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

Recommendations on the use of MF59-Adjuvanted Trivalent Influenza Vaccine (Fluad®)

Supplemental Statement of Seasonal Influenza Vaccine for 2011-2012

Preamble

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

[†] This statement was prepared by CADTH and approved by NACI.

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I. Introduction

In February 2011, Fluad® (Novartis), a trivalent inactivated subunit influenza vaccine (TIV) adjuvanted with MF59C.1[1] was authorized in Canada for use in adults 65 years of age and older for active immunization against influenza caused by specific strains of influenza virus contained in the vaccine. It is the first seasonal influenza vaccine in Canada to contain an adjuvant and will be used in the upcoming fall 2011 influenza season. Fluad® has been licensed and used extensively in Europe for adults 65 years and older since 1997.

This supplement to the National Advisory Committee on Immunization (NACI) statement on seasonal TIV for 2011-12 will:

- Provide information on the MF59-adjuvanted TIV vaccine (Fluad®)
- Provide recommendations for the use of Fluad®

For further details on influenza epidemiology and recommended recipients of influenza vaccine for the 2011-12 season, please refer to NACI's 2011-12 Statement on Seasonal Trivalent Influenza Vaccine (TIV).

Recommendations

- NACI recommends that Fluad® can be used for the prevention of influenza in adults 65 years of age and older. (NACI Recommendation Grade A)
- At this time, NACI concludes there is insufficient evidence to make a recommendation for the preferential use of Fluad® over other TIV products currently authorized for use in Canada. (NACI Recommendation Grade I)

[1] *MF59C.1 is the second generation of MF59, in which citrate was added to improve the stability of the adjuvant.*[2] MF59 is often used in clinical studies and the literature to describe the adjuvant contained in Fluad®. In this document, MF59C.1 will be referred to as MF59.

II. Methods

Details regarding NACI's evidence-based process for developing a statement are outlined in *Evidence-Based Recommendations for Immunization: Methods of the NACI, January 2009, CCDR*, available from: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/acs-1/index-eng.php. NACI reviewed the key questions for the literature review as proposed by the Influenza Working Group, including such considerations as the burden of illness of the disease to be prevented and the target population(s), safety, immunogenicity, efficacy, effectiveness of the vaccine, vaccine schedules, and other aspects of the overall immunization strategy. The knowledge synthesis was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH) and supervised by the Working Group. This supplement reflects published literature up to March 2011. Following critical appraisal of individual studies, summary tables with ratings of the quality of the evidence using NACI's methodological hierarchy (Table 8) were prepared, and proposed recommendations for vaccine use developed. The Working Group chair (Dr. Nadine Sicard) presented the evidence and proposed recommendations to NACI on June 1, 2011. Following thorough review of the evidence and consultation at the NACI meeting on June 1, 2011, the committee voted on specific recommendations. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described in the text.

III. Epidemiology

A summary of the epidemiology of the 2010-2011 influenza season is included in the 2011-2012 Seasonal Influenza Vaccine Statement.

IV. Vaccine

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

Fluad® is a subunit trivalent influenza vaccine, which is inactivated and adjuvanted with MF59. It is presented as a sterile, milky-white suspension in a prefilled syringe for intramuscular injection. The type of viral antigens contained in Fluad® conforms to the current requirements for the northern hemisphere recommended by the World Health Organization (WHO). Annual revaccination with an influenza vaccine is recommended because immunity declines over time and because circulating strains of influenza virus usually change from year to year.

Annual influenza vaccination with Fluad® consists of one dose of 0.5 mL for adults age 65 years and older. Each 0.5 mL dose contains 15 µg hemagglutinin (HA) of each of the A(H1N1), A(H3N2) and B influenza strains, propagated in embryonated chicken eggs, inactivated with formaldehyde, and adjuvanted with MF59.

MF59® is an oil-in-water emulsion licensed as a vaccine adjuvant for human use.[1] It is small (~160 nm in diameter) microvesicles, consisting of squalene, polysorbate 80, sorbitan trioleate, trisodium citrate dehydrate, citric acid monohydrate, and water.[2]

Subunit vaccines are highly purified products containing surface antigen only, with most (if not all) of the internal viral components removed compared to split vaccines. Split virus and subunit vaccines are standardized to contain the same HA content (15 µg for each strain). The amount of neuraminidase in the vaccines is not standardized. As a result of the manufacturing process of Fluad®, trace residuals may include kanamycin sulfate, neomycin sulfate, formaldehyde, chicken proteins, cetyltrimethylammonium bromide (CTAB), sucrose, and barium sulphate.[3] Fluad® does not contain thimerosal. The syringe plunger does not contain latex and Fluad® is considered safe for use in persons with latex allergies.[3]

Fluad® contains the equivalent antigenic content to that of Agrippal®, another subunit TIV product manufactured by Novartis, which is now marketed and authorized for use in Canada under the name of Agriflu®.

IV.2. Efficacy in adults 65 years and older

There are currently no published studies on the efficacy of Fluad®. Efficacy of inactivated influenza vaccines in general is reviewed in more detail in the 2011-12 Statement on TIV.

IV.2.1 Effectiveness in adults 65 years and older

Three published papers that assessed the effectiveness of Fluad® were identified; one uncontrolled observational study[4] compared Fluad® with non-adjuvanted subunit vaccine (Agrippal®); three case controlled studies published in one paper[5], and a fourth case control study in another paper[6], all by the same author, assessed the effectiveness of Fluad® in the elderly based on prevention of hospitalization compared to unvaccinated individuals. These studies are summarized in Table 8. In addition, an unpublished observational cohort study[7] compares the effectiveness of Fluad® with Agrippal®.

An uncontrolled observational study by Iob et al. 2005[4] assessed the effectiveness of Fluad® in 3,173 persons (3.65% < 65 years of age; mean age 85 ± 10 years) residing in 25 long-term care facilities. Among the study population, 2,965 (93.44%) had been vaccinated (1,487 with Fluad® and 1,478 with non-adjuvanted subunit vaccine Agrippal S1®). The clinical syndrome of influenza-like illness (ILI) without laboratory confirmation was observed. Residents had received no vaccine (because of refusal), or MF59 adjuvanted or non-adjuvanted vaccine. Selection of vaccine was by the facility and all residents within each facility either received the chosen vaccine for that facility or refused to be vaccinated; reasons for product choice by the facility were not known. Overall, 16.9% of vaccinated residents

had ILI compared to 30.4% of the unvaccinated (Vaccine effectiveness (VE) for any vaccine was 54%). The VE of MF59 adjuvanted vaccine was 94% although confidence intervals were wide (47-100%), and of non-adjuvanted vaccine 24.5% (95% CI 0, 45%). When stratifying for chronic illness (defined as current treatment of or past hospitalization for renal, heart, or lung disease) Fluad® was found to be more effective at preventing ILI than Agrippal S1® in patients with respiratory or heart disease with higher odds ratios than in the unstratified analysis.

There were several important methodologic limitations of this study. The decision regarding which vaccine a facility used was not randomized and was left to the discretion of the facility. The health status of residents in each of the vaccine groups was not provided so it is not possible to assess potential important differences among the groups. Reported effectiveness in this trial was against ILI and not lab-confirmed influenza. Occurrence of influenza outbreaks in participating facilities was not reported making interpretation of estimates of vaccine effectiveness difficult since the proportion of ILI caused by influenza may have varied considerably between facilities. Most importantly, the reported VE of 94% for Fluad® seems improbable since much ILI is not due to influenza even during influenza seasons. Likewise, effectiveness of the non-adjuvanted subunit vaccine may be an underestimate if a higher proportion of ILI in facilities using this vaccine were not due to influenza. Due to these limitations, the results of this study should be interpreted with caution.

Puig-Barbera et al. 2007[5] performed a series of three case-control studies to assess the effectiveness of Fluad® versus no vaccine in preventing hospitalization for pneumonia, acute coronary syndrome (ACS) and cerebrovascular accident (CVA) among the elderly (≥65 years) living in the community between November and March of the 2004-2005 influenza season. Results were adjusted for potential confounders including medical comorbidities, functional status, smoking, healthcare utilization, pneumococcal vaccination, and vaccination of the usual caregiver. No impact of vaccination on hospitalization due to pneumonia, CVA, or ACS was observed outside of influenza season. During periods in which influenza virus was circulating in the community, the adjusted odds ratio in participants who had received MF59® -adjuvanted vaccine was 0.13 (95%CI .03-.65) for ACS, .07 (.01-.48) for CVA, and .31 (.14-.71) for pneumonia giving a corresponding estimate of vaccine effectiveness of 87% for ACS, 93% for CVA, and 69% for pneumonia. Because this was not a randomized controlled trial, it is subject to confounding and bias. The authors attempt to control for as many confounding factors (including indication bias) as possible in the analysis. While the effectiveness of Fluad® in the prevention of hospitalization for pneumonia, ACS and CVA may be overestimated given this potential for bias, the results are epidemiologically and biologically plausible and consistent with other published data suggesting benefit of influenza vaccination in the prevention of the studied outcomes. A fourth case-control study by Puig-Barbera et al. 2004[6] for the period November 2002 to March 2003 also showed that Fluad® demonstrated a vaccine effectiveness of 48% in reducing emergency admission for pneumonia.

Since there were no comparator vaccines used in the Puig-Barbera studies, the added benefits of using adjuvanted vaccine over non-adjuvanted vaccines cannot be assessed.

An unpublished cohort study by Mannino et al. 2011[7], also known as the Lombardy Influenza Vaccine Effectiveness (LIVE) study, was conducted during three consecutive influenza seasons (2006-2008) in Italy. This study assessed the effectiveness of Fluad® versus non-adjuvanted subunit Agrippal® in preventing hospitalizations for influenza and pneumonia in 107,661 elderly (≥65 years) subjects, who contributed 170,988 person-seasons of observation. The included participants received either Fluad® or Agrippal® through general practitioners or local health authorities and provided written informed consent before vaccination. It is not known, however, how patients were selected to receive Fluad® or Agrippal®. After the exclusion of outliers (not defined in the information available), 164,007 person-seasons remained for analysis. During the peak influenza season, 115 hospitalizations for influenza or pneumonia per 84,564 person-seasons (0.136%) where identified in the Fluad® group and 112 hospitalizations for influenza or pneumonia per 79,443 person-seasons (0.141%) were identified in the Agrippal® group. During the influenza season, there was no significant difference in risk reduction for hospitalizations based on the crude estimate [relative risk (RR) 0.96; 95% CI 0.74-1.25]. However, participants

in the Fluad® cohort had more comorbidities and history of severe diseases than those in the Agrippal® cohort; after controlling for possible confounding, there was a reduction in hospitalizations for influenza and pneumonia during the influenza season in favor of Fluad® over Agrippal® (RR 0.77; 95% CI 0.59-0.99). For the time frame when influenza was mostly likely to be circulating, Fluad® use was associated with an estimated 23% reduction in hospitalization for pneumonia and influenza compared with the non-adjuvanted vaccine. No difference between Fluad® and Agrippal® was noted in the adjusted analysis outside of the influenza season. The relative low incidence of hospitalizations (112-115) from large cohorts (79,443 - 84,564 person-seasons) raises questions about the significance of any observed benefit of Fluad® over non-adjuvanted vaccine in the prevention of hospitalization. Since the information was derived from presentations and personal communications and has not been published, caution should be given to any interpretation of the results pending opportunity for a full critical appraisal and peer review of the study.

IV.3 Immunogenicity

IV.3.1 Mechanism of Action of Adjuvant

The mechanism of action of MF59® is not fully understood. It is suggested that MF59® facilitates the internalization of antigen by dendritic cells.[2] Animal studies show that administration of MF59® triggers a cascade of immune-stimulatory events and induces a significant influx of phagocytes (e.g., macrophages and monocytes) to the site of injection, which in turn upregulates the differentiation of monocytes to dendritic cells.[8] Thus, one of the effects of MF59® is to produce a local immune-stimulatory environment at the injection site by promoting the production of immune mediators in the muscle fibers.[1] [2] This is hypothesized to be the mechanism by which the adjuvant improves and broadens the immune response.

IV.3.2 Immunogenicity in adults 61 years and older

In clinical trials of Fluad®, haemagglutinin inhibition geometric mean titres (HI GMTs) were the primary outcome measurement for evaluation of antibody response. HI GMTs elicited by Fluad® were compared with those elicited by the control intramuscular influenza vaccine. In addition, the immune response to Fluad® vaccination was evaluated based upon the European Medicines Agency (EMA) immunogenicity criteria (Table 1).[9] EMA requires that at least one of the criteria must be met *for each strain* in order to grant an annual licensure for a specific influenza vaccine in the pre-defined age groups.

The immunogenicity of Fluad® has been evaluated for two groups of recipients, adults 61 years of age and older, and adults 18 to 60 years of age. Some of the studies included may have participants whose ages overlap these ranges, and were categorized for the relevant age group according to the ages of the majority of the participants, and the objective of the study.

Table 1: European Medicines Agency (EMA) immunogenicity criteria for annual licensing of influenza vaccine using HI (haemagglutinin inhibition) and SRH (single radial haemolysis) methods.[9]

Criteria	Definition	≥60 years
Seroconversion or significant increase rate	HI method: Percentage of vaccines with pre-vaccination titre <10 and post-vaccination titre of ≥40 OR ≥10 and at least 4-fold rise in post-vaccination titre SRH method: Percentage of vaccines with negative pre-vaccination titre and post-vaccination area ≥25 mm^2 OR ≥50% increase in area post-vaccination	>30%
Seroprotection	Percentage of vaccinees achieving post-vaccination HI titre of ≥40 OR SRH titre > 25 mm^2	>60%
Mean geometric increase	Post / prevaccination GMT ratio	>2.0

For the evidence of immunogenicity of Fluad® vaccine in adults 61 years of age and older, two meta-analyses were identified,[10][11]16 RCTs[12]-[27] and two cohort studies.[28] [29] The two meta-analyses by Banzhoff et al. 2003[10] and Podda 2001[11] reviewed first year and multi-year data, respectively, from trials participating in an integrated clinical program. Of note, these meta-analyses were an integrated clinical development program of the manufacturer, and therefore were not systematic reviews. Evidence related to immunogenicity of Fluad® vaccine in adults 61 years of age and older is shown in Table 8.

The comparator vaccines mentioned in the meta-analyses[10] [11] included non-adjuvanted subunit vaccines and split vaccines (Agrippal S1®, Influvac®, FluShield®, Vaxigrip®, Alpharix®, and Fluvirin®).

Pooled data from the first vaccination of 13 clinical trials reported in the meta-analyses[10][11] showed that Fluad® is more immunogenic than non-adjuvanted vaccines for all three antigens (B, A/H3N2,and A/H1N1), particularly in elderly subjects with chronic disease. Day-0 GMT values were similar in both groups. Table 2 shows results of Day-28 GMT and GMT ratios (GMRs) of Fluad® and comparator vaccines by health status for all three antigens. Fluad® induced a more significant increase in GMTs than comparator vaccines for B antigen (with or without comorbidities), A/H3N2 antigen (with or without comorbidities) and A/H1N1 antigen (with comorbidities). Across comparisons by health status, GMR values in subjects with comorbidities were more pronounced than those without comorbidities, demonstrating the additional effect of Fluad®, particularly for A/H3N2 antigen (p=0.004) and B antigen (p=0.065). The respective GMR values for those with and without co-morbidities were 1.37 vs. 1.17 for B antigens (p=0.065), 1.43 vs. 1.18 for A/H3N2 (p=0.004), and 1.17 vs. 1.10 for A/H1N1 antigen (p=0.41). It was concluded that, in elderly subjects (≥65 years) with or without underlying comorbidities, Fluad® provided higher antibody response than non-adjuvanted vaccines as shown by post-vaccination GMT, and GMR responses, particularly for the A/H3N2 and B strains.

Table 2: GMTs and GMRs by health status for B, A/H3N2 and A/H1N1 antigens[10][11]

Antigen	Day-28 GMTs		GMRs	P value (within each group)	P value (by health status)
	Fluad®	Comparator			
B					
With comorbidities	202	147	1.37	<0.001	
Without comorbidities	168	144	1.17	0.003	0.065
A/H3N2					
With comorbidities	260	182	1.43	<0.001	
Without comorbidities	198	167	1.18	0.002	0.004
A/H1N1					
With comorbidities	268	228	1.17	<0.001	
Without comorbidities	212	191	1.10	0.068	0.41

GMTs: geometric mean titers; GMRs: GMT ratios of Fluad® and comparator

Of the individual RCT studies reviewed, 10 compared Fluad® with non-adjuvanted subunit vaccines [Agrippal® (Chiron/Novartis),[12][13][18]-[22][25][29] and Influvac® (Solvay Pharmaceuticals)[17]]; one compared Fluad® with whole virus vaccine [Inflexal® Berna (Berna Biotech Co.) [23]], and eight compared Fluad® with split vaccines [Mutagrip® (Sanofi-Aventis),[14]-[16][30] Begrivac® (Wyeth),[29] Fluarix™(GlaxoSmithKline),[24] Vaxigrip® (Sanofi-Aventis),[26] and intradermal Intanza™ (Sanofi-Pasteur)[27]]. Data from at least five of these studies were included in the above mentioned meta-analyses.[16][18][19][22][30] Although virosomal vaccine formulations are not available in Canada, comparisons of Fluad® with this type of vaccine [Inflexal® V (Berna Biotech Co.),[14][16][23][24] Invivac® (Solvay Pharmaceuticals)[17] can be found in the studies listed in Table 8]. The study population consisted of elderly subjects with and without underlying disease, [10][11][14]-[17][19][23] or with unknown health status,[24][25][29][30] patients with chronic obstructive pulmonary disease[20] or healthy elderly subjects. [12][13][18][21][22][26][27] One cohort study evaluated the impact of systemic steroid use on the immunogenicity of Fluad® given to elderly chronic obstructive pulmonary disease (COPD) patients.[28]

Fluad® and non-adjuvanted split vaccines:

All studies showed that both Fluad® and split vaccines met EMA immunogenicity criteria as shown by seroconversion rates, seroprotection rates and post-vaccination GMTs and GMRs. Table 3 summarizes the immune response (post-vaccination GMTs and seroprotection rates) of Fluad® and split vaccines against homologous and heterologous strains. For studies whose population consisted of elderly with and without underlying health conditions, no subanalyses were conducted to evaluate potential differences in outcome between these groups

Compared with Mutagrip®, Fluad® was generally more immunogenic and induced higher post-vaccination GMTs for all three strains. Statistical significance was reached for A/H3N2 and B strains in one trial where participants were unprotected against at least one influenza virus strain at the start of the study,[15] for A/H3N2 and A/H1N1 strains in a second trial,[30] but it was not reached for any of the three strains in a third trial.[16] Participants from this third trial[16] were later retested for immunogenicity against 2006-2007 homologous and heterologous strains.[14] Individuals in the Mutagrip® group were generally healthier than the Fluad® group, with 60.2% and 87.5% of participants reporting at least one underlying disease, respectively. Fluad® induced a stronger and broader response in elderly subjects with chronic conditions than Mutagrip®, with significantly higher GMTs for A/H3N2 (p<0.01) and A/H1N1 (p<0.01).

Cross reactivity was also observed when comparing Fluad® to Bengrivac®. Fluad® had higher GMTs than Bengrivac® against heterologous strain A/H3N2 (A/Wyoming) circulating one year after vaccination (p=0.0064), although both vaccines had similarly high seroprotection rates against the

homologous strain (A/Panama).[29] Against Vaxigrip®, Fluad® had higher post-vaccination GMTs for all three strains in healthy elderly subjects 65 years of age and older.[26] The ratios of post-GMT to pre-GMT were similar for the two vaccines against the A/H3N2 strain, but higher for Fluad® for the A/H1N1 and B strains. Non-inferiority analysis showed that Vaxigrip® was equivalent to Fluad® regarding seroprotection rates and seroconversion rates against the A/H3N2 strain, but Fluad® was more immunogenic for the other two strains (A/H1N1 and B) in those < 75 years of age. For subjects 75 years of age or older, Fluad® was more immunogenic than Vaxigrip® for all three strains.[26]

In contrast, Fluarix™[24] had higher post-vaccination GMTs for A/H1N1 (p<0.0001) and A/H3N2 (p<0.0001), while Fluad® had higher GMTs for B strain (not significant). Both vaccines showed increased titres (over 10-fold) for all three strains compared to pre-vaccination. Data was collected up to eight months post-vaccination throughout which high seroprotection rates of both vaccines were maintained, although some degree of waning immunity was observable. For seroconversion rate at one month post vaccination, Fluarix™ showed a higher seroconversion rate for A/H1N1 (74.8% Fluarix™ vs. 70.2% Fluad®), and Fluad® for the A/H3N2 (69.5% Fluad® vs. 67.4% Fluarix™) and B (80.4% Fluad® vs. 78.0% Fluarix™) strains. Up to month eight, Fluad® demonstrated higher titres against the B strain, similar titres against A/H3N2, and lower titres against A/H1N1 compared to Fluarix™. It was concluded that split-virus vaccine (Fluarix™) was more immunogenic than MF59® -adjuvanted vaccine (Fluad®) for A/H1N1 and A/H3N2 strains.

A phase III randomized trial[27] in adults 65 years of age and older has compared Intanza™ to Fluad®. In this trial, two methods of immunogenicity assessment were used; haemagglutinin inhibition (HI) as the primary endpoint and single radial haemolysis (SRH) as the secondary endpoint. Samples were taken pre- and 21 days post-vaccination. Non-inferiority was defined as the upper bound of the 95% CIs around the post-vaccination ratios of GMTs (adjuvanted / intradermal vaccine) being < 1.5 for all three strains.

GMT non-inferiority criteria for Intanza™ were met for all three strains for SRH method and for H1N1 and B strains only using the HI method. Post-vaccination GMT ratios (Fluad® / Intanza™) using HI and SRH methods respectively were 1.13 (0.95, 1.34) / 1.16 (1.00, 1.34) for A/H1N1; 1.31 (1.13, 1.53) / 1.18 (1.03, 1.34) for A/H3N2; and 1.08 (0.95, 1.23) / 1.03 (0.91, 1.17) for B strain. Superiority of Intanza™ was not tested using the HI method as non-inferiority was not demonstrated for all three strains. Superiority using the SRH method was tested but not demonstrated for any of the strains. Post-hoc analysis to adjust for baseline antibody titres demonstrated non-inferiority of the ID vaccine using both HI and SRH methods for all three strains.

There were no significant differences between the two vaccine groups in GMT ratios, seroprotection rates and seroconversion rates for the three strains by either HI or SRH method with the exception of the seroprotection rate for the A/H1N1 strain. Seroprotection rates were high in both groups, but significantly higher in the Fluad® group (difference of 5.8% (0.7, 10.9) and 5.8% (1.1, 10.5) by HI and SRH method respectively).

Using the HI method, both vaccines satisfied all three EMEA criteria for the A/H1N1 and A/H3N2 strains GMTR criterion only for the B strain for both vaccines. With the SRH method, both vaccines satisfied all EMEA criteria for all three strains.

Fluad® and non-adjuvanted subunit vaccines:

Most studies showed that both Fluad® and non-adjuvanted subunit vaccines met EMA immunogenicity criteria as shown by seroconversion rates, seroprotection rates and post-vaccination GMTs and GMRs against homologous strains. Table 3 summarizes the immune response (post-vaccination GMTs) and seroprotection rates of Fluad® and non-adjuvanted subunit vaccines against homologous and heterologous strains.

Fluad® induced higher post-vaccination GMTs than Agrippal® for all three antigens, and was shown to be significantly different against one[13][22][29], two[19][21], and

all three influenza strains[18][21]. Fluad® provided higher seroprotection rates than Agrippal® that were statistically significant in a few studies for A/H3N2 antigen only[21][29], and for both A/H3N2 and B strains[18][19]. In a multi-year trial, Fluad® was significantly seroprotective against the B strain in year 1 and against A/H1N1 in year 3.[22] The immunogenicity of Fluad® has also been evaluated for heterologous strains. Fluad® had higher GMTs than Agrippal® against strains circulated one and two years after vaccination with the WHO recommended A/H3N2,[12][13][22][29] A/H1N1,[22] and B[22] strains . Fluad® also had higher seroprotection rates than Agrippal® against heterologous strain (A/H3N2)[13][29] Thus, compared with Agrippal®, Fluad® seemed to provide higher immunogenicity and broader cross-reactivity against heterologous influenza strains. In two studies, however, outbreaks due to drift variants were still identified among elderly individuals despite their having mounted high cross-reactive antibodies to the heterologous A/H3N2[31] or influenza B[32] virus causing outbreaks in their settings. This suggests cross-reactive antibodies are of uncertain clinical significance.

One trial[17] showed that the post-vaccination GMTs were comparable between Fluad® and Influvac®. Both vaccines induced a strong and comparable immune response as indicated by seroprotection rates (A/H3N2: 100% vs. 99.2%; A/H1N1: 84.1% vs. 88.8%; B: 94.4% vs. 89.6%).

Table 3: Post-vaccination GMTs and seroprotection rates of Fluad®, non-adjuvanted subunit vaccines and split vaccines against homologous and heterologous strains for adults 61 years of age and older

Study (Health status)	Comparator (Season)	Post-vaccination GMT and [Seroprotection rate, %] (Fluad® vs. comparator)		
		A/H3N2	A/H1N1	B
Fluad® and split vaccines				
Baldo et al. 2006[15] (With and without comorbidities)	Mutagrip® (2004-2005)	60.3 vs. 43.5, $p<0.05$ **[90 vs. 65, $p<0.005$]**	104.7 vs. 120.2, NS **[98.8 vs. 98.8, NS]**	51.5 vs. 40.2, $p<0.05$ **[88 vs. 74, $p<0.005$]**
Baldo et al. 2001[16] (With and without comorbidities)	Mutagrip® (1998-1999)	48.6 vs. 47.0 **[79.8 vs. 80.6, NS]**	157.8 vs. 123.3 **[100 vs. 100, NS]**	75.6 vs. 65.6 **[98 vs. 100, NS]**
Baldo et al. 2010[14] (With comorbidities)	Mutagrip® (1998-1999) retesting sera of elderly with comorbidities, who participated in the trial of Baldo et al. 2001[17]	Fluad® had higher GMT against 2006/2007 heterologous strain ($p<0.01$) **[77.8 vs. 79.5, NS]**	Fluad® had higher GMT against 2006/2007 heterologous strain ($p<0.01$) **[100 vs. 98.9, NS]**	Both vaccines had similar GMT against 2006/2007 heterologous strain (NS) **[100 vs. 97.7, NS]**
Del Giudice et al. 2006[29] (With and without comorbidities)	Begrivac® (2003-2004)	Fluad® had higher GMT against 2004/2005 heterologous strain ($p=0.006$) **[98.3 vs. 96.7, NS]**	Not determined	Not determined
Menegon et al. 1999[30] (with and without comorbidities)	Mutagrip® (1997-1998)	221.4 vs. 153.4, <0.05 **[NS difference; numerical data not reported]**	346.5 vs. 227.9, $p<0.005$ **[NS difference; numerical data not reported]**	54.5 vs. 49.0, NS **[Fluad® > Mutagrip, $p<0.05$]**
Ruf et al. 2004[24] (With and without comorbidities)	Fluarix® (2002-2003)	Fluad® had lower GMT ($p<0.0001$) **[88.4 vs. 90.1, overlap 95% CI]**	Fluad® had lower GMT ($p<0.0001$) **[89.8 vs. 93.8, overlap 95% CI]**	Fluad® had higher GMT (NS) **[94.9 vs. 91.2, overlap 95% CI]**

Study (Health status)	Comparator (Season)	Post-vaccination GMT and [Seroprotection rate, %] (Fluad® vs. comparator)		
		A/H3N2	A/H1N1	B
Squarcione et al. 2003[26] (Healthy)	Vaxigrip® (1998-1999)	214.3 vs. 183.2 **[94.0 vs. 90.4, NS]**	154.4 vs. 87.1 **[83.4 vs. 71.6, p not reported]**	24.0 vs. 18.9 **[38.0 vs. 29.5, p not reported]**
Van Damme et al. 2010[27] (Healthy)	Intanza™ (2007-2008)	332.8 vs. 266.5 GMR: 1.25 (non-inferiority was demonstrated; upper bound of 95% CI was <1.5) **[similar; numerical data not reported]**	121.6 vs. 108.8 GMR: 1.12 (non-inferiority was demonstrated; upper bound of 95% CI was <1.5) **[similar; numerical data not reported]**	38.9 vs. 37.9 GMR: 1.03 (non-inferiority was demonstrated; upper bound of 95% CI was <1.5) **[similar; numerical data not reported]**
Fluad® and non-adjuvanted subunit vaccines				
De Donato et al. 1999[18] (Healthy)	Agrippal® (1993-1994)	331 vs. 162, $p<0.001$ **[83 vs. 68, $p<0.001$]**	252 vs. 177, $p<0.001$ **[88 vs. 80, NS]**	137 vs. 84, $p<0.001$ **[71 vs. 43, $p<0.001$]**
Gasparini et al. 2001[19] (Healthy)	Agrippal® (1994-1995)	103 vs. 55, $p\leq0.001$ **[51 vs. 34, $p\leq0.001$]**	191 vs. 167, NS **[88 vs. 85, NS]**	102 vs. 70, $p\leq0.001$ **[54 vs. 35, $p\leq0.001$]**
Li et al. 2008[21] (Healthy)	Agrippal® (2005-2006)	274.61 vs. 110.85, $p<0.001$ **[88 vs. 72, $p<0.001$]**	1439.01 vs. 1197.39, $p=0.034$ **[99.7 vs. 99.5, NS]**	16.59 vs. 11.95, $p=0.0005$ **[35.7 vs. 28.3, NS]**
Minutello et al. 1999[22] (Healthy)	Agrippal® (1992/1993)	189 vs. 149, NS Fluad® had higher GMT against 1993/1994 heterologous strains (by 75%) **[83 vs. 61, NS]**	45 vs. 31, NS Fluad® had higher GMT against 1993/1994 strain* (103%) **[22 vs. 17, NS]**	115 vs. 74, $p\leq0.005$ Fluad® had higher GMT against 1993/1994 strain* (by 90%) **[63 vs. 41, $p\leq0.05$]**
Ansaldi et al. 2010[12] (Healthy)	Agrippal® (2005-2006)	Fluad® had higher GMT against 2004/2005 and 2006/2007 heterologous strains ($p<0.05$) **[Both vaccines met EMA criteria]**	Not determined	Not determined
Ansaldi et al. 2008[13] (Healthy)	Agrippal® (2004-2005)	Fluad® had higher GMT against 2005/2006 and 2007/2008 heterologous strains ($p<0.05$) **[Both vaccines met EMA criteria]**	Not determined	Not determined

Study (Health status)	Comparator (Season)	Post-vaccination GMT and [Seroprotection rate, %] (Fluad® vs. comparator)		
		A/H3N2	A/H1N1	B
Del Giudice et al. 2006[29] (With and without co-morbidities)	Agrippal® (2003/2004)	Fluad® had higher GMT against 2004/2005 heterologous strains (p=0.006) **[98.3 vs. 75.9, p=0.0001] for heterologous strains**	Not determined	Not determined
Giammanco et al. 2005[20] (Chronic obstructive pulmonary disease)	Agrippal® (2003-2004)	NS difference **[NS difference]**	NS difference **[NS difference]**	NS difference **[NS difference]**
Sindoni et al. 2009[25] (With and without co-morbidities)	Agrippal® (2002-2003)	378 vs. 257, p<0.05 **[98.9 vs. 98.9, NS]**	256 vs. 185, p<0.05 **[95.8 vs. 96, NS]**	160 vs. 170, NS **[96.6 vs. 98, NS]**
de Bruijn et al. 2007[17] (With and without co-morbidities)	Influvac® (2004-2005)	740 vs. 595, NS **[100 vs. 99.2, NS]**	109 vs. 136, NS **[84.1 vs. 88.8, NS]**	195 vs. 188, NS **[94.4 vs. 89.6, NS]**

Fluad® and whole virus vaccine:

One trial[23] compared the immunogenicity of Fluad® and whole virus vaccine (Inflexal® Berna), which were randomly given to elderly subjects in nursing homes. The seroprotection rates of Fluad® were higher than Inflexal® Berna for A/H1N1 at 4 weeks (98% vs. 73%, p=0.0038) and at 12 weeks (93% vs. 58%, p=0.0009) post-vaccination. There were no significant differences between groups for A/H3N2 (100% vs. 97%) and B (85% vs. 82%). Fluad® provided a better post-vaccination GMT than Inflexal® Berna for the A/H1N1 antigen at 4 weeks (157 vs. 66) and 12 weeks (124 vs. 42), and for B antigen at 4 weeks (100 vs. 63) and 12 weeks (100 vs. 62).

Fluad® in elderly COPD patients:

One cohort study was conducted to evaluate the impact of systemic steroid use on the immunogenicity of Fluad® given to elderly COPD patients.[28] COPD patients who received Fluad® in the season 2001-2002 were stratified into three groups according to the treatment regimen: systemic steroid therapy, inhaled steroid, and no steroid use (control group). Four weeks post-vaccination, mean GMTs were significantly increased in all groups for all strains (p≤0.05), but there were no significant differences between groups with regards to GMTs, seroconversion or seroprotection. At week 24, mean GMTs had fallen to baseline levels for A/H1N1 and A/H3N2, but remained significant for B (p≤0.05). The authors concluded that the use of systemic steroids in elderly patients with COPD did not affect immunogenicity to Fluad®.

IV.3.3 Immunogenicity in adults 18 to 60 years of age

Although the Fluad® vaccine has been authorized for use in individuals 65 years and older, several studies on populations aged 18 to 60 years were found.

For evidence of immunogenicity in adults 18 to 60 years of age, four RCTs were identified.[33]-[36]. Summary of immunogenicity of each trial is shown in Table 4 and detailed information can be found in the evidence table (Table 8).

When the immunogenicity of Fluad® and non-adjuvanted subunit vaccine (Influpozzi®; Biochine) was evaluated in adult subjects (18 to 60 years) with underlying chronic disease (cancer, diabetes, heart, lung),[33] both vaccines induced a significant increase in GMTs against all three strains. Compared to the non-adjuvanted vaccine, Fluad® provided significantly higher GMTs for A/H3N2 and B strains. Seroprotection rate >70% was met with Fluad® for both A strains (A/H1N1: 97.5% & A/H3N2: 75%), but was slightly below threshold for the B strain (69.2%). Seroprotection rate for Influpozzi® was only met for A/H1N1

strain (96.6%). Seroconversion rate >40% was met with Fluad® for all three strains and met with Influpozzi® for A/H1N1 strain only. It was concluded that while both vaccines have a good immunogenicity profile, the addition of MF59® enhances immunogenicity of subunit influenza vaccine in adults with chronic disease.

One study[35] showed that there was no significant difference in immunogenicity between Fluad® and non-adjuvanted split vaccine (Fluzone®) in healthy adults. Although both vaccines met EMA immunogenicity criteria, there were no significant differences with regard to seroprotection rates and post-vaccination GMTs. Seroconversion rates between Fluad® and Fluzone® reached significant difference for B strain only (83% vs. 71%, p=0.008). It was concluded that only minor immunogenicity differences were seen between the two groups at 28 days post-vaccination. In the following season, a subset of the same participants were revaccinated and a statistically higher immune response was only observed with the A/H3N2 strain in the Fluad® group at four weeks post-vaccination. The GMT was higher (112 vs. 71; p<0.001); the percentage of subjects who seroconverted was higher (55% vs. 32%, p=0.0005); and the percentage of subjects with seroprotection was higher (53% vs. 26%, p<0.0001) with Fluad® versus Fluzone® respectively. For the A/H1N1 and B strains the results were similar between the Fluad® and Fluzone® groups. Only minor immunogenicity differences between the two groups were seen at 180 days post-vaccination with the second dose.

Two studies assessed Fluad® in HIV seropositive patients (Durando et al and Gabutti et al).[34][36] For HIV-1-seronegative and HIV-1-seropositive subjects (the majority of whom were on highly active antiretroviral therapy (HAART), there was no difference in seroprotection and seroconversion rates between Fluad® and Agrippal®. Post-vaccination GMTs were higher in Fluad® than in Agrippal®,[34] but significant differences were reached only for A/H1N1 (p=0.005) and B (p=0.023) strains in HIV-1-seronegative subjects, and for A/H3N2 (p=0.003) strain in HIV-1-seropositive subjects. After correction for existing pre-vaccination antibody status, Fluad® exhibited better immunogenicity than Agrippal®, as shown from the analysis of the GMTs, with significant differences for some virus strains. Because the mathematical method to adjust for prevaccination antibodies (Beyer's correction) is currently not standard for influenza vaccine analyses, no definitive conclusions on the clinical significance of such results can be drawn. It was concluded that both vaccines had good immunogenicity for both uninfected and HIV-1-infected adults. However, there was insufficient evidence of superiority of Fluad® compared to Agrippal® in the population. Both studies assessed if there was a negative effect of vaccination based on viremia (HIV-1 RNA levels) or CD4+ T-lymphocyte counts and no clinically significant negative effect was noted. The Durando *et al* study also assessed cell-mediated immunity.

The immune response to influenza was assessed by measuring IgG and IgM antibodies in 58 heart transplant patients randomized to receive either Fluad® or Agrippal® versus a control non-vaccinated group[37]. The findings were consistent with other studies in that there was no significant difference in the rate of immune response between the Fluad® and Agrippal® group in this population. The mean antibody titers to influenza A virus were not modified by either Fluad® or Agrippal® treatment, whereas immunity to influenza B virus was increased following immunization by both vaccines.

Table 4: Post-vaccination GMTs and seroprotection rates of Fluad® and non-adjuvanted subunit vaccines against homologous strains in adults 18 to 60 years of age

Study (Health status)	Comparator (season)	Post-vaccination GMT and [Seroprotection rate, %] (Fluad® vs. comparator) at approximately 28 days post-vaccination		
		A/H3N2	A/H1N1	B
Baldo et al. 2007[33] (with comorbidities)	Influpozzi Subunita® (non-adjuvanted subunit vaccine) (2005-2006)	Higher, $p<0.001$ **[75.0% vs. 57.6%, $p=0.002$]**	NS difference **[97.5% vs. 96.6%, NS]**	Higher, $p<0.02$ **[69.2% vs. 61.0%, NS]**
Durando et al. 2008[34] (HIV-1-seronegative and HIV-1-seropositive)	Agrippal® (non-adjuvanted subunit vaccine) (2005-2006)	NS for HIV-1 negative Higher, $p=0.003$ for HIV-1 positive **[NS difference; numerical data not reported]**	Higher, $p=0.005$ for HIV-1 negative NS for HIV-1 positive **[NS difference; numerical data not reported]**	Higher, $p=0.023$ for HIV-1 negative NS for HIV-1 positive **[NS difference; numerical data not reported]**
Frey et al. 2003[35] (Healthy)	Fluzone™ (split vaccine) (1995-1996) Year 1	511 vs. 418, NS **[94% vs. 91%, NS]**	951 vs. 850, NS **[99% vs. 95%, NS]**	698 vs. 601, NS **[99% vs. 97%, NS]**
	(1996-1997) Year 2	Higher $p<0.001$ **[53% vs. 26%, $p<0.0001$]**	216 vs 263, NS **[79% vs. 86%, NS]**	160 vs 176, NS **[73% vs. 69%, NS]**
Gabutti et al. 2005[36] (HIV-1-seropositive)	Agrippal® (non-adjuvanted subunit vaccine) (2002-2003)	NS difference **[72% vs. 74%, NS]**	NS difference **[83% vs. 100%, NS]**	NS difference **[94% vs. 89%, NS]**

IV.4. Vaccine Administration and Schedule

IV.4.1 Schedule & dosage

The recommended dose of Fluad® is 0.5 mL (15 µg / strain) given once annually for adults 65 years of age and older. Fluad® is supplied in single-dose prefilled glass syringes.

IV.4.2 Route of administration

Fluad® should be administered by the intramuscular (IM) route into the deltoid muscle.

IV.5. Storage Requirements

Fluad® should be stored away from light at 2°C to 8°C and should not be frozen.

IV.6. Simultaneous Administration with Other Vaccines

No studies have been conducted regarding the concomitant administration of Fluad® with other vaccines. NACI states that in general, influenza vaccine may be given at the same time as other vaccines. Injections should be given if possible in opposite limbs. When multiple injections are given at one clinic visit, injections given in one limb should be separated by a distance of at least 2 cm. Different administration sets (needle and syringe) should be used for each injection.

IV.7. Adverse Events

Information on adverse events following immunization is available through clinical trials and passive reporting. Fluad® has been authorized for use since 1997 in Italy and subsequently in other European countries and so there is considerable post-marketing experience.

Local reactions (e.g., pain, erythema, and induration) were significantly more frequent with Fluad® than comparator non-adjuvanted vaccines. However, they were classified as mild and transient. Systemic reactions (myalgia, headache, fatigue, and malaise) were similar or more frequent with Fluad® compared to non-adjuvanted vaccines. The reactions were rated as mild-to-moderate and transient.

Similar rates of local and systemic reactions were seen with Fluad® after re-immunization in subsequent influenza seasons. Serious adverse events were uncommon and were comparable between Fluad® and comparator vaccines.

Through passive surveillance, the following adverse events following immunization were reported: local injection site reactions (e.g., redness, swelling, and pain), allergic reactions, infection, vasculitis, nervous system disorders (e.g., Guillain-Barré Syndrome, myelitis, neuritis, convulsion, and paresthesia), blood disorders (transient thrombocytopenia), and skin disorders.

A detailed summary of AEs with respect to inactivated influenza vaccine is available in the 2011-12 NACI Statement on TIV. Information on AEs from clinical trials of Fluad® is summarized below.

Adverse events associated with Fluad® have been evaluated for two groups of recipients, adults 61 years of age and older, and adults 18 to 60 years of age. Some of the studies included may have participants whose ages overlap these ranges, and were categorized for the relevant age group according to the ages of the majority of the participants, and the objective of the study.

IV.7.1 In adults (61 years of age or older)

Three meta-analyses,[10][11][38] thirteen RCTs,[16]-[27][30] and one cohort study[28] having safety data on Fluad® were identified. The meta-analyses by Banzhoff et al. 2003[10] and of Podda 2001[11] reviewed first year and multi-year data, respectively, from trials participating in an integrated clinical program. Safety data included local and systemic reactions during the first three days of vaccination and any adverse events at any time during the study, usually up to day 28 post-vaccination (Table 8).

Local reactions:

All meta-analyses included trials comparing Fluad® with non-adjuvanted influenza vaccines given to elderly subjects (≥65 years) with and without underlying disease. The comparator vaccines mentioned in the meta-analyses of Banzhoff et al. 2003[10] and Podda 2001[11] included non-adjuvanted subunit and split vaccines (Agrippal® S1, Influvac®, FluShield®, Vaxigrip®, Alpharix®, and Fluvirin®).

Pooled data of clinical trials reported by Banzhoff et al. 2003[10] (13 RCTs) and Podda 2001[11] (20 RCTs; 13 first immunization, 5 second immunization, and 2 third immunization) showed that local reactions were more frequent with Fluad® than comparator vaccines (15-32% vs. 10-14%), especially pain (33% vs. 13%, $p<0.001$), erythema (18% vs. 13%, $p<0.001$), and induration (15% vs. 9%, $p<0.001$). Table 5 shows selected local reactions after first, second and third vaccination. There was almost no difference in local reactions between Fluad® and the comparator groups by day 3. Similar rates of local reactions were seen after re-immunization in subsequent influenza seasons.

A large meta-analysis by Pellegrini et al. 2009[38] of an integrated database of 64 clinical trials between 1992-1993 and 2007-2008 also showed that local reactions were more frequent with Fluad®, with a RR of 1.74 (95% CI 1.57-1.94) in the elderly population (≥65 years of age). The reactions were found to be transient and mild to moderate.

Table 5: Selected local reactions after first, second and third vaccination[10][11]

	First vaccination		Second vaccination		Third vaccination	
Reaction (%)	Fluad® (n=2112)	Comparator (N=1437)	Fluad® (N=492)	Comparator (N=330)	Fluad® (N=150)	Comparator (N=87)
Pain	32	14	27	21	28	16
Erythema	18	13	22	19	22	9
Induration	15	10	11	8	13	6

Of the individual RCT studies reviewed, seven compared Fluad® with non-adjuvanted subunit vaccines (Influvac®[17] and Agrippal®[18]-[22][25]), one compared Fluad® with whole virus vaccine (Inflexal® Berna)[23], and five compared Fluad® with split vaccines (Mutagrip®,[16][30] Fluarix™,[24] Vaxigrip®,[26] and intradermal Intanza™[27]). Data from at least five of these studies were included in the above mentioned meta-analyses.[16][18][19][22][30] The elderly population of the RCTs were comprised of either healthy subjects,[18][19][21][22][26][27] patients with chronic obstructive pulmonary disease,[20] or individuals with or without underlying disease.[16][17][30] Four RCTs did not report the health status of their study populations.[23]-[25] One cohort study[28] examined the safety of Fluad® in elderly patients with COPD who received systemic steroid therapy. Six RCTs found that local reactions were more frequent in Fluad® than Influvac®,[17] and Agrippal®,[18][19][21][22][25] particularly pain, erythema at the site of injection, and induration. One RCT found no difference in local reactions between Fluad® and whole virus vaccine Inflexal® Berna.[23]

In comparing Fluad® to Fluarix™, Fluad® had a higher number of reactions overall (p=0.021),[24] while they were found to be similar to Vaxigrip® in another study, except for pain delayed 30 minutes to three days, which was more frequent in Fluad® (6.6% vs. 3.9%, p=0.005).[26] The differences in frequency of reactions between Fluad® and Mutagrip® were found to be statistically significant in one study[30] but not in the other.[16] When compared with intradermal Intanza™,[27] local reactions were less frequent in Fluad® for erythema, swelling, induration, and puritus. A cohort study[28] reported that 21% of all patients who received Fluad® had local reactions, which were mainly mild and transient. There were no significant differences of local reactions between groups receiving systemic steroid therapy, inhaled steroid, and no steroid in the study that assessed these populations.

Systemic reactions:

Two meta-analyses[10][11] showed that systemic reactions were uncommon in both Fluad® and comparator vaccines (<1 to 8% for Fluad® vs. <1 to 4% for comparator). Most of the systemic reactions were mild and transient. Table 6 shows the frequency of selected systemic reactions after first, second and third vaccination. There was a significant difference in malaise, headache, and myalgia in the first vaccination with higher rates noted for Fluad®, but similar rates of systemic reactions were seen after re-immunization in subsequent influenza seasons. There was almost no difference in systemic reactions between Fluad® and the comparator groups by day three.

The meta-analysis of 64 clinical trials between 1992-1993 and 2007-2008 found that systemic reactions including myalgia, headache, fatigue, and malaise were more frequent with Fluad® (RR 1.29; 95% CI 1.10-1.52) for the elderly (≥ 65 years) population compared with unadjuvanted trivalent influenza vaccines.[38]

Table 6: Selected systemic reactions after first, second and third vaccination[10][11]

Reaction	First vaccination		Second vaccination		Third vaccination	
	Fluad® (n=2112)	Comparator (N=1437)	Fluad® (N=492)	Comparator (N=330)	Fluad® (N=150)	Comparator (N=87)
Malaise*	6%	4%	8%	7%	7%	3%
Headache**	6%	4%	8%	7%	7%	3%
Myalgia***	8%	3%	3%	2%	1%	2%
Fever (≥38°C)	1%	<1%	1%	1%	1%	0%

Differences between Fluad® and comparator vaccine for the first vaccination only: *p=0.003; **p=0.010; ***p<0.001

Four RCTs[17][18][22][25] showed that systemic reactions, such as headache (10% vs. 3%, p<0.05 in year two only in a three year trial)[18] and malaise (15% vs. 0%, p=0.05)[22], were more frequent in Fluad® relative to the comparator unadjuvanted trivalent influenza vaccines, while three RCTs[17][19][21] showed there were no significant differences between groups. One RCT found no differences in systemic reactions between Fluad® and whole virus vaccine Inflexal® Berna.[23] Four RCTs comparing Fluad® with Mutagrip®,[16][30] Fluarix®,[24] or intradermal Intanza™[27] showed no significant differences between groups for systemic reactions. When comparing Fluad® to Vaxigrip®, no significant differences between groups for systemic reactions were found except for immediate systemic reactions (0.6% Fluad® vs. 0% Vaxigrip®, p=0.015)[26] No systemic reactions were reported in a study of elderly patients with COPD.[28]

Serious adverse events:

Incidents of serious adverse events related to influenza vaccination were not identified in a large majority of the studies. Only one report of high fever was identified in a Fluad® recipient.[21] One meta-analysis[11] reported that possible AEs related to vaccination were similar in Fluad® and comparator vaccines: 4% from day 0 to 6 and 1% from day 7 to 28 in both groups.

A meta-analysis of 64 clinical trials between 1992-1993 and 2007-2008 found that serious AEs (at any time during the study, usually 28 days) were less frequent with Fluad® (RR 0.89; 95% CI 0.80-0.99) for elderly populations compared to non-adjuvanted vaccines when data from all trials were included, but no difference was observed when looking at data from controlled trials only.[38] Of the unsolicited AEs, the pooled estimates showed a significantly lower risk of cardiovascular disease (RR 0.58; 95% CI 0.47-0.73), new onset chronic disease (RR 0.73; 95% CI 0.59-0.91), and death (RR 0.70; 95% CI 0.54-0.91) in the elderly population receiving Fluad® relative to non-adjuvanted vaccines. The incidence of hospitalization due to an adverse event was not significantly different between groups who received Fluad® compared to non-adjuvanted vaccine for elderly populations (RR 0.91; 95% CI 0.81-1.02).

IV.7.2 In adults (18 to 60 years)

Although the Fluad® vaccine has been authorized for use in individuals 65 years and older, several studies on populations aged 18 to 60 years were found.

Five RCTs were identified comparing Fluad® with non-adjuvanted subunit vaccines (Influpozzi[33], Agrippal®[34][36][37], and Fluzone®[35]) and one retrospective study[39] comparing MF59® -adjuvanted influenza vaccines with non-adjuvanted vaccines. The study population included subjects with chronic diseases,[33] HIV-1-seronegative or HIV-1-seropositive,[34][36] heart transplant recipients,[37] healthy subjects,[35] and females with unintended pregnancy.[39] Safety data included local and systemic reactions during the first three days of vaccination and any adverse events at any time during the study, usually 28 days post-vaccination (Table 8). Pregnancy outcomes (normal, abnormal, or induced abortion) are reported in the Other Considerations section of this statement.[39]

Local reactions:

As in the elderly population, local reactions (e.g., pain, erythema, induration, or warmth) were found to be more frequent in Fluad® than comparator vaccines in adults with chronic disease,[33] adults who were HIV-1-seronegative or HIV-1-seropositive,[34][36] and in healthy adults.[35] The reactions were classified as mild and transient.

Systemic reactions:

Systemic reactions (e.g., shivering, malaise, headache, fever, or myalgia) were found to be no different in three studies[33][36][37] but more frequent in two other studies[34][35] when Fluad® was assessed against comparator vaccines. These reactions were classified as mild and transient.

Serious adverse events:

No serious AEs related to vaccination were found in any of the RCTs.

IV.8. Contraindications and Precautions

Contraindications[3]

Fluad® is contraindicated in persons with a known hypersensitivity to the active substances and/or to any of the excipients (kanamycin and neomycin sulphate, formaldehyde, and cetyltrimethylammonium bromide (CTAB)). Fluad is also contraindicated for anyone who has had a life-threatening reaction to previous influenza vaccine.[3] For more information on vaccine safety and anaphylaxis, please see the Canadian Immunization Guide (http://www.phac-aspc.gc.ca/publicat/cig-gci/index-eng.php).

Precautions[3]

Egg allergy is no longer considered to be a contraindication for influenza vaccine. Egg-allergic individuals may be vaccinated for influenza, without a prior influenza vaccine skin test, based on an assessment of risk for a severe allergic reaction to guide the method of vaccination. For details see the 2011-2012 seasonal influenza statement.

Expert review of the risks and benefits should be sought for those who have previously experienced severe lower respiratory symptoms (e.g., wheezing, chest tightness, or difficulty breathing) within 24 hours of influenza vaccination, an apparent allergic reaction to the vaccine or any other symptoms (e.g., throat constriction, or difficulty swallowing) that raise concern regarding the safety of re-immunization. This advice may be obtained from local medical officers of health or other experts in infectious disease, allergy/immunology and/or public health.

Persons with serious acute febrile illness usually should not be vaccinated until their symptoms have abated. Those with mild non-serious febrile illness (such as mild upper respiratory tract infections) may be given influenza vaccine. Opportunities for immunization should not be lost because of inappropriate deferral of immunization.

It is not known whether influenza vaccination is causally associated with increased risk of recurrent Guillain-Barré Syndrome (GBS) in persons with a previous history of GBS due to any cause. Avoiding subsequent influenza vaccination of persons known to have had GBS within eight weeks of a previous influenza vaccination appears prudent at this time.

IV.9. Other considerations

Pregnancy

Fluad® has been authorized for use in individuals 65 years or older, which precludes use in pregnant woman. However, one study on pregnant women was found and is included for completeness.

A retrospective study[39] was conducted using data from Novartis Vaccines' pregnancy database from 1991 to 2009 of female subjects (16-42 years) with unintended pregnancy exposures to MF59® -adjuvanted influenza vaccines (n=43) and non-adjuvanted influenza vaccines (n=60). The pregnancy outcomes were similar in two groups who had been exposed to MF59® -adjuvanted influenza vaccines (which consisted of Fluad®, Aflunov®, Focetria® and experimental adjuvanted tetravalent influenza vaccines) and non-adjuvanted influenza vaccines (Agrippal® and Optaflu®). The outcomes were classified as normal (70% vs. 75%), abnormal (21% vs. 23%), and induced abortion (9% vs. 2%) in the adjuvanted and non-adjuvanted groups respectively. The differences between groups were not statistically significant. Similar results were found for analysis focused on exposures occurring within the interval of 30 days before to 45 days after the last menstrual period.

Individuals with Immune Compromising Conditions

As is the case with all vaccines, the efficacy of Fluad® may be lower in certain populations (e.g., persons with immune compromising conditions, or elderly persons) than in healthy adults. However, the possibility of lower efficacy should not prevent immunization in those at high risk of influenza-associated morbidity, since protection is still likely to occur. Evidence pertaining to HIV+ individuals is presented in other sections of this statement.

Recommendations

1) **NACI recommends that Fluad® can be used for the prevention of influenza in adults 65 years of age and older. (NACI Recommendation Grade A)**

   The efficacy of Fluad® has not been directly studied; however a few observational studies suggest that Fluad® maybe be effective at reducing the risk of hospitalization for influenza and its complications in the elderly compared to unvaccinated individuals.[5][6] However, these studies have significant methodological limitations that make their interpretation difficult.

   In clinical trials, Fluad® has met EMA immunogenicity criteria for adults 60 years and older established for influenza vaccines.

   The safety profile of Fluad® has also been deemed acceptable by licensing authorities. Most reactions were mild or moderate and were of short duration. Since Fluad® has been used in many other countries in Europe since 1997, there are several years of post-marketing surveillance data available.

   The decision to include Fluad® among the influenza vaccine products available to adults 65 years of age and older, as part of publicly funded Provincial / Territorial programs will depend on multiple factors such as cost-benefit evaluation and other local programmatic / operational factors.

2) **At this time, NACI concludes there is insufficient evidence to make a recommendation for the preferential use of Fluad® in adults 65 years of age and older over other TIV products currently authorized for use in Canada. (NACI Recommendation Grade I)**

   The efficacy of Fluad® has not been directly studied. There is one published[4] and one unpublished[7] study (both observational uncontrolled studies) that assess the relative effectiveness of Fluad compared to non-adjuvanted subunit vaccines in the elderly. However, these studies have significant methodological limitations that make their interpretation difficult.

   There is evidence from randomized controlled trials showing that Fluad® induced higher immunogenicity and broader cross-reactivity in adults 65 years of age and older compared to the non-adjuvanted subunit vaccines, with similar but less consistent results shown in terms of improvement in antibody response relative to split-virus vaccine, which is the type of influenza vaccine used most often in Canada. The studies which compare Fluad® to split-virus vaccine generally compared to a vaccine called Mutagrip®, which is not available in Canada. The one study[26] that compared Fluad® to Vaxigrip® found a similar seroprotection and seroconversion rate for H3N2 and a higher immune response for H1N1 and B for Fluad recipients < 75 years of age. For those 75 years of age and older, higher seroprotection and seroconversion rates were noted for all three strains in those receiving Fluad®. In a randomized clinical trial comparing Intanza™ (intradermal TIV) to Fluad®, Intanza™ was shown to be non-inferior.[27] The implication of these immunogenicity findings with regard to clinical efficacy is unknown and requires further study.

Local reactions pain (32% vs. 14%), erythema (18% vs. 13%), and induration (15% vs. 10%) and systemic reactions (myalgia (8% vs. 3%), headache (6% vs. 4%), malaise (6% vs. 4%) and fever (1% vs. <1%) were more frequent with Fluad® compared to non-adjuvanted vaccines. However, the reactions were mild or moderate and were of short duration.

Table 7: Summary of Information Contained in this NACI Statement

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

1. What a) Basic information about the Disease (e.g. agent, symptoms, epidemiology) b) Basic information about the Vaccine (e.g. efficacy, safety)	Influenza is a respiratory infection caused by influenza A and B viruses and occurs in Canada every year, generally during late fall and the winter months. Infection typically starts with a headache, chills and cough, followed rapidly by fever, loss of appetite, muscle aches and fatigue, running nose, sneezing, watery eyes and throat irritation. Nausea, vomiting and diarrhea may also occur, especially in children. Most people will recover from influenza within a week or ten days, but some - including those 65 years of age and older and adults and children with chronic conditions, such as diabetes and cancer - are at greater risk of more severe complications, such as pneumonia. Additional information about influenza can be accessed at: http://www.phac-aspc.gc.ca/im/vpd-mev/influenza-eng.php Fluad® is a trivalent, adjuvanted, subunit inactivated influenza vaccine (TIV) administered by the intramuscular route. It can be used for annual influenza vaccination for adults 65 years of age and older. It is given as one annual dose of 0.5 mL intramuscularly, which contains 15 µg of influenza virus hemagglutinin antigens (HA) of each of the A(H1N1), A(H3N2) and B influenza strains. There are no published studies available on the efficacy of Fluad® and no effectiveness studies to compare Fluad® to current split virus vaccine options in Canada. Clinical studies have demonstrated that the immune response to Fluad® is generally better compared to non-adjuvanted subunit TIV vaccines with similar but less consistent findings when compared to the split TIV vaccines. Fluad® meets / exceeds immunogenicity criteria established for licensure of seasonal TIV. Fluad® is generally safe and well-tolerated. An increased frequency of injection site reactions was observed in clinical trials; however these reactions were mild and resolved within a few days. Slightly more frequent systemic reactions with Fluad® compared to the non-adjuvanted vaccines have been observed; however these reactions were transient and considered to be of mild to moderate severity.
2. Who Groups recommended to immunize	NACI recommends that Fluad® (15 µg/strain) can be used for the prevention of influenza in adults 65 years of age and older. (NACI Recommendation Grade A) At this time, NACI concludes there is insufficient evidence to make a recommendation for the preferential use of Fluad® in adults 65 years of age and older over other TIV products currently authorized for use in Canada. (NACI Recommendation Grade I)

3. How • Dose, schedule • Co-administration	The recommended schedule is one dose of 0.5 mL of Fluad® for adults 65 years of age and older. Fluad® is supplied in single-dose prefilled glass syringes. Fluad® is administered intramuscularly in the deltoid muscle of the upper arm. No studies have been conducted regarding the concomitant administration of Fluad® with other vaccines. NACI states that in general, influenza vaccine may be given at the same time as other vaccines. Injections should be given if possible in opposite limbs. When multiple injections are given at one clinic visit, injections given in one limb should be separated by a distance of at least 2 cm. Different administration sets (needle and syringe) should be used for each injection.
4. Why "Counseling Points" for providers to emphasize with clients when discussing these recommendations	Vaccination is the most effective way to prevent influenza. Each year there is a new vaccine to protect against the influenza virus strains that are expected in the coming influenza season. Even if the vaccine strains have not changed, getting influenza vaccine every year reinforces optimal protection. Annual influenza vaccination is encouraged for all Canadians, particularly those at high risk of influenza complications, those who could transmit influenza to someone at risk and those who provide essential community services. Fluad® is generally safe and well-tolerated. Redness and / or swelling at the site of injection following receipt of Fluad® is common and should disappear within a few days.

Table 8: Summary of Evidence for NACI Recommendation(s)

Evidence related to effectiveness of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Iob et al. Evidence of increased clinical protection of an MF59® -adjuvant influenza vaccine compared to a non-adjuvant vaccine among elderly residents of long-term care facilities in Italy. Epidemiol Infect. 2005;133(4):687-93.[4]	Fluad® (MF59® -adjuvanted subunit influenza vaccine) vs. Agrippal S1® (non-adjuvanted subunit influenza vaccine) IM; 15µg of each of the A/ Sydney/5/97(H3N2); A/ Beijing/262/95(H1N1); B/Beijing/184/93 strains	Uncontrolled observational multi-center study Italy	3173 residents from 25 long-term care facilities (mean age 85 ± 10 years); 3.65% persons <65 years Categorized as having no underlying disease, heart disease alone, respiratory disease alone, renal disease alone, or having more than one of these diseases	Incidence of influenza-like illness; stratified based on respiratory, cardiovascular and renal disease. Vaccination effectiveness: Overall (vaccine vs. no vaccine): OR 2.16, 95% CI 1.56-2.98) Fluad®: 94% (47-100%) Agrippal S1®: 24.5% (0-45%) Influenza-like illness: • Agrippal S1® vs. Fluad® • Facilities reporting ILI and underlying chronic disease: OR 1.52 (95% CI 1.22-1.88) • Above + facilities reporting no ILI: OR 1.72 (95% CI 1.39-2.12) • Above + facilities missing information on chronic diseases: OR 1.80 (95% CI 1.47-2.21) • Underlying respiratory disease: OR 2.27, 95% CI 1.09-4.82) • Underlying heart disease: OR 1.88 95% CI 1.31-2.72) MF59-adjuvanted vaccine (Fluad®) provided better protection for elderly subjects, especially those with comorbidities in having influenza-like illness	• II-2	Poor (risk of bias; reason for choosing product by long term care facility unknown; frequency of risk factors for complications in each vaccine group unknown; impact of outbreaks not discussed)

Evidence related to effectiveness of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Mannino et al. Effectiveness of influenza vaccination with Fluad® versus a subunit influenza vaccine. Canadian Geriatrics Society 31st Annual Scientific Meeting; Vancouver; 2011.[7]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Agrippal® (non-adjuvanted subunit influenza vaccine)	Cohort study; multi-season (may have looked at the same patients for more than one season)	164,007 person-seasons, subjects ≥65 years with or without comorbidities	Hospitalization Fluad® group had more underlying co-morbidities and a higher risk of hospitalizations outside of influenza season vs. Agrippal® group (RR 1.19; 95% CI 0.98-1.45) A significantly lower risk of hospitalization during influenza season (RR 0.77; 95% CI 0.59-0.99) in population receiving Fluad® vs. Agrippal® A significantly lower risk of hospitalization for all respiratory disease during influenza season (RR 0.79; 95% CI 0.66-0.95) in population receiving Fluad® vs. Agrippal® During influenza season, vaccination with Fluad® reduced hospitalizations for influenza and pneumonia by 23% compared with Agrippal®.	II-2	Poor (Personal communication)

Evidence related to effectiveness of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Puig-Barbera et al. Effectiveness of MF59-adjuvanted subunit influenza vaccine in preventing hospitalisations for cardiovascular disease, cerebrovascular disease and pneumonia in the elderly. Vaccine. 2007;25(42):7313-21.[5]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. No vaccination	3 case-control studies; multi-center November 2004 to March 2005	Subjects >64 years; Cases n=134-198; Controls n=246-321 Cases: Consecutive non-institutionalized elderly living in hospital catchment area for previous 6 months, and admitted for emergency hospitalization between Nov 2004 and Mar 2005 acute coronary syndrome (ACS), cerebrovascular accidents (CVA) or pneumonia Controls: Hospital and gender matched with same inclusion criteria as cases for acute surgical process or trauma within 0-10 days of case admission date	Risk of hospitalization for ACS, CVA or pneumonia *Hospitalization for Fluad® vs. no vaccination* ACS - greater reduction in risk observed after peak of influenza circulation • OR: 0.89; 95% CI 0.37-2.08 • Adjusted OR: 0.13; 95% CI 0.03-0.65 CVA – greater reduction in risk during peak of influenza circulation • OR: 0.66; 95% CI 0.31-1.40 • Adjusted OR 0.07; 95% CI 0.01-0.48) Pneumonia – greater reduction in risk during peak influenza circulation • OR: 0.73; 95% CI 0.40-1.35 • Adjusted OR 0.31; 95% CI 0.14-0.71 Adjusted OR accounted for likelihood of vaccination and relevant confounding factors (e.g. underlying chronic disease, use of therapeutics, caregiver vaccination, smoking, etc.) *Vaccine effectiveness (Risk reduction)* ACS: 87%; 95% CI 35-97 CVA: 93%; 95% CI 52-99 Pneumonia: 69%; 95% CI 29-86	II-2	Fair Thorough methodology with identification of potential confounding factors and controlling potential bias using propensity score

Evidence related to effectiveness of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Puig-Barbera et al. Effectiveness of the MF59-adjuvanted influenza vaccine in preventing emergency admissions for pneumonia in the elderly over 64 years of age. Vaccine. 2004;23(3):283-9.[6]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. No vaccination	Case-control study; multi-center November 2002 to March 2003	Subjects ≥65 years; Cases n=290; Controls n=525 Cases: Non-institutionalized elderly living in hospital catchment area for previous 6 months, and admitted for emergency hospitalization between Nov 2002 and Mar 2003 with confirmed pneumonia Controls: Hospital and gender matched with same inclusion criteria as cases for surgical or traumatological acute condition within 0-7 days of case admission date	Risk of hospitalization (emergency admission) for pneumonia *Fluad® vs. no vaccination* Preventing emergency admission for pneumonia: Adjusted effectiveness of 48%; 95% CI 20-66% Adjusted for heart disease, COPD, asthma, Barthel index score <60, smoking, administered pneumococcal vaccine, attending out patient clinics	II-2	Fair

Evidence related to immunogenicity of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Banzhoff et al. A new MF59-adjuvanted influenza vaccine enhances the immune response in the elderly with chronic diseases: results from an immunogenicity meta-analysis. Gerontology. 2003;49(3):177-84. [10]	MF59 adjuvanted (Fluad®) compared with non-adjuvanted vaccines (Agrippal S1, Influvac, FluShield, Vaxigrip, Alpharix, and Fluvirin)	Meta-analysis of 13 clinical trials (12 phase II/III and a subset of one phase IV)	Subjects ≥65 years with or without underlying disease	GMT, GMR from HI assay at 28 days post-vaccination Day-28 GMT for B antigen (Fluad® vs. comparator): With disease: 202 vs. 147, p<0.001 (GMR: 1.37) Without disease: 168 vs. 144, p=0.003 (GMR: 1.17) Day-28 GMT for A/H3N2 antigen (Fluad®vs. comparator): With disease: 260 vs. 182, p<0.001 (GMR: 1.43) Without disease: 198 vs. 167, p=0.002 (GMR: 1.18) Day-28 GMT for A/H1N1 antigen (Fluad® vs. comparator): With disease: 268 vs. 228, p<0.001 (GMR: 1.17) Without disease: 212 vs. 191, p=0.068 (GMR: 1.10) Significant difference in GMR for A/H3N2 between those with and without underlying chronic disease (p=0.004), but not for A/H1N1 and B MF59-adjuvanted vaccine (Fluad®) is more immunogenic than non-adjuvanted vaccines	N/A	Poor (not systematic review)
Podda A. The adjuvanted influenza vaccines with novel adjuvants: experience with the MF59-adjuvanted vaccine. Vaccine. 2001;19(17-19):2673-80.[11]	MF59 adjuvanted (Fluad®) compared with non-adjuvanted vaccines 1st, 2nd, 3rd immunization	Meta-analysis (data from a clinical database) of observer-blind RCTs	Subjects ≥65 years with or without underlying disease	GMT, GMR, seroconversion rate, seroprotection rate from HI assay at 28 days post-vaccination Day-28 GMT (Fluad® vs. comparator): With disease: 260 vs. 182, p<0.001 (GMR: 1.43) Without disease: 198 vs. 167, p=0.002 (GMR: 1.18) Significant group difference between those with and without underlying chronic disease (p=0.004) Fluad® vaccine provided higher immune response than non-adjuvanted vaccines as shown by post-vaccination GMT, GMR, seroprotection rates and seroconversion rates, particularly for the A/H3N2 and B strains.	N/A	Poor (not systematic review)

Evidence related to immunogenicity of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Ansaldi et al. Antibody response against heterogeneous circulating influenza virus strains elicited by MF59- and non-adjuvanted vaccines during seasons with good or partial matching between vaccine strain and clinical isolates. Vaccine. 2010;28(25):4123-9.[12]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Agrippal® (non-adjuvanted subunit influenza vaccine) IM; A/California/7/04(H3N2) strain	RCT; two-arm; parallel group; single-center	50 healthy subjects (>65 years) randomly assigned (1:1) to receive single dose of vaccine	GMT, MFI, seroconversion rate, seroprotection rate from HI and NT assays at 22±2 days post-vaccination MFI (>2): Both vaccines Seroprotection (>60%): Both vaccines against circulating viruses isolated between 2004/2005 and 2006/2007. Seroconversion (>30%): Both vaccines against circulating viruses isolated between 2004/2005 and 2006/2007. Post-vaccination HI GMT: higher with Fluad® compared with Agrippal® against a drifted strains Addition of MF59 to subunit influenza vaccine when there is a good or partial match to circulating strains results in a high antibody response that will increase as the antigenic and molecular distance between vaccine and circulating strains grows	I	Poor (small and selected population; method of randomization not reported)

Evidence related to immunogenicity of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Ansaldi et al. Cross-protection by MF59-adjuvanted influenza vaccine: neutralizing and haemagglutination-inhibiting antibody activity against A(H3N2) drifted influenza viruses. Vaccine. 2008;26(12):1525-9.[13]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Agrippal® (non-adjuvanted subunit influenza vaccine) IM; 15µg of each of the A/New Caledonia/20/99(H1N1); A/Wyoming/3/03(H3N2); B/Shanghai/361/02 strains	RCT; two-arm; parallel group; single-center	50 healthy subjects (≥65 years) randomly assigned (1:1) to receive single dose of vaccine	GMT, MFI, seroconversion rate, seroprotection rate from HI and NT assays at 21 days post-vaccination MFI (>2): Both vaccines Seroprotection (>60%): Both vaccines against Woy/03 Seroconversion (>30%): Only met for Fluad® group Post-vaccination HI and NT GMT: Significantly higher with Fluad® group (p=0.01 for HI and p=0.03 for NT) and when corrected for pre-vaccination status for drifted strains (p<0.05) For drifted strains (Pan/99, Cal/04, Wisc/05), Fluad® met all CHMP requirements; induced significantly (p<0.05) higher HI GMT & seroprotection rates (for Cal/04, Wisc/05) and higher seroconversion rates (for Pan/99, Cal/04) Fluad® showed a broader serological protection against drifted strains that circulated 1 and 2 years after vaccination.	I	Poor (small sample size; patient characteristic and method of randomization not reported)

Evidence related to immunogenicity of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Baldo et al. Immunogenicity of three different influenza vaccines against homologous and heterologous strains in nursing home elderly residents. Clin Dev Immunol. 2010;2010:517198. [14]	Fluad® (MF59-adjuvanted subunit influenza vaccine; Sub/MF59) vs. Mutagrip® (split influenza vaccine; Split) 0.5 ml IM; 15µg of each of the A/Sydney/5/97(H3N2); A/Beijing/262/95(H1N1); B/Beijing/184/93 strains	DB RCT; parallel group; multicenter Retesting sera of subjects participated in previous RCT of Baldo et al. 2001	Nursing home residents (≥65 years with underlying disease) randomly assigned to single dose of Sub/MF59 (n=72) and Split (n=88)	GMT, MFI, seroconversion rate, seroprotection rate from HI assay at 4 weeks post-vaccination MFI: Fluad® higher for all homologous and heterologous strains Seroprotection (≥40%): Homologous (Sub/MF59 vs. split) A/H1N1: 100; 98.9 A/H3N2: 77.8; 79.5 B: 100; 97.7 Heterologous (Sub/MF59 vs. split) A/H1N1: 87.5; 68.2 A/H3N2: 79.2; 78.4 B: 69.4; 73.9 Seroconversion (≥4 fold): Homologous (Sub/MF59 vs. split) A/H1N1: 94.4; 85.2 A/H3N2: 76.4; 62.5 B: 66.7; 54.5 Heterologous (Sub/MF59 vs. split) A/H1N1: 68.1; 31.8 A/H3N2: 41.7; 27.3 B: 25.0; 26.1 Post-vaccination GMT: Fluad® significantly higher ($p<0.05$) than split vaccine For drifted strains (A/New Cal/99, A/Wisc/2005, B/Mal/2004), Fluad® had significantly higher GMT for the A/H3N2 ($p<0.01$) and A/H1N1 ($p<0.01$) strains than split vaccine. Fluad® induced a stronger and broader response in elderly subjects with chronic conditions than split vaccine, particularly for the A/H3N2 and A/H1N1 strains.	I	Poor (sera from a subset of previous population; baseline characteristics not balance between groups; method of randomization not reported)

Evidence related to immunogenicity of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Baldo et al. Response to influenza vaccine in people with non-protective HI antibody titers. Eur J Epidemiol. 2006;21(11):843-5.[15]	Fluad® (MF59-adjuvanted subunit influenza vaccine; Sub/MF59) vs. Mutagrip® (split influenza vaccine; Split) IM; A/New Caledonia/20/99(H1N1); A/Moscow/10/99(H3N2); B/Sichuan/379/99 strains	DB RCT; two-arm; parallel group; multi-center	338 subjects >64 years and unprotected against at least one of the three influenza virus strain	GMT, seroconversion rate, seroprotection rate from HI assay at 4 weeks post-vaccination Seroprotection (≥40%): Both vaccines met; Fluad® significantly higher than Mutagrip® for A/H3N2 (p<0.005) and B (p<0.005) strains Seroconversion (≥4 fold): Both vaccines met; Fluad® significantly higher than Mutagrip® for A/H3N2 (p<0.005) and B (p<0.005) strains Post-vaccination GMT: Fluad® significantly higher than Mutagrip® for A/H3N2 (p<0.05) and B (p<0.05) strains Adjuvanted vaccine (Fluad®) induced better immunogenicity in elderly previously lacking an protective antibody titer.	I	Fair (method of randomization not reported)
Baldo et al. Comparison of three different influenza vaccines in institutionalised elderly. Vaccine. 2001;19(25-26):3472-5.[16]	Fluad® (MF59-adjuvanted subunit influenza vaccine; Sub/MF59) vs. Mutagrip® (split influenza vaccine; Split) 0.5 ml IM; 15µg of each of the A/Sydney/5/97(H3N2); A/Beijing/262/95(H1N1); B/Beijing/184/93 strains	DB RCT; parallel group; multi-center	Nursing home residents (≥65 years healthy and with underlying disease) randomly assigned to single dose of Sub/MF59 (n=99) and Split (n=93)	GMT, MFI, seroconversion rate, seroprotection rate from HI assay at 4 weeks post-vaccination MFI (>2): Both vaccines met Seroprotection (≥40%): Both vaccines met Seroconversion (≥4 fold): Significant difference for H3N2 (Sub/MF59 92.9% vs. Split 78.5%, p<0.005) and B strains (Sub/MF59 62.6% vs. Split 50.5%, p<0.005) Post-vaccination GMT: Fluad® had higher GMT than split vaccine for all strains, but did not reach statistical significance	I	Fair (method of randomization not reported; no ITT analysis)

Evidence related to immunogenicity of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
de Bruijn et al. Antibody induction by virosomal, MF59-adjuvanted, or conventional influenza vaccines in the elderly. Vaccine. 2007;26(1):119-27. [17]	Fluad® (MF59-adjuvanted subunit influenza vaccine; adSIV) vs. Influvac® (non-adjuvanted subunit influenza vaccine; SIV) Vaccine composition: A/Fujian/411/2002(H3N2); A/New Caledonia/20/99(H1N1); B/Shanghai/361/2002	Observer-blind RCT; parallel group; multi-center	386 subjects >60 years with or without underlying disease randomly assigned to adSIV (n=126) and SIV (n=125)	GMT, GMR, seroconversion rate, seroprotection rate from HI assay at 3 weeks post-vaccination MFI (>2): Both vaccines met Seroprotection (≥60%): Both vaccines met Seroconversion (≥30%): Both vaccines met Post-vaccination GMT: Both vaccines showed increased titers for all three strains. No significant difference between groups. Post-vaccination GMRs: Immunogenicity of adSIV was comparable to SIV; sub-analysis of subjects 70 years of age and older showed >1.0 GMR for adSIV vs. SIV but not statistically significant The two trivalent inactivated subunit influenza vaccines (Fluad® and Influvac®) were equally immunogenic in elderly.	I	Good (per protocol analysis)

Evidence related to immunogenicity of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
De Donato et al. Safety and immunogenicity of MF59-adjuvanted influenza vaccine in the elderly. Vaccine. 1999;17(23-24):3094-101. [18]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Agrippal™ (non-adjuvanted subunit influenza vaccine) 0.5 ml IM; 15µg of each of the A/H1N1, A/H3N3, and B antigens 3 annual immunizations (1993/94-1995/96)	RCT; two-arm; parallel group; single center	211 subjects ≥65 years having no underlying disease randomly assigned to Fluad® (n=94) and Agrippal™ (n=98)	GMT, GMR, seroconversion rate from HI assay at 28 days post-vaccination (year 1 only) Seroprotection(≥1:120) Fluad® vs. Agrippal™ A/H1N1: 88% vs. 80%, *p*=NS A/H3N2: 93% vs. 68%, *p*<0.001 B: 71% vs. 43%, *p*<0.001 Seroconversion (≥4 fold) Fluad® vs. Agrippal™ A/H1N1: 32% vs. 32%, *p*=NS A/H3N2: 83% vs. 62%, *p*<0.01 B: 52% vs. 31%, *p*<0.001 Post-vaccination HI titres (1/GMT), Fluad® vs. Agrippal™ A/H1N1: 252 (214-298) vs. 177 (151-209), *p*<0.01 A/H3N2: 331 (267-411) vs. 162 (131-200), *p*<0.001 B: 137 (115-162) vs. 84 (71-99), *p*<0.001 Post-vaccination GMRs (Fluad® vs. Agrippal™ for all years): 7/9 GMRs by strain and year for subjects with pre-immunization titre ≤40 were between 1.5 and 2.4; 1/9 GMRs were >1.5 for subjects with pre-immunization titre >40 Difference in % of subjects with tire ≥1:120 and 4-fold rise between vaccines was higher in subjects with pre-titre ≤40 than pre-titre >40 for all strains (except for % 4-fold rise of A/H1N1)	I	Poor (baseline characteristics and method of randomization not reported; no ITT analysis)

Evidence related to immunogenicity of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
de Roux et al. Impact of corticosteroids on the immune response to a MF59-adjuvanted influenza vaccine in elderly COPD-patients. Vaccine. 2006;24(10):1537-42. [28]	Fluad® (MF59-adjuvanted subunit influenza vaccine) 0.5 ml IM; 15µg of each of the A/H1N1, A/H3N2 and B strains	Cohort study; single-center	162 COPD patients (≥60 years) who received systemic steroid therapy (SS, n=33), inhaled steroids (IS, n=87) or no steroid (CG, n=42)	GMT, seroconversion rate, seroprotection rate from HI assay at 4 weeks and 24 weeks post-vaccination Seroprotection (≥40%): At 4 weeks, all groups met for all 3 antigens (range 64% in CG to 93 in all groups for B strain). No significant difference between groups (p>0.05) Vaccine failed to induced protective HI titres in a significant number of patients (20-44% of groups) with pre-vaccination titre <40 for A strains, and some (11-18%) for B strain Seroconversion (≥40%): At 4 weeks, all groups met for all 3 antigens (range 56% in CG to 89% in IS). No significant difference between groups (p>0.05) Post-vaccination GMT: All groups had significant increase of mean HI titers 4 weeks after vaccination for all 3 antigens. No significant difference between groups (p>0.05); At 24 weeks, GMT fell close to baseline for both A strains, but remained high for B strain (p≤0.05) Systemic steroids did not influence the antibody response towards Fluad® vaccine in elderly COPD patients	II-3	Poor (small sample size; baseline characteristics not reported; risk of selection bias)

Evidence related to immunogenicity of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Del Giudice et al. An MF59-adjuvanted inactivated influenza vaccine containing A/Panama/1999 (H3N2) induced broader serological protection against heterovariant influenza virus strain A/Fujian/2002 than a subunit and a split influenza vaccine. Vaccine. 2006;24(16):3063-5.[29]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Agrippal™ (non-adjuvanted subunit influenza vaccine) vs. Begrivac™ (split subunit influenza vaccine) Vaccine composition: A/Caledonia/20/99(H1N1); A/Panama/2007/99(H3N2); B/Shangdong/7/97 strains	Cohort study; three-arm	119 subjects (61-91 years; patient characteristics not reported) received single dose of Fluad® (n=60), Agrippal™ (n=29) and Begrivac™ (n=30)	GMT from HI assay at 21 days post-vaccination Seroprotection rate (≥40%): Fluad® induced higher seroprotection rates against heterovariant A/Fujian-like strain than Agrippal™ (98.3% vs. 75.9%, *p*=0.0001) and Begrivac™ (98.3% vs. 80%, *p*=0.0001) All three vaccines had similar seroprotection rates against homologous strain Post-vaccination GMT: Fluad® had higher GMT against heterovariant A/Fujian-like strain than Agrippal™ (181.0 vs. 122.3, *p*=0.0064) and Begrivac™ (180.0 vs. 82.2, *p*=0.0064) Higher post-vaccination GMT against homologous strain observed for all vaccines Fluad® provided broader protection against influenza virus strains not matched with those included in the vaccine	II-2	Poor (small sample size; baseline characteristics not reported; risk of selection bias)

Evidence related to immunogenicity of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Gasparini et al. Increased immunogenicity of the MF59-adjuvanted influenza vaccine compared to a conventional subunit vaccine in elderly subjects. Eur J Epidemiol. 2001;17(2):135-40.[19]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Agrippal® (non-adjuvanted subunit influenza vaccine) IM; 15µg of each of the A/Shangdong/9/93(H3N2); A/Texas/36/91(H1N1); B/Panama/45/90 strains	DB RCT; two-arm; parallel group; multicenter	308 healthy subjects (≥65 years), non-institutionalized and mentally competent, randomly assigned to Fluad® (n=204) or Agrippal® (n=104)	GMT, GMR, seroconversion rate, seroprotection rate from HI assay at 28 days post-vaccination Fluad® (n=192) or Agrippal® (n=99) provided blood sample at day 0 and day 28 Seroconversion (≥4 fold), Fluad® vs. Agrippal™ A/H3N2: 52% (44.9-49.1) vs. 29% (20.1-37.9), $p \leq 0.001$ A/H1N1: 20% (14.3-25.6) vs. 11% (4.8-17.2), $p \leq 0.01$ B: 35% (28.3-41.7) vs. 27% (18.3-35.7), $p \leq 0.05$ Seroprotection (≥1/160) , Fluad® vs. Agrippal™ A/H3N2: 51% (43.9-58.1) vs. 34% (24.7-43.3), $p \leq 0.001$ A/H1N1: 88% (83.4-92.6) vs. 85% (78.0-92.0), p=NS B: 54% (46.9-61.0) vs. 35% (25.6-44.4), $p \leq 0.001$ Post-vaccination GMT: Fluad® had higher GMT against A/H3N2 (103 vs. 55, $p \leq 0.001$), and B (102 vs. 70, $p \leq 0.001$) antigens than Agrippal® Post-vaccination GMR: GMRs were greater than 1.0 in favor of Fluad® with a statistically significant difference for all three strains (H3N2 – 3.3, $p \leq 0.05$; H1N1 – 1.9, $p \leq 0.001$; B – 2.6, $p \leq 0.01$) Day 180 No significant difference in GMT between vaccines; Fluad® had higher percentage of subjects with titres ≥1/160 for B ($p<0.01$) and H3N2 ($p<0.05$)	I	Poor (selected population; method of randomization not reported; no ITT analysis)

Evidence related to immunogenicity of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Giammanco et al. Immunogenicity and tolerability of two subunit influenza vaccines in patients with chronic obstructive bronchopneumopathy. Journal of Preventive Medicine and Hygiene 2005;46(3):85-7. [20]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Agrippal® S1 (non-adjuvanted subunit influenza vaccine) 0.5 ml IM; 15µg of each of the A/New Caledonia/IVR116(H1N1); A/Mosca/Resvir2002(H3N2); B/Shangdong/7/97 strains	RCT; two-arm; parallel group; single-center	54 adult and elderly subjects (53-85 years) with chronic obstructive broncho-pneumopathy randomly assigned to receive Fluad® (n=27), Agrippal® (n=27)	GMT, GMR, seroconversion rate, seroprotection rate from HI assay at 28 days post-vaccination No significant differences in immunogenicity for both Agrippal and Fluad®.	I	Poor (small sample size; method of randomization not reported; safety data not properly reported)

Evidence related to immunogenicity of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Li et al. Safety and immunogenicity of an MF59-adjuvanted subunit influenza vaccine in elderly Chinese subjects. Immun Ageing. 2008;5:2. [21]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Agrippal® (non-adjuvanted subunit influenza vaccine) 0.5 ml IM; 15µg of each of the A/New Caledonia/20/99(H1N1); A/California/7/2004(H3N2); B/Shanghai/361/2002 strains	Phase II/III observer-blind RCT; two-arm; parallel group; multi-center	600 healthy Chinese subjects (≥65 years) randomly assigned (2:1) to Fluad® (n=400) or Agrippal® (n=200)	GMT, GMR, seroconversion rate, seroprotection rate from HI assay at 22 days post-vaccination Fluad® n=367; Agrippal® n=187 <u>Seroprotection rates (≥1/40)</u>: Fluad® (A/H1N1: 99.7%; A/H3N2: 88.0%; B: 35.7%) Agrippal® (A/H1N1: 99.5%; A/H3N2: 72.2%; B: 28.3%) Fluad® significantly higher than Agrippal® for A/H3N2 (p<0.001) <u>Seroconversion rates (in subjects without pre-vaccination immunoprotection)</u>: Fluad® (A/H1N1: 83.3%; A/H3N2: 85.1%; B: 33.4%) Agrippal® (A/H1N1: 80.0%; A/H3N2: 66.2%; B: 25.8%) Fluad® significantly higher than Agrippal® for A/H3N2 (p<0.001) <u>Post-vaccination GMT</u>: Fluad® had higher GMT against A/H1N1 (1439 vs. 1197, p=0.034), A/H3N2 (275 vs. 111, p<0.001), B (17 vs. 12, p=0.005) Higher post-vaccination GMTs also found in subjects without seroprotective titres at baseline for Fluad®, and significant for A/H3N2 (p<0.001) and B (p=0.008) <u>Post-vaccination GMR</u>: The ratios were in favor of Fluad® for all 3 antigens (A/H1N1, p<0.038; A/H3N2, p<0.001; B, p<0.006) MF53-adjuvanted vaccine (Fluad®) had higher level of immunogenicity in Chinese elderly subjects than non-adjuvanted subunit vaccine.	I	Poor (selected population; baseline characteristics and method of randomization not reported; no ITT analysis; risk of selection bias)

Evidence related to immunogenicity of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Menegon et al. Influenza vaccines: antibody responses to split virus and MF59-adjuvanted subunit virus in an adult population. Eur J Epidemiol 1999;15(6):573-6. [30]	Fluad® (MF59-adjuvanted subunit influenza vaccine; Sub/MF59) vs. Mutagrip® (split influenza vaccine; SVV) 0.5 ml IM; 15µg of each of the A/ Wuhan/359/95(H3N2); A/ Bayern/7/95(H1N1); B/ Beijing/184/93 strains	DB RCT; two-arm; paral-lel group; single-center	200 adult and elderly subjects (23-97 years) with or without comorbidi-ties randomly assigned to receive Fluad® (n=100), Mutagrip ® (n=100) 194 com-pleted the follow-up (96 in Fluad® and 98 in Muta-grip®)	GMT, seroconversion rate, seroprotection rate from HI assay at 4 weeks post-vaccination Seroprotection (≥1/40): Fluad® > Mutagrip for B strain (p<0.05) Seroconversion (≥4 fold): Both vaccines met for all 3 antigens. Fluad® > Mutagrip for all 3 strains (p<0.005) Factors associated with seroconversion for all strains include prevaccination titre ≥1:40, assignment to Fluad®, and previous vaccinations (except for B strain) Post-vaccination GMT: Fluad® > Mutagrip for A/H3N2 (221.4 vs. 153.4, p<0.05) and A/H1N1 (346.5 vs. 227.9, p<0.005); but not for B (54.5 vs. 49.0, NS) Both vaccines caused significant rises in GMTs (p<0.001); Fluad® induced greater immune response than Mu-tagrip	I	Fair (method of ran-domiza-tion not reported; baseline character-istics not appro-priate; no ITT analysis)

Evidence related to immunogenicity of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Minutello et al. Safety and immunogenicity of an inactivated subunit influenza virus vaccine combined with MF59 adjuvant emulsion in elderly subjects, immunized for three consecutive influenza seasons. Vaccine. 1999;17(2):99-104. [22]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Agrippal S1® (non-adjuvanted subunit influenza vaccine) 0.5 ml IM; 15µg of each of First vaccination: A/Taiwan/1/86(H1N1); A/Beijing/353/89(H3N2); B/Yamagata/16/88 strains Second vaccination: A/Texas/36/91(H1N1); A/Beijing/32/92(H3N2); B/Panama/45/90 strains Third vaccination: A/Texas/36/92(H1N1); A/Shangdong/9/93(H3N2); B/Panama/45/90 strains	Phase II, observer-blind RCT; two-arm; parallel group; single-center; 3 consecutive years of immunization	92 healthy ambulatory subjects (≥65 years) randomly assigned to Fluad® (n=46) or Agrippal® (n=46) in 1st vaccination; 74 subjects in 2nd vaccination and 67 in 3rd vaccination	GMT, GMR, seroprotection rate from HI assay at 28 days post-vaccination Seroconversion (≥4 fold) Fluad® showed higher rates of seroconversion than Agrippal® for all strains in all years except A/H3N2 in year 1 (70 vs. 72%). Significant difference only for A/H3N2 in year 3 (37 vs. 13%, $p \leq 0.05$) Seroprotection(≥1:128) Fluad® showed higher rates of seroprotection than Agrippal® for all strains in all years. Significant difference for B in year 1 (63 vs. 41%, $p \leq 0.05$) and H1N1 in year 3 (77 vs. 47%, $p \leq 0.05$) Post-vaccination GMT: 1st immunization: Fluad® had higher GMT against all 3 antigens than Agrippal® (by 55% for B, by 27% for A/H3N2, by 45% for A/H1N1). Significant difference for B ($p \leq 0.05$) 2nd immunization: Fluad® had higher GMT against all 3 antigens than Agrippal® (by 28% for B, by 52% for A/H3N2, by 56% for A/H1N1).Significant difference for A/H1N1 ($p \leq 0.05$). 3rd immunization: Fluad® had higher GMT against all 3 antigens than Agrippal® (by 30% for B, by 44% for A/H3N2, by 53% for A/H1N1). Significant difference for A/H1N1 ($p \leq 0.05$). Post-vaccination GMR: Similar day 28/day 0 GMRs between Fluad® and Agrippa, but higher month12/day 0 GMRs for Fluad® in year 1 for all 3 antigens. HI response to 1993/94 heterovariants: Fluad®/Agrippal GMT ratios against heterologous strains were higher compared with those seen against homologous vaccine strains (by 90% for B, by 75% for A/H3N2, by 103% for A/H1N1) MF53-adjuvanted vaccine (Fluad®) had higher level of immunogenicity not only against current season's strains, but also against heterologous strains.	I	Poor (small sample size; selected population of a phase II trial; method of randomization not reported)

Evidence related to immunogenicity of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Pregliasco et al. Immunogenicity and safety of three commercial influenza vaccines in institutionalized elderly. Aging (Milano). 2001;13(1):38-43. [23]	Fluad® (MF59-adjuvanted subunit influenza vaccine; aSUV) vs. Inflexal® Berna (whole virus vaccine; WVV) 0.5 ml IM; 15µg of each of the A/Beijing/262/95(H1N1); A/Sydney/5/97(H3N2); B/Beijing/184/93 strains	Observed-blind RCT; parallel group; multi-center	Subjects ≥64 years (health status not reported) from four nursing homes randomly assigned to vaccines. A subgroup of 74 subjects [aSUV (n=41) and WVV (n=33)] were assessed for immunogenicity	GMT, seroconversion rate, seroprotection rate from HI assay at 4 weeks and 12 weeks post-vaccination Seroprotection (≥40%): Both vaccines met. aSUV was higher than WVV for all strains at 4 and 12 weeks. Statistically significant for A/H1N1 at 4 weeks (98% vs. 73%, *p*=0.0038) and at 12 weeks (93% vs. 58%, *p*=0.0009) post-vaccination. Seroconversion (≥4-fold): Both vaccines met. Rates were higher for aSUV than WVV, but not statistically different. Post-vaccination GMT: Both vaccines showed increased titers for all three strains. aSUV higher than WVV for all strains at 4 and 12 weeks, particularly for A/H1N1 and B, but not statistically different.	I	Poor (small sample size; subset was selected for blood sampling; baseline characteristics not reported; risk of selection bias)

Evidence related to immunogenicity of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Ruf et al. Open, randomized study to compare the immunogenicity and reactogenicity of an influenza split vaccine with an MF59-adjuvanted subunit vaccine and a virosome-based subunit vaccine in elderly. Infection. 2004;32(4):191-8. [24]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Fluarix™ (split vaccine) 0.5 ml IM; 15µg of each of the A/New Caledonia/20/99(H1N1); A/Panama/2007/99(H3N2); B/Shangdong/7/97 strains	Open RCT; parallel group; multi-center	Subjects ≥60 years (health status not reported) who, in the previous season, did not receive the influenza vaccine and were not diagnosed with influenza, were randomly assigned to Fluad® (n=275) and Fluarix™ (n=273)	GMT, seroconversion rate from HI assay at 28 days post-vaccination Seroconversion rate (≥4-fold): Fluarix™ A/H1N1: 74.8 (74-84) A/H3N2: 67.4 (62-73) B: 78.0 (73-83) Fluad® A/H1N1: 70.2 (65-76) A/H3N2: 69.5 (64-75) B: 80.4 (76-85) Seroprotection rate ((≥1:40): Fluarix™ A/H1N1: 24.5 (19-30) A/H3N2: 34.1 (28-40) B: 28.9 (24-34) Fluad® A/H1N1:27.3 (22-33) A/H3N2: 30.2 (25-36) B: 32.0 (26-34) Post-vaccination GMT: Both vaccines showed increased titers (over 10-fold) for all three strains. Fluarix™ had higher GMTs for A/H1N1 and A/H3N2; Fluad® had higher GMTs for B Split vaccine (Fluarix™) was more immunogenic than MF59-adjuvanted vaccine (Fluad®) for A/H1N1 (p=0.0006) and A/H3N2 (p<0.0001) Persistence (up to 8 months) Split vaccine had higher titres for A/H1N1 than Fluad®, about the same for A/H3N2; Fluad® had higher titres for B up to month 8; high protection rates maintained	I	Good (health status not reported)

Evidence related to immunogenicity of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Sindoni et al. Comparison between a conventional subunit vaccine and the MF59-adjuvanted subunit influenza vaccine in the elderly: an evaluation of the safety, tolerability and immunogenicity. J Prev Med Hyg. 2009;50(2):121-6. [25]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Agrippal® (non-adjuvanted subunit influenza vaccine) 0.5 ml IM; 15µg of each of the A/New Caledonia/20/99(H1N1); A/Moscow/10/99(H3N2); B/Shandong/7/97 strains	Open RCT; two-arm; parallel group; multicenter	195 subjects ≥65 years (health status not reported) randomly assigned to Fluad® (n=96), and Agrippal® (n=99)	GMT, GMR, seroconversion rate, seroprotection rate from HI assay at 28 days post-vaccination Seroprotection (≥60%): Both vaccines met; similar rates in both vaccines for all three strains Seroconversion (≥4-fold): Both vaccines met; Fluad® showed higher rates than Agrippal® for all strains Post-vaccination GMT: Both vaccines showed increased titers for all three strains. Fluad® group had significantly higher GMT against A/H1N1 (256 vs. 185) and A/H3N2 (378 vs. 257) compared with Agrippal® Post-vaccination GMR: Fluad® had higher GMR than Agrippal® for all strains.z MF59-adjuvanted vaccine (Fluad®) provided greater protection for elderly	I	Fair (baseline characteristics not reported)

Evidence related to immunogenicity of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Squarcione et al. Comparison of the reactogenicity and immunogenicity of a split and a subunit-adjuvanted influenza vaccine in elderly subjects. Vaccine. 2003;21(11-12):1268-74. [26]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Vaxigrip® (split vaccine) 0.5 ml IM; 15µg of each of the A/Beijing/262/95(H1N1); A/Sydney/5/97(H3N2); B/Beijing/184/93 strains	Open RCT; phase IV; two-arm' parallel group; multi-center	2150 healthy subjects (≥65 years) randomly assigned to Fluad® (n=595) and Vaxigrip® (n=591)	GMT, GMR, seroconversion rate, seroprotection rate from HI assay at 21 days post-vaccination <u>Seroprotection (≥40%)</u>: Both vaccines met for all 3 strains. Vaxigrip® shown to be equivalent to Fluad® for A/H3N2, but Fluad® had higher responses to A/H1N1 and B in individuals <75 years. In individuals ≥75, Fluad® had higher response for all strains. <u>Seroconversion (≥4-fold)</u>: Both vaccines met for all 3 strains Vaxigrip® shown to be equivalent to Fluad® for A/H3N2, but Fluad® had higher responses to A/H1N1 and B in individuals <75 years. In individuals ≥75, Fluad® had higher response for all strains. <u>Post-vaccination GMT</u>: Both vaccines showed increased titers for all three strains. Fluad® group had higher GMT than Vaxigrip® against all 3 strains <u>Post-vaccination GMR</u>: Fluad® had higher GMR than Vaxigrip® against A/H1N1 and B stains, but both vaccines had similar GMR against A/H3N2 Both vaccines induced an effective immune response against A/H3N2 and A/H1N1, similar seroprotection and seroconversion against A/H3N2, and low response against B strain.	I	Fair (baseline characteristics and method of randomization note reported)

Evidence related to immunogenicity of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Van Damme et al. Evaluation of non-inferiority of intradermal versus adjuvanted seasonal influenza vaccine using two serological techniques: a randomised comparative study. BMC Infect Dis. 2010;10:134. [27]	Fluad® (MF59-adjuvanted subunit influenza vaccine; 0.5 ml IM) vs. Intanza™ (split vaccine; 0.1 ml ID) 15µg of each of the A/Solomon Islands/3/2006(H1N1); A/ Wisconsin/67/2005(H3N2); B/Malaysia/2506/2004 strains	Open RCT; phase III; two-arm; parallel group; multi-center	795 healthy subjects (≥65 years) randomly assigned to Fluad® (n=397) and Intanza™ (n=398)	GMT, GMR, seroconversion rate, seroprotection rate from HI or SRH assay at 21 days post-vaccination Seroprotection (≥60%): Both vaccines met for all 3 strains. Fluad® was higher than Intanza™for A/H1N1 strain Seroconversion (≥30%): Both vaccines met for all 3 strains. Post-vaccination GMT: Both vaccines showed increased titers for all three strains. Intanza™ (intradermal) was comparable with Fluad® for all 3 strains using SRH method and for A/H1N1 and B strains using HI method Post-vaccination GMR: No significant differences between the two vaccines The immunogenicity of the intradermal split vaccine (Intanza™) in elderly was comparable with that of the MF53-adjuvanted vaccine (Fluad®)	I	Good

Evidence related to safety of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Banzhoff et al. A new MF59-adjuvanted influenza vaccine enhances the immune response in the elderly with chronic diseases: results from an immunogenicity meta-analysis. Gerontology. 2003;49(3):177-84. [10]	MF59 adjuvanted (Fluad®) compared with non-adjuvanted vaccines (Agrippal S1, Influvac, FluShield, Vaxigrip, Alpharix, and Fluvirin)	Meta-analysis of 13 clinical trials (12 phase II/III and a subset of one phase IV)	Subjects ≥65 years with and without underlying diseases	Local and systemic reactions during the first 3 days after vaccination Local reactions: Most were mild and transient. More frequent with Fluad® than comparator vaccines (15-32% vs. 10-14%) Pain (33% vs. 13%, $p<0.001$) Erythema (18% vs. 13%, $p<0.001$) Induration (15% vs. 9%, $p<0.001$) Systemic reactions: Uncommon, most were mild and transient (<1 to 8% for Fluad® vs. <1 to 4% for comparator). Malaise (6% vs. 4%, $p=0.003$) Myalgia (8% vs. 3%, $p<0.001$) Headache (6% vs. 4%, $p=0.010$) Almost no difference in local or systemic reactions between adjuvanted and comparator groups by day 3	N/A	Poor (not systematic review)
Pellegrini et al. MF59-adjuvanted versus non-adjuvanted influenza vaccines: integrated analysis from a large safety database. Vaccine. 2009;27(49):6959-65. [38]	MF59 adjuvanted (Fluad®) compared with non-adjuvanted vaccines	Meta-analysis (Integrated database analysis) of 64 clinical trials between 1992-1993 and 2007-2008	Overall population (n=27,998), with 19,590 subjects ≥65 years with or without underlying disease	Local and systemic reactions at day 0 to day 3; AEs at any time during the study Potential autoimmune origin, and unsolicited AEs (diseases, hospitalization and death) occurring at any time during the trials Any reactions: More frequent with Fluad® (RR 1.34; 95% CI 1.28-1.40 for overall; RR 1.32; 95% CI 1.23-1.41 for elderly population) Local reactions: (Pain, injection-site warmth, induration, erythema; mild or moderate) More frequent with Fluad® (RR 1.71; 95% CI 1.61-1.82 for overall; RR 1.74; 95% CI 1.57-1.94 for elderly population) Systemic reactions: (Myalgia, headache, fatigue and malaise) More frequent with Fluad® (RR 1.33; 95% CI 1.22-1.46 for overall; RR 1.29; 95% CI 1.10-1.52 for elderly population)	N/A	Poor (not systematic review)

Evidence related to safety of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
				AEs: Serious AEs - All trials : Less frequent with Fluad® (RR 0.86; 95% CI 0.77-0.95 for overall; RR 0.89; 95% CI 0.90-0.99 for elderly population) Serious AEs - Control trials No difference (RR 0.96; 95% CI 0.86-1.06 for overall; RR 0.95; 95% CI 0.85-1.06 for elderly population) Potential autoimmune origin: No significant differences between MF59-adjuvanted (Fluad®) and non-adjuvanted vaccines for overall, non-elderly (<65 years) and elderly (≥65 years) Diseases: *All trials* CVD - RR 0.44; 95% CI 0.35-0.55 (overall); RR 0.58; 95% CI 0.47-0.73 (elderly) New onset chronic disease (NOCD) - RR 0.71; 95% CI 0.57-0.87 (overall); RR 0.73; 95% CI 0.59-0.91 (elderly) *Control trials* CVD - RR 0.78; 95% CI 0.63-0.97 (overall); RR 0.82; 95% CI 0.66-1.02 (elderly) New onset chronic disease (NOCD) - RR 0.76; 95% CI 0.62-0.95 (overall); RR 0.70; 95% CI 0.61-0.95 (elderly) Hospitalization: A significantly lower risk of hospitalization (RR 0.88; 95% CI 0.79-0.99) in overall population (but not elderly - all trials) receiving MF59-adjuvanted vs. non-adjuvanted vaccines; no difference in overall or elderly in controlled trials Death: A significantly lower risk of death in overall (RR 0.67; 95% CI 0.51-0.87) and elderly (RR 0.70; 95% CI 0.54-0.91) population receiving MF59-adjuvanted vs. non-adjuvanted vaccines; no difference in controlled trials in overall or elderly populations		

Evidence related to safety of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Podda A. The adjuvanted influenza vaccines with novel adjuvants: experience with the MF59-adjuvanted vaccine. Vaccine. 2001;19(17-19):2673-80. [11]	MF59 adjuvanted (Fluad®) compared with non-adjuvanted vaccines	Meta-analysis (data from a clinical database) of observer-blind RCTs	Subjects ≥65 years with or without underlying disease	Local and systemic reactions, and all AEs for 28 days post-vaccination Local reactions for Fluad®: % year 1/ % year 2/% year 3 Pain: 32/27/28 Erythema: 18/22/22 Induration: 15/11/13 Local reactions for comparator: % year 1/% year 2/% year 3 Pain: 14/21/16 Erythema: 13/19/9 Induration: 10/8/6 Almost no difference in reported local reactions by day 3 Systemic reactions for Fluad®: % year 1/ % year 2/% year 3 Malaise: 6/8/7 Headache: 6/8/7 Myalgia: 8/3/1 Fever (≥38ºC): 1/1/1 Systemic reactions for comparator: % year 1/ % year 2/% year 3 Malaise: 4/7/3 Headache: 4/7/3 Myalgia: 3/2/2 Fever (≥38ºC): <1/1/0 No difference in reported systemic reactions by day 3 AEs requiring physician visit within 7 days of vaccination: No differences between groups (Relative risk 0.92; 95% CI 0.66-1.30)	N/A	Poor (not systematic review)

Evidence related to safety of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Baldo et al. Comparison of three different influenza vaccines in institutionalised elderly. Vaccine. 2001;19(25-26):3472-5. [16]	Fluad® (MF59-adjuvanted subunit influenza vaccine; Sub/MF59) vs. Mutagrip® (split influenza vaccine; Split) 0.5 ml IM; 15µg of each of the A/Sydney/5/97(H3N2); A/Beijing/262/95(H1N1); B/Beijing/184/93 strains	DB RCT; parallel group; multi-center	Nursing home residents (≥65 years healthy and with underlying disease) randomly assigned to single dose of Sub/MF59 (n=100) and Split (n=100)	First week post-immunization reaction concerning local reactions, and systemic reactions 0.3% reported mild and transient local or systemic reactions within 1st week of immunization. No significant differences in frequency of reactions between vaccines	I	Fair (method of randomization not reported; no ITT analysis)
de Bruijn et al. Antibody induction by virosomal, MF59-adjuvanted, or conventional influenza vaccines in the elderly. Vaccine. 2007;26(1):119-27. [17]	Fluad® (MF59-adjuvanted subunit influenza vaccine; adSIV) vs. Influvac® (non-adjuvanted subunit influenza vaccine; SIV) Vaccine composition: A/Fujian/411/2002(H3N2); A/New Caledonia/20/99(H1N1); B/Shanghai/361/2002	Observer-blind RCT; parallel group; multi-center	Subjects >60 years with or without underlying disease randomly assigned to adSIV (n=130) and SIV (n=129)	Local and systemic reactions during the first 3 days after vaccination; AEs by spontaneous reporting <u>Local reactions</u>: adSIV vs. SIV: 46% vs.19% (p<0.001) Most frequent was pain (37% in adSIV and 9% in SIV) <u>Systemic reactions</u>: adSIV vs. SIV: 32% vs. 22% (p = NS) Most frequent was headache (18% in adSIV and 11% in SIV) and malaise (13.8% in adSIV and 8.6% in SIV) Most local and systemic reactions were mild, but lasted longer with adSIV (3 days). Moderate to severe reactions were more frequent in the adSIV group (7 reports of local and systemic reactions each for adSIV and 2 systemic reactions for SIV) <u>Treatment emergent adverse events:</u> adSIV: 13.8% SIV: 6.3% Most frequent was arthralgia (0.8% in adSIV and 1.6% in SIV) and injection site erythema (2.3% in adSIV and 0.0% in SIV) MF59-adjuvanted vaccine (Fluad®) was more reactogenic than non-adjuvanted subunit vaccine (Influvac®).	I	Good

Evidence related to safety of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
De Donato et al. Safety and immunogenicity of MF59-adjuvanted influenza vaccine in the elderly. Vaccine. 1999;17(23-24):3094-101. [18]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Agrippal™ (non-adjuvanted subunit influenza vaccine) 0.5 ml IM; 15µg of each of the A/H1N1, A/H3N3, and B antigens 3 annual immunizations	RCT; two-arm; parallel group; single center	192 subjects ≥65 years having no underlying disease randomly assigned to Fluad® (n=94) and Agrippal™ (n=98)	Reactions at 30 minutes after injection; local or systemic reactions at 6 h post-immunization; AEs were followed up until resolved. Local reactions: Pain (resolving within 48h, mild or moderate): more frequent in Fluad® than Agrippal™, with more reports of moderate pain in Fluad® (38%) than Agrippal™ (13%); significantly different in year 1 and 2 (data not provided, $p<0.01$) Erythema at site of injection: no difference between groups Induration: more frequent in Fluad® than Agrippal™ in year 2 (data not provided) and year 3 (16% vs. 4%, $p<0.05$). Systemic reactions: Low and the respective rates were similar in both groups. Headache: more frequent in Fluad® than Agrippal™ in year 2 only (10% vs. 3%, $p<0.05$) AEs: No serious AEs reported within 7 days of vaccination	I	Poor (baseline characteristics and method of randomization not reported; no ITT analysis)
de Roux et al. Impact of corticosteroids on the immune response to a MF59-adjuvanted influenza vaccine in elderly COPD-patients. Vaccine. 2006;24(10):1537-42. [28]	Fluad® (MF59-adjuvanted subunit influenza vaccine) 0.5 ml IM; 15µg of each of the A/H1N1, A/H3N2 and B strains	Cohort study; single-center	162 COPD patients (≥60 years) who received systemic steroid therapy (SS, n=33), inhaled steroids (IS, n=87) or no steroid (CG, n=42)	Local reactions, systemic reactions, and AEs from day 0 to 4 weeks and to 24 weeks Local reactions: Mild and transient in 21% of patients Systemic reactions: None reported AEs: No serious AEs. No documented case death during the study period	II-3	Poor (small sample size; baseline characteristics not reported; risk of selection bias)

Evidence related to safety of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Gasparini et al. Increased immunogenicity of the MF59-adjuvanted influenza vaccine compared to a conventional subunit vaccine in elderly subjects. Eur J Epidemiol. 2001;17(2):135-40.[19]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Agrippal® (non-adjuvanted subunit influenza vaccine) IM; 15µg of each of the A/Shangdong/9/93(H3N2); A/Texas/36/91(H1N1); B/Panama/45/90 strains	DB RCT; two-arm; parallel group; multi-center	308 healthy subjects (≥65 years) randomly assigned to Fluad® (n=204) or Agrippal® (n=104)	Local and selected systemic reactions at day 0 to day 6; AEs for 28 days requiring physician visit or consultation, with only hospitalizations and deaths considered a serious AE for days 28-180 post-immunization Local reactions: More frequent with Fluad® than Agrippal® Pain: 19% vs. 11%, NS Warmth: 13% vs. 9%, NS Injection-site pain was transient, mild and self-limited. Systemic reactions: No difference between groups. The incidence was low in both groups AEs: No serious AEs	I	Poor (selected population; method of randomization not reported)
Giammanco et al. Immunogenicity and tolerability of two subunit influenza vaccines in patients with chronic obstructive bronchopneumopathy. Journal of Preventive Medicine and Hygiene 2005;46(3):85-7. [20]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Agrippal® S1 (non-adjuvanted subunit influenza vaccine) 0.5 ml IM; 15µg of each of the A/New Caledonia/IVR116(H1N1); A/Mosca/Resvir2002(H3N2); B/Shangdong/7/97 strains	RCT; two-arm; parallel group; single-center	54 adult and elderly subjects (53-85 years) with chronic obstructive bronchopneumopathy randomly assigned to receive Fluad® (n=27), Agrippal® (n=27)	Local reactions and systemic reactions during 3 days post-vaccination, and monitoring of body temperature, oxygen saturation and ventilator function during 28 days post-vaccination Local reactions: Injection-site pain and erythema (13 patients total); number of patients in each group not reported Systemic reactions: 3 reports of fever, and 3 reports of ILI (rapid onset of fever, myalgia, sore throat) from Fluad® group AEs: No serious AEs Worsening of ventilator function in some patients without reported ILI in follow-up period (3 patients in Fluad® group, 4 patients in Agrippal® group) No significant differences in frequency of side effects in both groups	I	Poor (small sample size; method of randomization not reported; safety data not properly reported)

Evidence related to safety of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Li et al. Safety and immunogenicity of an MF59-adjuvanted subunit influenza vaccine in elderly Chinese subjects. Immun Ageing. 2008;5:2. [21]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Agrippal® (non-adjuvanted subunit influenza vaccine) 0.5 ml IM; 15µg of each of the A/New Caledonia/20/99(H1N1); A/California/7/2004(H3N2); B/Shanghai/361/2002 strains	Phase II/III observer-blind RCT; two-arm; parallel group; multi-center	600 healthy Chinese subjects (≥65 years) randomly assigned (2:1) to Fluad® (n=400) or Agrippal® (n=200)	Local and systemic reactions, and all AEs for 22 days post-vaccination Fluad® n=391; Agrippal® n=198 Local reactions: Mild or moderate and transient. Significantly more frequent with Fluad® than Agrippal® (24.0% vs. 15.2%, p=0.012) Induration (2.5% vs. 0.5%, p<0.05) Pain (10.2% vs. 3.0%, p≤0.005) Systemic reactions: Mild or moderate and transient. Fever (15.9% vs. 7.6%, p≤0.005) No difference in overall systemic reactions between groups. AEs: High fever: one subject (0.3%) in Fluad®	I	Poor (selected population; baseline characteristics and method of randomization not reported; no ITT analysis; risk of selection bias)
Menegon et al. Influenza vaccines: antibody responses to split virus and MF59-adjuvanted subunit virus in an adult population. Eur J Epidemiol 1999;15(6):573-6. [30]	Fluad® (MF59-adjuvanted subunit influenza vaccine; Sub/MF59) vs. Mutagrip® (split influenza vaccine; SVV) 0.5 ml IM; 15µg of each of the A/Wuhan/359/95(H3N2); A/Bayern/7/95(H1N1); B/Beijing/184/93 strains	DB RCT; two-arm; parallel group; single-center	200 adult and elderly subjects (23-97 years) with or without underlying disease randomly assigned to receive Fluad® (n=100), Mutagrip® (n=100) 194 completed the follow-up (96 in Fluad® and 98 in Mutagrip®)	Local reactions and systemic reactions collected by phone-interview 1 week post-vaccination Local reactions: More frequent with Fluad® than Mutagrip® (15.6% vs. 3.1%, p<0.05) All reactions were mild and transient Systemic reactions: No significant differences between groups (28.1% in Fluad® vs. 20.4% in Mutagrip®) All reactions were mild and transient AEs: No serious AEs	I	Fair (method of randomization not reported; baseline characteristics nor appropriate; no ITT analysis)

Evidence related to safety of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Minutello et al. Safety and immunogenicity of an inactivated subunit influenza virus vaccine combined with MF59 adjuvant emulsion in elderly subjects, immunized for three consecutive influenza seasons. Vaccine. 1999;17(2):99-104. [22]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Agrippal S1® (non-adjuvanted subunit influenza vaccine) 0.5 ml IM; 15µg of each of First vaccination: A/Taiwan/1/86(H1N1); A/Beijing/353/89(H3N2); B/Yamagata/16/88 strains Second vaccination: A/Texas/36/91(H1N1); A/Beijing/32/92(H3N2); B/Panama/45/90 strains Third vaccination: A/Texas/36/92(H1N1); A/Shangdong/9/93(H3N2); B/Panama/45/90 strains	Phase II, observer-blind RCT; two-arm; parallel group; single-center; 3 consecutive years of immunization	92 healthy ambulatory subjects (≥65 years) randomly assigned to Fluad® (n=46) or Agrippal® (n=46) in 1st vaccination; 74 subjects in 2nd vaccination and 67 in 3rd vaccination	Local and systemic reactions at day 0 to day 6, and all AEs Overall, reactions were mild and transient, occurring within first 48h. Local reactions: Significantly more frequent with Fluad® than Agrippal® for Soreness (41% vs. 6.5%, *p*=0.01) in 1st immunization Erythema (38.5% vs. 14%, *p*=0.05) in 2nd immunization Systemic reactions: Significantly more frequent with Fluad® than Agrippal® for Malaise (15% vs. 0%, *p*=0.05) in 1st immunization AEs: No serious AEs in all 3 immunizations	I	Poor (small sample size; selected population of a phase II trial; method of randomization not reported)
Pregliasco et al. Immunogenicity and safety of three commercial influenza vaccines in institutionalized elderly. Aging (Milano). 2001;13(1):38-43. [23]	Fluad® (MF59-adjuvanted subunit influenza vaccine; aSUV) vs. Inflexal® Berna (whole virus vaccine; WVV) 0.5 ml IM; 15µg of each of the A/Beijing/262/95(H1N1); A/Sydney/5/97(H3N2); B/Beijing/184/93 strains	Observed-blind RCT; parallel group; multi-center	Subjects ≥64 years (health status not reported) from four nursing homes randomly assigned to vaccines.	Local and systemic reactions within 72 hours of vaccination, and all AEs Local reactions: 4 in aSUV, 1 in WVV Systemic reactions: 2 in WVV AEs: No serious AEs in all 3 immunizations; cumulative ILI incidence of 8.3% equally distributed among sites Death: 30 deaths (1 due to respiratory complications); none related to vaccination	I	Poor (small sample size; subset was selected for blood sampling; baseline characteristics not reported; risk of selection bias)

Evidence related to safety of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Ruf et al. Open, randomized study to compare the immunogenicity and reactogenicity of an influenza split vaccine with an MF59-adjuvanted subunit vaccine and a virosome-based subunit vaccine in elderly. Infection. 2004;32(4):191-8. [24]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Fluarix™ (split vaccine) 0.5 ml IM; 15µg of each of the A/New Caledonia/20/99(H1N1); A/Panama/2007/99(H3N2); B/Shangdong/797/2001 strains	Open RCT; parallel group; multi-center	Subjects ≥60 years (health status not reported) who, in the previous season, did not receive the influenza vaccine and were not diagnosed with influenza, were randomly assigned to Fluad® (n=273) and Fluarix™ (n=272)	Local and systemic reactions during days 0-3 post-vaccination, and all AEs for 28±7 days post-vaccination Local reactions: Fluad® vs. Fluarix™ Redness: 20.1 vs. 14.3% Pain: 30.8 vs. 16.9% Induration: 20.5 vs. 14.7% Systemic reactions: Comparable between groups Overall reactions significantly more frequent with Fluad® than Fluarix™ (52.4% vs. 42.3%, *p*=0.021) AEs: No SAEs reported. Safety similar in subjects ≥60 years and ≥65 years	I	Good (health status not reported)
Sindoni et al. Comparison between a conventional subunit vaccine and the MF59-adjuvanted subunit influenza vaccine in the elderly: an evaluation of the safety, tolerability and immunogenicity. J Prev Med Hyg. 2009;50(2):121-6. [25]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Agrippal® (non-adjuvanted subunit influenza vaccine) 0.5 ml IM; 15µg of each of the A/New Caledonia/20/99(H1N1); A/Moscow/10/99(H3N2); B/Shandong/7/97 strains	Open RCT; two-arm; parallel group; multi-center	195 subjects ≥65 years (health status not reported) randomly assigned to Fluad® (n=96), and Agrippal® (n=99)	Local and systemic reactions during 7 days post-vaccination, and all AEs for 1 month post-vaccination Local reactions: More frequent with Fluad® than Agrippal® (50% vs. 27.27%, *p*<0.001, reporting at least one local reaction) Systemic reactions: More frequent with Fluad® than Agrippal® (23.96% vs. 18.2%, *p*<0.001) Reactions in both vaccines were mild or moderate and transient AEs: No serious AEs	I	Fair (baseline characteristics not reported)

Evidence related to safety of Fluad® vaccine in adults 61 years of age and older						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Squarcione et al. Comparison of the reactogenicity and immunogenicity of a split and a subunit-adjuvanted influenza vaccine in elderly subjects. Vaccine. 2003;21(11-12):1268-74. [26]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Vaxigrip® (split vaccine) 0.5 ml IM; 15µg of each of the A/Beijing/262/95(H1N1); A/Sydney/5/97(H3N2); B/Beijing/184/93 strains	Open phase IV RCT; two-arm' parallel group; multi-center	2150 healthy subjects (≥65 years) randomly assigned to Fluad® (n=1074) and Vaxigrip® (n=1076)	Local and systemic reactions at day 0 to day 3; AEs at day 0 to day 21 Local reactions: Similar between groups, except for delayed (30 min-3 d) pain (6.6% of Fluad® vs. 3.9% of Vaxigrip®, *p*=0.005) Systemic reactions: Similar for both groups (6.5% of Fluad® vs. 6.0% of Vaxigrip®), except for any immediate (within 30 min) systemic reaction (0.6% Fluad® vs. 0% Vaxigrip®, *p*=0.015) Overall, the frequency of local and systemic reactions was low in both vaccines. The reactions were mild or moderate and transient AEs: 9 SAE reported, but none considered related to vaccine	I	Fair (baseline characteristics and method of randomization note reported)
Van Damme P,et al. Evaluation of non-inferiority of intradermal versus adjuvanted seasonal influenza vaccine using two serological techniques: a randomised comparative study. BMC Infect Dis. 2010;10:134.[27]	Intanza™ (15 µg HA per strain)	Phase III RCT, open-label NCT00554333 Compared to Fluad® (split virion, MF59C.1 adjuvanted, IM) 2007-08	N=795 (n=398 ID, n=397 IM) Adults ≥65 years	• Erythema (63.1% versus 13.4%), swelling (34.2% versus 8.6%), induration (32.9% versus 10.6%) and pruritis (28.1% versus 6.5%) were reported more frequently in the ID group • Incidence of systemic reactions was comparable for the two groups • 2/6 serious adverse events were determined to be vaccine-related; pneumonia and facial herpes zoster in the ID and adjuvanted IM groups respectively	I	Good

Evidence related to immunogenicity of Fluad® vaccine in adults (18 – 60 years) with or without comorbidities						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Baldo et al. Family Medicine Group of Pianiga. MF59-adjuvanted influenza vaccine confers superior immunogenicity in adult subjects (18-60 years of age) with chronic diseases who are at risk of post-influenza complications. Vaccine. 2007;25(20):3955-61.[33]	Fluad® (MF59-adjuvanted subunit influenza vaccine; Sub/MF59) vs. Influpozzi Subunità® (non-adjuvanted subunit influenza vaccine; Sub) 0.5 ml IM; 15µg of each of the A/New Caledonia/20/99(H1N1); A/California/7/2004(H3N2); B/Shanghai/361/2002 strains	DB RCT; two-arm; parallel group; multi-center 2005-2006	238 adult subjects (18-60 years) with chronic diseases (cancer, diabetes, heart, lung) randomly assigned to Sub/MF59 (n=120) or Sub (n=118)	GMT, MFI, GMR, seroconversion rate, seroprotection rate from HI assay at 4 weeks post-vaccination <u>Seroprotection (>70%):</u> Sub/MF59 met for A/H1N1 and A/H3N2; Sub met for A/H1N1 only Sub/MF59 vs. Sub: A/H3N2: 75.0% vs. 57.6%, *p*=0.002 A/H1N1: 97.5% vs. 96.6%, NS B: 69.2% vs. 61.0%, NS <u>Seroconversion (>40%):</u> Sub/MF59 met for all 3 antigens; Sub met for A/H1N1 only Sub/MF59 vs. Sub: A/H3N2: 52.5% vs. 33.1%, *p*=0.02 A/H1N1: 57.5% vs. 55.9%, NS B: 46.7% vs. 36.4%, NS <u>Post-vaccination GMT</u>: Both Vaccines had significant increase in post-vaccination GMT against all 3 strains. <u>Post-vaccination GMR</u>: Sub/MF59 had significant higher GMT than Sub for A/H3N2 ($p<0.001$) and B ($p<0.02$) strains <u>MFI (>2.5)</u>: Both vaccines met for all 3 antigens Addition of MF59 enhances the immunogenicity of subunit influenza vaccine in adults with chronic disease	I	Good

Evidence related to immunogenicity of Fluad® vaccine in adults (18 – 60 years) with or without comorbidities						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Durando et al. Safety and immunogenicity of two influenza virus subunit vaccines, with or without MF59 adjuvant, administered to human immunodeficiency virus type 1-seropositive and -seronegative adults. Clin Vaccine Immunol. 2008 ;15(2):253-9. [34]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Agrippal® (non-adjuvanted subunit influenza vaccine) 0.5 ml IM; 15µg of each of the A/New Caledonia/20/99(H1N1); A/California/7/2004(H3N2); B/Shanghai/361/2002 strains	Open-label RCT; two-arm; parallel group; single-center 2005-2006	256 adult (18-65 years) with HIV-1-seronegative or HIV-1-seropositive randomly assigned to receive Fluad® (n=127) or Agrippal® (n=129) 4 groups: Fluad®, HIV-1(-) (n=81); Fluad®, HIV-1(+) (n=46); Agrippal®, HIV-1(-) (n=80); Agrippal®, HIV-1(+) (n=49)	GMT, GMR, seroconversion rate, seroprotection rate from HI assay at 4 weeks and 12 weeks post-vaccination Seroprotection (>70%): Both vaccines met for all 3 antigens. NS difference between groups Seroconversion (>40%): Both vaccines met for all 3 antigens. NS difference between groups Post-vaccination GMT: After Beyer's correction , Fluad® had significant higher GMT than Agrippal for all influenza vaccine subtypes, although statistical significant was reached for only AH1N1 (p=0.005) and B (p=0.023) strains in HIV-1-seronegative subjects; for seropositive subjects, Fluad had significantly higher GMT than Agrippal for A/H3N2 (p=0.003) strain only in HIV-1-seropositive subjects. A value near significance was observed for A/H1N1 strain in seropositive subjects (p=0.097) Both vaccines had good immunogenicity for both uninfected and HIV-1-infected adults. No definitive conclusions could be drawn for the superiority of Fluad® over Agrippal.	I	Poor (small sample size; method of randomization not reported)

Evidence related to immunogenicity of Fluad® vaccine in adults (18 – 60 years) with or without comorbidities						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Frey et al. Comparison of the safety, tolerability, and immunogenicity of a MF59-adjuvanted influenza vaccine and a non-adjuvanted influenza vaccine in non-elderly adults. Vaccine. 2003;21(27-30):4234-7. [35]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Fluzone™ (non-adjuvanted subunit influenza vaccine) 0.5 ml IM; 15µg of each of the A/Texas/39/91(H1N1); A/Johannesburg/33/94(H3N2); B/Harbin/7/94 strains (1st immunization) and A/Texas/39/91(H1N1); A/Nanchang/933/95(H3N2); B/Harbin/7/94 strains (2nd immunization)	Observer-blind RCT; two-arm; parallel group; multi-center 1995-1996 Study extension for a subsequent injection in year 2: 1996-1997	301 healthy adult subjects (18-64 years) randomly assigned to receive Fluad® (n=150) or Fluzone™ (n=151) Year 2: Fluad (n=99) Fluzone (n=94)	GMT, seroconversion rate, seroprotection rate from HI assay at 4 weeks post-vaccination and 180 days post-vaccination <u>Seroprotection (>70%):</u> Both vaccines met for all 3 antigens. NS difference between groups <u>Seroconversion (>40%):</u> Both vaccines met for all 3 antigens. Significant difference reached for B strain (Fluad®: 83% vs. Fluzone: 71%, *p*=0.008) <u>Post-vaccination GMT</u>: NS difference between groups Year 2: 28 days post-injection <u>Seroprotection:</u> Significant difference reached for A/H3N2 strain (Fluad 53% vs Fluzone 26%, *p*<0.0001) <u>Seroconversion:</u> Significant difference reached for A/H3N2 strain (Fluad® 55% vs. Fluzone 32%, *p*≤0.0005) <u>Post-vaccination GMT</u>: GMT higher for H3N2 strain in Fluad vs Fluzone (112 vs. 71, *p*≤0.001) No significant differences were seen at day 180 except in the % of subjects with a titer: 160 for A/H1N1 antigen (Fluad 57% vs Fluzone 73%, *p*=0.025) Fluad was slightly more immunogenic in healthy adults for the B strain after the 1st injection and for the A/H3N2 strain after the 2nd injection.	I	Poor (method of randomization not reported; not followed up for AEs)

Evidence related to immunogenicity of Fluad® vaccine in adults (18 – 60 years) with or without comorbidities						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Gabutti et al. Safety and immunogenicity of conventional subunit and MF59-adjuvanted influenza vaccines in human immunodeficiency virus-1-seropositive patients. J Int Med Res. 2005 ;33(4):406-16. [36]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Agrippal® (non-adjuvanted subunit influenza vaccine) 0.5 ml IM; 15µg of each of the A/New Caledonia/20/99(H1N1); A/Moscow/10/99(H3N2); B/Hong Kong/330/2001 strains	RCT; two-arm; parallel group; single-center 2002-2003	37 adult subjects (18-65 years) with HIV-1-seropositive randomly assigned to receive Fluad® (n=18) or Agrippal® (n=19)	GMT, GMR, seroconversion rate, seroprotection rate from HI assay at 4 weeks post-vaccination and 180 days post-vaccination Seroprotection (>70%): Both vaccines met for all 3 antigens. NS difference between groups Seroconversion (>40%): Both vaccines met for all 3 antigens. NS difference between groups Post-vaccination GMT: NS difference between groups Both Fluad and Agrippal were immunogenic, and there was prolonged persistence of antibodies towards all 3 strains after 180 days.	I	Poor (small sample size; method of randomization not reported

Evidence related to safety of Fluad® vaccine in adults (18 – 60 years) with or without comorbidities						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Baldo et al. Family Medicine Group of Pianiga. MF59-adjuvanted influenza vaccine confers superior immunogenicity in adult subjects (18-60 years of age) with chronic diseases who are at risk of post-influenza complications. Vaccine. 2007;25(20):3955-61. [33]	Fluad® (MF59-adjuvanted subunit influenza vaccine; Sub/MF59) vs. Influpozzi Subunità® (non-adjuvanted subunit influenza vaccine; Sub) 0.5 ml IM; 15µg of each of the A/New Caledonia/20/99(H1N1); A/California/7/2004(H3N2); B/Shanghai/361/2002 strains	DB RCT; two-arm; parallel group; multi-center 2005-2006	256 adult subjects (18-60 years) with chronic diseases (cancer, diabetes, heart, lung) randomly assigned to Sub/MF59 (n=128) or Sub (n=128)	Local reactions and systemic reactions during 7 days post-vaccination, and AEs during 4 weeks post-vaccination Local reactions: More frequent with Sub/MF59 than with Sub (46.9% vs. 24.2%. $p<0.001$) Pain (28.9% vs. 8.6%, $p<0.001$) Erythema (12.5% vs. 4.7%, $p<0.05$) Systemic reactions: No significant difference between groups(25.7% vs 18.8%) AEs: No serious AEs	I	Good

Evidence related to safety of Fluad® vaccine in adults (18 – 60 years) with or without comorbidities						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Durando et al. Safety and immunogenicity of two influenza virus subunit vaccines, with or without MF59 adjuvant, administered to human immunodeficiency virus type 1-seropositive and -seronegative adults. Clin Vaccine Immunol. 2008 ;15(2):253-9. [34]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Agrippal® (non-adjuvanted subunit influenza vaccine) 0.5 ml IM; 15µg of each of the A/New Caledonia/20/99(H1N1); A/California/7/2004(H3N2); B/Shanghai/361/2002 strains	Open-label RCT; two-arm; parallel group; single-center 2005-2006	256 adult (18-65 years) with HIV-1-seronegative or HIV-1-seropositive randomly assigned to receive Fluad® (n=127) or Agrippal® (n=129) 4 groups: Fluad®, HIV-1(-) (n=81); Fluad®, HIV-1(+) (n=46); Agrippal®, HIV-1(-) (n=80); Agrippal®, HIV-1(+) (n=49)	Local reactions and systemic reactions during 4 days post-vaccination, and AEs during 4 weeks post-vaccination Local reactions: More frequent with Fluad® than with Agrippal® ® in both HIV-1(-) and HIV-1(+) groups Significance noted for pain and induration (p<0.01 in HIV-1 (-), NS in HIV-1 (+)) Systemic reactions: More frequent with Fluad® than with Agrippal® ® in both groups. HIV-1 (negative) group: Shivering, malaise, asthenia (p<0.05), headache, fever (p<0.01) HIV-1 (positive) group: Shivering (p<0.05) Fever (p<0.01) AEs: No serious AEs Fluad was better tolerated in HIV(+) participants than in HIV(-) participants. Most symptoms and signs were classified as mild and disappeared within 48-72 hours No significant changes in CD4 cell counts and HIV-1 RNA levels, analyzed by vaccine group, were observed after immunization	I	Poor (small sample size; method of randomization not reported)

Evidence related to safety of Fluad® vaccine in adults (18 – 60 years) with or without comorbidities						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Frey et al. Comparison of the safety, tolerability, and immunogenicity of a MF59-adjuvanted influenza vaccine and a non-adjuvanted influenza vaccine in non-elderly adults. Vaccine. 2003;21(27-30):4234-7. [35]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Fluzone™ (non-adjuvanted subunit influenza vaccine) 0.5 ml IM; 15µg of each of the A/Texas/39/91(H1N1); A/Johannesburg/33/94(H3N2); B/Harbin/7/94 strains (1st immunization) and A/Texas/39/91(H1N1); A/Nanchang/933/95(H3N2); B/Harbin/7/94 strains (2nd immunization)	Observer-blind RCT; two-arm; parallel group; multi-center 2 seasons (1995-1996 and 1996-1997)	301 healthy adult subjects (18-64 years) randomly assigned to receive Fluad® (n=150) or Fluzone™ (n=151) Study extension in season 2: N=200 returning subjects Fluad® (n=104) or Fluzone™ (n=96)	Local reactions and systemic reactions during 7 days post-vaccination for 1st and 2nd injections.. Local reactions: More frequent with Fluad® than with Fluzone™ for pain (90% vs. 64%, $p \leq 0.001$) and warmth (28% vs. 18%, $p \leq 0.05$) during 1st immunization; and pain (84% vs. 69%, $p \leq 0.05$) during 2nd immunization) Systemic reactions: More frequent with Fluad® than with Fluzone™ for chills (5% vs. 1%, $p \leq 0.05$) and myalgia (15% vs. 6%, $p \leq 0.05$) and analgesic/antipyretic use (39% vs. 26%, $p \leq 0.05$) during 1st immunization; and no significant difference during 2nd immunization) In both groups, most local and systemic reactions were classified as mild	I	Poor (method of randomization not reported; not followed up for AEs)

Evidence related to safety of Fluad® vaccine in adults (18 – 60 years) with or without comorbidities						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Gabutti et al. Safety and immunogenicity of conventional subunit and MF59-adjuvanted influenza vaccines in human immunodeficiency virus-1-seropositive patients. J Int Med Res. 2005 ;33(4):406-16. [36]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Agrippal® (non-adjuvanted subunit influenza vaccine) 0.5 ml IM; 15µg of each of the A/New Caledonia/20/99(H1N1); A/Moscow/10/99(H3N2); B/Hong Kong/330/2001 strains	RCT; two-arm; parallel group; single-center 2002-2003	37 adult subjects (18-65 years) with HIV-1-seropositive randomly assigned to receive Fluad® (n=18) or Agrippal® (n=19)	Local reactions and systemic reactions during 4 days post-vaccination, and AEs during 30 days post-vaccination Local reactions: More frequent with Fluad®than with Agrippal® Pain and redness (5 vs. 2 patients) Systemic reactions: No significant differences between groups (fever (2 vs 1 patient) AEs: No serious AEs All reactions were resolved completely within 48-72 hours No significant changes in CD4 counts in subjects who received Fluad. No significant changes in viraemia at any time point in either group. Both Fluad® and Agrippal are safe and can be used in HIV-1-seropositive patients	I	Poor (small sample size; method of randomization not reported
Magnani et al. Safety and efficacy of two types of influenza vaccination in heart transplant recipients: a prospective randomised controlled study. J Heart Lung Transplant 2005;24(5):588-92. [37]	Fluad® (MF59-adjuvanted subunit influenza vaccine) vs. Agrippal® (non-adjuvanted subunit influenza vaccine) vs. no vaccinaton 0.5 ml IM; 15µg of each of the A/Beijing/262/95(H1N1); A/Sidney/5/97(H3N2); B/Beijing/184/93 strains	RCT; three-arm; parallel group; single-center 1999	58 adult heart transplant recipients (stable, > 6 months passed since transplant) randomly assigned to receive Fluad® (n=21), Agrippal® (n=21), or control (no vaccine; n=16)	Local reactions and systemic reactions during 4 days post-vaccination, and AEs during 30 days post-vaccination Local reactions: Not reported Systemic reactions: No significant differences between vaccine groups AEs: No serious AEs related to vaccination	I	Poor (small sample size; method of randomization not reported; safety data not completed)

Evidence related to safety of Fluad® vaccine in adults (18 – 60 years) with or without comorbidities						
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Tsai et al. Exposure to MF59-adjuvanted influenza vaccines during pregnancy--a retrospective analysis. Vaccine 2010;28(7):1877-80. [39]	MF59-adjuvanted influenza vaccines (Fluad®, Aflunov®, Focetria®, experimental adjuvanted tetravalent influenza vaccines) vs. non-adjuvanted influenza vaccines (Agrippal®, Optaflu®)	Retrospective study (data from Novartis Vaccines' pregnancy database from 1991 to 2009)	Female subjects (16-42 years) with unintended pregnancy exposures to MF59-adjuvanted influenza vaccines (n=43) and non-adjuvanted influenza vaccines (n=60)	Pregnancy outcomes (MF59-adjuvanted vs. non-adjuvanted): Normal: 70% vs. 75% Abnormal: 21% vs. 23% Induced abortion: 9% vs. 2% Similar results for analysis focused on exposures occurring within the interval of -30 to +45 days of the last menstrual period. Pregnancy outcomes were similar in both groups	II-2	Poor (small sample size; risk of selection bias)

Table 9: 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 10: Quality (internal validity) Rating of Evidence

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[43]

Table 11: NACI Recommendation for Immunization - Grades

A	NACI concludes that there is **good** evidence to recommend immunization.
B	NACI concludes that there is **fair** evidence to recommend immunization.
C	NACI concludes that the existing evidence is **conflicting** and does not allow making a recommendation for or against immunization, however other factors may influence decision-making.
D	NACI concludes that there is **fair** evidence to recommend against immunization.
E	NACI concludes that there is **good** evidence to recommend against immunization.
I	NACI concludes that there is **insufficient** evidence (in either quantity and/or quality) to make a recommendation, however other factors may influence decision-making.

Table 12: European Medicines Evaluation Agency (EMA) immunogenicity criteria for annual licensing of influenza vaccine using HI (haemagglutinin inhibition) and SRH (single radial haemolysis) methods.[10]

Criteria	Definition	18-59 years
Seroconversion or significant increase rate	*HI method:* Percentage of vaccines with pre-vaccination titre <10 and post-vaccination titre of ≥40 OR ≥10 and at least 4-fold rise in post-vaccination titre *SRH method:* Percentage of vaccines with negative pre-vaccination titre and post-vaccination area ≥25 mm^2 OR ≥50% increase in area post-vaccination	>40%
Seroprotection	Percentage of vaccinees achieving post-vaccination HI titre of ≥40 OR SRH titre > 25 mm^2	>70%
Mean geometric increase	Pre / post-vaccination GMT ratio	>2.5

List of Abbreviations

ACS	Acute coronary syndrome
AEs	Adverse events
BCG	Bacille Calmette-Guérin
CCDR	Canada Communicable Disease Report
CHMP	Committee for Medical Products for Human Use
CI	Confidence interval
CVA	cerebrovascular accident
DB	double blind
EMEA	European Medicines Evaluation Agency
GBS	Guillain-Barré syndrome
GMT	Geometric mean titre
GMR	geometric mean titre ratio
HA	Haemagglutinin antigen
HI	Haemagglutination inhibition
ID	Intradermal
ITT	intention-to-treat
IgE	Immune globulin E
IM	Intramuscular
MFI	mean-fold increase
mL	Millilitres
mm	Millimitre
MN	microneutralization
NACI	National Advisory Committee on Immunization
NS	not significant
NT	neutralization
ORS	Oculorespiratory syndrome
pH1N1	Pandemic H1N1
RCT	randomized controlled trial
SRH	Single radial haemolysis
TIV	Trivalent inactivated influenza vaccine
TIV-ID	Trivalent inactivated influenza vaccine administered by the intradermal route
µg	Microgram
WHO	World Health Organization

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