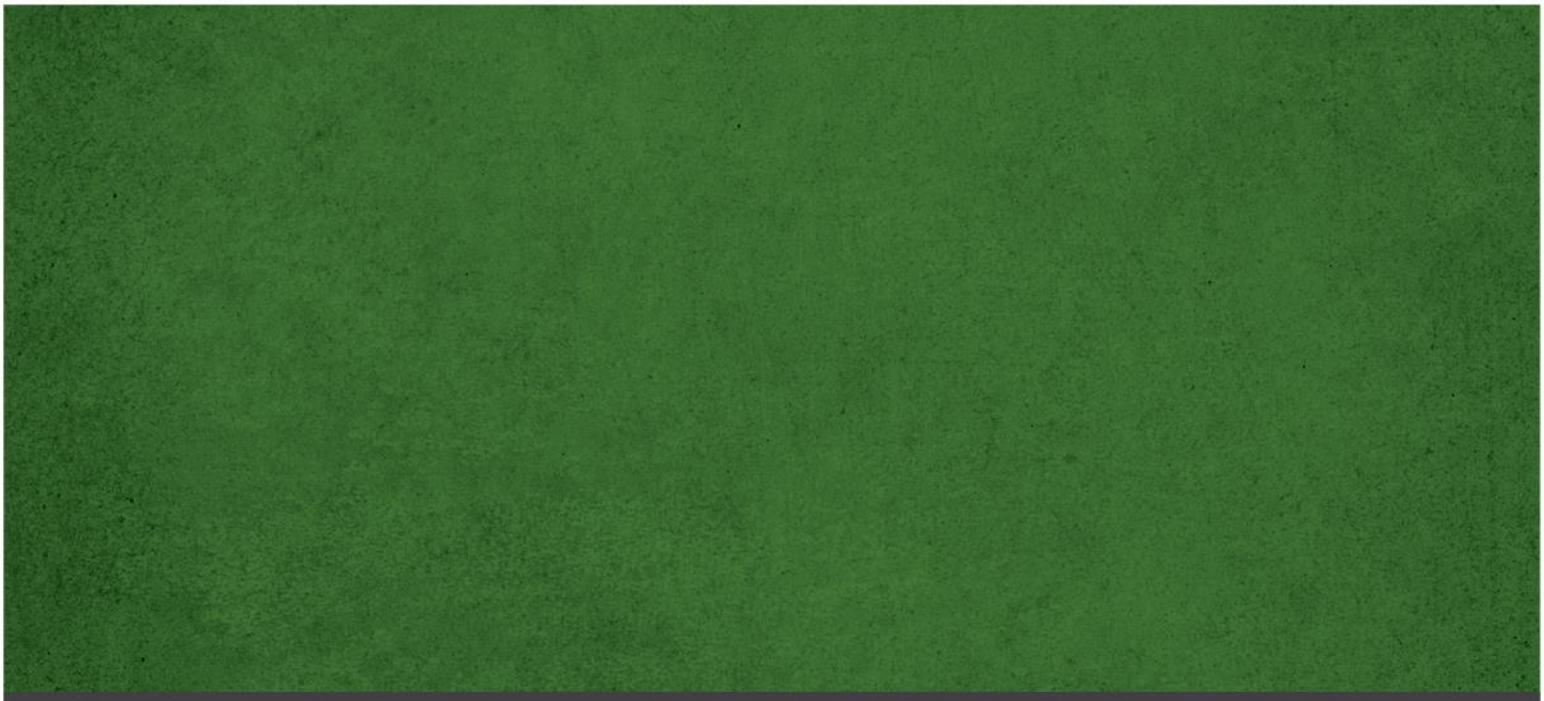
An Advisory Committee Statement (ACS)

National Advisory Committee on Immunization (NACI)

Supplemental guidance on influenza vaccination in adults 65 years of age and older



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PREAMBLE

The National Advisory Committee on Immunization (NACI) is an External Advisory Body that provides the Public Health Agency of Canada (PHAC) with independent, ongoing, and timely medical, scientific, and public health advice in response to questions from PHAC relating to immunization.

In addition to burden of disease and vaccine characteristics, PHAC has expanded the mandate of NACI to include the systematic consideration of programmatic factors in developing evidence based recommendations to facilitate timely decision-making for publicly funded vaccine programs at provincial and territorial levels.

The additional factors to be systematically considered by NACI include: economics, ethics, equity, feasibility, and acceptability. Not all NACI statements will require in-depth analyses of all programmatic factors. While systematic consideration of programmatic factors will be conducted using evidence-informed tools to identify distinct issues that could impact decision-making for recommendation development, only distinct issues identified as being specific to the vaccine or vaccine-preventable disease will be included.

This statement contains NACI's independent advice and recommendations, which are based upon the best current available scientific knowledge. This document is being disseminated for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph. Recommendations for use and other information set out herein may differ from that set out in the product monographs of the Canadian manufacturers of the vaccines. Manufacturer(s) have sought approval of the vaccines and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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SUMMARY OF INFORMATION CONTAINED IN THIS NACI STATEMENT

The following highlights key information for immunization providers. Please refer to the remainder of the statement for details.

1. What

The following recommendations for influenza vaccination in adults 65 years of age and older supplement the National Advisory Committee on Immunization (NACI)'s overarching recommendations for influenza vaccination, which are available in the NACI Seasonal Influenza Vaccine Statement. NACI recommends that high-dose inactivated influenza vaccine (IIV-HD), adjuvanted inactivated influenza vaccine (IIV-Adj) or recombinant influenza vaccine (RIV) should be offered, when available, over other influenza vaccines for adults 65 years of age and older. If a preferred product is not available, any of the available age-appropriate influenza vaccines should be used.

2. Who

Adults 65 years of age and older are prioritized to receive influenza vaccines because of the increased risks of severe disease in this population. This supplemental statement provides an evidence summary on the preferential use of 1 or more of the age-appropriate influenza vaccines for adults 65 years of age and older, over other age-appropriate influenza vaccines.

3. How

Inactivated high-dose, adjuvanted or recombinant influenza vaccines should be offered, when available, over other influenza vaccines for adults 65 years of age and older. If a preferred product is not available, any available age-appropriate influenza vaccines should be used. Influenza vaccination may be given at the same time as, or at any time before or after administration of another vaccine, including COVID-19 vaccine.

4. Why

Annual influenza vaccination is safe and the best way to prevent influenza and its complications. Adults 65 years of age and older are at higher risk of serious complications from influenza; therefore, NACI undertook a review of evidence to determine whether any age-appropriate influenza vaccines should be preferentially used in this age group. A systematic review of economic literature was also undertaken to inform public health program decision-making. Overall, the evidence supports IIV-HD, IIV-Adj and RIV as having increased benefit as compared to IIV-SD, with no difference in safety.

I. INTRODUCTION

Influenza is a respiratory infection caused primarily by influenza A and B viruses. Older adults are disproportionately affected by serious outcomes from influenza infection and may present with typical or atypical symptoms, as influenza causes respiratory and systemic illness. Prior to the -19 pandemic, influenza was estimated to cause 12,200 hospitalizations [1] and 3,500 deaths [2] annually in Canada, with the majority of deaths occurring in adults 65 years and older [3]. Considering the burden of influenza disease in this population, the National Advisory Committee on Immunization (NACI) has identified adults 65 years of age and older as 1 of the groups at higher risk of influenza complications and for whom influenza immunization is particularly important (Strong NACI recommendation) [4].

NACI has conducted several reviews over the years to evaluate the best available scientific and clinical evidence to develop recommendations for the use of influenza vaccines, with a focus on optimizing influenza protection among older adults in Canada [5, 6]. These recommendations have evolved over time due to the availability of new vaccine products, some of which are designed to enhance immunogenicity in specific age groups, as well as the expansion and accumulation of evidence on influenza vaccines. The most recent NACI literature review update on the efficacy and effectiveness of high-dose (Fluzone® High-Dose) and MF59-adjuvanted (Fluad®) trivalent inactivated influenza vaccines in adults 65 years of age and older was published in May 2018 [7].

The findings of this review supported the conclusions of previous reviews and led to a strengthened NACI recommendation for the use of high-dose egg-based trivalent inactivated influenza vaccine (IIV3-HD) as the preferred vaccine for Canadians 65 years of age and older. Therefore, on an individual level, NACI recommended that for older adults, IIV-HD should be used over standard-dose inactivated influenza vaccines (IIV-SD) given the burden of influenza A(H3N2) disease and the good evidence of IIV3-HD providing better protection compared to IIV3-SD in adults 65 years of age and older.

Other than a recommendation for using IIV-HD over IIV-SD formulations, NACI has not previously made comparative individual-level recommendations on the use of the other available vaccines in this age group. If a preferred product is not available, NACI has recommended that any of the available age-appropriate influenza vaccines should be used. On a public health program level, NACI has recommended that any of the available influenza vaccines authorized in this age group should be used, as there was insufficient evidence on the incremental value of different influenza vaccines to make comparative public health program-level recommendations on the use of the available vaccines.

Evidence on vaccine effectiveness (VE) in adults 65 years of age and older suggests a need for more effective vaccines targeted to this age group. For example, individuals 17 to 59 years of age showed a 2- to 4-fold higher immune response to influenza vaccine as measured by seroconversion and seroprotection rates compared to those 65 years of age and older [8]. Furthermore, a meta-analysis conducted in adults 65 years of age and older found a lower point estimate of VE against laboratory-confirmed influenza (pooled VE of 49%, 95% CI: 33-62%) [9] compared to a meta-analysis in healthy adults 18 to 64 years of age (pooled VE of 59%, 95% CI: 51-67%) [10].

The trigger for this NACI Supplemental Statement on the use of influenza vaccines in adults 65 years of age and older was the expressed desire by provincial and territorial programs for guidance on optimal product choice(s) for older adults. In consideration of the above factors, NACI has undertaken a review of evidence to determine whether any 1 or more of the age-appropriate influenza vaccines for adults 65 years of age and older should be preferentially used over other age-appropriate influenza vaccines. A systematic review of economic literature was also undertaken to inform public health program decision-making.

Guidance Objective

The following advisory committee statement on influenza vaccination in adults 65 years of age and older supplements NACI's overarching recommendations for influenza vaccination, which are available in the

NACI Seasonal Influenza Vaccine Statement. The objective of this supplemental statement is to provide updated guidance on the use of influenza vaccine in adults 65 years of age and older. This statement describes the disproportionate risk of morbidity and mortality for adults 65 years of age and older who acquire influenza compared to younger age groups; reviews the available evidence on the efficacy, effectiveness and safety of influenza vaccination in adults 65 years of age and older; and explores the economic, ethics, equity, feasibility, and acceptability considerations of immunizing adults 65 years of age and older against influenza.

II. METHODS

In brief, the broad stages in the preparation of a NACI advisory committee statement are:

1. Knowledge synthesis: retrieval and summary of literature, assessment of the quality of the evidence (summarized in Table 5: Summary of Evidence).
2. Synthesis of the body of evidence: benefits (efficacy and effectiveness) and potential harms (safety), considering the quality of the synthesized evidence and, where applicable, the magnitude of effects observed across the studies.
3. Use of a published, peer-reviewed framework and evidence-informed tools to ensure that issues related to ethics, equity, feasibility, and acceptability (EEFA) are systematically assessed and integrated into the guidance.
4. Use of the evidence to inform recommendations.

Further information on NACI's process and procedures is available elsewhere.

For this supplemental statement, NACI reviewed the key questions for the literature review as proposed by the Influenza Working Group, including such considerations as the burden of influenza illness to be prevented and the target population(s); safety, efficacy, effectiveness, economic evaluations of influenza vaccines; and other aspects of the overall immunization strategy. In preparation for this statement, the GRADE-ADOLOPMENT process was employed to adapt recommendations from the US Advisory Committee on Immunization Practices (ACIP) guideline panel where they assessed the relative benefits and harms of IIV-HD, IIV-Adj, and RIV compared to one another and with IIV-SD in adults 65 years of age and older [11].

ACIP applied the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess the strength and certainty of the evidence for critical outcomes included in their review. Evidence on the efficacy and cost-effectiveness of influenza vaccines in adults 65 years of age and older was further expanded with 2 additional systematic reviews, both developed in collaboration with the Methods and Applications Group for Indirect Comparisons (MAGIC) through the Drug Safety and Effectiveness Network (DSEN) and supervised by the NACI Influenza Working Group. One (1) review examined the efficacy of influenza vaccines in older adults, while the second review delved into the cost-effectiveness of seasonal influenza vaccines in older adults.

The ACIP conducted a literature search from 1990 through September 7, 2022, to identify eligible studies on the efficacy, effectiveness, and safety of influenza vaccines in older adults. Additionally, DSEN MAGIC performed an initial literature search on influenza vaccine efficacy in older adults, covering the period from inception to March 31, 2022, and subsequently conducted a second updated search on June 20, 2022.

Further details regarding the methodologies employed in both DSEN reviews are available in pre-specified written protocols [12, 13].

The evidence and proposed recommendations were presented to NACI for deliberation on September 27, 2023, and approved following a thorough review of the evidence. Relevant considerations, rationale for specific decisions, and knowledge gaps are further described in the following sections.

For a comprehensive description of the methodology and results of the reviews reporting on the safety, efficacy, and effectiveness of influenza vaccines, please refer to Grohskopf et al (2022) [14] and Veroniki et al (2023) [15]. Data are summarized in sections IV.3 and IV.4 of this statement. For details on the methodology and results on the economic evaluation findings for influenza vaccines in older adults, refer to Section V of this statement.

The overarching policy question addressed in this statement is: **Should any age-appropriate influenza vaccine(s) be preferentially used in adults 65 years of age and older? In addition, the following sub-questions were posed:**

- Do the relative benefits and harms of IIV-HD, IIV-Adj, IIV-cc and RIV, as compared with one another and with IIV-SD, favour the preferential use of any 1 or more of these vaccines over other age-appropriate influenza vaccines for adults 65 years of age and older?
- Does this recommendation vary by vaccine characteristic (e.g., high dose/standard dose, trivalent/quadrivalent, adjuvanted/unadjuvanted, egg-based/non-egg-based manufacturing?)
- Does this recommendation vary by risk group (e.g., populations with comorbid conditions, sex, previous vaccination, age 80 years and older)?

The literature search and data extraction were conducted according to the following PICO framework (Population, Intervention, Comparators and Outcomes):

P (Population):	Adults 65 years of age and older
I (Intervention):	Inactivated influenza vaccine (IIV)-not standard dose (not SD) and recombinant influenza vaccines: 1. High-dose inactivated influenza vaccine (IIV-HD) 2. MF-59 adjuvanted inactivated influenza vaccine (IIV-Adj) 3. Recombinant influenza vaccine (RIV) 4. Mammalian cell culture-based vaccine (IIV-cc)
C (Comparator):	Inactivated standard-dose influenza vaccines (IIV-SD) Inactivated influenza vaccine (IIV)-not SD and recombinant influenza vaccines
O (Outcome)[a]:	Vaccine efficacy/effectiveness: • Lab-confirmed influenza (LCI) • Influenza-associated outpatient/emergency department (ED) visits (LCI, influenza-like illness [ILI]) • Influenza-associated hospitalization (LCI, ILI) • Influenza-associated vascular events Vaccine safety: • Any solicited systemic adverse reaction grade ≥3 • Guillain-Barré Syndrome (GBS) • Any serious adverse events (SAE) • Any solicited injection site adverse reaction grade ≥3 Economics: • Vaccine cost-effectiveness (cost per life year saved, cost per influenza case averted) • Cost-utility (cost per quality-adjusted life year [QALY])

[a] Critical/important outcomes for decision making.
Abbreviations: ED, emergency department; GBS, Guillain-Barré Syndrome; IIV, inactivated influenza vaccine; IIV-Adj, adjuvanted inactivated influenza vaccine; IIV-cc, mammalian cell culture-based inactivated influenza vaccine; IIV-HD, high-dose inactivated influenza vaccine; IIV-SD, standard dose inactivated influenza vaccine; ILI, influenza-like illness; LCI, laboratory-confirmed influenza; QALY, quality-adjusted life year; RIV, recombinant influenza vaccine; SAE, serious adverse event.

To meet the objective of this statement, supplementary informal literature reviews were conducted as necessary, encompassing:

- The epidemiology and estimated burden of influenza illness among adults 65 years of age and older
- The efficacy, effectiveness, and safety of influenza vaccines in frail older adults 65 years of age and older
- Guidelines and considerations for the use of influenza vaccines in older adults across Canadian provinces, territories and globally

For additional information and NACI's current recommendations on the use of influenza vaccines in adults 65 years of age and older, please refer to the current NACI Statement on seasonal influenza vaccine and to the influenza vaccine chapter in the Canadian Immunization Guide (CIG).

III. EPIDEMIOLOGY

III.1 Estimated burden of influenza among adults 65 years of age and older

Although adults 65 years of age and older only comprise approximately 19% of the Canadian population, this population is over-represented among laboratory-confirmed influenza (LCI) cases, especially in seasons where the A(H3N2) influenza strain predominated (e.g., 2014-2015, 2016-2017, 2017-2018) before the COVID-19 pandemic [16]. Although influenza-associated morbidity and mortality vary each season, in general there is an increased burden of severe disease such as influenza-associated hospitalizations, intensive care unit (ICU) admissions, and deaths in adults 65 years of age and older, especially in seasons when influenza A(H3N2) predominates [16]. Data derived from Canada's national hospitalization database found that rates of respiratory hospitalizations attributed to influenza were highest among adults 65 years and older at 144.9 per 100,000 compared to 25.8 per 100,000 for adults 45 to 64 years of age [17]. With regard to influenza-attributable deaths, the annual average mortality rate for adults 65 years and older was estimated to be 108.8 per 100,000, which is substantially higher than the estimated mortality rate of 4.0 per 100,000 for adults 50 to 64 years of age [18].

Furthermore, among adults 65 years of age and older, the risk of influenza-related complications is significantly higher with increasing age, the presence and severity of chronic medical conditions, and higher level of frailty [19, 20]. As with LCI cases, adults 65 years of age and older had higher influenza-related hospitalization rates than younger age groups in most years before the COVID-19 pandemic [21]. During the 2022-2023 influenza season, adults 65 years of age and older had the highest cumulative hospitalization rate (136 per 100,000 population), followed by children under 5 years of age (130 per 100,000 population) [21]. For the relatively brief and unusually late 2021-2022 influenza season, the seasonal hospitalization rate was also highest in adults 65 years age [22]; and ICU admissions and deaths were most common among adults 65 years of age and older (30% and 59%, respectively) [22]. In the years when A(H3N2) was dominant, over 80% of influenza-associated deaths were in adults 65 years of age and older (e.g., seasons 2014-2015, 2016-2018) [23].

III.2 Influenza vaccination coverage among adults 65 years of age and older

Influenza vaccine coverage among adults 65 years of age and older in Canada is usually relatively high, at approximately 70% in the most recent years. During the 2022-2023 season, influenza vaccination coverage among adults 65 years of age and older was 74%. However, vaccination coverage in this age group still does not meet the national goal of 80% for those at high risk of influenza-related complications, such as older adults [24].

IV. VACCINE

IV.1 Preparation(s) authorized for use in Canada

Five (5) influenza vaccines are authorized and available for use in Canada in adults 65 years of age and older: IIV-Adj, IIV-SD, IIV-HD, RIV and IIV-cc.

Two (2) inactivated influenza vaccines (IIVs) are designed specifically to enhance immunogenicity in adults 65 years of age and older: IIV4-HD, a high-dose quadrivalent inactivated split virion vaccine (Fluzone® High-Dose Quadrivalent, Sanofi Pasteur) and IIV3-Adj, an MF59-adjuvanted trivalent inactivated subunit vaccine (Fluad®, Seqirus).

Fluzone® High-Dose contains 60 µg of haemagglutinin (HA) per strain (compared to 15 µg HA per strain in a standard dose) [25]. Fluzone® High-Dose Quadrivalent, authorized for use in Canada in 2020, is currently the only available high-dose inactivated split virion influenza vaccine in Canada [4, 26]. A literature review on the efficacy, effectiveness, immunogenicity and safety of high-dose seasonal influenza vaccines, including Fluzone® High-Dose, for adults 65 years of age and older was conducted in 2016 [6] as part of NACI's evidence-based process [27] to inform the inclusion of Fluzone® High-Dose in the Statement on Seasonal Influenza Vaccine for 2016–2017 [25].

Fluad® is a standard-dose inactivated subunit vaccine containing the adjuvant MF59, which is an oil-in-water emulsion composed of squalene as the oil phase and stabilized with the surfactants polysorbate 80 and sorbitan triolate in citrate buffer [28]. Fluad® and its pediatric formulation (Fluad Pediatric®, Seqirus) are the only seasonal influenza vaccines available for use in Canada with an adjuvant. Evidence on the efficacy, effectiveness, immunogenicity, and safety of Fluad® was first reviewed in 2011 [5] to inform the inclusion of Fluad® in the Statement on Seasonal Influenza for 2011–2012 [29] and subsequently supplemented with additional effectiveness evidence in the Statement on Seasonal Influenza for 2014–2015 [30].

All inactivated influenza vaccines (IIV) available in Canada are produced in eggs, except for Flucelvax Quad (IIV4-cc), which is a mammalian cell culture-based quadrivalent inactivated, **subunit influenza** vaccine that is prepared from viruses propagated in mammalian cell lines (proprietary 33016-PF Madin-Darby Canine Kidney [MDCK] cell lines) adapted to grow freely in suspension in culture medium.

There is currently only 1 RIV authorized for use in Canada: Supemtek (RIV4), a quadrivalent unadjuvanted, baculovirus-expressed seasonal influenza vaccine that contains 45 µg of HA per strain (compared to 15 µg HA per strain in a standard dose) and authorized for adults 18 years of age and older. RIV contains recombinant HAs produced in an insect cell line using genetic sequences from cell-derived influenza viruses. The production of RIV does not depend on egg supply.

The NACI annual statement on seasonal influenza vaccine contains a full description of vaccines available for use in Canada.

IV.2 Concurrent administration with other vaccines

The NACI annual statement on seasonal influenza vaccine contains a full description of concurrent administration of influenza vaccines with other vaccines. Briefly, all seasonal influenza vaccines may be given at the same time as, or any time before or after administration of other vaccines, including COVID-19 and pneumococcal vaccines.

Data are limited regarding concurrent administration of newer adjuvanted influenza vaccines with other adjuvanted or non-adjuvanted vaccines.

Recombinant zoster vaccine (RZV) (Shingrix®, GlaxoSmithKline) is authorized for use in Canada in adults 50 years of age and older, and in adults 18 years of age or older who are or will be at increased risk of herpes zoster (HZ) due to immunodeficiency or immunosuppression caused by known disease or therapy; therefore, the target age group for herpes zoster vaccine and influenza vaccine overlap. RZV has been shown to be safe and effective when given concurrently with unadjuvanted, standard dose influenza vaccines [31]. However, no studies have been conducted that have assessed the concurrent administration of RZV with adjuvanted or high dose influenza vaccine [32]. It should be noted that RZV and IIV-Adj contain the adjuvants AS01B and MF59 respectively. How these adjuvants may interact when RZV and IIV-Adj are administered concurrently is not known.

NACI will continue to review the evidence and update guidance accordingly.

IV.3 Efficacy and effectiveness

To answer the policy question addressed in this statement, ACIP and DSEN MAGIC results evaluating the relative benefits and harms of IIV-HD, IIV-Adj, IIV-cc and RIV, as compared with one another and with IIV-SD were presented in the narrative summary. Of note, DSEN MAGIC conducted a network meta-analysis (NMA) to evaluate the efficacy of influenza vaccines in adults 65 years of age and older. However, due to the difficulties in interpreting the NMA results arising from the presence of sparse and disconnected networks, and the challenges of comparing influenza efficacy in different seasons, only the pairwise meta-analysis and single study results were presented in the narrative summary. For further information, please refer to the original publication by Veroniki et al (2023) [15].

ACIP and DSEN MAGIC appraised articles using the Cochrane risk of bias tools. Study limitations of articles included in the evidence synthesis are reported in Table 6.

Overall, in the ACIP review the level of certainty of the evidence for outcomes reporting on vaccine efficacy and effectiveness was rated as low to very low and was primarily downgraded due to limited availability of randomized studies. For additional details regarding the summary of findings and assessments of the quality of the evidence please refer to GRADE: Higher Dose and Adjuvanted Influenza Vaccines for Persons Aged ≥65 Years and to the Evidence to Recommendations (EtR) Framework: Higher Dose and Adjuvanted Influenza Vaccines for Persons Aged ≥65 Years.

In the DSEN MAGIC review, certainty of evidence of NMA estimates was assessed using the Confidence in Network Meta-Analysis (CINeMA) approach and confidence in pairwise estimates for which a NMA could not be performed was assessed using the GRADE approach (i.e., IIV-HD vs. IIV-SD). The GRADE certainty of evidence for outcomes reporting on vaccine efficacy of IIV-HD compared to IIV-SD were rated low to high which were primarily downgraded due to imprecision and risk of bias. For additional details regarding the GRADE assessments and other supplementary materials for quality of evidence appraisals that were conducted, please refer to the original publication by Veroniki et al (2023) [15] and the Framework webpage.

Please note that analyses on vaccine efficacy and effectiveness were conducted on the overall population of adults 65 years of age and older, and not by risk groups (e.g., population with comorbid conditions, sex, previous vaccination, and adults 80 years of age and older) due to data limitation, including the number of studies reporting for each outcome.

IV.3.1 Efficacy and effectiveness of high dose, recombinant and adjuvanted influenza vaccines compared to standard-dose inactivated influenza vaccines

Summary of study characteristics

Overall, the ACIP review identified 31 studies (9 RCTs [33-41], including 2 cluster RCTs [40, 41], and 22 observational studies [42-63]) reporting data on influenza vaccine efficacy/effectiveness outcomes in adults 65 years of age and older. Their systemic review provided data on influenza illness (n=4) defined as LCI or influenza-like illness (ILI) syndrome without laboratory confirmation of viral etiology, influenza-associated outpatient and/or emergency department (ED) visits (n=8), influenza-associated hospitalization (n=21), and influenza-associated deaths (n=2).

The DSEN MAGIC systematic review considered only RCTs and identified 10 studies reporting data on influenza vaccine efficacy outcomes comparing IIV-HD, IIV-Adj, and RIV to IIV-SD in adults 65 years of age and older [33-35, 64-70]. Their systemic review provided data on influenza LCI (n=5), ILI syndrome without laboratory confirmation of viral etiology (n=5), influenza-associated outpatient visits (n=1), influenza-associated hospitalization (n=4), influenza-associated deaths (n=1), and influenza-associated vascular events (n=7).

Summary of vaccine efficacy/effectiveness against influenza

Overall, ACIP included 4 RCTs reporting data on influenza illness in adults 65 years of age and older. Of those, 1 RCT compared IIV3-HD to IIV3-SD against LCI [33], 1 compared IIV3-Adj to IIV3-SD against ILI [35], and 2 RCTs compared RIV to IIV-SD against LCI [34, 36]. The DSEN MAGIC included 4 RCTs reporting data comparing IIV-HD to IIV-SD against LCI (n=3) [33, 64, 65] and ILI (n=3) [33, 65, 66], as well as 2 RCTs comparing RIV4 to IIV-SD against LCI and ILI [34, 71] in adults 65 years of age and older.

Both the ACIP and DSEN MAGIC reviews found that IIV-HD was associated with relative vaccine efficacy of approximately 25% compared to IIV-SD against LCI. The ACIP review used data from 1 RCT by DiazGranados 2014 [33] while the DSEN MAGIC pooled estimates from 3 RCTs, also including DiazGranados 2014 RCT [33, 64, 65], with both groups demonstrating beneficial effects of IIV-HD compared to IIV-SD. ACIP reported a relative vaccine efficacy of 18% (95% CI: -17 to 43%) against LCI combining 2 RCTs [34, 36] comparing RIV to IIV-SD. The DSEN MAGIC observed a potential beneficial protective effect of RIV4 over IIV-SD against LCI combining 2 RCTs though the estimate lacked precision (pooled relative vaccine efficacy of 30%, 95% CI: -18 to 58%) [34, 71].

ACIP reported no difference in vaccine efficacy between IIV3-Adj and IIV-SD against ILI from 1 RCT (relative vaccine efficacy of -3%, 95% CI: -19 to 11%) [35]. Finally, the DSEN MAGIC did not identify a difference between IIV3-HD (pooled relative vaccine efficacy of 2%, 95% CI: -2 to 7%) [33, 64, 66] , RIV (relative vaccine efficacy of 1%, 95% CI: -9 to 11%, and 4%, 95% CI: -65 to 45%) [34, 71], and IIV-Adj (relative vaccine efficacy of -3%, 95% CI: -21 to 13%) [35] when compared to IIV-SD for the prevention of ILI syndrome without laboratory confirmation of viral etiology.

Summary of vaccine efficacy/effectiveness against influenza-associated outpatient and/or emergency department visits

Overall, ACIP included 8 observational studies reporting data on influenza-associated outpatient and/or ED visits defined by clinical diagnosis. Of those, 5 compared IIV3-HD to IIV-SD [43-47], and 4 compared IIV3-Adj to IIV-SD [42, 45, 48, 49]. The DSEN MAGIC included 1 RCT comparing IIV-HD to IIV-SD against influenza-associated outpatient visits defined by clinical diagnosis [64].

From the ACIP review, pooled results from 4 retrospective cohort studies demonstrated a beneficial effect of IIV-HD compared to IIV-SD with a relative vaccine effectiveness (rVE) of 13% (95% CI: 1 to 24%) [44-47]. They also identified 1 test-negative case-control study comparing IIV-HD to IIV-SD that found a rVE of 9% (95% CI: -12 to 27%) [43]. The DSEN MAGIC did not find a difference between IIV3-HD and IIV3-SD for the prevention of outpatient visits for ILI in 1 RCT (relative vaccine efficacy of 3%, 95% CI: -14 to 18%) [64].

Evidence comparing IIV-Adj to IIV-SD against outpatient and/or ED visits for ILI from the ACIP review was inconsistent. Evidence derived from 2 observational studies indicated a beneficial protective effect of IIV-Adj compared to IIV-SD (pooled rVE of 36%, 95% CI: 21 to 48%) [42, 48]. However, evidence derived from 2 retrospective cohort studies did not identify a difference between IIV-Adj and IIV-SD for the prevention of outpatient and/or ED visits for ILI (pooled rVE of 0%, 95% CI: -3 to 3%) [45, 49].

Summary of vaccine efficacy/effectiveness against influenza-associated hospitalizations

Overall, ACIP included 4 RCTs [38-40, 72] and 15 observational studies [45, 47, 50-62] reporting data on influenza-associated hospitalization including laboratory-confirmed, code-based, and clinical case definitions. Of those, 13 compared IIV3-HD to IIV-SD [38-40, 45, 47, 50-57], 7 compared IIV3-Adj to IIV-SD [45, 51, 58-61, 72], and 1 compared RIV to IIV-SD [51]. The DSEN MAGIC included 3 RCTs [33, 64, 66] comparing IIV-HD to IIV-SD and 1 comparing RIV to IIV-SD [34] against ILI (n=2) and LCI (n=3) hospitalization.

In the ACIP review, most data were available for influenza hospitalizations among all outcomes examined. Their evidence demonstrated protective beneficial effects for IIV-HD, IIV-Adj, and RIV when compared to IIV-SD, though the depth of data varied as most of the data were for IIV-HD (n=13), less for IIV-Adj (n=7), and least for RIV (n=1). The DSEN MAGIC review also demonstrated a beneficial protective effect of IIV-HD compared to IIV-SD against ILI hospitalization (pooled relative vaccine efficacy of 28%, 95%: 8 to 43%) [33, 64]. Evidence for IIV-HD (relative vaccine efficacy of 40%, 95% CI: -65 to 78%, and 0%, 95% CI: -1570 to 94%) [33, 66] and RIV (relative vaccine efficacy of 67%, 95% CI: -221 to 96%) [34] compared to IIV-SD against hospitalization for LCI was only available from single studies in the DSEN MAGIC review and did not demonstrate protective effects as estimates were imprecise with large confidence interval.

Summary of vaccine efficacy/effectiveness against influenza-associated deaths

Overall, ACIP included 2 retrospective cohort studies [46, 59] comparing IIV3-HD to IIV-SD, and the DSEN MAGIC included 1 RCT comparing IIV-Adj to IIV-SD against influenza-associated deaths defined by clinical diagnosis codes [35].

ACIP demonstrated a beneficial protective effect of IIV3-HD compared to IIV-SD against influenza-associated deaths (pooled rVE of 31%, 95% CI: 16 to 43%) [46, 59]. The DSEN MAGIC identified a study reporting a point estimate of lower influenza related deaths for IIV3-Adj compared with IIV3-SD, though the effect was very imprecise with wide confidence intervals (vaccine efficacy of 25%, 95% CI: -236 to 83%) [35].

Summary of vaccine efficacy/effectiveness against vascular events

Data on influenza-associated vascular events, which include various cardiovascular outcomes associated with influenza infection, as defined by the individual study (e.g., myocardial infarction, heart failure, stroke, etc.) were only available from the DSEN MAGIC review. Overall, they included 7 RCTs reporting data on vascular events [33-35, 64, 67, 68, 73]. Of those, 4 compared IIV3-HD to IIV-SD [33, 64, 68, 73], 2 compared IIV3-Adj to IIV-SD [35, 67], and 1 compared RIV to IIV-SD [34]. The 3 vaccines IIV-HD (pooled rate ratio of 0.75, 95% CI: 0.43 to 1.29), IIV-Adj (pooled rate ratio of 0.83, 95% CI: 0.54 to 1.27) and RIV (odds ratio of 0.89, 95% CI: 0.30 to 2.60) were associated with a lower number of vascular events compared to IIV-SD, though the associations were not statistically significant with wide confidence intervals.

IV.3.2 Efficacy and effectiveness of high dose, recombinant and adjuvanted influenza vaccines compared to one another

Summary of study characteristics

The ACIP systematic review identified 7 studies (1 RCT and 6 observational studies) that assessed the efficacy/effectiveness of IIV-HD, IIV-Adj and RIV against one another. Of those, 2 reported data comparing

IIV3-Adj to RIV4 [37, 51], 7 reported data comparing IIV3-HD to IIV3-Adj [37, 45, 49-51, 62, 63] and 2 reported data comparing IIV3-HD to RIV4 [37, 51]. Their systemic review provided data on LCI (n=1), influenza-associated outpatient and/or ED visits (n=3), and influenza-associated hospitalization (n=4).

The DSEN MAGIC identified 2 RCTs reporting on the efficacy of IIV-HD, IIV-Adj and RIV with one another against LCI. Of those studies, 1 reported data comparing IIV3-HD to IIV3-Adj and RIV4 [37], and another reported data comparing IIV3-HD to IIV3-Adj [74].

No studies were identified that compared the efficacy/effectiveness of these vaccines with one another against influenza-associated deaths and vascular events. Few studies reported data comparing the efficacy/effectiveness of IIV-HD, IIV-Adj and RIV against one another thus limiting the generalizability of findings to all or most influenza seasons.

Summary of vaccine efficacy/effectiveness against laboratory-confirmed influenza

The ACIP review identified a single RCT that compared the efficacy of IIV-HD vs IIV-Adj (relative vaccine efficacy of 66%, 95% CI: -213 to 96%), IIV-HD vs RIV (relative vaccine efficacy of 74%, 95% CI: -118 to 97%) and IIV-Adj vs RIV (relative vaccine efficacy of 25%, 95% CI: -207 to 82%) against LCI [37]. Nevertheless, the study did not demonstrate a beneficial protective effect associated with IIV-HD, IIV-Adj, or RIV compared with one another due to the important imprecision associated with these vaccine efficacy estimates.

The DSEN MAGIC review identified 2 RCTs comparing IIV-HD to IIV-Adj (relative vaccine efficacy of -210%, 95% CI: -3,080 to 70%), RIV to IIV-Adj (relative vaccine efficacy of 28%, 95% CI: -254 to 85%), and RIV to IIV-HD (relative vaccine efficacy of 77%, 95% CI: -121 to 98%) against LCI [37, 74]. Similar to the ACIP review, the studies did not demonstrate a beneficial protective effect against LCI associated with IIV-HD, IIV-Adj, or RIV compared with one another due to the wide confidence intervals associated with the vaccine efficacy estimates.

Summary of vaccine efficacy/effectiveness against influenza-associated outpatient and/or emergency department visits

The ACIP review included 3 retrospective cohort studies comparing IIV3-HD to IIV3-Adj against influenza-associated outpatient and/or ED visits defined using diagnostic and procedural codes associated with a prescription of antiviral (i.e., oseltamivir) [45, 49, 63]. A meta-analysis involving those studies did not demonstrate a beneficial protective effect against influenza-associated outpatient and/or ED visits with IIV-HD over IIV-Adj (pooled rVE of –6%, 95% CI: -23 to 8%).

The DSEN MAGIC review did not identify any RCTs reporting data on influenza-associated outpatient visits comparing IIV-HD, IIV-Adj, and RIV with one another.

Summary of vaccine efficacy/effectiveness against influenza-associated hospitalization

The ACIP review identified 4 retrospective cohort studies reporting data on influenza-associated hospitalizations defined by clinical diagnosis codes comparing IIV3-HD to IIV3-Adj (n=4) [45, 50, 51, 62], IIV3-HD to RIV4 (n=1) [51] and IIV3-Adj to RIV4 (n=1) [51]. All of these studies assessed influenza associated hospitalizations through diagnostic codes. The DSEN MAGIC review did not identify any RCTs reporting data on influenza-associated hospitalization comparing IIV-HD, IIV-Adj, and RIV to one another.

One (1) retrospective cohort study demonstrated a relative benefit of RIV compared to IIV-HD and IIV-Adj against influenza-associated hospitalizations during the 2019-20 influenza season [51]. A meta-analysis of 4 observational studies conducted over 4 influenza seasons did not find a difference between IIV3-HD and IIV3-Adj against influenza-associated hospitalization (rVE of 4%, 95% CI: -1 to 10%) [45, 50, 51, 62].

IV.4 Vaccine safety

Safety outcomes evaluated in the systematic review conducted by the US ACIP were rated as low to very low and most were downgraded for imprecision due to low number of events, small sample size, and wide confidence intervals around the effect estimate [14]. For additional details regarding the summary of findings and assessments of the quality of the evidence please refer to GRADE: Higher Dose and Adjuvanted Influenza Vaccines for Persons Aged ≥65 Years and to the Evidence to Recommendations (EtR) Framework: Higher Dose and Adjuvanted Influenza Vaccines for Persons Aged ≥65 Years.

Please note that subgroup analyses on vaccine safety were conducted on the overall population of adults 65 years of age and older, and not by risk groups (e.g., population with comorbid conditions, sex, previous vaccination, and adults 80 years of age and older) due to data limitations, including the number of studies reporting for each outcome.

IV.4.1 Vaccine safety of high dose, recombinant and adjuvanted influenza vaccines compared to standard-dose inactivated influenza vaccines

Summary of study characteristics

The ACIP review included 23 RCTs [33-36, 39, 67, 68, 71, 73, 75-88] and 1 retrospective cohort study [89] that reported safety data comparing IIV-HD, IIV-Adj, and RIV to IIV-SD in adults 65 years of age and older. Of those, 8 compared IIV-HD to IIV-SD [33, 36, 39, 68, 73, 78, 86, 87], 12 compared IIV-Adj to IIV-SD [35, 67, 71, 75, 79-82, 85, 87-89], and 7 compared RIV to IIV-SD [34, 71, 76, 77, 83, 84, 87]. Their systematic review provided data on any solicited systemic events grade 3 or higher (n=7), Guillain-Barré Syndrome (n=4), any serious adverse events (n=18), and any solicited injection site events grade 3 or higher (n=6).

Summary of vaccine safety

Any solicited systemic events grade 3 or higher following immunization

The ACIP review included 7 RCTs reporting data on solicited systemic adverse events grade 3 or higher comparing HD-IIV3 (n=3) [36, 86, 87], IIV3-Adj (n=5) [67, 71, 75, 87, 88] or RIV3 (n=1) [87] to IIV-SD in adults 65 years of age and older. Together, these studies showed that HD-IIV3, IIV3-Adj and RIV3 may lead to a decrease in solicited systemic adverse events grade 3 or higher when compared to IIV-SD though all the estimates lack precision (pooled risk ratio [RR] of 0.95, 95% CI: 0.20 to 4.53, 0.77, 95% CI: 0.34 to 1.76, and RR of 0.28, 95% CI: 0.05 to 1.67, respectively).

Guillain-Barré Syndrome

The ACIP review included 2 RCTs [35, 39] and 2 observational studies [77, 89] reporting data on Guillain-Barré Syndrome (GBS) comparing IIV3-HD, IIV3-Adj or RIV3 to IIV-SD. One (1) RCT comparing IIV3-HD (n=2,606) to IIV-SD (n=2,604) did not identify any cases of GBS among 5,210 vaccine recipients [39]. One (1) RCT found a non-significant decreased risk of GBS with IIV3-Adj compared to IIV-SD (RR of 0.33, 95% CI: 0.01 to 8.16) [35]. One (1) observational study comparing IIV3-Adj (n=88,449) to IIV-SD (n=82,539) did not identify any cases of GBS among 170,988 vaccine recipients [89]. Another observational study comparing RIV3 to IIV3-SD identified 4 GBS cases among 283,683 IIV3-SD recipients and none among 21,976 RIV3 recipients [77]. Of note, as GBS occurs very rarely in the general population, it is not expected that studies of these sizes would be sufficiently powered to detect a difference in the risk of GBS between groups.

Any serious adverse events (SAE) following immunization

The ACIP review included 18 RCTs reporting data on any SAE comparing IIV3-HD (n=7) [33, 36, 39, 68, 73, 78, 87], IIV3-Adj (n=8) [35, 67, 79-82, 85, 87] or RIV3 (n=5) [34, 71, 83, 84, 87] to IIV-SD in adults 65 years of age and older.

A meta-analysis of 7 RCTs showed that IIV-HD was associated with a lower risk of SAE compared to IIV-SD (pooled RR of 0.91, 95% CI: 0.85 to 0.97). No differences were observed in SAE with IIV-Adj and RIV compared to IIV-SD though the estimates lacked precision (pooled RR of 1.07, 95% CI: 0.92 to 1.26 and 1.03, 95% CI: 0.84 to 1.26, respectively).

Any solicited injection site events grade 3 or higher following immunization

The ACIP review included 6 RCTs reporting solicited injection site events grade 3 or higher comparing IIV3-HD, IIV3-Adj or RIV to IIV-SD in adults 65 years of age and older [36, 67, 71, 85, 87, 88]. A meta-analysis of 4 RCTs showed that IIV3-Adj led to an increase in reactogenicity events compared to IIV-SD (pooled RR of 3.39, 95% CI: 1.32 to 8.72) [67, 85, 87, 88]. Similarly, a meta-analysis of 2 RCTs showed that IIV3-HD may lead to an increase in reactogenicity events compared to IIV-SD though the estimate lacked precision (pooled RR of 5.03, 95% CI: 0.88 to 28.74) [36, 87]. Conversely, results suggested that RIV may lead to a decrease in solicited injection sites events grade 3 or higher when compared to IIV-SD, however the estimates also lacked precision (pooled RR of 0.67, 95% CI: 0.27 to 1.69) [71, 87].

IV.4.2 Vaccine safety of high dose, recombinant and adjuvanted influenza vaccines compared to one another

Summary of study characteristics

The ACIP review included 3 RCTs reporting safety data comparing IIV3-HD, IIV3-Adj, and RIV4 to one another [76, 87, 90]. Of those, 2 compared IIV3-HD to IIV3-Adj [76, 87], 2 compared IIV3-HD to RIV4 [87, 90], and 1 compared RIV4 to IIV3-Adj [87]. Their systematic review provided data on any solicited adverse events grade 3 or higher (n=3), any serious adverse events (n=3), and any solicited injection site events grade 3 or higher (n=3). No study comparing IIV3-HD, IIV3-Adj, and RIV4 to one another with data on GBS was identified in this review.

Summary of vaccine safety

Any solicited systemic adverse events grade 3 or higher following immunization

The ACIP review included 3 RCTs reporting data on solicited systemic adverse events grade 3 or higher comparing IIV3-HD, IIV3-Adj, and RIV4 to one another [76, 87, 90]. Two (2) meta-analyses showed that IIV3-HD was less likely to cause solicited systemic adverse events compared to IIV3-Adj (n=2) [76, 87] and RIV4 (n=2) [87, 90], however both estimates were imprecise (pooled RR of 0.73, 95% CI: 0.29 to 1.80, and pooled RR of 0.86, 95% CI: 0.22 to 3.32, respectively). Additionally, 1 RCT reported that IIV3-Adj may lead to an increased risk of solicited systemic adverse events when compared to RIV3 though the estimate lacked precision (RR of 4.62, 95% CI: 0.24 to 89.17) [87].

Any serious adverse events (SAEs) following immunization

The ACIP review included 3 RCTs reporting on SAEs comparing IIV3-HD to IIV3-Adj (n=2) [76, 87], IIV3-HD to RIV4 (n=2) [87, 90] and IIV3-Adj to RIV4 (n=1) [87]. One (1) meta-analysis and 1 single study showed that IIV3-HD and IIV3-Adj were associated with higher risks of SAEs when compared to RIV4, however the estimates lacked precision (pooled RR of 1.77, 95% CI: 0.73 to 4.27 and RR of 1.81, 95% CI: 0.58 to 5.65, respectively). Additionally, 1 meta-analysis reported that IIV3-HD may be associated with a lower risk of SAEs compared to IIV3-Adj though the pooled estimate also lacked precision (pooled RR of 0.65, 95% CI: 0.32 to 1.30).

Any solicited injection site events grade 3 or higher following immunization

The ACIP review included 3 RCTs that reported data on solicited injection site events grade 3 or higher comparing IIV3-HD to IIV3-Adj (n=2) [76, 87], IIV3-HD to RIV4 (n=2) [87, 90], and IIV3-Adj to RIV4 (n=1) [87].

One (1) meta-analysis and 1 RCT showed that IIV3-HD and IIV3-Adj may be associated with more reactogenicity compared to RIV4, however the estimates lacked precision (pooled RR of 5.92, 95% CI: 0.32 to 109.56, and RR of 4.62, 95% CI: 0.24 to 89.17, respectively). Additionally, 1 meta-analysis reported that IIV3-HD may be associated with less reactogenicity compared to IIV3-Adj though the estimate also lacked precision (pooled RR of 0.88, 95% CI: 0.45 to 1.75).

V. Economics

Two (2) economic analyses are summarized below. The first is a published systematic review of the cost-effectiveness of influenza vaccination among adults 65 years of age and older [91]. Studies on influenza vaccines approved for use in the United States or in Canada published as full-text peer reviewed articles up to October 29, 2020, were included. All included studies compared the cost-effectiveness of quadrivalent or high-dose/adjuvanted vaccine strategies to an IIV3-SD strategy. The second is an economic evaluation published by the Comité sur l'immunisation du Québec (CIQ) [92].

V.1 Systematic review of economic evaluations

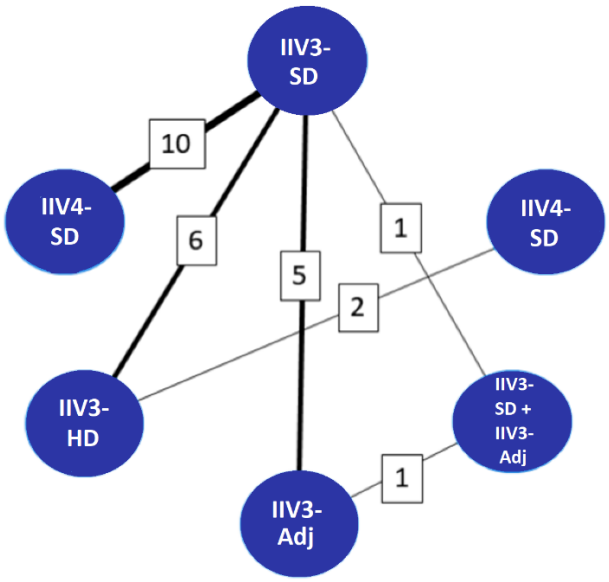
A high-level overview of the published systematic review [91] is presented here with additional NACI commentary. All costs are reported in 2019 Canadian dollars. For a primer on the interpretation of economic evaluation findings and cost-effectiveness thresholds, please refer to the NACI Interpretation Guide to Health Economics for Decision-Makers [93]. A brief overview of key terminology is presented in Appendix A.

V.1.1 Summary of included studies

Overall, 19 studies, consisting of 16 cost-utility analyses [94-109], 2 cost-benefit analyses [110, 111] and 1 cost-effectiveness analysis [112], were included. Among the included studies, 8 were conducted in North America [91, 92, 96, 97, 101, 103, 106, 107], 5 were conducted in Europe [97-99, 108, 112], 5 were conducted in Asia [94, 102-104, 106], and 1 was conducted in South America [109]. All studies but 1 [112] were published between 2014 and 2020. All included studies were appraised to be of high (n=13) [94-97, 100-105, 107-109] or moderate (n=6) [98, 99, 106, 110-112] quality.

Figure 1 shows the comparisons of vaccine products made (note multiple comparisons were possible within 1 study).

Figure 1. Number and distribution of vaccine comparisons in the 19 included studies



Note: "IIV3-SD + IIV3-Adj" refers to IIV3-SD for individuals aged 65 to 74 years and IIV3-Adj for adults aged 75 years of age and older [98]; IIV4-SD vs IIV3-SD [94, 97, 99, 101-106, 108]; IIV3-HD vs IIV3-SD [95, 96, 100, 107, 110, 111]; IIV3-Adj vs IIV3-SD [99, 104, 108, 109, 112]; IIV3-HD vs IIV4-SD [96, 107]. Line thickness represents the number of studies reporting data for a given comparison, also indicated in boxes.

The following perspectives were adopted for analyses:

- Societal perspective: n=13 studies [94-97, 99-107]
- Healthcare payer perspective: n=12 studies
- Healthcare provider perspective: n=1 study [102]

The time horizon used for analysis in the included studies varied from 1 influenza season [110] to lifetime [97, 99, 104], with 6 studies [94-96, 100, 107, 112] applying different time horizons for costs and effects (e.g., a time horizon of 1 influenza season for cost and a lifetime time horizon for effect). Four (4) studies did not report the time horizon used for analysis [98, 101, 102, 111].

Most studies were funded by industry (n=13) [95-97, 99-101, 103, 105, 108-112]. Three (3) [98, 104, 107] were supported by public funding sources and 1 reported a mix of both industry and public funding [94]. Two (2) studies did not specify the funding sources [102, 106].

V1.2 Model-specific appraisal

Key model parameters included influenza vaccine coverage, influenza attack rate, influenza-related complications (e.g., pneumonia, bronchitis, cardiovascular disease, central nervous system complications), need for prescription drugs to treat influenza-related complications, medical consultations, ED visits, hospitalizations, and influenza-associated mortality. Influenza vaccine coverage ranged from 27% [94] to 82% [103, 104] across the included studies.

A minority of studies accounted for cross protection (n=5) [97, 99, 101, 104, 105] and community immunity (i.e., herd effect) (n=1) [105]. No studies accounted for frailty, vaccine wastage, the availability of multi-dose and single-dose formats, and the availability of various influenza vaccines on the market.

V1.3 Summary of results

A summary of the findings from included cost-utility studies is provided in Table 1 (n=16) [94-109]. In general, IIV4-SD, IIV3-Adj, and IIV3-HD were found to be cost-effective options compared to IIV3-SD from the healthcare and societal perspectives. The included cost-effectiveness analysis (n=1) [112] and cost-benefit analyses (n=2) [110, 111] had similar conclusions which were that IIV3-HD and IIV3-Adj were cost-effective compared to IIV3-SD.

Table 1. Summary of findings from cost-utility studies examining the use of influenza vaccines among adults 65 years of age and older (n=16)

Outcome	Vaccine Comparisons					
	IIV4-SD vs IIV3-SD	**IIV3-Adj vs IIV3-SD**	**IIV3-HD vs IIV3-SD**	**IIV3-HD vs IIV4-SD**	**IIV-SD+IIV-Adj vs IIV-SD**	**IIV-Adj vs IIV-SD+IIV-Adj**
Healthcare payer perspective:						
Number of ICERs	4 [97, 99, 101, 108]	2 [108, 109]	3 [95, 96, 100]	1 [96]	1 [98]	1 [98]
ICER (Minimum)	$28 524/ QALY gained [97]	$3 406/ QALY gained [109]	IIV3-HD dominated IIV3-SD [95, 100]	$5 709/ QALY gained [96]	$9 771/ QALY gained [98]	$13 804/ QALY gained [98]
ICER (Maximum)	$224 000/ QALY gained [108]	$7 692/ QALY gained [108]	$13 537/ QALY gained [96]	-	-	-
Proportion of estimates CE at $10 000/QALY	0%	100% [108, 109]	67% [95, 100]	100% [96]	100% [98]	0%
Proportion of estimates CE at $40 000/QALY	75% [96, 97, 99]	100% [108, 109]	100% [95, 96, 100]	100% [96]	100% [98]	100% [98]
Proportion of estimates CE at $50 000/QALY	75% [96, 97, 99]	100% [108, 109]	100% [95, 96, 100]	100% [96]	100% [98]	100% [98]
Societal perspective:						
Number of ICERs	9 [94, 97, 99, 101-106]	2 [99, 104]	4 [95, 96, 100, 107]	2 [96, 107]	0	0
ICER (Minimum)	IIV4-SD dominated IIV3-SD [103, 105]	IIV3-Adj dominated IIV3-SD [99, 104]	IIV3-HD dominated IIV3-SD [95, 100]	IIV3-HD dominated IIV4-SD [96]	-	-
ICER (Maximum)	$55 865/QALY gained [106]	-	$36 967/QALY gained [107]	$40 824/QALY gained [107]	-	-
Proportion of estimates CE at $10 000/QALY	33% [94, 103, 105]	100% [99, 104]	75% [95, 100, 101]	50% [96]	-	-
Proportion of estimates CE at $40 000/QALY	89% [94, 97, 99, 101-105]	100% [99, 104]	100% [95, 100, 101, 107]	50% [96]	-	-
Proportion of estimates CE at $50 000/QALY	89% [94, 97, 99, 101-105]	100% [99, 104]	100% [95, 100, 101, 107]	100% [107]	-	-
Healthcare provider perspective:						
Number of ICERs	1 [102]	0	0	0	0	0
ICER (Minimum)	$29 562/QALY gained [102]	-	-	-	-	-
ICER (Maximum)	-	-	-	-	-	-
Proportion of estimates CE at $10 000/QALY	0%	-	-	-	-	-
Proportion of estimates CE at $40 000/QALY	100% [102]	-	-	-	-	-
Proportion of estimates CE at $50 000/QALY	100% [102]	-	-	-	-	-

Abbreviations: CE, cost-effective; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year
Notes: "IIV3-SD + IIV3-Adj" refers to IIV3-SD for individuals 65 to 74 years of age and IIV3-Adj for adults 75 years of age and older [98]. "Intervention A dominated Intervention B" means that Intervention A is less costly and more effective than Intervention B.

Results from studies considered highly generalizable to a Canadian setting

Four (4) studies were considered highly generalizable to a Canadian setting: 2 were conducted in Canada [95, 101] and 2 were conducted in the United Kingdom (UK) [97, 98], of which, only 1 was not industry-funded [98]. Details on how generalizability was assessed can be found in Appendix B. The findings from the 4 studies are presented below.

Healthcare Payer Perspective: All 4 studies conducted analyses from the healthcare payer perspective (Table 2) [95, 97, 98, 101]. Comparing a IIV4-SD to a IIV3-SD strategy, the incremental cost-effectiveness ratio (ICER) estimates ranged from $28 524 [97] to $39 599 [101] per quality-adjusted life year (QALY) gained. These estimates can be considered cost-effective under commonly used thresholds (Appendix A). Comparing the IIV3-HD strategy to the IIV3-SD strategy in Canada, the IIV3-HD strategy was less costly and more effective among adults (i) 65 years of age and older, (ii) living with a cardiorespiratory condition, and (iii) living with 1 or more comorbid conditions [95]. Further, the IIV3-HD strategy was cost-effective among adults 75 years and older compared to the IIV3-SD strategy [95]. Comparing a mixed intervention approach (IIV3-SD for individuals 65 to 74 years of age and IIV3-Adj for adults 75 years of age and older) to IIV3-Adj and to IIV3-SD, the mixed approach was cost-effective under commonly used thresholds ($9 771 per QA[99] to $13 084 per QALY) [98].

Societal Perspective: Three (3) studies conducted analyses from the societal perspective (Table 2) [95, 97, 101]. Comparing an IIV4-SD strategy to an IIV3-SD strategy, the ICER estimates ranged from $26 288 [101] to $36 115 [97] per QALY gained. Comparing an IIV3-HD strategy to an IIV3-SD strategy in Canada, IIV3-HD strategy was less costly and more effective in adults (i) 65 years of age and older, (ii) 75 years of age and older, (iii) living with a cardiorespiratory condition, and (iv) living with 1 or more comorbid conditions [95].

Estimated ICER values were consistently lower from a societal perspective than a healthcare payer perspective. The former often included productivity loss for patients and/or caregivers.

Table 2. Summary of study characteristics and findings from cost-utility studies that were considered highly generalizable to a Canadian setting (n=4)

Author, Year, Country	Funding	Population	Time horizon	Findings – Healthcare payer perspective	Findings – Societal perspective
IIV4-SD (Intervention) vs IIV3-SD (Comparator)					
Chit et al., 2015a [101], Canada	Sanofi Pasteur (Industry)	Adults 65 years of age and older	Not reported	$39 599/QALY gained	$36 115/QALY gained
Meier et al., 2015 [97], UK	GlaxoSmithKline Biologicals SA (Industry)	Adults 65 years of age and older	Lifetime	$28 524/QALY gained	$26 288/QALY gained
IIV3-HD (Intervention) vs IIV3-SD (Comparator)					
Becker et al., 2016 [95], Canada	Sanofi Pasteur (Industry)	Adults 65 years of age and older	One (1) influenza season for cost and lifetime for effect	All participants 65 years of age and older: IIV3-HD dominated IIV3-SD **Subgroup analyses** Participants 75 years of age and older: $87/QALY gained Participants living with a cardiorespiratory condition: IIV3-HD dominated IIV3-SD Participants living with 1 or more comorbidities: IIV3-HD dominated IIV3-SD	All participants 65 years of age and older: IIV3-HD dominated IIV3-SD **Subgroup analyses** Participants 75 years of age and older: IIV3-HD dominated IIV3-SD Participants living with a cardiorespiratory condition: IIV3-HD dominated IIV3-SD Participants living with 1 or more comorbidities: IIV3-HD dominated IIV3-SD
IIV3-SD + IIV3-Adj (Intervention)[a] vs IIV3-SD (Comparator)					
Thorrington et al., 2019 [98], UK	Multiple sources (Public)	Adults 65 years of age and older	Not reported	$9 771/QALY gained	Analysis not conducted
IIV3-Adj (Intervention) vs IIV3-SD + IIV3-Adj (Comparator)[a]					
Thorrington et al., 2019 [98], UK	Multiple sources (Public)	Adults 65 years of age and older	Not reported	$13 084/QALY gained	Analysis not conducted

[a] IIV3-SD (for adults aged 65 to 74 years) and IIV3-Adj (for adults age 75 years and older).
Note: "Intervention A dominated Intervention B" means that Intervention A is less costly and more effective than Intervention B.

Results from studies considered less generalizable to a Canadian setting

A summary of the 15 studies [94, 96, 99, 100, 102-112] deemed to have limited generalizability to a Canadian setting can be found in Appendix C. The findings from these 15 studies were broadly similar to the 4 studies above. These studies also found IIV4-SD, IIV3-Adj, and IIV3-HD strategies to be cost-effective compared to an IIV3-SD strategy.

Results from studies on higher risk older adults

Table 3 shows the 5 studies that assessed older adults with a higher risk of influenza infection and/or complications such as those with comorbidities or in congregate living [95, 100, 104, 110, 112]. IIV3-HD and IIV3-Adj strategies were either cost-effective or less costly and more effective compared to an IIV3-SD strategy depending on the population. An IIV4-SD strategy was cost-effective compared to an IIV3-SD strategy under commonly used thresholds.

Table 3. Summary of study characteristics and findings from studies conducted among older adults at high risk of seasonal influenza infection or influenza-related complications or hospitalizations (n=5)

Author, Year, Country	Funding	Study type	Time horizon	Findings – Healthcare payer perspective	Findings – Societal perspective
IIV4-SD (Intervention) vs IIV3-SD (Comparator)					
Yun et al., 2019 [104], South Korea	Korea Centers for Disease Control and Prevention (Public)	Cost-utility	Lifetime for cost and effect	Analysis not conducted	Participants at high risk of seasonal influenza infection and/or influenza-related complications or hospitalizations: $1 327/QALY gained
IIV3-Adj (Intervention) vs IIV3-SD (Comparator)					
Yun et al., 2019 [104], South Korea	Korea Centers for Disease Control and Prevention (Public)	Cost-utility	Lifetime for cost and effect	Analysis not conducted	Participants at high risk of seasonal influenza infection and/or influenza-related complications or hospitalizations: IIV3-Adj dominated IIV3-SD
Piercy et al., 2004 [112], France	Chiron Vaccines (Industry)	Cost-effectiveness	One (1) year for cost and lifetime for effect	Participants suffering from heart or lung disease: $44 492 per death avoided $8 943 per life year gained	Analysis not conducted
IIV3-HD (Intervention) vs IIV3-SD (Comparato[96] Becker et al., 2016 [95], Canada	Sanofi Pasteur (Industry)	Cost-utility	One (1) influenza season for cost and lifetime for effect	Participants living with a cardiorespiratory condition: IIV3-HD dominated IIV3-SD Participants living with 1 or more comorbidities: IIV3-HD dominated IIV3-SD	Participants living with a cardiorespiratory condition: IIV3-HD dominated IIV3-SD Participants living with 1 or more comorbidities: IIV3-HD dominated IIV3-SD
Chit et al., 2015b [100], US	Sanofi Pasteur (Industry)	Cost-utility	One (1) year for cost and lifetime for effect	Participants living with 1 or more comorbidities: IIV3-HD dominated IIV3-SD Participants living with a cardiorespiratory condition: IIV3-HD dominated IIV3-SD	Participants living with 1 or more comorbidities: IIV3-HD dominated IIV3-SD Participants living with a cardiorespiratory condition: IIV3-HD dominated IIV3-SD
Shireman et al., 2019 [110], US	Sanofi Pasteur (Industry)	Cost-benefit analysis	One (1) influenza season for cost and effect	Nursing home residents: Positive net monetary benefit	Analysis not conducted

V1.4 Influential factors that affect cost-effectiveness

Most of the included studies, apart from 2 [105, 106], conducted sensitivity analyses to test model assumptions and the robustness of study results. In most cases, the results from the sensitivity analyses supported the base case conclusions (i.e., interventions that were cost-effective under base case analysis remained cost-effective during sensitivity analyses). However, cost-effectiveness was found to be sensitive to a number of variables including mismatch between seasonal influenza vaccines and circulating strains [97, 99, 102-104], relative vaccine effectiveness (e.g., against symptomatic disease, hospitalizations, mortality) [94, 103, 104], vaccine costs [102, 104], level of vaccine cross protection in the event of type B lineage mismatch, and influenza mortality rate [99].

V.1.5 Discussion

The current review of economic evaluation studies summarizes the cost-effectiveness of seasonal influenza vaccines among adults 65 years of age and older. Studies on budget impact (i.e., analyses on the likely change in expenditure to a specific budget holder when a vaccination program is implemented) were not included. In total, 19 studies of moderate to high quality were included in this review. The directionality of cost-effectiveness results remained consistent across all studies. IIV4-SD, IIV3-HD, and IIV3-Adj strategies were cost-effective compared to an IIV3-SD strategy under commonly used thresholds. The findings of the current review are supported by 2 recent literature reviews in older adults conducted by Sugishita and Sugiwara (2021) [113] and Postma et al. (2023) [114].

A trend emerged in 2 studies showing that IIV4-SD became increasingly more cost-effective (i.e., lower ICER) compared to IIV3-SD with increasingly older age groups [102, 104]. Generally, immune function declines with older age, resulting in the increased risk of influenza infection and influenza-related hospitalization and/or complications among older adults [115-118]. Additionally, the average number of comorbidities and level of frailty per individual tend to increase with older age [119-122]. Individuals living with 1 or more comorbidity and/or higher levels of frailty are at increased risk for more severe influenza-related outcomes, including hospitalizations, functional decline, and death following infection [20, 123-125]. More effective vaccines administered to older adults can result in fewer influenza-related hospitalizations and complications, reducing associated healthcare utilization costs and resulting in more favourable cost-effectiveness results with increasing age.

Thirteen of the 19 included studies were conducted from a societal perspective, often incorporating productivity loss for the older adult and their caregiver(s). Other studies assumed that income loss was minimal among older adults who may be retired by 65 years of age [126]. The societal perspective resulted in additional cost-savings and lower ICER estimates.

Several studies conducted their analyses from a short time horizon based on the length of the influenza season [103, 108-110]. A short time horizon can be appropriate in many cases given that consequences and costs of influenza often occur within a single year [127]. However, long term consequences and costs associated with influenza infection would not be well-captured in these studies, such as long-term disability, loss of independence, reduced health-related quality of life, need for nursing home placement or home care, and death post-infection [128, 129].

No studies accounted for frailty in their analyses. Frailty is a complex, dynamic, multifactorial syndrome characterized by an increased risk of adverse outcomes compared to other individuals in the same age group [129-132]. While vaccine effectiveness and odds of recovery from influenza infection decline with increasing frailty, frailer adults tend to have increased vaccine coverage [133]. A previous Canadian study conducted among older adults found that influenza vaccination provided good protection against influenza hospitalization among non-frail older adults, and those on the milder end of the frailty spectrum [133]. Not adjusting for frailty tends to underestimate vaccine effectiveness in the older adult population [133]. The underestimation of vaccine effectiveness may subsequently impact cost-effectiveness results, particularly when indication bias is considered.

For instance, to improve immune response, frail older adults may be more likely to receive influenza vaccines designed specifically to enhance immunogenicity compared to non-frail older adults, and this indication bias is difficult to fully account for, especially in the absence of adjusting the models for frailty. The difference in type of influenza vaccine received between frail and non-frail adults (i.e., if frail older adults who are most at risk of adverse outcomes are also more likely to have received the enhanced vaccines) may underestimate the benefit of these vaccines compared to standard vaccine products, potentially underestimating their cost-effectiveness compared to standard vaccine strategies.

Four (4) of the 19 included studies (from Ontario, Canada [95, 101] and UK [97, 98]) were considered to be highly generalizable to a Canadian setting based on participant demographics, vaccine availability, and the healthcare resources consumed and associated costs, among other generalizability assessment criteria (Appendix B) [95, 97, 98, 101]. Several studies were conducted in non-OECD countries (n=4) [94, 102, 106, 109], 1 of which was conducted in the southern hemisphere [109] and may have limited generalizability due to differing formulations of the vaccine products, healthcare costs, and differing seasonality of influenza. Although the US has similar demographics and influenza epidemiology compared to Canada, there are differences in healthcare systems (e.g., payer) and discrepancies in the cost of vaccines and healthcare services. For economic evaluations conducted from a societal perspective, out-of-pocket costs and productivity loss can also vary across countries and regions.

The reported ICERs comparing IIV4-SD to IIV3-SD strategies may be of limited generalizability to the present time and setting considering the absence of confirmed detections of B/Yamagata since March 2020. The review included studies up until 2020 when both the B/Victoria and B/Yamagata lineages were still circulating. The relevance of IIV4-SD cost-effectiveness for the future is unclear. Further, Health Canada authorizations and industry determine which products are available on the Canadian market, and so at present, provinces and territories do not choose between IIV4 or IIV3 for the standard dose vaccines.

The small variation in ICER estimates may be due to assumptions and data sources used for influential variables such as vaccine mismatch, vaccine effectiveness, vaccine costs, level of vaccine cross protection, vaccine coverage, and influenza mortality rate. In particular, vaccine effectiveness, seasonality, and the match between the vaccine and circulating influenza strains within a single country or region vary across influenza seasons and by type of vaccine product, so outcome estimates may vary depending on the year(s) of data used and the vaccine products compared.

Notably, only 1 of the 19 included studies accounted for potential benefits of community immunity (also known as herd immunity) arising from immunization of older adults in their analysis [105]. Community immunity refers to the concept that once a certain proportion of the population is vaccinated against a specific disease, the remaining individuals in the population who are not immunized experience indirect protection against the disease because the infectious organism is less able to circulate. Its inclusion may be particularly important in economic evaluations of close congregate settings (e.g., nursing homes, long term care facilities) where residents are in close contact with shared caregivers and staff [134, 135]. A previously published conference abstract by Yang and Tan (2014) found that IIV4-SD cost US$35 851 more than IIV3-SD for each QALY gained when community immunity was not considered during data analysis [136]. This ICER estimate decreased to US$32 660 per QALY gained when community immunity was incorporated into the analysis [136]. Without accounting for community immunity, studies may be undervaluing vaccine effectiveness and the associated incremental benefit of vaccination, and subsequently undervaluing the cost-effectiveness of the vaccine.

Other factors including vaccine wastage (which may decrease vaccine availability and supply), and the availability of various influenza vaccines each season were not accounted for in any of the included studies. Vaccine wastage refers to the under-usage of purchased vaccines or the over-purchase of a vaccine product, which typically expires after each influenza season. As an example, in Canada, seasonal influenza vaccines are available in multi-dose and single-dose formats [137]. Compared to single-dose formats, multi-dose formats have been associated with increased safety concerns, increased risk of contamination, and potentially higher costs associated with waste disposal, storage, and vaccine waste [138]. The incorporation

of programmatic factors such as vaccine wastage, the availability and use of multi-dose and single-dose formats, and the availability of different seasonal influenza vaccine products may impact costs, leading to changes in cost-effectiveness estimates.

The current review had several limitations. First, most of the identified economic evaluations on the use of seasonal influenza vaccines in older adults used IIV3-SD as the comparator. There is a need for future economic analyses to compare newer vaccine products with comparators that are currently available in Canada for older adults. For example, Canadian provinces such as Alberta, Ontario, Prince Edward Island, Saskatchewan, Nova Scotia, Yukon, and New Brunswick, among others, provide IIV4-HD to all adults 65 years of age and older as part of their publicly funded seasonal influenza vaccination programs [139-144]. Other vaccine interventions of interest for comparison include IIV4-cc, RIV4, IIV3-Adj, IIV4-SD, and IIV4-Adj are needed. Second, the majority of the included studies were funded by industry. In this review, findings from industry-funded studies (n=13, 68%) were similar to non-industry-funded studies. There is also a lack of cost-effectiveness estimates by age subgroups, presence of comorbidities, and frailty within the older adult population. Finally, vaccine prices vary by product and jurisdiction. As such, vaccine prices used in studies conducted outside of Canada may not be applicable to a Canadian setting.

V.2 Economic evaluation by the Comité sur l'immunisation du Québec

A high-level overview of the Comité sur l'immunisation du Québec (CIQ) economic evaluation (cost-utility analysis) is presented below. The economic exercise was 1 component of CIQ's decision-making. A literature review of vaccine efficacy was also conducted, which found no head-to-head RCT comparing IIV3-Adj and IIV-SD against LCI and found the observational literature for IIV3-Adj was not of high quality. CIQ concluded that there is insufficient evidence to support that IIV3-Adj is superior to IIV-SD or that rVE of IIV3-Adj is similar to IIV-HD.

V.2.1 Decision problem and methods

The analysis assessed the cost-effectiveness of vaccinating the older adult population (65 years of age and older) in Quebec using enhanced vaccines compared to standard dose vaccines for the prevention of influenza morbidity and mortality. In the CIQ analyses, the terminology of "enhanced vaccines" was used, not specific to either high-dose or adjuvanted vaccines. Rather, they referred to vaccines that were designed to enhanced immunogenicity. As such, the same terminology is used here in the reporting of CIQ results. The enhanced vaccines had the following hypothetical characteristics: relative vaccine effectiveness compared to standard dose between 0% and 100% (base case 25%); price differential compared to standard dose between $0 and $50 (base case $30); duration of protection of 1 year. The standard dose vaccines had a VE of 40% (base case). The vaccination program had 100% coverage. The study population was stratified by age (65 to 74 years of age vs. 75 years of age and older) and by the presence of at least 1 chronic illness that increases the risk of influenza complications (specific chronic illnesses not listed; proportion of population with at least 1 condition 52% among 65 to 74 years of age, and 58% for 75 years of age and older).

The analysis was conducted from a publicly funded health system perspective, which included costs of hospitalization, ICU, medications, and the vaccination program. Costs and consequences of caregivers and productivity loss of the study population were not included. The analysis used burden data and other parameters based on a CIQ influenza report from 2018 [145].

V.2.2 Summary of results

Results are presented as ICERs using QALYs as well as numbers of consultations, hospitalizations and deaths averted. All costs are reported in 2022 Canadian dollars. Results presented are discounted at 3% (which deviates from NACI and other Canadian recommendations of 1.5% for base case analysis), but also

presented at 0% (in line with NACI and other Canadian recommendations for sensitivity analysis) [93, 146]. Discounting allows the analysis to account for time preferences (i.e., costs and consequences in the future are usually valued less than the present).

The base case results showed that among individuals 65 to 74 years of age, enhanced vaccines prevented 571 consultations, 155 hospitalization, and 4 deaths compared to standard dose vaccine. Among people 75 years of age and older, enhanced vaccines prevented 541 consultations, 533 hospitalizations, and 28 deaths. Table 4 shows the ICERs of enhanced vaccines compared to standard dose among older adults in Quebec, stratified by age and by presence of chronic illness. ICERs of non-base case analyses were not reported.

Table 4. Cost-effectiveness of enhanced vaccines compared to standard dose among older adults in Quebec (base case analysis)

Demographic	ICER ($ per QALY), discounted at 3%	ICER ($ per QALY), undiscounted
All ages (65 years of age and older)	**NR**	**NR**
65 to 74 years of age, all	**609,927**	**480,604**
With chronic illness(es)	345,297	270,784
Without chronic illness(es)	2,648,381	2,166,967
75 years of age and older, all	**100,618**	**84,805**
With chronic illness(es)	56,173	47,308
Without chronic illness(es)	496,177	421,085

Abbreviations: ICER, incremental cost-effectiveness ratio; NR, not reported; QALY, quality-adjusted life year
Base case used a relative VE of 25% for enhanced vaccines, VE of 40% for standard dose, price differential of $30, duration of protection of 1 year, vaccine coverage of 100%.

Individuals 75 years of age and older with chronic illness had the lowest ICER (i.e., most value for money) (discounted: $56,173 per QALY) among the stratified study populations. The other stratified groups had ICERs over 6 times that ICER (discounted range: $345,297 per QALY to $2,648,381 per QALY).

V2.3 Discussion

Based on commonly used cost-effectiveness thresholds, the use of enhanced vaccines (relative VE of 25%) in Quebec does not appear to be cost-effective compared to standard dose. Of the 4 stratified groups, use of enhanced vaccines among individuals 75 years of age and older with chronic illness was the most cost-effective strategy compared to standard dose ($56,173 per QALY).

The presence of chronic illness appeared to drive the ICERs lower (i.e., better value for money), more so than older age. However, implementing a vaccination strategy to identify individuals by chronic illness may not be feasible. Conversely, implementing a vaccination strategy that is age-based does not appear cost-effective (ICERs for individuals 65 to 74 years of age versus 75 years of age and older were $609,927 per QALY and $100,618 per QALY, respectively) in this analysis.

While the analysis used a previously recommended discount rate of 3% instead of current recommendations of 1.5% (as of 2017 and 2023) [93, 146], the discount rate does not appear to be an influential parameter as it did not change the results of enhanced vaccines from being not cost-effective to markedly cost-effective.

Results from the Quebec economic evaluation may be generalizable to other provinces and territories unless the decision-maker believes the epidemiology or health system costs are marked differently across Canadian jurisdictions. The authors of the analysis noted that the majority of model inputs were based on

parameters from the CIQ influenza report from 2018 [145]; hence, it is possible that there are changes in disease burden or changes in the management of the health system not reflected in the analysis.

As noted, cost-effectiveness is 1 consideration in CIQ's decision-making. Based on the clinical literature review, CIQ found that there was insufficient evidence to support that vaccine efficacy of adjuvanted vaccine is superior to that of standard dose. Based on the totality of evidence, CIQ preferentially recommends high dose vaccine over adjuvanted vaccine and standard dose vaccine for people 75 years of age and older with chronic illnesses. Given implementation considerations, CIQ recommends that high dose vaccine may be offered to all people 75 years of age and older despite the much higher costs and lack of cost-effectiveness.

VI. DISCUSSION

The present statement comprehensively examines the available evidence on the efficacy, effectiveness, and safety of influenza vaccines designed to enhance protection in older adults (i.e., IIV-HD and IIV-Adj), as well as those leveraging technology and heightened antigen concentrations to increase immune responses (i.e., RIV). The analysis focused on comparisons and evidence from studies conducted during regular influenza seasons. Only influenza vaccines approved for older adults were included, with the primary research question comparing IIV-HD, IIV-Adj, RIV and IIV-cc to IIV-SD, as well as against each other, to determine their relative performance in adults 65 years of age and older. Of note, no study included in this review compared IIV-cc to other influenza vaccines. RCTs identified in the DSEN MAGIC review that addressed IIV-cc did not report on critical outcomes or meaningful vaccine comparisons involving the desired vaccines of interest within their corresponding study arms [147-149]. Furthermore, the review conducted by ACIP did not evaluate evidence on IIV-cc. Consequently, it was not possible to make a recommendation on the preferential use of IIV-cc in adults 65 years of age and older.

Overall, the results presented suggest a general trend favouring influenza vaccines aimed at enhancing protection for older adults, pointing to potential benefits associated with IIV-HD, IIV-Adj, and RIV when compared to IIV-SD, with most available evidence for IIV-HD. However, evidence comparing IIV-HD, IIV-Adj and RIV to one another is limited. Both the ACIP and DSEN MAGIC reviews found that IIV-HD was approximately 25% more effective than IIV-SD against LCI (relative vaccine efficacy of 24%, 95% CI: 10 to 36%; and pooled relative vaccine efficacy of 25%, 95% CI: 12 to 37%, respectively). For RIV, DSEN MAGIC and ACIP reported a pooled relative vaccine efficacy for RIV versus IIV-SD of 30% (95% CI: -18 to 58%) and 18% (95% CI: -17 to 43%) against LCI, respectively.

However, there were no studies available reporting on the efficacy or effectiveness of IIV-Adj compared to IIV-SD against LCI. ACIP reported 2 meta-analyses of observational studies comparing IIV-Adj to IIV-SD against influenza-associated outpatient/ED visits defined by clinical diagnosis. One (1) meta-analysis of 2 studies demonstrated a beneficial protective effect of IIV-Adj compared to IIV-SD against influenza-associated outpatient/ED visits (pooled rVE of 36%, 95% CI: 21 to 48%). However, another meta-analysis of 2 retrospective cohort studies did not identify a difference between IIV-Adj and IIV-SD against this outcome (pooled rVE of 0%, 95% CI: -9 to 3%).

Nevertheless, IIV-Adj demonstrated effectiveness in reducing influenza-associated hospitalizations compared to IIV-SD in 2 meta-analyses of observational studies (pooled rVE of 12%, 95% CI: 3 to 20% and 25%, 95% CI: 3 to 42%). There are few RCTs comparing IIV-HD, IIV-Adj, and RIV to one another against LCI. Notably, both reviews did not demonstrate a beneficial protective effect against LCI associated with IIV-HD, IIV-Adj and RIV compared to one another due to the wide confidence intervals associated with the vaccine efficacy estimates. While the results from both reviews suggest potential advantages associated with IIV-HD, IIV-Adj and RIV compared to IIV-SD, the current available evidence directly comparing these vaccines to one another is insufficient to establish with certainty that 1 vaccine consistently outperforms the others.

This review also examined the comparative safety of seasonal influenza vaccines. Data for IIV-HD, IIV-Adj, and RIV against IIV-SD demonstrated a comparable safety profile with regards to SAEs. However, recipients of IIV-HD and IIV-Adj exhibited a higher frequency of injection site and systemic events when compared with those receiving IIV-SD. Conversely, evidence regarding RIV did not indicate an increase in injection site or systemic events in comparison to IIV-SD.

The NACI Secretariat applied the Committee's EEFA Framework to assess the implications of ethics, equity, feasibility, and acceptability of its recommendation on influenza vaccination in adults 65 years of age and older in Canada. There were no potential inequities or ethical considerations identified that could arise with the recommendation of age-appropriate preferential use of high-dose, adjuvanted, recombinant influenza vaccines. In fact, acceptability may be increased for certain sub-groups (i.e., frailty) who benefit by the preferential vaccine's real or perceived increased efficacy. Potential feasibility issues for providers

and policymakers are limited to the increased costs of the preferred vaccines but as these vaccines are already in use across some jurisdictions this is unlikely a wide-spread issue.

In addition to EEFA factors, economic considerations were evaluated to supplement the evidence base for programmatic factors. Published economic assessment determined that both IIV3-HD and IIV3-Adj are cost-effective in comparison to IIV3-SD. No economic evidence was available for RIV, resulting in the absence of data reporting on RIV's cost-effectiveness when compared to IIV-SD. Moreover, no economic evidence identified in this review directly compared IIV-HD, IIV-Adj and RIV to one another.

One (1) notable limitation in both reviews is the absence of data on frail older adults, an important factor for understanding the impact of influenza vaccination in adults 65 years of age and older at higher risk of severe influenza-related outcomes and complications. The efficacy and effectiveness of influenza vaccines in older adults can vary due to multiple factors, which may be more pronounced among frail older adults. As adults age, immune function declines, increasing the vulnerability to influenza infection and related complications [115-118].

Furthermore, among older age groups, an increase is observed in both the average number of comorbidities present, and the level of frailty exhibited. Individuals living with elevated levels of frailty, or 1 or more comorbidities are at increased risk for severe influenza-related outcomes, including hospitalizations, functional decline, and death following infection. Nonetheless, due to the complexities of the frailty spectrum, influenza-related morbidity in frail older adults might be underestimated [20, 123-125]. Limited studies exist that provide insights into the impact of influenza vaccines among frail older adults. Notably, 2 RCTs conducted in the US and Canada reported decreasing vaccine efficacy with increasing frailty, indicating an association between frailty and lower protection against influenza infection and its complications [133, 150].

A similar trend was observed in a case-control study comparing vaccine effectiveness in patients with low vs. high frailty scores, showing lower VE among those with higher scores [151]. Additionally, despite the previously reported reduced vaccine efficacy in frail older adults, DiazGranados et al. reported favourable relative efficacy for IIV-HD over IIV-SD in this population [150]. A recent test-negative study conducted in Canada found, in an exploratory analysis, a higher relative vaccine effectiveness comparing IIV-Adj to IIV-SD against LCI hospitalization among adults 65 years of age and older after accounting for frailty (rVE of 25%,95% CI: 8 to 39%) [152]. Similarly, Nace et al. reported higher geometric mean titers and seroconversion rates associated with IIV-HD as opposed to IIV-SD in frail residents of long-term care facilities [78]. These findings provide reassurance that the greater efficacy of IIV-HD and IIV-Adj observed across the literature in the general older population remains consistent in frail older adults. The mentioned studies offer valuable insight into the relationship between frailty and influenza vaccine efficacy/effectiveness. As frailty increases, influenza vaccine effectiveness and the probability of recovering from influenza infection tend to decline. However, the cited studies show a trend of improved vaccine protection associated with IIV-HD and IIV-Adj compared to IIV-SD among frail older adults. Taken together, these findings highlight the potential benefits of administering influenza vaccines designed to enhance protection in older adults to reduce the burden of influenza illness within this population. As further research is required, some of the following methodological considerations may be pertinent to the older adult population. For instance, the presence of a "frailty bias" in studies of vaccine efficacy/effectiveness – that is, the differential susceptibility to adverse health outcomes due to frailties, underlines the importance of accounting for frailty as a confounding factor in future research on influenza vaccines in older adults. Frail older adults tend to be under-represented in trials, especially RCTs; hence, literature reviews and meta-analyses that focus only on RCTs will tend to not fully represent frail populations - even if they do attempt to include a frailty measure. As such, well-designed and rigorously conducted observational studies continue to play an important role.

Other limitations include the limited number of studies reporting on the vaccine of interest; limited number of influenza seasons represented within each comparison; variability of vaccine formulations between influenza seasons; differences in outcome definitions within the 2 reviews; downgrading of certainty due to study design; and imprecise effect estimates. Most available studies focused on IIV-HD, less on IIV-Adj, while data on RIV was limited. The limited number of studies available per comparison resulted in the inclusion of a low number of influenza seasons for each, especially for pooled-effect estimates involving RCT data, which can affect the generalizability of the results. Another contributing factor influencing the

generalizability of findings is the variability in vaccine effectiveness in each influenza season. The differences in outcome definitions between the reviews are mostly attributed to the inclusion of influenza outcomes defined by LCI, clinical diagnostic or ILI in both reviews, leading to challenges in summarizing and interpreting the results due to differences in sensitivity, specificity, and the susceptibility to misclassification bias of the different influenza case definitions. Another difference between ACIP's review and DSEN MAGIC's is that DSEN MAGIC included only RCTs, which generally tend to exclude older and frailer adults. As such, downgrading certainty due to observational study design and imprecise effect estimates presents a limitation as it may make interpretation of the results less robust.

While randomized trials generally provide the highest certainty of evidence as they are less susceptible to bias, they are usually conducted over few influenza seasons. Therefore, it cannot be assumed that results from 1 or few seasons will be generalizable to all or most seasons due to the constant evolution of influenza viruses. Observational studies are more numerous and bring other advantages including representation of larger and more diverse populations and results across a larger range of influenza seasons than RCTs. Hence, it is important to recognize the value of observational studies in providing a more comprehensive understanding of the relative benefits of IIV-HD, IIV-Adj and RIV to one another and to IIV-SD within the real-world setting despite providing lower certainty of evidence.

VII. RECOMMENDATIONS

Following the thorough review of available evidence summarized above, as well as the assessment of ethics, equity, feasibility, and acceptability considerations with the EEFA Framework, the following section outlines the evidence-informed recommendation made by NACI regarding the use of influenza vaccines in adults 65 years of age and older. NACI will continue to carefully monitor the scientific developments related to influenza vaccines, as well as ongoing vaccine pharmacovigilance, and will update recommendations as evidence evolves.

Please note:

- A *strong recommendation* applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present
- A *discretionary recommendation* may be considered for some populations/individuals in some circumstances. Alternative approaches may be reasonable

Please see Table 8 for a more detailed explanation of strength of NACI recommendations and grade of the body of evidence.

The following recommendation for population-level and individual-level vaccination decisions regarding annual influenza vaccination for adults 65 years of age and older supplements NACI's overarching recommendation for influenza vaccination, available in the NACI Seasonal Influenza Vaccine Statement, which is that an age-appropriate influenza vaccine should be offered annually to anyone 6 months of age and older (Strong NACI Recommendation), noting product-specific contraindications.

1. NACI recommends that IIV-HD, IIV-Adj, or RIV should be offered over other influenza vaccines for adults 65 years of age and older. If a preferred product is not available, any of the available age-appropriate influenza vaccine should be used. (Strong NACI Recommendation)

- Where supply of IIV-HD, IIV-Adj, or RIV is limited, consideration can be given to prioritizing groups at highest risk of severe outcomes from influenza among adults 65 years of age and older, such as advanced-age older adults (e.g., 75 years of age and older), those with 1 or more comorbidities, older frail adults, and residents of nursing homes and other chronic care facilities.

Summary of evidence and rationale:

- IIV-HD, IIV-Adj, and RIV appear to have increased vaccine efficacy/effectiveness as compared to IIV-SD.
- No definitive conclusion can be reached regarding the superiority of any of these vaccines over one another as there is a limited number of studies directly comparing IIV-HD, IIV-Adj, and RIV against each other. Notably, IIV-HD has the most substantial body of supporting evidence, followed by IIV-Adj, and then RIV.
- IIV-HD, IIV-Adj, and RIV are effective alternatives to IIV-SD, with no identified difference in safety, based on direct evidence among adults 65 years of age and older.
- IIV-HD and IIV-Adj are cost-effective when compared to IIV-SD.

VIII. RESEARCH PRIORITIES

Research to address the following outstanding knowledge gaps is encouraged:

- Additional safety, efficacy, and effectiveness data for newer vaccine technologies, including cell culture and recombinant influenza vaccines among adults 65 years of age and older.
- Vaccine comparisons (pairwise or comparisons between multiple vaccines) of safety, efficacy and effectiveness between newer influenza vaccines approved for use among adults aged 65 years and older that are currently available in the Canadian market (e.g., IIV-cc, RIV, IIV-Adj, IIV-SD, and IIV-HD).
- Data on the efficacy and effectiveness of influenza vaccines in subpopulations of adults 65 years of age and older at higher risk of severe influenza-related outcomes and complications, such as older adults, individuals living with 1 or more chronic medical conditions, and that consider the role of frailty in older adults.
- Consideration of frailty on VE estimates and the impact of longer-term functional outcomes among adults 65 years of age and older.
- National-level influenza surveillance data among adults 65 years of age and older in Canada, which will help to better define the burden of disease for older adults, especially those at higher risk of severe influenza-related outcomes, such as individuals living with 1 or more chronic medical conditions, and frail older adults.
- Timing of influenza immunization in adults 65 years of age and older with respect to duration or waning of protection against infection and severe disease.
- Incorporation and investigation of the impact of community immunity on cost-effectiveness of seasonal influenza vaccines among adults 65 years of age and older.
- Consideration of frailty into cost-effectiveness and the impact of longer-term functional outcomes.
- Vaccine confidence and acceptability among adults 65 years of age and older in Canada, especially among racialized groups.
- Range and complex interplay of factors that influence acceptability of influenza immunization in general and for high-risk groups among adults 65 years of age and older.

IX. SURVEILLANCE ISSUES

Ongoing and systematic data collection, analysis, interpretation, and timely dissemination is fundamental to planning, implementation, evaluation, and evidence-based decision-making. To support such efforts, NACI encourages ongoing surveillance and continued expansion of surveillance details in the epidemiology of influenza in Canada.

In Canada, FluWatch, the national surveillance system, monitors the spread of influenza and influenza-like illness (ILI) by province/territory and age group, including adults 65 years of age and older. Robust enhanced surveillance data including health status and granularity for older age groups, who might be at higher risk of severe influenza-related outcomes due to the decline in immune function is limited. Therefore, initiatives are needed to collect data on influenza infection (e.g., ILI and LCI incidence, viral strain, hospitalization, detailed health status including frailty, and assessment of outcomes over both short- and long- time horizons) from adults 65 years of age and older who are at higher risk of severe influenza-related outcomes, to determine vaccine effectiveness in these groups and to inform appropriate public health efforts such as targeted vaccination campaigns and education. Importantly, increased use of enhanced influenza vaccine products will underscore the need for ongoing surveillance and research on product-specific effectiveness as well as continued rigorous product-specific safety monitoring. It will thus be all the more important to ensure robust and feasible means of verifying which product a person has received, such as through immunization registries that can be readily linked to both clinical and administrative data.

X. TABLES

Table 5. Summary of evidence for NACI recommendation(s)

Study details					
Study	**Outcome**	**Vaccine**	**Study design**	**Participants (n/N)**	**Summary of key findings**
Efficacy					
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Lab-confirmed influenza (LCI)	IIV3-HD vs. IIV-SD	RCT (n=1)	IIV3-HD: n=228/15,990 (1.4%) IIV-SD: n= 301/15,993 (1.9%)	The relative effect estimate (95% CI) was a RR: 0.76 (0.64 to 0.90)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Influenza-like illness (ILI)	IIV3-Adj vs. IIV-SD	RCT (n=1)	IIV3-Adj: n= 322/3479 (9.3%) IIV-SD: n=314/3482 (9.0%)	The relative effect estimate (95% CI) was a RR: 1.03 (0.89 to 1.19)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Lab-confirmed influenza (LCI)	RIV3 vs. IIV-SD	RCT (n=2)	RIV3: n= 53/2168 (2.4%) IIV-SD: n=64/2143 (3.0%)	The pooled relative effect estimate (95% CI) was a RR: 0.82 (0.57 to 1.17)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Lab-confirmed influenza (LCI)	IIV3-HD vs. IIV3-Adj	RCT (n=1)	IIV3-HD: n= 1/29 (3.4%) IIV3-Adj: n=3/30 (10.0%)	The relative effect estimate (95% CI) was a RR: 0.34 (0.04 to 3.13)

Study details					
Study	**Outcome**	**Vaccine**	**Study design**	**Participants (n/N)**	**Summary of key findings**
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Lab-confirmed influenza (LCI)	IIV3-HD vs. RIV4	RCT (n= 1)	IIV3-HD: n= 1/29 (3.4%) RIV4: n=4/30 (13.3%)	The relative effect estimate (95% CI) was a RR: 0.26 (0.03 to 2.18)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Lab-confirmed influenza (LCI)	IIV-Adj vs. RIV4	RCT (n= 1)	IIV-Adj: n= 3/30 (10.0%) RIV4: n= 4/30 (13.3%)	The relative effect estimate (95% CI) was a RR: 0.75 (0.18 to 3.07)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Influenza hospitalization	IIV3-HD vs. IIV-SD	RCT (n= 2)	IIV3-HD: n=14/18,596 (0.1%) IIV-SD: n=14/18,597 (0.1%)	The relative pooled effect estimate (95% CI) was a RR: 1.00 (0.48 to 2.09)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Influenza hospitalization	IIV3-HD vs. IIV-SD	Cluster RCT (n= 1)	IIV3-HD: n=247/19,127 IIV-SD: n=309/19,129	The relative effect estimate (95% CI) was a rate ratio of 0.79 (0.66 to 0.95)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Influenza hospitalization	IIV3-Adj vs. IIV-SD	RCT (n= 1)	IIV3-Adj: n=242/24,926 IIV-SD: n=309/25,806	The relative effect estimate (95% CI) was a rate ratio of 0.79 (0.65 to 0.96)

Study details					
Study	**Outcome**	**Vaccine**	**Study design**	**Participants (n/N)**	**Summary of key findings**
Veroniki/Tricco et al. (2023) [15] *Efficacy of the trivalent and quadrivalent influenza vaccines relative to one another among adults 60 years of age and older: A systematic review and network meta-analysis.* Submitted.	Lab-confirmed influenza (LCI)	IIV3-HD vs. IIV3-SD	RCT (n=3)	IIV3-HD: n=252/22,394 IIV3-SD: n=329/19,359	The relative pooled-effect estimate (95% CI) was an OR: 0.75 (0.63 to 0.88)
Veroniki/Tricco et al. (2023) [15] *Efficacy of the trivalent and quadrivalent influenza vaccines relative to one another among adults 60 years of age and older: A systematic review and network meta-analysis.* Submitted.	Lab-confirmed influenza (LCI)	RIV vs. IIV-SD	RCT (n=2)	RIV: n= -/- IIV-SD: n= -/-	The relative pooled effect estimate (95% CI) was an OR: 0.70 (0.42 to 1.18)
Veroniki/Tricco et al. (2023) [15] *Efficacy of the trivalent and quadrivalent influenza vaccines relative to one another among adults 60 years of age and older: A systematic review and network meta-analysis.* Submitted.	Influenza-like illness (ILI)	IIV-HD vs. IIV-SD	RCT (n=3)	IIV-HD: n=-/41,209 IIV-SD: n=-/41,209	The relative pooled effect estimate (95% CI) was an OR: 0.98 (0.93 to 1.02)
Veroniki/Tricco et al. (2023) [15] *Efficacy of the trivalent and quadrivalent influenza vaccines relative to one another among adults 60 years of age and older: A systematic review and network meta-analysis.* Submitted.	Influenza-like illness (ILI)	RIV vs. IIV-SD	RCT (n=1)	RIV4: n= -/9003 IIV4-SD: n= -/9003	The relative effect estimate (95% CI) was an OR: 0.99 (0.89 to 1.09)
Veroniki/Tricco et al. (2023) [15] *Efficacy of the trivalent and quadrivalent influenza vaccines relative to one another among adults 60 years of age and older: A systematic review and network meta-analysis.* Submitted.	Influenza-like illness (ILI)	RIV vs. IIV-SD	RCT (n=1)	RIV3: n= -/870 IIV3-SD: n= -/870	The relative effect estimate (95% CI) was an OR: 0.96 (0.55 to 1.65)
Veroniki/Tricco et al. (2023) [15] *Efficacy of the trivalent and quadrivalent influenza vaccines relative to one another among adults 60 years of age and older: A systematic review and network meta-analysis.* Submitted.	Influenza-like illness (ILI)	IIV3-Adj vs. IIV3-SD	RCT (n=1)	IIV3-Adj: n= -/6961 IIV3-SD n= -/6961	The relative effect estimate (95% CI) was an OR: 1.03 (0.87 to 1.21)

Study details					
Study	**Outcome**	**Vaccine**	**Study design**	**Participants (n/N)**	**Summary of key findings**
Veroniki/Tricco et al. (2023) [15] *Efficacy of the trivalent and quadrivalent influenza vaccines relative to one another among adults 60 years of age and older: A systematic review and network meta-analysis.* Submitted.	Hospitalization for LCI	IIV3-HD vs. IIV4-SD	RCT (n=1)	IIV3-HD: n= -/68 IIV4-SD: n= -/68	The relative effect estimate (95% CI) was an OR: 1 (0.06 to 16.7)
Veroniki/Tricco et al. (2023) [15] *Efficacy of the trivalent and quadrivalent influenza vaccines relative to one another among adults 60 years of age and older: A systematic review and network meta-analysis.* Submitted.	Hospitalization for LCI	IIV3-HD vs. IIV3-SD	RCT (n=1)	IIV3-HD: n= -/31,983 IIV3-SD: n= -/31,983	The relative effect estimate (95% CI) was an OR: 0.6 (0.22 to 1.65)
Veroniki/Tricco et al. (2023) [15] *Efficacy of the trivalent and quadrivalent influenza vaccines relative to one another among adults 60 years of age and older: A systematic review and network meta-analysis.* Submitted.	Hospitalization for LCI	RIV4 vs. IIV4-SD	RCT (n=1)	RIV4: n= -/ 9,003 IIV4-SD: n= -/9003	The relative effect estimate (95% CI) was an OR: 0.33 (0.04 to 3.21)
Veroniki/Tricco et al. (2023) [15] *Efficacy of the trivalent and quadrivalent influenza vaccines relative to one another among adults 60 years of age and older: A systematic review and network meta-analysis.* Submitted.	Hospitalization for ILI	IIV3-HD vs. IIV3-SD	RCT (n=2)	IIV3-HD: n=127/22,098 IIV3-SD: n=155/19,043	The relative pooled effect estimate (95% CI) was an OR: 0.72 (0.57 to 0.92)
Veroniki/Tricco et al. (2023) [15] *Efficacy of the trivalent and quadrivalent influenza vaccines relative to one another among adults 60 years of age and older: A systematic review and network meta-analysis.* Submitted.	Outpatient Visit	IIV3-HD vs. IIV3-SD	RCT (n=1)	IIV3-HD: n=439/6108 IIV3-SD: n=226/3050	The relative effect estimate (95% CI) was an OR: 0.97 (0.82 to 1.14)

Study details					
Study	**Outcome**	**Vaccine**	**Study design**	**Participants (n/N)**	**Summary of key findings**
Veroniki/Tricco et al. (2023) [15] *Efficacy of the trivalent and quadrivalent influenza vaccines relative to one another among adults 60 years of age and older: A systematic review and network meta-analysis.* Submitted.	Number of vascular events	IIV3-HD vs. IIV3-SD	RCT (n=4)	IIV3-HD: n=166/23,551* IIV3-SD: n= 169/19,847* *person-time	The relative pooled effect estimate (95% CI) was a rate ratio of 0.75 (0.43 to 1.29)
Veroniki/Tricco et al. (2023) [15] *Efficacy of the trivalent and quadrivalent influenza vaccines relative to one another among adults 60 years of age and older: A systematic review and network meta-analysis.* Submitted.	Number of vascular events	IIV3-Adj vs. IIV3-SD	RCT (n=2)	IIV3-Adj: n=39/3422* IIV3-SD: n= 47/3427* *person-time	The relative pooled effect estimate (95% CI) was a rate ratio of 0.83 (0.54 to 1.27)
Veroniki/Tricco et al. (2023) [15] *Efficacy of the trivalent and quadrivalent influenza vaccines relative to one another among adults 60 years of age and older: A systematic review and network meta-analysis.* Submitted.	Number of vascular events	RIV4 vs. IIV4-SD	RCT (n=1)	RIV4: n= -/ 9,003 IIV4-SD: n= -/9003 Total N= 9,003	The relative effect estimate (95% CI) was an OR: 0.89 (0.30 to 2.60)
Veroniki/Tricco et al. (2023) [15] *Efficacy of the trivalent and quadrivalent influenza vaccines relative to one another among adults 60 years of age and older: A systematic review and network meta-analysis.* Submitted.	Influenza-related death	IIV3-Adj vs. IIV3-SD	RCT (n=1)	IIV3-Adj: n= -/6961 IIV3-SD: n= -/6961 Total N= 6,961	The relative effect estimate (95% CI) was an OR: 0.75 (0.17 to 3.36)
Veroniki/Tricco et al. (2023) [15] *Efficacy of the trivalent and quadrivalent influenza vaccines relative to one another among adults 60 years of age and older: A systematic review and network meta-analysis.* Submitted.	Lab-confirmed influenza (LCI)	IIV-HD vs. IIV-Adj	RCT (n=1)	IIV-HD: n= -/152 IIV-Adj: n= -/152 Total N= 152	The relative effect estimate (95% CI) was an OR: 3.1 (0.30 to 31.8)

Study details					
Study	**Outcome**	**Vaccine**	**Study design**	**Participants (n/N)**	**Summary of key findings**
Veroniki/Tricco et al. (2023) [15] *Efficacy of the trivalent and quadrivalent influenza vaccines relative to one another among adults 60 years of age and older: A systematic review and network meta-analysis.* Submitted.	Lab-confirmed influenza (LCI)	RIV vs. IIV-Adj	RCT (n=1)	RIV: n= -/89 IIV-Adj: n= -/89	The relative effect estimate (95% CI) was an OR: 0.72 (0.15 to 3.54)
Veroniki/Tricco et al. (2023) [15] *Efficacy of the trivalent and quadrivalent influenza vaccines relative to one another among adults 60 years of age and older: A systematic review and network meta-analysis.* Submitted.	Lab-confirmed influenza (LCI)	RIV vs. IIV-HD	RCT (n=1)	RIV: n= -/89 IIV-HD: n=-/89 Total N= 89	The relative effect estimate (95% CI) was an OR: 0.23 (0.02 to 2.20)
Effectiveness					
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Influenza hospitalization	IIV3-HD vs. IIV-SD	Observational (n= 8)	IIV3-HD: n=-/43519,865* IIV-SD: n=-/20193,377* *person-time	The relative pooled effect estimate (95% CI) was a rate ratio of 0.92 (0.90 to 0.94)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Influenza hospitalization	IIV3-HD vs. IIV-SD	Observational (n= 2)	IIV3-HD: n=177/24,334 (0.7%) IIV-SD: n=201/24,197 (0.8%)	The relative pooled effect estimate (95% CI) was RR: 0.71 (0.57 to 0.88)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Influenza hospitalization	IIV3-Adj vs. IIV-SD	Observational (n= 4)	IIV3-Adj: n=/6,133,023* IIV-SD: n=-/4,861,653* *person-time	The relative pooled effect estimate (95% CI) was a rate ratio of 0.88 (0.80 to 0.97)

Study details					
Study	**Outcome**	**Vaccine**	**Study design**	**Participants (n/N)**	**Summary of key findings**
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Influenza hospitalization	IIV3-Adj vs. IIV-SD	Observational (n= 2)	IIV3-Adj: n=230/85,483 IIV-SD: n=35/79,610	The relative pooled effect estimate (95% CI) was a rate ratio of 0.75 (0.58 to 0.97)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Influenza hospitalization	RIV3 vs. IIV-SD	Observational (n=1)	RIV3: n=640/608,433 IIV-SD: n=2,309/1,584,451	The relative effect estimate (95% CI) was a rate ratio of 0.83 (0.76 to 0.91)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Influenza hospitalization	IIV3-HD vs. IIV-Adj	Observational (n= 4)	IIV3-HD: n=-/25,467,741* IIV-Adj: n=-/6,356,816* *person-time	The relative pooled effect estimate (95% CI) was a rate ratio of 0.96 (0.90 to 1.01)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Influenza hospitalization	IIV3-HD vs. RIV	Observational (n= 1)	IIV3-HD: n=81,492/7,173,433 RIV: n=640/608,433	The relative effect estimate (95% CI) was a rate ratio of 1.12 (1.03 to 1.21)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Influenza hospitalization	IIV-Adj vs. RIV	Observational (n= 1)	IIV-Adj: n=2,783/2,565,513 RIV: n=640/608,433	The relative effect estimate (95% CI) was a rate ratio of 1.12 (1.03 to 1.22)

Study details					
Study	**Outcome**	**Vaccine**	**Study design**	**Participants (n/N)**	**Summary of key findings**
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Influenza outpatient and/or ED visits	IIV3-Adj vs. IIV-SD	Observational (n= 2)	IIV3-Adj: n=-/1,701,231* IIV-SD: n=-/2,035,149* *person-time	The relative pooled effect estimate (95% CI) indicated a rate ratio of 1.00 (0.97 to 1.03)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Influenza outpatient and/or ED visits	IIV3-Adj vs. IIV-SD	Observational (n= 2)	IIV3-Adj: n=344/1333 IIV-SD: n=197/988	The relative pooled effect estimate (95% CI) was RR: 0.64 (0.52 to 0.79)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Influenza outpatient and/or ED visits	IIV3-HD vs. IIV-SD	Observational (n= 1)	IIV3-HD: n= 593/3141 (18.9%) IIV-SD: n= 580/2840 (20.4%)	The relative pooled effect estimate (95% CI) was RR: 0.91 (0.73 to 1.12)
Grohskopf et al. (2022) [16] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Influenza outpatient and/or ED visits	IIV3-HD vs. IIV-SD	Observational (n= 4)	IIV3-HD: n=-/11,001,581* IIV-SD: n=-/5,658,869* * person-time	The relative pooled effect estimate (95% CI) was a rate ratio of 0.87 (0.76 to 0.99)
Grohskopf et al. (2022) [16] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Influenza outpatient and/or ED visits	IIV3-HD vs. IIV3-Adj	Observational (n=3)	IIV3-HD: n=-/11,430,788* IIV-Adj: n=-/2,262,474* * person-time	The relative pooled effect estimate (95% CI) was a rate ratio of 1.06 (0.92 to 1.23)

Study details					
Study	**Outcome**	**Vaccine**	**Study design**	**Participants (n/N)**	**Summary of key findings**
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Influenza-related death	IIV3-HD vs. IIV-SD	Observational (n= 2)	IIV3-HD: n= -/2,755,395* IIV-SD: n= -/3,922,569* *person-time	The relative pooled effect estimate (95% CI) was a rate ratio of 0.69 (0.57 to 0.84)
Safety					
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Any Serious Adverse Event	IIV3-HD vs. IIV-SD	RCT (n=7)	IIV3-HD: n=1,518/22,109 (6.7%) IIV-SD: n=1,582/20,811 (7.5%)	The relative effect estimate (95% CI) was RR: 0.91 (0.85 to 0.97)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Any Serious Adverse Event	IIV3-Adj vs. IIV-SD	RCT (n=8)	IIV3-Adj: n=300/5266 (5.7%) IIV-SD: n=277/5055 (5.5%)	The relative effect estimate (95% CI) was RR: 1.07 (0.92 to 1.26)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Any Serious Adverse Event	RIV3 vs. IIV-SD	RCT (n=5)	RIV3: n=191/6513 (2.9%) IIV-SD: n=190/6697 (2.8%)	The relative effect estimate (95% CI) was RR: 1.03 (0.84 to 1.26)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Any Serious Adverse Event	IIV3-HD vs. IIV3-Adj	RCT (n=2)	IIV3-HD: n=13/887 (1.5%) IIV3-Adj: n=20/886 (2.3%)	The relative effect estimate (95% CI) was RR: 0.65 (0.32 to 1.30)

Study details					
Study	**Outcome**	**Vaccine**	**Study design**	**Participants (n/N)**	**Summary of key findings**
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Any Serious Adverse Event	IIV3-HD vs. RIV	RCT (n=2)	IIV3-HD: n=16/663 (2.4%) RIV: n=7/486 (1.4%)	The relative effect estimate (95% CI) was RR: 1.77 (0.73 to 4.27)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Any Serious Adverse Event	IIV-Adj vs. RIV	RCT (n=1)	IIV-Adj: n=11/508 (2.2%) RIV: n=4/335 (1.2%)	The relative effect estimate (95% CI) was RR: 1.81 (0.58 to 5.65)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Guillain-Barré syndrome	IIV3-Adj vs. IIV-SD	RCT (n= 1)	IIV3-Adj: n=0/3545 (0.0%) IIV-SD: n=1/3537 (0.0%)	The relative effect estimate (95% CI) was RR: 0.33 (0.01 to 8.16)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Guillain-Barré syndrome	IIV3-Adj vs. IIV-SD	Observational (n= 1)	IIV3-Adj: n=0/88,449 (0.0%) IIV-SD: n=0/82,539 (0.0%)	The relative effect estimate was not estimable
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Solicited injection site events grade 3 or higher	IIV3-HD vs. IIV-SD	RCT (n=2)	IIV3-HD: n=7/560 (1.3%) IIV-SD: n=1/559 (0.2%)	The relative effect estimate (95% CI) was RR: 5.03 (0.88 to 28.74)

Study details					
Study	**Outcome**	**Vaccine**	**Study design**	**Participants (n/N)**	**Summary of key findings**
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Solicited injection site events grade 3 or higher	IIV3-Adj vs. IIV-SD	RCT (n=4)	IIV3-Adj: n=18/952 (1.9%) IIV-SD: n=5/957 (0.5%)	The relative effect estimate (95% CI) was RR: 3.39 (1.32 to 8.72)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Solicited injection site events grade 3 or higher	RIV3 vs. IIV-SD	RCT (n=2)	RIV3: n=7/771 (0.9%) IIV-SD: n=11/941 (1.2%)	The relative effect estimate (95% CI) was RR: 0.67 (0.27 to 1.69)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Solicited injection site events grade 3 or higher	IIV3-HD vs. IIV3-Adj	RCT (n=2)	IIV3-HD: n=15/887 (1.7%) IIV3-Adj: n=17/886 (1.9%)	The relative effect estimate (95% CI) was RR: 0.88 (0.45 to 1.75)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Solicited injection site events grade 3 or higher	IIV3-HD vs. RIV	RCT (n=2)	IIV3-HD: n=4/663 (0.6%) RIV: n=0/486 (0.0%)	The relative effect estimate (95% CI) was RR: 5.92 (0.32 to 109.56)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Solicited injection site events grade 3 or higher	IIV-Adj vs. RIV	RCT (n=1)	IIV-Adj: n=3/508 (0.6%) RIV: n=0/335 (0.0%)	The relative effect estimate (95% CI) was RR: 4.62 (0.24 to 89.17)

Study details					
Study	**Outcome**	**Vaccine**	**Study design**	**Participants (n/N)**	**Summary of key findings**
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Solicited systemic events grade 3 or higher	IIV3-HD vs. IIV-SD	RCT (n=2)	IIV3-HD: n=3/766 (0.4%) IIV-SD: n=3/767 (0.4%)	The relative effect estimate (95% CI) was RR: 0.95 (0.20 to 4.53)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Solicited systemic events grade 3 or higher	IIV3-Adj vs. IIV-SD	RCT (n=4)	IIV3-Adj: n=10/1016(1.0%) IIV-SD: n=13/1026 (1.3%)	The relative effect estimate (95% CI) was RR: 0.77 (0.34 to 1.76)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Solicited systemic events grade 3 or higher	RIV3 vs. IIV-SD	RCT (n=2)	RIV3: n=1/771 (0.1%) IIV-SD: n=6/941 (0.6%)	The relative effect estimate (95% CI) was RR: 0.28 (0.05 to 1.67)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Solicited systemic events grade 3 or higher	IIV3-HD vs. IIV3-Adj	RCT (n=2)	IIV3-HD: n=8/887 (0.9%) IIV3-Adj: n=11/886 (1.2%)	The relative effect estimate (95% CI) was RR: 0.73 0.29 to 1.80)
Grohskopf et al. (2022) [14] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Solicited systemic events grade 3 or higher	IIV3-HD vs. RIV4	RCT (n=2)	IIV3-HD: n=4/663 (0.6%) RIV4: n=4/486 (0.8%)	The relative effect estimate (95% CI) was RR: 0.86 (0.22 to 3.32)

Study details					
Study	**Outcome**	**Vaccine**	**Study design**	**Participants (n/N)**	**Summary of key findings**
Grohskopf et al. (2022) [16] *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season.* MMWR Recomm Rep 2022	Solicited systemic events grade 3 or higher	IIV-Adj vs. RIV	RCT (n=1)	IIV-Adj: n=3/508 (0.6%) RIV: n=0/335 (0.0%)	The relative effect estimate (95% CI) was RR: 4.62 (0.24 to 89.17)

Abbreviations: CI, confidence interval; ED, emergency department; IIV3-Adj, adjuvanted trivalent inactivated influenza vaccine (egg-based); IIV3-HD, high-dose trivalent inactivated influenza vaccine (egg-based); IIV3-SD, standard-dose trivalent inactivated influenza vaccine (egg-based); IIV-Adj, adjuvanted inactivated influenza vaccine (egg-based); IIV-HD, high-dose inactivated influenza vaccine (egg-based); IIV-SD, standard-dose inactivated influenza vaccine (egg-based); ILI, influenza-like illness; LCI, laboratory-confirmed influenza infection; OR, odds ratio; RCT, randomized controlled trial; RIV, recombinant influenza vaccine; RIV3, trivalent recombinant influenza vaccine; RIV4, quadrivalent recombinant influenza vaccine; RR, risk ratio; vs, versus.

Table 6. Characteristics of studies included in evidence review

Author, Year	Funding	Study design	Country	Intervention	Comparison	Outcomes	Study limitations (Risk of Bias)[a, b]
Balasubramani 2020 [43]	US government	Observational (TNCC)	US	IIV3-HD	IIV3-SD IIV4-SD	Outpatient/ER	Moderate[a]
Belongia 2020 [37]	US government	RCT	US	IIV3-HD IIV3-Adj RIV4	IIV3-Adj RIV4	LCI	High[a]
Cocchio 2020 [58]	No external funding.	Observational (Retro. cohort)	Italy	IIV3-Adj	IIV-SD	Hospitalization	Serious[a]
Couch 2007 [86]	US government	RCT	US	IIV3-HD	IIV3-SD	Any Solicited Systemic AE Grade ≥3	Unclear[a]
Cowling 2020 [87]	US government	RCT	Hong Kong	IIV3-HD IIV3-Adj RIV4	IIV4-SD IIV3-Adj RIV4	Any Solicited Systemic AE Grade ≥3	Low[a]
						Any Solicited injection site AE Grade ≥3	Low[a]
						Any SAE	Low[a]

DiazGranados 2014 [33]	Sanofi Pasteur	RCT	US/ Canada	IIV3-HD	IIV3-SD	LCI	Low[a]
						Any SAE ER visits for ILI LCI ILI	Low[a, b]
						Hospitalizations for ILI Outpatient visit	Some concerns[b]
DiazGranados 2015 [38]	Sanofi Pasteur	RCT	US/ Canada	IIV3-HD	IIV3-SD	Hospitalization	Unclear[a]
De Bruijn 2007 [79]	Unclear; Solvay authors.	RCT	Germany, Sweden, Lithuania, Bulgaria	IIV3-Adj	IIV3-SD	Any SAE	High[a]
De Donato 1999 [80]	Unclear; Chiron authors.	RCT	Italy	IIV3-Adj	IIV3-SD	Any SAE	High[a]
Della Cioppa 2012 [85]	Novartis	RCT	Poland, Belgium, Germany	IIV3-Adj	IIV3-SD	Any SAE	High[a]
Doyle 2021 [52]	US government	Observational (TNCC)	US	IIV3-HD	IIV-SD	Hospitalization	Serious[a]
Dunkle 2017 [34]	BARDA; Protein Sciences authors	RCT	US	RIV4	IIV4-SD	LCI cases	Low[a] - High[b]
						ILI cases	High[b]
						Any SAE	Low[a]
Falsey 2009 [68]	Sanofi Pasteur	RCT	US	IIV3-HD	IIV3-SD	Any SAE	Unclear[a]
						Number of vascular events	Some concerns[b]
Frey 2014 [35]	Novartis	RCT	US Colombia, Panama Philippines	IIV3-Adj	IIV3-SD	ILI cases	Low[a] – Some concerns[b]
						Any SAE	Low[a]
						GBS	Low[a]
Gravenstein 2017 [40]	Sanofi Pasteur	Cluster RCT	US	IIV3-HD	IIV3-SD	Hospitalization	Unclear[a]
Hansen 2020 [77]	Protein Sciences	Observational (Retro. cohort)	US	RIV3	IIV3-SD	GBS	Moderate[a]
Iob 2005 [48]	Not stated	Observational (Cohort)	Italy	IIV3-Adj	IIV3-SD	Outpatient/ER Visit	Serious[a]
Izikson 2015 [83]	BARDA; Protein Sciences authors	RCT	US	RIV3	IIV3-SD	Any SAEs	Unclear [a]

Izurieta 2015 [44]	US government	Observational (Retro. cohort)	US	IIV3-HD	IIV3-SD	Outpatient/ER visit	Serious [a]
Izurieta 2019 [45]	US government	Observational (Retro. cohort)	US	IIV3-HD	IIV4-SD	Outpatient/ER visit, Hospitalization	Serious [a]
				IIV3-Adj	IIV4-SD	Hospitalization	Serious[a]
				IIV3-HD	IIV3-Adj	Hospitalization	Serious[a]
Izurieta 2020 [50]	US government	Observational (Retro. cohort)	US	IIV3-HD IIV3-Adj RIV4	IIV4-SD	Hospitalization	Serious[a]
				IIV3-HD	IIV3-Adj	Hospitalization	Serious[a]
				IIV3-Adj	IIV-SD	Hospitalization	Serious[a]
Izurieta 2021 [51]	US government	Observational (Retro. Cohort)	US	RIV4	IIV4-SD	Hospitalization	Serious[a]
				IIV3-HD	IIV3-Adj	Hospitalization	Serious[a]
				IIV3-HD	RIV4	Hospitalization	Serious[a]
				IIV3-Adj	RIV4	Hospitalization	Serious[a]
Keitel 2006 [36]	US government	RCT	US	IIV3-HD	IIV3-SD	Any SAEs	Unclear[a]
						Any Solicited Systemic AE Grade ≥3	Unclear[a]
						Any Solicited Injection Site AE Grade ≥3	Unclear[a]
Keitel 2010 [71]	Unclear; Protein Sciences author	RCT	US	RIV3	IIV3-SD	Any SAEs	Unclear[a]
						Any Solicited Systemic AE Grade ≥3	Unclear[a]
						Any Solicited Injection Site AE Grade ≥3	Unclear[a]
						LCI cases	Unclear[a] Some concerns[b]
						ILI cases	Some concerns[b]
Li 2008 [81]	Novartis	RCT	China	IIV3-Adj	IIV3-SD	Any SAEs	High[a]
Loeb 2020 [65]	National Institute on Aging, National Institutes of Health	RCT	US/Canada	IIV3-HD	IIV3-SD	LCI cases	Some concerns [a, b]
						Number of vascular events	Low[b]

Lu 2019 [53]	US government	Observational (Retro. cohort)	US	IIV3-HD	IIV-SD	Hospitalization	Serious[a]
Mannino 2012 [60]	Novartis	Observational (Prospective cohort)	Italy	IIV3-Adj	IIV-SD	Hospitalization	Serious [a]
McConeghy 2020 [72]	Seqirus	Cluster RCT	US	IIV3-Adj	IIV3-SD	Hospitalization	Unclear [a]
McLean 2021 [74]	Centers for Disease Control and Prevention and the Marshfield Clinic Research Institute	RCT	US	IIV3-HD	IIV3-Adj	LCI cases	Unclear [b]
Menegon 1999 [88]	Ministry grant	RCT	Italy	IIV3-Adj	IIV3-HD	Any Solicited injection Site AE Grade ≥3	Unclear [a]
Nace 2015 [78]	Sanofi Pasteur	RCT	US	IIV3-HD	IIV3-SD	Any SAEs	High [a]
Paudel 2020 [54]	Sanofi Pasteur	Observational (Retro. cohort)	US	IIV3-HD	IIV-SD	Hospitalization	Serious[a]
Pebody 2020 [61]	UK Government	Observational (TNCC)	UK	IIV3-Adj	IIV-SD	Hospitalization	Moderate [a]
Pelton 2020 [49]	Seqirus	Observational (Retro. cohort)	US	IIV3-HD	IIV3-Adj	Outpatient/ER visit	Serious [a]
				IIV3-Adj	IIV4-SD	Outpatient/ER visit	Serious[a]
Pelton 2021 [63]	Funding not stated. Seqirus authors.	Observational (Retro. cohort)	US	IIV3-HD IIV3-Adj	IIV3-Adj	Outpatient/ER visit	Serious[a]
Richardson 2015 [55]	US government	Observational (Retro. cohort)	US	IIV3-HD	IIV-SD	Hospitalization	Serious[a]
Robison 2018 [56]	Funding not stated. No industry authors.	Observational (Matched cohort)	US	IIV3-HD	IIV-SD	Hospitalization	Serious[a]
Shay 2017 [46]	US government	Observational (Retro. cohort)	US	IIV3-HD	IIV3-SD	Outpatient/ER visit Death	Serious[a]

Scheifele 2013 [67]	Canadian government	RCT	Canada	IIV3-Adj	IIV3-SD	Any SAEs	Low[a]
						Any Solicited Systemic AE Grade ≥3	Low[a]
						Any Solicited Injection Site AE Grade ≥3	Low[a]
Schmader 2021 [76]	US government	RCT	US	IIV3-HD	IIV3-Adj	Any SAEs	Low[a]
				IIV3-HD	IIV3-Adj	-	-
				IIV3-HD	IIV3-Adj	GBS	Low[a]
				IIV3-HD	IIV3-Adj	Any Solicited Injection Site AE Grade ≥3	Low[a]
Seo 2014 [75]	S. Korean government	RCT	S. Korea	IIV3-Adj	IIV3-SD	Any Solicited Systemic AE Grade ≥3	Unclear[a]
Sindoni 2009 [82]	Not stated. No industry authors.	RCT	Italy	IIV3-Adj	IIV3-SD	Any SAEs	Unclear [a]
Shinde 2022 [90]	Novavax	RCT	US	IIV3-HD	RIV4	Any SAEs GBS	Low[a]
						Any Solicited Systemic AE Grade ≥3	Low[a]
Teh 2021 [66]	Sanofi Pasteur	RCT	Australia	IIV3-HD	IIV4-SD	Hospitalization for LCI ILI cases LCI cases	Low[b]
Treanor 2006 [84]	US government; Protein Sciences author	RCT	US	RIV3	IIV3-SD	Any SAEs	Unclear [a]
Tsang 2014 [73]	Sanofi Pasteur	RCT	US	IIV3-HD	IIV3-SD	Any SAEs	Unclear [a]
						Number of vascular events	Some concerns[b]
Van Aalst 2020 [62]	Sanofi Pasteur	Observational (Retro. cohort)	US	IIV3-HD IIV3-Adj	IIV3-Adj	Hospitalization	Serious [a]
Van Buynder 2013 [42]	Unrestricted grant, Novartis; Fraser Health Authority	Observational (TNCC)	Canada	IIV3-Adj	IIV3-SD	Outpatient/ER	Serious [a]

Vardeny 2021 [39]	US government, Sanofi Pasteur	RCT	US, Canada	IIV3-HD	IIV4-SD	Hospitalization	Unclear [a]
Villa 2013 [89]	Unclear; Novartis authors.	Observational (Retro. cohort)	Italy	IIV3-Adj	IIV3-SD	GBS	Serious [a]
Young-Xu 2018 [47]	Sanofi Pasteur; Sanofi authors	Observational (Retro. cohort)	US	IIV3-HD	IIV3-SD	Outpatient/ER Hospitalizations	Serious [a]
Young-Xu 2019 [57]	Unrestricted grant, Sanofi Pasteur; Sanofi authors	Observational (Retro. cohort)	US	IIV3-HD	IIV3-SD	Hospitalization	Serious [a]
Young-Xu 2020 [59]	Unrestricted grant, Sanofi Pasteur; Sanofi authors	Observational (Retro. cohort)	US	IIV3-HD	IIV3-SD	Death	Moderate [a]

[a] For further information on study limitations identified in US ACIP review, please refer to the GRADE: Higher Dose and Adjuvanted Influenza Vaccines for Persons Aged ≥65 Years.

[b] For further information on the study limitations identified in DSEN MAGIC review, please refer to the original publication by Veroniki et al (2023) and the Open Science Framework webpage repository for this project.

Abbreviations: IIV3-Adj, adjuvanted trivalent inactivated influenza vaccine (egg-based); IIV3-HD, high-dose trivalent inactivated influenza vaccine (egg-based); IIV3-SD, standard-dose trivalent inactivated influenza vaccine (egg-based); IIV-Adj, adjuvanted inactivated influenza vaccine (egg-based); IIV-HD, high-dose inactivated influenza vaccine (egg-based); IIV-SD, standard-dose inactivated influenza vaccine (egg-based); ILI, influenza-like illness; LCI, laboratory-confirmed influenza infection; RCT, randomized controlled trial; RIV, recombinant influenza vaccine; RIV3, trivalent recombinant influenza vaccine; RIV4, quadrivalent recombinant influenza vaccine; Retro. Cohort, retrospective cohort; TNCC, test-negative case-control.

Table 7. Description of GRADE ratings for synthesised results

GRADE rating	Description
High	Very confident that the true effect lies close to that of the effect estimate.
Moderate	Moderately confident: the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low	Limited confidence: the true effect may be substantially different from the effect estimate.
Very low	Verry little confidence: the true effect is likely to be substantially different from the effect estimate.

Abbreviation: GRADE, Grading of Recommendations Assessment, Development and Evaluation.

Table 8. Strength of NACI Recommendations

Strength of NACI Recommendation *based on factors not isolated to strength of evidence* (e.g., public health need)	**STRONG**	**DISCRETIONARY**
Wording	"*should/should not be* offered"	"*may/may not be* offered"
Rationale	Known/anticipated advantages outweigh known/anticipated disadvantages ("should"), OR Known/Anticipated disadvantages outweigh known/anticipated advantages ("should not")	Known/anticipated advantages are closely balanced with known/anticipated disadvantages, OR uncertainty in the evidence of advantages and disadvantages exists
Implication	A strong recommendation applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present.	A discretionary recommendation may be considered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.

LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
cc	Cell cultured
CE	Cost-effectiveness
CI	Confidence interval
CIG	Canadian Immunization Guide
CINeMA	Confidence in network meta-analysis
CIQ	Comité sur l'immunisation du Québec
DSEN	Drug Safety and Effectiveness Network
ED	Emergency department
EEFA	Ethics, equity, feasibility, and acceptability
GBS	Guillain-Barré syndrome
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HA	Hemagglutinin
HZ	Herpes zoster
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IIV	Inactivated influenza vaccine
IIV3	Trivalent inactivated influenza vaccine
IIV4	Quadrivalent inactivated influenza vaccine
IIV-Adj	Adjuvanted inactivated influenza vaccine (egg-based)
IIV-cc	Mammalian cell culture-based inactivated influenza vaccine
IIV-HD	High-dose inactivated influenza vaccine (egg-based)
IIV-SD	Standard dose inactivated influenza vaccine (egg-based)
IIV3-Adj	Adjuvanted trivalent inactivated influenza vaccine (egg-based)
IIV3-HD	High-dose trivalent inactivated influenza vaccine (egg-based)
IIV3-SD	Standard dose trivalent inactivated influenza vaccine (egg-based)
IIV4-Adj	Adjuvanted quadrivalent inactivated influenza vaccine (egg-based)
IIV4-cc	Mammalian cell culture-based quadrivalent inactivated influenza vaccine
IIV4-HD	High-dose quadrivalent inactivated influenza vaccine (egg-based)
IIV4-SD	Standard dose quadrivalent inactivated influenza vaccine (egg-based)
ILI	Influenza-like illness
IM	Intramuscular
LCI	Laboratory-confirmed influenza
MDCK	Madin-Darby Canine Kidney
MAGIC	Methods and Applications Group for Indirect Comparisons

NACI	National Advisory Committee on Immunization
NMA	Network Meta-analysis
NOC	Notice of Compliance
OECD	Organisation for Economic Co-operation and Development
PHAC	Public Health Agency of Canada
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
RIV	Recombinant influenza vaccine
RIV3	Recombinant trivalent influenza vaccine
RIV4	Recombinant quadrivalent influenza vaccine
RR	Risk ratio
RT-PCR	Reverse transcription polymerase chain reaction
rVE	Relative vaccine efficacy
RZV	Recombinant zoster vaccine
SAE	Serious adverse event
UK	United Kingdom
US	United States
VE	Vaccine effectiveness

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NACI Influenza Working Group

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APPENDIX A. KEY TERMINOLOGY FOR UNDERSTANDING ECONOMIC EVALUATION EVIDENCE

Table A1. Key terms and descriptions for understanding economic evaluation evidence

Term	Description
Cost-benefit analysis	"In healthcare evaluation, cost-benefit analysis (CBA) is a comparison of interventions and their consequences in which both costs and resulting benefits (health outcomes and others) are expressed in monetary terms. This enables 2 or more treatment alternatives to be compared using the summary metric of net monetary benefit, which is the difference between the benefit of each treatment (expressed in monetary units) less the cost of each. Monetary valuations of benefits are commonly obtained through willingness to pay (WTP) surveys or discrete choice experiments (DCEs). Although popular in other fields, CBA is not commonly used in health technology assessment due to difficulty of associating monetary values with health outcomes such as (increased) survival. Most commonly CBAs have been used to assess large capital development projects (new hospital facilities) or interventions that improve waiting times or location/access to services [153]." The outcome of a CBA is expressed as the incremental net monetary benefit (NMB). "NMB is a summary statistic that represents the value of an intervention in monetary terms when a willingness to pay threshold for a unit of benefit (for example a measure of health outcome or QALY) is known. NMB is calculated as (incremental benefit x threshold) – incremental cost. Incremental NMB measures the difference in NMB between alternative interventions, a positive incremental NMB indicating that the intervention is cost-effective compared with the alternative at the given willingness-to-pay threshold. In this case the cost to derive the benefit is less than the maximum amount that the decision-maker would be willing to pay for this benefit [153]."
Cost-effectiveness analysis	"Cost-effectiveness analysis (CEA) evaluates the effectiveness of 2 or more treatments relative to their cost [153]." CEA is an economic evaluation in which health outcomes are expressed in natural units (e.g., infections avoided). The outcome of a CEA is expressed as the incremental cost-effectiveness ratio (ICER). The ICER is a ratio calculated by dividing the difference in mean expected costs by the difference in mean expected health outcomes or effects between 2 alternatives being compared in an economic evaluation.
Cost-utility analysis	Cost-utility analysis is an economic evaluation in which health outcomes are expressed in quality-adjusted life years (QALYs), or other generic measure of health-related utility. It is sometimes referred to as a cost-effectiveness analysis (CEA), or CEA with QALYs. This is the form of economic evaluation favoured by public health care decision-makers in Canada. The outcome of a CUA is expressed as an ICER, (also sometimes referred to as an incremental cost-utility ratio [ICUR] in a CUA specifically). The ICER is a ratio calculated by dividing the difference in mean expected costs by the difference in mean expected QALYs between 2 alternatives being compared in an economic evaluation. ICERs can be compared to cost-effectiveness thresholds (see below) to assess if the new intervention is an efficient use of resources.
Dominant	An intervention is dominant if it is less costly and more effective (i.e., results in relatively more benefits) than the comparator. Conversely, an intervention that is both more costly and less effective is said to be "dominated."
Perspective	The viewpoint from which an economic evaluation will be conducted. The perspective determines the outcomes and costs that will be included in the analysis. NACI's draft Guidelines for the Economic Evaluation of Vaccination Programs in Canada (2022) recommends the adoption of 2 reference case analyses: 1 conducted from the publicly funded health system perspective and the other conducted from the societal perspective. In these guidelines, health system refers to both healthcare treatment services and Public Health. The purpose of these reference cases is to encourage the use

	of a standard set of methods when conducting economic evaluations of vaccination programs and to ensure that decision-makers are able to compare results between different vaccination programs. The health system perspective includes all resources within the publicly funded health system that are consumed through the delivery of the vaccination program, and resources that are consumed or saved as a result of its implementation (e.g., healthcare costs, public health costs). The provider perspective is a narrower perspective that includes resources and outcomes associated with the healthcare provider (e.g., hospital). The societal perspective is broader and accounts for the full range of benefits associated with vaccination programs, including those that accrue to non-health sectors. It includes elements such as out-of-pocket costs, productivity loss (e.g., individual, caregiver, macroeconomic), and non-medical consumption.
Time horizon	"The time horizon used for an economic evaluation is the duration over which health outcomes and costs are calculated. The choice of time horizon is an important decision for economic modelling and depends on the nature of the disease and intervention under consideration and the purpose of the analysis. Longer time horizons are applicable to chronic conditions associated with on-going medical management, rather than a cure. A shorter time horizon may be appropriate for some acute conditions, for which long-term consequences are less important [(153)]."
Cost-effectiveness threshold	Cost-effectiveness thresholds can be used to assess if an intervention represents sufficient value for money to merit adoption into the health system. Some agencies advocate for their use because they are practical, whereas others dismiss their use arguing they are arbitrary. There are several approaches to estimating a cost-effectiveness threshold, basing it on: (i) willingness-to-pay for a unit of outcome; (ii) value of interventions already funded in the system; and (iii) opportunity costs in terms of forgone health benefits (e.g., cost per QALY gained forgone). In Canada, no explicit cost-effectiveness threshold has been formally adopted by federal or provincial/ territorial agencies. In the literature, common cost-effectiveness thresholds range from $20,000 to $100,000 CAD per QALY gained 40 with $50,000 per QALY being commonly cited [(154)].

APPENDIX B. METHODS FOR QUALITY APPRAISAL AND GENERALIZABILITY ASSESSMENT

The following sections contain additional information regarding the methods and findings of the quality appraisal and generalizability assessment of the included studies.

The systematic review methodology was developed in collaboration with the Methods and Applications Group for Indirect Comparisons (MAGIC) team through the Drug Safety and Effectiveness Network (DSEN). The systematic review followed existing NACI Guidelines for Systematic Reviews on Economic Evaluations of Vaccination Programs. The methods were specified a priori in a written protocol that included the research question, search strategy, inclusion and exclusion criteria, and quality assessment (registered in PROSPERO, CRD42020177337).

Quality appraisal

The quality of included studies was assessed using the 11-item Joanna Briggs Institute (JBI) Appraisal Checklist for Economic Evaluations [155]. All included studies were of high or moderate quality. Thirteen studies were considered to be high quality, reporting 10 or more of the 11 items (>90%) in the JBI Appraisal Checklist for Economic Evaluations [94-97, 100-105, 107-109]. The remaining 6 studies were of moderate quality and reported 7 to 9 of the 11 items (64% to 82%) in the JBI Appraisal Checklist for Economic Evaluations [98, 99, 106, 110-112]. Main issues related to quality assessment included unclear or insufficient information to confirm whether all important and relevant costs and outcomes for each intervention and comparator were identified (n=4) [98, 106, 111, 112] and whether the time horizon and discount rate were identified and justified (n=4) [98, 99, 106, 111].

Generalizability of studies to a Canadian setting

Using the Heyland Generalizability Assessment [156], 4 studies, including 2 conducted in Canada [95, 101] and 2 conducted in UK settings [97, 98] had high applicability to a Canadian setting. The remaining studies were found to have low generalizability to a Canadian setting. Most of the remaining studies satisfied less than half of the Heyland Generalizability Assessment criteria. The following elements of the Heyland Generalizability Assessment were scored poorly when comparing the article being assessed and the setting of interest (i.e., Canada):

- Similar patient preferences: n=19 studies [94-112]
- Exchange rates could be converted appropriately: n=17 studies [94, 96-100, 102-112]
- Similar average cost per patient: n=16 studies [94, 96, 98-100, 102-112]
- Similar resource consumption: n=15 studies [94, 96, 99, 100, 102-112]
- Similar unit price of relevant resources: n=15 studies [94, 96, 99, 100, 102-112]
- Similar perspective of analysis: n=14 studies [94, 96, 99, 100, 102-111]

APPENDIX C. FINDINGS FROM REMAINING INCLUDED ECONOMIC EVALUATION STUDIES DEEMED TO HAVE LESS GENERALIZABILITY TO A CANADIAN SETTING

Findings among cost-utility, cost-benefit, and cost-effectiveness studies that were deemed to have less generalizability to a Canadian setting are described below.

Results among cost-utility analysis studies considered less generalizable to a Canadian setting

Among the remaining 12 cost-utility studies conducted in settings with limited generalizability to a Canadian setting, the following perspectives were taken. Note that a single study can include multiple analyses from different perspectives.

- Healthcare payer: n=5 studies [96, 99, 100, 108, 109]
- Societal: n=10 studies [94, 96, 99, 100, 102-107]
- Healthcare provider: n=1 study [102]

The results are described below. Results were similar to the above studies deemed generalizable to the Canadian context.

Results among cost-utility analysis studies with limited generalizability to a Canadian setting – Healthcare Payer Perspective

The 2 Italian studies comparing an IIV4-SD strategy to an IIV3-SD strategy had differing results, with ICER estimates ranging from $32 617 per QALY gained over a lifetime time horizon [99] to $224 000 per QALY gained over a 1-year time horizon [108] (Table A2).

ICER values for an IIV3-Adj strategy versus an IIV3-SD strategy ranged from $3 406 [109] to $7 692 [108] per QALY gained (Table A2). These estimates can be considered cost-effective under commonly used thresholds.

Among the 2 studies comparing an IIV3-HD strategy to an IIV3-SD strategy, 1 [100] found an IIV3-HD strategy to be less costly and more effective than an IIV3-SD strategy and the other study [96] estimated an ICER value of $13 537 per QALY gained (Table A2).

One (1) study comparing an IIV3-HD strategy to an IIV4-SD strategy estimated an ICER value of $5 709 per QALY gained (Table A2) [96].

Table A2. Summary of study characteristics and findings from other included cost-utility studies that were conducted from a healthcare payer perspective (n=5)

Author, Year, Country	Funding	Population	Time horizon	Findings
IIV4-SD (Intervention) vs IIV3-SD (Comparator)				
Mennini et al., 2018 [99], Italy	Sanofi Pasteur (Industry)	Adults 65 years of age and older	Lifetime	$32,617/QALY gained
Capri et al., 2018 [108], Italy	Seqirus SRL (Industry)	Adults 65 years of age and older	One (1) year	$224,000/QALY gained
IIV3-Adj (Intervention) vs IIV3-SD (Comparator)				
Capri et al., 2018 [108], Italy	Seqirus SRL (Industry)	Adults 65 years of age and older	One (1) year	$7,692/QALY gained
Nguyen et al., 2020 [109], Argentina	Seqirus USA Inc. (Industry)	Adults 65 years of age and older	One (1) year	$3,406/QALY gained
IIV3-HD (Intervention) vs IIV3-SD (Comparator)				
Chit et al., 2015b [100], US	Sanofi Pasteur (Industry)	Adults 65 years of age and older	One (1) year for cost and lifetime for effect	IIV3-HD dominated IIV3-SD Participants living with 1 or more comorbidities: IIV3-HD dominated IIV3-SD Participants living with a cardiorespiratory condition: IIV3-HD dominated IIV3-SD
Chit et al., 2015c [96], US	Sanofi Pasteur (Industry)	Adults 65 years of age and older	One (1) influenza season for cost and lifetime for effect	$13,537/QALY gained
IIV3-HD (Intervention) vs IIV4-SD (Comparator)				
Chit et al., 2015c [96], US	Sanofi Pasteur (Industry)	Adults 65 years of age and older	One (1) influenza season for cost and lifetime for effect	$5,709/QALY gained

Note: "Intervention A dominated Intervention B" means that Intervention A is less costly and more effective than Intervention B.

Results among cost-utility analysis studies with limited generalizability to a Canadian setting – Societal Perspective

The following comparisons were analyzed from studies that carried out analyses from a societal perspective:

- IIV4-SD vs IIV3-SD: n=7 studies [94, 99, 102-106]
- IIV3-Adj vs IIV3-SD: n=2 studies [99, 104]
- IIV3-HD vs IIV3-SD: n=3 studies [96, 100, 107]
- IIV3-HD vs IIV4-SD: n=2 studies [96, 107]

Among the 7 studies comparing an IIV4-SD strategy to an IIV3-SD strategy, 2 found an IIV4-SD strategy to be less costly and more effective than an IIV3-SD strategy (Table A3) [103, 105]. ICER estimates for the remaining 6 studies ranged from $8 087 [94] to $55 865 [106] per QALY gained over time horizons ranging

from 1 year to lifetime. Notably, the 2 studies that conducted subgroup analyses by age group found an IIV4-SD strategy to be increasingly more cost-effective than an IIV3-SD strategy for older age groups [102, 104].

The 2 studies comparing an IIV3-Adj strategy to an IIV3-SD strategy found an IIV3-Adj strategy to be less costly and more effective than an IIV3-SD strategy over a lifetime time horizon for adults 65 years of age and older (Table A3) [99, 104]. These findings were robust in the 1 study that conducted subgroup analyses by age group (65–74 years, 75–84 years, and 85 years of age and older) and for individuals at high risk of seasonal influenza infection and/or influenza-related complications or hospitalization [104].

Of the 3 studies comparing an IIV3-HD strategy to an IIV3-SD strategy, 1 found an IIV3-HD strategy to be less costly and more effective than an IIV3-SD strategy (Table A3) [100]. The remaining 2 studies found an IIV3-HD strategy to cost $6 930 [96] to $36 967 [107] for each QALY gained compared to an IIV3-SD strategy.

Two (2) studies compared an IIV3-HD strategy to an IIV4-SD strategy (Table A3). One (1) study found an IIV3-HD strategy to be less costly and more effective than an IIV4-SD strategy [96] while the second study found an IIV3-HD strategy to cost $40 824 [107] more than an IIV4-SD strategy for each QALY gained.

Table A3. Summary of study characteristics and findings from other included cost-utility studies that were conducted from a societal perspective (n=10).

Author, Year, Country	Funding	Population	Time horizon	Findings
IIV4-SD (Intervention) vs IIV3-SD (Comparator)				
Jiang et al., 2020 [94], China	China Postdoctoral Science Foundation China (Public and Industry)	Adults 69 years of age and older	One (1) year for cost and lifetime for effect	$8 087/QALY gained
You et al., 2015 [102], Hong Kong	Not reported	Adults 65 years of age and older	Not reported	All participants 65 years of age and older: $16,424/QALY gained **Subgroup analyses** Participants 65-79 years of age: $40,221/QALY gained Participants 80 years of age and older: IIV4-SD dominated IIV3-SD
Kim et al., 2018 [103], South Korea	GlaxoSmithKline Biologicals SA (Industry)	Adults 65 years of age and older	One (1) year for cost and effect	Broad set of ICD-10 codes used to identify influenza infection: IIV4-SD dominated IIV3-SD Narrow set of ICD-10 codes used to identify influenza infection: IIV4-SD dominated IIV3-SD
Yun et al., 2019 [104], South Korea	Korea Centers for Disease Control and Prevention (Public)	Adults 65 years of age and older	Lifetime for cost and effect	All participants 65 years of age and older: $22,656/QALY gained **Subgroup analyses** Participants 65-74 years of age: $31,869/QALY gained Participants 75-84 years of age: $13,304/QALY gained Participants 85 years of age and older: $4,392/QALY gained Participants at high risk of seasonal influenza infection and/or influenza-related complications or hospitalizations: $1,327/QALY gained
Brogan et al., 2017 [105], US	GlaxoSmithKline Biologicals SA (Industry)	Adults 65 years of age and older	10 years for cost and effect	IIV4-SD dominated IIV3-SD
You et al., 2014 [106], Hong Kong	None	Adults 65 years of age and older	9 years for cost and effect	Assuming IIV4-SD cost an additional $1 USD compared to IIV3-SD in 2010, the ICER was $55,865/QALY gained for adults aged 65-79 and IIV4-SD dominated IIV3-SD for adults 85 years of age and older.

Mennini et al., 2018 [99], Italy	Sanofi Pasteur (Industry)	Adults 65 years of age and older	Lifetime for cost and effect	$32,617/QALY gained
IIV3-Adj (Intervention) vs IIV3-SD (Comparator)				
Yun et al., 2019 [104], South Korea	Korea Centers for Disease Control and Prevention (Public)	Adults 65 years of age and older	Lifetime for cost and effect	All participants 65 years of age and older: IIV3-Adj dominated IIV3-SD **Subgroup analyses** Participants 65-74 years of age: IIV3-Adj dominated IIV3-SD Participants 75-84 years of age: IIV3-Adj dominated IIV3-SD Participants 85 years of age and older: IIV3-Adj dominated IIV3-SD Participants at high risk of seasonal influenza infection and/or influenza-related complications or hospitalizations: IIV3-Adj dominated IIV3-SD
Mennini et al., 2018 [99], Italy	Sanofi Pasteur (Industry)	Adults 65 years of age and older	Lifetime for cost and effect	IIV3-Adj dominated IIV3-SD
IIV3-HD (Intervention) vs IIV3-SD (Comparator)				
Chit et al., 2015b [100], US	Sanofi Pasteur (Industry)	Adults 65 years of age and older	One (1) year for cost and lifetime for effect	IIV3-HD dominated IIV3-SD Participants living with 1 or more comorbidities: IIV3-HD dominated IIV3-SD Participants living with a cardiorespiratory condition: IIV3-HD dominated IIV3-SD
Chit et al., 2015c [96], US	Sanofi Pasteur (Industry)	Adults 65 years of age and older	One (1) year for cost and lifetime for effect	$6,930/QALY gained
Raviotta et al., 2016 [107], US	National Institute of General Medical Sciences of the National Institutes of Health Award (Industry)	Adults 65 years of age and older	One (1) year for cost and lifetime for effect	$36,967/QALY gained
IIV3-HD (Intervention) vs IIV4-SD (Comparator)				
Chit et al., 2015c [96], US	Sanofi Pasteur (Industry)	Adults 65 years of age and older	One (1) year for cost and lifetime for effect	IIV3-HD dominated IIV4-SD
Raviotta et al., 2016 [107], US	National Institute of General Medical Sciences of the National Institutes of Health Award (Industry)	Adults 65 years of age and older	One (1) year for cost and lifetime for effect	$40,824/QALY gained

Note: "Intervention A dominated Intervention B" means that Intervention A is less costly and more effective than Intervention B.

Results among cost-utility analysis studies with limited generalizability to a Canadian setting – Healthcare Provider Perspective

One (1) study was conducted from a healthcare provider perspective and did not report the time horizon used for analysis [102]. The study found an IIV4-SD strategy to cost $29 562 more than an IIV3-SD strategy for each QALY gained [102]. The study found an IIV4-SD strategy to be increasingly more cost-effective (i.e., lower ICER) compared to an IIV3-SD strategy with increasing age [102].

Results from cost-benefit analysis studies

The 2 cost-benefit analyses concluded that an IIV3-HD strategy was cost-effective (i.e., positive net monetary benefit) compared to an IIV3-SD strategy in the US (Table A4) [110, 111].

Table A4. Summary of study characteristics and findings from included cost-benefit analysis studies (n=2)

Author, Year, Country	Funding	Population	Perspective	Time horizon	Findings
IIV3-HD (Intervention) vs IIV3-SD (Comparator)					
Shireman et al., 2019 [110], US	Sanofi Pasteur (Industry)	Adults 65 years of age and older, nursing home residents	Healthcare payer	One (1) influenza season for cost and effect	Positive net monetary benefit
van Aalst et al., 2019 [111], US	Multiple sources (Industry)	Adults 65 years of age and older, veterans	Healthcare payer	Not specified	Positive net monetary benefit

Results from cost-effectiveness analysis studies

One (1) cost-effectiveness study comparing an IIV3-Adj strategy to an IIV3-SD strategy was identified [112]. The study was conducted from a French healthcare payer perspective over a 1 year time horizon for cost and lifetime time horizon for effect [112]. The study estimated ICERs of $44 492 per death avoided and $8 943 per life year gained for an IIV3-Adj strategy compared to an IIV3-SD strategy [112].