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# BMJ Open

## Safety and effectiveness of dose-sparing strategies for intramuscular seasonal influenza vaccine: A rapid scoping review

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1 **Safety and effectiveness of dose-sparing strategies for intramuscular seasonal influenza**  
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6 **vaccine:**

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8 **A rapid scoping review**

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## 35 ABSTRACT

36 **Background:** The objective of this rapid scoping review was to identify dose-sparing strategies  
37 for intramuscular administration of seasonal influenza vaccines in healthy individuals of all ages.

38 **Methods:** Comprehensive literature searches were executed in MEDLINE, EMBASE, and the  
39 Cochrane library. The grey literature was searched via international clinical trial registries for  
40 relevant studies published in English in the last 20 years. References of the included systematic  
41 reviews and their primary studies were also scanned. Title/abstract and full-text screening were  
42 carried out by pairs of reviewers independently. Data extraction was conducted by a single  
43 reviewer and verified by a second reviewer. Our outcomes of interest were influenza infections,  
44 ICU admission, pneumonia, hospitalizations, adverse events, and mortality. Results were  
45 summarized descriptively.

46 **Results:** A total of 13 studies with 10,351 participants were included in the review and all  
47 studies were randomized control trials (RCTs) conducted between 2006 and 2019. The most  
48 common interventions were the trivalent influenza vaccine (n=10), followed by the quadrivalent  
49 influenza vaccine (n=4). Nine studies included infants/toddlers 6-36 months old and one of these  
50 studies also included children and adolescents. In these nine studies, no clinical effectiveness  
51 outcomes were reported. Of the four adult studies ( $\geq 18$  years), two studies reported on  
52 effectiveness outcomes.

53 **Conclusions:** Due to the low number of studies in healthy adults and the lack of studies  
54 assessing confirmed influenza and influenza-like illness, there remains a need for further  
55 evaluation.

56 **Keywords:**

## 57 STRENGTHS AND LIMITATIONS OF THIS STUDY

### 58 Strengths:

- 59 • This rapid scoping review was conducted within a 6-week timeline and the methods were  
60 tailored to provide results to the stakeholders within 4 weeks.
- 61 • We did not restrict the search dates and study screening was completed in independently  
62 by two reviewers.

### 63 Limitations:

- 64 • We limited the selection of studies to those published in the English language, and data  
65 extraction was conducted by one abstractor and one verifier.
- 66 • Twelve dose-sparing RCTs were not included in the review because they did not include  
67 vaccines that were deemed of interest to the stakeholder, and/or did not provide sufficient  
68 data.

## 69 BACKGROUND

70 The symptoms of novel coronavirus disease (COVID-19) closely mimic those of seasonal  
71 influenza vaccine and health officials recommend vaccination against the flu to limit  
72 confounding of flu symptoms with COVID-19 symptoms. An anticipated shortage in influenza  
73 vaccine supplies was of concern.[1] This anticipated shortage did not happen however, and in the  
74 2019-2020 flu season, influenza vaccination coverage among adults (42%) was similar to the  
75 previous season (42%). This question of vaccine shortage remains relevant in Canada and other  
76 jurisdictions for future COVID-19 and flue seasons. As a potential solution, health officials were  
77 interested in assessing the effectiveness of fractional dosing (e.g., half-doses) of currently  
78 available intramuscular influenza vaccines.

79 Fractional dosing, or dose sparing, strategies are those where less than the standard dose of  
80 hemagglutinin (HA) antigen, and thus less volume of vaccine, is administered, increasing the  
81 overall number of influenza vaccine doses available. In Canada, influenza vaccines are currently  
82 authorized for intramuscular administration only, apart from the live-attenuated influenza  
83 vaccine, which is administered intranasally.[2] Standard dose influenza vaccines contain 15 mcg  
84 of HA per strain and are delivered in 0.5 mL volume. Therefore, the total amount of HA in  
85 standard dose trivalent vaccines is 45 mcg, and the total amount of HA in standard dose  
86 quadrivalent vaccines is 60 mcg.

87 A scoping review of all the available dose sparing strategies for intramuscular administration of  
88 seasonal influenza vaccines currently approved in Canada for healthy populations had not been  
89 systematically conducted. With the resource-constraints for the influenza season due to COVID-  
90 19, there is a need to scope the evidence on the safety and effectiveness of dose-sparing  
91 strategies for intramuscular administration of seasonal influenza vaccines. The objective of this



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3 92 rapid scoping review was to identify studies of dose-sparing strategies for administration of  
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5 93 intramuscular seasonal influenza vaccines in healthy individuals of all ages. The results of this  
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8 94 scoping review were used to inform a systematic review with meta-analysis by National  
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10 95 Advisory Committee on Immunization (NACI) on the same topic [3].

## 11 12 96 **METHODS**

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15 97 The Centre for Immunization and Respiratory Infectious Diseases of the Public Health Agency  
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17 98 of Canada (PHAC) commissioned a rapid scoping review on the available methods for fractional  
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19 99 dosing of seasonal influenza vaccines through the Canadian Institutes of Health Research  
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22 100 (CIHR) Drug Safety and Effectiveness Network (DSEN) with a 6-week timeline for preliminary  
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24 101 results.

### 25 26 102 **Protocol**

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29 103 The methods for this review were guided by the updated reviewer manual for scoping reviews  
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31 104 published by the Joanna Briggs Institute and the World Health Organization's guide to rapid  
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33 105 reviews.[4, 5] Results are reported according to the Preferred Reporting Items for Systematic  
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35 106 Reviews and Meta-analysis extension to scoping reviews (PRISMA-ScR).[6] A protocol for this  
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37 107 rapid review was disseminated through the Open Science Framework registry  
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40 108 (<https://osf.io/8mwz2/>).

### 41 42 109 **Literature search**

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45 110 Comprehensive literature searches were developed and executed by an experienced librarian in  
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47 111 Ovid MEDLINE (**Appendix 1**), EMBASE using the OVID interface (**Appendix 2**), and the  
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49 112 Cochrane library between 1946 and May 2020 (**Appendix 3**). The literature search was peer  
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51 113 reviewed by a second librarian using the PRESS checklist  
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54 114 (<https://www.cadth.ca/resources/finding-evidence/press>). The grey (i.e., difficult to locate or

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3 115 unpublished) literature was searched via international clinical trial registries (i.e.  
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5 116 clinicaltrials.gov, EU clinical trial register). References of relevant systematic reviews and  
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7 117 included studies were also scanned.  
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### 10 118 **Eligibility criteria**

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12 119 The eligibility criteria followed the Population, Intervention, Comparators, Outcome, Study  
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14 120 design (PICOS) framework as follows:

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17 121 • Population: Healthy humans of any age. Immunocompromised populations and animal  
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19 122 studies were excluded. Examples of persons with weakened immune systems include those  
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21 123 with HIV/AIDS; cancer and transplant patients who are taking certain immunosuppressive  
22  
23 124 drugs; and those with inherited diseases that affect the immune system (e.g., congenital  
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25 125 agammaglobulinemia, congenital IgA deficiency)[7].
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28 126 • Intervention: Any dose-sparing strategy used to administer intramuscular seasonal influenza  
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30 127 vaccines (eligible vaccines listed in **Appendix 4**). Eligible strategies included, but were not  
31  
32 128 limited to, administering less than the standard 15 ug HA antigen using multi-dose vials, half  
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34 129 dosing, or pre-formulated products with reduced antigen quantity, or with revised vaccine  
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36 130 dose schedules. Any studies examining monovalent pandemic vaccines,  
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38 131 specialty/experimental vaccines (e.g., high dose), whole virus vaccines, or other routes of  
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40 132 administration (e.g. intranasal, intradermal) were not eligible. Only vaccine products  
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42 133 approved for use in Canada or equivalent formulations approved for use in other countries  
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44 134 were eligible for inclusion. Concomitant administration with other vaccine products were  
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46 135 included only if administered to both the intervention and the comparator groups.  
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51 136 • Comparator: Any of the interventions listed above, no intervention, or placebo.  
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3 137 • Outcomes: Lab-confirmed influenza infection (primary outcome), influenza-like illness or  
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5 138 clinical/symptomatic diagnosis of influenza, hospitalization, intensive care unit (ICU)  
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7 139 admission, pneumonia, mortality, and adverse events (local/systemic reactogenicity,  
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9 140 vascular-related, serious). Reactogenicity represents the physical manifestation of the  
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11 141 inflammatory response to vaccination, and can include injection-site pain, redness, swelling  
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13 142 or induration at the injection site, as well as systemic symptoms, such as fever, myalgia, or  
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15 143 headache.[8]  
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19 144 • Study designs: Randomized controlled trials (RCTs), non-randomised studies (e.g., quasi-  
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21 145 RCTs, non-randomized trials, interrupted time series, controlled before after), and  
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23 146 observational studies (e.g., cohort, case control) were included. Studies must have had a  
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25 147 control or comparator group in order to be eligible for inclusion and as such, cross-sectional,  
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27 148 case series, case reports, and qualitative studies were excluded.  
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31 149 • Publication status: We included full text and abstracts if they included data on safety or  
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33 150 effectiveness.

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36 151 Inclusion was also limited to studies written in the English language due to the short timelines  
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38 152 for the conduct of this review.

### 39 40 153 **Study selection**

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42 154 A screening form based on the eligibility criteria was prepared and pilot-tested with 30 studies  
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44 155 with all members of the review team until sufficient agreement (>75%) was reached prior to both  
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46 156 title/abstract (level 1) and full-text (level 2) screening. Subsequent screening at level 1 and level  
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48 157 2 were completed by pairs of reviewers working independently using the Knowledge Translation  
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50 158 Program's proprietary screening software (synthesi.SR)[9]. Any discrepancies between  
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52 159 reviewers were consistently resolved by a third independent reviewer.  
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## 160 **Data extraction**

161 Items for data collection included study characteristics (study design, year of publication,  
162 country of conduct, multi-center vs. single site), patient characteristics (mean age, age range, sex,  
163 vaccination history), intervention details (type of vaccine, vaccine manufacturer, dose, timing  
164 and administration of treatment), comparator details (comparator intervention, dose), and  
165 outcome results (influenza infections, ICU admission, pneumonia, hospitalizations, adverse  
166 events, mortality) at the longest duration of follow-up.

167 A standardized form for data extraction was developed and pilot tested by the entire review team  
168 using two pre-selected full-text RCTs to ensure understanding of the data items to be extracted,  
169 and congruence among reviewers. All included studies were extracted by one reviewer  
170 independently and then verified by a second reviewer.

## 171 **Risk of bias assessment**

172 As this was a scoping review, the risk of bias of studies was not assessed.[4]

## 173 **Synthesis**

174 The synthesis involved providing a descriptive summary of included studies with summary  
175 tables and detailed tables of study results. Study results were organized and tabulated according  
176 to patients (children vs adults), interventions, and outcomes and where available information on  
177 relevant subgroups.

## 178 **RESULTS**

### 179 **Literature search**

180 We screened 2,378 titles and abstracts from our database search and an additional 13 citations  
181 located through searching the grey literature and scanning references. Of these, 144 potentially  
182 relevant full-text articles were screened for eligibility (**Figure 1**). Twelve studies that assessed

183 dose-sparing strategies were excluded during full-text screening because the vaccine under study  
 184 was not of interest or unclearly reported. We contacted authors of these 12 unclear studies and  
 185 received 1 response confirming the vaccine was not of interest (see list of excluded studies in  
 186 **Appendix 5**). Subsequently, 13 RCTs were included; five trial protocols were found and were  
 187 denoted as duplicate/companion reports. No non-randomised or observational studies were found  
 188 that fulfilled the eligibility criteria.

### 189 **Study characteristics**

190 **Table 1** summarizes the characteristics of the 13 RCTs published between 2006 and 2019; and  
 191 conducted mainly in the US, followed by Mexico, Canada and Finland. The majority of the  
 192 studies evaluated trivalent vaccines (10/13 [77%]) and most were conducted in the 6-36 month-  
 193 old pediatric population (9/13 [69%]). Almost all studies reported on reactogenicity and/or other  
 194 adverse events, but only two studies reported on the effectiveness of our outcomes of interest  
 195 (i.e., lab-confirmed influenza and influenza-like illness).

196 Full study and patient characteristic details for each study are reported in **Appendix 6** and  
 197 treatment and outcome details in **Appendix 7**.

198 **Table 1: Characteristics of included studies (n=13)**

Characteristics	Category	Frequency (%)
Date of publication	2006-2010	4 (30.8)
	2011-2015	5 (38.4)
	2016-2020	4 (30.8)
Multi-center or single site	Multi-centre	8 (61.5)
	Single centre	2 (15.4)
Countries of conduct <sup>a</sup>	USA	8 (61.5)
	Mexico	3 (23.1)
	Canada	2 (15.4)
	Finland	2 (15.4)
	Belgium	1 (7.7)
	Hong Kong	1 (7.7)
	Taiwan	1 (7.7)

	Thailand	1 (7.7)
Populations <sup>a,b</sup>	Infants/Toddlers (6-36 months)	9 (69.2)
	Children (37 months – 17 years)	1 (7.7)
	Adults (18-64 years)	3 (23.1)
	Older adults ( $\geq 65$ )	1 (7.7)
Treatments <sup>a,c</sup>	Trivalent influenza vaccine (TIV)	10 (76.9)
	Quadrivalent influenza vaccine (QIV)	4 (30.8)
Outcomes <sup>a</sup>	Effectiveness	2 (15.4)
	Local and Systemic Reactogenicity	12 (92.3)
	Adverse events	10 (76.9)

<sup>a</sup>Each study can fit into more than one category so the total percentage will not add up to 100%

<sup>b</sup>One study includes both infants/toddlers and children, and another includes both adults and seniors

<sup>c</sup>One study includes both TIV and QIV arms

## 199 RCTs in healthy children (<18 years old)

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Nine studies included infants/toddlers 6-36 months old and one study also included children and adolescents (**Table 2**). None of these studies reported results on the effectiveness outcomes that were relevant to our review and established *a priori*, however all of them reported on safety outcomes.

207 **Table 2: Nine RCTs conducted in children (6 months – 17 years)**

Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcomes	Author reported conclusions
<b>TRIVALENT AND QUADRIVALENT INFLUENZA VACCINES (TIV/QIV)</b>									
Cioppa, 2011[10]	October 2008 – March 2009	NR - TIV, <b>7.5-µg/strain</b> [2 x 0.25mL dose]	20.0 months (7.0)	6- <36 months	43.5	NR	25	Local and Systemic reactogenicity	Reactogenicity of the 7.5-µg TIV/QIV formulations was slightly lower than for the corresponding 15-µg formulations.  The majority of unsolicited AEs were mild or moderate in severity and none of the SAEs was considered to be related to the study vaccine.
	Belgium	Agrippal - TIV, <b>15-µg/strain</b> [2 x 0.5mL dose]	15.0 months (8.8)	6- <36 months	43.5	NR	22	Adverse events	
		NR - QIV, <b>7.5-µg/strain</b> [2 x 0.25mL dose]	18.0 months (8.9)	6- <36 months	43.5	NR	25		
		NR - QIV, <b>15-µg/strain</b> [2 x 0.5mL dose]	15.2 months (7.8)	6- <36 months	43.5	NR	28		
		Vaxigrip (Sanofi Pasteur), <b>7.5-µg/strain</b> [2 x 0.25mL dose]	16.1 months (8.5)	6- <36 months	43.5	NR	26		

Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcomes	Author reported conclusions
Skowronski, 2011[11]	September 2008 – December 2008  Canada	Vaxigrip (Sanofi-Pasteur), 15-µg/strain [2 x 0.5mL dose]	13.2 months (5.1)	6-23 months	53.2	0	124	Local and Systemic reactogenicity  Adverse events	Local reactions generally were less common in infants than toddlers and more common with full doses versus half doses, but none of these differences were significant.  One serious adverse event was reported: a toddler in the half dose group was hospitalized with pneumonia 28 days after the first vaccination. The event was deemed unlikely related to the vaccine.
		Vaxigrip (Sanofi-Pasteur), 15-µg/strain [2 x 0.25mL dose]	12.8 months (5.0)	6-23 months	53.2	0	128		



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Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcomes	Author reported conclusions
									Compared with 0.25-mL half-dosing, administration of 2 full 0.5-mL doses of trivalent inactivated influenza vaccine can increase antibody response without increasing reactogenicity in previously unimmunized infants aged 6 to 11 months.
Langley, 2012[12]	November 2008 – August 2009	Fluviral F1 (Sanofi-Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose]	18.2 months (9.06)	6-35 months	47.9	42.6	164	Local and Systemic reactogenicity	Fluviral F1 group had 1 case of pneumonia resolved. Fluviral F2 group had 1 case of
	Canada	Fluviral F2 (Sanofi-Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose]	17.5 months (8.27)	6-35 months	47.9	42.6	167	Adverse events	

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Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcomes	Author reported conclusions
		Vaxigrip (Sanofi-Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose]	17.0 months (8.33)	6-35 months	47.9	42.6	43		bronchial hyper-reactivity in resolving stage.  The 0.5-mL dose of the study vaccine, when administered to children aged 6–35 months, resulted in a modest but not statistically significant improvement in immunogenicity with clinically similar safety and reactogenicity compared with the 0.25-mL dose.
Pavia-Ruz, 2013[13]	October 2008-March 2009	Fluarix (GSK), <b>15-µg/strain</b> [1 x 0.5mL dose]	21.2 months (8.37)	6-35 months	51	30.1	1018	Local and Systemic reactogenicity	The reactogenicity and safety

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Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcomes	Author reported conclusions
	Hong Kong, Mexico, Taiwan, Thailand, and the USA	Fluarix (GSK), 7.5-µg/strain [1 x 0.25 mL dose]	21.2 months (8.03)	6-35 months	51	30.1	1018	Adverse events	<p>profile of the study vaccine did not appear to be affected by doubling the dose.</p> <p>One participant in the Flu-15µg group had two SAEs, (apnea and cyanosis) which were considered by the investigator to be possibly related to vaccination. The subject was hospitalized and the events resolved on the same day as they occurred.</p>
		Fluzone (Sanofi-Pasteur), 7.5-µg/strain [1 x 0.25 mL dose]	21.1 months (8.20)	6-35 months	51	30.1	1031		

Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcomes	Author reported conclusions
Halasa, 2015[14]	2010-2012  USA	Fluzone (Sanofi Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose]	13.5	6-35 months, 12-35 months	52	13.2	80	Local and Systemic reactogenicity	No significant differences between the full-dose or half-dose groups for either the fully primed or naive cohorts for systemic reactions or local reactions when both seasons were combined.  The only significant difference in the 2011–2012 season was that 8 of 48 (16.7%) participants in the half-dose group compared with 32 of 96 (33.3%) in the full-dose group had increased
		Fluzone (Sanofi Pasteur), <b>15-µg/strain</b> [1 x 0.5 mL dose]	14.5				163		

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Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcomes	Author reported conclusions
									redness at the injection site (P < .05).  No significant differences between the groups in AE, SAE, or onset of chronic medical conditions between the dose groups in either the naive or fully primed cohorts, and none of the SAEs were deemed related to the vaccine.
Phung, 2016[15]	September 2010- January 2011	FLUAD (NR), NR [1 x 0.5mL dose]	68.7 months (18)	6-35 months	55.8	85.7	60	Local and Systemic reactogenicity	<i>Trial protocol with no author conclusions.</i>
	Finland	FLUAD (NR), NR [1 x 0.25 mL dose]	60.4 months (23.2)	6-35 months	55.8	85.7	75	Adverse events	

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Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcomes	Author reported conclusions
		Agrippal S1 (NR), NR [1 x 0.5mL dose]	68 months (17.1)	6-35 months	55.8	85.7	51		
		Agrippal S1 (NR), NR [1 x 0.25mL dose]	32.4 months (1.9)	6-35 months	55.8	85.7	11		
Jain, 2017[16]	2014-2015 Influenza Season	Flulaval (GSK), 15-µg/strain [1 x 0.5mL dose]	19.7 months (8.7)	6-35 months	46.9	57.5	1013	Local and Systemic reactogenicity	None of the febrile seizures or the SAEs were considered by the investigator to be related to vaccination.
	USA and New Mexico	Fluzone (Sanofi Pasteur), 7.5-µg/strain [1 x 0.25 mL dose]	19.9 months (8.9)	6-35 months	46.9	57.5	1028	Adverse events	Double-dose vaccines may improve protection against influenza B in some young children and simplifies annual influenza vaccination by

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Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcomes	Author reported conclusions
									allowing the same vaccine dose to be used for all eligible children and adults.
Ojeda, 2019[17]	December 2017- January 2018  Mexico	Vaxigrip Tetra (Sanofi Pasteur) <b>PFS 15-µg/strain</b> [1 x 0.5mL dose]	NR (6 months – 17 years)	6 months – 17 years	46.4	NR	149	Local and Systemic reactogenicity  Adverse events	Solicited systemic reactions were reported in more infants aged 6 – 35 months in the MDV group than in the PFS group however this was not clinically significant.  AE not considered related to a study vaccine.  There were no differences in reactogenicity or safety
		Vaxigrip Tetra (Sanofi Pasteur) <b>MDV 15-µg/strain</b> [1 x 0.5mL dose]	NR (6 months – 17 years)	6 months – 17 years	46.4	NR	153		

Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcomes	Author reported conclusions
									between the two vaccine formats. These results showed that the MDV format of QIV was as safe and immunogenic as the PFS format in infants, children, and adolescents. These findings support the use of MDV QIV as a resource-saving alternative for seasonal influenza vaccination.
Robertson, 2019[18]	September 2016 – March 2017	Fluzone (Sanofi Pasteur) <b>15-µg/strain</b> [1x0.5mL dose]	20.5 months (8.55)	6-35 months	49.7	47.25	992	Local and Systemic reactogenicity	No significant differences between full- and half-dose



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Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcomes	Author reported conclusions
	USA	Fluzone (Sanofi Pasteur) 7.5-µg/strain [1x0.25 dose]	20.4 months (8.75)	6-35 months	49.7	47.25	949	Adverse events	groups.  AE leading to study discontinuation/ SAE not considered vaccine-related.  A full dose vaccine was immunogenic and had a safety profile comparable to that of a half dose, with no new safety concerns observed.

**Abbreviations:** AE – adverse events; GMR – geometric mean ratio; GMFR – geometric mean fold rise; GMT - geometric mean antibody titer; HA - hemagglutinin; HAI - hemagglutination inhibition; ID – intradermal; IM – intramuscular; ITT – intent-to-treat; MDV – multi-dose vials, n – number of people with condition, N – sample size of treatment arm, NR – not reported, PFS – prefilled dose, SAEs – serious adverse events

## 211 **Safety outcomes**

212 Trivalent influenza vaccines

213 Six of the included RCTs assessed trivalent influenza vaccines (TIV) in young children (6-36  
214 months) and reported on local and systemic reactogenicity outcomes and other adverse  
215 events.[10-14, 19] Two RCTs compared the administration of full (0.5mL) and half (0.25mL)  
216 doses of the same standard 15µg/strain vaccine.[11, 19] The first RCT compared two full versus  
217 two half doses of TIV in previously unimmunized infants (6-11 months) and toddlers (12-23  
218 months) using Vaxigrip (15µg/strain).[11] The study found that in the infants group, two full 0.5-  
219 mL doses of vaccine did not increase reactogenicity. Local reactions were less common in  
220 infants than toddlers and more common with full doses versus half doses, but the differences  
221 were not statistically significant. An identified clinical trial registry compared a single  
222 intramuscular injection of 0.5mL to 0.25mL of FLUAD or Agrippal and showed comparable  
223 numbers of children with reactogenicity outcomes and other adverse events across the groups,  
224 but no significance levels or conclusions were provided by the investigators upon contact.[19]  
225 The objective of three of the included RCTs was to examine the impact of administering the full  
226 adult dose of 15µg/strain vaccines compared with the usual children's dose of 7.5µg/strain in  
227 infants and toddlers.[12-14] A multicenter RCT was conducted in Canada assessing the safety of  
228 full-dose Fluviral TIV (15µg/strain) compared with the half-dose (7.5µg/strain) and an active  
229 comparator Vaxigrip (7.5µg/strain).[12] Compared with the half-dose, the full-dose vaccine  
230 resulted in clinically similar reactogenicity and safety. A similar three-arm RCT to assess the use  
231 of Fluarix at two different dose levels (7.5µg/strain and 15µg/strain) compared to an established  
232 control vaccine Fluzone (7.5µg/strain) also found the reactogenicity and safety profile of Fluarix  
233 did not appear to be affected by doubling the dose, but one participant in the 15µg group had two

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3 234 serious adverse events (apnea and cyanosis) that were considered by the investigator to be  
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5 235 possibly related to vaccination.[13] A third multicenter RCT compared the 15 µg/strain  
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7 236 formulation to the 7.5µg/strain formulation of Fluzone (Sanofi Pasteur) administered to young  
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10 237 children across multiple influenza seasons.[14] This study also found no statistically significant  
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12 238 differences between the full-dose or half-dose groups for systemic reactions, local reactions or  
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14 239 adverse events when both seasons were combined; however, in the 2011–2012 season, 8 of 48  
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16 240 (16.7%) participants in the half-dose group compared with 32 of 96 (33.3%) in the full-dose  
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18 241 group had increased redness at the injection site ( $P < .05$ ).

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21 242 Cioppa et al. (2009) was the only trial that compared the safety and tolerability of both TIV and  
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23 243 QIV vaccine formulations.[10] The vaccine arms of interest were a QIV 15-µg/strain, TIV 15-  
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25 244 µg/strain, QIV 7.5-µg/strain, TIV 7.5-µg/strain, and a control Vaxigrip TIV 7.5-µg/strain  
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27 245 vaccine. Reactogenicity of the 7.5-µg TIV/QIV formulations was slightly lower than for the  
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29 246 corresponding 15-µg formulations, but there was no difference in reactogenicity between TIV  
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31 247 and QIV vaccines.

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35 248 Quadrivalent influenza vaccines

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38 249 Four of the included RCTs evaluated quadrivalent influenza vaccines (QIV) in children.[10, 16-  
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40 250 18] All of the studies reported reactogenicity outcomes and other adverse events. The Cioppa et  
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42 251 al. (2009) RCT reported both TIV and QIV vaccines and the results are reported above.[10] Two  
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44 252 studies compared full-dose QIV to pediatric 7.5µg/strain Fluzone. In the first RCT, full dose  
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46 253 Fluzone had a similar safety profile to half-dose Fluzone with a single adverse event being  
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48 254 attributed to the study vaccine.[18] Similarly, the second study found that full-dose Flulaval may  
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50 255 improve protection against influenza in some young children when compared to low-dose  
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53 256 Fluzone, and in this RCT, none of the adverse events were considered to be study-related as

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3 257 reported by the investigator.[16] The final trial evaluated Vaxigrip Tetra (15µg/strain)  
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5 258 administered to children and adolescents in two different formats.[17] Vaxigrip administered as a  
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7 259 single dose using a pre-filled syringe (PFS) was compared to a 10-dose multi-dose vial (MDV).  
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10 260 Systemic reactions were reported in more infants aged 6 – 35 months in the MDV group than in  
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12 261 the PFS group; however this difference was not clinically significant. The authors concluded that  
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14 262 there was no difference in reactogenicity or safety between the two vaccine formats in infants,  
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16 263 children, and adolescents.  
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19 264 **RCTs in healthy adults (≥18 years old)**  
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21 265 One RCT included healthy adults over 18 years, two studies included healthy adults from 18-45  
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23 266 and 18-65 years old, and one study included older healthy adults (≥ 65 years) (**Table 3**). Two  
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25 267 studies reported on effectiveness outcomes and three on reactogenicity and other adverse events.  
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28 268 All four RCTs evaluated Fluzone QIV.  
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269 **Table 3: Four RCTs conducted in adults (≥18 years old)**

Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Relevant Outcomes	Author reported conclusions
<b>QUADRIVALENT INFLUENZA VACCINES (QIV)</b>									
Kramer, 2006[20]	October 2004 – November 2004  USA	Fluzone (Aventis Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose]	NR (>18 years)	>18 years	NR	NR	222	Lab-confirmed influenza	There was no significant difference between the full-dose and half-dose groups in the diagnosis of influenza or in the proportion of participants self-reporting four or more symptoms consistent with influenza-like illness.  No adverse events were noted by participants from either group or reported to the IRB during the course of the study
		Fluzone (Aventis Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose]	NR (>18 years)	>18 years	NR	NR	222	Influenza-like illness  Adverse events	

Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Relevant Outcomes	Author reported conclusions
Engler, 2008[21]	November 2004 – December 2004	Fluzone (Aventis Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose]	NR (18 – 64 years)	18-64 years	43.4	0	554	Influenza-like illness Hospital/ER visits	The relative risk of medical visits and hospitalizations for influenza-like illnesses were similar in the half- and full-dose group regardless of age, and there was no evidence of ILI symptom differences by sex or dose during the 21 days after immunizations.  Although injection site pain was greater for full- vs half-dose (19.9% vs 14.4%; p=.01), when analyzed for clinically significant pain levels significant
	USA	Fluzone (Aventis Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose]	NR (18 – 64 years)	18-64 years	43.4	0	556	Local and Systemic reactogenicity Adverse events	

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Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Relevant Outcomes	Author reported conclusions
									<p>dose-dependent pain differences were not identified.</p> <p>Joint and/or muscle pain were significantly different (p=.02 and p=.03, respectively) by dose.</p> <p>No other adverse event differed significantly by dose.</p>
Belshe, 2007[22]	NR  USA	Fluzone (Sanofi-Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose]	31.5 years (9.6)	18-49 years	71.2	0	31	Local and Systemic reactogenicity	Intradermal (ID) vaccine induced significantly more local inflammatory response than Intramuscular (IM) vaccine but this did not translate into an
		Fluzone (Sanofi-Pasteur), <b>9-µg/strain</b> [1 x 0.3mL dose]	31.2 years (9.4)	18-49 years	71.2	0	32		

Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Relevant Outcomes	Author reported conclusions
		Fluzone (Sanofi-Pasteur), <b>6-µg/strain</b> [1 x 0.2mL dose]	30.1 years (10.3)	18-49 years	71.2	0	31		increased immune response for ID vaccines compared to IM (primary comparison of this study was ID vs IM doses)
		Fluzone (Sanofi-Pasteur), <b>3-µg/strain</b> [1 x 0.1mL dose]	31.9 years (10.3)	18-49 years	71.2	0	31		
Chi, 2010[23]	August 2007-2008  USA	Fluzone (Sanofi Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose]	75.6 years (6.8)	>65 years	17.8	94.6	65	Local and Systemic reactogenicity	The two SAEs were acute coronary syndrome and appendicitis and neither were judged to be related to influenza vaccination
		Fluzone (Sanofi Pasteur), <b>9-µg/strain</b> [1 x 0.3mL dose]	75.2 years (7.7)	>65 years	17.8	94.6	64	Adverse events	

**Abbreviations:** AE – adverse events, GMT - geometric mean antibody titer; HA - hemagglutinin; ID – intradermal; ILI – influenza-like illness; IM – intramuscular; MDV – multi-dose vials, n – number of people with condition, N – sample size of treatment arm, NR – not reported, PFS – prefilled syringe, SAE – serious adverse events



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3 272 **Effectiveness outcomes**  
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5 273 Two of the included RCTs that examined the same vaccine (Fluzone manufactured by Aventis  
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7 274 Pasteur) in healthy adult populations reported effectiveness outcomes including lab-confirmed  
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10 275 influenza infections, influenza like illness, and/or hospitalizations or emergency room visits after  
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12 276 vaccination.[20, 21] The RCT by Kramer et al. (2006) found that 3.6% of participants receiving  
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14 277 a 15- $\mu$ g/strain dose of vaccine reported influenza like illness compared to 6.8% of participants  
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16 278 that received a 7.5- $\mu$ g/strain dose.[20] However, only one participant in the RCT that received  
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18 279 the 15- $\mu$ g/strain dose was confirmed via laboratory analysis to have influenza. The authors  
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20 280 concluded that half-dose and full-dose vaccinations appear to be similarly effective based on the  
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22 281 low rate of influenza infections and similar symptom surveys between both groups but  
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24 282 acknowledge that further studies examining immunogenicity are needed to confirm.  
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28 283 A similar RCT by Engler et al. (2008) that compared a 15- $\mu$ g/strain dose of Fluzone vaccine to a  
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30 284 7.5- $\mu$ g/strain dose found equal proportions of participants reporting influenza like illness (9.7%  
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32 285 vs 9.9%) and hospitalizations or emergency room visits (0.3% v 0.2%).[21] The authors found  
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34 286 the relative risk of medical visits or hospitalizations between both groups was the same even  
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36 287 when adjusting for age and that age, sex, nor dose had an influence on the severity of influenza  
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38 288 like illness symptoms.  
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42 289 **Safety outcomes**  
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44 290 Three of the included studies in adult populations reported adverse events that occurred during  
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46 291 the trial while one RCT indicated that no adverse events were recorded for the duration of their  
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48 292 trial.[20-23] All three studies reporting adverse events compared different doses of Fluzone  
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50 293 vaccine including 3- $\mu$ g, 6- $\mu$ g, 7.5- $\mu$ g, 9- $\mu$ g, and 15- $\mu$ g per strain doses.  
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3 295 Two of the studies were carried out in healthy adult populations and one RCT was conducted in  
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5 296 older healthy adults (>60 years of age).[21-23] One RCT found that joint or muscle pain  
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7 297 following vaccination was statistically significantly higher in the full dose (15- $\mu$ g) group  
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9 298 compared to the half-dose (7.5- $\mu$ g) group and that while injection site pain initially appeared to  
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11 299 be statistically significantly higher in the full dose group, when adjusted to include only  
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13 300 clinically significant pain levels (>3 out of 5 on a visual analogue scale) the difference was no  
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15 301 longer statistically significant.[21] The RCT found no differences in occurrence or severity of  
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17 302 any other adverse effects. Similarly, one RCT comparing four different doses of Fluzone (3- $\mu$ g,  
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19 303 6- $\mu$ g, 9- $\mu$ g, and 15- $\mu$ g per strain) did not report any differences between the IM vaccination  
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21 304 groups.[22] Finally, the RCT in older adults also found no difference in the occurrence or  
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23 305 severity of adverse events in the low dose (9- $\mu$ g) versus high dose (15- $\mu$ g) group and found no  
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25 306 serious adverse events that were considered related to the vaccine.[23]

## 31 **DISCUSSION**

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33 308 PHAC commissioned this rapid scoping review to identify the evidence for efficacy and safety of  
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35 309 fractional influenza vaccine dosing for intramuscular administration of seasonal influenza  
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37 310 vaccines in healthy individuals of all ages that have been evaluated in human trials. Thirteen  
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39 311 RCTs published between 2006 and 2019 comparing standard/full-dose and half/low-dose  
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41 312 vaccines were included in this scoping review after a comprehensive search of three electronic  
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43 313 databases, trial registries and references of relevant systematic reviews. The majority of the  
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45 314 included RCTs were conducted in children and evaluated trivalent influenza vaccines (TIV).  
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47 315 In young, healthy children, there were no effectiveness outcomes of interest reported. However,  
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49 316 local reactogenicity, systemic reactogenicity and adverse events were comparable across the full-  
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51 317 dose and half-dose TIV and QIV vaccine arms. In addition, the authors of one RCT in children  
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3 318 and adolescents that compared full-dose QIV using pre-filled syringes (PFS) versus multi-dose  
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5 319 vials (MDV) also found no statistically significant differences in safety outcomes between  
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7 320 administration formats. In healthy adults (including older adults), half-dose QIV was considered  
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9 321 equally effective as high-dose in the two RCTs that assessed clinical effectiveness. Safety  
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11 322 profiles were similar across groups in all 4 RCTs.

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14 323 A full systematic review with meta-analysis based on the studies included in this scoping review  
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16 324 was conducted by the NACI and the report was published in January of 2021.[3] The report  
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18 325 found that there is some, but still insufficient, evidence that fractional doses of influenza vaccine  
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20 326 provided via the intramuscular route are effective and immunogenic in healthy individuals.  
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22 327 NACI concludes that since many of those at high risk of influenza (e.g., adults 65 years of age  
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24 328 and older, individuals with specific underlying chronic health conditions) may have a lower  
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26 329 immune response to influenza vaccination already (due to immunosenescence in older adults or a  
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28 330 condition that alters immune function), it is important to ensure that those at high risk continue to  
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30 331 receive the full dose of influenza vaccine.

### 332 **Future research**

333 Dose-sparing approaches such as intradermal (ID) immunisation vaccination exhibits similar, or  
334 even enhanced, immunogenicity, when using a fractional dose only, as compared to  
335 intramuscular or subcutaneous immunisation, and should be explored in future scoping  
336 reviews.[24]

### 337 **CONCLUSIONS**

338 In our scoping review, we found 13 RCTs on the efficacy and safety of fractional doses of  
339 influenza vaccine provided via the intramuscular route to healthy adults and children. These  
340 studies were used to inform a systematic review with meta-analysis which were commissioned

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3 341 by the PHAC. We found that due to the low number of studies in healthy adults and the lack of  
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5 342 studies assessing confirmed influenza and influenza-like illness, there remains a need for further  
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7 343 evaluation of the clinical effectiveness of IM dose-sparing strategies using vaccines currently  
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9 344 available in this population.  
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For peer review only

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3 345 **LIST OF ABBREVIATIONS**  
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5 346 PHAC – Public Health Agency of Canada  
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8 347 CIHR – Canadian Institutes of Health Research  
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10 348 DSEN – Drug Safety and Effectiveness Network  
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12 349 MAGIC – Methods and Application Group in Indirect Comparisons  
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14 350 PRISMA-ScR – Preferred Reporting Items for Systematic Reviews and Meta-analysis extension  
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17 351 to scoping reviews  
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19 352 ICU – Intensive Care Unit  
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21 353 RCT – Randomized controlled trials  
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23 354 NRCTs – non-randomized controlled trials  
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25 355 TIV – Trivalent Influenza Vaccine  
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27 356 AE – Adverse Events  
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29 357 SAE – Serious adverse events  
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31 358 QIV – Quadrivalent Influenza Vaccine  
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33 359 PFS – Pre-filled syringe  
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35 360 MDV – Multi-dose vial  
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41 362 **Ethics approval and consent to participate**  
42

43 363 Not applicable  
44

45 364 **Consent for publication**  
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47 365 Not applicable  
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3 366 **Availability of data and materials**  
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6  
7  
8 368 additional file(s)).  
9

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11

12 370 The authors have no competing interests to declare.  
13

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38 382 <http://creativecommons.org/licenses/by-nc/4.0/>  
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41

42 383 **Authors' contributions**  
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44 384 CL wrote and revised the final manuscript. JA and PR screened citations and full-text articles,  
45  
46 385 abstracted and verified data, interpreted results and wrote the first draft manuscript. CW and NR  
47  
48 386 screened citations and full-text articles, abstracted data, and reviewed the manuscript. SES and  
49  
50 387 ACT developed the protocol, obtained funding, interpreted results, and edited the manuscript.  
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13

14 393 **Additional files**  
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18 395 **Title of Data:** Additional File 1 (Appendices 1-7)  
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21

22 397 Appendix 1 – MEDLINE search strategy  
23

24 398 Appendix 2 – EMBASE search strategy  
25

26 399 Appendix 3 – Cochrane search strategy  
27

28 400 Appendix 4 – List of eligible vaccines  
29

30 401 Appendix 5 – Excluded dose-sparing studies  
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32 402 Appendix 6 – Study and patient data  
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34 403 Appendix 7 – Treatment and outcome data  
35

36 404 **FIGURE LEGEND**  
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38 405 Figure 1. Flow chart of studies included in the review  
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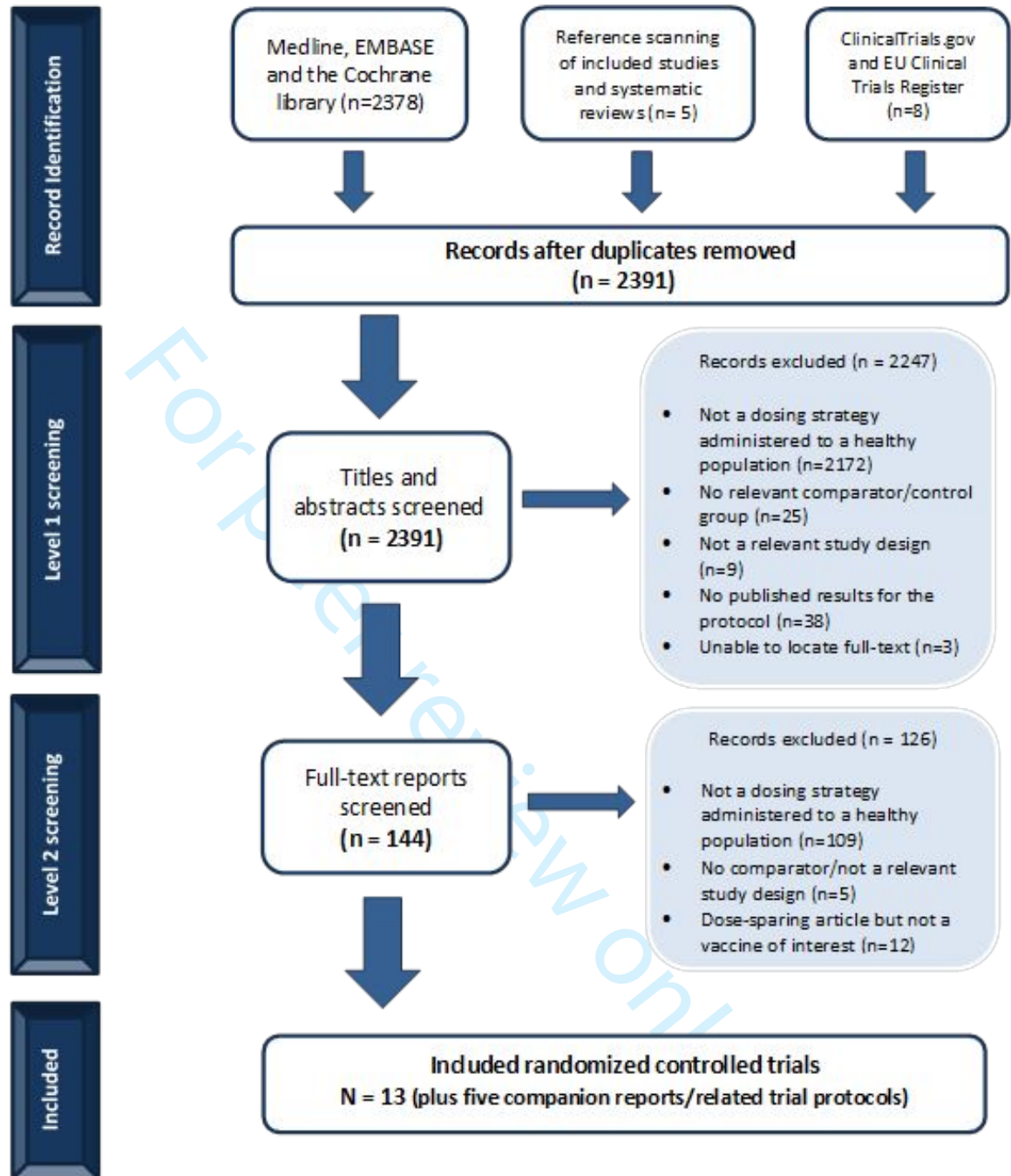
40 406 Study flow diagram.  
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443 intramuscular dose of FLUAD or Agridipal S1 influenza vaccines in healthy children  
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4 452 virion, Inactivated, Quadrivalent Influenza Vaccine in Healthy Children 6-35 Months of  
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26 473 [published Online First: 2020/09/09]



## APPENDIX 1 – MEDLINE search strategy

Database: Ovid MEDLINE(R) ALL <1946 to May 29, 2020>

### Search Strategy:

-----

- 1 influenza, human/ or exp influenza a virus/ or exp influenzavirus b/ or influenzavirus c/
- 2 (flu or flue or influenza\* or grippe).tw,kf.
- 3 1 or 2
- 4 exp Vaccines/ or Immunization/
- 5 (vaccin\* or immuni\* or inocula\* or shot or jab).tw,kf.
- 6 4 or 5
- 7 3 and 6
- 8 influenza vaccines/ or Adjuvants, Immunologic/
- 9 (LAIV or Fluenz or FluMist or Afluria or Fluad or Fluzone or Flulaval or Fluarix or Flublok or
- 10 Flucelvax or FluQuadri or Vaxigrip or Influvac or Fluvirin or Agrippal or Begrivac or Fluad or
- 11 agriflu or fluviral).tw,kf.
- 12 7 or 8 or 9
- 13 Injections, Intramuscular/
- 14 (intramuscular or intra-muscular).tw,kf.
- 15 or/11-12
- 16 10 and 13
- 17 limit 14 to yr=2000-current
- 18 animals/ not humans/
- 19 15 not 16
- 20 ad.fs.
- 21 11 or 12 or 18
- 22 10 and 19
- 23 exp dose-response relationship, immunologic/
- 24 dose-Response Relationship, Drug/
- 25 (Dos\* sparing or Dose -sparing or half-dose or dose-response or dose response or dose
- 26 effect\* or dose-effect\* or fractional dos\*).tw,kf.
- 27 ((reduc\* or lower or less) adj2 (quantity or strength or standard)).tw,kf.
- 28 ((dos\* adj3 change) or (half adj3 dos\*)).tw,kf.
- 29 ((down adj3 titrat\*) or (dose adj3 titrat\*) or (dose adj3 reduc\*) or (dose adj3 "de-escalat\*")
- 30 or (dose adj3 taper\*)).tw,kf.
- 31 or/21-26
- 32 20 and 27
- 33 animals/ not humans/
- 34 28 not 29
- 35 limit 30 to yr=2000-current
- 36 17 or 31

## APPENDIX 2 – EMBASE search strategy

Database: Ovid MEDLINE(R) Embase <2000 to June 11, 2020>

### Search Strategy:

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1 influenza, human/ or exp influenza a virus/ or exp influenzavirus b/ or influenzavirus c/  
 2 (flu or flue or influenza\* or grippe).tw,kf.  
 3 1 or 2  
 4 exp Vaccines/ or Immunization/  
 5 (vaccin\* or immuni\* or inocula\* or shot or jab).tw,kf.  
 6 4 or 5  
 7 3 and 6  
 8 influenza vaccines/ or Adjuvants, Immunologic/  
 9 (LAIV or Fluenz or FluMist or Afluria or Fluad or Fluzone or Flulaval or Fluarix or Flublok  
 or Flucelvax or FluQuadri or Vaxigrip or Influvac or Fluvirin or Agrippal or Begrivac or Fluad or  
 agriflu or fluviral).tw,kf.  
 10 7 or 8 or 9  
 11 Injections, Intramuscular/  
 12 (intramuscular or intra-muscular).tw,kf.  
 13 or/11-12  
 14 10 and 13  
 15 limit 14 to yr=2009-current  
 16 animals/ not humans/  
 17 15 not 16  
 18 ad.fs.  
 19 11 or 12 or 18  
 20 10 and 19  
 21 exp dose-response relationship, immunologic/  
 22 dose-Response Relationship, Drug/  
 23 (Dos\* sparing or Dose -sparing or half-dose or dose-response or dose response or dose  
 effect\* or dose-effect\* or fractional dos\*).tw,kf.  
 24 ((reduc\* or lower or less) adj2 (quantity or strength or standard)).tw,kf.  
 25 ((dos\* adj3 change) or (half adj3 dos\*)).tw,kf.  
 26 ((down adj3 titrat\*) or (dose adj3 titrat\*) or (dose adj3 reduc\*) or (dose adj3  
 "de-escalat\*") or (dose adj3 taper\*)).tw,kf.  
 27 or/21-26  
 28 20 and 27  
 29 animals/ not humans/  
 30 28 not 29  
 31 limit 30 to yr=2009-current  
 32 17 or 31  
 33 32 use ppez  
 34 exp Influenza virus/ or exp influenza/  
 35 (flu or flue or influenza\* or grippe).tw.  
 36 34 or 35  
 37 exp vaccine/  
 38 exp immunization/  
 39 influenza vaccination/ or vaccination/  
 40 (vaccin\* or immuni\* or inocula\* or shot or jab).tw.

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6 41 or/37-40  
7 42 36 and 41  
8 43 influenza vaccination/  
9 44 immunological adjuvant/  
10 45 (LAIV or Fluenz or FluMist or Afluria or Fluad or Fluzone or Flulaval or Fluarix or Flublok  
11 or Flucelvax or FluQuadri or Vaxigrip or Influvac or Fluvirin or Agrippal or Begrivac or Fluad or  
12 agriflu or fluviral).tw.  
13 46 or/42-45  
14 47 intramuscular drug administration/  
15 48 (intramuscular or intra-muscular).tw.  
16 49 47 or 48  
17 50 46 and 49  
18 51 limit 50 to yr="2009 -Current"  
19 52 animals/ not humans/  
20 53 51 not 52  
21 54 ad.fs.  
22 55 49 or 54  
23 56 46 and 55  
24 57 dose response/ or drug response/  
25 58 (Dos\* sparing or Dose -sparing or half-dose or dose-response or dose response or dose  
26 effect\* or dose-effect\* or fractional dos\*).tw.  
27 59 ((reduc\* or lower or less) adj2 (quantity or strength or standard)).tw.  
28 60 ((dos\* adj3 change) or (half adj3 dos\*)).tw.  
29 61 ((down adj3 titrat\*) or (dose adj3 titrat\*) or (dose adj3 reduc\*) or (dose adj3  
30 "de-escalat\*") or (dose adj3 taper\*)).tw.  
31 62 or/57-61  
32 63 56 and 62  
33 64 animals/ not humans/  
34 65 63 not 64  
35 66 limit 65 to yr="2009 -Current"  
36 67 53 or 66  
37 68 67 use emczd  
38 69 33 or 68  
39 70 remove duplicates from 69  
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### APPENDIX 3 – Cochrane search strategy

Database: Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to June 03, 2020>, EBM Reviews - ACP Journal Club

<1991 to May 2020>, EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>, EBM Reviews - Cochrane

Clinical Answers <May 2020>, EBM Reviews - Cochrane Central Register of Controlled Trials <May 2020>, EBM Reviews -

Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM

Reviews - NHS Economic Evaluation Database <1st Quarter 2016>

Search Strategy:

- 
- 1 (influenza, human or influenza a virus or influenzavirus b or influenzavirus c).kw.
  - 2 (flu or flue or influenza\* or grippe).ti,ab.
  - 3 1 or 2
  - 4 (Vaccines or Immunization).kw.
  - 5 (vaccin\* or immuni\* or inocula\* or shot or jab).ti,ab.
  - 6 4 or 5
  - 7 3 and 6
  - 8 (influenza vaccines or Adjuvants, Immunologic).kw.
  - 9 (LAIV or Fluenz or FluMist or Afluria or Fluad or Fluzone or Flulaval or Fluarix or Flublok or Flucelvax or FluQuadri or Vaxigrip or Influvac or Fluvirin or Agrippal or Begrivac or Fluad or agriflu or fluviral).ti,ab.
  - 10 7 or 8 or 9
  - 11 Injections, Intramuscular.kw.
  - 12 (intramuscular or intra-muscular).ti,ab.
  - 13 11 or 12
  - 14 10 and 13
  - 15 dose-response relationship, immunologic.kw.
  - 16 dose-Response Relationship, Drug.kw.
  - 17 (Dos\* sparing or Dose -sparing or half-dose or dose-response or dose response or dose effect\* or dose-effect\* or fractional dos\*).ti,ab.
  - 18 ((reduc\* or lower or less) adj2 (quantity or strength or standard)).ti,ab.
  - 19 ((dos\* adj3 change) or (half adj3 dos\*)).ti,ab.
  - 20 ((down adj3 titrat\*) or (dose adj3 titrat\*) or (dose adj3 reduc\*) or (dose adj3 "de-escalat\*") or (dose adj3 taper\*)).ti,ab.
  - 21 or/15-20
  - 22 10 and 21
  - 23 14 or 22
  - 24 limit 23 to yr="2009 -Current" [Limit not valid in DARE; records were retained]

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to June 03, 2020>, EBM Reviews - ACP Journal Club

<1991 to May 2020>, EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>, EBM Reviews - Cochrane

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6 **Clinical Answers <May 2020>, EBM Reviews - Cochrane Central Register of Controlled**  
7 **Trials <May 2020>, EBM Reviews -**  
8 **Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology**  
9 **Assessment <4th Quarter 2016>, EBM**  
10 **Reviews - NHS Economic Evaluation Database <1st Quarter 2016>**  
11 **Search Strategy:**  
12

- 
- 13 1 (influenza, human or influenza a virus or influenzavirus b or influenzavirus c).kw.  
14 2 (flu or flue or influenza\* or grippe).ti,ab.  
15 3 1 or 2  
16 4 (Vaccines or Immunization).kw.  
17 5 (vaccin\* or immuni\* or inocula\* or shot or jab).ti,ab.  
18 6 4 or 5  
19 7 3 and 6  
20 8 (influenza vaccines or Adjuvants, Immunologic).kw.  
21 9 (LAIV or Fluenz or FluMist or Afluria or Fluad or Fluzone or Flulaval or Fluarix or Flublok or  
22 Flucelvax or  
23 FluQuadri or Vaxigrip or Influvac or Fluvirin or Agrippal or Begrivac or Fluad or agriflu or  
24 fluviral).ti,ab.  
25 10 7 or 8 or 9  
26 11 Injections, Intramuscular.kw.  
27 12 (intramuscular or intra-muscular).ti,ab.  
28 13 11 or 12  
29 14 10 and 13  
30 15 dose-response relationship, immunologic.kw.  
31 16 dose-Response Relationship, Drug.kw.  
32 17 (Dos\* sparing or Dose -sparing or half-dose or dose-response or dose response or dose  
33 effect\* or dose-effect\* or  
34 fractional dos\*).ti,ab.  
35 18 ((reduc\* or lower or less) adj2 (quantity or strength or standard)).ti,ab.  
36 19 ((dos\* adj3 change) or (half adj3 dos\*)).ti,ab.  
37 20 ((down adj3 titrat\*) or (dose adj3 titrat\*) or (dose adj3 reduc\*) or (dose adj3 "de-escalat\*")  
38 or (dose adj3  
39 taper\*).ti,ab.  
40 21 or/15-20  
41 22 10 and 21  
42 23 14 or 22  
43 24 limit 23 to yr="2000 - 2008" [Limit not valid in DARE; records were retained]  
44 25 from 24 keep 1-173  
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## APPENDIX 4 – List of eligible vaccines

Product name (manufacturer)	Vaccine Characteristic				
	Vaccine type	Route of administration	Authorized ages for use	Antigen content for each vaccine strain	Formats available
Flulaval Tetra (GSK)	IIV4-SD (split virus)	IM	6 months and older	15 µg HA /0.5 mL dose	5 mL multi-dose vial Single dose pre-filled syringe
Fluzone Quadrivalent (Sanofi Pasteur)	IIV4-SD (split virus)	IM	6 months and older	15 µg HA /0.5 mL dose	5 mL multi-dose vial Single dose pre-filled syringe without attached needle
Afluria Tetra (Seqirus)	IIV4-SD (split virus)	IM	5 years and older	15 µg HA /0.5 mL dose	Up to expiry date indicate on vial label
Influvac Tetra (BGP Pharma ULC, operating as Mylan)	IIV4-SD (subunit)	IM or deep subcutaneous injection	3 years and older	15 µg HA /0.5 mL dose	Single dose pre-filled syringe with or without a needle
Vaxigrip Tetra	IIV4	IM	6 months and older	Pediatric: 7.5 µg HA /0.25 mL dose Adult: 15 µg HA /0.5 mL dose	0.5 mL pre-filled syringe
Fluarix Tetra/ Influsplit Tetra (GSK)	IIV4	IM	6 months and older	15 µg HA /0.5 mL dose	0.5 mL pre-filled syringe
Agriflu (Seqirus)	IIV3-SD (subunit)	IM	6 months and older	15 µg HA /0.5 mL dose	5 mL multi-dose vial Single dose pre-filled syringe without attached needle
Fluad Pediatric and Fluad (Seqirus)	IIV3-Adj (subunit)	IM	Pediatric: 6-23 months Adult: 65 years and older	Pediatric: 7.5 µg HA /0.25 mL dose Adult: 15 µg HA /0.5 mL dose	Single dose pre-filled syringe without a needle
Fluviral (GSK)	IIV3-SD (split virus)	IM	6 months and older	15 µg HA /0.5 mL dose	5 mL multi-dose vial
Fluzone TIV (Sanofi Pasteur)	IIV3-HD (split virus)	IM	65 years and older	Adult: 15 µg HA /0.5 mL dose	0.5 mL pre-filled syringe
Vaxigrip TIV	IIV3-SD	IM	6 months and older	Pediatric: 7.5 µg HA /0.25 mL dose Adult: 15 µg HA /0.5 mL dose	0.5 mL pre-filled syringe

**Note:** list of vaccines included in the review is based on feedback from PHAC and the 2020-2021 seasonal vaccine availability in Canada found here: <https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/canadian-immunization-guide-statement-seasonal-influenza-vaccine-2020-2021.html#appA>



## APPENDIX 5 – Excluded dose-sparing studies

Reference	Reason for exclusion
1 Euctr, H. U. A Randomized, Double-blind, Multi-Center Study to Evaluate Safety and Immunogenicity of One Dose of Four FLUVAL AB-like (Trivalent, Whole Virus, Aluminium Phosphate Gel Adjuvanted) Influenza Vaccines Containing 3.5[micro]gHA, 6[micro]gHA, 9[micro]gHA or 1. 2011. Available from: <a href="http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011">http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011</a>	exclude - dose-sparing but vaccine not of interest
2 Vajo Z, Tamas F, Jankovics I. A reduced-dose seasonal trivalent influenza vaccine is safe and immunogenic in adult and elderly patients in a randomized controlled trial. <i>Clin Vaccine Immunol.</i> 2012;19(3):313-318. doi:10.1128/CVI.05619-11	exclude - dose-sparing but vaccine not of interest
3 Treanor J, Keitel W, Belshe R, et al. Evaluation of a single dose of half strength inactivated influenza vaccine in healthy adults. <i>Vaccine.</i> 2002;20(7-8):1099-1105. doi:10.1016/s0264-410x(01)00440-6	exclude - dose-sparing but vaccine not of interest
4 Euctr. A Randomized, Active Controlled, Double-blind, Multi-Centre Study to Evaluate Safety and Immunogenicity of One Dose of FLUVAL AB-like (Trivalent, Whole Virus, Aluminium Phosphate Gel Adjuvanted) Influenza Vaccine Containing 6µgHA of Seasonal A/H1N1, A/H3N2 and B Influenza Antigens in Non-elderly Adult and Elderly Subjects. 2011. Available from: <a href="http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011-003314-16-HU">http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011-003314-16-HU</a>	exclude - dose-sparing but experimental vaccine
5 Euctr, E. S. Clinical study to compare the safety of two influenza vaccines in children and adolescents of 3 to less than 18 years of age at risk for influenza-related complications. 2013. Available from: <a href="http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2013">http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2013</a>	exclude - dose-sparing but experimental vaccine
6 Pillet S, Aubin É, Trépanier S, et al. A plant-derived quadrivalent virus like particle influenza vaccine induces cross-reactive antibody and T cell response in healthy adults. <i>Clin Immunol.</i> 2016;168:72-87. doi:10.1016/j.clim.2016.03.008	exclude - dose-sparing but experimental vaccine
7 Lee JH, Cho HK, Kim KH, et al. Evaluation of Waning Immunity at 6 Months after Both Trivalent and Quadrivalent Influenza Vaccination in Korean Children Aged 6-35 Months. <i>J Korean Med Sci.</i> 2019;34(46):e279. Published 2019 Dec 2. doi:10.3346/jkms.2019.34.e279	exclude - dose-sparing but experimental vaccine
8 Treanor JJ, Taylor DN, Tussey L, et al. Safety and immunogenicity of a recombinant hemagglutinin influenza-flagellin fusion vaccine (VAX125) in healthy young adults. <i>Vaccine.</i> 2010;28(52):8268-8274. doi:10.1016/j.vaccine.2010.10.009	exclude - dose-sparing but experimental vaccine
9 Vajo Z, Balaton G, Vajo P, Kalabay L, Erdman A, Torzsa P. Dose sparing and the lack of a dose-response relationship with an influenza vaccine in adult and elderly patients - a randomized, double-blind clinical trial. <i>Br J Clin Pharmacol.</i> 2017;83(9):1912-1920. doi:10.1111/bcp.13289	exclude - dose-sparing but vaccine not of interest
10 Ctri. Study of a Single Dose or Two Doses of a Quadrivalent Influenza Vaccine in Subjects Aged 6 Months or Older in India. 2015. Available from: <a href="http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI">http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI</a>	exclude - dose-sparing but unclear vaccine (waiting for author response)
11 Euctr, F. I. Safety and Immunogenicity of the Quadrivalent Influenza Vaccine Administered via the Intramuscular Route in Children Aged 3 to 8 Years. 2011. Available from: <a href="http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011">http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011</a>	exclude - dose-sparing but unclear vaccine (waiting for

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9	Euctr, C. Z. A randomized, double-blind, placebo-controlled, multi-	sparing but
10	country and multi-center, phase IV study to demonstrate the	unclear vaccine
11	efficacy of GSK Biologicals' influenza vaccine (Fluarix[TM])	(waiting for
12	administered intramuscularly in adults. - FluarixUS-006. 2006.	author
13	Available from: <a href="http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2006">http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2006</a>	response)
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## APPENDIX 6 – Study and patient data

Author, Year [Study design]	Study period; Setting and Country	Objective of study	Eligibility criteria	Sample size; % Female, % previously immunized	Ethnicities
Kramer, 2006 [RCT] <sup>1</sup>	October 2004 – November 2004; 760-bed tertiary care community teaching hospital in the USA	To compare the effectiveness of half-dose versus full dose TIV in health care workers	Age 18 years or older, hospital employee, staff member, or volunteer, and signed informed consent and authorization to use and disclose protected health information for research purposes	444; NR, NR	NR
Belshe, 2007 [RCT] <sup>2</sup>	USA; NR	To compare the immunogenicity and safety of injection of IM and ID TIV across different dose levels (3, 6, 9, and 15µg/antigen/dose)	Healthy adults 18-49 years of age	125; 71.2%, 0%	American Indian/Alaskan Native (0%), Asian (2.4%), Black/African American (9.6%), Hawaiian/Pacific Islander (0%), Hispanic (0%), Multi-racial (0.8%), Non-Hispanic (97.6%), Other/unknown (0%), White (87.2%)
Engler, 2008 [RCT] <sup>3</sup>	November 2004 – December 2004; Allergy-Immunology-Immunization Clinic, WRAMC, and Pentagon/DiLorenzo Health Clinic, Arlington, Virginia in the USA	To determine the effects of age, sex, and dose on the immunogenicity of intramuscular TIV	Healthy adults aged 18-64 years. Inclusion criteria were based on the remaining CDC and/or DoD priority prior to the shortage announcement which includes all children aged 6--23 months; adults aged >65 years; persons aged 2--64 years with underlying chronic medical conditions; all women who will be pregnant during the influenza season; residents of nursing homes and long-term--care facilities; children aged 2--18 years on chronic aspirin therapy; health-care workers involved in direct patient care; and out-of-home caregivers and household contacts of children aged <6 months	1316; 43.4%, 0%	African American (9%), Asian (2%), Hispanic (2%), Other/unknown (1.4%), White (85%)
	August 2007-2008; Seattle Division of the Department of	To determine pre vaccination and 4- week post-vaccination changes in antibody titer, and	Community-dwelling adults 65 years and older living in Puget Sound area in Washington State	129; 17.8%, 94.6%	African American (4.7%), Asian (1.6%), Hispanic (0.8%), Not reported

Author, Year [Study design]	Study period; Setting and Country	Objective of study	Eligibility criteria	Sample size; % Female, % previously immunized	Ethnicities
Chi, 2010 [RCT] <sup>4</sup>	Veterans Affairs Puget Sound Health Care System in Washington State, USA.	local and systemic reactions of full-dose compared to 60% dose of TIV by IM injection			(2.3%), Other (0.8%), White (90%)
Cioppa, 2011 [RCT] <sup>5</sup>	October 2008 – March 2009; 10 study centers in Finland and 5 centers in Belgium	To evaluate the safety, tolerability and immunogenicity of different vaccine formulations with different doses of MF59 adjuvant and/or a second B strain (QIV) when added to either high or low doses of a purified subunit influenza vaccine	Healthy children aged 6 to <36 months	126; 43.5%, NR	Asian (1.68%), Black (6.54%), White (84.2%)
Skowronski, 2011 [RCT] <sup>6</sup>	September 2008 – December 2008; 5 sites in 3 Canadian provinces (British Columbia, Quebec, and Nova Scotia)	To determine whether giving 2 full doses of split TIV to previously unimmunized infants and toddlers can improve immunogenicity without increasing reactogenicity compared with 2 half-doses	Healthy children 6–23 months of age	267; 53.2%, 0%	Asian (7.9%), Other (14.3%), White (77.8%)
Langley, 2012 [RCT] <sup>7</sup>	November 2008 – August 2009; 17 centers in Canada	To assess the immunogenicity and safety of a preservative-free, prefilled syringe formulation of TIV provided as the full adult dose of 0.50 mL compared with the usual children's dose of 0.25 mL in young children	Healthy children 6–35 months at the time of vaccination	390; 47.9%, 42.6%	Other (13.9%), White (86.1%)
Pavia-Ruz, 2015 [RCT] <sup>8</sup>	October 2008 – March 2009; Hong Kong, Mexico, Taiwan, Thailand, and the USA	To evaluate Fluarix at both the standard recommended TIV dose for young children in the US (0.25 ml) and also at double this dose (0.5 ml)	Healthy children aged 6 to 35 months at the time of the first vaccination; without acute illness at the time of enrollment and who had not been vaccinated during the 2008-2009 influenza season. Administration of influenza vaccine in a previous season was not however an exclusion criteria	3318; 51%, 30.1%	African heritage/African American (3.5%), American Indian or Alaskan native (0.1%), Asian-Central/South Asian heritage (0.1%), Asian-East Asian heritage (14.5%), Asian-Japanese heritage (0.1%), Asian-South East Asian heritage

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Author, Year [Study design]	Study period; Setting and Country	Objective of study	Eligibility criteria	Sample size; % Female, % previously immunized	Ethnicities
					(9.2%), Native Hawaiian or other Pacific Islander (0.2%), White - Arabic/North African heritage (0.5%), White-Caucasian/European heritage (29.9%), Hispanics and children of mixed race (42.1%)
Halasa, 2015 [RCT] <sup>9</sup>	2010-2012; 6 study sites in USA	To determine whether a higher dose of influenza vaccine would be safe in the 6 through 35 months age group. In addition, to determine whether immunization with 0.5 mL doses of TIV (15 µg of each HA) would improve the immunogenicity without increasing the reactogenicity of TIV when administered to children 6 through 35 months of age with and without a history of previous TIV vaccination	Healthy children 6 to 35 months of age (naïve cohort) or 12 through 35 months of age (fully primed cohort) who were available for the entire study period and whose parents or guardians provided informed consent were eligible to participate. Children who were eligible in the fully primed cohort also required a history of receiving 2 doses of 2009–2010 H1N1 influenza vaccine and 2 doses of TIV at any time in the past	243; 52%, 13.2%	African (26%), Asian (1%), Multiracial (5%), other (0%); Ethnicity: Hispanic (2%), Non-Hispanic (98%), White (67%)
Phung, 2016 [RCT] <sup>10</sup>	September 2010-January 2011; Finland	To evaluate the immunogenicity and safety following a single intramuscular dose of FLUAD or Agrippal S1 influenza vaccines in healthy children previously vaccinated	Healthy children 6–35 months at the time of vaccination	197; 55.8%, 85.7%	NR
Jain, 2017 [RCT] <sup>11</sup>	2014-2015 influenza season; 66 study locations in USA and Mexico	To compare the safety and immunogenicity of a double-dose IIV4 manufactured by GSK Vaccines with the United States-approved standard-dose IIV4 in children 6–35 months of age	Healthy children aged 6-35 months regardless of influenza vaccination history, but could not have received any seasonal or pandemic influenza vaccine within 6 months before the first dose of study vaccine	2424; 46.9%, 57.5%	African/African American (13.9%), American Indian or Alaskan Native (2.0%), Caucasian (64.3%), Other (17.9%), South East Asian (1.8%)
Ojeda, 2019 [RCT] <sup>12</sup>	December 2017 – January 2018; 3 study sites in Mexico	Reported the results of an open-label, randomized phase III study designed to evaluate the immunogenicity and safety	Children aged 6 months to 17 years of age	302; 46.4%, NR	NR

Author, Year [Study design]	Study period; Setting and Country	Objective of study	Eligibility criteria	Sample size; % Female, % previously immunized	Ethnicities
		of this thiomersal containing MDV format of QIV compared to the licensed thiomersal-free, single-dose PFS format in children and adolescents			
Robertson, 2019 [RCT] <sup>13</sup>	September 2016 – March 2017; 38 sites in the USA	To compare the safety and immunogenicity of full and half doses of quadrivalent, split-virion, inactivated influenza vaccine in children 6–35 months of age	Healthy children 6–35 months of age who had not been vaccinated against influenza during the current season (2016–2017). Children 6–11 months of age had to be born at full term of pregnancy (≥37 weeks) or with a birth weight ≥2.5 kg	1950; 49.7%, 47.3%	Race: American Indian or Alaska Native (0.98%), Asian (0.46%), Black (19.2%), Native Hawaiian or Other Pacific Islander (0.46%), White (74.3%), Ethnicity: Hispanic or Latino (22%), not Hispanic or Latino (77%)

**Abbreviations:** CDC- Centers for Disease Control and Prevention; DoD- Department of Defense; GSK -GlaxoSmithKline; HA- hemagglutinin; IIV4 – inactivated influenza vaccine; ID - intradermal; IM - intramuscular; MDV- multi-dose vial; PFS – pre-filled syringe; QIV-quadrivalent influenza vaccine; TIV-trivalent influenza vaccine; NR – not reported

**APPENDIX 7 – Treatment and outcome data**

<b>Author, Year; [Study design] Population</b>	<b>Treatment arms</b> Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	<b>Effectiveness and Safety</b> Outcome (definition): n/N (unless otherwise indicated)	<b>Conclusions</b>
Kramer, 2006 [RCT] <sup>1</sup>  Adults and Seniors (>18 years)	Fluzone (Aventis Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose (Intramuscular into the deltoid region)]  <i>A/Wyoming/3/2003 (H3N2), A/New Caledonia/20/99 (H1N1), and a new B strain, B/Jiangsu/10/2003</i>  Fluzone (Aventis Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose (Intramuscular into the deltoid region)]  <i>A/Wyoming/3/2003 (H3N2), A/New Caledonia/20/99 (H1N1), and a new B strain, B/Jiangsu/10/2004</i>	<b>Effectiveness</b> <i>Lab confirmed influenza</i> (Laboratory confirmation of influenza diagnosis was sought in participants reporting a clinical diagnosis by their physicians): 1/222  <i>Influenza like illness</i> (Clinical diagnosis of influenza. Participants self-reported four or more symptoms consistent with influenza-like illness (i.e., headache, extreme tiredness, dry cough, fever, muscle or body aches)): 8/222  <b>Effectiveness</b> <i>Lab confirmed influenza</i> (Laboratory confirmation of influenza diagnosis was sought in participants reporting a clinical diagnosis by their physicians): 0/222  <i>Influenza like illness</i> (Clinical diagnosis of influenza. Participants self-reported four or more symptoms consistent with influenza-like illness (i.e., headache, extreme tiredness, dry cough, fever, muscle or body aches)): 15/222	<ul style="list-style-type: none"> <li>There was no significant difference between the full-dose and half-dose groups in the diagnosis of influenza or in the proportion of participants self-reporting four or more symptoms consistent with influenza-like illness.</li> <li>No adverse events were noted by participants from either group or reported to the IRB during the course of the study</li> </ul>
Belshe, 2007 [RCT] <sup>2</sup>  Adults (18-49 years)	Fluzone (Sanofi-Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose (Intramuscular in the non-dominant arm)]  Fluzone (Sanofi-Pasteur), <b>9-µg/strain</b> [1 x 0.3mL dose (Intramuscular in the non-dominant arm)]	<b>Reactogenicity – injection site</b> <i>Pain</i> <sup>1</sup> : 15/31 <i>Redness</i> <sup>2</sup> : 8/31 <i>Swelling</i> <sup>2</sup> : 7/31  <b>Reactogenicity – systemic</b> <i>Fever</i> <sup>3</sup> : 1/31 <i>Headache</i> <sup>1</sup> : 15/31 <i>Malaise</i> <sup>1</sup> : 8/31 <i>Myalgia</i> <sup>1</sup> : 10/31  <b>Reactogenicity – injection site</b> <i>Pain</i> <sup>1</sup> : 11/31 <i>Redness</i> <sup>2</sup> : 11/31 <i>Swelling</i> <sup>2</sup> : 4/31  <b>Reactogenicity – systemic</b> <i>Fever</i> <sup>3</sup> : 1/31 <i>Headache</i> <sup>1</sup> : 6/31	<ul style="list-style-type: none"> <li>Intradermal vaccine induced significantly more local inflammatory response than Intramuscular vaccine (primary comparison of this study was ID vs IM doses)</li> </ul>

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety Outcome (definition): n/N (unless otherwise indicated)	Conclusions
	<p>Fluzone (Sanofi-Pasteur), <b>6-µg/strain</b> [1 x 0.2mL dose (Intramuscular in the non-dominant arm)]</p>	<p><i>Malaise</i><sup>1</sup>: 8/31 <i>Myalgia</i><sup>1</sup>: 6/31</p> <p><b>Reactogenicity – injection site</b> <i>Pain</i><sup>1</sup>: 14/31 <i>Redness</i><sup>2</sup>: 9/31 <i>Swelling</i><sup>2</sup>: 4/31</p> <p><b>Reactogenicity – systemic</b> <i>Fever</i><sup>3</sup>: 0/31 <i>Headache</i><sup>1</sup>: 9/31 <i>Malaise</i><sup>1</sup>: 7/31 <i>Myalgia</i><sup>1</sup>: 9/31</p>	
	<p>Fluzone (Sanofi-Pasteur), <b>3-µg/strain</b> [1 x 0.1mL dose (Intramuscular in the non-dominant arm)]</p>	<p><b>Reactogenicity – injection site</b> <i>Pain</i><sup>1</sup>: 15/31 <i>Redness</i><sup>2</sup>: 9/31 <i>Swelling</i><sup>2</sup>: 7/31</p> <p><b>Reactogenicity – systemic</b> <i>Fever</i><sup>3</sup>: 3/31 <i>Headache</i><sup>1</sup>: 8/31 <i>Malaise</i><sup>1</sup>: 3/31 <i>Myalgia</i><sup>1</sup>: 7/31</p>	
<p>Engler, 2008 [RCT]<sup>3</sup></p> <p><i>Adults</i> (18-64 years)</p>	<p>Fluzone (Aventis Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose (Intramuscular injection)]</p> <p><i>A/H1N1, A/New Caledonia/20/99; A/H3N2, A/Fujian/411/2002; B, B/Shanghai/361/2002</i></p>	<p><b>Effectiveness</b> <i>Influenza like illness</i> (Influenza-like illness and complications resulting in either inpatient or outpatient medical encounters were compared between dose groups (by age)): 61/632</p> <p><i>Hospitalization or Emergency visits</i>: 0.3%</p> <p><b>Reactogenicity – local/injection site</b> <i>Any local reactions</i> (NR): 8.9% <i>Arm weakness</i> (NR): 8.3% <i>Numbness or burning</i> (NR): 9.7% <i>Pain</i> (NR): 5.9% <i>Redness or swelling</i> (NR): 13.4%</p> <p><b>Reactogenicity – systemic</b> <i>Joint and/or muscle pain</i> (NR): 4.5%</p>	<ul style="list-style-type: none"> <li>▪ The relative risk of medical visits and hospitalizations for influenza-like illnesses were similar in the half- and full-dose group regardless of age, and there was no evidence of ILI symptom differences by sex or dose during the 21 days after immunizations.</li> <li>▪ Although injection site pain was greater for full vs half dose (19.9% vs 14.4%; p=.01), when analyzed for clinically significant pain levels significant dose-dependent pain differences were not</li> </ul>



Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety Outcome (definition): n/N (unless otherwise indicated)	Conclusions
	<p>Fluzone (Aventis Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose (Intramuscular injection)]</p> <p><i>A/H1N1, A/New Caledonia/20/99; A/H3N2, A/Fujian/411/2002; B, B/Shanghai/361/2003</i></p>	<p><b>Adverse events</b> SAE: 2/554</p> <p><b>Effectiveness</b> <i>Influenza like illness</i> (Influenza-like illness and complications resulting in either inpatient or outpatient medical encounters were compared between dose groups (by age): 64/644</p> <p><i>Hospitalization or Emergency visits</i>: 0.2%</p> <p><b>Reactogenicity – local/injection site</b> <i>Any local reactions</i> (NR): 7.5% <i>Arm weakness</i> (NR): 6.5% <i>Numbness or burning</i> (NR): 7.8% <i>Pain</i> (NR): 4.6% <i>Redness or swelling</i> (NR): 8.6%</p> <p><b>Reactogenicity – systemic</b> <i>Joint and/or muscle pain</i> (NR): 2.2%</p> <p><b>Adverse events</b> SAE: 1/556</p>	<p>identified.</p> <ul style="list-style-type: none"> <li>Joint and/or muscle pain were significantly different (p=.02 and p=.03, respectively) by dose.</li> <li>No other adverse event differed significantly by dose</li> </ul>
<p>Chi, 2010 [RCT]<sup>4</sup></p> <p>Seniors (&gt;65 years)</p>	<p>Fluzone (Sanofi Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose (intramuscular in deltoid of arm)]</p> <p><i>A/Solomon Islands/3/ 2006 (A/H1N1), A/Wisconsin/67/2005 (A/H3N2), and B/Malaysia/2506/2004</i></p>	<p><b>Reactogenicity – injection site, N=64</b> <i>Arm motion limitation</i>: 1 (grade I)<sup>4</sup> <i>Itching</i>: 4 (grade I)<sup>4</sup> <i>Pain</i>: 7 (grade I)<sup>4</sup> <i>Redness or discoloration</i>: 9 (grade I)<sup>4</sup> <i>Swelling</i>: 13 (grade I)<sup>4</sup></p> <p><b>Reactogenicity - systemic, N=64</b> <i>Chills</i>: 1 (grade I)<sup>4</sup>, 1 (grade II/III)<sup>5</sup> <i>Fatigue</i>: 4 (grade I)<sup>4</sup>, 2 (grade II/III)<sup>5</sup> <i>Fever</i>: 0 <i>General body ache/pain</i>: 6 (grade I)<sup>4</sup>, 1 (grade II/III)<sup>5</sup> <i>Headache</i>: 10 (grade I)<sup>4</sup> <i>Nausea</i>: 3 (grade I)<sup>4</sup>, 1 (grade II/III)<sup>5</sup></p> <p><b>Adverse events</b></p>	<ul style="list-style-type: none"> <li>The two SAEs were acute coronary syndrome and appendicitis and neither were judged to be related to influenza vaccination</li> </ul>

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety <i>Outcome</i> (definition): n/N (unless otherwise indicated)	Conclusions
	<p>Fluzone (Sanofi Pasteur), <b>9-µg/strain</b> [1 x 0.3mL dose (intramuscular in deltoid of arm)]</p> <p><i>A/Solomon Islands/3/ 2006 (A/H1N1), A/Wisconsin/67/2005 (A/H3N2), and B/Malaysia/2506/2004</i></p>	<p>SAE<sup>6</sup>: 0/64</p> <p><b>Reactogenicity – injection site, N=64</b> <i>Arm motion limitation</i>: 1 (grade I)<sup>4</sup> <i>Itching</i>: 5 (grade I)<sup>4</sup> <i>Pain</i>: 11 (grade I)<sup>4</sup> <i>Redness or discoloration</i>: 7 (grade I)<sup>4</sup> <i>Swelling</i>: 4 (grade I)<sup>4</sup></p> <p><b>Reactogenicity - systemic, N=64</b> <i>Chills</i>: 1 (grade I)<sup>4</sup>, 1 (grade II/III)<sup>5</sup> <i>Fatigue</i>: 6 (grade I)<sup>4</sup>, 1 (grade II/III)<sup>5</sup> <i>Fever</i>: 1 (grade I)<sup>4</sup> <i>General body ache/pain</i>: 5 (grade I)<sup>4</sup>, 2 (grade II/III)<sup>5</sup> <i>Headache</i>: 5 (grade I)<sup>4</sup>, 1 (grade II/III)<sup>5</sup> <i>Nausea</i>: 2 (grade I)<sup>4</sup>, 1 (grade II/III)<sup>5</sup></p> <p><b>Adverse events</b> SAE<sup>6</sup>: 2/64</p>	
<p>Cioppa, 2011 [RCT]<sup>5</sup></p> <p><i>Infants/ Toddlers (6-36 months)</i></p>	<p>NR - TIV, <b>7.5-µg/strain</b> [2 x 0.25mL dose (intramuscular in deltoid of arm (children 24-35 mo of age) or the anterolateral aspect of the thigh (children &lt;24 mo of age) using prefilled syringes)]</p> <p><i>A/Brisbane/59/2007 (A/H1N1)-like virus, A/Brisbane/10/2007 (A/H3N2)-like virus, and B/Florida/4/2006-like virus (of the influenza B/Yamagata lineage)</i></p> <p>Agrippal - TIV, <b>15-µg/strain</b> [2 x 0.5mL dose (intramuscular in deltoid of arm (children 24-35 mo of age) or the anterolateral aspect of the thigh (children &lt;24 mo of age) using prefilled syringes)]</p> <p><i>A/Brisbane/59/2007 (A/H1N1)-like virus, A/Brisbane/10/2007 (A/H3N2)-like virus, and B/Florida/4/2006-like virus (of the influenza B/Yamagata lineage)</i></p>	<p><b>Reactogenicity</b> <i>Any local reaction</i><sup>7</sup>: 47% <i>Any systemic reaction</i><sup>8</sup>: 68%</p> <p><b>Adverse events</b> AE (solicited/spontaneously reported): 84% SAE: 0/25</p> <p><b>Reactogenicity</b> <i>Any local reaction</i><sup>7</sup>: 59% <i>Any systemic reaction</i><sup>8</sup>: 50%</p> <p><b>Adverse events</b> AE (solicited/spontaneously reported): 82% SAE: 0/22</p>	<ul style="list-style-type: none"> <li>Reactogenicity of the 7.5-µg TIV/QIV formulations was slightly lower than for the corresponding 15-µg formulations.</li> <li>The majority of unsolicited AEs were mild or moderate in severity and none of the SAEs was considered to be related to the study vaccine.</li> </ul>

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety <i>Outcome</i> (definition): n/N (unless otherwise indicated)	Conclusions
	NR - QIV, <b>7.5-µg/strain</b> [2 x 0.25mL dose (intramuscular in deltoid of arm (children 24-35 mo of age) or the anterolateral aspect of the thigh (children <24 mo of age) using prefilled syringes)]  <i>A/Brisbane/59/2007 (A/H1N1)-like virus, A/Brisbane/10/2007 (A/H3N2)-like virus, B/Florida/4/2006-like virus (of the influenza B/Yamagata lineage), and B/Malaysia/2506/2004-like antigen virus (Victoria lineage)</i>	<b>Reactogenicity</b> <i>Any local reaction</i> <sup>7</sup> : 25% <i>Any systemic reaction</i> <sup>8</sup> : 50%  <b>Adverse events</b> <i>AE (solicited/spontaneously reported)</i> : 92% SAE: 1/25	
	NR - QIV, <b>15-µg/strain</b> [2 x 0.5mL dose (intramuscular in deltoid of arm (children 24-35 mo of age) or the anterolateral aspect of the thigh (children <24 mo of age) using prefilled syringes)]  <i>A/Brisbane/59/2007 (A/H1N1)-like virus, A/Brisbane/10/2007 (A/H3N2)-like virus, B/Florida/4/2006-like virus (of the influenza B/Yamagata lineage), and B/Malaysia/2506/2004-like antigen virus (Victoria lineage)</i>	<b>Reactogenicity</b> <i>Any local reaction</i> <sup>7</sup> : 39% <i>Any systemic reaction</i> <sup>8</sup> : 54%  <b>Adverse events</b> <i>AE (solicited/spontaneously reported)</i> : 71% SAE: 1/28	
	Vaxigrip pediatric - TIV (Sanofi Pasteur), <b>7.5-µg/strain</b> [2 x 0.25mL dose (intramuscular in deltoid of arm (children 24-35 mo of age) or the anterolateral aspect of the thigh (children <24 mo of age) using prefilled syringes)]	<b>Reactogenicity</b> <i>Any local reaction</i> <sup>7</sup> : 50% <i>Any systemic reaction</i> <sup>8</sup> : 46%  <b>Adverse events</b> <i>AE (solicited/spontaneously reported)</i> : 73% SAE: 1/26	
Skowronski, 2011 [RCT] <sup>6</sup>  <i>Infants/Toddlers (6-23 months)</i>	Vaxigrip (Sanofi-Pasteur), 15-µg/strain [ <b>2 x 0.5mL dose</b> (Intramuscular injection)]  <i>A/Brisbane/10/07 (H3N2); A/Brisbane/59/07 (H1N1); and B/Florida/4/06 (Yamagata lineage)</i>	<b>Reactogenicity – injection site</b> <i>Induration</i> (NR): 13.7% <i>Redness</i> (NR): 22.6% <i>Swelling</i> (NR): 15.3% <i>Tenderness</i> (NR): 22.6%  <b>Reactogenicity – systemic</b> <i>Fever (&gt;37.5°C)</i> : 8.06% <i>Irritability</i> (NR): 59.7% <i>Decreased appetite</i> (NR): 38.7%	<ul style="list-style-type: none"> <li>▪ Local reactions generally were less common in infants than toddlers and more common with full doses versus half doses, but none of these differences were significant.</li> <li>▪ One serious adverse event was reported: a toddler in the half dose group was</li> </ul>

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety <i>Outcome</i> (definition): n/N (unless otherwise indicated)	Conclusions
	<p>Vaxigrip (Sanofi-Pasteur), 15-µg/strain [2 x 0.25mL dose (Intramuscular injection)]</p> <p><i>A/Brisbane/10/07 (H3N2); A/Brisbane/59/07 (H1N1); and B/Florida/4/06 (Yamagata lineage)</i></p>	<p><i>Drowsiness</i> (NR): 39.5% <i>Sleep disturbance</i> (NR): 54.8%</p> <p><b>Adverse events</b> SAE: NR</p> <p><b>Reactogenicity – injection site</b> <i>Induration</i> (NR): 6.3% <i>Redness</i> (NR): 20.3% <i>Swelling</i> (NR): 8.6% <i>Tenderness</i> (NR): 25.8%</p> <p><b>Reactogenicity – systemic</b> <i>Fever (&gt;37.5°C)</i>: 11.7% <i>Irritability</i> (NR): 60.2% <i>Decreased appetite</i> (NR): 43% <i>Drowsiness</i> (NR): 41.4% <i>Sleep disturbance</i> (NR): 50%</p> <p><b>Adverse events</b> SAE: 1/128</p>	<p>hospitalized with pneumonia 28 days after the first vaccination. The event was deemed unlikely related to the vaccine.</p> <ul style="list-style-type: none"> <li>▪ All of the rate differences were significantly below the allowed 10% increase in reactogenicity for the full dose (p&lt; 0.001 for infant and combined analyses, p&lt;.005 for toddlers).</li> <li>▪ This randomized controlled trial in infants and toddlers shows that compared with 0.25-mL half-dosing, administration of 2 full 0.5-mL doses of trivalent inactivated influenza vaccine can increase antibody response without increasing reactogenicity in previously unimmunized infants aged 6 to 11 months.</li> </ul>
<p>Langley, 2012 [RCT]<sup>7</sup></p> <p><i>Infants/ Toddlers (6-35 months)</i></p>	<p>Fluviral F1 (Sanofi-Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose (Intramuscularly in the anterolateral part of the thigh (if the participant was less than 12 months) or in the deltoid region of the arm)]</p> <p><i>A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (an A/Brisbane/10/2007 [H3N2]-like virus), and B/Florida/4/2006</i></p>	<p><b>Reactogenicity – injection site</b> <i>Pain</i> (NR): 45/164 <i>Redness</i> (NR): 49/164 <i>Swelling</i> (NR): 22/164</p> <p><b>Reactogenicity – systemic</b> <i>Drowsiness</i> (NR) – 44/164 <i>Fever</i> (NR) – 10/164 <i>Irritability</i> (NR) – 62/164 <i>Loss of appetite</i> (NR) – 37/164</p> <p><b>Adverse events</b> SAE: 1/164</p>	<ul style="list-style-type: none"> <li>▪ Fluviral F1 group had 1 case of pneumonia resolved</li> <li>▪ Fluviral F2 group had 1 case of bronchial hyper-reactivity in resolving stage</li> <li>▪ The 0.5-mL dose of the study vaccine, when administered to children aged 6–35 months, resulted in a modest but not statistically significant improvement in</li> </ul>

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety Outcome (definition): n/N (unless otherwise indicated)	Conclusions
	<p>Fluviral F2 (Sanofi-Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose (Intramuscularly in the anterolateral part of the thigh (if the subject was less than 12 months) or in the deltoid region of the arm)]</p> <p><i>A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (an A/Brisbane/10/2007 [H3N2]-like virus), and B/Florida/4/2006</i></p>	<p><i>Unsolicted adverse events (NR): 108/164</i> <i>Medically attended events (NR): 52/164</i></p> <p><b>Reactogenicity – injection site</b> <i>Pain (NR): 55/167</i> <i>Redness (NR): 54/167</i> <i>Swelling (NR): 24/167</i></p> <p><b>Reactogenicity – systemic</b> <i>Drowsiness (NR) – 52/167</i> <i>Fever (NR) – 6/167</i> <i>Irritability (NR) – 69/167</i> <i>Loss of appetite (NR) – 43/167</i></p> <p><b>Adverse events</b> <i>SAE: 1/167</i> <i>Unsolicted adverse events (NR): 112/167</i> <i>Medically attended events (NR): 40/167</i></p>	<p>immunogenicity with clinically similar safety and reactogenicity compared with the 0.25-mL dose.</p>
	<p>Vaxigrip (Sanofi-Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose (Intramuscularly in the anterolateral part of the thigh (if the participant was less than 12 months) or in the deltoid region of the arm)]</p> <p><i>A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (an A/Brisbane/10/2007 [H3N2]-like virus), and B/Florida/4/2006</i></p>	<p><b>Reactogenicity – injection site</b> <i>Pain (NR): 17/43</i> <i>Redness (NR): 13/43</i> <i>Swelling (NR): 5/43</i></p> <p><b>Reactogenicity – systemic</b> <i>Drowsiness (NR) – 11/43</i> <i>Fever (NR) – 2/43</i> <i>Irritability (NR) – 15/43</i> <i>Loss of appetite (NR) – 9/43</i></p> <p><b>Adverse events</b> <i>SAE: NR/43</i> <i>Unsolicted adverse events (NR): 24/43</i> <i>Medically attended events (NR): 9/43</i></p>	
<p>Pavia-Ruz, 2013 [RCT]<sup>8</sup></p> <p><i>Infants/Toddlers</i></p>	<p>Fluarix (GSK), <b>15-µg/strain</b> [1 x 0.5mL dose (intramuscular injection into the right deltoid muscle or anterolateral thigh)]</p>	<p><b>Reactogenicity – injection site</b> <i>Any injection site reactions<sup>9</sup>: 514/1086</i> <i>Pain: 406/1086</i> <i>Redness: 249/1086</i> <i>Swelling: 170/1086</i></p>	<ul style="list-style-type: none"> <li>▪ The reactogenicity and safety profile of the study vaccine did not appear to be affected by doubling the dose.</li> <li>▪ One subject in the Flu-15µg</li> </ul>

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety Outcome (definition): n/N (unless otherwise indicated)	Conclusions
(6-35 months)	A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2) and B/Brisbane/3/2007	<b>Reactogenicity – systemic</b> Any general reactions <sup>10</sup> : 575/1086 Drowsiness: 317/1086 Fever: 69/1086 Irritability: 387/1086 Loss of appetite: 273/1086  <b>Adverse events</b> Any AE: 729/1086 SAE: 29/1086	group had two SAEs, (apnea and cyanosis) which were considered by the investigator to be possibly related to vaccination. The participant was hospitalized and the events resolved on the same day as they occurred.
	Fluarix (GSK), <b>7.5-µg/strain</b> [1 x 0.25 mL dose (intramuscular injection into the right deltoid muscle or anterolateral thigh)]  A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2) and B/Brisbane/3/2007	<b>Reactogenicity – injection site</b> Any injection site reactions <sup>9</sup> : 492/1081 Pain: 403/1081 Redness: 259/1081 Swelling: 152/1081  <b>Reactogenicity – systemic</b> Any general reactions <sup>10</sup> : 598/1081 Drowsiness: 293/1081 Fever: 67/1081 Irritability: 386/1081 Loss of appetite: 281/1081  <b>Adverse events</b> Any AE: 724/1081 SAE: 35/1081	
	Fluzone (Sanofi-Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose (intramuscular injection into the right deltoid muscle or anterolateral thigh)]  A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2) and B/Florida/4/2006	<b>Reactogenicity – injection site</b> Any injection site reactions <sup>9</sup> : 467/1090  Pain: 363/1090 Redness: 253/1090 Swelling: 129/1090  <b>Reactogenicity – systemic</b> Any general reactions <sup>10</sup> : 592/1090 Drowsiness: 298/1090 Irritability: 375/1090 Fever: 72/1090 Loss of appetite: 270/1090	

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety Outcome (definition): n/N (unless otherwise indicated)	Conclusions
		<b>Adverse events</b> Any AE: 722/1090 SAE: 31/1090	
Halasa, 2015 [RCT] <sup>9</sup>  Infants/Toddlers (6-35 months)	Fluzone (Sanofi Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose (intramuscular)]  A/California/7/09 (H1N1)-like virus, A/Perth/16/2009 (H3N2)-like virus, and B/Brisbane/60/2008-like virus	<b>Reactogenicity</b> Redness at injection site: 8/48 Fever (temperature >39°C after the first dose): 7/80	<ul style="list-style-type: none"> <li>No significant differences between the full-dose or half-dose groups for either the fully primed or naive cohorts for systemic reactions or local reactions when both seasons were combined.</li> <li>The only significant difference in the 2011–2012 season was that 8 of 48 (16.7%) participants in the half-dose group compared with 32 of 96 (33.3%) in the full-dose group had increased redness at the injection site (P &lt; .05).</li> <li>No significant differences between the groups in unsolicited AEs, serious adverse events (SAEs), or onset of chronic medical conditions between the dose groups in either the naive or fully primed cohorts, and none of the SAEs were deemed related to the vaccine.</li> </ul>
	Fluzone (Sanofi Pasteur), <b>15-µg/strain</b> [1 x 0.5 mL dose (intramuscular)]  A/California/7/09 (H1N1)-like virus, A/Perth/16/2009 (H3N2)-like virus, and B/Brisbane/60/2008-like virus	<b>Reactogenicity</b> Redness at injection site: 32/96 Fever (temperature >39°C after the first dose): 19/161	
Phung, 2016 [RCT] <sup>10</sup>  Infants/Toddlers (6-35 months)	FLUAD (NR), <b>NR [1 x 0.5mL dose]</b> (Intramuscular injection)  A/H1N1, A/H3N2, Strain B	<b>Reactogenicity</b> Any local reaction <sup>11</sup> : 45/61 Any systemic reaction <sup>12</sup> : 36/61  <b>Adverse events</b> SAE (based on MedDRA v 17.1 definition): 2/61  <b>Reactogenicity</b> Any local reaction <sup>11</sup> : 63/75	

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety Outcome (definition): n/N (unless otherwise indicated)	Conclusions
	A/H1N1, A/H3N2, Strain B	Any systemic reaction <sup>12</sup> : 42/75  <b>Adverse events</b> SAE (based on MedDRA v 17.1 definition): 2/75	
	Agrippal S1 (NR), NR [1 x 0.5mL dose (Intramuscular injection)]  A/H1N1, A/H3N2, Strain B	<b>Reactogenicity</b> Any local reaction <sup>11</sup> : 42/51 Any systemic reaction <sup>12</sup> : 24/51  <b>Adverse events</b> SAE (based on MedDRA v 17.1 definition): 0/51	
	Agrippal S1 (NR), NR [1 x 0.25mL dose (Intramuscular injection)] A/H1N1, A/H3N2, Strain B	<b>Reactogenicity</b> Any local reaction <sup>11</sup> : 6/10 Any systemic reaction <sup>12</sup> : 5/10  <b>Adverse events</b> SAE (based on MedDRA v 17.1): 0/10	
Jain, 2017 [RCT] <sup>11</sup>  Infants/Toddlers (6-35 months)	Flulaval Quadrivalent (GSK), <b>15-µg/strain</b> [1 x 0.5mL dose (intramuscular in deltoid region)]  A/California/7/2009 (A/H1N1), A/Texas/50/2012 (A/H3N2), B/Brisbane/60/2008 (B/Victoria), and B/Massachusetts/2/2012 (B/Yamagata)	<b>Reactogenicity – injection site (within 7 days)</b> Pain: 44.0% Redness: 1.4% Swelling: 1.0%  <b>Reactogenicity – systemic (within 7 days)</b> Drowsiness: 40.6% Fever (>=38.0C): 7.9% Irritability/fussiness: 54.4% Loss of appetite: 33.7%  <b>Adverse events</b> Any AE: 45.5% Vaccine-related AE: 5.9% Any SAE <sup>13</sup> : 1.8% Febrile seizures: 0.4% Medically attended event <sup>14</sup> : 60.2%	<ul style="list-style-type: none"> <li>▪ None of the febrile seizures or the SAEs were considered by the investigator to be related to vaccination</li> <li>▪ Double-dose IIV4 may improve protection against influenza B in some young children and simplifies annual influenza vaccination by allowing the same vaccine dose to be used for all eligible children and adults.</li> </ul>
	Fluzone Quadrivalent (Sanofi Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose (intramuscular in deltoid region)]	<b>Reactogenicity – injection site (within 7 days)</b> Pain: 40.1% Redness: 1.4% Swelling: 0.4%  <b>Reactogenicity – systemic (within 7 days)</b>	



Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety Outcome (definition): n/N (unless otherwise indicated)	Conclusions
	<p>A/California/7/2009 (A/H1N1), A/Texas/50/2012 (A/H3N2), B/Brisbane/60/2008 (B/Victoria), and B/Massachusetts/2/2012 (B/Yamagata)</p>	<p>Drowsiness: 40.9% Fever (<math>\geq 38.0^{\circ}\text{C}</math>): 7.5% Irritability/fussiness: 50.5% Loss of appetite: 33.4%</p> <p><b>Adverse events</b> Any AE: 44.1% Vaccine-related AE: 5.8% Any SAE<sup>13</sup>: 1.7% Febrile seizures: 0.3% Medically attended event<sup>14</sup>: 59.1%</p>	
<p>Ojeda. 2019 [RCT]<sup>12</sup>  Infants/Toddlers and Children (6 months – 17 years)</p>	<p>Vaxigrip Tetra (Sanofi Pasteur) – <b>PFS</b>, 15-<math>\mu\text{g}</math>/strain [1 x 0.5mL dose (intramuscular or deep subcutaneous injection)]</p> <p>A/Michigan/45/2015 (H1N1)pdm09-like virus, A/Hong Kong/4801/2014 (H3N2)-like virus, /Brisbane/60/2008-like virus (B/Victoria lineage), and B/Phuket/3073/2013 (B/Yamagata lineage)</p> <p>Vaxigrip Tetra (Sanofi Pasteur) - <b>MDV</b>, 15-<math>\mu\text{g}</math>/strain [1 x 0.5mL dose (intramuscular or deep subcutaneous injection)]</p> <p>A/Michigan/45/2015 (H1N1)pdm09-like virus, A/Hong Kong/4801/2014 (H3N2)-like virus, /Brisbane/60/2008-like virus (B/Victoria lineage), and B/Phuket/3073/2013 (B/Yamagata lineage)</p>	<p><b>Reactogenicity, N=142</b> Any injection-site reaction (solicited within 7 days): 26 (6-35mo), 16 (3-8yr), 42 (9-7yr) Any systemic reaction (solicited within 7 days): 25 (6-35mo), 15 (3-8yr), 35 (9-7yr)</p> <p><b>Adverse events, N=147</b> AE (immediate unsolicited): 1 (9-17 years) Non-serious AE: 25 (6-35mo), 9 (3-8yr), 8 (9-7yr) Vaccine-related non-serious AE: 1 (9-17 years) AE leading to study discontinuation: 0 SAE: 0</p> <p><b>Reactogenicity, N=139</b> Any injection-site reaction(solicited within 7 days): 27 (6-35mo), 16 (3-8yr), 26 (9-7yr) Any systemic reaction(solicited within 7 days): 33 (6-35mo), 13 (3-8yr), 30 (9-7yr)</p> <p><b>Adverse events, N=150</b> AE (immediate unsolicited): 0 Non-serious AE: 31 (6-35mo), 14 (3-8yr), 5 (9-7yr) Vaccine-related non-serious AE: 0 AE leading to study discontinuation: 0 SAE: 0</p>	<ul style="list-style-type: none"> <li>▪ Solicited reactions were mostly grade 1 (mild) in intensity and resolved within 3 days.</li> <li>▪ Solicited systemic reactions were reported in more infants aged 6 – 35 months in the MDV group than in the PFS group however, because the 95% CIs were overlapping, this was not thought clinically significant.</li> <li>▪ None of these unsolicited AEs were considered related to a study vaccine by the investigators.</li> <li>▪ There were no differences in reactogenicity or safety between the two vaccine formats. These results showed that the MDV format of QIV was as safe and immunogenic as the PFS format in infants, children, and adolescents. These findings support the use of MDV QIV</li> </ul>

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety Outcome (definition): n/N (unless otherwise indicated)	Conclusions
			as a resource-saving alternative for seasonal influenza vaccination.
Robertson, 2019 [RCT] <sup>13</sup>  Infants/Toddlers (6-35 months)	<p>Fluzone Quadrivalent (Sanofi Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose (intramuscular single-dose syringes in deltoid of arm)]</p> <p><i>A/California/07/2009 X-179A (H1N1), A/Hong Kong/4801/2014 X-263B (H3N2), B/Brisbane/60/2008 (Victoria lineage), B/Phuket/3073/2013 (Yamagata lineage)</i></p> <p>Fluzone Quadrivalent (Sanofi Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose (intramuscular single-dose syringes in deltoid of arm)]</p> <p><i>A/California/07/2009 X-179A (H1N1), A/Hong Kong/4801/2014 X-263B (H3N2), B/Brisbane/60/2008 (Victoria lineage), B/Phuket/3073/2013 (Yamagata lineage)</i></p>	<p><b>Reactogenicity</b> <i>Any injection-site reaction</i><sup>15</sup>: 533/939 <i>Any systemic reaction</i><sup>16</sup>: 561/941</p> <p><b>Adverse events</b> <i>Vaccine-related AE</i> (immediate within 30 mins): 0/992 <i>Vaccine-related AE</i> (within 28 days): 30/992 <i>AE leading to study discontinuation</i>: 0/992 SAE: 5/992</p> <p><b>Reactogenicity</b> <i>Any injection-site reaction</i><sup>15</sup>: 480/909 <i>Any systemic reaction</i><sup>16</sup>: 533/909</p> <p><b>Adverse events</b> <i>Vaccine-related AE</i> (unsolicited within 30 mins): 1/949 <i>Vaccine-related AE</i> (unsolicited within 28 days): 29/949 <i>AE leading to study discontinuation</i>: 3/949 SAE: 5/949</p>	<ul style="list-style-type: none"> <li>▪ Proportions of participants reporting solicited injection-site reactions, solicited systemic reactions, vaccine-related unsolicited AEs were similar for the full- and half-dose groups</li> <li>▪ None of the AEs leading to study discontinuation or the SAEs were considered related to vaccination</li> <li>▪ A single AE of special interest (chronic urticaria first appearing 3 days post-vaccination and continuing for &gt;6 weeks) was considered by the investigator to be related to vaccination</li> <li>▪ In children 6–35 months of age, a full dose of IIV4 was immunogenic and had a safety profile comparable to that of a half dose with no new safety concerns observed.</li> </ul>

**Abbreviations:** AE – adverse events, ID – intradermal; ILI – influenza-like illness; IM – intramuscular; MDV – multi-dose vials, n – number of people with condition, N – sample size of treatment arm, NR – not reported, PFS – prefilled syringe, SAE – serious adverse events

<sup>1</sup> Defined as mild (easily tolerated), moderate (interferes with normal behaviour or activities), severe (incapacitating, unable to perform usual activities, may require medical attention)

<sup>2</sup> Present at or near the approximate point of needle entry; small <2.5cm, medium >2.5cm to <5cm, large >5cm

<sup>3</sup> Oral temperature >37.5 C; mild >37.5 to 38 C, moderate >38.1 to 39 C, severe >39.1 C

<sup>4</sup> Grade I reactions defined as “present but easily tolerated” for fatigue, muscle ache, headache, itching or pain at injection site; oral temperature >=38 and <39 degrees Celsius; some limitation to arm motion due to stiffness or discomfort but easily tolerated; redness or swelling >= 8cm

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3 <sup>5</sup> Grade II/III reactions defined as “interferes with normal activity” to “severe and incapacitating” for fatigue, muscle ache, headache, itching or pain at  
4 injection site; oral temperature  $\geq 39$  degrees Celsius; limitation to arm motion due to stiffness or discomfort that interferes with normal activity; redness  
5 or swelling  $> 8$ cm

6 <sup>6</sup> Defined as serious adverse events resulting in hospitalization

7 <sup>7</sup> Solicited local reactions included ecchymosis, erythema, induration, swelling, and tenderness at injection site

8 <sup>8</sup> Solicited systemic reactions included sleepiness, diarrhea, vomiting, irritability, change in eating habits, shivering, and unusual crying

9 <sup>9</sup> Included injection site reactions of Grade 1, “minor reaction to touch”, Grade 2, “cries/protests on touch”, and Grade 3, “cries when limb  
10 moved/spontaneously painful”

11 <sup>10</sup> Included systemic reactions of Grade 1, “no effect on normal activity”, Grade 2, “interferes with normal activity”, and Grade 3, “prevents normal activity”

12 <sup>11</sup> Included injection site ecchymosis, injection site erythema, injection site induration, injection site swelling, tenderness, injection site pain

13 <sup>12</sup> Included change in eating habits, sleepiness, unusual crying, irritability, vomiting, diarrhea, chills/shivering, malaise, myalgia, arthralgia, headache,  
14 fatigue, fever ( $>37.3$  C)

15 <sup>13</sup> Defined serious adverse events as any untoward medical occurrence that results in death, is life-threatening, requires/prolongs hospitalization, or  
16 results in disability or incapacity during entire study period

17 <sup>14</sup> Defined as hospitalization, emergency room visit, and/or medical practitioner visit during entire study period

18 <sup>15</sup> Included tenderness, redness and/or swelling solicited within 7 days

19 <sup>16</sup> Included fever, vomiting, abnormal crying, drowsiness, loss of appetite, and/or irritability solicited within 7 days  
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## PRISMA ScR checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
<b>TITLE</b>			
<b>Title</b>	1	Identify the report as a scoping review.	<a href="#">Click here to enter text.</a>
<b>ABSTRACT</b>			
<b>Structured summary</b>	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	<a href="#">Click here to enter text.</a>
<b>INTRODUCTION</b>			
<b>Rationale</b>	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	<a href="#">Click here to enter text.</a>
<b>Objectives</b>	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	<a href="#">Click here to enter text.</a>
<b>METHODS</b>			
<b>Protocol and registration</b>	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	<a href="#">Click here to enter text.</a>
<b>Eligibility criteria</b>	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	<a href="#">Click here to enter text.</a>
<b>Information sources*</b>	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	<a href="#">Click here to enter text.</a>
<b>Search</b>	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	<a href="#">Click here to enter text.</a>
<b>Selection of sources of evidence†</b>	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	<a href="#">Click here to enter text.</a>
<b>Data charting process‡</b>	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	<a href="#">Click here to enter text.</a>

<b>Data items</b>	11	List and define all variables for which data were sought and any assumptions and simplifications made.	Click here to enter text.
<b>Critical appraisal of individual sources of evidence§</b>	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	Click here to enter text.
<b>Synthesis of results</b>	13	Describe the methods of handling and summarizing the data that were charted.	Click here to enter text.
<b>RESULTS</b>			
<b>Selection of sources of evidence</b>	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	Click here to enter text.
<b>Characteristics of sources of evidence</b>	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Click here to enter text.
<b>Critical appraisal within sources of evidence</b>	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	Click here to enter text.
<b>Results of individual sources of evidence</b>	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Click here to enter text.
<b>Synthesis of results</b>	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	Click here to enter text.
<b>DISCUSSION</b>			
<b>Summary of evidence</b>	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	Click here to enter text.
<b>Limitations</b>	20	Discuss the limitations of the scoping review process.	Click here to enter text.
<b>Conclusions</b>	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	
<b>FUNDING</b>			
<b>Funding</b>	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	Click here to enter text.

‡ JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

\* Where sources of evidence (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with information sources (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic

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3 reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review  
4 (e.g., quantitative and/or qualitative research, expert opinion, and policy document).  
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# BMJ Open

## Safety and effectiveness of dose-sparing strategies for intramuscular seasonal influenza vaccine: A rapid scoping review

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# 1 Safety and effectiveness of dose-sparing strategies for intramuscular seasonal influenza

## 2 vaccine:

### 3 A rapid scoping review

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## 25 ABSTRACT

26 **Background:** The objective of this rapid scoping review was to identify studies of dose-sparing  
27 strategies for administration of intramuscular seasonal influenza vaccines in healthy individuals  
28 of all ages.

29 **Methods:** Comprehensive literature searches were executed in MEDLINE, EMBASE, and the  
30 Cochrane library. The grey literature was searched via international clinical trial registries for  
31 relevant studies published in English in the last 20 years. We included studies in healthy humans  
32 of any age that used any dose-sparing strategy to administer intramuscular seasonal influenza  
33 vaccines. Title/abstract and full-text screening were carried out by pairs of reviewers  
34 independently. Data extraction was conducted by a single reviewer and verified by a second  
35 reviewer. Our outcomes of interest were influenza infections, ICU admission, pneumonia,  
36 hospitalizations, adverse events, and mortality. Results were summarized descriptively.

37 **Results:** A total of 13 studies with 10,351 participants were included in the review and all  
38 studies were randomized control trials (RCTs) conducted between 2006 and 2019. The most  
39 common interventions were the trivalent influenza vaccine (n=10), followed by the quadrivalent  
40 influenza vaccine (n=4). Nine studies included infants/toddlers 6-36 months old and one of these  
41 studies also included children and adolescents. In these nine studies, no clinical effectiveness  
42 outcomes were reported. Of the four adult studies ( $\geq 18$  years), two studies reported on  
43 effectiveness outcomes.

44 **Conclusions:** Due to the low number of studies in healthy adults and the lack of studies  
45 assessing confirmed influenza and influenza-like illness, there remains a need for further  
46 evaluation.

47 **Keywords:**

## 48 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

### 49 Strengths:

- 50 • This rapid scoping review was conducted within a 6-week timeline and the methods were  
51 tailored to provide results to the stakeholders within 4 weeks.
- 52 • We did not restrict the search dates and study screening was completed in independently  
53 by two reviewers.

### 54 Limitations:

- 55 • We limited the selection of studies to those published in the English language, and data  
56 extraction was conducted by one abstractor and one verifier.
- 57 • Twelve dose-sparing RCTs were not included in the review because they did not include  
58 vaccine interventions that were deemed of interest to the stakeholders, and/or did not  
59 provide sufficient data.

## 60 **BACKGROUND**

61 The symptoms of novel coronavirus disease (COVID-19) closely mimic those of seasonal  
62 influenza vaccine and health officials recommend vaccination against the flu to limit  
63 confounding of flu symptoms with COVID-19 symptoms. An anticipated shortage in influenza  
64 vaccine supplies was of concern.[1] This anticipated shortage did not happen however, and in the  
65 2019-2020 flu season, influenza vaccination coverage among adults (42%) was similar to the  
66 previous season (42%). This question of vaccine shortage remains relevant in Canada and other  
67 jurisdictions for future COVID-19 and flue seasons. As a potential solution, health officials were  
68 interested in assessing the effectiveness of fractional dosing (e.g., half-doses) of currently  
69 available intramuscular influenza vaccines.

70 Fractional dosing, or dose-sparing, strategies are those where less than the standard dose of  
71 hemagglutinin (HA) antigen, and thus less volume of vaccine, is administered, increasing the  
72 overall number of influenza vaccine doses available. In Canada, influenza vaccines are currently  
73 authorized for intramuscular administration only, apart from the live-attenuated influenza  
74 vaccine, which is administered intranasally.[2] Standard dose influenza vaccines contain 15 mcg  
75 of HA per strain and are delivered in 0.5 mL volume. Therefore, the total amount of HA in  
76 standard dose trivalent vaccines is 45 mcg, and the total amount of HA in standard dose  
77 quadrivalent vaccines is 60 mcg.

78 A scoping review of all the available dose-sparing strategies for intramuscular administration of  
79 seasonal influenza vaccines currently approved in Canada for healthy populations had not been  
80 systematically conducted. With the resource-constraints for the influenza season due to COVID-  
81 19, there was a need to scope the evidence on the safety and effectiveness of dose-sparing  
82 strategies for intramuscular administration of seasonal influenza vaccines. The objective of this

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3 83 rapid scoping review was to identify studies of dose-sparing strategies for administration of  
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5 84 intramuscular seasonal influenza vaccines in healthy individuals of all ages. The results of this  
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8 85 scoping review were used to inform a systematic review with meta-analysis by National  
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10 86 Advisory Committee on Immunization (NACI) on the same topic [3].

## 11 12 87 **METHODS**

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15 88 The Centre for Immunization and Respiratory Infectious Diseases of the Public Health Agency  
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17 89 of Canada (PHAC) commissioned a rapid scoping review on the available methods for fractional  
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19 90 dosing of seasonal influenza vaccines through the Canadian Institutes of Health Research  
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21 (CIHR) Drug Safety and Effectiveness Network (DSEN) with a 6-week timeline for preliminary  
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23 91 results.  
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### 26 92 **Protocol**

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29 94 The methods for this review were guided by the updated reviewer manual for scoping reviews  
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31 95 published by JBI and the World Health Organization's guide to rapid reviews.[4, 5] Results are  
32  
33 96 reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis  
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35 97 extension to scoping reviews (PRISMA-ScR).[6] A protocol for this rapid scoping review was  
36  
37 98 disseminated through the Open Science Framework registry (<https://osf.io/8mwz2/>).  
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### 40 99 **Patient and Public Involvement statement**

41  
42  
43 100 No patients or the public were involved in this rapid scoping review.  
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### 45 101 **Literature search**

46  
47 102 Comprehensive literature searches were developed and executed by an experienced librarian in  
48  
49 103 Ovid MEDLINE (**Appendix 1**), EMBASE using the OVID interface (**Appendix 2**), and the  
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51 104 Cochrane library between 1946 and May 2020 (**Appendix 3**). The literature search was peer  
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53 105 reviewed by a second librarian using the PRESS checklist  
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3 106 (<https://www.cadth.ca/resources/finding-evidence/press>). The grey (i.e., difficult to locate or  
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5 107 unpublished) literature was searched via international clinical trial registries (i.e.  
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7 108 clinicaltrials.gov, EU clinical trial register). References of relevant systematic reviews and  
8  
9 109 included studies were also scanned.

## 110 **Eligibility criteria**

111 The eligibility criteria followed the Population, Intervention, Comparators, Outcome, Study  
112 design (PICOS) framework as follows:

- 113 • Population: Healthy humans of any age. Immunocompromised populations and animal  
114 studies were excluded. Examples of persons with weakened immune systems include those  
115 with HIV/AIDS; cancer and transplant patients who are taking certain immunosuppressive  
116 drugs; and those with inherited diseases that affect the immune system (e.g., congenital  
117 agammaglobulinemia, congenital IgA deficiency)[7].
- 118 • Intervention: Any dose-sparing strategy used to administer intramuscular seasonal influenza  
119 vaccines (eligible vaccines listed in **Appendix 4**). Eligible strategies included, but were not  
120 limited to, administering less than the standard 15 ug HA antigen using multi-dose vials, half  
121 dosing, or pre-formulated products with reduced antigen quantity, or with revised vaccine  
122 dose schedules. Any studies examining monovalent pandemic vaccines,  
123 specialty/experimental vaccines (e.g., high dose), whole virus vaccines, or other routes of  
124 administration (e.g. intranasal, intradermal) were not eligible. Only vaccine products  
125 approved for use in Canada or equivalent formulations approved for use in other countries  
126 were eligible for inclusion. Concomitant administration with other vaccine products were  
127 included only if administered to both the intervention and the comparator groups.
- 128 • Comparator: Any of the interventions listed above, no intervention, or placebo.

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3 129 • Outcomes: Lab-confirmed influenza infection (primary outcome), influenza-like illness or  
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5 130 clinical/symptomatic diagnosis of influenza, hospitalization, intensive care unit (ICU)  
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7 131 admission, pneumonia, mortality, and adverse events (local/systemic reactogenicity,  
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9 132 vascular-related, serious). Reactogenicity represents the physical manifestation of the  
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11 133 inflammatory response to vaccination, and can include injection-site pain, redness, swelling  
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13 134 or induration at the injection site, as well as systemic symptoms, such as fever, myalgia, or  
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15 135 headache.[8]  
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19 136 • Study designs: Randomized controlled trials (RCTs), non-randomised studies (e.g., quasi-  
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21 137 RCTs, non-randomized trials, interrupted time series, controlled before after), and  
22  
23 138 observational studies (e.g., cohort, case control) were included. Studies must have had a  
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25 139 control or comparator group in order to be eligible for inclusion and as such, cross-sectional,  
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27 140 case series, case reports, and qualitative studies were excluded.  
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31 141 • Publication status: We included full text and abstracts if they included data on safety or  
32  
33 142 effectiveness.

34  
35 143 Inclusion was also limited to studies written in the English language due to the short timelines  
36  
37 144 for the conduct of this review.

### 38 39 40 145 **Study selection**

41  
42 146 A screening form based on the eligibility criteria was prepared and pilot-tested with 30 studies  
43  
44 147 with all members of the review team until sufficient agreement (>75%) was reached prior to both  
45  
46 148 title/abstract (level 1) and full-text (level 2) screening. Subsequent screening at level 1 and level  
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48 149 2 were completed by two reviewers working independently using the Knowledge Translation  
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50 150 Program's proprietary screening software (synthesi.SR)[9]. Any discrepancies between  
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52 151 reviewers were consistently resolved by a third independent reviewer.  
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## 152 **Data extraction**

153 Items for data collection included study characteristics (study design, year of publication,  
154 country of conduct, multi-center vs. single site), patient characteristics (mean age, age range, sex,  
155 vaccination history), intervention details (type of vaccine, vaccine manufacturer, dose, timing  
156 and administration of treatment), comparator details (comparator intervention, dose), and  
157 outcome results (influenza infections, ICU admission, pneumonia, hospitalizations, adverse  
158 events, mortality) at the longest duration of follow-up.

159 A standardized form for data extraction was developed and pilot tested by the entire review team  
160 using two pre-selected full-text RCTs to ensure understanding of the data items to be extracted,  
161 and congruence among reviewers. All included studies were extracted by one reviewer  
162 independently and then verified by a second reviewer.

## 163 **Risk of bias assessment**

164 As this was a scoping review, the risk of bias of studies was not assessed.[4]

## 165 **Synthesis**

166 The synthesis involved providing a descriptive summary of included studies with summary  
167 tables and detailed tables of study results. Study results were organized and tabulated according  
168 to patients (children vs adults), interventions, and outcomes and where available information on  
169 relevant subgroups.

## 170 **RESULTS**

### 171 **Literature search**

172 We screened 2,378 titles and abstracts from our database search and an additional 13 citations  
173 located through searching the grey literature and scanning references. Of these, 144 potentially  
174 relevant full-text articles were screened for eligibility (**Figure 1**). Twelve studies that assessed

175 dose-sparing strategies were excluded during full-text screening because the vaccine under study  
 176 was not of interest or unclearly reported. We contacted authors of these 12 unclear studies and  
 177 received 1 response confirming the vaccine was not of interest (see list of excluded studies in  
 178 **Appendix 5**). Subsequently, 13 RCTs were included; five trial protocols were found and were  
 179 denoted as duplicate/companion reports. No non-randomised or observational studies were found  
 180 that fulfilled the eligibility criteria.

### 181 **Study characteristics**

182 **Table 1** summarizes the characteristics of the 13 RCTs published between 2006 and 2019; and  
 183 conducted mainly in the US, followed by Mexico, Canada and Finland. The majority of the  
 184 studies evaluated trivalent vaccines (10/13 [77%]) and most were conducted in the 6-36 month-  
 185 old pediatric population (9/13 [69%]). Almost all studies reported on reactogenicity and/or other  
 186 adverse events, but only two studies reported on the effectiveness of our outcomes of interest  
 187 (i.e., lab-confirmed influenza and influenza-like illness).

188 Full study and patient characteristic details for each study are reported in **Appendix 6** and  
 189 treatment and outcome details in **Appendix 7**.

190 **Table 1: Characteristics of included studies (n=13)**

Characteristics	Category	Frequency (%)
Date of publication	2006-2010	4 (30.8)
	2011-2015	5 (38.4)
	2016-2020	4 (30.8)
Multi-center or single site	Multi-centre	8 (61.5)
	Single centre	2 (15.4)
Countries of conduct <sup>a</sup>	USA	8 (61.5)
	Mexico	3 (23.1)
	Canada	2 (15.4)
	Finland	2 (15.4)
	Belgium	1 (7.7)
	Hong Kong	1 (7.7)
	Taiwan	1 (7.7)
	Thailand	1 (7.7)

Populations <sup>a,b</sup>	Infants/Toddlers (6-36 months)	9 (69.2)
	Children (37 months – 17 years)	1 (7.7)
	Adults (18-64 years)	3 (23.1)
	Older adults (≥65)	1 (7.7)
Treatments <sup>a,c</sup>	Trivalent influenza vaccine (TIV)	10 (76.9)
	Quadrivalent influenza vaccine (QIV)	4 (30.8)
Outcomes <sup>a</sup>	Effectiveness	2 (15.4)
	Local and Systemic Reactogenicity	12 (92.3)
	Adverse events	10 (76.9)

<sup>a</sup>Each study can fit into more than one category so the total percentage will not add up to 100%

<sup>b</sup>One study includes both infants/toddlers and children, and another includes both adults and seniors

<sup>c</sup>One study includes both TIV and QIV arms

### 194 **RCTs in healthy children (<18 years old)**

195 Nine studies included infants/toddlers 6-36 months old and one study also included children and  
 196 adolescents (**Table 2**). None of these studies reported results on the effectiveness outcomes that  
 197 were relevant to our review and established *a priori*, however all of them reported on safety  
 198 outcomes.

199 **Table 2: Nine RCTs conducted in children (6 months – 17 years)**

Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcomes	Author reported conclusions
TRIVALENT AND QUADRIVALENT INFLUENZA VACCINES (TIV/QIV)									
Cioppa, 2011[10]	October 2008 – March 2009  Belgium	NR - TIV, <b>7.5-µg/strain</b> [2 x 0.25mL dose]	20.0 months (7.0)	6- <36 months	43.5	NR	25	Local and Systemic reactogenicity	Reactogenicity of the 7.5-µg TIV/QIV formulations was slightly lower than for the corresponding 15-µg formulations.  The majority of unsolicited AEs were mild or moderate in severity and none of the SAEs was considered to be related to the study vaccine.
		Agrippal - TIV, <b>15-µg/strain</b> [2 x 0.5mL dose]	15.0 months (8.8)	6- <36 months	43.5	NR	22	Adverse events	
		NR - QIV, <b>7.5-µg/strain</b> [2 x 0.25mL dose]	18.0 months (8.9)	6- <36 months	43.5	NR	25		
		NR - QIV, <b>15-µg/strain</b> [2 x 0.5mL dose]	15.2 months (7.8)	6- <36 months	43.5	NR	28		
		Vaxigrip (Sanofi Pasteur), <b>7.5-µg/strain</b> [2 x 0.25mL dose]	16.1 months (8.5)	6- <36 months	43.5	NR	26		

Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcomes	Author reported conclusions
Skowronski, 2011[11]	September 2008 – December 2008  Canada	Vaxigrip (Sanofi-Pasteur), 15-µg/strain [2 x 0.5mL dose]	13.2 months (5.1)	6-23 months	53.2	0	124	Local and Systemic reactogenicity  Adverse events	Local reactions generally were less common in infants than toddlers and more common with full doses versus half doses, but none of these differences were significant.  One serious adverse event was reported: a toddler in the half dose group was hospitalized with pneumonia 28 days after the first vaccination. The event was deemed unlikely related to the vaccine.
		Vaxigrip (Sanofi-Pasteur), 15-µg/strain [2 x 0.25mL dose]	12.8 months (5.0)	6-23 months	53.2	0	128		

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Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcomes	Author reported conclusions
									Compared with 0.25-mL half-dosing, administration of 2 full 0.5-mL doses of trivalent inactivated influenza vaccine can increase antibody response without increasing reactogenicity in previously unimmunized infants aged 6 to 11 months.
Langley, 2012[12]	November 2008 – August 2009	Fluviral F1 (Sanofi-Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose]	18.2 months (9.06)	6-35 months	47.9	42.6	164	Local and Systemic reactogenicity	Fluviral F1 group had 1 case of pneumonia resolved. Fluviral F2 group had 1 case of
	Canada	Fluviral F2 (Sanofi-Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose]	17.5 months (8.27)	6-35 months	47.9	42.6	167	Adverse events	

Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcomes	Author reported conclusions
		Vaxigrip (Sanofi-Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose]	17.0 months (8.33)	6-35 months	47.9	42.6	43		bronchial hyper-reactivity in resolving stage.  The 0.5-mL dose of the study vaccine, when administered to children aged 6–35 months, resulted in a modest but not statistically significant improvement in immunogenicity with clinically similar safety and reactogenicity compared with the 0.25-mL dose.
Pavia-Ruz, 2013[13]	October 2008-March 2009	Fluarix (GSK), <b>15-µg/strain</b> [1 x 0.5mL dose]	21.2 months (8.37)	6-35 months	51	30.1	1018	Local and Systemic reactogenicity	The reactogenicity and safety

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Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcomes	Author reported conclusions
	Hong Kong, Mexico, Taiwan, Thailand, and the USA	Fluarix (GSK), 7.5-µg/strain [1 x 0.25 mL dose]	21.2 months (8.03)	6-35 months	51	30.1	1018	Adverse events	<p>profile of the study vaccine did not appear to be affected by doubling the dose.</p> <p>One participant in the Flu-15µg group had two SAEs, (apnea and cyanosis) which were considered by the investigator to be possibly related to vaccination. The subject was hospitalized and the events resolved on the same day as they occurred.</p>
		Fluzone (Sanofi-Pasteur), 7.5-µg/strain [1 x 0.25 mL dose]	21.1 months (8.20)	6-35 months	51	30.1	1031		



Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcomes	Author reported conclusions
Halasa, 2015[14]	2010-2012  USA	Fluzone (Sanofi Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose]	13.5	6-35 months, 12-35 months	52	13.2	80	Local and Systemic reactogenicity	No significant differences between the full-dose or half-dose groups for either the fully primed or naive cohorts for systemic reactions or local reactions when both seasons were combined.  The only significant difference in the 2011–2012 season was that 8 of 48 (16.7%) participants in the half-dose group compared with 32 of 96 (33.3%) in the full-dose group had increased
		Fluzone (Sanofi Pasteur), <b>15-µg/strain</b> [1 x 0.5 mL dose]	14.5				163		

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Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcomes	Author reported conclusions
									redness at the injection site (P < .05).  No significant differences between the groups in AE, SAE, or onset of chronic medical conditions between the dose groups in either the naive or fully primed cohorts, and none of the SAEs were deemed related to the vaccine.
Phung, 2016[15]	September 2010- January 2011	FLUAD (NR), NR [1 x 0.5mL dose]	68.7 months (18)	6-35 months	55.8	85.7	60	Local and Systemic reactogenicity	<i>Trial protocol with no author conclusions.</i>
	Finland	FLUAD (NR), NR [1 x 0.25 mL dose]	60.4 months (23.2)	6-35 months	55.8	85.7	75	Adverse events	

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Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcomes	Author reported conclusions
		Agrippal S1 (NR), NR [1 x 0.5mL dose]	68 months (17.1)	6-35 months	55.8	85.7	51		
		Agrippal S1 (NR), NR [1 x 0.25mL dose]	32.4 months (1.9)	6-35 months	55.8	85.7	11		
Jain, 2017[16]	2014-2015 Influenza Season	Flulaval (GSK), 15-µg/strain [1 x 0.5mL dose]	19.7 months (8.7)	6-35 months	46.9	57.5	1013	Local and Systemic reactogenicity	None of the febrile seizures or the SAEs were considered by the investigator to be related to vaccination.  Double-dose vaccines may improve protection against influenza B in some young children and simplifies annual influenza vaccination by
	USA and New Mexico	Fluzone (Sanofi Pasteur), 7.5-µg/strain [1 x 0.25 mL dose]	19.9 months (8.9)	6-35 months	46.9	57.5	1028	Adverse events	

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Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcomes	Author reported conclusions
									allowing the same vaccine dose to be used for all eligible children and adults.
Ojeda, 2019[17]	December 2017- January 2018  Mexico	Vaxigrip Tetra (Sanofi Pasteur) <b>PFS 15-µg/strain</b> [1 x 0.5mL dose]	NR (6 months – 17 years)	6 months – 17 years	46.4	NR	149	Local and Systemic reactogenicity  Adverse events	Solicited systemic reactions were reported in more infants aged 6 – 35 months in the MDV group than in the PFS group however this was not clinically significant.  AE not considered related to a study vaccine.  There were no differences in reactogenicity or safety
		Vaxigrip Tetra (Sanofi Pasteur) <b>MDV 15-µg/strain</b> [1 x 0.5mL dose]	NR (6 months – 17 years)	6 months – 17 years	46.4	NR	153		

Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcomes	Author reported conclusions
									between the two vaccine formats. These results showed that the MDV format of QIV was as safe and immunogenic as the PFS format in infants, children, and adolescents. These findings support the use of MDV QIV as a resource-saving alternative for seasonal influenza vaccination.
Robertson, 2019[18]	September 2016 – March 2017	Fluzone (Sanofi Pasteur) <b>15-µg/strain</b> [1x0.5mL dose]	20.5 months (8.55)	6-35 months	49.7	47.25	992	Local and Systemic reactogenicity	No significant differences between full- and half-dose

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Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcomes	Author reported conclusions
	USA	Fluzone (Sanofi Pasteur) 7.5-µg/strain [1x0.25 dose]	20.4 months (8.75)	6-35 months	49.7	47.25	949	Adverse events	groups.  AE leading to study discontinuation/ SAE not considered vaccine-related.  A full dose vaccine was immunogenic and had a safety profile comparable to that of a half dose, with no new safety concerns observed.

**Abbreviations:** AE – adverse events; GMR – geometric mean ratio; GMFR – geometric mean fold rise; GMT - geometric mean antibody titer; HA - hemagglutinin; HAI - hemagglutination inhibition; ID – intradermal; IM – intramuscular; ITT – intent-to-treat; MDV – multi-dose vials, n – number of people with condition, N – sample size of treatment arm, NR – not reported, PFS – prefilled dose, SAEs – serious adverse events

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3 **203 Safety outcomes**  
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5 **204 Trivalent influenza vaccines**  
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8 **205** Six of the included RCTs assessed trivalent influenza vaccines (TIV) in young children (6-36  
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10 **206** months) and reported on local and systemic reactogenicity outcomes and other adverse  
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12 **207** events.[10-14, 19] Two RCTs compared the administration of full (0.5mL) and half (0.25mL)  
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14 **208** doses of the same standard 15µg/strain vaccine.[11, 19] The first RCT compared two full versus  
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16 **209** two half doses of TIV in previously unimmunized infants (6-11 months) and toddlers (12-23  
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18 **210** months) using Vaxigrip (15µg/strain).[11] The study found that in the infants group, two full 0.5-  
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20 **211** mL doses of vaccine did not increase reactogenicity. Local reactions were less common in  
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22 **212** infants than toddlers and more common with full doses versus half doses, but the differences  
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24 **213** were not statistically significant. An identified clinical trial registry compared a single  
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26 **214** intramuscular injection of 0.5mL to 0.25mL of FLUAD or Agrippal and showed comparable  
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28 **215** numbers of children with reactogenicity outcomes and other adverse events across the groups,  
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30 **216** but no significance levels or conclusions were provided by the investigators upon contact.[19]  
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32 **217** The objective of three of the included RCTs was to examine the impact of administering the full  
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34 **218** adult dose of 15µg/strain vaccines compared with the usual children's dose of 7.5µg/strain in  
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36 **219** infants and toddlers.[12-14] A multicenter RCT was conducted in Canada assessing the safety of  
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38 **220** full-dose Fluviral TIV (15µg/strain) compared with the half-dose (7.5µg/strain) and an active  
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40 **221** comparator Vaxigrip (7.5µg/strain).[12] Compared with the half-dose, the full-dose vaccine  
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42 **222** resulted in clinically similar reactogenicity and safety. A similar three-arm RCT to assess the use  
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44 **223** of Fluarix at two different dose levels (7.5µg/strain and 15µg/strain) compared to an established  
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46 **224** control vaccine Fluzone (7.5µg/strain) also found the reactogenicity and safety profile of Fluarix  
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48 **225** did not appear to be affected by doubling the dose, but one participant in the 15µg group had two  
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3 226 serious adverse events (apnea and cyanosis) that were considered by the investigator to be  
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5 227 possibly related to vaccination.[13] A third multicenter RCT compared the 15 µg/strain  
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7 228 formulation to the 7.5µg/strain formulation of Fluzone (Sanofi Pasteur) administered to young  
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9 229 children across multiple influenza seasons.[14] This study also found no statistically significant  
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11 230 differences between the full-dose or half-dose groups for systemic reactions, local reactions or  
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13 231 adverse events when both seasons were combined; however, in the 2011–2012 season, 8 of 48  
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15 232 (16.7%) participants in the half-dose group compared with 32 of 96 (33.3%) in the full-dose  
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17 233 group had increased redness at the injection site ( $P < .05$ ).

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19 234 Cioppa et al. (2009) was the only trial that compared the safety and tolerability of both TIV and  
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21 235 QIV vaccine formulations.[10] The vaccine arms of interest were a QIV 15-µg/strain, TIV 15-  
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23 236 µg/strain, QIV 7.5-µg/strain, TIV 7.5-µg/strain, and a control Vaxigrip TIV 7.5-µg/strain  
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25 237 vaccine. Reactogenicity of the 7.5-µg TIV/QIV formulations was slightly lower than for the  
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27 238 corresponding 15-µg formulations, but there was no difference in reactogenicity between TIV  
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29 239 and QIV vaccines.

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31 240 Quadrivalent influenza vaccines

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33 241 Four of the included RCTs evaluated quadrivalent influenza vaccines (QIV) in children.[10, 16-  
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35 242 18] All of the studies reported reactogenicity outcomes and other adverse events. The Cioppa et  
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37 243 al. (2009) RCT reported both TIV and QIV vaccines and the results are reported above.[10] Two  
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39 244 studies compared full-dose QIV to pediatric 7.5µg/strain Fluzone. In the first RCT, full dose  
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41 245 Fluzone had a similar safety profile to half-dose Fluzone with a single adverse event being  
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43 246 attributed to the study vaccine.[18] Similarly, the second study found that full-dose Flulaval may  
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45 247 improve protection against influenza in some young children when compared to low-dose  
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47 248 Fluzone, and in this RCT, none of the adverse events were considered to be study-related as  
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3 249 reported by the investigator.[16] The final trial evaluated Vaxigrip Tetra (15µg/strain)  
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5 250 administered to children and adolescents in two different formats.[17] Vaxigrip administered as a  
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7 251 single dose using a pre-filled syringe (PFS) was compared to a 10-dose multi-dose vial (MDV).  
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9 252 Systemic reactions were reported in more infants aged 6 – 35 months in the MDV group than in  
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11 253 the PFS group; however this difference was not clinically significant. The authors concluded that  
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13 254 there was no difference in reactogenicity or safety between the two vaccine formats in infants,  
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15 255 children, and adolescents.  
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19 256 **RCTs in healthy adults (≥18 years old)**

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21 257 One RCT included healthy adults over 18 years, two studies included healthy adults from 18-45  
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23 258 and 18-65 years old, and one study included older healthy adults (≥ 65 years) (**Table 3**). Two  
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25 259 studies reported on effectiveness outcomes and three on reactogenicity and other adverse events.  
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28 260 All four RCTs evaluated Fluzone QIV.  
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261 **Table 3: Four RCTs conducted in adults ( $\geq 18$  years old)**

Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Relevant Outcomes	Author reported conclusions
QUADRIVALENT INFLUENZA VACCINES (QIV)									
Kramer, 2006 [20]	October 2004 – November 2004  USA	Fluzone (Aventis Pasteur), <b>15-<math>\mu</math>g/strain</b> [1 x 0.5mL dose]	NR (>18 years)	>18 years	NR	NR	222	Lab-confirmed influenza	There was no significant difference between the full-dose and half-dose groups in the diagnosis of influenza or in the proportion of participants self-reporting four or more symptoms consistent with influenza-like illness.  No adverse events were noted by participants from either group or reported to the IRB during the course of the study
		Fluzone (Aventis Pasteur), <b>7.5-<math>\mu</math>g/strain</b> [1 x 0.25 mL dose]	NR (>18 years)	>18 years	NR	NR	222	Influenza-like illness  Adverse events	

Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Relevant Outcomes	Author reported conclusions
Engler, 2008 [21]	November 2004 – December 2004	Fluzone (Aventis Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose]	NR (18 – 64 years)	18-64 years	43.4	0	554	Influenza-like illness Hospital/ER visits	The relative risk of medical visits and hospitalizations for influenza-like illnesses were similar in the half- and full-dose group regardless of age, and there was no evidence of ILI symptom differences by sex or dose during the 21 days after immunizations.  Although injection site pain was greater for full- vs half-dose (19.9% vs 14.4%; p=.01), when analyzed for clinically significant pain levels significant
	USA	Fluzone (Aventis Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose]	NR (18 – 64 years)	18-64 years	43.4	0	556	Local and Systemic reactogenicity Adverse events	

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Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Relevant Outcomes	Author reported conclusions
									<p>dose-dependent pain differences were not identified.</p> <p>Joint and/or muscle pain were significantly different (p=.02 and p=.03, respectively) by dose.</p> <p>No other adverse event differed significantly by dose.</p>
Belshe, 2007 [22]	NR USA	Fluzone (Sanofi-Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose]	31.5 years (9.6)	18-49 years	71.2	0	31	Local and Systemic reactogenicity	Intradermal (ID) vaccine induced significantly more local inflammatory response than Intramuscular (IM) vaccine but this did not translate into an
		Fluzone (Sanofi-Pasteur), <b>9-µg/strain</b> [1 x 0.3mL dose]	31.2 years (9.4)	18-49 years	71.2	0	32		

Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Relevant Outcomes	Author reported conclusions
		Fluzone (Sanofi-Pasteur), <b>6-µg/strain</b> [1 x 0.2mL dose]	30.1 years (10.3)	18-49 years	71.2	0	31		increased immune response for ID vaccines compared to IM (primary comparison of this study was ID vs IM doses)
		Fluzone (Sanofi-Pasteur), <b>3-µg/strain</b> [1 x 0.1mL dose]	31.9 years (10.3)	18-49 years	71.2	0	31		
Chi, 2010[23]	August 2007-2008  USA	Fluzone (Sanofi Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose]	75.6 years (6.8)	>65 years	17.8	94.6	65	Local and Systemic reactogenicity	The two SAEs were acute coronary syndrome and appendicitis and neither were judged to be related to influenza vaccination
		Fluzone (Sanofi Pasteur), <b>9-µg/strain</b> [1 x 0.3mL dose]	75.2 years (7.7)	>65 years	17.8	94.6	64	Adverse events	

**Abbreviations:** AE – adverse events, GMT - geometric mean antibody titer; HA - hemagglutinin; ID – intradermal; ILI – influenza-like illness; IM – intramuscular; MDV – multi-dose vials, n – number of people with condition, N – sample size of treatment arm, NR – not reported, PFS – prefilled syringe, SAE – serious adverse events

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3 264 **Effectiveness outcomes**  
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7 266 Pasteur) in healthy adult populations reported effectiveness outcomes including lab-confirmed  
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10 267 influenza infections, influenza like illness, and/or hospitalizations or emergency room visits after  
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12 268 vaccination.[20, 21] The RCT by Kramer et al. (2006) found that 3.6% of participants receiving  
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14 269 a 15- $\mu$ g/strain dose of vaccine reported influenza like illness compared to 6.8% of participants  
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16 270 that received a 7.5- $\mu$ g/strain dose.[20] However, only one participant in the RCT that received  
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18 271 the 15- $\mu$ g/strain dose was confirmed via laboratory analysis to have influenza. The authors  
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20 272 concluded that half-dose and full-dose vaccinations appear to be similarly effective based on the  
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22 273 low rate of influenza infections and similar symptom surveys between both groups but  
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24 274 acknowledge that further studies examining immunogenicity are needed to confirm.  
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28 275 A similar RCT by Engler et al. (2008) that compared a 15- $\mu$ g/strain dose of Fluzone vaccine to a  
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30 276 7.5- $\mu$ g/strain dose found equal proportions of participants reporting influenza like illness (9.7%  
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32 277 vs 9.9%) and hospitalizations or emergency room visits (0.3% v 0.2%).[21] The authors found  
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34 278 the relative risk of medical visits or hospitalizations between both groups was the same even  
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36 279 when adjusting for age and that age, sex, nor dose had an influence on the severity of influenza  
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42 281 **Safety outcomes**  
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44 282 Three of the included studies in adult populations reported adverse events that occurred during  
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46 283 the trial while one RCT indicated that no adverse events were recorded for the duration of their  
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48 284 trial.[20-23] All three studies reporting adverse events compared different doses of Fluzone  
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50 285 vaccine including 3- $\mu$ g, 6- $\mu$ g, 7.5- $\mu$ g, 9- $\mu$ g, and 15- $\mu$ g per strain doses.  
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3 286 Two of the studies were carried out in healthy adult populations and one RCT was conducted in  
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5 287 older healthy adults (>60 years of age).[21-23] One RCT found that joint or muscle pain  
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7 288 following vaccination was statistically significantly higher in the full dose (15- $\mu$ g) group  
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9 289 compared to the half-dose (7.5- $\mu$ g) group and that while injection site pain initially appeared to  
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11 290 be statistically significantly higher in the full dose group, when adjusted to include only  
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13 291 clinically significant pain levels (>3 out of 5 on a visual analogue scale) the difference was no  
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15 292 longer statistically significant.[21] The RCT found no differences in occurrence or severity of  
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17 293 any other adverse effects. Similarly, one RCT comparing four different doses of Fluzone (3- $\mu$ g,  
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19 294 6- $\mu$ g, 9- $\mu$ g, and 15- $\mu$ g per strain) did not report any differences between the IM vaccination  
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21 295 groups.[22] Finally, the RCT in older adults also found no difference in the occurrence or  
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23 296 severity of adverse events in the low dose (9- $\mu$ g) versus high dose (15- $\mu$ g) group and found no  
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25 297 serious adverse events that were considered related to the vaccine.[23]

## 31 **DISCUSSION**

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33 299 PHAC commissioned this rapid scoping review to identify the evidence for efficacy and safety of  
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35 300 fractional influenza vaccine dosing for intramuscular administration of seasonal influenza  
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37 301 vaccines in healthy individuals of all ages that have been evaluated in human trials. Thirteen  
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39 302 RCTs published between 2006 and 2019 comparing standard/full-dose and half/low-dose  
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41 303 vaccines were included in this scoping review after a comprehensive search of three electronic  
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43 304 databases, trial registries and references of relevant systematic reviews. The majority of the  
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45 305 included RCTs were conducted in children and evaluated trivalent influenza vaccines (TIV).  
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47 306 In young, healthy children, there were no effectiveness outcomes of interest reported. However,  
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49 307 local reactogenicity, systemic reactogenicity and adverse events were comparable across the full-  
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51 308 dose and half-dose TIV and QIV vaccine arms. In addition, the authors of one RCT in children  
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3 309 and adolescents that compared full-dose QIV using pre-filled syringes (PFS) versus multi-dose  
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5 310 vials (MDV) also found no statistically significant differences in safety outcomes between  
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7 311 administration formats. In healthy adults (including older adults), half-dose QIV was considered  
8  
9 312 equally effective as high-dose in the two RCTs that assessed clinical effectiveness. Safety  
10  
11 313 profiles were similar across groups in all 4 RCTs.

12  
13  
14 314 A full systematic review with meta-analysis based on the studies and results of this scoping  
15  
16 315 review was conducted by the NACI and the report was published in January of 2021.[3] The  
17  
18 316 report found that there is some, but still insufficient, evidence that fractional doses of influenza  
19  
20 317 vaccine provided via the intramuscular route are effective and immunogenic in healthy  
21  
22 318 individuals. NACI concludes that since many of those at high risk of influenza (e.g., adults 65  
23  
24 319 years of age and older, individuals with specific underlying chronic health conditions) may have  
25  
26 320 a lower immune response to influenza vaccination already (due to immunosenescence in older  
27  
28 321 adults or a condition that alters immune function), it is important to ensure that those at high risk  
29  
30 322 continue to receive the full dose of influenza vaccine.

### 31 323 **Strengths and limitations**

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33  
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36  
37 324 A strength of this rapid scoping review was that it was conducted within a 6-week timeline and  
38  
39 325 the methods were tailored to provide results to the stakeholders within 4 weeks. We also did not  
40  
41 326 restrict the search dates and study screening was completed independently by two reviewers. We  
42  
43 327 developed a comprehensive search using three major databases, and searched the grey literature.  
44  
45 328 We engaged with the NACI stakeholder group, who provided input on the PICO criteria, and  
46  
47 329 funded this rapid scoping review.

48  
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50  
51 330 We were limited by the lack of studies providing objective outcome data. Only one RCT by  
52  
53 331 Kramer et al. reported the objective outcome “lab confirmed influenza”, and the other RCT by



1  
2  
3 332 Engler only reported the outcome “influenza like illness” [20, 21]. Since a 2014 review found  
4  
5 333 that less than 25% of cases diagnosed by physicians as influenza like illness were later laboratory  
6  
7 334 proven influenza cases [24], we are lacking RCTs examining fractional dosing of IM influenza  
8  
9 335 immunization. Further, twelve dose-sparing RCTs were not included because they did not  
10  
11 336 provide sufficient data, and did not include vaccines that were deemed of interest to the  
12  
13 337 stakeholders. Another limitation was that only studies published in the English language were  
14  
15 338 included, and data extraction was conducted by one abstractor and one verifier. Since this was a  
16  
17 339 scoping review, we did not appraise the methodological quality of the included studies.[25]  
18  
19  
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21

#### 22 340 **Future research**

23  
24 341 Dose-sparing approaches such as intradermal (ID) immunisation vaccination exhibits similar, or  
25  
26 342 even enhanced, immunogenicity, when using a fractional dose only, as compared to  
27  
28 343 intramuscular or subcutaneous immunisation, and should be explored in future scoping  
29  
30 344 reviews.[26]  
31  
32

#### 33 345 **CONCLUSIONS**

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35 346 In our scoping review, we found 13 RCTs on the efficacy and safety of fractional doses of  
36  
37 347 influenza vaccine provided via the intramuscular route to healthy adults and children. These  
38  
39 348 studies were used to inform a systematic review with meta-analysis which were commissioned  
40  
41 349 by the PHAC. We found that due to the low number of studies in healthy adults and the lack of  
42  
43 350 studies assessing confirmed influenza and influenza-like illness, there remains a need for further  
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45 351 evaluation of the clinical effectiveness of IM dose-sparing strategies using vaccines currently  
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47 352 available in this population.  
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3 353 **LIST OF ABBREVIATIONS**  
4

5 354 PHAC – Public Health Agency of Canada  
6

7  
8 355 CIHR – Canadian Institutes of Health Research  
9

10 356 DSEN – Drug Safety and Effectiveness Network  
11

12 357 MAGIC – Methods and Application Group in Indirect Comparisons  
13

14 358 PRISMA-ScR – Preferred Reporting Items for Systematic Reviews and Meta-analysis extension  
15

16  
17 359 to scoping reviews  
18

19 360 ICU – Intensive Care Unit  
20

21 361 RCT – Randomized controlled trials  
22

23 362 NRCTs – non-randomized controlled trials  
24

25 363 TIV – Trivalent Influenza Vaccine  
26

27 364 AE – Adverse Events  
28

29 365 SAE – Serious adverse events  
30

31 366 QIV – Quadrivalent Influenza Vaccine  
32

33 367 PFS – Pre-filled syringe  
34

35 368 MDV – Multi-dose vial  
36

37  
38  
39 369 **DECLARATIONS**  
40

41  
42 370 **Ethics approval and consent to participate**  
43

44 371 Not applicable  
45

46 372 **Consent for publication**  
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49 373 Not applicable  
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3 374 **Availability of data and materials**  
4

5 375 The dataset(s) supporting the conclusions of this article is(are) included within the article (and its  
6  
7  
8 376 additional file(s)).  
9

10 377 **Competing interests**  
11

12 378 The authors have no competing interests to declare.  
13

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15

16  
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18  
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20  
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22  
23 383 Translation and the Mary Trimmer Chair in Geriatric Medicine; ACT is funded by a Tier 2  
24  
25 384 Canada Research Chair in Knowledge Synthesis.  
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28 385 **Open Access**  
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33  
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36 389 provided the original work is properly cited and the use is non-commercial. See:  
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38 390 <http://creativecommons.org/licenses/by-nc/4.0/>  
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42 391 **Authors' contributions**  
43

44 392 CL wrote and revised the final manuscript. JA and PR screened citations and full-text articles,  
45  
46 393 abstracted and verified data, interpreted results and wrote the first draft manuscript. CW and NR  
47  
48 394 screened citations and full-text articles, abstracted data, and reviewed the manuscript. SES and  
49  
50 395 ACT developed the protocol, obtained funding, interpreted results, and edited the manuscript.  
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4

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11  
12 400 author's and formatting this manuscript.  
13

14  
15 401 **Additional files**

16  
17 402 **File Format:** Microsoft Word (.docx)  
18

19 403 **Title of Data:** Additional File 1 (Appendices 1-7)  
20

21 404 **Description of Data:** The appendices include the following additional information:  
22

23  
24 405 Appendix 1 – MEDLINE search strategy  
25

26 406 Appendix 2 – EMBASE search strategy  
27

28 407 Appendix 3 – Cochrane search strategy  
29

30  
31 408 Appendix 4 – List of eligible vaccines  
32

33 409 Appendix 5 – Excluded dose-sparing studies  
34

35 410 Appendix 6 – Study and patient data  
36

37  
38 411 Appendix 7 – Treatment and outcome data  
39

40 412 **FIGURE LEGEND**  
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42  
43 413 Figure 1. Flow chart of studies included in the review  
44

45 414 Study flow diagram.  
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11 418  
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16  
17 421 [immunization-naci/recommendations-fractional-influenza-vaccine-dosing.html](https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/recommendations-fractional-influenza-vaccine-dosing.html)  
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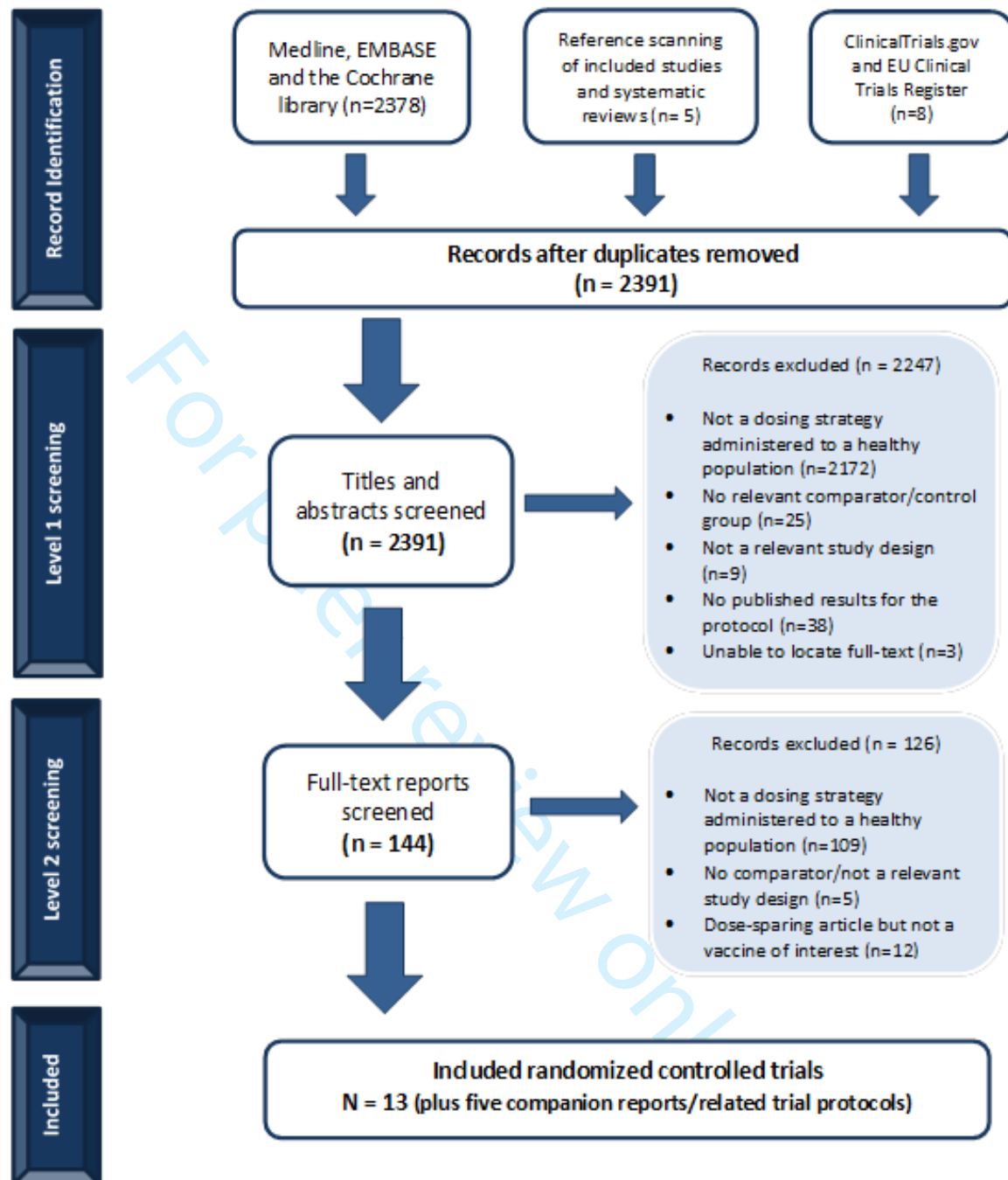
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For peer review only





## PRISMA ScR checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
<b>TITLE</b>			
<b>Title</b>	1	Identify the report as a scoping review.	1
<b>ABSTRACT</b>			
<b>Structured summary</b>	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2
<b>INTRODUCTION</b>			
<b>Rationale</b>	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	4
<b>Objectives</b>	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	4
<b>METHODS</b>			
<b>Protocol and registration</b>	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	4
<b>Eligibility criteria</b>	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	5-6
<b>Information sources*</b>	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	5
<b>Search</b>	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Appendix 1-3
<b>Selection of sources of evidence†</b>	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	6
<b>Data charting process‡</b>	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	6
<b>Data items</b>	11	List and define all variables for which data were sought and any assumptions and simplifications made.	6

<b>Critical appraisal of individual sources of evidence<sup>§</sup></b>	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	N/A
<b>Synthesis of results</b>	13	Describe the methods of handling and summarizing the data that were charted.	6
<b>RESULTS</b>			
<b>Selection of sources of evidence</b>	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	6
<b>Characteristics of sources of evidence</b>	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	7, Appendix 6-7
<b>Critical appraisal within sources of evidence</b>	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	N/A
<b>Results of individual sources of evidence</b>	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	8-25
<b>Synthesis of results</b>	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	25
<b>DISCUSSION</b>			
<b>Summary of evidence</b>	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	25-27
<b>Limitations</b>	20	Discuss the limitations of the scoping review process.	26
<b>Conclusions</b>	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	27
<b>FUNDING</b>			
<b>Funding</b>	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	28
<p>           JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.         </p> <p>           * Where sources of evidence (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.         </p> <p>           † A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with information sources (see first footnote).         </p> <p>           ‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.         </p> <p>           § The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).         </p>			

## APPENDIX 1 – MEDLINE search strategy

Database: Ovid MEDLINE(R) ALL <1946 to May 29, 2020>

### Search Strategy:

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- 1 influenza, human/ or exp influenza a virus/ or exp influenzavirus b/ or influenzavirus c/
- 2 (flu or flue or influenza\* or grippe).tw,kf.
- 3 1 or 2
- 4 exp Vaccines/ or Immunization/
- 5 (vaccin\* or immuni\* or inocula\* or shot or jab).tw,kf.
- 6 4 or 5
- 7 3 and 6
- 8 influenza vaccines/ or Adjuvants, Immunologic/
- 9 (LAIV or Fluenz or FluMist or Afluria or Fluad or Fluzone or Flulaval or Fluarix or Flublok or
- 10 Flucelvax or FluQuadri or Vaxigrip or Influvac or Fluvirin or Agrippal or Begrivac or Fluad or
- 11 agriflu or fluviral).tw,kf.
- 12 7 or 8 or 9
- 13 Injections, Intramuscular/
- 14 (intramuscular or intra-muscular).tw,kf.
- 15 or/11-12
- 16 10 and 13
- 17 limit 14 to yr=2000-current
- 18 animals/ not humans/
- 19 15 not 16
- 20 ad.fs.
- 21 11 or 12 or 18
- 22 10 and 19
- 23 exp dose-response relationship, immunologic/
- 24 dose-Response Relationship, Drug/
- 25 (Dos\* sparing or Dose -sparing or half-dose or dose-response or dose response or dose
- 26 effect\* or dose-effect\* or fractional dos\*).tw,kf.
- 27 ((reduc\* or lower or less) adj2 (quantity or strength or standard)).tw,kf.
- 28 ((dos\* adj3 change) or (half adj3 dos\*)).tw,kf.
- 29 ((down adj3 titrat\*) or (dose adj3 titrat\*) or (dose adj3 reduc\*) or (dose adj3 "de-escalat\*")
- 30 or (dose adj3 taper\*)).tw,kf.
- 31 or/21-26
- 32 20 and 27
- 33 animals/ not humans/
- 34 28 not 29
- 35 limit 30 to yr=2000-current
- 36 17 or 31

## APPENDIX 2 – EMBASE search strategy

Database: Ovid MEDLINE(R) Embase <2000 to June 11, 2020>

### Search Strategy:

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1 influenza, human/ or exp influenza a virus/ or exp influenzavirus b/ or influenzavirus c/  
 2 (flu or flue or influenza\* or grippe).tw,kf.  
 3 1 or 2  
 4 exp Vaccines/ or Immunization/  
 5 (vaccin\* or immuni\* or inocula\* or shot or jab).tw,kf.  
 6 4 or 5  
 7 3 and 6  
 8 influenza vaccines/ or Adjuvants, Immunologic/  
 9 (LAIV or Fluenz or FluMist or Afluria or Fluad or Fluzone or Flulaval or Fluarix or Flublok  
 10 or Flucelvax or FluQuadri or Vaxigrip or Influvac or Fluvirin or Agrippal or Begrivac or Fluad or  
 11 agriflu or fluviral).tw,kf.  
 12 7 or 8 or 9  
 13 Injections, Intramuscular/  
 14 (intramuscular or intra-muscular).tw,kf.  
 15 or/11-12  
 16 10 and 13  
 17 limit 14 to yr=2009-current  
 18 animals/ not humans/  
 19 15 not 16  
 20 ad.fs.  
 21 11 or 12 or 18  
 22 10 and 19  
 23 exp dose-response relationship, immunologic/  
 24 dose-Response Relationship, Drug/  
 25 (Dos\* sparing or Dose -sparing or half-dose or dose-response or dose response or dose  
 26 effect\* or dose-effect\* or fractional dos\*).tw,kf.  
 27 ((reduc\* or lower or less) adj2 (quantity or strength or standard)).tw,kf.  
 28 ((dos\* adj3 change) or (half adj3 dos\*)).tw,kf.  
 29 ((down adj3 titrat\*) or (dose adj3 titrat\*) or (dose adj3 reduc\*) or (dose adj3 "de-  
 30 escalat\*") or (dose adj3 taper\*)).tw,kf.  
 31 or/21-26  
 32 20 and 27  
 33 animals/ not humans/  
 34 28 not 29  
 35 limit 30 to yr=2009-current  
 36 17 or 31  
 37 32 use ppez  
 38 exp Influenza virus/ or exp influenza/  
 39 (flu or flue or influenza\* or grippe).tw.  
 40 34 or 35  
 41 exp vaccine/  
 42 exp immunization/  
 43 influenza vaccination/ or vaccination/  
 44 (vaccin\* or immuni\* or inocula\* or shot or jab).tw.  
 45 or/37-40  
 46 36 and 41  
 47 influenza vaccination/

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3 44 immunological adjuvant/  
4 45 (LAIV or Fluenz or FluMist or Afluria or Fluad or Fluzone or Flulaval or Fluarix or Flublok  
5 or Flucelvax or FluQuadri or Vaxigrip or Influvac or Fluvirin or Agrippal or Begrivac or Fluad or  
6 agriflu or fluviral).tw.  
7 46 or/42-45  
8 47 intramuscular drug administration/  
9 48 (intramuscular or intra-muscular).tw.  
10 49 47 or 48  
11 50 46 and 49  
12 51 limit 50 to yr="2009 -Current"  
13 52 animals/ not humans/  
14 53 51 not 52  
15 54 ad.fs.  
16 55 49 or 54  
17 56 46 and 55  
18 57 dose response/ or drug response/  
19 58 (Dos\* sparing or Dose -sparing or half-dose or dose-response or dose response or dose  
20 effect\* or dose-effect\* or fractional dos\*).tw.  
21 59 ((reduc\* or lower or less) adj2 (quantity or strength or standard)).tw.  
22 60 ((dos\* adj3 change) or (half adj3 dos\*)).tw.  
23 61 ((down adj3 titrat\*) or (dose adj3 titrat\*) or (dose adj3 reduc\*) or (dose adj3 "de-  
24 escalat\*") or (dose adj3 taper\*)).tw.  
25 62 or/57-61  
26 63 56 and 62  
27 64 animals/ not humans/  
28 65 63 not 64  
29 66 limit 65 to yr="2009 -Current"  
30 67 53 or 66  
31 68 67 use emczd  
32 69 33 or 68  
33 70 remove duplicates from 69  
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### APPENDIX 3 – Cochrane search strategy

Database: Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to June 03, 2020>, EBM Reviews - ACP Journal Club <1991 to May 2020>, EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>, EBM Reviews - Cochrane Clinical Answers <May 2020>, EBM Reviews - Cochrane Central Register of Controlled Trials <May 2020>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>  
**Search Strategy:**

1 (influenza, human or influenza a virus or influenzavirus b or influenzavirus c).kw.  
 2 (flu or flue or influenza\* or grippe).ti,ab.  
 3 1 or 2  
 4 (Vaccines or Immunization).kw.  
 5 (vaccin\* or immuni\* or inocula\* or shot or jab).ti,ab.  
 6 4 or 5  
 7 3 and 6  
 8 (influenza vaccines or Adjuvants, Immunologic).kw.  
 9 (LAIV or Fluenz or FluMist or Afluria or Fluad or Fluzone or Flulaval or Fluarix or Flublok or Flucelvax or FluQuadri or Vaxigrip or Influvac or Fluvirin or Agrippal or Begrivac or Fluad or agriflu or fluviral).ti,ab.  
 10 7 or 8 or 9  
 11 Injections, Intramuscular.kw.  
 12 (intramuscular or intra-muscular).ti,ab.  
 13 11 or 12  
 14 10 and 13  
 15 dose-response relationship, immunologic.kw.  
 16 dose-Response Relationship, Drug.kw.  
 17 (Dos\* sparing or Dose -sparing or half-dose or dose-response or dose response or dose effect\* or dose-effect\* or fractional dos\*).ti,ab.  
 18 ((reduc\* or lower or less) adj2 (quantity or strength or standard)).ti,ab.  
 19 ((dos\* adj3 change) or (half adj3 dos\*)).ti,ab.  
 20 ((down adj3 titrat\*) or (dose adj3 titrat\*) or (dose adj3 reduc\*) or (dose adj3 "de-escalat\*") or (dose adj3 taper\*)).ti,ab.  
 21 or/15-20  
 22 10 and 21  
 23 14 or 22  
 24 limit 23 to yr="2009 -Current" [Limit not valid in DARE; records were retained]

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to June 03, 2020>, EBM Reviews - ACP Journal Club <1991 to May 2020>, EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>, EBM Reviews - Cochrane Clinical Answers <May 2020>, EBM Reviews - Cochrane Central Register of Controlled Trials <May 2020>, EBM Reviews -

**Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>**  
**Search Strategy:**

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- 1 (influenza, human or influenza a virus or influenzavirus b or influenzavirus c).kw.
- 2 (flu or flue or influenza\* or grippe).ti,ab.
- 3 1 or 2
- 4 (Vaccines or Immunization).kw.
- 5 (vaccin\* or immuni\* or inocula\* or shot or jab).ti,ab.
- 6 4 or 5
- 7 3 and 6
- 8 (influenza vaccines or Adjuvants, Immunologic).kw.
- 9 (LAIV or Fluenz or FluMist or Afluria or Fluad or Fluzone or Flulaval or Fluarix or Flublok or Flucelvax or FluQuadri or Vaxigrip or Influvac or Fluvirin or Agrippal or Begrivac or Fluad or agriflu or fluviral).ti,ab.
- 10 7 or 8 or 9
- 11 Injections, Intramuscular.kw.
- 12 (intramuscular or intra-muscular).ti,ab.
- 13 11 or 12
- 14 10 and 13
- 15 dose-response relationship, immunologic.kw.
- 16 dose-Response Relationship, Drug.kw.
- 17 (Dos\* sparing or Dose -sparing or half-dose or dose-response or dose response or dose effect\* or dose-effect\* or fractional dos\*).ti,ab.
- 18 ((reduc\* or lower or less) adj2 (quantity or strength or standard)).ti,ab.
- 19 ((dos\* adj3 change) or (half adj3 dos\*)).ti,ab.
- 20 ((down adj3 titrat\*) or (dose adj3 titrat\*) or (dose adj3 reduc\*) or (dose adj3 "de-escalat\*") or (dose adj3 taper\*)).ti,ab.
- 21 or/15-20
- 22 10 and 21
- 23 14 or 22
- 24 limit 23 to yr="2000 - 2008" [Limit not valid in DARE; records were retained]
- 25 from 24 keep 1-173



## APPENDIX 4 – List of eligible vaccines

Product name (manufacturer)	Vaccine Characteristic				
	Vaccine type	Route of administration	Authorized ages for use	Antigen content for each vaccine strain	Formats available
Flulaval Tetra (GSK)	IIV4-SD (split virus)	IM	6 months and older	15 µg HA /0.5 mL dose	5 mL multi-dose vial Single dose pre-filled syringe
Fluzone Quadrivalent (Sanofi Pasteur)	IIV4-SD (split virus)	IM	6 months and older	15 µg HA /0.5 mL dose	5 mL multi-dose vial Single dose vial Single dose pre-filled syringe without attached needle
Afluria Tetra (Seqirus)	IIV4-SD (split virus)	IM	5 years and older	15 µg HA /0.5 mL dose	Up to expiry date indicate on vial label
Influvac Tetra (BGP Pharma ULC, operating as Mylan)	IIV4-SD (subunit)	IM or deep subcutaneous injection	3 years and older	15 µg HA /0.5 mL dose	Single dose pre-filled syringe with or without a needle
Vaxigrip Tetra	IIV4	IM	6 months and older	Pediatric: 7.5 µg HA /0.25 mL dose Adult: 15 µg HA /0.5 mL dose	0.5 mL pre-filled syringe
Fluarix Tetra/ Influxplit Tetra (GSK)	IIV4	IM	6 months and older	15 µg HA /0.5 mL dose	0.5 mL pre-filled syringe
Agriflu (Seqirus)	IIV3-SD (subunit)	IM	6 months and older	15 µg HA /0.5 mL dose	5 mL multi-dose vial Single dose pre-filled syringe without attached needle
Fluad Pediatric and Fluad (Seqirus)	IIV3-Adj (subunit)	IM	Pediatric: 6-23 months Adult: 65 years and older	Pediatric: 7.5 µg HA /0.25 mL dose Adult: 15 µg HA /0.5 mL dose	Single dose pre-filled syringe without a needle
Fluviral (GSK)	IIV3-SD (split virus)	IM	6 months and older	15 µg HA /0.5 mL dose	5 mL multi-dose vial
Fluzone TIV (Sanofi Pasteur)	IIV3-HD (split virus)	IM	65 years and older	Adult: 15 µg HA /0.5 mL dose	0.5 mL pre-filled syringe
Vaxigrip TIV	IIV3-SD	IM	6 months and older	Pediatric: 7.5 µg HA /0.25 mL dose Adult: 15 µg HA /0.5 mL dose	0.5 mL pre-filled syringe

**Note:** list of vaccines included in the review is based on feedback from PHAC and the 2020-2021 seasonal vaccine availability in Canada found here: <https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/canadian-immunization-guide-statement-seasonal-influenza-vaccine-2020-2021.html#appA>

## APPENDIX 5 – Excluded dose-sparing studies

	Reference	Reason for exclusion
1	Euctr, H. U. A Randomized, Double-blind, Multi-Center Study to Evaluate Safety and Immunogenicity of One Dose of Four FLUVAL AB-like (Trivalent, Whole Virus, Aluminium Phosphate Gel Adjuvanted) Influenza Vaccines Containing 3.5[micro]gHA, 6[micro]gHA, 9[micro]gHA or 1. 2011. Available from: <a href="http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011">http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011</a>	exclude - dose-sparing but vaccine not of interest
2	Vajo Z, Tamas F, Jankovics I. A reduced-dose seasonal trivalent influenza vaccine is safe and immunogenic in adult and elderly patients in a randomized controlled trial. <i>Clin Vaccine Immunol.</i> 2012;19(3):313-318. doi:10.1128/CVI.05619-11	exclude - dose-sparing but vaccine not of interest
3	Treanor J, Keitel W, Belshe R, et al. Evaluation of a single dose of half strength inactivated influenza vaccine in healthy adults. <i>Vaccine.</i> 2002;20(7-8):1099-1105. doi:10.1016/s0264-410x(01)00440-6	exclude - dose-sparing but vaccine not of interest
4	Euctr. A Randomized, Active Controlled, Double-blind, Multi-Centre Study to Evaluate Safety and Immunogenicity of One Dose of FLUVAL AB-like (Trivalent, Whole Virus, Aluminium Phosphate Gel Adjuvanted) Influenza Vaccine Containing 6µgHA of Seasonal A/H1N1, A/H3N2 and B Influenza Antigens in Non-elderly Adult and Elderly Subjects. 2011. Available from: <a href="http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011-003314-16-HU">http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011-003314-16-HU</a>	exclude - dose-sparing but experimental vaccine
5	Euctr, E. S. Clinical study to compare the safety of two influenza vaccines in children and adolescents of 3 to less than 18 years of age at risk for influenza-related complications. 2013. Available from: <a href="http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2013">http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2013</a>	exclude - dose-sparing but experimental vaccine
6	Pillet S, Aubin É, Trépanier S, et al. A plant-derived quadrivalent virus like particle influenza vaccine induces cross-reactive antibody and T cell response in healthy adults. <i>Clin Immunol.</i> 2016;168:72-87. doi:10.1016/j.clim.2016.03.008	exclude - dose-sparing but experimental vaccine
7	Lee JH, Cho HK, Kim KH, et al. Evaluation of Waning Immunity at 6 Months after Both Trivalent and Quadrivalent Influenza Vaccination in Korean Children Aged 6-35 Months. <i>J Korean Med Sci.</i> 2019;34(46):e279. Published 2019 Dec 2. doi:10.3346/jkms.2019.34.e279	exclude - dose-sparing but experimental vaccine
8	Treanor JJ, Taylor DN, Tussey L, et al. Safety and immunogenicity of a recombinant hemagglutinin influenza-flagellin fusion vaccine (VAX125) in healthy young adults. <i>Vaccine.</i> 2010;28(52):8268-8274. doi:10.1016/j.vaccine.2010.10.009	exclude - dose-sparing but experimental vaccine
9	Vajo Z, Balaton G, Vajo P, Kalabay L, Erdman A, Torzsa P. Dose sparing and the lack of a dose-response relationship with an influenza vaccine in adult and elderly patients - a randomized, double-blind clinical trial. <i>Br J Clin Pharmacol.</i> 2017;83(9):1912-1920. doi:10.1111/bcp.13289	exclude - dose-sparing but vaccine not of interest
10	Ctri. Study of a Single Dose or Two Doses of a Quadrivalent Influenza Vaccine in Subjects Aged 6 Months or Older in India. 2015. Available from: <a href="http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI">http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI</a>	exclude - dose-sparing but unclear vaccine (waiting for author response)
11	Euctr, F. I. Safety and Immunogenicity of the Quadrivalent Influenza Vaccine Administered via the Intramuscular Route in Children Aged 3 to 8 Years. 2011. Available from: <a href="http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011">http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011</a>	exclude - dose-sparing but unclear vaccine (waiting for author response)
12	Euctr, C. Z. A randomized, double-blind, placebo-controlled, multi-country and multi-center, phase IV study to demonstrate the efficacy of GSK Biologicals' influenza vaccine (Fluarix[TM])	exclude - dose-sparing but unclear vaccine (waiting for author response)

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administered intramuscularly in adults. - FluarixUS-006. 2006. Available from: <a href="http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2006">http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2006</a>	
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For peer review only

## APPENDIX 6 – Study and patient data

Author, Year [Study design]	Study period; Setting and Country	Objective of study	Eligibility criteria	Sample size; % Female, % previously immunized	Ethnicities
Kramer, 2006 [RCT] <sup>1</sup>	October 2004 – November 2004; 760-bed tertiary care community teaching hospital in the USA	To compare the effectiveness of half-dose versus full dose TIV in health care workers	Age 18 years or older, hospital employee, staff member, or volunteer, and signed informed consent and authorization to use and disclose protected health information for research purposes	444; NR, NR	NR
Belshe, 2007 [RCT] <sup>2</sup>	USA; NR	To compare the immunogenicity and safety of injection of IM and ID TIV across different dose levels (3, 6, 9, and 15µg/antigen/dose)	Healthy adults 18-49 years of age	125; 71.2%, 0%	American Indian/Alaskan Native (0%), Asian (2.4%), Black/African American (9.6%), Hawaiian/Pacific Islander (0%), Hispanic (0%), Multi-racial (0.8%), Non-Hispanic (97.6%), Other/unknown (0%), White (87.2%)
Engler, 2008 [RCT] <sup>3</sup>	November 2004 – December 2004; Allergy-Immunology-Immunization Clinic, WRAMC, and Pentagon/DiLorenzo Health Clinic, Arlington, Virginia in the USA	To determine the effects of age, sex, and dose on the immunogenicity of intramuscular TIV	Healthy adults aged 18-64 years. Inclusion criteria were based on the remaining CDC and/or DoD priority prior to the shortage announcement which includes all children aged 6--23 months; adults aged >65 years; persons aged 2--64 years with underlying chronic medical conditions; all women who will be pregnant during the influenza season; residents of nursing homes and long-term--care facilities; children aged 2--18 years on chronic aspirin therapy; health-care workers involved in direct patient care; and out-of-home caregivers and household contacts of children aged <6 months	1316; 43.4%, 0%	African American (9%), Asian (2%), Hispanic (2%), Other/unknown (1.4%), White (85%)
	August 2007-2008; Seattle Division of the Department of	To determine pre vaccination and 4- week post-vaccination changes in antibody titer, and	Community-dwelling adults 65 years and older living in Puget Sound area in Washington State	129; 17.8%, 94.6%	African American (4.7%), Asian (1.6%), Hispanic (0.8%), Not reported

Author, Year [Study design]	Study period; Setting and Country	Objective of study	Eligibility criteria	Sample size; % Female, % previously immunized	Ethnicities
Chi, 2010 [RCT] <sup>4</sup>	Veterans Affairs Puget Sound Health Care System in Washington State, USA.	local and systemic reactions of full-dose compared to 60% dose of TIV by IM injection			(2.3%), Other (0.8%), White (90%)
Cioppa, 2011 [RCT] <sup>5</sup>	October 2008 – March 2009; 10 study centers in Finland and 5 centers in Belgium	To evaluate the safety, tolerability and immunogenicity of different vaccine formulations with different doses of MF59 adjuvant and/or a second B strain (QIV) when added to either high or low doses of a purified subunit influenza vaccine	Healthy children aged 6 to <36 months	126; 43.5%, NR	Asian (1.68%), Black (6.54%), White (84.2%)
Skowronski, 2011 [RCT] <sup>6</sup>	September 2008 – December 2008; 5 sites in 3 Canadian provinces (British Columbia, Quebec, and Nova Scotia)	To determine whether giving 2 full doses of split TIV to previously unimmunized infants and toddlers can improve immunogenicity without increasing reactogenicity compared with 2 half-doses	Healthy children 6–23 months of age	267; 53.2%, 0%	Asian (7.9%), Other (14.3%), White (77.8%)
Langley, 2012 [RCT] <sup>7</sup>	November 2008 – August 2009; 17 centers in Canada	To assess the immunogenicity and safety of a preservative-free, prefilled syringe formulation of TIV provided as the full adult dose of 0.50 mL compared with the usual children's dose of 0.25 mL in young children	Healthy children 6–35 months at the time of vaccination	390; 47.9%, 42.6%	Other (13.9%), White (86.1%)
Pavia-Ruz, 2015 [RCT] <sup>8</sup>	October 2008 – March 2009; Hong Kong, Mexico, Taiwan, Thailand, and the USA	To evaluate Fluarix at both the standard recommended TIV dose for young children in the US (0.25 ml) and also at double this dose (0.5 ml)	Healthy children aged 6 to 35 months at the time of the first vaccination; without acute illness at the time of enrollment and who had not been vaccinated during the 2008-2009 influenza season. Administration of influenza vaccine in a previous season was not however an exclusion criteria	3318; 51%, 30.1%	African heritage/African American (3.5%), American Indian or Alaskan native (0.1%), Asian-Central/South Asian heritage (0.1%), Asian-East Asian heritage (14.5%), Asian-Japanese heritage (0.1%), Asian-South East Asian heritage

Author, Year [Study design]	Study period; Setting and Country	Objective of study	Eligibility criteria	Sample size; % Female, % previously immunized	Ethnicities
					(9.2%), Native Hawaiian or other Pacific Islander (0.2%), White - Arabic/North African heritage (0.5%), White-Caucasian/European heritage (29.9%), Hispanics and children of mixed race (42.1%)
Halasa, 2015 [RCT] <sup>9</sup>	2010-2012; 6 study sites in USA	To determine whether a higher dose of influenza vaccine would be safe in the 6 through 35 months age group. In addition, to determine whether immunization with 0.5 mL doses of TIV (15 µg of each HA) would improve the immunogenicity without increasing the reactogenicity of TIV when administered to children 6 through 35 months of age with and without a history of previous TIV vaccination	Healthy children 6 to 35 months of age (naïve cohort) or 12 through 35 months of age (fully primed cohort) who were available for the entire study period and whose parents or guardians provided informed consent were eligible to participate. Children who were eligible in the fully primed cohort also required a history of receiving 2 doses of 2009–2010 H1N1 influenza vaccine and 2 doses of TIV at any time in the past	243; 52%, 13.2%	African (26%), Asian (1%), Multiracial (5%), other (0%); Ethnicity: Hispanic (2%), Non-Hispanic (98%), White (67%)
Phung, 2016 [RCT] <sup>10</sup>	September 2010-January 2011; Finland	To evaluate the immunogenicity and safety following a single intramuscular dose of FLUAD or Agrippal S1 influenza vaccines in healthy children previously vaccinated	Healthy children 6–35 months at the time of vaccination	197; 55.8%, 85.7%	NR
Jain, 2017 [RCT] <sup>11</sup>	2014-2015 influenza season; 66 study locations in USA and Mexico	To compare the safety and immunogenicity of a double-dose IIV4 manufactured by GSK Vaccines with the United States-approved standard-dose IIV4 in children 6–35 months of age	Healthy children aged 6-35 months regardless of influenza vaccination history, but could not have received any seasonal or pandemic influenza vaccine within 6 months before the first dose of study vaccine	2424; 46.9%, 57.5%	African/African American (13.9%), American Indian or Alaskan Native (2.0%), Caucasian (64.3%), Other (17.9%), South East Asian (1.8%)
Ojeda, 2019 [RCT] <sup>12</sup>	December 2017 – January 2018; 3 study sites in Mexico	Reported the results of an open-label, randomized phase III study designed to evaluate the immunogenicity and safety	Children aged 6 months to 17 years of age	302; 46.4%, NR	NR

Author, Year [Study design]	Study period; Setting and Country	Objective of study	Eligibility criteria	Sample size; % Female, % previously immunized	Ethnicities
Robertson, 2019 [RCT] <sup>13</sup>	September 2016 – March 2017; 38 sites in the USA	of this thiomersal containing MDV format of QIV compared to the licensed thiomersal-free, single-dose PFS format in children and adolescents  To compare the safety and immunogenicity of full and half doses of quadrivalent, split- virion, inactivated influenza vaccine in children 6–35 months of age	Healthy children 6–35 months of age who had not been vaccinated against influenza during the current season (2016–2017). Children 6–11 months of age had to be born at full term of pregnancy (≥37 weeks) or with a birth weight ≥2.5 kg	1950; 49.7%, 47.3%	Race: American Indian or Alaska Native (0.98%), Asian (0.46%), Black (19.2%), Native Hawaiian or Other Pacific Islander (0.46%), White (74.3%), Ethnicity: Hispanic or Latino (22%), not Hispanic or Latino (77%)

**Abbreviations:** CDC- Centers for Disease Control and Prevention; DoD- Department of Defense; GSK -GlaxoSmithKline; HA- hemagglutinin; IIV4 – inactivated influenza vaccine; ID - intradermal; IM - intramuscular; MDV- multi-dose vial; PFS – pre-filled syringe; QIV-quadrivalent influenza vaccine; TIV-trivalent influenza vaccine; NR – not reported

**APPENDIX 7 – Treatment and outcome data**

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety Outcome (definition): n/N (unless otherwise indicated)	Conclusions
Kramer, 2006 [RCT] <sup>1</sup>  Adults and Seniors (>18 years)	<p>Fluzone (Aventis Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose (Intramuscular into the deltoid region)]</p> <p><i>A/Wyoming/3/2003 (H3N2), A/New Caledonia/20/99 (H1N1), and a new B strain, B/Jiangsu/10/2003</i></p> <p>Fluzone (Aventis Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose (Intramuscular into the deltoid region)]</p> <p><i>A/Wyoming/3/2003 (H3N2), A/New Caledonia/20/99 (H1N1), and a new B strain, B/Jiangsu/10/2004</i></p>	<p><b>Effectiveness</b> <i>Lab confirmed influenza</i> (Laboratory confirmation of influenza diagnosis was sought in participants reporting a clinical diagnosis by their physicians): 1/222</p> <p><i>Influenza like illness</i> (Clinical diagnosis of influenza. Participants self-reported four or more symptoms consistent with influenza-like illness (i.e., headache, extreme tiredness, dry cough, fever, muscle or body aches)): 8/222</p> <p><b>Effectiveness</b> <i>Lab confirmed influenza</i> (Laboratory confirmation of influenza diagnosis was sought in participants reporting a clinical diagnosis by their physicians): 0/222</p> <p><i>Influenza like illness</i> (Clinical diagnosis of influenza. Participants self-reported four or more symptoms consistent with influenza-like illness (i.e., headache, extreme tiredness, dry cough, fever, muscle or body aches)): 15/222</p>	<ul style="list-style-type: none"> <li>There was no significant difference between the full-dose and half-dose groups in the diagnosis of influenza or in the proportion of participants self-reporting four or more symptoms consistent with influenza-like illness.</li> <li>No adverse events were noted by participants from either group or reported to the IRB during the course of the study</li> </ul>
Belshe, 2007 [RCT] <sup>2</sup>  Adults (18-49 years)	<p>Fluzone (Sanofi-Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose (Intramuscular in the non-dominant arm)]</p> <p>Fluzone (Sanofi-Pasteur), <b>9-µg/strain</b> [1 x 0.3mL dose (Intramuscular in the non-dominant arm)]</p>	<p><b>Reactogenicity – injection site</b> <i>Pain</i><sup>1</sup>: 15/31 <i>Redness</i><sup>2</sup>: 8/31 <i>Swelling</i><sup>2</sup>: 7/31</p> <p><b>Reactogenicity – systemic</b> <i>Fever</i><sup>3</sup>: 1/31 <i>Headache</i><sup>1</sup>: 15/31 <i>Malaise</i><sup>1</sup>: 8/31 <i>Myalgia</i><sup>1</sup>: 10/31</p> <p><b>Reactogenicity – injection site</b> <i>Pain</i><sup>1</sup>: 11/31 <i>Redness</i><sup>2</sup>: 11/31 <i>Swelling</i><sup>2</sup>: 4/31</p> <p><b>Reactogenicity – systemic</b> <i>Fever</i><sup>3</sup>: 1/31 <i>Headache</i><sup>1</sup>: 6/31</p>	<ul style="list-style-type: none"> <li>Intradermal vaccine induced significantly more local inflammatory response than Intramuscular vaccine (primary comparison of this study was ID vs IM doses)</li> </ul>



Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety Outcome (definition): n/N (unless otherwise indicated)	Conclusions
	<p>Fluzone (Sanofi-Pasteur), <b>6-µg/strain</b> [1 x 0.2mL dose (Intramuscular in the non-dominant arm)]</p>	<p><i>Malaise</i><sup>1</sup>: 8/31 <i>Myalgia</i><sup>1</sup>: 6/31</p> <p><b>Reactogenicity – injection site</b> <i>Pain</i><sup>1</sup>: 14/31 <i>Redness</i><sup>2</sup>: 9/31 <i>Swelling</i><sup>2</sup>: 4/31</p> <p><b>Reactogenicity – systemic</b> <i>Fever</i><sup>3</sup>: 0/31 <i>Headache</i><sup>1</sup>: 9/31 <i>Malaise</i><sup>1</sup>: 7/31 <i>Myalgia</i><sup>1</sup>: 9/31</p>	
	<p>Fluzone (Sanofi-Pasteur), <b>3-µg/strain</b> [1 x 0.1mL dose (Intramuscular in the non-dominant arm)]</p>	<p><b>Reactogenicity – injection site</b> <i>Pain</i><sup>1</sup>: 15/31 <i>Redness</i><sup>2</sup>: 9/31 <i>Swelling</i><sup>2</sup>: 7/31</p> <p><b>Reactogenicity – systemic</b> <i>Fever</i><sup>3</sup>: 3/31 <i>Headache</i><sup>1</sup>: 8/31 <i>Malaise</i><sup>1</sup>: 3/31 <i>Myalgia</i><sup>1</sup>: 7/31</p>	
<p>Engler, 2008 [RCT]<sup>3</sup></p> <p><i>Adults</i> (18-64 years)</p>	<p>Fluzone (Aventis Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose (Intramuscular injection)]</p> <p><i>A/H1N1, A/New Caledonia/20/99; A/H3N2, A/Fujian/411/2002; B, B/Shanghai/361/2002</i></p>	<p><b>Effectiveness</b> <i>Influenza like illness</i> (Influenza-like illness and complications resulting in either inpatient or outpatient medical encounters were compared between dose groups (by age)): 61/632</p> <p><i>Hospitalization or Emergency visits</i>: 0.3%</p> <p><b>Reactogenicity – local/injection site</b> <i>Any local reactions</i> (NR): 8.9% <i>Arm weakness</i> (NR): 8.3% <i>Numbness or burning</i> (NR): 9.7% <i>Pain</i> (NR): 5.9% <i>Redness or swelling</i> (NR): 13.4%</p> <p><b>Reactogenicity – systemic</b> <i>Joint and/or muscle pain</i> (NR): 4.5%</p>	<ul style="list-style-type: none"> <li>▪ The relative risk of medical visits and hospitalizations for influenza-like illnesses were similar in the half- and full-dose group regardless of age, and there was no evidence of ILI symptom differences by sex or dose during the 21 days after immunizations.</li> <li>▪ Although injection site pain was greater for full vs half dose (19.9% vs 14.4%; p=.01), when analyzed for clinically significant pain levels significant dose-dependent</li> </ul>

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety Outcome (definition): n/N (unless otherwise indicated)	Conclusions
	<p>Fluzone (Aventis Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose (Intramuscular injection)]</p> <p><i>A/H1N1, A/New Caledonia/20/99; A/H3N2, A/Fujian/411/2002; B, B/Shanghai/361/2003</i></p>	<p><b>Adverse events</b> SAE: 2/554</p> <p><b>Effectiveness</b> <i>Influenza like illness</i> (Influenza-like illness and complications resulting in either inpatient or outpatient medical encounters were compared between dose groups (by age): 64/644</p> <p><i>Hospitalization or Emergency visits</i>: 0.2%</p> <p><b>Reactogenicity – local/injection site</b> <i>Any local reactions</i> (NR): 7.5% <i>Arm weakness</i> (NR): 6.5% <i>Numbness or burning</i> (NR): 7.8% <i>Pain</i> (NR): 4.6% <i>Redness or swelling</i> (NR): 8.6%</p> <p><b>Reactogenicity – systemic</b> <i>Joint and/or muscle pain</i> (NR): 2.2%</p> <p><b>Adverse events</b> SAE: 1/556</p>	<p>pain differences were not identified.</p> <ul style="list-style-type: none"> <li>Joint and/or muscle pain were significantly different (p=.02 and p=.03, respectively) by dose.</li> <li>No other adverse event differed significantly by dose</li> </ul>
<p>Chi, 2010 [RCT]<sup>4</sup></p> <p>Seniors (&gt;65 years)</p>	<p>Fluzone (Sanofi Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose (intramuscular in deltoid of arm)]</p> <p><i>A/Solomon Islands/3/ 2006 (A/H1N1), A/Wisconsin/67/2005 (A/H3N2), and B/Malaysia/2506/2004</i></p>	<p><b>Reactogenicity – injection site, N=64</b> <i>Arm motion limitation</i>: 1 (grade I)<sup>4</sup> <i>Itching</i>: 4 (grade I)<sup>4</sup> <i>Pain</i>: 7 (grade I)<sup>4</sup> <i>Redness or discoloration</i>: 9 (grade I)<sup>4</sup> <i>Swelling</i>: 13 (grade I)<sup>4</sup></p> <p><b>Reactogenicity - systemic, N=64</b> <i>Chills</i>: 1 (grade I)<sup>4</sup>, 1 (grade II/III)<sup>5</sup> <i>Fatigue</i>: 4 (grade I)<sup>4</sup>, 2 (grade II/III)<sup>5</sup> <i>Fever</i>: 0 <i>General body ache/pain</i>: 6 (grade I)<sup>4</sup>, 1 (grade II/III)<sup>5</sup> <i>Headache</i>: 10 (grade I)<sup>4</sup> <i>Nausea</i>: 3 (grade I)<sup>4</sup>, 1 (grade II/III)<sup>5</sup></p> <p><b>Adverse events</b></p>	<ul style="list-style-type: none"> <li>The two SAEs were acute coronary syndrome and appendicitis and neither were judged to be related to influenza vaccination</li> </ul>

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety <i>Outcome</i> (definition): n/N (unless otherwise indicated)	Conclusions
	<p>Fluzone (Sanofi Pasteur), <b>9-µg/strain</b> [1 x 0.3mL dose (intramuscular in deltoid of arm)]</p> <p><i>A/Solomon Islands/3/2006 (A/H1N1), A/Wisconsin/67/2005 (A/H3N2), and B/Malaysia/2506/2004</i></p>	<p>SAE<sup>6</sup>: 0/64</p> <p><b>Reactogenicity – injection site, N=64</b> <i>Arm motion limitation</i>: 1 (grade I)<sup>4</sup> <i>Itching</i>: 5 (grade I)<sup>4</sup> <i>Pain</i>: 11 (grade I)<sup>4</sup> <i>Redness or discoloration</i>: 7 (grade I)<sup>4</sup> <i>Swelling</i>: 4 (grade I)<sup>4</sup></p> <p><b>Reactogenicity - systemic, N=64</b> <i>Chills</i>: 1 (grade I)<sup>4</sup>, 1 (grade II/III)<sup>5</sup> <i>Fatigue</i>: 6 (grade I)<sup>4</sup>, 1 (grade II/III)<sup>5</sup> <i>Fever</i>: 1 (grade I)<sup>4</sup> <i>General body ache/pain</i>: 5 (grade I)<sup>4</sup>, 2 (grade II/III)<sup>5</sup> <i>Headache</i>: 5 (grade I)<sup>4</sup>, 1 (grade II/III)<sup>5</sup> <i>Nausea</i>: 2 (grade I)<sup>4</sup>, 1 (grade II/III)<sup>5</sup></p> <p><b>Adverse events</b> SAE<sup>6</sup>: 2/64</p>	
<p>Cioppa, 2011 [RCT]<sup>5</sup></p> <p><i>Infants/ Toddlers (6-36 months)</i></p>	<p>NR - TIV, <b>7.5-µg/strain</b> [2 x 0.25mL dose (intramuscular in deltoid of arm (children 24-35 mo of age) or the anterolateral aspect of the thigh (children &lt;24 mo of age) using prefilled syringes)]</p> <p><i>A/Brisbane/59/2007 (A/H1N1)-like virus, A/Brisbane/10/2007 (A/H3N2)-like virus, and B/Florida/4/2006-like virus (of the influenza B/Yamagata lineage)</i></p> <p>Agrippal - TIV, <b>15-µg/strain</b> [2 x 0.5mL dose (intramuscular in deltoid of arm (children 24-35 mo of age) or the anterolateral aspect of the thigh (children &lt;24 mo of age) using prefilled syringes)]</p> <p><i>A/Brisbane/59/2007 (A/H1N1)-like virus, A/Brisbane/10/2007 (A/H3N2)-like virus, and B/Florida/4/2006-like virus (of the influenza B/Yamagata lineage)</i></p>	<p><b>Reactogenicity</b> <i>Any local reaction</i><sup>7</sup>: 47% <i>Any systemic reaction</i><sup>8</sup>: 68%</p> <p><b>Adverse events</b> AE (solicited/spontaneously reported): 84% SAE: 0/25</p> <p><b>Reactogenicity</b> <i>Any local reaction</i><sup>7</sup>: 59% <i>Any systemic reaction</i><sup>8</sup>: 50%</p> <p><b>Adverse events</b> AE (solicited/spontaneously reported): 82% SAE: 0/22</p>	<ul style="list-style-type: none"> <li>▪ Reactogenicity of the 7.5-µg TIV/QIV formulations was slightly lower than for the corresponding 15-µg formulations.</li> <li>▪ The majority of unsolicited AEs were mild or moderate in severity and none of the SAEs was considered to be related to the study vaccine.</li> </ul>

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety Outcome (definition): n/N (unless otherwise indicated)	Conclusions
	NR - QIV, <b>7.5-µg/strain</b> [2 x 0.25mL dose (intramuscular in deltoid of arm (children 24-35 mo of age) or the anterolateral aspect of the thigh (children <24 mo of age) using prefilled syringes)]  <i>A/Brisbane/59/2007 (A/H1N1)-like virus, A/Brisbane/10/2007 (A/H3N2)-like virus, B/Florida/4/2006-like virus (of the influenza B/Yamagata lineage), and B/Malaysia/2506/2004-like antigen virus (Victoria lineage)</i>	<b>Reactogenicity</b> <i>Any local reaction</i> <sup>7</sup> : 25% <i>Any systemic reaction</i> <sup>8</sup> : 50%  <b>Adverse events</b> AE (solicited/spontaneously reported): 92% SAE: 1/25	
	NR - QIV, <b>15-µg/strain</b> [2 x 0.5mL dose (intramuscular in deltoid of arm (children 24-35 mo of age) or the anterolateral aspect of the thigh (children <24 mo of age) using prefilled syringes)]  <i>A/Brisbane/59/2007 (A/H1N1)-like virus, A/Brisbane/10/2007 (A/H3N2)-like virus, B/Florida/4/2006-like virus (of the influenza B/Yamagata lineage), and B/Malaysia/2506/2004-like antigen virus (Victoria lineage)</i>	<b>Reactogenicity</b> <i>Any local reaction</i> <sup>7</sup> : 39% <i>Any systemic reaction</i> <sup>8</sup> : 54%  <b>Adverse events</b> AE (solicited/spontaneously reported): 71% SAE: 1/28	
	Vaxigrip pediatric - TIV (Sanofi Pasteur), <b>7.5-µg/strain</b> [2 x 0.25mL dose (intramuscular in deltoid of arm (children 24-35 mo of age) or the anterolateral aspect of the thigh (children <24 mo of age) using prefilled syringes)]	<b>Reactogenicity</b> <i>Any local reaction</i> <sup>7</sup> : 50% <i>Any systemic reaction</i> <sup>8</sup> : 46%  <b>Adverse events</b> AE (solicited/spontaneously reported): 73% SAE: 1/26	
Skowronski, 2011 [RCT] <sup>6</sup>  <i>Infants/Toddlers (6-23 months)</i>	Vaxigrip (Sanofi-Pasteur), <b>15-µg/strain [2 x 0.5mL dose]</b> (Intramuscular injection)  <i>A/Brisbane/10/07 (H3N2); A/Brisbane/59/07 (H1N1); and B/Florida/4/06 (Yamagata lineage)</i>	<b>Reactogenicity – injection site</b> <i>Induration</i> (NR): 13.7% <i>Redness</i> (NR): 22.6% <i>Swelling</i> (NR): 15.3% <i>Tenderness</i> (NR): 22.6%  <b>Reactogenicity – systemic</b> <i>Fever</i> (>37.5°C): 8.06% <i>Irritability</i> (NR): 59.7% <i>Decreased appetite</i> (NR): 38.7%	<ul style="list-style-type: none"> <li>▪ Local reactions generally were less common in infants than toddlers and more common with full doses versus half doses, but none of these differences were significant.</li> <li>▪ One serious adverse event was reported: a toddler in the half dose group was</li> </ul>

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety <i>Outcome</i> (definition): n/N (unless otherwise indicated)	Conclusions
	<p>Vaxigrip (Sanofi-Pasteur), 15-µg/strain [2 x 0.25mL dose (Intramuscular injection)]</p> <p><i>A/Brisbane/10/07 (H3N2); A/Brisbane/59/07 (H1N1); and B/Florida/4/06 (Yamagata lineage)</i></p>	<p><i>Drowsiness</i> (NR): 39.5% <i>Sleep disturbance</i> (NR): 54.8%</p> <p><b>Adverse events</b> SAE: NR</p> <p><b>Reactogenicity – injection site</b> <i>Induration</i> (NR): 6.3% <i>Redness</i> (NR): 20.3% <i>Swelling</i> (NR): 8.6% <i>Tenderness</i> (NR): 25.8%</p> <p><b>Reactogenicity – systemic</b> <i>Fever (&gt;37.5°C)</i>: 11.7% <i>Irritability</i> (NR): 60.2% <i>Decreased appetite</i> (NR): 43% <i>Drowsiness</i> (NR): 41.4% <i>Sleep disturbance</i> (NR): 50%</p> <p><b>Adverse events</b> SAE: 1/128</p>	<p>hospitalized with pneumonia 28 days after the first vaccination. The event was deemed unlikely related to the vaccine.</p> <ul style="list-style-type: none"> <li>All of the rate differences were significantly below the allowed 10% increase in reactogenicity for the full dose (<math>p &lt; 0.001</math> for infant and combined analyses, <math>p &lt; .005</math> for toddlers).</li> <li>This randomized controlled trial in infants and toddlers shows that compared with 0.25-mL half-dosing, administration of 2 full 0.5-mL doses of trivalent inactivated influenza vaccine can increase antibody response without increasing reactogenicity in previously unimmunized infants aged 6 to 11 months.</li> </ul>
<p>Langley, 2012 [RCT]<sup>7</sup></p> <p><i>Infants/ Toddlers (6-35 months)</i></p>	<p>Fluviral F1 (Sanofi-Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose (Intramuscularly in the anterolateral part of the thigh (if the participant was less than 12 months) or in the deltoid region of the arm)]</p> <p><i>A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (an A/Brisbane/10/2007 [H3N2]-like virus), and B/Florida/4/2006</i></p>	<p><b>Reactogenicity – injection site</b> <i>Pain</i> (NR): 45/164 <i>Redness</i> (NR): 49/164 <i>Swelling</i> (NR): 22/164</p> <p><b>Reactogenicity – systemic</b> <i>Drowsiness</i> (NR) – 44/164 <i>Fever</i> (NR) – 10/164 <i>Irritability</i> (NR) – 62/164 <i>Loss of appetite</i> (NR) – 37/164</p> <p><b>Adverse events</b> SAE: 1/164</p>	<ul style="list-style-type: none"> <li>Fluviral F1 group had 1 case of pneumonia resolved</li> <li>Fluviral F2 group had 1 case of bronchial hyper-reactivity in resolving stage</li> <li>The 0.5-mL dose of the study vaccine, when administered to children aged 6–35 months, resulted in a modest but not statistically significant improvement in</li> </ul>

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety Outcome (definition): n/N (unless otherwise indicated)	Conclusions
	<p>Fluviral F2 (Sanofi-Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose (Intramuscularly in the anterolateral part of the thigh (if the subject was less than 12 months) or in the deltoid region of the arm)]</p> <p><i>A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (an A/Brisbane/10/2007 [H3N2]-like virus), and B/Florida/4/2006</i></p> <p>Vaxigrip (Sanofi-Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose (Intramuscularly in the anterolateral part of the thigh (if the participant was less than 12 months) or in the deltoid region of the arm)]</p> <p><i>A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (an A/Brisbane/10/2007 [H3N2]-like virus), and B/Florida/4/2006</i></p>	<p><i>Unsolicted adverse events (NR): 108/164</i> <i>Medically attended events (NR): 52/164</i></p> <p><b>Reactogenicity – injection site</b> <i>Pain (NR): 55/167</i> <i>Redness (NR): 54/167</i> <i>Swelling (NR): 24/167</i></p> <p><b>Reactogenicity – systemic</b> <i>Drowsiness (NR) – 52/167</i> <i>Fever (NR) – 6/167</i> <i>Irritability (NR) – 69/167</i> <i>Loss of appetite (NR) – 43/167</i></p> <p><b>Adverse events</b> <i>SAE: 1/167</i> <i>Unsolicted adverse events (NR): 112/167</i> <i>Medically attended events (NR): 40/167</i></p> <p><b>Reactogenicity – injection site</b> <i>Pain (NR): 17/43</i> <i>Redness (NR): 13/43</i> <i>Swelling (NR): 5/43</i></p> <p><b>Reactogenicity – systemic</b> <i>Drowsiness (NR) – 11/43</i> <i>Fever (NR) – 2/43</i> <i>Irritability (NR) – 15/43</i> <i>Loss of appetite (NR) – 9/43</i></p> <p><b>Adverse events</b> <i>SAE: NR/43</i> <i>Unsolicted adverse events (NR): 24/43</i> <i>Medically attended events (NR): 9/43</i></p>	<p>immunogenicity with clinically similar safety and reactogenicity compared with the 0.25-mL dose.</p>
<p>Pavia-Ruz, 2013 [RCT]<sup>8</sup></p> <p><i>Infants/Toddlers</i></p>	<p>Fluarix (GSK), <b>15-µg/strain</b> [1 x 0.5mL dose (intramuscular injection into the right deltoid muscle or anterolateral thigh)]</p>	<p><b>Reactogenicity – injection site</b> <i>Any injection site reactions<sup>9</sup>: 514/1086</i> <i>Pain: 406/1086</i> <i>Redness: 249/1086</i> <i>Swelling: 170/1086</i></p>	<ul style="list-style-type: none"> <li>The reactogenicity and safety profile of the study vaccine did not appear to be affected by doubling the dose.</li> </ul>

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety Outcome (definition): n/N (unless otherwise indicated)	Conclusions
(6-35 months)	A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2) and B/Brisbane/3/2007	<b>Reactogenicity – systemic</b> Any general reactions <sup>10</sup> : 575/1086 Drowsiness: 317/1086 Fever: 69/1086 Irritability: 387/1086 Loss of appetite: 273/1086  <b>Adverse events</b> Any AE: 729/1086 SAE: 29/1086	<ul style="list-style-type: none"> <li>One subject in the Flu-15µg group had two SAEs, (apnea and cyanosis) which were considered by the investigator to be possibly related to vaccination. The participant was hospitalized and the events resolved on the same day as they occurred.</li> </ul>
	Fluarix (GSK), <b>7.5-µg/strain</b> [1 x 0.25 mL dose (intramuscular injection into the right deltoid muscle or anterolateral thigh)]  A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2) and B/Brisbane/3/2007	<b>Reactogenicity – injection site</b> Any injection site reactions <sup>9</sup> : 492/1081 Pain: 403/1081 Redness: 259/1081 Swelling: 152/1081  <b>Reactogenicity – systemic</b> Any general reactions <sup>10</sup> : 598/1081 Drowsiness: 293/1081 Fever: 67/1081 Irritability: 386/1081 Loss of appetite: 281/1081  <b>Adverse events</b> Any AE: 724/1081 SAE: 35/1081	
	Fluzone (Sanofi-Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose (intramuscular injection into the right deltoid muscle or anterolateral thigh)]  A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2) and B/Florida/4/2006	<b>Reactogenicity – injection site</b> Any injection site reactions <sup>9</sup> : 467/1090  Pain: 363/1090 Redness: 253/1090 Swelling: 129/1090  <b>Reactogenicity – systemic</b> Any general reactions <sup>10</sup> : 592/1090 Drowsiness: 298/1090 Irritability: 375/1090 Fever: 72/1090 Loss of appetite: 270/1090	

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety Outcome (definition): n/N (unless otherwise indicated)	Conclusions
		<b>Adverse events</b> Any AE: 722/1090 SAE: 31/1090	
Halasa, 2015 [RCT] <sup>9</sup>  Infants/Toddlers (6-35 months)	Fluzone (Sanofi Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose (intramuscular)]  <i>A/California/7/09 (H1N1)-like virus, A/Perth/16/2009 (H3N2)-like virus, and B/Brisbane/60/2008-like virus</i>	<b>Reactogenicity</b> <i>Redness at injection site: 8/48</i> <i>Fever (temperature &gt;39°C after the first dose): 7/80</i>	<ul style="list-style-type: none"> <li>No significant differences between the full-dose or half-dose groups for either the fully primed or naive cohorts for systemic reactions or local reactions when both seasons were combined.</li> <li>The only significant difference in the 2011–2012 season was that 8 of 48 (16.7%) participants in the half-dose group compared with 32 of 96 (33.3%) in the full-dose group had increased redness at the injection site (<math>P &lt; .05</math>).</li> <li>No significant differences between the groups in unsolicited AEs, serious adverse events (SAEs), or onset of chronic medical conditions between the dose groups in either the naive or fully primed cohorts, and none of the SAEs were deemed related to the vaccine.</li> </ul>
	Fluzone (Sanofi Pasteur), <b>15-µg/strain</b> [1 x 0.5 mL dose (intramuscular)]  <i>A/California/7/09 (H1N1)-like virus, A/Perth/16/2009 (H3N2)-like virus, and B/Brisbane/60/2008-like virus</i>	<b>Reactogenicity</b> <i>Redness at injection site: 32/96</i> <i>Fever (temperature &gt;39°C after the first dose): 19/161</i>	
Phung, 2016 [RCT] <sup>10</sup>  Infants/Toddlers (6-35 months)	FLUAD (NR), <b>NR [1 x 0.5mL dose]</b> (Intramuscular injection)]  <i>A/H1N1, A/H3N2, Strain B</i>	<b>Reactogenicity</b> <i>Any local reaction<sup>11</sup>: 45/61</i> <i>Any systemic reaction<sup>12</sup>: 36/61</i>  <b>Adverse events</b> SAE (based on MedDRA v 17.1 definition): 2/61	
	FLUAD (NR), <b>NR [1 x 0.25 mL dose]</b> (Intramuscular injection)]	<b>Reactogenicity</b> <i>Any local reaction<sup>11</sup>: 63/75</i>	



Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety Outcome (definition): n/N (unless otherwise indicated)	Conclusions
	A/H1N1, A/H3N2, Strain B	Any systemic reaction <sup>12</sup> : 42/75  <b>Adverse events</b> SAE (based on MedDRA v 17.1 definition): 2/75	
	Agrippal S1 (NR), NR [1 x 0.5mL dose (Intramuscular injection)]  A/H1N1, A/H3N2, Strain B	<b>Reactogenicity</b> Any local reaction <sup>11</sup> : 42/51 Any systemic reaction <sup>12</sup> : 24/51  <b>Adverse events</b> SAE (based on MedDRA v 17.1 definition): 0/51	
	Agrippal S1 (NR), NR [1 x 0.25mL dose (Intramuscular injection)] A/H1N1, A/H3N2, Strain B	<b>Reactogenicity</b> Any local reaction <sup>11</sup> : 6/10 Any systemic reaction <sup>12</sup> : 5/10  <b>Adverse events</b> SAE (based on MedDRA v 17.1): 0/10	
Jain, 2017 [RCT] <sup>11</sup>  Infants/ Toddlers (6-35 months)	Flulaval Quadrivalent (GSK), <b>15-µg/strain</b> [1 x 0.5mL dose (intramuscular in deltoid region)]  A/California/7/2009 (A/H1N1), A/Texas/50/2012 (A/H3N2), B/Brisbane/60/2008 (B/Victoria), and B/Massachusetts/2/2012 (B/Yamagata)	<b>Reactogenicity – injection site (within 7 days)</b> Pain: 44.0% Redness: 1.4% Swelling: 1.0%  <b>Reactogenicity – systemic (within 7 days)</b> Drowsiness: 40.6% Fever (>=38.0C): 7.9% Irritability/fussiness: 54.4% Loss of appetite: 33.7%  <b>Adverse events</b> Any AE: 45.5% Vaccine-related AE: 5.9% Any SAE <sup>13</sup> : 1.8% Febrile seizures: 0.4% Medically attended event <sup>14</sup> : 60.2%	<ul style="list-style-type: none"> <li>▪ None of the febrile seizures or the SAEs were considered by the investigator to be related to vaccination</li> <li>▪ Double-dose IIV4 may improve protection against influenza B in some young children and simplifies annual influenza vaccination by allowing the same vaccine dose to be used for all eligible children and adults.</li> </ul>
	Fluzone Quadrivalent (Sanofi Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose (intramuscular in deltoid region)]	<b>Reactogenicity – injection site (within 7 days)</b> Pain: 40.1% Redness: 1.4% Swelling: 0.4%  <b>Reactogenicity – systemic (within 7 days)</b>	

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety Outcome (definition): n/N (unless otherwise indicated)	Conclusions
	A/California/7/2009 (A/H1N1), A/Texas/50/2012 (A/H3N2), B/Brisbane/60/2008 (B/Victoria), and B/Massachusetts/2/2012 (B/Yamagata)	<p>Drowsiness: 40.9% Fever (<math>\geq 38.0^{\circ}\text{C}</math>): 7.5% Irritability/fussiness: 50.5% Loss of appetite: 33.4%</p> <p><b>Adverse events</b> Any AE: 44.1% Vaccine-related AE: 5.8% Any SAE<sup>13</sup>: 1.7% Febrile seizures: 0.3% Medically attended event<sup>14</sup>: 59.1%</p>	
Ojeda. 2019 [RCT] <sup>12</sup>  Infants/ Toddlers and Children (6 months – 17 years)	<p>Vaxigrip Tetra (Sanofi Pasteur) – PFS, 15-<math>\mu\text{g}</math>/strain [1 x 0.5mL dose (intramuscular or deep subcutaneous injection)]</p> <p>A/Michigan/45/2015 (H1N1)pdm09-like virus, A/Hong Kong/4801/2014 (H3N2)-like virus, /Brisbane/60/2008-like virus (B/Victoria lineage), and B/Phuket/3073/2013 (B/Yamagata lineage)</p> <p>Vaxigrip Tetra (Sanofi Pasteur) - MDV, 15-<math>\mu\text{g}</math>/strain [1 x 0.5mL dose (intramuscular or deep subcutaneous injection)]</p> <p>A/Michigan/45/2015 (H1N1)pdm09-like virus, A/Hong Kong/4801/2014 (H3N2)-like virus, /Brisbane/60/2008-like virus (B/Victoria lineage), and B/Phuket/3073/2013 (B/Yamagata lineage)</p>	<p><b>Reactogenicity, N=142</b> Any injection-site reaction (solicited within 7 days): 26 (6-35mo), 16 (3-8yr), 42 (9-7yr) Any systemic reaction (solicited within 7 days): 25 (6-35mo), 15 (3-8yr), 35 (9-7yr)</p> <p><b>Adverse events, N=147</b> AE (immediate unsolicited): 1 (9-17 years) Non-serious AE: 25 (6-35mo), 9 (3-8yr), 8 (9-7yr) Vaccine-related non-serious AE: 1 (9-17 years) AE leading to study discontinuation: 0 SAE: 0</p> <p><b>Reactogenicity, N=139</b> Any injection-site reaction(solicited within 7 days): 27 (6-35mo), 16 (3-8yr), 26 (9-7yr) Any systemic reaction(solicited within 7 days): 33 (6-35mo), 13 (3-8yr), 30 (9-7yr)</p> <p><b>Adverse events, N=150</b> AE (immediate unsolicited): 0 Non-serious AE: 31 (6-35mo), 14 (3-8yr), 5 (9-7yr) Vaccine-related non-serious AE: 0 AE leading to study discontinuation: 0 SAE: 0</p>	<ul style="list-style-type: none"> <li>▪ Solicited reactions were mostly grade 1 (mild) in intensity and resolved within 3 days.</li> <li>▪ Solicited systemic reactions were reported in more infants aged 6 – 35 months in the MDV group than in the PFS group however, because the 95% CIs were overlapping, this was not thought clinically significant.</li> <li>▪ None of these unsolicited AEs were considered related to a study vaccine by the investigators.</li> <li>▪ There were no differences in reactogenicity or safety between the two vaccine formats. These results showed that the MDV format of QIV was as safe and immunogenic as the PFS format in infants, children, and adolescents. These findings support the use of MDV QIV</li> </ul>

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety <i>Outcome</i> (definition): n/N (unless otherwise indicated)	Conclusions
			as a resource-saving alternative for seasonal influenza vaccination.
Robertson, 2019 [RCT] <sup>13</sup>  Infants/ Toddlers (6-35 months)	<p>Fluzone Quadrivalent (Sanofi Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose (intramuscular single-dose syringes in deltoid of arm)]</p> <p><i>A/California/07/2009 X-179A (H1N1), A/Hong Kong/4801/2014 X-263B (H3N2), B/Brisbane/60/2008 (Victoria lineage), B/Phuket/3073/2013 (Yamagata lineage)</i></p> <p>Fluzone Quadrivalent (Sanofi Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose (intramuscular single-dose syringes in deltoid of arm)]</p> <p><i>A/California/07/2009 X-179A (H1N1), A/Hong Kong/4801/2014 X-263B (H3N2), B/Brisbane/60/2008 (Victoria lineage), B/Phuket/3073/2013 (Yamagata lineage)</i></p>	<p><b>Reactogenicity</b> <i>Any injection-site reaction</i><sup>15</sup>: 533/939 <i>Any systemic reaction</i><sup>16</sup>: 561/941</p> <p><b>Adverse events</b> <i>Vaccine-related AE</i> (immediate within 30 mins): 0/992 <i>Vaccine-related AE</i> (within 28 days): 30/992 <i>AE leading to study discontinuation</i>: 0/992 <i>SAE</i>: 5/992</p> <p><b>Reactogenicity</b> <i>Any injection-site reaction</i><sup>15</sup>: 480/909 <i>Any systemic reaction</i><sup>16</sup>: 533/909</p> <p><b>Adverse events</b> <i>Vaccine-related AE</i> (unsolicited within 30 mins): 1/949 <i>Vaccine-related AE</i> (unsolicited within 28 days): 29/949 <i>AE leading to study discontinuation</i>: 3/949 <i>SAE</i>: 5/949</p>	<ul style="list-style-type: none"> <li>▪ Proportions of participants reporting solicited injection-site reactions, solicited systemic reactions, vaccine-related unsolicited AEs were similar for the full- and half-dose groups</li> <li>▪ None of the AEs leading to study discontinuation or the SAEs were considered related to vaccination</li> <li>▪ A single AE of special interest (chronic urticaria first appearing 3 days post-vaccination and continuing for &gt;6 weeks) was considered by the investigator to be related to vaccination</li> <li>▪ In children 6–35 months of age, a full dose of IIV4 was immunogenic and had a safety profile comparable to that of a half dose with no new safety concerns observed.</li> </ul>

**Abbreviations:** AE – adverse events, ID – intradermal; ILI – influenza-like illness; IM – intramuscular; MDV – multi-dose vials, n – number of people with condition, N – sample size of treatment arm, NR – not reported, PFS – prefilled syringe, SAE – serious adverse events

<sup>1</sup> Defined as mild (easily tolerated), moderate (interferes with normal behaviour or activities), severe (incapacitating, unable to perform usual activities, may require medical attention)

<sup>2</sup> Present at or near the approximate point of needle entry; small <2.5cm, medium >2.5cm to <5cm, large >5cm

<sup>3</sup> Oral temperature >37.5 C; mild >37.5 to 38 C, moderate >38.1 to 39 C, severe >39.1 C

<sup>4</sup> Grade I reactions defined as “present but easily tolerated” for fatigue, muscle ache, headache, itching or pain at injection site; oral temperature >=38 and <39 degrees Celsius; some limitation to arm motion due to stiffness or discomfort but easily tolerated; redness or swelling >= 8cm

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3 <sup>5</sup> Grade II/III reactions defined as “interferes with normal activity” to “severe and incapacitating” for fatigue, muscle ache, headache, itching or pain at  
4 injection site; oral temperature  $\geq 39$  degrees Celsius; limitation to arm motion due to stiffness or discomfort that interferes with normal activity; redness  
5 or swelling  $> 8$ cm

6 <sup>6</sup> Defined as serious adverse events resulting in hospitalization

7 <sup>7</sup> Solicited local reactions included ecchymosis, erythema, induration, swelling, and tenderness at injection site

8 <sup>8</sup> Solicited systemic reactions included sleepiness, diarrhea, vomiting, irritability, change in eating habits, shivering, and unusual crying

9 <sup>9</sup> Included injection site reactions of Grade 1, “minor reaction to touch”, Grade 2, “cries/protests on touch”, and Grade 3, “cries when limb  
10 moved/spontaneously painful”

11 <sup>10</sup> Included systemic reactions of Grade 1, “no effect on normal activity”, Grade 2, “interferes with normal activity”, and Grade 3, “prevents normal activity”

12 <sup>11</sup> Included injection site ecchymosis, injection site erythema, injection site induration, injection site swelling, tenderness, injection site pain

13 <sup>12</sup> Included change in eating habits, sleepiness, unusual crying, irritability, vomiting, diarrhea, chills/shivering, malaise, myalgia, arthralgia, headache,  
14 fatigue, fever ( $>37.3$  C)

15 <sup>13</sup> Defined serious adverse events as any untoward medical occurrence that results in death, is life-threatening, requires/prolongs hospitalization, or  
16 results in disability or incapacity during entire study period

17 <sup>14</sup> Defined as hospitalization, emergency room visit, and/or medical practitioner visit during entire study period

18 <sup>15</sup> Included tenderness, redness and/or swelling solicited within 7 days

19 <sup>16</sup> Included fever, vomiting, abnormal crying, drowsiness, loss of appetite, and/or irritability solicited within 7 days  
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# BMJ Open

## Safety and effectiveness of dose-sparing strategies for intramuscular seasonal influenza vaccine: A rapid scoping review

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3 **1 Safety and effectiveness of dose-sparing strategies for intramuscular seasonal influenza**  
4 **2 vaccine:**  
5 **3 A rapid scoping review**  
6 **4**

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3 30 **ABSTRACT**

4 31 **Background:** The objective of this rapid scoping review was to identify studies of dose-sparing  
5 32 strategies for administration of intramuscular seasonal influenza vaccines in healthy individuals  
6 33 of all ages.

8 34 **Methods:** Comprehensive literature searches were executed in MEDLINE, Embase, and the  
9 35 Cochrane library. The grey literature was searched via international clinical trial registries for  
10 36 relevant studies published in English in the last 20 years. We included studies in healthy humans  
11 37 of any age that used any dose-sparing strategy to administer intramuscular seasonal influenza  
12 38 vaccines. Title/abstract and full-text screening were carried out by pairs of reviewers  
13 39 independently. Data extraction was conducted by a single reviewer and verified by a second  
14 40 reviewer. Our outcomes were influenza infections, ICU admission, pneumonia, hospitalizations,  
15 41 adverse events, and mortality. Results were summarized descriptively.

17 42 **Results:** A total of 13 studies with 10,351 participants were included in the review and all  
18 43 studies were randomized control trials (RCTs) conducted between 2006 and 2019. The most  
19 44 common interventions were the trivalent influenza vaccine (n=10), followed by the quadrivalent  
20 45 influenza vaccine (n=4). Nine studies included infants/toddlers 6-36 months old and one of these  
21 46 studies also included children and adolescents. In these nine studies, no clinical effectiveness  
22 47 outcomes were reported. Of the four adult studies ( $\geq 18$  years), two studies reported on  
23 48 effectiveness outcomes, however only one RCT reported on laboratory confirmed influenza.

25 49 **Conclusions:** Due to the low number of studies in healthy adults and the lack of studies  
26 50 assessing confirmed influenza and influenza-like illness, there remains a need for further  
27 51 evaluation.

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29 53 Keywords:  
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3 55 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

4 56 Strengths:

- 5 57 • This rapid scoping review was conducted within a 6-week timeline and the methods were  
6 58 tailored to provide results to the stakeholders within 4 weeks.  
7 59 • We did not restrict the search dates and study screening was completed in independently  
8 60 by two reviewers.

9 61 Limitations:

- 10 62 • We limited the selection of studies to those published in the English language, and data  
11 63 extraction was conducted by one abstractor and one verifier.  
12 64 • Twelve dose-sparing RCTs were not included in the review because they did not include  
13 65 vaccine interventions that were deemed of interest to the stakeholders, and/or did not  
14 66 provide sufficient data.

## 67 **BACKGROUND**

68 The symptoms of novel coronavirus disease (COVID-19) closely mimic those of seasonal  
69 influenza vaccine and health officials recommend vaccination against the flu to limit  
70 confounding of flu symptoms with COVID-19 symptoms. An anticipated shortage in influenza  
71 vaccine supplies was of concern.[1] This anticipated shortage did not happen however, and in the  
72 2019-2020 flu season, influenza vaccination coverage among adults (42%) was similar to the  
73 previous season (42%). This question of vaccine shortage remains relevant in Canada and other  
74 jurisdictions for future COVID-19 and flue seasons. As a potential solution, health officials were  
75 interested in assessing the effectiveness of fractional dosing (e.g., half-doses) of currently  
76 available intramuscular influenza vaccines.

77  
78 Fractional dosing, or dose-sparing, strategies are those where less than the standard dose of  
79 hemagglutinin (HA) antigen, and thus less volume of vaccine, is administered, increasing the  
80 overall number of influenza vaccine doses available. In Canada, influenza vaccines are currently  
81 authorized for intramuscular administration only, apart from the live-attenuated influenza  
82 vaccine, which is administered intranasally.[2] Standard dose influenza vaccines contain 15 mcg  
83 of HA per strain and are delivered in 0.5 mL volume. Therefore, the total amount of HA in  
84 standard dose trivalent vaccines is 45 mcg, and the total amount of HA in standard dose  
85 quadrivalent vaccines is 60 mcg.

86  
87 A scoping review of all the available dose-sparing strategies for intramuscular administration of  
88 seasonal influenza vaccines currently approved in Canada for healthy populations had not been  
89 systematically conducted. With the resource-constraints for the influenza season due to COVID-  
90 19, there was a need to scope the evidence on the safety and effectiveness of dose-sparing  
91 strategies for intramuscular administration of seasonal influenza vaccines. The objective of this  
92 rapid scoping review was to identify studies of dose-sparing strategies for administration of  
93 intramuscular seasonal influenza vaccines in healthy individuals of all ages. The results of this  
94 scoping review were used to inform a systematic review with meta-analysis by National  
95 Advisory Committee on Immunization (NACI) on the same topic [3].

## 97 **METHODS**

98 The Centre for Immunization and Respiratory Infectious Diseases of the Public Health Agency  
99 of Canada (PHAC) commissioned a rapid scoping review on the available methods for fractional  
100 dosing of seasonal influenza vaccines through the Canadian Institutes of Health Research  
101 (CIHR) Drug Safety and Effectiveness Network (DSEN) with a 6-week timeline for preliminary  
102 results.

### 104 **Protocol**

105 The methods for this review were guided by the updated reviewer manual for scoping reviews  
106 published by JBI and the World Health Organization's guide to rapid reviews.[4, 5] Results are  
107 reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis  
108 extension to scoping reviews (PRISMA-ScR).[6] A protocol for this rapid scoping review was  
109 disseminated through the Open Science Framework registry (<https://osf.io/8mwz2/>).

### 111 **Patient and Public Involvement statement**

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3 112  
4 113 No patients or the public were involved in this rapid scoping review.  
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### 6 114 **Literature search**

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8 115 Comprehensive literature searches were developed and executed by an experienced librarian in  
9 116 Ovid MEDLINE (**Appendix 1**), EMBASE using the OVID interface (**Appendix 2**), and the  
10 117 Cochrane library between 1946 and May 2020 (**Appendix 3**). The literature search was peer  
11 118 reviewed by a second librarian using the PRESS checklist  
12 119 (<https://www.cadth.ca/resources/finding-evidence/press>). The grey (i.e., difficult to locate or  
13 120 unpublished) literature was searched via international clinical trial registries (i.e.  
14 121 clinicaltrials.gov, EU clinical trial register). References of relevant systematic reviews and  
15 122 included studies were also scanned.  
16 123

### 17 124 **Eligibility criteria**

18 125 The eligibility criteria followed the Population, Intervention, Comparators, Outcome, Study  
19 126 design (PICOS) framework as follows:

- 20 127 • Population: Healthy humans of any age. Immunocompromised populations and animal  
21 128 studies were excluded. Examples of persons with weakened immune systems include those  
22 129 with HIV/AIDS; cancer and transplant patients who are taking certain immunosuppressive  
23 130 drugs; and those with inherited diseases that affect the immune system (e.g., congenital  
24 131 agammaglobulinemia, congenital IgA deficiency)[7].
- 25 132 • Intervention: Any dose-sparing strategy used to administer intramuscular seasonal influenza  
26 133 vaccines (eligible vaccines listed in **Appendix 4**). Eligible strategies included, but were not  
27 134 limited to, administering less than the standard 15 ug HA antigen using multi-dose vials, half  
28 135 dosing, or pre-formulated products with reduced antigen quantity, or with revised vaccine  
29 136 dose schedules. Any studies examining monovalent pandemic vaccines,  
30 137 specialty/experimental vaccines (e.g., high dose), whole virus vaccines, or other routes of  
31 138 administration (e.g. intranasal, intradermal) were not eligible. Only vaccine products  
32 139 approved for use in Canada or equivalent formulations approved for use in other countries  
33 140 were eligible for inclusion. Concomitant administration with other vaccine products were  
34 141 included only if administered to both the intervention and the comparator groups.
- 35 142 • Comparator: Any of the interventions listed above, no intervention, or placebo.
- 36 143 • Outcomes: Lab-confirmed influenza infection (primary outcome), influenza-like illness or  
37 144 clinical/symptomatic diagnosis of influenza, hospitalization, intensive care unit (ICU)  
38 145 admission, pneumonia, mortality, and adverse events (local/systemic reactogenicity,  
39 146 vascular-related, serious). Reactogenicity represents the physical manifestation of the  
40 147 inflammatory response to vaccination, and can include injection-site pain, redness, swelling  
41 148 or induration at the injection site, as well as systemic symptoms, such as fever, myalgia, or  
42 149 headache.[8] Immunogenicity outcomes were not abstracted, but these studies were flagged  
43 150 for NACI.
- 44 151 • Study designs: Randomized controlled trials (RCTs), non-randomised studies (e.g., quasi-  
45 152 RCTs, non-randomized trials, interrupted time series, controlled before after), and  
46 153 observational studies (e.g., cohort, case control) were included. Studies must have had a  
47 154 control or comparator group in order to be eligible for inclusion and as such, cross-sectional,  
48 155 case series, case reports, and qualitative studies were excluded.

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3 156 • Publication status: We included full text and abstracts if they included data on safety or  
4 157 effectiveness.  
5  
6 158 Inclusion was also limited to studies written in the English language due to the short timelines  
7 159 for the conduct of this review.  
8 160

### 9 161 **Study selection**

10 162 A screening form based on the eligibility criteria was prepared and pilot-tested with 30 studies  
11 163 with all members of the review team until sufficient agreement (>75%) was reached prior to both  
12 164 title/abstract (level 1) and full-text (level 2) screening. Subsequent screening at level 1 and level  
13 165 2 were completed by two reviewers working independently using the Knowledge Translation  
14 166 Program's proprietary screening software (synthesi.SR)[9]. Any discrepancies between  
15 167 reviewers were consistently resolved by a third independent reviewer.  
16 168

### 17 169 **Data extraction**

18 170 Items for data collection included study characteristics (study design, year of publication,  
19 171 country of conduct, multi-center vs. single site), patient characteristics (mean age, age range, sex,  
20 172 vaccination history), intervention details (type of vaccine, vaccine manufacturer, dose, timing  
21 173 and administration of treatment), comparator details (comparator intervention, dose), and  
22 174 outcome results (influenza infections, ICU admission, pneumonia, hospitalizations, adverse  
23 175 events, mortality) at the longest duration of follow-up.  
24 176

25 177 A standardized form for data extraction was developed and pilot tested by the entire review team  
26 178 using two pre-selected full-text RCTs to ensure understanding of the data items to be extracted,  
27 179 and congruence among reviewers. All included studies were extracted by one reviewer  
28 180 independently and then verified by a second reviewer.  
29 181

### 30 182 **Risk of bias assessment**

31 183 As this was a scoping review, the risk of bias of studies was not assessed.[4]  
32 184

### 33 185 **Synthesis**

34 186 The synthesis involved providing a descriptive summary of included studies with summary  
35 187 tables and detailed tables of study results. Study results were organized and tabulated according  
36 188 to patients (children vs adults), interventions, and outcomes and where available information on  
37 189 relevant subgroups.  
38 190

## 39 191 **RESULTS**

### 40 192 **Literature search**

41 193 We screened 2,378 titles and abstracts from our database search and an additional 13 citations  
42 194 located through searching the grey literature and scanning references. Of these, 144 potentially  
43 195 relevant full-text articles were screened for eligibility (**Figure 1**). Twelve studies that assessed  
44 196 dose-sparing strategies were excluded during full-text screening because the vaccine under study  
45 197 was not of interest or unclearly reported. We contacted authors of these 12 unclear studies and  
46 198 received 1 response confirming the vaccine was not of interest (see list of excluded studies in  
47 199 **Appendix 5**). Subsequently, 13 RCTs were included; five trial protocols were found and were  
48 200 denoted as duplicate/companion reports. No non-randomised or observational studies were found  
49 201 that fulfilled the eligibility criteria.  
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## 202 Study characteristics

203 **Table 1** summarizes the characteristics of the 13 RCTs published between 2006 and 2019; and  
 204 conducted mainly in the US, followed by Mexico, Canada and Finland. The majority of the  
 205 studies evaluated trivalent vaccines (10/13 [77%]) and most were conducted in the 6-36 month-  
 206 old pediatric population (9/13 [69%]). Almost all studies reported on reactogenicity and/or other  
 207 adverse events, but only two studies reported on the effectiveness of our outcomes of interest  
 208 (i.e., lab-confirmed influenza and influenza-like illness).  
 209 Full study and patient characteristic details for each study are reported in **Appendix 6** and  
 210 treatment and outcome details in **Appendix 7**.

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212 **Table 1: Characteristics of included studies (n=13)**

Characteristics	Category	Frequency (%)
Date of publication	2006-2010	4 (30.8)
	2011-2015	5 (38.4)
	2016-2020	4 (30.8)
Multi-center or single site	Multi-centre	8 (61.5)
	Single centre	2 (15.4)
Countries of conduct <sup>a</sup>	USA	8 (61.5)
	Mexico	3 (23.1)
	Canada	2 (15.4)
	Finland	2 (15.4)
	Belgium	1 (7.7)
	Hong Kong	1 (7.7)
	Taiwan	1 (7.7)
	Thailand	1 (7.7)
	Populations <sup>a,b</sup>	Infants/Toddlers (6-36 months)
Children (37 months – 17 years)		1 (7.7)
Adults (18-64 years)		3 (23.1)
Older adults (≥65)		1 (7.7)
Treatments <sup>a,c</sup>	Trivalent influenza vaccine (TIV)	10 (76.9)
	Quadrivalent influenza vaccine (QIV)	4 (30.8)
Outcomes <sup>a</sup>	Effectiveness	2 (15.4)
	Local and Systemic Reactogenicity	12 (92.3)
	Adverse events	10 (76.9)

213 <sup>a</sup>Each study can fit into more than one category so the total percentage will not add up to 100%

214 <sup>b</sup>One study includes both infants/toddlers and children, and another includes both adults and seniors

215 <sup>c</sup>One study includes both TIV and QIV arms

## 216 RCTs in healthy children (<18 years old)

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218 Nine studies included infants/toddlers 6-36 months old and one study also included children and  
 219 adolescents (**Table 2**). None of these studies reported results on the effectiveness outcomes that  
 220 were relevant to our review and established *a priori*, however all of them reported on safety  
 221 outcomes.

222 **Table 2: Nine RCTs conducted in children (6 months – 17 years)**

Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcome	Author reported conclusions
TRIVALENT AND QUADRIVALENT INFLUENZA VACCINES (TIV/QIV)									
Cioppa, 2011[10]	October 2008 – March 2009  Belgium	NR - TIV, <b>7.5-µg/strain</b> [2 x 0.25mL dose]	20.0 months (7.0)	6- <36 months	43.5	NR	25	Local and Systemic reactogenicity  Adverse events	Reactogenicity of the 7.5-µg TIV/QIV formulations was slightly lower than for the corresponding 15-µg formulations.  The majority of unsolicited AEs were mild or moderate in severity and none of the SAEs was considered to be related to the study vaccine.
		Agrippal - TIV, <b>15-µg/strain</b> [2 x 0.5mL dose]	15.0 months (8.8)	6- <36 months	43.5	NR	22		
		NR - QIV, <b>7.5-µg/strain</b> [2 x 0.25mL dose]	18.0 months (8.9)	6- <36 months	43.5	NR	25		
		NR - QIV, <b>15-µg/strain</b> [2 x 0.5mL dose]	15.2 months (7.8)	6- <36 months	43.5	NR	28		
		Vaxigrip (Sanofi Pasteur), <b>7.5-µg/strain</b> [2 x 0.25mL dose]	16.1 months (8.5)	6- <36 months	43.5	NR	26		
Skowronski, 2011[11]	September 2008 – December 2008  Canada	Vaxigrip (Sanofi-Pasteur), <b>15-µg/strain</b> [2 x <b>0.5mL dose</b> ]	13.2 months (5.1)	6-23 months	53.2	0	124	Local and Systemic reactogenicity  Adverse	Local reactions generally were less common in infants than toddlers and more common with full

Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcome	Author reported conclusions
		Vaxigrip (Sanofi-Pasteur), 15-µg/strain [2 x <b>0.25mL dose]</b>	12.8 months (5.0)	6-23 months	53.2	0	128	events	<p>doses versus half doses, but none of these differences were significant.</p> <p>One serious adverse event was reported: a toddler in the half dose group was hospitalized with pneumonia 28 days after the first vaccination. The event was deemed unlikely related to the vaccine.</p> <p>Compared with 0.25-mL half-dosing, administration of 2 full 0.5-mL doses of trivalent inactivated influenza vaccine can increase antibody response</p>

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Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcome	Author reported conclusions
									without increasing reactogenicity in previously unimmunized infants aged 6 to 11 months.
Langley, 2012[12]	November 2008 – August 2009	Fluviral F1 (Sanofi-Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose]	18.2 months (9.06)	6-35 months	47.9	42.6	164	Local and Systemic reactogenicity  Adverse events	Fluviral F1 group had 1 case of pneumonia resolved. Fluviral F2 group had 1 case of bronchial hyper-reactivity in resolving stage.  The 0.5-mL dose of the study vaccine, when administered to children aged 6–35 months, resulted in a modest but not statistically significant improvement in immunogenicity
	Canada	Fluviral F2 (Sanofi-Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose]	17.5 months (8.27)	6-35 months	47.9	42.6	167		
		Vaxigrip (Sanofi-Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose]	17.0 months (8.33)	6-35 months	47.9	42.6	43		



Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcome	Author reported conclusions
									with clinically similar safety and reactogenicity compared with the 0.25-mL dose.
Pavia-Ruz, 2013[13]	October 2008-March 2009  Hong Kong, Mexico, Taiwan, Thailand, and the USA	Fluarix (GSK), <b>15-µg/strain</b> [1 x 0.5mL dose]	21.2 months (8.37)	6-35 months	51	30.1	1018	Local and Systemic reactogenicity  Adverse events	The reactogenicity and safety profile of the study vaccine did not appear to be affected by doubling the dose.  One participant in the Flu-15µg group had two SAEs, (apnea and cyanosis) which were considered by the investigator to be possibly related to vaccination. The subject was hospitalized and the events resolved on the same day as they
		Fluarix (GSK), <b>7.5-µg/strain</b> [1 x 0.25 mL dose]	21.2 months (8.03)	6-35 months	51	30.1	1018		
		Fluzone (Sanofi-Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose]	21.1 months (8.20)	6-35 months	51	30.1	1031		

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Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcome	Author reported conclusions
									occurred.
Halasa, 2015[14]	2010-2012  USA	Fluzone (Sanofi Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose]	13.5	6-35 months, 12-35 months	52	13.2	80	Local and Systemic reactogenicity	No significant differences between the full-dose or half-dose groups for either the fully primed or naive cohorts for systemic reactions or local reactions when both seasons were combined.  The only significant difference in the 2011–2012 season was that 8 of 48 (16.7%) participants in the half-dose group compared with 32 of 96 (33.3%) in the full-dose group had
		Fluzone (Sanofi Pasteur), <b>15-µg/strain</b> [1 x 0.5 mL dose]	14.5				163		

Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcome	Author reported conclusions
									increased redness at the injection site (P < .05).  No significant differences between the groups in AE, SAE, or onset of chronic medical conditions between the dose groups in either the naive or fully primed cohorts, and none of the SAEs were deemed related to the vaccine.
Phung, 2016[15]	September 2010- January 2011  Finland	FLUAD (NR), NR [1 x 0.5mL dose]	68.7 months (18)	6-35 months	55.8	85.7	60	Local and Systemic reactogenicity	<i>Trial protocol with no author conclusions.</i>
		FLUAD (NR), NR [1 x 0.25 mL dose]	60.4 months (23.2)	6-35 months	55.8	85.7	75		
		Agrippal S1 (NR),	68 months (17.1)	6-35 months	55.8	85.7	51	Adverse events	

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Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcome	Author reported conclusions
		NR [1 x 0.5mL dose]							
		Agrippal S1 (NR), NR [1 x 0.25mL dose]	32.4 months (1.9)	6-35 months	55.8	85.7	11		
Jain, 2017[16]	2014-2015 Influenza Season  USA and New Mexico	Flulaval (GSK), 15-µg/strain [1 x 0.5mL dose]	19.7 months (8.7)	6-35 months	46.9	57.5	1013	Local and Systemic reactogenicity	None of the febrile seizures or the SAEs were considered by the investigator to be related to vaccination.
		Fluzone (Sanofi Pasteur), 7.5-µg/strain [1 x 0.25 mL dose]	19.9 months (8.9)	6-35 months	46.9	57.5	1028	Adverse events	Double-dose vaccines may improve protection against influenza B in some young children and simplifies annual influenza vaccination by allowing the same vaccine dose to be used for all eligible children

Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcome	Author reported conclusions
									and adults.
Ojeda, 2019[17]	December 2017- January 2018  Mexico	Vaxigrip Tetra (Sanofi Pasteur) <b>PFS 15-µg/strain</b> [1 x 0.5mL dose]	NR (6 months – 17 years)	6 months – 17 years	46.4	NR	149	Local and Systemic reactogenicity	Solicited systemic reactions were reported in more infants aged 6 – 35 months in the MDV group than in the PFS group however this was not clinically significant.  AE not considered related to a study vaccine.  There were no differences in reactogenicity or safety between the two vaccine formats. These results showed that the MDV
		Vaxigrip Tetra (Sanofi Pasteur) <b>MDV 15-µg/strain</b> [1 x 0.5mL dose]	NR (6 months – 17 years)	6 months – 17 years	46.4	NR	153	Adverse events	

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Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcome	Author reported conclusions
									format of QIV was as safe and immunogenic as the PFS format in infants, children, and adolescents. These findings support the use of MDV QIV as a resource-saving alternative for seasonal influenza vaccination.
Robertson, 2019[18]	September 2016 – March 2017	Fluzone (Sanofi Pasteur) <b>15-µg/strain</b> [1x0.5mL dose]	20.5 months (8.55)	6-35 months	49.7	47.25	992	Local and Systemic reactogenicity	No significant differences between full- and half-dose groups.
	USA	Fluzone (Sanofi Pasteur) <b>7.5-µg/strain</b> [1x0.25 dose]	20.4 months (8.75)	6-35 months	49.7	47.25	949	Adverse events	AE leading to study discontinuation/S AE not considered vaccine-related.  A full dose vaccine was immunogenic and

Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Outcome	Author reported conclusions
									had a safety profile comparable to that of a half dose, with no new safety concerns observed.

**Abbreviations:** AE – adverse events; GMR - geometric mean ratio; GMFR – geometric mean fold rise; GMT - geometric mean antibody titer; HA - hemagglutinin; HAI - hemagglutination inhibition; ID – intradermal; IM – intramuscular; ITT – intent-to-treat; MDV – multi-dose vials, n – number of people with condition, N – sample size of treatment arm, NR – not reported, PFS – prefilled dose, SAEs – serious adverse events

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## 226 **Safety outcomes**

### 227 Trivalent influenza vaccines

228 Six of the included RCTs assessed trivalent influenza vaccines (TIV) in young children (6-36  
229 months) and reported on local and systemic reactogenicity outcomes and other adverse  
230 events.[10-14, 19] Two RCTs compared the administration of full (0.5mL) and half (0.25mL)  
231 doses of the same standard 15µg/strain vaccine.[11, 19] The first RCT compared two full versus  
232 two half doses of TIV in previously unimmunized infants (6-11 months) and toddlers (12-23  
233 months) using Vaxigrip (15µg/strain).[11] The study found that in the infants group, two full 0.5-  
234 mL doses of vaccine did not increase reactogenicity. Local reactions were less common in  
235 infants than toddlers and more common with full doses versus half doses, but the differences  
236 were not statistically significant. An identified clinical trial registry compared a single  
237 intramuscular injection of 0.5mL to 0.25mL of FLUAD or Agrippal and showed comparable  
238 numbers of children with reactogenicity outcomes and other adverse events across the groups,  
239 but no significance levels or conclusions were provided by the investigators upon contact.[19]

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241 The objective of three of the included RCTs was to examine the impact of administering the full  
242 adult dose of 15µg/strain vaccines compared with the usual children's dose of 7.5µg/strain in  
243 infants and toddlers.[12-14] A multicenter RCT was conducted in Canada assessing the safety of  
244 full-dose Fluviral TIV (15µg/strain) compared with the half-dose (7.5µg/strain) and an active  
245 comparator Vaxigrip (7.5µg/strain).[12] Compared with the half-dose, the full-dose vaccine  
246 resulted in clinically similar reactogenicity and safety. A similar three-arm RCT to assess the use  
247 of Fluarix at two different dose levels (7.5µg/strain and 15µg/strain) compared to an established  
248 control vaccine Fluzone (7.5µg/strain) also found the reactogenicity and safety profile of Fluarix  
249 did not appear to be affected by doubling the dose, but one participant in the 15µg group had two  
250 serious adverse events (apnea and cyanosis) that were considered by the investigator to be  
251 possibly related to vaccination.[13] A third multicenter RCT compared the 15 µg/strain  
252 formulation to the 7.5µg/strain formulation of Fluzone (Sanofi Pasteur) administered to young  
253 children across multiple influenza seasons.[14] This study also found no statistically significant  
254 differences between the full-dose or half-dose groups for systemic reactions, local reactions or  
255 adverse events when both seasons were combined; however, in the 2011–2012 season, 8 of 48  
256 (16.7%) participants in the half-dose group compared with 32 of 96 (33.3%) in the full-dose  
257 group had increased redness at the injection site ( $P < .05$ ).

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259 Cioppa et al. (2009) was the only trial that compared the safety and tolerability of both TIV and  
260 QIV vaccine formulations.[10] The vaccine arms of interest were a QIV 15-µg/strain, TIV 15-  
261 µg/strain, QIV 7.5-µg/strain, TIV 7.5-µg/strain, and a control Vaxigrip TIV 7.5-µg/strain  
262 vaccine. Reactogenicity of the 7.5-µg TIV/QIV formulations was slightly lower than for the  
263 corresponding 15-µg formulations, but there was no difference in reactogenicity between TIV  
264 and QIV vaccines.

### 265 266 Quadrivalent influenza vaccines

267 Four of the included RCTs evaluated quadrivalent influenza vaccines (QIV) in children.[10, 16-  
268 18] All of the studies reported reactogenicity outcomes and other adverse events. The Cioppa et  
269 al. (2009) RCT reported both TIV and QIV vaccines and the results are reported above.[10] Two  
270 studies compared full-dose QIV to pediatric 7.5µg/strain Fluzone. In the first RCT, full dose  
271 Fluzone had a similar safety profile to half-dose Fluzone with a single adverse event being



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3 272 attributed to the study vaccine.[18] Similarly, the second study found that full-dose Flulaval may  
4 273 improve protection against influenza in some young children when compared to low-dose  
5 274 Fluzone, and in this RCT, none of the adverse events were considered to be study-related as  
6 275 reported by the investigator.[16] The final trial evaluated Vaxigrip Tetra (15µg/strain)  
7 276 administered to children and adolescents in two different formats.[17] Vaxigrip administered as a  
8 277 single dose using a pre-filled syringe (PFS) was compared to a 10-dose multi-dose vial (MDV).  
9 278 Systemic reactions were reported in more infants aged 6 – 35 months in the MDV group than in  
10 279 the PFS group; however this difference was not clinically significant. The authors concluded that  
11 280 there was no difference in reactogenicity or safety between the two vaccine formats in infants,  
12 281 children, and adolescents.  
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### 15 283 **RCTs in healthy adults (≥18 years old)**

16 284 One RCT included healthy adults over 18 years, two studies included healthy adults from 18-45  
17 285 and 18-65 years old, and one study included older healthy adults (≥ 65 years) (**Table 3**). Two  
18 286 studies reported on effectiveness outcomes and three on reactogenicity and other adverse events.  
19 287 All four RCTs evaluated Fluzone QIV.  
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288 **Table 3: Four RCTs conducted in adults ( $\geq 18$  years old)**

Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Relevant Outcomes	Author reported conclusions
QUADRIVALENT INFLUENZA VACCINES (QIV)									
Kramer, 2006 [20]	October 2004 – November 2004  USA	Fluzone (Aventis Pasteur), <b>15-<math>\mu</math>g/strain</b> [1 x 0.5mL dose]	NR (>18 years)	>18 years	NR	NR	222	Lab-confirmed influenza (one patient receiving the full dose)	There was no significant difference between the full-dose and half-dose groups in the diagnosis of influenza or in the proportion of participants self-reporting four or more symptoms consistent with influenza-like illness.  No adverse events were noted by participants from either group or reported to the IRB during the course of the study
		Fluzone (Aventis Pasteur), <b>7.5-<math>\mu</math>g/strain</b> [1 x 0.25 mL dose]	NR (>18 years)	>18 years	NR	NR	222	Influenza-like illness  Adverse events	

Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Relevant Outcomes	Author reported conclusions
Engler, 2008 [21]	November 2004 – December 2004	Fluzone (Aventis Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose]	NR (18 – 64 years)	18-64 years	43.4	0	554	Influenza-like illness Hospital/ER visits	The relative risk of medical visits and hospitalizations for influenza-like illnesses were similar in the half- and full-dose group regardless of age, and there was no evidence of ILI symptom differences by sex or dose during the 21 days after immunizations.  Although injection site pain was greater for full- vs half-dose (19.9% vs 14.4%; p=.01), when analyzed for clinically significant pain
	USA	Fluzone (Aventis Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose]	NR (18 – 64 years)	18-64 years	43.4	0	556	Local and Systemic reactogenicity Adverse events	

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Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Relevant Outcomes	Author reported conclusions
									<p>levels significant dose-dependent pain differences were not identified.</p> <p>Joint and/or muscle pain were significantly different (p=.02 and p=.03, respectively) by dose.</p> <p>No other adverse event differed significantly by dose.</p>
Belshe, 2007 [22]	NR USA	Fluzone (Sanofi-Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose]	31.5 years (9.6)	18-49 years	71.2	0	31	Local and Systemic reactogenicity	Intradermal (ID) vaccine induced significantly more local inflammatory response than Intramuscular (IM) vaccine but
		Fluzone (Sanofi-Pasteur),	31.2 years (9.4)	18-49 years	71.2	0	32		

Author, Year	Study period and countr(ies)	Treatment arms Brand name (manufacturer) HA/strain [dosing]	Mean age (SD)	Age range	Sex (overall % female)	Vaccination history (overall % previously immunized)	ITT sample size	Relevant Outcomes	Author reported conclusions
		<b>9-<math>\mu</math>g/strain</b> [1 x 0.3mL dose]							this did not translate into an increased immune response for ID vaccines compared to IM (primary comparison of this study was ID vs IM doses)
		Fluzone (Sanofi-Pasteur), <b>6-<math>\mu</math>g/strain</b> [1 x 0.2mL dose]	30.1 years (10.3)	18-49 years	71.2	0	31		
		Fluzone (Sanofi-Pasteur), <b>3-<math>\mu</math>g/strain</b> [1 x 0.1mL dose]	31.9 years (10.3)	18-49 years	71.2	0	31		
Chi, 2010[23]	August 2007-2008  USA	Fluzone (Sanofi Pasteur), <b>15-<math>\mu</math>g/strain</b> [1 x 0.5mL dose]	75.6 years (6.8)	>65 years	17.8	94.6	65	Local and Systemic reactogenicity	The two SAEs were acute coronary syndrome and appendicitis and neither were judged to be related to influenza vaccination
		Fluzone (Sanofi Pasteur), <b>9-<math>\mu</math>g/strain</b> [1 x 0.3mL dose]	75.2 years (7.7)	>65 years	17.8	94.6	64	Adverse events	

**Abbreviations:** AE – adverse events, GMT - geometric mean antibody titer; HA - hemagglutinin; ID – intradermal; ILI – influenza-like illness; IM – intramuscular; MDV – multi-dose vials, n – number of people with condition, N – sample size of treatment arm, NR – not reported, PFS – prefilled syringe, SAE – serious adverse events

### 291 **Effectiveness outcomes**

292 Two of the included RCTs that examined the same vaccine (Fluzone manufactured by Aventis  
293 Pasteur) in healthy adult populations reported effectiveness outcomes. Only one study by Kramer  
294 et al. included lab-confirmed influenza infection [20], two reported influenza like illness, [20,  
295 21] and one reported hospitalizations or emergency room visits after vaccination [21]. The RCT  
296 by Kramer et al. (2006) found that 3.6% of participants receiving a 15- $\mu$ g/strain dose of vaccine  
297 reported influenza like illness compared to 6.8% of participants that received a 7.5- $\mu$ g/strain  
298 dose.[20] However, only one participant that received the full dose 15- $\mu$ g/strain was confirmed  
299 via laboratory analysis to have influenza, and no patients in the half dose arm got lab  
300 confirmation. The authors concluded that half-dose and full-dose vaccinations appear to be  
301 similarly effective for influenza like illness and similar symptom surveys between both groups  
302 but acknowledge that further studies examining immunogenicity are needed to confirm.

304 A similar RCT by Engler et al. (2008) that compared a 15- $\mu$ g/strain dose of Fluzone vaccine to a  
305 7.5- $\mu$ g/strain dose found equal proportions of participants reporting influenza like illness (9.7%  
306 vs 9.9%) and hospitalizations or emergency room visits (0.3% v 0.2%).[21] The authors found  
307 the relative risk of medical visits or hospitalizations between both groups was the same even  
308 when adjusting for age and that age, sex, nor dose had an influence on the severity of influenza  
309 like illness symptoms.

### 311 **Safety outcomes**

312 Three of the included studies in adult populations reported adverse events that occurred during  
313 the trial while one RCT indicated that no adverse events were recorded for the duration of their  
314 trial.[20-23] All three studies reporting adverse events compared different doses of Fluzone  
315 vaccine including 3- $\mu$ g, 6- $\mu$ g, 7.5- $\mu$ g, 9- $\mu$ g, and 15- $\mu$ g per strain doses.

317 Two of the studies were carried out in healthy adult populations and one RCT was conducted in  
318 older healthy adults (>60 years of age).[21-23] One RCT found that joint or muscle pain  
319 following vaccination was statistically significantly higher in the full dose (15- $\mu$ g) group  
320 compared to the half-dose (7.5- $\mu$ g) group and that while injection site pain initially appeared to  
321 be statistically significantly higher in the full dose group, when adjusted to include only  
322 clinically significant pain levels (>3 out of 5 on a visual analogue scale) the difference was no  
323 longer statistically significant.[21] The RCT found no differences in occurrence or severity of  
324 any other adverse effects. Similarly, one RCT comparing four different doses of Fluzone (3- $\mu$ g,  
325 6- $\mu$ g, 9- $\mu$ g, and 15- $\mu$ g per strain) did not report any differences between the IM vaccination  
326 groups.[22] Finally, the RCT in older adults also found no difference in the occurrence or  
327 severity of adverse events in the low dose (9- $\mu$ g) versus high dose (15- $\mu$ g) group and found no  
328 serious adverse events that were considered related to the vaccine.[23]

## 330 **DISCUSSION**

331 PHAC commissioned this rapid scoping review to identify the evidence for efficacy and safety of  
332 fractional influenza vaccine dosing for intramuscular administration of seasonal influenza  
333 vaccines in healthy individuals of all ages that have been evaluated in human trials. Thirteen  
334 RCTs published between 2006 and 2019 comparing standard/full-dose and half/low-dose  
335 vaccines were included in this scoping review after a comprehensive search of three electronic

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3 336 databases, trial registries and references of relevant systematic reviews. The majority of the  
4 337 included RCTs were conducted in children and evaluated trivalent influenza vaccines (TIV).  
5 338 In young, healthy children, there were no effectiveness outcomes of interest reported. However,  
6 339 local reactogenicity, systemic reactogenicity and adverse events were comparable across the full-  
7 340 dose and half-dose TIV and QIV vaccine arms. In addition, the authors of one RCT in children  
8 341 and adolescents that compared full-dose QIV using pre-filled syringes (PFS) versus multi-dose  
9 342 vials (MDV) also found no statistically significant differences in safety outcomes between  
10 343 administration formats. In healthy adults (including older adults), half-dose QIV was considered  
11 344 equally effective as high-dose in the two RCTs that assessed clinical effectiveness. Safety  
12 345 profiles were similar across groups in all 4 RCTs.  
13 346

14 347 A full systematic review with meta-analysis based on the studies and results of this scoping  
15 348 review was conducted by the NACI and the report was published in January of 2021.[3] Briefly,  
16 349 the report found that there is some, but still insufficient, evidence that fractional doses of  
17 350 influenza vaccine provided via the intramuscular route are effective and immunogenic in healthy  
18 351 individuals. NACI concludes that since many of those at high risk of influenza (e.g., adults 65  
19 352 years of age and older, individuals with specific underlying chronic health conditions) may have  
20 353 a lower immune response to influenza vaccination already (due to immunosenescence in older  
21 354 adults or a condition that alters immune function), it is important to ensure that those at high risk  
22 355 continue to receive the full dose of influenza vaccine. With regard to the safety of intramuscular  
23 356 seasonal fractional doses of influenza vaccines, there is fair evidence that fractional doses do not  
24 357 result in significant differences compared to full dose with regard to severe adverse effects post-  
25 358 influenza vaccination. Readers are encouraged to reference the full NACI report on the Health  
26 359 Canada website [3].  
27 360

### 361 **Strengths and limitations**

362 A strength of this rapid scoping review was that it was conducted within a 6-week timeline and  
363 the methods were tailored to provide results to the stakeholders within 4 weeks. We also did not  
364 restrict the search dates and study screening was completed independently by two reviewers. We  
365 developed a comprehensive search using three major databases, and searched the grey literature.  
366 We engaged with the NACI stakeholder group, who provided input on the PICO criteria, and  
367 funded this rapid scoping review.  
368

369 We were limited by the lack of studies providing objective outcome data. Only one RCT by  
370 Kramer et al. reported the objective outcome “lab confirmed influenza”, and the other RCT by  
371 Engler only reported the outcome “influenza like illness” [20, 21]. Since a 2014 narrative review  
372 found that less than 25% of cases diagnosed by physicians as influenza like illness were later  
373 laboratory proven influenza cases [24], we are lacking RCTs examining fractional dosing of IM  
374 influenza immunization. Further, twelve dose-sparing RCTs were not included because they did  
375 not provide sufficient data, and did not include vaccines that were deemed of interest to the  
376 stakeholders. Another limitation was that only studies published in the English language were  
377 included, and data extraction was conducted by one abstractor and one verifier. Since this was a  
378 scoping review, we did not appraise the methodological quality of the included studies.[25]  
379

### 380 **Future research**

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3 381 Dose-sparing approaches such as intradermal (ID) immunisation vaccination exhibits similar, or  
4 382 even enhanced, immunogenicity, when using a fractional dose only, as compared to  
5 383 intramuscular or subcutaneous immunisation, and should be explored in future scoping  
6 384 reviews.[26]  
7  
8 385

## 9 386 **CONCLUSIONS**

10 387 In our scoping review, we found 13 RCTs on the efficacy and safety of fractional doses of  
11 388 influenza vaccine provided via the intramuscular route to healthy adults and children. These  
12 389 studies were used to inform a systematic review with meta-analysis which were commissioned  
13 390 by the PHAC. We found that due to the low number of studies in healthy adults, namely one  
14 391 study assessing laboratory confirmed influenza and two evaluating influenza-like illness in  
15 392 adults, there remains a need for further evaluation of the clinical effectiveness of IM dose-  
16 393 sparing strategies using vaccines currently available in this population.  
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3 394 **LIST OF ABBREVIATIONS**

4 395 PHAC – Public Health Agency of Canada

5 396 CIHR – Canadian Institutes of Health Research

6 397 DSEN – Drug Safety and Effectiveness Network

7 398 MAGIC – Methods and Application Group in Indirect Comparisons

8 399 PRISMA-ScR – Preferred Reporting Items for Systematic Reviews and Meta-analysis extension  
9 400 to scoping reviews

10 401 ICU – Intensive Care Unit

11 402 RCT – Randomized controlled trials

12 403 NRCTs – non-randomized controlled trials

13 404 TIV – Trivalent Influenza Vaccine

14 405 AE – Adverse Events

15 406 SAE – Serious adverse events

16 407 QIV – Quadrivalent Influenza Vaccine

17 408 PFS – Pre-filled syringe

18 409 MDV – Multi-dose vial

19 410

20 411 **DECLARATIONS**

21 412 **Ethics approval and consent to participate**

22 413 Not applicable

23 414 **Consent for publication**

24 415 Not applicable

25 416 **Availability of data and materials**

26 417 The dataset(s) supporting the conclusions of this article is(are) included within the article (and its  
27 418 additional file(s)).

28 419 **Competing interests**

29 420 The authors have no competing interests to declare.

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35 426 Canada Research Chair in Knowledge Synthesis.

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39 430 build upon this work non-commercially, and license their derivative works on different terms,  
40 431 provided the original work is properly cited and the use is non-commercial. See:

41 432 <http://creativecommons.org/licenses/by-nc/4.0/>

42 433 **Authors' contributions**

43 434 CL wrote and revised the final manuscript. JA and PR screened citations and full-text articles,  
44 435 abstracted and verified data, interpreted results and wrote the first draft manuscript. CW and NR  
45 436 screened citations and full-text articles, abstracted data, and reviewed the manuscript. SES and  
46 437 ACT developed the protocol, obtained funding, interpreted results, and edited the manuscript.

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6 441 executing searches and retrieving articles, and Navjot Mann for her assistance in contacting  
7 442 author's and formatting this manuscript.  
8 443

9 444 **Additional files**

10 445 **File Format:** Microsoft Word (.docx)

11 446 **Title of Data:** Additional File 1 (Appendices 1-7)

12 447 **Description of Data:** The appendices include the following additional information:

13 448 Appendix 1 – MEDLINE search strategy

14 449 Appendix 2 – EMBASE search strategy

15 450 Appendix 3 – Cochrane search strategy

16 451 Appendix 4 – List of eligible vaccines

17 452 Appendix 5 – Excluded dose-sparing studies

18 453 Appendix 6 – Study and patient data

19 454 Appendix 7 – Treatment and outcome data  
20 455

21 456 **FIGURE LEGEND**

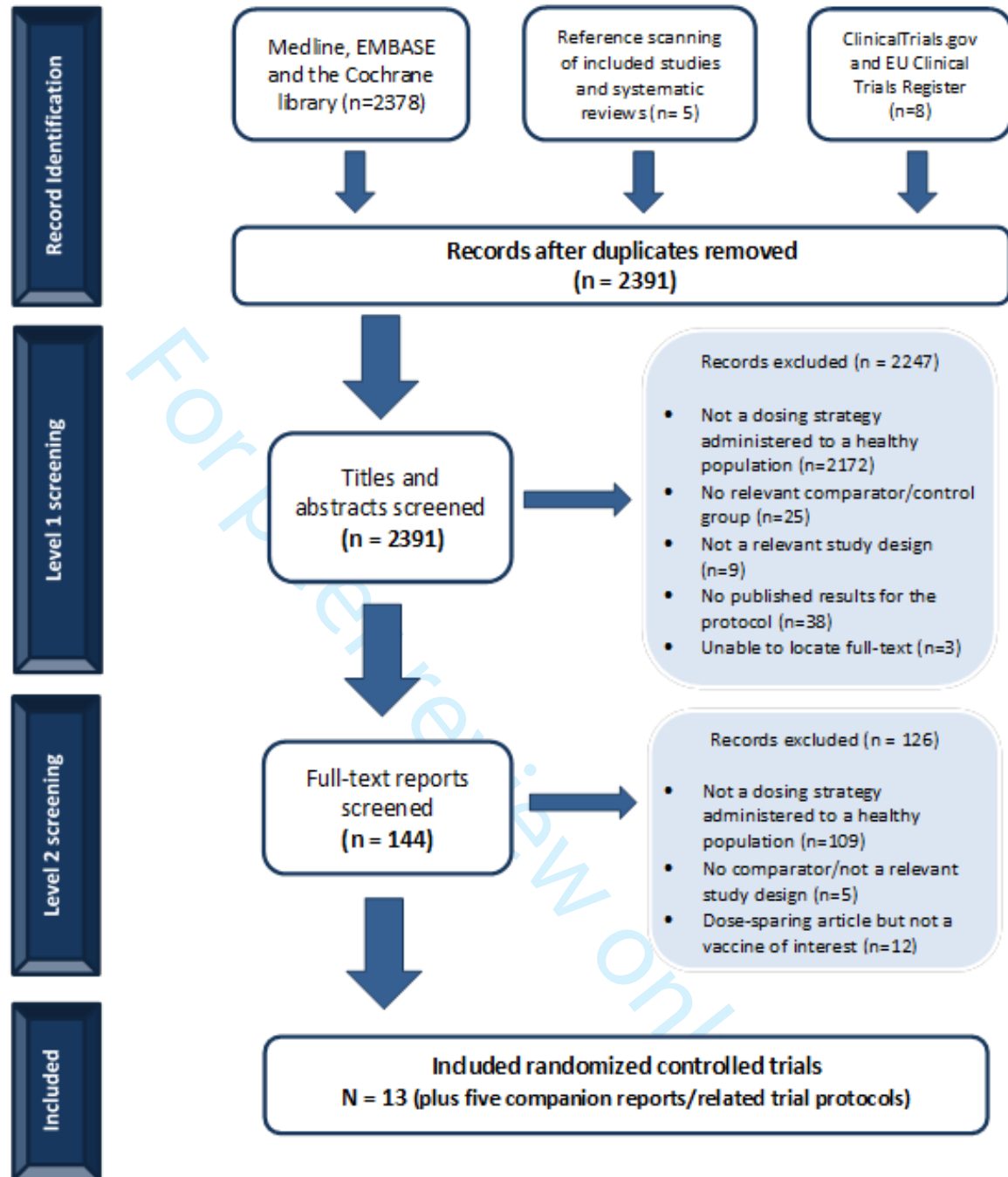
22 457 Figure 1. Flow chart of studies included in the review

23 458 Study flow diagram.  
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## APPENDIX 1 – MEDLINE search strategy

Database: Ovid MEDLINE(R) ALL <1946 to May 29, 2020>

### Search Strategy:

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- 1 influenza, human/ or exp influenza a virus/ or exp influenzavirus b/ or influenzavirus c/
- 2 (flu or flue or influenza\* or grippe).tw,kf.
- 3 1 or 2
- 4 exp Vaccines/ or Immunization/
- 5 (vaccin\* or immuni\* or inocula\* or shot or jab).tw,kf.
- 6 4 or 5
- 7 3 and 6
- 8 influenza vaccines/ or Adjuvants, Immunologic/
- 9 (LAIV or Fluenz or FluMist or Afluria or Fluad or Fluzone or Flulaval or Fluarix or Flublok or
- 10 Flucelvax or FluQuadri or Vaxigrip or Influvac or Fluvirin or Agrippal or Begrivac or Fluad or
- 11 agriflu or fluviral).tw,kf.
- 12 7 or 8 or 9
- 13 Injections, Intramuscular/
- 14 (intramuscular or intra-muscular).tw,kf.
- 15 or/11-12
- 16 10 and 13
- 17 limit 14 to yr=2000-current
- 18 animals/ not humans/
- 19 15 not 16
- 20 ad.fs.
- 21 11 or 12 or 18
- 22 10 and 19
- 23 exp dose-response relationship, immunologic/
- 24 dose-Response Relationship, Drug/
- 25 (Dos\* sparing or Dose -sparing or half-dose or dose-response or dose response or dose
- 26 effect\* or dose-effect\* or fractional dos\*).tw,kf.
- 27 ((reduc\* or lower or less) adj2 (quantity or strength or standard)).tw,kf.
- 28 ((dos\* adj3 change) or (half adj3 dos\*)).tw,kf.
- 29 ((down adj3 titrat\*) or (dose adj3 titrat\*) or (dose adj3 reduc\*) or (dose adj3 "de-escalat\*")
- 30 or (dose adj3 taper\*)).tw,kf.
- 31 or/21-26
- 32 20 and 27
- 33 animals/ not humans/
- 34 28 not 29
- 35 limit 30 to yr=2000-current
- 36 17 or 31

## APPENDIX 2 – EMBASE search strategy

Database: Ovid MEDLINE(R) Embase <2000 to June 11, 2020>

### Search Strategy:

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1 influenza, human/ or exp influenza a virus/ or exp influenzavirus b/ or influenzavirus c/  
 2 (flu or flue or influenza\* or grippe).tw,kf.  
 3 1 or 2  
 4 exp Vaccines/ or Immunization/  
 5 (vaccin\* or immuni\* or inocula\* or shot or jab).tw,kf.  
 6 4 or 5  
 7 3 and 6  
 8 influenza vaccines/ or Adjuvants, Immunologic/  
 9 (LAIV or Fluenz or FluMist or Afluria or Fluad or Fluzone or Flulaval or Fluarix or Flublok  
 10 or Flucelvax or FluQuadri or Vaxigrip or Influvac or Fluvirin or Agrippal or Begrivac or Fluad or  
 11 agriflu or fluviral).tw,kf.  
 12 7 or 8 or 9  
 13 Injections, Intramuscular/  
 14 (intramuscular or intra-muscular).tw,kf.  
 15 or/11-12  
 16 10 and 13  
 17 limit 14 to yr=2009-current  
 18 animals/ not humans/  
 19 15 not 16  
 20 ad.fs.  
 21 11 or 12 or 18  
 22 10 and 19  
 23 exp dose-response relationship, immunologic/  
 24 dose-Response Relationship, Drug/  
 25 (Dos\* sparing or Dose -sparing or half-dose or dose-response or dose response or dose  
 26 effect\* or dose-effect\* or fractional dos\*).tw,kf.  
 27 ((reduc\* or lower or less) adj2 (quantity or strength or standard)).tw,kf.  
 28 ((dos\* adj3 change) or (half adj3 dos\*)).tw,kf.  
 29 ((down adj3 titrat\*) or (dose adj3 titrat\*) or (dose adj3 reduc\*) or (dose adj3 "de-  
 30 escalat\*") or (dose adj3 taper\*)).tw,kf.  
 31 or/21-26  
 32 20 and 27  
 33 animals/ not humans/  
 34 28 not 29  
 35 limit 30 to yr=2009-current  
 36 17 or 31  
 37 32 use ppez  
 38 exp Influenza virus/ or exp influenza/  
 39 (flu or flue or influenza\* or grippe).tw.  
 40 34 or 35  
 41 exp vaccine/  
 42 exp immunization/  
 43 influenza vaccination/ or vaccination/  
 44 (vaccin\* or immuni\* or inocula\* or shot or jab).tw.  
 45 or/37-40  
 46 36 and 41  
 47 influenza vaccination/

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3 44 immunological adjuvant/  
4 45 (LAIV or Fluenz or FluMist or Afluria or Fluad or Fluzone or Flulaval or Fluarix or Flublok  
5 or Flucelvax or FluQuadri or Vaxigrip or Influvac or Fluvirin or Agrippal or Begrivac or Fluad or  
6 agriflu or fluviral).tw.  
7 46 or/42-45  
8 47 intramuscular drug administration/  
9 48 (intramuscular or intra-muscular).tw.  
10 49 47 or 48  
11 50 46 and 49  
12 51 limit 50 to yr="2009 -Current"  
13 52 animals/ not humans/  
14 53 51 not 52  
15 54 ad.fs.  
16 55 49 or 54  
17 56 46 and 55  
18 57 dose response/ or drug response/  
19 58 (Dos\* sparing or Dose -sparing or half-dose or dose-response or dose response or dose  
20 effect\* or dose-effect\* or fractional dos\*).tw.  
21 59 ((reduc\* or lower or less) adj2 (quantity or strength or standard)).tw.  
22 60 ((dos\* adj3 change) or (half adj3 dos\*)).tw.  
23 61 ((down adj3 titrat\*) or (dose adj3 titrat\*) or (dose adj3 reduc\*) or (dose adj3 "de-  
24 escalat\*") or (dose adj3 taper\*)).tw.  
25 62 or/57-61  
26 63 56 and 62  
27 64 animals/ not humans/  
28 65 63 not 64  
29 66 limit 65 to yr="2009 -Current"  
30 67 53 or 66  
31 68 67 use emczd  
32 69 33 or 68  
33 70 remove duplicates from 69  
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### APPENDIX 3 – Cochrane search strategy

Database: Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to June 03, 2020>, EBM Reviews - ACP Journal Club <1991 to May 2020>, EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>, EBM Reviews - Cochrane Clinical Answers <May 2020>, EBM Reviews - Cochrane Central Register of Controlled Trials <May 2020>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>  
**Search Strategy:**

1 (influenza, human or influenza a virus or influenzavirus b or influenzavirus c).kw.  
 2 (flu or flue or influenza\* or grippe).ti,ab.  
 3 1 or 2  
 4 (Vaccines or Immunization).kw.  
 5 (vaccin\* or immuni\* or inocula\* or shot or jab).ti,ab.  
 6 4 or 5  
 7 3 and 6  
 8 (influenza vaccines or Adjuvants, Immunologic).kw.  
 9 (LAIV or Fluenz or FluMist or Afluria or Fluad or Fluzone or Flulaval or Fluarix or Flublok or Flucelvax or FluQuadri or Vaxigrip or Influvac or Fluvirin or Agrippal or Begrivac or Fluad or agriflu or fluviral).ti,ab.  
 10 7 or 8 or 9  
 11 Injections, Intramuscular.kw.  
 12 (intramuscular or intra-muscular).ti,ab.  
 13 11 or 12  
 14 10 and 13  
 15 dose-response relationship, immunologic.kw.  
 16 dose-Response Relationship, Drug.kw.  
 17 (Dos\* sparing or Dose -sparing or half-dose or dose-response or dose response or dose effect\* or dose-effect\* or fractional dos\*).ti,ab.  
 18 ((reduc\* or lower or less) adj2 (quantity or strength or standard)).ti,ab.  
 19 ((dos\* adj3 change) or (half adj3 dos\*)).ti,ab.  
 20 ((down adj3 titrat\*) or (dose adj3 titrat\*) or (dose adj3 reduc\*) or (dose adj3 "de-escalat\*") or (dose adj3 taper\*)).ti,ab.  
 21 or/15-20  
 22 10 and 21  
 23 14 or 22  
 24 limit 23 to yr="2009 -Current" [Limit not valid in DARE; records were retained]

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to June 03, 2020>, EBM Reviews - ACP Journal Club <1991 to May 2020>, EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>, EBM Reviews - Cochrane Clinical Answers <May 2020>, EBM Reviews - Cochrane Central Register of Controlled Trials <May 2020>, EBM Reviews -

**Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>**  
**Search Strategy:**

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- 1 (influenza, human or influenza a virus or influenzavirus b or influenzavirus c).kw.
- 2 (flu or flue or influenza\* or grippe).ti,ab.
- 3 1 or 2
- 4 (Vaccines or Immunization).kw.
- 5 (vaccin\* or immuni\* or inocula\* or shot or jab).ti,ab.
- 6 4 or 5
- 7 3 and 6
- 8 (influenza vaccines or Adjuvants, Immunologic).kw.
- 9 (LAIV or Fluenz or FluMist or Afluria or Fluad or Fluzone or Flulaval or Fluarix or Flublok or Flucelvax or FluQuadri or Vaxigrip or Influvac or Fluvirin or Agrippal or Begrivac or Fluad or agriflu or fluviral).ti,ab.
- 10 7 or 8 or 9
- 11 Injections, Intramuscular.kw.
- 12 (intramuscular or intra-muscular).ti,ab.
- 13 11 or 12
- 14 10 and 13
- 15 dose-response relationship, immunologic.kw.
- 16 dose-Response Relationship, Drug.kw.
- 17 (Dos\* sparing or Dose -sparing or half-dose or dose-response or dose response or dose effect\* or dose-effect\* or fractional dos\*).ti,ab.
- 18 ((reduc\* or lower or less) adj2 (quantity or strength or standard)).ti,ab.
- 19 ((dos\* adj3 change) or (half adj3 dos\*)).ti,ab.
- 20 ((down adj3 titrat\*) or (dose adj3 titrat\*) or (dose adj3 reduc\*) or (dose adj3 "de-escalat\*") or (dose adj3 taper\*)).ti,ab.
- 21 or/15-20
- 22 10 and 21
- 23 14 or 22
- 24 limit 23 to yr="2000 - 2008" [Limit not valid in DARE; records were retained]
- 25 from 24 keep 1-173

## APPENDIX 4 – List of eligible vaccines

Product name (manufacturer)	Vaccine Characteristic				
	Vaccine type	Route of administration	Authorized ages for use	Antigen content for each vaccine strain	Formats available
Flulaval Tetra (GSK)	IIV4-SD (split virus)	IM	6 months and older	15 µg HA /0.5 mL dose	5 mL multi-dose vial Single dose pre-filled syringe
Fluzone Quadrivalent (Sanofi Pasteur)	IIV4-SD (split virus)	IM	6 months and older	15 µg HA /0.5 mL dose	5 mL multi-dose vial Single dose vial Single dose pre-filled syringe without attached needle
Afluria Tetra (Seqirus)	IIV4-SD (split virus)	IM	5 years and older	15 µg HA /0.5 mL dose	Up to expiry date indicate on vial label
Influvac Tetra (BGP Pharma ULC, operating as Mylan)	IIV4-SD (subunit)	IM or deep subcutaneous injection	3 years and older	15 µg HA /0.5 mL dose	Single dose pre-filled syringe with or without a needle
Vaxigrip Tetra	IIV4	IM	6 months and older	Pediatric: 7.5 µg HA /0.25 mL dose Adult: 15 µg HA /0.5 mL dose	0.5 mL pre-filled syringe
Fluarix Tetra/ Influxplit Tetra (GSK)	IIV4	IM	6 months and older	15 µg HA /0.5 mL dose	0.5 mL pre-filled syringe
Agriflu (Seqirus)	IIV3-SD (subunit)	IM	6 months and older	15 µg HA /0.5 mL dose	5 mL multi-dose vial Single dose pre-filled syringe without attached needle
Fluad Pediatric and Fluad (Seqirus)	IIV3-Adj (subunit)	IM	Pediatric: 6-23 months Adult: 65 years and older	Pediatric: 7.5 µg HA /0.25 mL dose Adult: 15 µg HA /0.5 mL dose	Single dose pre-filled syringe without a needle
Fluviral (GSK)	IIV3-SD (split virus)	IM	6 months and older	15 µg HA /0.5 mL dose	5 mL multi-dose vial
Fluzone TIV (Sanofi Pasteur)	IIV3-HD (split virus)	IM	65 years and older	Adult: 15 µg HA /0.5 mL dose	0.5 mL pre-filled syringe
Vaxigrip TIV	IIV3-SD	IM	6 months and older	Pediatric: 7.5 µg HA /0.25 mL dose Adult: 15 µg HA /0.5 mL dose	0.5 mL pre-filled syringe

**Note:** list of vaccines included in the review is based on feedback from PHAC and the 2020-2021 seasonal vaccine availability in Canada found here: <https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/canadian-immunization-guide-statement-seasonal-influenza-vaccine-2020-2021.html#appA>

## APPENDIX 5 – Excluded dose-sparing studies

	Reference	Reason for exclusion
1	Euctr, H. U. A Randomized, Double-blind, Multi-Center Study to Evaluate Safety and Immunogenicity of One Dose of Four FLUVAL AB-like (Trivalent, Whole Virus, Aluminium Phosphate Gel Adjuvanted) Influenza Vaccines Containing 3.5[micro]gHA, 6[micro]gHA, 9[micro]gHA or 1. 2011. Available from: <a href="http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011">http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011</a>	exclude - dose-sparing but vaccine not of interest
2	Vajo Z, Tamas F, Jankovics I. A reduced-dose seasonal trivalent influenza vaccine is safe and immunogenic in adult and elderly patients in a randomized controlled trial. <i>Clin Vaccine Immunol.</i> 2012;19(3):313-318. doi:10.1128/CVI.05619-11	exclude - dose-sparing but vaccine not of interest
3	Treanor J, Keitel W, Belshe R, et al. Evaluation of a single dose of half strength inactivated influenza vaccine in healthy adults. <i>Vaccine.</i> 2002;20(7-8):1099-1105. doi:10.1016/s0264-410x(01)00440-6	exclude - dose-sparing but vaccine not of interest
4	Euctr. A Randomized, Active Controlled, Double-blind, Multi-Centre Study to Evaluate Safety and Immunogenicity of One Dose of FLUVAL AB-like (Trivalent, Whole Virus, Aluminium Phosphate Gel Adjuvanted) Influenza Vaccine Containing 6µgHA of Seasonal A/H1N1, A/H3N2 and B Influenza Antigens in Non-elderly Adult and Elderly Subjects. 2011. Available from: <a href="http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011-003314-16-HU">http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011-003314-16-HU</a>	exclude - dose-sparing but experimental vaccine
5	Euctr, E. S. Clinical study to compare the safety of two influenza vaccines in children and adolescents of 3 to less than 18 years of age at risk for influenza-related complications. 2013. Available from: <a href="http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2013">http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2013</a>	exclude - dose-sparing but experimental vaccine
6	Pillet S, Aubin É, Trépanier S, et al. A plant-derived quadrivalent virus like particle influenza vaccine induces cross-reactive antibody and T cell response in healthy adults. <i>Clin Immunol.</i> 2016;168:72-87. doi:10.1016/j.clim.2016.03.008	exclude - dose-sparing but experimental vaccine
7	Lee JH, Cho HK, Kim KH, et al. Evaluation of Waning Immunity at 6 Months after Both Trivalent and Quadrivalent Influenza Vaccination in Korean Children Aged 6-35 Months. <i>J Korean Med Sci.</i> 2019;34(46):e279. Published 2019 Dec 2. doi:10.3346/jkms.2019.34.e279	exclude - dose-sparing but experimental vaccine
8	Treanor JJ, Taylor DN, Tussey L, et al. Safety and immunogenicity of a recombinant hemagglutinin influenza-flagellin fusion vaccine (VAX125) in healthy young adults. <i>Vaccine.</i> 2010;28(52):8268-8274. doi:10.1016/j.vaccine.2010.10.009	exclude - dose-sparing but experimental vaccine
9	Vajo Z, Balaton G, Vajo P, Kalabay L, Erdman A, Torzsa P. Dose sparing and the lack of a dose-response relationship with an influenza vaccine in adult and elderly patients - a randomized, double-blind clinical trial. <i>Br J Clin Pharmacol.</i> 2017;83(9):1912-1920. doi:10.1111/bcp.13289	exclude - dose-sparing but vaccine not of interest
10	Ctri. Study of a Single Dose or Two Doses of a Quadrivalent Influenza Vaccine in Subjects Aged 6 Months or Older in India. 2015. Available from: <a href="http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI">http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI</a>	exclude - dose-sparing but unclear vaccine (waiting for author response)
11	Euctr, F. I. Safety and Immunogenicity of the Quadrivalent Influenza Vaccine Administered via the Intramuscular Route in Children Aged 3 to 8 Years. 2011. Available from: <a href="http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011">http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011</a>	exclude - dose-sparing but unclear vaccine (waiting for author response)
12	Euctr, C. Z. A randomized, double-blind, placebo-controlled, multi-country and multi-center, phase IV study to demonstrate the efficacy of GSK Biologicals' influenza vaccine (Fluarix[TM])	exclude - dose-sparing but unclear vaccine (waiting for author response)

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	administered intramuscularly in adults. - FluarixUS-006. 2006. Available from: <a href="http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2006">http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2006</a>	
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## APPENDIX 6 – Study and patient data

Author, Year [Study design]	Study period; Setting and Country	Objective of study	Eligibility criteria	Sample size; % Female, % previously immunized	Ethnicities
Kramer, 2006 [RCT] <sup>1</sup>	October 2004 – November 2004; 760-bed tertiary care community teaching hospital in the USA	To compare the effectiveness of half-dose versus full dose TIV in health care workers	Age 18 years or older, hospital employee, staff member, or volunteer, and signed informed consent and authorization to use and disclose protected health information for research purposes	444; NR, NR	NR
Belshe, 2007 [RCT] <sup>2</sup>	USA; NR	To compare the immunogenicity and safety of injection of IM and ID TIV across different dose levels (3, 6, 9, and 15µg/antigen/dose)	Healthy adults 18-49 years of age	125; 71.2%, 0%	American Indian/Alaskan Native (0%), Asian (2.4%), Black/African American (9.6%), Hawaiian/Pacific Islander (0%), Hispanic (0%), Multi-racial (0.8%), Non-Hispanic (97.6%), Other/unknown (0%), White (87.2%)
Engler, 2008 [RCT] <sup>3</sup>	November 2004 – December 2004; Allergy-Immunology-Immunization Clinic, WRAMC, and Pentagon/DiLorenzo Health Clinic, Arlington, Virginia in the USA	To determine the effects of age, sex, and dose on the immunogenicity of intramuscular TIV	Healthy adults aged 18-64 years. Inclusion criteria were based on the remaining CDC and/or DoD priority prior to the shortage announcement which includes all children aged 6--23 months; adults aged >65 years; persons aged 2--64 years with underlying chronic medical conditions; all women who will be pregnant during the influenza season; residents of nursing homes and long-term--care facilities; children aged 2--18 years on chronic aspirin therapy; health-care workers involved in direct patient care; and out-of-home caregivers and household contacts of children aged <6 months	1316; 43.4%, 0%	African American (9%), Asian (2%), Hispanic (2%), Other/unknown (1.4%), White (85%)
	August 2007-2008; Seattle Division of the Department of	To determine pre vaccination and 4- week post-vaccination changes in antibody titer, and	Community-dwelling adults 65 years and older living in Puget Sound area in Washington State	129; 17.8%, 94.6%	African American (4.7%), Asian (1.6%), Hispanic (0.8%), Not reported

Author, Year [Study design]	Study period; Setting and Country	Objective of study	Eligibility criteria	Sample size; % Female, % previously immunized	Ethnicities
Chi, 2010 [RCT] <sup>4</sup>	Veterans Affairs Puget Sound Health Care System in Washington State, USA.	local and systemic reactions of full-dose compared to 60% dose of TIV by IM injection			(2.3%), Other (0.8%), White (90%)
Cioppa, 2011 [RCT] <sup>5</sup>	October 2008 – March 2009; 10 study centers in Finland and 5 centers in Belgium	To evaluate the safety, tolerability and immunogenicity of different vaccine formulations with different doses of MF59 adjuvant and/or a second B strain (QIV) when added to either high or low doses of a purified subunit influenza vaccine	Healthy children aged 6 to <36 months	126; 43.5%, NR	Asian (1.68%), Black (6.54%), White (84.2%)
Skowronski, 2011 [RCT] <sup>6</sup>	September 2008 – December 2008; 5 sites in 3 Canadian provinces (British Columbia, Quebec, and Nova Scotia)	To determine whether giving 2 full doses of split TIV to previously unimmunized infants and toddlers can improve immunogenicity without increasing reactogenicity compared with 2 half-doses	Healthy children 6–23 months of age	267; 53.2%, 0%	Asian (7.9%), Other (14.3%), White (77.8%)
Langley, 2012 [RCT] <sup>7</sup>	November 2008 – August 2009; 17 centers in Canada	To assess the immunogenicity and safety of a preservative-free, prefilled syringe formulation of TIV provided as the full adult dose of 0.50 mL compared with the usual children's dose of 0.25 mL in young children	Healthy children 6–35 months at the time of vaccination	390; 47.9%, 42.6%	Other (13.9%), White (86.1%)
Pavia-Ruz, 2015 [RCT] <sup>8</sup>	October 2008 – March 2009; Hong Kong, Mexico, Taiwan, Thailand, and the USA	To evaluate Fluarix at both the standard recommended TIV dose for young children in the US (0.25 ml) and also at double this dose (0.5 ml)	Healthy children aged 6 to 35 months at the time of the first vaccination; without acute illness at the time of enrollment and who had not been vaccinated during the 2008-2009 influenza season. Administration of influenza vaccine in a previous season was not however an exclusion criteria	3318; 51%, 30.1%	African heritage/African American (3.5%), American Indian or Alaskan native (0.1%), Asian-Central/South Asian heritage (0.1%), Asian-East Asian heritage (14.5%), Asian-Japanese heritage (0.1%), Asian-South East Asian heritage

Author, Year [Study design]	Study period; Setting and Country	Objective of study	Eligibility criteria	Sample size; % Female, % previously immunized	Ethnicities
					(9.2%), Native Hawaiian or other Pacific Islander (0.2%), White - Arabic/North African heritage (0.5%), White-Caucasian/European heritage (29.9%), Hispanics and children of mixed race (42.1%)
Halasa, 2015 [RCT] <sup>9</sup>	2010-2012; 6 study sites in USA	To determine whether a higher dose of influenza vaccine would be safe in the 6 through 35 months age group. In addition, to determine whether immunization with 0.5 mL doses of TIV (15 µg of each HA) would improve the immunogenicity without increasing the reactogenicity of TIV when administered to children 6 through 35 months of age with and without a history of previous TIV vaccination	Healthy children 6 to 35 months of age (naïve cohort) or 12 through 35 months of age (fully primed cohort) who were available for the entire study period and whose parents or guardians provided informed consent were eligible to participate. Children who were eligible in the fully primed cohort also required a history of receiving 2 doses of 2009–2010 H1N1 influenza vaccine and 2 doses of TIV at any time in the past	243; 52%, 13.2%	African (26%), Asian (1%), Multiracial (5%), other (0%); Ethnicity: Hispanic (2%), Non-Hispanic (98%), White (67%)
Phung, 2016 [RCT] <sup>10</sup>	September 2010-January 2011; Finland	To evaluate the immunogenicity and safety following a single intramuscular dose of FLUAD or Agrippal S1 influenza vaccines in healthy children previously vaccinated	Healthy children 6–35 months at the time of vaccination	197; 55.8%, 85.7%	NR
Jain, 2017 [RCT] <sup>11</sup>	2014-2015 influenza season; 66 study locations in USA and Mexico	To compare the safety and immunogenicity of a double-dose IIV4 manufactured by GSK Vaccines with the United States-approved standard-dose IIV4 in children 6–35 months of age	Healthy children aged 6-35 months regardless of influenza vaccination history, but could not have received any seasonal or pandemic influenza vaccine within 6 months before the first dose of study vaccine	2424; 46.9%, 57.5%	African/African American (13.9%), American Indian or Alaskan Native (2.0%), Caucasian (64.3%), Other (17.9%), South East Asian (1.8%)
Ojeda, 2019 [RCT] <sup>12</sup>	December 2017 – January 2018; 3 study sites in Mexico	Reported the results of an open-label, randomized phase III study designed to evaluate the immunogenicity and safety	Children aged 6 months to 17 years of age	302; 46.4%, NR	NR



Author, Year [Study design]	Study period; Setting and Country	Objective of study	Eligibility criteria	Sample size; % Female, % previously immunized	Ethnicities
Robertson, 2019 [RCT] <sup>13</sup>	September 2016 – March 2017; 38 sites in the USA	To compare the safety and immunogenicity of full and half doses of quadrivalent, split-virion, inactivated influenza vaccine in children 6–35 months of age	Healthy children 6–35 months of age who had not been vaccinated against influenza during the current season (2016–2017). Children 6–11 months of age had to be born at full term of pregnancy (≥37 weeks) or with a birth weight ≥2.5 kg	1950; 49.7%, 47.3%	Race: American Indian or Alaska Native (0.98%), Asian (0.46%), Black (19.2%), Native Hawaiian or Other Pacific Islander (0.46%), White (74.3%), Ethnicity: Hispanic or Latino (22%), not Hispanic or Latino (77%)

**Abbreviations:** CDC- Centers for Disease Control and Prevention; DoD- Department of Defense; GSK -GlaxoSmithKline; HA- hemagglutinin; IIV4 – inactivated influenza vaccine; ID - intradermal; IM - intramuscular; MDV- multi-dose vial; PFS – pre-filled syringe; QIV-quadrivalent influenza vaccine; TIV-trivalent influenza vaccine; NR – not reported

**APPENDIX 7 – Treatment and outcome data**

<b>Author, Year; [Study design] Population</b>	<b>Treatment arms</b> Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	<b>Effectiveness and Safety</b> Outcome (definition): n/N (unless otherwise indicated)	<b>Conclusions</b>
Kramer, 2006 [RCT] <sup>1</sup>  Adults and Seniors (>18 years)	Fluzone (Aventis Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose (Intramuscular into the deltoid region)]  A/Wyoming/3/2003 (H3N2), A/New Caledonia/20/99 (H1N1), and a new B strain, B/Jiangsu/10/2003  Fluzone (Aventis Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose (Intramuscular into the deltoid region)]  A/Wyoming/3/2003 (H3N2), A/New Caledonia/20/99 (H1N1), and a new B strain, B/Jiangsu/10/2004	<b>Effectiveness</b> Lab confirmed influenza (Laboratory confirmation of influenza diagnosis was sought in participants reporting a clinical diagnosis by their physicians): 1/222  Influenza like illness (Clinical diagnosis of influenza. Participants self-reported four or more symptoms consistent with influenza-like illness (i.e., headache, extreme tiredness, dry cough, fever, muscle or body aches)): 8/222  <b>Effectiveness</b> Lab confirmed influenza (Laboratory confirmation of influenza diagnosis was sought in participants reporting a clinical diagnosis by their physicians): 0/222  Influenza like illness (Clinical diagnosis of influenza. Participants self-reported four or more symptoms consistent with influenza-like illness (i.e., headache, extreme tiredness, dry cough, fever, muscle or body aches)): 15/222	<ul style="list-style-type: none"> <li>There was no significant difference between the full-dose and half-dose groups in the diagnosis of influenza or in the proportion of participants self-reporting four or more symptoms consistent with influenza-like illness.</li> <li>No adverse events were noted by participants from either group or reported to the IRB during the course of the study</li> </ul>
Belshe, 2007 [RCT] <sup>2</sup>  Adults (18-49 years)	Fluzone (Sanofi-Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose (Intramuscular in the non-dominant arm)]  Fluzone (Sanofi-Pasteur), <b>9-µg/strain</b> [1 x 0.3mL dose (Intramuscular in the non-dominant arm)]	<b>Reactogenicity – injection site</b> Pain <sup>1</sup> : 15/31 Redness <sup>2</sup> : 8/31 Swelling <sup>2</sup> : 7/31  <b>Reactogenicity – systemic</b> Fever <sup>3</sup> : 1/31 Headache <sup>1</sup> : 15/31 Malaise <sup>1</sup> : 8/31 Myalgia <sup>1</sup> : 10/31  <b>Reactogenicity – injection site</b> Pain <sup>1</sup> : 11/31 Redness <sup>2</sup> : 11/31 Swelling <sup>2</sup> : 4/31  <b>Reactogenicity – systemic</b> Fever <sup>3</sup> : 1/31 Headache <sup>1</sup> : 6/31	<ul style="list-style-type: none"> <li>Intradermal vaccine induced significantly more local inflammatory response than Intramuscular vaccine (primary comparison of this study was ID vs IM doses)</li> </ul>

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety Outcome (definition): n/N (unless otherwise indicated)	Conclusions
	<p>Fluzone (Sanofi-Pasteur), <b>6-µg/strain</b> [1 x 0.2mL dose (Intramuscular in the non-dominant arm)]</p>	<p><i>Malaise</i><sup>1</sup>: 8/31 <i>Myalgia</i><sup>1</sup>: 6/31</p> <p><b>Reactogenicity – injection site</b> <i>Pain</i><sup>1</sup>: 14/31 <i>Redness</i><sup>2</sup>: 9/31 <i>Swelling</i><sup>2</sup>: 4/31</p> <p><b>Reactogenicity – systemic</b> <i>Fever</i><sup>3</sup>: 0/31 <i>Headache</i><sup>1</sup>: 9/31 <i>Malaise</i><sup>1</sup>: 7/31 <i>Myalgia</i><sup>1</sup>: 9/31</p>	
	<p>Fluzone (Sanofi-Pasteur), <b>3-µg/strain</b> [1 x 0.1mL dose (Intramuscular in the non-dominant arm)]</p>	<p><b>Reactogenicity – injection site</b> <i>Pain</i><sup>1</sup>: 15/31 <i>Redness</i><sup>2</sup>: 9/31 <i>Swelling</i><sup>2</sup>: 7/31</p> <p><b>Reactogenicity – systemic</b> <i>Fever</i><sup>3</sup>: 3/31 <i>Headache</i><sup>1</sup>: 8/31 <i>Malaise</i><sup>1</sup>: 3/31 <i>Myalgia</i><sup>1</sup>: 7/31</p>	
<p>Engler, 2008 [RCT]<sup>3</sup></p> <p><i>Adults</i> (18-64 years)</p>	<p>Fluzone (Aventis Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose (Intramuscular injection)]</p> <p><i>A/H1N1, A/New Caledonia/20/99; A/H3N2, A/Fujian/411/2002; B, B/Shanghai/361/2002</i></p>	<p><b>Effectiveness</b> <i>Influenza like illness</i> (Influenza-like illness and complications resulting in either inpatient or outpatient medical encounters were compared between dose groups (by age)): 61/632</p> <p><i>Hospitalization or Emergency visits</i>: 0.3%</p> <p><b>Reactogenicity – local/injection site</b> <i>Any local reactions</i> (NR): 8.9% <i>Arm weakness</i> (NR): 8.3% <i>Numbness or burning</i> (NR): 9.7% <i>Pain</i> (NR): 5.9% <i>Redness or swelling</i> (NR): 13.4%</p> <p><b>Reactogenicity – systemic</b> <i>Joint and/or muscle pain</i> (NR): 4.5%</p>	<ul style="list-style-type: none"> <li>▪ The relative risk of medical visits and hospitalizations for influenza-like illnesses were similar in the half- and full-dose group regardless of age, and there was no evidence of ILI symptom differences by sex or dose during the 21 days after immunizations.</li> <li>▪ Although injection site pain was greater for full vs half dose (19.9% vs 14.4%; p=.01), when analyzed for clinically significant pain levels significant dose-dependent</li> </ul>

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety Outcome (definition): n/N (unless otherwise indicated)	Conclusions
	<p>Fluzone (Aventis Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose (Intramuscular injection)]</p> <p><i>A/H1N1, A/New Caledonia/20/99; A/H3N2, A/Fujian/411/2002; B, B/Shanghai/361/2003</i></p>	<p><b>Adverse events</b> SAE: 2/554</p> <p><b>Effectiveness</b> <i>Influenza like illness</i> (Influenza-like illness and complications resulting in either inpatient or outpatient medical encounters were compared between dose groups (by age): 64/644</p> <p><i>Hospitalization or Emergency visits</i>: 0.2%</p> <p><b>Reactogenicity – local/injection site</b> <i>Any local reactions</i> (NR): 7.5% <i>Arm weakness</i> (NR): 6.5% <i>Numbness or burning</i> (NR): 7.8% <i>Pain</i> (NR): 4.6% <i>Redness or swelling</i> (NR): 8.6%</p> <p><b>Reactogenicity – systemic</b> <i>Joint and/or muscle pain</i> (NR): 2.2%</p> <p><b>Adverse events</b> SAE: 1/556</p>	<p>pain differences were not identified.</p> <ul style="list-style-type: none"> <li>Joint and/or muscle pain were significantly different (p=.02 and p=.03, respectively) by dose.</li> <li>No other adverse event differed significantly by dose</li> </ul>
<p>Chi, 2010 [RCT]<sup>4</sup></p> <p>Seniors (&gt;65 years)</p>	<p>Fluzone (Sanofi Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose (intramuscular in deltoid of arm)]</p> <p><i>A/Solomon Islands/3/ 2006 (A/H1N1), A/Wisconsin/67/2005 (A/H3N2), and B/Malaysia/2506/2004</i></p>	<p><b>Reactogenicity – injection site, N=64</b> <i>Arm motion limitation</i>: 1 (grade I)<sup>4</sup> <i>Itching</i>: 4 (grade I)<sup>4</sup> <i>Pain</i>: 7 (grade I)<sup>4</sup> <i>Redness or discoloration</i>: 9 (grade I)<sup>4</sup> <i>Swelling</i>: 13 (grade I)<sup>4</sup></p> <p><b>Reactogenicity - systemic, N=64</b> <i>Chills</i>: 1 (grade I)<sup>4</sup>, 1 (grade II/III)<sup>5</sup> <i>Fatigue</i>: 4 (grade I)<sup>4</sup>, 2 (grade II/III)<sup>5</sup> <i>Fever</i>: 0 <i>General body ache/pain</i>: 6 (grade I)<sup>4</sup>, 1 (grade II/III)<sup>5</sup> <i>Headache</i>: 10 (grade I)<sup>4</sup> <i>Nausea</i>: 3 (grade I)<sup>4</sup>, 1 (grade II/III)<sup>5</sup></p> <p><b>Adverse events</b></p>	<ul style="list-style-type: none"> <li>The two SAEs were acute coronary syndrome and appendicitis and neither were judged to be related to influenza vaccination</li> </ul>

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety <i>Outcome</i> (definition): n/N (unless otherwise indicated)	Conclusions
	<p>Fluzone (Sanofi Pasteur), <b>9-µg/strain</b> [1 x 0.3mL dose (intramuscular in deltoid of arm)]</p> <p><i>A/Solomon Islands/3/2006 (A/H1N1), A/Wisconsin/67/2005 (A/H3N2), and B/Malaysia/2506/2004</i></p>	<p>SAE<sup>6</sup>: 0/64</p> <p><b>Reactogenicity – injection site, N=64</b> <i>Arm motion limitation</i>: 1 (grade I)<sup>4</sup> <i>Itching</i>: 5 (grade I)<sup>4</sup> <i>Pain</i>: 11 (grade I)<sup>4</sup> <i>Redness or discoloration</i>: 7 (grade I)<sup>4</sup> <i>Swelling</i>: 4 (grade I)<sup>4</sup></p> <p><b>Reactogenicity - systemic, N=64</b> <i>Chills</i>: 1 (grade I)<sup>4</sup>, 1 (grade II/III)<sup>5</sup> <i>Fatigue</i>: 6 (grade I)<sup>4</sup>, 1 (grade II/III)<sup>5</sup> <i>Fever</i>: 1 (grade I)<sup>4</sup> <i>General body ache/pain</i>: 5 (grade I)<sup>4</sup>, 2 (grade II/III)<sup>5</sup> <i>Headache</i>: 5 (grade I)<sup>4</sup>, 1 (grade II/III)<sup>5</sup> <i>Nausea</i>: 2 (grade I)<sup>4</sup>, 1 (grade II/III)<sup>5</sup></p> <p><b>Adverse events</b> SAE<sup>6</sup>: 2/64</p>	
<p>Cioppa, 2011 [RCT]<sup>5</sup></p> <p><i>Infants/ Toddlers (6-36 months)</i></p>	<p>NR - TIV, <b>7.5-µg/strain</b> [2 x 0.25mL dose (intramuscular in deltoid of arm (children 24-35 mo of age) or the anterolateral aspect of the thigh (children &lt;24 mo of age) using prefilled syringes)]</p> <p><i>A/Brisbane/59/2007 (A/H1N1)-like virus, A/Brisbane/10/2007 (A/H3N2)-like virus, and B/Florida/4/2006-like virus (of the influenza B/Yamagata lineage)</i></p> <p>Agrippal - TIV, <b>15-µg/strain</b> [2 x 0.5mL dose (intramuscular in deltoid of arm (children 24-35 mo of age) or the anterolateral aspect of the thigh (children &lt;24 mo of age) using prefilled syringes)]</p> <p><i>A/Brisbane/59/2007 (A/H1N1)-like virus, A/Brisbane/10/2007 (A/H3N2)-like virus, and B/Florida/4/2006-like virus (of the influenza B/Yamagata lineage)</i></p>	<p><b>Reactogenicity</b> <i>Any local reaction</i><sup>7</sup>: 47% <i>Any systemic reaction</i><sup>8</sup>: 68%</p> <p><b>Adverse events</b> AE (solicited/spontaneously reported): 84% SAE: 0/25</p> <p><b>Reactogenicity</b> <i>Any local reaction</i><sup>7</sup>: 59% <i>Any systemic reaction</i><sup>8</sup>: 50%</p> <p><b>Adverse events</b> AE (solicited/spontaneously reported): 82% SAE: 0/22</p>	<ul style="list-style-type: none"> <li>Reactogenicity of the 7.5-µg TIV/QIV formulations was slightly lower than for the corresponding 15-µg formulations.</li> <li>The majority of unsolicited AEs were mild or moderate in severity and none of the SAEs was considered to be related to the study vaccine.</li> </ul>

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety Outcome (definition): n/N (unless otherwise indicated)	Conclusions
	NR - QIV, <b>7.5-µg/strain</b> [2 x 0.25mL dose (intramuscular in deltoid of arm (children 24-35 mo of age) or the anterolateral aspect of the thigh (children <24 mo of age) using prefilled syringes)]  <i>A/Brisbane/59/2007 (A/H1N1)-like virus, A/Brisbane/10/2007 (A/H3N2)-like virus, B/Florida/4/2006-like virus (of the influenza B/Yamagata lineage), and B/Malaysia/2506/2004-like antigen virus (Victoria lineage)</i>	<b>Reactogenicity</b> <i>Any local reaction</i> <sup>7</sup> : 25% <i>Any systemic reaction</i> <sup>8</sup> : 50%  <b>Adverse events</b> AE (solicited/spontaneously reported): 92% SAE: 1/25	
	NR - QIV, <b>15-µg/strain</b> [2 x 0.5mL dose (intramuscular in deltoid of arm (children 24-35 mo of age) or the anterolateral aspect of the thigh (children <24 mo of age) using prefilled syringes)]  <i>A/Brisbane/59/2007 (A/H1N1)-like virus, A/Brisbane/10/2007 (A/H3N2)-like virus, B/Florida/4/2006-like virus (of the influenza B/Yamagata lineage), and B/Malaysia/2506/2004-like antigen virus (Victoria lineage)</i>	<b>Reactogenicity</b> <i>Any local reaction</i> <sup>7</sup> : 39% <i>Any systemic reaction</i> <sup>8</sup> : 54%  <b>Adverse events</b> AE (solicited/spontaneously reported): 71% SAE: 1/28	
	Vaxigrip pediatric - TIV (Sanofi Pasteur), <b>7.5-µg/strain</b> [2 x 0.25mL dose (intramuscular in deltoid of arm (children 24-35 mo of age) or the anterolateral aspect of the thigh (children <24 mo of age) using prefilled syringes)]	<b>Reactogenicity</b> <i>Any local reaction</i> <sup>7</sup> : 50% <i>Any systemic reaction</i> <sup>8</sup> : 46%  <b>Adverse events</b> AE (solicited/spontaneously reported): 73% SAE: 1/26	
Skowronski, 2011 [RCT] <sup>6</sup>  <i>Infants/Toddlers (6-23 months)</i>	Vaxigrip (Sanofi-Pasteur), <b>15-µg/strain [2 x 0.5mL dose]</b> (Intramuscular injection)  <i>A/Brisbane/10/07 (H3N2); A/Brisbane/59/07 (H1N1); and B/Florida/4/06 (Yamagata lineage)</i>	<b>Reactogenicity – injection site</b> <i>Induration</i> (NR): 13.7% <i>Redness</i> (NR): 22.6% <i>Swelling</i> (NR): 15.3% <i>Tenderness</i> (NR): 22.6%  <b>Reactogenicity – systemic</b> <i>Fever (&gt;37.5°C)</i> : 8.06% <i>Irritability</i> (NR): 59.7% <i>Decreased appetite</i> (NR): 38.7%	<ul style="list-style-type: none"> <li>▪ Local reactions generally were less common in infants than toddlers and more common with full doses versus half doses, but none of these differences were significant.</li> <li>▪ One serious adverse event was reported: a toddler in the half dose group was</li> </ul>

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety <i>Outcome</i> (definition): n/N (unless otherwise indicated)	Conclusions
	<p>Vaxigrip (Sanofi-Pasteur), 15-<math>\mu</math>g/strain [2 x 0.25mL dose (Intramuscular injection)]</p> <p><i>A/Brisbane/10/07 (H3N2); A/Brisbane/59/07 (H1N1); and B/Florida/4/06 (Yamagata lineage)</i></p>	<p><i>Drowsiness</i> (NR): 39.5% <i>Sleep disturbance</i> (NR): 54.8%</p> <p><b>Adverse events</b> SAE: NR</p> <p><b>Reactogenicity – injection site</b> <i>Induration</i> (NR): 6.3% <i>Redness</i> (NR): 20.3% <i>Swelling</i> (NR): 8.6% <i>Tenderness</i> (NR): 25.8%</p> <p><b>Reactogenicity – systemic</b> <i>Fever</i> (&gt;37.5°C): 11.7% <i>Irritability</i> (NR): 60.2% <i>Decreased appetite</i> (NR): 43% <i>Drowsiness</i> (NR): 41.4% <i>Sleep disturbance</i> (NR): 50%</p> <p><b>Adverse events</b> SAE: 1/128</p>	<p>hospitalized with pneumonia 28 days after the first vaccination. The event was deemed unlikely related to the vaccine.</p> <ul style="list-style-type: none"> <li>All of the rate differences were significantly below the allowed 10% increase in reactogenicity for the full dose (<math>p &lt; 0.001</math> for infant and combined analyses, <math>p &lt; .005</math> for toddlers).</li> <li>This randomized controlled trial in infants and toddlers shows that compared with 0.25-mL half-dosing, administration of 2 full 0.5-mL doses of trivalent inactivated influenza vaccine can increase antibody response without increasing reactogenicity in previously unimmunized infants aged 6 to 11 months.</li> </ul>
<p>Langley, 2012 [RCT]<sup>7</sup></p> <p><i>Infants/Toddlers (6-35 months)</i></p>	<p>Fluviral F1 (Sanofi-Pasteur), 7.5-<math>\mu</math>g/strain [1 x 0.25 mL dose (Intramuscularly in the anterolateral part of the thigh (if the participant was less than 12 months) or in the deltoid region of the arm)]</p> <p><i>A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (an A/Brisbane/10/2007 [H3N2]-like virus), and B/Florida/4/2006</i></p>	<p><b>Reactogenicity – injection site</b> <i>Pain</i> (NR): 45/164 <i>Redness</i> (NR): 49/164 <i>Swelling</i> (NR): 22/164</p> <p><b>Reactogenicity – systemic</b> <i>Drowsiness</i> (NR) – 44/164 <i>Fever</i> (NR) – 10/164 <i>Irritability</i> (NR) – 62/164 <i>Loss of appetite</i> (NR) – 37/164</p> <p><b>Adverse events</b> SAE: 1/164</p>	<ul style="list-style-type: none"> <li>Fluviral F1 group had 1 case of pneumonia resolved</li> <li>Fluviral F2 group had 1 case of bronchial hyper-reactivity in resolving stage</li> <li>The 0.5-mL dose of the study vaccine, when administered to children aged 6–35 months, resulted in a modest but not statistically significant improvement in</li> </ul>

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety <i>Outcome</i> (definition): n/N (unless otherwise indicated)	Conclusions
	<p>Fluviral F2 (Sanofi-Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose (Intramuscularly in the anterolateral part of the thigh (if the subject was less than 12 months) or in the deltoid region of the arm)]</p> <p><i>A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (an A/Brisbane/10/2007 [H3N2]-like virus), and B/Florida/4/2006</i></p> <p>Vaxigrip (Sanofi-Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose (Intramuscularly in the anterolateral part of the thigh (if the participant was less than 12 months) or in the deltoid region of the arm)]</p> <p><i>A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (an A/Brisbane/10/2007 [H3N2]-like virus), and B/Florida/4/2006</i></p>	<p><i>Unsolicted adverse events</i> (NR): 108/164 <i>Medically attended events</i> (NR): 52/164</p> <p><b>Reactogenicity – injection site</b> <i>Pain</i> (NR): 55/167 <i>Redness</i> (NR): 54/167 <i>Swelling</i> (NR): 24/167</p> <p><b>Reactogenicity – systemic</b> <i>Drowsiness</i> (NR) – 52/167 <i>Fever</i> (NR) – 6/167 <i>Irritability</i> (NR) – 69/167 <i>Loss of appetite</i> (NR) – 43/167</p> <p><b>Adverse events</b> SAE: 1/167 <i>Unsolicted adverse events</i> (NR): 112/167 <i>Medically attended events</i> (NR): 40/167</p> <p><b>Reactogenicity – injection site</b> <i>Pain</i> (NR): 17/43 <i>Redness</i> (NR): 13/43 <i>Swelling</i> (NR): 5/43</p> <p><b>Reactogenicity – systemic</b> <i>Drowsiness</i> (NR) – 11/43 <i>Fever</i> (NR) – 2/43 <i>Irritability</i> (NR) – 15/43 <i>Loss of appetite</i> (NR) – 9/43</p> <p><b>Adverse events</b> SAE: NR/43 <i>Unsolicted adverse events</i> (NR): 24/43 <i>Medically attended events</i> (NR): 9/43</p>	<p>immunogenicity with clinically similar safety and reactogenicity compared with the 0.25-mL dose.</p>
<p>Pavia-Ruz, 2013 [RCT]<sup>8</sup></p> <p><i>Infants/ Toddlers</i></p>	<p>Fluarix (GSK), <b>15-µg/strain</b> [1 x 0.5mL dose (intramuscular injection into the right deltoid muscle or anterolateral thigh)]</p>	<p><b>Reactogenicity – injection site</b> <i>Any injection site reactions</i><sup>9</sup>: 514/1086 <i>Pain</i>: 406/1086 <i>Redness</i>: 249/1086 <i>Swelling</i>: 170/1086</p>	<ul style="list-style-type: none"> <li>The reactogenicity and safety profile of the study vaccine did not appear to be affected by doubling the dose.</li> </ul>



Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety Outcome (definition): n/N (unless otherwise indicated)	Conclusions
(6-35 months)	A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2) and B/Brisbane/3/2007	<b>Reactogenicity – systemic</b> Any general reactions <sup>10</sup> : 575/1086 Drowsiness: 317/1086 Fever: 69/1086 Irritability: 387/1086 Loss of appetite: 273/1086  <b>Adverse events</b> Any AE: 729/1086 SAE: 29/1086	<ul style="list-style-type: none"> <li>One subject in the Flu-15µg group had two SAEs, (apnea and cyanosis) which were considered by the investigator to be possibly related to vaccination. The participant was hospitalized and the events resolved on the same day as they occurred.</li> </ul>
	Fluarix (GSK), <b>7.5-µg/strain</b> [1 x 0.25 mL dose (intramuscular injection into the right deltoid muscle or anterolateral thigh)]  A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2) and B/Brisbane/3/2007	<b>Reactogenicity – injection site</b> Any injection site reactions <sup>9</sup> : 492/1081 Pain: 403/1081 Redness: 259/1081 Swelling: 152/1081  <b>Reactogenicity – systemic</b> Any general reactions <sup>10</sup> : 598/1081 Drowsiness: 293/1081 Fever: 67/1081 Irritability: 386/1081 Loss of appetite: 281/1081  <b>Adverse events</b> Any AE: 724/1081 SAE: 35/1081	
	Fluzone (Sanofi-Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose (intramuscular injection into the right deltoid muscle or anterolateral thigh)]  A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2) and B/Florida/4/2006	<b>Reactogenicity – injection site</b> Any injection site reactions <sup>9</sup> : 467/1090  Pain: 363/1090 Redness: 253/1090 Swelling: 129/1090  <b>Reactogenicity – systemic</b> Any general reactions <sup>10</sup> : 592/1090 Drowsiness: 298/1090 Irritability: 375/1090 Fever: 72/1090 Loss of appetite: 270/1090	

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety Outcome (definition): n/N (unless otherwise indicated)	Conclusions
		<b>Adverse events</b> Any AE: 722/1090 SAE: 31/1090	
Halasa, 2015 [RCT] <sup>9</sup>  Infants/Toddlers (6-35 months)	Fluzone (Sanofi Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose (intramuscular)]  <i>A/California/7/09 (H1N1)-like virus, A/Perth/16/2009 (H3N2)-like virus, and B/Brisbane/60/2008-like virus</i>	<b>Reactogenicity</b> <i>Redness at injection site: 8/48</i> <i>Fever (temperature &gt;39°C after the first dose): 7/80</i>	<ul style="list-style-type: none"> <li>No significant differences between the full-dose or half-dose groups for either the fully primed or naive cohorts for systemic reactions or local reactions when both seasons were combined.</li> <li>The only significant difference in the 2011–2012 season was that 8 of 48 (16.7%) participants in the half-dose group compared with 32 of 96 (33.3%) in the full-dose group had increased redness at the injection site (P &lt; .05).</li> <li>No significant differences between the groups in unsolicited AEs, serious adverse events (SAEs), or onset of chronic medical conditions between the dose groups in either the naive or fully primed cohorts, and none of the SAEs were deemed related to the vaccine.</li> </ul>
	Fluzone (Sanofi Pasteur), <b>15-µg/strain</b> [1 x 0.5 mL dose (intramuscular)]  <i>A/California/7/09 (H1N1)-like virus, A/Perth/16/2009 (H3N2)-like virus, and B/Brisbane/60/2008-like virus</i>	<b>Reactogenicity</b> <i>Redness at injection site: 32/96</i> <i>Fever (temperature &gt;39°C after the first dose): 19/161</i>	
Phung, 2016 [RCT] <sup>10</sup>  Infants/Toddlers (6-35 months)	FLUAD (NR), <b>NR [1 x 0.5mL dose</b> (Intramuscular injection)]  <i>A/H1N1, A/H3N2, Strain B</i>  FLUAD (NR), <b>NR [1 x 0.25 mL dose</b> (Intramuscular injection)]	<b>Reactogenicity</b> <i>Any local reaction<sup>11</sup>: 45/61</i> <i>Any systemic reaction<sup>12</sup>: 36/61</i>  <b>Adverse events</b> SAE (based on MedDRA v 17.1 definition): 2/61  <b>Reactogenicity</b> <i>Any local reaction<sup>11</sup>: 63/75</i>	

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety Outcome (definition): n/N (unless otherwise indicated)	Conclusions
	A/H1N1, A/H3N2, Strain B	Any systemic reaction <sup>12</sup> : 42/75  <b>Adverse events</b> SAE (based on MedDRA v 17.1 definition): 2/75	
	Agrippal S1 (NR), NR [1 x 0.5mL dose (Intramuscular injection)]  A/H1N1, A/H3N2, Strain B	<b>Reactogenicity</b> Any local reaction <sup>11</sup> : 42/51 Any systemic reaction <sup>12</sup> : 24/51  <b>Adverse events</b> SAE (based on MedDRA v 17.1 definition): 0/51	
	Agrippal S1 (NR), NR [1 x 0.25mL dose (Intramuscular injection)] A/H1N1, A/H3N2, Strain B	<b>Reactogenicity</b> Any local reaction <sup>11</sup> : 6/10 Any systemic reaction <sup>12</sup> : 5/10  <b>Adverse events</b> SAE (based on MedDRA v 17.1): 0/10	
Jain, 2017 [RCT] <sup>11</sup>  Infants/ Toddlers (6-35 months)	Flulaval Quadrivalent (GSK), <b>15-µg/strain</b> [1 x 0.5mL dose (intramuscular in deltoid region)]  A/California/7/2009 (A/H1N1), A/Texas/50/2012 (A/H3N2), B/Brisbane/60/2008 (B/Victoria), and B/Massachusetts/2/2012 (B/Yamagata)	<b>Reactogenicity – injection site (within 7 days)</b> Pain: 44.0% Redness: 1.4% Swelling: 1.0%  <b>Reactogenicity – systemic (within 7 days)</b> Drowsiness: 40.6% Fever (>=38.0C): 7.9% Irritability/fussiness: 54.4% Loss of appetite: 33.7%  <b>Adverse events</b> Any AE: 45.5% Vaccine-related AE: 5.9% Any SAE <sup>13</sup> : 1.8% Febrile seizures: 0.4% Medically attended event <sup>14</sup> : 60.2%	<ul style="list-style-type: none"> <li>▪ None of the febrile seizures or the SAEs were considered by the investigator to be related to vaccination</li> <li>▪ Double-dose IIV4 may improve protection against influenza B in some young children and simplifies annual influenza vaccination by allowing the same vaccine dose to be used for all eligible children and adults.</li> </ul>
	Fluzone Quadrivalent (Sanofi Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose (intramuscular in deltoid region)]	<b>Reactogenicity – injection site (within 7 days)</b> Pain: 40.1% Redness: 1.4% Swelling: 0.4%  <b>Reactogenicity – systemic (within 7 days)</b>	

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety Outcome (definition): n/N (unless otherwise indicated)	Conclusions
	A/California/7/2009 (A/H1N1), A/Texas/50/2012 (A/H3N2), B/Brisbane/60/2008 (B/Victoria), and B/Massachusetts/2/2012 (B/Yamagata)	<p>Drowsiness: 40.9% Fever (<math>\geq 38.0^{\circ}\text{C}</math>): 7.5% Irritability/fussiness: 50.5% Loss of appetite: 33.4%</p> <p><b>Adverse events</b> Any AE: 44.1% Vaccine-related AE: 5.8% Any SAE<sup>13</sup>: 1.7% Febrile seizures: 0.3% Medically attended event<sup>14</sup>: 59.1%</p>	
Ojeda. 2019 [RCT] <sup>12</sup>  Infants/ Toddlers and Children (6 months – 17 years)	<p>Vaxigrip Tetra (Sanofi Pasteur) – PFS, 15-<math>\mu\text{g}</math>/strain [1 x 0.5mL dose (intramuscular or deep subcutaneous injection)]</p> <p>A/Michigan/45/2015 (H1N1)pdm09-like virus, A/Hong Kong/4801/2014 (H3N2)-like virus, /Brisbane/60/2008-like virus (B/Victoria lineage), and B/Phuket/3073/2013 (B/Yamagata lineage)</p> <p>Vaxigrip Tetra (Sanofi Pasteur) - MDV, 15-<math>\mu\text{g}</math>/strain [1 x 0.5mL dose (intramuscular or deep subcutaneous injection)]</p> <p>A/Michigan/45/2015 (H1N1)pdm09-like virus, A/Hong Kong/4801/2014 (H3N2)-like virus, /Brisbane/60/2008-like virus (B/Victoria lineage), and B/Phuket/3073/2013 (B/Yamagata lineage)</p>	<p><b>Reactogenicity, N=142</b> Any injection-site reaction (solicited within 7 days): 26 (6-35mo), 16 (3-8yr), 42 (9-7yr) Any systemic reaction (solicited within 7 days): 25 (6-35mo), 15 (3-8yr), 35 (9-7yr)</p> <p><b>Adverse events, N=147</b> AE (immediate unsolicited): 1 (9-17 years) Non-serious AE: 25 (6-35mo), 9 (3-8yr), 8 (9-7yr) Vaccine-related non-serious AE: 1 (9-17 years) AE leading to study discontinuation: 0 SAE: 0</p> <p><b>Reactogenicity, N=139</b> Any injection-site reaction(solicited within 7 days): 27 (6-35mo), 16 (3-8yr), 26 (9-7yr) Any systemic reaction(solicited within 7 days): 33 (6-35mo), 13 (3-8yr), 30 (9-7yr)</p> <p><b>Adverse events, N=150</b> AE (immediate unsolicited): 0 Non-serious AE: 31 (6-35mo), 14 (3-8yr), 5 (9-7yr) Vaccine-related non-serious AE: 0 AE leading to study discontinuation: 0 SAE: 0</p>	<ul style="list-style-type: none"> <li>▪ Solicited reactions were mostly grade 1 (mild) in intensity and resolved within 3 days.</li> <li>▪ Solicited systemic reactions were reported in more infants aged 6 – 35 months in the MDV group than in the PFS group however, because the 95% CIs were overlapping, this was not thought clinically significant.</li> <li>▪ None of these unsolicited AEs were considered related to a study vaccine by the investigators.</li> <li>▪ There were no differences in reactogenicity or safety between the two vaccine formats. These results showed that the MDV format of QIV was as safe and immunogenic as the PFS format in infants, children, and adolescents. These findings support the use of MDV QIV</li> </ul>

Author, Year; [Study design] Population	Treatment arms Brand name (manufacturer), HA/strain [dosing (administration)] Included strains	Effectiveness and Safety <i>Outcome</i> (definition): n/N (unless otherwise indicated)	Conclusions
			as a resource-saving alternative for seasonal influenza vaccination.
Robertson, 2019 [RCT] <sup>13</sup>  Infants/ Toddlers (6-35 months)	<p>Fluzone Quadrivalent (Sanofi Pasteur), <b>15-µg/strain</b> [1 x 0.5mL dose (intramuscular single-dose syringes in deltoid of arm)]</p> <p><i>A/California/07/2009 X-179A (H1N1), A/Hong Kong/4801/2014 X-263B (H3N2), B/Brisbane/60/2008 (Victoria lineage), B/Phuket/3073/2013 (Yamagata lineage)</i></p> <p>Fluzone Quadrivalent (Sanofi Pasteur), <b>7.5-µg/strain</b> [1 x 0.25 mL dose (intramuscular single-dose syringes in deltoid of arm)]</p> <p><i>A/California/07/2009 X-179A (H1N1), A/Hong Kong/4801/2014 X-263B (H3N2), B/Brisbane/60/2008 (Victoria lineage), B/Phuket/3073/2013 (Yamagata lineage)</i></p>	<p><b>Reactogenicity</b> <i>Any injection-site reaction</i><sup>15</sup>: 533/939 <i>Any systemic reaction</i><sup>16</sup>: 561/941</p> <p><b>Adverse events</b> <i>Vaccine-related AE</i> (immediate within 30 mins): 0/992 <i>Vaccine-related AE</i> (within 28 days): 30/992 <i>AE leading to study discontinuation</i>: 0/992 <i>SAE</i>: 5/992</p> <p><b>Reactogenicity</b> <i>Any injection-site reaction</i><sup>15</sup>: 480/909 <i>Any systemic reaction</i><sup>16</sup>: 533/909</p> <p><b>Adverse events</b> <i>Vaccine-related AE</i> (unsolicited within 30 mins): 1/949 <i>Vaccine-related AE</i> (unsolicited within 28 days): 29/949 <i>AE leading to study discontinuation</i>: 3/949 <i>SAE</i>: 5/949</p>	<ul style="list-style-type: none"> <li>▪ Proportions of participants reporting solicited injection-site reactions, solicited systemic reactions, vaccine-related unsolicited AEs were similar for the full- and half-dose groups</li> <li>▪ None of the AEs leading to study discontinuation or the SAEs were considered related to vaccination</li> <li>▪ A single AE of special interest (chronic urticaria first appearing 3 days post-vaccination and continuing for &gt;6 weeks) was considered by the investigator to be related to vaccination</li> <li>▪ In children 6–35 months of age, a full dose of IIV4 was immunogenic and had a safety profile comparable to that of a half dose with no new safety concerns observed.</li> </ul>

**Abbreviations:** AE – adverse events, ID – intradermal; ILI – influenza-like illness; IM – intramuscular; MDV – multi-dose vials, n – number of people with condition, N – sample size of treatment arm, NR – not reported, PFS – prefilled syringe, SAE – serious adverse events

<sup>1</sup> Defined as mild (easily tolerated), moderate (interferes with normal behaviour or activities), severe (incapacitating, unable to perform usual activities, may require medical attention)

<sup>2</sup> Present at or near the approximate point of needle entry; small <2.5cm, medium >2.5cm to <5cm, large >5cm

<sup>3</sup> Oral temperature >37.5 C; mild >37.5 to 38 C, moderate >38.1 to 39 C, severe >39.1 C

<sup>4</sup> Grade I reactions defined as “present but easily tolerated” for fatigue, muscle ache, headache, itching or pain at injection site; oral temperature >=38 and <39 degrees Celsius; some limitation to arm motion due to stiffness or discomfort but easily tolerated; redness or swelling >= 8cm

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3 <sup>5</sup> Grade II/III reactions defined as “interferes with normal activity” to “severe and incapacitating” for fatigue, muscle ache, headache, itching or pain at  
4 injection site; oral temperature  $\geq 39$  degrees Celsius; limitation to arm motion due to stiffness or discomfort that interferes with normal activity; redness  
5 or swelling  $> 8$ cm

6 <sup>6</sup> Defined as serious adverse events resulting in hospitalization

7 <sup>7</sup> Solicited local reactions included ecchymosis, erythema, induration, swelling, and tenderness at injection site

8 <sup>8</sup> Solicited systemic reactions included sleepiness, diarrhea, vomiting, irritability, change in eating habits, shivering, and unusual crying

9 <sup>9</sup> Included injection site reactions of Grade 1, “minor reaction to touch”, Grade 2, “cries/protests on touch”, and Grade 3, “cries when limb  
10 moved/spontaneously painful”

11 <sup>10</sup> Included systemic reactions of Grade 1, “no effect on normal activity”, Grade 2, “interferes with normal activity”, and Grade 3, “prevents normal activity”

12 <sup>11</sup> Included injection site ecchymosis, injection site erythema, injection site induration, injection site swelling, tenderness, injection site pain

13 <sup>12</sup> Included change in eating habits, sleepiness, unusual crying, irritability, vomiting, diarrhea, chills/shivering, malaise, myalgia, arthralgia, headache,  
14 fatigue, fever ( $>37.3$  C)

15 <sup>13</sup> Defined serious adverse events as any untoward medical occurrence that results in death, is life-threatening, requires/prolongs hospitalization, or  
16 results in disability or incapacity during entire study period

17 <sup>14</sup> Defined as hospitalization, emergency room visit, and/or medical practitioner visit during entire study period

18 <sup>15</sup> Included tenderness, redness and/or swelling solicited within 7 days

19 <sup>16</sup> Included fever, vomiting, abnormal crying, drowsiness, loss of appetite, and/or irritability solicited within 7 days  
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## PRISMA ScR checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
<b>TITLE</b>			
<b>Title</b>	1	Identify the report as a scoping review.	1
<b>ABSTRACT</b>			
<b>Structured summary</b>	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2
<b>INTRODUCTION</b>			
<b>Rationale</b>	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	4
<b>Objectives</b>	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	4
<b>METHODS</b>			
<b>Protocol and registration</b>	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	4
<b>Eligibility criteria</b>	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	5-6
<b>Information sources*</b>	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	5
<b>Search</b>	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Appendix 1-3
<b>Selection of sources of evidence†</b>	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	6
<b>Data charting process‡</b>	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	6
<b>Data items</b>	11	List and define all variables for which data were sought and any assumptions and simplifications made.	6

<b>Critical appraisal of individual sources of evidence<sup>§</sup></b>	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	N/A
<b>Synthesis of results</b>	13	Describe the methods of handling and summarizing the data that were charted.	6
<b>RESULTS</b>			
<b>Selection of sources of evidence</b>	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	6
<b>Characteristics of sources of evidence</b>	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	7, Appendix 6-7
<b>Critical appraisal within sources of evidence</b>	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	N/A
<b>Results of individual sources of evidence</b>	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	8-25
<b>Synthesis of results</b>	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	25
<b>DISCUSSION</b>			
<b>Summary of evidence</b>	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	25-27
<b>Limitations</b>	20	Discuss the limitations of the scoping review process.	26
<b>Conclusions</b>	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	27
<b>FUNDING</b>			
<b>Funding</b>	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	28
<p>           JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.         </p> <p>           * Where sources of evidence (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.         </p> <p>           † A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with information sources (see first footnote).         </p> <p>           ‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.         </p> <p>           § The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).         </p>			