

***FluMist Delivery System: the First
Nasal Vaccine in the U.S.***

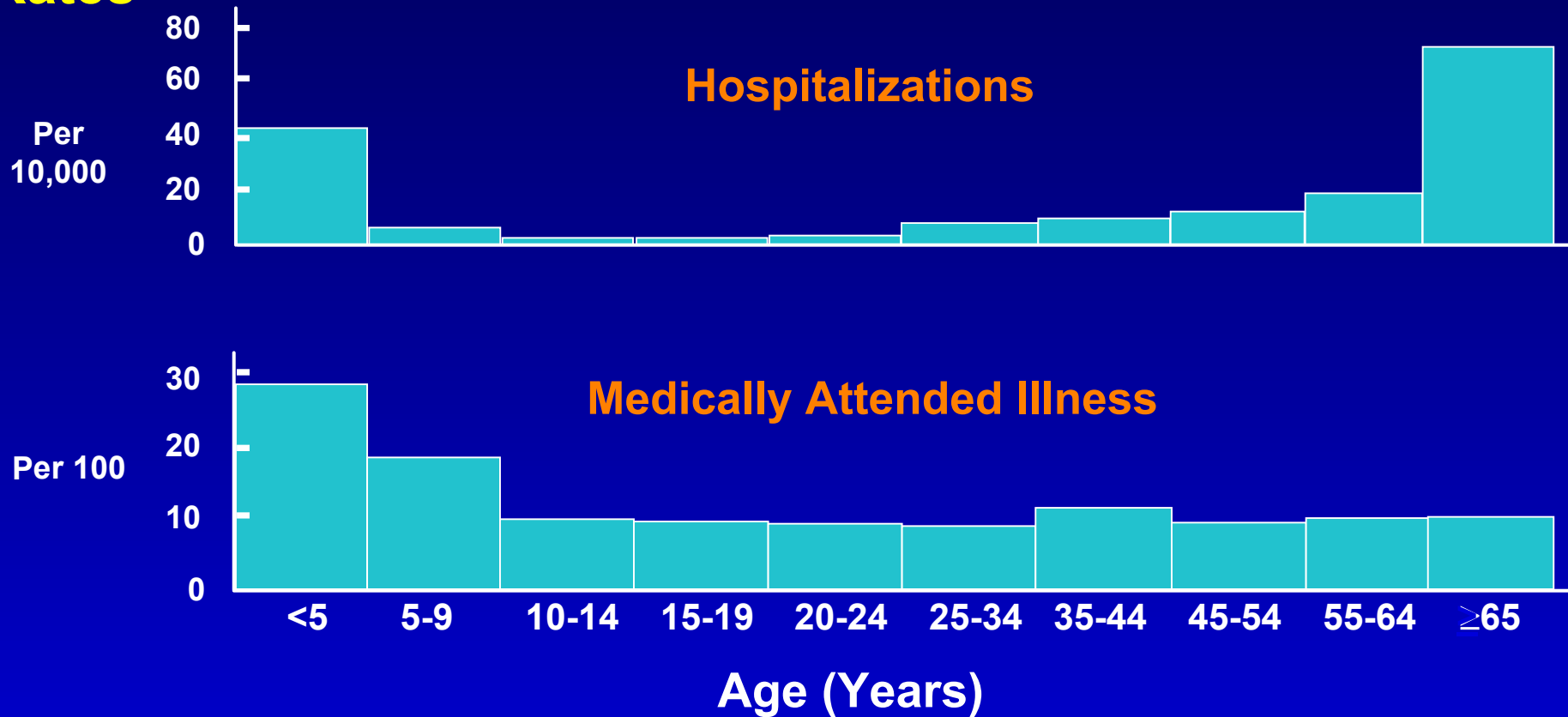
***James Young, PhD
President, Research and Development
MedImmune, Inc.***

Influenza

- **Most common medically attended acute respiratory illness**
Fever, chills, myalgia, cough, sore throat, nasal congestion, headache, malaise
- **Annual U.S. disease burden**
 - 20-50M people infected
 - 20,000-50,000 deaths
 - 70M lost work days and 38M lost school days
 - Costs nearly \$12B

Influenza Burden

Rates



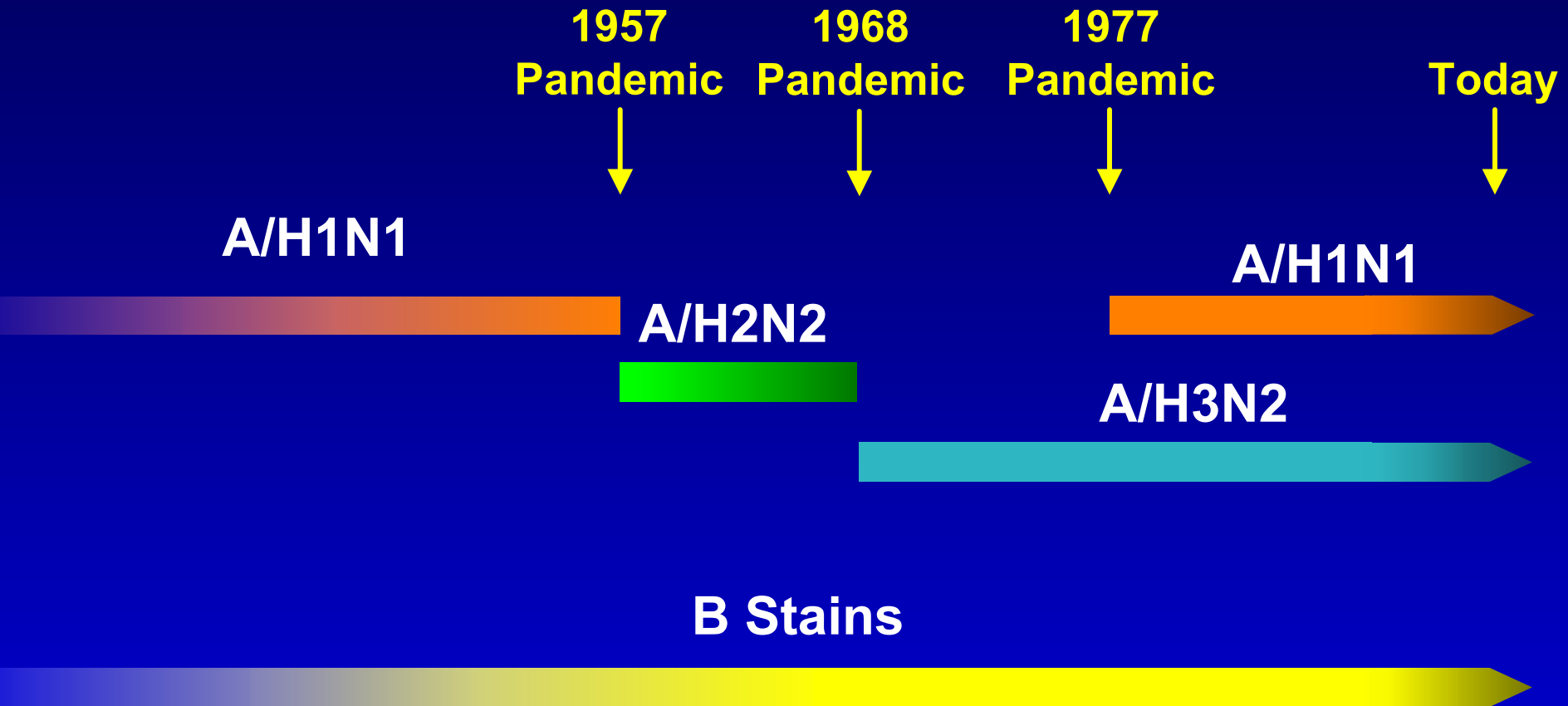
Influenza Virus

- Orthomyxovirus
- Negative-stranded, RNA genome of eight segments
- Enveloped virus with two surface glycoproteins
- Protective immunity directed against hemagglutinin (HA) surface glycoprotein
- Type A strains differentiated by HA and NA proteins
 - Avian, porcine, equine and human
 - 15 HA types
 - 9 NA types
- Three different virus types currently co-circulating
A/H1N1, A/H3N2, B

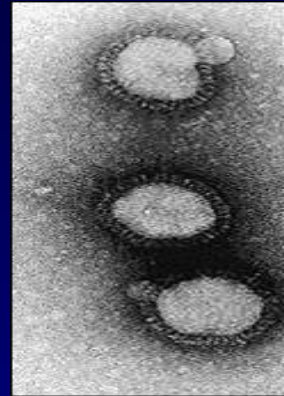


Influenza Virus Epidemiology

“Shift” and “Drift”



Influenza Vaccine



- **Vaccination is primary method for prevention**
 - **Trivalent inactivated intramuscular vaccine**
 - **Recommended 6-24 months, >50 years**
 - **Virus “drift” dictates annual vaccination**
- **Two manufacturers**
 - **Aventis Pasteur**
 - **Chiron (Powderject/Evans/Medeva)**
- **80M doses sold annually in U.S.**
 - **Growing at 7%**





FluMist™

First Nasal Flu Vaccine

- **Live, cold-adapted, attenuated influenza virus vaccine**
- **Delivered by intranasal mist**
- **Trivalent blend of $10^{7.0}$ infectious particles of each strain
A/H1N1, A/H3N2, B**
- **Induction of systemic IgG, cytotoxic T cell and local
secretory IgA responses**
- **20 clinical trials completed; >20,000 subjects**





FluMist™

First Nasal Flu Vaccine



- **Approved June 2003**
- **Launched September 2003**
- **Initial target healthy 5 - 49 year olds**
 - Working adults
 - Prevention-minded families
 - School-aged children





FluMist™

Live Virus

Active viral replication

Attenuated

Mild Infection

**Cold-adapted
Temperature-sensitive**

**Replication restricted
mainly to the nasopharynx**

Trivalent

**A/H1H1
A/H3N2
B**



Derivation of the Master Donor Viruses

Wild-type Viruses

(A/Ann Arbor/6/60 (H2N2))

(B/Ann Arbor/1/66)

↓
Adaptation to Efficient Growth at 25°C (Primary chick kidney cells)

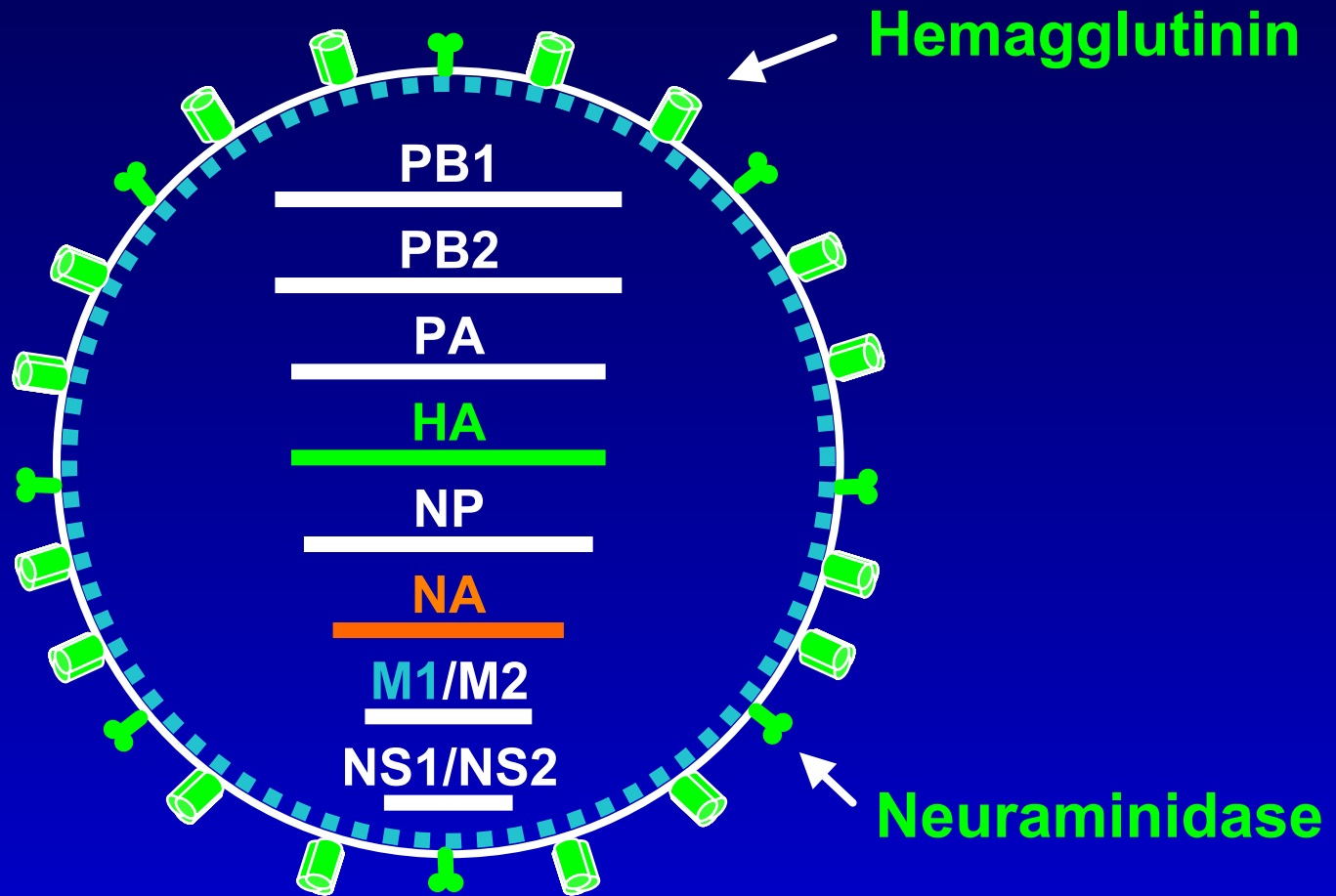
↓
Plaque Purification at 25°C

↓
Amplification in SPF Eggs

Master Donor Viruses

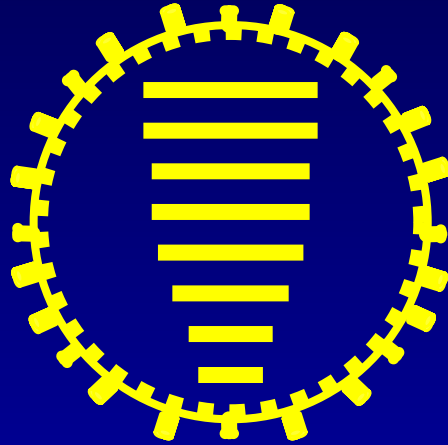
- *ca and ts* phenotype in cell culture
- *att* phenotype in ferrets

Influenza Virus Genomic Structure

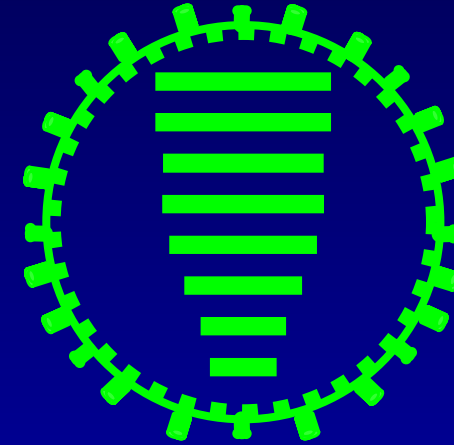


Derivation of New Master Virus Strain

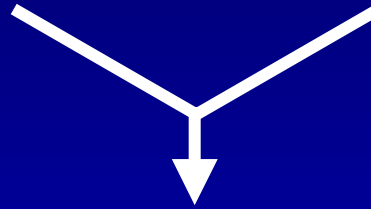
Master Donor Virus



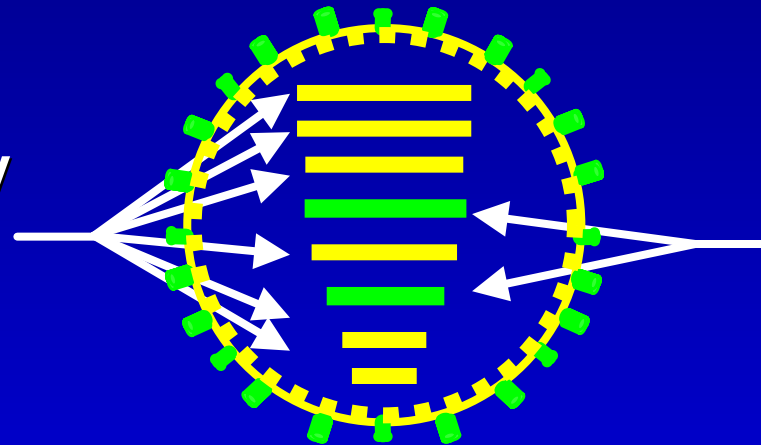
New Wild Type Strain



Co-infect Cells



Six genes from MDV confer *ca*, *ts*, *att* phenotype



Hemagglutinin and Neuraminidase Genes from Wild Type

6:2 Master Virus Strain (ca, ts, att)



Intranasal Administration of Live Attenuated Influenza Vaccine

- Proprietary Becton-Dickenson spray device (AccuSpray)
 - Sensation of nasal spray - none, like fog
- 0.25 ml administered in each nostril (0.5 ml dose)
- Infectious dose $_{50}$
 - Adults: 10^5 – $10^{6.4}$ TCID $_{50}$
 - Children: $10^{2.5}$ – $10^{4.5}$ TCID $_{50}$



Intranasal Administration



In a Time & Motion study* of 497 pediatric subjects receiving intranasal flu vaccine, 12/497, or 2% cried

** Unpublished data, A Personnel Time-Motion Study of Intranasal Influenza Vaccination in Healthy Children*

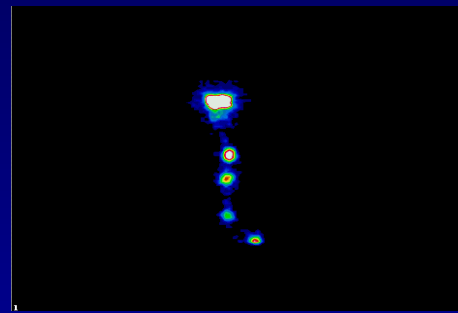
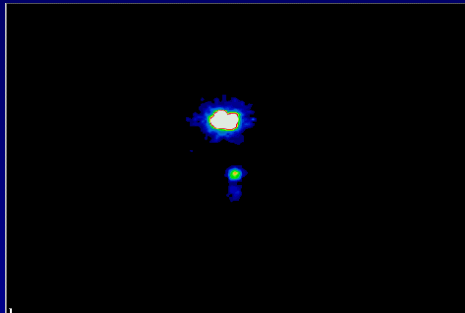


MedImmune,

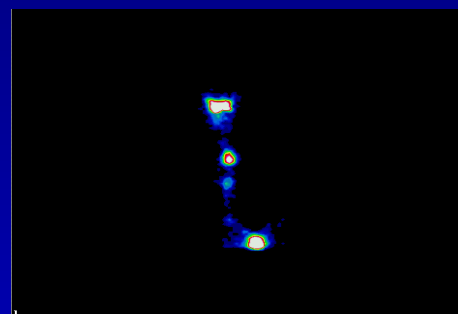
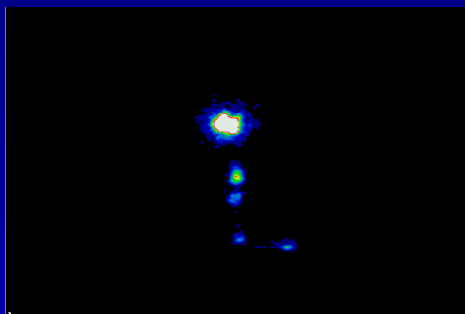
Scintiscans of the Deposition And Clearance FluMist

SPRAY

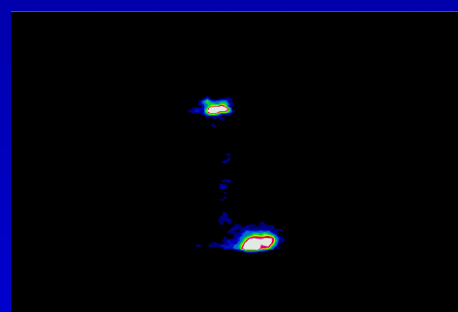
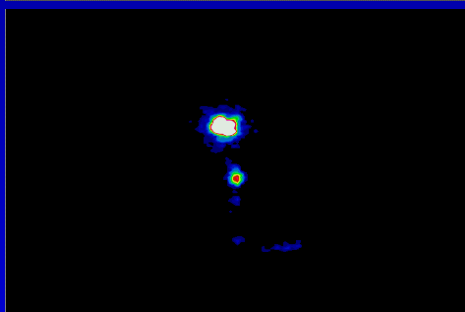
DROPS



0 MIN



5 MIN



10 MIN

Safety of FluMist in Indicated Populations

(Ages 5-49 years)

- **Generally safe and well tolerated**
- **Most common side effects are mild and temporary**
 - **Runny nose and other various cold-like symptoms**
- **No related serious adverse events**

FluMist Effectiveness Against Febrile Upper Respiratory Illness in Healthy Adults

Endpoint	Reduction	p-value^a
Occurrence of:	21.9 %	0.010
Episodes of:	23.6 %	<0.0001
Days^b of:	24.8 %	<0.0001
Illness Associated Days of:		
Missed Work	28.4 %	<0.0001
Health-care Provider Visits	40.9 %	<0.0001
Prescription Antibiotics	45.2 %	<0.0001
OTC Medication Use	28.0 %	<0.0001

^a Unadjusted for multiple comparisons.

^b Days per 1,000 participants per 7-week outbreak period.

FluMist Efficacy Against Culture-Confirmed Influenza in Children Year One

Strains*	Dosing Group	Percent Efficacy	95% Confidence Interval
All	One Dose	89	65, 96
All	Two Doses	94	88, 97

Belshe et al. NEJM 1998;338:1405-12.

*** Circulating strains matched those represented in the vaccine**

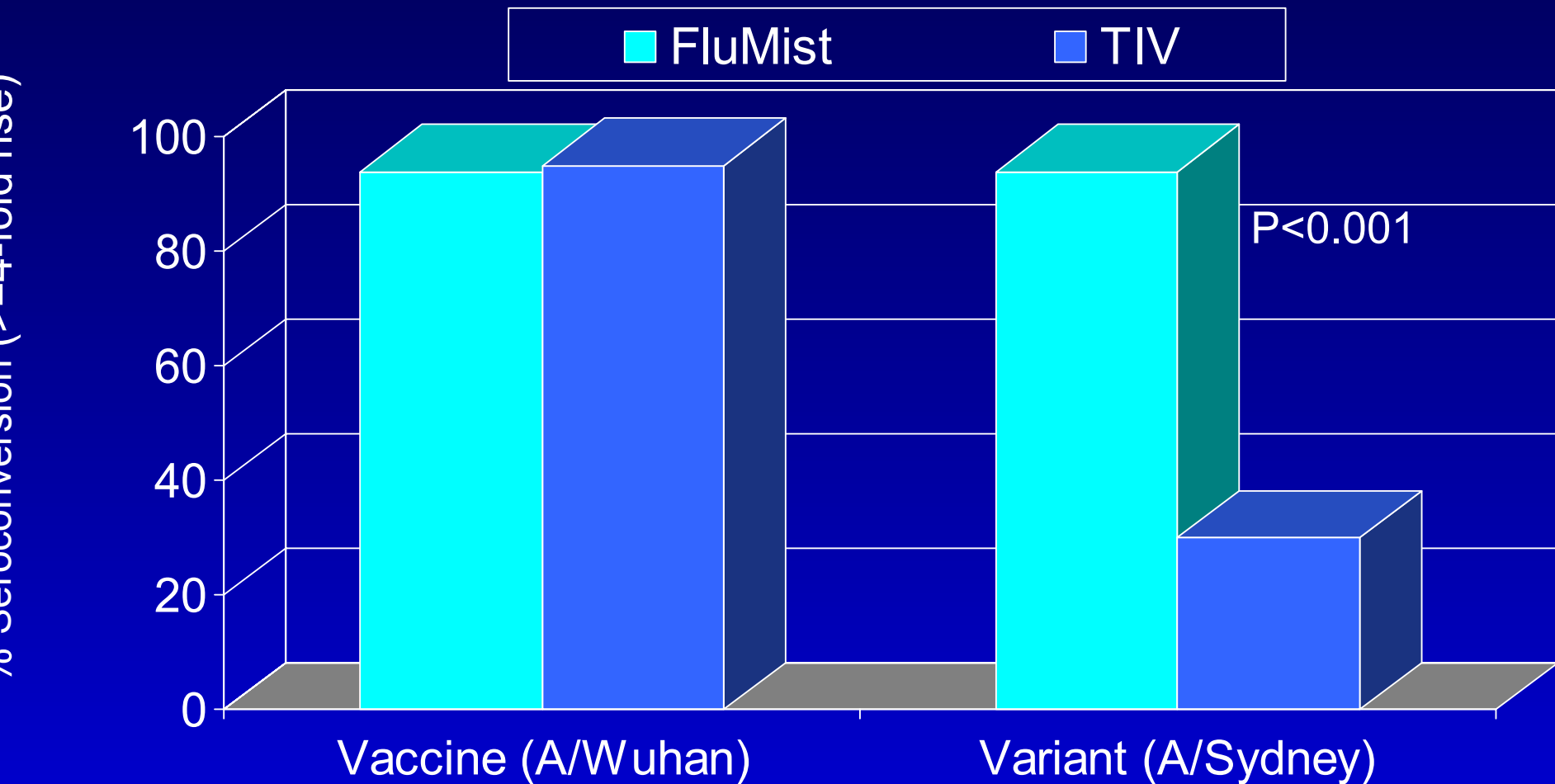
FluMist Efficacy Against Culture-Confirmed Influenza in Children

Year Two

Strains	Percent Efficacy	95% Confidence Interval
All	87.1	(77.7, 92.6)
Matched Strains	100	(63.1, 100)
A/Sydney Variant	85.9	(75.3, 91.9)

HAI Antibody to H3N2 Strains

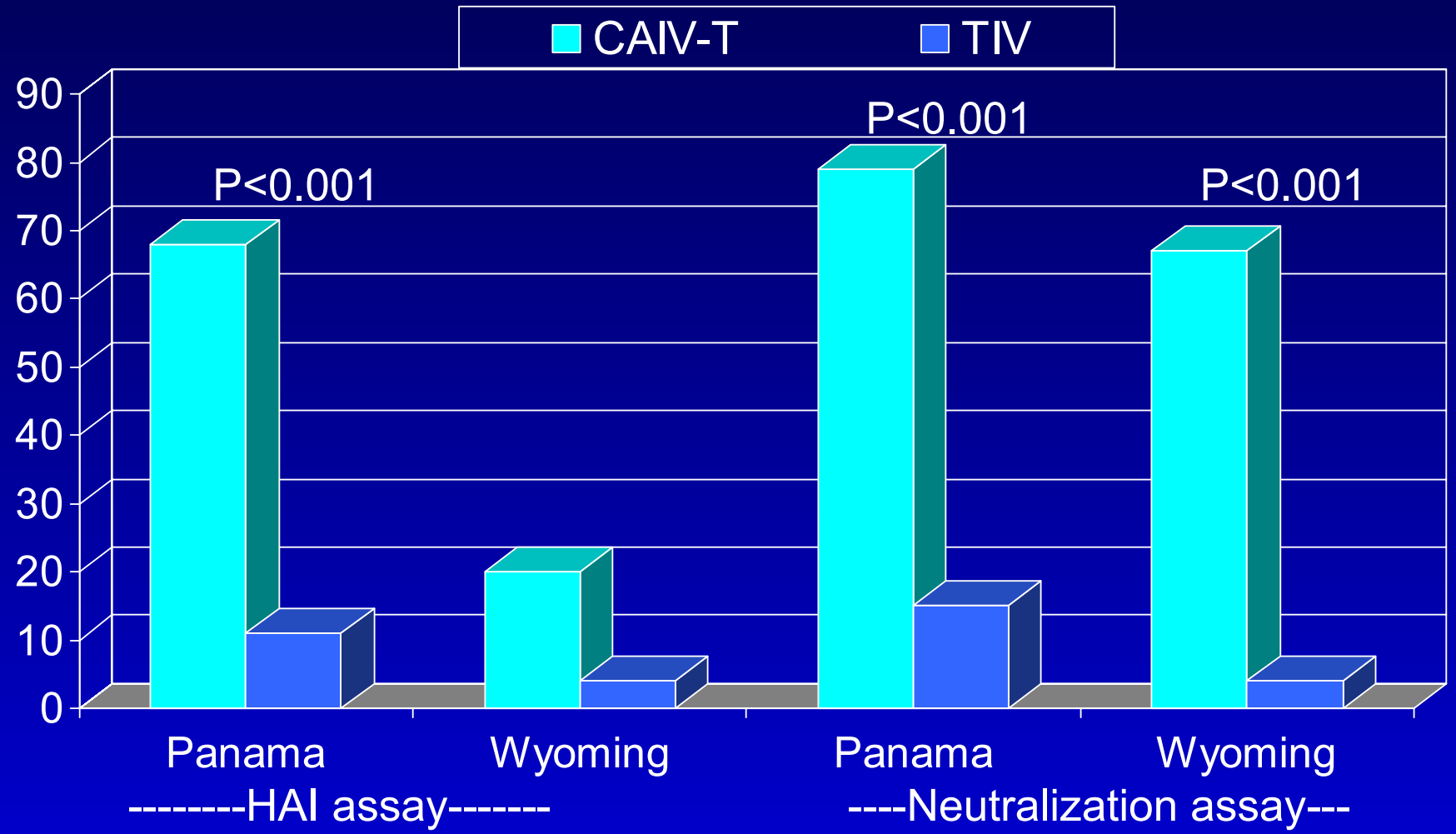
Two dose regimen in seronegative children



Antibody Response to A/Panama H3N2 Vaccine Strain and A/Wyoming (Fujian-Like) Variant Strain in Children

- **Sample size: ~25 seronegative children per group**
- **Age: 6-36 months**
- **One dose regimen: Randomized to CAIV-T or TIV which contained A/Panama/ /strain**
- **Sera obtained prior to and 28 days after vaccination**
- **Hemagglutination inhibition (HAI) and neutralizing antibody titers determined**

Antibody to H3N2 After One Dose of CAIV-T or TIV in Seronegative Infants

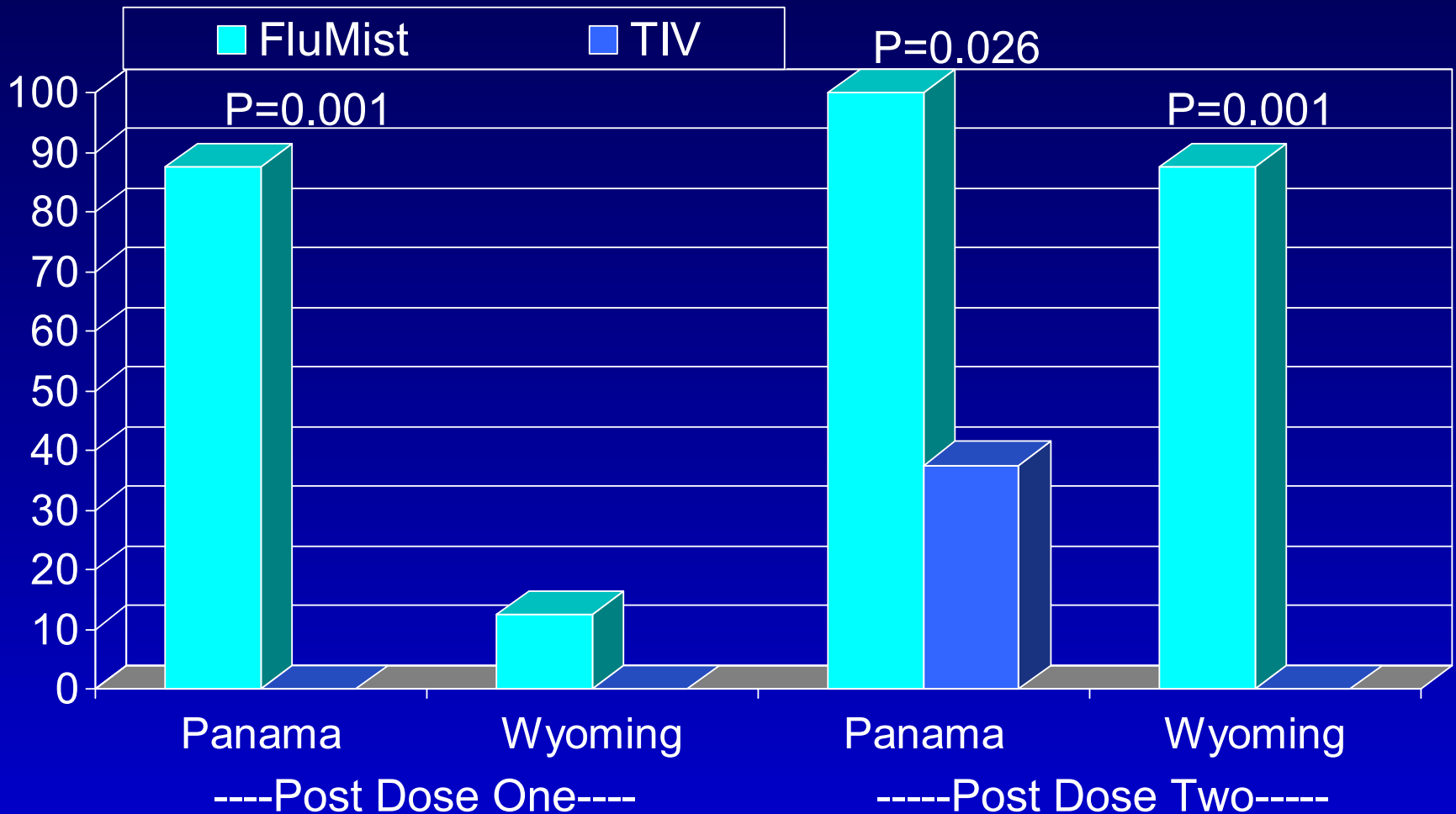


Wyoming strain is a Fujian-like antigenic variant to the Panama vaccine strain

Antibody Responses to A/Panama H3N2 Vaccine and A/Wyoming Variant Strain in Ferrets

- **Sample size: 8 seronegative ferrets/group**
- **Two dose regimen: one human dose of FluMist or TIV at day 0 and 14**
- **Sera obtained on Days 0, 14, and 21**
- **Hemagglutination inhibition (HAI) and neutralizing antibody titers determined**

Antibody to H3N2 Strains after FluMist or TIV in Ferrets



Wyoming strain is a Fujian-like antigenic variant to the Panama vaccine strain

Conclusions

FluMist is safe and highly efficacious and effective in healthy children and healthy adults

FluMist containing A/Wuhan (H3N2) provided high cross-reactive antibody in children and high cross-protection in children and adults to the H3N2 variant A/Sydney strains in the 1997-98 season

CAIV-T containing A/Panama (H3N2) provided higher cross-reactive antibody than inactivated vaccine in children to the H3N2 variant strain A/Wyoming (A/Fujian-like) following one dose of either

FluMist is an important vaccine with the potential to prevent influenza even when wild-type strains are not matched to those in the vaccine

Acknowledgements

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- **National Institutes of Health**
- **Investigators of FluMist Clinical Studies**
- **MedImmune Vaccines, Inc.**
- **Wyeth**