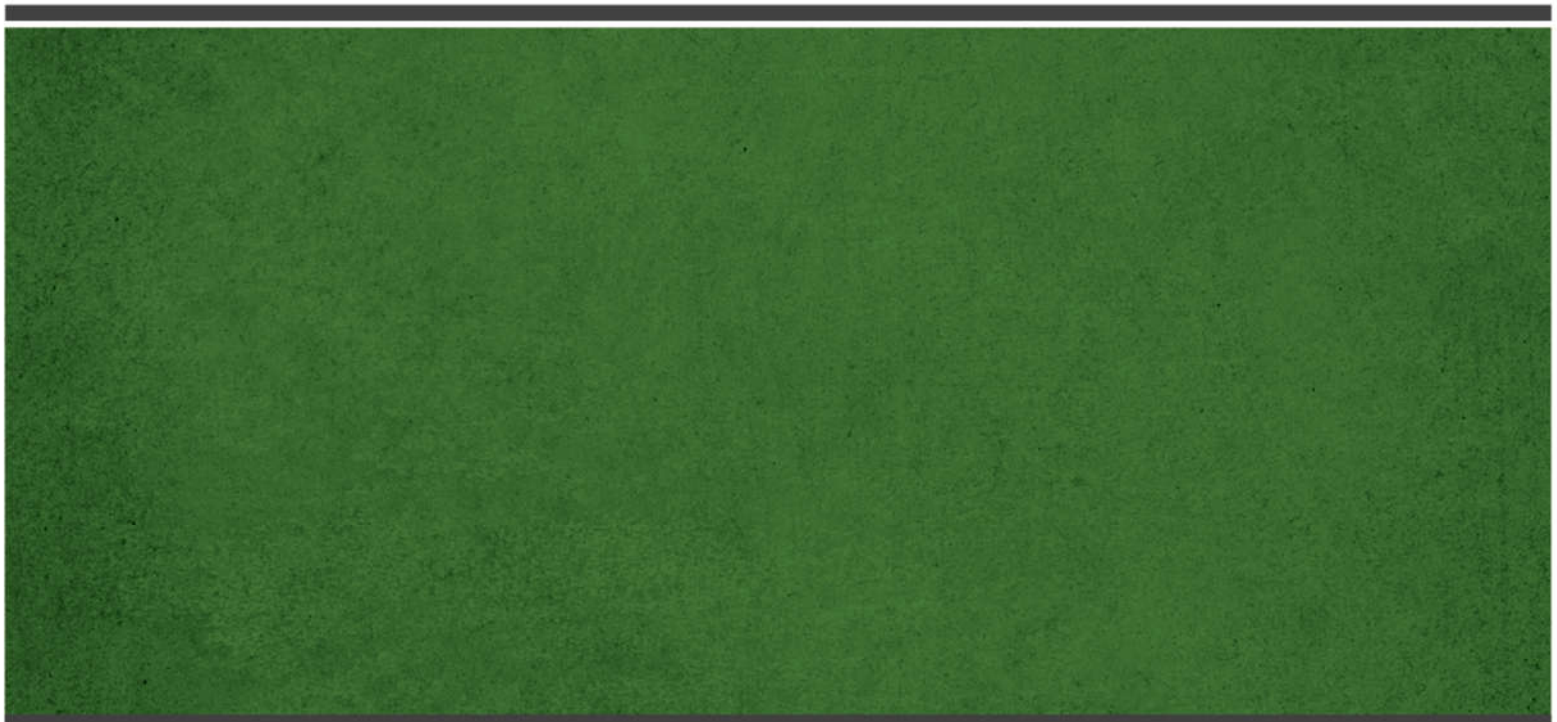
An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

Recommendations on Fractional Influenza Vaccine Dosing



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PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (PHAC) with ongoing and timely medical, scientific, and public health advice relating to immunization.

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

The additional factors to be considered by NACI include: economics, ethics, equity, feasibility, and acceptability. Over the coming years NACI will be refining methodological approaches to include these factors. Not all NACI Statements will require in-depth analyses of all programmatic factors. As NACI works towards full implementation of the expanded mandate, select Statements will include varying degrees of programmatic analyses for public health programs.

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

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SUMMARY OF THE INFORMATION CONTAINED IN THIS NACI SUPPLEMENTAL STATEMENT

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

1. What

Influenza vaccination in Canada is provided annually through provincial and territorial seasonal influenza vaccine programs. Due to the rapid timelines required for vaccine production each year, any significant impact to the manufacturing process may cause delays in influenza vaccine delivery or decrease the overall number of doses produced, potentially resulting in vaccine shortages for a season. A significant and unexpected increase in demand for the influenza vaccine may also lead to insufficient supply, as the number of doses available is based on orders made primarily in the spring months. A strategy for the administration of fractional influenza vaccine doses (i.e., less than a full dose) might be considered in these situations, as the use of fractional doses would provide vaccine programs the ability to vaccinate a larger number of people with the amount of vaccine that is available.

2. Who

This supplemental statement provides an evidence summary and recommendations on the topic of fractional influenza vaccine doses for consideration by public health programs during a significant influenza vaccine shortage.

3. How

In the event of a significant population-level shortage of the currently available influenza vaccine products, NACI recommends that full dose influenza vaccine should continue to be used and existing vaccine supply should be prioritized for those considered to be at high risk or capable of transmitting to those at high risk of influenza-related complications or hospitalizations. NACI recommends against the use of fractional doses of influenza vaccines in any population.

4. Why

There is some, but still insufficient, evidence that fractional doses of influenza vaccine provided via the intramuscular (IM) route are effective and immunogenic in healthy individuals. Although there is some evidence on the use of fractional intradermal (ID) doses in adults $\geq$ 65 years of age, including those with chronic health conditions, that demonstrates that lower doses may be immunogenic in this population, there is no evidence regarding the use of fractional dosing in other adult high-risk groups. Moreover, administering influenza vaccines through the ID route, while using regular syringes, has been determined to not be feasible.

Since many of those at high risk of influenza (e.g., adults 65 years of age and older, individuals with specific underlying chronic health conditions) may have a lower immune response to influenza vaccination already (due to immunosenescence in older adults or a condition that alters

immune function), it is important to ensure that those at high risk continue to receive the full dose of influenza vaccine.

There is fair evidence that fractional doses of influenza vaccine administered via the IM and ID routes do not result in a significant difference with regard to severe systemic adverse events (AEs) post-influenza vaccination; however, ID administration of influenza vaccine will likely result in a higher proportion of individuals who experience local AEs.

There are feasibility issues when considering fractional dosing of current influenza immunizations or administration of ID doses of influenza vaccines. Pre-filled syringes cannot be used for fractional dosing. ID administration of vaccine requires a different gauge needle than IM administration, and training and skill in ID administration that not all vaccinators will have. The volume of vaccine to be administered is high, requiring two ID injections if regular needles and syringes are used. The majority of studies of administration of influenza vaccine by the ID route used micro-needle injectors for administration. The use of fractional doses is not covered within influenza vaccine product monographs and would therefore require a novel communication and consent plan for any off-label dosing if it were adopted. Moreover, implementation of such an ID immunization program would require monitoring for any potential modification to a seasonal influenza vaccine program running low on vaccine supply and thus would be a challenge without significant advanced planning.

I. INTRODUCTION

Influenza is a viral infection that is estimated to cause approximately 12,200 hospitalizations[1] and 3,500 deaths[2] in Canada annually. All provinces and territories in Canada have implemented seasonal influenza vaccination programs, with the aim of reducing morbidity and mortality caused by influenza-associated illness[3]. Although influenza programs vary across the country, all programs cover individuals who are at high risk of severe outcomes due to influenza and individuals that are capable of transmitting influenza to those at high risk (e.g., household members, healthcare workers).

Influenza vaccine for use in publicly funded programs in Canada is coordinated by the federal government's Public Services and Procurement Canada, and vaccine orders are completed in the spring in advance of the next influenza season[4]. The schedule for finalizing influenza vaccine orders is generally consistent for all countries in the Northern Hemisphere, as vaccine manufacturers must follow strict timelines to produce influenza vaccine with the recommended strain composition for the next season. The strain composition for the upcoming Northern Hemisphere season is announced by the World Health Organization annually in February[5]. Significant changes to the amount of influenza vaccine ordered are, therefore, difficult once the influenza season has begun. In addition, unforeseen influenza vaccine production issues or an unexpected increase in demand for influenza vaccine could result in a delay or decrease in vaccine available for Canadians. In the event that a significant shortage of influenza vaccine were to occur in Canada, guidance on appropriate strategies for fractional dosing, or dose sparing, would be needed. However, significant global influenza vaccine shortages are extremely rare, given the variety of influenza vaccine products available on the market, with any issues that do arise typically being isolated to only one vaccine product or manufacturer.

In Canada, influenza vaccines are currently authorized for IM administration only, apart from the live-attenuated influenza vaccine (LAIV), which is administered intranasally[6]. The stated dose of an influenza vaccine is based on the hemagglutinin (HA) content within the vaccine. Standard dose influenza vaccines contain 15 mcg of HA per strain and are delivered in 0.5 mL volume. Therefore, the total amount of HA in standard dose trivalent vaccines is 45 mcg, and the total amount of HA in standard dose quadrivalent vaccines is 60 mcg. Fractional dosing strategies are those where less than the standard amount of HA antigen and thus less volume of vaccine is administered during influenza vaccination, increasing the overall number of doses available. For the purposes of these recommendations, NACI considered two different strategies:

1) Fractional intramuscular (IM) administration of influenza vaccine
2) Fractional intradermal (ID) administration of influenza vaccine

Guidance Objective

The objective of this advisory committee supplemental statement is to review the available evidence for efficacy, effectiveness, immunogenicity, and safety of fractional influenza vaccine dosing, and to provide guidance on potential fractional dosing strategies in the event of a significant influenza vaccine shortage in Canada.

II. METHODS

In brief, the broad stages in the preparation of a NACI Advisory Committee Statement are:

1. Knowledge synthesis - individual studies were retrieved and key data abstracted, and the level (i.e., study design) and quality of the evidence assessed. This information is summarized in Summary of Evidence Tables.
2. Synthesis of the body of evidence of benefits and harms, considering the quality of the evidence and magnitude of effects observed.
3. Translation of evidence into recommendations.

Further information on NACI's evidence-based methods is available in: *Evidence-Based Recommendations for Immunization: Methods of the NACI, January 2009, CCDR*.

In preparation for this Statement, two reviews were conducted to gather evidence to inform NACI's recommendations regarding the use of fractional dosing strategies. The review methodologies were developed in collaboration with the Methods and Applications Group for Indirect Comparisons (MAGIC) through the Drug Safety and Effectiveness Network (DSEN). The methods were specified *a priori* in a written protocol that included the research questions, search strategy, inclusion and exclusion criteria, and quality assessment. The reviews were completed by MAGIC, with additional data extraction (notably immunogenicity outcomes as indirect evidence for effectiveness for IM administration of fractional doses) completed by PHAC.

Research question #1

What is the safety and effectiveness* of using fractional dosing strategies to deliver IM seasonal influenza vaccines?

Research question #2

What is the safety and effectiveness* of using fractional dosing strategies to deliver seasonal influenza vaccine by ID administration?

* Although not explicitly stated in the research questions, immunogenicity evidence was also included in both reviews to supplement efficacy and effectiveness data.

The search strategies were developed based on the research questions and pre-defined PICOST[7,8], in conjunction with an experienced librarian. For both reviews, EMBASE and MEDLINE electronic databases were searched for research articles, with the review of IM studies looking at publications in the last 20 years and the review of ID studies looking at publications in the last 10 years. The Cochrane library, the Cochrane Central Register of Controlled Trials, and international clinical trial registries were also searched for additional studies. Searches were restricted to articles published in English. Additionally, hand-searching of the reference lists of included articles and relevant systematic reviews were performed.

Screening of citations and full-text articles were completed using a standard form based on study eligibility criteria. The forms were pilot-tested between two reviewers until 70% or greater agreement was reached, after which screening was completed by one reviewer.

One reviewer extracted data from the studies included for review into an evidence table using a piloted data abstraction template designed to capture information on study design, vaccine characteristics, population and outcomes of interest. A second reviewer independently validated the abstracted data.

For the review of ID administration of fractional influenza vaccine, the DSEN MAGIC team conducted all data extraction and performed a meta-analysis for effectiveness, immunogenicity, and safety outcomes[8]. The risk of bias for the studies included as part of the ID review was assessed using the Cochrane Tool for Risk of Bias in Randomized Controlled Studies.

For the IM fractional dose review, the DSEN MAGIC team extracted and narratively summarized the data for effectiveness and safety, and provided PHAC with a list of studies that assessed immunogenicity outcomes. PHAC then extracted the immunogenicity data from the studies provided, and summarized the evidence narratively. The level of evidence (i.e., study design) and methodological quality of studies included in the IM review were assessed independently by two reviewers with PHAC using the design-specific criteria outlined by Harris et al.(2001)[9], which has been adopted by NACI for rating the internal validity of individual studies.

Development of Recommendations

Following critical appraisal of individual studies, summary tables (Tables 9, 10, and 11) were prepared with ratings of the quality of the evidence using NACI's methodological hierarchy, and proposed recommendations for vaccine use were developed. The evidence and proposed recommendations were discussed by the NACI Influenza Working Group (IWG) and considered the Ethics, Equity, Feasibility, and Acceptability (EEFA) framework[10]. Following a thorough review of the evidence, NACI approved the recommendation contained in this statement on November 2, 2020. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described in the following sections.

III. FRACTIONAL INFLUENZA VACCINE DOSES

Intramuscular fractional dosing

Thirteen studies were identified through the DSEN MAGIC team review on IM fractional dosing[7], including 5 related reports or trial protocols. Twelve of the studies were randomized controlled trials (RCT), and were assessed as being of good quality, according to the criteria defined by Harris et al. One trial was considered as having a high risk of bias due to significant issues with the randomization process and concerns with missing outcome data and selection of the reported outcomes[11] This trial was later excluded from the PHAC analysis because it did not have any peer-reviewed published results.

Intradermal fractional dosing

The DSEN MAGIC team rapid review on fractional ID influenza vaccination identified 29 studies. Most of the 29 RCTs were rated as having some concerns with bias (n=17), based on the Cochrane Risk of Bias tool for RCTs[12], and two studies (Chuaychoo, 2010 and Han 2013) had a high risk of bias. Issues were most often noted for the randomization process, deviations from the intended intervention, and bias in the selection of reported results[7].

Evidence from the DSEN MAGIC team reviews and additional analyses by PHAC technical staff are presented in Tables 9, 10, and 11.

III.1 Vaccine Efficacy and Effectiveness

III.1.1 Fractional intramuscular dosing

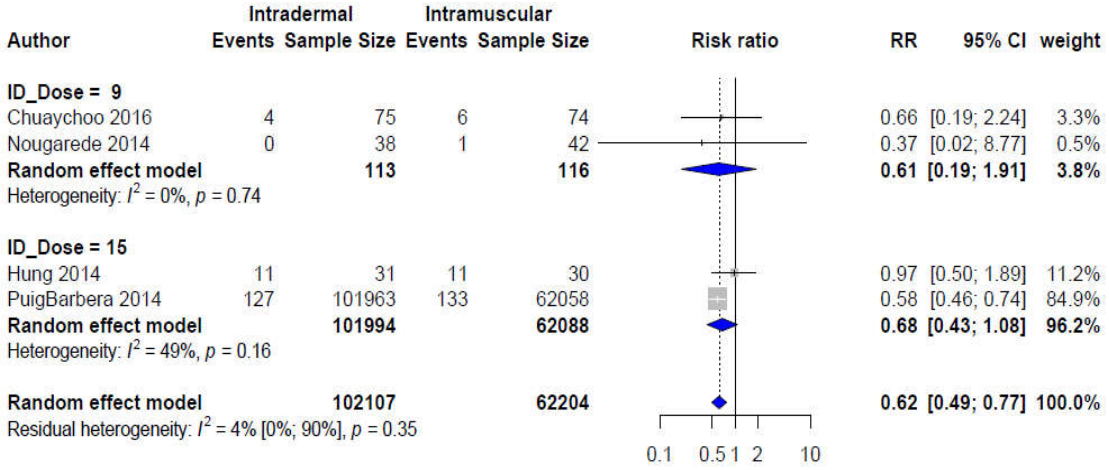
There were no studies included in the rapid review that assessed the efficacy of fractional IM administration of influenza vaccine. Two studies were identified that assessed the effectiveness of fractional IM administration of influenza vaccine[13,14]. Both studies were RCTs that assessed the efficacy of a 7.5 mcg of HA per strain dose of a quadrivalent influenza vaccine versus a 15 mcg of HA per strain dose in adults.

The first study was conducted by Kramer et al. (2006), in a population of adult healthcare workers 18 years of age and older. The study reported on clinical diagnoses of influenza-like illness (ILI) and laboratory-confirmed influenza (type of test not specified). Laboratory testing was only completed for individuals who had a clinical diagnosis of influenza. This RCT study found that 6.8% (n=15 of 222) of individuals who received the half-dose received a clinical diagnosis of ILI compared to 3.6% (n=8 of 222) of those that received the standard 15 mcg of HA per strain dose; however, only one participant in the study (an individual that received the 15 mcg of HA per strain dose) had laboratory-confirmed influenza infection and this difference for the laboratory-confirmed outcome was not statistically significant (relative risk [RR]: 0.53, 95% confidence interval [CI]: 0.23-1.23)[13]. The second study by Engler et al. (2008) assessed the efficacy of a half dose compared to a full dose of influenza vaccine against medical visits for ILI involving the upper and lower respiratory tract, but with no laboratory confirmation, in adults 18 to 49 (n=558) and 50 to 64 years of age (n=556), and there was no statistically significant difference in the relative risk between vaccine groups, before and after adjusting for confounders (18-49 year olds: adjusted RR: 1.01, 95% CI: 0.70-1.46; 50-64 year olds: adjusted RR: 1.07, 95% CI: 0.53-2.18).

III.1.2 Fractional intradermal dosing

Two studies assessed the efficacy of fractional ID administration of influenza vaccine against laboratory-confirmed influenza infection or ILI in adults using trivalent influenza vaccine[15,16]. A meta-analysis of these two studies[8] indicated no significant difference in the risk of influenza infection/ILI from the ID administration of a 9 mcg of HA per strain dose of influenza vaccine compared to 15 mcg of HA per strain IM dose (Figure 1). Note that the figure below also describes the comparison of 15 mcg of HA per strain ID and IM. These data were not used to inform this Statement, as it was not considered a fractional dose.

Figure 1. Risk ratio of influenza infection and/or ILI of ID administration compared to 15 mcg of HA per strain dose IM*



* Figure reproduced from MAGIC report.

III.2 Immunogenicity

The serological assessments of antibody responses to vaccination are based on the geometric mean titres (GMT) assessed using a hemagglutinin inhibition assay (HI). The assessments used by regulators are: GMT ratio, seroprotection rate, and seroconversion rate. The United States (US) Food and Drug Administration (FDA) has published definitions for these serological assessments and define criteria for the immunogenicity data required for influenza vaccine licensure in the US[17] (Table 5). Correlates of protection that are not based on HI antibody titres have not been well established.

III.2.1 Fractional intramuscular dosing

Ten published studies were identified that assessed immunogenicity outcomes for fractional doses of influenza vaccines administered intramuscularly[14, 18-26]. The 10 studies were all RCTs and were considered to be of good quality according to Harris et al. criteria. Of the 10 studies, two were conducted in adults within the range of ages of 18 and 64[14,18] and one was conducted in adults 65 years of age and older[19]. The other seven studies were all conducted in children within the range of 6 to 35 months of age[20-26]. Only one study in adults and four studies in children assessed the difference in immunogenicity between fractional and standard dose IM administration of influenza vaccine statistically.

One study statistically compared the immune response following the IM administration of a fractional dose (7.5 mcg of HA per strain) of influenza vaccine to the standard dose in adults[14]. Engler et al. (2008) reported that the study groups that received a fractional dose of 7.5 mcg of HA per strain had statistically lower proportions of seroconversion and seroprotection post-vaccination when compared to the groups that had received the full dose for all strains. The exception to this was seroprotection against influenza B in the 18 to 49 years of age subgroup and seroconversion for influenza A(H1N1) in the 50 to 64 years of age subgroup, which showed no significant difference between 7.5 mcg of HA per strain and 15 mcg of HA per strain.

Four studies statistically assessed the difference in immunogenicity between a full dose and a half dose of influenza vaccine in children 6 to 35 months of age[21-23,25]. Results from these studies were mixed. Langley et al. (2012) reported no significant difference based on GMT ratios (GMT of full dose/GMT of fractional dose) post-vaccination between the two study groups, and Halasa et al. (2015) found no significant difference in the absolute difference in GMTs. Robertson et al. (2019) reported better GMTs in groups that received the full dose compared to the half dose of influenza vaccine based on GMT ratios (lower limit of 95% CI was greater than 1 for all strains); however, they reported non-significant differences in seroconversion rates between the two study groups for all strains except for influenza A(H1N1) (difference in seroconversion for A(H1N1): 5.1, 95% CI: 0.189 to 10.0). Pavia-Ruz et al. (2013) reported contradictory results, with the group receiving a half dose experiencing higher GMTs and seroconversion rates compared to the group that received the full dose of vaccine, with the exception of influenza B (Yam) with regard to seroconversion rates, for which there was no statistically significant difference between the two groups. In a non-statistical comparison, the group that received 7.5 mcg of HA per strain of Fluarix® appeared to have similar immunogenicity to those that received 15 mcg of HA per strain Fluarix® (i.e., 95% CI were widely overlapping).

Additional studies (one in adults and two in children) that assessed varying fractional doses of influenza vaccine (3 mcg, 6 mcg, 7.5 mcg, and 9 mcg of HA per strain) reported on GMT rise, seroprotection rates, and seroconversion rates for the different study groups, but did not compare them statistically. In general, as the dose of influenza vaccine decreased, the immunogenic response also decreased[20,24,26]; however, most lower doses continued to meet criteria set for non-inferiority, despite the reduced response compared to full dose (according to current US FDA or previous European Medicines Agency criteria).

III.2.2 Fractional intradermal dosing

Of the thirty studies identified in the rapid review, 16 studies assessed immunogenicity outcomes for fractional doses of influenza vaccine administered intradermally[15,16,19,27-39], all of which were RCTs.

A meta-analysis[8] demonstrated no significant difference in the seroconversion rate for the study groups that had received fractionated doses (3 mcg, 6 mcg, 7.5 mcg or 9 mcg of HA per strain) by ID administration compared to 15 mcg of HA per strain dose given intramuscularly for influenza A(H1N1), A(H3N2), or B (Table 1).

A meta-analysis was also performed for seroprotection rates compared to a full 15 mcg of HA per strain per IM dose, and found no significant difference in seroprotection rates against influenza A(H1N1), A(H3N2), or B for groups that had received ID administration of influenza vaccine at doses of 3 mcg of HA per strain, 7.5 mcg of HA per strain, or 9 mcg of HA per strain (Table 1). However, rates of seroprotection were significantly lower for those that had received a dose of 6

mcg of HA per strain for influenza A(H1N1) (risk ratio [RR]: 0.93, 95% confidence interval [CI]: 0.88-0.99) and influenza B (RR: 0.92, 95% CI: 0.86-0.98) compared to the full IM dose.

A further sub-analysis was performed by the DSEN MAGIC team to assess immunogenicity in adults 60 years of age and older. The only fractional ID dose assessed by the studies that had sufficient data for inclusion in the sub-analysis was 9 mcg of HA per strain dose[19,29,30]. Similar to the overall results, there was no significant difference in seroconversion or seroprotection rates between older adults that had received the fractional 9 mcg of HA per strain ID dose compared to those that received the full, 15 mcg of HA per strain IM dose (Table 2).

Table 1. Risk ratios of seroconversion and seroprotection rates for ID compared to standard dose of IM administration**

	ID Dose vs. 15mcg IM	Number of Studies	Risk Ratio [95% CI]	I^2
Seroconversion H1N1	3 mcg	2	1.77 [0.43-7.28]	82.6
	6 mcg	3	1.00 [0.78-1.28]	87.7
	7.5 mcg	3	1.01 [0.80-1.28]	0
	9 mcg	10	1.02 [0.93-1.12]	59
Seroconversion H3N2	3 mcg	2	1.14 [0.56-2.31]	81.3
	6 mcg	3	0.98 [0.97-1.00]	0
	7.5 mcg	3	0.92 [0.63-1.33]	63.8
	9 mcg	11	1.01 [0.95-1.06]	38
Seroconversion B Strain	3 mcg	2	1.46 [0.67-1.99]	53.5
	6 mcg	3	0.95 [0.68-1.32]	88.3
	7.5 mcg	3	1.21 [0.79-1.85]	43.9
	9 mcg	11	0.95 [0.84-1.08]	57.1
Seroprotection H1N1	3 mcg	3	1.00 [0.78-1.28]	87.7
	6 mcg	3	0.93 [0.88-0.99]	37.5
	7.5 mcg	3	1.07 [1.01-1.12]	0
	9 mcg	12	1.00 [0.98-1.03]	33
Seroprotection H3N2	3 mcg	3	0.98 [0.97-1.00]	0
	6 mcg	3	1.00 [0.99-1.01]	0
	7.5 mcg	3	1.01 [0.96-1.06]	36.6
	9 mcg	12	1.00 [0.99-1.00]	0
Seroprotection B Strain	3 mcg	3	0.95 [0.68-1.32]	88.3
	6 mcg	3	0.92 [0.86-0.98]	0
	7.5 mcg	3	1.13 [0.78-1.66]	58.2
	9 mcg	12	0.99 [0.95-1.03]	50

Outcome significantly higher with ID administration
No significant difference in outcome between ID and IM administration
Outcome significantly lower with ID administration

** Table reproduced from MAGIC report with modifications.

Table 2. Risk ratios of seroconversion and seroprotection rates for ID compared to standard dose of IM administration in adults 60 years of age and older **

	ID Dose vs. 15 mcg IM	Number of Studies Pooled	Risk Ratio [95% CI]	I^2
Seroconversion H1N1	9 mcg	2	1.01 [0.58-1.77]	87
Seroconversion H3N2	9 mcg	2	1.02 [0.83-1.25]	0
Seroconversion B	9 mcg	2	1.00 [0.60-1.67]	0
Seroprotection H1N1	9 mcg	4	0.98 [0.88-1.09]	24.1
Seroprotection H3N2	9 mcg	4	1.03 [0.94-1.12]	0
Seroprotection B	9 mcg	4	0.95 [0.71-1.27]	0

Outcome significantly higher with ID administration
No significant difference in outcome between ID and IM administration
Outcome significantly lower with ID administration

** Table reproduced from MAGIC report with modifications.

III.3 Safety

III.3.1 Adverse Events with IM administration

Children

The rapid review found 9 studies that assessed safety outcomes (local, systemic, and severe AEs) of fractional IM influenza vaccine (IIV3: 5 studies, IIV4: 3 studies, IIV3 and IIV4: 1 study) in infants or toddlers in the range of 6 to 36 months of age[20-26]. Children that received one or two half doses (7.5 mcg of HA per strain) of influenza vaccine (dependent on whether they had ever received an influenza vaccine previously) generally reported similar levels of reactogenicity and AEs when compared to those that received one or two standard doses. In some instances, AEs appeared to be slightly more common with the full dose of influenza vaccine compared to the half dose, however there was no consistent trend.

Adults

Three studies were identified in the rapid review that assessed safety of fractional IM influenza vaccination in adults: 2 of the studies involved adults between the ages of 18 to 64 (18 to 49 and 18 to 65)[14, 18] and one study included older adults >65 years of age[19]. Belshe et al. (2008) reported no differences in the occurrence of AEs between any of the study groups (doses assessed: 3 mcg, 6 mcg, 9 mcg, and 15 mcg of HA per strain)[18]. The other study, by Engler et al. (2008), that assessed safety in adults less than 65 years of age also found no statistically significant difference in the occurrence of AEs after adjusting to only include clinically significant pain levels ($\geq$ 3 out of 5 using a visual analog scale)[14]. The study conducted in older adults found no significant difference in the proportion of individuals that experienced AEs or in the severity of the AEs between the group that received the fractional dose (9 mcg of HA per strain) and the group that received the full standard dose[19].

III.3.2 Adverse events associated with ID administration

Twenty-four studies were identified that assessed the safety of ID administration of influenza vaccine and were able to be included in a meta-analysis performed by the DSEN MAGIC

team[15,16,19,27-31,33-37,39-49]. The studies identified included various fractional doses (3 mcg, 6 mcg, 9 mcg of HA per strain), as well as a full non-fractional dose (i.e. 15 mcg of HA per strain) of ID administered influenza vaccine. Because ID administration of influenza vaccine is not authorized in Canada, there is a lack of data not only for ID administration of fractional doses, but of the full, non-fractional dose as well. Since the safety of ID administration of a full dose of influenza vaccine is likely comparable to that of fractional doses, evidence regarding safety for the full non-fractional dose was also considered to enhance the evidence base for this outcome.

Overall, the risk of ecchymosis, erythema, pruritus, and swelling occurring post-vaccination at the injection site was significantly higher with ID administration of influenza vaccine compared to IM administration. However, the risk of pain at the injection site was not significantly different for ID administration of 6 mcg, 9 mcg and 15 mcg of HA per strain compared to administration of 15 mcg per strain IM; whereas the risk of pain after the ID administration of a 3 mcg of HA per strain dose was significantly lower (Table 3). Unlike with local AEs, there was in general no significant difference in the risk of systemic events with ID influenza vaccine administration compared to IM administration, with the exception of chills and fever which were higher for ID administration but only at the 9 mcg per strain dose level and not at the lower or higher dose levels (Table 4).

Table 3. Risk of Local Adverse Events with ID compared to IM administration**

	ID Dose vs 15 mcg IM	Number of Studies Pooled	Risk Ratio [95% CI]	I^2
Ecchymosis	9 mcg	7	1.67 [1.12-2.48]	55
	15 mcg	9	1.06 [0.73-1.57]	0
Erythema	3 mcg	3	9.62 [1.07-86.56]	97.2
	6 mcg	2	23.79 [14.42-39.23]	0
	9 mcg	14	4.56 [3.05-6.82]	93.9
	15 mcg	16	3.68 [3.19-4.25]	8.8
Induration	9 mcg	5	3.27 [1.65-6.46]	95.4
	15 mcg	9	2.98 [2.32-3.84]	42.6
Pain	3 mcg	4	0.34 [0.20-0.56]	21.9
	6 mcg	2	0.98 [0.38-2.49]	68.3
	9 mcg	12	0.95 [0.86-1.05]	34.4
	15 mcg	16	0.94 [0.72-1.21]	61.3
Pruritus	6 mcg	2	15.22 [4.77-48.54]	0
	9 mcg	9	4.24 [3.16-5.70]	56.2
	15 mcg	6	4.01 [3.13-5.15]	0
Swelling	3 mcg	2	20.16 [4.68-86.82]	51.3
	9 mcg	13	5.23 [3.58-7.62]	84.4
	15 mcg	12	3.47 [2.21-5.45]	71.9

AE significantly lower with ID administration
No significant difference between ID and IM
AE significantly higher with ID administration

** Table reproduced from MAGIC report with modifications.

Table 4. Risks of Systemic Adverse Events with ID compared to IM administration**

	ID Dose vs 15 mcg IM	Number of Studies Pooled	Risk Ratio [95% CI]	I^2
Arthralgia	15 mcg	3	1.17 [0.39-3.53]	22.7
Chills and shivering	9 mcg	7	1.24 [1.03-1.50]	0
	15 mcg	10	1.08 [0.78-1.51]	0
Fever	6 mcg	2	0.54 [0.17-1.71]	34.5
	9 mcg	11	1.36 [1.03-1.80]	0
	15 mcg	13	0.89 [0.59-1.34]	0
Headache	3 mcg	2	1.09 [0.86-1.37]	0
	6 mcg	2	0.83 [0.39-1.78]	68
	9 mcg	13	1.03 [0.96-1.11]	0
	15 mcg	9	1.16 [0.94-1.45]	0
Malaise	9 mcg	7	1.05 [0.94-1.20]	7.1
	15 mcg	14	0.97 [0.78-1.22]	0
Myalgia	9 mcg	12	1.24 [0.93-1.65]	74.8
	15 mcg	9	0.84 [0.63-1.12]	29.4
Nausea	9 mcg	3	0.93 [0.37-2.31]	0
	15 mcg	2	1.05 [0.33-3.33]	0

AE significantly lower with ID administration
No significant difference between ID and IM
AE significantly higher with ID administration

** Table reproduced from MAGIC report with modifications.

IV. FEASIBILITY

An assessment of EEFA of influenza vaccine fractional dosing strategies was conducted according to established NACI methods[10]. The assessment of feasibility in particular identified several significant issues that warrant further discussion within the Statement.

Logistics for fractional dosing strategies

Both fractional dosing strategies (IM and ID) assessed in this Statement would require using influenza vaccine that has been packaged in the format and of an antigen concentration authorized for use in Canada. Therefore, administering a fractional dose would require administering a lower volume of vaccine to achieve the desired lower dose, which is only possible when influenza immunizations have been packaged as multi-dose vials (MDV), and not as pre-filled syringes. A significant proportion of the influenza vaccine supply purchased for public programs is in MDV format; however, the distribution of MDV of influenza vaccine may not be equal across jurisdictions, and varies between provinces, based on provincial vaccine orders. When vaccine has already been ordered in a given season, there is not typically the opportunity to change the supply to MDV mid-season.

Using standard doses, MDVs contain 5 mL of vaccine solution, sufficient to vaccinate 10 individuals. The volume of vaccine for some fractional doses (e.g., 9 mcg of HA per strain is 0.3 mL), would not split evenly from 5 mL vials. Therefore, using fractional doses that do not divide evenly into 5 mL could result in unnecessary vaccine wastage, which would not allow for the full advantage of implementing fractional dosing as a dose sparing strategy. A half dose of influenza vaccine (7.5 mcg of HA per strain) is likely the most feasible fractional dose for influenza vaccine programs, regardless of route of administration, as this dose could allow the full use of the vial without wastage.

ID administration of vaccine requires a different needle gauge than IM administration. Most immunization venues providing influenza vaccines are unlikely to be equipped with a sufficient number of needles necessary for ID administration for the seasonal influenza vaccine program. Depending on the syringe used, different volumes may be more clearly marked (e.g., 0.5 mL, 0.25 mL). Therefore, fractional doses that require a vaccine volume that is not as clearly marked on the syringe may be more difficult to measure accurately in a vaccination setting, leading to variation in the amount of vaccine administered.

Intradermal administration of influenza vaccine

In addition to the logistical considerations above, the ID administration of fractional doses has further implementation issues.

ID administration requires skill to administer the vaccine correctly. Influenza vaccines in Canada are only authorized for IM administration or nasal spray in the case of LAIV. As such, many influenza vaccinators may be unfamiliar with the requisite technique for ID administration. Inexperience could lead to vaccine administration errors or wasted vaccine product. ID administration also requires creation of an ID wheal or “bleb” and it can be more difficult to perform in older adults, which may slow down the immunization process. As shown in Section III.4.2, ID administration is also associated with a significant increase in local adverse reactions across almost all fractionated dose levels, which could reduce uptake of the vaccine. ID administration by needle and syringe may also require 2 or more injections to administer the full dose, further

exacerbating the issues with ID. A needle-free jet injector has been authorized for use in Canada for ID injections[50]. NACI is actively reviewing the evidence on the use of this device to determine if it could potentially be used as an alternative method for administering ID vaccine. Novel technologies for ID injection, such as the needle-free jet injector, may be an option in the future that would facilitate delivery of ID dosing but are not yet widely available in Canadian settings.

Since fractional influenza vaccines doses are considered off-label for all ages, discussion with the patient and additional information in the vaccination consent form would be required. Finally, given that ID is not an authorized route of administration for influenza vaccine, many immunization registries/surveillance systems do not currently have the capacity to input ID as the route of administration, and would therefore require system-level changes before being able to effectively implement ID administration of influenza vaccine. This option would need to be added to these systems in advance of implementing ID administration to ensure the ability to evaluate the safety and effectiveness of ID administration of influenza vaccine.

V. RECOMMENDATION

The following section outlines recommendations made by NACI regarding potential fractional influenza vaccine dosing strategies. Additional information on the strength of NACI recommendations and the grading of evidence is available in Table 6.

The following recommendations are meant to be considered in situations of influenza vaccine shortage when it is not possible to procure additional vaccine doses. Policies regarding fractional dosing strategies should be implemented at a jurisdictional level, and vaccination should be consistent with the policy and not subject to individual preference. All recommendations should be considered in the context of a given shortage situation. The extent of the shortage and its potential impact will need to be assessed prior to deciding on the best course of action.

V.1 Public Health Program Decision-Making

1. NACI recommends that, in the event of a significant population-level shortage of influenza vaccine, a full dose influenza vaccine should continue to be used, and existing vaccine supply should be prioritized for those considered to be at high risk or capable of transmitting to those at high risk* of influenza-related complications or hospitalizations (Strong NACI Recommendation).

- NACI concludes that there is fair evidence to recommend the use of a full dose influenza vaccine (15 mcg or 60 mcg HA per strain, dependent on vaccine product) compared to a fractional dose for individuals at high risk or those capable of transmitting to those at high risk of influenza-related complications or hospitalizations (Grade B Evidence).

*A full list of people considered to be at high risk or capable of transmitting to those at high risk of influenza-related complications or hospitalizations is available in the Annual NACI Statement on Seasonal Influenza Vaccine (Refer to List 1 therein).

Summary of Evidence and Rationale

- Influenza vaccine has previously been shown to be effective in the prevention of morbidity and mortality in individuals who are at high risk of influenza-related complications and hospitalizations.

- Since many of those at high risk of influenza (e.g., older adults, immunocompromised individuals) may have a lower response to influenza vaccination already (due to immunosenescence in older adults or other conditions that alter immune function), it is important to ensure this group continues to receive the full dose of influenza vaccine.

- Although there is some limited evidence on the use of fractional ID doses in adults ≥ 65 years of age, including those with chronic health conditions, there is no evidence of fractional dosing in other adult high risk-groups.

- There are some efficacy, effectiveness, and immunogenicity data regarding fractional dosing of current influenza vaccine products, but overall insufficient evidence that fractional doses of influenza vaccine provided via IM or ID are effective in healthy individuals. The majority of the evidence identified on fractional dosing is from studies

conducted in healthy individuals, particularly in infants and young children, with no underlying chronic conditions.

2. NACI recommends against the use of fractional doses of influenza vaccine in any population (Discretionary NACI Recommendation)

- NACI concludes that there is insufficient overall evidence at this time to recommend the use of fractional IM influenza vaccine doses (Grade I Evidence)
- NACI concludes that there is fair evidence that fractional ID influenza vaccine doses provide a sufficient immune response, but this route of administration is not feasible at this time (Grade B Evidence)

Summary of Evidence and Rationale

- There are some efficacy, effectiveness, and immunogenicity data regarding fractional dosing of current influenza vaccine products, but overall, there is insufficient evidence that fractional doses of influenza vaccine provided via the IM route is effective in healthy individuals. The majority of the evidence identified on fractional dosing is from studies conducted in healthy individuals, mainly young children and infants, with no underlying chronic conditions.

- ID administration of influenza vaccine may be more effective at lower doses than IM and would be reasonable to recommend based on efficacy, effectiveness, immunogenicity, and safety data; however, significant system-level changes are needed to address the feasibility issues associated with this route of administration before it can be considered at a large scale.

- With regard to the safety of fractional doses of influenza vaccines, there is fair evidence that fractional doses of influenza vaccine administered via IM or ID routes do not result in significant differences compared to full dose with regard to severe AEs post-influenza vaccination; however, ID administration of influenza vaccine will likely result in a higher proportion of individuals who experience local AEs.

- Pre-filled syringes cannot be used for IM or ID fractional dosing.

- ID administration of vaccine by syringe and needle requires a different gauge needle than IM administration. Therefore, immunization venues providing influenza vaccines may not be equipped with a sufficient number of needles necessary for ID administration for a seasonal influenza vaccine program unless prepared in advance.

- Significant training would be required to ensure vaccinators are equipped to provide ID influenza vaccinations and feel comfortable doing so. Without training, it is possible that a greater number of vaccine administration errors could occur with ID administration.

- Not all vaccinators are authorized to provide ID administration. The number of vaccinators who are able to provide ID vaccination will vary by jurisdiction.

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TABLES

Table 5. Serological Assay Definitions and Thresholds for Protection Specified by the United States Food and Drug Administration[19]

Serological assay	Definition	Threshold
GMT ratio	Ratio of GMT post-vaccination of licensed vaccine to GMT post-vaccination of new vaccine	Non-inferiority: The upper bound of the two-sided 95% CI on the ratio of the GMTs should not exceed 1.5.
Seroprotection	Proportion of subjects achieving an HI titre of ≥1:40 post-vaccination	Placebo-controlled: Lower limit of the two-sided 95% CI for the percent of subjects achieving seroprotection should meet or exceed 70% (for adults <65 and children) or 60% (for adults ≥65)
Seroconversion	Proportion of subjects achieving an increase from ≤1:10 HI titre pre-vaccination to ≥1:40 post-vaccination or achieving at least four-fold rise in HI titres	Non-inferiority: Upper limit of the two-sided 95% CI on the difference between the seroconversion rates (rate of licensed vaccine – rate of new vaccine) should not exceed 10 percentage points. Placebo-controlled: Lower limit of the two-sided 95% CI for the percent of subjects achieving seroprotection should meet or exceed 40% (for adults <65 and children) or 30% (for adults ≥65)

Abbreviations: CI: confidence interval, GMT: geometric mean titre, HI: hemagglutination inhibition

Table 6. NACI Recommendations: Strength of Recommendation and Grade of Evidence

STRENGTH OF NACI RECOMMENDATION	GRADE OF EVIDENCE
Based on factors not isolated to strength of evidence (e.g., public health need)	***Based on assessment of the body of evidence***
Strong "*should/should not be* offered" ➢ Known/Anticipated advantages outweigh known/anticipated disadvantages ("should"), OR Known/Anticipated disadvantages outweigh known/anticipated advantages ("should not") ➢ Implication: A strong recommendation applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present	A - *good evidence* to recommend
	B – *fair evidence* to recommend
	C – *conflicting evidence*, however other factors may influence decision-making
	D – *fair evidence* to recommend against
	E – *good evidence* to recommend against
	I – *insufficient evidence* (in quality or quantity), however other factors may influence decision-making
Discretionary "*may be* considered" ➢ Known/Anticipated advantages closely balanced with known/anticipated disadvantages, OR uncertainty in the evidence of advantages and disadvantages exists ➢ Implication: A discretionary recommendation may be considered for some populations/individuals in some circumstances. Alternative approaches may be reasonable	A - *good evidence* to recommend
	B – *fair evidence* to recommend
	C – *conflicting evidence*, however other factors may influence decision-making
	D – *fair evidence* to recommend against
	E – *good evidence* to recommend against
	I – *insufficient evidence* (in quality or quantity), however other factors may influence decision-making

Table 7. Ranking Individual Studies: Levels of Evidence Based on Research Design

Level	Description
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. Ranking Individual Studies: Quality (internal validity) Rating of Evidence

Quality Rating	Description
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 RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, Atkins D. Current methods of the US Preventive Services Task Force: A review of the process. Am J Prev Med. 2001;20(3):21-35.[9]

Table 9. Summary of Evidence Related to the Comparative Efficacy and Effectiveness of Fractional vs Full-dose Influenza Vaccine for IM and ID

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Intramuscular						
Kramer JS, Durham C, Schroeder T, Garrelts JC. *Effectiveness of half-dose versus full-dose influenza vaccine in health care workers*. American journal of health-system pharmacy. 2006 Nov 1;63(21):2111-5.	IIV3 (Fluzone) Doses: 7.5 mcg 15 mcg	RCT US single site 2004–2005 influenza season No funding declared	Healthy adults ≥18 years of age 7.5 group: n=222 15 group: n=222	Study participants self-reported their physician's diagnosis of influenza to the study investigators, who then attempted to obtain laboratory confirmation of the physician's diagnosis. There was no difference between the full-dose (15 mcg) and half-dose (7.5 mcg) groups in clinical diagnosis of influenza (4% versus 7%; p = 0.198; relative risk = 0.53 [95% CI 0.23–1.23]). Of those that had a clinical diagnosis of influenza, none of the participants who received 7.5 mcg dose had laboratory-confirmed influenza, and one of the participants who received 15 mcg dose had laboratory-confirmed influenza (13%).	I	Good
Engler RJ, Nelson MR, Klote MM, VanRaden MJ, Huang CY, Cox NJ, Klimov A, Keitel WA, Nichol KL, Carr WW, Treanor JJ. *Half-vs full-dose trivalent inactivated influenza vaccine (2004-2005): age, dose, and sex effects on immune responses.* Archives of internal medicine. 2008 Dec 8;168(22):2405-14.	IIV3 (Fluzone) Doses: 7.5 mcg 15 mcg	RCT US multi-center 2004-2005 influenza season This study was supported by the Office of the Army Surgeon General in collaboration with Walter Reed Army	Healthy adults 18–64 years of age 18–49 year old subgroup: Mean age: 42.3 44.3% female 7.5 mcg group: n=284 15 mcg group: n= 274 50–64 year old subgroup: Mean age: 55.6 42.6% female	Relative risk of 1 or more medical visits for ILI involving the upper or lower respiratory tract: Age group | Relative risk (95% CI) 18-49 | 1.01 (0.70-1.46) 50-64 | 1.07 (0.53-2.18)	I	Good

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
		Medical Center and Healthcare System; the North Atlantic Regional Medical Command; the US Army Medical Research and Materiel Command; the NIAID, the NIH, and the US CDC	7.5 mcg group: n=276 15 mcg group: n= 280			
Intradermal						
Oluwaseun Egunsola, John Taplin, Liza Mastikhina, Joyce Li, Diane Lorenzetti, Laura E. Dowsett, Tom Noseworthy, Fiona Clement. Intradermal versus intramuscular administration of influenza vaccination. University of Calgary, Health Technology Assessment Unit. Produced for DSEN MAGIC Team. July 21, 2020.	Seasonal inactivated influenza vaccine	Rapid review and meta-analysis Random effects model Included: RCTs, non-RCTs, observational studies Funding: Canadian Institute for Health Research (DSEN)	Number of participants (RCTs): 13,759 Number of participants (observational): 164,021 Age range: all ages Sub-analysis: 60 years of age and older	Primary findings: Meta-analysis included a total of 2 RCTs (no observational studies) on the effectiveness of a 9 mcg of HA per strain fractional dose of ID influenza vaccine. Refer to the ID Dose = 9 portion of figure 1 within this statement for results on the effectiveness of 9 mcg of HA per strain ID dosing in adults against influenza infection and ILI. Effectiveness estimates for influenza infection and ILI were combined in this analysis.	Meta-analysis	N/A

Abbreviations: CI: confidence interval, IIV3: trivalent inactivated influenza vaccine, RCT: randomized controlled trial

Table 10. Summary of Evidence Related to the Comparative Immunogenicity of Fractional vs Full-dose Influenza Vaccine for IM and ID

<table>
<tr><th colspan="5">STUDY DETAILS</th><th colspan="2">SUMMARY</th></tr>
<tr><th>Study</th><th>Vaccine</th><th>Study Design</th><th>Participants</th><th>Summary of Key Findings</th><th>Level of Evidence</th><th>Quality</th></tr>
<tr><td colspan="7">Intramuscular</td></tr>
<tr><td>Belshe RB, Newman FK, Wilkins K, Graham IL, Babusis E, Ewell M, Frey SE. Comparative immunogenicity of trivalent influenza vaccine administered by intradermal or intramuscular route in healthy adults. Vaccine. 2007 Sep 17;25(37-38):6755-63.</td><td>IIV3
(Fluzone)

Doses:
3 mcg
6 mcg
9 mcg
15 mcg</td><td>RCT

US
single site

2006-2007 influenza season

Funding provided by N01-AI-25464.</td><td>Healthy adults 18–49 years of age

mean age: 30
68% female

3mcg group:
n=29

6mcg group:
n=30

9mcg:
n=32

15mcg:
n=31</td><td>Proportion that achieved seroconversion 28 days post-vaccination:
<table><tr><th rowspan="2">Strain</th><th colspan="4">Proportion that achieved seroconversion (95% CI)</th></tr><tr><th>3mcg</th><th>6mcg</th><th>9mcg</th><th>15mcg</th></tr><tr><td>A(H1N1)</td><td>62.1 (42.3-79.3)</td><td>60.0 (40.6-77.3)</td><td>66.7 (47.2-82.7)</td><td>67.7 (48.6-83.3)</td></tr><tr><td>A(H3N2)</td><td>58.6 (38.9-76.5)</td><td>60.0 (40.6-77.3)</td><td>90.0 (73.5-97.9)</td><td>93.5 (78.6-99.2)</td></tr><tr><td>B</td><td>51.7 (32.5-70.6)</td><td>70.0 (50.6-85.3)</td><td>66.7 (47.2-82.7)</td><td>67.7 (48.6-83.3)</td></tr></table>
Proportion that achieved seroprotection 28 days post-vaccination:
<table><tr><th rowspan="2">Strain</th><th colspan="4">Proportion that achieved seroprotection (95% CI)</th></tr><tr><th>3mcg</th><th>6mcg</th><th>9mcg</th><th>15mcg</th></tr><tr><td>A(H1N1)</td><td>72.4 (52.8-87.3)</td><td>80 (61.4-92.3)</td><td>83.3 (65.3-94.4)</td><td>77.4 (58.9-90.4)</td></tr><tr><td>A(H3N2)</td><td>79.3 (60.3-92.0)</td><td>80 (61.4-92.3)</td><td>93.3 (77.9-99.2)</td><td>100 (88.8-100)</td></tr><tr><td>B</td><td>89.7 (72.6-97.8)</td><td>86.7 (69.3-96.2)</td><td>93.3 (77.9-99.2)</td><td>90.3 (74.2-98.0)</td></tr></table></td><td>I</td><td>Good</td></tr>
<tr><td>Engler RJ, Nelson MR, Klote MM, VanRaden MJ, Huang CY, Cox NJ, Klimov A, Keitel WA, Nichol KL, Carr WW, Treanor JJ. Half-vs full-dose trivalent inactivated influenza vaccine (2004-2005): age, dose, and sex effects on immune responses. Archives of internal medicine. 2008 Dec 8;168(22):2405-14.</td><td>IIV3
(Fluzone)

Doses:
7.5 mcg
15 mcg</td><td>RCT

US
multi-center

2004-2005 influenza season

This study was supported by the Office of</td><td>Healthy adults 18–64 years of age

18–49 year old subgroup:
Mean age: 42.3
44.3% female

7.5 mcg group: n=284
15 mcg group: n= 274

50–64 year old subgroup:</td><td>Difference in proportions (% in 15 mcg group - % in 7.5 mcg group) that achieved seroconversion 21 days post-vaccination in 18-49 year old age group:
<table><tr><th>Strain</th><th>Difference in seroconversion (95% CI)</th><th>p value</th></tr><tr><td>A(H1N1)</td><td>6.6 (1.0-12.2)</td><td>0.02</td></tr><tr><td>A(H3N2)</td><td>8.4 (0.5-16.2)</td><td>0.04</td></tr><tr><td>B</td><td>1.27 (1.08-1.50)</td><td>0.002</td></tr></table>
Difference in proportions that achieved seroconversion 21 days post-vaccination in 50-64 year old age group:</td><td>I</td><td>Good</td></tr>
</table>

<table>
<tr><th colspan="4">STUDY DETAILS</th><th colspan="2">SUMMARY</th></tr>
<tr><th>Study</th><th>Vaccine</th><th>Study Design</th><th>Participants</th><th>Summary of Key Findings</th><th>Level of Evidence</th><th>Quality</th></tr>
<tr><td></td><td></td><td>the Army Surgeon General in collaboration with Walter Reed Army Medical Center and Healthcare System; the North Atlantic Regional Medical Command; the US Army Medical Research and Materiel Command; the NIAID, the NIH, and the US CDC</td><td>Mean age: 55.6
42.6% female

7.5 mcg group: n=276
15 mcg group: n= 280</td><td>
<table>
<tr><th>Strain</th><th>Difference in seroconversion (95% CI)</th><th>p value</th></tr>
<tr><td>A(H1N1)</td><td>4.8 (-0.8-10.5)</td><td>0.09</td></tr>
<tr><td>A(H3N2)</td><td>12.9 (5.2-20.5)</td><td>0.001</td></tr>
<tr><td>B</td><td>14.6 (6.8-22.5)</td><td><0.001</td></tr>
</table>
Difference in proportions that achieved seroprotection 21 days post-vaccination in 18-49 year old age group:
<table>
<tr><th>Strain</th><th>Difference in seroprotection (95% CI)</th><th>p value</th></tr>
<tr><td>A(H1N1)</td><td>11.8 (3.5-20.0)</td><td>0.005</td></tr>
<tr><td>A(H3N2)</td><td>8.3 (0.8-15.8)</td><td>0.03</td></tr>
<tr><td>B</td><td>5.0 (-1.6-11.7)</td><td>0.19</td></tr>
</table>
Difference in proportions that achieved seroprotection 21 days post-vaccination in 50-64 year old age group:
<table>
<tr><th>Strain</th><th>Difference in seroprotection (95% CI)</th><th>p value</th></tr>
<tr><td>A(H1N1)</td><td>15.7 (8.1-23.4)</td><td><0.001</td></tr>
<tr><td>A(H3N2)</td><td>9.5 (1.7-17.2)</td><td>0.02</td></tr>
<tr><td>B</td><td>8.8 (0.9-16.6)</td><td>0.03</td></tr>
</table>
</td><td></td><td></td></tr>
<tr><td>Chi RC, Rock MT, Neuzil KM.
Immunogenicity and safety of intradermal influenza vaccination in healthy older adults. Clinical infectious diseases. 2010 May 15;50(10):1331-8.</td><td>IIV3 (Fluzone)

Doses:
9 mcg
15 mcg</td><td>RCT

US

2007-2008 influenza season

Funded by PATH</td><td>Adults ≥65 year of age, excluding those with serious or unstable conditions

9 mcg group: n=64
17.2% female
Mean age: 75.2

15 mcg group: n=65</td><td>Proportion that achieved seroprotection 4 weeks post-vaccination:
<table>
<tr><th rowspan="2">Strain</th><th colspan="2">Number that achieved seroprotection (%)</th></tr>
<tr><th>9 mcg</th><th>15 mcg</th></tr>
<tr><td>A(H1N1)</td><td>37(57.8%)</td><td>42 (65.5%)</td></tr>
<tr><td>A(H3N2)</td><td>48 (75%)</td><td>49 (76.6%)</td></tr>
<tr><td>B</td><td>11(17.2%)</td><td>17 (26.6%)</td></tr>
</table>
</td><td></td><td></td></tr>
</table>

<table>
<tr><th colspan="5">STUDY DETAILS</th><th colspan="2">SUMMARY</th></tr>
<tr><th>Study</th><th>Vaccine</th><th>Study Design</th><th>Participants</th><th>Summary of Key Findings</th><th>Level of Evidence</th><th>Quality</th></tr>
<tr><td></td><td></td><td></td><td>16.9% female
Mean age: 75.6</td><td></td><td></td><td></td></tr>
<tr><td>Skowronski DM, Hottes TS, Chong M, De Serres G, Scheifele DW, Ward BJ, Halperin SA, Janjua NZ, Chan T, Sabaiduc S, Petric M. Randomized controlled trial of dose response to influenza vaccine in children aged 6 to 23 months. Pediatrics. 2011 Amcg 1;128(2):e276-89.</td><td>IIV3
(Vaxigrip)

Doses:
7.5 mcg
15 mcg</td><td>RCT

Canada multi-center

2008-2009 influenza season

Funding for this study was provided by PHAC and the Ministère de la Santé et des Services Sociaux du Québec.</td><td>Healthy children 6-23 months of age

7.5 mcg group:
n=124
50.8% female
Mean age: 12.8 months

15 mcg group:
n=128
55.5% female
Mean age: 13.2 months</td><td>Proportion that achieved seroprotection 27-45 days after the 2nd dose of influenza vaccine:
<table>
<tr><th rowspan="2">Strain</th><th colspan="2">Proportion that achieved seroprotection (95% CI)</th></tr>
<tr><th>7.5 mcg</th><th>15 mcg</th></tr>
<tr><td>A(H1N1)</td><td>70.5 (61.6-78.4)</td><td>81.2 (72.9-87.8)</td></tr>
<tr><td>A(H3N2)</td><td>67.2 (58.1-75.4)</td><td>83.8 (75.8-89.9)</td></tr>
<tr><td>B (Yam)</td><td>66.4 (57.3-74.7)</td><td>80.3 (72-87.1)</td></tr>
</table>
Proportion that achieved seroconversion 27-45 days after the 2nd dose of influenza vaccine:
<table>
<tr><th rowspan="2">Strain</th><th colspan="2">Proportion that achieved seroconversion (95% CI)</th></tr>
<tr><th>7.5 mcg</th><th>15 mcg</th></tr>
<tr><td>A(H1N1)</td><td>70.5 (61.6-78.4)</td><td>80.3 (72-87.1)</td></tr>
<tr><td>A(H3N2)</td><td>67.2 (58.1-75.4)</td><td>81.2 (72.9-87.8)</td></tr>
<tr><td>B (Yam)</td><td>65.6 (56.4-73.9)</td><td>80.3 (72-87.1)</td></tr>
</table>
GMT rise (post-vaccination GMT / pre-vaccination GMT) after the 2nd dose of influenza vaccine:
<table>
<tr><th rowspan="2">Strain</th><th colspan="2">GMT rise (95% CI)</th></tr>
<tr><th>7.5 mcg</th><th>15 mcg</th></tr>
<tr><td>A(H1N1)</td><td>10.2 (8.2-12.7)</td><td>12.2 (9.8-15.2)</td></tr>
<tr><td>A(H3N2)</td><td>9.1 (7.5-11.0)</td><td>13.0 (10.9-15.7)</td></tr>
<tr><td>B</td><td>8.4 (6.7-10.6)</td><td>13.6 (10.8-17.1)</td></tr>
</table></td><td>I</td><td>Good</td></tr>
</table>

<table>
<tr><th colspan="5">STUDY DETAILS</th><th colspan="2">SUMMARY</th></tr>
<tr><th>Study</th><th>Vaccine</th><th>Study Design</th><th>Participants</th><th>Summary of Key Findings</th><th>Level of Evidence</th><th>Quality</th></tr>
<tr>
<td>Langley JM, Vanderkooi OG, Garfield HA, Hebert J, Chandrasekaran V, Jain VK, Fries L. Immunogenicity and safety of 2 dose levels of a thimerosal-free trivalent seasonal influenza vaccine in children aged 6–35 months: a randomized, controlled trial. Journal of the Pediatric Infectious Diseases Society. 2012 Mar 1;1(1):55-63.</td>
<td>IIV3 (Flulaval or Vaxigrip)

Doses:
7.5 mcg
15 mcg</td>
<td>RCT

Canada multi-center

2008-2009 influenza season

Funded by GlaxoSmith Kline Biologicals</td>
<td>Healthy children 6-35 months of age

Flulaval 7.5 mcg group:
n=164
42.7% female
Mean age: 18.2 months

Flulaval 15 mcg group:
n=167
49.3% female
Mean age: 17.5 months

Vaxigrip 7.5 mcg group:
n=43
60.5% female
Mean age: 17.0 months</td>
<td>Proportion that achieved seroprotection 28 days post-vaccination:
<table>
<tr><th rowspan="2">Strain</th><th colspan="3">Proportion that achieved seroprotection (95% CI)</th></tr>
<tr><th>7.5 mcg (Vaxigrip)</th><th>7.5 mcg (Flulaval)</th><th>15 mcg (Flulaval)</th></tr>
<tr><td>A(H1N1)</td><td>80.6 (64.0-91.8)</td><td>51.1 (42.3-60)</td><td>62.1 (53.3-70.4)</td></tr>
<tr><td>A(H3N2)</td><td>77.8 (60.8-89.9)</td><td>61.8 (52.9-70.2)</td><td>74.2 (65.9-81.5)</td></tr>
<tr><td>B (Yam)</td><td>86.1 (70.5-95.3)</td><td>80.9 (73.1-87.3)</td><td>86.4 (79.3-91.7)</td></tr>
</table>
Proportion that achieved seroconversion 28 days post-vaccination:
<table>
<tr><th rowspan="2">Strain</th><th colspan="3">Proportion that achieved seroconversion (95% CI)</th></tr>
<tr><th>7.5 mcg (Vaxigrip)</th><th>7.5 mcg (Flulaval)</th><th>15 mcg (Flulaval)</th></tr>
<tr><td>A(H1N1)</td><td>83.3 (67.2-93.6)</td><td>53.4 (44.5-62.2)</td><td>63.6 (54.8-71.8)</td></tr>
<tr><td>A(H3N2)</td><td>83.3 (67.2-93.6)</td><td>62.6 (53.7-70.9)</td><td>75.0 (66.7-82.1)</td></tr>
<tr><td>B (Yam)</td><td>91.7 (77.5-98.2)</td><td>84.7 (77.4-90.4)</td><td>92.4 (86.5-96.3)</td></tr>
</table>
GMT ratios (Flulaval 15 mcg / Flulaval 7.5 mcg) 28 days post-vaccination (adjusted for prior influenza vaccination, baseline titre – pooled variance):
<table>
<tr><th>Strain</th><th>GMT ratio (95% CI)</th></tr>
<tr><td>A(H1N1)</td><td>1.25 (0.9-1.75)</td></tr>
<tr><td>A(H3N2)</td><td>1.11 (0.83-1.49)</td></tr>
<tr><td>B (Yam)</td><td>1.27 (0.93-1.74)</td></tr>
</table>
Children received 1 or 2 doses, depending on previous influenza vaccination.</td>
<td>I</td>
<td>Good</td>
</tr>
</table>

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<tr><th>Study</th><th>Vaccine</th><th>Study Design</th><th>Participants</th><th>Summary of Key Findings</th><th>Level of Evidence</th><th>Quality</th></tr>
<tr>
<td>Pavia-Ruz N, Angel Rodriguez Weber M, Lau YL, Nelson EA, Kerdpanich A, Huang LM, Silas P, Qaqundah P, Blatter M, Jeanfreau R, Lei P. A randomized controlled study to evaluate the immunogenicity of a trivalent inactivated seasonal influenza vaccine at two dosages in children 6 to 35 months of age. Human vaccines & immunotherapeutics. 2013 Sep 19;9(9):1978-88.</td>
<td>IIV3 (Fluarix or Fluzone)

Doses:
7.5 mcg
15 mcg</td>
<td>RCT

US, Hong Kong, Mexico, Thailand, and Taiwan

Multi-centre

2008-2009 influenza season

Funded by GlaxoSmith Kline Biologicals</td>
<td>Healthy children 6-35 months of age

Fluarix 7.5 mcg group:
n=1017
50.7% female
Mean age: 21.2 months

Fluarix 15 mcg group:
n=1013
53.3% female
Mean age: 21.2 months

Fluzone 7.5 mcg group:
n=1031
49.1% female
Mean age: 21.1 months</td>
<td>Proportion that achieved seroprotection 28 days (or 56 for unprimed children) post-vaccination:
<table>
<tr><th rowspan="2">Strain</th><th colspan="3">Proportion that achieved seroprotection (95% CI)</th></tr>
<tr><th>7.5 mcg (Fluzone)</th><th>7.5 mcg (Fluarix)</th><th>15 mcg (Fluarix)</th></tr>
<tr><td>A(H1N1)</td><td>95.6 (94.2-96.8)</td><td>68.7 (65.7-71.5)</td><td>74.2 (71.4-76.9)</td></tr>
<tr><td>A(H3N2)</td><td>98.2 (97.1-98.9)</td><td>77.4 (74.7-79.9)</td><td>83.3 (80.8-85.5)</td></tr>
<tr><td>B (Yam)[a]</td><td>90.7 (88.7-92.4)</td><td>85.7 (83.4-87.8)</td><td>88.8 (86.7-90.7)</td></tr>
<tr><td>B (Yam)[b]</td><td>92.3 (90.5-93.9)</td><td>88 (85.9-89.9)</td><td>90.6 (88.6-92.3)</td></tr>
</table>
[a] B/Florida/4/2006, which is a B/Florida/4/2006-like strain, as recommended by WHO for influenza season of this study
[b] B/Brisbane/3/2007, which is a B/Florida/4/2006-like strain, as recommended by WHO for influenza season of this study

Proportion that achieved seroconversion 28 days (or 56 for unprimed children) post-vaccination:
<table>
<tr><th rowspan="2">Strain</th><th colspan="3">Proportion that achieved seroconversion (95% CI)</th></tr>
<tr><th>7.5 mcg (Fluzone)</th><th>7.5 mcg (Fluarix)</th><th>15 mcg (Fluarix)</th></tr>
<tr><td>A(H1N1)</td><td>90.2 (88.2-91.9)</td><td>62.5 (59.5-65.5)</td><td>69 (66.1-71.8)</td></tr>
<tr><td>A(H3N2)</td><td>95.9 (94.5-97)</td><td>73.5 (70.6-76.1)</td><td>79.8 (77.2-82.2)</td></tr>
<tr><td>B (Yam)[a]</td><td>87.8 (85.6-89.7)</td><td>79.8 (77.2-82.3)</td><td>85.3 (83-87.4)</td></tr>
<tr><td>B (Yam)[b]</td><td>89.3 (87.3-91.1)</td><td>82.6 (80.1-84.9)</td><td>87.1 (84.8-89.1)</td></tr>
</table>
[a] B/Florida/4/2006
[b] B/Brisbane/3/2007</td>
<td>I</td>
<td>Good</td>
</tr>
</table>

<table>
<tr><th colspan="4">STUDY DETAILS</th><th colspan="2">SUMMARY</th></tr>
<tr><th>Study</th><th>Vaccine</th><th>Study Design</th><th>Participants</th><th>Summary of Key Findings</th><th>Level of Evidence</th><th>Quality</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
GMT rise (post-vaccination GMT / pre-vaccination GMT) post-vaccination:
<table>
<tr><th rowspan="2">Strain</th><th colspan="3">GMT rise (95% CI)</th></tr>
<tr><th>7.5 mcg (Fluzone)</th><th>7.5 mcg (Fluarix)</th><th>15 mcg (Fluarix)</th></tr>
<tr><td>A(H1N1)</td><td>21.4 (19.9-23.1)</td><td>10.2 (9.2-11.4)</td><td>12.4 (11.2-13.7)</td></tr>
<tr><td>A(H3N2)</td><td>24.1 (22.6-25.7)</td><td>10.4 (9.6-11.3)</td><td>14.2 (13.1-15.4)</td></tr>
<tr><td>B (Yam)[a]</td><td>21.4 (19.7-23.1)</td><td>13.4 (12.4-14.5)</td><td>18.4 (17-20)</td></tr>
<tr><td>B (Yam)[b]</td><td>23.1 (21.4-24.9)</td><td>14.9 (13.7-16.1)</td><td>19.7 (18.2-21.4)</td></tr>
</table>
[a] B/Florida/4/2006
[b] B/Brisbane/3/2007

Difference in immune response of 15 mcg Fluarix compared to 7.5 mcg Fluzone 28 days (or 56 for unprimed children) post-vaccination:
<table>
<tr><th>Strain</th><th>GMT ratio[a] (95% CI)</th><th>Difference in seroconversion rate[b] (95% CI)</th></tr>
<tr><td>A(H1N1)</td><td>1.74 (1.54–1.98)</td><td>21.19 (17.82–24.58)</td></tr>
<tr><td>A(H3N2)</td><td>1.72 (1.57–1.89)</td><td>16.16 (13.46–18.98)</td></tr>
<tr><td>B (Yam)[c]</td><td>1.13 (1.01–1.25)</td><td>2.48 (-0.49–5.45)</td></tr>
<tr><td>B (Yam)[d]</td><td>1.13 (1.02–1.25)</td><td>2.25 (-0.55–5.07)</td></tr>
</table>
[a] calculated as post-vaccination GMT in 7.5 mcg Fluzone / 15 mcg Fluarix, adjusted for baseline titre – pooled variance)
[b] calculated as seroconversion rate in 7.5 mcg Fluzone – 15 mcg Fluarix
[c] B/Florida/4/2006
[d] B/Brisbane/3/2007

Children received 1 or 2 doses, depending on previous influenza vaccination.
</td><td></td><td></td></tr>
</table>

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<tr><th>Study</th><th>Vaccine</th><th>Study Design</th><th>Participants</th><th>Summary of Key Findings</th><th>Level of Evidence</th><th>Quality</th></tr>
<tr>
<td>Halasa NB, Gerber MA, Berry AA, Anderson EL, Winokur P, Keyserling H, Eckard AR, Hill H, Wolff MC, McNeal MM, Edwards KM. Safety and immunogenicity of full-dose trivalent inactivated influenza vaccine (TIV) compared with half-dose TIV administered to children 6 through 35 months of age. Journal of the Pediatric Infectious Diseases Society. 2015 Sep 1;4(3):214-24.</td>
<td>IIV3 (Fluzone)

Doses:
7.5 mcg
15 mcg</td>
<td>RCT

US Multi-center

October 5, 2010 and March 2, 2012; The studies were conducted before the 2010–2011 and 2011–2012 influenza seasons.

Funded by the National Institutes of Health Clinical and Translational Science Awards Program, the National Center for Advancing Translational Sciences, and the National Institute of Allergy and</td>
<td>Healthy children 6-35 months of age

N=204
52% female
Mean age: 14.2 months

Primed subgroup:

7.5 mcg group:
n=9
66.7% female
Mean age: 23.4 months

15 mcg group:
n=21
45.4% female
Mean age: 25.3 months

Influenza vaccine naïve subgroup:

7.5 mcg group:
n=55
50.7% female

15 mcg group:
n=119
52.9% female</td>
<td>Proportion of primed individuals that achieved seroprotection 28 days post-vaccination:
<table>
<tr><th rowspan="2">Strain</th><th colspan="2">Proportion that achieved seroprotection (95% CI)</th></tr>
<tr><th>7.5 mcg</th><th>15 mcg</th></tr>
<tr><td>A(H1N1)</td><td>89 (0.52-1.00)</td><td>100 (0.84-1.0)</td></tr>
<tr><td>A(H3N2)</td><td>89 (0.52-1.00)</td><td>90 (0.7-0.99)</td></tr>
<tr><td>B (Yam)</td><td>33 (0.07-0.70)</td><td>14 (0.03-0.36)</td></tr>
</table>
Proportion of naïve individuals that achieved seroprotection 28 days after the 2nd dose of influenza vaccine:
<table>
<tr><th rowspan="2">Strain</th><th colspan="2">Proportion that achieved seroprotection (95% CI)</th></tr>
<tr><th>7.5 mcg</th><th>15 mcg</th></tr>
<tr><td>A(H1N1)</td><td>85 (73-94)</td><td>89 (82-94)</td></tr>
<tr><td>A(H3N2)</td><td>15 (6-27)</td><td>15 (9-23)</td></tr>
<tr><td>B (Yam)</td><td>44 (30-58)</td><td>50 (40-59)</td></tr>
</table>
Proportion of primed individuals that achieved seroconversion 28 days post-vaccination:
<table>
<tr><th rowspan="2">Strain</th><th colspan="2">Proportion that achieved seroconversion (95% CI)</th></tr>
<tr><th>7.5 mcg</th><th>15 mcg</th></tr>
<tr><td>A(H1N1)</td><td>89 (52-100)</td><td>90 (70-99)</td></tr>
<tr><td>A(H3N2)</td><td>78 (40-97)</td><td>86 (64-97)</td></tr>
<tr><td>B (Yam)</td><td>22 (3-60)</td><td>10 (1-30)</td></tr>
</table>
Proportion of naïve individuals that achieved seroconversion 28 days after the 2nd dose of influenza vaccine:
<table>
<tr><th rowspan="2">Strain</th><th colspan="2">Proportion that achieved seroconversion (95% CI)</th></tr>
<tr><th>7.5 mcg</th><th>15 mcg</th></tr>
<tr><td>A(H1N1)</td><td>78 (65-88)</td><td>85 (77-91)</td></tr>
</table>
</td>
<td>I</td>
<td>Good</td>
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</table>

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<tr><td></td><td></td><td>Infectious Diseases</td><td></td><td>
<table>
<tr><td>A(H3N2)</td><td>7 (2-18)</td><td>11 (6-18)</td></tr>
<tr><td>B (Yam)</td><td>31 (19-45)</td><td>42 (33-51)</td></tr>
</table>
Difference in GMT (15 mcg - 7.5 mcg) 28 days after last vaccination:
<table>
<tr><th rowspan="2">Strain</th><th colspan="2">Difference in GMT (95% CI)</th></tr>
<tr><th>Primed</th><th>Naive</th></tr>
<tr><td>A(H1N1)</td><td>-267.5
(-527.9 to -3.9)</td><td>−5.7
(−94.9 to 90.2)</td></tr>
<tr><td>A(H3N2)</td><td>−11.0
(−105.1 to 122.2)</td><td>−1.9
(−2.0 to 5.2)</td></tr>
<tr><td>B (Yam)</td><td>3.0
(−7.5 to 14.8)</td><td>−3.7
(−5.1 to12.0)</td></tr>
</table>
</td><td></td><td></td></tr>
<tr><td>Jain VK, Domachowske JB, Wang L, Ofori-Anyinam O, Rodríguez-Weber MA, Leonardi ML, Klein NP, Schlichter G, Jeanfreau R, Haney BL, Chu L. Time to change dosing of inactivated quadrivalent influenza vaccine in young children: evidence from a phase III, randomized, controlled trial. Journal of the Pediatric Infectious Diseases Society. 2017 Mar 1;6(1):9-19.</td><td>IIV4 (Fluzone quadrivalent)

Doses:
7.5 mcg
15 mcg</td><td>RCT

US and Mexico

Multi-centre

2014-2015 influenza season

Funded by GlaxoSmith Kline Biologicals</td><td>Healthy children 6-35 months of age

7.5 mcg group:
n=1028
48.2% female
Mean age: 19.9 months

15 mcg group:
n=1013
45.6% female
Mean age: 19.7 months</td><td>Proportion that achieved seroprotection 28 days (or 56 days for unprimed individuals) post-vaccination:
<table>
<tr><th rowspan="2">Strain</th><th colspan="2">Proportion that achieved seroprotection (95% CI)</th></tr>
<tr><th>7.5 mcg</th><th>15 mcg</th></tr>
<tr><td>A(H1N1)</td><td>75.4 (72.6-78)</td><td>80.4 (77.8-82.8)</td></tr>
<tr><td>A(H3N2)</td><td>77.8 (75.2-80.3)</td><td>82.2 (79.7-84.5)</td></tr>
<tr><td>B (Yam)</td><td>88.6 (86.5-90.5)</td><td>97 (95.8-98)</td></tr>
<tr><td>B (Vic)</td><td>49.8 (46.7-52.9)</td><td>66 (63-69)</td></tr>
</table>
Proportion that achieved seroconversion 28 days (or 56 days for unprimed individuals) post-vaccination:
<table>
<tr><th rowspan="2">Strain</th><th colspan="2">Proportion that achieved seroconversion (95% CI)</th></tr>
<tr><th>7.5 mcg</th><th>15 mcg</th></tr>
<tr><td>A(H1N1)</td><td>67.3 (64.3-70.3)</td><td>73.7 (70.8-76.4)</td></tr>
<tr><td>A(H3N2)</td><td>69.4 (66.4-72.3)</td><td>76.1 (73.3-78.8)</td></tr>
<tr><td>B (Yam)</td><td>73.8 (70.9-76.5)</td><td>85.5 (83.2-87.7)</td></tr>
<tr><td>B (Vic)</td><td>48.5 (45.3-51.6)</td><td>64.9 (61.8-67.9)</td></tr>
</table>
GMT rise 28 days (or 56 days for unprimed individuals) post-vaccination:</td><td>I</td><td>Good</td></tr>
</table>

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<table>
<tr><th rowspan="2">Strain</th><th colspan="2">GMT rise (95% CI)</th></tr>
<tr><th>7.5 mcg</th><th>15 mcg</th></tr>
<tr><td>A(H1N1)</td><td>7.7 (7.1-8.3)</td><td>9 (8.4-9.7)</td></tr>
<tr><td>A(H3N2)</td><td>8.9 (8.2-9.7)</td><td>10.7 (10-11.6)</td></tr>
<tr><td>B (Yam)</td><td>8.1 (7.5-8.8)</td><td>12.7 (11.7-13.7)</td></tr>
<tr><td>B (Vic)</td><td>5.4 (5.0-5.8)</td><td>8.7 (8.1-9.4)</td></tr>
</table>
</td><td></td><td></td></tr>
<tr><td>Robertson CA, Mercer M, Selmani A, Klein NP, Jeanfreau R, Greenberg DP. Safety and immunogenicity of a full-dose, split-virion, inactivated, quadrivalent influenza vaccine in healthy children 6-35 months of age: a randomized controlled clinical trial. The Pediatric infectious disease journal. 2019 Mar;38(3):323.)</td><td>IIV4

Doses:
7.5 mcg
15 mcg</td><td>RCT

US
Multi-center

2016-2017 influenza season

Funded by Sanofi Pasteur</td><td>Healthy children 6-35 months of age

7.5 mcg group:
n=682
49.4% female
Mean age: 20.4 months

15 mcg group:
n=682
49.9% female
Mean age: 20.5 months</td><td>Difference in seroconversion rate (% in 15 mcg group – % 7.5 mcg group) post-vaccination:
<table>
<tr><th>Strain</th><th>Difference in seroconversion rate (95% CI)</th></tr>
<tr><td>A(H1N1)</td><td>5.1 (0.189 to 10.0)</td></tr>
<tr><td>A(H3N2)</td><td>4.3 (-0.283 to 8.99)</td></tr>
<tr><td>B (Yam)</td><td>3.4 (-2.78 to 5.56)</td></tr>
<tr><td>B (Vic)</td><td>1.4 (-0.465 to 7.36)</td></tr>
</table>
GMT ratios (15 mcg group / 7.5 mcg group) post-vaccination:
<table>
<tr><th>Strain</th><th>GMT ratio (95% CI)</th></tr>
<tr><td>A(H1N1)</td><td>1.45 (1.19 to 1.77)</td></tr>
<tr><td>A(H3N2)</td><td>1.50 (1.23 to 1.83)</td></tr>
<tr><td>B (Yam)</td><td>1.44 (1.20 to 1.73)</td></tr>
<tr><td>B (Vic)</td><td>1.33 (1.10 to 1.62)</td></tr>
</table>
</td><td>I</td><td>Good</td></tr>
<tr><td>Della Cioppa G, Vesikari T, Sokal E, Lindert K, Nicolay U. Trivalent and quadrivalent MF59®-adjuvanted influenza vaccine in young children: a dose-and schedule-finding study. Vaccine. 2011 Nov 3;29(47):8696-704.</td><td>IIV3 or IIV4

Doses:
7.5 mcg
15 mcg</td><td>RCT

Finland and Belgium

Multi-center

2008-2009 influenza season</td><td>Healthy children 6-35 months of age

(Note: only a subset of study groups relevant for this review are presented here. Authors combined the IIV3 and IIV4 groups for analysis in the publication)</td><td>Proportion that had achieved seroprotection on day 50:
<table>
<tr><th rowspan="2">Strain</th><th colspan="3">Number that achieved seroprotection (%)</th></tr>
<tr><th>7.5 mcg (Vaxigrip)</th><th>7.5 mcg</th><th>15 mcg</th></tr>
<tr><td>A(H1N1)</td><td>96</td><td>65</td><td>79</td></tr>
<tr><td>A(H3N2)</td><td>92</td><td>70</td><td>71</td></tr>
<tr><td>B (Yam)</td><td>42</td><td>19</td><td>12</td></tr>
<tr><td>B (Vic)</td><td>Not reported</td><td>17</td><td>14</td></tr>
</table>
</td><td>I</td><td>Good</td></tr>
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<tr><th colspan="5">STUDY DETAILS</th><th colspan="2">SUMMARY</th></tr>
<tr><th>Study</th><th>Vaccine</th><th>Study Design</th><th>Participants</th><th>Summary of Key Findings</th><th>Level of Evidence</th><th>Quality</th></tr>
<tr><td></td><td></td><td>Funded by Novartis</td><td>IIV3 7.5 mcg group:
n=25
66% female
Mean age: 20 months

IIV3 15 mcg group:
n=22
27% female
Mean age: 15 months

IIV4 7.5 mcg group:
n=25
36% female
Mean age: 18 months

IIV4 15 mcg group:
n=28
46% female
Mean age: 15.2 months

IIV3 15 mcg group (Vaxigrip):
n=26
50% female
Mean age: 16.1 months</td><td>Proportion that achieved seroconversion on day 50:<table><tr><th rowspan="2">Strain</th><th colspan="3">Number that achieved seroconversion (%)</th></tr><tr><th>7.5 mcg (Vaxigrip)</th><th>7.5 mcg</th><th>15 mcg</th></tr><tr><td>A(H1N1)</td><td>96</td><td>62</td><td>79</td></tr><tr><td>A(H3N2)</td><td>92</td><td>62</td><td>71</td></tr><tr><td>B (Yam)</td><td>42</td><td>4 / 19</td><td>21</td></tr><tr><td>B (Vic)</td><td>Not reported</td><td>17</td><td>14</td></tr></table>GMT rise (post-vaccination GMT / pre-vaccination GMT) on day 50:<table><tr><th rowspan="2">Strain</th><th colspan="3">GMT rise</th></tr><tr><th>7.5 mcg (Vaxigrip)</th><th>7.5 mcg</th><th>15 mcg</th></tr><tr><td>A(H1N1)</td><td>25</td><td>8.15</td><td>10</td></tr><tr><td>A(H3N2)</td><td>27</td><td>8.7</td><td>9.91</td></tr><tr><td>B (Yam)</td><td>4.06</td><td>2.39</td><td>2.07</td></tr><tr><td>B (Vic)</td><td>Not reported</td><td>2.16</td><td>1.94</td></tr></table></td><td></td><td></td></tr>
<tr><td colspan="7">Intradermal</td></tr>
<tr><td>Oluwaseun Egunsola, John Taplin, Liza Mastikhina, Joyce Li, Diane Lorenzetti, Laura E. Dowsett, Tom Noseworthy, Fiona Clement. Intradermal versus intramuscular</td><td>Seasonal inactivated influenza vaccine</td><td>Rapid review and meta-analysis

Random effects model</td><td>Number of participants (RCTs): 13,759

Number of participants (observational): 164,021

Age range: all ages</td><td>Primary findings:
Meta-analysis included a total of 16 RCTs (no observational studies) on the immunogenicity of fractional doses of IM influenza vaccine (includes 3 mcg, 6 mcg, 7.5 mcg, and 9 mcg).

Refer to tables 1 and 2 within this statement for results on seroconversion and seroprotection in all</td><td>Meta-analysis</td><td>N/A</td></tr>
</table>

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
administration of influenza vaccination. University of Calgary, Health Technology Assessment Unit. Produced for DSEN MAGIC Team. July 21, 2020.		Included: RCTs, non-RCTs, observational studies Funding: Canadian Institute for Health Research (DSEN)	Sub-analysis: 60 years of age and older	ages and in adults 60 years of age and older respectively.		

Abbreviations: CI: confidence interval; GMT: geometric mean titre; IIV3: trivalent inactivated influenza vaccine; IIV4: quadrivalent inactivated influenza vaccine; mcg: microgram; RCT: randomized controlled trial; US: United States

Table 11. Summary of Evidence Related to the Safety of Fractional Influenza Vaccine for IM and ID

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Intramuscular						
Antony J, Rios P, Williams C, Ramkissoon N, Straus SE, Tricco AC. Safety and effectiveness of dose-sparing strategies for seasonal influenza vaccine: a rapid scoping review of fractional dosing of the intramuscular influenza vaccine. medRxiv. 2020 Jan 1.	Standard dose inactivated seasonal influenza vaccines	Scoping review Included: RCTs, non-RCTs, observational studies Funding: Canadian Institute for Health Research (DSEN)	Age range: all ages	Primary findings: 13 RCTs were included in the scoping review, including 10 RCTs that had safety data relevant for this Statement (3 in adults, 9 in children). All studies in children assessed the safety of 7.5 mcg of HA per strain fractional dose compared to standard dose (15 mcg of HA per strain). None of the studies identified in this review reported statistical differences in local or systemic AEs between study groups. One study compared 3 fractional doses of Fluzone (3 mcg, 6 mcg, 9 mcg of HA per strain) to standard dose, and did not report any differences between the IM vaccination groups. A second in adults less than 65 years of age found no significant differences after adjusting for clinically significant pain levels (determined as ≥3 out of 5 on a visual analogue scale) between groups that had received a 7.5 mcg of HA per strain dose compared to standard dose. A single study in older adults was identified, and found no difference in the occurrence or severity of AEs between groups that received a fractional dose of 9 mcg of HA per strain versus standard dose. No serious AEs that were considered related to the vaccine were found.	Review	N/A
Intradermal						
Oluwaseun Egunsola, John Taplin, Liza Mastikhina, Joyce Li, Diane Lorenzetti, Laura E.	Seasonal inactivated influenza vaccine	Rapid review and meta-analysis	Number of participants (RCTs): 13,759	Primary findings: Meta-analysis included a total of 24 RCTs (no observational studies) on the safety of fractional doses	Meta-analysis	N/A

STUDY DETAILS					SUMMARY	
Study	***Vaccine***	***Study Design***	***Participants***	***Summary of Key Findings***	***Level of Evidence***	***Quality***
Dowsett, Tom Noseworthy, Fiona Clement. Intradermal versus intramuscular administration of influenza vaccination. University of Calgary, Health Technology Assessment Unit. Produced for DSEN MAGIC Team. July 21, 2020.		Random effects model Included: RCTs, non-RCTs, observational studies Funding: Canadian Institute for Health Research (DSEN)	Number of participants (observational): 164,021 Age range: all ages Sub-analysis: 60 years of age and older	of IM influenza vaccine (includes 3 mcg, 6 mcg, 7.5 mcg, and 9 mcg). Refer to tables 3 and 4 within this statement for results on local and systemic AEs respectively. No sub-analysis by age is available for this outcome.		

Abbreviations: AE: Adverse Event; DSEN: Drug Safety Effectiveness Network; HA: hemagglutinin; mcg: microgram; N/A: not applicable; RCT: randomized controlled trial

LIST OF ABBREVIATIONS

Abbreviation	***Term***
AE	Adverse event
CI	Confidence interval
DSEN	Drug Safety Effectiveness Network
EEFA	Ethics, equity, feasibility, and acceptability
FDA	Food and Drug Administration
GMT	Geometric mean titre
HA	Hemagglutinin
HI	Hemagglutination inhibition
ID	Intradermal
IIV3	Trivalent inactivated influenza vaccine
IIV4	Quadrivalent inactivated influenza vaccine
ILI	Influenza-like illness
IM	Intramuscular
IWG	Influenza Working Group
MAGIC	Methods and Applications Group for Indirect Comparisons
mcg	Micrograms
MDV	Multi-dose vial
mL	Milliliter
N/A	Not applicable
NACI	National Advisory Committee on Immunization
PHAC	Public Health Agency of Canada
RCT	Randomized controlled trial
RR	Relative risk (also known as risk ratio)
US	United States

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