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

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ABSTRACT

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

Methods Comprehensive literature searches were executed in MEDLINE, Embase and the Cochrane library. The grey literature was searched via international clinical trial registries for relevant studies published in English in the last 20 years. We included studies in healthy humans of any age that used any dose-sparing strategy to administer intramuscular seasonal influenza vaccines. Title/abstract and full-text screening were carried out by pairs of reviewers independently. Data extraction was conducted by a single reviewer and verified by a second reviewer. Our outcomes were influenza infections, intensive care unit admission, pneumonia, hospitalisations, adverse events and mortality. Results were summarised descriptively.

Results A total of 13 studies with 10 351 participants were included in the review and all studies were randomised controlled trials (RCTs) conducted between 2006 and 2019. The most common interventions were the trivalent influenza vaccine (n=10), followed by the quadrivalent influenza vaccine (n=4). Nine studies included infants/toddlers 6–36 months old and one of these studies also included children and adolescents. In these nine studies, no clinical effectiveness outcomes were reported. Of the four adult studies (≥18 years), two studies reported on effectiveness outcomes, however, only one RCT reported on laboratory-confirmed influenza.

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

Strengths and limitations of this study

- ► This rapid scoping review was conducted within a 6-week timeline and the methods were tailored to provide results to the stakeholders within 4 weeks.
- ► We did not restrict the search dates and study screening was completed in independently by two reviewers.
- ► We limited the selection of studies to those published in the English language, and data extraction was conducted by one abstractor and one verifier.
- ► Twelve dose-sparing randomised control trials were not included in the review because they did not include vaccine interventions that were deemed of interest to the stakeholders and/or did not provide sufficient data.

BACKGROUND

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

Fractional dosing, or dose-sparing, strategies are those where less than the standard dose of haemagglutinin (HA) antigen, and thus less volume of vaccine, is administered, increasing the overall number of influenza vaccine doses available. In Canada, influenza vaccines are currently authorised for IM administration only, apart from the live-attenuated influenza vaccine, which is administered intranasally.[2] Standard dose influenza vaccines contain 15 µg of HA per strain and are delivered in 0.5 mL volume. Therefore, the total amount of HA in

standard dose trivalent vaccines is 45 µg, and the total amount of HA in standard dose quadrivalent vaccines is 60 µg.

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

METHODS

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

Protocol

The methods for this review were guided by the updated reviewer manual for scoping reviews published by JBI (https://jbi.global/) and the WHO's guide to rapid reviews.[4 5] Results are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension to Scoping Reviews.[6] A protocol for this rapid scoping review was disseminated through the Open Science Framework registry (https://osf.io/8mwz2/).

Patient and public involvement statement

No patients or the public were involved in this rapid scoping review.

Literature search

Comprehensive literature searches were developed and executed by an experienced librarian in Ovid MEDLINE (online supplemental appendix 1, EMBASE using the OVID interface (online supplemental appendix 2), and the Cochrane library between 1946 and May 2020 (online supplemental appendix 3). The literature search was peer reviewed by a second librarian using the PRESS checklist (https://www.cadth.ca/resources/finding-evidence/press). The grey (ie, difficult to locate or unpublished) literature was searched via international clinical trial registries (ie, clinicaltrials.gov, European Union clinical trial register). References of relevant systematic reviews and included studies were also scanned.

Eligibility criteria

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

- Population: Healthy humans of any age. Immunocompromised populations and animal studies were excluded. Examples of persons with weakened immune systems include those with HIV/AIDS; cancer and transplant patients who are taking certain immunosuppressive drugs; and those with inherited diseases that affect the immune system (eg, congenital agammaglobulinaemia, congenital IgA deficiency).[7]
- Intervention: Any dose-sparing strategy used to administer IM seasonal influenza vaccines (eligible vaccines listed in online supplemental appendix 4). Eligible strategies included, but were not limited to, administrating less than the standard 15 ug HA antigen using multidose vials (MDV), half dosing or preformulated products with reduced antigen quantity, or with revised vaccine dose schedules. Any studies examining monovalent pandemic vaccines, specialty/experimental vaccines (eg, high dose), whole virus vaccines or other routes of administration (eg, intranasal, intradermal (ID)) were not eligible. Only vaccine products approved for use in Canada or equivalent formulations approved for use in other countries were eligible for inclusion. Concomitant administration with other vaccine products were included only if administered to both the intervention and the comparator groups.
- Comparator: Any of the interventions listed above, no intervention or placebo.
- Outcomes: Lboratory-confirmed influenza infection (primary outcome), influenza-like illness or clinical/symptomatic diagnosis of influenza, hospitalisation, intensive care unit (ICU) admission, pneumonia, mortality and adverse events (local/systemic reactogenicity, vascular-related, serious). Reactogenicity represents the physical manifestation of the inflammatory response to vaccination, and can include injection-site pain, redness, swelling or induration at the injection site, as well as systemic symptoms, such as fever, myalgia or headache.[8] Immunogenicity outcomes were not abstracted, but these studies were flagged for NACI.
- Study designs: Randomised controlled trials (RCTs), non-randomised studies (eg, quasi-RCTs, non-randomised trials, interrupted time series, controlled before after) and observational studies (eg, cohort, case control) were included. Studies must have had a control or comparator group in order to be eligible for inclusion and as such, cross-sectional, case series, case reports and qualitative studies were excluded.
- Publication status: We included full text and abstracts if they included data on safety or effectiveness.

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

Study selection

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

Data extraction

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

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

Risk of bias assessment

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

Synthesis

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

RESULTS

Literature search

We screened 2378 titles and abstracts from our database search and an additional 13 citations located through searching the grey literature and scanning references. Of these, 144 potentially relevant full-text articles were screened for eligibility (figure 1). Twelve studies that assessed dose-sparing strategies were excluded during full-text screening because the vaccine under study was not of interest or unclearly reported. We contacted authors of these 12 unclear studies and received 1 response confirming the vaccine was not of interest (see list of excluded studies in online supplemental appendix 5). Subsequently, 13 RCTs were included; 5 trial protocols were found and were denoted as duplicate/companion reports. No non-randomised or observational studies were found that fulfilled the eligibility criteria.

Study characteristics

Table 1 summarises the characteristics of the 13 RCTs published between 2006 and 2019 and and conducted mainly in the USA, followed by Mexico, Canada and Finland. The majority of the studies evaluated trivalent vaccines (10/13 (77%)) and most were conducted in the 6–36 months old paediatric population (9/13 (69%)). Almost all studies reported on reactogenicity and/or other adverse events, but only two studies reported on the effectiveness of our outcomes of interest (ie, laboratory-confirmed influenza and influenza-like illness).

Full study and patient characteristic details for each study are reported in online supplemental appendix 6 and treatment and outcome details in online supplemental appendix 7.

RCTs in healthy children (<18 years old)

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.

Safety outcomes

Trivalent influenza vaccines

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

The objective of three of the included RCTs was to examine the impact of administering the full adult dose of 15 µg/strain vaccines compared with the usual children's dose of 7.5 µg/strain in infants and toddlers.[12–14] A multicentre RCT was conducted in Canada assessing the safety of full-dose Fluviral TIV (15 µg/strain) compared with the half-dose (7.5 µg/strain) and an active comparator Vaxigrip (7.5 µg/strain).[12] Compared with the half-dose, the full-dose vaccine resulted in clinically similar reactogenicity

and safety. A similar three-arm RCT to assess the use of Fluarix at two different dose levels (7.5 µg/strain and 15 µg/strain) compared with an established control vaccine Fluzone (7.5 µg/strain) also found the reactogenicity and safety profile of Fluarix did not appear to be affected by doubling the dose, but one participant in the 15 µg group had two serious adverse events (apnea and cyanosis) that were considered by the investigator to be possibly related to vaccination.[13] A third multicentre RCT compared the 15 µg/strain formulation to the 7.5 µg/strain formulation of Fluzone (Sanofi Pasteur) administered to young children across multiple influenza seasons.[14] This study also found no statistically significant differences between the full-dose or half-dose groups for systemic reactions, local reactions or adverse events when both seasons were combined; however, in the 2011–2012 season, 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 ($p<0.05$).

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

Quadrivalent influenza vaccines

Four of the included RCTs evaluated QIV in children.[10 16–18] All of the studies reported reactogenicity outcomes and other adverse events. Della Cioppa *et al* RCT reported both TIV and QIV vaccines and the results are reported above.[10] Two studies compared

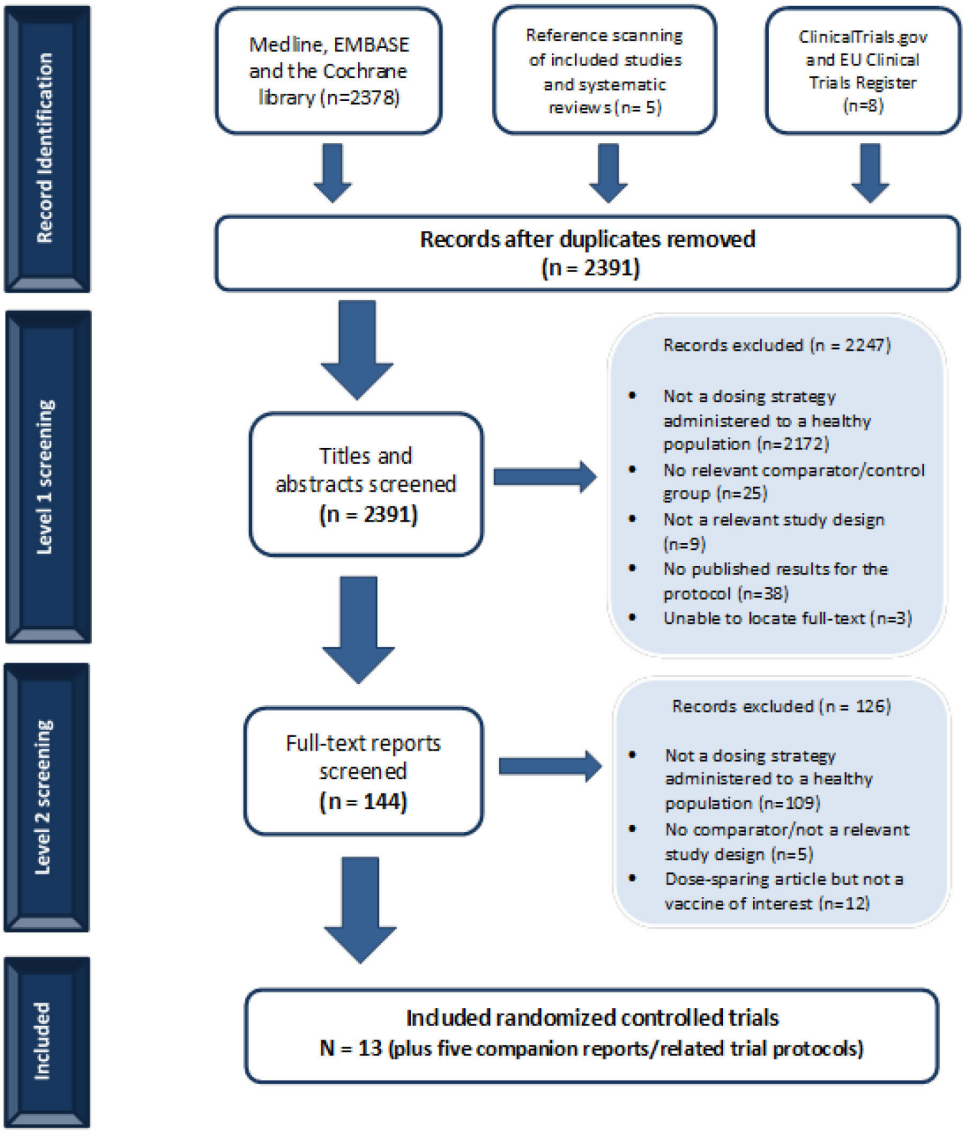

Figure 1 Flow chart of studies included in the review. Study flow diagram.

full-dose QIV to paediatric 7.5 µg/strain Fluzone. In the first RCT, full dose Fluzone had a similar safety profile to half-dose Fluzone with a single adverse event being attributed to the study vaccine.[18] Similarly, the second study found that full-dose Flulaval may improve protection against influenza in some young children when compared with low-dose Fluzone, and in this RCT, none of the adverse events were considered to be study related as reported by the investigator.[16] The final trial evaluated Vaxigrip Tetra (15 µg/strain) administered to children and adolescents in two different formats.[17] Vaxigrip administered as a single dose using a prefilled syringe (PFS) was compared with a 10-dose MDV. Systemic reactions were reported in more infants aged 6–35 months in the MDV group than in the PFS group; however, this difference was not clinically significant. The authors concluded that there was no difference in reactogenicity or safety between the two vaccine formats in infants, children and adolescents.

RCTs in healthy adults (≥18 years old)

One RCT included healthy adults over 18 years, two studies included healthy adults from 18 to 45 and 18–65 years old, and one study included older healthy adults (≥65 years) (table 3). Two studies reported on effectiveness outcomes and three on reactogenicity and other adverse events. All four RCTs evaluated Fluzone QIV.

Effectiveness outcomes

Two of the included RCTs that examined the same vaccine (Fluzone manufactured by Aventis Pasteur) in healthy adult populations reported effectiveness outcomes. Only one study by Kramer *et al* included lab-confirmed influenza infection,[19] two reported influenza like illness,[19 20] and one reported hospitalisations or emergency room visits after vaccination.[20] The RCT by Kramer *et al* found that 3.6% of participants receiving a 15 µg/strain dose of vaccine reported influenza like illness compared with 6.8% of participants that received a 7.5 µg/strain dose.[19] However, only one participant that received the full dose 15 µg/strain was confirmed via laboratory analysis to have influenza, and no patients in the half-dose arm got laboratory confirmation. The authors concluded that half-dose and full-dose vaccinations appear to be similarly effective for influenza like illness and similar symptom surveys between both groups but acknowledge that further studies examining immunogenicity are needed to confirm.

A similar RCT by Engler *et al* that compared a 15 µg/strain dose of Fluzone vaccine to a 7.5 µg/strain dose found equal proportions of participants reporting influenza like illness (9.7% vs 9.9%) and hospitalisations or emergency room visits (0.3% vs 0.2%).[20] The authors found the relative risk of medical visits or hospitalisations between both groups was the same even when adjusting for age and that age, sex, nor dose had an influence on the severity of influenza like illness symptoms.

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)
Multicentre or single site	Multicentre	8 (61.5)
	Single centre	2 (15.4)
Countries of conduct*	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*†	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*‡	Trivalent influenza vaccine (TIV)	10 (76.9)
	Quadrivalent influenza vaccine (QIV)	4 (30.8)
Outcomes*	Effectiveness	2 (15.4)
	Local and systemic reactogenicity	12 (92.3)
	Adverse events	10 (76.9)

*Each study can fit into more than one category so the total percentage will not add up to 100%.
†One study includes both infants/toddlers and children, and another includes both adults and seniors.
‡One study includes both TIV and QIV arms.

Safety outcomes

Three of the included studies in adult populations reported adverse events that occurred during the trial while one RCT indicated that no adverse events were recorded for the duration of their trial.[19–22] All three studies reporting adverse events compared different doses of Fluzone vaccine including 3 µg, 6 µg, 7.5 µg, 9 µg and 15 µg per strain doses.

Two of the studies were carried out in healthy adult populations and one RCT was conducted in older healthy adults (>60 years of age).[20–22] One RCT found that joint or muscle pain following vaccination was statistically significantly higher in the full dose (15 µg) group compared with the half-dose (7.5 µg) group and that while injection site pain initially appeared to be statistically significantly

Table 2 Nine RCTs conducted in children (6 months to 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 immunised)	ITT sample size	Outcome	Author reported conclusions
Trivalent and quadrivalent influenza vaccines (TIV/QIV)									
Della Cioppa, 2011[10]	October 2008–March 2009 Belgium	NR—TIV, 7.5 µg/strain (2×0.25 mL dose)	20.0 months (7.0)	6 to <36 months	43.5	NR	25	Local and systemic reactogenicity AEs	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, 15 µg/strain (2×0.5 mL dose)	15.0 months (8.8)	6 to <36 months	43.5	NR	22		
		NR—QIV, 7.5 µg/strain (2×0.25 mL dose)	18.0 months (8.9)	6 to <36 months	43.5	NR	25		
		NR—QIV, 15 µg/strain (2×0.5 mL dose)	15.2 months (7.8)	6 to <36 months	43.5	NR	28		
		Vaxigrip (Sanofi Pasteur), 7.5 µg/strain (2×0.25 mL dose)	16.1 months (8.5)	6 to <36 months	43.5	NR	26		
Skowronski, 2011[11]	September 2008–December 2008 Canada	Vaxigrip (Sanofi-Pasteur), 15 µg/strain (2×0.5 mL dose)	13.2 months (5.1)	6–23 months	53.2	0	124	Local and systemic reactogenicity AEs	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 AE was reported: a toddler in the half dose group was hospitalised with pneumonia 28 days after the first vaccination. The event was deemed unlikely related to the vaccine. 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 unimmunised infants aged 6 to 11 months.
		Vaxigrip (Sanofi-Pasteur), 15 µg/strain (2×0.25 mL dose)	12.8 months (5.0)	6–23 months	53.2	0	128		
Langley, 2012[12]	November 2008–August 2009 Canada	Fluviral F1 (Sanofi-Pasteur), 7.5 µg/strain (1×0.25 mL dose)	18.2 months (9.06)	6–35 months	47.9	42.6	164	Local and Systemic reactogenicity AEs	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 with clinically similar safety and reactogenicity compared with the 0.25 mL dose.
		Fluviral F2 (Sanofi-Pasteur), 15 µg/strain (1×0.5 mL dose)	17.5 months (8.27)	6–35 months	47.9	42.6	167		
		Vaxigrip (Sanofi-Pasteur), 7.5 µg/strain (1×0.25 mL dose)	17.0 months (8.33)	6–35 months	47.9	42.6	43		
Pavia-Ruz, 2013[13]	October 2008–March 2009 Hong Kong, Mexico, Taiwan, Thailand and the USA	Fluarix (GSK), 15 µg/strain (1×0.5 mL dose)	21.2 months (8.37)	6–35 months	51	30.1	1018	Local and systemic reactogenicity AEs	The reactogenicity and safety profile of the study vaccine did not appear to be affected by doubling the dose. One participant in the Flu-15 µg group had two SAEs, (apnea and cyanosis) which were considered by the investigator to be possibly related to vaccination. The subject was hospitalised and the events resolved on the same day as they occurred.
		Fluarix (GSK), 7.5 µg/strain (1×0.25 mL dose)	21.2 months (8.03)	6–35 months	51	30.1	1018		
		Fluzone (Sanofi-Pasteur), 7.5 µg/strain (1×0.25 mL dose)	21.1 months (8.20)	6–35 months	51	30.1	1031		
Halasa, 2015[14]	2010–2012 USA	Fluzone (Sanofi Pasteur), 7.5 µg/strain (1×0.25 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 redness at the injection site ($p<0.05$). 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.
		Fluzone (Sanofi Pasteur), 15 µg/strain (1×0.5 mL dose)	14.5				163		

Continued

Table 2 Continued

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 immunised)	ITT sample size	Outcome	Author reported conclusions
Phung, 2016[26]	September 2010–January 2011 Finland	FLUAD (NR), NR (**1×0.5 mL dose**)	68.7 months (18)	6–35 months	55.8	85.7	60	Local and systemic reactogenicity AEs	Trial protocol with no author conclusions.
		FLUAD (NR), NR (1×0.25 mL dose)	60.4 months (23.2)	6–35 months	55.8	85.7	75		
		Agrippal S1 (NR), NR (**1×0.5 mL dose**)	68 months (17.1)	6–35 months	55.8	85.7	51		
		Agrippal S1 (NR), NR (**1×0.25 mL 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 (1×0.5 mL dose)	19.7 months (8.7)	6–35 months	46.9	57.5	1013	Local and systemic reactogenicity AEs	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 allowing the same vaccine dose to be used for all eligible children and adults.
		Fluzone (Sanofi Pasteur), 7.5 µg/strain (1×0.25 mL dose)	19.9 months (8.9)	6–35 months	46.9	57.5	1028		
Ojeda, 2019[17]	December 2017–January 2018 Mexico	Vaxigrip Tetra (Sanofi Pasteur) PFS 15 µg/strain (1×0.5 mL dose)	NR (6 months to 17 years)	6 months to 17 years	46.4	NR	149	Local and systemic reactogenicity AEs	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 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.
		Vaxigrip Tetra (Sanofi Pasteur) MDV 15 µg/strain (1×0.5 mL dose)	NR (6 months to 17 years)	6 months to 17 years	46.4	NR	153		
Robertson, 2019[18]	September 2016–March 2017 USA	Fluzone (Sanofi Pasteur) 15 µg/strain (1×0.5 mL dose)	20.5 months (8.55)	6–35 months	49.7	47.25	992	Local and systemic reactogenicity AEs	No significant differences between full-dose and half-dose 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.
		Fluzone (Sanofi Pasteur) 7.5 µg/strain (1×0.25 dose)	20.4 months (8.75)	6–35 months	49.7	47.25	949		

AE, adverse events; HA, haemagglutinin; ID, intradermal; IM, intramuscular; ITT, intention to treat; MDV, multidose vials; NR, not reported; PFS, prefilled dose; RCT, randomised controlled trial; SAEs, serious adverse events.

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 immunised)	ITT sample size	Relevant outcomes	Author reported conclusions
Quadrivalent influenza vaccines (QIV)									
Kramer, 2006[19]	October 2004–November 2004 USA	Fluzone (Aventis Pasteur), 15 µg/strain (1×0.5 mL dose)	NR (>18 years)	>18 years	NR	NR	222	Lab-confirmed influenza (one patient receiving the full dose) Influenza-like illness Adverse events	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), 7.5 µg/strain (1×0.25 mL dose)	NR (>18 years)	>18 years	NR	NR	222		
Engler, 2008[20]	November 2004–December 2004 USA	Fluzone (Aventis Pasteur), 15 µg/strain (1×0.5 mL dose)	NR (18–64 years)	18–64 years	43.4	0	554	Influenza-like illness Hospital/ER visits local and systemic reactogenicity adverse events	The relative risk of medical visits and hospitalisations for influenza-like illnesses were similar in the half-dose 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 immunisations. Although injection site pain was greater for full-dose versus half-dose (19.9% vs 14.4%; p=0.01), when analysed for clinically significant pain levels significant dose-dependent pain differences were not identified. Joint and/or muscle pain were significantly different (p=0.02 and p=0.03, respectively) by dose. No other adverse event differed significantly by dose.
		Fluzone (Aventis Pasteur), 7.5 µg/strain (1×0.25 mL dose)	NR (18–64 years)	18–64 years	43.4	0	556		
Belshe, 2007[21]	NR USA	Fluzone (Sanofi-Pasteur), 15 µg/strain (1×0.5 mL dose)	31.5 years (9.6)	18–49 years	71.2	0	31	Local and systemic reactogenicity	ID vaccine induced significantly more local inflammatory response than intramuscular (IM) vaccine but this did not translate into an increased immune response for ID vaccines compared with IM (primary comparison of this study was ID vs IM doses)
		Fluzone (Sanofi-Pasteur), 9 µg/strain (1×0.3 mL dose)	31.2 years (9.4)	18–49 years	71.2	0	32		
		Fluzone (Sanofi-Pasteur), 6 µg/strain (1×0.2 mL dose)	30.1 years (10.3)	18–49 years	71.2	0	31		
		Fluzone (Sanofi-Pasteur), 3 µg/strain (1×0.1 mL dose)	31.9 years (10.3)	18–49 years	71.2	0	31		
Chi, 2010[22]	August 2007–2008 USA	Fluzone (Sanofi Pasteur), 15 µg/strain (1×0.5 mL dose)	75.6 years (6.8)	>65 years	17.8	94.6	65	Local and systemic reactogenicity adverse events	The two SAEs were acute coronary syndrome and appendicitis and neither were judged to be related to influenza vaccination
		Fluzone (Sanofi Pasteur), 9 µg/strain (1×0.3 mL dose)	75.2 years (7.7)	>65 years	17.8	94.6	64		

HA, haemagglutinin; ID, intradermal; ILI, influenza-like illness; ITT, intention to treat; MDV, multidose vials; N, sample size of treatment arm; NR, not reported; PFS, prefilled syringe; RCT, randomised controlled trial; SAE, serious adverse events.

higher in the full dose group, when adjusted to include only clinically significant pain levels (>3 out of 5 on a Visual Analogue Scale) the difference was no longer statistically significant.[20] The RCT found no differences in occurrence or severity of any other adverse effects. Similarly, one RCT comparing four different doses of Fluzone (3 µg, 6 µg, 9 µg, and 15 µg per strain) did not report any differences between the IM vaccination groups.[21] Finally, the RCT in older adults also found no difference in the occurrence or severity of adverse events in the low-dose (9 µg) vs high-dose (15 µg) group and found no serious adverse events that were considered related to the vaccine.[22]

DISCUSSION

PHAC commissioned this rapid scoping review to identify the evidence for efficacy and safety of fractional influenza vaccine dosing for IM administration of seasonal influenza vaccines in healthy individuals of all ages that have been evaluated in human trials. Thirteen RCTs published between 2006 and 2019 comparing standard/full-dose and half/low-dose vaccines were included in this scoping review after a comprehensive search of three electronic databases, trial registries and references of relevant systematic reviews. The majority of the included RCTs were conducted in children and evaluated TIV.

In young, healthy children, there were no effectiveness outcomes of interest reported. However, local reactogenicity, systemic reactogenicity and adverse events were comparable across the full-dose and half-dose TIV and QIV vaccine arms. In addition, the authors of one RCT in children and adolescents that compared full-dose QIV using PFS vs MDV also found no statistically significant differences in safety outcomes between administration formats. In healthy adults (including older adults), half-dose QIV was considered equally effective as high-dose in the two RCTs that assessed clinical effectiveness. Safety profiles were similar across groups in all four RCTs.

A full systematic review with meta-analysis based on the studies and results of this scoping review was conducted by the NACI and the report was published in January of 2021.[3] Briefly, the report found that there is some, but still insufficient, evidence that fractional doses of influenza vaccine provided via the IM route are effective and immunogenic in healthy individuals. NACI concludes that since many of those at high risk of influenza (eg, adults 65 years of age and older, individuals with specific underlying chronic health conditions) may have a lower immune response to influenza vaccination already (due to immunosenescence in older adults or a condition that alters immune function), it is important to ensure that those at high risk continue to receive the full dose of influenza vaccine. With regard to the safety of IM seasonal fractional doses of influenza vaccines, there is fair evidence that fractional doses do not result in significant differences compared with full dose with regard to severe adverse effects post-influenza vaccination. Readers are encouraged to reference the full NACI report on the Health Canada website.[3]

Strengths and limitations

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

We were limited by the lack of studies providing objective outcome data. Only one RCT by Kramer *et al* reported the objective outcome 'laboratory-confirmed influenza', and the other RCT by Engler only reported the outcome 'influenza like illness'.[19 20] Since a 2014 narrative review found that less than 25% of cases diagnosed by physicians as influenza like illness were later laboratory proven influenza cases,[23] we are lacking RCTs examining fractional dosing of IM influenza immunisation. Further, twelve dose-sparing RCTs were not included because they did not provide sufficient data, and did not include vaccines that were deemed of interest to the stakeholders. Another limitation was that only studies published in the English language were included, and data extraction was conducted by one abstractor and one verifier. Since this was a scoping review, we did not appraise the methodological quality of the included studies.[24]

Future research

Dose-sparing approaches such as ID immunisation vaccination exhibits similar, or even enhanced, immunogenicity, when using a fractional dose only, as compared with IM or subcutaneous immunisation, and should be explored in future scoping reviews.[25]

CONCLUSIONS

In our scoping review, we found 13 RCTs on the efficacy and safety of fractional doses of influenza vaccine provided via the IM route to healthy adults and children. These studies were used to inform a systematic review with meta-analysis which were commissioned by the PHAC. We found that due to the low number of studies in healthy adults, namely one study assessing laboratory confirmed influenza and two evaluating influenza-like illness in adults, there remains a need for further evaluation of the clinical effectiveness of IM dose-sparing strategies using vaccines currently available in this population.

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Contributors CL wrote and revised the final manuscript. JA and PR screened citations and full-text articles, abstracted and verified data, interpreted results and wrote the first draft manuscript. CW and NR screened citations and full-text articles, abstracted data and reviewed the manuscript. SES and ACT developed the protocol, obtained funding, interpreted results and edited the manuscript.

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Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

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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 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=2000-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=2000-current
32 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.
41 or/37-40
42 36 and 41
43 influenza vaccination/

44 immunological adjuvant/
45 (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.
46 or/42-45
47 intramuscular drug administration/
48 (intramuscular or intra-muscular).tw.
49 47 or 48
50 46 and 49
51 limit 50 to yr="2009 -Current"
52 animals/ not humans/
53 51 not 52
54 ad.fs.
55 49 or 54
56 46 and 55
57 dose response/ or drug response/
58 (Dos* sparing or Dose -sparing or half-dose or dose-response or dose response or dose effect* or dose-effect* or fractional dos*).tw.
59 ((reduc* or lower or less) adj2 (quantity or strength or standard)).tw.
60 ((dos* adj3 change) or (half adj3 dos*)).tw.
61 ((down adj3 titrat*) or (dose adj3 titrat*) or (dose adj3 reduc*) or (dose adj3 "de-escalat*") or (dose adj3 taper*)).tw.
62 or/57-61
63 56 and 62
64 animals/ not humans/
65 63 not 64
66 limit 65 to yr="2009 -Current"
67 53 or 66
68 67 use emczd
69 33 or 68
70 remove duplicates from 69

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:
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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="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
VaxigripTetra	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: http://www. who. int/trialsearch/Trial2. aspx?TrialID=EUCTR2011	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. *Clin Vaccine Immunol*. 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. Vaccine. 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: http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011-003314-16-HU	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: http://www. who. int/trialsearch/Trial2. aspx?TrialID=EUCTR2013	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. Clin Immunol. 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. J Korean Med Sci. 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. Vaccine. 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. Br J Clin Pharmacol. 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: http://www. who. int/trialsearch/Trial2. aspx?TrialID=CTRI	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: http://www. who. int/trialsearch/Trial2. aspx?TrialID=EUCTR2011	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)

	administered intramuscularly in adults. - FluarixUS-006. 2006. Available from: http://www. who. int/trialsearch/Trial2. aspx?TrialID=EUCTR2006	

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][1]	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][2]	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][3]	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][4]	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][5]	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][6]	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][7]	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][8]	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][9]	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][10]	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][11]	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][12]	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][13]	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

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][1] *Adults and Seniors (>18 years)*	Fluzone (Aventis Pasteur), **15-µg/strain** [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*	**Effectiveness** *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	▪ 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), **7.5-µg/strain** [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*	**Effectiveness** *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	
Belshe, 2007 [RCT][2] *Adults (18-49 years)*	Fluzone (Sanofi-Pasteur), **15-µg/strain** [1 x 0.5mL dose (Intramuscular in the non-dominant arm)]	**Reactogenicity – injection site** *Pain*[1]: 15/31 *Redness*[2]: 8/31 *Swelling*[2] :7/31 **Reactogenicity – systemic** *Fever*[3]: 1/31 *Headache*[1]: 15/31 *Malaise*[1]: 8/31 *Myalgia*[1]: 10/31	▪ Intradermal vaccine induced significantly more local inflammatory response than Intramuscular vaccine (primary comparison of this study was ID vs IM doses)
	Fluzone (Sanofi-Pasteur), **9-µg/strain** [1 x 0.3mL dose (Intramuscular in the non-dominant arm)]	**Reactogenicity – injection site** *Pain*[1]: 11/31 *Redness*[2]: 11/31 *Swelling*[2] :4/31 **Reactogenicity – systemic** *Fever*[3]: 1/31 *Headache*[1]: 6/31	

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**
		Malaise[1]: 8/31 *Myalgia*[1]: 6/31	
	Fluzone (Sanofi-Pasteur), **6-µg/strain** [1 x 0.2mL dose (Intramuscular in the non-dominant arm)]	**Reactogenicity – injection site** *Pain*[1]: 14/31 *Redness*[2]: 9/31 *Swelling*[2] :4/31 **Reactogenicity – systemic** *Fever*[3]: 0/31 *Headache*[1]: 9/31 *Malaise*[1]: 7/31 *Myalgia*[1]: 9/31	
	Fluzone (Sanofi-Pasteur), **3-µg/strain** [1 x 0.[1mL dose (Intramuscular in the non-dominant arm)]	**Reactogenicity – injection site** *Pain*[1]: 15/31 *Redness*[2]: 9/31 *Swelling*[2]:7/31 **Reactogenicity – systemic** *Fever*[3]: 3/31 *Headache*[1]: 8/31 *Malaise*[1]: 3/31 *Myalgia*[1]: 7/31	
Engler, 2008 [RCT][3] *Adults (18-64 years)*	Fluzone (Aventis Pasteur), **15-µg/strain** [1 x 0.5mL dose (Intramuscular injection)] *A/H1N1, A/New Caledonia/20/99; A/H3N2, A/Fujian/411/2002; B, B/Shanghai/361/2002*	**Effectiveness** *Influenza like illness* (Influenza-like illness and complications resulting in either inpatient or outpatient medical encounters were compared between dose groups (by age)): 61/632 *Hospitalization or Emergency visits*: 0.3% **Reactogenicity – local/injection site** *Any local reactions* (NR): 8.9% *Arm weakness* (NR): 8.3% *Numbness or burning* (NR): 9.7% *Pain* (NR): 5.9% *Redness or swelling* (NR): 13.4% **Reactogenicity – systemic** *Joint and/or muscle pain* (NR): 4.5%	▪ 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 dose-dependent

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**
		Adverse events *SAE*: 2/554	pain differences were not identified. ▪ Joint and/or muscle pain were significantly different (p=.02 and p=.03, respectively) by dose. ▪ No other adverse event differed significantly by dose
	Fluzone (Aventis Pasteur), **7.5-µg/strain** [1 x 0.25 mL dose (Intramuscular injection)] *A/H1N1, A/New Caledonia/20/99; A/H3N2, A/Fujian/411/2002; B, B/Shanghai/361/2003*	**Effectiveness** *Influenza like illness* (Influenza-like illness and complications resulting in either inpatient or outpatient medical encounters were compared between dose groups (by age): 64/644 *Hospitalization or Emergency visits*: 0.2% **Reactogenicity – local/injection site** *Any local reactions* (NR): 7.5% *Arm weakness* (NR): 6.5% *Numbness or burning* (NR): 7.8% *Pain* (NR): 4.6% *Redness or swelling* (NR): 8.6% **Reactogenicity – systemic** *Joint and/or muscle pain* (NR): 2.2% **Adverse events** *SAE*: 1/556	
Chi, 2010 [RCT][4] *Seniors (>65 years)*	Fluzone (Sanofi Pasteur), **15-µg/strain** [1 x 0.5mL dose (intramuscular in deltoid of arm)] *A/Solomon Islands/3/ 2006 (A/H1N1), A/Wisconsin/67/2005 (A/H3N2), and B/Malaysia/2506/2004*	**Reactogenicity – injection site, N=64** *Arm motion limitation*: 1 (grade I)[4] *Itching:* 4 (grade I)[4] *Pain:* 7 (grade I)[4] *Redness or discoloration:* 9 (grade I)[4] *Swelling:* 13 (grade I)[4] **Reactogenicity - systemic, N=64** *Chills:* 1 (grade I)[4], 1 (grade II/III)[5] *Fatigue:* 4 (grade I)[4], 2 (grade II/III)[5] *Fever:* 0 *General body ache/pain:* 6 (grade I)[4], 1 (grade II/III)[5] *Headache:* 10 (grade I)[4] *Nausea:* 3 (grade I)[4], 1 (grade II/III)[5] **Adverse events**	▪ The two SAEs were acute coronary syndrome and appendicitis and neither were judged to be related to influenza vaccination

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**
		SAE[6]: 0/64	
	Fluzone (Sanofi Pasteur), **9-µg/strain** [1 x 0.3mL dose (intramuscular in deltoid of arm)] *A/Solomon Islands/3/ 2006 (A/H1N1), A/Wisconsin/67/2005 (A/H3N2), and B/Malaysia/2506/2004*	**Reactogenicity – injection site, N=64** *Arm motion limitation:* 1 (grade I)[4] *Itching:* 5 (grade I)[4] *Pain:* 11 (grade I)[4] *Redness or discoloration:* 7 (grade I)[4] *Swelling:* 4 (grade I)[4] **Reactogenicity - systemic, N=64** *Chills:* 1 (grade I)[4], 1 (grade II/III)[5] *Fatigue:* 6 (grade I)[4], 1 (grade II/III)[5] *Fever:* 1 (grade I)[4] *General body ache/pain:* 5 (grade I)[4], 2 (grade II/III)[5] *Headache:* 5 (grade I)[4], 1 (grade II/III)[5] *Nausea:* 2 (grade I)[4], 1 (grade II/III)[5] **Adverse events** *SAE*[6]*:* 2/64	
Cioppa, 2011 [RCT][5] *Infants/ Toddlers (6-36 months)*	NR - TIV, **7.5-µg/strain** [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)] *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)*	**Reactogenicity** *Any local reaction*[7]: 47% *Any systemic reaction*[8]: 68% **Adverse events** *AE* (solicited/spontaneously reported): 84% *SAE*: 0/25	▪ 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, **15-µg/strain** [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)] *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)*	**Reactogenicity** *Any local reaction*[7]: 59% *Any systemic reaction*[8]: 50% **Adverse events** *AE* (solicited/spontaneously reported): 82% *SAE*: 0/22	

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, **7.5-µg/strain** [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)] *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)*	**Reactogenicity** *Any local reaction*[7]: 25% *Any systemic reaction*[8]: 50% **Adverse events** *AE* (solicited/spontaneously reported): 92% SAE: 1/25	
	NR - QIV, **15-µg/strain** [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)] *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)*	**Reactogenicity** *Any local reaction*[7]: 39% *Any systemic reaction*[8]: 54% **Adverse events** *AE* (solicited/spontaneously reported): 71% *SAE*: 1/28	
	Vaxigrip pediatric - TIV (Sanofi Pasteur), **7.5-µg/strain** [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)]	**Reactogenicity** *Any local reaction*[7]: 50% *Any systemic reaction*[8]: 46% **Adverse events** *AE* (solicited/spontaneously reported): 73% *SAE*: 1/26	
Skowronski, 2011 [RCT][6] *Infants/ Toddlers (6-23 months)*	Vaxigrip (Sanofi-Pasteur), 15-µg/strain **[2 x 0.5mL dose** (Intramuscular injection)] *A/Brisbane/10/07 (H3N2); A/Brisbane/59/07 (H1N1); and B/Florida/4/06 (Yamagata lineage)*	**Reactogenicity – injection site** *Induration* (NR): 13.7% *Redness* (NR): 22.6% *Swelling* (NR): 15.3% *Tenderness* (NR): 22.6% **Reactogenicity – systemic** *Fever* (>37.5°C): 8.06% *Irritability* (NR): 59.7% *Decreased appetite* (NR): 38.7%	▪ 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

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**
		Drowsiness (NR): 39.5% *Sleep disturbance* (NR): 54.8% **Adverse events** *SAE:* NR	hospitalized with pneumonia 28 days after the first vaccination. The event was deemed unlikely related to the vaccine. ▪ All of the rate differences were significantly below the allowed 10% increase in reactogenicity for the full dose (p< 0.001 for infant and combined analyses, p<.005 for toddlers). ▪ 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.
	Vaxigrip (Sanofi-Pasteur), 15-µg/strain **[2 x 0.25mL dose** (Intramuscular injection)] *A/Brisbane/10/07 (H3N2); A/Brisbane/59/07 (H1N1); and B/Florida/4/06 (Yamagata lineage)*	**Reactogenicity – injection site** *Induration* (NR): 6.3% *Redness* (NR): 20.3% *Swelling* (NR): 8.6% *Tenderness* (NR): 25.8% **Reactogenicity – systemic** *Fever* (>37.5°C): 11.7% *Irritability* (NR): 60.2% *Decreased appetite* (NR): 43% *Drowsiness* (NR): 41.4% *Sleep disturbance* (NR): 50% **Adverse events** *SAE:* 1/128	
Langley, 2012 [RCT][7] *Infants/ Toddlers (6-35 months)*	Fluviral F1 (Sanofi-Pasteur), **7.5-µg/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)] *A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (an A/Brisbane/10/2007 [H3N2]–like virus), and B/Florida/4/2006*	**Reactogenicity – injection site** *Pain* (NR): 45/164 *Redness* (NR): 49/164 *Swelling* (NR): 22/164 **Reactogenicity – systemic** *Drowsiness* (NR) – 44/164 *Fever* (NR) – 10/164 *Irritability* (NR) – 62/164 *Loss of appetite* (NR) – 37/164 **Adverse events** *SAE:* 1/164	▪ 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

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**
		Unsolicited adverse events (NR): 108/164 *Medically attended events* (NR): 52/164	immunogenicity with clinically similar safety and reactogenicity compared with the 0.25-mL dose.
	Fluviral F2 (Sanofi-Pasteur), **15-µg/strain** [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)] *A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (an A/Brisbane/10/2007 [H3N2]–like virus), and B/Florida/4/2006*	**Reactogenicity – injection site** *Pain* (NR): 55/167 *Redness* (NR): 54/167 *Swelling* (NR): 24/167 **Reactogenicity – systemic** *Drowsiness* (NR) – 52/167 *Fever* (NR) – 6/167 *Irritability* (NR) – 69/167 *Loss of appetite* (NR) – 43/167 **Adverse events** *SAE*: 1/167 *Unsolicited adverse events* (NR): 112/167 *Medically attended events* (NR): 40/167	
	Vaxigrip (Sanofi-Pasteur), **7.5-µg/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)] A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (an A/Brisbane/10/2007 [H3N2]–like virus), and B/Florida/4/2006	**Reactogenicity – injection site** *Pain* (NR): 17/43 *Redness* (NR): 13/43 *Swelling* (NR): 5/43 **Reactogenicity – systemic** *Drowsiness* (NR) – 11/43 *Fever* (NR) – 2/43 *Irritability* (NR) – 15/43 *Loss of appetite* (NR) – 9/43 **Adverse events** *SAE:* NR/43 *Unsolicited adverse events* (NR): 24/43 *Medically attended events* (NR): 9/43	
Pavia-Ruz, 2013 [RCT][8] *Infants/ Toddlers*	Fluarix (GSK), **15-µg/strain** [1 x 0.5mL dose (intramuscular injection into the right deltoid muscle or anterolateral thigh)]	**Reactogenicity – injection site** *Any injection site reactions*[9]: 514/1086 *Pain:* 406/1086 *Redness*: 249/1086 *Swelling:* 170/1086	▪ The reactogenicity and safety profile of the study vaccine did not appear to be affected by doubling the dose.

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*	**Reactogenicity – systemic** *Any general reactions*[10]: 575/1086 *Drowsiness:* 317/1086 *Fever:* 69/1086 *Irritability:* 387/1086 *Loss of appetite:* 273/1086 **Adverse events** *Any AE*: 729/1086 *SAE*: 29/1086	▪ 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.
	Fluarix (GSK), **7.5-µg/strain** [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*	**Reactogenicity – injection site** *Any injection site reactions*[9]: 492/1081 *Pain:* 403/1081 *Redness*: 259/1081 *Swelling:* 152/1081 **Reactogenicity – systemic** *Any general reactions*[10]*:* 598/1081 *Drowsiness:* 293/1081 *Fever:* 67/1081 *Irritability:* 386/1081 *Loss of appetite:* 281/1081 **Adverse events** *Any AE*: 724/1081 *SAE*: 35/1081	
	Fluzone (Sanofi-Pasteur), **7.5-µg/strain** [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*	**Reactogenicity – injection site** *Any injection site reactions*[9]*:* 467/1090 *Pain:* 363/1090 *Redness:* 253/1090 *Swelling:* 129/1090 **Reactogenicity – systemic** *Any general reactions*[10]: 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**
		Adverse events *Any AE:* 722/1090 *SAE:* 31/1090	
Halasa, 2015 [RCT][9] *Infants/ Toddlers (6-35 months)*	Fluzone (Sanofi Pasteur), **7.5-µg/strain** [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*	**Reactogenicity** *Redness at injection site*: 8/48 *Fever* (temperature >39°C after the first dose): 7/80	▪ 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 redness at the injection site (P < .05). ▪ 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.
	Fluzone (Sanofi Pasteur), **15-µg/strain** [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*	**Reactogenicity** *Redness at injection site*: 32/96 *Fever* (temperature >39°C after the first dose): 19/161	
Phung, 2016 [RCT][10] *Infants/ Toddlers (6-35 months)*	FLUAD (NR), NR [**1 x 0.5mL dose** (Intramuscular injection)] *A/H1N1, A/H3N2, Strain B*	**Reactogenicity** *Any local reaction*[11]: 45/61 *Any systemic reaction*[12]: 36/61 **Adverse events** *SAE* (based on MedDRA v 17.1 definition): 2/61	
	FLUAD (NR), NR [**1 x 0.25 mL dose** (Intramuscular injection)]	**Reactogenicity** *Any local reaction*[11]: 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*[12]: 42/75 **Adverse events** *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*	**Reactogenicity** *Any local reaction*[11]: 42/51 *Any systemic reaction*[12]: 24/51 **Adverse events** *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*	**Reactogenicity** *Any local reaction*[11]: 6/10 *Any systemic reaction*[12]: 5/10 **Adverse events** *SAE* (based on MedDRA v 17.1): 0/10	
Jain, 2017 [RCT][11] *Infants/ Toddlers (6-35 months)*	Flulaval Quadrivalent (GSK), **15-µg/strain** [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)*	**Reactogenicity – injection site (within 7 days)** *Pain*: 44.0% *Redness*: 1.4% *Swelling*: 1.0% **Reactogenicity – systemic (within 7 days)** *Drowsiness:* 40.6% *Fever (>=38.0C):* 7.9% *Irritability/fussiness:* 54.4% *Loss of appetite:* 33.7% **Adverse events** *Any AE*: 45.5% *Vaccine-related AE*: 5.9% *Any SAE*[13]: 1.8% *Febrile seizures*: 0.4% *Medically attended event*[14]: 60.2%	▪ None of the febrile seizures or the SAEs were considered by the investigator to be related to vaccination ▪ 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.
	Fluzone Quadrivalent (Sanofi Pasteur), **7.5-µg/strain** [1 x 0.25 mL dose (intramuscular in deltoid region)]	**Reactogenicity – injection site (within 7 days)** *Pain*: 40.1% *Redness:* 1.4% *Swelling*: 0.4% **Reactogenicity – systemic (within 7 days)**	

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)	*Drowsiness:* 40.9% *Fever (>=38.0C):* 7.5% *Irritability/fussiness:* 50.5% *Loss of appetite:* 33.4% **Adverse events** *Any AE:* 44.1% *Vaccine-related AE:* 5.8% *Any SAE*[13]*:* 1.7% *Febrile seizures*: 0.3% *Medically attended event*[14]: 59.1%	
Ojeda. 2019 [RCT][12] *Infants/ Toddlers and Children (6 months – 17 years)*	Vaxigrip Tetra (Sanofi Pasteur) – **PFS**, 15-µg/strain [1 x 0.5mL dose (intramuscular or deep subcutaneous injection)] *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)*	**Reactogenicity, N=142** *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) **Adverse events, N=147** *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	▪ Solicited reactions were mostly grade 1 (mild) in intensity and resolved within 3 days. ▪ 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. ▪ None of these unsolicited AEs were considered related to a study vaccine by the investigators. ▪ 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
	Vaxigrip Tetra (Sanofi Pasteur) - **MDV,** 15-µg/strain [1 x 0.5mL dose (intramuscular or deep subcutaneous injection)] *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)*	**Reactogenicity, N=139** *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) **Adverse events, N=150** *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	

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][13] *Infants/ Toddlers (6-35 months)*	Fluzone Quadrivalent (Sanofi Pasteur), **15-µg/strain** [1 x 0.5mL dose (intramuscular single-dose syringes in deltoid of arm)] *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)*	**Reactogenicity** *Any injection-site reaction*[15]: 533/939 *Any systemic reaction*[16]: 561/941 **Adverse events** *Vaccine-related AE* (immediate within 30 mins): 0/992 *Vaccine-related AE* (within 28 days): 30/992 *AE leading to study discontinuation*: 0/992 *SAE*: 5/992	▪ Proportions of participants reporting solicited injection-site reactions, solicited systemic reactions, vaccine-related unsolicited AEs were similar for the full- and half-dose groups ▪ None of the AEs leading to study discontinuation or the SAEs were considered related to vaccination ▪ A single AE of special interest (chronic urticaria first appearing 3 days post-vaccination and continuing for >6 weeks) was considered by the investigator to be related to vaccination ▪ 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.
	Fluzone Quadrivalent (Sanofi Pasteur), **7.5-µg/strain** [1 x 0.25 mL dose (intramuscular single-dose syringes in deltoid of arm)] *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)*	**Reactogenicity** *Any injection-site reaction*[15]: 480/909 *Any systemic reaction*[16]: 533/909 **Adverse events** *Vaccine-related AE* (unsolicited within 30 mins): 1/949 *Vaccine-related AE* (unsolicited within 28 days): 29/949 *AE leading to study discontinuation*: 3/949 *SAE*: 5/949	

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

[1] Defined as mild (easily tolerated), moderate (interferes with normal behaviour or activities), severe (incapacitating, unable to perform usual activities, may require medical attention)
[2] Present at or near the approximate point of needle entry; small <2.5cm, medium >2.5cm to <5cm, large >5cm
[3] Oral temperature >37.5 C; mild >37.5 to 38 C, moderate >38.1 to 39 C, severe >39.1 C
[4] 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

[5] Grade II/III reactions defined as “interferes with normal activity” to “severe and incapacitating” for fatigue, muscle ache, headache, itching or pain at injection site; oral temperature >/=39 degrees Celsius; limitation to arm motion due to stiffness or discomfort that interferes with normal activity; redness or swelling > 8cm
[6] Defined as serious adverse events resulting in hospitalization
[7] Solicited local reactions included ecchymosis, erythema, induration, swelling, and tenderness at injection site
[8] Solicited systemic reactions included sleepiness, diarrhea, vomiting, irritability, change in eating habits, shivering, and unusual crying
[9] Included injection site reactions of Grade 1, “minor reaction to touch”, Grade 2, “cries/protests on touch”, and Grade 3, “cries when limb moved/spontaneously painful”
[10] Included systemic reactions of Grade 1, “no effect on normal activity”, Grade 2, “interferes with normal activity”, and Grade 3, “prevents normal activity”
[11] Included injection site ecchymosis, injection sit erythema, injection site induration, injection site swelling, tenderness, injection site pain
[12] Included change in eating habits, sleepiness, unusual crying, irritability, vomiting, diarrhea, chills/shivering, malaise, myalgia, arthralgia, headache, fatigue, fever (>37.3 C)
[13] Defined serious adverse events as any untoward medical occurrence that results in death, is life-threatening, requires/prolongs hospitalization, or results in disability or incapacity during entire study period
[14] Defined as hospitalization, emergency room visit, and/or medical practitioner visit during entire study period
[15] Included tenderness, redness and/or swelling solicited within 7 days
[16] Included fever, vomiting, abnormal crying, drowsiness, loss of appetite, and/or irritability solicited within 7 days