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

Addendum to the 2010-2011 Seasonal Trivalent Inactivated Influenza Vaccine

Recommendations on the use of intradermal trivalent inactivated influenza vaccine (TIV-ID)

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 Tara Harris and Dr. Nadine Sicard and approved by NACI.

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Introduction

In May 2010, a trivalent inactivated influenza vaccine administered by the intradermal route (TIV-ID) (Intanza®, Sanofi Pasteur)(1) was authorized in Canada for use in adults 18 years of age and older for active immunization against influenza caused by specific strains of influenza virus contained in the vaccine.

This addendum to the National Advisory Committee on Immunization (NACI) statement on seasonal trivalent influenza vaccine (TIV) for 2010-2011 will:

- Provide a brief overview of 2010-2011 NACI recommendations on the use of TIV
- Provide information on the recently-authorized TIV-ID vaccine (Intanza®) which is administered using a micro-injection system
- Provide recommendations for the use of Intanza®

For further detail on the epidemiology of influenza and recommended recipients of influenza vaccine for the 2010-2011 season please refer to NACI's 2010-2011 Statement on Seasonal Trivalent Influenza Vaccine (TIV) available from: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10vol36/acs-6/index-eng.php.

Recommendations

- NACI recommends that Intanza® (9 µg/strain) can be used for the prevention of influenza in healthy adults 18 to 59 years of age. (NACI Recommendation Grade A)
- NACI recommends that Intanza® (9 µg/strain) can be used for the prevention of influenza in adults 18 to 59 years of age with chronic health conditions including diabetes, heart, pulmonary, renal and neurological diseases. (NACI Recommendation Grade B)
- NACI recommends that Intanza® (15 µg/strain) can be considered for the prevention of influenza in adults 18 to 59 years of age with immune compromising conditions. (NACI Recommendation Grade I)
- NACI recommends that Intanza® (15 µg/strain) can be used for the prevention of influenza in adults 60 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 Intanza® over other TIV products currently authorized for use in Canada. (NACI recommendation grade I)

Intradermal injection has long been considered a potentially viable route for immunization. While it is most commonly used for rabies, Bacille Calmette Guérin (BCG) and hepatitis B vaccines (although not in Canada), variability in immune response and difficulties with performing intradermal injection have limited its use.(2)

Recently, interest has been renewed in influenza vaccines delivered via cutaneous routes due to ease of access, potential for dose-sparing capacity and the unique immunological characteristics of the skin which may provide for enhanced immune response, particularly among those most vulnerable to complications from influenza.(2, 3) In addition, recent advances in delivery methods for intradermal injection using microneedle injection systems address issues related to the traditional Mantoux method of intradermal injection.(4)

Intanza® is the first TIV-ID vaccine authorized for use in Canada.

Overview of 2010-11 TIV recommendations

The seasonal trivalent vaccine for 2010-2011 incorporates the pandemic 2009 influenza A (pH1N1) component, a new influenza A (H3N2) component and the same B component as 2009-2010.

NACI's recommendations for the 2010-2011 season relate to use of four vaccines authorized in Canada that are formulated for intramuscular use: Fluviral® (GlaxoSmithKline), Vaxigrip® (Sanofi Pasteur), Agriflu® (Novartis) and Influvac® (Abbott). Since these recommendations have been published, four additional vaccines have been authorized for use in Canada including Intanza®, and Fluzone® (Sanofi Pasteur), Fluad® (Novartis) and FluMist® (AstraZeneca). Recommendations regarding the use of these products will be addressed in separate supplements. For the 2010-2011 influenza season, NACI continues to recommend that immunization programs focus on those persons at high risk of influenza-related complications, those capable of transmitting influenza to individuals at high risk of complications and those who provide essential community services. In addition, NACI recommends that three additional groups that experienced a higher incidence of severe outcomes during both waves of the pH1N1 pandemic be considered as priority recipients for influenza vaccine. These new groups are persons with morbid obesity, Aboriginal peoples and children two to four years of age.

For further details on recommended recipients of influenza vaccine for the 2010-2011 season please refer to NACI's 2010-11 Statement on Seasonal Trivalent Influenza Vaccine (TIV) available from: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10vol36/acs-6/index-eng.php.

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 performed by Ms. Tara Harris and supervised by the Working Group. Following critical appraisal of individual studies, summary tables with ratings of the quality of the evidence using NACI's methodological hierarchy (Table 6) 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 February 9, 2011. Following thorough review of the evidence and consultation at the NACI meeting on February 9, 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

Review of the epidemiology of influenza is available in previous NACI statements on Seasonal Trivalent Influenza Vaccine (TIV). A summary of the 2009 pH1N1 pandemic virus is included in the 2010-11 Statement on TIV.

IV. Vaccine

IV.1. Preparation(s) authorized for use in Canada (e.g. description, composition)

Intanza® [Influenza Vaccine (Split Virion, Inactivated)] is a sterile, colourless and opalescent suspension containing three strains of influenza virus. The type of viral antigens contained in Intanza® conform to the current requirements of the World Health Organization (WHO). The strains for the 2010-2011 season are: A/California/7/2009 (H1N1)-like strain, A/Perth/16/2009 (H3N2)-like strain and B/Brisbane/60/2008.(5)

Two different dosing formulas are available for Intanza®. Each 0.1 mL dose contains either 9 µg or 15 µg of influenza virus haemagglutinin antigens (HA) for each strain, indicated for adults 18 to 59 years of age or adults 60 years of age and older respectively. Manufacturing process residuals including neomycin, formaldehyde, ovalbumin and Triton® X-100 may be present in trace amounts. Intanza® does not contain thimerosal. The micro-injection system does not include any latex-containing or latex-derived component.

Intanza® is manufactured using the same process as Vaxigrip®, another TIV product manufactured by Sanofi Pasteur, authorized for use in Canada and administered by the intramuscular (IM) route.

IV.2. Efficacy

There are currently no published studies on the efficacy of Intanza®. Efficacy of inactivated influenza vaccines in general is reviewed in more detail in the 2010-2011 Statement on TIV;(5) however, the data refer to TIV products administered by the intramuscular (IM) route only. In general, given a good match, influenza vaccination given via the IM route has been estimated to prevent influenza illness in 73% (95% CI (confidence interval); 54, 84) of healthy adults (6) and 58% (95% CI; 34, 73) of the elderly.(7) Without a good match, efficacy is estimated at 44% (95% CI; 23, 59) for healthy adults.(6) Systematic reviews also demonstrate that influenza vaccine decreases the incidence of pneumonia, hospital admissions and death in the elderly.(7) Previously, NACI has advised caution when interpreting the results of observational studies and has recommended that more studies are needed to assess vaccine protection against laboratory-confirmed influenza and its serious complications.(5)

It is generally accepted that a serum haemagglutination-inhibiting (HI) titre of 1:40 correlates with 50% protection against infection, while higher antibody titres (1:120 - 1:160) are associated with higher protection of up to 90%.(8-11) A recent publication by Coudeville *et al.* (11) presents a model developed using a meta-analytic approach, of clinical protection against laboratory-confirmed influenza at any HI titre. This model estimates a significant, positive relationship between HI titre and clinical protection which remains consistent regardless of strain or vaccination status. In another recent publication by Coudeville *et al.*,(12) the above model is used along with results from two clinical trials (13, 14) to predict the efficacy of ID (Intanza®) and IM (Vaxigrip®) influenza vaccine among those 60 years of age and older based upon their immunogenicity profile. Based on this pooled data, predicted efficacy was 63.3% (95% CI; 58.1, 68.7) for the ID route and 54.4% (95% CI; 49.4, 59.2) for the IM route, with a relative increase in efficacy of 16.5% (95% CI; 12.7, 20.1) of ID versus IM vaccine. Relative predicted increase in efficacy for those 70 years of age and older was 18.0% (95% CI; 12, 24). While this data suggests potential clinical benefit of Intanza®, more studies are needed to directly assess the efficacy of Intanza® against laboratory-confirmed influenza and its serious complications.

IV.3. Immunogenicity

The exact mechanisms involved in intradermal immunization are not fully understood; however, it is known that the skin generates both innate and adaptive immune system responses. Two types of professional antigen-presenting cells (Langerhans cells in the epidermis and dermal dendritic cells in the dermis) play a pivotal role in skin's innate immune response and induction of the adaptive immune response against pathogens.(2, 3) These dendritic cells, present in high densities in the skin, favour rapid capture and movement of antigen via lymphatic vessels to lymph nodes. The migration of dermal dendritic cells to the lymph nodes facilitates lymph node T and B cell activation / expansion and induction of antigen-specific humoral and cellular

immunity.(3, 15, 16) Antigen can also drain into the lymph nodes without involvement of peripheral tissue dendritic cells and be captured by lymph node resident dendritic cells, or alternatively is transferred to resident dendritic cells from the skin migratory dendritic cells, with subsequent priming of naive T cells.(17)

In clinical trials of Intanza®, HI GMTs (geometric mean titres) were the primary objectives for evaluation of immune response. HI GMTs elicited by Intanza® were compared to those elicited by the control IM influenza vaccine. In addition, the immune response to Intanza® vaccination was evaluated based upon the European Medicines Evaluation Agency (EMEA) immunogenicity criteria (see Table 1 below).(18) EMEA requires that for annual licensure to be granted for a specific influenza vaccine in the pre-defined age groups (below), at least one of the criteria must be met *for each strain*.

Table 1: European Medicines Evaluation Agency (EMEA) immunogenicity criteria for annual licensing of influenza vaccine using HI (haemagglutinin inhibition) and SRH (single radial haemolysis) methods.(18)

Criteria	Definition	Age group	
		18 to 60 years	>60 years
Seroconversion or significant increase rate	*HI method:* Percentage of vaccinees 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 vaccinees with negative pre-vaccination titre and post-vaccination area ≥25 mm^2 OR ≥50% increase in area post-vaccination	>40%	>30%
Seroprotection	Percentage of vaccinees achieving post-vaccination HI titre of ≥40 OR SRH titre > 25 mm^2	>70%	>60%
Mean geometric increase	Post / pre-vaccination GMT ratio	>2.5	>2.0

Adults 18 to 59 years of age

Immunogenicity of Intanza® among adults 18 to 59 years of age is summarized from phase II and III clinical trials by Beran *et al.*(19), Leroux-Roels *et al.*(20) (Phase II) and Arnou *et al.*(21) (Phase III).

In Beran *et al*.(19), a phase II multicentre, randomized dose-ranging trial was conducted to compare 3 µg, 6 µg and 9 µg/strain of inactivated influenza vaccine administered by the ID route using a microinjection system, with 15 µg/strain of inactivated influenza vaccine (Vaxigrip®) administered by the IM route. The 6 µg/strain ID vaccine satisfied EMEA immunogenicity criteria except for seroprotection and seroconversion for the B strain. When comparing to the IM formulation, neither the 3 µg nor the 6 µg/strain ID vaccines met the predefined non-inferiority criteria (lower boundary of the 95% CI of the ratio of post-vaccination GMTs (ID/IM) greater than 0.667 in both groups for each strain). Response following the 9 µg/strain dose of ID vaccine was immunogenic and met EMEA criteria for all three strains, therefore subsequent trials focused exclusively on 9 µg/strain ID vaccine.

The subsequent trials(20, 21) compared Intanza® (9 µg/strain) administered ID (microinjection system), with Vaxigrip® (15 µg/strain) administered IM as the control vaccine. In both the Leroux-Roels *et al*.(20) and Arnou *et al*.(21) trials, prevaccination titres were comparable between ID and IM groups for all three strains. Prior immunization status was also comparable between groups for both studies with between 39.1% and 47.5% having ever received an influenza vaccine.

The primary end-points were strain-specific GMTs, 21 days following vaccination, and were tested using a non-inferiority approach. Immunogenicity was non-inferior if the lower bound of the 95% CI of the difference of the log transformed post-vaccination GMT between the ID and IM groups was above -0.176 ($\log_{10}$ (GMT_{ID}) - $\log_{10}$ (GMT_{IM}) > -0.176) for all three strains. Immunogenicity was considered statistically superior for a given strain if the lower bound of the 95% CI of the difference of the log transformed post-vaccination GMT between the ID and IM groups was above 0 ($\log_{10}$ (GMT_{ID}) - $\log_{10}$ (GMT_{IM})>0).

In both trials, at 21 days post-vaccination, Intanza® met all three EMEA criteria for each of the three strains and was non-inferior to the Vaxigrip® for all three strains (A/H1N1, A/H2N3 and B). Lower bound values (as per above non-inferiority description) were 0.006 / -0.084 for A/H1N1; 0.087, -0.059 for A/H3N2 and -0.003, -0.064 for B for the Leroux-Roels *et al*.(20) and Arnou *et al.*(21) studies respectively.

Seroprotection rate, seroconversion rate and GMT ratios were all higher in the ID vaccine group compared with IM vaccine group in the Leroux-Roels *et al*.(20) study and statistical superiority was demonstrated for both of the A strains (H1N1 and H3N2) but not B. Antibody persistence was tested at 3, 6 and 12 months. Seroprotection rates in the ID group were 82%, 98% and 61% at 6 months and 68%, 96% and 50% at 12 months for A/H1N1, A/H3N2 and B strains respectively. Both the IM and ID groups had an almost identical kinetic profile.

In the Arnou *et al.*(21) study, seroprotection rate, seroconversion rate and GMT ratios between the ID and IM vaccine groups were comparable but not consistently higher or statistically superior in the ID group as was demonstrated by Leroux-Roels *et al*.(20)

Table 2: Immunogenicity of Intanza® (9 µg/strain) among adults 18 to 59 years of age 21 days post-vaccination.(1, 20, 21)

	EMEA criteria	Phase II		Phase III	
		9 µg ID n=381	15 µg IM n=379	9 µg ID n=1255	15 µg IM n=421
A/H1N1					
Seroprotection (95% CI)	>70%	92.4% (89.3, 94.9)	88.8% (85.3, 91.8)	87.2% (85.2, 89.0)	86.2% (82.6, 89.3)
Seroconversion (95% CI)	>40%	74.3% (69.7, 78.7)	70.4% (65.6, 74.9)	57.5% (54.7, 60.2)	56.4% (51.6, 61.1)
GMT ratios (95% CI) Post/pre-vaccination	>2.5	16.2 (13.7, 19.2)	13.8 (11.6, 16.4)	9.17 (8.33, 10.1)	9.71 (8.19, 11.5)
A/H3N2					
Seroprotection (95% CI)	>70%	99.7% (98.6, 100)	98.7% (97.0, 99.6)	93.5% (92.0, 94.8)	95.4% (93.0, 97.2)
Seroconversion (95% CI)	>40%	85.1% (81.2, 88.5)	79.2% (74.8, 83.1)	66.5% (63.8, 69.0)	69.3% (64.7, 73.6)
GMT ratios (95% CI) Post/pre-vaccination	>2.5	28.2 (23.7, 33.5)	20.7 (17.5, 24.4)	11.5 (10.4, 12.7)	11.2 (9.58, 13.1)
B					
Seroprotection (95% CI)	>70%	90.6% (87.2, 93.3)	85.5% (81.5, 88.8)	72.9% (70.4, 75.3)	74.8% (70.4, 78.8)
Seroconversion (95% CI)	>40%	76.4% (71.9, 80.6)	73.5% (68.8, 77.8)	56.7% (54.0, 59.4)	60.8% (56.0, 65.4)
GMT ratios (95% CI) Post/pre-vaccination	>2.5	12.1 (10.5, 13.8)	10.8 (9.6, 12.3)	6.39 (5.96, 6.84)	6.63 (5.90, 7.46)

ID=intradermal, IM=intramuscular, CI=confidence interval

60 years of age and older

Immunogenicity of Intanza® among elderly adults 60 years of age and older is summarized from phase II and III clinical trials by Holland *et al.*(13) and Arnou *et al.*(14) respectively. In Holland *et al.*(13), two dosage strengths of Intanza® (15 µg and 21 µg/strain) administered by the ID route were compared to Vaxigrip® (15 µg/strain) administered by the IM route. In Arnou *et al.*(14), Intanza® (15 µg/strain) was compared to Vaxigrip® (15 µg/strain) over three consecutive years in which 4 groups were compared (ID-ID-ID, IM-ID-ID, IM-IM-ID and IM-IM-IM) based on which vaccine was received in each year of the study.

Pre-vaccination titres were comparable between groups for all three strains in both Phase II and III studies.(13, 14) Prior immunization status was also comparable between groups in both trials with between 79.0% and 85.0% having received an influenza vaccine in the previous year.

Those with congenital or acquired immunodeficiency, treatment with immunosuppressive therapy within the last 6 months; long-term treatment with systemic corticosteroids or an unstable chronic illness were excluded from both phase II and III trials. At least one condition which increases the risk of influenza complications (including diabetes, cardiac, pulmonary, renal and neurological diseases) was present in approximately 40% of participants of the phase II trial and 65% of participants for the phase III trial(13, 14).

Primary endpoints were GMTs and seroprotection rate against all three strains, 21 days following vaccination. Immunogenicity endpoints were non-inferior if the lower bound of the 95% CI of the ratio of GMTs between the ID and IM groups (GMT_{ID}: GMT_{IM}) was above 0.667 for each strain OR the difference of the log transformed post-vaccination GMT between the ID and IM groups was above -0.176 for each strain. In the Holland *et al.* study(13), statistical superiority was demonstrated if the 95% CI of the GMT_{ID}: GMT_{IM} ratio was >1 for at least 2 strains. Arnou *et al.*(14) defined statistical superiority as being demonstrated if the lower bound of the 95% CI of the difference in post-vaccination seroprotection rate between the ID and IM group was greater than 0 for at least two strains.

In Holland *et al.*(13), both ID vaccines (15 µg and 21 µg/strain) met EMEA immunogenicity criteria for those >60 years of age, were non-inferior and subsequently demonstrated to be statistically superior compared with the IM vaccine. Seroprotection rate, seroconversion rate and GMT ratios as a result of both 15 µg and 21 µg of ID vaccine were significantly higher than the IM vaccine for all three strains, with the exception of seroprotection for A/H1N1 in the 15 µg ID group which did not reach significance. GMT_{ID}: GMT_{IM} ratios for 15 µg and 21 µg respectively were 1.517 (1.285, 1.786) / 1.592 (1.368, 1.849) for A/H1N1; 1.702 (1.419, 20.46) / 1.706 (1.429, 2.037) for A/H3N2 and 1.493 (1.276, 1.746) / 1.406 (1.205, 1.641) for B strains. No significant effects on the superiority analysis were detected when immunization status was added as a covariate.

In Arnou *et al.*(14), Intanza® (15 µg/strain) ID met all EMEA criteria and was shown to be non-inferior to the control IM vaccine. Lower bound values (as per above non-inferiority description) were 0.038 for A/H1N1; 0.171 for A/H3N2 and 0.026 for B. Statistical superiority was demonstrated for all three strains with seroprotection rate differences (ID – IM) of 5.78% (2.74, 9.08), p=0.0003 for A/H1N1; 5.49% (3.40, 7.76), p<0.0001 for A/H3N2; and 6.60% (3.05, 10.1), p=0.0003 for the B strain. Post-hoc analyses to examine the effect of age on superiority found that superiority was maintained when two age strata (60 to 70 years and ≥70 years) were analyzed separately.

Table 3: Immunogenicity of Intanza® (15 µg/strain) among adults 60 years of age and older 21 days post-vaccination.* (1, 13, 14)

	EMEA criteria	Phase II			Phase III	
		15 µg ID N=365	21 µg ID N=369	15 µg IM N=363	15 µg ID	15 µg IM
A/H1N1						
Seroprotection (95% CI)	>60%	77.5 (72.9, 81.7)	N/A	72.2 (67.3, 76.7)	77.0 (75.3, 78.6)	71.2 (68.4, 73.9)
Seroconversion (95% CI)	>30%	41.3 (39.2, 46.6)	N/A	22.3 (18.1, 26.9)	38.7 (36.8, 40.6)	30.0 (27.3, 32.9)
GMT (95% CI)	N/A	86.7 (76.7, 98.1)	90.9 (81.7, 101)	57.1 (51.2, 63.7)	81.9 (78.2, 85.8)	69.1 (64.1, 74.4)
GMT ratios (95% CI) Post/pre-vaccination	>2.0	3.73 (3.28, 4.24)	N/A	2.37 (2.13, 2.63)	3.97 (3.77, 4.18)	3.19 (2.94, 3.45)
A/H3N2						
Seroprotection (95% CI)	>60%	98.1 (96.1, 99.2)	N/A	93.4 (90.3, 95.7)	93.3 (92.3, 94.3)	87.8 (85.7, 89.7)
Seroconversion (95% CI)	>30%	42.3 (36.2, 46.6)	N/A	27.2 (22.7, 32.1)	61.3 (59.3, 63.1)	46.9 (43.9, 49.9)
GMT (95% CI)	N/A	400 (354, 452)	403 (359, 452)	235 (205, 268)	298 (282, 315)	181 (167, 197)
GMT ratios (95% CI) Post/pre-vaccination	>2.0	4.14 (3.56, 4.83)	N/A	2.68 (2.36, 3.04)	8.19 (7.68, 8.74)	5.35 (4.87, 5.88)
B						
Seroprotection (95% CI)	>60%	84.7 (80.6, 88.2)	N/A	73.9 (69.2, 78.4)	55.7 (53.7, 57.6)	49.1 (46.0, 52.1)
Seroconversion (95% CI)	>30%	43.1 (39.0, 48.4)	N/A	29.9 (25.2, 34.8)	36.4 (34.5, 38.3)	30.7 (28.0, 33.6)
GMT (95% CI)	N/A	100 (89.6, 112)	95.5 (85.7, 106)	67.7 (60.6, 75.7)	39.9 (38.2, 41.6)	34.9 (32.7, 37.3)
GMT ratios (95% CI) Post/pre-vaccination	>2.0	3.65 (3.26, 4.10)	N/A	2.69 (2.43, 2.98)	3.61 (3.47, 3.76)	3.04 (2.85, 3.24)

ID=intradermal, IM=intramuscular, CI=confidence interval

N/A = Values not provided in either Arnou *et al.*, 2009 or Sanofi Pasteur, 2010

*Where values differ between the product monograph and the corresponding publication, product monograph are taken as most correct

Further analysis of Phase III trial data was done to determine the effect on the immune response to Intanza® of either the absence of a wheal or liquid at the injection site following vaccine administration. In both instances, no differences in post-vaccination GMTs were noted among those with / without the above circumstances.(1)

In addition to the above trials comparing Intanza® to Vaxigrip®, a phase III randomized trial in adults 65 years of age and older has also been conducted comparing Intanza® to Fluad® an inactivated influenza vaccine adjuvanted with an oil-in-water adjuvant, MF59®, administered by the IM route.(22) In this trial, two methods of immunogenicity assessment were used; haemagglutinin inhibition (HI) and single radial haemolysis (SRH). 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 was not tested using the HI method (non-inferiority not demonstrated for all three strains) and 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.(22)

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 adjuvanted group (difference of 5.8% (0.7, 10.9) and 5.8% (1.1, 10.5) by HI and SRH method respectively).(22)

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.(22)

Adults with chronic health conditions

There are five published studies that assess the use of intradermally administered influenza vaccine in those with chronic health conditions, including immunocompromising conditions, known to increase the risk for influenza complications (Table 6). In four of these studies,(23-26) antibody response to ID-administered influenza vaccine was comparable to the standard IM vaccine and no significant safety issues were identified. However, variations in the product used, ID vaccine antigen dose administered and the use of the Mantoux injection method limit the generalizeability of these findings to Intanza®.

In a phase II descriptive study, Morelon *et al.*(27) assessed the immunogenicity and safety of Intanza® in renal transplant patients known to be prior non-responders to conventional influenza vaccines. Two hundred and one adult renal transplant patients were enrolled to receive IM influenza immunization during the 2006-2007 influenza season. From this group, 62 vaccine non-responders were identified and randomized to receive Intanza® (15 µg/strain, ID) or Vaxigrip® (15 µg/strain, IM) the following influenza season (2007-2008). In this selected, vaccine hyporesponsive population, ID dosing of Intanza® was well tolerated and demonstrated trends toward improved immunogenicity compared to IM Vaxigrip® for each of the three antigens evaluated. Antibody response on day 21 following vaccination with Intanza® (ID) met EMEA criteria for licensing of seasonal influenza vaccines in this population (with the exception of not having a minimum of 50 subjects), while the same criteria were not met in the Vaxigrip® comparison group. GMT ratios, seroprotection and seroconversion tended to be higher in the ID group with the exception of seroconversion for the B strain which was identical between groups. In the ID group GMT ratios were greater than 2.5 for A/H1N1 and A/H3N2 strains and seroprotection was greater than 70% for A/H1N1 and B strains. Equal doses of antigen (15 µg/strain) were used for each of the ID and IM vaccine (ID vaccine formulated in a reduced volume of 0.1 mL) which is notable as previous studies in this population evaluated reduced-dose ID influenza vaccine to the full-dose IM influenza vaccine.

A post-hoc analysis was conducted comparing persons with and without high risk conditions participating in the Intanza® Phase III trial in adults 60 years of age and over.(28) Those with risk conditions (at least one chronic health condition including diabetes as well as heart, pulmonary, renal and neurological diseases) had a similar or higher degree of seroprotection after receipt of Intanza® when compared to healthy participants (77.2%/76.6%; 93.1%/93.7%; 58.7%/50.0% high risk versus no risk for H1N1, H3N2 and B strains respectively. Of note, this trial excluded those with an unstable chronic illness (defined as an illness requiring hospitalization or clinically significant change in medication in the previous 12 weeks), congenital or acquired immunodeficiency, treatment with immunosuppressive therapy within the previous 6 months and long-term treatment with systemic corticosteroids.(14)

IV.4. Vaccine Administration and Schedule

IV.4.1 Schedule and dosage

Annual influenza vaccination consists of one dose. The recommended vaccine dosage is 0.1 mL (9µg / strain) for adults 18 to 59 years of age and 0.1 mL (15 µg/strain) for adults 60 years of age and over.

Intanza® is not authorized for use in persons <18 years of age.

IV.4.2 Route of administration

Intanza® is administered by the ID route. The recommended site of injection is in the deltoid region. Intanza® is supplied in a micro-injection system for intradermal injection which consists of a pre-filled syringe with a micro-needle (1.5 mm) and a needle shielding system designed to cover the micro-needle after use.

The micro-injection system used for Intanza® (BD Soluvia ™ Micro Injection System, BD Medical Pharmaceutical Systems) has been evaluated by Laurent and colleagues (4) using the following clinical investigation models: injection site imaging, (X-ray and 3D ultrasound echography), histological examination of injection sites, fluid injection volume accuracy measurement, subject perceived pain and local skin reactivity. The BD Soluvia ™ Micro Injection System is able to consistently inject the delivered dose into the deltoid region of the dermis correctly and a needle length of 1.5 mm has been validated in a large (n=645) multi-ethnic adult population.(4)

IV.5. Storage Requirements

Intanza® should be stored at 2° 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 Intanza® with other vaccines. NACI states that in general, influenza vaccine may be given at the same time as other vaccines, preferably in opposite limbs. If injections are given in the same limb, different sites on the limb should be chosen. Different administration sets (needle and syringe) must be used.

The target groups for influenza and pneumococcal polysaccharide vaccines overlap considerably. Health care providers should take the opportunity to vaccinate eligible persons against pneumococcal disease when influenza vaccine is given, according to the *Canadian Immunization Guide*.(CIG, 2006: http://www.phac-aspc.gc.ca/publicat/cig-gci/index-eng.php)

IV.7. Adverse Events

A detailed summary of adverse events as they relate to inactivated influenza vaccine is available in the 2010-2011 NACI Statement on TIV.(5) Information on adverse events from pre-market clinical trials of Intanza® is summarized below.

Among adults 18 to 59 years of age and adults ages 60 years and over, systemic reactions following receipt of Intanza® were comparable with the IM control vaccine in all four trials. (13, 14, 20, 21) Injection site reactions were consistently more frequent and more extensive in the ID vaccine groups, generally beginning the day following vaccination, lasting up to 3 days and resolving spontaneously.

In a randomized controlled trial of adults 18 to 59 years of age(20), solicited injection site reactions of erythema, induration and swelling in the seven days following immunization were reported more frequently in ID compared with IM vaccine recipients. Erythema was the most frequently reported injection site reaction with 9.6% of ID vaccine recipients and 0.8 % of IM vaccine recipients reporting erythema of 5 cm or larger. Among those who

received ID vaccine, 44% had erythema lasting more than 4 days compared with 1.3% of those who received IM vaccine. The frequency of systemic reactions was comparable between the two groups with the exception of myalgia, which was more frequent in the IM vaccine group (29.4% of IM recipients versus 19.7% of ID recipients).

The Phase III trial of adults 18 to 59 years showed similar results.(21) Erythema (84.4% versus 25.5%), swelling (61.9% versus 20.7%), induration (60.8 versus 26.1%) and pruritis (44.8% versus 13.1%) were all more frequent in the ID group compared with IM, while pain appeared to be slightly more frequent in the IM group (48.4% versus 43.1%). Most injection site reactions appeared the day following immunization and resolved by day four. As in the randomized controlled study by Leroux-Roels *et al.*,(20) systemic reactions were comparable between the ID and IM groups except for myalgia, which was slightly more frequent in the IM vaccine group (29.5% versus 23.5% in IM and ID groups respectively).(21)

Adults 60 years of age and older experienced a similar adverse event profile as younger adults summarized above. In Phase II, injection site erythema (78.8% versus 19.1%), swelling (62.3% versus 13.4%), induration (64.6% versus 16.7%) and pruritis (27.7% versus 8.7%) were all more frequent 7 days following immunization in those who received Intanza® 15 mg ID compared to Vaxigrip® 15 mg IM.(13) The frequency of systemic adverse reactions was also similar between groups with 30.2% experiencing at least one systemic reaction in the ID group compared to 27.4% in the IM group. Headache was the most commonly reported reaction in both groups (18.1% versus 7.4%) in the ID and IM groups respectively.

Injection site reactions reported in Phase III were consistent. Pruritis, erythema (³2.5 cm and >5 cm), swelling and induration were all more frequent in the ID vaccine group, while ecchymosis was comparable between groups. These reactions lasted less than three days for the majority of cases, with less than 1% of subjects in either group reporting reactions lasting longer than three days.(14) This trial was conducted over three consecutive years; therefore, assessment of reactogenicity after two and three years of receiving ID vaccine was possible. Following three consecutive ID vaccines over three years (ID-ID-ID) the rate of injection site reactions (71.3%; 95 % CI 69.4, 73.2) appears higher when compared with the IM-ID-ID (67.4%, 95% CI 62.9, 71.6) and IM-IM-ID (57.3%, 95% CI 50.6, 63.8) groups. However, rates in the ID-ID-ID groups were lower overall compared with the rates observed following the first ID vaccine group in year one of the trial (77.9%). No significant difference in systemic reactions was noted between the ID and IM vaccine groups. In both groups, headache, myalgia and malaise were most frequently reported.

Pooled data from four clinical trials (Phase II and III) are presented below. Trials were conducted in adults 18 to 59 years of age and 60 years of age and older representing 2384 and 2974 subjects who received Intanza® 9 mg and 15 mg respectively, compared with 843 and 1458 subjects respectively who received the control vaccine Vaxigrip® (15 mg).

Table 4: Injection site and systemic reactions following vaccination with either Intanza® (9 µg) in adults 18 to 59 years of age or Intanza® (15 µg) in adults 60 years of age and over compared with Vaxigrip® (15 µg). Combined data from Phase II and III clinical trials.(1, 13, 14, 20, 21)

Symptom	Adults 18 -59 years		Adults 60 years and over	
	9 µg ID n=2384	15 µg IM n=843	15 µg ID n=2974	15 µg IM n=1458
Injection site reactions (%)				
Pain	41.9	44.0	22.2	17.1
Erythema	85.0	19.0	71.9	16.1
Swelling	62.7	14.9	39.0	9.7
Induration	61.5	19.9	40.9	12.6
Ecchymosis	8.3	6.5	4.3	4.2
Pruritis	42.7	9.1	29.2	6.8
Systemic reactions				
Fever	3.8	3.5	2.4	3.5
Headache	30.2	30.1	13.7	13.9
Malaise	17.3	18.4	9.0	8.4
Myalgia	22.6	29.5	10.8	11.2
Shivering	8.7	8.0	4.1	4.8

ID=intradermal; IM=intramuscular

In Arnou *et al*.(21) (Phase III, adults 18 to 64 years), a post-hoc analysis was conducted to determine if there was any direct relationship between injection sites reactions and seroprotection. Seroprotection rates were subdivided by four categories of subjects who received ID vaccine: (1) subjects reporting no injection site reactions,(2) subjects reporting only mild injection site reactions, (3) subjects reporting at least one moderate injection site reaction but none that were severe, and (4) subjects reporting at least one severe injection site reaction.

Seroprotection rates were shown to be lower in the group with no injection site reactions compared with the other three groups (mild, moderate and severe) in two out of three strains; however, no direct correlation between injection site reactogenicity and seroprotection was demonstrated.

For A/H3N2, the group with no injection site reactions, seroprotection was comparable (93.1%) with the other three groups (92.7%, 93.9% and 94.4% for mild, moderate and severe respectively). Whereas seroprotection rates for A/H1N1 and B strains were lower in the group with no injection site reactions (79.2% and 58.4% respectively) compared with the other three groups (89.3%, 85.1% and 91.2% for A/H1N1 and 75.4%, 72.9% and 74.4% for B strain for mild, moderate and severe reactions respectively).(21)

To date there is no post-marketing data available for Intanza®. For a review of post-marketing data related to the use of Vaxigrip® and other TIV products in use in Canada please refer to the 2010-11 NACI TIV statement.(5)

IV.9. Contraindications and Precautions

Contraindications

Intanza® should not be given to people who have had an anaphylactic reaction to a previous dose or to any of the vaccine components. For more information on vaccine safety and anaphylaxis, please see the *Canadian Immunization Guide* (CIG 2006: http://www.phac-aspc.gc.ca/publicat/cig-gci/index-eng.php).

Precautions

Persons with known IgE-mediated hypersensitivity to eggs (manifested as hives, swelling of the mouth and throat, difficulty in breathing, hypotension or shock) should not be routinely vaccinated with influenza vaccine. Egg-allergic individuals who are at risk of the complications of influenza should be evaluated by an allergy specialist, as vaccination might be possible after careful evaluation, skin testing and graded challenge or desensitization. If such an evaluation is not possible, the risk of an allergic reaction to the vaccine must be weighed against the risk of influenza disease. See the *Canadian Immunization Guide*'s recommendations for those with a known hypersensitivity to eggs.(5) (CIG 2006: http://www.phac-aspc.gc.ca/publicat/cig-gci/index-eng.php)

Expert review of the risks and benefits of vaccination should be sought for those who have previously experienced severe lower respiratory symptoms (wheeze, chest tightness, difficulty breathing) within 24 hours of influenza vaccination, an apparent allergic reaction to the vaccine or any other symptoms (e. g., throat constriction, 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.

Individuals who have experienced the oculorespiratory syndrome (ORS), including those with a severe presentation (bilateral red eyes, cough, sore throat, hoarseness, facial swelling) but without lower respiratory tract symptoms, may be safely re-immunized with influenza vaccine. Persons who experienced ORS with lower respiratory tract symptoms should have an expert review as described in the previous paragraph. Health care providers who are unsure whether an individual previously experienced ORS versus an IgE-mediated hypersensitivity immune response should seek advice. In view of the considerable morbidity and mortality associated with influenza, a diagnosis of influenza vaccine allergy should not be made without confirmation (which may involve skin testing) from an allergy/immunology expert.

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.

Although the influenza vaccine can inhibit the clearance of warfarin and theophylline, clinical studies have not shown any adverse effects attributable to these drugs in people receiving influenza vaccine. Therapy with beta-blocker medication is not a contraindication to influenza vaccination. Individuals who have an allergy to substances that are not components of the influenza vaccine are not at increased risk of allergy to influenza vaccine.

There are no known precautions related to the use of Intanza® in those with skin diseases.

IV.10. Other considerations

There is no clinical data available on the use of Intanza® in pregnant women. It is not known whether Intanza® is excreted in human milk. However, NACI has reviewed the available safety data on the use of trivalent inactivated influenza vaccine during pregnancy and finds that studies to date have not shown evidence of harm to the mother or fetus associated with influenza immunization.(5)

Serious maternal morbidity (namely hospitalization) during the seasonal influenza season supports a recommendation for seasonal TIV vaccine for healthy pregnant women since rates of influenza-associated hospitalization increase with length of gestation after the first trimester. Pregnant women with chronic health conditions are recommended by NACI as a high priority group for immunization at any stage of pregnancy.(5)

V. Recommendations

NACI continues to recommend that in order to reduce the morbidity and mortality associated with influenza, immunization programs should focus on those at high risk of influenza-related complications, those capable of transmitting influenza to individuals at high risk of complications and those who provide essential community services.

For a detailed list of recommended recipients of influenza vaccine for the 2010-11 season, please see Table 3 in NACI's 2010-11 Statement on Seasonal Trivalent Influenza Vaccine (TIV), available from: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10vol36/acs-6/index-eng.php.(5)

Based on the available evidence, NACI makes the following recommendations with respect to the use of Intanza® (TIV-ID). These recommendations are intended to be considered in combination with NACI's existing recommendations regarding recommended recipients of influenza vaccine.

1. **NACI recommends that Intanza® (9 µg/strain) can be used for the prevention of influenza in healthy adults 18-59 years of age. (NACI Recommendation Grade A)**

   Clinical trial data show that Intanza® is statistically non-inferior to Vaxigrip®, a TIV product authorized and in use in Canada for many years, and meets established immunogenicity criteria for licensure of seasonal trivalent inactivated influenza vaccines (TIV).

   While Intanza® is associated with an increased frequency of injection site reaction, clinical trial data indicate that the large majority of these reactions were mild and resolved spontaneously within a few days.(20, 21) No difference in systemic reactions between Intanza® and the control vaccine were observed.

   The decision to include Intanza® among the influenza vaccine products available to adults 18 to 59 years of age, as part of publicly funded Provincial/Territorial (P/T) programs will depend on multiple factors such as cost-benefit evaluation and other local programmatic/operational factors.

   As part of this evaluation, P/Ts may consider the following:

   - Administration of Intanza® using the micro-injection system appears to be intuitive and requires very little training. In a study by Laurent et al.,(4) immunizers (general practitioners and nurses) with varying levels of training were compared with one another. The levels of training ranged from those with no training and no opportunity to practice to those with correct written instruction, personal training and strict instruction to follow step-by-step written instructions. In all groups, Intanza® was administered correctly more than 96% of the time regardless of the level of training received prior to administration.
   - Assessment of Intanza® clinical trial subjects' perception of injection site reactions indicated that >96% of participants rated injection site reactions following both ID and IM vaccination as either 'totally acceptable' or 'very acceptable' and that willingness to get vaccinated the following year and satisfaction with the ID micro-injection system or the conventional IM syringe was high and not adversely affected by the occurrence of injection site reactions.(29)

2. **NACI recommends that Intanza® (9 µg/strain) can be used for the prevention of influenza in adults 18 to 59 years of age with chronic health conditions including diabetes, heart, pulmonary, renal and neurological diseases. (NACI Recommendation Grade B)**

   Data on the use of Intanza® in adults 18 to 59 years of age with chronic conditions is limited. However, currently available literature suggests that Intanza® (ID) is safe and at least as immunogenic as inactivated IM influenza vaccine in vaccine hyporesponsive populations with chronic health conditions. Further studies to assess response to Intanza® in those with specific chronic conditions/immune suppression would strengthen recommendations for this heterogeneous population.

3. **NACI recommends that Intanza® (15 µg/strain) can be considered for the prevention of influenza in adults 18-59 years of age with immune compromising conditions (NACI Recommendation Grade I).**

   NACI concludes that there is insufficient evidence (in quantity and quality) to make a recommendation, however other factors influence decision-making.

   There is limited safety and immunogenicity data in kidney transplant patients where non-responders to a 15 µg IM influenza vaccine did respond to the Intanza® 15 µg ID formulation.(27) EMEA criteria were met with the exception of the number of patients in the study. The safety profile was similar to trials of healthy subjects where injection site reactions in the ID group were more

frequent than the IM group while systemic reactions were comparable between groups. Other clinical trials of Intanza® (15 µg ID) excluded immune compromised patients. Some experts would recommend Intanza® (15 µg ID) for individuals with immune compromising conditions based on this evidence and theoretical concepts on immunology and vaccinology.

Further evaluation of Intanza® in these populations is advised.

4. NACI recommends that Intanza® (15 µg/strain) can be used for the prevention of influenza in all adults 60 years of age and older. (NACI Recommendation Grade A)

Data from two clinical trials with over 4800 participants demonstrated that immune response to Intanza® is statistically superior to Vaxigrip® and meets established immunogenicity criteria for licensure of seasonal trivalent inactivated influenza vaccines (TIV).

In the Phase III Intanza® trial(14) conducted in adults 60 years of age and older, seroprotection rates following receipt of Intanza® were consistently higher compared to IM vaccine, with percentage differences of 5.78 ($p=0.0003$); 5.49 ($p<0.0001$); and 6.60 ($p=0.0003$) for A/H1N1, A/H3N2 and B strains respectively. Statistical superiority remained consistent among more elderly participants, as no effect of age on superiority was shown when two age strata (60-70 years and ≥70 years) were analyzed separately.

No difference in immunogenicity was noted between healthy participants and those with chronic conditions. Those with at least one chronic condition, including diabetes and cardiac, pulmonary renal or neurological diseases represented approximately 65% of phase III trial participants; however, those with congenital / acquired immunodeficiency as well as treatment with immunosuppressive therapy within the last six months were excluded.

5. At this time, NACI concludes there is insufficient evidence to make a recommendation for the preferential use of Intanza® over other TIV products currently authorized for use in Canada. (NACI recommendation grade I)

There are no published studies available on the efficacy of Intanza®. While statistically significant increases in the point estimate of seroprotection ranging between 5.49 and 6.60% (depending on the strain) have been demonstrated with the use of Intanza® in adults over 60 years of age, the clinical significance in terms of protection against laboratory-confirmed influenza illness is not known.

Table 5: 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 over 65 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 Intanza® is a trivalent inactivated influenza vaccine (TIV) administered by the intradermal (ID) route. There are two dosing formulas available containing either 9 µg of influenza virus haemagglutinin antigens (HA) of each strain or 15 µg of influenza virus HA of each strain indicated for adults 18 to 59 years of age and adults 60 years of age and older respectively. There are no published studies available on the efficacy of Intanza®. Clinical trials have demonstrated that immune response to Intanza® is comparable to TIV administered by the intramuscular (IM) route. Intanza® meets/exceeds immunogenicity criteria established for licensure of seasonal TIV. Intanza® is generally safe and well-tolerated. No difference in systemic reactions between Intanza® and the control vaccine have been observed. An increased frequency of injection site reactions was observed in clinical trials; however, these reactions were mild and resolved spontaneously within a few days.
2. Who Groups recommended to immunize	• NACI recommends that Intanza® (9 µg/strain) can be used for the prevention of influenza in healthy adults 18 to 59 years of age. (NACI Recommendation Grade A) • NACI recommends that Intanza® (9 µg/strain) can be used for the prevention of influenza in adults 18 to 59 years of age with chronic health conditions including diabetes, heart, pulmonary, renal and neurological diseases. (NACI Recommendation Grade B) • NACI recommends that Intanza® (15 µg/strain) can be considered for the prevention of influenza in adults 18 to 59 years of age with immune compromising conditions (NACI Recommendation Grade I) • NACI recommends that Intanza® (15 µg/strain) can be used for the prevention of influenza in adults 60 years of age and older. (NACI Recommendation Grade A)

3. How • Dose, schedule • Precautions, contraindications • Co-administration	Annual influenza vaccination consists of one dose. The recommended vaccine dosage is 0.1 mL (9 µg/strain) for adults 18 to 59 years of age and 0.1 mL (15 µg/strain) for adults 60 years of age and over. Intanza® is administered intradermally. The preferred site of injection is in the deltoid region. Intanza® is supplied in a micro-injection system for intradermal injection which consists of a pre-filled syringe with a micro-needle (1.5 mm) and a needle shielding system designed to cover the micro-needle after use. No studies have been conducted regarding the concomitant administration of Intanza® with other vaccines. NACI states that in general, influenza vaccine may be given at the same time as other vaccines, preferably in opposite limbs. If injections are given in the same limb, different sites on the limb should be chosen.
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 new strains of the influenza virus - that's why you need a flu shot every year. 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. Intanza® is safe and well-tolerated. Redness and / or swelling at the site of injection following receipt of Intanza® is common and should disappear within a few days.

Table 6: Summary of Evidence for NACI Recommendation(s)

Evidence related to immunogenicity of Intanza®						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Leroux-Roels I, Vets E, Freese R, *et al*. Seasonal influenza vaccine delivered by intradermal microinjection: A randomized controlled safety and immunogenicity trial in adults. *Vaccine*. 2008;26(51):6614-6619.(20)	Intanza® (9 µg HA per strain)	Phase II RCT, open-label NCT00258934 Control vaccine: Vaxigrip® IM (intramuscular) 15 µg HA per strain	N=978 (n=588 ID, n=390 IM) Healthy adults 18 to 57 years Excluded those in receipt of influenza vaccine in the last 6 months	Primary endpoint was strain-specific GMT 21 days post-vaccination for each strain; secondary endpoints were EMEA criteria* for GMT ratios, seroconversion and seroprotection <u>Seroprotection:</u> H1N1 - ID 92.4% (89.3, 94.9); IM 88.8% (85.3, 91.8) H3N2 - ID 99.7% (98.6, 100); IM 98.7% (97.0, 99.6) B - ID 90.6% (87.2, 93.3); IM 85.5% (81.5, 88.8) <u>Seroconversion:</u> H1N1 - ID 74.3% (69.7, 78.7); IM 70.4% (65.6, 74.9) H3N2 - ID 85.1% (81.2, 88.5); IM 79.2% (74.8, 83.1 B - ID 76.4% (71.9, 80.6); IM 73.5% (68.8, 77.8) <u>GMT ratio (pre/post-vaccination):</u> H1N1 - ID 16.2 (13.7, 19.2); IM 13.8 (11.6, 16.4) H3N2 - ID 28.2 (23.7, 33.5); IM 20.7 (17.5, 24.4) B - ID 12.1 (10.5, 13.8); IM 10.8 (9.56, 12.29)	Level 1	Good

Evidence related to immunogenicity of Intanza®						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Arnou R, Eavis P, Pardo JR, *et al*. Immunogenicity, large scale safety and lot consistency of an intradermal influenza vaccine in adults aged 18-60 years: Randomized, controlled, phase III trial. *Hum vaccin*. 2010;6(4):346-354.(21)	Intanza® (9 µg HA per strain)	Phase III RCT, double blind for lot consistency, open label for administration route (ID versus IM) NCT00383539 Control vaccine: Vaxigrip® IM (intramuscular) 15 µg HA per strain	N=2255 (n=1803 ID; three lots pooled, n=452 IM) Healthy adults 18-60 years Excluded those in receipt of influenza vaccine in the last 6 months	Primary endpoint was strain-specific GMT 21 days post-vaccination for each strain and lot; secondary endpoints were EMEA criteria* for GMT ratios, seroconversion and seroprotection (lots pooled) <u>Seroprotection:</u> H1N1 - ID 87.2% (85.2, 89.0); IM 86.2% (82.6, 89.3) H3N2 - ID 93.5% (92.0, 94.8); IM 95.4% (93.0, 97.2) B - ID 72.9 (70.4, 75.3); IM 74.8% (70.4, 78.8) <u>Seroconversion:</u> H1N1 - ID 57.5% (54.7, 60.2); IM 56.4% (51.6, 61.1) H3N2 - ID 66.5% (63.8, 69.0); IM 69.3% (64.7, 73.6) B - ID 56.7% (54.0, 59.4); IM 60.8% (56.0, 65.4) <u>GMT ratio (pre/post-vaccination):</u> H1N1 - ID 9.17 (8.33, 10.1); IM 9.71 (8.19, 11.5) H3N2 - ID 11.5 (10.4, 12.7); IM 11.2 (9.58, 13.1) B - ID 6.39 (5.96, 6.84); IM 6.63 (5.90, 7.46)	Level 1	Good

Evidence related to immunogenicity of Intanza®						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Holland D, Booy R, De Looze F, *et al*. Intradermal influenza vaccine administered using a new microinjection system produces superior immunogenicity in elderly adults: a randomized controlled trial. *J Infect Dis*. 2008;198(5):650-658. (13)	Intanza® (15 and 21 µg HA per strain)	Phase II RCT; double-blind for ID dose, open-label for route NCT00296829 Control vaccine: Vaxigrip® IM (intramuscular) 15 µg HA per strain	N=1107 (n=370 ID 15 µg, n=369 ID 21 µg, n=368 IM 15 µg) Medically stable adults 60-85 years Excluded those in receipt of influenza vaccine in the last six months	Primary endpoint was strain-specific GMT 21 days post-vaccination for each strain; secondary endpoints were EMEA criteria* for GMT ratios, seroconversion and seroprotection • seroprotection rates for ID 15 and 21 µg significantly higher ($p<0.05$) for H3N2 and B strains compared with 15 µg IM; for H1N1 strain, ID 21 µg was significantly higher and 15 µg ID was non-inferior compared with 15 µg IM • seroconversion for ID 15 and 21 µg was significantly higher ($p<0.05$) for all three strains compared with 15 µg IM <u>GMTs pre / post-vaccination:</u> H1N1 - ID 15 µg 23.2 (20.8, 26.0) / 86.6 (76.5, 98.1); ID 21 µg 21.3 (19.1, 23.7) / 90.9 (81.7-101); IM 15 µg 24.1 (21.6, 26.8) / 57.1 (51.2, 63.7) H3N2 - ID 15 µg 96.5 (83.5, 112) / 402 (355, 455); ID 21 µg 85.0 (72.9, 99.2) / 403 (359, 452); IM 15 µg 87.1 (75.1, 101) / 236 (206, 271) B - ID 15 µg 27.4 (24.4, 30.7) / 101 (90.8, 113); ID 21 µg 22.2 (19.8, 24.9) / 95.5 (85.7, 106); IM 15 µg 25.1 (22.5, 28.1) / 67.9 (60.7, 76.0)	Level 1	Good

Evidence related to immunogenicity of Intanza®						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Arnou R, Icardi G, De Decker M, *et al*. Intradermal influenza vaccine for older adults: a randomized controlled multicenter phase III study. *Vaccine*. 2009;27(52):7304-7312.(14)	Intanza® (15 µg HA per strain)	Phase III RCT, open-label 3 seasons: 2006-2007, 2007-2008, 2008-2009 NCT00383526 Control vaccine: Vaxigrip® IM (intramuscular) 15 µg HA per strain	N=3707 (n=2618 ID, n=1089 IM for the first season, randomized 1:1 for each subsequent season) Medically stable adults ≥60 years	Primary endpoints was strain-specific GMT and seroprotection 21 days post-vaccination for each strain; secondary endpoints were EMEA criteria* for GMT ratios and seroconversion • seroprotection rate for ID 15 µg was statistically superior for all three strains compared with 15 µg IM • difference in seroprotection rates (ID minus IM) were 5.78 (2.74-9.08), p=0.0003 for the A/H1N1 strain; 5.49 (3.40-7.76) p<0.0001 for the A/H3N2 strain, and 6.60 (3.05-10.1) p=0.0003 for the B strain. • superiority maintained in age strata 60 to 70 and ≥70 years • seroprotection in years 2 and 3 also consistently higher for ID compared with IM with no consistent trend for higher seroprotection in any sub-group • GMT ratios significantly higher for ID compared with IM (p < 0.0001 for all three strains)	Level 1	Good

Evidence related to immunogenicity of Intanza®						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Beran J, Ambrozaitis A, Laiskonis A, *et al*. Intradermal influenza vaccination of healthy adults using a new microinjection system: a 3-year randomised controlled safety and immunogenicity trial. *BMC Med*. 2009;7:13. 10.1186/1741-7015-7-13.(19)	Intanza® (3, 6, 9 and 15 µg HA per strain)	Phase II RCT (dose ranging study) 3 seasons NCT00703651 Control vaccine: Vaxigrip® IM (intramuscular) 15 µg HA per strain	N=1150 18 to 57 years	Primary endpoint was strain-specific GMT 21 days post-vaccination for each strain and each dose group; secondary endpoints were EMEA criteria* for GMT ratios, seroconversion and seroprotection • 3 and 6 µg ID formulations did not meet pre-defined EMEA non-inferiority criteria (lower boundary of the 95% CI post-vaccination GMT ratio (ID/IM) was lower than 1/1.5 in both ID vaccine groups for each strain) • 9 µg ID met EMEA criteria* in both years 2 and 3 GMT pre / post-vaccination ratio: (9 µg ID / 15 µg IM) H1N1: 4.3 (3.8, 4.8) / 4.7 (4.2, 5.3) H3N2: 4.4 (4.0, 5.0) / 4.4 (3.9, 5.0) B: 7.8 (7.0, 8.8) / 8.3 (7.5, 9.1) Seroprotection H1N1: 90.0 (87.1, 92.4) / 93.4 (90.0, 95.3) H3N2: 97.2 (95.4, 98.4) / 99.4 (98.4, 99.9) B: 73.0 (69.1, 76.8) / 74.4 (70.5, 78.0) Seroconversion H1N1: 43.0 (38.8, 47.3) / 45.7 (41.4, 50.0) H3N2: 53.1 (48.8, 57.4) / 50.8 (46.5, 55.1) B: 63.4 (59.2, 67.5) / 66.6 (62.5, 70.6)	Level 1	Good

Evidence related to immunogenicity of Intanza®						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Van Damme P, Arnou R, Kafeja F, *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. (22)	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	Primary endpoint was strain-specific GMT 21 days post-vaccination for each strain; secondary endpoints were anti-HA antibody titres using SRH (single radial haemolysis) method, GMTRs, seroconversion and seroprotection using HI (haemagglutinin inhibition) and SRH methods • GMT non-inferiority criteria met for all three strains for SRH method and for H1N1 and B strains for HI method (non-inferiority criteria not met for H3N2 using HI method) <u>Post-vaccine GMT ratio (ID versus adjuvanted IM) HI / SRH method:</u> A/H1N1 - 1.13 (0.95, 1.34) / 1.16 (1.00, 1.34) A/H3N2 - 1.31 (1.13, 1.53) / 1.18 (1.03, 1.34) B - 1.08 (0.95, 1.23) / 1.03 (0.91, 1.17) • All strains non-inferior using both methods when post-vaccination GMTs were adjusted for pre-vaccination titres and ratios of GMT (IM/ID) • Superiority not tested for HI method (non-inferiority not shown) and tested but not shown using SRH method	Level 1	Good

Evidence related to immunogenicity of Intanza®						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Leroux-Roels I, Vets E, Freese R, *et al*. Seasonal influenza vaccine delivered by intradermal microinjection: A randomised controlled safety and immunogenicity trial in adults. *Vaccine*. 2008;26(51):6614-6619. (20)	Intanza® (9 µg HA per strain)	Phase II NCT00258934	N=978 (n=588 ID, n=390 IM) Healthy adults 18 to 57 years Excluded those in receipt of influenza vaccine in the last 6 months	• Erythema, induration and swelling were more frequent after Intanza® ID (intradermal) compared with Vaxigrip® IM (intramuscular) • 9.6% versus 0.8% reported erythema >5 cm compared with 0.8% while 44% versus 1.3% had erythema >4 days for ID and IM vaccine respectively • Frequency of reported systemic adverse events was comparable except for myalgia which was more frequent after IM (29.4 versus 19.7%) • 7 SAEs (serious adverse events) observed; 6 unrelated, one peritonsillar abcess, likely unrelated to vaccination	Level 1	Good

Evidence related to immunogenicity of Intanza®						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Arnou R, Eavis P, Pardo JR, *et al*. Immunogenicity, large scale safety and lot consistency of an intradermal influenza vaccine in adults aged 18-60 years: Randomized, controlled, phase III trial. *Hum vaccin*. 2010;6(4):346-354.(21)	Intanza® (9 µg HA per strain)	Phase III RCT, double blind for lot consistency, open label for administration route (ID versus IM) NCT00383539	N=2255 (n=1803 ID; three lots pooled, n=452 IM) Healthy adults 18 to 60 years Excluded those in receipt of influenza vaccine in the last 6 months	• Injection site erythema (84.4 versus 25.5%), swelling (61.9 versus 20.7%), induration 60.8 versus 26.1%) and pruritis (44.8 versus 13.1%) were more frequent after ID vaccine compared with IM • Frequency of reported systemic adverse events was comparable with the exception of myalgia which appeared more frequent after IM 29.5% (25.3, 34.0) versusID23.5% (21.6, 25.6) although confidence intervals overlap slightly • 39 (2.2%) SAEs reported (compared with 1.8% for IM group), none considered related to vaccination • Post-hoc analysis conducted to determine relationship between injection site reactogenicity and antibody response showed that while lower seroprotection rates were observed for 2/3 strains among those reporting no injection site reaction, no direct correlation was found	Level 1	Good

Evidence related to immunogenicity of Intanza®						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Holland D, Booy R, De Looze F, *et al*. Intradermal influenza vaccine administered using a new microinjection system produces superior immunogenicity in elderly adults: a randomized controlled trial. *J Infect Dis*. 2008;198(5):650-658.(13)	Intanza® (15 and 21 µg HA per strain)	Phase II RCT; double-blind for ID dose, open-label for route NCT00296829 Compared to Vaxigrip®	N=1107 (n=370 ID 15 µg, n=369 ID 21 µg, n=368 IM 15 µg) Medically stable adults 60 to 85 years Excluded those in receipt of influenza vaccine in the last 6 months	• Incidence of erythema (78.8 and 77.7 versus 19.1%), swelling (62.3 and 58.2 versus 13.4 %), induration (64.6 and 65.2 versus 16.7%) and pruritis (27.7 and 32.1 versus 8.7%) were more frequent for ID (15 / 21 µg respectively) compared with IM 15 µg • Incidence of systemic reactions was comparable between groups	Level 1	Good

Evidence related to immunogenicity of Intanza®						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Arnou R, Icardi G, De Decker M, *et al*. Intradermal influenza vaccine for older adults: a randomized controlled multicenter phase III study. *Vaccine*. 2009;27(52):7304-7312. (14)	Intanza® (15 µg HA per strain)	Phase III RCT, open-label 3 seasons: 2006-2007, 2007-2008, 2008-2009 NCT00383526 Compared to Vaxigrip®	N=3707 (n=2618 ID, n=1089 IM for the first season, randomized 1:1 for each subsequent season)	• Injection site reactions pruritis (29.5 versus 6.1%, p<0.0001), erythema (70.9 versus 15.1%, p<0.0001), swelling (35.8 versus 8.4%, p<0.0001), pain (22.7 versus 17.2%, p=0.0002)and induration (37.6 versus 11.3%, p<0.0001) were more frequent the ID group compared with IM • majority of cases lasted ≤3 days (1% lasted >3 days) • no significant differences between systemic reactions in the ID group compared to IM • reactogenicity comparable after 2nd season between ID-ID and IM-ID groups however overall rate of injection site reactions appeared higher in the third season for the ID-ID-ID group (71.3%, 95% CI: 69.4–73.2) compared with IM-ID-ID (67.4%, 95% CI: 62.9–71.6) and IM-IM-ID (57.3%, 95% CI: • 50.6–63.8) primarily due to more frequent reports of erythema and swelling • 2 SAEs evaluated as vaccine-related, both in ID group; myopericarditis and facial neuralgia	Level 1	Good

Evidence related to immunogenicity of Intanza®						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Van Damme P, Arnou R, Kafeja F, *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. (22)	Intanza®	Phase III RCT, open-label NCT00554333 Compared to Fluad® (split virion, MF59C.1 adjuvanted, IM)	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	Level 1	Good

Evidence related to immunogenicity of Intanza®						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Beran J, Ambrozaitis A, Laiskonis A, *et al*. Intradermal influenza vaccination of healthy adults using a new microinjection system: a 3-year randomised controlled safety and immunogenicity trial. *BMC Med*. 2009;7:13. 10.1186/1741-7015-7-13.(19)	Intanza® (3, 6, 9 or 15 µg HA per strain)	Phase II RCT (dose ranging study) 3 years (Year 1 3 µg versus 6 µg ID; year 2 9 µg ID versus 15 µg IM; year 3 9 µg ID versus 15 µg IM) NCT00703651 Compared to Vaxigrip®	N=1150 18 to 57 years	• Erythema (74.9% versus 10.3% year 2; 71.6% versus 12.7% year 3), swelling • (44.5% versus 5.5% year 2; 37.6% versus 8.5% year 3), induration (40.3% versus 9.0% in year 2; 40.2% versus 12.5% in year 3) and pruritis (32.2% versus 7.3% in year 2; 30.3% versus 7.8% in year 3) were reported more frequently in the 9 µg ID group compared with 15 µg IM • Incidence of systemic reactions was comparable for the two groups for years 2 and 3 • 1 or 2 previous ID vaccinations • did not increase the reactogenicity to ID vaccination in Year 3 (in comparison with vaccinated with the IM control vaccine in the first 2 years)	Level 1	Good

Evidence related to immunogenicity of Intanza®						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Manuel O, Humar A, Chen MH, *et al*. Immunogenicity and safety of an intradermal boosting strategy for vaccination against influenza in lung transplant recipients. *Am J Transplant*. 2007;7(11):2567-2572.(23)	Vaxigrip® 15 µg IM followed by 3 µg ID (Mantoux method) 4 weeks later	Observational study	N=60 Mean age 47.3 years Adult lung transplant recipients (>3 months post-transplant)	• 63% (38/60) subjects had a response after IM vaccination • GMTs increased for all three vaccine antigens • following the first dose (p<0.001) • No significant increases in titre observed after the booster dose for all three antigens. • Among non-responders, 3/22 (13.6%) additional patients responded after the intradermal booster (p=0.14). • Use of basiliximab was associated with a positive response (p=0.024).	Level II-3	Good Small, uncontrolled observational study

Evidence related to immunogenicity of Intanza®						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Jo YM, Song JY, Hwang IS, *et al*. Dose sparing strategy with intradermal influenza vaccination in patients with solid cancer. *J Med Virol*. 2009;81(4):722-727.(24)	Fluarix® 15 µg IM, 7.5 µg ID (Mantoux method)	RCT	N=113 (n=59 15 µg IM, n=54 7.5 µg ID (Mantoux method) Adults 19 to 64 years with carcinoma of solid organs	• No significant differences between ID and IM route for HI response and the fold increase in titre for A/H1N1, A/H3N2, and B 4 to 6 weeks post-vaccination • seroprotection rates were above 70% against all three influenza strains in both the intradermal and intramuscular groups. Seroprotection rate (15 µg IM versus 7.5 µg ID) H1N1: 94.5% versus 96.1% (p=1.00) H3N2: 98.1% versus 96.1% (p=0.61) B: 81.8% versus 78.8% (p=0.80) Seroconversion rate (15 µg IM versus 7.5 µg ID) H1N1: 74.5% versus 73.0% (p=1.00) H3N2: 43.6% versus 53.8% (p=0.34) B: 67.3% versus 53.8% (p=0.11)	Level I	Good No 7.5 µg IM comparison group

Evidence related to immunogenicity of Intanza®						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Chuaychoo B, Wongsurakiat P, Nana A, *et al*. The immunogenicity of intradermal influenza vaccination in COPD patients. *Vaccine*. 2010;28(24):4045-4051.(25)	TIV (Merieux Biological Products, Thailand) 15 µg IM, 6 µg ID (Mantoux method; half -dose administered in each arm)	RCT, unblinded	N=156 Adults 36 to 91 years Dx of COPD with ratio FEV_1 to FVC of <0.70	• GMTs, seroconversion factors, seroconversion rates and seroprotection rates at 4 weeks post-vaccination were less in the ID group compared to the IM group; however only the seroconversion factor to influenza B in the ID group was statistically significant <u>Seroprotection rate (15 µg IM versus 6 µg ID)</u> H1N1: 93.3% (85.3, 97.1) / 92.6 (84.8, 96.6) H3N2: 88.0% (78.7, 93.6) / 87.7 (78.7, 93.2) B: 72.0% (61.0, 80.9) / 67.9 (57.1, 77.1) <u>Seroconversion rate (15 µg IM versus 6 µg ID)</u> H1N1: 80.0% (69.6, 87.5) / 71.6 (61.0, 80.3) H3N2: 84.0% (74.1, 90.6) / 72.8 (62.3, 81.3) B: 61.3% (50., 71.5) / 56.8 (45.9, 67.0) Each strain of the ID vaccination met all the Committee for Proprietary Medicinal Products (CPMP) criteria	Level I	Fair Unblinded, no single-site ID dose comparison group

Evidence related to immunogenicity of Intanza®						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Gelinck LB, van den Bemt BJ, Marijt WA, *et al*. Intradermal influenza vaccination in immunocompromised patients is immunogenic and feasible. *Vaccine*. 2009;27(18):2469-2474.(26)	TIV (Influvac™) 2005-06 15 µg IM, 3 µg ID (Mantoux method)	RCT, open-label	N=197 Immuno-compromised adults (n=81 HIV, n=50 rheumotologic treated with anti-TNF (tumour necrosis factor), n=26 haematologic stem cell transplantation(HSCT)) + 41 healthy controls	• Post-vaccination titres were similar between ID and IM recipients in all four groups • Overall hierarchy of titres was shown for both ID and IM with healthy controls the highest, followed by those on anti-TNF, HIV and HSCT patients • Injection site reactions after ID less frequent and milder in immunocompromised patients compared to healthy subjects predictive of response to at least one out of three antigens ($p<0.05$)	Level 1	Fair Unblinded

Evidence related to immunogenicity of Intanza®						
STUDY DETAILS					**SUMMARY**	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Morelon E, Noble CP, Daoud S, *et al*. Immunogenicity and safety of intradermal influenza vaccination in renal transplant patients who were non-responders to conventional influenza vaccination. Vaccine. 2010 Oct 4;28(42):6885-90. (27)	Vaxigrip® 2006-07 15 µg IM, Versus Intanza®15 µg ID	Randomized controlled trial nested in a larger descriptive study	N=62 non-responders randomized 1:1 to ID and IM groups Larger study had 201 adults 18 to 60 years (non-responder group was 40 to 56 years)	• GMT and seroprotection rates tended to be higher in the ID group compared with IM; met EMEA criteria with the exception of not having a min. of 50 subjects <u>Seroprotection rate (15 µg IM versus 15 µg ID)</u> H1N1: 52% (33.1, 69.8) / 71% (52.0, 85.8) H3N2: 36% (19.2, 54.6) / 52% (33.1, 69.8) B: 61% (42.2, 78.2) / 71% (52.0, 85.8) <u>Seroconversion rate (15 µg IM versus 15 µg ID)</u> H1N1: 19% (7.5, 37.5) / 35% (19.2, 54.6) H3N2: 19% (7.5, 37.5) / 35% (19.2, 54.6) B: 19% (7.5, 37.5) / 19% (7.5, 37.5) <u>GMT ratio pre/post-vaccination (15 µg IM versus 15 µg ID)</u> H1N1: 1.93 (1.30, 2.88) / 3.09 (2.17, 4.40) H3N2: 2.34 (1.56, 3.51) / 3.50 (2.29, 5.34) B: 1.77 (1.38, 2.27) / 1.96 (1.57, 2.44)	Level I	Fair Small study , unblinded, lack of healthy control group

Table 7: 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 8: 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[1].	

Table 9: 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.

[1] Harris RP, Helfand M, Woolf SH, *et al.* Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev* Med 2001;20:21-35.

List of Abbreviations

BCG	Bacille Calmette-Guérin
CCDR	Canada Communicable Disease Report
CI	Confidence interval
EMEA	European Medicines Evaluation Agency
GBS	Guillain-Barré syndrome
GMT	Geometric mean titre
HA	Haemagglutinin antigen
HI	Haemagglutination inhibition
ID	Intradermal
IgE	Immune globulin E
IM	Intramuscular
mL	Millilitres
mm	Millimetre
NACI	National Advisory Committee on Immunization
ORS	Oculorespiratory syndrome
pH1N1	Pandemic H1N1
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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Footnote

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