

Excerpts from:
"Strategies for improvements on
the back 40; Can we vaccinate
more HCWs?"

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Comparing TIV & LAIV

	TIV	LAIV
FDA-approved	Since 1960s	Since 2003
Route of administration	Intramuscular	Intranasal
Immunity	Primarily humoral	Mucosal and humoral
Virus	Split-virus or subunit inactivated virus	Cold-adapted, temperature-sensitive, live attenuated virus
Growth Medium	Chick embryos	Chick embryos
Indication	Persons ≥ 6 months	Healthy persons 5–49 years

Live Attenuated Influenza Virus Vaccine - Trivalent

- Content Updated yearly to protect against anticipated strains, consists of:
 - type A (2) and
 - type B (1)
- Process Attenuated influenza virus grown in embryonated chicken eggs

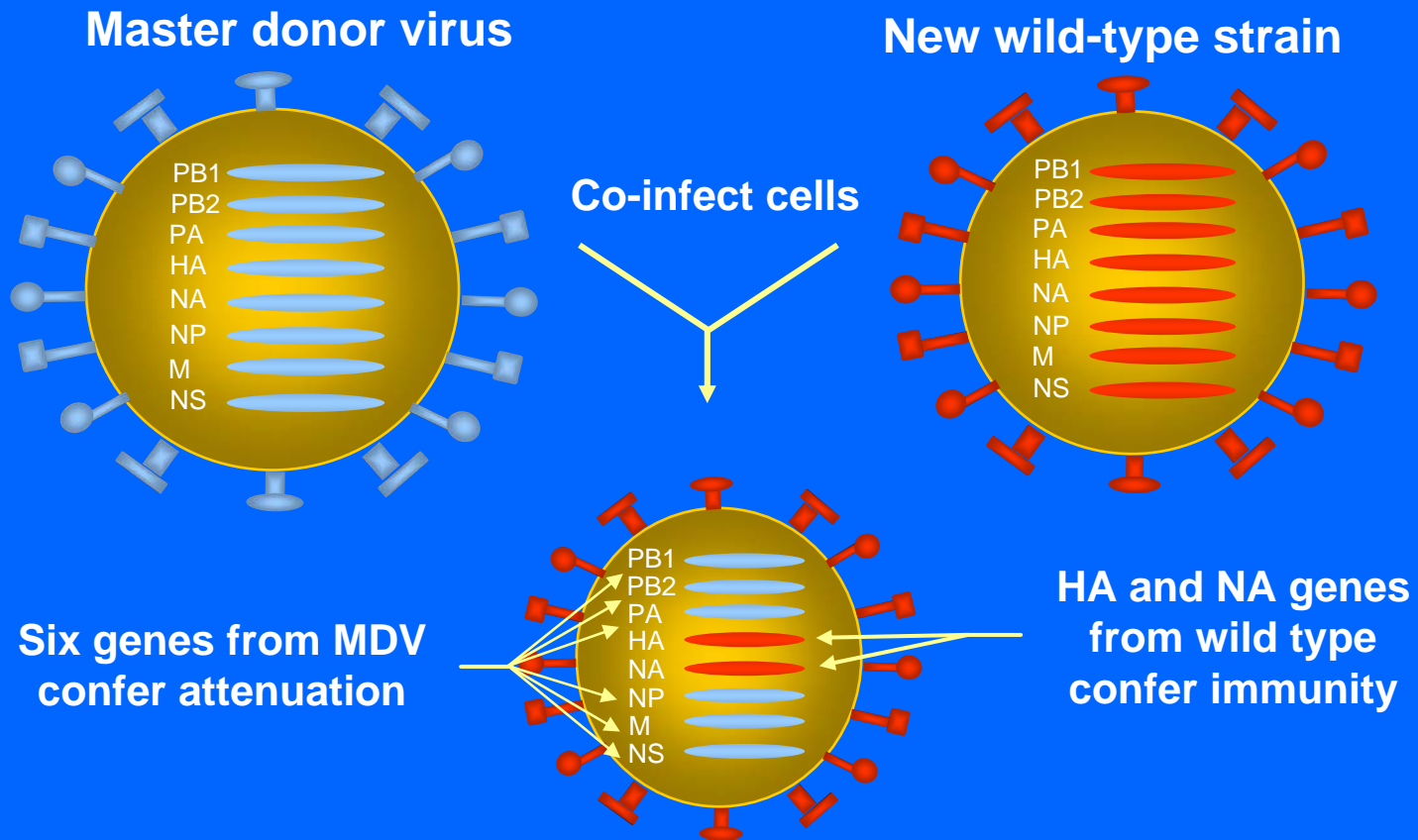
Why a Live, Attenuated Vaccine?

- Improved immunogenicity and vaccine efficacy
- Improved protection against drifted and mismatch, antigenically different strains
- Improved patient acceptance, which would reduce barriers to vaccination
 - needle-free intranasal, influenza vaccine,
 - thimersol free



FluMist®: Preparation of Vaccine Strains

Reassortants for each of three vaccine strains are derived by coinfection

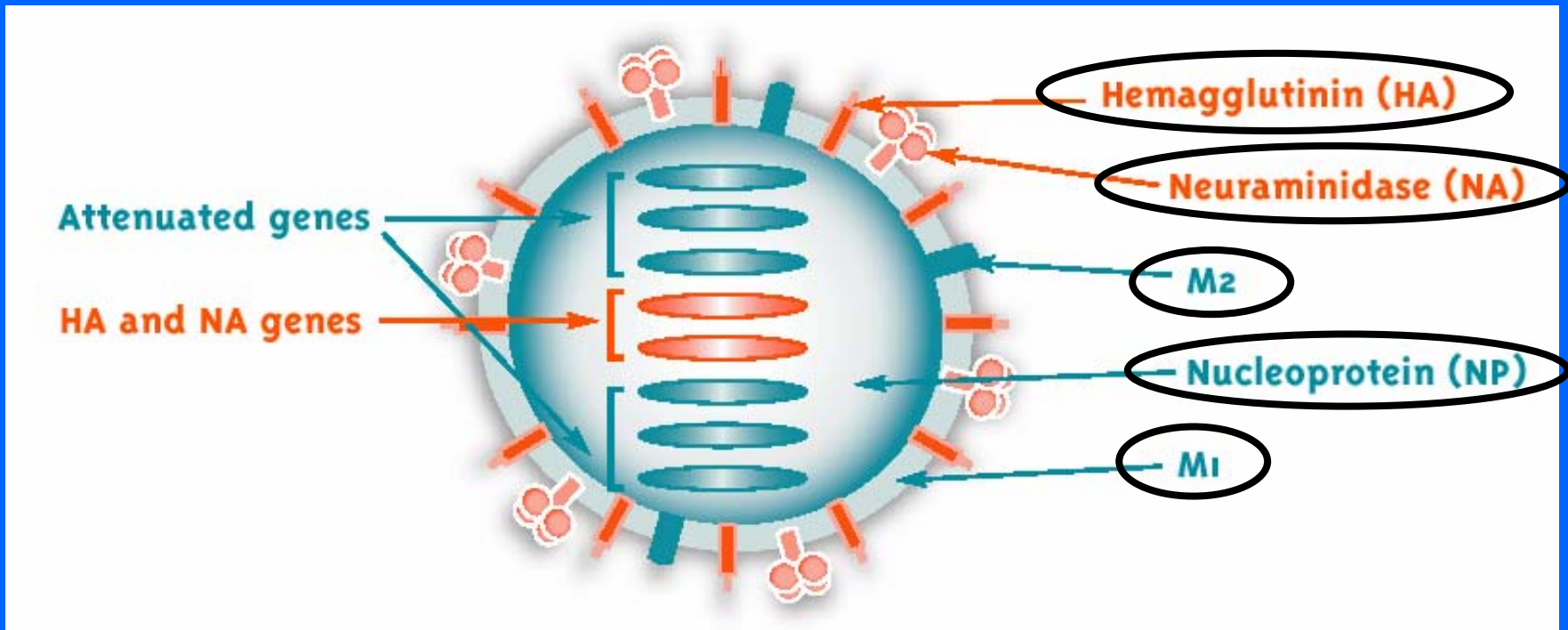


FluMist: Engineered for Safety and Efficacy

- Each of the 3 vaccine strains in FluMist are modified in multiple ways:
 1. Attenuated: weakened so as not to cause influenza-like illness
 2. Cold-adapted: replicates efficiently only in the cooler temperatures of the nasopharynx
 3. Temperature-sensitive: does not replicate efficiently in the warmer temperatures of the lower respiratory tract

FluMist Contains Multiple Antigens

- Contains multiple influenza antigens in their natural configuration



FluMist[®] Herd Immunity Study

- Open-label, nonrandomized community-based trial
- Children 18 months – 18-years-old
- Intervention with FluMist[®]; TIV for children at high risk (~1%)
- Temple-Belton intervention community vs Waco, Bryan and College Station as controls
- Baseline community data 1997-1998, intervention 1998-1999, 1999-2000, 2000-2001
 - N = 4,298, 5,251 and 5,150 respectively; 1 dose of FluMist[®]
- End point: MAARI
 - Including URTI, LRTI, AOM and sinusitis
 - Throat culture, if febrile illness

FluMist[®] Herd Immunity Study: Conclusions

Vaccination of ~20-25% of children
reduced MAARI in adults ≥ 35 years-old by 8-18%

	Reduction in MAARI (1- RR)	95% CI
Year 1	0.08	0.04-0.13
Year 2	0.18	0.14-0.22
Year 3	0.15	0.12-0.19

FluMist™ Effectiveness in Adults

- Double-blind, vaccine:placebo, 2:1 randomization
- N = 4,561 healthy working adults aged 18 to 64 years
- Mismatched A(H3N2) strain
 - Vaccine strain: A/Wuhan/359/95 (H3N2)
 - Circulating strain: A/Sydney/5/97 (H3N2)

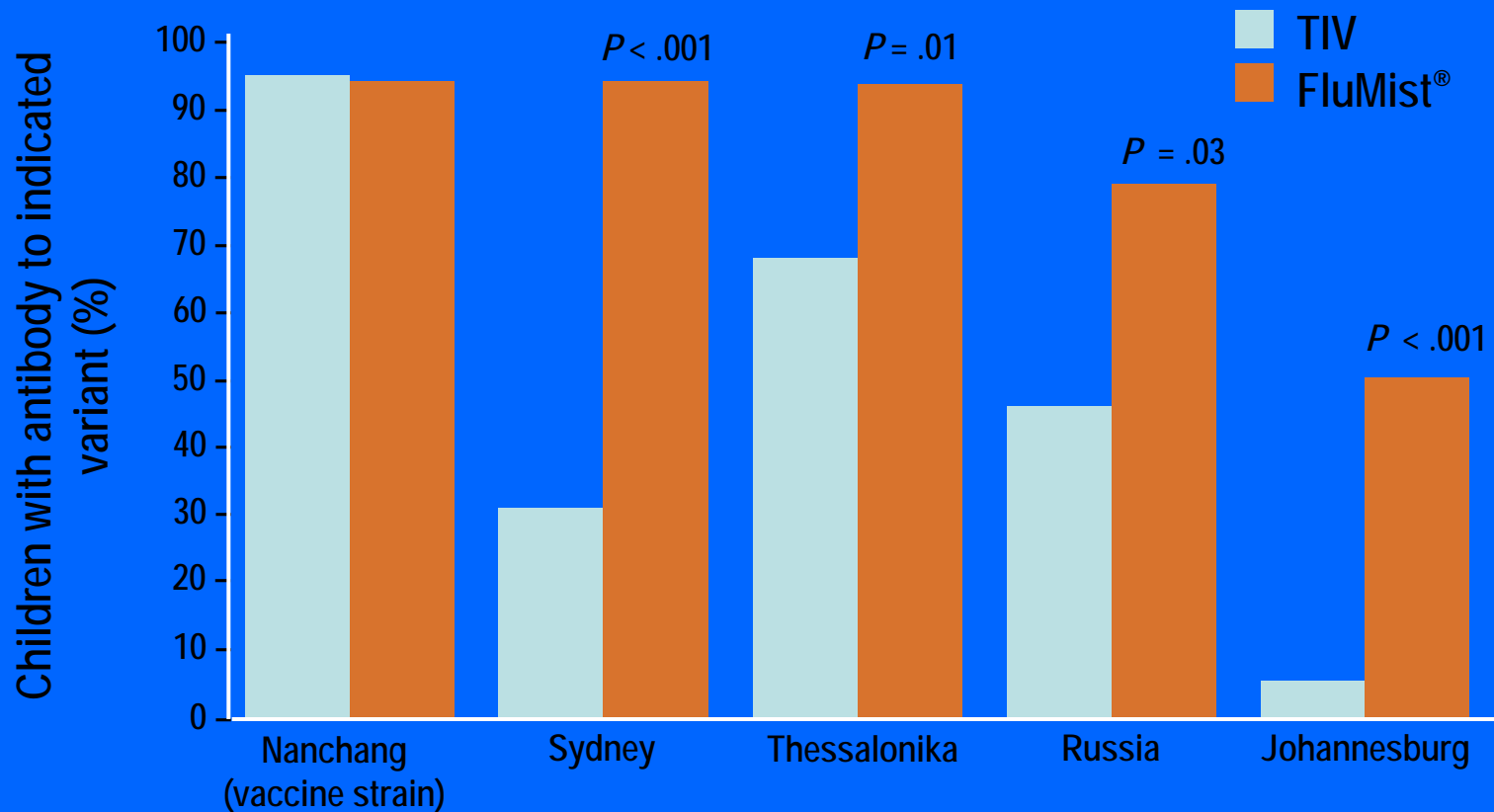
LAIIV Effectiveness in Mismatch Year

Outcomes (vaccine n = 2,833; placebo n = 1,420)	% Reduction	95% CI
Febrile Illness episodes	10.0	-2.1, 20.7 [†]
Severe febrile illness episodes	18.8	7.4, 28.8*
Febrile upper respiratory illness (FURI) episodes	23.6	12.7, 33.2**
- Work missed because of FURI	28.4	16.3, 38.8**
- At least 1 healthcare provider visit for FURI	40.9	30.1, 50.0**
- Taking antibiotics for FURI	45.2	35.2, 53.6**
- Taking over-the-counter medication for FURI	28.0	16.8, 37.7**

[†] not significant, * p=0.002; ** p<0.001

Heterotypic Protection by Influenza Vaccines

More children develop HA antibodies to drifted A(H3N2) variants after immunization with FluMist®



Additional FluMist Safety Data

- Temple Belton Heard Immunity - NIH Funded study
- Reviewed 4 years of safety data in healthy children with specified endpoints (reviewed 4 years prior to licensure)
 - Asthma, SAE's, MAARI
- 42 SAE's identified, none judged to be associated with FluMist
- No increased in HC utilization associated with MAARI
- Increased risk of asthma observed in 1 of 4 years
 - Only in 18 mo-4 yrs of age, 15-42 days after immunization
 - LAIV-T associated with asthma hypothesis not supported by data.

Does FluMist® Transmit from Person to Person?

Definitions

- “Shedding” = the ability to detect virus in respiratory secretions via invasive specimen collection techniques (nasal wash or nasal swab)
- “Transmission” = the spreading of virus from person to person
- “Influenza Like Illness” (ILI) = fever (>100°F, oral), plus either cough or sore throat on the same or consecutive days
- Shedding ≠ transmission ≠ ILI

Finnish Daycare Trial: Transmission of FluMist® Viral Strains

- Randomized, double-blind, placebo-controlled study designed to investigate the likelihood of transmission of FluMist strains from vaccinated to unvaccinated children (worst case scenario)
- 8-36 months olds
 - n=98 FluMist: n=99 placebo
 - Close contact, 4.1 children/playgroup >12h/week
 - Nasal washes samples ~3 per week for 3 weeks
 - Wild type influenza A virus circulated in community

Results

Finnish Daycare Study

- 80% of FluMist® recipients shed vaccine virus
 - 32% H1N1, 12% H3N2, 74% Type B
 - Mean days shedding = 7.6 (range 1-21 days)
- One placebo recipient shed Type B vaccine virus at day 15 visit only-- confirmed to be vaccine virus
- Four placebo recipients shed Type A viruses that were not available for further characterization as vaccine or wild-type strains thus, vaccine strains could not be excluded
- In the day care setting, the probability of transmission was estimated to be 0.6% to 2.4%

Characteristics of Recovered and Transmitted FluMist® Viruses

- Recovered FluMist® viruses
 - Retained ts and ca phenotypes
 - No reversions in attenuating mutations
- Transmitted virus
 - Identical genetic sequence to virus isolate from vaccine recipient in same playgroup
 - Retained the ca, ts, and att phenotype
 - Not associated with increase in adverse events

Risk of Transmission Summary

- Probability of transmission in daycare setting (worst case scenario) very low (0.6% to 2.4%)
- Even lower probability expected in older children and adults (indicated population)
- No documented cases of transmission within indicated population
- No documented transmission events in indicated population
- No concerns regarding reversion
- No documented transmission in adults
- Transmitted FluMist® isolate retained the ca, ts, and att phenotype and was not associated with increase in adverse events

Vaccination of Close Contacts of Persons at High Risk for Complications from Influenza

Close contacts of persons at high risk for complications from influenza should receive influenza vaccine to reduce transmission of wild-type influenza viruses to persons at high risk.

- Use of inactivated influenza vaccine is preferred for vaccinating household members, health-care workers, and others who have close contact with severely immunocompromised persons (e.g., patients with hematopoietic stem cell transplants) during those periods in which the immunocompromised person requires care in a protective environment.
- The rationale for not using LAIV among healthcare workers caring for such patients is the theoretical risk that a live, attenuated vaccine virus could be transmitted to the severely immunocompromised person. If a health-care worker receives LAIV, that worker should refrain from contact with severely immunocompromised patients for 7 days after vaccine receipt. Hospital visitors who have received LAIV should refrain from contact with severely immunocompromised persons for 7 days after vaccination;
- however, such persons need not be excluded from visitation of patients who are not severely immunocompromised. ACIP has not indicated a preference for inactivated influenza vaccine use by health-care workers or other persons who have close contact with persons with *lesser degrees* of immunodeficiency (e.g., persons with diabetes, persons with asthma taking corticosteroids, or persons infected with HIV) or for inactivated influenza vaccine use by health-care workers or other healthy persons aged 5–49 years in close contact with all other groups at high risk.

Case Study I

- **Ms Johnson is a 31 YO nurse in her 2nd trimester of pregnancy presenting in mid-Jan w/ 3 days of febrile, URI symptoms.**
 - **Has missed 2 days of work due to illness**
 - **Last week missed 2 days of work due to ill child**
 - **She is feeling miserable and knows that her absence from work has resulted in mandatory overtime for others at the hospital. She is desperate to feel better so that things at home can get back on track and she can return to work.**

Case Study II

- **Last week her 8 yo child was ill with fever, runny nose, cough & diarrhea (rapid test – positive)**
 - **Child could not attend school and had to stay home for 3 days**
 - **66 YO grandmother came over to care for the child 2 days (she does this frequently), mother covered other 1 day (husband is out of town)**
 - **Over the week-end, child developed otitis media, was seen in urgent care & given antibiotics**
- **No one in the family has received an influenza vaccination**

Case Study III

- **On exam, Ms Johnson has a low-grade fever, non-productive cough, and mild pharyngeal injection.**
- **Recent reports from the health dept indicate that influenza is widely circulating.**
- **Physician makes a diagnosis of influenza & prescribes rest, fluids, and analgesics for symptoms.**

Case Study IV

- **Follow-up**
 - **Child recovered uneventfully (s/p abx and missed school)**
 - 22% of classmates were out sick w/in 10 days of event
 - **Ms Johnson returned to work the next day**
 - Still having some symptoms for another 3 days
 - 1 other nurse became ill 4 days later and missed 2 days of work
 - **Grandmother developed fever, myalgia and cough 4 days after watching grandson.**
 - Hospitalized x 1 week
 - Required 2 weeks of additional care in home setting to return to ADL