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Strengthening our Defense Against Influenza: The LAIV Option

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25 September 2008

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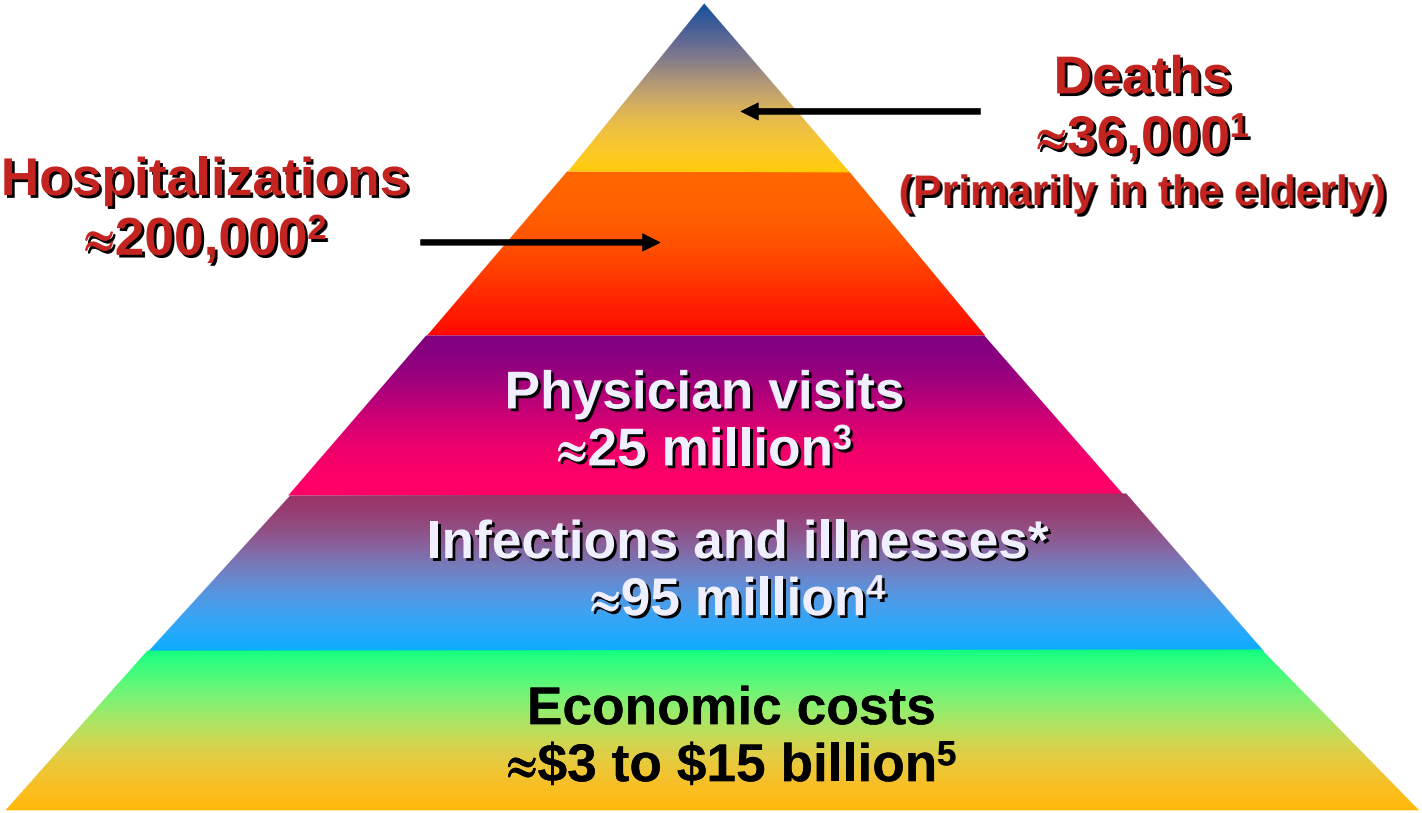
Vaccine-Preventable Disease is Unacceptable for Influenza in the US

Diseases	Estimated Annual Cases	Average Annual Deaths
Influenza[1]	**31,000,000**	**38,000**
Hepatitis B[2,3]	78,000	5000
Hepatitis A[2]	93,000	100
Varicella[4]	67,400	54
Pneumococcal disease[2]	175,000	5500
Meningococcal disease[2]	2500 - 3000	150
Pertussis[5]	800,000 - 3,300,000	7
HPV[6,7]	6,200,000	4000

1. Weycker D, et al. *Vaccine*. 2005;23:1284. 2. CDC. *Pink Book*. 8th Edition. 2005. 3. American Liver Foundation. Hepatitis and Liver Disease in the United States. Available at http://www.liverfoundation.org. Accessed April 2005. 4. CDC. *MMWR*. 2005;52:73. 5. Cherry JD. *Pediatrics*. 2005;115:1422. 6. CDC. Genital HPV Infection – CDC Fact Sheet. Available at www.cdc.gov/std/HPV/STDFact-HPV.htm. Accessed June 2005. 7. American Cancer Society. *Cancer Facts and Figures 2005*.

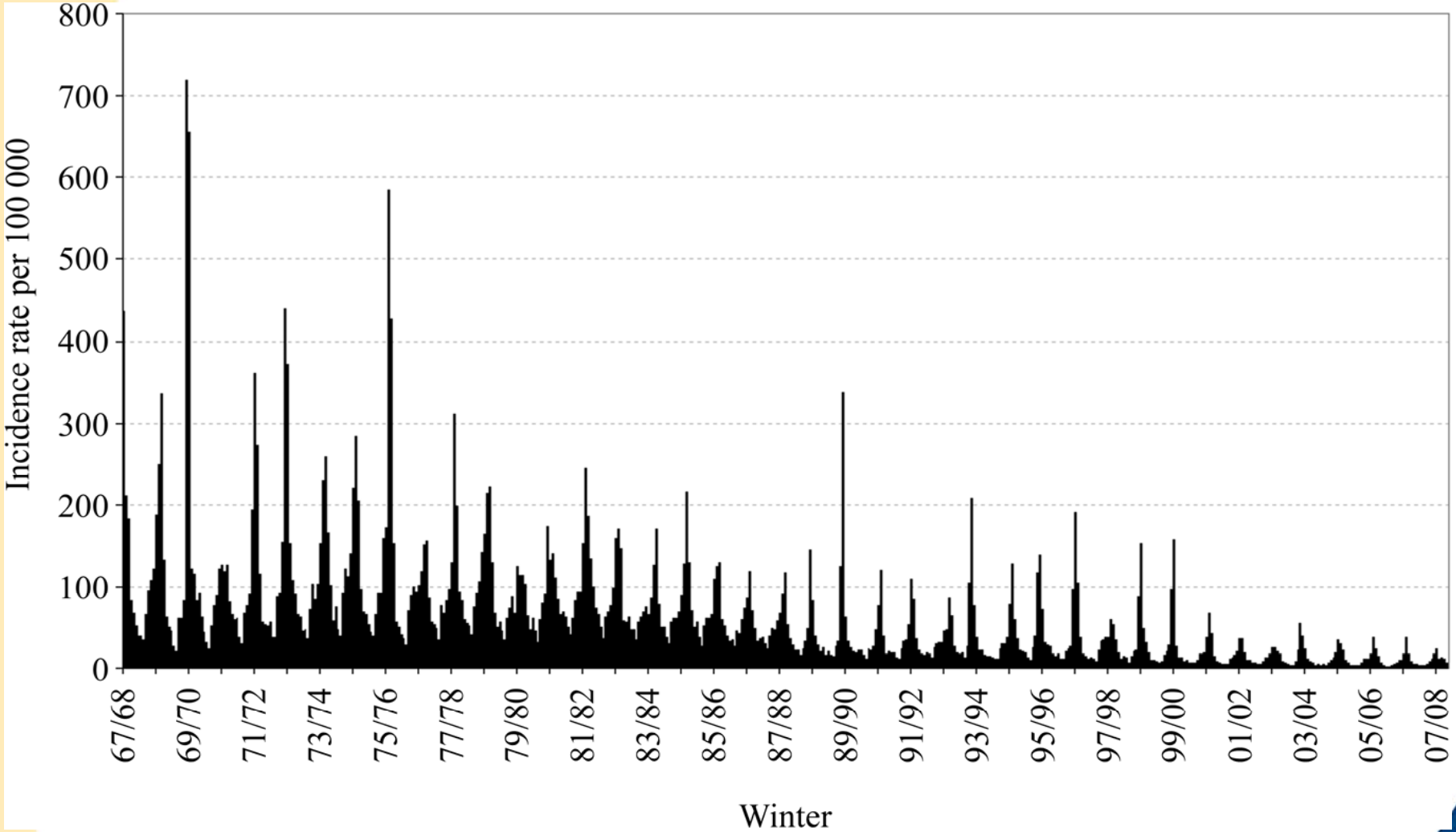
The High Annual Toll of Influenza Disease in the United States



***According to the CDC National Health Interview Survey, individuals may have more than 1 influenza illness annually**

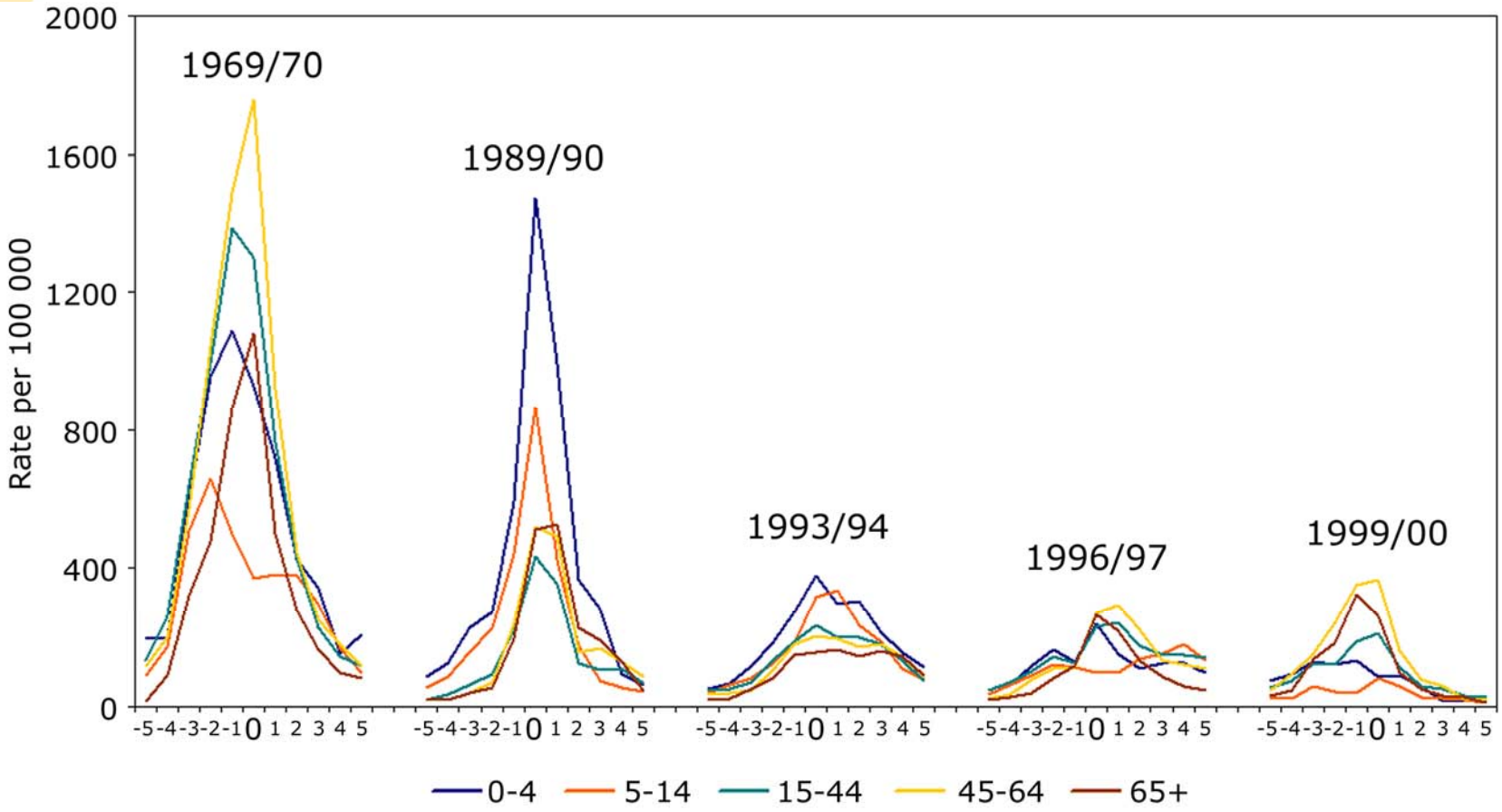
1. Thompson WW et al. *JAMA*. 2003;289:179-186.
2. CDC website.
3. Couch RB. *Ann Intern Med*. 2000;133:992-998.
4. Adams PF et al. *Vital Health Stat 10*. 2005;224:1-104.
5. Szucs TD. *Pharmocoeconom*. 1999;16(suppl 1):27-32.

Influenza like illness: mean weekly incidence: 1967/68 - 2007/08



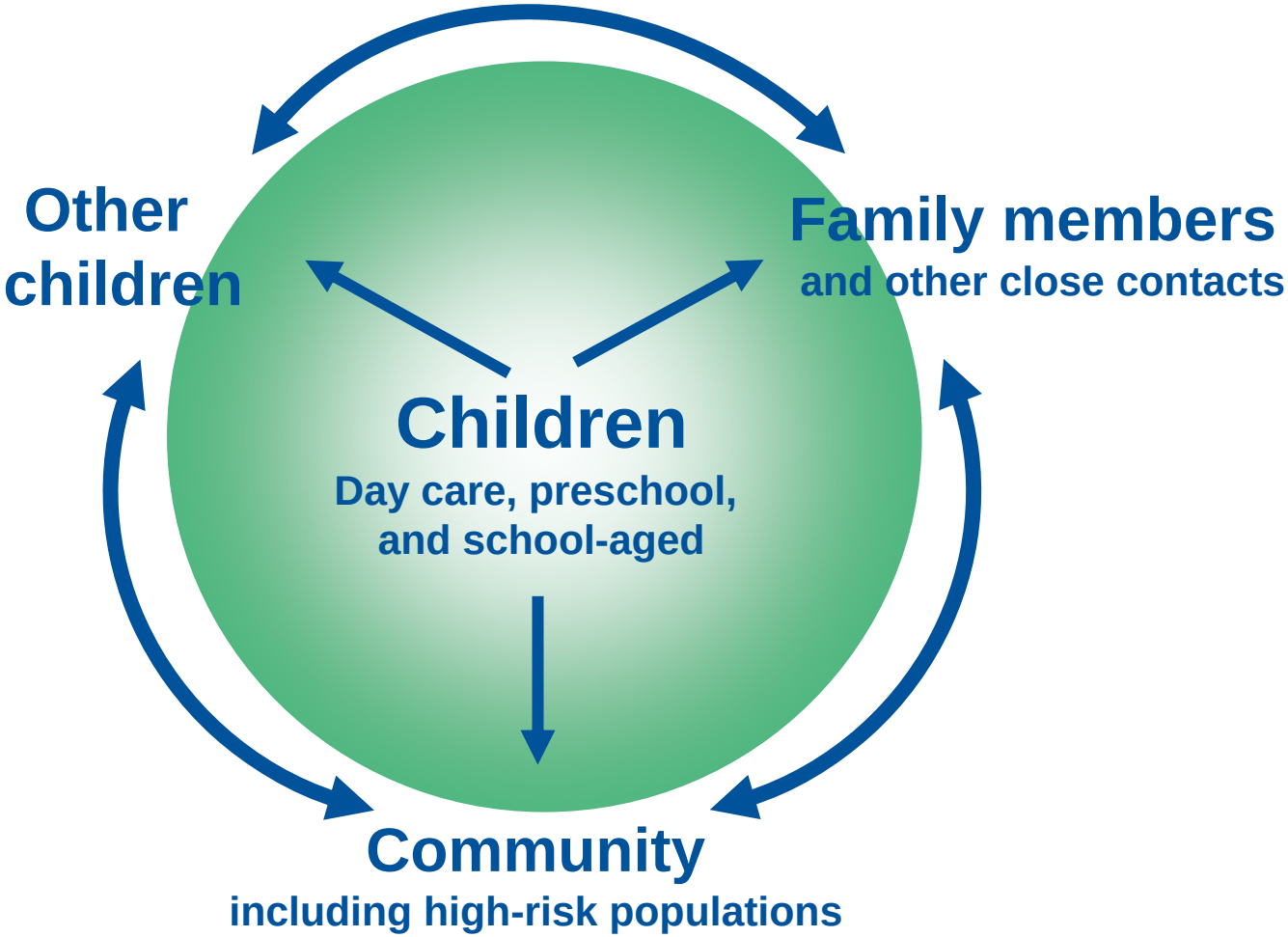
Source: Elliot AJ & Fleming DM *Eurosurveil* (2007); **11**(10): 249-50

Incidence of ILI by age in influenza H3years (courtesy D. Fleming)



Elliot AJ *et al. Options for the Control of Influenza VI* (2007) Abstract 124

Children are Primary Vectors



1. Glezen WP, et al. *N Engl J Med*. 1978;298:587-592.
2. Weycker D, et al. *Vaccine*. 2005;23:1284-1293.

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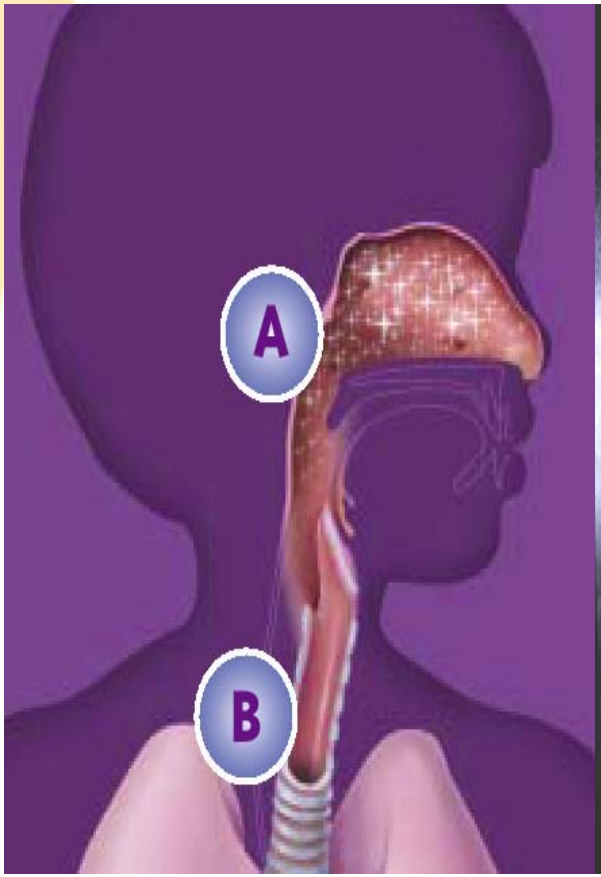
Disclaimer

- This presentation contains discussion of MedImmune's proprietary live attenuated influenza virus vaccine (LAIV).
- LAIV has been approved by the United States Food and Drug Administration since 2003.
- **LAIV has not been registered and is not available outside of the United States.**

Live, Attenuated, Intranasal Influenza (LAIV) Vaccine

A. Cold adapted

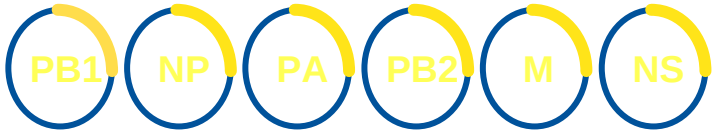
Large particle fine mist spray



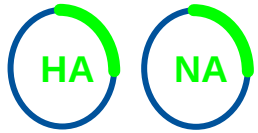
B. Temperature Sensitive, Attenuated

Manufacturing Master Vaccine Strains

Master Donor Virus Plasmids



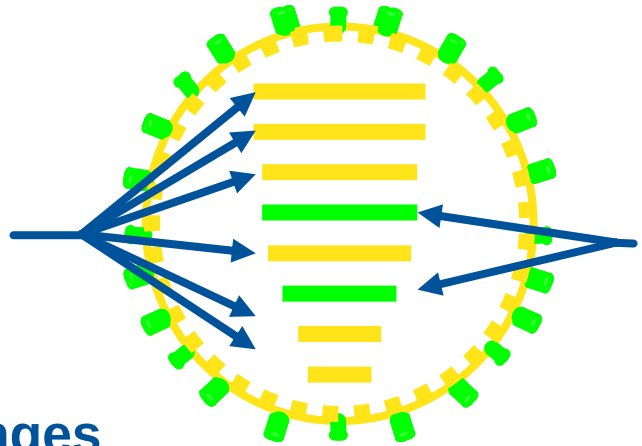
New Wild Type Strain Plasmids



Electroporate Vero Cells

Only One Possible Combination

Six MDV genes:
Cold adapted,
Temperature sensitive,
Attenuated,
19 amino acid changes



Hemagglutinin and Neuraminidase Genes from Wild Type for immunity

6:2 Master Virus Strain

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LAIV Is Engineered Not to Cause Disease

- Each of the 3 vaccine strains in LAIV is[1]
  - Attenuated
    - > Weakened so as not to cause influenza-like illness
  - Cold adapted
    - > Replicates efficiently in the cooler temperatures of the nasopharynx
  - Temperature sensitive
    - > Does not replicate efficiently in the warmer temperatures of the lower respiratory tract
- Odds of reversion to wild-type are 1 in 10^{20} replication cycles[2,3]

1. FluMist [prescribing information]. Gaithersburg, MD: MedImmune Vaccines, Inc.; 2007.
2. Smith DB et, al. *J Gen Virol*. 1987;68:2729-2740.
3. Data on file. MedImmune, Inc.

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Registration Status

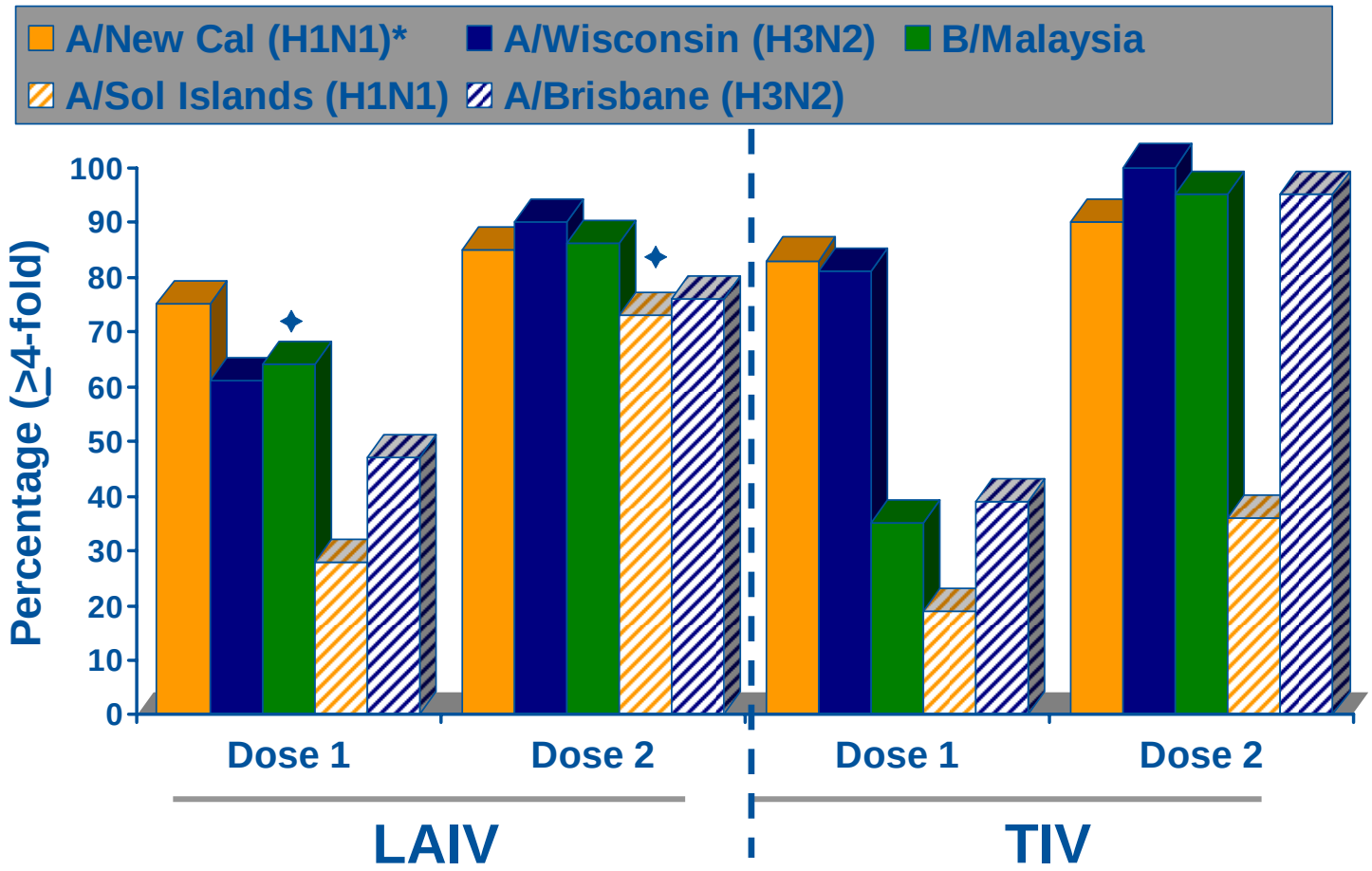
- **U.S. indication:** Prevention for ages 2-49 yrs
  - 2003: Frozen formulation licensed for ages 5-49 yrs
  - 2007: Refrigerated formulation licensed and age expanded to 2-49 years of age
  - 10MM Doses Distributed through 07/08 Season
- **E.U. registration:** Submission planned 4Q08
- **Global registrations**: Future submissions planned

LAIV: Clinical Program Summary

Encompasses data from:

- 54 completed clinical studies of both frozen and refrigerated formulations
- > 46,000 subjects from 6 weeks to >90 years who received 10^7 $TCID_{50}$ or FFU dosage
  - > 7,500 adults 18 to >90 years of age
  - > 13,000 children 6 to <18 years of age
  - >14,000 children 24 months to 5 years of age
  - > 9,000 toddlers 12 to <24 months of age
  - > 1,900 infants 6 weeks to <12 months of age

Serum HAI Responses: Seroconversion Rates in Seronegative Children

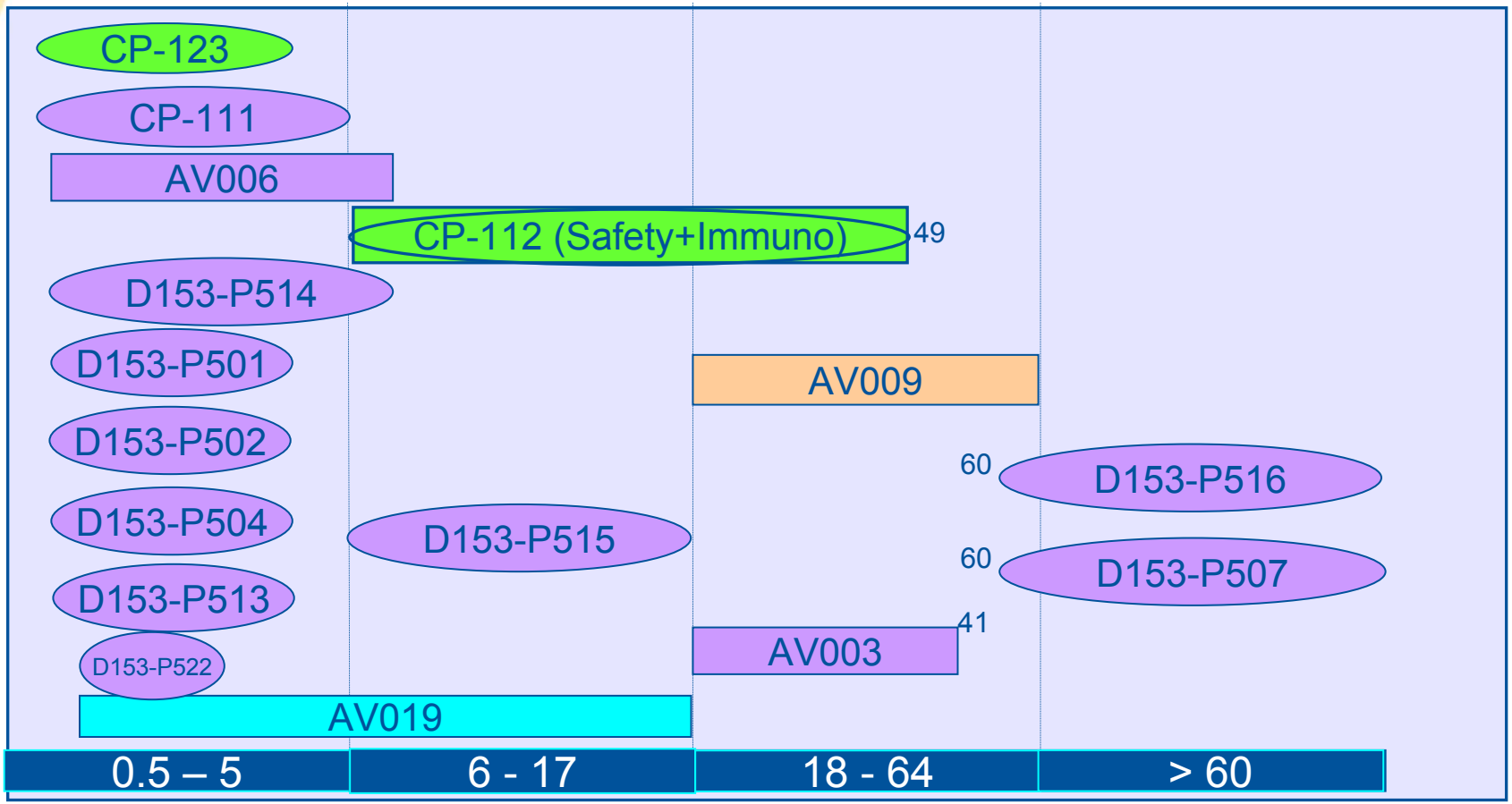


*Each vaccine tested with vaccine-like antigen (ca vs. wt)

✦Statistically Significant

Vaccine Strains shown in solid bars
Mismatched Strains shown in hashed bars

Overview of Key LAIV Clinical Studies



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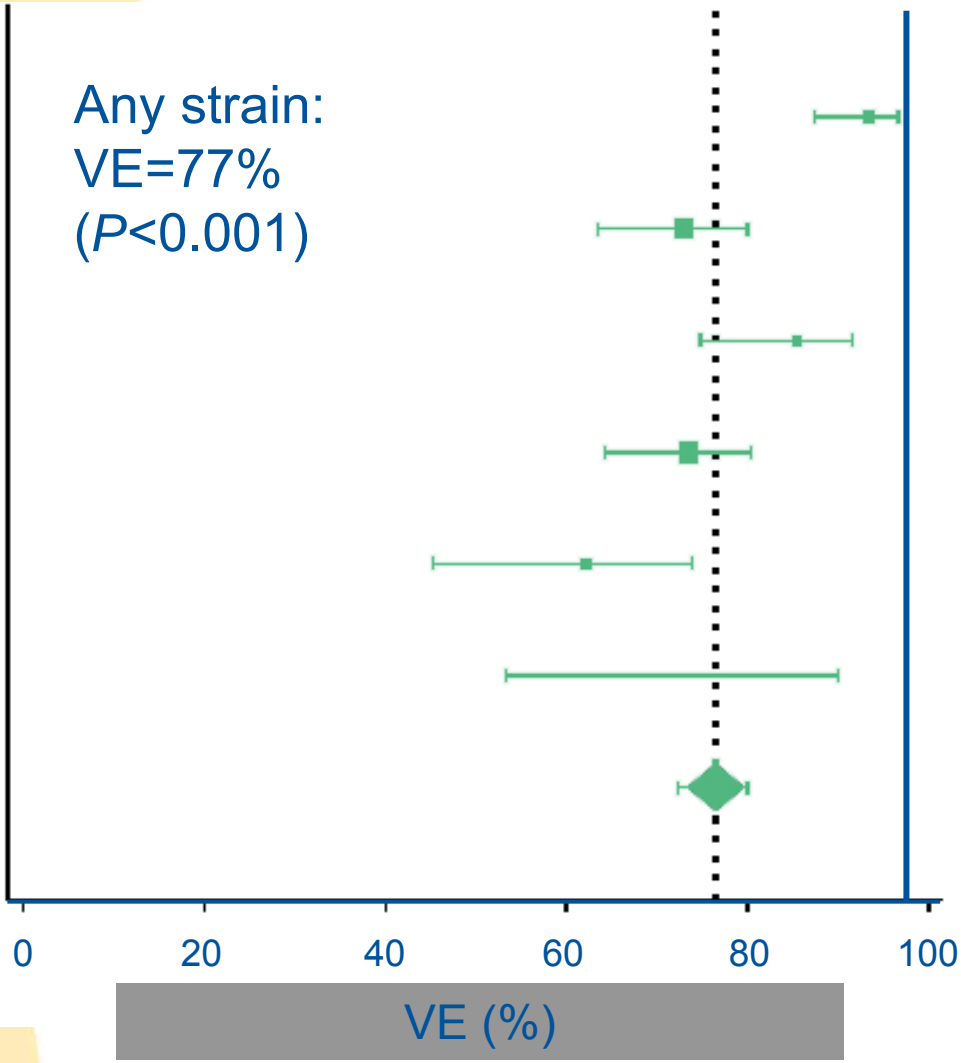
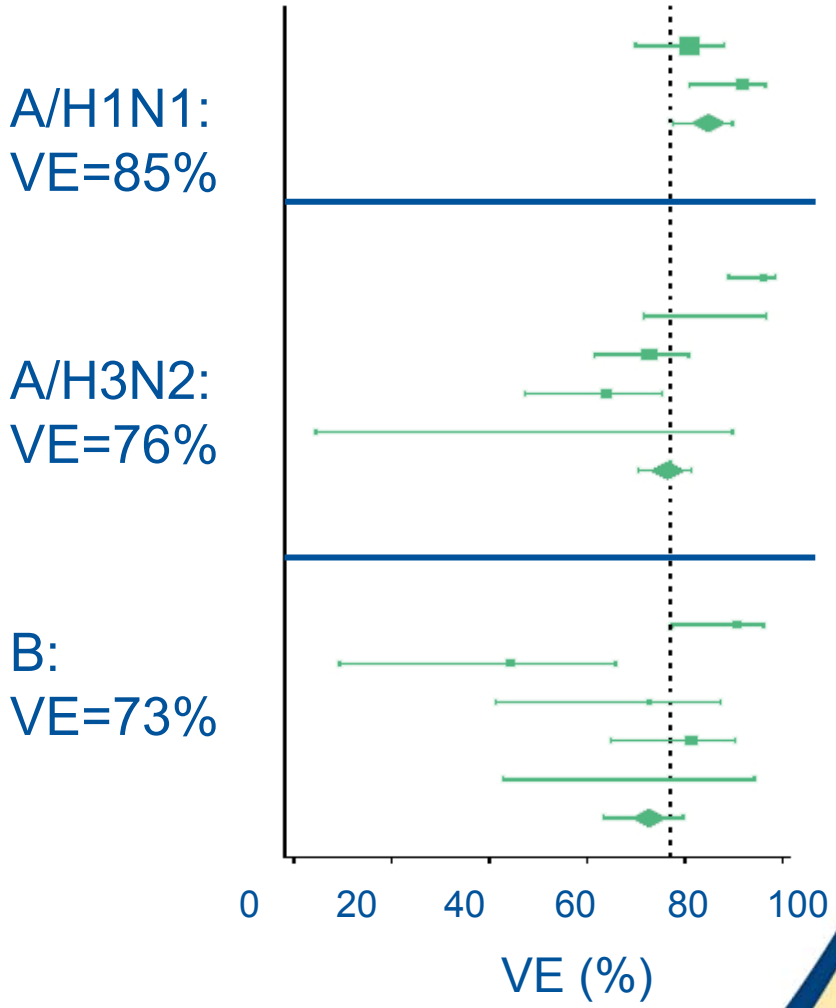
Pediatric Meta-Analysis

- 9 RCT of LAIV in children between 1997 and 2005
  - 6 placebo controlled
  - 3 TIV controlled
- Asia, Europe, Middle East, South America, US
- Each trial involved at least 1000 children
- Mostly healthy children with no prior influenza vaccination
  - 25,000 children aged 6 to 71 months
  - 2000 children aged 6 to 17 years
- Many different strains circulated
- Outcome: rates of culture-confirmed influenza

Rhorer et al. 2007 ESPR abstract

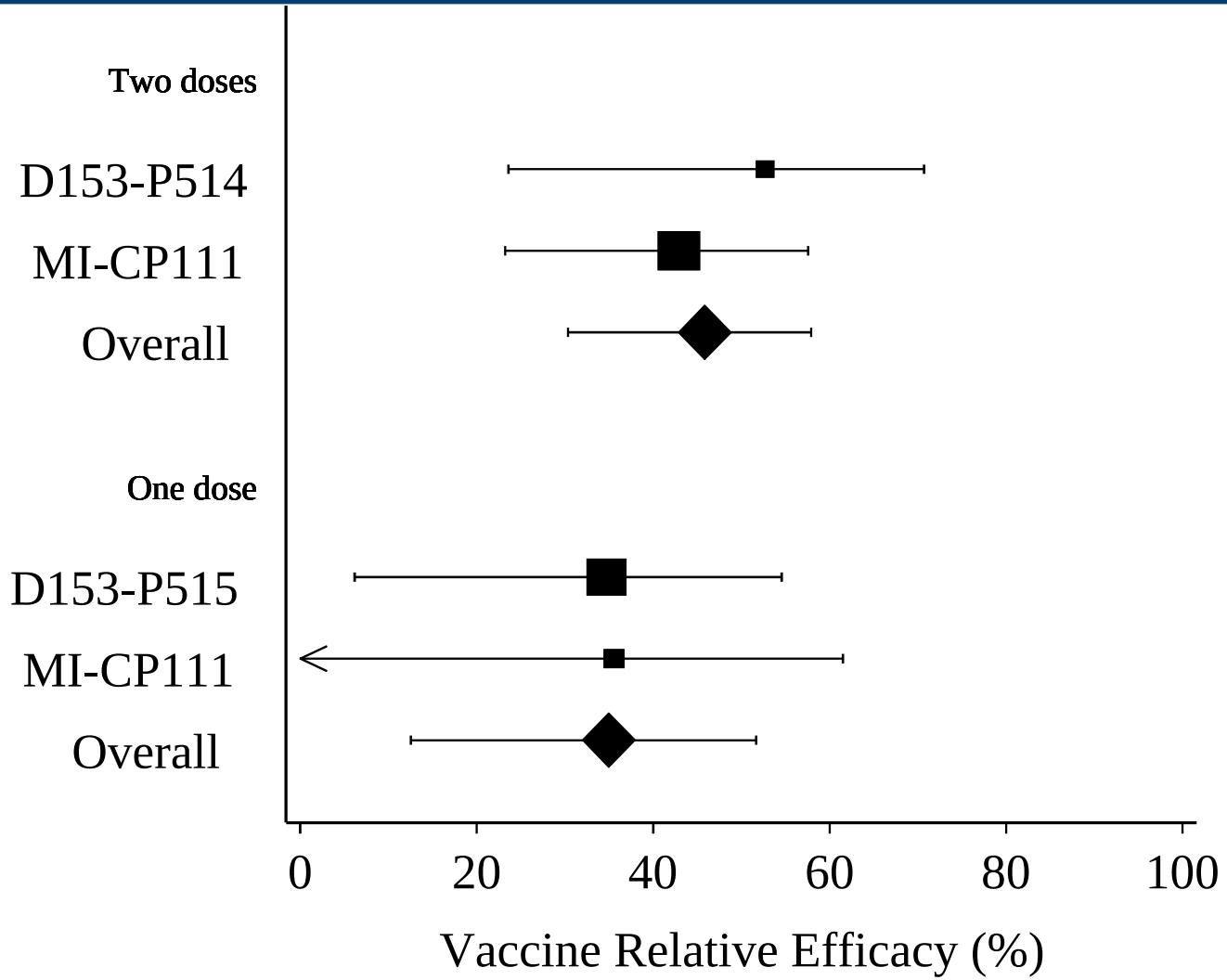
Vaccine Efficacy Against Placebo By Strain (Two Doses)





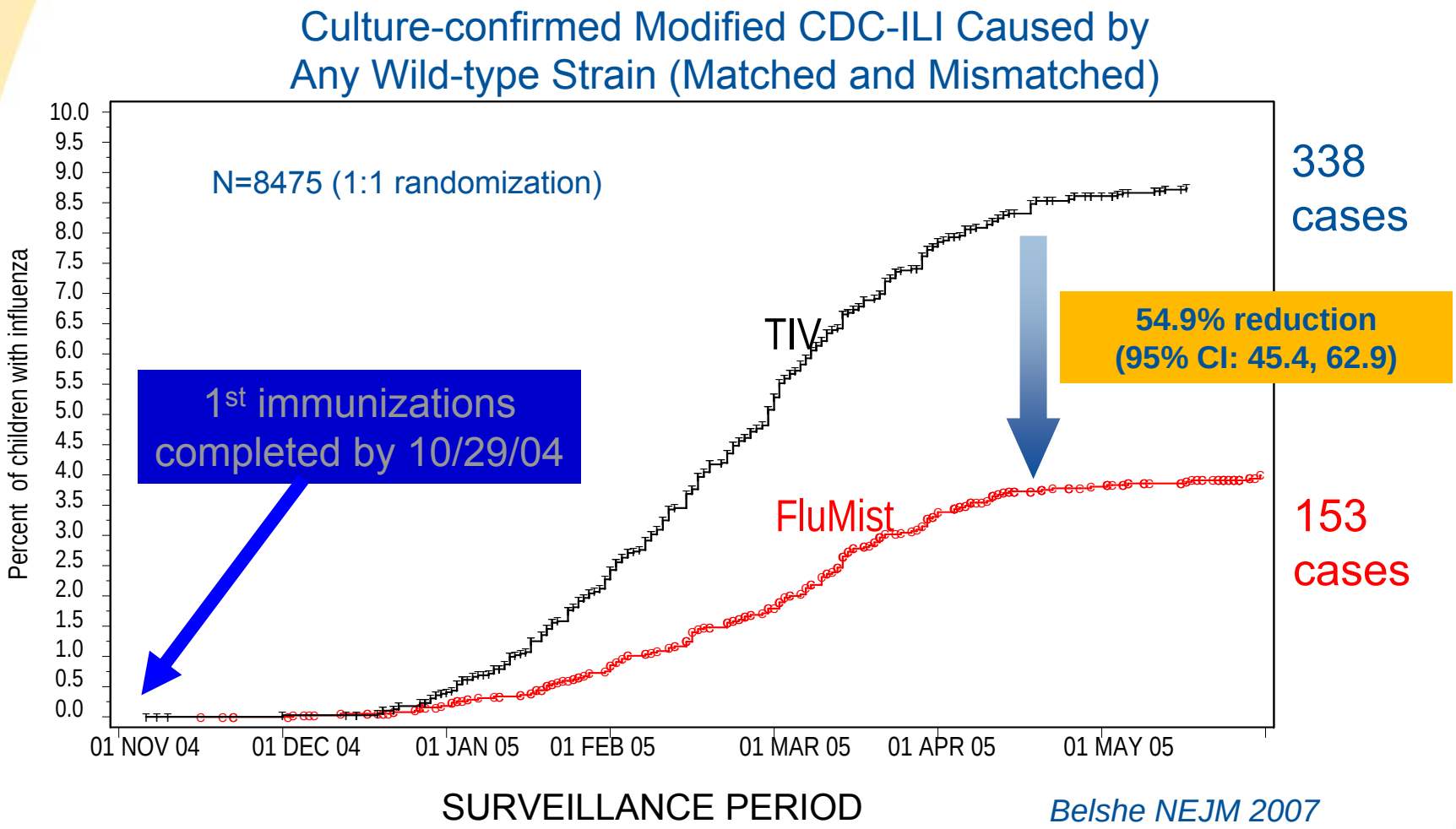
Rhorer et al. 2007 ESPR abstract

LAIV vs. Injectable Vaccine (TIV)
3 Studies in Children



Rhorer et al. 2007 ESPR abstract

LAIV: Reduced Cases of Influenza vs. TIV in Children 6-59 Months of Age in Study MI-CP111



Belshe NEJM 2007

Summary of Solicited Events in Children Aged 2 to 6 Years

- LAIV safety profile generally comparable to the flu shot and placebo in over 7,000 children studied

Event	Placebo studies 2 years to 6 years of age[1-2]		Active-controlled study 2 years to 5 years of age[3]	
	LAIV (N=876-1,764) %	Placebo (N=424-1,036) %	**LAIV** (N=2,170) %	Flu shot (N=2,165) %
Runny nose/nasal congestion*	58	50	51	42
Decreased appetite	21	17	13	12
Irritability	21	19	12	11
Decreased activity (lethargy)	14	11	7	6
Sore throat	11	9	5	6
Headache	9	7	3	3
Muscle aches	6	3	2	2
Chills	4	3	2	2
Fever*				
100º-101ºF Oral	9	6	6	4
101º-102ºF Oral	4	3	4	3

*Most common adverse reactions (≥10% in FluMist and at least 5% greater than in control) are runny nose or nasal congestion and fever >100°F in children 2-6 years of age and sore throat in adults.

Studies reflect the data collected between 2 pooled studies and 1 active-controlled study

1. Belshe RB, et al. *N Engl J Med.*1998;338:1405-1412
2. Tam J, et al. *Pediatr Infect Dis J*. 2007;26:619-628.
3. Belshe RB, et al. *N Engl J Med*. 2007;356:685-696.
4. Data on file. MedImmune, LLC.
5. FluMist [prescribing information]. Gaithersburg, MD: MedImmune Vaccines, Inc; 2007.

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LAIV: Safety Observations in Children

- **40 studies evaluated the safety and tolerability of LAIV in children 2 years of age:**
  - Solicited events and adverse events were mostly mild and transient upper respiratory and systemic symptoms
- **Study MI-CP111:**
  - Rates of medically significant wheezing were higher in LAIV vs. TIV in children 6-23 months (pre-specified analysis)
  - A trend towards increased hospitalization was observed in children 6-23 months, driven mostly by those <12 months
  - An increase in medically significant wheezing was not observed in children 24 to 59 months, and there was no trend towards increased hospitalization in this age group

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LAIV: Summary of Pediatric Studies

- 6 placebo controlled studies
  - Results similar across age, strain, population analyzed
- Reductions in cases of influenza vs. TIV seen in all 3 TIV-controlled studies conducted in 2 different seasons
- Reduced cases of influenza in second season revaccination studies (87% efficacy in mis-matched year)
- Cross-protection demonstrated against mismatched (overall attack rate of 3.2 vs. 7.1 with TIV; 54% reduction)
- Mild, self limited reactogenicity
- Limited use in young asthmatics/persistent wheezing

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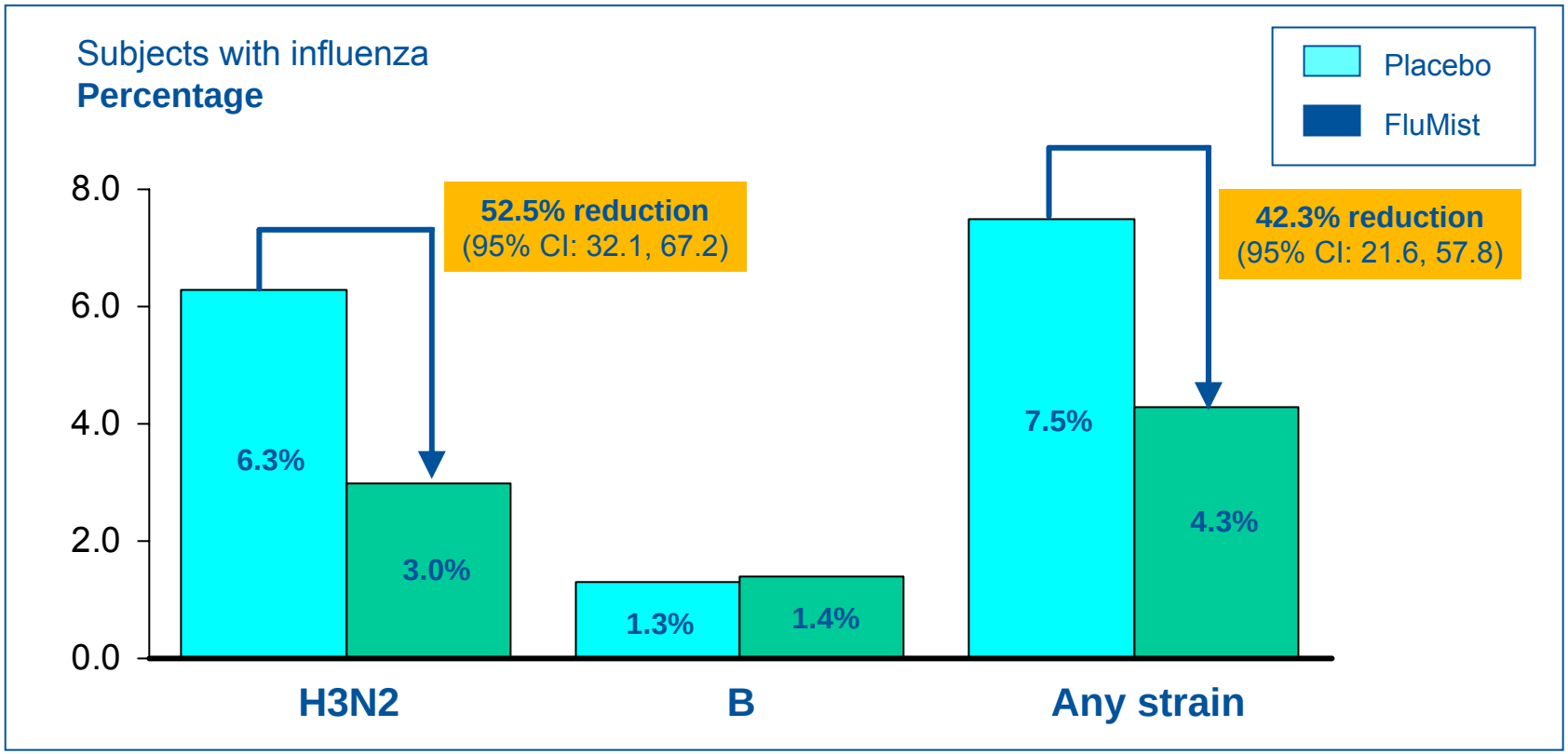
LAIV in Adults

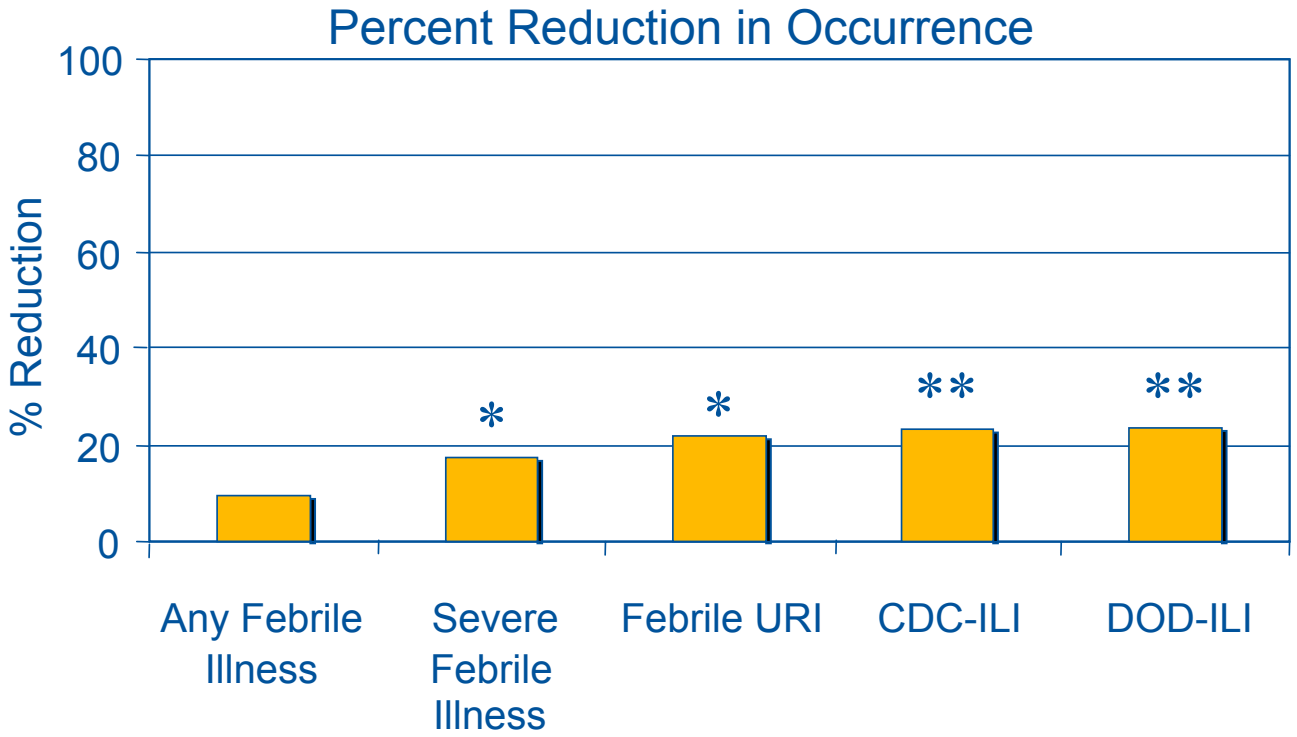
LAIV: D153-P507 Placebo Controlled Efficacy Study in Adults

- Double blind, randomized (1:1), placebo controlled study
- 3,242 adults ≥60 years of age (mean age 70; range 60-98)
- Conducted in South Africa in 2001



LAIV: Results Against Influenza-like Illness in Study AV009 in Adults

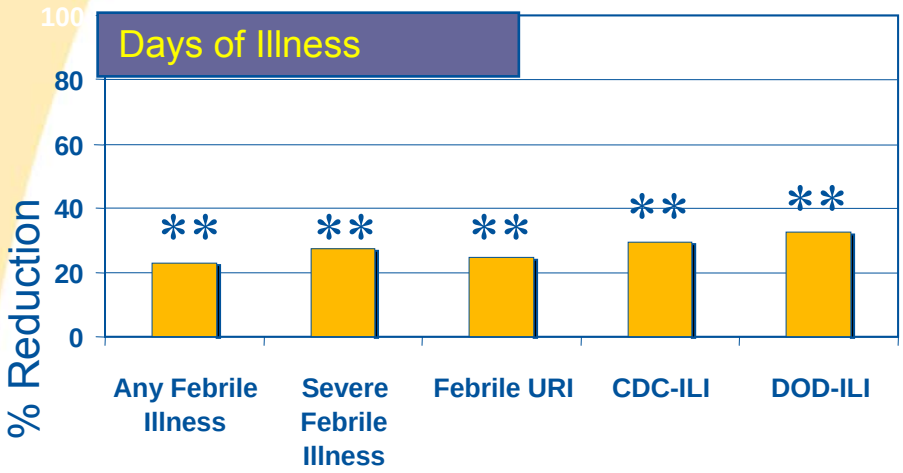
- No significant reduction in “Any Febrile Illness” endpoint
- Significant reductions in more influenza-specific syndromes

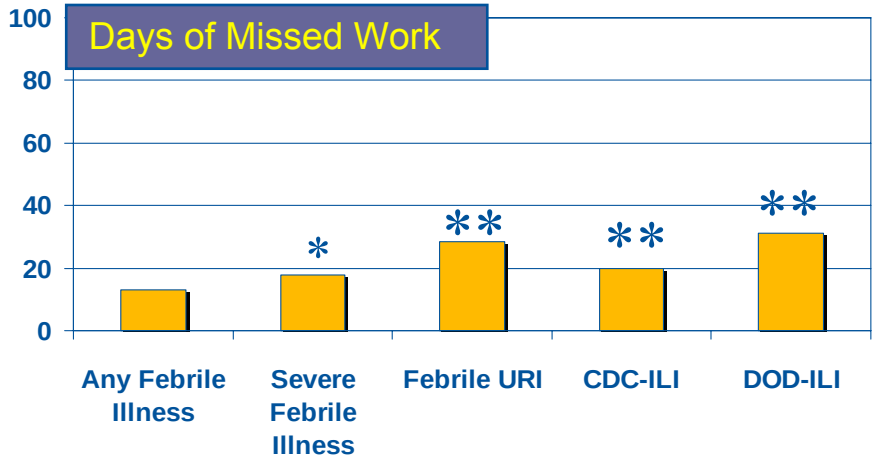


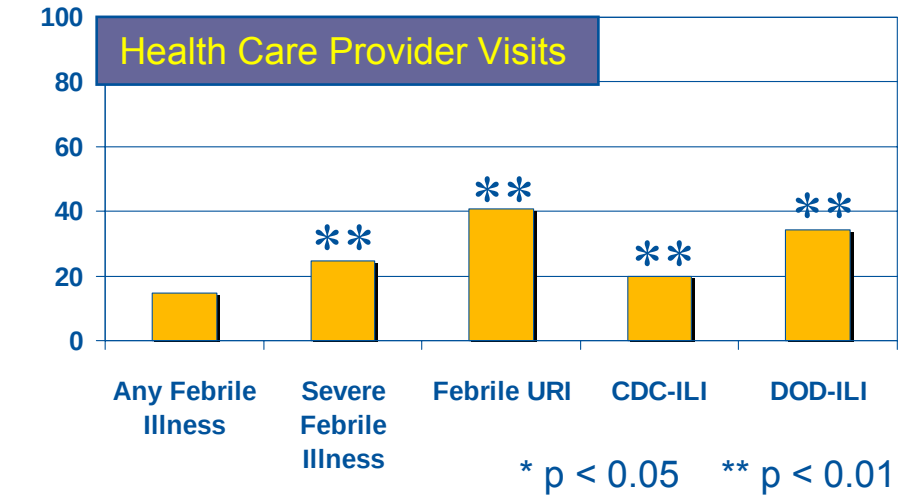
Nichol J Amer Med Assoc 1999

* $p < 0.05$ ** $p < 0.01$

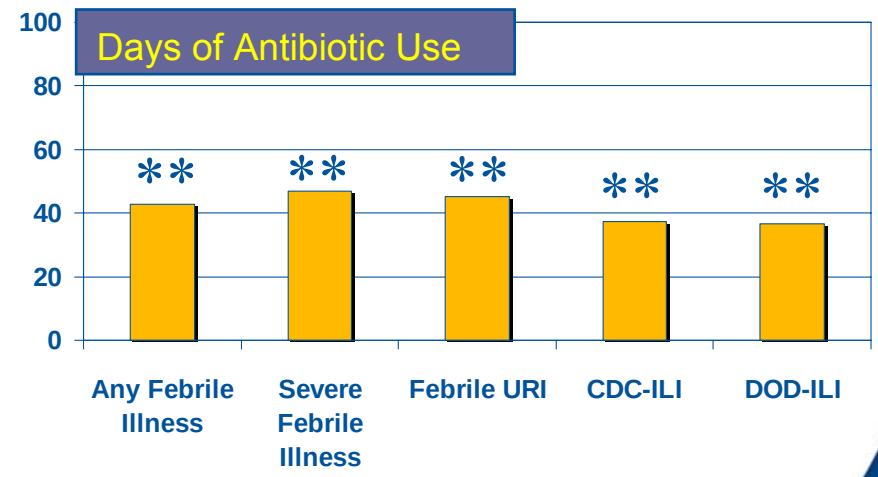
LAIV: Observations of Health Economic Endpoints in Adult Study AV009







* $p < 0.05$ ** $p < 0.01$



Nichol J Amer Med Assoc 1999

LAIV Safety and Tolerability in Adults

Summary of solicited adverse events in healthy adults aged 18 years to 49 years

Event	LAIV (n=2,458) %	Placebo (n=1,290) %
Runny nose*	44	27
Headache*	40	38
Sore throat*	28	17
Tiredness/weakness	26	22
Muscle aches	17	15
Cough	14	11
Chills	9	6

Summary of solicited events reported within 7 days of either vaccine or placebo (normal egg allantoic fluid) administration in healthy adults 18 years to 49 years of age.

All solicited events were transient.

*Most common adverse reactions (occurring at ≥10% in individuals receiving FluMist and at least 5% greater than in placebo) are runny nose or nasal congestion in recipients of all ages, fever >100°F in children 2-6 years of age, and sore throat in adults.

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School-based (Post-licensure) Reduction in Family Burden of Influenza

- Multicenter (4 states) cluster randomized, open-label school based community intervention trial (2004-05 Season)
  - 11 target schools: LAIV offered free to students (46% received it)
  - 17 control schools: LAIV not offered
- Significant direct & indirect benefits for families in target schools:
  - Children:
    - > 23% reduction in Influenza-Like-Illness (ILI)*
    - > 38% reduction in ILI-related elementary school days missed
  - Adults:
    - > 27% reduction in ILI
    - > 25% reduction in ILI-related work days missed by adults
  - Overall 38% reduction in ILI-related prescription medications

*ILI defined as fever or symptoms of runny nose, nasal congestion, sinus problems, earache, ear infection, cough, sore throat, muscle aches, chills, or wheezing. *King JC, et al. N Engl J Med. 2006;355:2523-2532*.

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Post Licensure Study to Help Define Extent of Off Label Use

- This is a retrospective descriptive cohort study of four dynamic cohorts conducted with health insurance claims data
- Children are screened for vaccination and type of influenza vaccine (Intranasal vs. Injectable) provided through routine practice
- LAIV use monitored from August through January for three influenza vaccination seasons
- Data for each cohort is screened over 20.5 month period
  - 7 months of the influenza vaccination season
  - 12 months prior to the influenza vaccination season (obtain Hx)
  - 1.5 months of follow-up after influenza vaccination

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Interim Data:

Incidence per 10,000 Child-Days of Vaccination With LAIV or With Inactivated Influenza Vaccine (TIV) in the Four Cohorts

Cohort (Subpopulation)	Number of Child-Days	LAIV		TIV Vaccination		Unknown Influenza Vaccine	
		n[a]	Incidence Rate[b] (95% CI)	n[a]	Incidence Rate[b] (95% CI)	n[a]	Incidence Rate[b] (95% CI)
Aged < 24 months	24,759,557	65	0.026 (0.020-0.033)	64,034	25.9 (25.7-26.1)	2,735	1.10 (1.06-1.15)
Aged 24-59 months, with claim for asthma	2,375,191	155	0.65 (0.55-0.76)	6,912	29.1 (28.4-29.8)	260	1.09 (0.97-1.24)
Aged 24-59 months, without any claim for asthma and receiving medication for wheezing	1,249,068	161	1.29 (1.10-1.50)	3,258	26.1 (25.2-27.0)	106	0.85 (0.69-1.03)
Aged 24-59 months, with claim for immunosuppression	79,734	5	0.63 (0.20-1.46)	275	34.5 (30.5-38.8)	21	2.63 (1.63-4.03)

n = number of children contributing to the numerator for each cohort; TIV = trivalent inactivated influenza vaccine.

[a] Number of vaccinated children.

[b] Incident rate per 10,000 child-days.

Note: Incidence = number of children vaccinated divided by number of child-days.

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Can Shedding or Transmission of LAIV Lead to Illness?

- "In rare instances, shed vaccine viruses can be transmitted from vaccine recipients to nonvaccinated persons. However, serious illnesses have not been reported among unvaccinated persons who have been infected inadvertently with vaccine viruses"[1]

- A study of 197 children aged 9 to 36 months in close contact in a day care setting demonstrated a vaccine virus transmission rate of only 0.58% to 2.4%.
  - One single confirmed case:[2,3]
  - The transmitted virus did not revert to wild-type[2,3]
  - The child exhibited a mild cough and runny nose, but showed no other reactogenicity events or safety concerns[2]

1. CDC. *MMWR.* 2007;56(RR-6):1-54.
2. Vesikari T, et al. *Pediatr Infect Dis J.* 2006;25:590-595.
3. FluMist [prescribing information]. Gaithersburg, MD: MedImmune Vaccines, Inc.; 2007.

Finnish Day Care Study: Transmission of Live, Attenuated Influenza Virus Strains

- Randomized (1:1), double-blind, placebo-controlled[1]
- N=197 children aged 9 to 36 months attending day care[1]
- Nasal cultures on the first 2 days after dosing and at least 3 times per week for 3 weeks[1]

Transmission in Finnish Day Care Children[2]	Probability (95% CI)*	Comments
1 confirmed Type B	0.58% (0%-1.7%)	1 of 11 swabs positive (Day 15). Retained *ts, ca, att* phenotypes of the vaccine strain
4 unconfirmed A strains plus 1 confirmed B	2.4% (0.13%-4.6%)	Samples not available for further characterization

*Reed-Frost Model.

1. Vesikari T, et al. *Pediatr Infect Dis J.* 2006;25:590-595.

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LAIV: Summary

- LAIV has been evaluated in children ≥1 year of age, in adolescents, and in adults
- Efficacy in both placebo and active control studies
- Cross-protection demonstrated against mismatched A/H3N2
- Needle-free, intranasal administration is convenient
- 4 years of post marketing experience in the U.S. shows consistent safety profile (> 10 million doses distributed)

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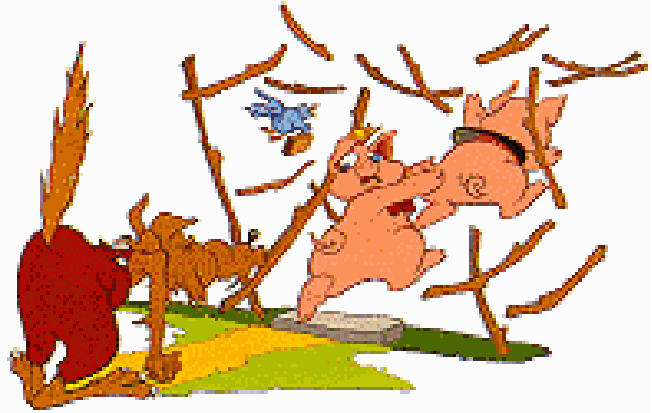
Options for Influenza Prevention



House of Straw

- Current Recommendations
  - Elderly, high risk, children in some countries
- Current Vaccine Options
  - Injectable ± adjuvant
- Current Reimbursement
- Current Utilization
  - Variable % uptake
- Current Public Awareness
  - Not priority

House of Sticks

- Expanding Recommendations
  - All children to 3 years?
- More Vaccine Options
  - Adding LAIV (for those eligible)
- Expanded Reimbursement
- Expanded Utilization
- Expanded Public Awareness

House of Bricks

- Optimal Recommendations
  - All ages
- Optimal Vaccine Options
  - New vaccines
- Optimal Reimbursement
  - Complete
- Optimal Utilization
  - Target 100%
- Optimal Public Awareness