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

Recommendations on the use of live, attenuated influenza vaccine (FluMist®)

Supplemental Statement on Seasonal Influenza Vaccine for 2011-2012

Preamble

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

† This statement was prepared and approved by NACI.

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I. Introduction

I.1 Overview of Statement

This supplement to the National Advisory Committee on Immunization (NACI) Statement on Seasonal Influenza Vaccine for 2011-2012 will:

- Provide information on the authorized live attenuated influenza vaccine (LAIV) product (FluMist®), which is administered by intranasal spray.
- Provide recommendations for the use of LAIV

NACI Recommendations

Children

Healthy Children 2-17 years of age

- Based on effectiveness, efficacy and immunogenicity data, NACI recommends LAIV for use in healthy children and adolescents 2-17 years of age. Available data indicates that LAIV would be preferred over TIV in this population, although NACI recognizes that other programmatic considerations will impact the implementation of this recommendation in publicly-funded programs. (NACI Recommendation Grade A)

Children with Immune Compromising Conditions

- NACI recommends against LAIV for individuals with immune compromising conditions. (NACI Recommendation Grade D)

Live vaccines have generally been contraindicated in people with immune compromising conditions, with some exceptions. NACI concludes that there is insufficient evidence supporting the use of LAIV in those with immune compromising conditions in terms of both safety and effectiveness. Based on expert opinion, NACI concludes that the use of LAIV in this population is contraindicated.

Children with Asthma

- NACI recommends that LAIV can be used in children 24 months and older with stable, non-severe asthma. (NACI Recommendation Grade B)
- LAIV should not be used in those with severe asthma (as defined as currently on oral or high dose inhaled glucocorticosteriods or active wheezing) and those with medically attended wheezing in the seven days prior to vaccination.

Children with other chronic health conditions

- NACI recommends that LAIV can be used in children with chronic health conditions (excluding those with immune compromising conditions and severe asthma, as defined above). (NACI Recommendation Grade B)
    - › A limited number of immunogenicity and efficacy studies have been conducted in these populations. Based on expert review, it is expected that LAIV should be as safe, immunogenic and efficacious in immune competent children with chronic health conditions as it is in healthy children. At this time there is insufficient evidence to recommend LAIV preferentially over TIV in children with chronic health conditions.

Adults

Healthy Adults 18 to 59 years of age

- NACI recommends that LAIV can be used for the prevention of influenza in healthy adults 18 to 59 years of age. (NACI Recommendation Grade A)
  - › There is some evidence that TIV may provide better efficacy than LAIV in healthy adults, although this finding is not consistent across available studies.

Adults with Immune Compromising Conditions

- NACI recommends against LAIV for individuals with immune compromising conditions. (NACI Recommendation Grade D)

Live vaccines have generally been contraindicated in people with immune compromising conditions, with some exceptions. NACI concludes that there is insufficient evidence supporting the use of LAIV in those with immune compromising conditions in terms of both safety and effectiveness. Based on expert opinion, NACI concludes that the use of LAIV in this population is contraindicated.

Adults with other chronic health conditions

- At this time NACI concludes that there is insufficient evidence to recommend LAIV in adults with chronic health conditions. (NACI Recommendation Grade I)
- The potentially better immune response following TIV compared to LAIV in healthy adults in some studies should be considered when selecting an influenza vaccine for adults at high risk for influenza complications.

Health Care Workers providing care to individuals with immune compromising conditions

- NACI recommends that TIV, instead of LAIV, should be used for health care workers providing care to those with immune compromising conditions, unless the individual will only accept LAIV. (NACI Recommendation Grade B)
- NACI recommends that if a health care worker, or another caregiver, receives LAIV and is providing care to individuals with severe immune compromising conditions (defined as hospitalized and requiring care in a protected environment), they should wait two weeks following receipt of LAIV before continuing to provide care to such individuals. (NACI Recommendation Grade D)

Egg Allergy/hypersensitivity

- Given the lack of data around egg allergy and the intranasal vaccine FluMist®, TIV is the currently recommended product for egg-allergic individuals. Ovalbumin concentrations in FluMist® are documented to be very low and a study is currently underway to assess the use of FluMist® in egg-allergic individuals. The use of FluMist® in egg-allergic individuals will be reevaluated when further data becomes available. If FluMist® is the only option that will be considered by an egg-allergic individual, consultation with a specialist with expertise in allergies should be sought.

I.2 Background

In June 2010, an intranasal, live, attenuated, trivalent influenza vaccine (FluMist® AstraZeneca Canada)[1] was authorized in Canada. FluMist® is indicated for active immunization of individuals 2 to 59 years of age against influenza caused by specific influenza virus strains contained in the vaccine. It was first approved for use in the United States in 2003 for individuals 5 to 49 years of age, and was extended to those 2 to 49 years of age in 2007.

Two formulations of FluMist®[1] have been studied worldwide: first a frozen formulation (0.5 mL/dose) and later a refrigerated formulation (0.2 mL/dose). Both formulations were derived from the same attenuated, cold-adapted master donor virus and are designed to have comparable potency per dose and have demonstrated comparable clinical efficacy. The 0.2 mL/dose is the formulation authorized for use in Canada.

Most influenza vaccines are administered by injection and stimulate the production of immunoglobulin G (IgG) antibodies. The intranasal administration route directly stimulates local immunity [mucosal response including production of IgA and cell-mediated immune response (CMI)] and induces a systemic immune response (production of IgG and CMI).[2]

[1] FluMist® has been described in clinical studies using various terminology and acronyms such as CAIV-T, LAIV, and LAIV-T. In this document, FluMist will be referred to as LAIV (live, attenuated, influenza vaccine), except in the evidence tables, where the terminology will be consistent with the study citation.

I.3 Overview of 2011-2012 seasonal influenza recommendations

For further detail on the epidemiology of influenza and recommended recipients of influenza vaccine for the 2011-2012 season, refer to NACI's Statement on Seasonal Influenza Vaccine for 2011-2012 (at http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/acs-dcc-5/index-eng.php).

II. Methods

Details regarding NACI's evidence-based process for developing a statement are outlined in *Evidence-Based Recommendations for Immunization: Methods of the NACI, January 2009, CCDR*, available at: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/acs-1/index-eng.php).

NACI reviewed the key questions for the literature review as proposed by the Influenza Working Group, including such considerations as the burden of illness of the disease to be prevented and the target population(s), safety, immunogenicity, efficacy, effectiveness of the vaccine, vaccine schedules, and other aspects of the overall immunization strategy. The knowledge synthesis was performed by PHAC and supervised by the Working Group. This supplement reflects published literature up to April 2011. Following critical appraisal of individual studies, summary tables with ratings of the quality of the evidence using NACI's methodological hierarchy were prepared (Table 9), and proposed recommendations for vaccine use developed. The Working Group chair (Dr. Nadine Sicard) presented the evidence and proposed recommendations to NACI on June 1 and 2, 2011. Following thorough review of the evidence and consultation at the NACI meeting on June 1 and 2, 2011, the committee voted on specific recommendations. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described in the text.

III. Epidemiology

Review of the epidemiology of influenza is available in NACI's Statement on Seasonal Influenza Vaccine for 2011-2012.

IV. Vaccine

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

FluMist® [influenza vaccine (live, attenuated)] is a colourless to pale yellow liquid and is clear to slightly cloudy. It is a live, trivalent vaccine for administration by intranasal spray by a healthcare professional. Each 0.2 mL dose contains $10^{6.5\text{-}7.5}$ FFU[2] (fluorescent focus units) of live attenuated influenza virus reassortants of each of three strains of virus: influenza virus type A (H1N1); influenza virus type A (H3N2); and influenza virus type B.

LAIV is indicated for the active immunization of individuals 2 to 59 years of age against two strains of influenza A and one strain of influenza B contained in the vaccine for that influenza season. The types of viral antigens contained in LAIV conform to the current requirements for the northern hemisphere as per the World Health Organization (WHO). Annual revaccination with an influenza vaccine is recommended because immunity declines over time and because circulating strains of influenza virus can change from year to year.

[2] The strength may change with the selection of the contained influenza strains for the specific season but will always be within the specification of $10^{6.5\text{-}7.5}$ FFU.

Non-medicinal ingredients contained in each 0.2 mL dose include sucrose, dibasic potassium phosphate, monobasic potassium phosphate, gelatin hydrolysate (porcine Type A), arginine hydrochloride, monosodium glutamate, and gentamicin (a trace residual). See package insert for specific amounts of each ingredient. FluMist® contains no preservatives (e.g. thimerosal). The intranasal sprayer does not contain latex.

LAIVs are produced in specific pathogen-free (SPF) embryonated eggs. When the WHO recommends a new strain for the annual influenza vaccine, a new master seed (used to inoculate the SPF eggs) is created by reverse genetics. In this process, the haemagglutinin (HA) and neuraminidase (NA) genes of the new strain are reassorted with an appropriate master donor strain. These master donor strains have been previously cold adapted by serial passages in tissue culture cells in sequentially lower temperatures. During this process, the viruses acquire multiple mutations in internal protein gene segments yielding viruses that are (a) *cold-adapted (ca)* - they replicate efficiently at 25ºC, a temperature that is restrictive for replication of many wild-type influenza viruses; (b) *temperature-sensitive (ts)* – they are restricted in replication at 37ºC (Type B strains) or 39ºC (Type A strains), temperatures at which many wild-type influenza viruses grow efficiently; (c) *attenuated (att)* – they do not produce classic influenza-like illness. The cumulative effect of the mutations associated to the *ca, ts*, and *att* phenotypes ensure that the attenuated vaccine viruses replicate in the ciliated epithelial cells of the nasopharyngeal mucosa with no or restricted replication in the lungs due to the higher temperature in the lower respiratory airways. These biological properties enable the vaccine to elicit a protective immune response (via mucosal immunoglobulin IgA, serum IgG antibodies, and cellular immunity) without causing clinical disease.

IV.2 Stability of live attenuated viruses

Viruses isolated from vaccine recipients have demonstrated genetic stability by retaining attenuated phenotypes. In one study, nasal and throat swab specimens were collected from 17 study participants for two weeks after vaccine receipt.[3] Virus isolates were analyzed by multiple genetic techniques. All isolates retained the LAIV genotype after replication in the human host, and all retained the cold-adapted and temperature-sensitive phenotypes. A study conducted in a child-care setting demonstrated that limited genetic change occurred in the LAIV strains following replication in vaccine recipients.[4]

IV.3 Efficacy

Live attenuated influenza vaccine has been administered to over 30,000 people in controlled clinical studies over multiple years, in various regions, using different vaccine strains. Many clinical studies evaluated the primary efficacy endpoint of the incidence of culture-confirmed influenza compared to placebo or an injectable influenza vaccine (commonly referred to as TIV or trivalent inactivated vaccine) against strains that match or do not match the circulating influenza virus that season. The term "absolute efficacy" refers to comparisons of LAIV to placebo. The term "relative efficacy" is used when comparing LAIV to TIV. Since the evidence shows variability in efficacy with children and adults, this section addresses them separately.

IV.3.1 Absolute efficacy in children 2 to 17 years of age (placebo comparison)

Several placebo controlled (LAIV versus placebo) and TIV controlled studies (LAIV versus TIV) have been conducted in over 20,000 healthy and asthmatic children over seven influenza seasons to determine absolute and relative efficacy against influenza illness and complications. The first section below describes six placebo controlled randomized studies and three community-based non-randomized studies analyzed for absolute vaccine efficacy. The following section on relative vaccine efficacy describes three TIV controlled studies measuring the relative efficacy of LAIV when compared to TIV.

Belshe *et al*, in the two year (1996 & 1997) pivotal randomized placebo controlled trial, demonstrated that LAIV was highly efficacious against well-matched circulating strains in healthy young children 15 to 71 months of age[5] and also against mismatched strains in children who returned for a booster dose in the subsequent season.[6] Overall, the vaccine was 92% efficacious in preventing culture-confirmed influenza (95% CI: 88,94) and exhibited some cross-protection properties against a variant strain in

year two. In year one of the study and after two doses of LAIV, there was 96% (95% CI: 90,99) efficacy against A/H3N2 and 91% (95% CI: 78,96) efficacy against influenza B viruses. Even after a single dose, efficacy was demonstrated (89%, CI: 65,96) against antigenically matched A/H3N2 and B viruses, although protection increased when two doses were administered (94%, 95% CI: 88,97). Efficacy was also demonstrated against a mismatched strain during year two when the influenza epidemic consisted largely of influenza A/Sydney/5/97, a variant not contained in the vaccine. This variant strain caused 66/71 total influenza cases in the study population, with the remaining cases associated with A/Wuhan/359/95-like strain or influenza B strain (both strains were contained in the vaccine). In that year, the vaccine was 100% efficacious against matched strains (A/H3N2: 95% CI: 54,100) (B: 95% CI: 79,100) and 86% efficacious against the mismatched strain (95% CI: 77,93).

Two other randomized, multi-year, placebo controlled studies by Tam *et al* and Vesikari *et al* conducted in two seasons (2000 to 2002) also found that LAIV is efficacious in preventing culture-confirmed influenza caused by antigenically matched strains in vaccinated and revaccinated children. The first study by Tam *et al* was conducted in eight Asian countries with healthy children 12 to 35 months of age (first year overall vaccine efficacy 73%, 95% CI: 62,80; second year overall efficacy 84%, 95% CI: 70,92)[7]. The second study by Vesikari *et al* involved healthy children 6 to 35 months of age attending daycare in five European countries (first year overall vaccine efficacy 85%, 95% CI: 74,92; second year overall efficacy 89%, 95% CI: 82,93).[8] In Tam *et al*, there were insufficient cases of A/H1N1 or B strains to determine statistical significance, but efficacy against those strains was later determined by assessing reductions in medically attended acute respiratory illness (MAARI) against a drifted A/H1N1 and B strain by Gaglani *et al* and Halloran *et al*.[9][10] In Vesikari *et al*, when there was a good match between vaccine and circulating strains, efficacy against A/H1N1 strains was 91.8% (95% CI: 80.8,97.1) in year one, and 90.0% (95% CI: 56.3, 98.9) in year two. Efficacy against influenza B strains was 72.6% (95% CI: 38.6,88.9) in year one and 81.7% (95% CI: 53.7,91.9) in year two. Efficacy against A/H3N2 was not assessed in the first year, but in the second year when it was the predominantly circulating strain, efficacy was 90.3% (95% CI: 82.9,94.9).

Similarly, a study by Bracco Neto *et al* was conducted with healthy vaccine-naïve children 6 to <36 months of age during the 2001 and 2002 influenza seasons in South Africa, Brazil and Argentina and found a reduction in culture-confirmed influenza caused by matched and mismatched strains.[11] In year one, vaccine efficacy versus placebo in children vaccinated with one or two doses of LAIV was 57.7% (95% CI: 44.7,67.9) and 73.5% (95% CI: 63.6,81.0) respectively, against matched strains. In year two, absolute efficacy of a single dose of LAIV was 65.2% (95% CI: 31.2,82.8) and 73.6% (95% CI: 33.3,91.2) respectively, in recipients of one or two doses of LAIV in year one. Year two efficacy in recipients who received two doses of LAIV in year one and placebo in year two was 57% (95% CI: 6.1,81.7) against antigenically similar strains compared to those who received placebo in both years. Efficacy was 35.3% (95% CI: -0.3,58.7) and 20.4% against any community acquired strain and antigenically dissimilar influenza B strains, respectively. In addition, when the groups who received placebo in year one and either one dose of LAIV or placebo in year two were compared, efficacy of a single dose of LAIV was 60.3% against matched strains and 59.4% (95% CI: 32.3,76.4) against any community strain and 54.9% (95% CI:16.6,76.6) against mismatched B strains.

Lum *et al*, in 2002-2003 examined the safety and efficacy of LAIV when co-administered with measles, mumps and rubella (MMR) vaccine in 1,150 healthy children 11-24 months in Europe/Asia.[12] The safety profile of this study is discussed in the Adverse Events section of this statement. Overall vaccine efficacy against a similar subtype was 78.4% (95% CI: 50.9,91.3) and 63.8% (95% CI: 36.2, 79.8) against any subtype. LAIV efficacy was not adversely affected by the concomitant administration with another live vaccine (MMR).

The absolute efficacy of LAIV in young children outlined above has been further documented by a 2009 meta-analysis by Rhorer *et al* examining efficacy against culture-confirmed influenza as compared to placebo in randomized clinical

trials in 25,000 children 6 to 71 months of age.[13] In this analysis, combined year one vaccine efficacy (relative to placebo) for two doses in vaccine-naïve young children was 77% (p<.001) against matched strains and 72% (p<.001) against strains regardless of antigenic match in the per protocol population. It was noted that efficacy varied by strain, showing that vaccine efficacy versus placebo after two doses was 85% (95% CI: 78,90), 76% (95% CI: 70,81), and 73% (95% CI: 63,80) against antigenically similar A/H1N1, A/H3N2, and B respectively. In summary, LAIV shows high vaccine efficacy in children across all age groups when compared with placebo regardless of circulating subtype.

Rhorer *et al* also examined four multi-year placebo controlled studies to determine the combined efficacy of second-season revaccination. Considering combined results from all four trials [Belshe[5][6], Tam[7], Vesikari[8], and Bracco Neto *et al*[11]], the efficacy of LAIV following second season re-vaccination ranged from 74 to 100% for matched strains and from 47 to 87% for all strains regardless of antigenic match. Efficacy against matched strains after re-vaccination in the second year was either the same as, or higher than, efficacy after the primary (first season) vaccination. In two studies, two doses of LAIV in the first year were associated with some protection persisting through a second season without revaccination. The effectiveness rates in year two ranged from 44.8% (95% CI: 18.2,62.9) when the vaccine was mismatched on one of the circulating strains in both seasons[7] to 57.0% (95% CI: 6.1,81.7) when the vaccine was well matched to the circulating strains in both seasons.[11] Regardless, annual vaccination is recommended because protection is lower in the second year following vaccination, and because circulating strains of influenza can change from year to year.

The above studies measure the frequency of culture-confirmed influenza to assess vaccine efficacy in children. In non-randomized, community-based studies, other measures of vaccine effectiveness have been evaluated. Gaglani *et al*[9] studied healthy children aged 18 months to 18 years across three influenza seasons (1998 to 2001) in Texas, USA. The study measured the *direct* effectiveness of LAIV against influenza A/H1N1 and B infections by comparing rates of medically attended acute respiratory illness (MAARI) in LAIV recipients and age-eligible non-recipients in the intervention communities. A single dose of LAIV was received by 9,765/19,700 children aged 1.5 to 18 years during the study. It also measured the *total* effectiveness of LAIV by comparing MAARI for LAIV recipients with that of non-recipients in comparison communities where LAIV was not offered. Individuals who had received LAIV for three consecutive years up to and including 2000-2001 demonstrated overall direct effectiveness of 20% (95% CI, 14,25) on decreasing MAARI during the weeks in the 2000-2001 influenza season with an identified influenza A and B epidemic, and 17% (95% CI: 9,27) during the weeks where only influenza A (H1N1) was predominant. The estimated total effectiveness was 18% (95% CI 13, 24) and 26% (95% CI: 18,33) in the same respective periods.

In a subsequent paper, Halloran *et al* examined one of the Texan regions studied in Gagani *et al* during the 2003-2004 influenza season to determine the effect of LAIV against drift variant influenza strain in children aged 5 to 18 years.[10] Vaccine effectiveness against MAARI was similar among children 5 to 9 years (0.31, 95% CI: 0.11,0.47) and older children 10 to 18 years (0.24, 95% CI: 0.03,0.40). The overall vaccine effectiveness of LAIV compared to non-vaccinated children against MAARI was 0.26 (95% CI: 0.11,0.39). When comparing surveillance data for culture confirmed influenza for children who received LAIV and non-vaccinated children, the overall vaccine effectiveness was 0.56 (95% CI: 0.24,0.84) using data from children with a health plan only, and 0.56 (95% CI: 0.32,0.75) in all children. Although some children in this study received TIV because LAIV was contraindicated, the direct comparison of LAIV and TIV should be interpreted with caution as the LAIV and TIV groups differed in their baseline characteristics (i.e. higher percentage of individuals in the TIV group with chronic obstructive pulmonary disease (COPD) and other chronic or congenital conditions).

The Texas trial evolved into a largely school-based program for children 4 to <18 years of age, and was evaluated by Glezen *et al* for the 2007-2008 season.[14] The intervention sites (schools with LAIV administration) were compared to the comparison sites (schools without LAIV administration) during four periods in the influenza season: before the start of the vaccine program, after the start of the vaccine program but prior to the start of the influenza epidemic as determined

by regional surveillance data, during the epidemic, and after the epidemic. The risk ratios for MAARI were 0.97 (95%CI: 0.95, 1.00), 0.89 (95%CI: 0.86, 0.91), 0.90 (95%CI: 0.88, 0.92), and 0.91 (95%CI: 0.88, 0.93) for each time period respectively. A total 2,500 medical encounters were estimated to have been prevented at the intervention sites.

Other studies using LAIV in a school-based immunization program also saw reductions in outcomes related to medically-attended influenza infection[15], MAARI[16][17] and ILI[18].

IV.3.2 Relative efficacy of LAIV in children 2 to 17 years of age (TIV comparison)

Three randomized TIV-comparison studies conducted in over 12,000 children from 6 months to 18 years of age consistently demonstrated statistically significant superior efficacy of LAIV relative to an injectable, trivalent inactivated influenza vaccine, against culture-confirmed influenza[19]-[21] and MAARI[10] caused by wild-type virus strains antigenically matched to those in the vaccine, as well as against all strains regardless of match.

The relative protection provided by LAIV and TIV was first studied in two trials by Ashkenazi *et al* and Fleming *et al* in Europe and Israel during the 2002-2003 influenza season. [20][21] Ashkenazi *et al* randomized 2,187 children 6 to 71 months of age with a history of recurrent respiratory tract infections (RTIs), including, but not limited to, common colds, acute otitis media, bronchitis, pneumonia, and bronchiolitis. From this population, 2,085 children were evaluated for efficacy in the per protocol population. Treatment groups were well matched with respect to baseline characteristics, including the proportion of children with a history of wheezing in the prior 12 months (34–36%) or asthma (23%). Active surveillance for influenza was conducted during the influenza season and viral cultures were obtained to determine culture-confirmed influenza. They found that there were 53% (95% CI: 22,72) fewer cases of culture-confirmed influenza caused by vaccine-matched strains among recipients of LAIV compared with recipients of TIV (24/1,050 versus 50/1,035, respectively). Although not powered to look at efficacy across age groups, higher culture-confirmed rates of influenza in children who received TIV compared to LAIV were found in 7 of 11 age groups assessed. In the study's evaluation of health outcomes related to all-cause respiratory illness (i.e. influenza and non-influenza), LAIV recipients reported 9% (95% CI: 2,16) fewer health care provider visit days and 16% (95% CI: 10,22) fewer missed days from school or child care, compared with TIV recipients. There was no impact noted on medication or antibiotic treatment for respiratory tract infections, overnight hospitalizations or wheezing associated with influenza-like illness. In a post hoc analysis[22], LAIV was found to decrease the severity of influenza illness that occurred despite vaccination (breakthrough influenza) compared to TIV.

Concurrently, Fleming *et al* evaluated the relative efficacy of a single dose of LAIV or TIV in a randomized, open-label trial in Europe in 2,220 children 6 to 17 years of age who had a prior clinical diagnosis of asthma.[21] Subjects were excluded if they had serious chronic disease, altered immune function, and were currently receiving immunosuppressive therapy, including high-dose systemic corticosteroids (≥2 mg/kg per days or ≥20 mg/days of prednisolone or its equivalent). Of note, in spite of these exclusion criteria, in each treatment group, 69% of participants reported current inhaled steroid use and 43% had a history of systemic steroid treatment. LAIV recipients experienced 35% (95% CI: 4,56) fewer cases of influenza caused by matched strains than TIV recipients (46/1,109 versus 70/1102, respectively). In this study, the relative efficacy of LAIV versus TIV was similar for children 6 to 11 and 12 to 17 years of age. Unlike the observations by Ashkenazi *et al*, Fleming *et al* found no significant differences for any other outcome measures (e.g. health care provider visits, medication use, and days missed from school or work). As well, no difference in illness severity was noted between LAIV and TIV recipients who developed breakthrough influenza.[22]

In 2004–2005, Belshe *et al* compared the efficacy of LAIV and TIV in a multinational, randomized, double-blind study in 7,852 children 6 to 59 months of age.[19] Vaccine-naïve children were given two doses of vaccine while previously vaccinated received one dose. Study groups were well matched with regard to history of prior influenza vaccination (22–23%), history of wheezing (21–22%), recurrent wheezing (6–7%), and asthma (4%). The primary endpoint was the incidence of culture-confirmed influenza, with illness being investigated upon report of fever plus ≥1 other symptom of cough, sore throat, or runny nose/nasal

congestion. There were 45% (95% CI: 22,61) fewer cases of influenza caused by matched strains in LAIV recipients than TIV recipients (53/3,916 versus 93/3,936, respectively), and 58% (95% CI: 47,67) fewer cases caused by mismatched strains (102/3916 versus 245/3936, respectively). Comparing LAIV to TIV, this study also noted a reduction in otitis media of 51% (95% CI:22-70%) and lower respiratory tract illness of 46% (95%CI: 4-70%) for all strains combined regardless of match to the vaccine[23]. In a post-hoc analysis of the relative efficacy of LAIV versus TIV across age groups, the efficacy for all strains combined regardless of antigenic match to the vaccine was found to be similar across age groups and ranged from 42% to 57% across the four age groupings assessed.[24]

In their meta-analysis of the above studies, Rhorer *et al* also examined relative efficacy when two doses of LAIV were compared to two doses of TIV which showed vaccine-naïve children who received LAIV experienced 46% fewer cases of ILI caused by matched strains.[13] Similarly, for studies including older children who had been previously vaccinated, those receiving one LAIV dose experienced 35% fewer cases of ILI than those receiving one TIV dose. Ambrose *et al*, in 2011, also reviewed comparative studies in children 6 months to 18 years of age and concluded that each of the four comparative studies reviewed (including the three reviewed above) demonstrated that LAIV was more protective than TIV.[22]

IV.3.3 Protection from Acute Otitis Media

Since influenza is known to be associated with acute otitis media (AOM) in children, many of the abovementioned studies examined the impact of LAIV on the incidence of AOM. Block *et al* pooled and analyzed data from six placebo controlled and two TIV controlled studies with children 6 to 83 months of age.[25] The pre-specified secondary endpoint was efficacy against AOM. Of 24,046 children, 47% were younger than 24 months of age, 84% were healthy, 11% had a history of wheezing, 11% attended daycare ≥12 hours per week and 9% reported a history of two or more respiratory tract infections (e.g. common colds, AOM, bronchitis, pneumonia, and bronchiolitis) in the previous 12 months.

For the pooled analysis of the six placebo controlled studies, a total of 36 cases of AOM associated with culture-confirmed influenza due to any strain were found in 8,353 (0.4%) LAIV recipients and 165 cases were found in 5,756 (2.9%) placebo recipients. Therefore, the overall efficacy of LAIV against influenza-associated AOM was 85% (95% CI: 78.3,89.8). When analyzed by age at the time of vaccination, the incidence of AOM in influenza-positive subjects was similar in placebo-recipient children ≥24 months of age (18%) when compared with placebo-recipient children 6 to 23 months of age (16%). The incidence of AOM in influenza-positive subjects in LAIV recipients ≥24 months of age was 8%, and 12% in children 6-23 months of age. In LAIV recipients, there was higher overall efficacy against developing AOM in influenza-positive children ≥24 months of age (91%) versus 6 to 23 months (78%) of age.

In the two TIV controlled studies examined by Block *et al* (Belshe et al[19] and Ashkenazi et al[20] referred to above), 28 cases of AOM associated with culture-confirmed influenza due to any influenza strain, were found in 4,966 (0.6%) LAIV recipients and 61 cases were found in 4,971 (1.2%) TIV recipients. The relative efficacy of LAIV compared with TIV for influenza-associated AOM was 54.0% (95% CI: 27.0,71.7). As with the placebo controlled studies, the relative efficacy of LAIV compared with TIV was higher in children ≥24 months of age versus 6 to 23 months of age (61.7% versus 47.5%).

Block *et al* also examined whether LAIV had any effect on the incidence of AOM beyond simply preventing influenza illness, and analyzed the rates of AOM among placebo, LAIV and TIV recipients who developed culture-confirmed influenza. In placebo controlled trials, among children who acquired influenza despite vaccination, AOM was diagnosed in 10.3% of LAIV recipients and 16.8% of placebo recipients, representing a 38.2% (95% CI: 11.0,58.2) relative reduction in the development of AOM. The difference was statistically significant in children ≥24 months of age but not among those 6 to 23 months of age. In TIV controlled studies, among children with breakthrough influenza illness, the proportions of LAIV and TIV recipients who developed AOM were similar and not statistically significant.

IV.4 Absolute efficacy in adults 18 to 59 years of age (placebo comparison)

Clinical trial data provide evidence of efficacy and effectiveness of LAIV in adults. Over 10,000 adults were included in four randomized trials, which included one placebo controlled trial[26] and four TIV controlled studies[27-30], one of which was a wild-type challenge study[30].

Nichol *et al* conducted a large randomized, double-blind, placebo controlled trial of LAIV effectiveness during the 1997-98 influenza season in 4,561 healthy working adults 18 to 64 years of age across thirteen centres in the US.[26] There was no laboratory confirmation of influenza during this study, and the season experienced a drifted variant of the A/Wuhan/359/95 vaccine strain (A/Sydney/05/97 was the predominant circulating strain). An observed reduction of 9.7% in any febrile illness in LAIV recipients compared to placebo recipients was not statistically significant (95% CI: -2.1,20.7); however, there were significant reductions in the incidence of severe febrile illness (18% reduction; 95% CI: 7.4,28.8), and febrile upper respiratory illnesses (23.6% reduction; 95% CI: 12.7,33.2). Vaccination also led to substantial reductions in days of illness, days of work lost, days with health-care provider visits, and use of prescription antibiotics and over-the-counter medications among LAIV recipients. This study also demonstrated that LAIV provided cross-protection against the variant strain but since it did not compare LAIV with TIV, it is not known how the degree of cross-protection compared with that offered by the TIV vaccine.

IV.4.1 Relative efficacy in adults 18 to 59 years of age (TIV comparison)

In contrast to children, most comparative studies in individuals 18 to 59 years of age have found LAIV and TIV were similarly efficacious[27][30-32] or that TIV was more efficacious. [28] One study found LAIV to be somewhat more efficacious in a cohort of vaccine-naïve adults (no previous influenza vaccination).[29] A possible reason for this difference between children and adults may be that adults generally have pre-existing immunity which may interfere with response to a live virus vaccine; by comparison, children, who are generally naïve to influenza, will mount a more robust immune response.

The primary limitation of the current analysis in adults 18 to 59 years of age is that a small number of prospective randomized studies have been conducted in this age group, therefore fewer data are available and results are more variable when compared to studies in children.

One of the first randomized placebo controlled studies to determine relative protection was by Edwards *et al* over five years (1985 to 1989) in 5,201 people (n=809 under 15 years of age) in seven sites in the US.[27] For A/H1N1 disease, there were no statistically significant differences in efficacy between LAIV and TIV (85% versus 76%, respectively) regardless of illness definition. In general, relative efficacy rates were higher when there was a better vaccine match to the circulating strains than when there was poor match. For A/H3N2 disease, no significant differences were found between LAIV and TIV for preventing culture-confirmed influenza, but TIV was more efficacious than LAIV (73% versus 32%, respectively) in preventing H3N2 seroconversion. Efficacy rates for A/H3N2 disease did not differ from year to year.

Treanor *et al* conducted a TIV-comparison study during the 1995-1996 influenza season which included a wild-type influenza challenge in 103 adult volunteers 18 to 45 years of age.[30] The study evaluated protection against documented influenza, defined as viral shedding (evaluated daily for seven days after challenge) and/or ≥4-fold increase in hemagglutination-inhibition (HAI) titre (28 days after challenge) in the presence of respiratory symptoms. Subjects with baseline serum HAI antibody titers of ≤1:8 to the vaccine strains were randomized to receive LAIV, TIV, or placebo and challenged intranasally with one vaccine-like wild-type virus (A/H1N1, A/H3N2, or B) approximately 28 days later. Culture confirmed influenza occurred in 45% (14/31) of placebo recipients following wild-type virus challenge, compared with 6.9% (2/29) and 12.5% (4/32) of those given LAIV and TIV, respectively (p=.001 for LAIV versus placebo; p=.006 for TIV versus placebo; p=.67 for LAIV versus TIV). Protective efficacy was 85% (95% CI: 28,100) for LAIV and 71% (95% CI: 2,97) for TIV. There were trends toward less severe illness among LAIV recipients compared with TIV recipients and less severe illness in both vaccinated groups compared with placebo recipients. Both LAIV and TIV demonstrated statistically significant efficacy against laboratory-documented influenza compared to placebo.

A randomized, culture-confirmed field trial with healthy adults 18 to 49 years of age during three influenza seasons was evaluated by Monto *et al* and Ohmit *et al* (2004-2008). Monto *et al* reported on the 2007-2008 season and demonstrated that TIV was more efficacious than LAIV with a statistically significant difference.[28] The absolute efficacy of LAIV was estimated to be 36-51% compared to 68-73% for TIV. TIV recipients experienced a 50% (95% CI: 20,69) reduction in culture-confirmed or PCR-identified influenza compared to the LAIV cohort. Ohmit *et al* studied vaccine efficacy in the same trial for two influenza seasons. In 2004-2005, depending on whether culture, PCR or both were used to detect influenza, the observed efficacies were 48-57% for LAIV and 74-77% for TIV; the difference between TIV and LAIV were not statistically significant.[31] In 2005-2006, Ohmit *et al* noted the influenza attack rate observed in the placebo group was much lower than in the previous year (1.8% versus 7.8% respectively), rendering the study underpowered to detect vaccine efficacy.[32] Absolute efficacies ranged from 8% (95% CI: -194,67) to 61% (95% CI: -48,89) for LAIV and 16% (95% CI: -171,70) to 23% (95% CI: -153,73) for TIV and were statistically similar. No analysis of illness severity among breakthrough cases was reported for any study season.

Wang *et al* conducted a large multi-year retrospective cohort study in the United States with over three million healthy, active duty military service members 17 to 49 years of age who received LAIV or TIV during 2004-2005, 2005-2006, or 2006-2007.[29] Pregnant women were excluded from the study. The primary outcome was the first medical encounter with a diagnosis code (ICD-9 code) associated with pneumonia or influenza. The incidence rate for health care encounters, pneumonia/hospitalization were highest for the unimmunized groups and lower in the TIV cohort versus the LAIV cohort, during each season. In all three seasons, immunization with TIV was associated with lower incidence rates of health care encounters for pneumonia and influenza when compared with LAIV: 8.6 versus 18.3 (2004-2005), 7.8 versus 10.6 (2005-2006) and 8.0 versus 11.1 (2006-2007) per 1,000 person-years (all $p<.001$). Vaccine-naive (no history of influenza vaccination in previous one or two seasons) and unimmunized cohorts (no documented influenza vaccination during the season of interest) were matched by propensity scoring determined by age, sex, service branch, medical encounter history, and immunization history. The incidence rates of hospitalization for pneumonia and influenza were similar between the previously unimmunized and vaccine-naïve cohorts in both LAIV recipients (9.5 and 9.3/1,000 person-years) and the TIV recipients (7.4 and 8.2/1,000 person-years). In contrast to the general trend that TIV was more efficacious than LAIV, this study found LAIV had an effect similar to TIV in the vaccine-naïve cohort (new recruits), which further supports previous studies demonstrating that children and adults who were seropositive at baseline were less likely to have a serologic response to LAIV compared with those who were seronegative.[33]-[35]

The 2005-2006 and 2006-2007 seasons in the study by Wang *et al*, were subsequently analyzed by Eick *et al*.[36] A slightly greater protection from ILI was found in both seasons for non-recruits who received TIV compared to LAIV (adjusted incidence rate ratio, 1.17 [95% CI, 1.14-1.20] and 1.33 [95% CI: 1.30-1.36], 2005-2006 and 2006-2007 influenza seasons, respectively). However, for recruits (who were less likely to have received prior influenza vaccine, as most were 20 years of age or younger), LAIV was found to provide significantly greater protection from ILI compared to TIV, with adjusted incidence rates of ILI 22-51% and 18-47% lower among LAIV compared to TIV recipients for the 2005-2006 and 2006-2007 seasons respectively. This suggests that pre-existing immunity may play a role in determining effectiveness of LAIV, in that it may be more effective when there has been minimal lifetime exposure to the influenza virus or vaccine.

In the same meta-analysis referenced in relative efficacy for children, Ambrose *et al* concluded that in individuals 17 to 49 years of age, most comparative studies have demonstrated that LAIV and TIV were similarly efficacious or that TIV was more efficacious and that the relative efficacy of LAIV and TIV among young adults may vary depending on the specific population and the antigenic match between the vaccines and circulating strains.[22]

IV.5 Immunogenicity

LAIV administered by the intranasal route results in an immune response that is thought to mimic the immune response induced by natural infection with wild-type viruses. Resistance to influenza infection and disease results from both mucosal and systemic immunity. The biological properties of LAIV (cold-adapted; temperature-sensitive; attenuated) enable a protective immune response without causing clinical disease.

Although serum antibodies are primarily responsible for lower respiratory tract protection and are the most commonly measured correlates of protection from illness, local mucosal antibodies are critical for protection of the upper respiratory tract and may be more important to overall protection against influenza.[37] Local mucosal antibodies may also be a better indicator of immunogenicity for LAIV than serum antibody.[38] Studies have demonstrated that presence of an HAI antibody response after the administration of LAIV is predictive of protection (see Table 1). However, the absence of an antibody response after the administration of LAIV does not reflect the absence of protection, as clinical efficacy studies have shown protection in the absence of a significant antibody response.[27][30]

The immunogenicity of LAIV has been assessed in multiple studies conducted among children and adults[33][34][38]-[48] including studies where LAIV was co-administered with other live vaccines.[12][49][50] Immunogenicity was measured based on immune responses elicited by the vaccine as measured by the serum level of antibodies against the HA envelope protein of the influenza viruses (as detected by the HAI assay). LAIV has predominately been shown to be equally if not more immunogenic than TIV in children, whereas TIV was typically more immunogenic in adults. Greater rates of seroconversion to LAIV occur in baseline seronegative individuals compared to baseline seropositive individuals in both child and adult populations. As well, the duration of TIV-induced immunity has been found to be more durable in adult compared with pediatric populations, and although the decline of TIV-induced serum antibody titres in adults occurs, it is less substantial than with children.[51]

Table 1: Comparison of the serum hemagglutination-inhibition antibody responses and vaccine efficacy in children receiving LAIV against three influenza outbreaks

Season	Vaccine virus	Circulating Virus	Percent of seronegative children who seroconverted		VE% (95% CI)
			A/Wuhan/359/95	A/Sydney	
1996-1997 (Belshe)	A/Wuhan/359/95 (H3N2)	Closely matched	96	-	95 (88,97)
1996-1997 (Belshe)	B/Harbin/7/94	Closely matched	96	-	91 (78, 96)
1997-1998 (Belshe)	A/Wuhan/359/95 (H3N2)	A/Sydney/5/97 (H3N2)	100	98	86 (77, 93) vs. Sydney 100 (54, 100) vs. A/Wuhan

Naturally acquired immunity against influenza is typically longer-lived and broader than that induced by inactivated vaccines, providing protection to both antigenically similar and drifted influenza strains. LAIV has demonstrated efficacy during seasons where there was a mismatch between vaccine and circulating strains. It is suggested that LAIV may trigger immunogenic activity similar to natural infection resulting from exposure to more antigens presented by a live vaccine virus compared to an inactivated vaccine.[52] LAIV may stimulate a mucosal IgA and/or T-cell-mediated immune response, and the production of more broadly cross-reactive humoral antibodies that can confer cross-protection in circumstances where there is a suboptimal match of the vaccine and epidemic influenza strains.[26]

IV.6 Vaccine Administration and Schedule

IV.6.1 Schedule & dosage

The recommended vaccine dosage is 0.2 mL (0.1 mL per nostril) for individuals 2 to 59 years of age. For children 2 to 8 years of age inclusive who have not previously received a seasonal influenza vaccine, the recommended dosage schedule for nasal administration is one 0.2 mL dose (0.1 mL in each nostril) followed by a second 0.2 mL dose (0.1 mL in each nostril) administered at least 4 weeks later. For all other individuals, including children 2 to 8 years of age who have previously received a seasonal influenza vaccine, the recommended schedule is one 0.2 mL dose (0.1 mL in each nostril).

If the vaccine recipient sneezes immediately after administration, the dose should not be repeated.

LAIV should be administered according to the following schedule:		
Age Group	**Vaccination Status**	**Dosage Schedule**
Children* (2 to 8 years of age)	Not previously vaccinated with seasonal influenza vaccine	Two doses (0.2 mL[a] each, at least 4 weeks apart)
	Previously vaccinated with seasonal influenza vaccine	Single dose (0.2 mL[a])
Children, adolescents and adults 9 to 59 years of age	Not applicable	Single dose (0.2 mL[a])

[a] Administer as 0.1 mL per nostril

** LAIV is not recommended in persons <2 years of age due to increased risk of wheezing (See Adverse Events).*

IV.6.2 Route of administration

LAIV is administered by the intranasal route by a healthcare provider. Each pre-filled glass sprayer contains a single dose of LAIV; approximately one-half of the contents should be administered into each nostril. There is a dose divider clip in the plunger to ensure that 0.1 mL is administered in each nostril. Refer to the product monograph for administration instructions. Once LAIV has been administered; the sprayer should be disposed of according to the standard procedures for medical waste.

IV.7 Storage Requirements

LAIV should be stored in a refrigerator between 2° to 8°C upon receipt and until use. The product must be used before the expiration date on the sprayer label. Do not freeze.[1]

IV.8 Simultaneous Administration with Other Vaccines

Three studies evaluated the immune response and safety after concomitant administration of LAIV with MMR,[12][49] varicella,[49] and the oral polio virus (OPV).[50] Seroresponse rates and GMT titres for MMR (≥96%) and varicella (≥82%) vaccines were found to be similar with concurrent administration of LAIV or placebo. The results of these studies demonstrated that LAIV can be safely administered concurrently with MMR and varicella vaccines to young children in routine clinical practice without reducing the immunogenicity or safety of any of the vaccines. If not administered during the same visit as other live virus vaccines (e.g. MMR or varicella), administration of the two live vaccines should be separated by at least four weeks.

IV.9 Adverse Events

In clinical studies, the safety of LAIV was evaluated in over 28,500 children and adolescents 2 to 17 years of age and over 4,350 adults 18 to 59 years of age. The most common adverse reaction observed in clinical studies in all ages was nasal congestion/rhinorrhea.[1] Adverse events have been identified in different age groups and time periods post-vaccination.

IV.9.1 Post-Market Adverse Drug Reactions

Since the authorization of FluMist® in June 2010, only a small number of post-marketing adverse events have been reported by the manufacturer, mostly involving non-serious events such as nasal symptoms with or without subsequent complaints of a “cold”. Due to the limited Canadian data

at this point in time, post-market adverse drug reactions observed in the US will be detailed here for information purposes as it has been licensed there since 2003.

The US Vaccine Adverse Event Reporting System (VAERS), a passive surveillance system, conducted an analysis of reported adverse events from 2003-2005[53] representing over 2.5 million persons who received LAIV during this timeframe. Table 2 provides the reactions identified during this post-marketing evaluation. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to estimate their incidence or establish a causal relationship to vaccine exposure.

Table 2: Summary of reported adverse events in VAERS, 2003-2005, following administration of LAIV[54]

Main condition	All reports: No. (% of all LAIV –associated reports) N = 460	All serious reports: No. (% of all serious LAIV-associated reports) N = 40
Respiratory (influenza-like illness, vaccine failure, rhinitis, pharyngitis, tracheitis, secondary transmission, sinusitis, asthma, pneumonia, other)	217 (47.2)	15 (37.5)
Constitutional (weakness/tiredness, fever, headache, dizziness, arthritis)	67 (14.6)	4 (10.0)
Allergic (possible anaphylaxis, other)	54 (11.7)	6 (15.0)
Abdominal symptoms (vomiting, nausea)	33 (7.2)	1 (2.5)
Ear–nose–throat (epistaxis, nose ulcer, redness, ear infection, oral herpes simplex)	18 (3.9)	0 (0.0)
Ocular (edema, retinal hemorrhage, eye pain)	7 (1.5)	1 (2.5)
Neurological (Guillain–Barré syndrome, Bell's palsy, febrile seizures, encephalomyelitis, encephalitis, other)	10 (2.2)	7 (17.5)
Cardiovascular (pericarditis, myocardial infarction, chest pain/discomfort)	10 (2.2)	3 (7.5)
Other (vaccine administration error, other)	44 (9.6)	3 (7.5)

A follow-up analysis on data from the VAERS for the period October 2007-April 2009 was conducted looking specifically into adverse event reports in children 24 to 59 months of age.[55] After over 10 million doses distributed to people of all ages, there were 222 relevant reports in children and the most frequently reported adverse event was fever (47%), vomiting (28%) and rhinitis (21%). Six reports identified asthma exacerbation in children with a history of asthma, and eight reports identified wheezing in children without a history of asthma. No serious adverse events, such as death, anaphylaxis, Guillain-Barré Syndrome, or encephalitis were reported.

A post-licensure evaluation of LAIV by MedImmune is nearing completion.[56] The evaluation assesses outcomes in children and adults age 5 to 49 years from October 2003 to March 2008. It compares 63,061 unique subjects who received LAIV to 62,492 subjects receiving TIV and 71,949 unvaccinated subjects. Preliminary results have identified 114 serious adverse events in 107 individuals within 42 days post-vaccination, including one death. Five serious adverse events were considered potentially related to LAIV, including three cases of Bell's Palsy, one case of nonspecific paroxysmal spell, and one case of migraine/sinusitis. Nine deaths occurred within 180 days of LAIV vaccination, but were considered unrelated to LAIV (three deaths in subjects 9 to 17 years, six deaths in subjects 18 to 49 years). The rate of death was not considered statistically significant when compared to four deaths each occurring in the TIV and unvaccinated cohorts. Asthma and wheezing events were not statistically increased in the LAIV cohort, and no anaphylactic events were reported within 36 hours post-vaccination.

IV.9.2 Adverse Events in Children and Adolescents 2 to 17 years of age in Clinical Trials

Several placebo controlled studies[7][8][11][50][57]-[59] and TIV controlled studies[19]-[21] were pooled to evaluate solicited events occurring in children and adolescents 2 to 17 years of age. Table 3 presents the solicited events that occurred within ten days of administering the first dose of LAIV in at least 1% of recipients, and compares rates from placebo and TIV-controlled studies. A total of 7,336 children and adolescents 2 to 17 years of age received at least one dose of LAIV in year one of dosing in controlled studies and provided data for the pooled safety analysis. In these studies, solicited events were documented within 10 days post vaccination. Solicited events after the second dose of LAIV were similar to those after the first dose, and were generally observed at a lower frequency. Similar findings were noted by Ambrose *et al* after their analysis of LAIV reactogenicity during second season revaccination, which is that side effects were lessened in year two.[22] The most common solicited adverse events, observed during days 0-10 after the first dose, included runny/stuffy nose, cough, decreased appetite, irritability, abdominal pain, decreased activity, headache, vomiting, sore throat, muscle ache, chills, and fever. There were no observed differences in adverse events following LAIV administration between age groups in the 2 to 17 year age bracket.

Table 3: Summary of solicited events observed during days 0 to 10 after first dose for LAIV and either placebo or TIV control recipients; children and adolescents 2 to 17 years of age.[1]

	Placebo Controlled Studies		TIV Controlled Studies	
Solicited Event	**LAIV N=258-3,245[a] %**	**Placebo N=191-1,994[a] %**	**LAIV N=3,931-4,108[a] %**	**Injectable Influenza Vaccine N=3,982-4,118[a] %**
Any solicited event	74.2	69.5	70.4	64.8
Runny/stuffy nose	63.7	56.9	56.7	45
Cough	39.9	41.6	33.6	35.6
Decreased Appetite	24.1	21.7	15.9	15.2
Irritability	21.2	19.7	13.8	12.5
Abdominal Pain	14.1	12.3	12.3	11.5
Decreased Activity[b]	13.8	11.7	13.1	11.8
Headache	13.4	6.5	13.8	12.3
Vomiting	12.3	13.7	6.8	6.9
Sore Throat	10.1	8.2	11.6	11.2
Muscle Aches	8.1	5.2	5.7	6.9
Chills	6.2	7.8	5.8	5.1
Fever				
≥38.0ºC	11.2	9.7	9.3	8.6
≥38.5ºC	6.0	5.6	5.1	5.1
≥39.0ºC	2.5	2.5	2.3	2.4
≥39.5ºC	1.1	1.0	0.8	0.9

[a] Number of subjects evaluated for the specific solicited event. Range reflects differences in data collection between the pooled studies, which have different sample sizes.

[b] Collected as decreased activity/tiredness/weakness/malaise

IV.9.2.1 Serious Adverse Events (children/adolescents)

Days 0-42

In the same pooled safety analysis for children and adolescents, 0.45% (129/28,873) of those who received LAIV reported at least one serious adverse event (SAE) during days 0 to 42 post-dose in the first year of dosing. The majority of these were either infectious (0.23%) or respiratory (0.05%) events, including gastroenteritis, pneumonia, otitis media, and asthma. During days 0 to 42 post dosing in TIV controlled studies, 0.75% (32/4,245) of individuals who received LAIV and 1.01% (43/4,278) individuals who received injectable influenza vaccine reported at least 1 SAE, and in placebo controlled studies, 0.49% (52/10,693) of individuals who received LAIV and 0.55% (31/5,677) of individuals who received placebo reported at least one SAE.

Days 0-180

Of the 2.22% (182/8,202) individuals who received LAIV and reported at least one SAE during days 0 to 180 post-dose in the first year of dosing, the majority reported infectious (1.52%), respiratory (0.28%) or gastrointestinal (0.23%) events, including pneumonia, gastroenteritis, asthma, and otitis media. During days 0-180 post dosing in TIV controlled studies, 2.28% (94/4,130) of individuals who received injectable influenza vaccine reported at least one SAE, and in placebo controlled studies, 2.91% (70/2,408) of individuals who received LAIV and 2.72% (42/1,546) of individuals who received placebo reported at least one SAE.

IV.9.3 Wheezing

Earlier studies[60] have suggested an association with wheezing in young children after receipt of LAIV while others have not. [20][61] A pivotal multi-centre efficacy trial[19] was conducted in over 7,800 children 6 to 59 months of age in 2004-2005 by Belshe *et al* and showed the percentage of all subjects reporting medically significant wheezing (MSW)[3] through 42 days post-vaccination was similar between groups (3.9% for LAIV versus 3.1% for TIV recipients). Upon analysis by subgroup, however, the rates of wheezing were statistically higher among children 6 to 23 months of age (5.9% LAIV versus 3.8% TIV) during weeks 2, 3, and 4 after vaccination. The rate of wheezing was not increased in LAIV recipients 24 months of age and older (2.1% LAIV versus 2.5% TIV).

Among vaccine-naïve children in this study, wheezing after the first dose was more common with LAIV than with TIV, primarily among children 6 to 11 months of age; in this age group, 12 additional episodes of wheezing were noted within 42 days after receipt of dose one in recipients of LAIV (3.8%) than among recipients of TIV (2.1%, p=.076).

A total of 18 children were hospitalized (11/4,179 [0.3%] LAIV versus 7/4173 [0.2%] TIV) in association with an adverse event that met the protocol definition of MSW within 42 days of dosing. Two-thirds (12/18) of the children were 6 to 23 months of age, of whom nine [0.5%] were in the LAIV group and three [0.2%] were in the TIV group. Of the nine children in the LAIV group, two had a past history of wheezing or asthma, one had Respiratory Syncytial Virus (RSV) infection, and two children had both a past history of wheezing or asthma and RSV infection. Of the three children in the TIV group, one had RSV infection, one had a past history of wheezing or asthma and RSV infection, and one had a past history of wheezing or asthma and *Mycoplasma* infection. No deaths resulted from these events and none of the hospitalized children required mechanical ventilation or admission to an intensive care unit. There was no difference in severity of outcomes between LAIV and TIV groups. The rate of hospitalizations was not increased in LAIV recipients ≥12 months of age.

[3] MSW defined as the presence of wheezing on a physical examination conducted by a health care provider, accompanied by at least one of the following: sign of respiratory distress: tachypnea, retractions, or dyspnea; hypoxemia (O_2 saturation <95%); or a new prescription for a daily bronchodilator.

Table 4: Comparison of LAIV and TIV on hospitalizations and medically significant wheezing[19]

Adverse Reaction	Age Group	LAIV	TIV Control[i]
All cause hospitalizations[ii]	6-23 months (n=3967)	4.2%	3.2%
	24-59 months (n=4385)	2.1%	2.5%
Wheezing[iii]	6-23 months (n=3967)	5.9%	3.8%[iv]
	24-59 months (n=4385)	2.1%	2.5%

[i] Injectable influenza vaccine made by Sanofi Pasteur inc
[ii] from randomization through 180 days post last vaccination
[iii] wheezing requiring bronchodilator therapy or with significant respiratory symptoms evaluation from randomization through 42 days post last vaccination
[iv] statistically significant difference, (95% CI: 7.2-3.38)

IV.9.4 Children with Asthma

In 1976, a small study by Storms *et al* with 20 asthmatics and 9 controls 18 to 57 years of age examined safety and immunogenicity of LAIV.[62] This vaccine was derived from the strains A/England/42/72 and A/PR8/34. In subjects with a low influenza type A antibody titer, there was a 4-fold rise in titer to the vaccine, whereas those subjects with a high baseline titer showed no rise. There were no significant changes in pulmonary function and no significant adverse reactions reported. Redding *et al* also examined LAIV safety in 1997 with 48 moderate to severely (but stable) asthmatic children and adolescents 9 to 17 years of age.[63] The percent change in forced expiratory volume at one second (FEV_1) scores and on days two to five thereafter were similar in vaccine and placebo groups (0.2 versus 0.4%, p=.78). The groups were similar in terms of post-vaccination symptoms (night-time awakenings, daily use of rescue medication) within 10 days and there were no serious adverse events in either group though two individuals in the LAIV group had a recurrence of asthma post-vaccination which could not be definitively associated with the vaccine due to small sample size. In a large multi-year trial (1998-2002) with over 12,000 healthy children 1.5 to 18 years of age, a cohort each year (range 11-18%) with a history of intermittent wheezing were examined to assess safety and effectiveness of LAIV in this population.[64] This study assessed rates of medically-attended acute respiratory illness (MAARI), including asthma exacerbation, at several reference points (days 0-14 and 0-42 days post LAIV) and found no increased risk for MAARI, including asthma exacerbation. This did not differ between single dose recipients and those receiving two to four consecutive annual doses.

Subsequently, Fleming *et al* compared LAIV to TIV in over 2,000 children and adolescents with a clinical diagnosis of asthma.[21] In this 2002-2003 study, not only was LAIV well tolerated, but it was shown to have higher relative efficacy versus TIV with matched strains (34.7%) as well as any strain (31.9%). Similar to Redding's findings, there was no significant difference between LAIV and TIV groups in the incidence of asthma exacerbations post-vaccination.

IV.10 Adverse Events in Adults 18 to 59 years of age

Twelve placebo controlled studies and three TIV controlled studies including over 3,300 adults ≥18 to 59 years of age were pooled to evaluate solicited events.[1] Table 5 summarizes solicited events and rates occurring in at least 1% of LAIV recipients. In these studies, solicited events were documented for six days post vaccination. The solicited AEs observed during days 0-6 post-dose were runny/stuffy nose, headache, sore throat (note, the incidence of sore throat was higher in adults than in children), malaise, muscle ache, cough, chills, fever, decreased appetite, abdominal pain/stomach ache, and vomiting.

Table 5: Summary of solicited events observed during days 0 to 6 after dose for LAIV and either placebo or TIV control recipients; Adults 18 to 59 years of age.[1]

	Placebo Controlled Studies		TIV Controlled Studies	
Solicited Event	LAIV N=64 – 3,265[a] %	Placebo N=65 – 1,711[a] %	LAIV N=10 - 80a %	Injectable Influenza Vaccine N=11 - 77[a] %
Any solicited event	69.1	58.9	62.5	58.4
Runny/stuffy nose	43.6	26.2	40.0	33.8
Headache	37.5	34.5	25.0	36.4
Sore throat	24.7	15.2	15.0	11.7
Malaise[b]	23.8	19.3	11.4	20.5
Muscle ache	15.4	13.7	16.3	18.2
Cough	13.1	10.2	18.8	14.3
Chills	7.7	5.6	6.3	6.5
Decreased appetite	5.8	8.9	2.3	9.1
Abdominal pain/stomach ache	4.7	6.2	0.0	9.1
Vomiting	3.5	3.8	2.3	2.3
Fever				
≥38.0ºC	0.9	1.2	2.5	0.0
≥38.5ºC	0.2	0.4	1.3	0.0
≥39.0ºC	0.1	0.0	1.3	0.0

[a] Number of subjects evaluated for the specific solicited event. Range reflects differences in data collection between the pooled studies, which have different sample sizes.

[b] Collected as decreased activity/tiredness/weakness/malaise

IV.10.1 Serious Adverse Events (Adults 18 to 59 years of age)

In the pooled safety analysis for individuals 18 to 59 years of age, 0.18% (8/4,376) of individuals exposed to LAIV reported at least one SAE during days 0-28 post-dose. Two gastroenteritis events were reported; all other events occurred in one individual each. In placebo controlled studies, 0.18% (6/3,315) of individuals who received LAIV and 0.29% (5/1,740) of individuals who received placebo reported at least one SAE during days 0-28 post-dose.[1]

There were two deaths reported within 180 days of receipt of LAIV: one due to homicide and one due to drowning. In addition, four subjects died within 180 days of receipt of concurrent LAIV and injectable influenza vaccine in a study that enrolled subjects with stable COPD[65]; two due to COPD; one due to a gastrointestinal hemorrhage; and one due to an acute myocardial infarction. None of these deaths were considered to be related to LAIV.

IV.11 Special populations

IV.11.1 Adults ≥60 years of age

The use of LAIV in adults ≥60 years of age does not have regulatory approval in Canada; however data on use of LAIV in this population is published and are included in this statement because they provide some information regarding adults with chronic conditions.

Forrest *et al* directly compared the safety and efficacy of LAIV versus TIV in over 3,000 adults ≥60 years of age in South Africa in 2002. Over 90% of participants reported underlying medical conditions, including cardiovascular disease (64%), endocrine/metabolic disease (36%), and respiratory conditions (18%). The relative efficacy for LAIV versus TIV was -49% (95% CI: -259,35).[66] Results for this study should be interpreted with caution since there was low incidence of influenza during that season in South Africa, however individuals with breakthrough illness showed less feverishness and less fever in LAIV recipients than in TIV recipients.

An earlier (2001) placebo controlled randomized study by De Villiers *et al,* also conducted in South Africa, investigated the absolute efficacy, safety and immunogenicity of LAIV in 3,242 adults ≥60 years of age.[67] Many of the participants had chronic underlying conditions (hypertension, cardiac disease, diabetes, hypothyroidism, asthma and COPD). Reactogenicity events were higher in LAIV than placebo recipients during 11 days post-vaccination (p=.042), including runny nose/nasal congestion, cough, sore throat, headache, muscle aches, tiredness, and decreased appetite. However, this was the first study in this age group to demonstrate efficacy of LAIV against culture-confirmed influenza. Overall efficacy against well matched strains was 42.3% (95% CI: 21.6,57.8). Post-hoc analysis in subjects 60 to <70 years of age was 41.8% and -22.7% against A/H3N2 and B, respectively and 65.7% and 9.9% respectively for subjects ≥70 years.

In 2008-2009, Gorse *et al*[65] studied 2,215 veterans ≥50 years of age with COPD and found the relative efficacy of TIV + LAIV compared with TIV + placebo in the prevention of laboratory-documented influenza illness was 16%, with confidence intervals overlapping zero (95% CI: –22,43) for any influenza strain. Although this study did not show efficacy of LAIV against laboratory-confirmed influenza, recipients who were administered both TIV and LAIV had improved chronic lung disease severity index scores.

The efficacy of LAIV administered simultaneously with TIV has also been studied in older adults.[68] Treanor *et al* randomized 523 residents of a nursing home to receive TIV + intranasal placebo versus TIV + monovalent A/H3N2 LAIV over three years (1987-1989). Relative protective efficacy of TIV + LAIV versus TIV+placebo recipients against laboratory-confirmed influenza A was 61% (95% CI: 18,82). In 1997, Jackson *et al* also conducted a study involving co-administration of TIV with either LAIV or placebo to 200 individuals aged 65 years and older to assess the safety and tolerability of LAIV in individuals with at least one additional risk factor for influenza morbidity (chronic cardiovascular or pulmonary conditions or diabetes mellitus). The safety and tolerability of LAIV plus TIV following vaccination was similar to that of placebo plus TIV with the exception of a higher incidence of sore throat, which is a similar finding in studies with younger adults.[69] No other reactogenicity symptom was statistically associated with receipt of LAIV. These studies demonstrate that there may be additional protective benefits against influenza A when LAIV is combined with TIV in the elderly. These findings, though relatively small sample size, demonstrate the need for further research with LAIV in this age group.

IV.11.2 Individuals with chronic health conditions

There are very limited data available on the use of LAIV in children and young adults with underlying chronic medical conditions. Although safety in children two years of age and older with mild to moderate asthma has been established, data in children with other pulmonary diseases or with chronic cardiovascular, metabolic or renal diseases are limited.

A post-marketing evaluation was conducted by Tennis et al[70] on the frequency of use and safety of LAIV in children for whom the vaccine was not recommended, as defined by the Advisory Committee on Immunization Practices in children under 24 months of age, or children with asthma, recurrent wheezing or altered immune competence. Data was obtained from a health insurance database on vaccinations between 2007 to 2009. Reports of LAIV vaccination in

children <24 months of age or children 24-59 months with asthma or immune compromising conditions were infrequent. However, LAIV immunization in children aged 24-59 months with wheezing occurred at a similar frequency as in the populations of children recommended for the vaccine. No safety signals were identified. The number of children vaccinated was insufficient to detect rare events.

In the studies outlined above in adults with chronic underlying medical conditions, the safety profile of LAIV was similar to the safety profile in individuals without these conditions. The absolute or relative efficacy of LAIV in older adults with chronic conditions, as in the healthy adult population, remains questionable.

IV.12 Contraindications and Precautions

IV.12.1 Contraindications

Children <2 years of age

Do not administer LAIV to children <24 months of age due to increased risk of wheezing (see Section IV.9.3).

Hypersensitivity

LAIV should not be administered to anyone with a history of anaphylaxis to a previous dose of the vaccine or have a history of hypersensitivity (especially anaphylactic reactions) to any of the non-medicinal ingredients contained in the vaccine (see Section IV.1)

Use of Aspirin with LAIV

LAIV is also contraindicated in children and adolescents (2 to 17 years of age) currently receiving aspirin therapy or aspirin-containing therapy because of the association of Reye's syndrome with aspirin and wild-type influenza infection.

Pregnancy

LAIV should not be administered to pregnant women because of the lack of safety data at this time. However, no unexpected patterns of pregnancy complications or fetal outcomes have been identified after the inadvertent administration of LAIV to pregnant women. A 19-year (1990-2009) review of the US Vaccine Adverse Event Reporting System (VAERS) was completed by Moro *et al* examining the reported incidence of adverse events after receipt of TIV and LAIV in pregnant women.[71] From July 1, 2003 through June 30, 2009 VAERS received 27 reports of pregnant women who inadvertently received LAIV. No AEs were noted in 16 of the 27 reports. Seven reports were systemic/generalized reactions, three were spontaneous abortions, and one was a serious event with a threatened abortion. Since causality cannot be determined in passive surveillance systems such as VAERS, data should be interpreted with caution. The effect of LAIV on embryo-fetal and pre-weaning development was evaluated in developmental toxicity studies of pregnant rats and pregnant ferrets showing no observed adverse effects on pregnancy, parturition, lactation or embryo-fetal development.[2] No adverse effects on pre-weaning development were observed in the rat study and no fetal malformations or other evidence of teratogenesis were observed. Until additional safety data on the use of LAIV in pregnant women become available it should not be administered to these individuals.

It is not known whether LAIV is excreted in human milk; however LAIV is not contraindicated in breastfeeding women.

Asthma

LAIV should not be administered to individuals with severe asthma (as defined as currently on oral or high dose inhaled glucocorticosteriods or active wheezing) and those with medically attended wheezing in the seven days prior to vaccination. Based on the trial results, LAIV can be considered safe and efficacious in stable asthmatics.

Immune Compromising Conditions

Live vaccines have generally been contraindicated in people with immune compromising conditions, with some exceptions. LAIV is not recommended for individuals with immune compromising conditions since data supporting the safety and efficacy of LAIV in people who are immune compromised are limited. The available data in individuals with immune compromising conditions are detailed below. Studies include evaluation in patients with HIV and a small cohort of children with cancer.

Safety of LAIV was first evaluated in 57 HIV+ and 54 HIV- adults 18 to 58 years of age in a randomized, double-blind, placebo controlled study.[72] HIV infected participants were to have a CDC class of A1-2 and a plasma HIV RNA polymerase

chain reaction (PCR) measurement of <10,000 copies/mL and 1200 CD4 cells/mm3 within 3 months prior to vaccination and were to be on a stable antiretroviral regimen if they had <500 CD4 cells/mm3. In this study, there were no serious adverse events attributable to LAIV, and vaccine shedding in HIV+ individuals was comparable to that seen in healthy populations. No adverse effects on HIV viral load or CD4 counts were identified following LAIV administration. King *et al* also assessed the safety of LAIV to 59 relatively asymptomatic or mildly symptomatic HIV+ children and HIV- children.[73] There were no significant differences found in rates of reactogenicity and vaccine-related adverse events after placebo or LAIV within each group. There were no significant changes in geometric mean HIV RNA concentrations, CD4 counts or CD4% or prolonged or increased quantity of LAIV virus shedding.

Subsequently Levin *et al*[74] assessed the comparative safety and antibody responses in 243 HIV+ children ≥5 to <18 years of age receiving stable antiretroviral therapy. Participants were stratified by immunologic status and randomly assigned to receive LAIV or TIV. The safety profile after LAIV or TIV closely resembled the previously reported tolerability to these vaccines in children without HIV infection. Post-vaccination HAI antibody responses and shedding of LAIV virus were also similar, regardless of immunological stratum, to children without HIV infection.

The effectiveness of LAIV in preventing influenza-like illness in HIV+ individuals has not been evaluated.[2]

Halasa *et al* conducted a multicentre, randomized, double-blind study of LAIV versus placebo in children 5 to 17 years of age with cancer to assess reactogenicity, adverse events, immunogenicity, and shedding in 20 subjects (n=10 LAIV, 10 placebo).[75] Ten of these subjects had hematologic malignancy (LAIV, n=4, placebo n=6); ten had solid tumors (LAIV, n=6; placebo, n=4). LAIV resulted in an increased incidence of runny nose/nasal congestion occurring in all LAIV recipients; no related SAEs were observed. Four of ten LAIV recipients shed vaccine virus, with none exceeding 7-10 days duration. LAIV demonstrated modest immunogenicity by HAI (≥4 fold rise for any strain, 33%) and microneutralization assays ((≥4 fold rise for any strain, 44%).

IV.12.2 Precautions

Egg Allergy/hypersensitivity

Given the lack of data around egg allergy and the intranasal vaccine LAIV, TIV is the currently recommended product for egg-allergic individuals. Ovalbumin concentrations in LAIV are documented to be very low and a study is currently underway to assess the use of LAIV in egg-allergic individuals. The use of LAIV in egg-allergic individuals will be reevaluated when further data becomes available. If LAIV is the only option that will be considered by an egg-allergic individual, consultation with a specialist with expertise in allergies should be sought.

Neurologic

It is not known whether influenza vaccination is causally associated with increased risk of recurrent Guillain-Barré Syndrome (GBS) in persons with a previous history of GBS due to any cause. Avoiding subsequent influenza vaccination of persons known to have had GBS within eight weeks of a previous influenza vaccination appears prudent at this time.

Drug Interactions

Although no data exists on Reye's syndrome and LAIV, because of a theoretical risk, it is recommended that aspirin-containing medications given to children younger than 18 years be delayed for four weeks after vaccination with LAIV. For children or adolescents <18 years of age who are receiving ongoing aspirin therapy or aspirin-containing therapy, vaccination with TIV should be considered instead of using LAIV.

It is also recommended that LAIV not be administered until 48 hours after antiviral agents active against influenza (e.g. oseltamivir and zanamivir) are stopped, and that antiviral agents not be administered until two weeks after receipt of LAIV unless medically indicated. If antiviral agents are administered within this time frame (from 48 hours before to two weeks after LAIV) revaccination should take place at least 48 hours after the antivirals are stopped.[76]

Nasal congestion & Illness

Persons with serious acute febrile illness should usually not be vaccinated until their symptoms have abated. Those with non-serious febrile illness (such as mild upper respiratory tract infections) may be given influenza vaccine. However,

if nasal congestion is present that might impede delivery of the vaccine to the nasopharyngeal mucosa, deferral of administration should be considered until resolution of the illness, or TIV should be considered instead.

No data exist about concomitant use of nasal corticosteroids or other intranasal medications.

Health Care Workers or others providing care to persons with severe immune compromising conditions

TIV should be used for health care workers providing care to those with immune compromising conditions, unless LAIV is the only product the health care worker will accept. If a health care worker, or another caregiver, receives LAIV and is providing care to individuals with severe immune compromising conditions (hospitalized and receiving care in a protected environment), they should wait two weeks following receipt of LAIV before continuing to provide care to such individuals.

IV.12.3 Other considerations

Shedding/transmission

There is an inversely proportional relationship observed between age and incidence of shedding vaccine virus. [77]-[79] Although both children and adults may shed vaccine virus when vaccinated with LAIV,[72]-[74][78]-[81] younger individuals are more likely to shed and shed higher titers than older individuals. The frequency of shedding decreases with age, with 69%, 44%, 27%, and 17% of individuals 2-4 years, 5-8 years, 9-17 years, and 18-49 years of age shedding virus following vaccination.[77,78] Shedding is rare after day 11 following vaccination, although children may shed for a mean duration of 7.6 days. [80]

Peak titers of viral shedding occur around the second day post-vaccination, but in lower amounts than would occur with infection by wild-type influenza virus. Talbot *et al* showed that viral titers ranged from 0.4 to 3.0 TCID/mL (tissue culture infective dose) in adults in the respiratory tract, while the mean titers of virus needed for infectivity range from 4.9 to 6.4 TCID/mL in adults.[79]

Shedding is not synonymous with transmission; however in rare instances, shed vaccine viruses can be transmitted from vaccine recipients to unvaccinated persons. A study conducted in a Finnish daycare of 197 children 8 to 36 months of age resulted in one instance of transmission of a vaccine strain to a placebo recipient.[80] Symptoms reported for this child were similar to those reported in the treatment group and included runny nose/nasal congestion, irritability, and cough. Statistical modeling estimated the probability of transmission to a subject in a contact group containing a single subject vaccinated with LAIV to be 0.58% (95% CI: 0,1.7). For subjects in contact with two, three, four, or five subjects vaccinated with LAIV, the probability of transmission was estimated to be 1.16%, 1.73%, 2.30% or 2.87% respectively. Serious illness has not been reported among unvaccinated persons who have been infected inadvertently with vaccine viruses.

Although no transmission of LAIV in a health care setting has ever been reported, vaccine recipients should be informed that LAIV is an attenuated live virus vaccine and has the theoretical potential for transmission to immune compromised contacts. Because the vaccine is cold-adapted, cannot replicate at normal body temperature, and fairly low viral titers are shed, the risk of transmitting the vaccine virus to a severely immune compromised person and causing severe infection appears to be extremely low. However, due to the theoretical risk of transmission, health care providers and other close contacts of severely immune compromised hospitalized patients requiring care in a protected environment should avoid contact with these patients for at least two weeks following vaccination.

V. Recommendations

Based on the available evidence NACI makes the following recommendations with respect to the use of LAIV. These recommendations are intended to be considered in combination with NACI's existing recommendations regarding recommended recipients of influenza vaccine.

For a detailed list of recommended recipients of influenza vaccine, refer to NACI's Statement on Seasonal Influenza Vaccine for 2011-2012 (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/acs-dcc-5/index-eng.php).

Children

V.1 Healthy Children and Adolescents 2 to 17 years of age

Healthy Children 2-17 years of age

- Based on effectiveness, efficacy, and immunogenicity data, NACI recommends LAIV for use in healthy children and adolescents 2-17 years of age. Available data indicates that LAIV would be preferred over TIV in this population, although NACI recognizes that other programmatic considerations will impact the implementation of this recommendation in publicly-funded programs (NACI Recommendation Grade A)

Numerous randomized placebo controlled studies in children have demonstrated efficacy, immunogenicity and safety of LAIV in the prevention of culture-confirmed influenza in children. These studies assessed reactogenicity and side effects of the vaccine, which demonstrated minimal side effects. Any reactogenicity events (e.g. runny/stuffy nose; headache, tiredness) that were experienced after the first dose of LAIV were reduced with successive dosing. In these studies, LAIV consistently demonstrated superior efficacy against culture-confirmed influenza as compared to placebo or TIV in children. In a 2009 meta-analysis of placebo controlled studies (comprising over 25,000 children), LAIV efficacy in vaccine-naïve children was 77% (95% CI: 72,80) against culture-confirmed influenza for antigenically similar subtypes for all strains, and 72% (P<0.001) against culture-confirmed influenza for subtypes regardless of antigenic similarity[13].

The same meta-analysis[13] examined the relative efficacy of LAIV compared to TIV in children. All studies examined in the meta-analysis (comprising over 13,000 children) showed a lower risk of contracting influenza among children given LAIV than among those given TIV for matched and mismatched strains.

Based on the absolute efficacy of LAIV and relative efficacy of LAIV versus TIV in controlled studies and post-marketing safety data, NACI considers LAIV to be safe, efficacious, and immunogenic in children. . The decision to include LAIV among the influenza vaccine products available to children aged 2 to 17 years of age as part of publicly funded Provincial/Territorial programs will depend on multiple factors such as cost-benefit evaluation and other local programmatic and operational factors such as increased cost, shorter shelf-life and the development of implementation strategies. Factors to consider include that administration of LAIV is well received by children and caregivers in clinical trials. Young children would require minimal cooperation or very brief restraint to allow administration of the vaccine intranasally[52]. Research has shown that even a single dose of LAIV is efficacious and offers protection in children who often are non-compliant with the more optimal two-dose regime[7][11], an issue noted by Jackson *et al* in evaluating compliance to two-dose recommendations for influenza vaccines.[83]

V.2 Children with Immune Compromising Conditions

- NACI recommends against LAIV for individuals with immune compromising conditions. (NACI Recommendation Grade D)

Live vaccines have generally been contraindicated in people with immune compromising conditions, with some exceptions. NACI concludes that there is insufficient evidence supporting the use of LAIV in those with immune compromising conditions in terms of both safety and effectiveness. LAIV has been administered to approximately 170 children and adults with mild to moderate immune suppression due to HIV infections and 10 children with mild to moderate immune suppression due to cancer. Although these small studies demonstrated a similar safety profile as in healthy individuals, based on expert opinion, NACI concludes that the use of LAIV in this population is contraindicated.

V.3 Children with Asthma

- NACI recommends that LAIV can be used in children 24 months and older with stable, non-severe asthma. (NACI Recommendation Grade B)
  - › LAIV should not be used in those with severe asthma (as defined as currently on oral or high dose inhaled glucocorticosteriods or active wheezing) and those with medically attended wheezing in the 7 days prior to vaccination

A study of LAIV found increased rates of wheezing in children 6-23 months of age when compared to TIV. Children 2 years of age and older and adolescents with asthma who received LAIV in clinical trials showed there was no significant difference between LAIV and TIV in the exacerbation of asthma post-vaccination. Several studies demonstrated that LAIV is well tolerated in asthmatics, and it has been demonstrated to have a higher relative efficacy versus TIV with matched and mismatched strains. NACI's review of current evidence on the use of LAIV in children 2 years of age and over with asthma and wheezing supports the use of LAIV in stable, non-severe asthmatics; however, NACI recommends against LAIV in those with severe asthma or medically attended wheezing in the previous seven days.

V.4 Children with other chronic health conditions

- NACI recommends that LAIV can be used in children with chronic health conditions (excluding those with immune compromising conditions and severe asthma, as defined above). (NACI Recommendation Grade B)
    - A limited number of immunogenicity and efficacy studies have been conducted in this population as a result of these conditions being fairly limited in this age group. Based on expert review, it is expected that LAIV should be as immunogenic and efficacious in immune competent children with chronic health conditions as it is in healthy children.

At this time there is insufficient evidence to recommend LAIV preferentially over TIV in children with chronic health conditions

Adults

V.5 Healthy Adults 18 to 59 years of age

- NACI recommends that LAIV can be used for the prevention of influenza in healthy adults 18 to 59 years of age. (NACI recommendation Grade A)
    - There is some evidence that TIV may provide better efficacy than LAIV in healthy adults, although not all studies are consistent on this point.

The combined data from LAIV trials in over 10,000 people confirmed evidence of immunogenicity, efficacy and effectiveness in adults 18 to 59 years of age.

There are limited data from randomized controlled trials in adults on relative efficacy of LAIV versus TIV, and those that are available show that LAIV and TIV were similarly efficacious or that TIV was more efficacious. Most studies demonstrated that LAIV was less effective than TIV in the adult population; however in one large observational study, LAIV was shown to be more protective than TIV in a cohort of new military recruits (who are generally a younger adult population and are likely to be vaccine-naïve).[29] Pre-existing immunity to the virus from infection or vaccine, which may interfere with the LAIV response, may also be a contributing factor.[22]

V.6 Adults with Immune Compromising Conditions

- NACI recommends against LAIV for individuals with immune compromising conditions. (NACI Recommendation Grade D)

Live vaccines have generally been contraindicated in people with immune compromising conditions, with some exceptions. NACI concludes that there is insufficient evidence supporting the use of LAIV in those with immune compromising conditions in terms of both safety and effectiveness. LAIV has been administered to approximately 170 children and adults with mild to moderate immune suppression due to HIV infections and 10 children with mild to moderate immune suppression due to cancer. Although these small studies demonstrated a similar safety profile as in healthy individuals, based on expert opinion, NACI concludes that the use of LAIV in this population is contraindicated.

V.7 Adults with other chronic health conditions

- At this time NACI concludes that there is insufficient evidence to recommend LAIV in adults with chronic health conditions. (NACI Recommendation Grade I)
    - › The potentially better immune response following TIV compared to LAIV in healthy adults in some studies should be considered when the choice of an influenza vaccine for adults at high risk for complications is made.

Data on the use of LAIV in adults 18 to 59 years of age with chronic underlying medical conditions are limited; however some research has been done on older adults (age 60 and older) with chronic conditions. Although not an indicated age group, the studies in older adults demonstrate a similar safety profile of LAIV in these individuals to individuals without these conditions but the absolute efficacy of LAIV or relative efficacy of LAIV compared to TIV, as in the healthy adult population, remains questionable.

V.8 Health Care Workers providing care to individuals with immune compromising conditions

- NACI recommends that TIV, instead of LAIV, should be used for health care workers providing care to those with immune compromising conditions, unless the individual will only accept LAIV. (NACI Recommendation Grade B)
- NACI recommends that if a health care worker, or another caregiver, receives LAIV and is providing care to individuals with severe immune compromising conditions (defined as hospitalized and requiring care in a protected environment), they should wait 2 weeks following receipt of LAIV before continuing to provide care to such individuals. (NACI Recommendation Grade D)

The rationale for these recommendations is two-fold. First, although limited, the existing evidence suggests that TIV may be more efficacious in adults than LAIV. Secondly, there is a theoretical concern that shed vaccine virus could be transmitted to a person with an immune compromising condition who could theoretically develop serious illness. However, shedding is generally below the levels needed to transmit infection and the duration of shedding after receipt of LAIV is shorter in adults than in children. This transmission of vaccine viruses from vaccine recipients to unvaccinated persons has occurred in rare instances, although serious illnesses have not been reported among unvaccinated persons who have been inadvertently infected with vaccine viruses. No transmission has ever been reported in a health care setting.[84]

Table 6: Summary of Information Contained in This NACI Statement

The following table highlights key information for immunization providers.
Please refer to the remainder of the Statement for details.

1. What a) Basic information about the Disease (e.g. agent, symptoms, epidemiology) b) Basic information about the Vaccine (e.g. efficacy, safety)	Influenza is a respiratory infection caused by influenza A and B viruses and occurs in Canada every year, generally during late fall and the winter months. Infection typically starts with a headache, chills and cough, followed rapidly by fever, loss of appetite, muscle aches and fatigue, running nose, sneezing, watery eyes and throat irritation. Nausea, vomiting and diarrhea may also occur, especially in children. Most people will recover from influenza within a week or ten days, but some - including those 65 years of age and older and adults and children with chronic conditions, such as diabetes and cancer - are at greater risk of more severe complications, such as pneumonia. Additional information about influenza can be accessed at: http://www.phac-aspc.gc.ca/im/vpd-mev/influenza-eng.php FluMist® is a live, attenuated, trivalent influenza vaccine administered by the intranasal route as a spray. There is a single dosing formula available containing $10^{6.5-7.5}$ fluorescent focus units of each influenza strain in a 0.2 mL dose (administered as 0.1 mL dose in each nostril). FluMist® was approved in Canada in 2010, and as been available for use in the United States since 2003. Efficacy and safety studies have demonstrated that FluMist® is safe and well tolerated.
2. Who Groups recommended to immunize	NACI recommends that FluMist® can be used for the prevention of influenza in: • Healthy children and adolescents 2-17 years of age (NACI Recommendation Grade A). • Children 24 months and older with stable, non-severe asthma (NACI Recommendation Grade B) • Children with chronic health conditions (excluding severe asthma and immune compromising conditions) (NACI Recommendation Grade B) • Healthy adults 18-59 years of age (NACI Recommendation Grade A)

3. How • Dose, schedule • Precautions, contraindications • Co-administration	The recommended vaccine dosage per administration is 0.2 mL (0.1 mL per nostril) for individuals 2-59 years of age. • Children 2-8 years of age inclusive who have not previously received seasonal influenza vaccine are recommended to receive a two dose schedule. An initial dose of 0.2 mL (0.1 mL in each nostril) is followed by a second 0.2 mL dose (0.1 mL in each nostril) administered at least 4 weeks later. • For all other individuals, including children 2-8 years of age who have previously received seasonal influenza vaccine, the recommended schedule is one 0.2 mL dose (0.1 mL in each nostril). The use of FluMist® should be carefully evaluated in individuals: • Persons with serious acute febrile illness should not be vaccinated until their symptoms have abated. If nasal congestion is present that might impede delivery of the vaccine, deferral of FluMist® or administration of trivalent inactivated influenza vaccine (TIV) should be considered instead. The use of FluMist® is contraindicated in: • Children <24 months of age • Individuals with a history of anaphylaxis to a previous dose of influenza vaccine or have a history of hypersensitivity to the non-medicinal ingredients contained in the vaccine, including those with egg allergy • Children and adolescents 2-17 years of age receiving ongoing aspirin therapy or aspirin-containing therapy. The use of aspirin-containing medications in individuals <18 years should be delayed at least four weeks after vaccination with FluMist®. • Pregnant women • Individuals with severe asthma (as defined as currently on oral or high dose inhaled glucocorticosteriods or active wheezing) and those with medically attended wheezing in the 7 days prior to vaccination • Individuals with occurrence of Guillain-Barré Syndrome within eight weeks of any prior influenza vaccination. • Individuals with immune compromising conditions • Health care workers providing care to individuals with severe immune compromising conditions. FluMist® may be administered concurrently with the MMR and varicella vaccines. • If not administered at the same time, the administration of another live vaccine should only be administered at least four weeks prior to, or after the receipt of FluMist®. FluMist® should not be administered until 48 hours after antiviral agents active against influenza (e.g. oseltamivir and zanamivir) are stopped, and antiviral agents should not be administered until two weeks after receipt of FluMist® unless medically indicated. If antiviral agents are administered within this time frame (from 48 hours before to two weeks after FluMist®), revaccination should take place at least 48 hours after the antivirals are stopped. No data currently exist about the concomitant use of nasal corticosteroids or other intranasal medications.
4. Why • "Counseling Points" for providers to emphasize with clients when discussing these recommendations	Vaccination is the most effective way to prevent influenza. Each year there is a new vaccine to protect against the influenza virus strains that are expected in the coming influenza season. Even if the vaccine strains have not changed, getting influenza vaccine every year reinforces optimal protection. Annual influenza vaccination is encouraged for all Canadians, particularly those at high risk of influenza complications, those who could spread influenza to someone at risk and those who provide essential community services. FluMist® is administered through the intranasal route which may increase compliance during administration. It can be used in children 2-17 years of age inclusive, and in healthy adults 18-59 years of age inclusive. Nasal congestion and rhinorrhea are the most common adverse reactions observed.

Table 7: Levels of Evidence Based on Research Design

I	Evidence from randomized controlled trial(s).
II-1	Evidence from controlled trial(s) without randomization.
II-2	Evidence from cohort or case–control analytic studies, preferably from more than one centre or research group using clinical outcome measures of vaccine efficacy.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

Table 8: Quality (internal validity) Rating of Evidence

Good	A study (including meta-analyses or systematic reviews) that meets all design- specific criteria* well.
Fair	A study (including meta-analyses or systematic reviews) that does not meet (or it is not clear that it meets) at least one design-specific criterion* but has no known "fatal flaw".
Poor	A study (including meta-analyses or systematic reviews) that has at least one design-specific* "fatal flaw", or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations.

* General design specific criteria are outlined in Harris et al., 2001[4]

Table 9: NACI Recommendation for Immunization - Grades

A	NACI concludes that there is **good** evidence to recommend immunization.
B	NACI concludes that there is **fair** evidence to recommend immunization.
C	NACI concludes that the existing evidence is **conflicting** and does not allow making a recommendation for or against immunization, however other factors may influence decision-making.
D	NACI concludes that there is **fair** evidence to recommend against immunization.
E	NACI concludes that there is **good** evidence to recommend against immunization.
I	NACI concludes that there is **insufficient** evidence (in either quantity and/or quality) to make a recommendation, however other factors may influence decision-making.

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

Table 10: Summary of Evidence for NACI Recommendation(s)

Evidence related to efficacy of FluMist®						
STUDY DETAILS					SUMMARY	
Study	Vaccine	Study Design	Participants	Summary of Key Findings Using Text or Data	Level of Evidence	Quality
Children						
Belshe RB, Mendelman PM, Treanor J, et al. The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenza-virus vaccine in children. N Engl J Med. 1998;338(20):1405-12.[5]	LAIV Aviron 0.25mL per nostril ($10^{6.7}$ TCID) Vaccine and circulating strains well-matched	RCT, double-blind, placebo controlled, multi-centre AV006 Year 1 1996/97 season USA	N=1602 (pp) n_{LAIV}= 1070 $n_{placebo}$= 532 Both groups received 1 (n=288) or 2 doses (n=1314); second dose 60d ± 14d apart Healthy children ≥ 15-71 months	Primary endpoint: Incidence of CCI (≥28 days after receipt of first dose or any time after second dose) caused by matched strains. Secondary endpoint: Efficacy of one or two dose regimen Vaccine Efficacy: Overall efficacy: 93% (88, 96) (One dose: 89% (65, 96) / Two doses: 94% (88, 97)) *Strain-specific efficacy* A/H1N1 – No cases in vaccine group A/H3N2: 95% (88, 97) B: 91% (79, 96) Efficacy in reducing febrile illness: 21% (11, 30) Efficacy in reducing AOM:30% (18, 45) Breakthrough illness in vaccinated recipients was milder than illnesses in placebo recipients.	Level I	Fair Participants not randomized into 1 or 2 dose groups, and equivalency between 1 and 2 dose was not established
Belshe RB, Gruber WC, Mendelman PM, et al. Efficacy of vaccination with live attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine against a variant (A/Sydney) not contained in the vaccine. J Pediatr. 2000;136(2):168-75.[6]	*LAIV* Aviron, Mountain View, CA, USA 0.25mL per nostril ($10^{7.0}$ $TCID_{50}$ per strain) Single dose Vaccine and circulating strains not well-matched (A/H3N2/ Sydney not contained in vaccine)	RCT, double-blind, placebo controlled, multicentre AV006 Year 2 1997/98 season	N=1358 n_{LAIV} = 917 $n_{placebo}$ =441 Both groups received 1 dose of vaccine or placebo, based on assignment in year 1 Healthy children 26-85 months from year 1 of trial (85% return rate)	Primary endpoint: First episode of CCI after receipt of revaccination (Year 2 of multi-year study by Belshe et al) Vaccine Efficacy (Year 2): Overall efficacy: 87% (78, 93) *Strain-specific efficacy (Year 2):* A/H1N1 – No cases in study group A/H3N2 (Wuhan/359/95-like): 100% (54, 100) B: 100% (79, 100) Efficacy against A/H3N2 (Sydney/5/97-like) not contained in vaccine: 86% (75, 92) Vaccine Efficacy (Years 1 and 2 combined): Overall efficacy: 92% (88, 94) Efficacy of LAIV to reduce AOM: 94% Efficacy of LAIV to reduce LRTD: 95%	Level I	Good

Evidence related to efficacy of FluMist®

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Tam JS, Capeding MR, Lum LC, et al. Efficacy and safety of a live attenuated, cold-adapted influenza vaccine, trivalent against culture-confirmed influenza in young children in Asia. Pediatr Infect Dis J. 2007;26(7):619-28.[7]	CAIV-T Wyeth, Marietta, PA, USA 0.1mL per nostril (10^7 $TCID_{50}$ per strain) Year 1: 2 doses ≥28 days apart Year 2: Single dose B-component of vaccine was not well matched in either year. (29.2% distinct in year 1, 77% in year 2)	RCT, double-blind, placebo controlled, multi-centre 2000/01 & 2001/02 seasons 16 sites, Asia NCT00192244 D153-P501	Year 1 N=2784 n_{CAIV-T} =1653 $n_{placebo}$ =1111 Both groups received 2 doses Year 2 (re-randomized) N=2527 $n_{CAIV-T/CAIV-T}$ = 771 $n_{CAIV-T/placebo}$ = 759 $n_{placebo/CAIV-T}$= 503 $n_{placebo/placebo}$ = 494 Healthy children aged 12 to <36 months	Primary endpoint: CCI caused by matched strains after 2nd dose Secondary endpoints: CCI caused by any subtype after 2nd dose in year 1 and single dose in year 2 Year 1 Vaccine Efficacy (matched strains): Overall efficacy – 72.9% (62.8, 80.5) *Strain-specific efficacy:* A/H1N1: 80.9% (69.4, 88.5) A/H3N2: 90.0% (71.4, 97.5) B: 44.3% (6.2, 67.2) (vaccine mismatch) Efficacy against any subtype was 70.1% (60.9, 77.3) Year 2 Vaccine Efficacy (matched strains): *Overall efficacy (Year 1 / Year 2 group comparisons)* CAIV/CAIVT vs. plac./plac.: 84.3% (70.1, 92.4) CAIVT/plac. vs. plac./plac.: 56.2% (30.5, 72.7) CAIVT/CAIVT vs. CAIVT/plac: 64.2% (28.9, 83.2) CAIVT/CAIVT vs. plac./CAIVT:60.9% (15.9, 82.6) Plac./CAIVT vs. plac./plac: 59.9% (31.1, 77.4) Vaccine Efficacy (any strains): *Overall efficacy (Year 1 / Year 2 group comparisons)* CAIVT/CAIVT vs. plac./plac.: 64.2% (44.2, 77.3) CAIVT/plac. vs. plac/plac.: 44.8% (18.2, 62.9) CAIVT/CAIVT vs. CAIVT/plac.: 35.0% (-2.9, 59.5) CAIVT/CAIVT vs. plac./CAIVT: 17.2% (-4.2, 52.0) Plac./CAIVT vs. plac./plac. : 56.7% (30.3, 73.8) Revaccination in second year has greater efficacy than only vaccinating in first year	Level I	Good
Vesikari T, Fleming DM, Aristegui JF, et al. Safety, efficacy, and effectiveness of cold-adapted influenza vaccine-trivalent against community-acquired, culture-confirmed influenza in young children attending day care. Pediatrics. 2006;118(6):2298-312.[8]	CAIV-T Wyeth Vaccines Research 0.1mL per nostril (10^7TCID) Vaccine and circulating strains well-matched (H3N2/A substituted in Year 2)	RCT, prospective, double-blind, placebo controlled, multicentre 2000-01 & 2001/02 seasons Belgium, Finland, Israel, Spain, UK NCT00192283 D153-P502	Year 1 N=1616 n_{CAIV-T} = 951 $n_{placebo}$ = 665 2 doses with second dose 35d ± 7d apart Year 2 (one dose) N=1090 n_{CAIV-T} = 640 $n_{placebo}$ = 450 1 dose based on assignment in year 1 Healthy children aged 6 to <36 months attending day care ≥12hours/week	Primary endpoint: CCI caused by matched strains (year 1) Year 1 Vaccine efficacy after 2 doses (matched strains): Overall efficacy: 85.4% (74.3, 92.2) *Strain-specific efficacy:* A/H1N1:91.8% (80.8, 97.1) B:72.6% (38.6, 88.9) Vaccine efficacy against any subtype 83.8% (74.2, 90.2) Year 2 Vaccine efficacy (matched strains): Overall efficacy: 88.7% (82.0, 93.2) *Strain-specific efficacy:* A/H1N1: 90.0% (56.3, 98.9) A/H3N2: 90.3% (82.9, 94.9) (predominant circulating strain) B: 81.7% (53.7, 93.9) (lower attack rate this year) Efficacy against any subtype 85.3% (78.3, 90.4) Efficacy against AOM associated with CCI Year 1: 90.6% (68.7, 97.2) Year 2: 97% (77.6, 99.6)	Level I	Good

Evidence related to efficacy of FluMist®

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Bracco Neto H, Farhat CK, Tregnaghi MW, et al. Efficacy and safety of 1 and 2 doses of live attenuated influenza vaccine in vaccine-naive children. Pediatr Infect Dis J. 2009;28(5):365-71.[11]	*LAIV* Wyeth Vaccines, Marietta, PA, USA 0.1mL per nostril ($10^{7\pm0.5}$FFU per strain) 2 doses in Year 1, single dose in Year 2 Vaccine and circulating strains well-matched	RCT, double-blind, placebo controlled, multi-centre 2001 and 2002 influenza seasons South Africa, Brazil, Argentina NCT00192283 D153-P502	Year 1 N=2821 $n_{LAIV-LAIV}$=944 $n_{LAIV-placebo}$=935 $n_{placebo-placebo}$=942 Year 2 (one dose) N = 2202 n_{LAIV} = 1467 $n_{placebo}$ = 735 Healthy influenza vaccine-naïve children aged 6 to <36 months	Primary endpoint: CCI caused by subtype antigenically similar to vaccine (year 1) Secondary endpoints: CCI caused by subtype antigenically similar to vaccine (year 2) and CCI caused by any subtype (both years); efficacy against AOM Year 1 vaccine efficacy (similar subtype): LAIV-LAIV: 73. 5% (63.6, 81.0) LAIV-Placebo: 57.7% (44.7, 67.9) LAIV-LAIV vs LAIV/Placebo:37.3% (9.5, 56.9) Year 1 efficacy against any subtype: LAIV-LAIV: 72.0% (61.9, 79.8) LAIV-Placebo: 56.3% (43.1, 66.7) Year 2 vaccine efficacy (similar subtype): LAIV-LAIV/LAIV: 73.6% (33.3, 91.2) LAIV-Placebo/LAIV: 65.2% (31.2, 82.8) LAIV-LAIV/Placebo: 57% (6.1, 81.7) Year 2 efficacy against any subtype: LAIV-LAIV/LAIV: 46.6%% (14.9, 67.2) LAIV-Placebo/LAIV: 46.4% (21.1, 63.5) Efficacy against AOM associated with CCI Year 1: LAIV-LAIV: 73.5% (52.4, 85.3) Year 1 : LAIV-Placebo: 69.6% (46.9, 82.6) Year 2: LAIV-LAIV/LAIV: 59.8% (-106.7, 92.2) - small sample size due to study error) Year 2 : LAIV-Placebo/LAIV: 90.1% (15.0, 98.8)	Level I	Good Error in treatment allocation coding and labelling in Year 2 resulted in 2 additional treatment protocols
Lum LC, Borja-Tabora CF, Breiman RF, et al. Influenza vaccine concurrently administered with a combination measles, mumps, and rubella vaccine to young children. Vaccine. 2010;28(6):1566-74.[12]	LAIV Wyeth Vaccines Research, Marietta, PA, USA 0.1mL per nostril (10^7 $TCID_{50}$) 2 doses 35±7 days apart Vaccine and circulating A/H3N2 not well matched	Phase III RCT, double-blind, placebo controlled, multicentre Non-inferiority trial (lower bound -10.0%) Co-vaccine: MMR (Priorix®) 2002/03 season 13 countries (Europe/Asia) NCT:00192166 D153-P522	N=1150 $n_{LAIV+MMR}$ = 765 $n_{placebo+MMR}$=385 Both groups received MMR with dose 1 Healthy vaccine-naïve children aged 11-<24 months	Primary endpoint: CCI caused by subtype antigenically similar to vaccine ≥15 days after receipt of dose 2 of vaccine/ placebo Secondary endpoints: CCI caused by any subtype ≥15 days after receipt of dose 2 of vaccine or placebo, efficacy against AOM Overall vaccine efficacy (similar subtype): 78.4% (50.9, 91.3) Vaccine efficacy against any subtype: 63.8%% (36.2, 79.8) *Strain-specific efficacy (similar subtype):* A/H1N1: insufficient cases A/H3N2: insufficient cases B: 81.7% (38.2, 95.8) LAIV efficacy was not adversely affected by the concomitant administration with MMR Protection against AOM could not be measured due to low incidence of influenza-associated AOM.	Level I	Good

Evidence related to efficacy of FluMist®						
STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Relative Efficacy (Children)						
Ashkenazi S, Vertruyen A, Aristegui J, et al. Superior relative efficacy of live attenuated influenza vaccine compared with inactivated influenza vaccine in young children with recurrent respiratory tract infections. Pediatr Infect Dis J. 2006;25(10):870-9.[20]	CAIV-T 0.1mL per nostril (10^7 $TCID_{50}$)	RCT, open-label, active controlled, multicentre Control vaccine: TIV, 0.25mL/dose or 0.50mL/dose based on participant age 2002/03 influenza season Europe, Israel NCT00192205 D153- P514	N = 2085 n_{TIV}= 1035 n_{CAIV-T}= 1050 2 doses: 35d ± 7d apart Vaccine naïve children 6 to 71 months, 45% of sample had history of recurrent respiratory tract infections (≥2 RTIs in past 12 months or since birth)	Primary endpoint: CCI caused by subtype antigenically similar to vaccines Secondary endpoints: CCI caused by any subtype, incidence of AOM, incidence of RTI Overall relative efficacy for CAIV-T (similar subtype): 52.7% (21.6, 72.2) – similar ITT value *Strain-specific efficacy (similar subtype)* A/H1N1: 100% (42.3, 100.0) A/H3N2: -97.1% (-540, 2:31.5) B: 68% (37.3, 84.8) Similar results seen for efficacy against any subtype. Relative to TIV, CAIV-T reduced the number of RTI healthcare visits by 8.9% (90% CI: 1.5, 15.8); missed days of school by 16.2% (90% CI: 10.4, 21.6) Few reports of influenza-associated AOM reported; no significant difference between groups for all AOM episodes	Level I	Good
Fleming DM, Crovari P, Wahn U, et al. Comparison of the efficacy and safety of live attenuated cold-adapted influenza vaccine, trivalent, with trivalent inactivated influenza virus vaccine in children and adolescents with asthma. Pediatr Infect Dis J. 2006;25(10):860-9.[21]	CAIV-T FluMist® 0.1mL per nostril ($10^7$$TCID_{50}$ per strain) Single dose	RCT, open-label, active-controlled, multicentre Control vaccine: TIV Aventis Pasteur 2002/03 season Europe NCT:00192257 D153-P515	N = 2220 n_{TIV}=1109 n_{CAIV-T}=1111 Children with asthma (not all influenza vaccine-naïve children) ≥6 years to ≤17 years of age	Primary endpoint: CCI >14 days after vaccination caused by matched strains Overall relative efficacy for CAIV-T (matched): 34.7% (3.9, 56.0) – similar ITT value *Strain-specific efficacy* A/H1N1: 100% (-8.4, 100) A/H3N2: 0.6% (141.8, 59.2) B: 36.3% (0.1, 59.8) Overall relative efficacy for CAIV-T (any subtype): 31.9% (1.1, 53.5) *Strain-specific efficacy* A/H1N1: 100% (15.6, 100) A/H3N2: -29.9% (-190.9, 40.6) B: 36.8% (1.6, 59.8)	Level I	Good

Evidence related to efficacy of FluMist®

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Belshe RB, Edwards KM, Vesikari T, et al. Live attenuated versus inactivated influenza vaccine in infants and young children. N Engl J Med. 2007;356(7):685-96.[19]	CAIV-T FluMist® 0.1mL per nostril (10^7 $TCID_{50}$) Vaccine and circulating A/H3N2 not well matched	RCT, prospective, double-blind, active controlled, multi-centre Control vaccine: TIV Fluzone® (US/Asia) Vaxigrip® (Europe/ Middle East), 0.25mL or 0.5mL/ dose based on age 2004/05 season 249 sites in 16 countries (US, Europe/Middle East, Asia) NCT00128167 MI-CPIII	N=7852 n_{TIV}=3936 n_{CAIV-T}=3916 1 or 2 doses for both groups. Second dose given to vaccine-naive children 28-42 days after first dose Children aged ≥6-≤59 months, both groups included some children with underlying medical conditions (5.7% of total) mild/ moderate asthma (4%) or a history of recurrent (6%) or any wheezing(21%). Exclusions: wheezing within 42 days of study	Primary endpoint: efficacy of CAIV-T versus TIV in preventing CCI illness (oral temperature of 37.8°C or higher or equivalent in presence of cough, sore throat, running nose/ nasal congestion occurring on the same or consecutive days) caused by well-matched strains. Secondary endpoints: efficacy of CAIV-T versus TIV in preventing CCI by mismatched and all flu viruses; any CCI symptom due to matched or mismatched strains, AOM, LRI Relative efficacy for CAIV-T (well-matched): 44.5% (22.4, 60.6) *Strain-specific efficacy (similar subtype):* A/H1N1: 89.2% (67.7, 97.4) A/H3N2: no cases B: 27.3% (-4.8, 49.9) Relative efficacy for CAIV-T (not well matched): 58.2% (47.4, 67.0) *Strain-specific efficacy (similar subtype):* A/H1N1: no cases A/H3N2: 79.2% (70.6, 85.7) B: 6.3% (-31.6, 33.3) Overall relative efficacy for CAIV-T (regardless of match): 54.9% (45.4, 62.9) *Strain-specific efficacy:* A/H1N1: 89.2% (67.7, 97.4) A/H3N2: 79.2% (70.6, 85.7) B: 16.1% (-7.7, 34.7) Reductions in AOM regardless of match: 50.6% (21.5, 69.5) (data in Supplementary Appendix [23]) - antigenically similar strains: 0.4% (-146, 59.6) - antigenically dissimilar strains: 61.4% (32.2, 78.8) Reductions in LRI regardless of match: 45.9% (4.4, 70.2) (data in Supplementary Appendix [23]) - antigenically similar strains: 24.5% (-89.8, 71.0) - antigenically dissimilar strains: 63.4% (18.9, 84.7)	Level I	Good

Evidence related to efficacy of FluMist®						
STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Adults						
Nichol KL, Mendelman PM, Mallon KP, et al. Effectiveness of live, attenuated intranasal influenza virus vaccine in healthy, working adults: a randomized controlled trial. JAMA. 1999;282(2):137-44.[26]	LAIV 0.25mL per nostril 1 dose A/H3N2 strains not well matched to vaccine. (A/Sydney/H3N2 predominantly circulating strain)	Randomized double-blind placebo controlled trial, multi-centre AV009 1997-1998 influenza season, 13 centres in USA	N=4,561 n_{LAIV}= 3041 $n_{placebo}$=1520 healthy working (≥30 hrs/week) adults aged 18-65	Primary endpoint: any febrile illness (AFI) during 14-wk outbreak period. Culture confirmation of influenza was not performed Secondary endpoints: severe febrile illness (SFI), febrile upper respiratory illness (FURI) work loss, use of health care facilities **Outcomes during peak outbreak periods (LAIV vs placebo)** Reduction of AFI: 10% (95%CI: -2.1, 20.7) Reduction of SFI: 18.8% (95%CI, 7.4, 28.8) Reduction in FURI: 23.6% (95%CI, 12.7, 33.2) **Efficacy (reported in % reduction) for all illnesses combined:** Total days ill (22.9% to 27.3%, p<0.001) Work-loss days (13.1% to 28.4%, p=.07 for AFI, p≤.01 for SFI, FURI) Prescription antibiotic use (42.9% to 47%, p<.001) Use of OTC medications (23.3% to 28%, p<.001)	Level I	Good
Relative Efficacy (Adults)						
Edwards KM, Dupont WD, Westrich MK, et al. A randomized controlled trial of cold-adapted and inactivated vaccines for the prevention of influenza A disease. J Infect Dis. 1994;169(1):68-76.[27]	LAIV 0.5mL per nostril (0.25mL per strain; 10^{7}-$10^{7.6}$ pfu/mL) Children <3 received same volume with 1/10 dilution Bivalent for A strains only throughout study Single dose per strain Nasal drops delivery	RCT, double-blind, active and placebo controlled, multi-centre Control vaccine: TIV (15µg HA per strain), Year 1 vaccine (bivalent A), trivalent thereafter 1985/86 to 1988-89 seasons 7 sites, Nashville, Tennessee. USA	N=5210 $Group_{TIV}$ 1 (n=1739) $Group_{LAIV}$ 2 (n=1733) $Group_{placebo}$ 3 (n=1738) Persons aged 1-65 years ($n_{<15\ years}$=809)	Primary endpoint: culture-positive illness and seroconversion. Retrospective reports of ILI (only 48-64% of those reporting ILI post-season had presented for culture during acute illness) Strain-specific efficacy (1986/1988 combined): A/H1N1: LAIV (85%, 70-92) vs TIV (76%, 58-87) Strain-specific efficacy (1987/1989 combined): A/H3N2: LAIV (58%, 29-75) vs TIV (74%, 52-86) LAIV demonstrated protection against natural influenza A infection among children and adults that was approximately equivalent to that of TIV.	Level I	Good

Evidence related to efficacy of FluMist®

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Treanor JJ, Kotloff K, Betts RF, et al. Evaluation of trivalent, live, cold-adapted (CAIV-T) and inactivated (TIV) influenza vaccines in prevention of virus infection and illness following challenge of adults with wild-type influenza A (H1N1), A (H3N2), and B viruses. Vaccine. 1999;18(9-10):899-906.[30]	CAIV-T Flu Mist® 0.25mL per nostril (10^7 $TCID_{50}$ per strain)	RCT, active and placebo controlled double-blind wild type challenge study Control vaccine: TIV: Fluvirin® 0.5mL (15µg HA per strain) 1995/96 season **AV003** NCT: 2 sites, USA	N=92 n_{CAIV-T}=29 n_{TIV}=32 $n_{placebo}$=31 Groups challenged with 1 strain of virus 28 days after vaccination (then placed in group isolation x7 days) Healthy adult volunteers aged 18-40 years who were seronsusceptible (HAI ≤1:8) to at least 1 of 3 strains	<u>Primary endpoint</u>: lab documented influenza <u>Secondary endpoints</u>: viral shedding on 1+ days following challenge and/or 4-fold+ increase in serum HAI antibody titer between pre/post challenge; 1+ respiratory symptoms %response (Serum)(CAIV-T;TIV;placebo) A/H1N1 (23%; 91%; 16%) A/H3N2 (33%; 76%; 6%) B (3%, 76%, 0%) % response (Nasal) (CAIV-T;TIV;placebo) A/H1N1 (14.3%; 23.3%; 12.9) A/H3N2 (32.1%; 16.7%; 9.7%) B (17.9%; 16.7%; 3.2%) Both FluMist and TIV demonstrated statistically significant efficacy against lab-documented illness compared to placebo TIV vs CAIV-T ; 71% ((p=0.006) vs 85% (P=0.001). No comparison of efficacy between TIV/CAIV-T conducted.	Level I	Good Limited sample size, low rates of infection/ illness in placebo recipients
Monto AS, Ohmit SE, Petrie JG, et al. Comparative efficacy of inactivated and live attenuated influenza vaccines. N Engl J Med. 2009;361(13):1260-7.[28]	LAIV FluMist® 0.1mL per nostril ($10^{6.5}$-$10^{7.6}$ FFU per strain) Single dose H3N2 predominant strain (90%)	RCT, double-blind, active and placebo controlled, community-based Control vaccine: *TIV,* Fluzone®, 0.5mL (15µg HA per strain) 2007/08 season NCT 00538512 Michigan, USA	N=1952 n_{LAIV}= 814 n_{TIV}= 813 $n_{placebo}$=325 Healthy adults aged 18-49 years	<u>Primary endpoint:</u> a case of symptomatic illness that was confirmed as influenza A or B by either isolation by cell culture or PCR assay. <u>Absolute efficacy for both strains (A/H3N2 and B) by positive culture, PCR, or both:</u> CAIV-T: 51% (19, 70). 36% (0, 59), 36% (0, 59) TIV: 73% (51, 85) 68% (46, 81). 68% (46,81) Relative efficacy of TIV compared to LAIV: 45%(3, 69), 50% (20, 69), 50% (20, 69) <u>Absolute efficacy for A/H3N2 strain</u>: CAIV-T: 29% (-14, 55) TIV: 72% (49, 84) Relative efficacy of TIV compared to LAIV: 60% (33, 77)	Level I	Good

Evidence related to efficacy of FluMist®

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Ohmit S, Victor J, Rotthoff J, et al. Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines. N Engl J Med. 2006;355(24):2513-22.[31]	LAIV FluMist® 0.25mL per nostril ($10^{6.5}$-$10^{7.6}$ $TCID_{50}$ per strain) Single dose A/H3N2 strains not well matched to vaccine, two lineages of type B were circulating (one in vaccine)	RCT, double-blind, active and placebo controlled, community-based Control vaccine: TIV, Fluzone®, 0.5mL (15µg HA per strain) 2004/05 season NCT: 00133523 4 sites, Michigan, USA Year 1 of 2	N=1247 n_{LAIV}= 519 $n_{placebo}$=103 (IN spray) n_{TIV}= 522 $n_{placebo}$=103 (IM injection) Healthy adults aged 18-46 years (mean age 24.9)	Primary endpoint: a case of symptomatic illness that was confirmed as influenza A or B by either isolation by cell culture or rise in antibody titer ≥4 times against circulating strain or HI serology Efficacy for all strains (95% CI): % relative reduction of TIV vs placebo: Cell culture +ve: 77% (37, 92) Culture +ve or PCR+: 75% (42, 90) Culture or serologic +: 67% (16,87) % relative reduction of LAIV vs placebo: Cell culture +ve: 57% (-3, 82) Culture +ve or PCR+: 48% (-7, 74) Culture or serologic +: 30% (-57, 67) % relative reduction of LAIV vs TIV: Cell culture +ve: 46% (-44, 82) Culture +ve or PCR+: 53% (-5, 80) Culture or serologic +: 53% (-4, 80) Difference in efficacy of LAIV not statistically significant and attributable primarily to a difference in efficacy against influenza B.	Level I	Good
Ohmit S, Victor J, Teich E, et al. Prevention of symptomatic seasonal influenza in 2005-2006 by inactivated and live attenuated vaccines. J Infect Dis. 2008;198(3):312-7.[32]	LAIV FluMist® 0.25mL per nostril ($10^{6.5}$-$10^{7.6}$ $TCID_{50}$ per strain) Single dose A/H3N2 similar to vaccine	RCT, double-blind, active and placebo controlled, community-based Control vaccine: TIV, Fluzone®, 0.5mL (15µg HA per strain) 2005/06 season NCT:00133523 6 sites, Michigan, USA Year 2 of 2	N=2058 n_{LAIV}= 853 n_{TIV}= 867 $n_{placebo}$=338 (IN spray or IM injection) (participants assigned to same group as in year 1, additional subjects enrolled) Healthy adults aged 18-48 years	Primary endpoint: a case of symptomatic illness that was confirmed as influenza A or B by either isolation by cell culture or rise in antibody titer ≥4 times against circulating strain or HI serology. Secondary endpoints: illness confirmed by virus identification on PCR Efficacy for all strains (95% CI): % relative reduction of TIV vs placebo: Cell culture +ve: 23% (-153, 73) Culture +ve and/or PCR+: 16% (-171, 70) Culture or serologic +: 54% (4, 77) % relative reduction of LAIV vs placebo: Cell culture +ve: 61% (-48, 89) Culture +ve and/or PCR+: 8% (-194, 67) Culture or serologic +: 43% (-15, 71) % relative reduction of LAIV vs TIV: Cell culture +ve: -95% (-539, 32) Culture +ve and/or PCR+: 9% (-110, 60) Culture or serologic +: 19% (-56, 58) Efficacy of live attenuated vaccine was slightly less than that of TIV but not statistically greater than that of placebo. Identified no significant difference in vaccine efficacy	Level I	Good Lower than expected attack rate, low power

Evidence related to efficacy of FluMist®

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Wang Z, Tobler S, Roayaei J, et al. Live attenuated or inactivated influenza vaccines and medical encounters for respiratory illnesses among US military personnel. JAMA. 2009;301(9):945-53.[29]	LAIV Single dose	Population-based, active control, retrospective, observational Control vaccine: TIV 2004/05 to 2006/07 seasons	2004/05 N=1,061,728 n_{TIV}=366,201 n_{LAIV}=184,707 $N_{unimmunized}$=510,820 2005/06 N=1,041,264 n_{TIV}=626,478 n_{LAIV}=143,054 $N_{unimmunized}$=271,732* 2006/07 N=1,067,959 n_{TIV}=436,600 n_{LAIV}=400,630 $N_{unimmunized}$=230,729* *includes personnel unimmunized in current & previous years Military personnel Aged 17-49 years over three influenza seasons Exclusions: pregnant women, >1 dose of flu vaccine in current season (vaccine-naïve=no immunization in prior 1 or 2 seasons)	<u>Primary endpoint</u>: Incidence of health care encounters for pneumonia or influenza illness. <u>Incidence (IR/1000 person-years) (TIV; LAIV; unimmunized)</u>: <u>Health care encounters</u> 2004/05 (8.6%; 18.3%; 19.4%) 2005/06 (7.8%; 10.6%; 10.9%) 2006/07 (8.0%; 11.1%; 11.7%) <u>Pneumonia/hospitalization</u>: 2004/05 (.38%; .90%; .46%) 2005/06 (.28%; .56%; .38%) 2006/07 (.29%; .48%; .38%) In all 3 seasons, TIV was associated with lower rates of health care encounters for pneumonia and influenza when compared to no immunization <u>Effect of vaccination in vaccine groups (propensity matched) (95% CI)</u> (TIV vs unimmunized) (LAIV vs unimmunized) (TIV vs LAIV) **2004/05** (53.7%: 49.8, 57.3) (7.3%, -9.21, 21.3) (31.6%: 21.6, 40.8) **2005/06** (33.5%: 26.3, 39.9) (5.9%: -9.25, 18.9) (15.9%: 4.77, 25.6) **2006/07** (33.1%: 25.6, 40.0) (11.8%, 0.85, 21.5) (13.3%: 5.78, 20.1) <u>Effect of vaccination in vaccine-naïve cohorts (propensity-matched) (unimmunized in last year or last 2 years) (95% CI)</u> **2005/06** (34.6%: 23.8, 43.9) (31.9%, 10.0, 48.3) (-6.7%: -44.1, 21.0) **2006/07** (39.3%: 19.9, 54.0) (38.2%, 12.8, 56.2) (-1.8%: -53.1, 32.3) Incidence rates of pneumonia and ILI similar between unimmunized and vaccine-naïve cohorts. Correlation between years of being vaccine-naïve and effect of vaccination was statistically significant for LAIV (P=0.04) but not for TIV (p=.63) Pre-existing vaccine immunity may play a role in determining effectiveness of LAIV (also see Bernstein, Lee, Block)	Level II-2	Fair Could not control for some confounding variables, use of ICD-9 codes, different uptake of LAIV during the observation period

Evidence related to efficacy of FluMist®						
STUDY DETAILS					SUMMARY	
Study	Vaccine	Study Design	Participants	Summary of Key Findings Using Text or Data	Level of Evidence	Quality
Adults aged 60+						
De Villiers PJ, Steele AD, Hiemstra LA, et al. Efficacy and safety of a live attenuated influenza vaccine in adults 60 years of age and older. Vaccine. 2009;28(1):228-34.[67]	LAIV FluMist® 0.2mL (10^7TCID$_{50}$ per strain) B strains not well matched to vaccine (production issues) Low incidence of influenza this season	Randomized, prospective, double-blind, placebo controlled, multicentre NCT00217230 D153-P507 2001 31 sites in South Africa	N=3,136 n_{LAIV}= 1567 $n_{placebo}$= 1569 Healthy adults ≥60 years (median age 69) Many with chronic underlying medical conditions Sera obtained pre-vaccination, 35±7 days post-vaccination, at study completion	Primary endpoint: efficacy of LAIV against CCI (≥15 days post-vaccination) caused by subtypes antigenically matched to vaccine. Secondary endpoint: efficacy against CCI caused by all subtypes; efficacy against ILI/pneumonia/mortality without culture confirmation. Efficacy against CCI to matched strains (95% CI): Overall: 42.3% (21.6, 57.8) A/H1N1: not determined A/H3N2: 52.5% (32.1, 67.2) B: -10.1% (-113, 42.7) (could be due to low # cases, antigenic differences in vaccine, lack of protective immune response) Efficacy against CCI to all strains (95% CI): Overall: 41.6% (20.9, 57.1) A/H1N1 : not determined A/H3N2: 52.5% (32.1, 67.2) B: -9.7% (-108.0, 42.0) Protective efficacy of LAIV (95% CI): All ILI: 4.3% (-4.8, 12.7) Hospitalizations: 8.2% (-127, 63.3) Pneumonia: -0.1% (-155, 60.6) Death: 66.6%, (-316, 99.4) Post-hoc analysis: Efficacy in subjects 60-<70 years of age A/H3N2: 41.8% B: -22.7% Efficacy in subjects ≥70 years A/H3N2: 65.7% B: 9.9%	Level I	Good
Treanor JJ, Mattison HR, Dumyati G, et al. Protective efficacy of combined live intranasal and inactivated influenza A virus vaccines in the elderly. Ann Intern Med. 1992;117(8):625-33.[68]	LAIV 0.25mL per nostril ($10^{7.2}$ $TCID_{50}$ per strain) A/H3N2 strains only Intranasal drops	RCT, double-blind, active and placebo controlled, multicentre Control vaccine: TIV, 0.5mL (15µg HA per strain) 1987-88, 1988-89 seasons 3 large nursing homes in NY	N=523 TIV + placebo TIV+intranasal monovalent LAIV Participants received TIV and were re-randomized for placebo or LAIV each year Elderly - 95% >65 years, 75% female	Participants were given monovalent intranasal influenza A/H3N2 vaccine + TIV vs placebo + TIV Primary endpoint: Laboratory-documented influenza A (CCI plus culture isolation + serology) Protective Efficacy (95% CI) Lab-documented Influenza A Overall = 60.6%, 18-82) TIV + LAIV (9/162) TIV + placebo (24/169) Respiratory Illness (outbreak-associated) Overall = 56.8%, 95% CI: 23,76) TIV + LAIV (13/162) TIV + placebo (34/169) ILI (outbreak-associated) Overall = 65.0%, 95% CI: 17, 86) TIV + LAIV (6/162) TIV + placebo (18/169)	Level I	Good

Evidence related to efficacy of FluMist®

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Vesikari T, Fleming DM, Aristegui JF, et al. Safety, efficacy, and effectiveness of cold-adapted influenza vaccine-trivalent against community-acquired, culture-confirmed influenza in young children attending day care. Pediatrics. 2006;118(6):2298-312.[8]	CAIV-T Wyeth Vaccines Research 0.1mL per nostril (10^7TCID) Vaccine and circulating strains well-matched (H3N2/A substituted in Year 2)	RCT, prospective, double-blind, placebo controlled, multicentre 2000-01 & 2001/02 seasons Belgium, Finland, Israel, Spain, UK NCT00192283 D153-P502	Year 1 N=1616 n_{CAIV-T} = 951 $n_{placebo}$ = 665 2 doses with second dose 35d ± 7d apart Year 2 (one dose) N=1090 n_{CAIV-T} = 640 $n_{placebo}$ = 450 1 dose based on assignment in year 1 Healthy children aged 6 to <36 months attending day care ≥12hours/week	Effectiveness endpoints: CCI caused by any strain (both years); efficacy against AOM, effectiveness measures (parent/guardian time off to care for sick child; missed paid work days; days child missed from daycare; incidence of ≥1outpatient/emergency visit from acute febrile and/or respiratory illness; incidence of related antibiotic prescriptions; days of antibiotic use) Effectiveness Impact of CAIV-T most visible in year 2 45.1% reduction in parent/guardian time off work 47.5% reduction in days of work lost 36.3% reduction in missed day care 24.0% reduction in days of antibiotic use	Level I	Good

Evidence related to efficacy of FluMist®

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Gaglani MJ, Piedra PA, Herschler GB, et al. Direct and total effectiveness of the intranasal, live-attenuated, trivalent cold-adapted influenza virus vaccine against the 2000-2001 influenza A(H1N1) and B epidemic in healthy children. Arch Pediatr Adolesc Med. 2004;158(1):65-73.[9]	CAIV-T MedImmune, Mountain View, CA, USA 0.25mL per nostril (10^{6-7} $TCID_{50}$ per strain) Single dose In 2000, A/H1N1 strain A/Beijing/262/95 was replaced by A/New Caledonia/20/99	Community-based non-randomized open-label trial 1998/99 to 2000/01 (3 seasons) Texas, USA	$N_{intervention}$=3212 $N_{Comparison}$ =25,589 (20-25% coverage) Healthy vaccine-naïve children aged 18 months to 18 years (Children <5 had no natural infection with A/H1N1)	Study designed to measure herd immunity (indirect effectiveness) Primary endpoint: direct effectiveness of CAIV-T by comparing medically attended acute respiratory illness (MAARI) for CAIV-T recipients with that in age-eligible non-recipients in intervention communities Secondary endpoint: total effectiveness of CAIV-T by comparing MAARI for CAIV-T recipients with that in non-recipients in comparison communities where CAIV-T was not offered. Direct effectiveness *Year 3 cumulative group (n=2281)* During H1N1/B epidemic: 20% (95% CI: 14,25) During H1N1 epidemic: 17% (95% CI: 9,27) *Year 2 cumulative vs. Year 2 only* During H1N1/B epidemic: 18% (95% CI: 9,27) During H1N1 epidemic: 22% (95% CI: 11,32) Total effectiveness *Year 3 cumulative group (n=2281)* During H1N1/B epidemic: 18% (95% CI: 13,24) During H1N1 epidemic: 26% (95% CI: 18,33 *Year 2 cumulative vs. Year 2 only* During H1N1/B epidemic: 18% (95% CI: 13,24) During H1N1 epidemic: 26% (95% CI: 18,33) Reductions in MAARI were observed among children who received 1 dose of CAIV-T during the 1990-00 and 2000-01 influenza seasons even though antigenically drifted influenza A/H1N1 and B viruses were circulating during that season.	Level II-1	Good
Glezen WP, Gaglani MJ, Kozinetz CA, et al. Direct and indirect effectiveness of influenza vaccination delivered to children at school preceding an epidemic caused by 3 new influenza virus variants. J Infect Dis. 2010;202(11):1626-33.[14]	LAIV 0.1mL per nostril Single dose	Nonrandomized, open label, active controlled community-based trial Control vaccine: TIV, 0.5mL 2007 Bell County, TX NCT00138294	N = 6191 Intervention Site: 6191 of 10,418 students (48% coverage) LAIV 84.8% TIV 15.2% Healthy children aged 4 to 11 years	Primary endpoint: rates of medically attended acute respiratory illness (assessing direct and indirect protection) Risk ratio (MAARI rates in intervention vs. comparison communities): Vaccination period: 0.89 (0.86, 0.91) During epidemic: 0.90 (0.88, 0.92) Post-epidemic: 0.91 (0.88, 0.93) LAIV protection more evident in children 5-11 Indirect protection detected for all age groups, except 12-17 year olds (were not offered free vaccine)	Level II-2	Good

Evidence related to efficacy of FluMist®						
STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Fleming DM, Crovari P, Wahn U, et al. Comparison of the efficacy and safety of live attenuated cold-adapted influenza vaccine, trivalent, with trivalent inactivated influenza virus vaccine in children and adolescents with asthma. Pediatr Infect Dis J. 2006;25(10):860-9.[21]	CAIV-T FluMist® 0.1mL per nostril (10^7TCID$_{50}$ per strain) Single dose	RCT, open-label, active-controlled, multicentre Control vaccine: TIV Aventis Pasteur 2002/03 season Europe NCT:00192257 D153-P515	N = 2220 n_{TIV}=1109 n_{CAIV-T}=1111 Children with asthma (not all influenza vaccine-naïve children) ≥6 years to ≤17 years of age	Effectiveness endpoints: Use of prescribed medication/antibiotics, incidence of healthcare provider visits, incidence of hospitalizations, # days missed from school/work No significant difference between CAIV-T and TIV groups in incidence of asthma exacerbations post-vaccination or any of the identified endpoints.	Level I	Good
Halloran ME, Piedra PA, Longini IM, Jr., et al. Efficacy of trivalent, cold-adapted, influenza virus vaccine against influenza A (Fujian), a drift variant, during 2003-2004. Vaccine. 2007;25(20):4038-45.[10]	LAIV 0.1mL per nostril (10^7FFU per strain) Circulating H3N2 strains were poorly matched with strains in the vaccine	Open-label, prospective, nonrandomized community-based trial Comparator vaccine: *TIV* (0.5mL) 2003-2004 influenza season Within the county of Temple-Belton, TX	N=6403 n_{LAIV} 1706 n_{TIV} 548 n_{PREV} (previously vaccinated in 1998-2001) n=983 $n_{unimmunized}$=3166 Healthy children aged 5-18 years	Examined direct protective effects of LAIV against drift variant Primary endpoint: incidence of MAARI during 10 week outbreak period Overall effectiveness against MAARI Received LAIV in 2003: 0.26 (0.11, 0.39) Previous vaccinated but not in 2002 or 2003: -0.13 (-0.30, 0.03) Overall effectiveness in culture confirmed children Received LAIV in 2003: 0.56 (0.32, 0.75) Previous vaccinated but not in 2002 or 2003: -0.11 (-0.19, 0.37) LAIV was cross-protective against a drift variant	Level II-1	Good

Evidence related to efficacy of FluMist®						
STUDY DETAILS					SUMMARY	
Study	Vaccine	Study Design	Participants	Summary of Key Findings Using Text or Data	Level of Evidence	Quality
Children						
Belshe RB, Swierkosz EM, Anderson EL, et al. Immunization of infants and young children with live attenuated trivalent cold-recombinant influenza A H1N1, H3N2, and B vaccine. J Infect Dis. 1992;165(4):727-32.[47]	Cold-adapted trivalent influenza vaccine 0.5mL (H1N1 $10^{4.5}$ $TCID_{50}$, H3N2 $10^{4.4}$, B $10^{5.0}$) by nasal droplet delivery Single dose	RCT, double blind, vaccine diluent (placebo) controlled	N = 49 $n_{vaccine}$=32 $n_{placebo}$=17 Healthy children 6 months-13 years	Serum collected at baseline and 28-31 days post-vaccination First clinical trial of trivalent vaccine in infants and young children <u>Seroconversion</u> 8/17 (47%) triply baseline seronegative participants developed an antibody response to all three strains ELISA more sensitive in detecting antibody increase in baseline seropositive children than HAI compared to baseline seronegatives	Level I	Good
Belshe RB, Mendelman PM, Treanor J, et al. The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenzavirus vaccine in children. N Engl J Med. 1998;338(20):1405-12.[5]	LAIV Aviron, Mountain View, CA, USA 0.25mL per nostril ($10^{6.7}$ $TCID_{50}$ per strain) 2 dose, 60±14 days apart Vaccine and circulating strains well-matched	RCT, double-blind, placebo controlled, multicentre, AV006 Year 1 1996/97 season	N=203 n_{LAIV}=136 $n_{placebo}$=67 Healthy children 15-71 months	Serum collected at baseline and 4 weeks after dose 2 Primary endpoint was strain-specific GMT factor of ≥4 after dose 2 Baseline seronegative (LAIV) A(H1N1): 89/136 A(H3N2): 66/136 B: 93/136 Baseline seronegative (Placebo) A(H1N1): 47/67 A (H3N2): 30/67 B: 42/67 LAIV highly immunogenic for H3N2 and B after first dose 2 dose required to induce serum antibodies to H1N1 in most children In baseline seronegative children receiving LAIV, 61% had antibodies to H1N1 and 96% had antibodies to H3N2 and B after 2 doses	Level I	Good
Belshe RB, Gruber WC, Mendelman PM, et al. Correlates of immune protection induced by live, attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine. J Infect Dis. 2000;181(3):1133-7.[39]	Intranasal trivalent live, attenuate, cold-adapted influenza vaccine Dosage not reported (10^{7} $TCID_{50}$ per strain) Single dose	RCT, double-blind, placebo controlled, multicentre Year 2 Challenge study (A/H1N1) 1997/98 season	N=199 5-71 months old Children from year 1 of trial, (healthy and 34-91 months at Year 1 recruitment)	Specimens collected pre- and post-challenge 6 months after vaccination Significant difference in serum HAI antibody and nasal wash IgA antibody levels between vaccine and placebo groups Presence of IgA antibody in pre-challenge nasal wash specimens significantly correlated with protection from vaccine virus challenge	Level I	Good

Evidence related to efficacy of FluMist®

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Belshe RB, Gruber WC, Mendelman PM, et al. Efficacy of vaccination with live attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine against a variant (A/Sydney) not contained in the vaccine. J Pediatr. 2000;136(2):168-75.[6]	LAIV Aviron, Mountain View, CA, USA 0.25mL per nostril ($10^{7.0}$ $TCID_{50}$ per strain) Single dose Vaccine and circulating strains not well-matched (A/H3N2/ Sydney not contained in vaccine)	RCT, double-blind, placebo controlled, multicentre AV006 Year 2 1997/98 season	N=159 Groups based on assignment in year 1 Healthy children 26-85 months from immunogenicity substudy in Year 1	Serum collected at baseline and 4 weeks post-vaccination Immunogenicity in LAIV vs. placebo: H1N2: 82% vs 20% H3N2 100% vs 65% B: 100% vs 46% GMT of HAI antibodies LAIV vs. placebo: A/Sydney: 68 vs 12 ($p<0.01$)	Level I	Good
Boyce TG, Gruber WC, Coleman-Dockery SD, et al. Mucosal immune response to trivalent live attenuated intranasal influenza vaccine in children. Vaccine. 1999;18(1-2):82-8.[38]	Trivalent, cold-adapted influenza vaccine Aviron, Mountain View, CA, USA 0.25mL per nostril ($10^{6.5}$ $TCID_{50}$ per strain) 2 doses 54 days (48-74d) apart	RCT, double-blind, placebo controlled, multicentre 1996/97 season	N=19 $n_{vaccine}$=13 $n_{placebo}$=6 Healthy children 15-71 months	Specimens collected at baseline, 4 weeks after dose 1 and 4 weeks after dose 2 <u>Mucosal antibody response</u> Vaccine generated higher IgA values than placebo for all three antigens Percentage of subjects with response was statistically significant for A/H3N2 and B <u>Seroconversion (≥ 4 fold)</u> A/H3N2 ($p=0.01$) B ($p=0.01$) A/H1N1 ($p = 0.09$) Patients seropositive at baseline were 4.5 times more likely to develop a mucosal response than an HAI response ($p = 0.015$)	Level I	Good
Bracco Neto H, Farhat CK, Tregnaghi MW, et al. Efficacy and safety of 1 and 2 doses of live attenuated influenza vaccine in vaccine-naive children. Pediatr Infect Dis J. 2009;28(5):365-71.[11]	LAIV Wyeth Vaccines, Marietta, PA, USA 0.1mL per nostril ($10^{7\pm0.5}$FFU per strain) 2 doses in Year 1, single dose in Year 2 Vaccine and circulating strains well-matched	RCT, double-blind, placebo controlled, multi-centre 2001 and 2002 seasons South Africa, Brazil, Argentina NCT00192283 D153-P502	<u>Year 1</u> N=334 <u>Year 2</u> N=524 Healthy influenza vaccine-naïve children 6 to <36 months	Serum collected at baseline and 35±7 days after final dose in each year <u>Year 1</u> Seroconversion rates ($p>0.03$), GMTs, GMFRs, GMFR ratios higher in LAIV-LAIV and LAIV-placebo than placebo only Seroconversion rates ($p\leq0.037$) and GMFRs ($p<0.001$) after 2 LAIV doses were higher than after one dose compared to LAIV-LAIV and LAIV-placebo <u>Year 2</u> Seroconversion rates and GMTs increased in each LAIV group postvaccination <u>Overall</u> Baseline seronegative patients had higher seroconversion rates than all subjects in both years	Level I	Good

Evidence related to efficacy of FluMist®

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Forrest BD, Pride MW, Dunning AJ, et al. Correlation of cellular immune responses with protection against culture-confirmed influenza virus in young children. Clin Vaccine Immunol 2008;15(7):1042-53.[57]	CAIV-T Wyeth, Marietta, PA, USA 0.1 mL per nostril (107.0±0.5, 105.0±0.5FFU per strain) A strains antigenically identical, B strains differ: TIV B: Sichuan/379/99 LAIV B: Victoria/504/2000	Active and placebo controlled, dose-ranging, exploratory study (immunogenicity) Control vaccine: TIV: FluShield™ 0.25mL (15 µg HA per strain in adult dose of 0.5mL) 2001/02 season NCT00192374 D153-P513	N = 162 nCAIV-T 107= 40 nCAIV-T <105= 40 nTIV= 42 nplacebo= 40 Young children	Serum collected at baseline and 28 days post-vaccination GMFR among all subjects Higher among subjects receiving CAIV-T (107 FFU) for H3N2 and B compared to CAIV-T (105 FFU), TIV and placebo TIV had highest GMFR for H1N1 strain only GMFR among baseline sereonegative subjects Higher among subjects receiving CAIV-T (107 FFU) for all strains Seroconversion CAIV-T (107 FFU) conversation rates higher for H3N2 and B compared to all groups ($p<0.042$) TIV conversion rates higher for H1N1 (not significant)	Level III	Poor Study protocol and population unclear
King JC,Jr, Lagos R, Bernstein DI, et al. Safety and immunogenicity of low and high doses of trivalent live cold-adapted influenza vaccine administered intranasally as drops or spray to healthy children. J Infect Dis. 1998 May;177(5):1394-1397.[40]	CAIV-T Aviron, Mountain View, CA, USA 0.25mL per nostril (104, 105, 106, 107 TCID50 per strain) Single dose Dropper or spray delivery	RCT, placebo controlled, double-blind, multicentre 3 stages: Stage 1: March 1995 Stage 2 & 3: March – May 1996 USA (dropper or spray), Chile (spray only)	N= 356 <u>Stage 1</u> n104=57 n105=53 <u>Stage 2</u> n106=54 <u>Stage 3</u> n107=60 nplacebo=118 Healthy children 18-71 months	Serum collected at baseline and 42±7 days post-vaccination Seroconversion Seroconversion for H3N2 and B significantly higher compared to placebo at all doses except H3N2 at 104 TCID Seroconversion for H1N1 occurred only at 107 TCID No significant difference in HAI response at any dose between drop and spray methods	Level I	Good US participants removed from H1N1 analysis as wild type began circulating before post-vaccination serum collection occurred

Evidence related to efficacy of FluMist®						
STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Levin MJ, Song LY, Fenton T, et al. Shedding of live vaccine virus, comparative safety, and influenza-specific antibody responses after administration of live attenuated and inactivated trivalent influenza vaccines to HIV-infected children. Vaccine. 2008 Aug; 26(33):4210-4217.[74]	LAIV FluMist® 0.25mL per nostril Single dose	Randomized, active controlled, open label clinical trial, stratified by CD4% Active vaccine: TIV: Fluzone® 0.5mL 2004/05 season Note: Stratification into 3 groups (CD4%<15 at nadir and ≥15 at screening; CD4% ≥15 at nadir and <25 at screening; CD4% ≥25 at nadir and screening)	N=243 nLAIV=122 nTIV=121 Children ≥5 to <18 years old on a stable highly active antiretroviral therapy for ≥16 weeks; HIV-1 plasma <60,000 copies/mL within 60 days prior to screening; and received at least one TIV within previous 2 years	Serum collected at baseline, 28 days and 6 months post-vaccination; Nasal swab days 3, 14, and 28 post-vaccination No significant increases in median/mean plasma HIV viral load from baseline in any group Median CD4% did not change significantly at any point as a result of vaccination HAI GMT at 4 weeks post-vaccination correlated with HAI GMT prior to vaccination for all strains in both interventions (p<0.0001) LAIV: Inverse relationship between entry HIV RNA plasma levels and HAI GMT for H3N2 TIV: Inverse relationship between entry HIV RNA plasma levels and HAI GMT for all strains TIV induced higher serum HAI titers for H3N2 and B strains, and greater increases in antibody titer compared to LAIV in baseline seropositive children	Level I	Good
Lum LC, Borja-Tabora CF, Breiman RF, et al. Influenza vaccine concurrently administered with a combination measles, mumps, and rubella vaccine to young children. Vaccine. 2010;28(6):1566-74.[12]	LAIV Wyeth Vaccines Research, Marietta, PA, USA 0.1mL per nostril (107 TCID50 per strain) 2 doses 35±7 days apart Vaccine and circulating A/H3N2 not well matched	Phase III RCT, double-blind, placebo controlled, multicentre Non-inferiority trial (lower bound -10.0%) Co-vaccine: MMR (Priorix®) 2002/03 season NCT:00192166 D153-P522 13 countries (Europe/Asia)	N=1120 nLAIV+MMR=747 nplacebo+MMR=373 Both groups received MMR with dose 1 Healthy vaccine-naïve children 11-<24 months	Serum collected before dose 1 and dose 2 Rubella Per-protocol study definition failed to show non-inferiority: Seroconversion rate for LAIV (78%) vs. placebo (83.9%) had difference in rates with 95% confidence interval (-10.5, -1.0) Post-hoc analysis using ELISA threshold: Seroconversion rate for LAIV (89.8%) vs. placebo (93.4%) had difference in rates with 95% confidence interval (-6.9, -0.1) Mumps Seroconversion rate for LAIV (86.6%) vs. placebo (84.5%) had difference in rates with 95% confidence interval (-2.1, 6.8) Measles Seroconversion rate for LAIV (90.8%) vs. placebo (85.3%) had difference in rates with 95% confidence interval (1.5, 9.9)	Level I	Good

Evidence related to efficacy of FluMist®						
STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Rudenko LG, Lonskaya NI, Klimov AI, et al. Clinical and epidemiological evaluation of a live, cold-adapted influenza vaccine for 3-14-year-olds. Bull World Health Organ. 1996;74(1):77-84.[46]	LAIV (Master donor virus A/Leningrad/134/47/57) Institute of Experimental Medicine, St. Petersburg, Russia 0.25mL per dose 2 doses 21-28 days apart Monovalentbivalent, trivalent	RCT, placebo controlled, multicentre	N=131,930 School children 3-15 years 2 doses given 21-28 days apart Serum and urine sample taken 3 days and 1 month after each dose	Specimens collected at baseline, 3 days and 1 month after dose 1, 3 days and 1 month after dose 2 Protective levels of antibody induced in mono, bi and trivalent participants Seroconversion Among baseline seronegative individuals: H1N1: 61.0-63.6% seroconverted H3N2: 69.8-73.7% B: 43.7-54.5%	Level I	Good
Schiff GM, Linnemann CC, Jr., shea L, et al. Evaluation of a live, attenuated recombinant influenza vaccine in high school children. Infect Immun. 1975;11(4):754-7.[45]	LAIV Experimental lot (Derived from A/England/42/72 and A/PR8/34) 5 drops per nostril (107.5 TCID)	Active and placebo controlled trial, open label Control vaccine: Bivalent inactivated vaccine (BIV) : Fluogen® 0.5mL Wyoming High School, Wyoming, Ohio	N=126 nLAIV=74 nBIV=24 nplacebo =28 High school students (Gr. 9-12)	Blood samples collected at beginning and after 30 days; also collected at the end of the study if influenza-like illness reported LAIV 62.2% experienced fourfold or greater rise in antibody titer GMT rose from 30.2 to 189.6 Nine participants lacked pre-existing antibody and developed GMT of 276.2 BIV 79.2% developed increase in antibody titer from GMT 32.9 to 361.8 Placebo No significant seroconversion (GMT 38.1 to 42.0 post-placebo)	Level II-1	Poor Relevant inclusion/exclusion criteria not considered; comparability of groups unclear; Randomization feasible but not used

Evidence related to efficacy of FluMist®						
STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Tam JS, Capeding MR, Lum LC, et al. Efficacy and safety of a live attenuated, cold-adapted influenza vaccine, trivalent against culture-confirmed influenza in young children in Asia. Pediatr Infect Dis J. 2007;26(7):619-28.[7]	CAIV-T Wyeth, Marietta, PA, USA 0.1mL per nostril (107TCID) 2 doses in Year 1 ≥28d apart 1 dose in Year 2 Vaccine and circulating B strain not well matched in either year (29.2% distinct in year 1, 77% in year 2)	RCT, double-blind, placebo controlled, multicentre, cross-over 2000/01 and 2001/02 seasons Asia NCT00192244 D153-P501	nCAIV-T=111 nplacebo = 52-75 Groups were re-randomized in Year 2 Healthy children 12-<36 months	Specimens collected pre- and post-vaccination after dose 2 in Year 1 and dose 1 in Year 2 Year 1 GMFR – All (CAIV-T vs placebo) H1N1: 5.0 (3.9, 6.5) vs. 1.2 (1.0, 1.5) H3N2: 17.0 (11.0, 26.4) vs. 1.1 (1.0, 1.4) B: 6.8 (4.9, 9.4) vs. 1.0 (0.9, 1.2) GMFR – Baseline Seronegative (CAIV-T vs. placebo) H1N1: 9.6 (7.2, 12.8) vs. 1.4 (1.1, 1.8) H3N2: 91.0 (64.0, 129.6) vs. 1.2 (0.9, 1.5) B: 11.7 (8.1, 16.8) vs. 1.1 (0.9, 1.3) Seroconversion Seroconversion rates higher in baseline seronegative subjects compared to all subjects with CAIV-T Rate of seroconversion higher in CAIV-T (56.8-95.1%) than placebo (2.1-13.5%) Year 2 Rate of seroconversion and fold-increases statistically significant only in treatments groups receiving CAIV-T in year 2, regardless of serostatus and year 1 treatment	Level I	Good

Evidence related to efficacy of FluMist®						
STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Weinberg A, Song LY, Walker R, et al. Anti-influenza serum and mucosal antibody responses after administration of live attenuated or inactivated influenza vaccines to HIV-infected children. J Acquir Immune Defic Syndr. 2010;55(2):189-96.[44]	LAIV FluMist® 0.25mL per nostril	RCT, active controlled, open label Control vaccine: TIV: Fluzone® 0.5mL 2004-05 season Note: Stratification into 3 groups by nadir: CD4<15; CD4 ≥15 at and <25; CD4 ≥25)	N=243 nLAIV=122 nTIV=121 Children and adolescents 5-18 years, HIV-infected on a stable highly active antiretroviral therapy for ≥16 weeks; plasma viral load <60,000 copies/mL, CD4 ≥15% within 60 days prior to enrollment; and received at least one TIV within previous 2 years	Specimens collected at baseline, week 4 and week 24 post-vaccination; nasal shedding monitored on days 3, 14, and 28 post-vaccination Magnitude of response to TIV and LAIV most correlated with baseline microneutralization titers ($p<0.0001$) and baseline viral load Significant increases in microneutralization titers at 4 and 24 weeks for TIV and LAIV ($p\leq0.02$) Week 4 titers higher in TIV recipients than LAIV ($p\leq0.002$) No significant associations between salivary influenza-IgA concentrations with baseline plasma viral load, CD4%, CD8% or CD19% Week 4 salivary anti-influenza-IgG response were associated with baseline concentrations and baseline plasma HIV viral load LAIV and TIV both demonstrated heterotypic HAI responses, with TIV inducing significantly higher HAI titers than LAIV at 4 and 24 weeks post-vaccination	Level I	Good
Children and Adults						
Block SL, Yogev R, Hayden FG, et al. Shedding and immunogenicity of live attenuated influenza vaccine virus in subjects 5-49 years of age. Vaccine. 2008;26(38):4940-6.[78]	LAIV FluMist® 0.25mL per nostril (10^7 $TCID_{50}$) Single dose	Phase IV, open-label clinical trial, multicentre 2004/05 season 11 sites , USA	N=343 n_{5-8}=102 n_{9-17}=126 n_{18-49}=115 3 age cohorts (5-8, 9-17, 18-49 years)	Serum collected at baseline and day 28 post vaccination <u>Study endpoints</u>: Strain-specific HAI titers at 28 days immunization and seroresponse (≥4 fold rise in HAI compared to baseline) <u>Seroresponse to any strain in all subjects</u> Age 5-8: 67.7% (57.4, 76.9) Age 9-17: 63.7% (54.6, 72.2) Age 18-49: 47.0% (37.6, 56.5) <u>Seroresponse in baseline seronegative subjects</u> H1N1: 81.1% H3N2: 70.3% B: 29.8% Seroresponse higher in 5-8 and 9-17 groups than 18-49	Level II-2	Good

Evidence related to efficacy of FluMist®

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Edwards KM, Dupont WD, Westrich MK, et al. A randomized controlled trial of cold-adapted and inactivated vaccines for the prevention of influenza A disease. J Infect Dis. 1994;169(1):68-76.[27]	LAIV 0.5mL per nostril (0.25mL per strain; 10^7-$10^{7.6}$ pfu/mL) Children <3 received same volume with 1/10 dilution Bivalent for A strains only throughout study Single dose per strain Nasal drops delivery	RCT, double-blind, active and placebo controlled, multicentre Control vaccine: TIV (15µg HA per strain), Year 1 vaccine (bivalent A), trivalent thereafter 1985/86 to 1988-89 seasons 7 sites, Nashville, Tennessee. USA	N=5210 $Group_{TIV}$ 1 (n=1739) $Group_{LAIV}$ 2 (n=1733) $Group_{placebo}$ 3 (n=1738) Healthy persons aged 1-65 years ($n_{<15\ years}$=809)	Serum collected pre-immunization, ~1 month post vaccination, spring after end of influenza season Postimmunization titers increased significantly for TIV and LAIV groups each year, but were higher for TIV than LAIV in all years except 1985 Control group more likely to seroconvert and have confirmed or retrospectively reported illness for all years LAIV group more likely to seroconvert and have confirmed or retrospectively reported illness than TIV group, when H3N2 was circulating, but not when H1N1 was circulating <u>First vaccination: % of participants ≥4-fold increase in HAI; Post-vaccination titer ≥32</u> H1N1 Control: 5.5 (4.0, 7.3); 60.0 (57.0, 63.0) LAIV: 24.4 (31.0, 38.0); 84.4 (82.0, 87.0) TIV: 69.4 (66.0, 73.0); 91.9 (90.0, 94.0) H3N2 Control: 10.0 (7.5, 13.0); 35.8 (32.0, 40.0) LAIV: 14.2 (11.0, 18.0); 42.2 (38.0, 47.0) TIV: 72.7 (68.9, 77.0); 82.4 (79.0, 86.0) <u>Subsequent vaccination: % of participants ≥4-fold increase in HAI; Post-vaccination titer ≥32</u> H1N1 Control: 5.21 (3.8, 7.0); 47.1 (44.0, 51.0) LAIV: 17.8 (15.0, 21.0); 82.8 (80.0, 85.0) TIV: 19.4 (17.0, 22.0); 96.8 (95.0, 98.0) H3N2 Control: 5.3 (4.2, 6.6); 23.0 (21.0, 25.0) LAIV: 6.8 (5.5, 8.1); 31.9 (29.0, 34.0) TIV: 16.8 (15.0, 19.0); 73.5 (71.0, 76.0)	Level I	Good

Evidence related to efficacy of FluMist®						
STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Mallory RM, Malkin E, Ambrose CS, et al. Safety and immunogenicity following administration of a live, attenuated monovalent 2009 H1N1 influenza vaccine to children and adults in two randomized controlled trials. PLoS ONE. 2010;5(10):e13755.[48]	LAIV MedImmune 0.25mL per nostril (10^7 FFU) Monovalent (H1N1)	RCT, double-blind, placebo controlled, multicentre 2 trials: children (NCT00946101) and adults (NCT00945893) Randomization stratified by site in adults and by age groups (2-8y, 9-17y) in children 2009 season	Child trial N=326 n_{LAIV}=261 $n_{placebo}$=65 Adult trial N=300 n_{LAIV}=240 $n_{placebo}$=60	Serum collected at days 0 and 57, and participants were randomized for collection for day 15 or 29 Primary endpoint: Proportion of subjects experiencing postvaccination seroresponse in baseline seronegative and in all subjects Secondary endpoint: proportion of subjects with HAI titer ≥32 and HAI GMTs Seroconversion rate (%) in baseline seronegative LAIV (placebo): Children at day 57 – 34.8 (16.1) Children GM ≥32: 19.0% (7.1%) Adults at day 57 – 16.9 (7.1) Adults GM ≥32: 7.4% (2.4%) Seroconversion rate (%) in all LAIV (placebo): Children (all) at day 57 – 32.0 (14.5) GM ≥32: 26.4% (9.7%) Children (2-9y) at day 57 – 28.0 (6.7) GM ≥32: 23.1% (6.7%) Adults at day 57 – 14.9 (5.6) Adults GM ≥32: 13.5% (11.1%)	Level I	Good

Evidence related to efficacy of FluMist®

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Sasaki S, Jaimes MC, Holmes TH, et al. Comparison of the influenza virus-specific effector and memory B-cell responses to immunization of children and adults with live attenuated or inactivated influenza virus vaccines. J Virol. 2007;81(1):215. [43]	LAIV FluMist® Single dose (2 dose for vaccine naïve children)	RCT, active controlled serology Control vaccine: TIV: Fluzone® 2003/04 and 2004/05 seasons	N=108 n_{adult}=44 $n_{older\ children}$=39 $n_{younger\ children}$=25 Adults: 21-49 years Older children: 5-9 years Younger children: 6 months-4 years Influenza vaccine naive children given 2nd dose 28 days (TIV) or 42 days (LAIV) after first dose Younger children only immunized with TIV (LAIV not licensed for this group)	Specimens collected for adults and older children at baseline, days 9 (7-12 in adults, 9-11 in older children, 30 (27-42); specimens collected in younger children at baseline and at random on day 9 (9-11) No detectable difference in effector IgA B-cell response in adults or older children after LAIV (p=.125) Adults had higher effector IgA B-cell response than older children after TIV (p=.024) IgG antibody secreting cell (ASC) responses in adults higher after TIV (IgG ASC/million PBMC 41±11) than LAIV (12± 4) (p=.005); no significant difference in older children between TIV and LAIV (p=.152) IgG ASC response in adults and older children not significantly different after TIV (p=.287), but children had higher IgG response on average than adults after LAIV (p=.028) IgG B-cell response numerically greater than IgA ASC (p≤.011) after TIV in adults and older children, and after LAIV in children (p=.004) IgA and IgG ASC not detectably different in adults after LAIV (p=.109) No statistical difference in B-cell response, effector IgA, IgG B-cell response, IgA ASC or IgG ASC in younger children after first vs. second dose of TIV IgG ASC response lower in younger children than older children and adults <u>Serum antibody response with ≥4 fold rise in HAI/neutralization (LAIV vs. TIV)</u> Adults: 15.8/21.1% vs. 43.5/52.2%; p≤.048 Children: 26.7/37.5% vs. 78.9/78.9%l; p≤.012	Level I	Good

Evidence related to efficacy of FluMist®						
STUDY DETAILS					SUMMARY	
Study	Vaccine	Study Design	Participants	Summary of Key Findings Using Text or Data	Level of Evidence	Quality
Adults						
King JC, Jr., Treanor J, Fast PE, et al. Comparison of the safety, vaccine virus shedding, and immunogenicity of influenza virus vaccine, trivalent, types A and B, live cold-adapted, administered to human immunodeficiency virus (HIV)-infected and non-HIV-infected adults. J Infect Dis. 2000;181(2):725-8.[72]	LAIV Aviron, Mountain View, CA, USA 0.25mL per nostril (10^7 $TCID_{50}$ per strain) Single dose	RCT, double-blind, placebo controlled	N=111 n_{HIV}=57 $n_{control}$=54 Adults in good general health 18-58 years; HIV participants with CDC class of A1-2 and plasma HIV RNA PCR measurement of <10,000 copies/mL and >200 CD4 cells/mm^3 within 4 months, and on stable antiretroviral regimen if ≤500 CD4 cells/mm^3	Plasma HIV RNA PCR levels stable in LAIV and placebo HIV-infected individuals Slight decline in CD4 cells post-vaccination in HIV-infected, but magnitude of difference was not significant between placebo and LAIV groups Few participants had seroresponse to LAIV (≥4-fold rise in HAI titer)	Level I	Good
Ohmit S, Victor J, Rotthoff J, et al. Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines. N Engl J Med. 2006;355(24):2513-22.[31]	LAIV FluMist® 0.25mL per nostril ($10^{6.5}$-$10^{7.6}$ $TCID_{50}$ per strain) Single dose A/H3N2 strains not well matched to vaccine, two lineages of type B were circulating (one in vaccine)	RCT, double-blind, active controlled, community-based Control vaccine: TIV: Fluzone® 0.5mL (15µg HA per strain) 2004/05 season NCT: 00133523 4 sites, Michigan, USA Year 1 of 2	N=1247 n_{LAIV}= 519 $n_{placebo}$=103 (IN spray) n_{TIV}= 522 $n_{placebo}$=103 (IM injection) Healthy adults aged 18-46 years (mean age 24.9)	Specimens collected at baseline, 3-5 weeks post-vaccination and end of influenza season (April-May 2005) <u>Participants (%) showing ≥4-fold increase in HAI (TIV vs. LAIV)</u> A/H3: 348 (66.7) vs. 110 (21.2), p<.001 B: 445 (85.2) vs. 70 (13.5), p<.001 A/H1: 367 (70.3) vs. 44 (8.5), p<.001	Level I	Good

Evidence related to efficacy of FluMist®

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Treanor JJ, Kotloff K, Betts RF, et al. Evaluation of trivalent, live, cold-adapted (CAIV-T) and inactivated (TIV) influenza vaccines in prevention of virus infection and illness following challenge of adults with wild-type influenza A (H1N1), A (H3N2), and B viruses. Vaccine. 1999;18(9-10):899-906.[30]	CAIV-T Flu Mist® 0.25mL per nostril (10^7 $TCID_{50}$ per strain)	RCT, active and placebo controlled double-blind wild type challenge study Control vaccine: TIV: Fluvirin® 0.5mL (15µg HA per strain) 1995/96 season **AV003** NCT: 2 sites, USA	N=92 n_{CAIV-T}=29 n_{TIV}=32 $n_{placebo}$=31 Groups challenged with 1 strain of virus 28 days after vaccination (then placed in group isolation x7 days) Healthy adult volunteers aged 18-40 years who were serosusceptible (HAI ≤1:8) to at least 1 of 3 strains	Serum collected at baseline and on day 28 post-vaccination Serum HAI response in placebo significantly different from TIV but not CAIV-T Nasal secretion antibody response (sIgA) more frequent in CAIV-T and TIV compared to placebo, but were not significantly different from each other <u>Serum antibody response in all subjects (pre GMT, post GMT; % response with ≥4-fold increase in HAI)</u> H1N1 CAIV-T – 4.8, 9.8; 23 TIV – 4.9, 199.0; 91 Placebo – 5.8, 11.8; 16 H3N2 CAIV-T – 6.1, 14.3; 33 TIV – 11.0, 99.5; 76 Placebo – 9.3, 11.9; 6 B CAIV-T – 18.8, 19.4; 3 TIV – 17.4, 133.5; 76 Placebo – 15.3, 15.3; 0	Level I	Good Limited sample size, low rates of infection/ illness in placebo recipients
Treanor JJ, Mattison HR, Dumyati G, et al. Protective efficacy of combined live intranasal and inactivated influenza A virus vaccines in the elderly. Ann Intern Med. 1992;117(8):625-33.[68]	LAIV 0.25mL per nostril ($10^{7.2}$ $TCID_{50}$ per strain) A/H3N2 strains only Intranasal drops	RCT, double-blind, active and placebo controlled, multi-centre Control vaccine: TIV, 0.5mL (15µg HA per strain) 1987-88, 1988-89 seasons 3 large nursing homes in NY	N=523 TIV + placebo TIV+intranasal monovalent LAIV Participants received TIV and were re-randomized for placebo or LAIV each year Elderly - 95% >65 years, 75% female	Serum collected at baseline, day 28 after vaccination and 1 month after end of influenza season in years 2 and 3 No difference observed in frequency of serum HAI or IgG EIA titers in TIV + placebo vs. TIV+ LAIV groups No correlation found between pre-vaccine HA titers and HAI response post-vaccination	Level I	Fair Nasal secretory antibody titers not determined

Evidence related to safety of FluMist®						
		STUDY DETAILS			SUMMARY	
Study	Vaccine	Study Design	Participants	Summary of Key Findings Using Text or Data	Level of Evidence	Quality
Children						
Belshe RB, Mendelman PM, Treanor J, et al. The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenzavirus vaccine in children. N Engl J Med. 1998;338(20):1405-12.[5]	LAIV Aviron, Mountain View, CA, USA 0.25mL per nostril ($10^{6.7}$ $TCID_{50}$ per strain) 2 dose, 60±14 days apart Vaccine and circulating strains well-matched	RCT, double-blind, placebo controlled, multicentre, AV006 Year 1 1996/97 Influenza season	N=1602 n_{LAIV}= 1070 $n_{placebo}$= 532 Both groups received 1 or 2 doses; second dose 60d ± 14d apart Healthy children ≥ 15-71 months	After 1st dose (LAIV vs placebo): Rhinorrhea (Days 2,3,8,9) (27% vs 18%, p=0.001) (30% vs 20%, p<0.001) (30% vs 22%, p=0.01) (29% vs 21%, p=0.02) respectively Fever (Day 2) (mean duration 1.4 days, low grade)(6.5% vs 1.6%, p<0.001) Decreased activity (Day 2) (6.0% vs 2.1%, p=0.008) No significant differences in other symptoms (cough, headache, sore throat, irritability, chills, vomiting, muscle aches). No significant differences in any variable after 2nd dose in year 1. No SAE attributed to vaccine	Level I	Fair Participants not randomized into 1 or 2 dose groups, and equivalency between 1 and 2 dose was not established
Belshe RB, Gruber WC, Mendelman PM, et al. Correlates of immune protection induced by live, attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine. J Infect Dis. 2000;181(3):1133-7.[39]	Intranasal trivalent live, attenuate, cold-adapted influenza vaccine Dosage not reported (10^7 $TCID_{50}$ per strain) Single dose	RCT, double-blind, placebo controlled, multicentre Year 2 Challenge study (A/H1N1) 1997/98 influenza season	N=222 n_{LAIV}=144 $n_{placebo}$=78 5-71 months old Children from year 1 of trial, (healthy and 34-91 months at Year 1 recruitment)	Primary endpoint: shedding of vaccine virus in respiratory secretions on days 1-4, ORP (overall rate of protection) Shedding of vaccine vs. placebo: 4.2% vs. 24.4% ORP 83% (95%CI, 60% to 93%) No serious adverse events occurred No significant differences in occurrence of runny nose, nasal congestion or fever between vaccine and placebo groups	Level I	Good
Belshe RB, Gruber WC, Mendelman PM, et al. Efficacy of vaccination with live attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine against a variant (A/Sydney) not contained in the vaccine. J Pediatr. 2000;136(2):168-75.[6]	LAIV Aviron, Mountain View, CA, USA 0.25mL per nostril ($10^{7.0}$ $TCID_{50}$ per strain) Single dose Vaccine and circulating strains not well-matched (A/H3N2/ Sydney not contained in vaccine)	RCT, double-blind, placebo controlled, multicentre AV006 Year 2 1997/98 influenza season	N=1358 n_{LAIV} = 917 $n_{placebo}$ =441 Both groups received 1 dose of vaccine or placebo, based on assignment in year 1 Healthy children 26-85 months from year 1 of trial (85% return rate)	No significant differences in rhinorrhea (LAIV 19% vs placebo 14%), fever (LAIV: 2.0% vs placebo:1.8%) or decreased activity were present in year 2 revaccination.	Level I	Good

Evidence related to safety of FluMist®

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Belshe RB, Edwards KM, Vesikari T, et al. Live attenuated versus inactivated influenza vaccine in infants and young children. N Engl J Med. 2007;356(7):685-96.[19]	CAIV-T FluMist® 0.1mL per nostril (10^7 $TCID_{50}$)	RCT, prospective, double-blind, active controlled, multi-centre Control vaccine: TIV Fluzone® (US/Asia) Vaxigrip® (Europe/ Middle East), 0.25mL or 0.5mL/ dose based on age 2004/05 season 249 sites in 16 countries (US, Europe/Middle East, Asia) NCT00128167 MI-CPIII	N=8352 n_{TIV}=4173 n_{CAIV-T}=4179 1 or 2 doses for both groups. Second dose given to vaccine-naive children 28-42 days after first dose Placebo saline injection or intranasal mist given concurrently with active intervention Children aged ≥6-≤59 months Both groups included some children with underlying medical conditions (5.7% of total) mild/ moderate asthma (4%) or a history of recurrent (6%) or any wheezing(21%)	<u>Significant reactogenicity events (LAIV vs TIV)</u> <u>Fever on day 2 after 1st dose: 5.4% vs 2.0%, (p<0.001)</u> <u>Significant increases in MSW ≤42 days after Dose 1 (LAIV vs TIV, 95% CI)</u> **Vaccine-naïve children (6-59 mos)** (2.3% vs 1.5%) (adjusted difference of 0.77%, 0.12, 1.46). Seen after weeks 2, 3, 4 **Vaccine-naïve children (6-24 mos)** (3.2% vs 2.0%) (adjusted difference of 1.18%, 0.13, 2.29) **Vaccine-naïve children (6-12 mos)** **(3.8% vs 2.1%) (p=-.08)** Beyond 42 days, rates of MSW did not differ between groups. <u>Rates of hospitalization for any cause within 180 days after vaccination (LAIV vs TIV):</u> 6-59 mos: 3.1% vs 2.9% 12-59 mos: 2.5% vs 2.9% **6-11 mos: 6.1% vs 2.6% (95% CI, 1.4, 5.8)** Trends were higher hospitalization for any cause among LAIV children aged 6 to 46 mos with hx of wheezing compared to same age TIV recipients with hx of wheezing (not significant). Children aged 12-59 mos with no hx wheezing, hospitalization for any cause lower in LAIV than TIV (p=0.07) SAEs: similar incidence between groups (136: LAIV & 128 TIV) 6 SAEs in LAIV (n=2 bronchiolitis, n=1 asthma exacerbation, n=1 wheezing, n=1 acute gastroenteritis, n=1 RAD) 5 SAEs in TIV (1 of each of pneumonia, wheezing, febrile convulsion, febrile convulsion and pneumonia, viral gastroenteritis). Two deaths in each group not related to study.	Level I	Good

Evidence related to safety of FluMist®

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Bergen R, Black S, Shinefield H, et al. Safety of cold-adapted live attenuated influenza vaccine in a large cohort of children and adolescents. Pediatr Infect Dis J. 2004;23(2):138-44.[60]	*CAIV-T* FluMist® 0.25mL per nostril (10^7TCID$_{50}$ per strain) 1 or 2 doses, depending on age	Randomized, double-blind, placebo controlled AV019 2000 Excluded those who received TIV in 2000 or any live virus within 1 month of study or inactivated vaccine within 2 weeks.	N = 9,689 Children aged 1-8 years $n_{TCAIV-T}$=3,769 $n_{placebo}$=1,868 Children aged 9-17 years $n_{TCAIV-T}$=2,704 $n_{placebo}$=1,348 Healthy children aged 12 months to 17 years (2nd dose given 28 to 42 days after 1st dose)	None of the 4 prespecified diagnostic categories (acute respiratory tract events, systemic bacterial infections, acute gastrointestinal tract events, rare events) associated with vaccine. Healthcare utilization rates similar between groups. **Signal detected in children 18 to 35 months within 42 days of vaccination** Asthma/Reactive Airway Disease incidence: FluMist: 2.2% Placebo: 0.54% Relative Risk: 4.06 (90% CI: 1.29, 17.86) • 8.8% of CAIV participants in this age group had prior hx of asthma/RAD. No increased asthma risk found with CAIV-T. Statistically significant AEs URI (18-35 mos) (Relative Risk 1.30, 90%CI: 1.01, 1.67) Musculoskeletal pain, Otitis media with effusion, Adenitis/adenopathy potentially related but low incidence. No SAE deemed related to study in either group.	Level I	Good
Bracco Neto H, Farhat CK, Tregnaghi MW, et al. Efficacy and safety of 1 and 2 doses of live attenuated influenza vaccine in vaccine-naive children. Pediatr Infect Dis J. 2009;28(5):365-71.[11]	LAIV Wyeth Vaccines, Marietta, PA, USA 0.1mL per nostril ($10^{7\pm0.5}$FFU per strain) 2 doses in Year 1, single dose in Year 2 Vaccine and circulating strains well-matched	RCT, double-blind, placebo controlled, multi-centre 2001 and 2002 influenza seasons South Africa, Brazil, Argentina NCT00192283 D153-P502	<u>Year 1</u> N=2821 <u>Year 2</u> N = 2054 Healthy influenza vaccine-naïve children aged 6 to <36 months	Significant reactogenicity events within 11 days were cough and rhinorrhea. No statistically significant differences among treatment and placebo groups for AE (fever, upper respiratory tract infections, rhinitis, coughing) Year 2 only significant AE was bronchitis (3.1% LAIV and 1.6% placebo; p=0.046) SAEs in year 1 related to study (n=29), including pneumonia, bronchopneumonia, bronchiolitis and bronchitis. 3 deaths, not related to study.	Level I	Good Error in treatment allocation coding and labelling in Year 2 resulted in 2 additional treatment protocols
Nolan T, Lee MS, Cordova JM, et al. Safety and immunogenicity of a live-attenuated influenza vaccine blended and filled at two manufacturing facilities. Vaccine. 2003;21(11-12):1224-31.[42]	CAIV-T 0.25mL per nostril (10^7TCID$_{50}$ per strain) Vaccine from different facilities (Medeva vs. Aviron-PA)	RCT, CAIV-T (Medeva) control, double-blind AV018 1997, off-season Australia	N=225 n_{Medeva}=135 n_{Aviron}=90 Healthy children aged 12-42 months 2 doses given 4-6 weeks apart.	Only significant adverse event: Vomiting after dose 1: (3% (Aviron) vs 13% (Medeva), p=0.01)	Level I	Good

Evidence related to safety of FluMist®						
STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Tam JS, Capeding MR, Lum LC, et al. Efficacy and safety of a live attenuated, cold-adapted influenza vaccine, trivalent against culture-confirmed influenza in young children in Asia. Pediatr Infect Dis J. 2007;26(7):619-28.[7]	CAIV-T Wyeth, Marietta, PA, USA 0.1mL per nostril (10^7 $TCID_{50}$ per strain) Year 1: 2 doses ≥28 days apart Year 2: Single dose B-component of vaccine was not well matched in either year. (29.2% distinct in year 1, 77% in year 2)	RCT, double-blind, placebo controlled, multicentre 2000/01 & 2001/02 seasons 16 sites, Asia NCT00192244 D153-P501	<u>Year 1</u> N=3174 n_{CAIV-T} =1900 $n_{placebo}$ =1274 Both groups received 2 doses <u>Year 2 (re-randomized)</u> N=2527 $n_{CAIV-T/CAIV-T}$= 881 $n_{CAIV-T/placebo}$ = 876 $n_{placebo/CAIV-T}$= 596 $n_{placebo/placebo}$ = 594 Healthy children aged 12 to <36 months	Significant reactogenicity events within 11 days (Year 1) 1st Dose (CAIV-T vs placebo) Fever ≥37.5ºC (22.0% vs 17.6%; p=0.004) Rhinorrhea (62.0% vs 52.0%; p<0.001) Decreased activity (13.4% vs 10.7%; p=0.026) Decreased appetite (24.2% vs 19.7%; p=0.003) Use of fever medication (21.3% vs 18.4%; p=0.044) **(Year 1) 2nd dose:** Rhinorrhea/Nasal congestion (49.8% vs 45.6%; p=0.030) **Year 2:** Rhinorrhea (62.0% vs 55.4%; p=0.019) AEs (year 1, dose 1) Fever (15.4% vs 11.7%; p=0.003) AEs (year 2) Fever (12.7% vs 9.8%; p=0.017) Year 1 cases of SAE Bronchospasm (7 vs 3) Bronchitis (3 vs 2) Rhinitis (3 vs 0) Fever x 3 days in 20 month old (1 vs 0) – withdrew 2 deaths, both unrelated Year 2 cases of SAE Pneumonia 6 days after vaccine (1 in CAIV-T group)	Level I	Good
Vesikari T, Karvonen A, Korhonen T, ***et al***. A randomized, double-blind study of the safety, transmissibility and phenotypic and genotypic stability of cold-adapted influenza virus vaccine. Pediatr.Infect. Dis.J. 2006 July 2006; 25(7):590-595.[80]	LAIV 0.25 mL per nostril ($10^7$$TCID_{50}$ per strain)	Prospective, randomized, double-blind, placebo controlled study NCT00192322 D153-P002 1999 Finland	N=197 N_{CAIV-T}=98 $n_{placebo}$=99 Healthy children in daycare aged 9-36 months Second dose was offered 42 days after 1st	Nasal swab specimens collected on day 0, and on days 1,3 alternating weeks for 21 days. SAE (42 days after vaccination) Placebo: acute laryngitis CAIV-T: pyelonephritis, acute gastroenteritis. All unrelated to vaccine. Other (not statistically significant) adverse events among CAIV-T/placebo groups: Otitis media (12.2% vs 16.2%, p=0.54) Cough (8.2% vs 8.1%, p>0.99) Fever (7.1% vs 3.0%, p-0.21) Rhinitis (6.1% vs 8.1%, p-0.78) Viral shedding: 80% of vaccine recipients shed at least one virus strain.	Level I	Good

Evidence related to safety of FluMist®						
		STUDY DETAILS			SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Vesikari T, Fleming DM, Aristegui JF, et al. Safety, efficacy, and effectiveness of cold-adapted influenza vaccine-trivalent against community-acquired, culture-confirmed influenza in young children attending day care. Pediatrics. 2006;118(6):2298-312. [8]	CAIV-T 0.1mL per nostril (10^7TCID$_{50}$ per strain) Vaccine and circulating strains well-matched (H3N2/A substituted in Year 2)	RCT, prospective, double-blind, placebo controlled, multicentre NCT00192283 D153-P502 2000-2001 & 2001-2002 influenza seasons Belgium, Finland, Israel, Spain, UK	<u>Year 1 Dose 1</u> N=1784 <u>Year 1 Dose 2</u> N=1784 2 doses with second dose 35d ± 7d apart <u>Year 2</u> N=1119 1 dose based on assignment in year 1 Healthy children aged 6 to <36 months attending day care ≥12hours/week	The only significant reactogenicity events within 11 days occurred in Year 1 after first dose: rhinorrhea (82.3% vs 75.4%, p=0.001)	Level I	Good
Adults						
De Villiers PJ, Steele AD, Hiemstra LA, et al. Efficacy and safety of a live attenuated influenza vaccine in adults 60 years of age and older. Vaccine. 2009;28(1):228-34.[67]	LAIV FluMist® 0.1mL per nostril (10^7TCID$_{50}$ per strain) B strains not well matched to vaccine (production issues)	Randomized, prospective, double-blind, placebo controlled, multicentre NCT:00217230 D153-P507 2001 31 sites in South Africa	N=3242 n_{LAIV}= 1620 $n_{placebo}$= 1622 Healthy adults ≥60 years (median age 69) Sera obtained pre-vaccination, 35±7 days post-vaccination, at study completion	Significant reactogenicity events (within 11 days post-vaccination): (LAIV vs placebo) Cough (20.3% vs 14.7%) (p<0.001) Sore throat (14.9% vs 10.1%) (p<0.001) Runny nose/nasal congestion (41.3% vs 22.7%) (p<0.001) (greatest on days 2-4) Headache (28.8% vs 24.1%) (p=0.003) (greatest on days 2-4) Muscle ache (16.6% vs 11.8%) (p<0.001) Tiredness (19.0% vs 15.6%) (p=0.12) Decreased appetite (7.7% vs 5.2%) (p=0.003) No fever ≥40.0ºC SAEs during first 28 days post-vaccination LAIV (n=16) Placebo (n=24) SAEs reported during 8 months study period: LAIV (351 SAEs in 163 LAIV recipients and 139 placebo) 7 events possibly related (4 cases of pneumonia, 1 case GBS in placebo and 1 case bronchopneumonia and 1 asthma in LAIV)	Level I	Good

Evidence related to safety of FluMist®						
STUDY DETAILS					SUMMARY	
Study	Vaccine	Study Design	Participants	Summary of Key Findings Using Text or Data	Level of Evidence	Quality
Forrest BD, Steele AD, Hiemstra L, et al. A prospective, randomized, open-label trial comparing the safety and efficacy of trivalent live attenuated and inactivated influenza vaccines in adults 60 years of age and older. Vaccine. 2011;29(20):3633-9.[66]	LAIV 0.1mL per nostril (10^7TCID$_{50}$ per strain)	Randomized, prospective, open-label, active controlled, multi-centre Control vaccine: TIV, 0.5mL (15µg HA per strain) NCT00192413 D153-P516 2002 30 sites in South Africa	N=3009 n_{TIV}=1501 n_{LAIV}=1508 ≥60-95 years (median age 68)	Significant reactogenicity events (within 11 days post-vaccination): (LAIV vs TIV) Cough (17.5% vs 12.3%) (p<0.000) Sore throat (15.3% vs 10.2%) (p<0.000) Runny nose/nasal congestion (36.7% vs 24.0%) (p=0.000) Decreased activity (lethargy) (18.7% vs 15.5%) (p=0.023) Decreased appetite (7.2% vs 5.3%) (p=0.031) Fever similar in both groups (none above 40ºC) AEs Rhinitis (3.7% LAIV and 1.5% TIV) (p<0.001) SAEs: LAIV (1 case of bronchopneumonia possibly related to study) 29 deaths not related to study.	Level I	Good Insufficient number of endpoints collected to demonstrate non-inferiority as a result of low incidence of influenza
Monto AS, Ohmit SE, Petrie JG, et al. Comparative efficacy of inactivated and live attenuated influenza vaccines. N Engl J Med. 2009;361(13):1260-7.[28]	LAIV FluMist® 0.1mL per nostril ($10^{6.5}$-$10^{7.6}$ FFU per strain) Single dose H3N2 predominant strain (90%)	RCT, double-blind, active and placebo controlled, community-based Control vaccine: *TIV,* Fluzone®, 0.5mL (15µg HA per strain) 2007/08 season NCT 00538512 Michigan, USA	N=1952 n_{LAIV}= 814 n_{TIV}= 813 $n_{placebo}$=325 Healthy adults aged 18-49 years	Runny Nose/congestion (52.3% LAIV vs 37.7% placebo, p=0.001) Arm soreness (52.6% TIV vs 21.3% placebo, p<0.001) SAE within 30 days: Placebo: Hospitalization for depression/anxiety (unrelated to study) SAE within 6 months: TIV (n=8) LAIV (n=4) Placebo (n=2) None related to study.	Level I	Good
Nichol KL, Mendelman PM, Mallon KP, et al. Effectiveness of live, attenuated intranasal influenza virus vaccine in healthy, working adults: a randomized controlled trial. JAMA. 1999;282(2):137-44.[26]	LAIV Dosage unreported A/H3N2 strains not well matched to vaccine.	Randomized double-blind placebo controlled trial, multi-centre AV009 1997-1998 influenza season, 13 centres in USA	N=4,561 N_{LAIV}= 3041 $n_{placebo}$=1520 healthy working (≥30 hrs/week) adults aged 18-64	75% vaccine and 69% placebo recipients self administered without difficulty. Reactogenicity Data (7 days following vaccination)(LAIV vs placebo) Runny Nose (44.3% vs 26.6%, CI 95%: 14.7, 20.7) Sore throat (26.6% vs 16.3%, 95% CI: 7.2, 12.9) Equivalent rates of other symptoms # SAE 28 days post-immunization: 9 (LAIV: 5, placebo: 4) (0.18% vs 0.27%, p=0.50). None related to study. #SAE 14 weeks post-immunization 49 (LAIV: 30, placebo: 19) (1.0% vs 1.3%, p=0.50). No hospitalizations related to study.	Level I	Good

Evidence related to safety of FluMist®

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Ohmit S, Victor J, Rotthoff J, et al. Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines. N Engl J Med. 2006;355(24):2513-22. [31]	LAIV FluMist® 0.25mL per nostril ($10^{6.5}$-$10^{7.6}$ $TCID_{50}$ per strain) Single dose A/H3N2 strains not well matched to vaccine, two lineages of type B were circulating (one in vaccine)	RCT, double-blind, active and placebo controlled, community-based Control vaccine: *TIV,* Fluzone®, 0.5mL (15µg HA per strain) 2004/05 season NCT: 00133523 4 sites, Michigan, USA Year 1 of 2	N=1247 n_{LAIV}= 519 $n_{placebo}$=103 (IN spray) n_{TIV}= 522 $n_{placebo}$=103 (IM injection) Healthy adults aged 18-46 years (mean age 24.9)	Significant reactogenicity events: Runny Nose/congestion (48.8% LAIV vs 30.3% IN placebo, p=0.001) Cough (18.2% LAIV vs 8.1% IN placebo, p=0.01) Headache (37.9% LAIV vs 25.3% IN placebo, p=0.02) Muscle aches (13.2% LAIV vs 5.1% IN placebo, p=0.02) Arm soreness (53.9%TIV vs 20.2% IM placebo, p<0.001) SAE within 30 days (n=4): LAIV: hospitalization for acute pericarditis (possibly related to study) Other 3 not related	Level I	Good
Ohmit S, Victor J, Teich E, et al. Prevention of symptomatic seasonal influenza in 2005-2006 by inactivated and live attenuated vaccines. J Infect Dis. 2008;198(3):312-7. [32]	LAIV FluMist® 0.25mL per nostril ($10^{6.5}$-$10^{7.6}$ $TCID_{50}$ per strain) Single dose A/H3N2 similar to vaccine	RCT, double-blind, placebo controlled, community-based Control vaccine: *TIV,* Fluzone®, 0.5mL (15µg HA per strain) 2005/06 season NCT:00133523 6 sites, Michigan, USA Year 2 of 2	N=1917 n_{LAIV}= 787 n_{TIV}= 818 $n_{placebo\ (IN)}$=157 $n_{placebo\ (IM)}$=155 (participants assigned to same group as in year 1, additional subjects enrolled) Healthy adults aged 18-48 years (mean age 24.9)	Significant reactogenicity events: LAIV Runny Nose/congestion (42.7% LAIV vs 31.2% IN placebo, p=0.008) Sore throat (26.9% LAIV vs 16.6% IN placebo, p=0.006) TIV Arm soreness (50.4%TIV vs 14.2% IM placebo, p<0.001) Arm redness (7.1%TIV vs 0.7% IM placebo, p=0.002) Muscle Aches (13.5%TIV vs 20.2% IM placebo, p=0.008) SAE within 30 days (n=3) SAE within 6 months (n=18) Only one hospitalization for viral meningitis was considered possibly related to study. Others were not.	Level I	Good Lower than expected attack rate, low power

Evidence related to safety of FluMist®						
STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Treanor JJ, Kotloff K, Betts RF, et al. Evaluation of trivalent, live, cold-adapted (CAIV-T) and inactivated (TIV) influenza vaccines in prevention of virus infection and illness following challenge of adults with wild-type influenza A (H1N1), A (H3N2), and B viruses. Vaccine. 1999;18(9-10):899-906.[30]	CAIV-T Flu Mist® 0.25mL per nostril (10^7 $TCID_{50}$ per strain)	RCT, active and placebo controlled double-blind wild type challenge study Control vaccine: TIV: Fluvirin® 0.5mL (15µg HA per strain) 1995/96 season **AV003** NCT: 2 sites, USA	N=103 n_{CAIV-T}=36 n_{TIV}=33 $n_{placebo}$=34 Groups challenged with 1 strain of virus 28 days after vaccination (then placed in group isolation x7 days) Healthy adult volunteers aged 18-40 years who were serosusceptible (HAI ≤1:8) to at least 1 of 3 strains	Reactogenicity within 7 days post-vaccination (fever, systemic symptoms, respiratory symptoms) CAIV-T (3%, 25%, 61%) Any symptom: 67% TIV- (0%, 12%, 48%) Any symptom: 52% Placebo- (9%, 21%, 53%) Any symptom: 62%	Level I	Good
Concurrent administration with other live vaccines						
Lum LC, Borja-Tabora CF, Breiman RF, et al. Influenza vaccine concurrently administered with a combination measles, mumps, and rubella vaccine to young children. Vaccine. 2010;28(6):1566-74.[12]	LAIV Wyeth Vaccines Research, Marietta, PA, USA 0.1mL per nostril (10^7 $TCID_{50}$ per strain) 2 doses 35±7 days apart Vaccine and circulating A/H3N2 not well matched	Phase III RCT, double-blind, placebo controlled, multicentre Non-inferiority trial (lower bound -10.0%) Co-vaccine: MMR (Priorix®) 2002/03 season NCT:00192166 D153-P522 13 countries (Europe/Asia)	N=1233 Dose 1: $n_{LAIV+MMR}$ = 753-806 $n_{placebo+MMR}$=378-406 Dose 1: $n_{LAIV+MMR}$ = 733-765 $n_{placebo+MMR}$=357-383 Both groups received MMR with dose 1 Healthy vaccine-naïve children 11 to <24 months	Receipt of LAIV/Priorix did not increase injection site reactions <u>Significant reactogenicity events (within 11 days post-dose 1):</u> (LAIV/Priorix vs Placebo/Priorix) Fever ≥37.5°C (49.9% vs 41.7%) (p<0.009) Use of medication to treat fever (37.7% vs 29.2%) (p=0.004) Runny nose/nasal congestion (70.1% vs 51.6%) (p=<0.001) Decreased appetite (33.6% vs 27.7%) (p=0.036) <u>Significant reactogenicity events after dose 2</u> (LAIV/Priorix vs Placebo/Priorix) Fever ≥40°C (0.0% vs 0.8%)(p=0.035) Unsolicited AEs (LAIV vs placebo) Fever (24.3% vs 18.4%, p=0.020) Rhinitis (9.6% vs 6.0%, p=0.039) SAEs across both treatment groups (no statistical difference): Gastroenteritis, convulsion, bronchospasm, pneumonia, pharyngitis, bronchitis, fever. 2 deaths, not attributed to study.	Level I	Good

Evidence related to safety of FluMist®						
STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Nolan T, Bernstein DI, Block SL, et al. Safety and immunogenicity of concurrent administration of live attenuated influenza vaccine with measles-mumps-rubella and varicella vaccines to infants 12 to 15 months of age. Pediatrics. 2008;121(3):508-16.[49]	LAIV MedImmune 0.25mL per nostril (10^7TCID$_{50}$ per strain)	RCT, prospective, placebo controlled, multicentre 2 influenza seasons (2001/2002) Co-vaccines: MMR: M-M-RII, Merck Varicella: Varivax, Merck NCT00192491 AV-018 US/Australia	N=1245 MMR/varicella group (n=411) (Day 0) MMR/Varicella/ placebo (Day 42) LAIV (Day 72) LAIV MMR/varicella/ LAIV group (n=422) (Day 0) MMR/Varicella/ LAIV (Day 42) LAIV (Day 72) placebo LAIV group (n=412) (Day 0) LAIV (Day 42) LAIV (Day 72) MMR/ Varicella Healthy children aged 12 to 15 months	Significant reactogenicity events 42 days after 1st dose LAIV or placebo concurrent with MMR and varicella vaccines:: Runny Nose/Nasal congestion (84% MMR/varicella/LAIV vs 77.6% MMR/Varicella) Incidence of ≥1 AE MMR/varicella/LAIV (overall: 47%) Diarrhea (17%) Otitis media (8%) Wheezing (1.2%) MMR/varicella/placebo (overall: 49%) Diarrhea (15%) Otitis media (11%) Wheezing (2.5%) SAEs (n=9) possibly related to study include: MMR/varicella: 2 cases croup, 1 case pneumonia, 1 bronchiolitis MMR/varicella/LAIV: 1 case croup, 1 case bronchiolitis LAIV: 1 case viral chest infection, bronchiolitis, bronchospasm 9 children experienced 9 significant new medical conditions MMR/varicella: asthma, excessive language delay MMR/varicella/LAIV: cerebral palsy LAIV: 3 cases asthma, 2 cases speech delay, seizure No deaths	Level I	Good

Evidence related to safety of FluMist®

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Breiman RF, Brooks WA, Goswami D, et al. A multinational, randomized, placebo-controlled trial to assess the immunogenicity, safety, and tolerability of live attenuated influenza vaccine coadministered with oral poliovirus vaccine in healthy young children. Vaccine. 2009;27(40):5472-9.[50]	LAIV 0.1mL per nostril ($10^{7\pm5}$FFU per strain)	RCT, LAIV blinded, placebo controlled, multicentre Co-vaccine: OPV (various sources) open label NCT00192491 D153-P511 2002 Asia, South America (OPV still used)	N=2503 <u>Dose 1</u> $n_{LAIV+OPV}$=787-818 $n_{Placebo + OPV}$=794-826 (blinded) n_{LAIV}=777-814 <u>Dose 2</u> $n_{LAIV+OPV}$=725-753 $n_{Placebo + OPV}$=748-769 (blinded) n_{LAIV}=740-760 2nd dose LAIV (or placebo) given 28-42 days after 1st dose Healthy influenza vaccine-naïve children aged 6 to <36 months receiving routine OPV Exclusions included administration of any live vaccine within 1 month and no other live vaccine during study	Reactogenicity (≥1 solicited systemic event within 11 days of any vaccination) Runny nose/nasal congestion (68.6% LAIV vs 62.7% placebo) (p=0.003) after dose 1 only Fever ≥40C and decreased activity more frequent with placebo and OPV than with LAIV recipients combined (p=0.037 and p=0.017) after dose 1 AEs (majority mild to moderate) LAIV + OPV = 38.3% Placebo + OPV = 36.0% LAIV = 35.9% Most common: upper respiratory tract infections, rhinitis. Dose 1 conjunctivitis significant: LAIV: 0.7%; LAIV+OPV: 0.1%; placebo+OPV: 0.1% (p=0.04). Onset between days 0 and 38, duration 3-19 days. SAEs (p=0.552) LAIV+OPV : 1.8% Placebo+OPV : 2.5% LAIV: 1.9% 17 SAEs included pneumonia (n=4), acute gastroenteritis (n=8), bronchospasm (n=2), acute tonsillitis (n=1), febrile seizure (n=1), and acute gastritis (n=1). Receipt of LAIV not associated with disproportionate incidence of SAE	Level I	Good

Evidence related to safety of FluMist®						
		STUDY DETAILS			SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Safety in Populations with Respiratory Conditions (including asthma)						
Belshe RB, Edwards KM, Vesikari T, et al. Live attenuated versus inactivated influenza vaccine in infants and young children. N Engl J Med. 2007;356(7):685-96.[19]	CAIV-T FluMist® 0.1mL per nostril (10^7 $TCID_{50}$)	RCT, prospective, double-blind, active controlled, multi-centre Control vaccine: TIV Fluzone® (US/Asia) Vaxigrip® (Europe/ Middle East), 0.25mL or 0.5mL/ dose based on age 2004/05 season 249 sites in 16 countries (US, Europe/Middle East, Asia) NCT00128167 MI-CPIII	N=7852 n_{TIV}=3936 n_{CAIV-T}=3916 1 or 2 doses for both groups. Second dose given to vaccine-naive children 28-42 days after first dose Children aged ≥6-≤59 months, both groups included some children with underlying medical conditions (5.7% of total) mild/moderate asthma (4%) or a history of recurrent (6%) or any wheezing(21%). Exclusions: wheezing within 42 days of study	Primary endpoint: efficacy of CAIV-T versus TIV in preventing CCI illness (oral temperature of 37.8°C or higher or equivalent in presence of cough, sore throat, running nose/nasal congestion occurring on the same or consecutive days) caused by well-matched strains. Secondary endpoints: efficacy of CAIV-T versus TIV in preventing CCI by mismatched and all flu viruses; any CCI symptom due to matched or mismatched strains, AOM, LRI Relative efficacy for CAIV-T (well-matched): 44.5% (22.4, 60.6) *Strain-specific efficacy (similar subtype):* A/H1N1: 89.2% (67.7, 97.4) A/H3N2: no cases B: 27.3% (-4.8, 49.9) Relative efficacy for CAIV-T (not well matched): 58.2% (47.4, 67.0) *Strain-specific efficacy (similar subtype):* A/H1N1: no cases A/H3N2: 79.2% (70.6, 85.7) B: 6.3% (-31.6, 33.3) Overall relative efficacy for CAIV-T (regardless of match): 54.9% (45.4, 62.9) *Strain-specific efficacy:* A/H1N1: 89.2% (67.7, 97.4) A/H3N2: 79.2% (70.6, 85.7) B: 16.1% (-7.7, 34.7) Reductions in AOM regardless of match: 50.6% (21.5, 69.5) Reductions in LRI regardless of match: 45.9% (4.4, 70.2)	Level I	Good

Evidence related to safety of FluMist®						
STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Redding G, Walker R, Hessel C, et al. Safety and tolerability of cold-adapted influenza virus vaccine in children and adolescents with asthma. Pediatr Infect Dis J. 2002;21(1):44-8.[63]	CAIV-T 0.25mL per nostril (10^7 TCID)	Randomized, double-blind, placebo controlled 1997 2 pediatric allergy practices in Seattle, WA	N=48 n_{CAIV-}T=24 $n_{placebo}$=24 Children 9-17 years of age with stable moderate to severe asthma.	Safety endpoints: percent change in predicted FEV_1 7 days before and 28 days after vaccination. Secondary measures: morning PEFR; asthma rescue medication; asthma exacerbations; daily clinical asthma sx scores; nighttime awakening scores; changes in FVC. % change in percent predicted FEV1 scores (CAIV-T vs placebo) 0.2% vs 0.4%, (p=0.78) Other endpoints were not significant between 2 groups. Post-vaccination symptoms were similar between groups. No serious adverse event. 2 LAIV recipients had mild asthma exacerbations within 28 days after vaccination that required increased bronchodilator or oral steroid usage but did not require emergency department visits or hospitalizations. Concluded CAIV-T is safe for administration to children with stable asthma.	Fair Small sample size	Fair Small sample size
Piedra PA, Gaglani MJ, Riggs M, et al. Live attenuated influenza vaccine, trivalent, is safe in healthy children 18 months to 4 years, 5 to 9 years, and 10 to 18 years of age in a community-based, nonrandomized, open-label trial. Pediatrics. 2005;116(3):e397-407. [61]	LAIV Aviron 0.25mL per nostril ($10^{7.6}$-$TCID_{50}$ per strain)	Prospective, multi-year open label, non- randomized trial 4 years (1998 to 2002) Templeton-Belton	N= 18,780 doses to 11,096 children 18mos-4 years (4529 doses) 5-9 years (7036 doses) 10-18 years (7215 doses) Healthy children aged 1.5-18 years. Children with a history of intermittent wheezing, medically attended acute-respiratory illness, including asthma exacerbation, not excluded.	Assessed medical records for 6 weeks post-vaccination No significant increase in healthcare utilization for MAARI in 0-14 or 15-42 days post-vaccination in any age group in any year. 18 mos-4 years - no significant increase in health care utilization for MAARI, MAARI subcategories, asthma on days 0-14 or days 15-42, **except:** **Asthma events in year 1: RR 2.85 (95% CI, 1.01-8.03) days 15 to 42 post-vaccination.** No statistically significant increase in subsequent years. This is most likely due to chance. No SAE attributed to study	Good	Good

Evidence related to safety of FluMist®

STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Ashkenazi S, Vertruyen A, Aristegui J, et al. Superior relative efficacy of live attenuated influenza vaccine compared with inactivated influenza vaccine in young children with recurrent respiratory tract infections. Pediatr Infect Dis J. 2006;25(10):870-9.[20]	CAIV-T Wyeth Vaccines Research (Marietta, PA) 0.1mL per nostril (10^7TCID$_{50}$ per strain)	RCT, open-label, active controlled, multi-centre Control vaccine: TIV, Aventis Pasteur, 0.25mL/dose or 0.50mL/dose based on participant age NCT00192205 D153-P514 2002-2003 influenza season Europe, Israel	N = 2187 n_{TIV}= 1086 n_{CAIV-T}= 1101 2 doses: 35d ± 7d apart Vaccine naïve children 6 to 71 months, with history of recurrent respiratory tract infections (≥2 RTIs in past 12 months of since birth if under 12 months) 23% had prior diagnosis of asthma	Reactogenicity events 11 days after dose 1 (CAIV vs TIV) Overall: (87.2% vs 83.7%) (p=0.033) Runny nose/nasal congestion (68.3% vs 55.1%) (p<0.001) Reactogenicity events after dose 2 (CAIV vs TIV) Overall: (76.2% vs 73.6%) (p=210) Runny nose/nasal congestion (52.1% vs 44.4%) (p=0.0001) Decreased appetite (23.9% vs 19.8%) (p=0.031) <u>AEs within 11 days (dose 1)</u> Overall: 33.8% vs 29.6%) (p=0.039) • Rhinitis (8.7% vs 5.3%, p=0.002) <u>AEs within 11 days (dose 2)</u> Overall: 32.4% vs 28.6%) (p=0.059) • Rhinitis (6.1% vs 3.8%, p=0.021) • Otitis media (3.7% vs 1.8%, p=0.011) Incidence of wheezing similar in both groups. SAEs reported in CAIV-T (n=104 in 64 subjects) and TIV (n=76 in 51 subjects) 2 CAIV-T and 4 TIV recipient SAEs possibly related to vaccine. No deaths.		Good

Evidence related to safety of FluMist®						
STUDY DETAILS					SUMMARY	
Study	Vaccine	Study Design	Participants	Summary of Key Findings Using Text or Data	Level of Evidence	Quality
Fleming DM, Crovari P, Wahn U, et al. Comparison of the efficacy and safety of live attenuated cold-adapted influenza vaccine, trivalent, with trivalent inactivated influenza virus vaccine in children and adolescents with asthma. Pediatr Infect Dis J. 2006;25(10):860-9.[21]	CAIV-T Wyeth Vaccines Research (Marietta, PA) 0.1mL per nostril (10^7TCID)	RCT, Open-label, active-controlled, multicentre Control vaccine: TIV, Aventis Pasteur, 0.5mL (15µg HA per strain) NCT00192257 D153-P515 2002/2003 influenza season Europe	N = 2229 n_{TIV}=1114 n_{CAIV-T}=11115 **Children with asthma** (not all influenza vaccine-naïve children) ≥6 years to ≤17 years of age	Primary endpoint: incidence of asthma exacerbation (acute wheezing associated with hospitalization, unscheduled clinic visit or new prescription) within 15 days post-vaccination. Secondary endpoints: recurrent wheezing during entire study (until May); first asthma exacerbation within 42 days; PEFR scores; nighttime awakenings; asthma symptoms. Reactogenicity events 15 days after dose 1 (CAIV vs TIV) Overall: (84.2% vs 78.9%) (p=0.002) Runny nose/nasal congestion (66.2% vs 52.5%) (p<0.001) Wheeze (19.5% vs 23.8%, p=0.020) Pharmacoeconomic Events: No difference between CAIV-T vs TIV in use of medications; unscheduled visits; hospitalizations or days off school/work. Asthma Events: Entire Study: no difference in asthma exacerbations between CAIV-T (31.2%, 90% CI: -1.6, 4.8) vs TIV (29.6%, 95% CI: -2.2, 5.4). No difference noted from days 0-42. PEFR findings, asthma symptoms, nighttime awakening scores similar. AE's (day 15 to 28 post-vaccination) Rhinitis (7.4% vs 3.9%, p=0.000) and headache (6.5% vs 4.2%, p=0.023) only significant events SAEs Respiratory (0.9% in both groups) 4 SAES (nCAIV-T=3, pneumonia with severe asthma attack, acute pansinusitis, painful gland behind L ear) (nTIV=1, hypergylcemia with nausea) possibly related to study		Good

Evidence related to safety of FluMist®						
STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
Gorse GJ, O'Connor TZ, Young SL, et al. Efficacy trial of live, cold-adapted and inactivated influenza virus vaccines in older adults with chronic obstructive pulmonary disease: a VA cooperative study. Vaccine. 2003;21(17-18):2133-44.[65]	CAIV-T 0.25mL per nostril (10^7TCID$_{50}$ per strain)	RCT, placebo controlled, double blinded, stratified by site Co- vaccine: TIV, Fluvirin™ 0.5mL (15µg HA per strain) 1998-1999 20 VA Medical Center sites	N=2215 n_{CAIV-T}=1107 $n_{placebo}$=1108 Adults ≥50 years meeting the spirometric criteria for COPD Excluded if received TVV in previous 6 months	Mean number of days for signs and symptoms higher for CAIV-T vs. placebo: Stuffy or runny nose: 1.9±2.6 vs. 1.5±2.4; p=0.0001 Increased shortness of breath: 1.0±2.0 vs. 0.75±1.7; p=0.0001 Chills: 0.35±1.1 vs. 0.29±1.0 p<0.05 Headache: 0.86±1.8 vs. 0.69±1.6; p<0.05 Itchiness at TVV injection site: 0.13±0.65 vs. 0.08±0.54; p<0.05 Statistically significantly higher recorded signs and symptoms for CAIV-T vs. placebo: Increase in sputum production, stuffy or runny nose, increased shortness of breath, chills, itchiness at TVV injection site No significant difference between adverse events possibly attributed to vaccination when comparing CAIV-T and placebo groups 64 subject deaths during trial (34 received LAIV-T, 30 received placebo); 1/6 deaths within 28 days post-vaccination was potentially attributed to placebo immunization No difference in estimate of survival from immunization to end of study participation between treatment groups No significant differences in spirometry post-immunization between groups		Good
Immune compromised						
Halasa N, Englund JA, Nachman S, et al. Safety of live attenuated influenza vaccine in mild to moderately immunocompromised children with cancer. Vaccine. 2011;29(24):4110-5.[75]	*LAIV* 0.5mL ($10^{6.5-7.5}$ TCID$_{50}$) 2 formulations: 2004/05 (n=2) in first year 2005/06 (n=8) in subsequent years	Phase 1 RCT, double-blind, placebo controlled, multicentre, multi-year Off-season (conducted during summers of 2005-07) NCT: 00112112	N=19 n_{LAIV}=9 $n_{placebo}$=10 Mild to moderately immunocompromised children with cancer aged 5-17 years with life expectancy >1 year on chemotherapy and/or radiation therapy for treatment of cancer (or received within the past 12 weeks)	Runny nose/nasal congestion occurred more frequently in LAIV recipients between Days 0-10 (p<0.02) Placebo group reported more adverse events overall than LAIV group (24 events in 10 subjects vs. 10 events in 6 subjects) <u>Shedding</u> Influenza positive nasal swabs detected in 4 LAIV recipients No viral shedding detected after day 10		Good

Evidence related to safety of FluMist®						
STUDY DETAILS					SUMMARY	
Study	**Vaccine**	**Study Design**	**Participants**	**Summary of Key Findings Using Text or Data**	**Level of Evidence**	**Quality**
King JC, Jr., Fast PE, Zangwill KM, et al. Safety, vaccine virus shedding and immunogenicity of trivalent, cold-adapted, live attenuated influenza vaccine administered to human immunodeficiency virus-infected and noninfected children. Pediatr Infect Dis J. 2001;20(12):1124-31.[73]	LAIV Aviron, Mountain View, CA, USA 0.25mL per nostril (10^7 $TCID_{50}$ per strain) Three doses administered 28-35 days apart Two protocols: LAIV-placebo-LAIV and placebo-LAIV-LAIV	RCT, double-blind, placebo controlled, cross-over	N=49 n_{HIV}=24 $n_{non\text{-}HIV}$=25 HIV-infected and non-infected children aged 1-7 years in good general health	No fevers >38.9°C observed Rates of fever, reactogenicity events or ILI not significantly different between non-HIV-infected and HIV-infected children after administration of LAIV 3 serious adverse events occurred in 2 HIV-infected children (wheezing requiring 2 hospitalizations in a known asthmatic and hospitalization for abdominal pain, vomiting and fever) determined unrelated to LAIV and resolved without sequelae <u>Shedding</u> 7 (28%) of non-HIV infected children shed type A or B LAIV virus 3 (13%) of HIV-infected children shed type A or B virus		Good
King JC, Jr., Treanor J, Fast PE, et al. Comparison of the safety, vaccine virus shedding, and immunogenicity of influenza virus vaccine, trivalent, types A and B, live cold-adapted, administered to human immunodeficiency virus (HIV)-infected and non-HIV-infected adults. J Infect Dis. 2000;181(2):725-8.[72]	LAIV Aviron, Mountain View, CA, USA 0.25mL per nostril (10^7 $TCID_{50}$ per strain) Single dose	RCT, double-blind, placebo controlled	N=111 n_{HIV}=57 $n_{control}$=54 Adults in good general health 18-58 years; HIV participants with CDC class of A1-2 and plasma HIV RNA PCR measurement of <10,000 copies/mL and >200 CD4 cells/mm^3 within 4 months, and on stable antiretroviral regimen if ≤500 CD4 cells/mm^3	Similar rates of reactogenicity events LAIV and placebo groups regardless of HIV status Occurrence of runny nose/nasal congestion higher in LAIV ($p<0.05$) No significant difference between events in HIV infected and non-infected receiving LAIV <u>Adverse events</u> No serious adverse events 4 adverse events reported potentially related to vaccine • 2 in HIV-infected LAIV (clinical sinusitis, wheezing) • 1 in HIV-infected placebo (wheezing) • 1 non-HIV-infected placebo (bronchitis) 1 case of vaccine virus shedding in HIV-infected LAIV		Good

Evidence related to safety of FluMist®						
STUDY DETAILS					SUMMARY	
Study	Vaccine	Study Design	Participants	Summary of Key Findings Using Text or Data	Level of Evidence	Quality
Levin MJ, Song LY, Fenton T, et al. Shedding of live vaccine virus, comparative safety, and influenza-specific antibody responses after administration of live attenuated and inactivated trivalent influenza vaccines to HIV-infected children. Vaccine. 2008;26(33):4210-7.[74]	LAIV FluMist® 0.25mL per nostril Single dose	Randomized, active controlled, open label clinical trial, stratified by CD4% Active vaccine: TIV: Fluzone® 0.5mL 2004/05 season Note: Stratification into 3 groups (CD4%<15 at nadir and ≥15 at screening; CD4% ≥15 at nadir and <25 at screening; CD4% ≥25 at nadir and screening)	N=243 n_{LAIV}=122 n_{TIV}=121 Children ≥5 to <18 years old on a stable highly active antiretroviral therapy for ≥16 weeks; HIV-1 plasma <60,000 copies/mL within 60 days prior to screening; and received at least one TIV within previous 2 years	Similar adverse events reported within 28 days post-vaccination abdominal, constitutional, ear or eye, and pulmonary signs and symptoms, skin abnormality and other reactions TIV had most injection reactions (23% overall) LAIV had most nasopharyngeal reactions compared to TIV (52% vs. 31%, p=0.002) No statistically significant differences between stratified groups for either LAIV or TIV in toxicity grades (from DAIDS Toxicity Manual) of adverse events 3 LAIV subjects had Grade 3 events (1 considered vaccine-related) 2 TIV subjects had Grade 3 events (both considered vaccine-related) 2 cases of radiographically confirmed pneumonia (1 in TIV subject and 1 in LAVI subject) No significant increase from baseline in median/mean plasma HIV viral load or CD4% resulting from vaccination <u>Shedding</u> Did not correlate with age, CD4 count or CD4% or HIV viral load at any time during vaccination, or subsequent boost in any specific antibody measured at 4 weeks post-vaccination		Good
Weinberg A, Song LY, Walker R, et al. Anti-influenza serum and mucosal antibody responses after administration of live attenuated or inactivated influenza vaccines to HIV-infected children. J Acquir Immune Defic Syndr. 2010;55(2):189-96.[44]	LAIV FluMist® 0.25mL per nostril	RCT, active controlled, open label Control vaccine: TIV: Fluzone® 0.5mL 2004-05 season Note: Stratification into 3 groups by nadir: CD4<15; CD4 ≥15 at and <25; CD4 ≥25)	N=243 n_{LAIV}=122 n_{TIV}=121 Children and adolescents 5-18 years, HIV-infected on a stable highly active antiretroviral therapy for ≥16 weeks; plasma viral load <60,000 copies/mL, CD4 ≥15% within 60 days prior to enrollment; and received at least one TIV within previous 2 years	Specimens collected at baseline, week 4 and week 24 post-vaccination; nasal shedding monitored on days 3, 14, and 28 post-vaccination Magnitude of response to TIV and LAIV most correlated with baseline microneutralization titers (p<0.0001) and baseline viral load Significant increases in microneutralization titers at 4 and 24 weeks for TIV and LAIV (p≤0.02) Week 4 titers higher in TIV recipients than LAIV (p≤0.002) No significant associations between salivary influenza-IgA concentrations with baseline plasma viral load, CD4%, CD8% or CD19% Week 4 salivary anti-influenza-IgG response were associated with baseline concentrations and baseline plasma HIV viral load LAIV and TIV both demonstrated heterotypic HAI responses, with TIV inducing significantly higher HAI titers than LAIV at 4 and 24 weeks post-vaccination		Good

List of Abbreviations

ca	cold-adapted
att	attenuated
CAIV-T	Cold-adapted, influenza vaccine, trivalent (refrigerated formulation)
CCDR	Canada Communicable Disease Report
CCI	Culture-confirmed influenza
CI	Confidence interval
CMI	Cell-mediated immune response
EIA	Enzyme immunoassay
EMEA	European Medicines Evaluation Agency
FFU	Fluorescent focus units
GBS	Guillain-Barré syndrome
GMT	Geometric mean titre
GMR	Geometric mean ratio
HA	Haemagglutinin antigen
HI	Haemagglutination inhibition
IgG	Immuneglobulin G
ITT	Intent-to-treat
LAIV	Live attenuated influenza vaccine (frozen formulation)
LRTD	Lower respiratory tract disease
mL	Millilitres
MAARI	Medically attended acute respiratory illness
MDV	Master donor virus strain
MSW	Medically significant wheezing
MVS	Master virus seed
NACI	National Advisory Committee on Immunization
pp	per protocol (population evaluated in final analysis)
SAE	Serious adverse event
SPF	Specific pathogen-free
TCID	Tissue-culture infective dose
TIV	Trivalent inactivated influenza vaccine (injectable)
ts	temperature sensitive
µg	Microgram
WHO	World Health Organization

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