An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)†

A Review of the Literature of High Dose Seasonal Influenza Vaccine for Adults 65 Years and Older

PROTECTING CANADIANS FROM ILLNESS

Public Health Agency of Canada
Agence de la santé publique du Canada

Canada

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PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (hereafter referred to as the Agency) with ongoing and timely medical, scientific, and public health advice relating to immunization. The Agency 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 the Agency's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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EXECUTIVE SUMMARY

Adults 65 years of age and older are at higher risk of becoming seriously ill or dying if they become sick with influenza, and their immune response to influenza vaccines is lower than that of younger people. Several influenza vaccines have been developed in an attempt to induce higher antibody responses that may increase effectiveness in older adults, including Fluad®, which is an adjuvanted vaccine with the same amount of antigen (15µg haemagglutinin [HA] per virus strain) as the standard inactivated influenza vaccine, Intanza®, which is an intradermally administered vaccine (15µg HA/strain), and Fluzone® High Dose vaccine, which has four times the concentration of influenza virus antigen as the standard inactivated influenza vaccine. As noted in the Statement on Seasonal Influenza Vaccine for 2015-2016 (subsequent to the completion of the initial review of the literature), Sanofi Pasteur confirmed that Intanza® is no longer available on the Canadian market, however studies involving Intanza® are still summarized in this review as this announcement was not made until after the preparation of this report. Additionally, Fluzone® High Dose vaccine has since (Autumn 2015) received authorization for use in Canada.

In one large randomized controlled trial, people 65 years and older who received Fluzone® High Dose were 18-24% less likely to have laboratory-confirmed influenza than people who received Fluzone® (standard dose). Fluzone® High Dose vaccine has been shown to have significantly higher rates of antibody production (seroconversion, seroprotection, and post-vaccination geometric mean antibody titres) than Fluzone® (15µg HA/strain) and the intradermal inactivated influenza vaccine, Intanza® (15 µg HA/strain). The high dose vaccine and the intradermal vaccine did induce higher rates of reaction post-injection than the standard dose, but they were short-lived.

In conclusion, in people 65 years of age and older, the inactivated influenza vaccine containing higher doses of antigen (15 µg HA/strain for intradermal vaccine and >15 µg HA/strain for intramuscular vaccine) induced relatively higher serologic responses. Reduced influenza illness compared to the standard dose intramuscular inactivated vaccine was demonstrated in a few studies. A higher rate of post-injection local adverse events was noted with the higher dose product.

Note: An update to the literature review was conducted to find new studies indexed between June 27, 2014 and June 22, 2015. The additional literature included support to the original findings (see Section VII for more details).

I. INTRODUCTION

Background

The risk of becoming severely ill or dying when infected with influenza increases as adults age. During the influenza seasons from 2003-04 through 2010-11, excepting the pandemc of 2009, 55-65% of hospital separations in Canada and about 87% of deaths due to influenza occurred in citizens 65 years or older, although this age group only made up about 14% of the population[1]. Although vaccination against influenza is the best strategy to prevent illness[2], studies show a reduced response to vaccines as people age[3], with the presence of one or more chronic diseases a marker for reduced response[4, 5]. Immunosenescence is hypothesized to play a role in older adults' response to vaccines. Goodwin et al.[3] estimate that, after adjusting for vaccine and host factors, rates of seroconversion and seroprotection in older adults were 50-75% lower than that of younger adults.

In a recent meta-analysis, Beyer et al.[6] estimate that vaccine effectiveness against laboratory-confirmed influenza was about 49% ($CI_{95\%}$ 33, 62) in adults 65 years and older. This is lower than the effectiveness of 59% ($CI_{95\%}$ 51, 67) for healthy adults 18-64 years old as estimated by Osterholm et al.[7] in their meta-analysis of the literature. There is growing pressure to improve influenza vaccine effectiveness, especially in older adults who are at higher risk of complications when they contract influenza.

There are influenza vaccines specifically formulated for older adults. Fluad®, which is available in Canada, is an adjuvanted vaccine that has 15µg haemagglutinin of each strain in the vaccine and is injected intramuscularly; Intanza®, which was previously available in Canada, has 15µg haemagglutinin of each strain and is injected intradermally. The 15µg formulation of Intanza® is considered high-dose compared to the 9µg formulation that was intended for adults aged 18 to 59 years of age. Both the 9µg and 15µg intradermal products are no longer available in Canada. Fluzone® High Dose, which is authorized for use in Canada as of Autumn 2015, contains 60µg of haemagglutinin per strain and is injected intramuscularly. Another vaccine referred to in this review is Flublok®. It is an intramuscular, recombinant influenza vaccine that uses insect cells in the replication process rather than chicken eggs and contains 45µg of haemagglutinin of each strain. It is authorized in the United States of America for adults 18 years of age and older, but is not authorized in Canada.

Purpose and Objectives

The purpose of this report is to review, to assess, and to synthesize the currently available literature to determine whether the burden of influenza-related disease is lower in people 65 years and older (or subgroups thereof) who receive high dose trivalent inactivated influenza vaccine compared with those who receive standard dose inactivated trivalent, adjuvanted inactivated trivalent, or quadrivalent inactivated influenza vaccines.

II. METHODS

This project includes information for adults 65 years and older, with no limit on their underlying health conditions. Publications with data from a wider range of age groups are included when subgroup data are available for some or all of the target age group (65 years and older). The review includes all high dose influenza vaccines, whether authorized or not, but with clear explication of whether they are authorized in Canada, experimental, or authorized in other

countries[a]. The review excludes the 2009 H1N1pdm vaccine and experimental pandemic vaccines (e.g., H5N1 or H7N9).

The literature search was conducted in three databases: Medline, Embase, and EBM reviews-Cochrane Central Register of Controlled Trials. The search strategy was designed with the keywords and limits intended to capture all the articles in these databases that were relevant to the systematic review's disease, interventions, outcomes, population and time period of interest. The search strategy applied to each of the three databases on June 27, 2014 to capture records published since January 1, 2000 is detailed in Appendix A. Clinical trials registered on clinicaltrials.gov were also downloaded and matched, as possible, with existing publications. Two studies had data available but were not yet published, or published only as abstract. These data were included in the review.

The search yielded 8338 non-duplicate records (Appendix B). Two individuals screened the titles and abstracts for relevance. Records were excluded if it was clear from their title and abstract that their study population did not contain at least some proportion of adults aged 65 years and older, they were not influenza vaccine related, or if it was only about pandemic influenza vaccines and did not investigate seasonal influenza in any analyses. Finally, records were excluded if it was clear that their outcomes did not include any of: efficacy or effectiveness information (laboratory-confirmed influenza, clinic orphysician visit, hospitalization, influenza-related mortality), immunological data (seroconversion, seroprotection, or antibody titres), or safety (reactogenicity, local, systemic, or adverse reactions). Upon applying these criteria, 7779 records were excluded. The remaining records were retrieved for full-text review.

Each of the 559 articles retrieved for full-text review were screened again for relevance by two reviewers. Articles were only excluded if they were assessed as ineligible by both reviewers. If the first and second reviewers could not agree on the article's eligibility, the article was assessed by a third reviewer. Articles were designated as ineligible if they had greater than 10% of their study population either outside the age range or did not provide separate analysis for the age group of interest. Articles were also excluded if they did not present some data, whether through sub-group analyses or otherwise, that were about seasonal influenza vaccines, including data about vaccine efficacy or effectiveness, immunogenicity, or safety or reactogenicity. In addition, secondary research articles were excluded, as well as articles that analyzed data that were already included in the review via another article (unless it added information pertinent to the review). Lastly, studies were excluded if they contained insufficient information to assess its eligibility for the review or if it was a foreign language article that could not be reliably translated to and assessed in English. Based on these criteria 531 articles were excluded upon full-text review.

All remaining articles were assessed with regard to the level of evidence (see Appendix C, Table 1) and the quality of the study (see Appendix C, Table 2). Appendix D contains extracted information on efficacy and effectiveness, Appendix E on immunogenicity, and Appendix F on safety.

[a] At the time of preparation of the initial report, Intanza® was authorized and available for use in Canada. As of the 2015-16 influenza season, Intanza® is no longer available in Canada, but studies using this vaccine as a high-dose comparator are still summarized in this review.

III. RESULTS

III.1 Epidemiology

Illnesses caused by influenza viruses occur throughout the year with widespread seasonal waves happening almost every year. The annual global attack rate of influenza is estimated at 5-10% in adults and 20-30% in children[8]. Although rates of influenza infection are higher in children, rates of serious morbidity and mortality are highest in children younger than 2 years of age, adults 65 years of age or older, and people with underlying medical conditions[8, 9].

Molinari et al.[12] estimated attack rates of 20% of American children under 5 years of age, 10% in children 5-17 years, 6.6% in adults 18 to 64 years, and 9% in adults 65 years and older. Using the Canadian national surveillance system for monitoring influenza, FluWatch, from the 2011-12 to 2013-14 influenza season, seniors accounted for 21-44% of all influenza detections per season. A larger proportion of seniors tested positive for influenza A(H3) subtype (range: 35-56% per season) compared to influenza A(H1) (8-12%) or influenza B (20-37%) in the past three seasons, however this is also attributed in part to the predominance of A(H3N2) during 2011-12 and 2012-13. The number of laboratory-confirmed outbreaks in long-term care facilities reported to FluWatch ranged from 180 in the predominantly A(H1N1) 2013-2014 season to 676 in the predominantly A(H3N2) 2012-2013 season[13].

An estimated 175,000 emergency department visits per year are attributable to influenza-related illnesses in Canada[11, 14 1]. Between 1997 and 2004, rates of visits to healthcare practitioners and emergency rooms for pneumonia and influenza-related illnesses were higher for Canadian children younger than 5 years of age (107/1000) and adults 65 years and older (81/1000) than for people 5 to 64 years old (34/1000)[15].

It is also estimated that an average of 12,200 influenza related hospital admissions occur annually in Canada[1,11, 14]. Rates of hospitalization due to influenza are highest in adults 65 years and older (18/1000), followed by rates of 8/1000 for children younger than 5 years and 1/1000 in people 5 to 64 years old[15]. Data reported to FluWatch from the PHAC/CIHR Influenza Research Network (PCIRN) Serious Outcomes Surveillance (SOS) network indicates that for the 2011-12 through 2013-14 influenza seasons, people 65 years and older accounted for 33-68% of people hospitalized and 34-58% of people admitted to ICU who had laboratory-confirmed influenza. Adults 65 years and older account for approximately 15% of the Canadian population[61].

In Canada, as many as 4,000 deaths (range 300 to 6700 annually) may be caused, directly or indirectly, by influenza[14, 16]. The highest mortality rates are in people 65 years and older (108.8/100,000) followed by people 50-64 years old (4.0/100,000) and people younger than 50 years (0.04/100,000)[16]. Even among older adults, the estimated risk of influenza-attributable death increases with age, from 23/100,000 Canadians 65-69 years old to 831/100,000 in people 90 years and older[17]. The estimated risk of death due to influenza is about 12 times higher in older adults with chronic lung disease than those without chronic lung disease and about 5 times higher for those with heart disease than those without heart disease[17]. Data reported to FluWatch from the SOS network indicates that for the 2011-12 through 2013-14 influenza seasons, of people who had laboratory-confirmed influenza, people 65 years and older accounted for 55-85% of those who died.

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

III.2 Efficacy and Effectiveness

Four studies comparing the relative efficacy of high dose vaccines were identified and described below.

The relative efficacy of Fluzone® High Dose (60µg HA/strain) compared with Fluzone® (15µg HA/strain) has been evaluated in two studies to date. The first study of 9158 ambulatory, medically-stable adults 65 years and older was conducted in 2009-2010 during the H1N1 pandemic[21]. The relative efficacy was 12.5% in favour of Fluzone® High Dose against laboratory-confirmed influenza, but with exceedingly wide confidence bounds ($CI_{95\%}$ -140, 66); in this study 21 of the 22 symptomatic cases of influenza were caused by the A(H1N1)pdm09 strain, which was not in the seasonal vaccine.

The second study was conducted in 2011-2012 and 2012-2013[22]. In this study of almost 32,000 older adults, 18-24% fewer illnesses caused by influenza occurred in people who received Fluzone® High Dose compared with those who received Fluzone® (standard dose). The relative efficacy against laboratory-confirmed influenza of the high dose vaccine compared to the standard dose vaccine was 18% ($CI_{95\%}$ 5,30) in participants who provided swabs when they had an acute respiratory illness, with 2.0% and 2.4%, respectively, diagnosed with influenza. The relative efficacy against laboratory-confirmed influenza was 24% ($CI_{95\%}$ 10,36), with 1.4% and 1.9%, respectively, diagnosed with influenza, in those who provided swabs when they had an influenza-like illness (i.e., acute respiratory illness with systemic symptom(s)).

The relative efficacy of FluBlok® (~45 µg HA/strain), compared with Fluzone® (15µg HA/strain) against culture-confirmed influenza was 25%($CI_{95\%}$ -448, 96) in adults 65 years and older and 50% ($CI_{95\%}$ -76, 68) against culture- or serologic-confirmed influenza in this small (N=836) trial conducted in the USA[23]. FluBlok® is not authorized for use in Canada; in the USA, it is only authorized for use in adults 18-49 years of age[24].

The relative effectiveness of Intanza® (15µg HA/strain) compared with Inflexal® V (15µg HA/strain), a virosome-adjuvanted subunit influenza vaccine, was 33% ($CI_{95\%}$ 15, 48) against influenza-related hospitalization, for community-dwelling older adults in Spain[25]. This large (N=164,021) retrospective cohort study limited analysis to hospital admissions with either laboratory-confirmed influenza or a main hospital discharge diagnosis of influenza in 2011-2012. Neither of these vaccines are currently available in Canada.

III.3 Serological criteria for assessment of influenza vaccines

A common measure of immunogenicity is to assess the level of serum antibodies produced in response to antigens included in the vaccine through a laboratory test called a hemagglutination inhibition (HI) assay. Seroconversion is measured as the proportion of participants with a minimum of a four-fold increase from pre- to post-immunization titres (≤1:10 to ≥1:40 or at least 4-fold rise in antibody titres). Seroprotection is a measure of the proportion of participants with a HI titre of ≥1:40 (or ≥1:32 in some studies) post-vaccination[26] and is generally accepted as being correlated with a 50% reduction in the risk of influenza[27]. The geometric mean titre (GMT) is the geometric mean of the participants' (average of the logarithmic values of the titres) serum antibodies. The geometric mean fold rise (GMFR) is the ratio of the post-vaccination/pre-vaccination serum anti-haemagglutinin antibody titres.

When comparing two vaccines, there are two commonly used assessments: 1) the geometric mean titre ratio (GMTR), which uses the ratio of the post-vaccination GMT of people receiving each vaccine, and 2) the difference in the proportion of people who seroconvert in each group[27].

Non-inferiority of a new vaccine when comparing it to a licensed vaccine requires that: 1) the ratio of the post-vaccine GMT (GMT_1/GMT_0) has an upper-bound of 2-sided 95% confidence interval (CI) of <1.5 [or lower bound of >0.67], and 2) the difference in seroconversion rates ($seroconversion_1 – seroconversion_0$) has an upper bound of 2-sided 95% CI of <10 percentage points.

Table 1: Criteria for assessment of seasonal influenza vaccines for adults 60 years and older (not for assessment of live attenuated vaccines)

Committee	Seroconversion (or significant increase)	Seroprotection (1:40 HA)	GMFR	Requirement
Committee for Proprietary Medicinal Products (Europe)[26]	>30% of participants	>60% of participants	>2.0	At least one of three measures
Center for Biologics Evaluation & Research (USA)[27]	Lower bound of 2-sided 95% CI ≥30%	Lower bound of 2-sided 95% CI ≥60%	NA	Meets both

III.4 Immunogenicity

Immunogenicity refers to the ability of a vaccine to induce an immune response and is used to predict vaccine efficacy. As stated in the previous section, there are three common measures of immune response: seroprotection, seroconversion, and level of antibody titres as measured by geometric means.

High (>15 µg HA/strain) versus Standard Dose (15 µg HA/strain) Intramuscular Vaccines

60µg HA/strain Inactivated Intramuscular Vaccines

Four studies available at the time of this review compared the rates of seroconversion for study participants receiving vaccine containing 60µg (high dose) versus 15µg (standard dose) haemagglutinin (HA) per influenza strain. Rates of seroconversion were about 19% higher (ranging from 10-28%) for those receiving the higher dose vaccine - across all three strains in the vaccines and in all four studies[28-32]. In the two studies that assessed significance, the rates of seroconversion were significantly higher for all three strains in the vaccine[28, 29]. Similarly, rates of seroconversion were higher for those receiving the high compared to standard dose vaccines for participants 75 years and older and for a cohort of participants with underlying cardiopulmonary disease[28].

Five studies report higher rates of seroprotection for older adults vaccinated with the 60µg/strain product compared to those vaccinated with 15µg/strain vaccines[21, 28-33]. Four of the five studies assessed significance in these, seroprotection was significantly higher in the groups receiving the high dose vaccine for all three strains in three of the studies [28, 33, 34], but only against A(H1N1) in the fourth study[29]. The relative lack of difference in response to the high dose vaccine in the fourth study may be attributable to the fact that 78% of participants were vaccinated against the same influenza strains within 6 months prior to the study.

Geometric mean titre ratios (GMTR) of participants' responses to the high versus the standard dose influenza vaccines were reported by several authors and were calculated for those that provided group-specific post-vaccination titres for each of the vaccines. Seroresponse to the B strains in the vaccines was about 1.5 times greater (1.3-1.7) to the high dose vaccines than the standard dose vaccines. The GMTR of the A strains was about 1.8 times higher for those

receiving the high dose vaccines compared to the standard dose vaccines; ranging from 1.6-2.3, depending on the study[21, 28-33].

One unpublished study[35] followed older adults for two years following vaccination with either 15- or 60µg HA/strain. There were no differences between the small (N=50) groups in their geometric mean antibody titres two years after vaccination.

Authors of one study reported that older adults vaccinated with Fluzone® High Dose had higher rates of seroconversion and seroprotection and the ratio of post-vaccination geometric mean titres was significantly higher (1.3-1.4 to 1.0) for all three strains compared with those who received Intanza® (15µg HA per strain)[32].

30µg HA/strain Inactivated Intramuscular Vaccines
Della Cioppa et al.[36, 37] conducted a trial comparing the immune responses of a small number of older adults to a range of levels of H3N2 antigen (6- versus 12- and 15- versus 30µg HA), a range of amounts of adjuvant (0-100% of the amount used in the licensed vaccine, Fluad®), and intradermal compared with intramuscular administration. There were no significant differences in seroresponse between people who received 15µg versus 30µg HA of A(H3N2) antigen intramuscularly or people who received 6µg versus 12µg HA of A(H3N2) antigen intradermally.

A trial comparing nursing home resident who received a double dose (two injections of 15µg HA/strain licensed influenza vaccine in the same arm on the same day) were compared with residents who received the standard single dose[38]. A significantly higher proportion of residents who received a double dose seroconverted and were seroprotected against the A(H3N2) strain 25 days after vaccination, and remained so 84 days afterwards. There were no differences between the groups 106 days after vaccination. Only results for the A(H3N2) strain were reported.

60µg HA/strain Subunit Intramuscular Vaccines
In 1988 Palache et al.[39] conducted a randomized controlled trial in which older adults living in nursing homes in the Netherlands received 10-, 20-, or 60µg HA/strain trivalent subunit influenza vaccine (Duphar BV). The rates of seroprotection were higher for those who received the 60µg HA/strain vaccine than the vaccines with lower doses. The geometric mean titre ratio did not change by dose for the A(H1N1) antigen. However, for people receiving the 60µg/strain vaccine, the GMTR was 1.6 for A(H3N2) and 2.1 for the B strain compared to those receiving the 10µg/strain vaccine.

Recombinant Haemagglutinin Intramuscular Vaccines
A randomized controlled trial comparing the recombinant influenza vaccine Flublok®, containing ~45µg HA/strain with Fluzone® containing 15µg/strain was conducted with community-dwelling people 65 years and older[23]. The rates of seroconversion were significantly higher for both A strains of influenza for those receiving the higher dose vaccine. On the other hand, the rates of seroprotection were similar for the two vaccines. The B strain could not be compared since the strains were not the same in the two vaccines.

A randomized controlled trial compared the immunogenicity of several antigen levels of a recombinant influenza vaccine with Fluzone® containing 15µg/strain in participants 65 years and older[40]. The rates of seroprotection and seroconversion were higher for those receiving the 45µg and 135µg HA/strain of the recombinant vaccine than those receiving Fluzone® for the A(H3N2) strain but rates were similar for the A(H1N1) and B strains. In comparison, participants

receiving the 15µg/strain of recombinant vaccine had similar responses to the A(H3N2) strain and lower responses to both the A(H1N1) and B strains than those receiving Fluzone®.

High (>9µg HA/strain) Intradermal Influenza Vaccines

15µg HA/strain Inactivated Intradermal versus Standard Dose Inactivated Intramuscular Vaccines

Seven randomized controlled trials have been conducted with older adults comparing the immune responses of 15µg HA/strain intradermal influenza vaccines with 15µg HA/strain intramuscular vaccines[41-47]. The rates of seroconversion, seroprotection, and the GMTR were generally higher for people who received the high dose intradermal vaccine than those receiving standard dose intramuscular vaccines. However, in only two of the studies, both with large sample sizes, were the differences statistically significant[42, 46]. Arnou et al.[46] vaccinated older adults with the same vaccine annually for three years. Although rates of seroconversion and seroprotection were higher for those receiving the intradermal vaccine in the first year of the study, the rates were similar between the groups in the next two years when the sample size greatly diminished. Holland et al.[42] reported superior response to the intradermal vaccine compared with the standard dose intramuscular vaccine based on GMTR and significantly higher rates of serconversion for all three strains. The ratio of post-vaccination geometric mean titres for those vaccinated with the intradermal compared with intramuscular vaccines was about 1.3 times higher (range 1.0 to 1.8) across all studies.

15µg HA/strain Inactivated Intradermal versus 60µg HA/strain Inactivated Intramuscular Vaccine

In the one study that compared seroresponses, a higher percentage of participants receiving the 60µg HA/strain intramuscular vaccine seroconverted and were seroprotected than those receiving the 15µg HA/strain intradermal vaccine[32]. The post-vaccination geometric mean titres for those receiving the 60µg HA/strain intramuscular vaccine were significantly higher than those receiving the 15µg HA/strain intradermal vaccine.

15µg HA/strain Inactivated Intradermal versus Adjuvanted Standard Dose Intramuscular Vaccines

Five randomized trials compared serological responses for older adults vaccinated with 15µg HA/strain intradermal influenza vaccines and 15µg HA/strain adjuvanted intramuscular vaccines[41, 45, 48-50]. In one study with 905 participants, the adjuvanted intramuscular vaccine produced significantly higher rates of immunological response than the intradermal vaccine[41] while the participants in the other four studies had similar rates of seroconversion, seroprotection, and had similar GMFR. The post-vaccination ratio of geometric mean titres for those vaccinated with inactivated intramuscular influenza vaccine with an adjuvant was slightly higher than those vaccinated with an intradermal vaccine - about 1.1-1.2 (range 0.9 to 1.3).

III.5 Safety and adverse events

In adults 60 years and older, common local reactions to influenza vaccines without adjuvant that are injected intramuscularly include redness, swelling, pain, and induration. Local reactions common to vaccines injected intradermally include itchiness, soreness, redness, swelling, pain, and induration. These reactions last 2-3 days and rarely interfere with normal activities. Systemic reactions common to adults 60 years and older who receive influenza vaccines include headache, malaise, myalgia, fatigue, arthralgia, and fever.

High (>15µg HA/strain) versus Standard Dose (15µg HA/strain) Intramuscular Vaccines

60µg HA/strain Inactivated Intramuscular Influenza Vaccines

The 60µg HA/strain vaccines produce a significantly higher rate of systemic reactions than the 15µg HA/strain vaccines to which they were compared. One study reported a higher rate of systemic reaction without specifying the specific reaction[32]. Other studies reported significantly higher rates of malaise[28], myalgia[28, 31], and moderate/severe fever[28].

Rates of systemic reactions in the first 7 days after vaccination include (15µg versus 60µg, respectively): myalgia (15-18% vs. 13-29%), malaise (13-14% vs. 16-18%), headache (14-17% vs. 11-17%), and fever (0.5-2.3% vs. 0.7-4.4%)[28, 29, 31]. Rates of local reactions include: (15µg versus 60µg, respectively): pain (14-24% vs. 36-53%), redness (5-28 v 9-29%), and swelling (3-18% v 6-24%)[28, 29, 31].

Serious adverse events were similar in frequency between the 15- and 60-µg HA/strain vaccines. In 25,440 older adults who received the 60µg HA/strain vaccines, 6 (2.36/10,000) vaccine-related serious adverse events were reported including cardiac chest pain[21], oculorespiratory syndrome[29], cranial nerve VI palsy[33], hypovolemic shock[33], acute disseminated encephalomyelitis[33], and Crohn's disease exacerbation[28]. These events were classified by the study investigators as being vaccine-related.

30µg HA/strain Inactivated Intramuscular Influenza Vaccines

In the two studies there were no reported differences in the rate of local or systemic reactions for people who received the 15- or 30- µg HA/strain vaccines. There were no reported serious adverse events related to the vaccine among the 80 people who received the 30µg HA/strain vaccines[30, 37].

Recombinant Haemagglutinin Vaccines

Recombinant subunit influenza vaccines elicited significantly higher rates of injection site pain[40] and immediate injection site redness[23] than standard dose inactivated influenza vaccines. No serious adverse events were reported in the 730 recipients.

High (>9µg HA/strain) Dose Intradermal Vaccines

15µg HA/strain Intradermal

The intradermal administration of influenza vaccines produces significantly higher rates of local reaction including redness, swelling, induration, and pruritus than either of the standard dose inactivated vaccines (i.e. those with and those without adjuvant)[41-46, 49, 50]. Rates of systemic and local reactions (non-adjuvanted intramuscular versus intradermal, respectively) include: headache (11-18% vs. 4-17%), myalgia (6-19% vs. 6-23%), malaise (6-13% vs. 5-20%), fever (0-4% vs. 1-3%), and pain (6-21% vs. 4-30%), redness (4-15% vs. 26-76%), swelling (2-13% vs. 19-62%), induration (5-17% vs. 25-64%), and pruritus (2-9% vs. 20-29%)[41-43, 46, 50].

Four severe adverse events that may have been related to receipt of the intradermal vaccine were reported in 4815 older adults (8.31/10,000) including myopericarditis[46], facial neuralgia[46], brachial neuritis[42], and pneumonia[49].

For an overview of contraindications and precautions for influenza vaccines in general, please see the NACI annual statement on seasonal influenza vaccines.

IV. EVIDENCE GAPS

IV.1 Older Adults with Risk Factors

The majority of studies reviewed for this report were conducted with ambulatory, community-dwelling older adults without immune suppressing diseases and who were not using immune suppressing medication. Also, the mean age of the participants is in the early 70s, when the immune response is expected to be better than for older adults. Studies need to be completed in older adults with immune suppressing conditions or using immune suppressing medications, people who are institutionalized, and adults who are 75 years of age and older to determine whether these vaccines are as effective in these cohorts as they are in the younger, healthier cohorts of seniors.

IV.2 Types of Vaccines Compared

There are no studies, at present, to compare the efficacy or effectiveness of 60µg HA/strain inactivated intramuscular influenza vaccine to 1) 15µg HA/strain inactivated intramuscular influenza vaccine containing an adjuvant, or 2) 15µg HA/strain inactivated intradermal vaccine. Since these vaccines are manufactured specifically for use in older adults, a head-to-head comparison would be informative for decision-makers. Only one study compared the immune responses of older adults vaccinated with 60µg HA/strain to those vaccinated with 15µg HA/strain intradermal vaccine and none have compared the immunogenicity of the 60µg HA/strain product to 15µg HA/strain intramuscular influenza vaccine containing an adjuvant.

There are also no studies that compare any of these vaccines with the quadrivalent influenza vaccines. Although a previous review found similar immune responses and safety profiles for inactivated quadrivalent compared with inactivated trivalent influenza vaccines in older adults, no studies have assessed the efficacy or effectiveness of the quadrivalent vaccines in seniors.

V. DISCUSSION/SUMMARY

In one large randomized controlled trial, people 65 years and older who received Fluzone® High Dose were 18-24% less likely to have laboratory-confirmed influenza than people who received Fluzone® (standard dose)[33]. The high dose vaccine was shown to have significantly higher rates of seroconversion and seroprotection than its 15µg HA/strain standard dose counterpart. The post-vaccination geometric mean titres of people receiving the high dose vaccine was about 1.5-1.8 times higher than those receiving the standard dose vaccine, indicating higher relative antibody immune response 28 days after vaccination. The high dose vaccine does, however, induce higher rates of reaction post-injection but they were short-lived.

Intanza® (15µg HA/strain), which was produced for adults 60 years and older, was shown in one retrospective cohort study to reduce influenza-related hospitalization by 33% compared to the standard dose virosomal subunit trivalent influenza vaccine in community-dwelling adults 65 years and older[25]. Compared with standard dose intramuscular influenza vaccines, the rates of seroconversion and seroprotection are slightly higher in those receiving Intanza®. The post-vaccination geometric mean titres of people receiving Intanza® is about 1.3 times higher than those receiving the standard dose intramuscular vaccine. In comparison, people vaccinated with Intanza® (15µg HA/strain) had lower serological responses than those vaccinated with Fluzone® High Dose, but similar to those receiving adjuvanted formulations of influenza vaccines. The intradermal vaccine induced higher rates of reactogenicity than the non-adjuvanted intramuscular influenza vaccines.

VI. CONCLUSIONS

Higher dose intramuscular, trivalent inactivated influenza vaccine for older adults[b] should provide superior protection compared with the standard dose intramuscular vaccines, but whether it is superior to the currently-available adjuvanted intramuscular formulations is, as-yet, unknown. The higher dose intradermal influenza vaccine indicated for older adults induces higher serological immune responses than the standard dose intramuscular vaccines to which it has been compared, similar responses as adjuvanted inactivated influenza vaccines, but lower responses than the high dose intramuscular inactivated influenza vaccine. The intradermal product is no longer available in Canada. Fluzone® High Dose and Intanza® (15µg) influenza vaccines induce higher rates of post-injection reactions, but these reactions are short-lived.

[b] Fluzone High-Dose® was authorized for use in Canada in the Autumn of 2015.

VII. UPDATE TO THE REVIEW OF THE LITERATURE

Although anticipated, an intramuscular high dose seasonal influenza vaccine was not available on the market in Canada at the completion of the initial literature review. An update was conducted to ensure recommendations for the use of such a vaccine would be informed by a body of evidence that included the most current literature. The initial search strategy was replicated in Medline and EMBASE for literature indexed between June 27, 2014 and June 22, 2015. With the intradermal vaccine (Intanza®) no longer offered in Canada, studies using intradermal influenza vaccine as the high dose comparator were excluded.

The search yielded 1,003 non-duplicate records, with 73 articles undergoing full-text review. The review of the search results was conducted by two reviewers. Articles were only excluded if they were assessed as ineligible by both reviewers. If the first and second reviewers could not agree on the article's eligibility, the article was assessed by a third reviewer. Titles and abstracts, and full-text articles were screened for relevance and reasons for exclusion were the same as the initial review by two reviewers (see Methods section). Also excluded were articles that had previously been included in the review.

Two articles were subsequently selected for inclusion and were assessed for level of evidence (Appendix C, Table 1) and the quality of the study (Appendix C, Table 2). Appendix D contains extracted information on efficacy and effectiveness, and Appendix E on immunogenicity.

One study compared the relative efficacy of high dose vaccine and one assessed immunogenicity. Both are described below.

Izurieta et al. (2015) evaluated the relative efficacy of a high dose influenza vaccine [Fluzone® High Dose (60µg HA/strain)] and any standard dose influenza vaccine (15µg HA/strain) administered during the 2012-13 influenza season against probable influenza-related illness (community medical encounter with a rapid influenza diagnostic test and dispensing of oseltamivir), and hospital-in patient admission or emergency department visit with an influenza diagnosis[62]. The study participants included 2,545,275 community-based adults 65 years and older who were enrolled in Medicare in the United States. Fewer events were observed in recipients of the high dose vaccine for both outcomes and the relative efficacy was 22% in favour of the high dose vaccine for both outcomes (95% CI: 15, 29 for probable influenza-related illness, and 95% CI:16, 27 for hospitalization or emergency department visit). Relative efficacy for probable influenza-related illness increased to 36% (95% CI: 13, 54) in those 85 years and older.

Measures of immunogenicity were assessed in a study by Nace et al. (2015) comparing high dose influenza vaccine [Fluzone® High Dose (60µg HA/strain)] and a standard dose influenza vaccine (15µg HA/strain) in 187 frail adults 65 years and older residing in long-term care facilities over two influenza seasons (2011-12, 2012-13)[63]. While comparable at baseline, at Day 30, GMTs were significantly higher in recipients of the high dose vaccine during both seasons, except for H1N1 in 2012-13 and seroprotection was significantly higher for H3N2 and B during both seasons. At Day 180, GMTs were only significantly higher for H3N2 and seroprotection was only higher for H1N1 and H3N2, during the 2011-12 season in high dose vaccine recipients.

These two studies further support the conclusion of the original review that higher dose intramuscular, trivalent inactivated influenza vaccine for older adults should provide superior protection compared with the standard dose intramuscular vaccine. Izurieta et al (2015) demonstrates that this superior relative protection in older adults is enhanced in those 85 years and older. Nace et al. (2015) was also the first study to look at the use of high dose intramuscular influenza vaccine in a population of frail older adults, and begins to address an identified evidence gap. However, there continues to be a need for studies of high dose intramuscular trivalent inactivated influenza vaccine in high risk patients of all ages and for head-to-head trials of high dose intramuscular influenza vaccine, adjuvanted influenza vaccine, and the quadrivalent influenza vaccine.

VIII. LIST OF ABBREVIATIONS

Abbreviation	***Term***
AE	Adverse event
ADV	Adjuvanted vaccine
ARI	Acute respiratory illness
GMFR	Geometric mean fold rise (post-vaccine GMT/pre-vaccine GMT)
GMT	Geometric mean titre
GMTR	Geometric mean titre ratio (post-vaccine GMT_1/post-vaccineGMT_0)
HI	Haemagglutination inhibition
ID	Intradermally-administered vaccine
ILI	Influenza-like illness
IM	Intramuscularly-administered vaccine
LAIV	Live attenuated influenza vaccine
SAE	Serious adverse event
v	Versus

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Appendix A: Search strategy and results

Set	History	Results	Comments
	MEDLINE		
1	([influenza* or flu or "caiv-t" or laiv or grippe or "h1n1" or "h3n2"] adj5 [vaccin* or inocul* or inject*]).mp.	23003	Influenza vaccine textword Terms
2	(admune or afluria or agrippal or agriflu or alorbat or adiugrip or berigripina or biaflu-zonale or celvapan or chiromas or evagrip or flu-imune or fluogen or fluvaccin or gripavac or grippe-impfstoff or grippeimpfstoff or imovax or inflexal or influenzainum or influmix or influpozzi or influsplit or influvac or influvirus or isiflu or miniflu or nasalflu or niligrip or prodigrip or sandovac or anflu or batrevac or begrivac or "flu immune" or "flu imune" or "flu-vac" or flulaval or fluvirin or fluzone or fluarix or alluria or fluad or fluarix or fluax or "adju-fluax" or flublok or flucelvax or fluenz or flumist or fluinsure or "intranasal TIV" or flulaval or fluogen or flushield or fluvax or fluviral or fluvirin* or fluzone or gammaflu or grippovac or idflu or intanza or inflexal or influject or influpozzi or influsplit or influvac or intanza or invivac or mastaflu or "mfv ject" or munevan or mutagrip or niligrip or optaflu or preflucel or previgrip or trivalent or vacciflu or vaxigrip or "x-flu").mp.	5006	Specific vaccine textword Terms
3	(fluvax or Imuvac or Viroflu or Fluval or virosome or virosomal or Enzira or fluvirix or AS03 or MF59 or AS04 or virsomes).mp.	946	Specific vaccine textword Terms
4	Influenza Vaccines/	16309	Influenza Vaccines MeSH terms
5	orthomyxoviridae infections/ or influenza, human/	41942	Influenza Virus MeSH terms
6	influenzavirus a/ or influenza a virus/ or influenza a virus, h1n1 subtype/ or influenza a virus, h3n2 subtype/ or influenzavirus b/ or influenza b virus/	28418	Influenza Virus MeSH terms
7	or/1-6	64873	MEDLINE influenza vaccine or virus terms*
8	limit 7 to ("all aged [65 and over]" or "aged [80 and over]")	7844	Age group limit
9	nursing homes/ or Homes for the Aged/ or (aged or senior* or "older adult*" or geriatric or retired or retiree* or elder* or pensioner*).ti,ab.	561491	Aged MeSH or textword terms
10	8 or (7 and 9)	10017	Geriatric age group results - Base Clinical Set
11	(clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or meta analysis or multicenter study or randomized controlled trial or pragmatic clinical trial).pt. or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or pragmatic clinical trials as topic/ or multicenter studies as topic/ or observational study as topic/ or meta-analysis as topic/ or double-blind method/ or single-blind method/ or (rct or rcts or random* or multicent* or placebo* or metaanalysis* or "meta-analysis" or sham or effectiveness or efficacy or compare*).mp. or (meta adj5 analysis).mp. or ([singl: or doubl: or tripl: or trebl:) adj5 (mask:	3492788	Clinical Trial MeSH and Textword Terms

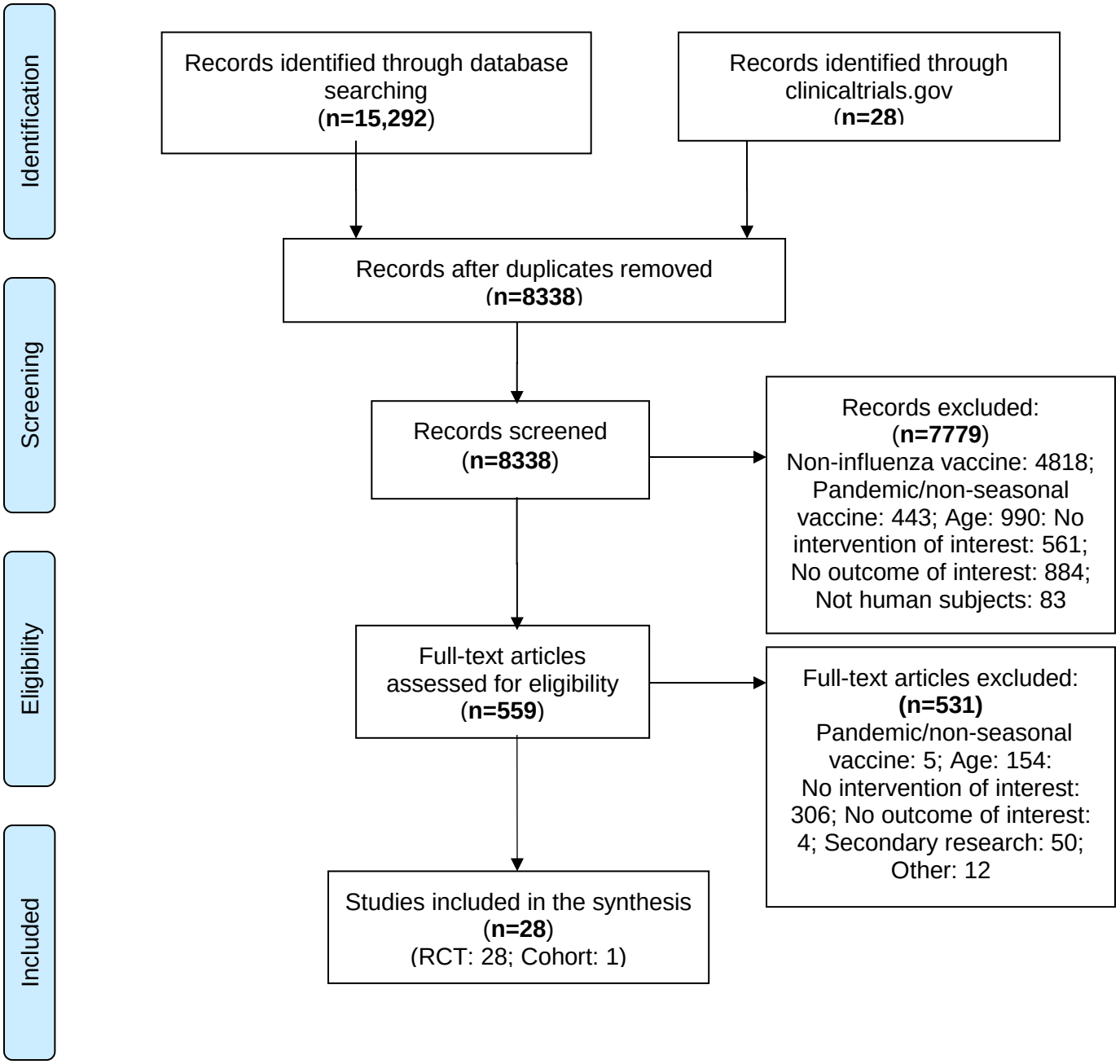
Set	History	Results	Comments
	or blind:]) mp.		
12	**10 and 11**	**3982**	**Unique Clinical trial results**
13	case-control studies/ or cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/ or ([observational or evaluation or comparative] adj3 [study or studies or studied]).mp.	3167204	Cohort/Observational Study MeSH and textword terms
14	10 and 13	2732	Cohort study results
15	**14 not 12**	**1154**	**Unique cohort results**
	EMBASE		
1	([influenza* or flu or "caiv-t" or laiv or grippe or "h1n1" or "h3n2") adj5 (vaccin* or inocul* or inject*]).mp.	45225	Influenza vaccine textword Terms
2	(admune or afluria or agrippal or agriflu or alorbat or adiugrip or berigripina or biaflu-zonale or celvapan or chiromas or evagrip or flu-imune or fluogen or fluvaccin or gripavac or grippe-impfstoff or grippeimpfstoff or imovax or inflexal or influenzainum or influmix or influpozzi or influsplit or infuvac or influvirus or isiflu or miniflu or nasalflu or niligrip or prodigrip or sandovac or anflu or batrevac or begrivac or "flu immune" or "flu imune" or "flu-vac" or flulaval or fluvirin or fluzone or fluarix or alluria or fluad or fluarix or fluax or "adju-fluax" or flublok or flucelvax or fluenz or flumist or fluinsure or "intranasal TIV" or flulaval or fluogen or flushield or fluvax or fluviral or fluvirin* or fluzone or gammaflu or grippovac or idflu or intanza or inflexal or influject or influpozzi or influsplit or influvac or intanza or invivac or mastaflu or "mfv ject" or munevan or mutagrip or niligrip or optaflu or preflucel or previgrip or trivalent or vacciflu or vaxigrip or "x-flu").mp.	9190	Specific vaccine textword Terms
3	(fluvax or Imuvac or Viroflu or Fluval or virosome or virosomal or Enzira or fluvirix or AS03 or MF59 or AS04 or virsomes).mp.	1478	Specific vaccine textword Terms
4	influenza vaccination/ or influenza vaccine/	30200	Influenza Vaccines EMBASE terms
5	influenza/ or orthomyxovirus infection/ or seasonal influenza/	56842	Influenza Virus EMBASE terms
6	influenza virus/ or influenza a/ or 1977 russian influenza/ or 2009 h1n1 influenza/ or asian influenza/ or hong kong influenza/ or "influenza a (h1n1)"/ or "influenza a (h2n2)"/ or "influenza a (h3n2)"/ or influenza virus a h1n2/ or influenza virus a h2n2/ or influenza virus a h3n2/ or influenza virus a h3n8/ or influenza virus b/ or influenza b/ or "influenza b virus (b/jing fang/76/98)"/	34222	Influenza Virus EMBASE terms
7	or/1-6	103871	EMBASE influenza vaccine or virus terms*
8	limit 7 to aged <65+ years>	8936	Age group limit
9	nursing home/ or nursing home patient/ or elderly care/ or exp geriatric care/ or home for the aged/ or (aged or senior* or "older adult*" or geriatric or retired or retiree* or elder* or pensioner*).ti,ab.	840992	Aged EMBASE or textword terms
10	8 or (7 and 9)	13301	Geriatric age

Set	History	Results	Comments
			group results - Base Clinical Set
11	limit 10 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 3 clinical trial or phase 4 clinical trial)	2223	Clinical Trial EMBASE limit
12	limit 10 to (meta analysis or "systematic review")	165	Meta-analysis EMBASE limit
13	clinical trial/ or controlled clinical trial/ or randomized controlled trial/ or multicenter study/ or phase 3 clinical trial/ or phase 4 clinical trial/ or meta analysis/ or "clinical trial (topic)"/ or "controlled clinical trial (topic)"/ or "randomized controlled trial (topic)"/ or "multicenter study (topic)"/ or "phase 3 clinical trial (topic)"/ or "phase 4 clinical trial (topic)"/ or "meta analysis (topic)"/ or control group/ or crossover procedure/ or double blind procedure/ or single blind procedure/ or triple blind procedure/ or (rct or rcts or random* or multicent* or placebo* or metaanalysis* or "meta-analysis" or sham or effectiveness or efficacy or compare*).mp. or (meta adj5 analysis).mp. or ([singl: or doubl: or tripl: or trebl:] adj5 [mask: or blind:]).mp.	5442758	Clinical Trial EMBASE and textword terms
14	**11 or 12 or (10 and 13)**	**6349**	**Unique Clinical trial results**
15	cohort analysis/ or observational study/ or comparative study/ or comparative effectiveness/ or case control study/ or hospital based case control study/ or population based case control study/ or longitudinal study/ or postmarketing surveillance/ or drug surveillance program/ or ([observational or evaluation or comparative] adj3 [study or studies or studied]).mp.	1151928	Cohort/Observational Study EMBASE and textword terms
16	10 and 15	1522	Cohort study results
17	**16 not 14**	**534**	**Unique cohort results**
	EBM reviews - Cochrane Central Register of Controlled Trials		
1	([influenza* or flu or "caiv-t" or laiv or grippe or "h1n1" or "h3n2"] adj5 [vaccin* or inocul* or inject*]).mp.	2187	Influenza vaccine textword Terms
2	(admune or afluria or agrippal or agriflu or alorbat or adiugrip or berigripina or biaflu-zonale or celvapan or chiromas or evagrip or flu-imune or fluogen or fluvaccin or gripavac or grippe-impfstoff or grippeimpfstoff or imovax or inflexal or influenzainum or influmix or influpozzi or influsplit or influvac or influvirus or isiflu or miniflu or nasalflu or niligrip or prodigrip or sandovac or anflu or batrevac or begrivac or "flu immune" or "flu imune" or "flu-vac" or flulaval or fluvirin or fluzone or fluarix or alluria or fluad or fluarix or fluax or "adju-fluax" or flublok or flucelvax or fluenz or flumist or fluinsure or "intranasal TIV" or flulaval or fluogen or flushield or fluvax or fluviral or fluvirin* or fluzone or gammaflu or grippovac or idflu or intanza or inflexal or influject or influpozzi or influsplit or influvac or intanza or invivac or mastaflu or "mfv ject" or munevan or mutagrip or niligrip or optaflu or preflucel or previgrip or trivalent or vacciflu or vaxigrip or "x-flu").mp.	537	Specific vaccine textword Terms
3	(fluvax or Imuvac or Viroflu or Fluval or virosome or virosomal or Enzira or fluvirix or AS03 or MF59 or AS04 or	277	Specific vaccine textword Terms

Set	History	Results	Comments
	virsomes).mp.		
4	Influenza Vaccines/ or influenza vaccination/ or influenza vaccine/	1071	Influenza Vaccines MEDLINE and EMBASE terms
5	orthomyxoviridae infections/ or influenza, human/ or influenza/ or orthomyxovirus infection/ or seasonal influenza/	1049	Influenza Virus MEDLINE and EMBASE terms
6	influenzavirus a/ or influenza a virus/ or influenza a virus, h1n1 subtype/ or influenza a virus, h3n2 subtype/ or influenzavirus b/ or influenza b virus/ or influenza virus/ or influenza a/ or 1977 russian influenza/ or 2009 h1n1 influenza/ or asian influenza/ or hong kong influenza/ or "influenza a (h1n1)"/ or "influenza a (h2n2)"/ or "influenza a (h3n2)"/ or influenza virus a h1n2/ or influenza virus a h2n2/ or influenza virus a h3n2/ or influenza virus a h3n8/ or influenza virus b/ or influenza b/ or "influenza b virus (b/jing fang/76/98)"/	708	Influenza Virus EMBASE terms
7	0r/1-6	2724	MEDLINE, EMBASE and textword influenza vaccine or virus terms*
8	nursing homes/ or Homes for the Aged/ or nursing home/ or nursing home patient/ or elderly care/ or exp geriatric care/ or home for the aged/ or (aged or senior* or "older adult*" or geriatric or retired or retiree* or elder* or pensioner*).ti,ab.	46889	Age group terms
9	**7 and 8**	**707**	**FINAL Results**

Appendix B: Flow diagram

Title: A Review of the Literature of High Dose Seasonal Influenza Vaccine for Adults 65 Years and Older



Appendix C: Level of evidence based on research design and quality (internal validity) rating of evidence

Table 1: 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 2: 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[1].	

Appendix D: Summary of evidence related to efficacy/effectiveness of high dose influenza vaccines in adults 65 years and older

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Diaz Granados (2013)[21] NCT00976027	60µg: Fluzone® High-Dose (Sanofi Pasteur) 60µg HA/strain 0.5mL/dose 15µg: Fluzone® (Sanofi Pasteur) 15µg HA/strain 0.5mL/dose Strains A/Brisbane/59/07 (H1N1) A/Uruguay/716/2007 (H3N2) B/Brisbane/60/2008	RCT Double-blind Multi-centre Phase 3b Country USA 99 centres Year 2009-10	Age ≥65 yrs Mean 72.8 yrs (64–99 yrs) Male 46.3% N=9158 60µg=6107 15µg=3051 85% Caucasian 89% vaccinated last season Ambulatory, medically stable Excluded Bed-ridden, Immune suppressing disease	**Follow up**: 7 months, during 2009pdm **Outcome:** ILI with lab-confirmed NP swab **PCR-confirmed influenza (any subtype)** Attack rates (per protocol) 15 v 60µg 2.66/1000 v 2.33/1000 **Relative vaccine efficacy** ILI 12.5% (-140.9,65.7) Notes: 21/22 cases were A/California/7/2009-like 24% of 60µg and 15µg participants received the H1N1 2009pdm vaccine respectively ILI defined as: ≥ 1 of temperature >37.2°C, feverishness, chills, tiredness, headaches or myalgia; and ≥ 1 of nasal congestion, rhinorrhoea, sore throat, cough, sputum production, wheezing, chest tightness, shortness of breath, or chest pain with breathing	Level 1	Good
Diaz Granados (2014)[33] NCT01427309	60µg: Fluzone® High Dose 60µg HA/strain 0.5mL/dose 15µg: Fluzone® 15µg HA/strain 0.5mL/dose 2011-12 strains	RCT Double-blind Multicenter Phase 3b–4 Country USA, Canada 126 centres Year 2011-12	Age ≥65 yrs Mean: 73.3 yrs Male 43.4% N=31,983 60µg=15,990 15µg=15,993 95% Caucasian 74% previous	**Follow-up:** active weekly January-April 30 **Outcome:** ILI with lab-confirmed NP swab **Lab-confirmed influenza** Attack rates: (any subtype) 15 v 60µg ILI 1.9 v 1.4% ARI 2.4 v 2.0% **Relative efficacy** 60µg:15µg	Level 1	Good

	A/California/ 7/2009 (H1N1) A/Victoria/210/2 009 (H3N2) B/Brisbane/60/2 008 2012-13 strains A/California/7/20 09 (H1N1) A/Victoria/361/ 2011 (H3N2) B/Texas/6/2011	& 2012-13	vaccination 67% ≥ 1 chronic condition	ILI 24.2% (9.7,36.5)[S] ARI 18.3% (5.0,29.8) Notes: ILI: ≥1 of sore throat, cough, sputum production, wheezing, or difficulty breathing *and* ≥1 of temperature >37.2°C, chills, tiredness, headaches, or myalgia ARI: sneezing, nasal congestion, rhinorrhoea, sore throat, cough, sputum production, wheezing, or difficulty breathing		
Izurieta (2015)[62]	IM: Fluzone High-Dose (Sanofi Pasteur) (60µg HA/strain) IM: Standard-dose vaccine (15 µg HA/strain)	Retrospective cohort Country USA Year: 2012-2013	Community based adults, ≥65 years of age N=2,545,275 60µg=929,730 15µg=1,615,545 Participants had to meet Medicare enrollment, duration and survival criteria, and have received vaccine from a community pharmacy that vaccinated at least one other beneficiary with the alternative vaccine within two weeks of index	**Primary outcome:** Probable episode of influenza-related illness defined as a community medical encounter with provision of a rapid influenza diagnostic test, followed by therapeutic dispensing of oseltamivir within a 2-day period) **Secondary outcome:** Hospital in-patient admission or emergency department visit diagnosis of influenza **Outcomes per 10,000 person-weeks (60µg v. 15µg)** Primary: 1.01 v. 1.30 [risk difference: 0.29 (0.19, 0.38)] Secondary: 0.86 v. 1.10 [risk difference: 0.24 (0.17, 0.30)] **Relative vaccine effectiveness (60 µg v. 15 µg):** Primary: 22% (15, 29) Secondary: 22% (16, 27) Notes: • Groups well balanced, with only substantial differences being noted in geographic region • Effect estimates consistent whether from univariate or multivariate Poisson regression • Relative VE for primary outcome increased to 36% (13, 54) for those aged ≥85yrs	II-2	Good

			vaccination			
Keitel (2009)[23] NCT00395174	45µg: FluBlok® (Protein Sciences Corp) ~45µg rHA/strain 0.5mL/dose Strains A/Wisconsin (H3N2) A/New Caledonia (H1N1) B/Ohio 15µg: Fluzone® (Sanofi Pasteur). 15µg HA/strain 0.5mL/dose Strains A/Wisconsin (H3N2) A/New Caledonia (H1N1) B/Malaysia	RCT Double-blind Multi-centre Phase 3 Country USA 7 centres Year 2006-07	Age ≥65 yrs Mean: 45µg 72.9 yrs 15µg 73.9 yrs Male 47% N=869 45µg N=436 15µg N=433 98% Caucasian 83% vaccinated last season Ambulatory, medically-stable, community dwelling	**Follow-up** 2006-2007 season **Outcome:** ILI with culture-confirmed nasal and throat swabs **Lab-confirmed influenza** Attack rates (any subtype) 15 v 45µg Culture 0.5 v 0.2% Serological 2.8 v 2.1%; **Relative VE** (computed) Culture 0.50 (0.01,9.56) Serological 0.79 (0.27,2.25) Either 0.74 (0.27,1.94) **Notes:** ILI: fever with cough and/or sore throat	Level 1	Good
Puig-Barberà (2014)[25]	ID: Intanza® (Sanofi Pasteur) 15µg HA/strain 0.1mL/dose IM: Inflexal-V® (Crucell) virosomal, subunit 15µg HA/strain	Retrospective cohort Country Spain 9 hospital service areas Year 2011-12	Age ≥65 yrs Mean: 76.7 yrs Male: 44.7% N=164,021 ID=101,963 IM= 62,058 87% vaccinated last season	**Follow up** Dec 2011–Mar 2012 **Influenza-related *hospitalization*** Rate/100,000 person-week ID v IM; RR($CI_{95\%}$) All ages 8.8 v 13.9 0.64 (0.50,0.81) 65-69 yrs 1.9 v 6.0 0.31 (0.12,0.83) 70-74 yrs 5.9 v 8.8 0.67 (0.36,1.27) 75-79 yrs 10.4 v 15.5 0.67 (0.42,1.07) 80-84 yrs 12.9 v 20.1 0.64 (0.40,1.02) ≥85 yrs 16.0 v 23.4 0.68 (0.42,1.14)	Level II-2	Good

	0.5mL/dose Strains A/California/7/2009 (H1N1) A/Perth/16/2009 (H3N2) B/Brisbane/60/2008		Excluded readmissions within 30 days, institutionalized, receipt of other influenza vaccines	**Relative effectiveness** ID:IM Crude 36% (19,50) Adjusted 33% (15,48) Notes: Influenza-related admission: Vaccine ≥15 days before hospitalization & one of: 1) main discharge diagnosis of influenza 2) admission with PCR-confirmed influenza		

Appendix E: Summary of evidence related to immunogenicity of high dose seasonal influenza vaccines in adults 65 years and older

STUDY DETAILS						
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Couch (2007)[29] NCT00115531 NCT00170508 NCT00170482	60µg: Experimental 60µg HA/strain 0.5mL/dose IM 15µg: Fluzone® (Sanofi Pasteur) 15µg HA/strain 0.5mL/dose IM Strains A/New Caledonia/20/99 (H1N1), A/Wyoming/03/2003 (H3N2) B/Jiangsu/10/2003	RCT Double blind Multi-site Phase II Country USA Year 2004-05 Stratified by receipt of influenza vaccine in <u>same</u> season	Age ≥65 Mean: 73-74 yrs Male 51% N=414 60µg=206 15µg=208 78% vaccinated in fall of 2004 (same season) 96% Caucasian	**Follow-up** 28 days **Seroconversion** 15 v 60µg A(H1N1) 23.6 v 51.5%* A(H3N2) 24.5 v 41.3* B 16.8 v 35.0* **Seroprotection** ≥1:32; 15 v 60µg A(H1N1) 48.1 v 62.6%* A(H3N2) 91.8 v 94.7 B 57.2 v 62.1 **GMTR** Significantly higher for 60µg, all strains* Notes: Same participants included in Chen et al. 2011	Level I	Good
DiazGranados (2013)[21] NCT00976027	60µg: Fluzone® High-Dose (Sanofi Pasteur) 60µg HA/strain 0.5mL/dose 15µg: Fluzone® (Sanofi Pasteur) 15µg HA/strain 0.5mL/dose Strains A/Brisbane/59/0	RCT Double-blind Multi-centre Phase 3b Country USA 99 centres Year 2009-10	Age ≥65 yrs Mean 72.8 yrs (64–99 yrs) Male 46.3 % N=9158 60µg=6107 15µg=3051 85% Caucasian 89% vaccinated	**Follow up** 28 days **Seroprotection** 15 v 60µg A(H1N1) 87.4 (85.2,89.4) v 94.9 (93.9,95.9)* A(H3N2) 94.8 (93.2,96.1) v 97.3 (96.5,98.0)* B 84.5 (82.1,86.7) v 93.4 (92.2,94.4)* **GMFR** 60/15µg A(H1N1) 1.57 (1.44; 1.71)* A(H3N2) 1.74 (1.57; 1.94)* B 1.61 (1.48; 1.75)*	Level 1	Good

	7 (H1N1) A/Uruguay/716/2007 (H3N2) B/Brisbane/60/2008		last season Ambulatory, medically stable Excluded Bed-ridden, Immune suppressing disease			
DiazGranados, (2014)[33] NCT01427309	60µg: Fluzone® high dose (Sanofi Pasteur) 60µg HA/strain 0.5mL/dose 15µg: Fluzone® 15µg HA/strain 0.5mL/dose 2011-12 strains A/California/7/2009 (H1N1) A/Victoria/210/2009 (H3N2) B/Brisbane/60/2008 2012-13 strains A/California/7/2009 (H1N1) A/Victoria/361/2011 (H3N2) B/Texas/6/2011	RCT Double-blind Multicenter Phase IIIb–IV Country USA, Canada 126 centres Yr 1 2011-12 Yr 2 2012-13	Age ≥65 yrs Mean 73.3 yrs Male 43.4% Immuno-genicity subset Year 1 60µg=2375 15µg=2382 Year 2 60µg=2879 15µg=2872 95% Caucasian 74% previously vaccinated 67% ≥ 1 chronic condition	**Follow-Up:** 28 days **Seroprotection** 15 v 60µg <u>Year 1</u> A(H1N1) 94.2 (93.2,95.1) v 98.1 (97.5,98.6)* A(H3N2) 96.5 (95.6,97.2) v 99.2 (98.7,99.5)* B 83.9 (82.3,85.3) v 91.6 (90.4,92.7)* <u>Year 2</u> A(H1N1) 93.3 (92.3,94.2) v 98.8 (98.3, 99.2)* A(H3N2) 95.0 (94.2,95.8) v 98.6 (98.2, 99.0)* B 72.8 (71.1,74.4) v 86.2 (84.9, 87.4)* **GMFR** 60:15µg <u>Year 1</u> A(H1N1) 1.8 (1.6,1.9)* A(H3N2) 2.0 (1.8, 2.1)* B 1.4 (1.3,1.5)* <u>Year 2</u> A(H1N1) 1.8 (1.7,1.9)* A(H3N2) 1.8 (1.7,1.9)* B 1.6 (1.5,1.7)*	Level 1	Good
Falsey (2009)[28] NCT0091053	60µg: Experimental TIV split-virus 60µg/strain 0.5mL/dose	RCT Double-blind Multi-centre Phase III	Age ≥65 years (65-97) Mean 73 yrs Male 52%	**Follow-up** 28 days **Seroconversion** % ($CI_{95\%}$) 15 v 60µg A(H1N1) 23.1 (20.2,25.6) v 48.6 (46.6,50.5)[S] A(H3N2) 50.7 (47.9,53.5) v 69.1 (67.3,70.9)[S]	Level I	Good

	15µg: Fluzone® (Sanofi Pasteur) 15µg HA/strain 0.5mL /dose Strains A/New Caledonia/20/99 (H1N1) A/Wisconsin/67/2005 (H3N2) B/Malaysia/2506/04	Country USA 30 centres Year 2006-07	N=3876 60µg=2576 15µg=1275 82% vaccinated last season 79% underlying condition Medically stable, community dwelling	B 29.9 (27.4.32.6) v 41.8 (39.8,43.7)[N] **Seroprotection** 15 v 60µg A(H1N1) 76.8 (74.3,79.1) v 89.9 (88.7,91.0)* A(H3N2) 96.5 (95.3,97.4) v 99.3 (98.9,99.6)* B 67.6 (64.9,70.2) v 79.3 (77.6,80.3)* **GMFR** 60/15µg A(H1N1) 1.7 (1.6,1.8)[S] A(H3N2) 1.8 (1.7,2.0)[S] B 1.3 (1.2,1.4)[N] **Cohort of ≥75 years of age** **Seroconversion** 15 v 60µg A(H1N1) 20.7 (17.1,24.8) v 46.8 (43.5,50.2) A(H3N2) 15.2 (9.6,20.7) v 52.5 (47.7,57.2) B 10.1 (5.0,15.2) v 25.4 (21.4,29.7) **GMT Ratio ≥75;** 60:15µg A(H1N1) 1.8 (1.7,2.0)[S] A(H3N2) 1.8 (1.6,2.0)[S] B 1.3 (1.2,1.4)[N] **Cohort with cardiopulmonary disease** **Seroconversion** 15 v 60µg A(H1N1) 22.0 (19.3,24.8) v 48.4 (46.0,50.7)* A(H3N2) 48.5 (45.5,52.2) v 68.5 (66.3,70.6)* B 13.1 (9.4,16.8) v 28.4 (25.5,31.4)* **GMT ratio** 60:15µg A(H1N1) 1.8 (1.6,1.9)[S] A(H3N2) 1.8 (1.7,2.0)[S] B 1.3 (1.2,1.4)[N]		
Nace (2015)[63] NCT01654224	IM: Fluzone High-Dose (Sanofi Pasteur) (60µg HA/strain) IM: Standard-dose vaccine (15 µg	RCT Single blind 15 community-based LTCFs Country USA Years: 2011-2012 & 2012-	Age: ≥65 years Mean: 86.7 (71% ≥85 yrs) Male: 32% N at 30 days =187 60µg = 89	**Follow up: 30 and 180 (±14) days from baseline** **GMT 60µg v. 15µg** **Year 1 – Day 0** A(H1N1) 17.1 (11.3, 25.9) v. 16.6 (10.3, 26.7) A(H3N2) 8.9 (6.5, 12.3) v. 7.3 (5.3, 10.0) B 15.3 (10.3, 22.6) v. 11.6 (8.6, 15.5) **Year 1 – Day 30**	I	Fair

	HA/strain)	13	15µg =98 Frail and residing in LTCFs	A(H1N1) 78.2 (45.1, 135.7) v. 27.4 (17,44.3)* A(H3N2) 26.2 (17.1, 40.0) v. 10.2 (7.0, 14.8)* B 25.6 (18.7, 34.9) v. 14.3 (11.1, 18.4)* **Year 1 – Day 180** A(H1N1) 59.7 (33.5, 106.3) v. 28.3 (15.3, 52.4) A(H3N2) 22.3 (14.5, 34.3) v. 9.4 (6, 14.8)* B 22.9 (16.3, 32) v. 15.4 (11.8, 20.2) **Year 2 – Day 0** A(H1N1) 23.6 (16.7, 33.4) v. 32.3 (23.8, 43.9) A(H3N2) 7.2 (6.1, 8.3) v. 6.2 (5.4, 7.1) B 7.9 (6.5, 9.5) v. 9.1 (7.5, 11) **Year 2 – Day 30** A(H1N1) 45.6 (32.9, 63.2) v. 50.0 (37.4, 67) A(H3N2) 23.4 (17.6, 31) v. 14.2 (11.0, 18.4)* B 26.0 (21.2, 31.9) v. 17.4 (13.9, 21.9)* **Year 2 – Day 180** A(H1N1) 46.8 (33.2, 65.9) v. 51.8 (37.8, 71.1) A(H3N2) 24.7 (18.3, 33.2) v. 13.4 (10.3, 17.5)* B 25.3 (20.8, 30.9) v. 18.9 (14.9, 23.9) **Seroprotection (%) 60µg v. 15µg** **Year 1 – Day 0 (n=31 v. 33)** A(H1N1) 32.3 v. 36.4 A(H3N2) 6.5 v. 6.1 B 25.8 v. 15.2 **Year 1 – Day 30 (n=31 v. 33)** A(H1N1) 71.0 v. 51.5 A(H3N2) 45.2 v. 18.2* B 45.2 v. 21.2* **Year 1 – Day 180 (n=26 v. 24)** A(H1N1) 76.9 v. 45.8* A(H3N2) 42.3 v. 12.5* B 23.1 v. 4.2		

				Year 2 – Day 0 (n=58 v. 65) A(H1N1) 44.8 v. 53.8 A(H3N2) 3.4 v. 4.6 B 8.6 v. 6.2 **Year 2 – Day 30 (n=58 v. 65)** A(H1N1) 58.6 v. 72.3 A(H3N2) 51.7 v. 24.6* B 48.3 v. 29.2* **Year 2 – Day 180 (n=53 v. 59)** A(H1N1) 47.2 v. 52.5 A(H3N2) 52.8 v. 39.0 B 32.1 v. 33.9		
Sanofi Pasteur (2013)[57] Robertson (2012)[58] NCT01430819	60µg: Fluzone® High-Dose (Sanofi Pasteur) 60µg HA/strain 0.5mL/dose 15µg:Fluzone® (Sanofi Pasteur) 15µg HA/strain 0.5mL/dose Strains A/California/07/2009 (H1N1) A/Victoria/210/2009 (H3N2) B/Brisbane/60/2008	RCT Double-blind Multi-centre Phase IV Country USA 6 centres Year 2011-12	Age ≥ 65 yrs Mean 72.1 yrs Male: 39% N=300 60µg=145 15µg=147 96% Caucasian	**Follow up** 21 days **Seroconversion** 15 v 60µg A(H1N1) 36 (28,44) v 61 (53,69) A(H3N2) 41 (33,49) v 69 (61,76) B 22 (15,29) v 41 (33,50) **Seroprotection (≥1 :40)** 15 v 60µg A(H1N1) 94 v 97 A(H3N2) 99 v 100 B 80 v 88 **≥1 :160** 15 v 60µg A(H1N1) 71 v 86 A(H3N2) 82 v 95 B 28 v 39 **GMTR** 15 v 60µg A(H1N1) 3.3 (2.7,4.0) v 7.1 (5.6,9.1) A(H3N2) 3.5 (2.9,4.2) v 8.2 (6.4,10.5) B 2.1 (1.9,2.4) v 3.1 (2.7,3.7)	Level 1	Good
Talbot (2014)[59] NCT01189123	60µg: Fluzone® High-Dose (Sanofi Pasteur) 60µg HA/strain 0.5mL/dose	RCT Double-blind Single centre Country	Age 67-79 yrs Mean 73 yrs Male 51.4% N=105	**Follow-up** 2 years **GMT** 15 v 60µg A(H1N1) 40 (10,80) v 80 (40,140) A/H3H2 20 (20,40) v 80 (10,160)	Level 1	Good Small sample size

	15µg: Fluzone® (Sanofi Pasteur) 15µg HA/strain 0.5mL/dose Strains not stated	USA Years: not stated	60µg=47 15µg=50	B 40 (20,80) v 40 (40,80) Notes: CD4+ and CD8+ data not abstracted		
Tsang (2014)[32] NCT00551031	60IM: High Dose IM15 (Sanofi Pasteur) 60µg/strain 0.5mL IM ID15: (Sanofi Pasteur) 15µg/strain 0.1 mL/dose ID 21ID: (Sanofi Pasteur) 21µg/strain 0.1 mL/dose ID 15IM: FluZone® (Sanofi Pasteur) 15µg/strain 0.5mL/dose IM Strains A/Solomon Islands/3/2006 (H1N1) A/Wisconsin/67/2005 (H3N2) B/Malaysia/2506/2004	RCT Open label for route Double-blind for dose Multi-centre Phase II Country USA 31 centres Year 2007-08	Age 47-99 yrs Mean 73 yrs Male 44% N=1912 60µg IM=319 15µg IM=320 15µg ID=635 21µg ID=635 87% previously vaccinated 94% Caucasian Medically stable Ambulatory	**Follow-up** 28 days **<u>60 vs 15µg IM</u>** **Seroconversion** Difference in rates (60-15µg) A(H1N1) 19.7 (12.8,26.6) A(H3N2) 16.8 (9.2,24.5) B 16.4 (10.7,22.1) **Seroprotection** Difference in rates (60-15µg) A(H1N1) 13.6 (8.4,18.8) A(H3N2) 1.9 (-0.2,4.0) B 15.6 (8.5,22.7) **GMTR ratios** (60/15IM) A(H1N1) 2.1 (1.7,2.6)* A(H3N2) 1.8 (1.5,2.1)* B 1.4 (1.2,1.6)* **<u>60IM vs 15ID</u>** **Seroconversion** Difference in rates (60IM-15ID) A(H1N1) 9.2 (3.6,14.7) A(H3N2) 13.7 (7.0,20.4) B 10.5 (5.0,16.1) **Seroprotection** Difference in rates A(H1N1) 5.7 (2.0,9.5) A(H3N2) 1.0 (-0.6,2.5) B 12.4 (6.4,18.3) **GMTR** (60IM/15ID) A(H1N1) 1.4 (1.2,1.6)* A(H3N2) 1.4 (1.2,1.6)* B 1.3 (1.2,1.5)* **<u>60IM vs 21ID</u>** **Seroconversion** Difference in rates (60IM-21ID)	Level 1	Good

				A(H1N1) 6.3 (0.8,11.8) A(H3N2) 13.1 (6.4,19.8) B 10.2 (4.6,15.7) **Seroprotection** Difference in rates A(H1N1) 3.7 (0,7.3) A(H3N2) 1.6 (0,3.3) B 10.6 (4.7,16.6) **GMTR** (60IM/21ID) A(H1N1) 1.3 (1.1,1.5)* A(H3N2) 1.3 (1.1,1.5)* B 1.2 (1.1,1.4)* **15ID vs 15IM** **Seroconversion** Difference in rates (ID-IM) A(H1N1) 10.5 (4.1,16.9) A(H3N2) 3.5 (-3.0,10.1) B 5.8 (1.7,10.0) **GMTR** (15ID/15IM) A(H1N1) 1.50 (1.3,1.8)[S] A(H3N2) 1.23 (1.1,1.4)[S] B 1.04 (0.9,1.2)[N] **21ID vs 15IM** **Seroconversion** Difference in rates (ID-IM) A(H1N1) 13.4 (7.0,19.8) A(H3N2) 4.2 (-2.4,10.8) B 6.2 (2.0,10.4) **GMTR** (21ID/15IM) A(H1N1) 1.6 (1.4,1.9)[S] A(H3N2) 1.3 (1.2,1.5)[S] B 1.1 (1.0,1.2)[N]		

Intramuscular, Other

Della Cioppa (2012) Della Cioppa (2014)[37] NCT00848848	IM15: 15µg HA/strain 0.5mL/dose no adjuvant IM30: 30µg	RCT Observer-blind Multicenter Countries Poland	Age ≥65 yrs Mean 69 yrs Male 40-68% N=450 IM15=43	**Follow-up** 22 days **Seroconversion** A(H3N2) only IM15 v IM30 70 v 63 ADV15 v ADV30 87 v 95 ID6 v ID12 77 v 71	Level 1	Good Small sample size

	H3N2 & 15µg each of H1N1 & B; 0.5mL/dose no adjuvant ADV15: Fluad® (Novartis) 15µg/strain 0.5mL/dose 100% of MF59 ADV30: 30µg H3N2 & 15µg each of H1N1 & B 0.5mL/dose 100% of MF59 ID6: 6µg HA/strain 0.2mL/dose ID12: 12µg H3N2 & 6µg each of H1N1 & B; 0.2mL/dose Strains A/Brisbane/59/2007 (H1N1) A/Uruguay/716/2007 (H3N2) B/Florida/4/2006	Belgium Germany Year 2008-09	IM30=43 ADV15=46 ADV30=42 ID6=43 ID12=46 (other groups excluded) 73-81% previously vaccinated Healthy volunteers Excluded impaired immune system	**Seroprotection** IM15 v IM30 93 v 80 ADV15 v ADV30 96 v 100 ID6 v ID12 88 v 90 **GMFR** IM15 v IM30 9.0 v 7.3 ADV15 v ADV30 15.0 v 19.0 ID6 v ID12 16.0 v 13.0 **Seroconversion** IM v ADV v ID A(H1N1) 30 v 62 v 44 B 30 v 49 v 36 **Seroprotection** IM v ADV v ID A(H1N1) 77 v 95 v 84 B 49 v 66 v 61 **GMTR** IM v ADV v ID A(H1N1) 2.8 v 7.1 v 5.1 (ID>IM*) B 2.5 v 4.1 v 3.0 A(H1N1) ADV:ID=1.6 (1.1,2.3)* IM:ID=0.7 (0.5,1.0)* B ADV:ID=1.4 (1.0,1.8)* Notes: -Increase in H3N2 antigen dose did not affect the antibody response to H1N1 and B strains -Increase in H3N2 antigen level did not increase responses -Inclusion of adjuvant improved serological response		
Keitel (2006)[30]	60µg: subvirion TIV (Aventis	RCT Single-center	Age ≥65 years Mean 72.4 yrs (65-88 yrs)	**Follow up** 28 days **Seroconversion** 15 v 30 v 60µg	Level 1	Good

	Pasteur) 60µg HA/strain 0.5mL/dose 30µg: subvirion TIV (Aventis Pasteur) 30µg HA/strain 0.5mL/dose 15µg: subvirion TIV (Aventis Pasteur) 15µg HA/strain 0.5mL/dose Placebo: saline Strains A/NewCaledonia/20/99 (H1N1) A/Panama/2007/99 (H3N2) B/Victoria/504/2000	Country USA Year 2001-02	Male 59 % N=202 60µg=50 30µg=51 15µg=51 Saline=50 97% Caucasian 82% vaccinated last season Ambulatory, medically stable .	A(H1N1) 17.6 v 31`.4 v 38.0 A(H3N2) 21.6 v 27.5 v 32.0 B 23.5 v 21.6 v 42.0 **Seroprotection** ≥1:32 Dose-related increases for all subtypes **GMFR** Significant differences for all subtypes (p<0.01) Dose-related increases for all subtypes		Small sample size Same antigens as previous season
60µg "experimental" Sub unit Intramuscular						
Palache (1993)[39]	60µg : Experimental trivalent subunit (Duphar BV) 60µg HA/strain 0.5mL/dose 10µg: 10µg HA/strain	RCT Double-blind Multi-centre Placebo-controlled Country Netherlands Israel	Data for 65+ yrs Age 68-99 yrs Mean 80 yrs N=262 60µg=66 10µg=67 20µg=64 Saline=65	**Follow-up** 21 days **Seroconversion** N/A **Seroprotection** (≥1:100 for A; ≥1:200 for B) 10 v 20 v 60µg A(H1N1) 33 v 33 v 42 A(H3N2) 72 v 75 v 80 B 52 v 67 v 77	Level 1	Good Small sample size

	20µg: 20µg HA/strain Experimental trivalent subunit Saline/placebo 0.5mL/dose Strains A/Taiwan/2/86 (H1N1) A/Sichuan/2/87 (H3N2) B/Beijing/1/87	Year 1988 See Remarque (1993) for same participants – for IgG, IgA, IgM responses to H3N2 strain	22% previously vaccinated Nursing home residents Excluded Immune suppressing drug treatment	**GMFR** 20/10µg v 60/10µg A(H1N1) No dose response effect A(H3N2) 1.3 v 1.6 B 1.4 v 2.1		
Recombinant Vaccines						
Keitel (2009)[23] NCT00395174	FluBlok® (Protein Sciences Corp.) ~45µg rHA/strain 0.5mL/dose (Total: 131µg) Strains A/Wisconsin (H3N2) A/New Caledonia (H1N1) B/Ohio 15µg: Fluzone® (Sanofi Pasteur). 15µg HA/strain 0.5mL/dose	RCT Double-blind Multi-centre Phase 3 Country USA 7 centres Year 2006-07	Age ≥65 yrs Mean 45µg 72.9 yrs 15µg 73.9 yrs Male 47% N=869 (all) 45µg=431 15µg=430 ≥75 years 45µg=163 15µg=159 98% Caucasian 83% vaccinated last season Ambulatory, medically-stable, community dwelling	**Follow-up**: 28 days **Seroconversion** 15 v 45µg A(H1N1) 33(28,37) v 43(39,48)[N] A(H3N2) 58(53,62) v 78(74,82)[N] B/Ohio 39(34,44) v 29(25,34) B/Malaysia 10(7,12.8) v 20(16,23.5) **Seroprotection** 15 v 45µg A(H1N1) 95(92,97) v 95(92,97) A(H3N2) 93(90,95) v 97(94,98) B/Ohio 97(95,99) v 92(89,94) B/Malaysia 30(26,34) v 40(35,45) **GMFR** (CI_{95}) 15:45µg A(H1N1) 0.84 (0.81, 0.86)[N] A(H3N2) 0.59 (0.57, 0.60)[N] B/Ohio 1.30 (1.26, 1.34)[N] B/Malaysia 1.37 (1.0, 1.7) **Seroconversion** 45µg v 15µg A(H1N1) 43(39,48) v 33(28,37)*[N] A(H3N2) 78(74,82) v 58(53,62)*[N] B/Ohio 29(25,34) v 39(34,44)	Level 1	Good Different B strains in vaccines

	Strains A/Wisconsin (H3N2) A/New Caledonia (H1N1) B/Malaysia			B/Malaysia 10(7,13) v 20(16,23) **Cohort of ≥75 years** **Seroprotection** 15µg v 45µg A(H1N1) 94(91,98) v 91(87,96) A(H3N2) 93(89,97) v 96(93,99) B/Ohio 99(98,100) v 96(93,99) B/Malaysia 31(24,38) v 47(39,54) **GMFR** 15:45µg A(H1N1) 0.82 (0.79, 0.85)[N] A(H3N2) 0.59 (0.58, 0.61)[N] B/Ohio 1.21 (1.18, 1.24)[N] B/Malaysia 1.40 (1.1, 1.7)		
Treanor (2006)[40]	Baculovirus-expressed (rHA) 135µg rHA/strain 45µg rHA/strain 15µg rHA/strain 0.5mL/dose IM15: Fluzone® (Sanofi Pasteur). 15µg HA/strain 0.5mL/dose Strains A/Panama/2007/99 (H3N2) A/NewCaledonia/20/99 (H1N1) B/HongKong/330/2001	RCT Double-blind Country USA Year not stated (2002-03 or 2003-04)	Age 65-90 yrs Mean: 72 yrs 49% male N=399 135rHA=101 45rHA= 99 15rHA=98 IM15=98 96% Caucasian Community-dwelling, medically stable	**Follow-up** 28 days **Seroconversion** IM15 v 15 v 45 v 135rHA A(H1N1) 37 v 16 v 32 v 37 A(H3N2) 33 v 38 v 55 v 88* B 63 v 51 v 65 v 66 **Seroprotection** ≥1:128 A(H1N1) 21 v 12 v 26 v 20 A(H3N2) 49 v 95 v 76 v 88* B 63 v 51 v 65 v 66 *Significantly higher (p ≤0.01) compared to IM15	Level 1	Good

Double dose; TIV 15µg/strain						
Cools (2009)[38] Roos-van Eijndhoven (2001)[60]	30µg : 15µg HA/strain 0.5mL/dose x 2 doses (same arm) Split virion (Pasteur Mérieux) 15µg : 15µg HA/strain 0.5mL/dose Split virion (Pasteur Mérieux) Strains: A/Nanchang/933/95 (H3N2), A/Johannes-burg/82/96 (H1N1), and B/Harbin/7/94	RCT Multi-centre Country: Netherlands 14 nursing homes Year 1997-98	Age 96% were ≥65 years Median 83-84 Male 25% N=815 30µg (15*2) Day 25=360 Day 84=340 Day106=155 15µg Day 25=347 Day 84=325 Day106=158 39% previously vaccinated Long-term care residents	**Follow-up:** 25, 84, 109 days **DATA for A(H3N2) strain only** **Seroconversion** 15 v 30µg Day 25 33.3 v 45.3* Day 84 28.6 v 37.1* Day 106 27.1 v 35.4 **Seroprotection** 15 v 30µg Day 25 66.3 v 73.3* Day 84 61.2 v 67.6 Day 106 63.9 v 64.6 **GMT** 15 v 30µg Day 25 57.8 (49.2,68.2) v 70.6 (61.1,81.7) Day 84 48.6 (41.1,56.9) v 53.5 (45.9,61.9) Day 106 49.3 (39.5,61.9) v 46.9 (37.6,58.8) Notes: Significantly greater rates of seroprotection and seroconversion at Day 25 & 84 for participants with pre-vaccination titres of <1:40 (only at Day 25 for ≥1:40) Data regarding 'booster' doses not abstracted	Level 1	Good
15µg Intradermal						
Arnou (2009)[46] NCT00383526	ID:(Sanofi Pasteur; experimental) 15ug HA/strain 0.1mL/dose 15IM: Vaxigrip® (Sanofi Pasteur) 15ug HA/strain 0.5mL/dose Strains as recommended	RCT Open-label Multi-centre Country: France, Belgium, Lithuania, Italy Years 2006-2009	Age 60-95 years Mean 71 years Male 20% N=3707 Year 1 ID=2604 IM=1081 Year 2 ID→ID =133 IM→IM =143 Year 3	**Follow-up:** 21 days post vaccination **First vaccination 2006** GMT non-inferior for all 3 strains (ID vs IM) Seroprotection superior for all 3 strains (ID vs IM) GMTR All 3 strains ID significantly higher (p<0.0001) than IM Seroconversion ID significantly higher (p<0.001) than IM **Second Vaccination 2007** **Seroconversion** ID→ID v IM→IM A(H1N1) 74.2 (65.9,81.5) v 63.6 (55.2,71.5) A(H3N2) 36.6 (28.4,45.5) v 40.1 (32.0,48.7)	Level I	Good

	for 2006-2007 2007-2008 2008-2009 *Analysis includes only participants vaccinated with the same vaccine sequentially		ID→ID→ID=121 IM→IM→IM=67 65% chronic condition Excluded congenital or acquired immuno-deficiency ID→ID signifies ID injection in first year followed by ID in second year	B 14.3 (8.8,21.4) v 9.8 (5.5,15.9) **Seroprotection** ID→ID v IM→IM A(H1N1) 95.5 (90.4,98.3) v 81.8 (74.5,87.8) A(H3N2) 98.5 (94.6,99.8) v 95.8 (91.0,98.4) B 55.6 (46.8,64.2) v 53.1 (44.6,61.5) **GMFR** ID→ID v IM→IM A(H1N1) 9.64 (7.70,12.1) v 7.24 (5.82,9.02) A(H3N2) 2.92 (2.43,3.51) v 2.88 (2.43,3.41) B 1.77 (1.57,2.00) v 1.67 (1.50,1.86) **<u>Third Vaccination 2008</u>** **Seroconversion** ID→ID→ID v IM→IM→IM A(H1N1) 37.2 (28.6,46.4) v 31.8 (20.9,44.4) A(H3N2) 73.6 (64.8,81.2) v 60.6 (47.8,72.4) B 47.1 (38.0,56.4) v 26.9 (16.8,39.1) **Seroprotection** ID→ID→ID v IM→IM→IM A(H1N1) 81.8 (73.8,88.2) v 74.2 (62.0,84.2) A(H3N2) 92.6 (86.3,96.5) v 77.3 (65.3,86.7) B 70.2 (61.3,78.2) v 55.2 (42.6,67.4) **GMFR** ID→ID→ID v IM→IM→IM A(H1N1) 2.88 (2.43,3.41) v 2.86 (2.31,3.54) A(H3N2) 8.45 (6.79,10.5) v 6.94 (5.15,9.36) B 3.76 (3.16,4.46) v 2.40 (1.93,2.98)		
Chan (2014)[44] NCT01967368	ID: Intanza® (Sanofi Pasteur) 15µg HA/strain 0.1mL/dose IM: Vaxigrip® (Sanofi Pasteur) 15µg HA/strain 0.5mL/dose Strains A/California/7/ 2009 (H1N1), A/Victoria/361/	RCT Open-label Single center Country: China (Hong Kong) Year 2013-14	Age: ≥65 years Mean 83 years Male 36% Total: n=100 ID=50 IM=50 Nursing home residents	**Follow-up**: 21 days **<u>Day 21</u>** **Seroconversion** ID v IM A(H1N1) 60 v 36* A(H3N2) 30 v 16 B 20 v 22 **Seroprotection** ID v IM A(H1N1) 96 v 90 A(H3N2) 96 v 98 B 98 v 94 **GMT** ID v IM A(H1N1) 8.6 (5.1,12.1) v 5.2 (2.4,7.9) A(H3N2) 2.7 (1.9,3.5) v 2.3 (1.0,3.5) B 4.9 (1.4,8.4) v 2.0 (1.6,2.4) **GMTR** IM/ID	Level I	Good

	2011 (H3N2) B/Massachus-etts/2/2012			A(H1N1) 0.85 (0.55,1.01) A(H3N2) 0.60 (0.47,0.65) B 0.28 (0.40,1.13) **<u>Day 180</u>** **Seroconversion** ID v IM A(H1N1) 38 v 22 A(H3N2) 16 v 2* B 20 v 6 **Seroprotection** ID v IM A(H1N1) 82 v 78 A(H3N2) 96 v 98 B 90 v 86 **GMT** ID v IM A(H1N1) 3.8 (2.3,5.3) v 2.6 (1.8,3.3) A(H3N2) 2.0 (1.4,2.7) v 1.2 (0.9,1.5)* B 2.4 (1.6,3.2) v 1.4 (0.0,1.8)*		
Hoon Han (2013)[43] NCT01215669	ID: Intanza® (IDflu) 15µg HA/strain 0.1mL/dose IM: Vaxigrip® (Sanofi Pasteur) 15µg HA/strain 0.5 mL/dose Strains A/California/7/2009 (H1N1) A/Perth/16/2009 (H3N2) B/Brisbane/60/2008	RCT Open-label Multicentre Phase IV Country South Korea 6 sites Year 2010-11	Age: 18+ years Data for ≥60 years Mean 64.5-64.9 yrs Male 38% N: 120 ID=60 IM= 60 38% vaccinated past year	**Follow up:** 21 days Data in figures only - CHMP criteria for all three strains met for ID and IM vaccines - No statistically significant differences in rates of seroprotection, seroconversion, or for GMTR for ID and IM vaccines	Level I	Fair-Good (limited data could be abstracted)
Holland (2008)[42]	15ID: 15µg HA/strain 21ID: 21µg	RCT Open label for route	Age 65-85 yrs Males 47%	**Follow-up** 21 days **Seroconversion**	Level I	Good

NCT00296829	HA/ strain Intradermal split-virion (Sanofi Pasteur) 0.1mL/dose 15IM: 15µg HA/strain VaxiGrip® (Sanofi Pasteur) 0.5mL/dose Strains A/New Caledonia/20/99 (H1N1) A/Wellington/1/2004 (H3N2) B/Jiangsu/10/2003	Double blind for dose Multicenter Phase II Country New Zealand Australia Year 2006	Total n=1101 15ID=366 21ID=369 15IM=366 ~85% vaccinated previous season Medically stable	Significantly higher (p<0.05) in the ID than in the IM, for all strains and both strengths **Seroprotection** A(H1N1) no difference A(H3N2) significantly higher for ID vs IM B significantly higher for ID vs IM **GMTR** 15ID/15IM & 21ID/15IM A(H1N1) 1.52 (1.28,1.78)^{S} & 1.59 (1.36,1.84)^{S} A(H3N2) 1.70 (1.41,2.04)^{S} & 1.70 (1.42,2.03)^{S} B 1.49 (1.27,1.74)^{S} & 1.40 (1.20,1.64)^{S} Notes: The 21µg ID vaccine did not induce a statistically significant difference in responses compared with the 15µg ID vaccine		
Seo (2014)[45]	ID : (Sanofi Pasteur) 15µg HA/strain 0.1mL/dose Comparator IM15: Aggripal S1® (Novartis) 15µg HA/strain 0.1mL/dose ADV: Fluad® (Novartis) 15µg HA/strain 0.1mL/dose adjuvant	RCT Multicenter Country South Korea	Age ≥65 years Median 71-73 years Male 32-39% N=335 IM15 =113 ADV=111 ID =111 Community-dwelling Good health	**<u>28 day follow-up</u>** **Seroconversion** ID v IM15 v ADV A(H1N1) 42.5 (34, 52) v 38.7 (30,49) v 54.1 (45,63) A(H3N2) 43.2 (34.2,54.3) v 26.5 (18.6,34.5) v 45.0 (36.0,54.1) B 7.2 (2.7,12.6) v 1.8 (0,4.4) v 7.2 (2.7,11.7) **Seroprotection** ID v IM15 v ADV A(H1N1) 78.8 (71.7,86.7) v 72.1 (63.1,80.2) v 84.7 (78.4,91.0) A(H3N2) 83.8 (75.7,91.0) v 71.7 (63.7,79.6) v 89.2 (82.9,94.6) B 18.6 (12.4,25.7) v 18.0 (10.8,25.2) v 24.3 (17.1,33.3) **GMTR** ID v IM15 v ADV A(H1N1) 3.6 (2.3,5.6) v 3.5 (2.2,5.7)	Level I	Good

	Year 2011-12 Strains A/California/7/2009 (H1N1) A/Perth/16/2009 (H3N2) B/Brisbane/60/2008			v 4.4 (2.7,6.3) A(H3N2) 3.5 (2.4,5.2) v 1.9 (1.3,2.8) v 3.4 (2.2,5.2), B 1.4 (1.0,1.9) v 1.2 (0.8,1.6) v 1.6 (1.1,2.4) **<u>180 day follow-up</u>** **Seroconversion** A(H1N1) 8.8 (3.5,15.0) v 10.8 (5.4,17.1) v 5.4 (1.8,9.9) A(H3N2) 34.2 (25.2,43.2) v 37.8 (27.9,47.7) v 28.3 (20.4,37.2) B 1.8 (0,4.5) v 1.8 (0,4.5) v 2.7 (0,5.3) **Seroprotection** A(H1N1) 53.1 (44.2,61.9) v 51.4 (42.3,61.3) v 37.8 (28.8,46.8) A(H3N2) 74.8 (66.7,82.9) v 77.5 (70.3,84.7) v 64.6 (56.6,73.5) B 18.6 (12.4,25.7) v 16.2 (9.9,24.3) v 9.9 (4.5,16.2) **GMFR** A(H1N1) 1.4 (0.9,2.2) v 1.6 (1.0,2.6) v 1.3 (0.8,2.1) A(H3N2) 2.5 (1.7,3.7) v 2.1 (1.4,3.2) v 1.3 (0.6,1.7) B 1.0 (0.8,1.4) v 1.2 (0.8,1.7) v 1.0 (0.7,1.4)		
Scheifele (2013)[41] NCT01368796	ID: Intanza® 15µg HA/strain 0.1mL/dose Comparators: ADV Fluad® (Novartis) 15µg HA/strain MF59 adjuvant 0.5mL/dose IM:15 Agriflu® (Novartis)	RCT Evaluator-blind Multicenter Country: Canada 8 centres) Year 2011-12	Age ≥65 years Mean 74 years 41% male ID=301 ADV=299 IM15=305 95% Caucasian 100% vaccinated in 1 or 2 of previous	**21 day follow-up** **Seroconversion** ID v ADV v IM15 A(H1N1) 39.0 v 49.5 v 36.3 A(H3N2) 35.3 v 44.7 v 24.7 B 15.8 v 16.6 v 10.9 **Seroprotection** ID v ADV v IM15 A(H1N1) 81.0 v 91.2 v 78.7 A(H3N2) 76.1 v 87.9 v 76.5 B 98.3 v 98.6 v 98.7 **GMFR** ID v ADV v IM15 A(H1N1) 3.1 (2.9,3.5) v 4.2 (3.7,4.8)* v 2.7 (2.5,3.0) A(H3N2)	Level I	Good

	15µg HA/strain 0.5mL/dose Strains A/California/7/2009 (H1N1) A/Perth/16/2009 (H3N2) B/Brisbane/60/2008		two seasons Community-dwelling or at facilities with minimal assistance	2.7 (2.5,3.1) v 3.4 (3.1,3.8)* v 2.3 (2.1,2.5) B 1.6 (1.5,1.8) v 1.6 (1.5,1.7) v 1.4 (1.3,1.5)* **180 day follow-up** Seroprotection rates declined by 21.3-25.6% for A(H1N1), 17.4-26.7% for H3N2 and <3% for B strains. Notes: Data for single radial hemolysis and microneutralization assays not abstracted but were generally similar to HAI testing ID & IM15 alike re: SP;		
Sibunruang (2011)[47]	ID12: 12µg/strain (6µg/strain /site x 2 sites) ID6: 6µg HA/strain (3µg/strain/site x 2 sites) IM: (Sanofi Pasteur) 15 µg HA/strain 0.5mL/dose Strains A/California/7/2009 (H1N1) A/Perth/16/2009 (H3N2) B/Brisbane/60/2008	RCT Open-label Country: Thailand Year: 2010	Age 60-90 years Mean 67 years Male 20% N=180 12ID=60 6ID=60 IM=60 Healthy, community dwelling	**28 day follow-up** **Seroconversion** 12ID vs 6ID vs IM A(H1N1) 45.0 v 33.3 v 43.3 A(H3N2) 25.0 v 28.3 v 35.0 B 71.7 v 75.0 v 86.7 **Seroprotection** 12ID vs 6ID vs IM A(H1N1) 23.3 v 25.0 v 36.0 A(H3N2) 26.7 v 23.3 v 38.3 B 76.7 v 73.3 v 76.7 **GMFR** 12ID vs 6ID vs IM A(H1N1) 2.4 v 2.3 v 2.7 A(H3N2) 2.0 v 2.2 v 2.4 B 5.2 v 5.4 v 7.3	Level 1	Fair-Good Small sample size Abstract (Limited data avail-able)
Camilloni (2014)[48]	ID: Intanza® (Sanofi Pasteur)	Randomized Blinding not stated	Age ≥65 years Mean 85 years Male 15%	Follow-up 1 & 6 months **<u>One month</u>** **Seroprotection** ID v ADV	Level II	Good Small

	15µg HA/strain 0.1mL/dose Comparator: ADV Fluad® (Novartis) 15µg/strain 0.5mL dose MF59	Country Italy Nursing homes Season 2011,2012	N=80 ID=40 ADV=40 100% previously vaccinated 100% chronic underlying disease Live in nursing home	H1N1 70.0 (57.1,80.3) v 72.5 (59.7,82.4) H3N2 92.5 (82.6,97.0) v 87.5 (76.4,93.8) B 75.0 (62.4,84.4) v 75.0 (62.4,84.4) **Seroconversion** ID vs ADV H1N1 42.5 (30.5,55.5) v 50.0 (37.3,62.6) H3N2 60.0 (47.0,71.7) v 47.5 (35.1,60.2) B 40.0 (28.3,53.0) v 10.0 (4.6,20.5)* **GMFR** ID v ADV H1N1 3.8 (2.2,6.8) v 3.7 (2.4,5.6) H3N2 4.6 (2.8,7.8) v 3.3 (1.9,5.7) B 3.2 (1.7,6.0) v 1.6 (1.3,2.0) **6 month follow-up** **Seroprotection** ID v ADV H1N1 50.0 (37.3,62.6) v 40.0 (28.3,53.0) H3N2 67.5 (54.5,78.2) v 66.5 (52.0,76.1) B 60.0 (47.0,71.7) v 57.5 (44.5,69.5) **Seroconversion** ID v ADV H1N1 7.5 (3.0,17.4) v 17.5 (9.8,29.4) H3N2 17.5 (9.8,29.4) v 30.0 (19.6,42.9) B 0.0 (0,6.3) v 17.5 (9.8,29.4)* **GMFR** ID v ADV H1N1 1.9 (1.2,2.8) v 1.5 (1.1,2.0) H3N2 2.4 (1.3,4.4) v 2.1 (1.1,4.1) B 1.8 (1.0,3.1) v 1.0 (0.9,1.1)		sample size
Ansaldi (2013)[50] EUDRACT: 2009–014637–24	ID: Intanza® (Sanofi Pasteur) 15µg HA/strain 0.1ml dose Comparator: ADV Inflexal® V (Crucell) 15µg HA/strain 0.5mL/dose Adjuvant: virosome Strains	RCT Open-label Multicenter Phase IV Country: Italy Year 2010	Age: ≥60 Mean 75-77 years Total: N=50 for serology ID=24 ADV=23 Excluded: alcoholic, unstable chronic illness	**Follow-up**: 28 days **Seroconversion** ID v ADV A(H1N1) 50 (31,69) v 43 (26,43) A(H3N2) 50 (31,69) v 35 (19,55) B 46 (28,65) v 0 (0,14) **Seroprotection** ID v ADV A(H1N1) 63 (43,79) v 57 (37,74) A(H3N2) 71 (51,85) v 48 (29,67) B 100 (86,100) v 100 (86,100) **GMFR** ($CI_{95\%}$) ID v ADV A(H1N1) 3.4 (1.9,5.9) v 2.3 (1.3,3.8) A(H3N2) 2.9 (1.8,4.8) v 2.1 (1.4,3.1)	Level I	Fair-Good Small number for serology

	A/California/7/2009(H1N1) A/Perth/16/2009 (H3N2) B/Brisbane/60/2008			B 2.7 (1.5,4.9) v 1.5 (1.0,2.3) **3 month follow-up** **Seroprotection** ID v IM A(H1N1) 45 (26,66) v 47 (27,68) A(H3N2) 60 (39,78) v 32 (15,54) B 95 (76,99) v 100 (83,100)		
Van Damme (2010)[49] NCT00554333	ID: Intanza® (Sanofi Pasteur) 15µg HA/strain 0.1 mL/dose ADV: Fluad® (Novartis) 15µg HA/strain MF59 adjuvant 0.5mL/dose Strains A/Solomon Islands/3/2006 (H1N1) A/Wisconsin/67/2005 (H3N2) B/Malaysia/2506/2004	RCT Open-label Parallel-group Multi-centre Phase II Country Belgium, France 10 centres Year 2007-08	Age ≥65 yrs Mean 74.3 yrs Male 46.5% N 795 ID=390 ADV=385 72% vaccinated last year 53% underlying disease	**Follow-up**: 21 days **Seroprotection** ID v ADV A(H1N1) 81.3 v 87.1 **GMFR** ($CI_{95\%}$) ADV/ID A(H1N1) 1.13 (0.95,1.34)[N] A(H3N2) 1.31 (1.13,1.53) B 1.08 (0.95,1.23)[N] **GMTR** (ADV/ID) A(H1N1) 1.12 A(H3N2) 1.31 B 1.07	Level 1	Good

Appendix F: Summary of evidence related to safety of high dose seasonal influenza vaccines in adults 65 years and older

STUDY DETAILS						
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
60µg HA/strain inactivated intramuscular						
Couch (2007)[29] NCT00115531 NCT00170508	Experimental IM: 60µg HA/strain 0.5mL/dose Comparator: Fluzone® (Sanofi Pasteur) 15µg HA/strain 0.5mL/dose Strains A/New Caledonia/20/99 (H1N1), A/Wyoming/03/2003 (H3N2) B/Jiangsu/10/2003	RCT Double blind Multi-site Phase II Country USA Year 2004-05 Stratified by receipt of influenza vaccine in <u>same</u> season	Age ≥65 Mean: 73-74 yrs Male 51% N=414 60µg=206 15µg=208 78% vaccinated in fall of 2004 (same season) 96% Caucasian	**Follow up**: 7 days active; 210 days passive **Reactogenicity** 15µg *v* 60µg <u>*Systemic*</u> Fever (≥37.5°C) 0.5 v 4.4 Myalgia 15.4 v 12.6 Headache 17.3 v 11.1 Malaise 13.0 v 16.5 <u>Local</u> Pain 19.7 v 40.3 Redness 27.9 v 29.1 Swelling 18.3 v 23.8 <u>Vaccine-related SAE</u> 60µg: oculo-respiratory syndrome day of vaccination	Level 1	Good
DiazGranados (2013)[21] NCT00976027	Fluzone® High-Dose (Sanofi Pasteur) 60µg HA/strain 0.5mL/dose Comparator: Fluzone® (Sanofi Pasteur)	RCT Double-blind Multi-centre Phase 3b Country USA 99 centres Year 2009-10	Age ≥65 yrs Mean 72.8 yrs (64–99 yrs) Male 46.3% N=9158 60µg N=6107 15µg N=3051 85% Caucasian 89% vaccinated	**Follow-up** 180 days, weekly calls **Adverse events** 60µg -3 cases of Bell's Palsy (116, 126, & 178 days post-vaccination) 15µg -2 cases of Bell's Palsy (34 & 176 days post-vaccination) **Serious adverse events** 15µg v 60µg At least one 197 (6.5%) v 408 (6.7%)	Level 1	Good

	15µg HA/strain 0.5mL/dose Strains A/Brisbane/59/07 (H1N1) A/Uruguay/716/2007 (H3N2) B/Brisbane/60/2008		last season Ambulatory, medically stable Key Exclusion Criteria: Bed-ridden, Immune suppressing disease	Fatal SAE 10 (0.3%) v 24 (0.4%) Vaccine-related 2 v 1 **Vaccine-related SAE** 60µg -cardiac chest pain starting one day after vaccination (recovered in 2 days) 15µg -Bell's palsy 34 days after injection and unresolved at study completion -immune thrombocytopenia 13 days after injection and recovered after 5 days No reactogenicity data gathered		
DiazGranados (2014)[33] NCT01427309	Fluzone® High- Dose (Sanofi Pasteur) 60µg HA/strain 0.5mL/dose Fluzone® 15µg HA/strain 0.5mL/dose	RCT Double-blind Multicenter Phase IIIb–IV Country USA, Canada 126 centres Yr 1 2011-12 Yr 2 2012-13	Age ≥65 yrs Mean: 73.3 yrs Male 43.4% N=31,983 60µg=15,990 15µg=15,993 95% Caucasian 74% previous vaccination 67% ≥ 1 chronic condition	**Follow-up:** ~180 days <u>Vaccine-related SAE</u> 60µg v 15µg 3 v 0 60µg: - cranial-nerve VI palsy (1 day post-vaccination) - hypovolemic shock including diarrhoea (1 day post-vaccination - acute disseminated encephalomyelitis (117 days post-vaccination)	Level 1	Good
Falsey (2009)[28] NCT00391053	Experimental TIV split-virus 60µg/strain 0.5mL/dose Comparator : Fluzone® (Sanofi Pasteur) 15µg HA/strain	RCT Double-blind Multi-centre Phase III Country USA 30 centres Year 2006-07	Age 65-97 years Mean 73 years Male 52% N=3876 60µg=2576 15µg=1275 82% vaccinated last season	**Follow-up** 7 days active, 180 days passive **Reactogenicity** 60µg v 15µg <u>Systemic</u> Fever (≥ *37.5* ^{o}C) 3.6 (2.9,4.4) v 2.3 (1.5,3.3) 1.1 (0.8,1.6) v 0.3 (0.1,0.8)* mod/severe Myalgia 21.4 (19.8,23.0) v 18.3 (16.2,20.5) 5.8 (5.0,6.8) v 3.4 (2.5,4.6)* mod/severe	Level 1	Good.

	0.5mL /dose Strains A/New Caledonia/20/99 (H1N1) A/Wisconsin/67/ 2005 (H3N2) B/Malaysia/2506 /04		79% underlying condition Medically stable, community dwelling	Headache 16.8 (16.5,19.5) v 14.4 (12.1,16.0) Malaise 18.0 (16.5,19.5) v 14.0 (12.1,16.0)* Any systematic reaction 34.3 (32.5,36.2) v 29.4 (26.9,32.0)* <u>Local</u> Pain 36 v 24 Redness 15 v 11 Swelling 6 v 4 **SAE** 60µg v 15µg 6% v 7% **Vaccine related SAE** 60µg: Crohn's disease exacerbation requiring hospitalization (2 days post-vaccination) 15µg: Myasthenia gravis (~ 1 month post-vaccination)		
Sanofi Pasteur (2013)[57] Robertson (2012)[58] NCT01430819	Fluzone® High-Dose (Sanofi Pasteur) 60µg HA/strain 0.5mL/dose Comparator: Fluzone® (Sanofi Pasteur) 15µg HA/strain 0.5mL/dose Strains A/California/07 /2009 (H1N1) A/Victoria/210/ 2009 (H3N2) B/Brisbane/60/ 2008	RCT Double-blind Multi-centre Phase IV Country USA 6 centres Year 2011-12	Age ≥ 65 yrs Mean: 72.1 yrs Male: 39% N=300 60µg=145 15µg=147 96% Caucasian	**Follow-up** 7 days active, 21 days passive **Reactogenicity** 60µg v 15µg <u>Systemic</u> Fever (undefined) 0.7 v 1.3 Myalgia 29.3 v 16.7* Headache 16.7 v 17.3 Malaise 16.0 v 14.0 <u>Local</u> Pain 52.7 v 24.0* Erythema 8.7 v 4.7 Swelling 6.7 v 2.7 **Vaccine-related SAE** None	Level 1	Good

Talbot (2014)[59] NCT01189123	Fluzone® High-Dose (Sanofi Pasteur) 60µg HA/strain 0.5mL/dose Comparator: Fluzone® (Sanofi Pasteur) 15µg HA/strain 0.5mL/dose Strains not stated	RCT Double-blind Single centre Country USA Years: not stated (possibly 2010-2012)	Age 67-79 yrs Mean 73 yrs Male 51.4% N=105 60µg=47 15µg=50	**Follow-up** Not specified **Vaccine-related SAE** No SAE	Level 1	Fair Small sample size
Tsang (2014)[32] NCT00551031	60IM: High Dose IM15 (Sanofi Pasteur) 60µg/strain 0.5mL IM Investigational ID (Sanofi Pasteur) 15ID: 15µg/strain 0.1 mL/dose ID 21ID: 21µg/strain 0.1 mL/dose Comparator: FluZone® (Sanofi Pasteur) 15IM: 15µg/strain	RCT Open label for route Double-blind for dose Multi-centre Phase II Country USA 31 centres Year 2007-08	Age 47-99 years Mean 73 years Male 44% N=1912 60IM=319 15IM=320 15ID=635 21ID=635 87% previously vaccinated 94% Caucasian Medically stable Ambulatory	**Follow-up** 7 days active; 180 days passive **Reactogenicity** <u>Local</u> 15ID v 21 ID 76.5 (73.0, 79.8) v 77.3 (73.8, 80.5) 60 v 15IM 34.5 (29.3, 40.0) v 49.5 (43.9, 55.2)* <u>Systemic</u> 15ID v 21ID 27.2 (23.8, 30.9) v 31.1 (27.5, 34.9) 15IM v 60IM 25.7 (21.0, 30.9) v 36.4 (31.1, 41.9)* <u>Immediate unsolicited events</u> 15ID: Moderate dizziness lasting one day 15IM: Moderate jaw pain lasting one day **Vaccine-related unsolicited AE** 15ID v 21ID 2.7 (1.6, 4.3) v 2.4 (1.3, 3.9) 15IM v 60IM 1.6 (0.5, 3.6) v 1.6 (0.5, 3.6) **Severe vaccine-related non-serious AE** 21ID: severe injection-site rash 60IM: Severe vomiting (on vaccination day)	Level I	Good

	0.5mL/dose Strains A/Solomon Islands/3/2006 (H1N1) A/Wisconsin/67/2005 (H3N2) B/Malaysia/2506/2004			60IM; Severe cough (9 days post-vaccination) **SAE** 15ID v 21ID 5.4 (3.7,7.4) v 6.0 (4.3,8.1) 15IM v 60IM 6.6 (4.1,9.9) v 5.0 (2.9,8.0) **Vaccine related SAE** None reported		
30µg inactivated, intramuscular						
Keitel (2006)[30]	Subvirion TIV (Aventis Pasteur) 30µg HA/strain 60µg HA/strain 0.5mL/dose Comparator: subvirion TIV (Aventis Pasteur) 15µg HA/strain 0.5mL/dose Placebo: saline Strains A/NewCaledonia/20/99 (H1N1) A/Panama/2007/99 (H3N2) B/Victoria/504/2000	RCT Single-center Country USA Year 2001-02	Age ≥65 years Mean 72.4 yrs (65-88 yrs) Male 59 % N=202 60µg=50 30µg=51 15µg=51 Saline=50 97% Caucasian 82% vaccinated last season Ambulatory, medically stable.	**Follow-up** 7 days; 180 passive **Local Reaction** 60 v 30 v 15µg v saline Any 12 v 24 v 20 v 22 (not significant) Redness/swelling 6% of high dose Significant dose-related increases in discomfort and redness/swelling (p<0.005) **Systemic Reaction (%)** No significant differences among groups **SAE** 3 in each of the vaccine groups **Vaccine-related SAE** None	Level 1	Good
60µg Intramuscular - subunit						
Palache (1993)[39]	Experimental trivalent subunit (Duphar BV) 60 µg	RCT Double-blind Multi-centre Placebo-controlled	Data for 65+ yrs Age 68-99 yrs Mean 80 yrs N=262	**Follow-up** 2 days of active **Reactogenicity** Placebo v 10 v 20 v 60µg Systemic Any 1 v 0 v 2 v 0	Level I	Good

	HA/strain 0.5mL/dose Comparator(s) 10µg HA/strain 20 µg HA/strain Saline (placebo) 0.5mL/dose Strains A/Taiwan/2/86 (H1N1) A/Sichuan/2/87 (H3N2) B/Beijing/1/87	Country Netherlands Israel Year 1988 See Remarque (1993) for same participants – for IgG, IgA, IgM responses to H3N2 strain	60 µg=66 10 µg=67 20 µg=64 Saline=65 22% previously vaccinated Nursing home residents Excluded Immune suppressing drug treatment	Local Any 3 v 1 v 5 v 6 **SAE** none reported		
Recombinant vaccines						
Keitel (2009)[23] NCT00395174	FluBlok® (Protein Sciences Corp.) ~45µg rHA/strain 0.5mL/dose (Total: 131µg) Strains A/Wisconsin (H3N2) A/New Caledonia (H1N1) B/Ohio IM15: Fluzone® (Sanofi Pasteur)	RCT Double-blind Multi-centre Phase 3 Country USA 7 centres Year 2006-07	Age ≥65 yrs Mean: 45µg 72.9 yrs 15µg 73.9 yrs Male 47% N=869 rHA45=431 IM15=430 98% Caucasian 83% vaccinated last season Ambulatory, medically-stable, community dwelling	**Follow-up:** 7 days active, 180 days passive **Reactogenicity** rHA45 v IM15 Any 47 v 50% Systemic Fever (≥37.6°C) 2.5 v 2.1 Headache 11 v 10 Tiredness 14 v 15 Fatigue 9 v 10 Local Discomfort 22 v 23 Erythema 10 v 12 Swelling 7 v 10 Erythema immediately after injection 6.1 v 0.6* **Unsolicited AE** 21% v 20% **Vaccine-related SAE** None	Level 1	Good

	15µg HA/strain 0.5mL/dose					
Treanor (2006)[40]	Baculovirus-expressed (rHA) 135µg rHA/strain 45µg rHA/strain 15µg rHA/strain 0.5mL/dose Comparator IM15: Fluzone® (Sanofi Pasteur). 15µg HA/strain 0.5mL/dose Strains A/Panama/2007/99 (H3N2) A/NewCaledonia/20/99 (H1N1) B/HongKong/330/2001	RCT Double-blind Country USA Year not stated (2002-03 or 2003-04)	Age 65-90 yrs Mean: 72 yrs 49% male N=399 135rHA=101 45rHA= 99 15rHA=98 IM=98 96% Caucasian Community-dwelling, medically stable	**Follow-up** 7 days active, 28 days passive **Reactogenicity** 135 v 45 v 15rHA v IM <u>Systemic</u> Fever (≥37.5°C) 4.0 v 4.0 v 3.0 v 2.0 Myalgia 15.0 v 8.0 v 11.1 v 8.1 Headache 15.0 v 14.0 v 15.2 v 10.1 Malaise 15.0 v 14.0 v 13.1 v 7.1 <u>Local</u> Pain 19.0 v 15.0 v 11.1 v 6.1* Swelling 11.0 v 0 v 1.0 v 3.0 Tenderness 29.0 v 20.0 v 14.1 v 29.3 **Vaccine-related SAE** None	Level 1	Good
15µg inactivated intradermal						
Ansaldi (2013)[50] EUDRACT: 2009–014637–24	ID: Intanza® (Sanofi Pasteur) 15µg HA/strain 0.1ml dose Comparator: Inflexal® V (Crucell) 15µg HA/strain 0.5mL/dose	RCT Open-label Multicenter Phase IV Country: Italy Year 2010	Age: ≥60 Mean 75-77 years Total: N=500 ID: n=250 IM: n=250 Excluded: alcoholic, unstable chronic	**Follow-up** 21 days active; 180 days passive **Reactogenicity** IM v ID <u>Systemic</u> Any 10 (7,15) v 11 (7,15) Fever (≥38°C): 2 (1,14) v 2 (1,14) Chills/shivering: 5 (3,9) v 3 (2,6) Myalgia: 7 (4,11) v 6 (4,10) Headache: 6 (3,10) v 4 (2,8) Malaise: 6 (3,10) v 5 (3,9) <u>Local</u>	Level I	Good

	Strains A/California/7/2009(H1N1) A/Perth/16/2009 (H3N2) B/Brisbane/60/2008		illness	Any: 20 (15,26) v 43 (36,49) Pain: 12 (8,17) v 13 (9,18) Redness: 7 (4,11)* v 33 (27,39) Swelling: 5 (2, 8)* v 19 (14,24) Lump: 7 (4,11)* v 25 (20,31) Pruritus: 5 (3,9)* v 20 (16,26) **Unsolicited Events,** days 0-21 2.0 (0.8,5.3) v 0.9% (0.2,3.1) **Serious adverse events** None reported		
Arnou (2009)[46] NCT00383526	Experimental ID: (Sanofi Pasteur) 15ug HA/strain 0.1mL/dose Comparator: Vaxigrip® (Sanofi Pasteur) 15ug HA/strain 0.5mL/dose Strains as recommended for 2006-2007 2007-2008 2008-2009 *Analysis includes only participants vaccinated with the same vaccine sequentially	RCT Open-label Multi-centre Country: France, Belgium, Lithuania, Italy Years 2006-2009	Age 60-95 years Mean 71 years Male 20% N=3707 Year 1 ID =2604 IM =1081 Year 2 ID→ID =133 IM→IM =143 Year 3 ID→ID→ID=121 IM→IM→IM=67 65% chronic condition Excluded congenital or acquired immuno-deficiency	**Follow up** 7 days active; 21 days passive **Reactogenicity** IM v ID <u>Systemic</u> Fever (>37.5°C & ≥24 hr) 3.4 (2.4,4.7) v 2.5 (1.9,3.1) Chills 6.1 (4.7,7.7) v 4.6 (3.8,5.5) Myalgia 10.9 (9.1,12.9) v 10.6 (9.5,11.9) Headache 12.7 (10.8,14.9) v 13.0 (11.8,14.4) Malaise 7.8 (6.3,9.6) v 8.5 (7.4,9.6) <u>Local</u> Pain 17.2 (15.0,19.6) v 22.7 (21.1,24.4) Redness 15.1 (13.0,17.3)* v 70.9 (69.1,72.7) Swelling 8.4 (6.8,10.2)* v 35.8 (33.9,37.7) Lump 11.3 (9.5,13.3)* v 37.6 (35.8,39.5) Pruritus 6.1 (4.7,7.7)* v 29.5 (27.7,31.2) Bruising 3.7 (2.7,5.0) v 3.4 (2.7,4.2) Unsolicited reactions (Day 0-21) 1.8 (1.1,2.8) v 1.6 (1.2,2.2) **SAE** IM v ID 0.6 (0.2,1.2) v 0.5 (0.3,0.9) **SAE possibly vaccine-related** IM=0 v ID=2 -myopericarditis 4 months post-vaccination in a person with history of MI -facial neuralgia 8 weeks post-vaccination	Level 1	Good

Chan (2014)[44] NCT01967368	Intanza® (Sanofi Pasteur) 15µg HA/strain 0.1mL/dose Comparator: Vaxigrip® (Sanofi Pasteur) 15µg HA/strain 0.5mL/dose Strains A/California/7/2009 (H1N1), A/Victoria/361/2011 (H3N2) B/Massachus-etts/2/2012	RCT Open-label Single center Country: China (Hong Kong) Year 2013-14	Age ≥65 years Mean 83 years Male 36% Total: n=100 ID=50 IM=50 Nursing home residents	**Follow-up:** 7 days active; 180 days passive **Reactogenicity** IM v ID <u>Systemic</u> Fever (≥37.5°C) 4 v 2 Myalgia 6 v 10 Arthralgia 4 v 8 Headache 6 v 6 Malaise 8 v 12 <u>Local</u> Pain 6 v 4 Redness 4 v 26* Swelling 2 v 20* Lump 0 v 0 **Serious adverse events:** No vaccine-related SAE	Level I	Good
Hoon Han (2013)[43] NCT01215669	Intanza® (IDflu) 15µg HA/strain 0.1mL/dose Comparator: Vaxigrip® (Sanofi Pasteur) 15µg HA/strain 0.5 mL/dose Strains A/California/7/2009 (H1N1) A/Perth/16/2009 (H3N2) B/Brisbane/60/2008	RCT Open-label Multicentre Phase IV Country South Korea 6 sites Year 2010-11	Age: 18+ years Data for ≥60 years Mean 64.5-64.9 yrs Male 38% N: 120 ID: n= 60 IM: n= 60 38% vaccinated past year	**Follow-up:** 7 days active, 21 days passive **Reactogenicity** IM v ID <u>Systemic</u> Fever (>38.0°C & ≥1 day) 0 v 0 Shivering 13.3 v 18.3 Malaise 13.3 v 20.0 <u>Local</u> Induration (≥50mm & ≥3 days) 0 v 0 Pain, erythema, swelling, induration, and pruritus were higher in ID than IM recipients **Unsolicited AE** IM v ID Any 25 V 23.3 Vaccine-related 3.3 v 3.3 **SAE** None	Level I	Good

Holland (2008)[42] NCT00296829	Intradermal split-virion (Sanofi Pasteur) 15µg HA/strain 21µg HA/ strain 0.1mL/dose Comparator: VaxiGrip® (Sanofi Pasteur) 15µg HA/strain 0.5mL/dose Strains A/New Caledonia/20/ 99 (H1N1) A/Wellington/1 /2004 (H3N2) B/Jiangsu/10/2 003	RCT Open label for route Double blind for dose Multicenter Phase II Country New Zealand Australia Year 2006	Age 65-85 yrs Males 47% Total n=1101 15ID=366 21ID=369 15IM=366 ~85% vaccinated previous season Medically stable	**Follow-up** 7 days reactogenicity; 180 days SAE **Reactogenicity** 15IM v 15ID v 21ID <u>Systemic</u> Any 27.4 v 30.2 v 29.1 Fever (>37.5°C & >24hr) 4.1 v 3.9 v 4.1 Chills 0.8 v 0.5 v 2.2 Myalgia 12.2 v 12.4 v 12.2 Headache 17.4 v 18.1 v 16.0 Malaise 10.1 v 13.2 v 10.1 <u>Local</u> Any 39.7* v 89.6 v 88.0 Pain 16.8 v 18.4 v 16.3 Erythema 19.1* v 78.8 v 77.7 Swelling 13.4* v 62.3 v 58.2 Pruritus 8.7* v 27.2 v 32.1 Induration 16.7* v 64.6 v 65.2 **Vaccine-related SAE** (180 days) 15ID - 1 vaccine-related, brachial neuritis	Level 1	Good
Seo (2014)[45]	ID: (Sanofi Pasteur) 15µg HA/strain 0.1mL/dose IM15: Aggripal S1® (Novartis) 15µg HA/strain 0.1mL/dose ADV: Fluad® (Novartis) 15µg HA/strain 0.1mL/dose adjuvant	RCT Multicenter Country South Korea	Age ≥65 years Median 71-73 years Male 32-39% N=335 IM =113 ADV=111 ID =111 Community-dwelling Good health	**Follow-up:** 7 day active **Reactogenicity** IM v ID v ADV <u>Systemic</u> Fever (≥38°C) 0 v 0.9 v 0 Chills/shivering 1.2 v 0 v 2.7 Myalgia 0.9 v 5.4 v 8.1 Arthralgia 0.9 v 2.7 v 5.4 Headache 0.9 v 4.5 v 2.7 Fatigue 0.9 v 5.4 v 5.4 Malaise 0 v 4.5 v 5.4 <u>Local</u> Pain 7.1 v 6.3 v 10.8 Redness 3.5 v 9.9 v 5.4 Swelling 3.5 v 6.3 v 2.7	Level I	Fair Short follow-up of SAE

	Year 2011-12 Strains A/California/7/2009 (H1N1) A/Perth/16/2009 (H3N2) B/Brisbane/60/2008			**SAE** None reported		
Scheifele (2013)[41] NCT01368796	ID: Intanza® (Sanofi Pasteur) 15µg HA/strain 0.1mL/dose Comparators ADV: Fluad® (Novartis) 15µg HA/strain MF59 adjuvant 0.5mL/dose IM15: Agriflu® (Novartis) 15µg HA/strain 0.5mL/dose Strains A/California/7/2009 (H1N1) A/Perth/16/2009 (H3N2) B/Brisbane/60/2008	RCT Evaluator-blind Multicenter Country: Canada 8 centres) Year 2011-12	Age ≥65 years Mean 74 years 41% male ID=301 ADV=299 IM=305 95% Caucasian 100% vaccinated in 1 or 2 of previous two seasons Community-dwelling or at facilities with minimal assistance	**Follow-up** Active 7 days; passive 180 days **Reactogenicity** IM v ID v ADV <u>Systemic</u> Any 39.4 (34.1,45.0) v 43.6 (38.1,49.2)* v 39.9 (34.5,45.5) Fever 0.7-1.7% across groups Myalgia 18.9 (14.9,23.6) v 22.8 (18.4,27.8)* v 25.9 (21.3,31.1)* Headache 11.4 (8.3,15.4) v 14.5 (11.0,18.9) v 9.6 (6.8,13.5) Malaise 11.4 (8.3,15.4)* v 16.2 (12.5,20.7)* v 11.0 (7.9,15.0)* Tiredness 21.2 (17.0, 26.1)* v 23.8(19.3,28.9)* v 18.6 (14.6,23.4)* Arthralgia 11.1 (8.0, 15.1) v 14.2 (10.7,18.6) v 12.6 (9.3,16.9) Sleep disturbance 7.2 (4.8,10.6) v 7.9 (5.4,11.5) v 8.3 (5.7,12.0) <u>Local</u> Pain 20.8 v 29.7 v 37.9 Redness 12.7 v 76.2* v 13.0 Swelling 6.2 v 49.2* v 12.0 Lump 4.6 v 46.5* v 8.0 Itchiness 1.6 v 20.8* v 3.0 **SAE** Day 0-20 8 Day 21-180 37 **Vaccine-related SAE** None	Level 1	Good

Van Damme (2010)[49] NCT00554333	ID: Intanza® (Sanofi Pasteur) 15µg HA/strain 0.1 mL/dose Comparator ADV: Fluad® (Novartis) 15µg HA/strain MF59 adjuvant 0.5mL/dose Strains A/Solomon Islands/3/2006 (H1N1) A/Wisconsin/67/2005 (H3N2) B/Malaysia/2506/2004	RCT Open-label Parallel-group Multi-centre Phase II Country Belgium, France 10 centres Year 2007-08	Age ≥65 yrs Mean 74.3 yrs Male 46.5% N 795 ID=390 ADV=385 72% vaccinated last year 53% underlying disease	**Follow up** 7 days active, 21 days passive **Reactogenicity** ID v ADV <u>Systemic</u> Fever (≥38°C) 4.0 v 5.8 Chills/shivering* 6.0 (3.9, 8.8) v 5.8 (3.7, 8.6) Malaise 4.8 (2.9, 7.4) v 5.0 (3.1 v 7.7) <u>Local</u> Pain 19.8 v 20.9 Redness 63.1 v 13.4* Swelling 34.2 v 8.6* Lump (induration) 32.9 v 10.6* Pruritis 28.1 v 6.5* At least one 70.1 v 33.8* No immediate AE **Unsolicited AE** Total 26.4 v 25.9 Severe 2.0 v 1.8 **Vaccine-related SAE** ID: Pneumonia (one day post vaccination) ADV: Facial herpes zoster (three days post vaccination)	Level I	Good
Della Cioppa (2012)[36] Della Cioppa (2014)[37] NCT00848848	IM30: 30µg H3N2 with 15µg each of H1N1 & B strains (no adjuvant) 0.5mL/dose ADV30: 30µg H3N2 with 15µg each of H1N1 & B strains & MF59 (100%) 0.5mL/dose IM15: 15µg /strain (no	RCT Observer-blind Multicenter Countries Poland Belgium Germany Year 2008-09	Age ≥65 yrs Mean 69 yrs Male 40-68% N=450 IM30=43 ADV30=42 IM15=43 ADV15=46 ID12=46 (other groups excluded) 73-81% previously vaccinated	**Follow-up** 7 days active, 21 days passive <u>Systemic</u>:IM30 v ADV30 v IM15 v ADV15 v ID12 Fever (≥38.0°C) 0 v 0 v 0 v 0 v NR Chills 0 v 2 v 0 v 2 v NR Myalgia 2 v 2 v 0 v 2 v 6 Headache 2 v 0 v 0 v 0 v NR Malaise 0 v 2 v 0 v 0 v NR Arthralgia 0 v 2 v 0 v 2 v NR <u>Local</u> Pain ADV significantly higher than IM or ID Erythema 0 v 2 v 0 v 0 v 47-52 Swelling ID significantly higher Induration ID significantly higher Pruritus Not stated for IM; ID12-2-6%	Level 1	Good

	adjuvant) 0.5mL/dose ADV15:15µg /strain & MF59 (100%) Fluad ® (Novartis) 0.5mL/dose Strains A/Brisbane/59/ 2007 (H1N1) A/Uruguay/716 /2007 (H3N2) B/Florida/4/20 06		Healthy volunteers	<u>Vaccine-related SAE</u> None NR: not reported		

ADV: adjuvant; ID: intradermal; IM: intramuscular;
AE: adverse event; SAE: serious adverse event