## 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 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:**

---

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:**
**----------**

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:**

---

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<br><br>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<br><br>Single dose vial<br><br>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<br><br>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]<br><br>*Adults and Seniors (>18 years)* | Fluzone (Aventis Pasteur), **15-µg/strain** [1 x 0.5mL dose (Intramuscular into the deltoid region)]<br><br>*A/Wyoming/3/2003 (H3N2), A/New Caledonia/20/99 (H1N1), and a new B strain, B/Jiangsu/10/2003* | **Effectiveness**<br>*Lab confirmed influenza* (Laboratory confirmation of influenza diagnosis was sought in participants reporting a clinical diagnosis by their physicians): 1/222<br><br>*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.<br><br>▪ 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)]<br><br>*A/Wyoming/3/2003 (H3N2), A/New Caledonia/20/99 (H1N1), and a new B strain, B/Jiangsu/10/2004* | **Effectiveness**<br>*Lab confirmed influenza* (Laboratory confirmation of influenza diagnosis was sought in participants reporting a clinical diagnosis by their physicians): 0/222<br><br>*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]<br><br>*Adults (18-49 years)* | Fluzone (Sanofi-Pasteur), **15-µg/strain** [1 x 0.5mL dose (Intramuscular in the non-dominant arm)] | **Reactogenicity – injection site**<br>*Pain*[1]: 15/31<br>*Redness*[2]: 8/31<br>*Swelling*[2] :7/31<br><br>**Reactogenicity – systemic**<br>*Fever*[3]: 1/31<br>*Headache*[1]: 15/31<br>*Malaise*[1]: 8/31<br>*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**<br>*Pain*[1]: 11/31<br>*Redness*[2]: 11/31<br>*Swelling*[2] :4/31<br><br>**Reactogenicity – systemic**<br>*Fever*[3]: 1/31<br>*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<br>*Myalgia*[1]: 6/31 | |
| | Fluzone (Sanofi-Pasteur), **6-µg/strain** [1 x 0.2mL dose (Intramuscular in the non-dominant arm)] | **Reactogenicity – injection site**<br>*Pain*[1]: 14/31<br>*Redness*[2]: 9/31<br>*Swelling*[2] :4/31<br><br>**Reactogenicity – systemic**<br>*Fever*[3]: 0/31<br>*Headache*[1]: 9/31<br>*Malaise*[1]: 7/31<br>*Myalgia*[1]: 9/31 | |
| | Fluzone (Sanofi-Pasteur), **3-µg/strain** [1 x 0.[1mL dose (Intramuscular in the non-dominant arm)] | **Reactogenicity – injection site**<br>*Pain*[1]: 15/31<br>*Redness*[2]: 9/31<br>*Swelling*[2]:7/31<br><br>**Reactogenicity – systemic**<br>*Fever*[3]: 3/31<br>*Headache*[1]: 8/31<br>*Malaise*[1]: 3/31<br>*Myalgia*[1]: 7/31 | |
| Engler, 2008 [RCT][3]<br><br>*Adults (18-64 years)* | Fluzone (Aventis Pasteur), **15-µg/strain** [1 x 0.5mL dose (Intramuscular injection)]<br><br>*A/H1N1, A/New Caledonia/20/99; A/H3N2, A/Fujian/411/2002; B, B/Shanghai/361/2002* | **Effectiveness**<br>*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<br><br>*Hospitalization or Emergency visits*: 0.3%<br><br>**Reactogenicity – local/injection site**<br>*Any local reactions* (NR): 8.9%<br>*Arm weakness* (NR): 8.3%<br>*Numbness or burning* (NR): 9.7%<br>*Pain* (NR): 5.9%<br>*Redness or swelling* (NR): 13.4%<br><br>**Reactogenicity – systemic**<br>*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.<br><br>▪ 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**<br>*SAE*: 2/554 | pain differences were not identified.<br>▪ Joint and/or muscle pain were significantly different (p=.02 and p=.03, respectively) by dose.<br>▪ No other adverse event differed significantly by dose |
| | Fluzone (Aventis Pasteur), **7.5-µg/strain** [1 x 0.25 mL dose (Intramuscular injection)]<br><br>*A/H1N1, A/New Caledonia/20/99; A/H3N2, A/Fujian/411/2002; B, B/Shanghai/361/2003* | **Effectiveness**<br>*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<br><br>*Hospitalization or Emergency visits*: 0.2%<br><br>**Reactogenicity – local/injection site**<br>*Any local reactions* (NR): 7.5%<br>*Arm weakness* (NR): 6.5%<br>*Numbness or burning* (NR): 7.8%<br>*Pain* (NR): 4.6%<br>*Redness or swelling* (NR): 8.6%<br><br>**Reactogenicity – systemic**<br>*Joint and/or muscle pain* (NR): 2.2%<br><br>**Adverse events**<br>*SAE*: 1/556 | |
| Chi, 2010 [RCT][4]<br><br>*Seniors (>65 years)* | Fluzone (Sanofi Pasteur), **15-µg/strain** [1 x 0.5mL dose (intramuscular in deltoid of arm)]<br><br>*A/Solomon Islands/3/ 2006 (A/H1N1), A/Wisconsin/67/2005 (A/H3N2), and B/Malaysia/2506/2004* | **Reactogenicity – injection site, N=64**<br>*Arm motion limitation*: 1 (grade I)[4]<br>*Itching:* 4 (grade I)[4]<br>*Pain:* 7 (grade I)[4]<br>*Redness or discoloration:* 9 (grade I)[4]<br>*Swelling:* 13 (grade I)[4]<br><br>**Reactogenicity - systemic, N=64**<br>*Chills:* 1 (grade I)[4], 1 (grade II/III)[5]<br>*Fatigue:* 4 (grade I)[4], 2 (grade II/III)[5]<br>*Fever:* 0<br>*General body ache/pain:* 6 (grade I)[4], 1 (grade II/III)[5]<br>*Headache:* 10 (grade I)[4]<br>*Nausea:* 3 (grade I)[4], 1 (grade II/III)[5]<br><br>**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)]<br><br>*A/Solomon Islands/3/ 2006 (A/H1N1), A/Wisconsin/67/2005 (A/H3N2), and B/Malaysia/2506/2004* | **Reactogenicity – injection site, N=64**<br>*Arm motion limitation:* 1 (grade I)[4]<br>*Itching:* 5 (grade I)[4]<br>*Pain:* 11 (grade I)[4]<br>*Redness or discoloration:* 7 (grade I)[4]<br>*Swelling:* 4 (grade I)[4]<br><br>**Reactogenicity - systemic, N=64**<br>*Chills:* 1 (grade I)[4], 1 (grade II/III)[5]<br>*Fatigue:* 6 (grade I)[4], 1 (grade II/III)[5]<br>*Fever:* 1 (grade I)[4]<br>*General body ache/pain:* 5 (grade I)[4], 2 (grade II/III)[5]<br>*Headache:* 5 (grade I)[4], 1 (grade II/III)[5]<br>*Nausea:* 2 (grade I)[4], 1 (grade II/III)[5]<br><br>**Adverse events**<br>*SAE*[6]*:* 2/64 | |
| Cioppa, 2011 [RCT][5]<br><br>*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)]<br><br>*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**<br>*Any local reaction*[7]: 47%<br>*Any systemic reaction*[8]: 68%<br><br>**Adverse events**<br>*AE* (solicited/spontaneously reported): 84%<br>*SAE*: 0/25 | ▪ Reactogenicity of the 7.5-µg TIV/QIV formulations was slightly lower than for the corresponding 15-µg formulations.<br><br>▪ 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)]<br><br>*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**<br>*Any local reaction*[7]: 59%<br>*Any systemic reaction*[8]: 50%<br><br>**Adverse events**<br>*AE* (solicited/spontaneously reported): 82%<br>*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)]<br><br>*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**<br>*Any local reaction*[7]: 25%<br>*Any systemic reaction*[8]: 50%<br><br>**Adverse events**<br>*AE* (solicited/spontaneously reported): 92%<br>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)]<br><br>*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**<br>*Any local reaction*[7]: 39%<br>*Any systemic reaction*[8]: 54%<br><br>**Adverse events**<br>*AE* (solicited/spontaneously reported): 71%<br>*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**<br>*Any local reaction*[7]: 50%<br>*Any systemic reaction*[8]: 46%<br><br>**Adverse events**<br>*AE* (solicited/spontaneously reported): 73%<br>*SAE*: 1/26 | |
| Skowronski, 2011 [RCT][6]<br><br>*Infants/ Toddlers (6-23 months)* | Vaxigrip (Sanofi-Pasteur), 15-µg/strain **[2 x 0.5mL dose** (Intramuscular injection)]<br><br>*A/Brisbane/10/07 (H3N2); A/Brisbane/59/07 (H1N1); and B/Florida/4/06 (Yamagata lineage)* | **Reactogenicity – injection site**<br>*Induration* (NR): 13.7%<br>*Redness* (NR): 22.6%<br>*Swelling* (NR): 15.3%<br>*Tenderness* (NR): 22.6%<br><br>**Reactogenicity – systemic**<br>*Fever* (>37.5°C): 8.06%<br>*Irritability* (NR): 59.7%<br>*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.<br><br>▪ 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%<br>*Sleep disturbance* (NR): 54.8%<br><br>**Adverse events**<br>*SAE:* NR | hospitalized with pneumonia 28 days after the first vaccination. The event was deemed unlikely related to the vaccine.<br><br>▪ 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).<br><br>▪ 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)]<br><br>*A/Brisbane/10/07 (H3N2); A/Brisbane/59/07 (H1N1); and B/Florida/4/06 (Yamagata lineage)* | **Reactogenicity – injection site**<br>*Induration* (NR): 6.3%<br>*Redness* (NR): 20.3%<br>*Swelling* (NR): 8.6%<br>*Tenderness* (NR): 25.8%<br><br>**Reactogenicity – systemic**<br>*Fever* (>37.5°C): 11.7%<br>*Irritability* (NR): 60.2%<br>*Decreased appetite* (NR): 43%<br>*Drowsiness* (NR): 41.4%<br>*Sleep disturbance* (NR): 50%<br><br>**Adverse events**<br>*SAE:* 1/128 | |
| Langley, 2012 [RCT][7]<br><br>*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)]<br><br>*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**<br>*Pain* (NR): 45/164<br>*Redness* (NR): 49/164<br>*Swelling* (NR): 22/164<br><br>**Reactogenicity – systemic**<br>*Drowsiness* (NR) – 44/164<br>*Fever* (NR) – 10/164<br>*Irritability* (NR) – 62/164<br>*Loss of appetite* (NR) – 37/164<br><br>**Adverse events**<br>*SAE:* 1/164 | ▪ Fluviral F1 group had 1 case of pneumonia resolved<br><br>▪ Fluviral F2 group had 1 case of bronchial hyper-reactivity in resolving stage<br><br>▪ 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<br>*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)]<br><br>*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**<br>*Pain* (NR): 55/167<br>*Redness* (NR): 54/167<br>*Swelling* (NR): 24/167<br><br>**Reactogenicity – systemic**<br>*Drowsiness* (NR) – 52/167<br>*Fever* (NR) – 6/167<br>*Irritability* (NR) – 69/167<br>*Loss of appetite* (NR) – 43/167<br><br>**Adverse events**<br>*SAE*: 1/167<br>*Unsolicited adverse events* (NR): 112/167<br>*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)]<br><br>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**<br>*Pain* (NR): 17/43<br>*Redness* (NR): 13/43<br>*Swelling* (NR): 5/43<br><br>**Reactogenicity – systemic**<br>*Drowsiness* (NR) – 11/43<br>*Fever* (NR) – 2/43<br>*Irritability* (NR) – 15/43<br>*Loss of appetite* (NR) – 9/43<br><br>**Adverse events**<br>*SAE:* NR/43<br>*Unsolicited adverse events* (NR): 24/43<br>*Medically attended events* (NR): 9/43 | |
| Pavia-Ruz, 2013 [RCT][8]<br><br>*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**<br>*Any injection site reactions*[9]: 514/1086<br>*Pain:* 406/1086<br>*Redness*: 249/1086<br>*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**<br>*Any general reactions*[10]: 575/1086<br>*Drowsiness:* 317/1086<br>*Fever:* 69/1086<br>*Irritability:* 387/1086<br>*Loss of appetite:* 273/1086<br><br>**Adverse events**<br>*Any AE*: 729/1086<br>*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),<br>**7.5-µg/strain** [1 x 0.25 mL dose (intramuscular injection into the right deltoid muscle or anterolateral thigh)]<br><br>*A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2) and B/Brisbane/3/2007* | **Reactogenicity – injection site**<br>*Any injection site reactions*[9]: 492/1081<br>*Pain:* 403/1081<br>*Redness*: 259/1081<br>*Swelling:* 152/1081<br><br>**Reactogenicity – systemic**<br>*Any general reactions*[10]*:* 598/1081<br>*Drowsiness:* 293/1081<br>*Fever:* 67/1081<br>*Irritability:* 386/1081<br>*Loss of appetite:* 281/1081<br><br>**Adverse events**<br>*Any AE*: 724/1081<br>*SAE*: 35/1081 | |
| | Fluzone (Sanofi-Pasteur),<br>**7.5-µg/strain** [1 x 0.25 mL dose (intramuscular injection into the right deltoid muscle or anterolateral thigh)]<br><br>*A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2) and B/Florida/4/2006* | **Reactogenicity – injection site**<br>*Any injection site reactions*[9]*:* 467/1090<br><br>*Pain:* 363/1090<br>*Redness:* 253/1090<br>*Swelling:* 129/1090<br><br>**Reactogenicity – systemic**<br>*Any general reactions*[10]: 592/1090<br>*Drowsiness:* 298/1090<br>*Irritability:* 375/1090<br>*Fever:* 72/1090<br>*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**<br>*Any AE:* 722/1090<br>*SAE:* 31/1090 | |
| Halasa, 2015 [RCT][9]<br><br>*Infants/ Toddlers (6-35 months)* | Fluzone (Sanofi Pasteur),<br>**7.5-µg/strain** [1 x 0.25 mL dose (intramuscular)]<br><br>*A/California/7/09 (H1N1)-like virus, A/Perth/16/2009 (H3N2)-like virus, and B/Brisbane/ 60/2008-like virus* | **Reactogenicity**<br>*Redness at injection site*: 8/48<br>*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.<br><br>▪ 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).<br><br>▪ 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),<br>**15-µg/strain** [1 x 0.5 mL dose (intramuscular)]<br><br>*A/California/7/09 (H1N1)-like virus, A/Perth/16/2009 (H3N2)-like virus, and B/Brisbane/ 60/2008-like virus* | **Reactogenicity**<br>*Redness at injection site*: 32/96<br>*Fever* (temperature >39°C after the first dose): 19/161 | |
| Phung, 2016 [RCT][10]<br><br>*Infants/ Toddlers (6-35 months)* | FLUAD (NR),<br>NR [**1 x 0.5mL dose** (Intramuscular injection)]<br><br>*A/H1N1, A/H3N2, Strain B* | **Reactogenicity**<br>*Any local reaction*[11]: 45/61<br>*Any systemic reaction*[12]: 36/61<br><br>**Adverse events**<br>*SAE* (based on MedDRA v 17.1 definition): 2/61 | |
| | FLUAD (NR),<br>NR [**1 x 0.25 mL dose** (Intramuscular injection)] | **Reactogenicity**<br>*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<br><br>**Adverse events**<br>*SAE* (based on MedDRA v 17.1 definition): 2/75 | |
| | Agrippal S1 (NR),<br>NR [**1 x 0.5mL dose** (Intramuscular injection)]<br><br>*A/H1N1, A/H3N2, Strain B* | **Reactogenicity**<br>*Any local reaction*[11]: 42/51<br>*Any systemic reaction*[12]: 24/51<br><br>**Adverse events**<br>*SAE* (based on MedDRA v 17.1 definition): 0/51 | |
| | Agrippal S1 (NR),<br>NR [**1 x 0.25mL dose** (Intramuscular injection)]<br>*A/H1N1, A/H3N2, Strain B* | **Reactogenicity**<br>*Any local reaction*[11]: 6/10<br>*Any systemic reaction*[12]: 5/10<br><br>**Adverse events**<br>*SAE* (based on MedDRA v 17.1): 0/10 | |
| Jain, 2017 [RCT][11]<br><br>*Infants/ Toddlers (6-35 months)* | Flulaval Quadrivalent (GSK),<br>**15-µg/strain** [1 x 0.5mL dose (intramuscular in deltoid region)]<br><br>*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)**<br>*Pain*: 44.0%<br>*Redness*: 1.4%<br>*Swelling*: 1.0%<br><br>**Reactogenicity – systemic (within 7 days)**<br>*Drowsiness:* 40.6%<br>*Fever (>=38.0C):* 7.9%<br>*Irritability/fussiness:* 54.4%<br>*Loss of appetite:* 33.7%<br><br>**Adverse events**<br>*Any AE*: 45.5%<br>*Vaccine-related AE*: 5.9%<br>*Any SAE*[13]: 1.8%<br>*Febrile seizures*: 0.4%<br>*Medically attended event*[14]: 60.2% | ▪ None of the febrile seizures or the SAEs were considered by the investigator to be related to vaccination<br><br>▪ 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),<br>**7.5-µg/strain** [1 x 0.25 mL dose (intramuscular in deltoid region)] | **Reactogenicity – injection site (within 7 days)**<br>*Pain*: 40.1%<br>*Redness:* 1.4%<br>*Swelling*: 0.4%<br><br>**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%<br>*Fever (>=38.0C):* 7.5%<br>*Irritability/fussiness:* 50.5%<br>*Loss of appetite:* 33.4%<br><br>**Adverse events**<br>*Any AE:* 44.1%<br>*Vaccine-related AE:* 5.8%<br>*Any SAE*[13]*:* 1.7%<br>*Febrile seizures*: 0.3%<br>*Medically attended event*[14]: 59.1% | |
| Ojeda. 2019 [RCT][12]<br><br>*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)]<br><br>*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**<br>*Any injection-site reaction* (solicited within 7 days)*:* 26 (6-35mo), 16 (3-8yr), 42 (9-7yr)<br>*Any systemic reaction* (solicited within 7 days): 25 (6-35mo), 15 (3-8yr), 35 (9-7yr)<br><br>**Adverse events, N=147**<br>*AE* (immediate unsolicited): 1 (9-17 years)<br>*Non-serious AE:* 25 (6-35mo), 9 (3-8yr), 8 (9-7yr)<br>*Vaccine-related non-serious AE*: 1 (9-17 years)<br>*AE leading to study discontinuation*: 0<br>*SAE*: 0 | ▪ Solicited reactions were mostly grade 1 (mild) in intensity and resolved within 3 days.<br><br>▪ 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.<br><br>▪ None of these unsolicited AEs were considered related to a study vaccine by the investigators.<br><br>▪ 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)]<br><br>*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**<br>*Any injection-site reaction*(solicited within 7 days)*:* 27 (6-35mo), 16 (3-8yr), 26 (9-7yr)<br>*Any systemic reaction*(solicited within 7 days): 33 (6-35mo), 13 (3-8yr), 30 (9-7yr)<br><br>**Adverse events, N=150**<br>*AE* (immediate unsolicited): 0<br>*Non-serious AE:* 31 (6-35mo), 14 (3-8yr), 5 (9-7yr)<br>*Vaccine-related non-serious AE*: 0<br>*AE leading to study discontinuation*: 0<br>*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<br>▪ None of the AEs leading to study discontinuation or the SAEs were considered related to vaccination<br>▪ 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<br>▪ 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