



MedImmune

Medical Affairs Department

Phone: 800-949-3789 Fax: 800-959-4033

One MedImmune Way, Gaithersburg, MD 20878

Website: <http://www.medimmune.com>

October 2, 2009

Debbie Elliott, MSN
SCG Regional Public Health Coordinator
132 Hocking Mall
Logan, OH 43138

Dear Debbie Elliott:

Thank you for your recent inquiry concerning the use of Pandemic Influenza 2009 (MedImmune).

Attached are individual answers and a bibliography for each of the questions you asked. These are itemized below:

**• Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal.
and issues related to healthcare providers [PAN09CT142]**

Your interest in Pandemic Influenza 2009 (MedImmune) is appreciated. This letter and citations are not intended to offer an opinion or advice on administering our products in a manner inconsistent with product labeling. A copy of the currently approved U.S. package insert(s) and designated (*) literature reprints are enclosed for your review. Please feel free to call us if we can be of further assistance.

Sincerely,

Eddie Carver, PharmD
Senior Information Specialist
(Phone: 800-949-3789 / e-mail: CarverE@medimmune.com)

GENERAL PRODUCT INFORMATION: Influenza A (H1N1) 2009 Monovalent Live, Intranasal is a live monovalent nasally-administered influenza virus vaccine with several characteristics that differ from injectable monovalent inactivated influenza vaccine (MIV). The single influenza strain contained in Influenza A (H1N1) 2009 Monovalent Live, Intranasal is *cold-adapted* in that it replicates efficiently at low temperatures such as 25°C, is *temperature-sensitive* in that its replication is reduced at higher temperatures of 37°C (for influenza B) and 39°C (for influenza A), and is *attenuated* in that it does not produce classical influenza-like illness in the ferret model of human influenza infection (*package insert*). Influenza A (H1N1) 2009 Monovalent Live, Intranasal, FluMist® and its earlier prototype formulations are commonly referred to by the CDC (Center for Disease Control & Prevention) as Live Attenuated Influenza Vaccine (LAIV).

Influenza A (H1N1) 2009 Monovalent Live, Intranasal is stored at 2-8°C/35-46°F. Influenza A (H1N1) 2009 Monovalent Live, Intranasal is concentrated by centrifugation, sterile filtered, and blended in stabilizing buffers containing monosodium glutamate, hydrolyzed porcine gelatin, arginine, sucrose and phosphate. The dose volume is 0.2 mL (0.1 mL per nostril). Influenza A (H1N1) 2009 Monovalent Live, Intranasal contains the CDC recommended strain for the 2009-10 pandemic vaccine: **A/California/04/2009**.

Influenza A (H1N1) 2009 Monovalent Live, Intranasal is indicated for the active immunization of children and adults, 2-49 years of age against influenza disease caused by pandemic (H1N1) 2009 virus (*package insert*). The relative efficacy of FluMist in preventing culture-confirmed influenza in a multinational, randomized, double-blind, active-controlled (inactivated influenza vaccine) study in healthy children <5 years of age at enrollment was 44.5% (*package insert*). In a multi-center, randomized, double-blind, placebo-controlled study in healthy adults, the protection afforded by FluMist against a challenge of a single strain of wild-type influenza virus was 85% (*Treanor 2000*). Vaccination with FluMist has been demonstrated to induce both serum (IgG) and nasal secretory (IgA) antibodies (*Belshe 2000, Boyce 2000, Treanor 2000*).

FluMist has been extensively studied in people 6 weeks to 98 years of age and has a well documented safety & efficacy profile. The most common adverse reactions are runny nose or nasal congestion in all ages, fever > 100°F in children 2-6 years of age and sore throat in adults. See the enclosed prescribing information for a complete description of the CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS for Influenza A (H1N1) 2009 Monovalent Live, Intranasal. Recommendations of the **CDC Advisory Committee on Immunization Practices (CDC-ACIP)** for the use of influenza A (H1N1) 2009 monovalent vaccine were published August 28, 2009 (*CDC-ACIP 2009*). Each pre-filled Influenza A (H1N1) 2009 Monovalent Live, Intranasal sprayer must be stored at 2-8° C (35-46°F). **FOR NASAL ADMINISTRATION ONLY. DO NOT ADMINISTER PARENTERALLY.**

RE: Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal and issues related to healthcare providers [PAN09CT142]

Although not specifically addressed in the Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal labeling (*package insert*), we are providing the following information per your request. Several commonly asked questions are discussed below on this topic.

Given that Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is similar in construct to the FluMist® formulation (which is trivalent for seasonal influenza strains), it may be noteworthy to review the issues related to healthcare providers of FluMist®.

Full guidance concerning FluMist and HCPs is available from the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC), which publishes annually its recommendations for the Prevention and Control of Influenza (*CDC/ACIP 2009*). In addition, ACIP together with the Healthcare Infection Control Practices Advisory Committee (HICPAC) has published its recommendations for Influenza Vaccination of Healthcare Personnel (*CDC-ACIP/HICPAC 2006*). Finally, the Society for Healthcare Epidemiology of America (SHEA) has published a position paper with guidance for vaccinating HCPs and allocating influenza vaccine during shortages (*SHEA 2005*). The CDC-ACIP/HICPAC 2006 states:

“LAIV [FluMist®] has demonstrated similar benefits in randomized trials among healthy working adults aged 18-64 years. In one study, vaccination with LAIV reduced severe febrile illnesses 19% and upper respiratory tract illness 24%; LAIV use also was associated with fewer days of illness and of work lost, fewer health-care provider visits, and reduced use of prescription antibiotics and over-the-counter medications [Nichol 1999]. These results were recorded during a season in which the vaccine and circulating influenza A (H3N2) strains were not well matched. In the same study, LAIV vaccination yielded similar benefits among a subset of healthy adults ages 18-49 years, and antibiotic use in this age group decreased 41-51% [Nichol 1999]. In one study, overall efficacy of LAIV and inactivated influenza vaccine [“flu shot”] in preventing laboratory-documented influenza was 85% and 71%, respectively [Treanor 1999].”

Can healthcare workers be vaccinated with Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal?

Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is an acceptable influenza vaccine for HCPs who fit the labeling criteria (see **INDICATIONS** section of the enclosed Package Insert).

The CDC/ACIP recommendations also state that:

“No preference is indicated for TIV use by persons who have close contact with persons with lesser degrees of immunosuppression (e.g., persons with diabetes, persons with asthma who take corticosteroids, persons who have recently received chemotherapy or radiation but who are not being cared for in a protective environment as defined above, or persons infected with HIV) or for TIV use by HCP or other healthy nonpregnant persons aged 2–49 years in close contact with persons in all other groups at high risk.” (CDC/ACIP 2009, p. 30)

Can HCPs Who Administer Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal to Others Become “Infected” with Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal Strains?

Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal contains an “attenuated” vaccine strain which is too weak to cause severe symptoms associated with influenza illness (Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal induces immunity, not influenza disease) (<http://www.cdc.gov/flu/keyfacts.htm>). By virtue of its cold-adapted, temperature sensitive phenotype, the vaccine strain is impaired from replicating at core body temperature after passage from the nasal airways (Murphy 2002).

With proper intranasal administration, it is unlikely that the HCP administrator would be exposed to Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal spray. If accidentally exposed to Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal spray, the likelihood of clinical infection – or even self-induced vaccination – resulting from such exposure is virtually nil.

Can Vaccinated HCPs Transmit Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal Strains to Immunocompromised Contacts?

CDC/ACIP has noted that “***LAIV [FluMist®] transmission from a recently vaccinated person causing clinically important illness in an immunocompromised contact has not been reported.***” They only specify a preference for TIV (“flu shots”) in persons have close contact with severely immunosuppressed persons (e.g., patients with hematopoietic stem cell transplants) during those periods in which the immunosuppressed person requires care in a protective environment (typically defined as a specialized patient care area with a positive airflow relative to the corridor, high efficiency particulate air filtration, and frequent air changes).

The CDC goes on to note that this is based on a “theoretical risk” and, as a precautionary measure, “***HCP’s who receive LAIV should avoid providing care for severely immunosuppressed patients for 7 days after vaccination.***” Persons who were previously in a protective environment but who are no longer in that protective environment are exempt from this precaution (CDC/ACIP 2009, p. 30). Note - The 7 day avoidance period is derived from studies that show this as the timeframe when any possible shedding and transmission might occur (Talbot 2004 & 2005).

Because of the lack of clinical data, some experts have concluded it advisable to avoid LAIV in health-care workers “whose primary responsibility is the care of highly immunosuppressed patients with hematopoietic stem cell transplants, patients with acute leukemia, and premature infants” (Cosgrove 2005). In this review of the “severely” immunocompromised, it is especially notable that the authors indicate that patients meeting the criteria for immunodeficiency (e.g., HIV with CD4 cell counts <100mcg/mL) also are “likely to have an adequate immunologic response to influenza vaccine.”

With respect to NICU exposure, it should be emphasized that “***neonates in an NICU are not considered severely immunocompromised. NICU personnel may receive LAIV [FluMist] if otherwise eligible (younger than 50 years, healthy, and not pregnant)***” according to CDC officials. (Immunization Action Coalition 2005).

The FDA’s Vaccine Adverse Event Reporting System (VAERS) recently published its final report of the first 2 years post-licensing experience (August 1, 2003 to July 31, 2005) involving an estimated 2.5 million FluMist recipients (Izurieta 2005). It specifically stated “***there were no reports of possible secondary transmission to an immunosuppressed individual.***” (Of further note, the 1 case that had a lab culture performed showed the infection not to be from a FluMist vaccine strain.)

Can Vaccinated Lay Person (non-HCP) Transmit Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal Strains When Visiting A Hospitalized Patient?

There should be no ban for Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal vaccinee to visit somebody or receive care in a hospital.

The CDC/ACIP Recommendations state:

“Hospital visitors who have received LAIV should avoid contact with severely immunosuppressed persons for 7 days after vaccination but should not be restricted from visiting less immunosuppressed patients.” (CDC/ACIP 2009, p. 30)

Clinical experience of healthcare workers vaccinated with FluMist

In a review of post-marketing adverse events with FluMist, it was concluded *“These and other studies substantiate the current recommendations that LAIV is safe for close contacts of high-risk patients except the most highly immunocompromised, such as hematopoietic stem cell transplant recipients receiving care in protected environments (Neuzil 2005).”*

The results of a comprehensive institutional influenza immunization campaign for health care workers in a pediatric cancer hospital were recently reported (McCullers 2006). FluMist was offered during the 2004–2005 influenza season to employees who had no direct contact with hematopoietic stem cell transplant recipients or other less severe immunosuppression along with TIV. An 80% vaccination rate was achieved where the mean rate for the previous five years was 43.6% of all employees (44.7% of HCP’s with direct patient care). A total of 1429 vaccine doses were administered with 348 receiving FluMist including 5 who had direct patient care duties.

In a similar type of program in a community hospital, intranasal and intramuscular vaccines were used in a mandatory influenza vaccination program for direct patient care employees during the 2005–2006 influenza season. A total of 3201 out of 4152 employees were designated as direct patient care employees. Hospital-employed physicians were included in the program; non-hospital employed physicians and all other staff were vaccinated voluntarily but vaccination was not required. Only 2.5% of employees met criteria for deferral because of a anaphylactic allergy to eggs or egg protein, a severe allergic reaction to previous influenza vaccination, a history of Guillian Barre Syndrome, or severe latex allergy. Three individuals declined because of religious objection. (Van Enk 2006).

Should HCPs Who Administer Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal to Others Be Previously Vaccinated Against Influenza?

The Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices met on July 29, 2009 to make recommendations for use of vaccine against novel influenza A /H1N1 (CDC 2009). The committee met to develop recommendations on who should receive vaccine against novel influenza A/H1N1 when it becomes available, and included health care and emergency services personnel in the population that should be prioritized if the vaccine is initially available in extremely limited quantities.

Can HCPs Who Are Pregnant or Breast-feeding, Have Asthma, or Are Immunocompromised Administer Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal?

Yes, many of these underlying conditions are acceptable in a HCP who will be administering Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal. In their 2009 Recommendations, the CDC/ACIP Recommendations state:

“Severely immunosuppressed persons should not administer LAIV. However, other persons at high risk for influenza complications may administer LAIV. These include persons with underlying medical conditions placing them at high risk or who are likely to be at risk, including pregnant women, persons with asthma, and persons aged ≥50 years.” (CDC/ACIP 2009, p. 33)

On their website under Influenza (flu) vaccine, the CDC provides the following language regarding use of FluMist in breastfeeding mothers (<http://www.cdc.gov/flu/about/qa/nasalspray.htm>):

Q. *“Are there any contraindications to giving breastfeeding mothers LAIV (sold commercially as FluMist)?”*

A. *“Breast feeding is not a contraindication for FluMist.”* See www.cdc.gov/mmwr/preview/mmwrhtml/rr5306a1.htm for a list of contraindications for FluMist.

The CDC/ACIP states that:

“Women who are breastfeeding may receive either TIV or LAIV unless contraindicated because of other medical conditions.” (CDC/ACIP 2009, p. 30).

As noted in the Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal labeling (package insert) in the section entitled **USE IN SPECIFIC POPULATIONS/Nursing Mothers**,

“It is not known whether Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is excreted in human milk. Therefore, as some viruses are excreted in human milk and additionally, because of the possibility of shedding of vaccine virus and the close proximity of a nursing infant and mother, caution should be exercised if Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal is administered to nursing mothers.”

Can HCPs Who Are 50 Years of Age or Older Administer Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal?

Yes, see CDC/ACIP recommendation above. There is no age restriction for the HCP who may administer Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal.

LITERATURE CITED: (reprints enclosed as marked below with an * - no reprints attached for FAX or e-m)

* Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal. MedImmune, LLC. Product/prescribing information as of September 2009. [[MRM46400](#)]

MMWR 2009/August 21;58 (Early Release):1-8 [[MRM46128](#)]

Ali T, Scott N, Kallas W, et al. Detection of influenza antigen with rapid antibody-based tests after intranasal influenza vaccination (FluMist). *Clin Infect Dis*. 2004;38:760-762. [[MRM 25,151](#)]

*Belshe RB, Gruber WC, Mendelman PM, et al. Correlates of immune protection induced by live, attenuated, cold-adapted intranasal influenza virus vaccine. *J Infect Dis*. 2000;181:1133-1137. [[MRM 19,176](#)]

*Boyce TG, Gruber WC, Coleman-Dokerty SD, et al. Mucosal immune response to trivalent live attenuated intranasal influenza vaccine in children. *Vaccine*. 2000;18:82-88. [[MRM 19,385](#)]

CDC. Guidelines for large-scale influenza vaccination clinic planning: Guidelines for the tiered use of inactivated influenza vaccine. Available at: http://www.cdc.gov/flu/professionals/vaccination/vax_priority.htm. Accessed on August 3, 2007 [MRM]

*CDC-ACIP (Centers for Disease Control and Prevention/Advisory Committee on Immunization Practices). Tiered use of inactivated influenza vaccine in the event of a vaccine shortage. *MMWR Morb Mortal Wkly Rep*. 2005/August 5;54: 749-750. [[MRM 29,880](#)]

CDC-ACIP/HICPAC. Influenza vaccination of health-care personnel. *MMWR Morb Mortal Wkly Rep*. 2006/February 24;55:1-15. [[MRM31615](#)]

*CDC-ACIP (Centers for Disease Control and Prevention/Advisory Committee on Immunization Practices). Prevention and Control of Influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2009/July 31;58 (RR-8):1-52 [[MRM45649](#)]

*Cosgrove SE, et al. : Strategies for use of a limited influenza vaccine supply. *JAMA*. 2005/Jan 12; 293:229-232. [[MRM27641](#)]

Immunization Action Coalition. Ask the experts – immunization questions. *Needle Tips* 2005;15:19-21. [[MRM 30,286](#)]

*Izurieta HS, et.al. Adverse events reported following live, cold-adapted, intranasal influenza vaccine. *JAMA* 2005;294:2720-2725 [[MRM 30,809](#)]

Kamboj M, sepkowitz KA. Risk of transmission associated with live attenuated vaccines given to healthy persons caring for or residing with an immunocompromised patient. *Infect Control Hosp Epidemiol* 2007;28:702-707 [[MRM36596](#)]

MedImmune . FluMist® Influenza Virus Vaccine Live, Intranasal. Summary for Presentation the Vaccinations and Related Biological Products Advisory Committee (VRBPAC). Part I. December 17, 2002. [[MRM 22,137](#)]

McCullers JA, et al. Increased influenza vaccination of healthcare workers at a pediatric cancer hospital: results of a comprehensive influenza vaccination campaign. *Infect Control Hosp Empidemiol* 2006;27:77-79. [[MRM 31,319](#)]

Murphy BR, Coelingh K. Principles underlying the development and use of live attenuated cold-adapted influenza A and B virus vaccines. *Viral Immunol*. 2002;15:295-323. [[MRM 20,527](#)]

Neuzil KM, Griffin MR. Vaccine safety – achieving the proper balance. *JAMA* 2005;294:2763-2765. [[MRM 30,810](#)]

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;282:137-144 [[MRM19468](#)]

SHEA Position Paper: Influenza Vaccination of Healthcare Workers [article on the Internet]. Alexandria, VA: The Society for Healthcare Epidemiology of America [cited 2005 Nov 1]. Available from: <http://www.shea-online.org/index.cfm>. [[MRM 30751](#)]

*Talbot TR, Crocker DD, Peters J, Doersam JK, Wright PF, Edwards KM. Degree and duration of mucosal shedding following use of the trivalent intranasal live attenuated influenza vaccine in adults. *The Society for Healthcare Epidemiology of America*, Philadelphia, 2004. [[MRM 25,211](#)]

*Talbot TR, et al. Duration of virus shedding after trivalent intranasal live attenuated influenza vaccination in adults. *Infection Control & Hospital Epidemiology*. 2005;26: 494-500. [[MRM29207](#)]

*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*. 2000;18(9-10):899-906. [[MRM 19,170](#)]

Van Enk RA, Potgiesser M, Corder W. Implementation of a hospital-wide employee influenza vaccination program. Abstract of the 33rd Association for Professionals in Infection Control and Epidemiology, 2006, 13-132[MRM]

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;25:590-595. [[MRM 33227](#)]

Vesikari T, Karvonen A, Korhonen T, et al. A randomized, double-blind, placebo-controlled trial of the safety, transmissibility and phenotypic stability of a live, attenuated, influenza virus vaccine in children attending day care. Fifth International Options for the Control of Influenza Conference in Okinawa, Japan, 2003. [[MRM 23,881](#)]