lineages (Yamagata and Victoria). Type A viruses account for about two-thirds of annual infections, though type B can occasionally predominate every few years. Traditional vaccines included both A subtypes and only one B lineage, making the selection of the correct B strain challenging. To address this, quadrivalent vaccines—covering both B lineages—were introduced [21].

In September 2023, the WHO recommended excluding the B/Yamagata component from vaccines for the Southern Hemisphere's 2024 flu season, transitioning back to trivalent formulations. This decision, and as mentioned before, was based on the absence of circulating B/Yamagata strains and concerns over potential reintroduction through reassortment between vaccine and wild-type viruses [22] [2].

1.7. National Immunization Programs and Evidence-Based Recommendations

As influenza vaccines have evolved to address changing viral patterns and age-related immunological challenges, their integration into public health policy has become increasingly

[1] Refer to Table 1 in the appendix for an overview of the enhanced influenza vaccines.
[2] Refer to Figures 1 and 2, on the evolution of influenza vaccines from the 1930s until today, and the framework of improving them.

important [23]. In response to the growing complexity of vaccine-related decisions, National Immunization Technical Advisory Groups (NITAGs) were established to offer independent, evidence-based recommendations to guide national health authorities [24].

The WHO's 2011–2020 Global Vaccine Action Plan (GVAP) recognized NITAGs as key indicators of national commitment to immunization [25]. These advisory bodies operate independently from implementing authorities, offering guidance on vaccine introductions, immunization schedules, evidence gaps, and public confidence [24]. Their performance is evaluated using six GVAP process indicators, such as multidisciplinary membership, annual meetings, and formal terms of reference [26].

The number of fully functional NITAGs grew from 41 in 2010 to 120 in 2019, covering 87% of the global population [27]. Despite this growth, many countries still face limitations in funding, technical expertise, and integration into national decision-making [24]. The Strategic Advisory Group of Experts (SAGE)— the principal advisory group to World Health Organization (WHO) for vaccines and immunization, in 2017, made recommendations along with World Health Assembly resolution, reinforcing the global support for NITAG development [27,28]. Moving forward, the Immunization Agenda 2030 and Global Alliance for Vaccines and immunization's (GAVI's) 2021–2025 strategy highlight the importance of NITAGs in promoting sustainable, evidence-based vaccine policies [29,30].

As NITAGs gain a more prominent role in shaping national immunization policies, the quality and rigor of their evidence review processes become increasingly critical. For instance, according to the European Centre for Disease Prevention and Control (ECDC), only a few countries in Europe have outlined specific and structured prerequisites to guide their evidence review processes [31]. These often reflect each country's internal systems and may include predefined search strategies, clear criteria for including or excluding studies, and most importantly, the use of standardized tools or rating frameworks—such as the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) [31]. These approaches are aimed at enhancing the transparency and rigor of the review process within National Immunization Technical Advisory Groups (NITAGs) [31].

Since 2008, the WHO has adopted the GRADE framework to inform its immunization policy recommendations [32]. Both the WHO and the Global NITAG Network (GNN) support NITAGs through guidance [33] and training on evidence-to-recommendation processes, emphasizing the importance of assessing evidence quality [34].

The GRADE working group has continuously refined this methodology since its launch in 2000, as outlined in the GRADE Handbook [35]. Although originally developed for general clinical guidelines, GRADE has only been applied to vaccine-related recommendations [32].

A GRADE assessment begins with a clearly defined research question using the PICO format (Population, Intervention, Comparator, Outcomes), a standard in evidence-based

medicine [36,37]. A systematic review follows to identify relevant studies. Evidence for each outcome is then graded for certainty as *very low, low, moderate, or high* [38]. Study methods are taken into consideration during the assessment. For instance, Randomized Controlled Trials (RCTs) typically start at high certainty but may be downgraded due to bias or imprecision. Observational studies begin at low certainty and are adjusted accordingly. These outcome-level ratings inform an overall certainty grade, guiding strong or weak recommendations for or against the intervention [38].

As NITAGs continue to navigate the complexities of evaluating currently available influenza vaccines, emerging technologies—such as mRNA-based influenza vaccines—are poised to add a new dimension to evidence review [39]. These developments are occurring alongside existing challenges; for instance, despite relying on similar GRADE-like assessments, countries vary in their recommendations for enhanced influenza vaccines for older adults [40–44]. These differences highlight the complexity of evidence assessment and NITAG decision-making, reflecting how scientific evidence interacts with national priorities, economic considerations, and logistical constraints [45]. While some NITAGs recommend high-dose or adjuvanted vaccines based on stronger efficacy/ effectiveness data, others prefer broader flexibility in vaccine choice [40].

1.8. Scope and Objectives

This narrative review aims to synthesize and interpret the influenza vaccine evaluation criteria and recommendations utilized by National Immunization Technical Advisory Groups (NITAGs) for older adults during the 2024–2025 influenza season in Canada, Germany, the United States, and Australia. The selection of the 2024–2025 season is deliberate, as recommendations for the 2025–2026 season had not yet been published by Canadian and U.S. NITAGs at the time of writing (as of March 24, 2025).

These four countries were selected because they represent a unique subset of countries whose NITAGs issue recommendations grounded in recent GRADE-like evaluations, as noted by Ricciardi et al. (2015) and corroborated by internal Sanofi documentation [46]. In addition to this methodological alignment, the NITAGs in Canada, Germany, the U.S., and Australia share a notable organizational feature: each has established internal subcommittees or working groups composed of multidisciplinary experts to support evidence-based decision-making [46].

This review focuses on evaluation criteria related to scientific evidence appraisal, economic evaluations, and public health impact assessments. By examining recent recommendations and building on Ricciardi et al.'s (2015) foundational analysis, the review aims to provide nuanced insights into how national contexts, healthcare priorities, and interpretative frameworks shape current influenza vaccine policy trends.

To address this objective, the review is structured around the following research question: **What are the differences in influenza vaccine evaluation criteria and recommendations adopted by NITAGs in Canada, Germany, the United States, and Australia for older adults for the 2024–2025 seasonal influenza vaccination campaign?**

2. Methods

2.1. Study Design

This study is a comparative narrative review. Given the limited availability of peer-reviewed articles specifically addressing NITAG structures, methodologies, and decision-making processes in the context of influenza vaccination, conducting a full systematic review was not feasible.

2.2. Data Collection

Primary data for this review were collected from the official websites of the public health authorities responsible for hosting the national immunization technical advisory groups (NITAGs) in the selected countries. Specifically, data were obtained from: the Government of Canada's official website for Canada; the Robert Koch Institute (RKI) and the European Centre for Disease Prevention and Control (ECDC) for Germany; the Centers for Disease Control and Prevention (CDC) for the United States; and both the Department of Health and Aged Care and the National Centre for Immunisation Research and Surveillance (NCIRS) for Australia. These sources provided information on the structure and role of each NITAG, official influenza vaccine recommendations, technical reports, and relevant policy documents for the 2024–2025 season.

2.3. Data Analysis

To clearly communicate the findings, narrative summary has been developed, supported by a comparative summary table. These serve to highlight both commonalities and differences in vaccine evaluation and policy across the four countries. Documents originally published in German were translated into English using Google Translate to facilitate analysis.

3. Results

3.1. Case 1: Canada

3.1.1. National Advisory Committee on Immunization (NACI): Structure and Role

Established in 1964 as the National Advisory Committee on Immunizing Agents to advise the Department of National Health and Welfare, the committee initially focused on identifying agents warranting special attention by the Dominion Council of Health [47]. Its mandate expanded in 1975 to support the introduction of new vaccines and development of immunization programs, prompting its renaming to the National Advisory Committee on Immunization (NACI) in 1978 to reflect this broader role [47].

NACI comprises 14 voting members—including a chair, vice-chair, and 12 other experts—plus an executive secretary. It also includes around a dozen industry liaisons and a similar number of ex-officio public service members from Health Canada [48]. Voting members are experts in immunization, public health, vaccine-preventable diseases, infectious diseases, allergy/immunology, and related fields [49]. The committee reports to the Vice-President of the Infectious Disease Prevention and Control Branch and collaborates with the Centre for Immunization and Respiratory Infectious Diseases at the Public Health Agency of Canada (PHAC). Its evidence syntheses, analyses, and vaccine recommendations are shared via literature reviews, official statements, updates, and the *Canadian Immunization Guide* [49].

NACI also maintains an Influenza Working Group (IWG) responsible for annual influenza vaccine recommendations, assessing disease burden, target populations, vaccine safety, efficacy, effectiveness, immunogenicity, and scheduling [50]. In recent years, NACI's scope has expanded to include programmatic elements such as ethics, equity, feasibility, and acceptability (EEFA), as well as cost-effectiveness. To support these considerations, NACI uses a structured, peer-reviewed EEFA framework and specialized tools, including the Ethics Integrated Filters, Equity Matrix, Feasibility Matrix, and Acceptability Matrix [51].

3.1.2. NACI Guidance on Vaccination in Adults Aged 65 and Older

The Burden of Disease in Canada

Although people aged 65 and over make up only 19% of Canada's population, they consistently bear the highest burden of influenza, particularly in A(H3N2)-dominant seasons such as 2014–2015, 2016–2017, and 2017–2018 [52]. Hospitalization rates due to influenza are highest among seniors—144.9 per 100,000 compared to 25.8 per 100,000 in the 45–64 age group [53]. Mortality is also significantly higher in seniors, with rates of 108.8 per 100,000 versus 4.0 per 100,000 among those aged 50–64 [54].

In the 2022–2023 season, hospitalization rates for seniors and children under five both reached 130 per 100,000 [55]. During the shorter 2021–2022 season, seniors again accounted for the highest hospitalization rates, 30% of ICU admissions, and 59% of deaths [56]. In past A(H3N2)-dominant seasons, more than 80% of influenza-related deaths occurred among adults aged 65 and older [57].

Systematic Review and Enhanced Vaccine Evaluation

In preparation for the 2024–2025 influenza season, Canada's National Advisory Committee on Immunization (NACI) conducted a systematic review to assess the comparative effectiveness, safety, and cost-effectiveness of enhanced influenza vaccines—high-dose (HD-IIV), adjuvanted (Adj-IIV), and recombinant (RIV)—versus standard-dose

(SD-IIV) vaccines in adults aged ≥65 years. An initial supplemental guidance[3] was published in July 2024, followed by a February 2025 update to correct minor data labeling errors, without changing the conclusions [57].

Using the GRADE-ADOLOPMENT approach[4], NACI adapted recommendations from the U.S. Advisory Committee on Immunization Practices (ACIP), which had applied the GRADE framework to evaluate outcomes such as lab-confirmed influenza, hospitalizations, and adverse events. ACIP's review included 31 studies (9 RCTs—including 2 cluster RCTs—and 22 observational studies) based on literature from 1990 to September 7, 2021 [58]. To supplement these findings, NACI commissioned two systematic reviews by the Methods and Applications Group for Indirect Comparisons (MAGIC) through the Drug Safety and Effectiveness Network (DSEN): one focused on vaccine efficacy and safety, and the other on economic impact. MAGIC used the Cochrane Risk of Bias Tool and applied both GRADE (for direct comparisons) and Confidence in Network Meta-Analysis (CINeMA; for network meta-analyses). Their literature search covered studies through March 31, 2022, with an update on June 20, 2022 [59]. The efficacy and safety review included 41 RCTs with 206,032 participants, of which 26 were included in the quantitative analysis.

Comparative Efficacy, Effectiveness and Safety of Enhanced Vaccines Compared to Standard-Dose Inactivated Influenza Vaccines

Efficacy/Effectiveness Against Lab-Confirmed Influenza (LCI)

Both reviews found that HD-IIV provided approximately 25% greater rVE than SD-IIV, with ACIP rating the evidence as high certainty (based on DiazGranados et al., 2014) [60]. For RIV, ACIP reported a relative vaccine effectiveness (rVE) of 18% (95% CI: -17 to 43%) against LCI from two trials with moderate certainty [61,62], while DSEN MAGIC estimated a higher but imprecise pooled rVE of 30% (95% CI: -18 to 58%) against LCI, rated as low certainty [61,63].

Efficacy/Effectiveness Against Influenza-Like Illness (ILI)

Adj-IIV did not show difference in efficacy vs SD-IIV against ILI, with an rVE of -3% (95% CI: -19 to 11%) in one RCT, and was rated as low certainty [64]. None of the enhanced vaccines demonstrated significant differences from SD-IIV in preventing ILI, with rVEs ranging from -3% to 2% and all comparisons rated as low certainty [61–66].

Efficacy/Effectiveness Against Outpatient/Emergency Department (ED) Visits

In terms of outpatient/ED visits, HD-IIV showed modest benefit for reducing outpatient and emergency department visits in four cohort studies (rVE: 13%, 95% CI: 1 to 24%) [67–70] but not in a case-control study [71] or RCT [72]. Findings for Adj-IIV were inconsistent, with

[3] PICO clearly mentioned in the summary table of results
[4] Refer to Figure 3 of the appendix, for the detailed GRADE-ADOLOPMENT process.

some studies showing protective effects (pooled rVE: 36%, 95% CI: 21 to 48%) [73,74] and others showing none [69,75].

Efficacy/Effectiveness Against Hospitalizations

ACIP reviewed four RCTs [76–79] and 15 observational studies [67,68,70,80–91], indicating that all three enhanced vaccines offered some protection, particularly HD-IIV, which was supported by moderate-certainty evidence. DSEN MAGIC found a 28% pooled rVE (95% CI: 8 to 43%) for HD-IIV against ILI-related hospitalization [60,72], though estimates for LCI-related hospitalization and for RIV were imprecise, with wide confidence intervals [60,61,92].

Efficacy/Effectiveness Against Influenza-Associated Deaths

ACIP also found that HD-IIV reduced influenza-associated deaths (pooled rVE: 31%, 95% CI: 16 to 43%) in two cohort studies [69,88], while DSEN MAGIC reported a non-significant effect for Adj-IIV (rVE of 25%, 95% CI: -236 to 83%) [64].

Efficacy/Effectiveness Against Vascular Events

Only DSEN MAGIC assessed vascular outcomes, finding non-significant trends toward fewer events with HD-IIV (pooled RR: 0.75 , 95%CI: 0.43 to 1.29) [60,72,93,94], Adj-IIV (pooled RR: 0.83, 95% CI: 0.54 to 1.27) [64,95], and RIV (OR: 0.89, , 95% CI: 0.30 to 2.60) [61], based on seven RCTs [60,61,64,72,93–95].

Safety Outcomes

ACIP's review of 23 RCTs and one retrospective cohort study found most safety outcomes to be of low to very low certainty due to small sample sizes and wide confidence intervals.

No consistent increase in grade ≥3 systemic adverse events was observed for any of the enhanced vaccines compared to SD-IIV [62,63,95–99].

For serious adverse events (SAEs), HD-IIV was associated with a significantly lower risk than SD-IIV (pooled RR: 0.91, 95% CI: 0.85 to 0.97) [60,62,77,93,94,97,100], while Adj-IIV [64,95,97,101–105] and RIV [61,63,97,106,107] showed no significant differences.

Four studies found no increased risk of Guillain-Barré Syndrome with any enhanced vaccine [64,77,108,109]; notably, no cases were reported in RCTs of HD-IIV [77] or in large observational studies of Adj-IIV [109], and none among RIV recipients compared to four cases among SD-IIV recipients [108].

Injection site reactions were more common with Adj-IIV (pooled RR: 3.39, 95% CI: 1.32 to 8.72) [95,97,105,110] and possibly HD-IIV (pooled RR: 5.03, 95% CI: 0.88 to 28.74), whereas RIV showed a potential reduction (pooled RR: 0.67, 95% CI: 0.27 to 1.69) [62,97], though all estimates were imprecise.

Comparative Efficacy, Effectiveness, and Safety of Enhanced Vaccines Compared to One Another

Seven studies — one RCT and six observational studies—compared these vaccines against each other in terms of laboratory-confirmed influenza (LCI), outpatient/emergency

department (ED) visits, and hospitalizations. These included comparisons of Adj-IIV3 vs RIV4 [65,67], HD-IIV3 vs Adj-IIV3 [65,67,68,75,80,91,111], and HD-IIV3 vs RIV4 [80,111].

Efficacy/Effectiveness Against Lab-Confirmed Influenza (LCI)

One RCT reported wide and imprecise confidence intervals for LCI outcomes: HD-IIV3 vs Adj-IIV3 (rVE: 66%, 95% CI: –213 to 96), HD-IIV3 vs RIV (rVE 74%, 95% CI: –118 to 97), and Adj-IIV3 vs RIV (rVE 25%, 95% CI: –207 to 82), with no statistically significant differences [111]. DSEN MAGIC also found no significant protective effect among the three vaccines due to similarly wide confidence intervals and low precision [66,111].

Efficacy/Effectiveness Against Outpatient/Emergency Department (ED) Visits

For outpatient and ED visits, ACIP analyzed three retrospective cohort studies comparing HD-IIV3 to Adj-IIV3 and found no significant difference (pooled rVE: –6%, 95% CI: –23 to 8%) [65,68,75]. DSEN MAGIC did not report head-to-head data for this outcome.

Efficacy/Effectiveness Against Hospitalizations

Regarding hospitalizations, four observational studies compared HD-IIV3 to Adj-IIV3 [68,80,91,112], HD-IIV3 to RIV [112], and Adj-IIV3 to RIV [112]. One study from the 2019–2020 season suggested a relative advantage for RIV, but a meta-analysis of four studies showed no meaningful difference between HD-IIV3 and Adj-IIV3 (rVE: 4%, 95% CI: –1 to 10%) [112]. DSEN MAGIC included no RCTs on hospitalizations for these comparisons.

Safety Outcomes

ACIP review included three RCTs [97,113,114] that compared the safety of the enhanced vaccines in adults aged ≥65 years. These trials assessed grade 3 or higher solicited systemic adverse events (AEs), serious adverse events (SAEs), and grade 3 or higher injection site reactions. No data were available on comparisons for Guillain-Barré Syndrome (GBS).

HD-IIV3 showed a lower risk of systemic AEs compared to Adj-IIV3 and RIV4, though results were imprecise RR: 0.73 (95% CI: 0.29 to1.80) vs Adj-IIV3; 0.86 (95% CI: 0.22 to 3.32) vs RIV4. One trial suggested Adj-IIV3 may have a higher risk than RIV4 (RR: 4.62, 95% CI: 0.24 to 89.17), but the estimate was highly imprecise [97].

For SAEs, two studies compared HD-IIV3 to both Adj-IIV3 and RIV4 [83, 84], while one compared Adj-IIV3 to RIV4 [97]. HD-IIV3 and Adj-IIV3 appeared to have higher SAE risks than RIV4 (RRs: 1.77 and 1.81), but confidence intervals were wide. HD-IIV3 may carry a slightly lower SAE risk compared to Adj-IIV3 (RR: 0.65, 95% CI: 0.32 to 1.30), though this too was not statistically significant.

For grade ≥3 injection site reactions, two studies compared HD-IIV3 to Adj-IIV3 and RIV4 [113,114], and one compared Adj-IIV3 to RIV4 [97]. Both HD-IIV3 and Adj-IIV3 appeared more reactogenic than RIV4 (RRs: 5.92 and 4.62, respectively), while HD-IIV3 may be slightly less

reactogenic than Adj-IIV3 (RR: 0.88, 95% CI: 0.45 to 1.75); however, all estimates were imprecise.

Economic Evaluations of Enhanced Influenza Vaccines

The 2024–2025 NACI supplemental guidance incorporated two economic evaluations on influenza vaccination in adults aged ≥65 years. The first was a systematic review (literature up to October 29, 2020) encompassing 19 studies: 16 cost-utility analyses [115–123,123–129], 2 cost-benefit [130,131], and 1 cost-effectiveness analysis [132]. These studies, mostly published between 2014 and 2020, evaluated SD-IIV4, Adj-IIV3, and HD-IIV3 compared to IIV3-SD and were conducted across North America, Europe, Asia, and South America [131,139–141,149]. Thirteen were rated high quality and six moderate.

From a healthcare payer perspective, at a $40,000/QALY threshold, 75–100% of estimates found SD-IIV4, Adj-IIV3, and HD-IIV3 cost-effective. HD-IIV3 was also cost-effective versus SD-IIV4. Mixed strategies yielded ICERs between $9,771/QALY and $13,084/QALY [119]. Societal perspective findings were consistent, showing 89–100% cost-effectiveness at the same threshold. One healthcare provider analysis of SD-IIV4 vs IIV3-SD gave an ICER of $29,562/QALY [121], within Canadian cost-effectiveness standards.

Four studies were deemed highly relevant to Canada: two Canadian [116,117] and two UK-based [118,119], published between 2015–2019. Canadian study [116] showed HD-IIV3 dominated IIV3-SD, especially in adults ≥75 or with comorbidities. UK-based analysis [119] estimated QALY gains for Adj-IIV3 at $9,771–$13,084. Comparisons of SD-IIV4 vs IIV3-SD reported ICERs between $26,288 [118] and $39,599 [121].

Fifteen additional studies [115,117,120,122–131,133,134], though less directly applicable to Canada, supported similar conclusions: HD-IIV3, Adj-IIV3, and SD-IIV4 were generally cost-effective vs IIV3-SD. Sensitivity analyses supported base case findings, though results varied with strain match, vaccine cost, cross-protection, and mortality assumptions.

The second evaluation, by Québec's Comité sur l'immunisation du Québec (CIQ), was published August 17, 2023 [135], using burden estimates and parameters from a 2018 CIQ report [136]. This economic exercise—part of CIQ's decision-making—also included a literature review of vaccine efficacy. Using 2022 Canadian dollars and 3% discounting (with 0% for sensitivity), the analysis showed that among adults aged 65–74, enhanced vaccines prevented 571 consultations, 155 hospitalizations, and 4 deaths. The ICERs ranged from $480,604 to $609,927/QALY (undiscounted to 3% discounted). Among adults ≥75, enhanced vaccines prevented 541 consultations, 533 hospitalizations, and 28 deaths, with ICERs of $84,905 to $100,618/QALY. The most favorable result was $56,173/QALY (discounted) for adults ≥75 with chronic conditions. However, other subgroups had ICERs over six times higher—ranging from $345,297 to $2,648,381/QALY.

Given a 25% rVE, the use of enhanced vaccines in Quebec did not appear cost-effective compared to standard-dose vaccines under typical thresholds. CIQ's literature review also found no RCTs comparing Adj-IIV3 to SD-IIV for lab-confirmed influenza (LCI), and existing observational studies were low quality. CIQ concluded there was insufficient evidence to support Adj-IIV3's superiority over SD-IIV or equivalence with HD-IIV3.

EEFA Framework Consideration

In its 2024–2025 seasonal influenza vaccine statement**,** NACI notes that offering higher-efficacy vaccines to older adults at increased risk of severe influenza outcomes may help improve equity in this population.

However, feasibility could be a concern for healthcare providers and policymakers due to the higher costs and uncertain magnitude of added efficacy of enhanced vaccines.

Acceptability may be greater among high-risk groups who perceive greater benefits from the preferred vaccines in adults aged 65 and over. At the same time, acceptability from providers and policymakers could improve if these vaccines effectively reduce disease burden—but may decline given the limited supporting data and potential financial constraints.

3.1.3. NACI Recommendations for 2024/2025

As published in the *Statement on Seasonal Influenza Vaccine for 2024* [137], adults aged 65 years and older were strongly recommended to receive a HD-IIV, an Adj-IIV, or a RIV over standard-dose options. This recommendation was released by the Public Health Agency of Canada (PHAC) in May 2024. In cases of limited supply of the preferred vaccines, priority should be given to high-risk subgroups, such as adults aged 75 and older, individuals with comorbidities or frailty, and residents of long-term care facilities. If none of the preferred products are available, any age-appropriate influenza vaccine may be used.

3.2. Case 2: Germany

3.2.1. The German Standing Committee on Vaccination (STIKO): Structure and Role

Established in 1972 and legally anchored under the Infection Protection Act (IfSG) since 2001, the Standing Committee on Vaccination (STIKO) is Germany's national immunization advisory body [138]. Hosted by the Robert Koch Institute (RKI), STIKO provides science-based national vaccine recommendations. While not legally binding, these recommendations guide public vaccination programs and influence reimbursement decisions under statutory health insurance through the Federal Joint Committee (G-BA) [139].

STIKO comprises 12 to 18 independent, unpaid experts appointed by the Federal Ministry of Health, representing fields such as pediatrics, family medicine, virology, immunology, epidemiology, occupational medicine, public health, and evidence-based medicine [139]. The committee meets at least twice a year in closed sessions attended by non-voting representatives from institutions like the RKI, Paul-Ehrlich-Institut, Federal Ministry of Health,

Bundeswehr, and Federal Foreign Office [139]. The Executive Secretariat, located in the RKI's Immunization Unit, provides administrative and scientific support, prepares meetings, conducts systematic reviews and meta-analyses, and drafts background documents [139].

STIKO's recommendations are developed following a Standard Operating Procedure (SOP), first introduced in 2011 and last updated in 2018 (version 3.1) [140]. Topics are prioritized based on disease burden, vaccine availability, and public health relevance. Working groups—composed of STIKO members, secretariat staff, and external experts—formulate PICO questions and perform systematic literature reviews across databases, trial registries, and conference proceedings [140]. Notably, STIKO has a dedicated Influenza Working Group responsible for evaluating seasonal influenza vaccines and informing annual recommendations [138]. Studies are evaluated using the Cochrane Risk of Bias Tool (for RCTs) and ROBINS-I (for non-RCTs), and the quality of evidence is graded using the GRADE framework. An Evidence-to-Decision (EtD) Table informs committee discussions. Final recommendations are adopted by majority vote and published with detailed background papers in the *Epidemiologisches Bulletin*, ensuring transparency and public access [140].

3.2.2. Scientific Rationale for Influenza Vaccine Recommendations in Older Adults

Burden of Influenza in Germany

In 2019, around 233 influenza cases per 100,000 people were officially reported in Germany under the Infection Protection Act (IfSG), equating to about 200,000 total cases according to the Robert Koch Institute (RKI) [138]. However, this figure significantly underrepresents the true burden, as many cases go undiagnosed or unreported. The Influenza Working Group (AGI) estimated that influenza-related medical visits were approximately 20 times higher than reported [141].

Among individuals aged 60 and over, there was a median of around 400,000 additional medical consultations per flu season over the past decade, with a range between 70,000 and 1.3 million. This age group also experienced most of the excess hospitalizations—ranging from under 500 to 21,000 per year—and accounted for about 85% of influenza-related excess deaths, which have fluctuated between 0 and 25,000 annually across all ages [142].

Systematic Review on Enhanced Influenza Vaccines

In 2020, STIKO's Influenza Working Group undertook a comprehensive evaluation of the comparative effectiveness and safety of enhanced influenza vaccines, including adjuvanted, high-dose, and recombinant vaccines [138]. This assessment was based on a systematic review conducted by the Health Information and Quality Authority (HIQA) in collaboration with the European Centre for Disease Prevention and Control (ECDC) and the Robert Koch

Institute (RKI). The review included literature published up to February 7, 2020, with an additional exploratory update conducted on May 27, 2020 [143]. This was done in the *Epidemiologisches Bulletin* 01/2021 which they referred to for Germany's 2024/2025 Northern Hemisphere (NH) Influenza season (*Epidemiologisches Bulletin* 04/2024).

The systematic review followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and included a total of 110 studies for qualitative analysis, of which 51 studies were incorporated into meta-analyses. Study quality was assessed separately for RCTs using the Cochrane Risk of Bias Tool and for observational studies using ROBINS-I. Evidence quality for each endpoint was graded using the GRADE approach[5].

Comparative Efficacy/Effectiveness and Safety of the MF-59-Adjuvanted Vaccine vs SD

Nine observational studies from multiple countries assessed the MF-59-adjuvanted vaccine in adults aged 65 and over.

Efficacy/Effectiveness Against Lab-Confirmed Influenza (LCI)

Five studies using a test-negative design reported rVE estimates ranging from 0% to 88% (95% CI: 59–100%), though only two were statistically significant. Certainty was rated as low.

Efficacy/Effectiveness Against Hospitalizations

Three cohort studies and one case-control study reported rVE estimates for hospitalization ranging from 3% to 49% (95% CI: 30 to 60%); however, most results were not statistically significant, and the certainty of evidence was rated as low to very low.

Safety Outcomes Compared to SD

Safety assessments from RCTs indicated increased risks of local reactions (pooled RR: 1.90; 95% CI: 1.50 to 2.39, based on 4 RCTs), injection site pain (RR: 2.02; 95% CI: 1.53 to 2.67, based on 12 RCTs), and systemic events (RR: 1.18; 95% CI: 1.02 to 1.38, based on 5 RCTs), all with moderate certainty. For fever, results showed an RR: 1.97 (95% CI: 1.07 to 3.61), based on 9 RCTs of low certainty.

Comparative Efficacy/Effectiveness and Safety of the High-Dose Vaccine vs SD

Efficacy/Effectiveness Against Lab-Confirmed Influenza (LCI)

One RCT and eight observational studies evaluated the high-dose vaccine across multiple Northern Hemisphere countries. The RCT found an rVE of 24% (CI: 9.7 to 36.5%), where "laboratory-confirmed influenza-like illness" was the primary endpoint investigated, with high certainty, but this dropped to 20.6% (95% CI: -4.6 to 39.9%) and lost significance under CDC's modified definition of including "fever" criteria. The same trial reported protective effects against hospitalization (rVE: 6.9%; 95% CI: 0.5 to 12.8%), severe

[5] PICO clearly mentioned in the summary table of results

cardiorespiratory events (rVE: 17.7%; 95% CI: 6.6 to 27.4%), and pneumonia (rVE: 39.8%; 95% CI: 19.3 to 55.1%), all with high certainty.

Efficacy/Effectiveness Against Hospitalizations

Observational data on hospitalizations yielded very low-certainty pooled rVE estimates of 11.8% (95% CI: 6.4 to 17.0%) for influenza-related based on two cohort studies and pooled rVE of 13.7% (95% CI: 9.5 to 17.7%) for pneumonia-related cases, based on three cohort studies.

Safety Outcomes

Safety data showed increased local reactions (RR: 1.40; 95% CI: 1.20 to 1.64, low certainty of three RCTs) and injection site pain (RR: 1.48; 95% CI: 1.21 to 1.82, moderate certainty of eight RCTS), but no significant increase in systemic reactions or fever, based on thirteen studies.

A U.S. study found a slightly increased risk of Guillain-Barré syndrome following high-dose influenza vaccination during the secondary analysis period (8–21 days post-vaccination), but no increased risk was observed in the primary analysis. The absolute risk increase was minimal, with 1.11 cases per million doses for the high-dose vaccine compared to 0.87 for the SD vaccine.

Comparative Efficacy/Effectiveness and Safety of the Recombinant Vaccine vs SD

Efficacy/Effectiveness Against Lab-Confirmed Influenza (LCI)

A single RCT conducted in the U.S. during the 2014–2015 season evaluated the recombinant with the SD vaccine, with the endpoint "laboratory-confirmed influenza-like illness". Among adults aged 50 and over, the rVE was 30% (95% CI: 10 to 47%) overall, 36% (95% CI: 14 to 53%) against influenza A, and 4% (95% CI: –72 to 46%) against influenza B. In those aged 65+, rVE was 17% (95% CI: –20 to 43%) but not statistically significant. Certainty was rated moderate.

Safety Outcomes

Safety results from RCTs showed a slight reduction in local adverse events (RR: 0.94 95% CI:0.90 to 0.98, low certainty) compared to SD vaccines, with no difference in pain.

Transmission Modeling of Enhanced Influenza Vaccines

STIKO used the Weidemann et al. (2017) transmission model [(144)] to simulate the impact of enhanced influenza vaccines on population health in Germany from 2003/04 to 2018/19, excluding the 2009 pandemic season. Assuming a 15% higher rVE for enhanced vaccines, the model estimated that each influenza season could see 23,013 additional physician consultations prevented, along with 314 hospitalizations and 162 deaths. Sensitivity analyses indicated that if rVE improved to 30%, about 45,881 consultations, 625 hospitalizations, and 324 deaths could be prevented each season. Increasing vaccination coverage by 10% alone would also yield substantial benefits, while a combination of better coverage and improved vaccine effectiveness would maximize health gains.

Health Economic Analysis of Enhanced Influenza Vaccines

Building on the transmission modeling results, a health economic evaluation assessed the cost-effectiveness of using enhanced influenza vaccines in Germany. Using a decision tree model populated with epidemiological data and healthcare cost inputs, the incremental cost-effectiveness ratio (ICER) was calculated from a societal perspective. The analysis concluded that, for vaccination of individuals over 60 years of age and an RVE of 15%, enhanced influenza vaccines would remain cost-effective if priced at twice the cost of SD vaccines, assuming a willingness-to-pay threshold of €50,000 per quality-adjusted life year (QALY). If the rVE were 30%, enhanced vaccines would still be cost-effective even at 2.5 times the cost of standard vaccines.

3.2.3. STIKO Recommendations for 2024/2025

In the *Epidemiologisches Bulletin* 04/2024, published by Robert Koch Institute (RKI) in January 2024, STIKO recommended that all individuals aged 60 and older receive an inactivated quadrivalent high-dose influenza vaccine with the WHO-recommended antigen combination. This advice, adopted at STIKO's 106th meeting [145], is grounded in evidence showing superior vaccine effectiveness in older adults. In case of supply constraints, alternative inactivated quadrivalent vaccines—such as cell culture-based, split virus, subunit, recombinant, or adjuvanted types—may be used.

3.3. Case 3: United States

3.3.1. The Advisory Committee on Immunization Practices (ACIP): Structure and Role

The Advisory Committee on Immunization Practices (ACIP) was established in March 1964 under Section 222 of the Public Health Service Act (PHSA; 42 U.S.C. §217a), which grants the Secretary of Health and Human Services (HHS) the authority to form advisory committees. ACIP was formed to provide expert, ongoing guidance to the Secretary on federal immunization policies, particularly considering growing national vaccination programs and the approval of new vaccines. The committee can have up to 19 voting members [146].

ACIP advises the CDC Director on the use of vaccines and related biologics to prevent vaccine-preventable diseases in the U.S. population. Once the CDC Director reviews and approves ACIP's recommendations, they become official CDC/HHS policy and are published in the *Morbidity and Mortality Weekly Report* (MMWR)[147].

The ACIP Influenza Work Group includes ACIP voting members, along with representatives from partner organizations and consultants. It meets one to two times per month via teleconference throughout the year. The group discusses issues such as influenza surveillance, vaccine safety and efficacy, vaccination coverage, feasibility of implementation, cost-effectiveness, and vaccine supply. External experts are often invited to present, and both published and unpublished data are evaluated [148].

3.3.2. EtR Framework on Enhanced Vaccines for Adults Aged ≥65 Years

The influenza vaccine recommendations for the 2024–2025 season were published in August 2024 under the title *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2024–25 Influenza Season* in the *Morbidity and Mortality Weekly Report* (MMWR Recomm Rep 2024;73[No. RR-5]) [(149)].

In this new recommendation publication, they refer to the EtR framework[6], as a guidance to their recommendation. This framework is detailed in the EtR document titled *Evidence to Recommendations (EtR) Framework: Higher Dose and Adjuvanted Influenza Vaccines for Persons Aged ≥65 Years*, initially published on August 26, 2022, and most recently updated on September 5, 2024[(150)]. The GRADE assessment supporting this framework includes articles published between 1990 and September 7, 2021, with one additional study published in 2022. The defined PICO question guided the analysis of 51 studies, including 25 RCTs, 2 cluster-RCTs, and 24 observational studies[7].

Comparative Effectiveness of Enhanced Vaccines

The ACIP evaluated the comparative benefits and harms of high-dose inactivated influenza vaccine (HD-IIV), MF59-adjuvanted inactivated influenza vaccine (Adj-IIV), and recombinant influenza vaccine (RIV) for adults aged ≥65 years, relative to each other and to standard-dose unadjuvanted inactivated influenza vaccines (SD-IIVs).

Evidence on Benefits and Harms

Evidence from RCTs outside pandemic contexts was limited. A large two-season RCT with 32,000 participants aged ≥65 years found HD-IIV3 to be 24% more effective than SD-IIV3 in preventing PCR- or culture-confirmed ILI (95% CI: 10% to 36%), and was rated as high certainty [(151)]. Conversely, two single-season RCTs comparing RIV3 and RIV4 to SD-IIVs showed no significant benefit among those aged ≥65 years, with a pooled relative efficacy of 18% (95% CI: −17% to 43%) [(152,153)]. However, RIV4 demonstrated improved efficacy in broader populations aged ≥50 years (30%; 95% CI: 10% to 47%) and among adults ≥65 years for culture-confirmed ILI (42%; 95% CI: 9% to 65%), with moderate certainty [(153)].

Though no individually RCTs have compared Adj-IIV to SD-IIV in non-pandemic settings, two cluster-RCTs U.S. nursing home studies found both HD-IIV3 and Adj-IIV3 to reduce hospitalizations for pneumonia and influenza (RR: 0.79; HD-IIV3 95% CI: 0.66 to 0.95; Adj-IIV3 95% CI: 0.65 to 0.96), both with moderate certainty [(154,155)]. Observational studies further suggested modest benefit, particularly for HD-IIV, followed by Adj-IIV and then RIV [(156–169).]

[6] Refer to Table 2 of the Appendices, for the full ACIP EtR framework
[7] PICO clearly mentioned in the summary table of results

The ACIP work group rated the anticipated benefits of enhanced vaccines over SD-IIVs as "moderate" for most members, with a few considering them "small." Evidence comparing enhanced vaccines directly was limited and inconsistent; one study favored RIV4 over both HD-IIV3 and Adj-IIV3 in a single season [158].

RCTs showed that the risk of severe systemic and serious adverse events was generally similar across vaccine types. However, HD-IIV and Adj-IIV were associated with higher frequencies of injection site reactions compared to SD, however, they were of low certainty [170,171]. Data on Guillain-Barré syndrome were sparse and inconclusive. The WG judged the anticipated undesirable effects as "minimal."

Certainty of Evidence

The certainty of evidence for benefits was rated as Level 3 (low) for HD-IIV, Adj-IIV, and RIV vs. SD-IIVs, and Level 4 (very low) for direct comparisons between the enhanced vaccines (e.g., HD-IIV vs. Adj-IIV, HD-IIV vs. RIV, Adj-IIV vs. RIV). Similarly, for harms, most comparisons were rated Level 3 (low), with Level 4 (very low) for RIV vs. SD-IIVs. Downgrades were due to limited RCTs, small sample sizes, and low event rates.

The WG ultimately concluded that the desirable effects of enhanced influenza vaccines outweigh the undesirable ones. Although no direct evidence supported public value judgments, the group believed that older adults would likely perceive the net benefit as favorable. They also found little to no variability in how these outcomes are valued.

Acceptability and Feasibility

The intervention was deemed acceptable by key stakeholders. Medicare data from the 2018–2019 and 2019–2020 seasons showed that ~80% of community-dwelling seniors had received a high-dose or adjuvanted vaccine. While these studies excluded nursing home residents and may not represent the entire ≥65 population, they offer indirect support for acceptability [156–158].

The WG also found the intervention feasible. The high uptake of enhanced vaccines in recent seasons suggests that infrastructure and provider acceptance are already in place. However, limitations of Medicare data and excluded populations (e.g., nursing homes) led some WG members to respond, "Probably Yes," acknowledging minor feasibility concerns.

Resource Use and Economic Efficiency

Although no direct cost-effectiveness studies assessed recommending all enhanced vaccines as a group, modeling based on past seasons showed variable outcomes. Twenty percent of modeled scenarios were cost-saving (ICER = $0/QALY), while the 95th percentile ICER reached $195,000/QALY [156–158]. Most WG members judged the intervention a reasonable use of resources; a smaller group responded "Varies," citing context-specific differences such as seasonal severity and baseline vaccine effectiveness.

Equity Considerations

The WG concluded that a preferential recommendation could probably improve health equity, although no direct evidence supported this. Past data indicated disparities in vaccine uptake: in the 2015–16 season, Black, Asian, and Hispanic Medicare beneficiaries were less likely than White beneficiaries to receive HD-IIV3 [172–174]. Some WG members expected equity gains, while others anticipated neutral impact.

Balance of Consequences

Most WG respondents agreed that the desirable consequences clearly outweigh the undesirable ones in most settings. A smaller subset concluded they "probably outweigh" the undesirable effects, reflecting consensus on the favorable benefit-risk profile of enhanced influenza vaccines for older adults.

3.3.3. ACIP Recommendations for 2024/2025

The influenza vaccine recommendations for the 2024–2025 season were published in August 2024 under the title *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2024–25 Influenza Season*, published by the Centers for Disease Control and Prevention (CDC) in the MMWR Recommendations and Reports [*149*].

The Advisory Committee on Immunization Practices (ACIP) recommended that adults aged 65 years and older preferentially receive one of the following enhanced influenza vaccines: HD-IIV4, RIV4, or Adj-IIV4. If none of these preferred options is available at the time of vaccination, any other age-appropriate influenza vaccine may be used [149,150].

3.4. Case 4: Australia

3.4.1. Australian Technical Advisory Group on Immunisation (ATAGI): Structure and Role

Established in 1997 by the Commonwealth Minister for Health [175], the Australian Technical Advisory Group on Immunisation (ATAGI) is composed of experts in research, clinical practice, and immunisation program implementation, alongside consumer representatives and ex-officio members [176]. Members are appointed by the Minister for Health and Aged Care [176], and the current composition includes 14 voting members and 6 ex-officio members [177]. ATAGI advises the Minister on the medical use of vaccines in Australia, particularly those under the National Immunisation Program (NIP), and identifies immunisation topics for further research [176]. It also provides pre-submission guidance to vaccine manufacturers seeking approval from the Pharmaceutical Benefits Advisory Committee (PBAC), especially regarding vaccine effectiveness and contextual use. In collaboration with stakeholders such as the National Centre for Immunisation Research and Surveillance (NCIRS), ATAGI helps develop the *Australian Immunisation Handbook* and supports immunisation policy, implementation strategies, and vaccine safety initiatives.

3.4.2. Burden of Influenza in Australia

According to the *Australian Immunisation Handbook*, influenza causes an estimated 100 deaths and 5,100 hospitalizations annually in Australia [178], though these figures likely underestimate the true burden [179]. A 2019 Australian modelling study covering 2006–2015 reported an average influenza-attributable excess respiratory mortality rate of 2.61 per 100,000, with the highest rate in adults aged ≥65 years (16.4 per 100,000), and the highest hospitalization rates in those aged ≥65 (195.42 per 100,000) and infants under 6 months (153.84 per 100,000) [180]. Another model estimated that mortality could reach 26.8 per 100,000 in Australians aged ≥75 [181]. Consistent with trends in other high-income countries, hospitalization rates in Australia are highest among older adults and children under 5 [178,182,183]. Additionally, Aboriginal and Torres Strait Islander peoples face a higher influenza burden than non-Indigenous Australians across all age groups [178].

3.4.3. Insights from GRADE Reviews

In February 2021 and March 2022, the National Centre for Immunisation Research and Surveillance (NCIRS) conducted three separate GRADE evidence reviews in support of ATAGI, comparing: 1. adjuvanted influenza vaccine (Adj-IIV) vs standard-dose influenza vaccine (sIV) in February 2021, based on 21 studies [184]; 2. high-dose influenza vaccine (HD-IV) vs sIV in March 2022, based on 37 studies [185]; and 3. High dose vs adjuvanted vaccine also in March 2022, based on 11 studies [186]. These reviews provide a comprehensive assessment of the comparative effectiveness and safety of influenza vaccines in adults aged 65 years and older[8].

Adjuvanted vs. Standard-Dose Influenza Vaccine

Hospitalization Outcomes

Four observational studies comparing Adj-IIV to sIV for influenza- or pneumonia-related hospitalizations reported adjusted risk ratios ranging from 0.75 (95% CI: 0.57 to 0.98) to 0.95 (95% CI: 91.7 to 99.1), indicating reduced hospitalization with Adj-IIV [187–190]. However, the certainty of this evidence was rated low due to concerns about bias, indirectness, and inconsistency.

Three additional studies assessing influenza-related hospital encounters, including inpatient and emergency department visits, showed probable benefit of Adj-IIV (RRs: 0.88 to 0.96), with moderate-certainty evidence [189–191].

One study also found a significant reduction in pneumonia, stroke, or myocardial infarction with Adj-IIV (OR: 0.61; 95% CI: 0.39 to 0.96), though the evidence was judged to be of very low certainty due to serious methodological limitations [192].

[8] PICO clearly mentioned in the summary table of results

Outpatient Visits and Influenza-like Illness (ILI)

One large observational study involving almost 2.5 million participants found that adjuvanted influenza vaccine may slightly increase in influenza-related office visits among Adj-IIV recipients compared with sIV (RR: 1.12; 95% CI: 1.08 to 1.16), with low certainty of evidence [189].

For ILI outcomes, an RCT found little to no difference between Adj-IIV and sIV (RR: 0.91; 95% CI: 0.71 to 1.16), with low-certainty evidence [193]. In contrast, one observational study showed a possible reduction in ILI for Adj-IIV compared to sIV (OR: 0.66; 95% CI: 0.53 to 0.82), but the certainty of this result was very low due to methodological limitations [194].

Laboratory-Confirmed Influenza (LCI)

A single small case-control observational study (65 cases, 162 controls) evaluated laboratory-confirmed influenza and found that Adj-IIV may reduce the odds of infection compared to sIV (OR: 0.37; 95% CI: 0.14 to 0.96) [195]. However, due to the limited sample size, wide confidence intervals, and high risk of bias, the certainty of evidence was rated very low.

Vaccine Safety

For local adverse events, 10 RCTs [193,196–204] and one observational study [205] showed that Adj-IIV was associated with slightly higher rates of events such as injection site pain. The pooled risk ratio was 1.27 (95% CI: 1.22 to 1.33), supporting a high-certainty conclusion that local reactions are more common with Adj-IIV.

Systemic adverse events, such as fatigue, myalgia, and fever, were similar between groups, with high-certainty evidence [193,196–205].

For serious adverse events (SAEs), data from 9 RCTs showed that most studies did not report any SAEs in either group, and the evidence was of high certainty [193,196–200,202–205].

Adverse events of special interest (AESIs), including Guillain-Barré syndrome (GBS), were assessed in two observational studies [206,207]. One suggested an elevated GBS risk with Adj-IIV, while the other did not. Due to inconsistencies and methodological limitations, the certainty of this evidence was very low.

High-Dose vs. Standard-Dose Influenza Vaccine

Mortality Outcomes

An observational study conducted over two influenza seasons (2012/13–2013/14) found mixed results: an rVE of 36.5% (95% CI: 9 to 56%) in 2012/13 and only 2.5% (95% CI: -47 to 35%) in 2013/14; the evidence was judged very low certainty [208]. In contrast, another observational study across three influenza seasons estimated that HD-IV may reduce influenza- or pneumonia-associated mortality, reporting a pooled rVE of 42% (95% CI: 24 to 59%), with low certainty [209]. As for all-cause mortality, one cluster RCT found no significant

difference between HD-IV and sIV, with an rVE of 1.5% (95% CI: -3.8 to 6.9%) and high certainty [210].

Hospitalization Outcomes

Regarding laboratory-confirmed influenza hospitalizations, HD-IV may reduce risk compared with sIV, although the evidence was very low [211,212]. One observational study showed an rVE of 27% (95% CI: -1 to 48%), while another reported inconsistent modelling results [211,212]. A cluster RCT provided moderate-certainty evidence that HD-IV likely decreases non-laboratory-confirmed respiratory-related hospitalizations (rVE: 12.7%; 95% CI: 1.8 to 22.4%) and pneumonia-related hospitalizations (rVE: 20.9%; 95% CI: 4.7 to 73.3%) [210].

Eight observational studies also suggest HD-IV may slightly reduce respiratory- or pneumonia-related hospitalizations compared to sIV, with rVEs ranging from 2% to 25%, and low certainty [213–219]. Additional observational studies indicate that HD-IV may decrease hospitalizations and emergency department (ED) visits for influenza, pneumonia, or respiratory conditions, with low certainty [190,208,215,218,220–223].

Concerning all-cause hospitalization, two RCTs showed a slight benefit for HD-IV, with moderate-certainty estimates of rVE: 7% (95% CI: 0 to 13%) and 8.5% (95% CI: 3 to 13.7%) [210,224]. Five observational studies found low-certainty evidence of modest reductions, with rVEs up to 11% (95% CI: 8 to 15%) [213,214,216,225,226].

Outpatient and Emergency Department Visits

HD-IV was found to be slightly reducing influenza and/or pneumonia-related outpatient or office visits or ED visits compared to sIV, though the evidence was very low [208,214,215,221]. Across six studies and nine influenza seasons, rVEs for such outcomes ranged from 4.9% (95% CI: 1.8 to 8.1%) to 21.6% (95% CI: 16.1 to 26.7%) [208,214,215,221].

Laboratory-Confirmed Influenza (LCI) Outcomes

Evidence from two RCTs shows that HD-IV likely results in a slight reduction in laboratory-confirmed influenza compared with sIV, with moderate certainty, reporting rVEs of 12.6% (95% CI: -140.5 to 65.8%) and 24.2% (95% CI: 9.7 to 36.5%) [224,227]. One observational study estimated an rVE of 38% (95% CI: -5 to 65%) with low certainty [225], and another study reported a 35% rVE against PCR-confirmed influenza A, also with low certainty [228].

Cardiovascular Events

HD-IV may have little to no effect on cardiovascular events compared with sIV, though evidence from two RCTs was very low. The DiazGranados (2015) trial reported negligible effects, while Saade (2018) found an 8% reduction in events; however, serious risk of bias and imprecision limited the certainty of these findings [224,229].

Vaccine Safety

In terms of serious adverse events (SAEs) and adverse events of special interest **(**AESIs), ten RCTs provided moderate-certainty evidence that HD-IV likely results in little to no difference compared with sIV [196,227,230–237]. While AESIs such as GBS occurred slightly more frequently among HD-IV recipients in some seasons, two observational studies suggested a possibly elevated risk—but with very low certainty due to serious risk of bias.

Systemic adverse events—including fatigue, fever, and myalgia—were slightly more common with HD-IV, based on six RCTs and two observational studies, with moderate-certainty evidence [196,230,232,234–236,238]. Local adverse events, such as injection site reactions, were also more common with HD-IV than with sIV, supported by the same set of studies and with moderate certainty [196,230,232,234–236,238].

High-Dose vs. Adjuvanted Influenza Vaccine

Hospitalization Outcomes

Three observational studies comparing high-dose (HD-IV) and MF59-adjuvanted (Adj-IIV) influenza vaccines for influenza-related hospitalizations found little to no difference, with adjusted rVE estimates ranging from –1.4% (95% CI: –5.4 to 2.4%) to 7.7% (95% CI: 5.1 to 10.2%) and moderate-certainty evidence [189,219,222].

Similarly, six observational studies assessing influenza-related hospital encounters—including emergency department visits and hospitalizations—also found no significant difference between the two vaccines, with rVEs ranging from –1.6% (95% CI: –4.8 to 1.6%) to 7.7% (95% CI: 2.3 to 12.8%) and moderate certainty [189–191,219,223,239].

One large study (van Aalst et al., 2019) indicated that HD-IV may slightly reduce respiratory-related hospitalizations compared to Adj-IIV (RR: 0.88; 95% CI: 0.80 to 0.97), though the certainty of this evidence was low.

Outpatient Visits

For influenza-related office visits, a large observational study found that HD-IV may slightly reduce visits compared to Adj-IIV(RR: 0.93; 95% CI: 0.91 to 0.95), equating to approximately 38 fewer visits per 100,000 people, and the certainty of this evidence was low [215].

Vaccine Safety

Two RCTs and one observational study found that HD-IV results in little to no difference in solicited local adverse events compared to Adj-IIV, with high-certainty evidence. One RCT reported slightly higher rates of moderate to severe injection site pain with HD-IV (5.8%) than with Adj-IIV (3.2%) [113], and another study supported these findings [196].

Systemic adverse events such as fatigue were also similar between the two vaccines, with high-certainty evidence [196,200,205]. For adverse events of special interest, one observational study suggested a possible elevated risk of GBS with Adj-IIV (OR: 3.75; 95%

CI: 1.01 to 13.96), though this was not statistically significant after multiplicity adjustment. No such risk was observed with HD-IV (OR: 0.89; 95% CI: 0.48 to 1.65), and the certainty of this evidence was rated low [206].

EtD Framework Summary: Individual Perspective

Across all three Evidence-to-Decision (EtD) frameworks[9]—each conducted from an individual perspective—the burden of influenza among older adults was identified as a high-priority public health issue. When comparing Adj-IIV to sIV, desirable effects were considered small, undesirable effects probably small, and the overall certainty of evidence was low, though the balance of effects probably favored Adj-IIV. The vaccine was deemed acceptable and feasible. For HD-IIV versus sIV, desirable effects were judged to be probably moderate and undesirable effects probably small, with moderate certainty of evidence. The balance of effects probably favored HD-IIV, which was also considered probably acceptable and feasible, with consistent values placed on outcomes by older adults. In comparing HD-IIV to Adj-IIV, HD-IIV showed only small improvements in effectiveness and trivial undesirable effects. The certainty of evidence ranged from low to moderate for effectiveness and was high for safety, but no clear preference was found between the two. Older adults were judged to consistently value vaccine protection, and HD-IIV was considered acceptable and feasible to implement given its previous high uptake and minimal delivery barriers.

3.4.4. ATAGI Recommendations for 2025

The Australian Technical Advisory Group on Immunisation (ATAGI) published its recommendation under the title *Statement on the Administration of Seasonal Influenza Vaccines in 2025* [240]. On March 3, 2025, ATAGI recommended that adults aged 65 years and older should preferentially receive either the adjuvanted influenza vaccine or the high-dose influenza vaccine. These two vaccines were equally preferred over standard influenza vaccines for this age group. If neither of these enhanced vaccines is available, any other age-appropriate influenza vaccine may be used [240].

[9] Refer to Table 3 of the Appendices, for the full GRADE EtD framework

Summary Table: Comparative Evaluation of Influenza Vaccine Recommendations and Evaluation Critera for Older Adults— Insights from Canada, Germany, the U.S., and Australia

	Country	Canada	Germany	United States	Australia
Recommendations	**Issuing Body**	National Advisory Committee on Immunization (NACI)	Standing Committee on Vaccination (STIKO)	Advisory Committee on Immunization Practices (ACIP)	Australian Technical Advisory Group on Immunisation (ATAGI)
	Recommended Vaccines	**NH 2024/2025:** High-dose inactivated influenza vaccine (IIV-HD), adjuvanted inactivated influenza vaccine (IIV-Adj), or recombinant influenza vaccine (RIV) in 65+ population	**NH 2024/2025:** High-dose inactivated influenza vaccine (IIV-HD) in 60+ population	**NH 2024/2025:** High-dose inactivated influenza vaccine (IIV-HD), adjuvanted inactivated influenza vaccine (IIV-Adj), or recombinant influenza vaccine (RIV) in 65+ population	**SH 2025:** Adjuvanted influenza vaccine (IIV-Adj) or the high-dose (IIV-HD) influenza vaccine in 65+ population
	Publication Details	*NACI Seasonal Influenza Vaccine Statement 2024–2025*	*Epidemiologisches Bulletin 04/2024*	*Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2024–25 Influenza Season*	*Statement on the Administration of Seasonal Influenza Vaccines in 2025*
		May 2024	January 2024	August 2024	March 2025
Evaluation Criteria	**Evidence Basis & Methodology**	GRADE ADOLOPMENT framework of US ACIP-based review + 2 DSEN MAGIC systematic reviews, including an economic review; GRADE and CINeMA used	Systematic review by HIQA, ECDC, and RKI with GRADE application, and economic evaluation based on transmission modeling	GRADE-based review; EtR framework applied	Separate GRADE-based reviews; EtR framework applied from an individual perspective
	Body of Evidence	31 studies from the US ACIP-based review and 41 RCTs , of which 26 included in the quantitative synthesis from 2 DSEN MAGIC sytematic reviews	110 studies included, of which 51 meta-analyzed	51 studies: 25 RCTs, 2 cluster-RCTs, 24 observational	37 studies for IIV-HD vs IIV-SD, 21 studies for IIV-Adj vs IIV-SD and 11 studies for IIV-HD vs IIV-Adj

Evalaution Criteria	**PICO**	**Population:** Persons aged 65 years and older	**Population:** Adults aged 18 years and older, regardless of health status or setting.	**Population:** Persons aged 65 years and older	**Population:** Adults aged 65 years and older
		Intervention: • Inactivated influenza vaccines (IIV) that are not standard dose (e.g., high-dose [IIV-HD], adjuvanted [IIV-Adj]) • Recombinant influenza vaccine (RIV) • Mammalian cell culture-based inactivated vaccine (IIV-cc)	**Intervention:** Vaccination with an enhanced (trivalent or quadrivalent) influenza vaccine.	**Intervention:** • High-dose inactivated influenza vaccine (HD-IIV) • Recombinant influenza vaccine (RIV) • MF59-adjuvanted inactivated influenza vaccine (aIIV)	**Intervention:** • MF59-adjuvanted influenza vaccine (aIV) • High-dose influenza vaccine (HD-IIV)
		Comparator: • Standard-dose inactivated influenza vaccines (IIV-SD) • Inactivated non-standard dose and recombinant vaccines (for head-to-head comparisons)	**Comparator:** Placebo, no vaccination, or SD influenza vaccine (head-to-head comparisons).	**Comparator:** • Standard-dose unadjuvanted inactivated influenza vaccines (SD-IIVs) • HD-IIV, RIV, and aIIV (for head-to-head comparisons)	**Comparator:** • Standard-dose influenza vaccines (sIV) • MF59-adjuvanted influenza vaccine (when HD-IIV is the intervention)
		Outcomes: • **Vaccine efficacy/effectiveness:** ○ Laboratory-confirmed influenza (LCI) ○ Influenza-associated outpatient or emergency department (ED) visits (LCI or influenza-like illness [ILI]) ○ Influenza-associated hospitalizations (LCI or ILI) ○ Influenza-associated vascular events • **Vaccine safety:** ○ Any solicited serious adverse reaction (SAR) of grade ≥3 ○ Guillain-Barré Syndrome (GBS) ○ Any serious adverse event (SAE) ○ Any solicited injection site adverse reaction (AR) of grade ≥3 • **Economics:** ○ Vaccine cost-effectiveness (e.g., cost per life year saved,	**Outcomes:** • Laboratory-confirmed influenza (LCI) • Influenza-related mortality (laboratory-confirmed) • Influenza-related hospitalization (laboratory-confirmed) • Laboratory-confirmed influenza-associated cardiovascular disease • Laboratory-confirmed influenza-associated pneumonia or lower respiratory tract disease • Influenza-like illness (ILI) • ICD-coded respiratory or cardiovascular mortality • Exacerbation of underlying respiratory or cardiovascular conditions • Serious adverse reactions (SAR) and local adverse reactions (LAR)	**Outcomes:** • **Critical outcomes:** ○ Influenza illness ○ Influenza-associated outpatient or emergency room (ER) visits ○ Influenza-associated hospitalizations ○ Influenza-associated deaths ○ Any solicited serious adverse event (SAE) of grade ≥3 ○ Guillain-Barré Syndrome (GBS) • **Important outcomes:** ○ Any solicited injection site adverse event (AE) of grade ≥3 ○ Any SAE	**Main Outcomes:** **Effectiveness outcomes:** • Laboratory-confirmed influenza (LCI) • PCR-confirmed Influenza A • Influenza-like illness (ILI) • Influenza- or pneumonia-related hospitalisation • Influenza-related hospitalisation and/or emergency department (ED) visits • Influenza-related outpatient, office, or medical encounters • Respiratory-related hospitalisations • Hospitalisations for pneumonia, stroke, or myocardial infarction (during influenza season) • Influenza/pneumonia/respiratory-related hospitalisations or ED visits (with or without laboratory confirmation) • Post-influenza mortality • Influenza- or pneumonia-associated mortality • Cardiovascular events

		cost per influenza case averted) Cost-utility (e.g., cost per quality-adjusted life year [QALY] gained)			• Cardiorespiratory events • All-cause hospitalisation • All-cause mortality **Safety outcomes:** • Local adverse events • Systemic adverse events • Serious adverse events (SAEs) • Adverse events of special interest (AESIs) Solicited local and systemic adverse events
	Literature Search	Up to June 2022	Up to February 2020	Up to September 2021	Up to March 2022
	Efficacy and Effectiveness (Moderate to High Certainty)	**Enhanced Vaccines vs SD:** ***LCI*** **HD vs SD**: rVE ~25% vs SD (high certainty, ACIP) **RIV vs SD**: rVE = 18% (95% CI: -17 to 43%) – moderate certainty (ACIP) ***Hospitalizations ILI*** **HD vs SD**: rVE = 28% (CI: 8 to 43%) for ILI-related hospitalization (moderate certainty**,** ACIP & DSEN MAGIC)	**Enhanced Vaccines vs SD:** **1- Adj vs SD:** None was found to be of moderate-high certainty **2- HD vs SD:** ***LCI*** **HD vs SD:** rVE = 24% (95% CI: 9.7 to 36.5%; high certainty) ***Hospitalizations LCI*** **HD vs SD:** rVE = 6.9% (95% CI: 0.5 to 12.8%; high certainty) ***Severe cardiorespiratory events*:** **HD vs SD in LCI:** rVE = 17.7% (95% CI: 6.6 to 27.4%) **Pneumonia:** **HD vs SD in LCI:** rVE = 39.8% (95% CI: 19.3 to 55.1%; high certainty) **3- RIV vs SD:** ***LCI*** **RIV vs SD:** rVE= 30% (95% CI: 10 to 47%; moderate certainty) in adults ≥50 years and rVE= 17% (95% CI: –20 to 43%) in adults ≥65 years (not statistically significant)	**Enhanced Vaccines vs SD:** **1- HD vs SD:** ***LCI*** **HD vs SD:** rVE = 24% (95% CI: 10 to 36%; high certainty) ***Hospitalizations P&I*** **HD vs SD:** RR = 0.79 (95% CI: 0.66 to 0.95; moderate certianty) **2- Adj vs SD:** ***Hospitalizations P&I*** **Adj vs SD**: RR = 0.79 (95% CI: 0.65 to 0.96; moderate certainty)	**Enhanced Vaccines vs SD:** **1- Adj vs SD:** ***Influenza-related hospital encounters*** RRs ranged from 0.88 (95%CI: 0.806 to 0.977) to 0.96 (95%CI: 0.936 to 0.993) – Moderate certainty **2- HD vs SD:** ***LCI*** (Moderate Certainty) **HD vs SD:** rVE = 12.6% (95% CI: -140.5 to 65.8%) and 24.2% (95% CI: 9.7 to 36.5%) ***All-cause mortality*** **HD vs SD: no significant differnece** rVE = 1.5% (95% CI: –3.8 to 6.9%; high certainty) ***Hospitalizations*** (Moderate certainty) **HD vs SD (Non-lab confirmed influenza):** rVE = 12.7% (95% CI: 1.8 to 22.4%) **HD vs SD (Pneumonia)**: rVE = 20.9% (95% CI: 4.7 to 73.3%) **HD vs SD (All-cause hospitalizations)**: rVE = 7(95% CI: 0 to 13%) to 8.5% (95% CI: 3 to 13.7%)

		Head-to-Head Enhanced Vaccines Among Each other: None was found to be of moderate-high certainty		**Head-to-Head Enhanced Vaccines Among Each other:** None was found to be of moderate-high certainty	**Head-to-Head Enhanced Vaccines Among Each other:** **1- HD vs Adj** ***Hospitalizations (Influenza-related)*** rVEs ranged from –1.4% (95% CI: –5.4 to 2.4%) to 7.7% (95% CI: 5.1 to 10.2%): **no significant differences (moderate certainty)**
	Safety Summary (Moderate to High Certainty)	**Enhanced Vaccines vs SD**: None was found to be of moderate-high certainty	**Enhanced Vaccines vs SD:** **1- Adj vs SD:**(Moderate certainty) ***Local reactions*:** Pooled RR = 1.90 (95% CI: 1.50 to 2.39) ***Injection site pain*:** RR = 2.02 (95% CI: 1.53 to 2.67) ***Systemic events*:** RR = 1.18 (95% CI: 1.02 to 1.38) **2- HD vs SD: (**Moderate certainty) ***Injection site pain :*** RR = 1.48 (95% CI : 1.21 to 1.82)	**Enhanced Vaccines vs SD:** None was found to be of moderate-high certainty	**Enhanced Vaccines vs SD:** **1- Adj vs SD:** ***Local Adverse Events*** Pooled RR = 1.27 (95% CI: 1.22 to 1.33; high certainty) ***Systemic Adverse Events*** No meaningful difference between Adj and SD (high certainty) ***Systemic Adverse Events*** No meaningful difference between Adj and SD (high certainty) ***Serious Adverse Events*** Most studies did not report any SAEs in both groups (high certainty) **2- HD vs SD:** ***Serious Adverse Events*** No major difference in SAEs (moderate certainty) ***Systemic Adverse Events*** Slightly more common with HD (moderate certainty) ***Local Adverse Events*** More common with HD (moderate certainty)
		Head-to-Head Enhanced Vaccines Among Each other: None was found to be of moderate-high certainty		**Head-to-Head Enhanced Vaccines Among Each other:** None was found to be of moderate-high certainty	**Head-to-Head Enhanced Vaccines Among Each other:** **2- HD vs Adj:** ***Local Adverse Events*** Little to no difference (high certainty) ***Systemic Adverse Events*** Similar frequency between HD and Adj (high certainty)

Evaluation Criteria	**Economic Evaluation Summary**	**National-level:** IIV3-HD dominated IIV3-SD (lower cost, higher effectiveness). At a $40,000/QALY threshold, IIV3-HD, IIV3-Adj, and IIV4-SD were cost-effective in 75–100**%** of estimates. **Quebec (CIQ):** Discounted ICER ranged from $56,173/QALY (for 75+ with comorbidities) to > $2.6 million/QALY in other subgroups. CIQ found limited evidence for IIV3-Adj superiority over IIV3-SD or parity with IIV3-HD. And based on commonly used cost-effectiveness thresholds, enhanced vaccines were not considered to be cost-effective.	High-dose vaccines considered cost-effective from a societal perspective. At 15% rVE, cost-effective up to €50,000/QALY if priced at 2 times the cost of standard vaccine. At 30% rVE, cost-effective even at 2.5 times the price. Used a decision tree model with data from 2003–2019 (excluding 2009 pandemic). Costs included outpatient care, medications, and productivity loss. Analyses were robust to sensitivity variations.	No direct cost-effectiveness studies assessed. 20% of modeled scenarios were cost saving. ICER up to $195,000/QALY Generally considered reasonable resource use.	None is mentioned
	Programmatic Considerations	EEFA factors: equity, feasibility and acceptability are explicitly considered via structured matrices.	Not mentioned in the scientific rationale document.	As part of the ACIP EtR framework: acceptability, feasability and equity were considered.	As part of the GRADE EtD framework: acceptability and feasability were considered.

Acronyms: NACI: National Advisory Committee on Immunization; STIKO: Standing Committee on Vaccination; ACIP: Advisory Committee on Immunization Practices; ATAGI: Australian Technical Advisory Group on Immunisation; NITAG: National Immunization Technical Advisory Group; NH: Northern Hemisphere; SH: Southern Hemisphere; CIQ: Comité sur l'immunisation du Québec;ECDC: European Centre for Disease Prevention and Control; HIQA: Health Information and Quality Authority; RKI: Robert Koch Institute; DSEN: Drug Safety and Effectiveness Network; MAGIC: Methods and Applications Group for Indirect Comparisons; IIV: Inactivated Influenza Vaccine; IIV-HD / IIV3-HD/ HD-IIV: High-Dose Inactivated Influenza Vaccine; IIV-Adj /IIV3-Adj /aIIV / aIV: Adjuvanted Inactivated Influenza Vaccine; RIV: Recombinant Influenza Vaccine; IIV-cc: Cell Culture-Based Inactivated Influenza Vaccine; IIV-SD / SD-IIV / sIV: Standard-Dose Inactivated Influenza Vaccine; GRADE: Grading of Recommendations Assessment, Development and Evaluation; EtR: Evidence to Recommendations; EtD: Evidence to Decision; CINeMA: Confidence in Network Meta-Analysis; EEFA: Ethics, Equity, Feasibility, Acceptability; PICO: Population, Intervention, Comparator, Outcomes; RCT: Randomized Controlled Trial; RR: Risk Ratio; rVE: Relative Vaccine Effectiveness; ICD: International Classification of Diseases; ICER: Incremental Cost-Effectiveness Ratio; QALY: Quality-Adjusted Life Year; LCI: Laboratory-Confirmed Influenza; ILI: Influenza-Like Illness; ED: Emergency Department; SAR: Serious Adverse Reaction; SAE: Serious Adverse Event; AR: Adverse Reaction; AE: Adverse Event; LAR: Local Adverse Reaction; AESI: Adverse Event of Special Interest; GBS: Guillain-Barré Syndrome; P&I: Pneumonia and Influenza

Discussion

This thesis aimed to examine how four high-income countries—Canada, Germany, the United States, and Australia—evaluated and recommended enhanced influenza vaccines for adults aged 65 years and older during the 2024–2025 influenza season. The analysis revealed differences in methodologies, strength of evidence, economic considerations, and recommendation specificity, all rooted in distinct national frameworks.

Despite a shared goal of improving influenza-related outcomes in older adults, the four countries employed somewhat distinct evaluative approaches. All four NITAGs applied GRADE-based frameworks, though with varying depth and supplemental methodologies. Canada used a GRADE-ADOLOPMENT approach to adapt U.S. evidence while incorporating additional systematic reviews (MAGIC) and a cost-effectiveness analysis; Germany, collaborating with the ECDC, used meta-analytic modeling and dynamic transmission models to assess both clinical and economic outcomes. The U.S. conducted its own GRADE assessment and used the ACIP EtR framework—similar to GRADE's EtD—which incorporates structured consideration of public health problem (burden of disease), values, equity, feasibility, and resource use. Australia applied GRADE and used the EtD framework from an individual perspective, excluding equity and resource use criteria.

To improve clarity and comparability in this analysis, only moderate- to high-certainty evidence was included in the summary table for efficacy, effectiveness, and safety. A large portion of available data was rated low to very low certainty and including it would have reduced the practical value of the comparison. Focusing on stronger evidence allowed clearer insight into how each country weighed robust findings in shaping recommendations.

Although most clinical studies assessed were common across countries, the size and scope of the body of evidence varied. Literature search timeframes also differed, with Canada having conducted the most recent review, including studies published through June 2022. This variability reflects a key contextual consideration: the application of systematic literature reviews and GRADE methodology is generally limited to circumstances where new vaccines are introduced or when substantial changes occur to existing formulations, as explicitly stated by the NITAGs of the four countries.

All four countries recommended enhanced vaccines (high-dose, adjuvanted, or recombinant) over standard-dose influenza vaccines for older adults. However, differences emerged in vaccine preference and recommendation specificity. For example, Germany clearly prioritized high-dose vaccines for those aged 60 and above, based on high-certainty evidence of effectiveness and good economic justification. This had been the case since the NH 2020/2021 STIKO recommendation [241]; however, in its latest NH 2025/2026 recommendation, this unique prioritization has shifted, with the MF59-adjuvanted vaccine

now included alongside the high-dose vaccine, based on both the scientific rationale from 2021 and new evidence published in *Epidemiologisches Bulletin* 44/2024 [242].

In contrast, Australia and the United States expressed equal preference for either adjuvanted or high-dose vaccines, acknowledging similar effectiveness and safety profiles, while US recommending also the recombinant with equal acknowledgement of effectiveness, but not Australia, as the recombinant is not already in its PICO as an intervention. Canada's recommendation aligned with these two, endorsing any of the three enhanced options for those aged 65+, but did so with more extensive evidence synthesis and economic scrutiny. This recommendation has remained consistent in the most recent NH 2025/2026 update, continuing to support all three enhanced vaccines without prioritization among them.

Despite relying on a largely overlapping body of clinical evidence, countries reported different estimates of vaccine effectiveness and assessed the quality of evidence differently. For example, all four NITAGs referenced the DiazGranados et al. (2014) randomized controlled trial comparing high-dose versus standard-dose influenza vaccines, but their reporting of relative vaccine effectiveness (rVE) and certainty ratings varied. Canada cited an rVE of approximately 25% against laboratory-confirmed influenza (LCI) with high certainty, referencing ACIP's interpretation. Germany reported 24% (95% CI: 9.7 to 36.5%), the U.S. 24% (95% CI: 10 to 36%), and Australia 24.2% (95% CI: 9.7 to 36.5%), all closely aligning with the original trial results. However, Australia rated the certainty of this evidence as moderate, highlighting differences in the appraisal of the same trial across countries. Additionally, Germany's documents used the term "laboratory-confirmed influenza-like illness," which appears to combine LCI (virologically confirmed) with ILI (syndromic diagnosis), potentially affecting interpretive clarity and scientific precision.

Additional inconsistencies emerged when comparing STIKO's 2021 rationale document with the ECDC's 2020 technical report. STIKO referenced only nine observational studies on MF59-adjuvanted vaccine effectiveness, while the ECDC listed 22 studies—11 of which addressed lab-confirmed influenza in older adults using a test-negative design. Similarly, for high-dose vaccines' effectiveness, STIKO mentioned one RCT and eight observational studies but did not align with the ECDC's classification, which included 2 efficacy RCTs, 1 effectiveness case-control study and 8 effectiveness cohort studies. For recombinant vaccines, STIKO cited only one RCT for rVE, whereas the ECDC reported two efficacy RCTs, all during the same time period for study inclusion. These mismatches suggest a tendency in the German rationale to underreport available evidence.

These inconsistencies illustrate both the challenges of evidence harmonization and the nuanced differences in how national advisory groups extract, frame, and report identical data. While these may seem like minor discrepancies, they have important implications for stakeholders such as pharmaceutical manufacturers, who invest significantly in these studies

and rely on accurate and consistent representation of their trial results. Most importantly, they also impact governments, which make vaccination decisions based on public health priorities and economic considerations.

Evaluation criteria and priority outcomes also varied. While all NITAGs included LCI and influenza-related hospitalization as core outcomes, Germany uniquely prioritized also disease severity outcomes (e.g., pneumonia, cardiorespiratory complications). Canada's evaluations were distinguished by incorporating economic models and explicitly integrating equity, feasibility, and acceptability considerations (EEFA framework).

When it came to head-to-head comparisons of enhanced vaccines, no country found high-certainty evidence favoring one product over another. Moderate-certainty observational data showed minimal differences in hospitalization rates, adverse events, and reactogenicity between adjuvanted and high-dose vaccines. This underpinned flexible recommendations in Canada, Australia, and the U.S., allowing for equal preference between options.

Cost-effectiveness data were considered to varying degrees. Canada and Germany conducted or cited detailed economic evaluations that supported the cost-effectiveness of enhanced vaccines under standard willingness-to-pay thresholds. The U.S. relied on modeled estimates and assessed resource use as reasonable within its EtR framework. Australia did not cite economic evaluations in its ATAGI recommendation, consistent with its structural division: economic review is the responsibility of the Pharmaceutical Benefits Advisory Committee (PBAC). Notably, PBAC analyses are not referenced in ATAGI's influenza vaccine recommendations [243]. Furthermore, Quebec's subnational analysis in Canada raised concerns about cost-effectiveness for certain subpopulations, suggesting that real-world value may vary by age group and health status.

Finally, programmatic and ethical factors also shaped recommendations. Canada and the U.S. explicitly integrated feasibility, equity, and acceptability into their decision-making through EEFA and EtR frameworks. Australia addressed feasibility and acceptability, while Germany focused more narrowly on clinical and economic data.

Limitations

In the case of STIKO, it was difficult to identify all the studies referenced in the scientific rationale document, as no direct citations were provided for those included in the ECDC's review. However, all new studies not covered by the ECDC review were directly cited. Despite this, it was not feasible to trace all the studies used or to assess their respective GRADE evaluations. In the ACIP recommendation, direct referencing was provided through a link to a supporting Background Document, which serves as the scientific rationale. However, the reference led only to archived publications of previous influenza vaccine recommendations, and we were unable to access the specific document cited.

Additionally, while Denmark met all inclusion criteria for this review based on our research and internal Sanofi documentation, it was ultimately excluded. This was because the GRADE evaluation was conducted by the Health Technology Assessment (HTA) body, which is a separate entity from the NITAG, and thus did not align with the study's focus on NITAG-based assessments [244].

Conclusion

This analysis shows that while frameworks like GRADE and EtD or EtR aim to standardize vaccine policy, their application still resulted in differences across countries. Even among high-income countries, similar data led to subtle differences in interpretation, terminology, and vaccine recommendations—raising important questions about global harmonization and equity in immunization decision-making.

Canada's case stands out: despite strong resources, it adapted much of its evaluation from the U.S. ACIP, highlighting that even advanced NITAGs may rely on external assessments due to practical constraints. This prompts reflection on what can be expected of low- and middle-income countries, where funding is limited, data infrastructure may be weak, and technical expertise is still being developed?

Future research should include a systematic literature review of these four countries, or qualitative studies based on semi-structured interviews with former NITAG members to better understand the decision-making processes beyond what is publicly documented. Additionally, research should explore how low- and middle-income countries (LMICs) conduct evidence synthesis and the extent to which they rely on recommendations from higher-income nations.

Strengthening cross-country collaboration, ensuring greater transparency, and providing technical support can contribute to building more autonomous and resilient NITAGs globally.

Ultimately, this study underscores that vaccine policy is not just technical, scientific or medical—it is political and ethical. Improving evaluation tools must go hand-in-hand with rethinking global health cooperation to promote shared capacity, mutual learning, and equitable access to decision-making resources.

Appendices

Table 1: Overview of enhanced influenza vaccines' approval and target age groups: United States, Canada, Australia, and Germany

Vaccine Technology[10]	Mechanism[10]Error! Bookmark not defined.	Antigen Content per Strain [10]Error! Bookmark not defined.	United States	Canada	Australia	Germany
High-dose inactivated influenza vaccine (HD-IIV) Split virus vaccine	Contains four times the amount of hemagglutinin (HA) antigen compared to standard-dose vaccines to elicit a stronger immune response, particularly in older adults.	60 µg HA	Licensed in 2009 for adults ≥65 years[11].	Licensed in 2015 for adults ≥65 years[12].	Licensed in 2020 for adults ≥65 years[13].	Licensed in 2020 for adults ≥60 years[14].
Adjuvanted inactivated influenza vaccine (Adj-IIV) Subunit vaccine	An adjuvant (MF59, an oil-in-water emulsion) is added to enhance the immune response to the vaccine antigen.	15 µg HA	Licensed in 2015 for adults ≥65 years[15].	Licensed in 2011 for adults ≥65 years[16].	Licensed in 2019 for adults ≥65 years[17].	Licensed in 2020 for adults ≥50 years[14].
Recombinant influenza vaccine (RIV)	Utilizes recombinant DNA technology where the gene encoding the influenza HA antigen is inserted into a baculovirus vector, which is then expressed in an insect cell line, producing the HA protein without the use of eggs. It contains three times the amount of HA.	45 µg HA	Licensed in 2013 for adults ≥18 years[18].	Licensed in 2021 for adults ≥18 years[19].	Licensed in 2021 for adults ≥18 years [20].	Licensed in 2020 for adults ≥18 years[21].

[10] https://pubmed.ncbi.nlm.nih.gov/39369576/

[11] https://www.sciencedirect.com/science/article/pii/S0264410X20311476#:~:text=Fluzone®%20High%2DDose%20was,the%20prevention%20of%20influenza%20disease.

[12] https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/a-review-literature-high-dose-seasonal-influenza-vaccine-adults-65-years-older.html

[13] https://www.tga.gov.au/resources/auspmd/fluzone-high-dose-quadrivalent

[14] https://www.pei.de/EN/medicinal-products/vaccines-human/influenza-flu/influenza-flu-node.html

[15] https://www.fda.gov/media/179766/download?attachment

[16] https://www.canada.ca/content/dam/phac-aspc/migration/phac-aspc/publicat/ccdr-rmtc/11vol37/acs-dcc-6/assets/pdf/acs-dcc-6-eng.pdf

[17] https://www.tga.gov.au/resources/auspmd/fluad-quad

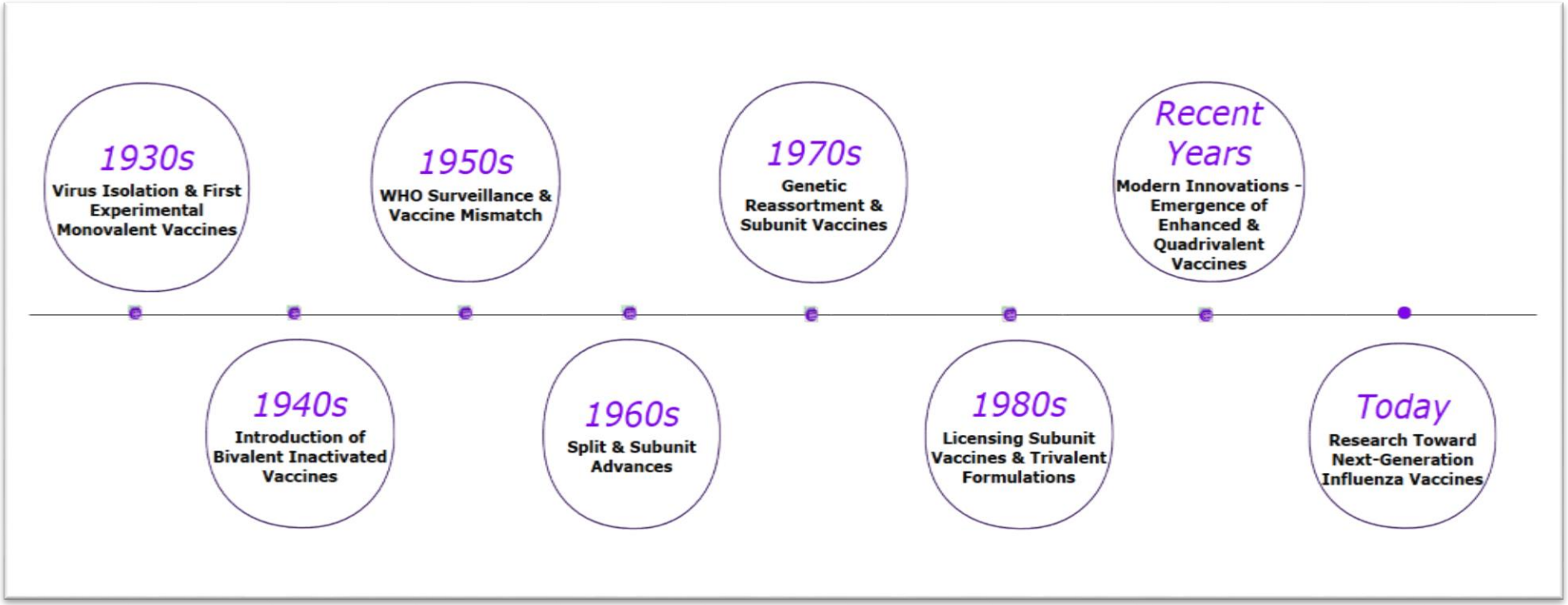
[18] https://www.cdc.gov/flu/vaccine-types/flublok-vaccine.html

[19] https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/recombinant-influenza-vaccines-supplemental-statement-canadian-immunization-guide-seasonal-influenza-vaccine-2022-2023.html#a4.1

[20] https://www.tga.gov.au/resources/auspmd/flublok-quadrivalent

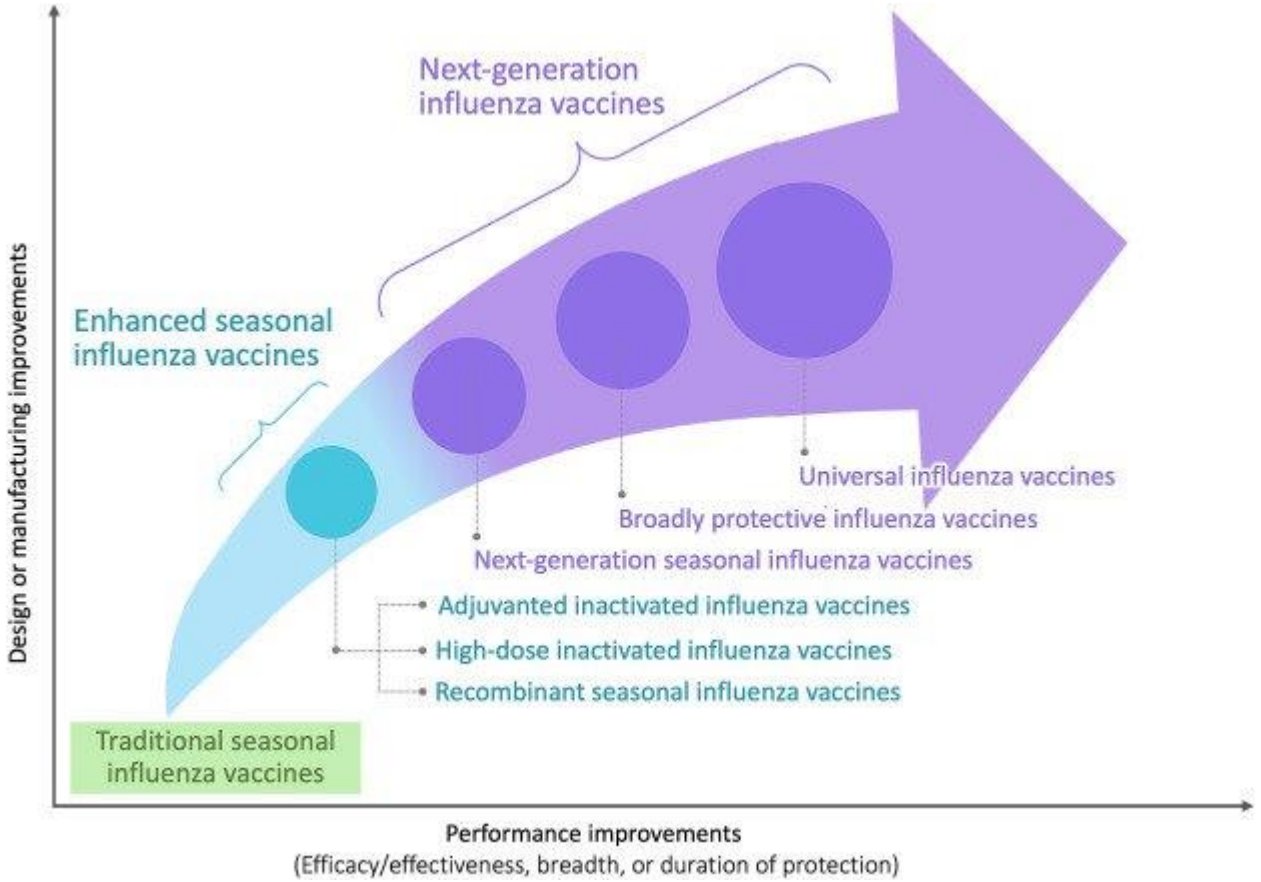
[21] Homepage - Supemtek - Paul-Ehrlich-Institut

Figure 1: Evolution of influenza vaccines from the 1930s until today



Reference: Barberis, I., Myles, P., Ault, S., Bragazzi, N. L., & Martini, M. (2016). History and evolution of influenza control through vaccination: from the first monovalent vaccine to universal vaccines. *PubMed*, *57*(3), E115–E120. https://pubmed.ncbi.nlm.nih.gov/27980374

Figure 2: Framework of improving influenza vaccines



Reference: Taaffe, J., Ostrowsky, J. T., Mott, J., Goldin, S., Friede, M., Gsell, P., & Chadwick, C. (2024). Advancing influenza vaccines: A review of next-generation candidates and their potential for global health impact. *Vaccine*, *42*(26), 126408. https://doi.org/10.1016/j.vaccine.2024.126408

Table 2: ACIP Evidence to Recommendations Framework

Question: Overarching policy question to be answered by the guideline panel (ACIP) using the Evidence to Recommendations (EtR) framework. The question should be precise and identify the specific intervention, comparison, and outcome, as well as the target population and the setting (specific subpopulations) in PICO format. **Population:** Target population for vaccine (e.g., age range, sex, immune status, pregnancy) **Intervention:** Vaccination (if applicable, dosage and schedule) **Comparison(s):** No Vaccination/Standard of care/An existing vaccine/Other prevention option **Outcome:** Outcome(s) associated with vaccination (e.g., prevention outcomes or adverse effects)			
Background: The addressed PICO question should be described in detail, and important background information for understanding the question and why a recommendation or decision is needed should be briefly provided. If a recommendation is preferential or represents off-label use, this should be indicated. *Include sample language: Additional background information supporting the ACIP recommendations on the use of xxx vaccine can be found in the relevant publication of the recommendation referenced on the ACIP website.*			
	WORK GROUP JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	**Is the problem of public health importance?** ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Provide available scientific evidence on burden of disease, preferably within the target population for the recommendation. If no published evidence is available, provide expert judgment on the public health priority considerations.	Identify any additional public health priority considerations, including consideration of disparities.

	WORK GROUP JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
BENEFITS & HARMS	**How substantial are the desirable anticipated effects?** o Minimal o Small o Moderate o Large o Varies o Don't know	Describe the magnitude of the beneficial effects of vaccination on individual (vaccine effectiveness, duration of protection) and population (herd immunity) levels.	Take into consideration: Is the baseline benefit similar across subgroups (by age, sex, pregnancy or lactation status, occupation[i.e., healthcare workers], immune status, race, SES, and other groups)? Are there indirect effects that should be considered (e.g., herd immunity)?
	How substantial are the undesirable anticipated effects? o Minimal o Small o Moderate o Large o Varies o Don't know	Are there undesirable effects of the vaccine, either on the individual (e.g., adverse events following immunization) or population (e.g., age-shift of disease, serotype replacement) levels?	Take into consideration: Is the baseline risk for harm similar across subgroups (see above)? Should there be separate recommendations for subgroups based on harms?
	Do the desirable effects outweigh the undesirable effects? o Favors interventionl o Favors comparison o Favors both o Favors neither o Varies o Don't know	Describe the balance of benefits of the vaccine with possible harms (individual and population level).	

	WORK GROUP JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
	What is the overall certainty of this evidence for the critical outcomes? *Effectiveness of the intervention* ○ No studies found ○ 4 (very low) ○ 3 (low) ○ 2 (moderate) ○ 1 (high) *Safety of the intervention* ○ No studies found ○ 4 (very low) ○ 3 (low) ○ 2 (moderate) ○ 1 (high)	Please refer to GRADE evidence profiles for detailed assessment of the certainty of the evidence. For more information, please see the ACIP Handbook for Developing Evidence- Based Recommendations.	If GRADE was not used to evaluate the certainty of evidence, please provide justification and the method and outcome of any other tools used to evaluate the body of evidence relevant to the critical outcomes.
VALUES	**Does the target population feel that the desirable effects are large relative to undesirable effects?** ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Provide any available evidence on target population values & preferences related to vaccination and comparative health benefits and risks. Describe the source of these estimates.	Are values and preferences for relevant outcomes measured? Are the benefits, harms and costs of vaccination valued differently by different subgroups? If the target group doesn't value the intervention, or attributes little value to the harms and benefits, consider whether potential education measures are needed.

	WORK GROUP JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
	Is there important uncertainty about or variability in how much people value the main outcomes? o Important uncertainty or variability o Probably important uncertainty or variability o Probabl not important uncertainty or variability o No important uncertainty or variability o No known undesireable outcomes	Please provide available data used to determine the relative importance that the target population attributes to the desirable and the undesirable outcomes related to the intervention as well as the comparison.	Describe the source of variability, if any. Are there methods for determining values satisfactory for this recommendation? If not, systematic assessment of values and preferences of target group may be considered.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** o No o Probably no o Probably yes o Yes o Varies o Don't know	Provide assessment of whether intervention would be acceptable to stakeholders (ethically, programmatically, financially, etc.)	
RESOURCE USE	**Is the intervention a reasonable and efficient allocation of resources?** o No o Probably no o Probably yes o Yes o Varies o Don't know	Provide summary of cost-effectiveness analyses (CEAs) of the vaccine in the target population. Include base case results and a sensitivity range. Include any other notable findings, for example, specific policy- relevant scenarios.	Overall findings: Summarize the findings from available CEAs, including major differences in baseline assumptions. Uncertainty: Does the analysis capture the full range of uncertainty? For example, are the findings from the uncertainty of evidence analysis, identified earlier in this document (the EtR Framework), appropriately represented in the methods of the CEAs? Multiple assessments: Are there multiple CEAs? If so, what are the major differences in methods and results?

	WORK GROUP JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
EQUITY	**What would be the impact on health equity?** o Reduced o Probably reduced o Probably no impact o Probably increased o Increased o Varies o Don't know	Summarize the findings from a review of the literature addressing issues of health inequities or groups who may be disadvantaged.	Consider from the evidence or guideline panel: • Are there any groups or settings that might be disadvantaged in relation to the problem or options that are considered? • Are there plausible reasons for anticipating differences in the relative effectiveness of the option for disadvantaged groups or settings? • Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the option or the importance of the problem for disadvantaged groups or settings? • Are there important considerations that should be made when implementing the intervention (option) in order to ensure that inequities are reduced, if possible, and that they are not increased?
FEASIBILITY	**Is the intervention feasible to implement?** o No o Probably no o Probably yes o Yes o Varies o Don't know	Are there any barriers to implementation?	Please refer to the Implementation Considerations checklist.

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings O	Undesirable consequences *probably outweigh* desirable consequences in most settings O	The balance between desirable and undesirable consequences *is closely balanced* or *uncertain* O	Desirable consequences *probably outweigh* undesirable consequences in most settings O	Desirable consequences *clearly outweigh* undesirable consequences in most settings O	There is insufficient evidence to determine the balance of consequences O
Is there sufficient information to move forward with a recommendation? Yes O No O						
Policy options for ACIP consideration	ACIP does not recommend the intervention* *Intervention may be used within FDA licensed indications O	ACIP recommends the intervention for individuals based on shared clinical decision-making O	ACIP recommends the intervention O			
Draft recommendation (text)	Please provide the draft recommendations proposed to ACIP.					
Additional considerations (optional)	Please outline any significant additional considerations (e.g., aspects related to implementation, monitoring and evaluation, research priorities, etc.).					

Final deliberation and decision by the ACIP

Final ACIP recommendation	ACIP does not recommend the intervention* *Intervention may be used within FDA licensed indications ○	ACIP recommends the intervention for individuals based on shared clinical decision-making ○	ACIP recommends the intervention ○
Additional ACIP considerations	Wording as accepted in the guide		

Reference: https://www.cdc.gov/acip/media/pdfs/2024/09/ACIP-Evidence-to-Recommendations-Framework-cdc.pdf

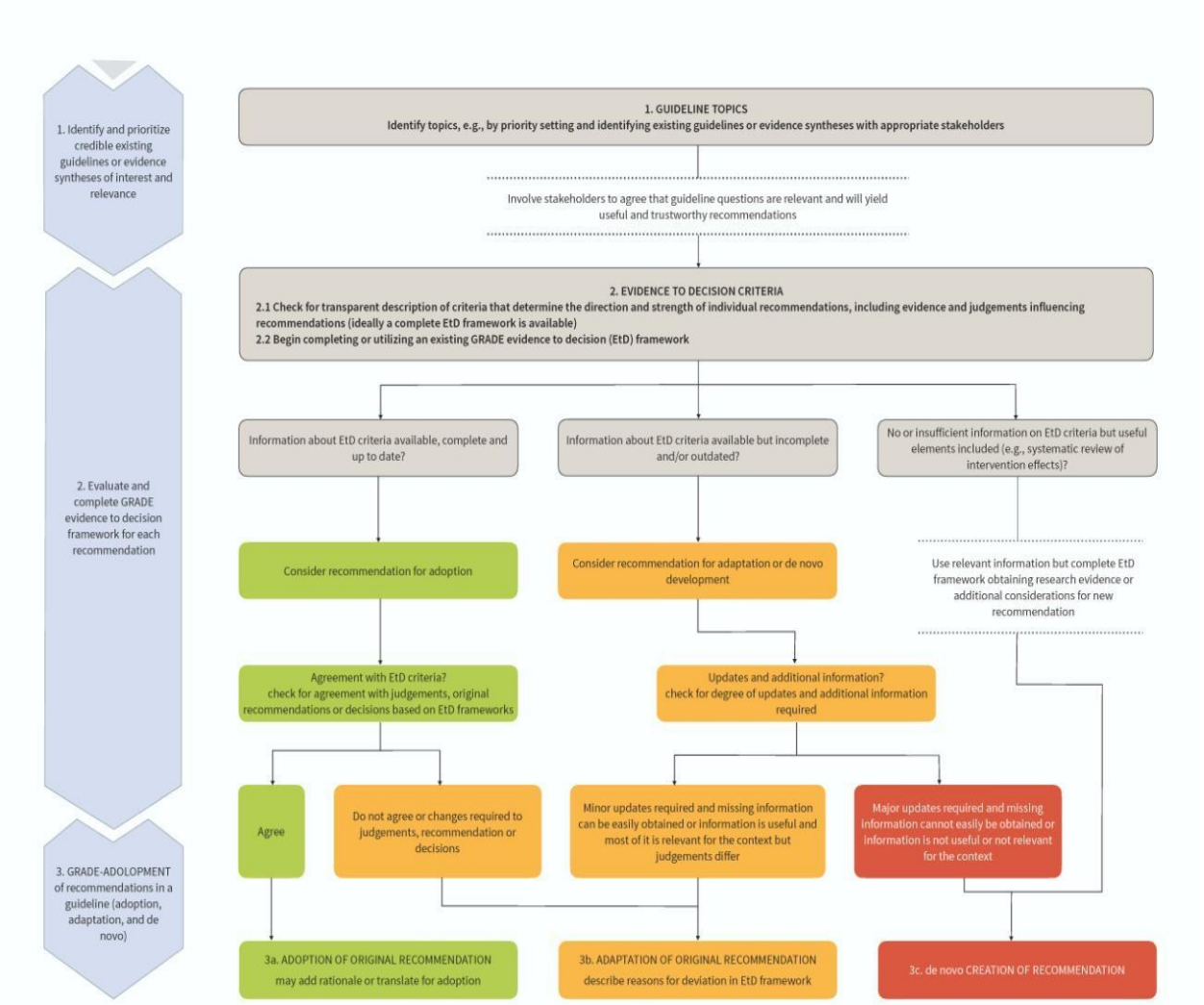
Table 3: GRADE's Evidence to Decision (EtD) Framework

<table>
<tr><th></th><th>Criteria</th><th>Judgements</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td>Problem</td><td>Is there a problem priority?</td><td>○ No
○ Probably no
○ Uncertain
○ Probably yes
○ Yes
○ Varies</td><td></td><td></td></tr>
<tr><td rowspan="2">Benefits & harms of the options</td><td>What is the overall certainty of this evidence?</td><td>○ No included studies
○ Very low
○ Low
○ Moderate
○ High</td><td>The relative importance or values of the main outcomes of interest:
<table>
<tr><th>Outcome</th><th>Relative importance</th><th>Certainty of the evidence (GRADE)</th></tr>
<tr><td>Outcome 1</td><td>CRITICAL</td><td>⊕⊕⊕⊕ HIGH</td></tr>
<tr><td>Outcome 2</td><td>CRITICAL</td><td>⊕⊕⊕◯ MODERATE</td></tr>
</table>
Summary of findings: intervention C
<table>
<tr><th>Outcome</th><th>Without intervention I</th><th>With intervention I</th><th>Difference (95% CI)</th><th>Relative effect (RR) (95% CI)</th></tr>
<tr><td>Outcome 1</td><td>61 per 1000</td><td>37 per 1000 (25 to 49)</td><td>25 fewer per 1000(from 12 fewer to 37 fewer)</td><td>RR 0.6 (0.4 to 0.8)</td></tr>
<tr><td>Outcome 2</td><td>108 per 1000</td><td>99 per 1000 (80 to 134)</td><td>9 fewer per 1000(from 26 more to 28 fewer)</td><td>RR 0.92 (0.74 to 1.24)</td></tr>
</table></td><td></td></tr>
<tr><td>Is there important uncertainty about how much people value the main outcomes?</td><td>○ Important uncertainty or variability
○ Possibly important uncertainty or variability
○ Probably no important uncertainty of variability
○ No important uncertainty of variability
○ No known undesirable</td><td></td><td></td></tr>
</table>

	Are the desirable anticipated effects large?	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies		
	Are the undesirable anticipated effects small?	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies		
	Are the desirable effects large relative to undesirable effects?	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies		
Resource use	**Are the resources required small?**	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies		
	Is the incremental cost small relative to the net benefits?	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies		
Equity	**What would be the impact on health inequities?**	○ Increased ○ Probably increased ○ Uncertain ○ Probably reduced ○ Reduced ○ Varies		
Acceptability	**Is the option acceptable to key stakeholders?**	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies		
Feasibility	**Is the option feasible to implement?**	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies		

Reference: https://gdt.gradepro.org/app/handbook/handbook.html#h.33qgws879zw

Figure 3: Detailed GRADE-ADOLOPMENT process



Reference: https://www.jclinepi.com/cms/10.1016/j.jclinepi.2016.09.009/attachment/d8c1c473-fceb-4d1d-a258-ed7f592cf998/mmc2.pdf

Abstract in French

Titre : Revue narrative des critères d'évaluation et des recommandations des vaccins contre la grippe pour les personnes âgées par les Groupes Techniques Consultatifs Nationaux sur la Vaccination : regards croisés entre le Canada, l'Allemagne, les États-Unis et l'Australie

Contexte

La grippe saisonnière entraîne des taux élevés de morbidité et de mortalité dans le monde entier, en particulier chez les personnes âgées de 65 ans et plus. Ce groupe est plus vulnérable en raison d'un système immunitaire affaibli. Pour mieux les protéger, de nombreux pays recommandent des vaccins antigrippaux améliorés, tels que les formulations à haute dose, adjuvantées ou recombinantes. Ce projet vise à comparer la manière dont quatre pays à revenu élevé — le Canada, l'Allemagne, les États-Unis et l'Australie — ont évalué et recommandé ces vaccins pour la saison grippale 2024–2025.

Méthodes

Une revue narrative a été menée afin de collecter des données à partir des sites officiels des autorités nationales de santé publique, dans le but de mieux comprendre et comparer la manière dont les pays formulent leurs recommandations vaccinales contre la grippe pour les personnes âgées. Les sources comprenaient des déclarations de recommandations, des rapports techniques et des documents d'évaluation des preuves. La revue s'est concentrée sur la manière dont les Groupes Techniques Consultatifs Nationaux sur la Vaccination (NITAG) de chaque pays ont utilisé les données scientifiques—en particulier les évaluations basées sur GRADE—pour orienter leurs décisions.

Résultats

Les quatre pays ont recommandé des vaccins antigrippaux améliorés pour les personnes âgées, mais leurs préférences et justifications différaient. L'Allemagne a recommandé exclusivement le vaccin à haute dose. Les États-Unis ont accordé la même préférence aux vaccins à haute dose, adjuvantées ou recombinants. L'Australie a recommandé uniquement les vaccins à haute dose et adjuvantées, tandis que le Canada a approuvé les trois options. Certains pays ont intégré des critères d'équité, de faisabilité et d'acceptabilité dans leurs cadres de décision, tandis que d'autres se sont davantage concentrés sur les données cliniques ou ont complété leurs décisions par des évaluations plus explicites de coût-efficacité. Même en s'appuyant plus ou moins sur les mêmes études, les pays ont rapporté des résultats ou des interprétations différents.

Conclusions

Cette étude montre que le contexte national influence fortement les recommandations vaccinales, même lorsque les données scientifiques sont similaires. Une collaboration internationale renforcée, des outils standardisés et des processus transparents pourraient favoriser des politiques vaccinales plus cohérentes et équitables. Les recherches futures devraient explorer comment les NITAGs prennent leurs décisions au-delà des documents publics, et comment les pays à revenu faible ou intermédiaire s'appuient sur les preuves produites par les pays à revenu élevé.

Mots-clés : Grippe, Personnes âgées, Politique vaccinale, Cadre GRADE, NITAG

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