

**FLUMIST<sup>®</sup>**

**LIVE-ATTENUATED INFLUENZA VACCINE**

# LEARNING OBJECTIVES

- Understand different influenza virus types and changes resulting in new strains
- Understand the annual impact of influenza infections in Canada
- List the different types of vaccines available for use in Canada for prevention of seasonal influenza
- Provide information on the authorized use of live-attenuated influenza vaccine (LAIV) product, FluMist® and FluMist® Quadrivalent
- Describe the Health Canada approved indications for use as well as the BC Centre for Disease Control policies on public use of LAIV
- Understand the efficacy and safety data for LAIV
- Know the storage and stability, administration, contraindications, precautions for use, and drug interactions of LAIV
- Know the approved indications of LAIV as well as the Provincial policy on publicly-funded use of LAIV

# INFLUENZA INFECTION

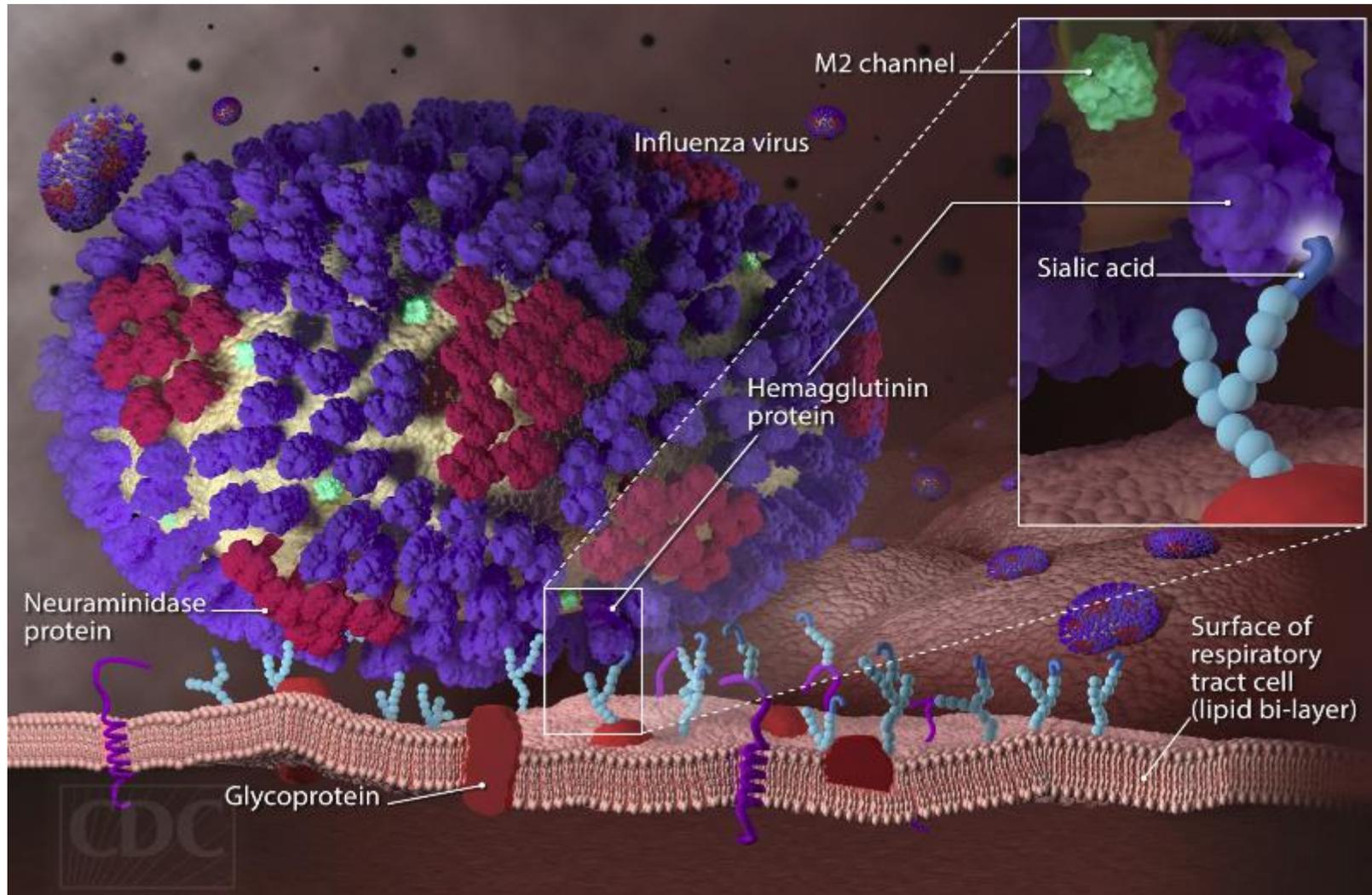
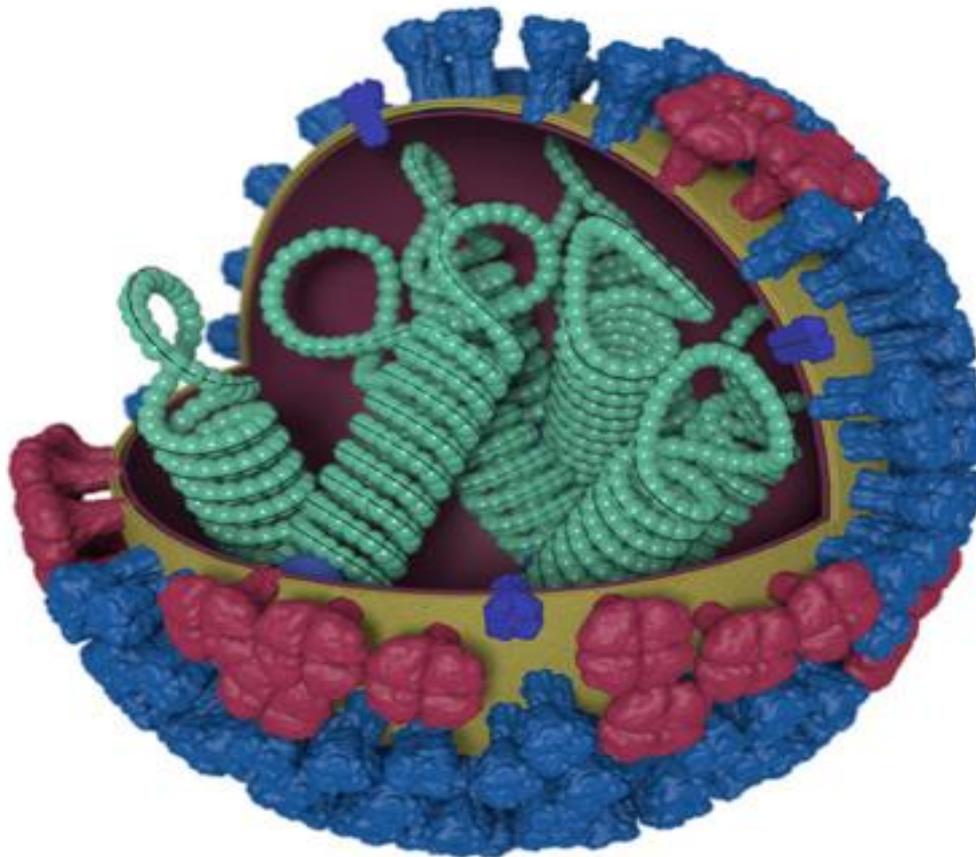


Image obtained from: [cdc.gov](https://www.cdc.gov)

# ANTIGENIC SITES

## AN INFLUENZA VIRUS



Hemagglutinin



Neuraminidase



M2 ion channel



Ribonucleoprotein

Image obtained from: [cdc.gov](http://cdc.gov)

# INFLUENZA TYPES

## Type A

- Classified into sub types based on the two surface proteins, H and N
- Epidemics and pandemics
- Animals and humans
- Infects all age groups

## Type B

- Milder epidemics
- Humans only
- Primarily affects children
- Evolved into two antigenically distinct lineages
  - B/Yamagata/16/88-like
  - B/Victoria/2/87-like viruses

# ANTIGENIC DRIFT AND SHIFT

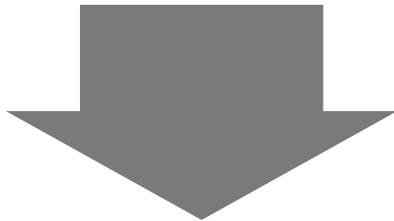
## Drift

Minor change, within subtype

Point mutations

Occurs in A and B subtypes

Can cause an epidemic



**Occurs  
Continuously**

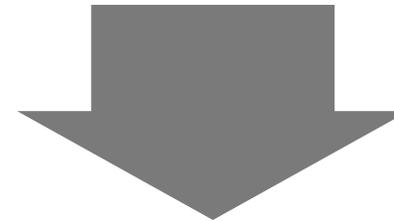
## Shift

Major change, new subtype

Exchange of gene segments

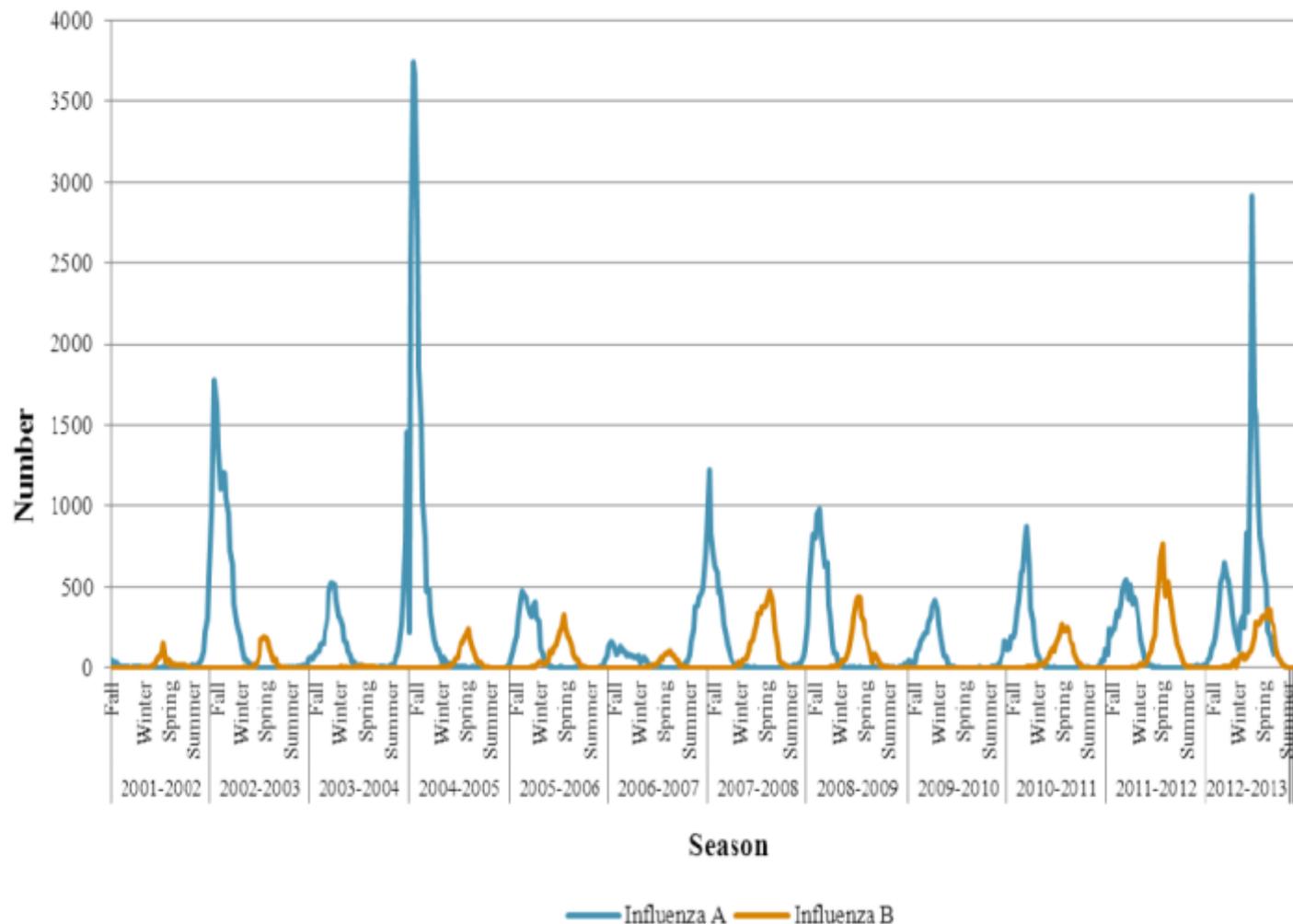
Occurs in A subtypes only

Can cause a pandemic



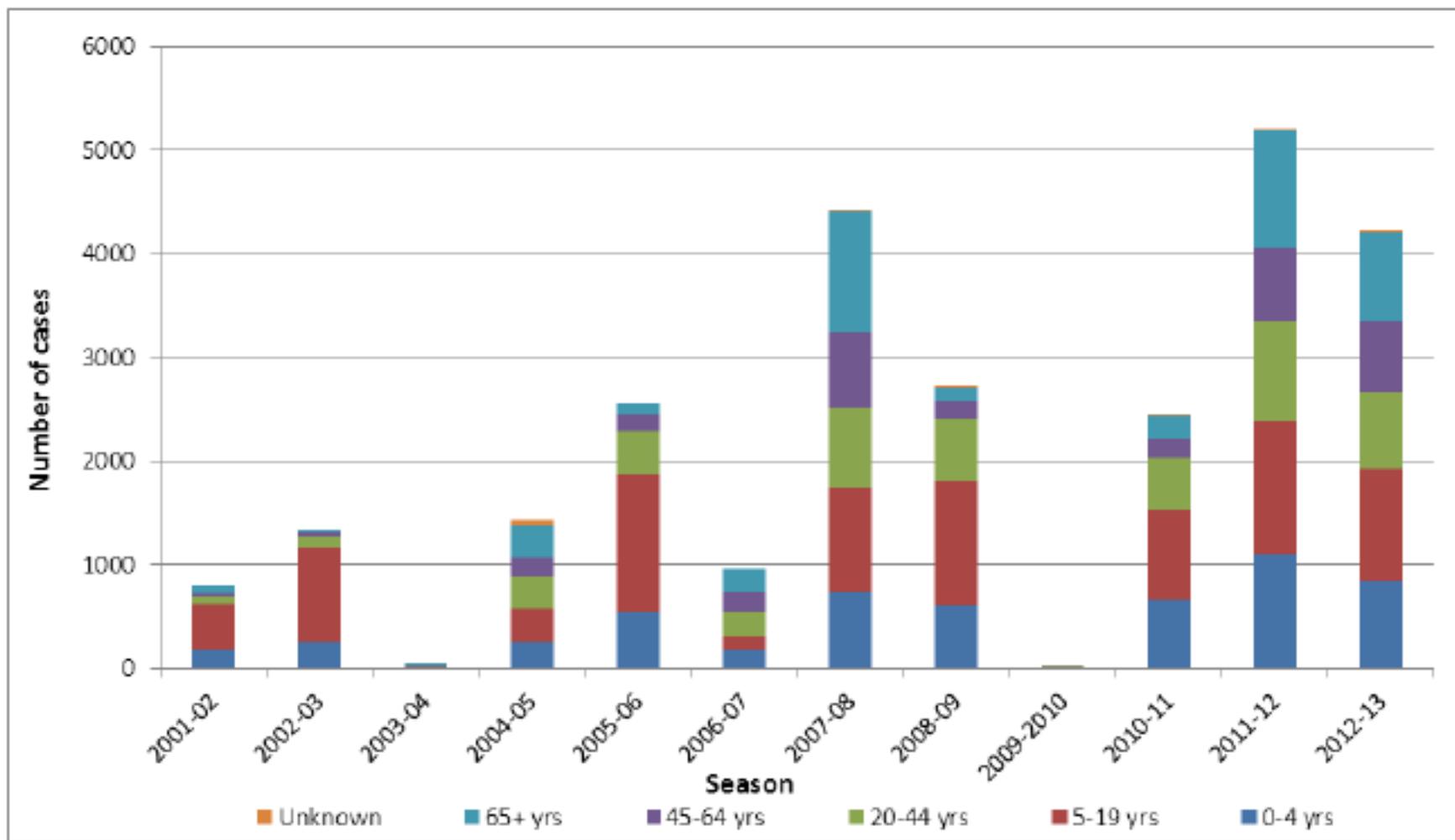
**Occurs  
Infrequently**

# LABORATORY-CONFIRMED INFLUENZA CASES IN CANADA BY TYPE AND SEASON

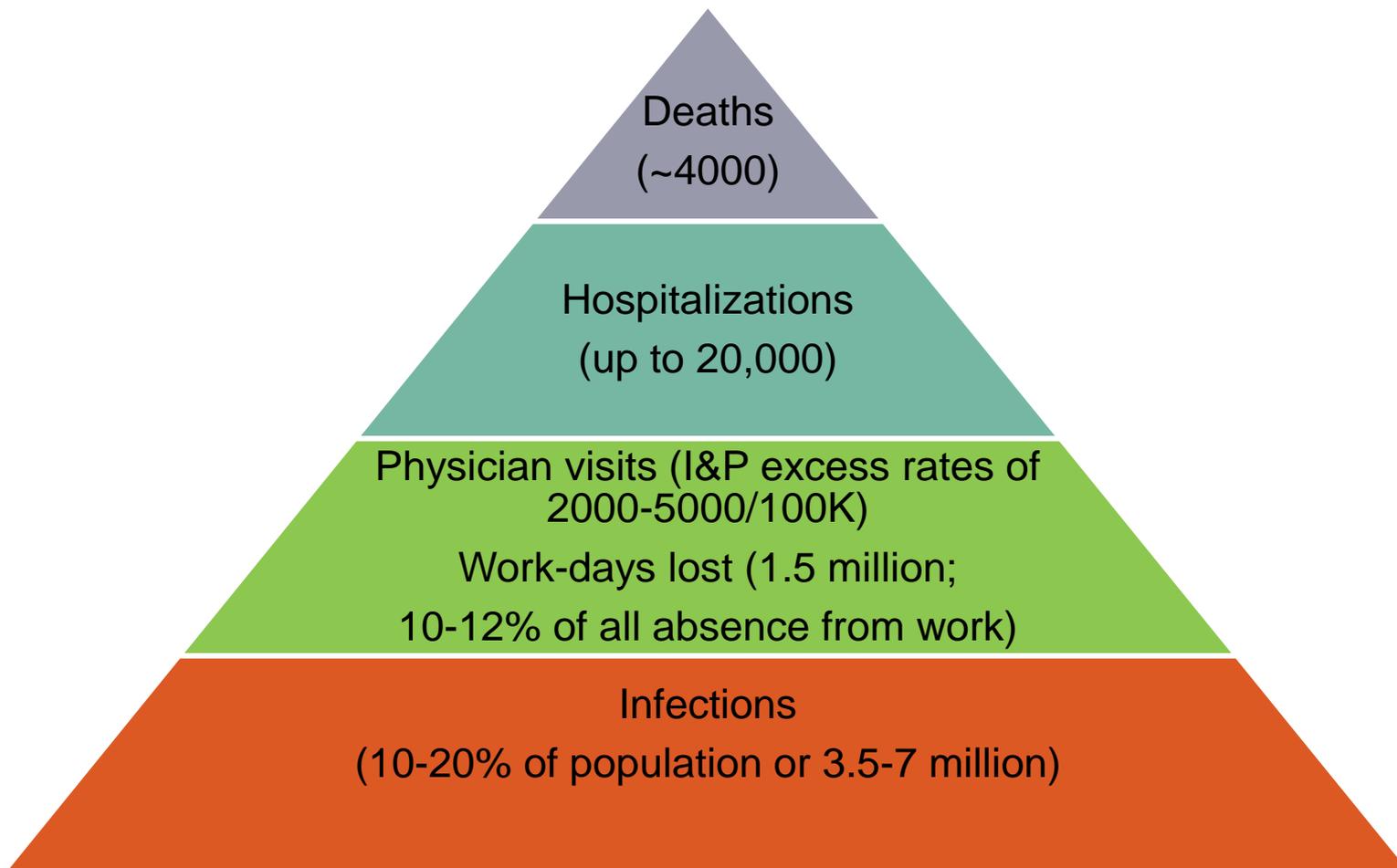


NACI Statement on Seasonal Influenza Vaccine for 2014-2015  
 FluWatch Weekly Reports on Influenza Surveillance, 2014-2015

# LABORATORY-CONFIRMED INFLUENZA B



# INFLUENZA AFFECTS MILLIONS OF PEOPLE EACH YEAR IN CANADA



# INFLUENZA B

Isolate testing by the National Microbiology Laboratory has also demonstrated that the predominantly circulating B lineage has differed from the WHO recommended B lineage for the Northern hemisphere influenza vaccine in seven out of the last 12 seasons.

For this reason, the World Health Organization (WHO) now recommends that both B lineages of the circulating influenza viruses maybe included in the vaccines. Vaccine manufacturers can therefore manufacture the trivalent influenza vaccine (TIV) or a quadrivalent influenza vaccine (QIV).

# INFLUENZA VACCINES

## An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)<sub>±</sub>

Statement on Seasonal Influenza Vaccine for  
2014-2015



### Trivalent Influenza Vaccine

#### Inactivated, non-adjuvanted

- Agriflu® (Novartis)
- Fluviral® (GSK)
- Fluzone® (Sanofi Pasteur)
- Influvac® (Abbott)
- Vaxigrip® (Sanofi Pasteur)
- Intanza® (Sanofi Pasteur)

#### Inactivated, MF59-adjuvanted

- Fluad® (Novartis)

#### Activated, non-adjuvanted

- FluMist® (AstraZeneca)

### Quadrivalent Influenza Vaccine

#### Inactivated, non- adjuvanted

- Flulaval™ Tetra (GSK)
- Fluzone® Quadrivalent (Sanofi Pasteur)

#### Activated, non- adjuvanted

- FluMist® Quadrivalent (AstraZeneca)

# INFLUENZA TYPES IN THE VACCINE

For the 2014-15 (Last) Season:

A/California/7/2009 (H1N1)pdm09-like virus

A/Texas/50/2012 (H3N2)-like virus

B/Massachusetts/2/2012-like virus

B/Brisbane/60/2008-like virus (in quadrivalent vaccines only)

For the 2015-16 (New) Season:

A/California/7/2009 (H1N1)pdm09-like virus

*A/Switzerland/9715293/2013 (H3N2)-like virus*

*B/Phuket/3073/2013-like virus*

B/Brisbane/60/2008-like virus (in quadrivalent vaccines only)

# ELIGIBLE RECIPIENTS OF INFLUENZA VACCINE

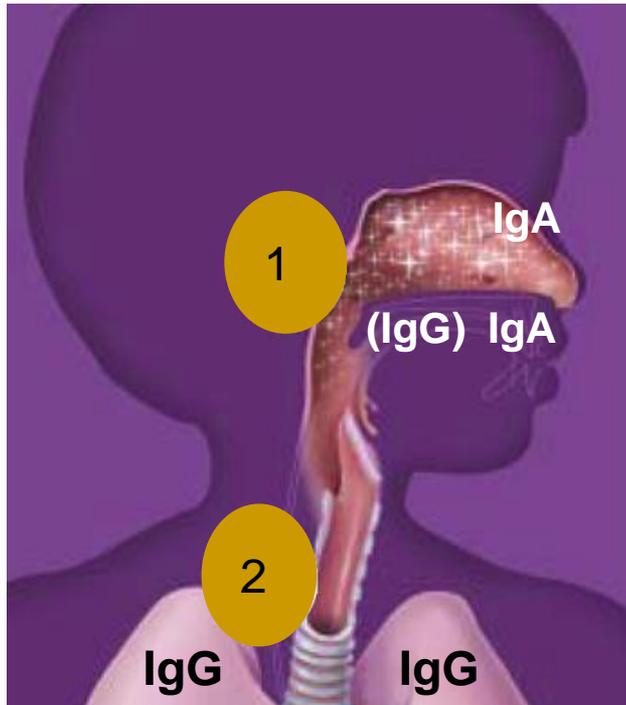
NACI recommends that influenza vaccine be given to all individuals aged 6 months and older, with particular focus on people at high risk of influenza-related complications or hospitalization, people capable of transmitting influenza to those at high risk.

In British Columbia, eligible individuals for publicly-funded influenza vaccine are similar to those suggested by NACI and include:

- Individuals at high risk for influenza infection.
- Individuals capable of transmitting influenza to those at high risk.
- Individuals who provide essential community services.

For further information on these groups, please click [here](#) for specifics on BC-specific guidelines.

# WHAT IS FLUMIST®?



FluMist® is a live, attenuated, cold-adapted (1), temperature-sensitive (2), trivalent or quadrivalent intranasal- mist influenza virus vaccine.

Contains attenuated live vaccine strains that are engineered not to cause disease.<sup>1</sup>

Designed to stimulate an immune response that more closely resembles the body's response to natural infection, although the exact mechanism conferring protection are not fully understood.<sup>2</sup>

Two types of live, attenuated influenza vaccine (LAIV) products are available, the trivalent influenza vaccine (FluMist®) and the quadrivalent vaccine (FluMist Quadrivalent®)

1. FluMist [Product Monograph]. Licensed product of MedImmune LLC, used under license by AstraZeneca Canada Inc. Available at: <http://www.astrazeneca.ca>
2. FluMist Quadrivalent [Product Monograph]. Licensed product of MedImmune LLC, used under license by AstraZeneca Canada Inc. Available at: <http://www.astrazeneca.ca>
3. Cox RJ, et al. *Scand J Immunol*. 2004;59:1-15.

**EFFICACY AND SAFETY OF LAIV  
AND TIV IN CHILDREN 6 MONTHS  
TO 17 YEARS OF AGE**

# EFFICACY IN CHILDREN

Study	Design	Age	Dosage	Study Population
Ashkenazi et al. <sup>1</sup>	R, OL, MC	6–71mo	2 doses of IN LAIV or IM TIV	Recurrent RTI
Belshe et al. <sup>2</sup>	R, DB, MC	6–59mo	1-2 doses of IN LAIV or IM TIV	Mild asthmatics
Fleming et al. <sup>3</sup>	R, OL, MC	6–17 yrs	1 dose of IN LAIV or IM TIV	Without wheezing or asthma prior to study enrollment

Abbreviations: R=randomised; OL=open-label; DB=double-blind; MC=multicentre; MO=months; Y=years; IN=intra-nasal; IM=intramuscular; LAIV=live attenuated influenza vaccine; TIV=trivalent inactivated vaccine; ILI=influenza-like-illness; RTI=respiratory tract infection

1. Ashkenazi S, Vertruyen A, Aristegui J, et al. *Pediatr Infect Dis J* 2006 Oct; 25 (10): 870-9.

2. Belshe RB, Edwards KM, Vesikari T, et al. *N Engl J Med* 2007 Feb 15; 356 (7): 685-96.

3. Fleming DM, Crovari P, Wahn U, et al. *Pediatr Infect Dis J* 2006 Oct; 25 (10): 860-9

# EFFICACY IN CHILDREN

Study	Ashkenazi <sup>1</sup>	Fleming <sup>2</sup>	Belshe <sup>3</sup>
Primary Endpoint	Incidence of culture-confirmed influenza illness caused by subtypes in the vaccine	Incidence of culture-confirmed influenza illness caused by subtypes in the vaccine	Efficacy of LAIV vs TIV in preventing culture-confirmed ILI
Subjects (N) LAIV	1050	1109	3916
Subjects (N) TIV	1035	1102	3936
Attack Rate (%) LAIV a/m strain [any viral strain]	2.3 [2.8]	4.1 [4.5]	1.4 [3.9]
Attack Rate (%) TIV a/m strain [any viral strain]	4.8 [5.8]	6.4 [6.6]	2.4 [8.6]
Relative Efficacy (%) [95%CI] LAIV a/m strain	52.7 [21.6, 72.2]	34.7 [3.9, 56.0]	44.5 [22.4, 60.6]
Relative Efficacy (%) [95%CI] LAIV any viral strain	52.4 [24.6, 70.5]	31.9 [1.1, 53.5]	54.9 [45.4, 62.9]

Abbreviations: LAIV=live attenuated influenza vaccine; TIV=trivalent inactivated vaccine; A/M=antigen-matched influenza strain; CI=confidence interval; SS=statistically significant

1. Ashkenazi S, Vertruyen A, Aristegui J, et al. *Pediatr Infect Dis J* 2006 Oct; 25 (10): 870-9.
2. Fleming DM, Crovari P, Wahn U, et al. *Pediatr Infect Dis J* 2006 Oct; 25 (10): 860-9
3. Belshe RB, Edwards KM, Vesikari T, et al. *N Engl J Med* 2007 Feb 15; 356 (7): 685-96.

**Original Article**

# **Live Attenuated versus Inactivated Influenza Vaccine in Infants and Young Children**

**Robert B. Belshe, M.D., Kathryn M. Edwards, M.D., Timo Vesikari, M.D., Steven V. Black, M.D., Robert E. Walker, M.D., Micki Hultquist, M.S., George Kemble, Ph.D., Edward M. Connor, M.D., for the CAIV-T Comparative Efficacy Study Group**

**N Engl J Med  
Volume 356(7):685-696  
February 15, 2007**



**The NEW ENGLAND  
JOURNAL of MEDICINE**

# LANDMARK TRIAL

Randomized, double-blind, double-dummy, multinational study, 2004-2005 influenza season (enrollment October 2004)<sup>1</sup>

8475 children aged 6 to 59 months were enrolled<sup>1</sup>

Principal exclusion criteria<sup>1,2</sup>

- Children with wheezing, steroid use (systemic or inhaled), or bronchodilator use within 42 days of enrollment
- Children with a history of severe asthma
- Children with a known immunosuppressive condition
- Children with a history of hypersensitivity to any component of the live attenuated vaccine or the inactivated vaccine
- Children with body temperature higher than 37.8°C (100°F) measured orally or the equivalent within 3 days of enrollment
- Use of aspirin or salicylate-containing products within 30 days of enrollment

Randomization was stratified by the following baseline characteristics:

- Age on receipt of first dose
  - 6-23 months or 24-35 months or 36-59 months
- Presence or absence of previous influenza vaccination
- Presence or absence of history of recurrent wheezing
  - $\geq 3$  wheezing episodes, each requiring medical follow-up or hospitalization
- Country of residence

## Efficacy

### Primary endpoint

- Culture-confirmed modified CDC-influenza-like-illness against antigenically matched influenza virus strains

### Secondary endpoint

- Culture-confirmed modified CDC-influenza-like-illness against antigenically mismatched influenza virus strains

## Safety

### Medically significant wheezing (MSW)

- Prospectively defined safety endpoint of primary interest
- Defined as the presence of wheezing on a physical examination conducted by a healthcare provider, with a prescription for a daily bronchodilator; respiratory distress; or hypoxemia

# Influenza Attack Rates in the According-to-Protocol Population

**Table 2. Influenza Attack Rates in the According-to-Protocol Population.\***

Variable	Similarity to Vaccine†	Live Attenuated Vaccine (N=3916)‡		Inactivated Vaccine (N=3916)§		Reduction in Attack Rate with Live Vaccine¶ % (95% CI)
		Cases	Attack Rate	Cases	Attack Rate	
		no.	%	no.	%	
Virus	Well matched	53	1.4	93	2.4	44.5 (22.4 to 60.6)
A/H1N1		3	0.1	27	0.7	89.2 (67.7 to 97.4)
A/H3N2		0	0	0	0	—
B		50	1.3	67	1.7	27.3 (-4.8 to 49.9)
Age at first vaccination (any influenza virus)	Well matched					
6-23 mo		23	1.3	32	1.7	29.1 (-21.2 to 59.1)
24-35 mo		17	1.3	24	1.8	32.6 (-23.8 to 64.5)
36-59 mo		13	1.7	37	4.7	65.6 (36.3 to 82.4)
Previous vaccination (any influenza virus)	Well matched					
Yes		18	1.9	29	3.1	39.3 (-9.2 to 66.9)
No		35	1.2	64	2.1	46.9 (20.0 to 65.2)
Virus	Not well matched	102	2.6	245	6.2	58.2 (47.4 to 67.0)
A/H1N1		0	0	0	0	—
A/H3N2		37	0.9	178	4.5	79.2 (70.6 to 85.7)
B		66	1.7	71	1.8	6.3 (-31.6 to 33.3)
Virus	Regardless of match	153	3.9	338	8.6	54.9 (45.4 to 62.9)
A/H1N1		3	0.1	27	0.7	89.2 (67.7 to 97.4)
A/H3N2		37	0.9	178	4.5	79.2 (70.6 to 85.7)
B		115	2.9	136	3.5	16.1 (-7.7 to 34.7)

\* Children had influenza-like illness and culture-positive infection. Modified CDC influenza-like illness was defined as the presence of an increased oral temperature ( $\geq 100.4^{\circ}\text{F}$  [ $37.8^{\circ}\text{C}$ ] or the equivalent) in the presence of cough, sore throat, runny nose, or nasal congestion occurring on the same or consecutive days. The analysis of the primary end point in subgroups (stratified according to age, vaccination status, and presence or absence of a history of recurrent wheezing) provided estimates of the relative efficacy of live attenuated vaccine of 34.0 to 65.6%, a finding consistent with the relative efficacy of 44.5% observed in the overall according-to-protocol population. Higher estimates of the relative efficacy of live attenuated vaccine, as compared with inactivated vaccine, against matched influenza strains were seen in 13 of the 15 countries in which matched strains were isolated.

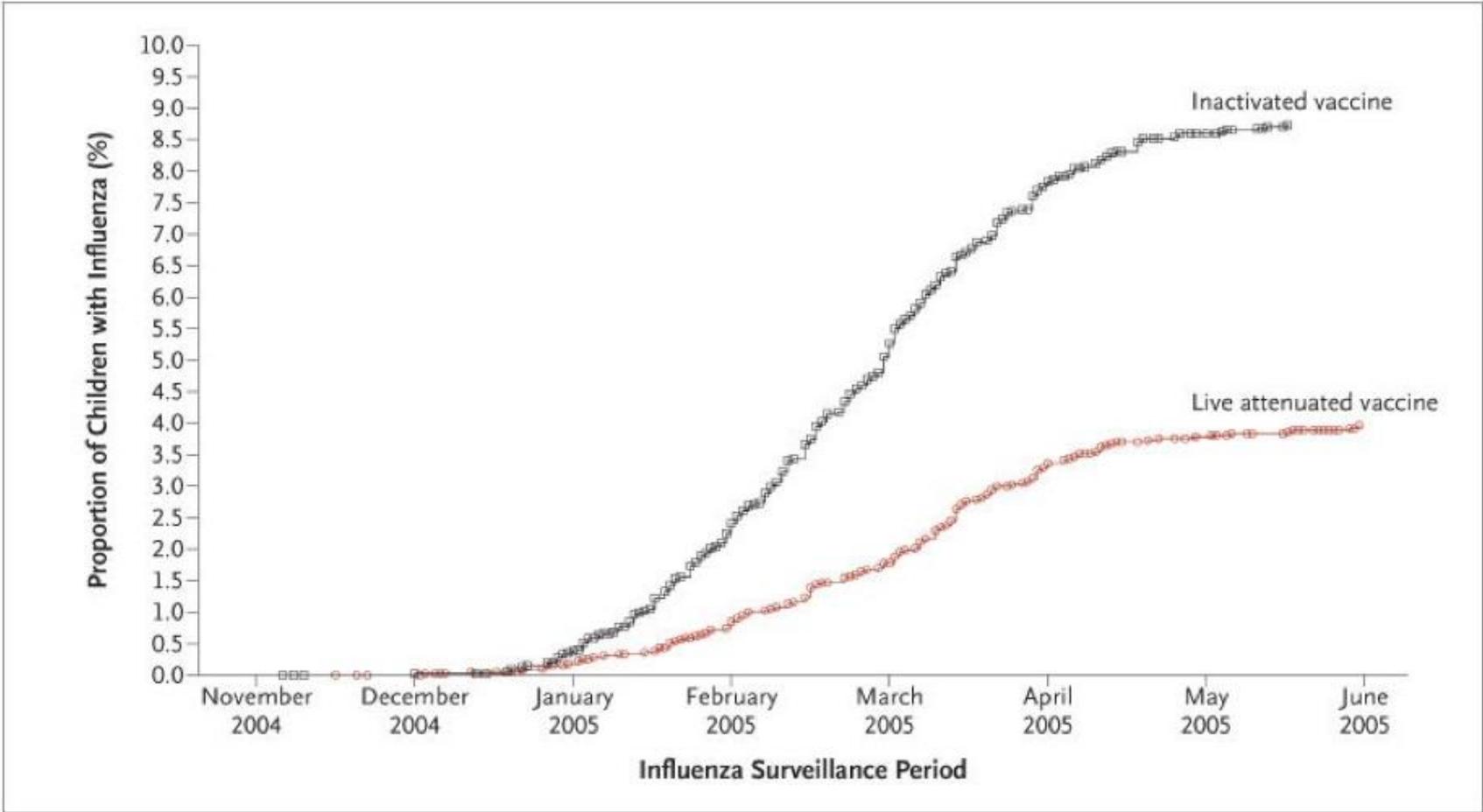
† Viruses were characterized as antigenically similar to vaccine or not well matched to vaccine. Reference antiserum provided by the CDC was used to characterize isolates antigenically and a difference by a factor of 4 or more in the hemagglutination-inhibition titers was considered indicative of antigenic variation between two viruses.

‡ Four subjects had both influenza A/H3N2 and influenza B virus infections; two isolates could not be characterized as antigenically well matched or not well matched to vaccine virus antigen.

§ Two subjects had both influenza A/H1N1 and influenza B virus infections; six subjects had both influenza A/H3N2 and influenza B virus infections; five isolates could not be characterized as antigenically well matched or not well matched to vaccine virus antigen.

¶ The analysis of subjects in the intention-to-treat population confirmed the results in the according-to-protocol population. The observations were robust in all subgroups (stratified according to age, vaccination status, presence or absence of a history of recurrent wheezing, and country of residence). Among children 6 to 23 months of age, in whom the overall attack rates of influenza were 3.2% in the live-attenuated-vaccine group and 7.2% in the inactivated-vaccine group, the relative efficacy of live attenuated vaccine of 55.7% was significant.

# Kaplan-Meier Curves for the Time to the First Culture-Confirmed Report of Influenza in the Two Vaccine Groups



Belshe RB et al. N Engl J Med 2007;356:685-696



## Medically Significant Wheezing, Serious Adverse Events, and Rates of Hospitalization According to Age Group, through 180 Days after the Last Dose of Vaccine

**Table 4.** Medically Significant Wheezing, Serious Adverse Events, and Rates of Hospitalization According to Age Group, through 180 Days after the Last Dose of Vaccine.\*

Age	Event	Live Attenuated Vaccine	Inactivated Vaccine
		<i>no./total no. (%)</i>	
6–11 mo	Medically significant wheezing	93/684 (13.6)	71/683 (10.4)
	Any serious adverse event	44/684 (6.4)	23/683 (3.4)
	Hospitalization for any cause	42/684 (6.1)	18/683 (2.6)
12–59 mo	Medically significant wheezing	272/3495 (7.8)	255/3490 (7.3)
	Any serious adverse event	92/3495 (2.6)	105/3490 (3.0)
	Hospitalization for any cause	88/3495 (2.5)	101/3490 (2.9)
6–59 mo	Medically significant wheezing	365/4179 (8.7)	326/4173 (7.8)
	Any serious adverse event	136/4179 (3.3)	128/4173 (3.1)
	Hospitalization for any cause	130/4179 (3.1)	119/4173 (2.9)

\* Medically significant wheezing, serious adverse events, and hospitalizations were analyzed from the day of the first dose through 180 days after the last dose of vaccine (for a breakdown according to causes of hospitalization and diagnostic category, see Table 4 in the Supplementary Appendix).

# Study Overview

- An intranasally administered influenza vaccine may be useful in efforts toward universal vaccination of children less than 5 years of age
- In this trial involving 8352 young children, the attack rate for symptomatic influenza was 5% with the live attenuated vaccine, as compared with 10% with the inactivated influenza vaccine administered intramuscularly
- However, with the live vaccine, as compared with the inactivated influenza vaccine, there was a higher rate of hospitalization for any cause among children younger than 12 months of age



# PROTECTION FROM AOM

Block *et al*<sup>1</sup> pooled and analyzed data from 6 placebo controlled and 2 TIV controlled studies with children 6 to 83 months of age. He evaluated acute otitis media (AOM) associated with culture-confirmed influenza due to any influenza strain.

The pooled analysis of the 6 placebo controlled studies found 36/8,353 (0.4%) cases of AOM in LAIV recipients and 165/5,756 (2.9%) cases in placebo recipients (overall efficacy of LAIV 85% (95% CI: 78.3,89.8)). In LAIV recipients, there was higher overall efficacy against developing AOM in children  $\geq 24$  months of age (91%) versus 6 to 23 months (78%) of age.

In the 2 TIV controlled studies,<sup>2,3</sup> the pooled analysis showed 28/4,966 (0.6%) cases of AOM in LAIV recipients and 61/4,971 (1.2%) cases in TIV recipients. The relative efficacy of LAIV compared with TIV 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  $\geq 24$  months of age versus 6 to 23 months of age (61.7% versus 47.5%).

1. Block SL, Heikkinen T, Toback SL, et al. *Pediatr Infect Dis J*. 2011;30(3):203-7.

2. Ashkenazi S, Vertruyen A, Aristegui J, et al. *Pediatr Infect Dis J* 2006 Oct; 25 (10): 870-9.

3. Belshe RB, Edwards KM, Vesikari T, et al. *N Engl J Med* 2007 Feb 15; 356 (7): 685-96.

# COMMON AND SERIOUS EVENTS

Runny nose (or nasal congestion), headache, and malaise were the most common adverse events occurring in individual trials of placebo-controlled trials<sup>1-6</sup> and active comparator<sup>7-9</sup> studies in children and adolescents aged 2–6 years or 2–17 years. These occurred in the first 10 days after vaccine administration. Events were similar after one dose or second dose of LAIV, although the incidence was less with the second dose. Similar findings were also seen in a pooled analyses of all LAIV trials.<sup>10</sup>

Serious adverse events, evaluated between days 0-42, were uncommon in LAIV recipients, with no significant differences between LAIV (0.5%) and placebo (0.6%) recipients in the larger pooled analysis.<sup>10</sup> The majority of these were either infectious (0.23%) or respiratory (0.05%) events, including gastroenteritis, pneumonia, otitis media, and asthma.

# WHEEZING AND ASTHMA

LAIV is associated with an increased incidence of wheezing in young children, aged 6-23 months of age (5.9% LAIV versus 3.8% TIV) and vaccine-naïve children (3.8% LAIV versus 2.1% TIV).<sup>1</sup>

Several studies have studied the safety profile of LAIV in children with asthma. These studies have not found LAIV to exacerbate asthma.<sup>2-4</sup>

1. *Belshe RB, Edwards KM, Vesikari T, et al. N Engl J Med 2007 Feb 15; 356 (7): 685-96.*
2. *Redding G, Walker R, Hessel C, et al. Pediatr Infect Dis J. 2002;21(1):44-8.*
3. *Gaglani MJ, Piedra PA, Riggs M, et al. Pediatr Infect Dis J. 2008;27(5):444-52.*
4. *Fleming DM, Crovari P, Wahn U, et al. Pediatr Infect Dis J 2006 Oct; 25 (10): 860-9.*

# SUMMARY IN CHILDREN

“There is more evidence that directly compares TIV and LAIV efficacy and that shows superior efficacy of LAIV in children younger than 6 years of age than in older children. Also, for children under 6 years of age the evidence for the superiority of LAIV is of higher quality and the estimate of efficacy is higher compared to the study performed on children 6 to 17 years old.”<sup>1</sup>

LAIV has shown decreased incidence of AOM, particularly in children 24 months of age and over.

Runny nose (or nasal congestion), headache, and malaise occurred more commonly with LAIV.

LAIV is associated with an increased incidence of wheezing in young children, aged 6-23 months of age and vaccine-naïve children.

<sup>1</sup> NACI Statement on Seasonal Influenza Vaccine for 2014-2015

**EFFICACY AND SAFETY OF LAIV  
AND TIV IN ADULTS 18 TO 59  
YEARS OF AGE**

# EFFICACY IN ADULTS

In contrast to children, most comparative studies in individuals 18 to 59 years of age have found LAIV and TIV were similarly efficacious<sup>1-5</sup> or that TIV was more efficacious.<sup>3</sup> One study found LAIV to be somewhat more efficacious in a cohort of vaccine-naïve adults (no previous influenza vaccination).<sup>5</sup>

This difference between children and adults may be related to the fact that adults have pre-existing influenza-related immunity which may interfere with response to a live virus vaccine; in contrast children, who are generally naïve to influenza, will mount a more robust immune response.

1. Edwards KM, Dupont WD, Westrich MK, et al. *J Infect Dis.* 1994;169(1):68-76.
2. Treanor JJ, Kotloff K, Betts RF, et al. *Vaccine.* 1999;18(9-10):899-906.
3. Monto AS, Ohmit SE, Petrie JG, et al.. *N Engl J Med.* 2009;361(13):1260-7.
4. Ohmit S, Victor J, Teich E, et al. *J Infect Dis.* 2008;198(3):312-7.
5. Wang Z, Tobler S, Roayaei J, et al. *JAMA.* 2009;301(9):945-53.

# EFFICACY IN ADULTS

Study	Design	Age	Total Patients	Primary Outcome¶
Edwards et al. <sup>1</sup>	R, DB, MC	1-65y	5210	<u>H1N1 serotypes</u> LAIV 85% [95%CI: 70,92] TIV 76% [95%CI: 58,87] <u>H3N2 serotypes</u> LAIV 58% [95%CI: 29,75] TIV 74% [95%CI: 52,86]
Treanor et al. <sup>2</sup>	R, DB, PC	18-45y	103	LAIV 85% [95%CI: 28,100] TIV 71% [95%CI: 2,97]
Monto et al. <sup>3</sup>	R, PC, DB	18-49y	1952	LAIV 51% [95%CI: 19,70] TIV 73% [95%CI: 51,85]
Ohmit et al. <sup>4</sup>	R, PC, DB	18-49y	2058	LAIV 8% [95%CI:-194,67] TIV 16% [95%CI: -171,70]
Wang et al. <sup>5</sup>	Cohort	17-49y	3 million	<u>Entire cohort</u> TIV vs LAIV (2004/05): 8.6 vs 18.3 TIV vs LAIV (2005/06): 7.8 vs 10.6 TIV vs LAIV (2006/07): 8.0 vs 11.1

Abbreviations: R=randomised; DB=double-blind; MC=multicentre; PC=placebo-controlled; Y=years; LAIV=live attenuated influenza vaccine; TIV=trivalent inactivated vaccine

¶ Primary Outcome was culture confirmed and/or PCR confirmed influenza for all trials except Wang et al. whose outcome was incidence rate (per 1000 person-years) of health care encounters for pneumonia and influenza

<sup>1</sup> Edwards KM, Dupont WD, Westrich MK, et al. *J Infect Dis.* 1994;169(1):68-76; <sup>2</sup>Treanor JJ, Kotloff K, Betts RF, et al. *Vaccine.* 1999;18(9-10):899-906; <sup>3</sup>Monto AS, Ohmit SE, Petrie JG, et al.. *N Engl J Med.* 2009;361(13):1260-7; <sup>4</sup> Ohmit S, Victor J, Teich E, et al. *J Infect Dis.* 2008;198(3):312-7; <sup>5</sup>Wang Z, Tobler S, Roayaei J, et al. *JAMA.* 2009;301(9):945-53.

From: **Live Attenuated or Inactivated Influenza Vaccines and Medical Encounters for Respiratory Illnesses Among US Military Personnel**

JAMA. 2009;301(9):945-953. doi:10.1001/jama.2009.265

**Table 3.** Vaccine Effects During 3 Influenza Seasons: 2004-2005, 2005-2006, and 2006-2007<sup>a</sup>

	Vaccine Effect (95% CI)		
	TIV vs Unimmunized	LAIV vs Unimmunized	TIV vs LAIV
2004-2005			
Total cohort	54.8 (51.3 to 58.1)	20.8 (12.3 to 28.5)	43.0 (36.4 to 48.9)
Propensity-matched <sup>b</sup>	53.7 (49.8 to 57.3)	7.3 (-9.21 to 21.3)	31.6 (21.0 to 40.8)
2005-2006			
Total cohort	30.7 (24.7 to 36.2)	12.0 (1.75 to 21.3) <sup>c</sup>	21.2 (13.5 to 28.2)
Propensity-matched <sup>b</sup>	33.5 (26.3 to 39.9)	5.9 (-9.25 to 18.9)	15.9 (4.77 to 25.6)
Unimmunized in last year <sup>d</sup>	35.3 (25.9 to 43.6)	30.2 (11.2 to 45.2)	7.3 (-18.0 to 26.9)
Propensity-matched <sup>b</sup>	34.6 (23.8 to 43.9)	31.9 (10.0 to 48.3)	-6.7 (-44.1 to 21.0)
2006-2007			
Total cohort	28.4 (21.9 to 34.3)	10.7 (2.72 to 18.1) <sup>e</sup>	19.8 (13.6 to 25.5)
Propensity-matched <sup>b</sup>	33.1 (25.6 to 40.0)	11.8 (0.85 to 21.5) <sup>f</sup>	13.3 (5.78 to 20.1)
Unimmunized in last year <sup>d</sup>	32.1 (17.3 to 44.3)	26.9 (9.37 to 41.1)	7.1 (-19.0 to 27.7)
Propensity-matched <sup>b</sup>	34.5 (18.8 to 47.2)	27.8 (6.53 to 44.2)	10.0 (-20.2 to 32.6)
Unimmunized in last 2 years <sup>d</sup>	35.7 (17.0 to 50.2)	37.3 (15.4 to 53.5)	-2.4 (-46.0 to 28.0)
Propensity-matched <sup>b</sup>	39.3 (19.9 to 54.0)	38.2 (12.8 to 56.2)	-1.8 (-53.1 to 32.3)

Abbreviations: CI, confidence interval; LAIV, live attenuated influenza vaccine; TIV, trivalent inactivated vaccine.

<sup>a</sup>Vaccine effect was calculated as 1 minus the adjusted incident rate ratio.

<sup>b</sup>Propensity score based on age, sex, service branch, ever hospitalized, immunization history status (excluded in vaccine-naïve cohorts), and number of medical encounters and influenza-like illness encounters in the 12 months prior to the influenza season.

<sup>c</sup>*P* = .07, adjusted by Bonferroni method.

<sup>d</sup>Vaccine-naïve cohort.

<sup>e</sup>*P* = .03, adjusted by Bonferroni method.

<sup>f</sup>*P* = .04.

From: **Live Attenuated or Inactivated Influenza Vaccines and Medical Encounters for Respiratory Illnesses Among US Military Personnel**

JAMA. 2009;301(9):945-953. doi:10.1001/jama.2009.265

**Table 3.** Vaccine Effects During 3 Influenza Seasons: 2004-2005, 2005-2006, and 2006-2007<sup>a</sup>

	Vaccine Effect (95% CI)		
	TIV vs Unimmunized	LAIV vs Unimmunized	TIV vs LAIV
<b>2004-2005</b>			
Total cohort	54.8 (51.3 to 58.1)	20.8 (12.3 to 28.5)	43.0 (36.4 to 48.9)
Propensity-matched <sup>b</sup>	53.7 (49.8 to 57.3)	7.3 (-9.21 to 21.3)	31.6 (21.0 to 40.8)
<b>2005-2006</b>			
Total cohort	30.7 (24.7 to 36.2)	12.0 (1.75 to 21.3) <sup>c</sup>	21.2 (13.5 to 28.2)
Propensity-matched <sup>b</sup>	33.5 (26.3 to 39.9)	5.9 (-9.25 to 18.9)	15.9 (4.77 to 25.6)
Unimmunized in last year <sup>d</sup>	35.3 (25.9 to 43.6)	30.2 (11.2 to 45.2)	7.3 (-18.0 to 26.9)
Propensity-matched <sup>b</sup>	34.6 (23.8 to 43.9)	31.9 (10.0 to 48.3)	-6.7 (-44.1 to 21.0)
<b>2006-2007</b>			
Total cohort	28.4 (21.9 to 34.3)	10.7 (2.72 to 18.1) <sup>e</sup>	19.8 (13.6 to 25.5)
Propensity-matched <sup>b</sup>	33.1 (25.6 to 40.0)	11.8 (0.85 to 21.5) <sup>f</sup>	13.3 (5.78 to 20.1)
Unimmunized in last year <sup>d</sup>	32.1 (17.3 to 44.3)	26.9 (9.37 to 41.1)	7.1 (-19.0 to 27.7)
Propensity-matched <sup>b</sup>	34.5 (18.8 to 47.2)	27.8 (6.53 to 44.2)	10.0 (-20.2 to 32.6)
Unimmunized in last 2 years <sup>d</sup>	35.7 (17.0 to 50.2)	37.3 (15.4 to 53.5)	-2.4 (-46.0 to 28.0)
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Abbreviations: CI, confidence interval; LAIV, live attenuated influenza vaccine; TIV, trivalent inactivated vaccine.

<sup>a</sup>Vaccine effect was calculated as 1 minus the adjusted incident rate ratio.

<sup>b</sup>Propensity score based on age, sex, service branch, ever hospitalized, immunization history status (excluded in vaccine-naïve cohorts), and number of medical encounters and influenza-like illness encounters in the 12 months prior to the influenza season.

<sup>c</sup>*P* = .07, adjusted by Bonferroni method.

<sup>d</sup>Vaccine-naïve cohort.

<sup>e</sup>*P* = .03, adjusted by Bonferroni method.

<sup>f</sup>*P* = .04.

# COMMON AND SERIOUS EVENTS

Data was pooled from 12 placebo-controlled studies and 3 TIV controlled studies for adults 18 to 59 years of age (N=3,300) to evaluate solicited events occurring 0-6 days post-vaccination.<sup>1,2</sup> Runny nose, headache, sore throat, malaise, muscle ache, and cough were common reactions to both vaccines. At least one serious adverse event, evaluated between days 0-28, was reported in 0.18% of LAIV recipients and 0.29% of placebo recipients in the pooled analysis.<sup>1,2</sup>

	Placebo Studies		TIV Studies	
	LAIV (%)	Placebo (%)	LAIV (%)	TIV (%)
Any AE	69.1	58.9	62.5	58.4
Runny 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	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
Less appetite	5.8	8.9	2.3	9.1
Abdominal pain	4.7	6.2	0.0	9.1
Vomiting	3.5	3.8	2.3	2.3

1. *Can Comm Dis Rep. FluMist. 2011;Vol 37(ACS-7)*

2. *FluMist [Product Monograph]. AstraZeneca Canada Inc. Available at: <http://www.astrazeneca.ca>*

# SUMMARY IN ADULTS

“In contrast to children, most comparative studies have found that LAIV and TIV had similar efficacy or that TIV was more efficacious in persons 18 to 59 years of age.”<sup>1</sup>

In adults, adverse events mainly include runny nose (or nasal congestion), headache, sore throat, malaise, muscle ache, and cough.

<sup>1</sup> NACI Statement on Seasonal Influenza Vaccine for 2014-2015

# INDICATIONS

FluMist® is a live attenuated influenza virus vaccine indicated for the active immunization of individuals aged 2 to 59 years against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

# PROVINCIAL POLICY FOR LAIV

LAIV products are publicly funded for the following group:

- Children 2 to 17 years old, inclusive

Although the product is approved for use in 2-59 year olds, NACI does not recommend it's use in adults (i.e., 18-59 year olds) as TIV provides better protection.

LAIV is not provided free in BC for this age group.

# DOSAGE SCHEDULE

Age	Vaccination Status	Dosage
Children (2-8 years) <sup>1</sup>	Not previously vaccinated with seasonal influenza vaccine <sup>2</sup>	2 doses (0.2 mL <sup>3</sup> each), at least 4 weeks apart)
	Previously vaccinated with seasonal influenza vaccine	1 dose (0.2 mL <sup>3</sup> )
Children, adolescents and adults 9-59 years	Not Applicable	1 dose (0.2 mL <sup>3</sup> )

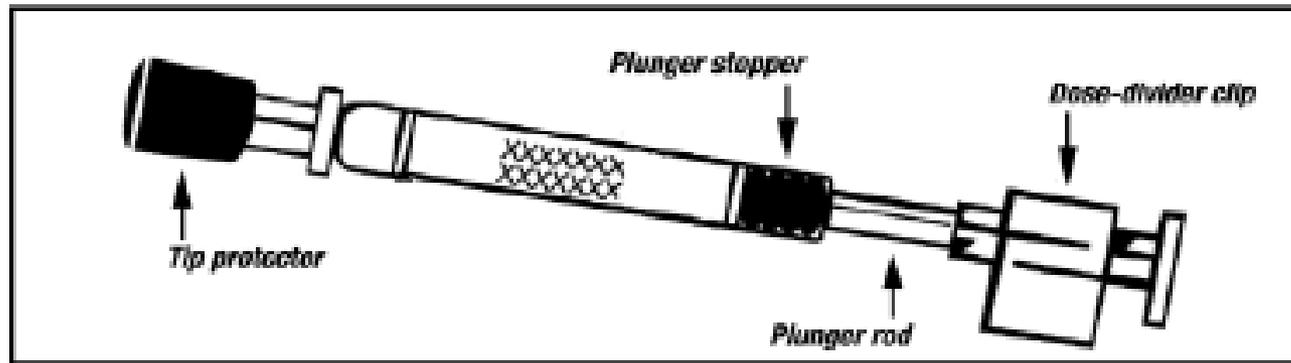
<sup>1</sup> BCCDC recommends preferential use of LAIV in children 2-8 years of age.

<sup>2</sup> If the child has received 1 or more doses in any previous season, only a single dose is required.

<sup>3</sup> Administer 0.1 mL in each nostril

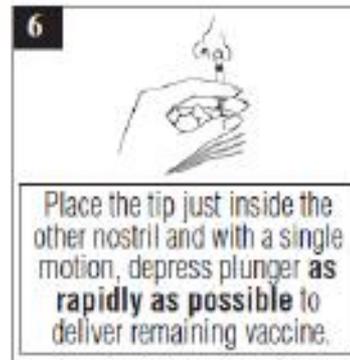
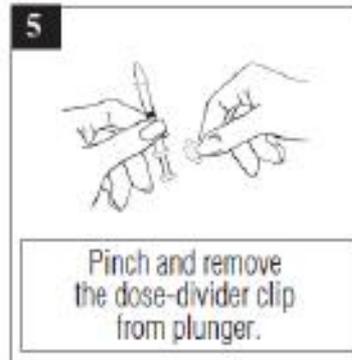
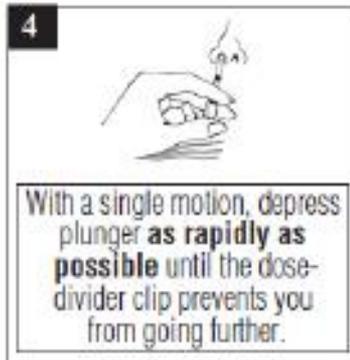
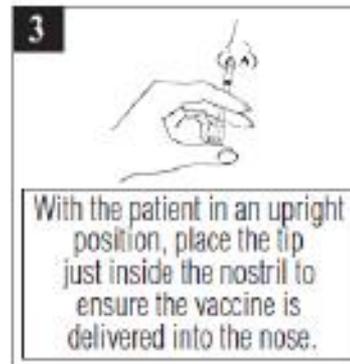
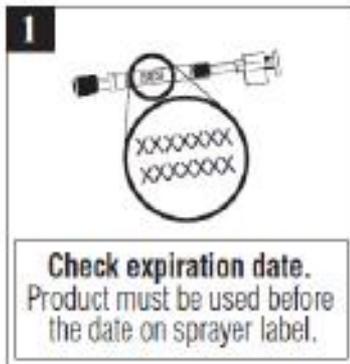
# DOSAGE FORM AND PACKAGING

FluMist® is supplied as a 0.2 mL pre-filled, single use glass sprayer  
Available in packages of 10 or 5 sprayers or a package of 1 sprayer.



# ADMINISTRATION

**DO NOT INJECT PRODUCT AS IT IS FOR INTRA-NASAL USE ONLY**



**Active inhalation (i.e., sniffing) is NOT required**

# COMPOSITION

Each 0.2 mL dose of FluMist® contains  $10^{6.5-7.5}$  FFU (fluorescent focus units) of live attenuated influenza virus reassortants of each of the four strains for the specific season.

Excipients include: sucrose, dibasic potassium phosphate, monobasic potassium phosphate, gelatin hydrolysate (porcine Type A), arginine hydrochloride, monosodium glutamate, gentamicin (a trace residual) and ovalbumin (a trace residual).

FluMist® contains no preservatives (e.g., no thimerosal). The intranasal sprayer contains no latex.

# CONTRAINDICATIONS

LAIV is contraindicated in individuals with a history of hypersensitivity, especially anaphylactic reactions, to eggs, egg proteins. TIV is recommended for use in these individuals.

LAIV is contraindicated in individuals with a history of hypersensitivity, especially anaphylactic reactions, to gentamicin, gelatin, or arginine or with life-threatening reactions to previous influenza vaccinations.

# WARNINGS AND PRECAUTIONS

Please see Product Monograph for Complete Information

**Do not administer LAIV** to children **<2 years of age**. In clinical trials, an increased risk of wheezing post-vaccination was observed in LAIV recipients <24 months of age. An increase in hospitalizations was observed in children <24 months of age after vaccination with LAIV.

LAIV should not be administered to any individuals with severe **asthma (those on oral corticosteroids, high-dose inhaled steroids or those with active wheezing in the 7 days prior to vaccination)** because these individuals have not been studied in clinical trials.

If Guillain-Barré syndrome has occurred within 6 weeks of any prior influenza vaccination, the decision to give LAIV should be based on careful consideration of the potential benefits and potential risks

# IMMUNOCOMPROMISED POPULATIONS

Data supporting the safety and effectiveness of LAIV in immunocompromised individuals are limited.

The effectiveness of LAIV in preventing influenza in HIV (+) individuals has not been studied. Halasa et al<sup>1</sup> evaluated 20 children 5-17 years of age with mild cancer and found LAIV demonstrated modest immunogenicity by HAI and microneutralization assays.

The safety of LAIV has been studied in 3 small studies that recruited children or adults with HIV infection (categorized as mild to moderate immunosuppression).<sup>2-4</sup> There were no significant differences found in rates of reactogenicity and vaccine-related adverse events after placebo or LAIV within either HIV(+) or HIV(-) subjects. There were no significant changes in geometric mean HIV RNA concentrations, CD4 counts or CD4%, or increased quantity of LAIV virus shedding.

Administration of LAIV, a live virus vaccine, to immunocompromised persons should be based on careful consideration of potential benefits and risks.

# PREGNANCY AND LACTATION

## Pregnancy Category C

Animal reproduction studies have not been conducted with LAIV. It is not known whether LAIV can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. LAIV should be given to pregnant or nursing women only if clearly needed.

LAIV is not contraindicated in lactating women.

# CONTACT WITH IMMUNOCOMPROMISED INDIVIDUALS

Studies have shown LAIV vaccinated recipients shed the influenza virus.<sup>1,2</sup>

Shedding is not synonymous with transmission but as a precaution vaccine recipients or their parents/guardians should be informed by the healthcare provider that LAIV is an attenuated live virus vaccine and has the potential for transmission to immunocompromised household contacts.<sup>3</sup>

Although no transmission of LAIV in a health care setting has ever been reported, vaccine recipients (and healthcare workers working with immunocompromised populations) should attempt to avoid close association with severely immunocompromised individuals (e.g., bone marrow transplant recipients requiring isolation) for at least 2 weeks following vaccination.<sup>3,4</sup>

If such contact cannot be avoided offer an inactivated influenza vaccine instead of LAIV.

1. Talbot TR, Crocker DD, Peters J, et al. *Infect Control Hosp Epidemiol.* 2005;26(5):494-500.

2. Vesikari T, Karvonen A, Korhonen T, et al. *Pediatr Infect Dis J.* 2006;25(7):590-5.

3. *Can Comm Disease Report. FluMist.* 2011;Vol 37(ACS-7)

4. *FluMist [Product Monograph]. AstraZeneca Canada Inc.* Available at: <http://www.astrazeneca.ca>

# CONCOMITANT USE WITH LIVE VACCINES

Concurrent administration of LAIV with the measles, mumps and rubella (MMR) vaccine was studied in children 11-23 months of age, the MMR-varicella vaccine in children 12-15 months of age,<sup>1,2</sup> and oral polio vaccine.<sup>3</sup>

Adverse events were similar to those seen in other clinical trials with LAIV.

No evidence of interference with immune responses to measles, mumps, rubella, varicella and LAIV vaccines was observed and thus can be given on the same visit.

LAIV can be administered with or at any time before or after live attenuated or inactivated vaccines.<sup>4</sup>

<sup>1</sup> FluMist [Product Monograph]. AstraZeneca Canada Inc. Available at: <http://www.astrazeneca.ca>

<sup>2</sup> Nolan T, Bernstein DI, Block SL, et al. *Pediatrics*. 2008;121(3):508-16.

<sup>3</sup> Breiman RF, Brooks WA, Goswami D, et al. *Vaccine*. 2009;27(40):5472-9.

<sup>4</sup> NACI Statement on Seasonal Influenza Vaccine for 2014-2015

# DRUG INTERACTIONS

Concurrent administration of LAIV should be avoided in those <18 years of age receiving aspirin therapy or aspirin-containing therapy, because of the association of Reye's syndrome with aspirin and wild-type influenza infection.

It is recommended that aspirin-containing medications given to children <18 years be delayed for four weeks after vaccination with LAIV.<sup>1,2</sup> For individuals who are receiving ongoing aspirin therapy or aspirin-containing therapy, vaccination with TIV should be considered.<sup>1</sup>

It is recommended to not administer influenza-related antiviral agents (i.e., oseltamivir and zanamivir) until two weeks after administration of LAIV.<sup>1,2</sup> If on antiviral therapy, administer LAIV at least 48 hours after the cessation of antiviral therapy. If these two are administered incorrectly, revaccination should take place.<sup>1</sup>

1. *Can Comm Dis Report. FluMist. 2011;Vol 37(ACS-7)*

2. *FluMist [Product Monograph]. AstraZeneca Canada Inc. Available at: <http://www.astrazeneca.ca>*

# STORAGE AND STABILITY

LAIV should be stored in a refrigerator between 2-8°C upon receipt and until use.

Do not freeze.

Vaccine remains stable after a single temperature excursion up to 25°C for 12 hours. Return vaccine to the fridge, after a temperature excursion, and use as soon as feasible.

Subsequent excursions are not permitted.

Expiration date is short (4 months).

Use the product by the expiration date on the sprayer label.

# **ASSESSMENT**

# QUESTION 1

Which of the following statement(s) is/are correct with respect to influenza B?

- a. The circulation of influenza B predominantly follows influenza A and typically peaks in the spring.
- b. Individuals who have influenza B are more likely to be older than 20 years of age.
- c. Individuals who have influenza B are more likely to be younger than 20 years of age
- d. (a) and (b)
- e. (a) and (c)

# QUESTION 2

Which of the following individuals are eligible for publicly-available influenza vaccination in British Columbia?

- a. Individuals at high risk for influenza infection.
- b. Individuals capable of transmitting influenza to those at high risk.
- c. Individuals who provide essential community services.
- d. All of the above
- e. None of the above

# QUESTION 3

Which of the following statement(s) is/are true?

- a. LAIV should be avoided in children <24 months of age due to increased risk of wheezing.
- b. It is recommended that acetylsalicylic acid -containing products in children <18 years of age be delayed for four weeks after receipt of LAIV.
- c. LAIV is contraindicated in nursing mothers
- d. (a) and (b)
- e. (b) and (c)

# QUESTION 4

FluMist contains the following ingredients (place True or False beside each sentence):

- a.  $10^{6.5-7.5}$  FFU of live attenuated reassortants \_\_\_\_\_
- b. MF-59 adjuvant \_\_\_\_\_
- c. Thimerosal \_\_\_\_\_
- d. Traces of antibiotics (eg gentamicin) \_\_\_\_\_
- e. Latex \_\_\_\_\_

# QUESTION 5

Evidence from randomized clinical trials evaluating efficacy of LAIV and TIV in children evaluated the following:

- a. None of the active-comparator studies evaluated children less than 2 years of age.
- b. All of the active-comparator studies used 1 dose of LAIV only.
- c. The primary endpoint of all the studies was development of laboratory-confirmed influenza.
- d. All of the studies included children with severe asthma.
- e. All of the studies included children up to 17 years of age.

# QUESTION 6

FluMist is indicated for use in the following individuals:

- a. Children 2 to 17 years of age.
- b. Adults 18 to 59 years of age.
- c. Children 6 to 23 months of age.
- d. (b) and (c)
- e. (a) and (b)

# QUESTION 7

Which of the following statement(s) is/are true?

- a. LAIV should be avoided in persons with immune compromising conditions.
- b. Patients on TIV experienced more adverse events than those on LAIV, particularly runny nose/congestion.
- c. LAIV may be used in those with severe asthma.
- d. All of the above
- e. None of the above

# QUESTION 8

Which of the following statement(s) is/are true with respect to use of LAIV in health care workers (HCW)?

- a. LAIV should be avoided in HCW with immune compromising conditions.
- b. TIV should be used for HCW providing care to those with immune compromising conditions, unless LAIV is the only product they will accept.
- c. If a HCW receives LAIV and is providing care to individuals with severe immune compromising conditions, they should wait two weeks following receipt of LAIV before continuing to provide care to such individuals.
- d. All of the above
- e. None of the above

# QUESTION 9

Which of the following statement is the correct process to use for administering LAIV intranasally?

- a. Remove the rubber tip protector. Remove the dose-divider clip at the other end of the sprayer. With the patient in an upright position, place the tip just inside the nostril to ensure LAIV is delivered into the nose. The patient should breathe normally. With a single motion, depress the plunger as rapidly as possible until the dose-divider clip prevents you from going further. Pinch the plunger. Repeat process with the next nostril.
- b. Remove the rubber tip protector. Do not remove the dose-divider clip at the other end of the sprayer. With the patient in an upright position, place the tip just inside the nostril to ensure LAIV is delivered into the nose. The patient should breathe normally. With a single motion, depress the plunger as rapidly as possible until the dose-divider clip prevents you from going further. Pinch and remove the dose-divider clip from the plunger. Repeat process with the next nostril.
- c. Remove the rubber tip protector. Do not remove the dose-divider clip at the other end of the sprayer. With the patient's head tilted back, place the tip just inside the nostril to ensure LAIV is delivered into the nose. The patient should breathe normally. With a single motion, depress the plunger as rapidly as possible until the dose-divider clip prevents you from going further. Pinch and remove the dose-divider clip from the plunger. Repeat process with the next nostril.
- d. Remove the rubber tip protector. Do not remove the dose-divider clip at the other end of the sprayer. With the patient in an upright position, place the tip just inside the nostril to ensure LAIV is delivered into the nose. The patient should take a deep breath. With a single motion, depress the plunger as rapidly as possible until the dose-divider clip prevents you from going further. Dispose the applicator in the sharps container.

# QUESTION 10

Which of the following statement(s) is/are correct regarding evidence for use of LAIV in adults?

- a. Individuals 18-59 years of age are capable of mounting a better immune response to LAIV and thus have a better response to LAIV than TIV.
- b. Individuals 18-59 years of age probably mount less of an immune response to LAIV than TIV.
- c. Active comparator studies in adults of LAIV and TIV have found the two products to be equally efficacious or TIV to be better
- d. (a) and (b)
- e. (b) and (c)

# ANSWERS

Question 1: **e** (a) and (c)

Question 2: **d** All of the above

Question 3: **d** (a) and (b)

Question 4: **a – true, b – false, c – false, d – true, e - false**

Question 5: **c** The primary endpoint of all the studies was development of laboratory-confirmed influenza.

Question 6: **e** (a) and (b)

Question 7: **a** LAIV should be avoided in persons with immune compromising conditions.

Question 8: **d** All of the above

Question 9: **b** Remove the rubber tip protector. Do not remove the dose-divider clip at the other end of the sprayer. With the patient in an upright position, place the tip just inside the nostril to ensure LAIV is delivered into the nose. The patient should breathe normally. With a single motion, depress the plunger as rapidly as possible until the dose-divider clip prevents you from going further. Pinch and remove the dose-divider clip from the plunger. Repeat process with the next nostril.

Question 10: **e** (b) and (c)