

# Influenza Vaccine and Possible Neurological Complications: Intranasal Vaccines

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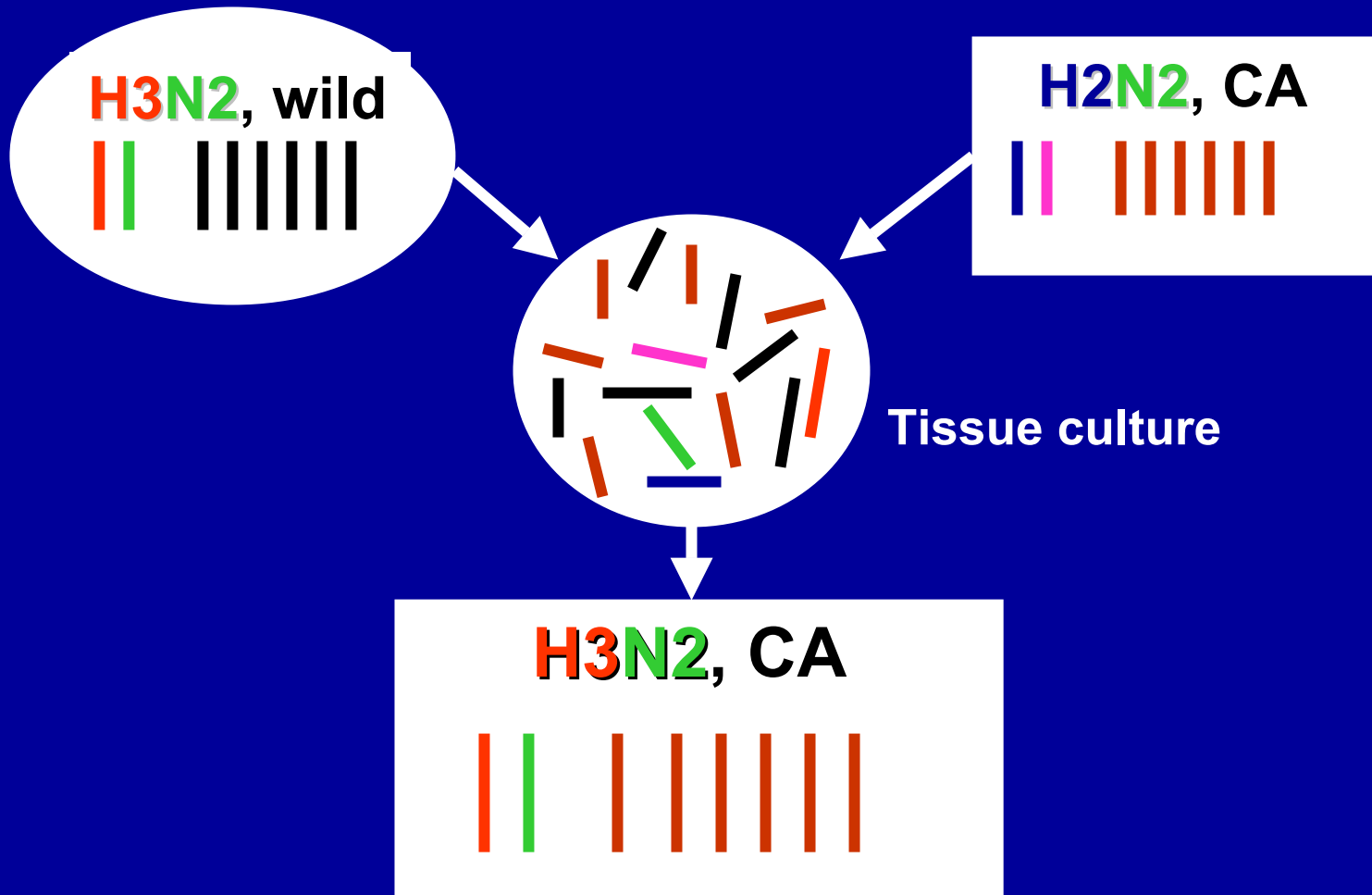
# Overview of Presentation

- Cold-adapted, live, attenuated vaccine
  - Summary of Studies and Safety Results
- Viroosomal vaccine with heat-labile toxin
  - Summary of published safety reports

# Live, Attenuated Cold-Adapted Influenza Vaccine

- **Developed in 1960's by Dr. Maassab**
- **Cold adapted**
  - **serial passage in tissue culture at successively lower temperatures**
  - **will grow in the nose (32-35°C)**
- **Temperature sensitive**
  - **ceases replication at 37°C**
- **Induces local mucosal immunity**

# Production of CAIV from Master Strain



# CAIV Development

**NIH studies 1976-**

**NIH / Wyeth 1991-93**

**NIH / Aviron 1995 – 2002**

**Medimmune 2002 - present**

# Randomized Controlled Trial of Inactivated and Cold- Adapted Vaccines for the Prevention of Influenza A

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# Methods

- Randomized, controlled trial of cold-adapted and inactivated vaccines
- Subjects between ages of 1-65 years
- Safety and immunogenicity studied
- Subjects completed a vaccine reaction form to indicate any systemic or local symptoms for 5 days after vaccination

# Results

- During the 5 years of the study, 5210 subjects participated in the trial and received a total of 12,500 doses of vaccine
- This included 791 children < 16 years of age who received 1,809 doses of vaccine
- Both cold adapted and inactivated vaccines were both well-tolerated with no serious adverse events noted

# Percentage of subjects with reactions in the 5 days after vaccination

Reaction	Control N=1738	CAIV N=1733	TIV N=1739
Fever >38°	3.7	3.9	4.1
Redness	8.3	7.8	10.5
Coryza	19.8	26.2	19.9
Lethargy	16.7	21.7	18.4
Myalgia	13.3	15.3	14.1
Cough	8.4	9.5	9.6

# FluMist

- Influenza Virus Vaccine consisting of 3 strains of live, attenuated, cold-adapted, temperature-sensitive influenza viruses
- Each dose contains  $10^7$  TCID<sub>50</sub> of each strain; two influenza A and one influenza B

# Number of Subjects Given FluMist

Age (yrs)	Dose 1	Dose 2	Placebo
1-4	5963	3145	3323
5-8	4418	2643	1970
9-17	5903	1028	1371
18-49	3322	38	1495
50-64	511	0	209
➤65	111	0	101
Total	20,228	7354	8469

# Studies Conducted with FluMist

- 20 studies submitted to the FDA
- 14 randomized, double-blinded, placebo controlled and 6 non-controlled studies
- For purposes of safety assessment, four trials will be summarized
  - AV019 Pediatric Safety Trial
  - AV012 Herd Immunity Trial
  - AV006 Pediatric Efficacy Trial
  - AV009 Adult Effectiveness Trial

# AV019

- Randomized, double-blinded, placebo-controlled study of the safety of FluMist
- Healthy children (1-17 yrs); no asthma
- 2:1 randomization to FluMist or placebo
- Children < 9 years received 2 doses
- Medically attended events obtained from Northern California Kaiser database

# AV019 Safety Methods

- No active monitoring for solicited reactions
- NCKP database searched for Serious Adverse Events (SAE) and Medically Attended Events (MAE)
- 9689 subjects (6473 FluMist, 3216 control)
- 58% between 1-8 years
- 42% between 9-17 years

# AV019 Results: % MAE by Setting

	FluMist N=6473	Placebo N=3216
Setting		
Hospital	0.5	0.6
ED	2.9	3.2
Clinic	35.6	37

# AV019 Results: SAE

- No deaths reported
- 20 Severe Adverse Events reported- 0.02% in both vaccine and placebo groups
- Events included 11 hospitalizations, 6 psychiatric admissions, 1 ED, 1 clinic, 1 outpatient surgery

# AV019 Neurologic Events

- No cases of encephalitis, encephalopathy, Guillain-Barre or Reye's Syndrome, or other influenza-associated disorders
- 10 subjects (7 FluMist, 3 placebo) reported seizure events
- RR of seizures = 1.16 (90% CI .38, 4.09)

# AV012 Texas HMO Trial

- Open-label, non-randomized
- Subjects 18 mos-18 years of age
- History of mild asthma permitted
- Vaccine single dose each year
- Planned to assess herd immunity
- Safety monitoring was secondary
- 9549 doses administered to 7448 subjects

# AV012 Safety Assessment

- Severe adverse events captured for 42 days after vaccination by postcards and database review
- No deaths reported
- 24 SAEs but 15 occurred after day 21
- Only 2 SAE related to CNS in first 21 days
  - 1 hospitalization for depression
  - 1 hospitalization for aseptic meningitis

# AV006

- Phase 3 randomized, double-blind, placebo-controlled study in healthy children aged 15-71 months of age
- 2:1 randomization
- Year 1 enrolled 1602 subjects
- Year 2 enrolled 1358 subjects
- Efficacy of culture-confirmed influenza

# % Post-vaccination Reactions in Children: AV006

	Dose 1		Dose 2	
	FluMist	Control	FluMist	Control
Any rx	74	66	69	62
URI	59	48	51	46
Myalgia	5	3	3	2
Fever $\geq$ 101° C	16	12	11	11

# AV009

- Phase 3 randomized, double-blind, placebo controlled study in 18-64 yr olds
- 2:1 randomization to FluMist or controls
- 4561 subjects enrolled in one year
- Endpoint was effectiveness in reducing influenza-like illness, absenteeism, health care utilization in adults

# % Post-vaccination Reactions in Adults: AV009

	FluMist	Control
Any Rx	71	62
URI	44	27
Sore throat	27	16
Cough	14	10
Myalgia	16	15
Fever $\geq 101^{\circ}$ C	0.6	0.6

# Rare Adverse Events Seen in 20 Studies of FluMist

- No reported cases of encephalitis, encephalopathy, Guillain Barre, Reyes
- No increase in the Relative Risk for CNS events, including seizures following the receipt of FluMist

# Nasalflu Berna: Intranasal Virosomal Influenza Vaccine

- Consists of influenza virosomes (small suspended spheres with a lipid bilayer) formulated to contain influenza hemagglutinin and neuraminidase from three contemporary influenza strains
- Vaccine contains E. coli heat-labile toxin as an adjuvant
- Safety studies conducted in 5400 subjects

# Studies of Nasalflu

- Elicited both local and systemic immunity
- Well tolerated locally and systemically by most of the vaccinated subjects
- Four SAE seen during development
- One subject had hypotension after vaccine, possibly related to vaccine

# Efficacy of Virosomes for Prevention of Acute Otitis in Children

- Children aged 1-5 years with history of recurrent acute otitis media enrolled
- Single center, prospective, randomized single blind study conducted in Italy in 1999-2000 influenza season
- Children randomly assigned to vaccine or placebo group
- Parents recorded local and systemic symptoms for 4 days after vaccination

# % Subjects with Indicated Reaction

<b>Local Events</b>	<b>After dose 1</b>	<b>After dose 2</b>
Nasal irritation	10	10
Sneezing	30	28
Stuffy nose	43	33
Runny nose	43	40
> 1 local event	64	49

# % Subjects with Indicated Reaction

Systemic Event	After dose 1	After dose 2
Fever $\geq 38.1^{\circ}\text{C}$	9	3
Shivering	6	8
Irritability	18	25
Earache	8	10
Nausea	2	3
Cough	43	28
$\geq 1$ event	54	49

# Summary

- Studies of cold-adapted, live, attenuated influenza vaccine in children and adults have not demonstrated a significant increase in adverse neurologic events in the subjects studied
- Studies of virosome influenza vaccine with heat-labile toxin adjuvant have been less extensive