An Advisory Committee Review
National Advisory Committee on Immunization (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

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Examen du comité consultatif
Comité consultatif national de l'immunisation (CCNI)
Mise à jour sur la revue de la littérature portant sur l'efficacité potentielle et réelle des vaccins antigrippaux trivalents inactivés à forte dose (Fluzone[MD] Haute dose) et contenant l'adjuvant MF59 (Fluad[MD]) chez les adultes âgés de 65 ans et plus

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PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (hereafter referred to as PHAC) with ongoing and timely medical, scientific, and public health advice relating to immunization. PHAC acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccine(s). Manufacturer(s) have sought approval of the vaccine(s) 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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EXECUTIVE SUMMARY

Two trivalent inactivated influenza vaccines (TIVs) designed specifically for adults 65 years of age and older are currently authorized for use in Canada: a high-dose vaccine (Fluzone® High-Dose, Sanofi Pasteur) and an MF59-adjuvanted vaccine (Fluad®, Seqirus). Previous literature reviews on the efficacy and effectiveness, immunogenicity and safety of Fluzone® High-Dose and Fluad® have been conducted to inform NACI's recommendations on the use of these vaccines in the annual NACI Advisory Committee Statement: Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine. To ensure that these recommendations continue to be informed with the most current literature, the present literature review was conducted to identify additional efficacy and effectiveness evidence published since the original literature reviews. Five additional studies regarding Fluzone® High-Dose and four additional studies regarding Fluad® were identified, all of which assessed vaccine effectiveness for the two vaccines. Several methodological concerns were identified that warrant cautious interpretation of study findings for both vaccines. In consideration of these concerns, the present literature review update did not identify evidence that warrants changing the conclusions of the previous reviews and concludes that: 1) there is good evidence that Fluzone® High-Dose provides superior protection compared with standard-dose TIV in the elderly (Grade A Evidence); 2) there is fair evidence that the MF59-adjuvanted Fluad® may be effective at reducing the risk of hospitalization for influenza and influenza complications in the elderly compared to unvaccinated individuals (Grade B Evidence); 3) there is insufficient evidence that Fluad® is effective at reducing the risk of hospitalization for influenza and influenza complications in the elderly compared to those who received unadjuvanted trivalent inactivated subunit vaccine (Grade I Evidence); and 4) there is no identified evidence on how the high-dose vaccine directly compares to the MF59-adjuvanted vaccine (Grade I Evidence).

I. INTRODUCTION

Background

In Canada, during the pre-pandemic (2003–2004 through 2008–2009) and post-pandemic (2010–2011) influenza seasons, 55–65% of hospital admissions and about 87% of deaths due to influenza occurred in adults aged 65 years and older, even though this age group only comprised about 14% of the population[1, 2]. Statistical modelling using data from Canada's national hospitalization database found adults 65 years of age and older to have the highest influenza-related hospitalization rate at 270–340 per 100,000 compared to rates of 10–20 per 100,000 for adults 20–49 years of age and 50–70 per 100,000 for adults 50–64 years of age[3]. For influenza-attributable deaths, the annual average mortality rate for adults 65 years of age 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 50–64 years of age[4]. Considering the burden of influenza disease in this population, NACI includes adults 65 years of age and older among the high-risk groups for whom influenza vaccination is particularly recommended[5].

Although vaccination remains the most effective way to prevent influenza and its complications[5], there is evidence of reduced elicited immune response and effectiveness of influenza vaccines in older versus younger adults due to immunosenescence in the elderly. For example, individuals 17–59 years of age showed a two- to four-fold higher immune response to influenza vaccine as measured by seroconversion and seroprotection rates compared to those 65 years of age and older[6]. A meta-analysis of adults 65 years of age and older found a lower point estimate of vaccine effectiveness (VE) against laboratory-confirmed influenza (VE: 49%,

95% CI: 33–62%)[7] compared to a meta-analysis of healthy adults 18–64 years of age (VE: 59%, 95% CI: 51–67%)[8]. As such, the evidence is suggestive of a need for more effective influenza vaccines targeted for adults 65 years of age and older.

There are two trivalent inactivated influenza vaccines (TIVs) available for use in Canada that are designed to enhance immunogenicity in adults 65 years of age and older: a high-dose inactivated split virion vaccine (Fluzone® High-Dose, Sanofi Pasteur) and an MF59-adjuvanted inactivated subunit vaccine (Fluad®, Seqirus).

Fluzone® High-Dose was authorized for use in Canada for the 2016–2017 influenza season[9] and contains 60 µg of haemagglutinin (HA) per strain (compared to 15 µg HA per strain in a standard dose) administered as a 0.5 mL dose by intramuscular injection delivered by single dose pre-filled syringes. Fluzone® High-Dose is currently the only available high-dose inactivated split virion influenza vaccine in Canada. A literature review on the efficacy and effectiveness, immunogenicity and safety of high-dose seasonal influenza vaccines, including Fluzone® High-Dose, for adults 65 years of age and older was prepared in 2016[1] as part of NACI's evidence-based process[10] to inform the inclusion of Fluzone® High-Dose in the Statement on Seasonal Influenza Vaccine for 2016–2017[11].

Authorized for use in Canada in September 2011, 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[12]. Fluad® is administered as a 0.5 mL dose by intramuscular injection delivered by single dose pre-filled syringes. 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 and effectiveness, immunogenicity and safety of Fluad® was first reviewed in 2011[13] to inform the inclusion of Fluad® in the Statement on Seasonal Influenza for 2011–2012[14] and subsequently supplemented with additional effectiveness evidence in the Statement on Seasonal Influenza for 2014–2015[15].

Based on the previous reviews of the literature, NACI includes Fluzone® High-Dose and Fluad® among the recommended products for adults 65 years of age and older. NACI concluded that there was evidence that high-dose TIV for older adults should provide superior protection compared with the standard-dose intramuscular vaccine and that the MF59-adjuvanted Fluad® may be effective at reducing the risk of hospitalization for influenza and influenza complications in the elderly compared to unvaccinated individuals and those who received unadjuvanted trivalent inactivated subunit vaccine[11]. These conclusions were based on the available evidence at the time of recommendation development, with evidence gaps and methodological concerns identified for the body of efficacy and effectiveness evidence for these vaccines[1, 11]. There was a lack of evidence directly comparing the relative efficacy or effectiveness of high-dose TIV with MF59-adjuvanted TIV[1] and high-dose or MF59-adjuvanted TIV with QIV[1, 11]. There was some evidence of an observed age effect found for the high-dose vaccine in the elderly, where the very elderly (e.g., 75 years of age and older) may have better relative protection compared to the younger elderly (e.g., 65–74 years of age) from the high-dose vaccine[11]. A similar effect was not identified for the MF59-adjuvanted vaccine. Methodological concerns of previously identified efficacy and effectiveness studies that warranted cautious interpretation of findings include the absence of randomized controlled trials (RCTs) for Fluad®, the use of clinical outcomes that are less (e.g., influenza-like illness [ILI]) or not specific to influenza (e.g., all-cause hospitalization), inherent limitations of observational studies of influenza vaccination as well as other study-specific limitations[1, 13, 15]. Furthermore, experience with efficacy and effectiveness findings for the live attenuated influenza vaccine emphasizes the

need for the ongoing monitoring of VE[11]. An update to the reviews of the literature on the efficacy and effectiveness of Fluzone® High-Dose and Fluad® ensure that the recommendations for the use of these vaccines in the elderly continue to be informed by a body of evidence that includes the most current literature.

Purpose and Objectives

The purpose of this literature review update is to systematically identify, review and synthesize newly available evidence on the efficacy and effectiveness of high-dose (Fluzone® High-Dose) and of MF59-adjuvanted (Fluad®) TIV in adults 65 years of age and older compared with each other, standard-dose TIV (without any adjuvant), QIV or no vaccination.

II. METHODS

Search Strategy

MEDLINE, EMBASE, Global Health, ProQuest Public Health Database and Scopus electronic databases were searched using search strategies for Fluzone® High-Dose and Fluad® adapted from the previously conducted NACI Literature Review of High Dose Seasonal Influenza Vaccine for Adults 65 Years and Older[1]. Separate searches were performed for the high-dose and MF59-adjuvanted TIVs as different publication date restrictions were applied: from 1 June 2014 to 22 March 2017 for the high-dose vaccine and from 1 January 2012 to 22 March 2017 for the MF59-adjuvanted vaccine. These publication date restrictions were chosen in order to have at least one year of overlap with the most recent literature search updates to the efficacy and effectiveness evidence for these vaccines (i.e., 22 June 2015 for Fluzone® High-Dose[1] and an unspecified date in 2013 for Fluad®[16]). The searches were further restricted to articles published in the English and French languages. Eligibility restriction was not imposed on publication type. The full electronic search strategies are presented in Appendix A.

Identification of Eligible Studies

Studies retrieved from the database searches were loaded into RefWorks (ProQuest LLC, Ann Arbor, MI) with duplicate records removed. Record screening and eligibility assessment for the present literature review were performed independently by two reviewers. Title and abstract information returned by the database searches was screened for potential eligibility. Full-text reports of studies deemed potentially eligible after title and abstract screening, or for which insufficient information was available to determine eligibility (e.g., no abstract), were obtained and further reviewed for eligibility. Exclusion criteria for the literature identification and selection process for Fluzone® High-Dose and Fluad® were adapted from the criteria used in the 2016 literature review on high-dose influenza vaccines for the elderly[1].

Records were excluded if it was clear from the title and abstract that the record met one or more of the following criteria:

1. Study population does not contain at least some proportion of adults aged 65 years and older;
2. Influenza vaccines were not investigated;
3. Only pre-pandemic or pandemic influenza vaccines were investigated;
4. Influenza vaccine efficacy or effectiveness against influenza or its complications was not investigated;
5. Article is an editorial, opinion or news report; or
6. Article was included in the previous literature reviews.

Articles were further excluded from review if it was clear from the full-text that the article met one or more of the following criteria:

1. Greater than 10% of the study population was outside of the age range of interest (65 years and older) or separate analysis was not conducted for the age group of interest;
2. Influenza vaccine efficacy or effectiveness against influenza or its complications was not investigated and reported for the high-dose (Fluzone® High-Dose) or MF59-adjuvanted (Fluad®) seasonal influenza vaccines; or
3. Article only reported secondary research (e.g., literature review, systematic review, meta-analysis).

Handsearching of included studies was performed by checking reference lists to identify additional relevant publications. Handsearching of reference lists was also performed for any relevant retrieved secondary research articles.

Data Extraction

One reviewer extracted data from the studies included for review into an evidence table using a piloted data abstraction template designed to capture information on study design, population and outcomes of interest as well as any information as appropriate on ascertainment of influenza vaccination status, method of influenza virus testing, influenza vaccine formulation and influenza season. A second reviewer independently validated the abstracted data, with any disagreements or discrepancies resolved by discussion and consensus.

Qualitative Synthesis

The present literature review narratively synthesized information extracted from the included studies, including summaries of the direction, size and statistical significance of reported effect estimates for various study-defined outcomes, and explored overall patterns in the data.

Methodological Quality Assessment

The methodological quality of studies was assessed independently by two reviewers based on reported study methodology using the design-specific parameters outlined by Harris et al. (2001)[17] for rating the internal validity of individual studies (Appendix B).

III. RESULTS

The study identification and selection process as well as study details are summarized in section III.1. Newly and previously identified efficacy and effectiveness evidence relating to the Fluzone® High-Dose and MF59-adjuvanted Fluad® vaccines are summarized in section III.2.

III.1 Study Inclusion and Characteristics

The study identification, screening and eligibility assessment process is summarized visually in Appendix C for Fluzone® High-Dose and Appendix D for MF59-adjuvanted Fluad®. All included studies were available as English language publications. For Fluzone® High-Dose, five studies were deemed eligible for qualitative synthesis[18-22], including one study by Shay et al. (2017) which was in press at time of electronic database searching (i.e., not indexed in the searched databases) and was identified by an external stakeholder. For the MF59-adjuvanted Fluad®, four studies were included for qualitative synthesis[23-26], including two studies identified from alternative sources. One study was identified from the reference list of a relevant retrieved review article[26] and the other, an interim report from the Canadian Serious Outcomes

Surveillance (SOS) Network, was presented to the NACI Influenza Working Group and at the 2016 Canada Immunization Conference[25].

Extracted study data are presented in the evidence table in Appendix E for Fluzone® High-Dose and the evidence table in Appendix F for the MF59-adjuvanted Fluad®. All studies included for qualitative synthesis received a "good" rating according to the Harris et al. design-specific parameters[17], with the exception of the study by Spadea et al., which received a "poor" rating[23].

III.2 Efficacy and Effectiveness

III.2.1 High-Dose Trivalent Inactivated Influenza Vaccine (Fluzone® High-Dose)

Updated Evidence

The updated literature review identified five additional studies[18-22] that assessed the effectiveness of Fluzone® High-Dose in adults 65 years of age and older[11]. Of the five studies, two were conducted by DiazGranados et al.[18, 20] as supplementary analyses using data from their previously published phase IIIb/IV RCT, which compared the relative efficacy of Fluzone® High-Dose to standard-dose Fluzone®[27]; the previously published RCT was included in the previous literature review[11]. The present review also identified a nursing home cluster RCT by Gravenstein et al. (2017) with only interim findings available at time of review[21] (now published[28]) and two prospective cohort studies, one by Richardson et al. (2015)[19] and another by Shay et al. (2017)[22]. The retrospective cohort study by Shay et al. (2017)[22] was conducted as a follow-up to the study by Izurieta et al. (2015)[29]; the Izurieta et al. study was also included in the previous literature review[11]. The Shay et al. study used an expanded dataset (two influenza seasons instead of one season) to investigate mortality as the primary outcome.

The first supplementary analysis conducted by DiazGranados et al. (2015) compared the relative effectiveness of Fluzone® High-Dose with standard-dose Fluzone® to prevent all-cause hospitalization and serious cardiorespiratory events possibly related to influenza (defined as events leading to death or hospitalization; considered as life-threatening or medically important; or resulting in disability) in adults 65 years of age and older, 6–8 months post-vaccination, over two influenza seasons[20]. Fluzone® High-Dose was statistically significantly more effective than the standard-dose formulation in preventing all-cause hospitalization (relative VE: 6.9%, 95% CI: 0.5–12.8%) and serious cardiorespiratory events overall (relative VE: 17.7%, 95% CI: 6.6–27.4%), as well as pneumonia events (relative VE: 39.8%, 95% CI: 19.3–55.1%), but not other specific cardiorespiratory outcomes (e.g., serious laboratory-confirmed influenza, coronary artery events, congestive heart failure, cerebrovascular events). The second supplementary analysis conducted by DiazGranados et al. (2016) in the same study population compared the relative effectiveness of vaccination with Fluzone® High-Dose or standard-dose Fluzone® in the previous and current influenza seasons on the prevention of laboratory-confirmed influenza of any strain in the current season[18]. Participants were randomized to receive either high-dose or standard-dose vaccine in the first season and high-dose or standard-dose vaccine in the second season for a total of four vaccination patterns. Relative to persons who received standard-dose vaccine in both study seasons, though not statistically significant, relative VE against influenza infection in the second season was higher for persons receiving high-dose vaccine in the first season and standard-dose vaccine in the second season (relative VE: 11.2%, 95% CI: -27.4–38.2%), standard-dose vaccine in the first season and high-dose vaccine in the second season

(relative VE: 31.6%, 95% CI: -0.8–53.9%) and high-dose vaccine in both seasons (relative VE: 25.1%, 95% CI: -8.9–48.8%). However, a statistically significant protection against influenza infection was observed when data was pooled to include persons who received any vaccine in the first season and high-dose vaccine in the second season compared to those who received standard-dose vaccine for both seasons (relative VE: 28.3%, 95% CI: 1.0–47.8%). Logistic regression modelling confirmed that the type of vaccine received in the previous season was not a statistically significant modifier of current season VE (p=0.43), but current season vaccination with high-dose vaccine was statistically significantly associated with lower influenza risk (p=0.043).

Interim findings from a multicentre, cluster RCT that randomized 823 nursing homes in the 2013–2014 influenza season by Gravenstein et al. (2015) compared the relative effectiveness of Fluzone® High-Dose to standard-dose Fluzone® in preventing all-cause hospitalizations (primary outcome), all-cause mortality and functional decline (secondary outcomes) in elderly (65 years of age and older), long-stay nursing home residents[21]. All-cause hospitalization was statistically significantly reduced among residents receiving high-dose vaccine compared to standard-dose vaccine (adjusted odds ratio [OR]: 0.930, 95% CI: 0.875–0.988), but no statistically significant differences for all-cause mortality or functional decline were found.

A retrospective cohort study by Richardson et al. (2015) compared the propensity score-adjusted relative risk (RR) of hospitalization for influenza or pneumonia (primary outcome) and of all-cause hospitalization or all-cause mortality (secondary outcomes) in community-dwelling patients who were 65 years of age and older and had received either Fluzone® High-Dose (n=25,714) or a standard-dose influenza vaccine (n=139,511) during the 2010–2011 influenza season[19]. The study found no statistically significant differences between high-dose or standard-dose vaccine groups for any of the primary or secondary outcomes (propensity score-adjusted RR: 0.98 to 1.05). By age-stratified analysis however, receipt of the high-dose vaccine, compared to receipt of the standard-dose influenza vaccine, was statistically significantly associated with a lower risk of hospitalization for influenza or pneumonia in patients 85 years of age and older (adjusted RR: 0.52, 95% CI: 0.29–0.92), but not for patients 65–74 years of age (adjusted RR: 1.16, 95% CI: 0.71–1.88) and 75–84 years of age (adjusted RR: 1.44, 95% CI: 0.82–2.52) .

In another retrospective cohort study using Medicare administrative data, Shay et al. (2017)[22] performed a follow-up analysis to the study by Izurieta et al. (2015)[29], in which Medicare beneficiaries 65 years of age and older who received either Fluzone® High-Dose or standard-dose influenza vaccine from a community-located pharmacy were compared for the outcomes of post-influenza death (primary outcome), hospitalization or emergency department visit for influenza, and ILI-related office visit (secondary outcomes) by influenza season and overall. Influenza status was based upon ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification) codes without laboratory confirmation. Fluzone® High-Dose was found to be statistically significantly more effective than the standard-dose vaccine in preventing post-influenza death (adjusted relative VE: 24.0%, 95% CI: 0.6–41.8%), hospitalization or emergency department visit for influenza (adjusted relative VE: 18.6%, 95% CI: 14.1–22.9%), and ILI (adjusted relative VE: 15.3%, 95% CI: 9.7–20.6%). However, results appeared to vary by influenza season, with high-dose vaccine being consistently more effective across outcomes during the influenza A(H3N2)-dominant 2012–2013 season (adjusted relative VE: 22.0 to 36.4%), rather than during the influenza A(H1N1)-dominant 2013–2014 season (adjusted relative VE: 2.5 to 12.7%). Influenza season-vaccine interaction analysis found that comparative effectiveness varied significantly by season for ILI (p=0.006) and hospital-diagnosed influenza (p=0.041), but was not statistically significantly different for post-influenza death (p=0.12).

Previous Evidence

The previous NACI review of literature identified two RCTs[30, 31] and one retrospective cohort study[29] that assessed the relative efficacy or effectiveness of Fluzone® High-Dose compared to standard-dose TIV in adults 65 years of age and older[1]. A phase IIIb RCT by DiazGranados et al. (2013) found the relative efficacy of Fluzone® High-Dose versus standard-dose Fluzone® against laboratory-confirmed influenza to be 12.5% (95% CI: -140.9–65.7%) during the 2009–2010 influenza season, in which the pandemic A(H1N1) influenza virus predominated and represented a vaccine strain mismatch[30]. Canadian authorization of Fluzone® High-Dose was based on a second, larger phase IIIb/IV RCT by DiazGranados et al. (2014) conducted over two influenza seasons (2011–2012 and 2012–2013) in which the relative efficacy of the high-dose vaccine against laboratory-confirmed influenza was found to be 24.2% (95% CI: 9.7–36.5%) compared to standard-dose Fluzone®[27, 31]. In a retrospective cohort study of Medicare beneficiaries in the US by Izurieta et al. (2015), conducted using administrative data, Fluzone® High-Dose was estimated to be 21.9% (95% CI: 15.0–28.7%) more effective than any standard-dose vaccine in preventing probable influenza-related illness and 21.6% (95% CI: 16.1–26.7%) more effective than any standard-dose vaccine in preventing hospital admission due to an influenza diagnosis[29]. Further details of these studies can be found in the NACI Literature Review of High Dose Seasonal Influenza Vaccine for Adults 65 Years of Age and Older[1].

Age Effect

The previous review of the literature found preliminary indications that the high-dose vaccine may provide greater benefit in the very elderly (e.g., 75 years of age and older) compared to younger elderly (e.g., 65–74 years of age)[1]. For example, in a supplementary analysis conducted using data from the large phase IIIb/IV efficacy trial by DiazGranados et al. (2014)[27], relative VE estimates against laboratory-confirmed influenza infection by any strain were found to be higher in individuals 75 years of age and older (relative VE: 32.4 to 32.7%) compared to individuals 65–74 years of age (relative VE: 18.0 to 19.7%)[31]. Although the differences between these age-stratified estimates were not statistically significant, the authors noted the original trial was also not adequately powered to address this supplementary analysis. In the retrospective cohort study by Izurieta et al. (2015), the relative VE of high-dose vaccine compared to standard-dose TIV was 35.6% (95% CI: 13.1–53.9%) in adults 85 years of age and older with lower relative VE point estimates observed for adults 65–74 years of age (relative VE: 21.5%, 95% CI: 12.1–30.3%) and 75–84 years of age (relative VE: 17.9%, 95% CI: 4.8–29.6%)[29]. However, the difference in relative VE estimates between the overall study and adults 85 years of age and older was not statistically significant. The study by Richardson et al. (2015), identified in the present review, also found a benefit of high-dose vaccine in preventing hospitalization for influenza or pneumonia in persons 85 years of age and older, but not in persons from 65 to 84 years of age[19].

III.2.2 MF59-Adjuvanted Trivalent Inactivated Influenza Vaccine (Fluad®)

Updated Evidence

The present literature review update identified four additional observational studies that assessed the effectiveness of Fluad® in adults 65 years of age and older[23-26] available since the original literature reviews[14, 15]. Two of four studies investigated VE of Fluad® against laboratory-confirmed influenza[24, 25] while two studies investigated less influenza-specific outcomes (i.e., hospitalization for influenza or pneumonia)[23, 26].

In a matched case-control study by Gasparini et al. (2013), patients 65 years of age and older hospitalized for influenza or pneumonia (cases) were matched 1:1 with subjects who were not hospitalized for influenza or pneumonia (controls) on a number of variables (e.g., age,

socioeconomic status, gender, type of influenza vaccine received)[26]. A vaccine registry was used to identify whether cases and controls had received influenza vaccine and the type of vaccine received. Excluding those who received unadjuvanted vaccines, the study found that, compared to unimmunized individuals, receipt of adjuvanted vaccine (Fluad® or Inflexal® V, an inactivated subunit virosomal vaccine not available in Canada) was associated with a statistically significant reduction in the risk of hospitalization for influenza or pneumonia, based upon ICD-9 codes; however, in an analysis restricted to Fluad®, the adjusted VE point estimate did not reach statistical significance (adjusted VE: 87.8%, 95% CI: 0.0–98.9%).

A multicentre, hospital-based, case-control study using a test-negative design was conducted as part of the Canadian SOS Network by McNeil et al. (2016)[25]. Hospitalized adult patients with a positive test for influenza (cases) or a negative test for influenza (test-negative controls) were matched by admission date, enrollment site and age of the case (aged 65 years and older versus less than 65 years). For the 2011–2012 through 2013–2014 influenza seasons, in patients 65 years of age and older, the adjusted VE was 61.3% (95% CI: 17.5–81.9%) for adjuvanted TIV and 32.5% (95% CI: 18.9–43.7%) for unadjuvanted TIV. This difference was not statistically significant due to wide and overlapping 95% confidence intervals. McNeil et al. found an adjusted VE of 61.3% in those 65 years of age and older compared with 20.7% in those younger than 65 years of age. These age-stratified estimates have wide and overlapping 95% confidence intervals (values are not available).

In a retrospective cohort study comparing adjuvanted influenza vaccines, Puig-Barberà et al. (2013) found that there was no statistically significant difference in effectiveness between MF59-adjuvanted TIV and a virosomal TIV (Inflexal® V) in reducing influenza-related hospitalizations based upon ICD-9-CM codes of community-dwelling persons 65 years of age and older (adjusted relative VE: 15%, 95% CI: -34–46%)[24]. This finding held when the analysis was confined to laboratory-confirmed influenza-related hospitalizations (adjusted relative VE: 25%, 95% CI: -24–54%).

Spadea et al. (2014) assessed the effectiveness of adjuvanted TIV (Fluad®) in the 2011–2012 influenza season and unadjuvanted TIV in the 2010–2011 influenza season compared to no vaccination in reducing the risk of hospitalization for influenza or pneumonia, based on ICD-9-CM codes, using a matched case-control design for each influenza season (and therefore for each vaccine type)[23]. Although the authors estimated VE for unadjuvanted TIV compared to no immunization in each season, the design of the study was not appropriate to compare the VE estimates for the adjuvanted and unadjuvanted vaccines as the assessments were conducted in different influenza seasons. Patients 65 years of age and older hospitalized for influenza or pneumonia (cases) were matched according to age and sex to patients hospitalized in the same period as cases for another condition (controls). Compared to no immunization, receipt of MF59-adjuvanted vaccine was associated with a statistically significant overall adjusted VE of 49% (95% CI: 30–60%) against hospitalization for influenza or pneumonia in adults 65 years of age and older in a mismatched influenza season. In age-stratified analysis, Fluad® was statistically significantly effective at reducing hospitalization for influenza or pneumonia in patients 75 years of age and older (adjusted VE: 53%, 95% CI: 33–68%), but not in subjects 65–74 years of age (adjusted VE: 34%, 95% CI: -24–65%). These age-stratified estimates have wide and overlapping 95% confidence intervals

Previous Evidence

The initial NACI review of published literature up to March 2011[13] identified four publications that assessed the effectiveness of Fluad® in the elderly against non-specific outcomes, such as ILI[32] and hospitalization for pneumonia[33, 34], influenza and pneumonia[35], acute coronary

syndrome or cerebrovascular accidents[34]. These publications all reported studies of observational designs, including one uncontrolled observational study by Iob et al. (2005)[32], a cohort study by Mannino et al. (2012)[35], and case-control studies by Puig-Barberà et al. (2004; 2007)[33, 34]. Findings from these observational studies suggest that the MF59-adjuvanted Fluad® subunit vaccine may be effective in reducing the risk of ILI and hospitalization for influenza and its complications in the elderly compared to unvaccinated individuals or individuals vaccinated with unadjuvanted subunit vaccine[13]. Further details of these studies can be found in the NACI Recommendations on the use of MF59-Adjuvanted Trivalent Influenza Vaccine (Fluad®): Supplemental Statement of Seasonal Influenza Vaccine for 2011–2012[13].

A subsequent literature review up to January 2013 identified a Canadian case-control study by Van Buynder et al. (2013)[36]. This observational study evaluated the comparative effectiveness of Fluad® to unadjuvanted TIV against laboratory-confirmed influenza in elderly individuals (65 years of age and older) residing in long-term care facilities or in the community for the 2011–2012 influenza season. The relative effectiveness of Fluad® compared with unadjuvanted TIV was 63% (95% CI: 4–86%) against laboratory-confirmed influenza[36]. Van Buynder et al. noted several limitations for their study, including small sample size and lack of control for external factors that may determine choice of vaccine. A detailed assessment of this study can be found in the NACI Statement on Seasonal Influenza Vaccine for 2014–2015[15].

IV. DISCUSSION

The present update to previous NACI reviews of the literature on the efficacy and effectiveness of Fluzone® High-Dose and MF59-adjuvanted Fluad® identified five studies of Fluzone® High-Dose[18-22] and four studies of Fluad®[23-26], all of which assessed VE for the two vaccines.

Findings from the newly identified studies suggest that Fluzone® High-Dose is significantly more effective than standard-dose vaccine in preventing ILI[22], non-laboratory-confirmed influenza-related death[22] and all-cause hospitalization[20-22]. Studies to date have not identified a benefit for vaccination with the high-dose vaccine over the standard-dose vaccine for hospitalization for influenza or pneumonia[19], all-cause mortality[19, 21] or functional decline[21]. However, there is some evidence to suggest that Fluzone® High-Dose is likely to provide current season clinical benefit over standard-dose vaccine irrespective of vaccination in the previous season with high-dose or standard-dose vaccine[18] and that high-dose vaccine is more effective than standard dose in preventing serious cardiorespiratory events possibly related to influenza[20]. There is now some further evidence in support of the preliminary indication for an age effect in that the high-dose vaccine may provide additional benefit in the very elderly[19].

For Fluad®, the newly identified observational studies provide some additional evidence of clinical benefit against hospitalization for influenza or pneumonia[23, 26] and laboratory-confirmed influenza infection[25] compared to a lack of vaccination in adults 65 years of age and older. The potential added benefit of using the MF59-adjuvanted vaccine over unadjuvanted vaccines could not be assessed in these studies due to either a lack of a comparison against an unadjuvanted vaccine[26] or due to methodological[23] or sample size[25] limitations.

Despite “good” quality ratings for studies included in the present literature review update according to the Harris et al. design-specific criteria for assessing the internal validity of individual studies[17], the previously noted methodological concerns for the body of efficacy and effectiveness evidence for these two vaccines[1, 13, 15] have not been adequately addressed by

the newly identified evidence. Observational studies comprise a majority of the identified VE evidence in the elderly and these study designs may be particularly susceptible to residual confounding, selection bias and other biases that may complicate the interpretation of effectiveness estimates[37]. Observational studies may also be prone to the healthy vaccinee bias if differences in functional status or health-related behaviors are not appropriately measured and controlled[38]. There are also factors inherent to investigations of influenza vaccination that may impact estimates of VE, such as influenza seasonality (temporal and geographic differences), vaccine mismatch with circulating influenza strains, and indirect protection from vaccination[39]. Other study-specific limitations such as sample size and data source (e.g., administrative data) that may impact estimates of VE are of additional concern. Therefore, these methodological limitations should be considered when interpreting the current body of efficacy and effectiveness evidence for Fluzone® High-Dose and Fluad®.

A study-specific limitation of particular concern is in the observational study by Spadea et al. (2014), rated as "poor" according to the Harris et al. criteria, in which the authors estimated the VE of the MF59-adjuvanted Fluad® and unadjuvanted TIV against hospitalization for influenza or pneumonia by comparing each vaccine type to unvaccinated individuals[23]. Although the Spadea et al. study was framed as a comparative study of adjuvanted TIV and unadjuvanted TIV by the authors, this study is of limited value as a comparative study since each vaccine type was assessed in a different influenza season (2010–2011 for unadjuvanted TIV and 2011–2012 for adjuvanted TIV). However, as the adjusted VE estimates compared to no vaccination were separately estimated for the adjuvanted and unadjuvanted vaccines (i.e., two matched case-control analyses were conducted, one for each influenza season and therefore for each vaccine type), despite a "poor" quality rating, the estimate of the effectiveness of Fluad® compared to no vaccination in preventing hospitalization for influenza or pneumonia in the 2011–2012 season remains relevant to the body of evidence.

Previously noted evidence gaps have not been addressed by the newly identified evidence. There remain no studies that compare high-dose vaccine with MF59-adjuvanted vaccine or either of these trivalent vaccines with QIV. Therefore there continues to be a need for head-to-head trials of high-dose vaccine, MF59-adjuvanted vaccine and QIV. Additional evidence of the efficacy or effectiveness of high-dose or MF59-adjuvanted vaccines in protecting persons with immune suppression and in those who are institutionalized, frail or very elderly is needed. Although a newly available study[19] bolstered the preliminary indications of better protection[28, 30] afforded by vaccination with Fluzone® High-Dose for elderly 75 or 85 years of age and older, further studies are needed to validate this purported age effect.

Overall, considering the potential methodological limitations of the body of evidence, the present literature review update did not identify evidence that warrants changing the conclusions of the previous reviews and concludes that:

1. There is good evidence that Fluzone® High-Dose provides superior protection (e.g., decrease in ILI[22], influenza-related death[22] and all-cause hospitalization[20-22]) compared with standard-dose TIV in the elderly (Grade A Evidence);
2. There is fair evidence that the MF59-adjuvanted Fluad® may be effective at reducing the risk of hospitalization for influenza and influenza complications in the elderly compared to unvaccinated individuals (Grade B Evidence);
3. There is insufficient evidence that Fluad® is effective at reducing the risk of hospitalization for influenza and influenza complications in the elderly compared to those who received unadjuvanted trivalent inactivated subunit vaccine (Grade I Evidence); and

4. There is no identified evidence on how the high-dose vaccine directly compares to the MF59-adjuvanted Fluad® (Grade I Evidence).

V. LIST OF ABBREVIATIONS

Abbreviation	Term
CDC	Centers for Disease Control and Prevention (US)
CI	Confidence interval
HA	Haemagglutinin
HD	High dose
ICD	International Classification of Diseases
ILI	Influenza-like illness
NACI	National Advisory Committee on Immunization
NP	Nasopharyngeal
OR	Odds ratio
PCR	Polymerase chain reaction
PHAC	Public Health Agency of Canada
QIV	Quadrivalent inactivated influenza vaccine
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard dose
SOS	Serious Outcomes Surveillance
STD	Standard deviation
TIV	Trivalent inactivated influenza vaccine
US	United States
VE	Vaccine effectiveness
VHA	Veterans Health Administration (US)

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Appendix A: Search Strategy and Results

Search 1: High-Dose Trivalent Inactivated Influenza Vaccine (Fluzone® High-Dose)

Limits:

- Vaccine efficacy or effectiveness
- Elderly only
- All countries
- English or French
- June 2014 to present

Set #	Searches	Results
MEDLINE (1 June 2014 to 22 March 2017)		
1	Influenza Vaccines/	19640
2	Influenza, Human/dt, pc, th [Drug Therapy, Prevention & Control, Therapy]	19577
3	exp Influenzavirus A/de [Drug Effects]	3155
4	exp Influenzavirus B/de [Drug Effects]	378
5	1 or 2 or 3 or 4	30968
6	Vaccines/ or Vaccines, Inactivated/ or Vaccination/	88143
7	Influenza, Human/ or exp influenzavirus a/ or exp influenzavirus b/	62126
8	(6 and 7) or 5	31548
9	(((influenza* or flu* or H?N?) adj5 (vaccin* or inocula*)) or fluzone).tw,kf.	26709
10	8 or 9	42406
11	high dose.tw,kf.	92569
12	dose-response relationship, immunologic/	11976
13	Dose-Response Relationship, Drug/	373572
14	11 or 12 or 13	463854
15	10 and 14	904
16	limit 15 to ("all aged (65 and over)" or "aged (80 and over)")	110
17	exp Nursing Homes/ or Homes for the Aged/ or exp Aged/	2729653
18	(senior* or older adult* or geriatric or retired or retiree* or elder* or pensioner* or nursing home*).tw,kf.	339163
19	15 and (17 or 18)	143
20	16 or 19	143
21	limit 20 to (english or french)	133
22	21 and (201406* or 201407* or 201408* or 201409* or 20141* or 2015* or 2016* or 2017*).dc.	40
23	remove duplicates from 22	35
EMBASE (1 June 2014 to 22 March 2017)		
1	influenza vaccine/ or influenza vaccination/	36365
2	exp influenza/dt, pc, th [Drug Therapy, Prevention, Therapy]	29210
3	exp Influenza virus/pc [Prevention]	1
4	1 or 2 or 3	47896
5	vaccine/ or virus vaccine/ or inactivated virus vaccine/ or vaccination/	218645
6	exp influenza/ or exp Influenza virus/	94913

Set #	Searches	Results
7	(5 and 6) or 4	52861
8	(((influenza* or flu* or H?N?) adj5 (vaccin* or inocula*)) or fluzone).tw,kw.	32239
9	7 or 8	60587
10	high dose.tw,kw.	128041
11	drug megadose/ or drug dose increase/ or "effective dose (pharmacology)"/ or maximum permissible dose/ or maximum tolerated dose/ or recommended drug dose/ or dose response/	562021
12	10 or 11	611263
13	9 and 12	2316
14	limit 13 to aged <65+ years>	283
15	nursing home/ or exp elderly care/ or exp aged/	2651419
16	(senior* or older adult* or geriatric or retired or retiree* or elder* or pensioner* or nursing home*).tw,kw.	450836
17	13 and (15 or 16)	362
18	14 or 17	362
19	limit 18 to (english or french)	352
20	19 and (201406* or 201407* or 201408* or 201409* or 20141* or 2015* or 2016* or 2017*).dc.	90
21	remove duplicates from 20	72
Global Health (1 June 2014 to 22 March 2017)		
1	influenza/	13415
2	Immunization/ or vaccination/ or vaccines/ or inactivated vaccines/	77941
3	exp influenza viruses/ or exp Influenzavirus A/ or exp Influenzavirus B/	27460
4	(((influenza* or flu* or H?N?) adj5 (vaccin* or inocula*)) or fluzone).tw,hw.	11141
5	(2 and 3) or 4	12824
6	high dose.tw,kw.	10623
7	Dosage/	8654
8	6 or 7	18361
9	nursing homes/ or elderly/ or old age/ or retired people/	41432
10	(senior* or older adult* or geriatric or retired or retiree* or elder* or pensioner* or nursing home*).tw,kw.	57681
11	9 or 10	59138
12	5 and 8 and 11	43
13	limit 12 to (english or french)	42
14	limit 13 to yr="2014 -Current"	19
15	remove duplicates from 14	19
ProQuest Public Health Database (1 June 2014 to 22 March 2017)		
-	AB,TI,SU(((influenza* or flu* or H?N?) NEAR/5 (vaccin* or inocula*)) or fluzone) AND AB,TI,SU("high dose") AND AB,TI,SU(senior* or "older adult*" or geriatric or retired or retiree* or elder* or pensioner* or "nursing home*" or "long term care") Applied filters: Publication date: 2014–2017 Source type: NOT Newspapers	26

Set #	Searches	Results
Scopus (1 June 2014 to 22 March 2017)		
-	TITLE-ABS-KEY(((influenza* OR flu* OR h?n?) W/5 (vaccin* OR inocula*)) OR fluzone) AND TITLE-ABS-KEY("high dose") AND TITLE-ABS-KEY(senior* OR "older adult*" OR geriatric OR retired OR retiree* OR elder* OR pensioner* OR "nursing home*" OR "long term care") AND (LIMIT-TO(PUBYEAR, 2017) OR LIMIT-TO(PUBYEAR, 2016) OR LIMIT-TO(PUBYEAR, 2015) OR LIMIT-TO(PUBYEAR, 2014)) AND (LIMIT-TO(LANGUAGE, "English"))	28

Search 2: MF59-Adjuvanted Trivalent Inactivated Influenza Vaccine (Fluad®)

Limits:

- Vaccine efficacy or effectiveness
- Not MF59-adjuvanted pandemic A(H1N1)pdm09 influenza vaccine
- Elderly only
- All countries
- English or French
- 2012 to present

Set #	Searches	Results
MEDLINE (1 January 2012 to 22 March 2017)		
1	Influenza Vaccines/	19640
2	Influenza, Human/dt, pc, th [Drug Therapy, Prevention & Control, Therapy]	19577
3	exp Influenzavirus A/de [Drug Effects]	3155
4	exp Influenzavirus B/de [Drug Effects]	378
5	1 or 2 or 3 or 4	30968
6	Vaccines/ or Vaccines, Inactivated/ or Vaccination/ or Adjuvants, Immunologic/	119410
7	Influenza, Human/ or exp influenzavirus a/ or exp influenzavirus b/	62126
8	(6 and 7) or 5	31650
9	(((influenza* or flu* or H?N?) adj5 (vaccin* or inocula*)) or fluad).tw,kf.	26710
10	8 or 9	42488
11	MF59*.tw,kf.	470
12	10 and 11	295
13	limit 12 to ("all aged (65 and over)" or "aged (80 and over)")	94
14	exp Nursing Homes/ or Homes for the Aged/ or exp Aged/	2729653
15	(senior* or older adult* or geriatric or retired or retiree* or elder* or pensioner* or nursing home*).tw,kf.	339163
16	12 and (14 or 15)	126
17	13 or 16	126
18	limit 17 to (english or french)	123
19	18 and (2012* or 2013* or 2014* or 2015* or 2016* or 2017*).dc.	54
20	remove duplicates from 19	51

Set #	Searches	Results
EMBASE (1 January 2012 to 22 March 2017)		
1	influenza vaccine/ or influenza vaccination/	36365
2	exp influenza/dt, pc, th [Drug Therapy, Prevention, Therapy]	29210
3	exp Influenza virus/pc [Prevention]	1
4	1 or 2 or 3	47896
5	vaccine/ or virus vaccine/ or inactivated virus vaccine/ or vaccination/ or immunological adjuvant/	228444
6	exp influenza/ or exp Influenza virus/	94913
7	(5 and 6) or 4	52893
8	(((influenza* or flu* or H?N?) adj5 (vaccin* or inocula*)) or fluad).tw,kw.	32175
9	7 or 8	60617
10	MF59*.tw,kw.	587
11	9 and 10	366
12	limit 11 to aged <65+ years>	112
13	nursing home/ or exp elderly care/ or exp aged/	2651419
14	(senior* or older adult* or geriatric or retired or retiree* or elder* or pensioner* or nursing home*).tw,kw.	450836
15	11 and (13 or 14)	137
16	12 or 15	137
17	limit 16 to (english or french)	132
18	17 and (2012* or 2013* or 2014* or 2015* or 2016* or 2017*).dc.	63
19	remove duplicates from 18	54
Global Health (1 January 2012 to 22 March 2017)		
1	Immunization/ or vaccination/ or vaccines/ or inactivated vaccines/ or adjuvants/	79402
2	exp influenza viruses/ or exp Influenzavirus A/ or exp Influenzavirus B/	27460
3	(((influenza* or flu* or H?N?) adj5 (vaccin* or inocula*)) or fluad).tw,hw.	11140
4	(1 and 2) or 3	12830
5	MF59*.tw,kw.	237
6	nursing homes/ or elderly/ or old age/ or retired people/	41432
7	(senior* or older adult* or geriatric or retired or retiree* or elder* or pensioner* or nursing home*).tw,kw.	57681
8	6 or 7	59138
9	4 and 5 and 8	56
10	limit 9 to (english or french)	55
11	limit 10 to yr="2012 -Current"	23
12	remove duplicates from 11	23
ProQuest Public Health Database (1 January 2012 to 22 March 2017)		
-	AB,TI,SU(((influenza* or flu* or H?N?) NEAR/5 (vaccin* or inocula*)) or fluad) AND AB,TI,SU(MF59*) AND AB,TI,SU(senior* or "older adult*" or geriatric or retired or retiree* or elder* or pensioner* or "nursing home*" or "long term care") Applied filters: Publication date: 2012–2017	21

Set #	Searches	Results
Scopus (1 January 2012 to 22 March 2017)		
-	TITLE-ABS-KEY(((influenza* OR flu* OR h?n?) W/5 (vaccin* OR inocula*)) OR fluad) AND TITLE-ABS-KEY(mf59*) AND TITLE-ABS-KEY(senior* OR "older adult*" OR geriatric OR retired OR retiree* OR elder* OR pensioner* OR "nursing home*" OR "long term care") AND (LIMIT-TO(PUBYEAR, 2017) OR LIMIT-TO(PUBYEAR, 2016) OR LIMIT-TO(PUBYEAR, 2015) OR LIMIT-TO(PUBYEAR, 2014) OR LIMIT-TO(PUBYEAR, 2013) OR LIMIT-TO(PUBYEAR, 2012)) AND (LIMIT-TO(LANGUAGE, "English"))	43

Appendix B: Level of Evidence Based on Research Design and Quality (Internal Validity) Rating of Evidence

Table B1: Levels of evidence based on research design

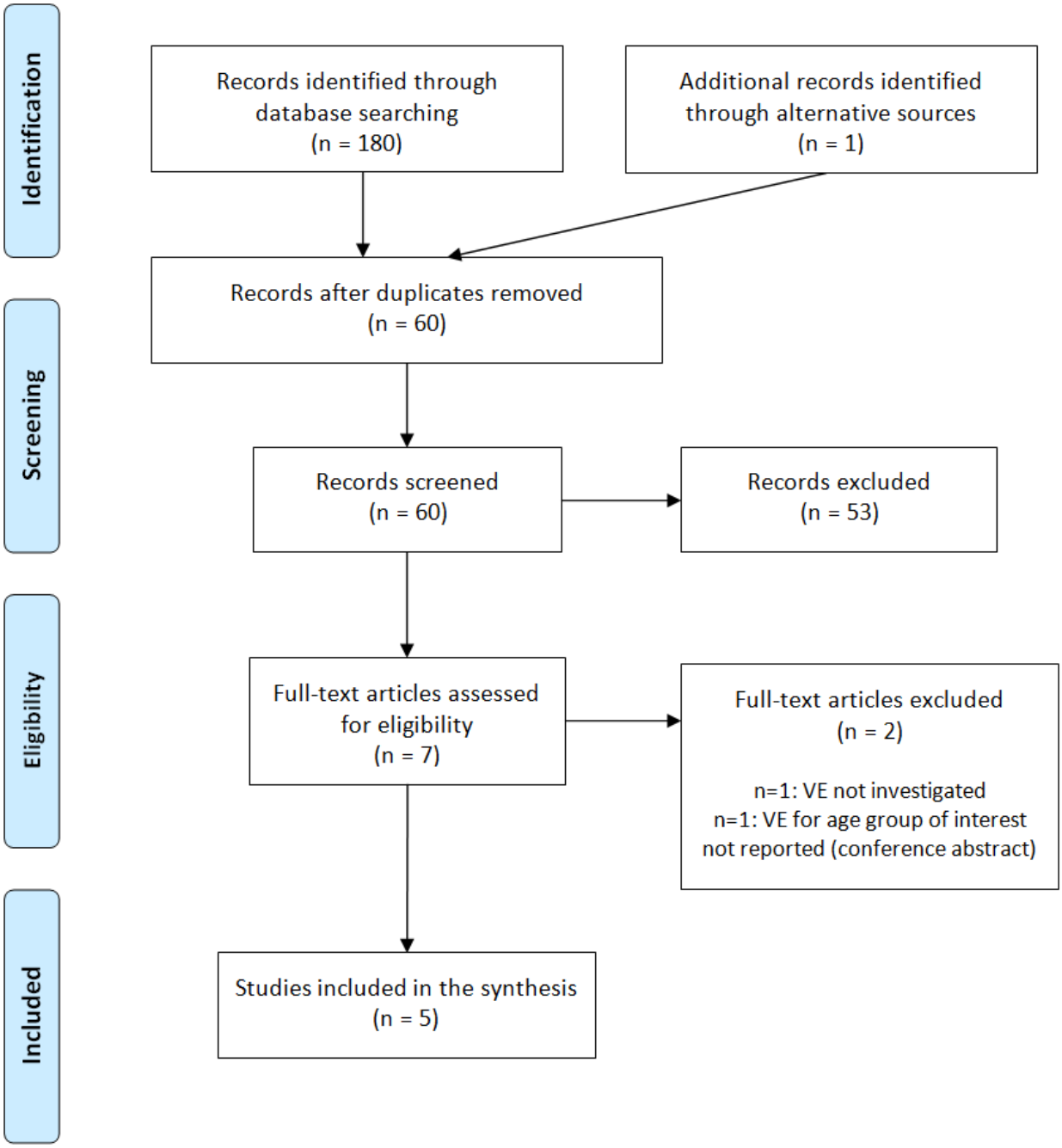
I	Evidence from randomized controlled trial(s).
II-1	Evidence from controlled trial(s) without randomization.
II-2	Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group using clinical outcome measures of vaccine efficacy.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

Table B2: Definition of overall study quality

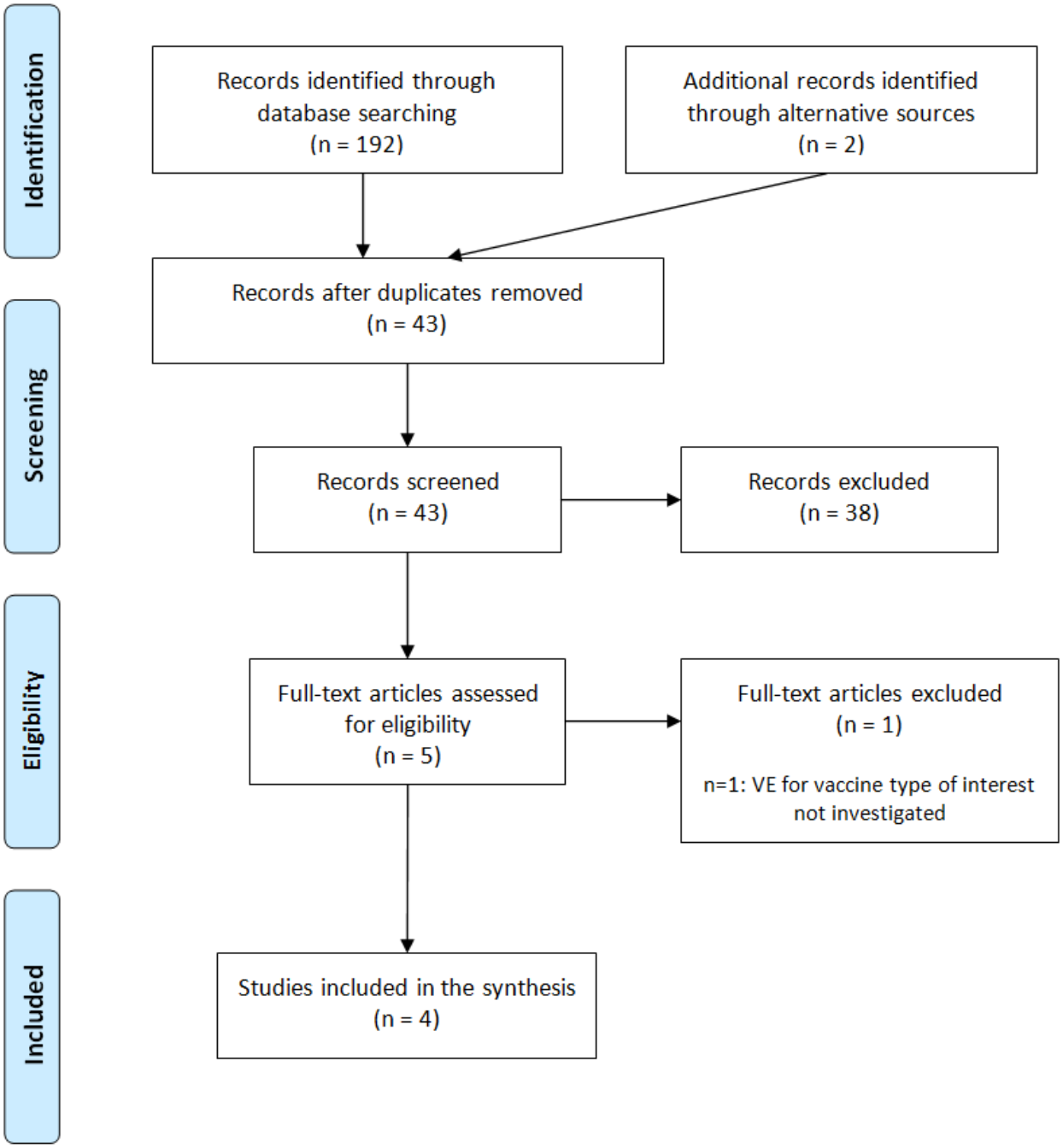
Good	A study (including meta-analyses or systematic reviews) that meets all design-specific criteria* well.
Fair	A study (including meta-analyses or systematic reviews) that does not meet (or it is not clear that it meets) at least one design-specific criterion but has no known "fatal flaw".
Poor	A study (including meta-analyses or systematic reviews) that has at least one design-specific "fatal flaw", or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations.

* General design-specific criteria are outlined in Harris et al. (2001)[17].

Appendix C: Flow Diagram of the Study Selection Process for Literature Evidence on the Efficacy and Effectiveness of High-Dose Trivalent Inactivated Influenza Vaccine (Fluzone® High-Dose) in Adults 65 Years of Age and Older



Appendix D: Flow Diagram of the Study Selection Process for Literature Evidence on the Efficacy and Effectiveness of MF59-Adjuvanted Trivalent Inactivated Influenza Vaccine (Fluad®) in Adults 65 Years of Age and Older



Appendix E: Summary of Literature Evidence Related to the Efficacy and Effectiveness of High-Dose Trivalent Inactivated Influenza Vaccine (Fluzone® High-Dose) in Adults 65 Years of Age and Older

<table>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level and quality of evidence</th></tr>
<tr>
<td>DiazGranados et al. (2015)[20]</td>
<td>Design
Supplementary analysis using data from a double blind RCT on prevention of serious cardiorespiratory events related to influenza following influenza vaccination

Influenza seasons
2011–2012
2012–2013

Location
US/Canada (126 centres)</td>
<td>HD:
• Fluzone® High-Dose (60 µg HA/strain)

SD:
• Fluzone® (15 µg HA/strain)</td>
<td>Population definition
Adults 65 years of age and older

Follow up
6–8 months post-vaccination each season

Sample size
Total: 31,989 participants randomized 1:1 into two arms:
• HD: 15,991
• SD: 15,998

Age
Mean:
• HD: 73.3 years
• SD: 73.3 years

Sex
56–57% female

Baseline characteristics
Baseline clinical and demographic characteristics were noted to be well balanced between groups</td>
<td>Outcomes
• All-cause hospitalization
• Serious cardiorespiratory events possibly related to influenza defined as events leading to death or hospitalization (or its prolongation); considered as life-threatening or medically important; or resulting in disability

<table>
<tr><th>Outcome</th><th>Relative VE* (95% CI) (%)</th></tr>
<tr><td>All-cause hospitalization</td><td>6.9 (0.5–12.8)</td></tr>
<tr><td>Serious cardiorespiratory events (overall)</td><td>17.7 (6.6–27.4)</td></tr>
<tr><td>Pneumonia events</td><td>39.8 (19.3–55.1)</td></tr>
<tr><td>Asthma/COPD/bronchial events</td><td>1.3 (-36.0–28.4)</td></tr>
<tr><td>Influenza events**</td><td>33.3 (-36.0–28.4)</td></tr>
<tr><td>Coronary artery events</td><td>2.4 (-25.3–24.0)</td></tr>
<tr><td>Congestive heart failure</td><td>24.0 (-7.2–46.1)</td></tr>
<tr><td>Cerebrovascular events</td><td>6.5 (-28.9–32.1)</td></tr>
<tr><td>Other respiratory events</td><td>34.0 (-3.8–58.1)</td></tr>
</table>
* Comparing HD with SD vaccine for both influenza seasons (2011–2012 and 2012–2013)
** Serious laboratory-confirmed influenza diagnosed outside study procedures by a participant's health-care provider

Narrative summary
• HD vaccine was statistically significantly more effective than SD vaccine in preventing all-cause hospitalization, but the point estimate of the relative VE is low and the lower limit of the 95% CI is close to the null value (i.e., "borderline statistical significance")
• HD vaccine was statistically significantly more effective than SD vaccine in preventing serious cardiorespiratory events possibly related to influenza overall and pneumonia events, but not other specific serious cardiorespiratory events

Note
• Supplementary analysis to DiazGranados et al. (2014)[27]</td>
<td>I

Good</td>
</tr>
<tr>
<td>DiazGranados et al. (2016)[18]</td>
<td>Design
Supplementary analysis using data from a double blind RCT on the</td>
<td>HD:
• Fluzone® High-Dose (60 µg HA/strain)

SD:</td>
<td>Population definition
Adults 65 years of age and older

Sample size
Total: 7643 of 14,500</td>
<td>Primary outcome
• Laboratory-confirmed influenza associated with a protocol-defined ILI caused by any strain (regardless of matching) in Y2</td>
<td>I

Good</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level and quality of evidence</th></tr>
<tr>
<td></td>
<td>effect of previous-year vaccination on current season VE

Influenza seasons
2011–2012 (Y1)
2012–2013 (Y2)

Location
US/Canada (126 centres)</td>
<td>• Fluzone® (15 µg HA/strain)</td>
<td>participants vaccinated in Y1 re-enrolled in Y2 and included in four possible vaccination patterns:
• Y1 HD/Y2 HD: 1943
• Y1 SD/Y2 HD: 1880
• Y1 HD/Y2 SD: 1890
• Y1 SD/Y2 SD: 1930

Age
Mean (STD):
• Y1 HD/Y2 HD: 74.3 (5.6) years
• Y1 SD/Y2 HD: 74.1 (5.5) years
• Y1 HD/Y2 SD: 74.2 (5.7) years
• Y1 SD/Y2 SD: 74.3 (5.7) years

Sex
56.6–58.0% female

Baseline characteristics
Baseline clinical and demographic characteristics were noted to be well balanced between groups and similar to those reported in the full study; no striking differences were observed among the vaccination patterns</td>
<td>
<table>
<tr><th>Vaccination pattern</th><th>Relative VE (95% CI) (%)</th></tr>
<tr><td>Y1 HD or SD/Y2 HD (pooled)</td><td>28.3 (1.0–47.8)</td></tr>
<tr><td>Y1 HD/Y2 HD</td><td>25.1 (-8.9–48.8)</td></tr>
<tr><td>Y1 SD/Y2 HD</td><td>31.6 (-0.8–53.9)</td></tr>
<tr><td>Y1 HD/Y2 SD</td><td>11.2 (-27.4–38.2)</td></tr>
<tr><td>Y1 SD/Y2 SD</td><td>Reference</td></tr>
</table>
Secondary outcomes
• Culture-confirmed influenza associated with a protocol-defined ILI caused by any strain in Y2
• Laboratory-confirmed influenza associated with a protocol-defined ILI caused by vaccine-similar (matched) strains in Y2
• Culture-confirmed influenza associated with a protocol-defined ILI caused by vaccine-similar (matched) strains in Y2

<table>
<tr><th rowspan="2">Vaccination pattern</th><th colspan="3">Relative VE (95% CI) (%)</th></tr>
<tr><th>Culture-confirmed influenza, any strain</th><th>Laboratory-confirmed influenza, vaccine-similar strains</th><th>Culture-confirmed influenza, vaccine-similar strains</th></tr>
<tr><td>Y1 HD or SD/Y2 HD (pooled)</td><td>30.1 (2.3–49.38)</td><td>22.0 (-40.0–55.7)</td><td>26.6 (-32.6–58.6)</td></tr>
<tr><td>Y1 HD/Y2 HD</td><td>28.2 (-6.2–51.7)</td><td>23.2 (-51.4–61.7)</td><td>27.8 (-44.0–64.5)</td></tr>
<tr><td>Y1 SD/Y2 HD</td><td>32.1 (-1.4–54.9)</td><td>20.7 (-56.4–60.5)</td><td>25.3 (-48.8–63.3)</td></tr>
<tr><td>Y1 HD/Y2 SD</td><td>13.6 (-25.7–40.8)</td><td>-25.3 (-131–31.3)</td><td>-20.7 (-123–34.2)</td></tr>
<tr><td>Y1 SD/Y2 SD</td><td>Reference</td><td>Reference</td><td>Reference</td></tr>
</table>
Narrative summary
• Relative to participants who received SD for both seasons, VE against influenza infection was higher for HD vaccine
• Logistic regression modeling found that Y1 vaccination was not a significant modifier of Y2 VE (p=0.43), but Y2 HD vaccination was significantly associated with lower influenza risk (p=0.043)
• HD vaccine is likely to provide clinical benefit over SD vaccine irrespective of previous season vaccination with HD or SD vaccine

Notes
• Protocol-defined ILI was defined as acute illness with at least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing or difficulty breathing; and concurrent with at
</td>
<td></td>
</tr>
</table>

Study	Study design	Influenza vaccine	Participants	Summary of key findings	Level and quality of evidence
				least one of the following systemic signs or symptoms: temperature greater than 37.2°C, chills, tiredness, headaches, or myalgia • Laboratory confirmation of influenza in nasopharyngeal specimens was defined as a positive result for tissue culture and/or PCR • Supplementary analysis to DiazGranados et al. (2014)[27]	
Gravenstein et al. (2015)[21]	**Design** 2x2 factorial-cluster RCT **Influenza season** 2013–2014 **Location** US (38 states)	HD: • Fluzone® High-Dose (60 µg HA/strain) SD: • Fluzone® (15 µg HA/strain)	**Population definition** Residents 65 years of age and older living in study nursing homes (i.e., Medicare certified nursing homes within 50 miles of a CDC influenza reporting city) for greater than 90 days Excluded nursing homes already using HD vaccine in the prior year; having less than 50 long-stay residents; having greater than 20% of residents less than 65 years of age; that are hospital-owned; or did not submit Minimum Data Set data **Sample size** 823 nursing homes randomized into four arms: • Resident HD/staff free SD*: 193 • Resident HD/staff usual care*: 216 • Resident SD/staff free SD*: 226 • Resident SD/staff usual care*: 188 Total: 53,035 residents * Study also evaluated access to free SD vaccine for staff in long-term care setting	**Primary outcome** • All-cause hospitalization obtained from the nursing home Minimum Data Set discharge records **Secondary outcomes** • All-cause mortality obtained from the vital status indicator in the Medicare Vital Status file • Functional decline defined as the probability of declining at least 4 points on the 28-point Activities of Daily Living Scale **Narrative summary** • All-cause hospitalization was statistically significantly reduced among HD group residents compared to SD group residents (adjusted OR: 0.930, 95% CI: 0.875–0.988, p=0.020) • No statistically significant differences between HD and SD group residents were observed for all-cause mortality or functional decline rates (details are unpublished at time of review, but were presented to the NACI Influenza Working Group) **Notes** • Intent-to-treat analysis performed at the resident level • Findings for the primary outcome of resident-level incidence of hospitalization with a primary diagnosis of pulmonary and ILI based upon Medicare claims (ICD-9-CM codes 460–466, 480–488, 490–496, 500–518) as described in the methods paper is not reported in the published conference abstract or in the presentation to the NACI Influenza Working Group • Final analysis not available/published at time of review; study data extracted from published conference abstract[21] and methods paper[40]	I Good (based on preliminary reporting)

<table>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level and quality of evidence</th></tr>
<tr><td></td><td></td><td></td><td>(findings not included in the present review)

Age
Mean (STD):
• HD for residents: 83.3 (8.7) and 83.1 (8.8) years
• SD for residents: 83.1 (8.8) and 83.1 (8.9) years

Sex
72.2% female overall (71.8–72.7%)

Baseline characteristics
Similar group characteristics were observed</td><td></td><td></td></tr>
<tr><td>Richardson et al. (2015)[19]</td><td>Design
Retrospective cohort study

Influenza season
2010–2011

Location
US</td><td>HD:
• Fluzone® High-Dose (60 µg HA/strain)

SD:
• No specified (15 µg HA/strain)

Influenza vaccination status
Health insurance billing codes</td><td>Population definition
Community-dwelling elderly patients aged 65 years and older who received primary care at the VHA medical centres

Included patients who received a single dose of inactivated influenza vaccine as an outpatient between 1 August 2010 and the end of the 2010–2011 regional influenza season; aged 65 years and older at time of vaccination; had at least one primary care visit in the VHA in the year prior to vaccination; and from VHA facilities in which at least 50 patients received HD vaccine

Excluded patients who</td><td>Primary outcome
• Hospitalization for influenza or pneumonia defined as presence of inpatient record having ICD-9-CM codes 480–487 as the primary diagnosis

<table><tr><th>Age group</th><th>Propensity score-adjusted RR* (95% CI)</th><th>p-value</th></tr><tr><td>Overall</td><td>0.98 (0.68–1.40)</td><td>0.92</td></tr><tr><td>65–74 years</td><td>1.16 (0.71–1.88)</td><td>0.55</td></tr><tr><td>75–84 years</td><td>1.44 (0.82–2.52)</td><td>0.20</td></tr><tr><td>≥85 years</td><td>0.52 (0.29–0.92)</td><td>0.02</td></tr></table>* Comparing HD with SD vaccine

Secondary outcomes
• All-cause hospitalization
• All-cause mortality

<table><tr><th>Outcome</th><th>Propensity score-adjusted RR* (95% CI)</th><th>p-value</th></tr><tr><td>All-cause hospitalization</td><td>0.99 (0.86–1.16)</td><td>0.94</td></tr><tr><td>All-cause mortality</td><td>1.05 (0.87–1.26)</td><td>0.61</td></tr></table>* Comparing HD with SD vaccine</td><td>II-2

Good</td></tr>
</table>

Study	Study design	Influenza vaccine	Participants	Summary of key findings	Level and quality of evidence
			received more than one dose of influenza vaccine or who received live attenuated influenza vaccine **Sample size** • HD: 25,714 • SD: 139,511 **Age** Mean (STD): • HD: 75.5 (7.45) years • SD: 75.0 (7.43) years % 85 years of age and older: • HD: 14.1 • SD: 13.1 **Sex** • HD: 1.5% female • SD: 1.8% female **Baseline characteristics** HD recipients were slightly older, more likely to be black, assessed with higher Elixhauser comorbidity scores and more likely to have HIV and exposure to immunosuppressive drugs	**Narrative summary** • Risk of hospitalization for influenza or pneumonia was not statistically significantly lower among patients receiving HD vaccine vs. those receiving SD vaccine • There was no statistically significant difference between those who received HD and SD vaccines for all-cause hospitalization and all-cause mortality • In age-stratified analysis, receipt of HD vaccine was statistically significantly associated with lower rates of hospitalization for influenza or pneumonia in patients 85 years of age and older **Notes** • Outcomes were included if they occurred greater than two weeks after vaccination and in the period of the regional influenza season • Propensity score was derived from a logistic regression model for the probability of receiving HD vaccine, including patient age, sex, race, Elixhauser comorbidity score, HIV infection, use of immunosuppressive medication and other predictor variables	
Shay et al. (2017)[22]	**Design** Retrospective cohort study **Influenza seasons** 2012–2013 2013–2014	HD: • Fluzone® High-Dose (60 µg HA/strain) SD: • Unspecified (15 µg HA/strain)	**Population definition** Medicare beneficiaries aged 65 years and older enrolled in fee-for-service care who received influenza vaccines in community-located pharmacies offering both HD and SD	**Primary outcome** • Post-influenza death defined as death occurring within 30 days following a Medicare claim for an inpatient hospitalization or an emergency department visit with a diagnosis of influenza (ICD-9-CM codes 487.xx and 488.xx)	II-2 Good

<table>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level and quality of evidence</th></tr>
<tr>
<td></td>
<td>Location
US</td>
<td>Influenza vaccination status
Health insurance billing codes</td>
<td>vaccines

Excluded beneficiaries who first enrolled in Medicare for any reason other than reaching 65 years of age (e.g., specifically being disabled or having end-stage renal disease) and those who did not receive HD or SD vaccine at a community-located pharmacy that vaccinated at least one beneficiary with the alternative influenza vaccine in the 14 days preceding or following each vaccination date in order to help adjust for temporal and geographical factors that influenced the availability of or access to HD vaccine

Sample size
Total: 5,797,090

2012–2013:
• HD: 1,039,645
• SD: 1,683,264

2013–2014:
• HD: 1,508,176
• SD: 1,877,327

Sex
2012–2013:
• HD: 57.9% female
• SD: 59.3% female

2013–2014:
• HD: 58.3% female
• SD: 59.7% female</td>
<td>
<table>
<tr><th>Season</th><th>Adjusted relative VE* (95% CI) (%)</th></tr>
<tr><td>Overall</td><td>24.0 (0.6–41.8)</td></tr>
<tr><td>2012–2013</td><td>36.4 (9–55.6)</td></tr>
<tr><td>2013–2014</td><td>2.5 (-46.8–35.3)</td></tr>
</table>
* Comparing HD with SD vaccine

Secondary outcomes
• Hospitalized influenza defined as hospitalization or emergency department visit listing an ICD-9-CM code for influenza

<table>
<tr><th>Season</th><th>Adjusted relative VE* (95% CI) (%)</th></tr>
<tr><td>Overall</td><td>18.6 (14.1–22.9)</td></tr>
<tr><td>2012–2013</td><td>22.1 (16.6–27.3)</td></tr>
<tr><td>2013–2014</td><td>12.7 (4.9–19.9)</td></tr>
</table>
* Comparing HD with SD vaccine

• ILI defined as likely influenza-related office visit with claims for rapid influenza diagnostic test and for dispensing of a treatment regimen of oseltamivir within two days of the test

<table>
<tr><th>Season</th><th>Adjusted relative VE* (95% CI) (%)</th></tr>
<tr><td>Overall</td><td>15.3 (9.7–20.6)</td></tr>
<tr><td>2012–2013</td><td>22.0 (14.8–28.6)</td></tr>
<tr><td>2013–2014</td><td>6.8 (-2.3–15.1)</td></tr>
</table>
* Comparing HD with SD vaccine

Narrative summary
• HD vaccine was statistically significantly more effective in preventing post-influenza deaths overall and for the A(H3N2)-dominant 2012–2013 influenza season, but not for the A(H1N1)-dominant 2013–2014 influenza season
• Consistently higher estimates of comparative effectiveness for the HD vaccine vs. SD vaccine were observed across outcomes during the A(H3N2)-dominant 2012–2013 influenza season compared to the A(H1N1)-dominant 2013–2014 influenza season
• Comparative effectiveness varied significantly by influenza season for ILI (season-vaccine interaction: p=0.006) and hospital-diagnosed influenza (p=0.041), but was only suggestively different for post-influenza death (p=0.12)

Notes
• Authors indicated that influenza vaccines and circulating viruses were similar during the 2012–2013 and 2013–2014 seasons
• Follow-up study to Izurieta et al. (2015)[29]; age-stratified analysis not investigated or reported in this follow-up study
</td>
<td></td>
</tr>
</table>

Abbreviations: CDC, Centers for Disease Control and Prevention; CI, confidence interval; HA, haemagglutinin; HD, high dose; ICD, International Classification of Diseases; ILI, influenza-like illness; PCR, polymerase chain reaction; RCT, randomized controlled trial; SD, standard dose; STD, standard deviation; US, United States; VE, vaccine effectiveness; VHA, Veterans Health Administration.

Appendix F: Summary of Literature Evidence Related to the Efficacy and Effectiveness of MF59-Adjuvanted Trivalent Inactivated Influenza Vaccine (Fluad®) in Adults 65 Years of Age and Older

<table>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level and quality of evidence</th></tr>
<tr>
<td>Gasparini et al. (2013)[26]</td>
<td>Design
Matched case-control study

Season
2010–2011

Location
Italy (Genoa; multicentre)</td>
<td>Adjuvanted:
• MF59-adjuvanted TIV (Fluad®)
• Virosomal TIV (Inflexal® V; 15 µg HA/strain), considered as an adjuvanted vaccine in this study

Unadjuvanted (not included in study analysis):
• Instanza® TIV (15 µg HA/strain)
• Other

Influenza vaccination status
Vaccination registry</td>
<td>Population definition
Case: Patient 65 years of age and older hospitalized for influenza or pneumonia with ICD-9 codes 480–487

Control: Subject who was not hospitalized for influenza or pneumonia in the study period

Cases and controls were matched 1:1 according to gender, age, socioeconomic status and type of influenza vaccine and matched cases and controls had the same general practitioner

Sample size
187 case-control pairs

Vaccination status
• Cases: 46.5% vaccinated
• Controls: 79.1% vaccinated

Age
Mean age (STD):
• Cases: 78.6 (8.3) years
• Controls: 77.7 (8.0) years

Sex
• Cases: 44.4% female
• Controls: 44.4%</td>
<td>Outcome
• Hospitalization for influenza or pneumonia

<table>
<tr><th>Vaccine type</th><th>Adjusted VE* (95% CI) (%)</th><th>p-value</th></tr>
<tr><td>Fluad® + Inflexal® V</td><td>94.8 (77.1–98.8)</td><td><0.001</td></tr>
<tr><td>Inflexal® V</td><td>95.2 (62.8–99.4)</td><td>0.004</td></tr>
<tr><td>Fluad®</td><td>87.8 (0.0–98.9)</td><td>0.09</td></tr>
</table>
* Comparing vaccinated with unvaccinated individuals

Narrative summary
• Adjuvanted vaccines (Fluad® and Inflexal® V) were associated with a statistically significant reduction in the risk of hospitalization for influenza or pneumonia
• In analysis restricted to MF59-adjuvanted Fluad®, the adjusted VE point estimate remained high, but did not reach statistical significance (p=0.09)

Notes
• The virosomal vaccine, Inflexal® V, is not available for use in Canada and was considered an adjuvanted vaccine in this study
• VE analysis was restricted to those vaccinated with adjuvanted vaccines (i.e., Fluad® or Infexal® V); therefore, 29 case-control pairs were excluded</td>
<td>II-2

Good</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level and quality of evidence</th></tr>
<tr><td></td><td></td><td></td><td>female

Baseline characteristics
Smoking and drinking were statistically significantly more common among cases than controls. More cases than controls suffered from heart disease, respiratory disease and renal disease, while more controls were affected by rheumatologic disease. The number of subjects with three or more risk factors was statistically significantly higher among cases.</td><td></td><td></td></tr>
<tr><td>McNeil et al. (2016)[25]</td><td>Design
Test-negative design case-control study

Influenza seasons
2011–2012
2012–2013
2013–2014

Location
Canada (14–45 academic and community hospitals)</td><td>Adjuvanted:
• MF59-adjuvanted TIV (Fluad®; although unspecified in the conference presentation, Fluad® is the sole MF59-adjuvanted TIV licensed for use in Canada)

Unadjuvanted:
• Unadjuvanted TIV

Influenza vaccination status
Self-report with verification with immunization provider or immunization registry (if</td><td>Population definition
Case: Patient 16 years of age and older with a positive test for influenza whose admission is attributable to influenza or a complication of influenza

Control: Patient at same site as cases with diagnosis compatible with influenza (i.e., eligible for NP swab at admission); NP swab obtained within seven days of onset of symptoms; negative test for influenza; admission date within 14 days of admission date of case; and same age strata as case (65 years and older or less than 65 years)

Sample size</td><td>Primary outcome
• Laboratory-confirmed influenza infection

<table><tr><th rowspan="2">Age group</th><th colspan="2">Adjusted VE* (%)</th></tr><tr><th>MF59-adjuvanted TIV**</th><th>Unadjuvanted TIV</th></tr><tr><td>Overall</td><td>61.0</td><td>35.8</td></tr><tr><td><65 years</td><td>20.7***</td><td>50.0</td></tr><tr><td>≥65 years</td><td>61.3</td><td>32.5</td></tr></table>* Comparing vaccinated with unvaccinated individuals across three influenza seasons (2011–2012 through 2013–2014)
** Wide and overlapping 95% CI for all age-stratified estimates
*** 95% CI crosses the null (i.e., lower limit less than 0%)

Narrative summary
• VE of MF59-adjuvanted influenza vaccine was about 61.3% in patients 65 years of age and older, representing an increase of approximately 30% over unadjuvanted vaccines, though the difference in VEs was not statistically significant (wide and overlapping 95% CIs)

Notes
• Laboratory confirmation of influenza A or B was defined as positive PCR or viral culture
• NP swab obtained from all patients with an admitting diagnosis of community-acquired pneumonia, exacerbation of chronic obstructive</td><td>II-2

Good (based on preliminary reporting)</td></tr>
</table>

<table>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level and quality of evidence</th></tr>
<tr><td></td><td></td><td>information is available)</td><td>• Cases: 3394
• Controls: 4560

Vaccination status
• Cases: 46.7% vaccinated
• Controls: 61.5% vaccinated

Age
Mean age (range):
• Cases: 67.7 (16–105) years
• Controls: 68.8 (16–104) years

% 65 years of age and older:
• Cases: 61.2
• Controls: 64.5</td><td>pulmonary disease/asthma, unexplained sepsis or any respiratory diagnosis of symptom
• Assumed protection from vaccine from 14 days post-vaccination
• Final analysis not available/published at time of review; study data extracted from published conference presentation[25]</td><td></td></tr>
<tr><td>Puig-Barberà et al. (2013)[24]</td><td>Design
Retrospective cohort study

Influenza season
2010–2011

Location
Spain (multicentre)</td><td>Adjuvanted:
• MF59-adjuvanted TIV (Fluad®; named Chiromas® in study location)
• Virosomal TIV (Inflexal® V)

Influenza vaccination status
Vaccination registry</td><td>Population definition
Community-dwelling elderly adults aged 65 years and older who were registered in a population-based register as vaccinated with any of the available seasonal influenza vaccines

Excluded institutionalized adults, individuals given unadjuvanted vaccines (i.e., non-virosomal or non-MF59-adjuvanted)

Sample size
• MF59-adjuvanted TIV: 197,180
• Virosomal TIV: 176,618

Sex
• MF59-adjuvanted</td><td>Outcome
• Influenza-related hospitalization defined as ICD-9-CM codes 487-488.89 from hospital discharges at least 15 days following vaccination date and linked to positive laboratory results for influenza

<table><tr><th>Outcome</th><th>Adjusted relative VE* (95% CI) (%)</th><th>p-value</th></tr><tr><td>All influenza-related hospitalization</td><td>15 (-34–46)</td><td>0.497</td></tr><tr><td>Laboratory-confirmed influenza-related hospitalization</td><td>25 (-24–54)</td><td>0.261</td></tr></table>* Comparing MF59-adjuvanted TIV with virosomal TIV

Narrative summary
• There was no statistically significant difference in the adjusted relative VE of MF59-adjvuanted TIV compared to virosomal TIV against influenza-related hospitalization in subjects 65 years of age and older

Notes
• The comparator virosomal vaccine, Inflexal® V, is not available for use in Canada and was considered an adjuvanted vaccine in this study
• Not all influenza-related hospitalizations were laboratory confirmed: 78% (n=29 of 37) of MF59-adjuvanted TIV-vaccinated cases had laboratory-confirmed influenza infection and 90% (n=36 of 40) of virosomal TIV-vaccinated cases had laboratory-confirmed influenza infection; study authors performed subgroup analysis restricted to</td><td>II-2

Good</td></tr>
</table>

<table>
<tr><th>Study</th><th>Study design</th><th>Influenza vaccine</th><th>Participants</th><th>Summary of key findings</th><th>Level and quality of evidence</th></tr>
<tr><td></td><td></td><td></td><td>TIV: 56% female
• Virosomal TIV: 55% female

Baseline characteristics
Similar age and sex distributions were observed for the two vaccinated groups and similar to that of the overall cohort</td><td>laboratory-confirmed influenza-related hospitalizations</td><td></td></tr>
<tr><td>Spadea et al. (2014)[23]</td><td>Design
Matched case-control study

Influenza seasons
2010–2011
2011–2012

Location
Italy</td><td>Adjuvanted:
• MF59-adjuvanted TIV (Fluad®; used for the 2011–2012 season)

Unadjuvanted:
• Unadjuvanted TIV, split virus preparation (used for the 2010–2011 season)

Influenza vaccination status
Cross-matching of hospitalization and immunization record databases</td><td>Population definition
Case: Patient 65 years of age and older hospitalized for influenza or pneumonia with ICD-9-CM codes 480–487

Case definition did not include positive laboratory confirmation of influenza virus

Control: Patient 65 years of age and older hospitalized in the same period as cases, but not for influenza or pneumonia

Cases and controls matched at least 1:3 for the 2010–2011 season and at least 1:4 for the 2011–2012 season according to age and sex

Sample size
2010–2011:
• Cases: 269
• Controls: 1247

2011–2012:
• Cases: 365
• Controls: 1227</td><td>Outcome
• Hospitalization for influenza or pneumonia
<table><tr><th rowspan="2">Age group</th><th colspan="2">Adjusted VE* (95% CI) (%)</th></tr><tr><th>MF59-adjuvanted TIV</th><th>Unadjuvanted TIV</th></tr><tr><td>Overall</td><td>49 (30–60)</td><td>48 (29–62)</td></tr><tr><td>65–74 years</td><td>34 (-24–65)</td><td>53 (3–78)</td></tr><tr><td>≥75 years</td><td>53 (33–68)</td><td>46 (24–62)</td></tr></table>* Comparing vaccinated with unvaccinated individuals

Narrative summary
• MF59-adjuvanted TIV was statistically significantly effective in preventing hospitalization for influenza or pneumonia compared to no vaccination (vaccine mismatch season)
• In age-stratified analysis, MF59-adjuvanted TIV was statistically significantly effective at reducing influenza-related hospitalization in patients 75 years of age and older, but not in subjects 65–74 years of age, suggesting a possible age effect in the elderly

Note
• Vaccine strain was well-matched for the 2010–2011 influenza season (unadjuvanted TIV use), but mismatched for the 2011–2012 influenza season (MF59-adjuvanted TIV use)</td><td>II-2

Poor

Adjuvanted and unadjuvanted vaccines were evaluated in different influenza seasons.</td></tr>
</table>

Study	Study design	Influenza vaccine	Participants	Summary of key findings	Level and quality of evidence
			Vaccination status 2010–2011: • Cases: 36.4% vaccinated • Controls: 46.5% vaccinated 2011–2012: • Cases: 21.4% vaccinated • Controls: 35.9% vaccinated **Sex** 2010–2011: • Cases: 50.6% female • Controls: 69.4% female 2011–2012: • Cases: 54.5% female • Controls: 67.2% female **Age** % 75 years of age and older: 2010–2011: • Cases: 78.4 • Controls: 55.3 2011–2012: • Cases: 78.4 • Controls: 64.5		

Abbreviations: CI, confidence interval; ICD, International Classification of Diseases; NP, nasopharyngeal; PCR, polymerase chain reaction; TIV, trivalent inactivated influenza vaccine; VE, vaccine effectiveness.