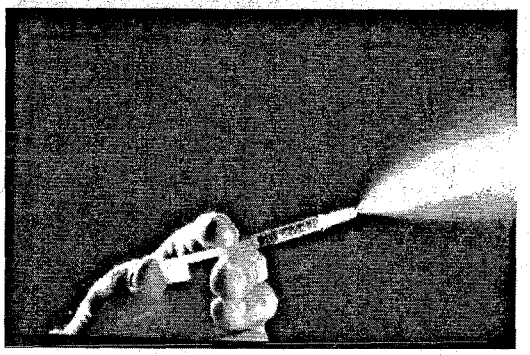
Aviron  **FluMist**

An Influenza Vaccine
For Use in Healthy Children
Age 1 – 17

Efficacy in Children

Robert B. Belshe, MD
Saint Louis University

Efficacy and Effectiveness In Healthy Children

AV006
AV011

- **Efficacy in Year One**
  - 1996-1997 type A/H3N2 and type B circulated that matched strains in the vaccine
- **Efficacy in Year Two**
  - 1997-1998 type A/H3N2 circulated that was not closely matched to the strain in the vaccine
- **Efficacy in both years combined**
- **Efficacy following an H1N1 challenge**

Pediatric Protective Efficacy Trial Group

Investigators

R. Belshe	Saint Louis Univ.
D. Bernstein	Childrens Hosp., Cinn.
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Sponsors

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	R. Rabinovich
Aviron	P. Mendelman

Biostatistics

EMMES	M. Wolff
Statistics Collaborative	J. Wittes
NIAID	W. Blackwelder
Aviron	I. Cho

Efficacy Trial in Young Children Study Design

Healthy Children AV006

- Two year field trial conducted jointly by NIAID and Aviron
- Double-blind placebo controlled
- Randomized 2:1 FluMist to placebo
- Healthy children 15-71 months of age
- Regimen
  - One or two doses in Year One
  - One revaccination dose in Year Two
    - Remained in the same treatment group
- Primary endpoint
  - Protection against culture-positive influenza in children who received two doses of vaccine or placebo
- Immune responses were measured in a subset of 203 children

Active Surveillance for Influenza

Healthy Children AV006

Weekly calls during the influenza season

- **To remind parents to report illness**
- **To trigger a home or office visit for viral culture if sufficient symptoms**

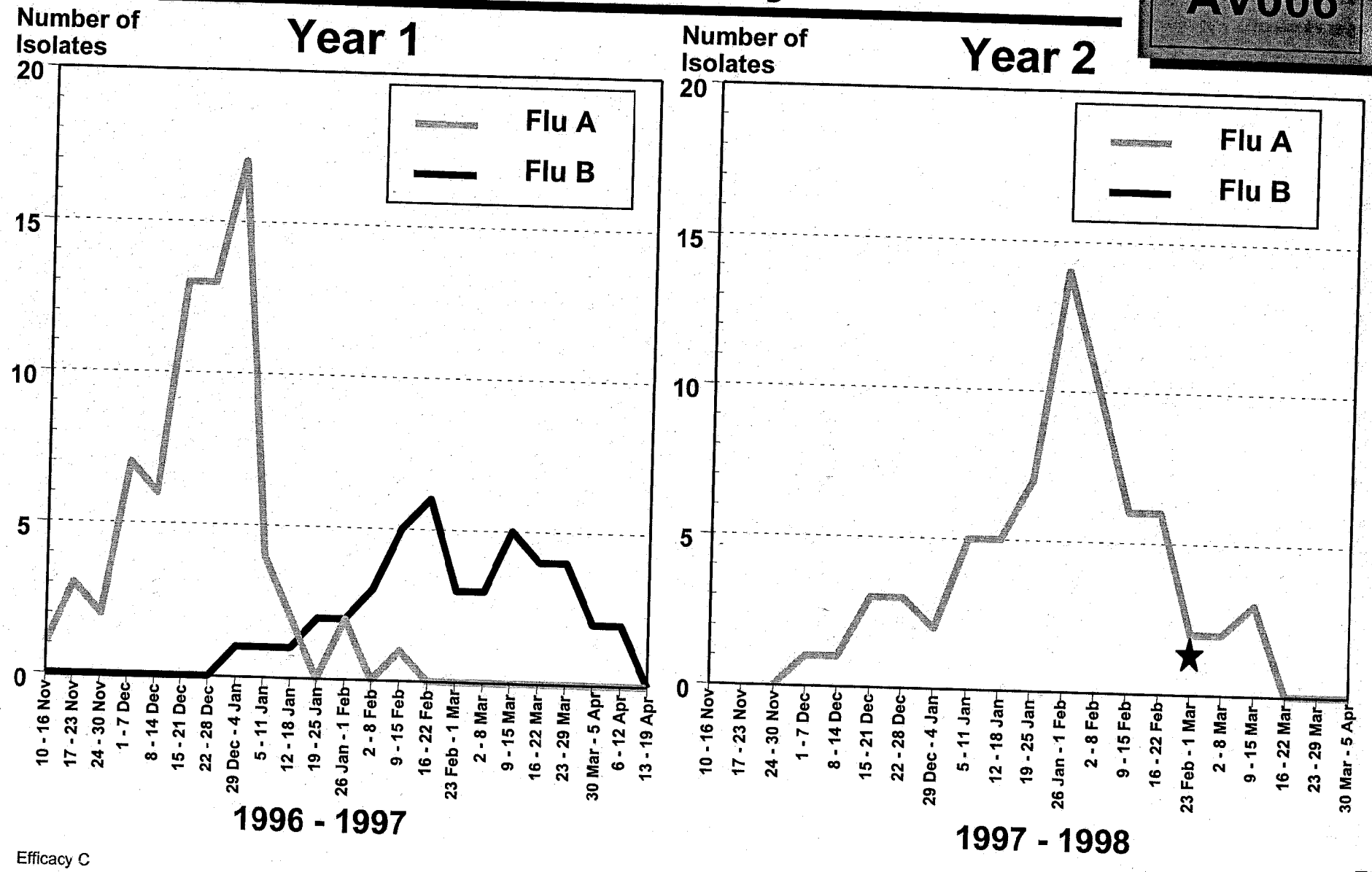
Participant Enrollment

Healthy Children AV006 Year One

Treatment Group	One-Dose Regimen	Two-Dose Regimen	Total
FluMist	189	881	1070
Placebo	99	433	532
Total	288	1314	1602

Influenza Activity by Week

Healthy Children AV006



Efficacy C

Cases of Culture-Confirmed Influenza

Healthy Children AV006 Year One

All Year One Participants

Treatment Group	Number with Influenza (%)		
	A/H3N2	B	Either
FluMist N = 1070	7 (0.7)	7 (0.7)	14 (1.3)
Placebo N = 532	63 (11.8)	37 (7.0)	94 (17.7)

Note: A/Wuhan/359/95 (H3N2) and B/Harbin/7/94 were the circulating strains.
Six children in the placebo group had both H3N2 and B influenza.

Efficacy of FluMist in Preventing Culture-Confirmed Influenza Illness

Healthy Children AV006 Year One

Analysis Group	Strain	Estimated Efficacy %	95% Confidence Interval %
Two Doses Received	Any	93.4	(87.5, 96.5)
One-Dose Regimen	Any	88.8	(64.5, 96.5)
All Participants (Intent to Treat)	Any	92.6	(87.3, 95.7)

Note: Primary Endpoint was efficacy in children who received two doses.

Efficacy of FluMist Preventing Events Associated with Culture-Confirmed Influenza

Healthy Children AV006 Year One

Endpoint	FluMist N = 1070	Placebo N = 532	% Efficacy (95% CI)
Febrile Illness	8 (0.7%)	80 (15%)	95.0 (90.0, 97.5)
Otitis Media	1 (0.1%)	20 (3.8%)	97.5 (85.5, 99.6)

Note: Mean number of days with fever in culture-confirmed influenza cases.

FluMist 2.4
Placebo 4.1
} P = 0.05

Febrile defined as temperature ≥ 101°F, rectal, or ≥ 101°F, oral, or ≥ 100.4°F, axillary.

Participant Enrollment

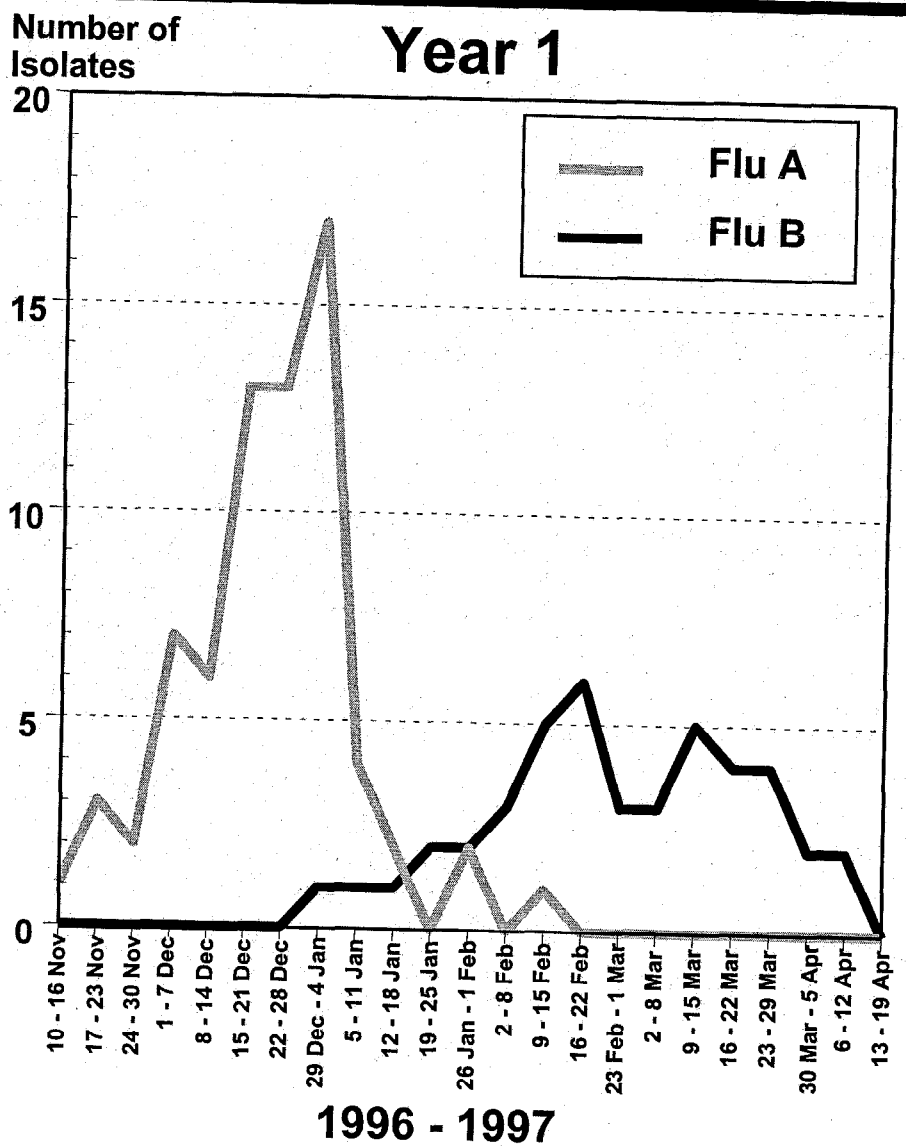
Healthy Children AV006 Year Two

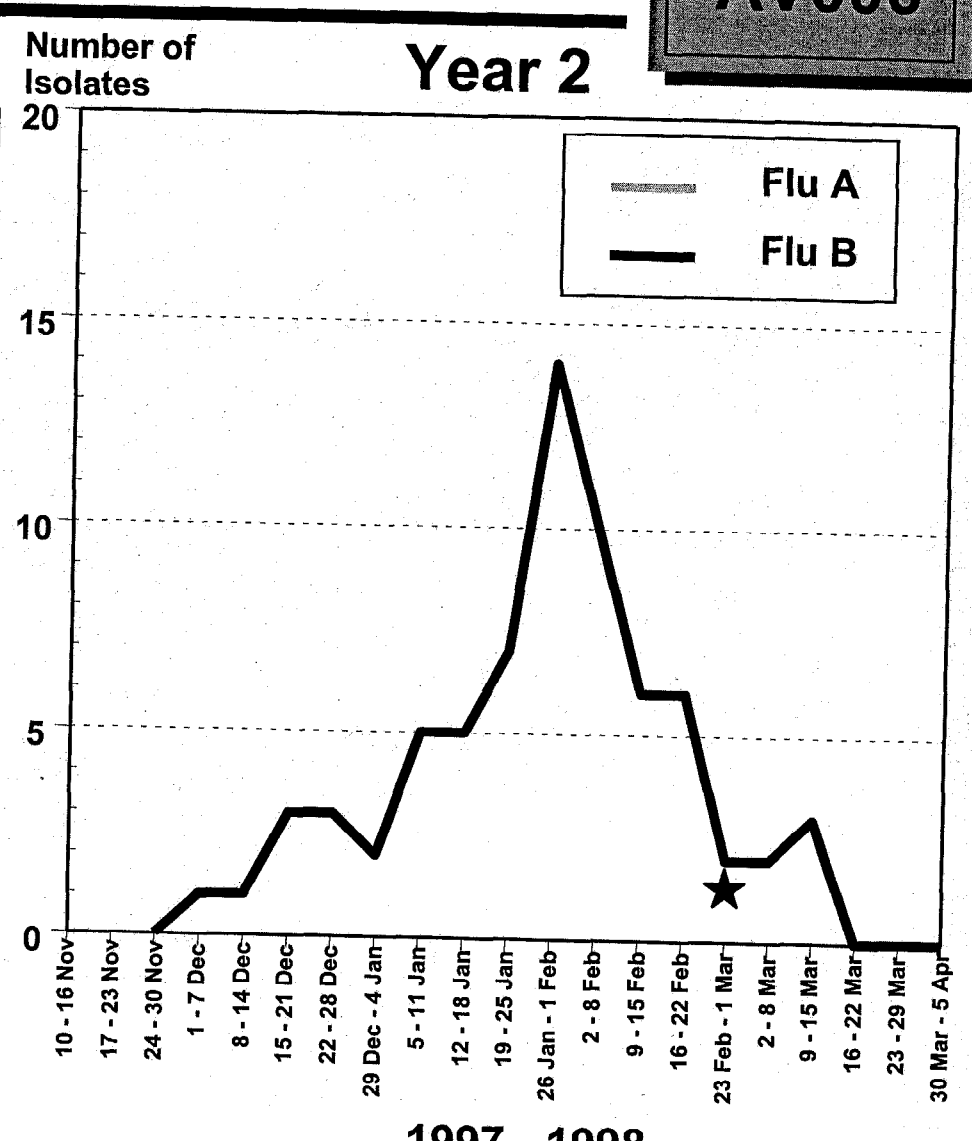
Treatment Group	One-Dose Regimen in Year One	Two-Dose Regimen in Year One	Total in Year Two
FluMist	162	755	917
Placebo	77	364	441
Total	239	1119	1358

Note: 85% (1358 / 1602) of children, were re-enrolled in Year Two of the trial.

Influenza Activity by Week

Healthy Children AV006





Cases of Culture-Confirmed Influenza

Healthy Children AV006 Year Two

FluMist N = 917	Placebo N = 441
15 (1.6%)	56 (12.7%)

Note: A/Wuhan/359/95 (H3N2), A/Sydney/05/97 (H3N2), and B/Harbin/7/94 circulated.

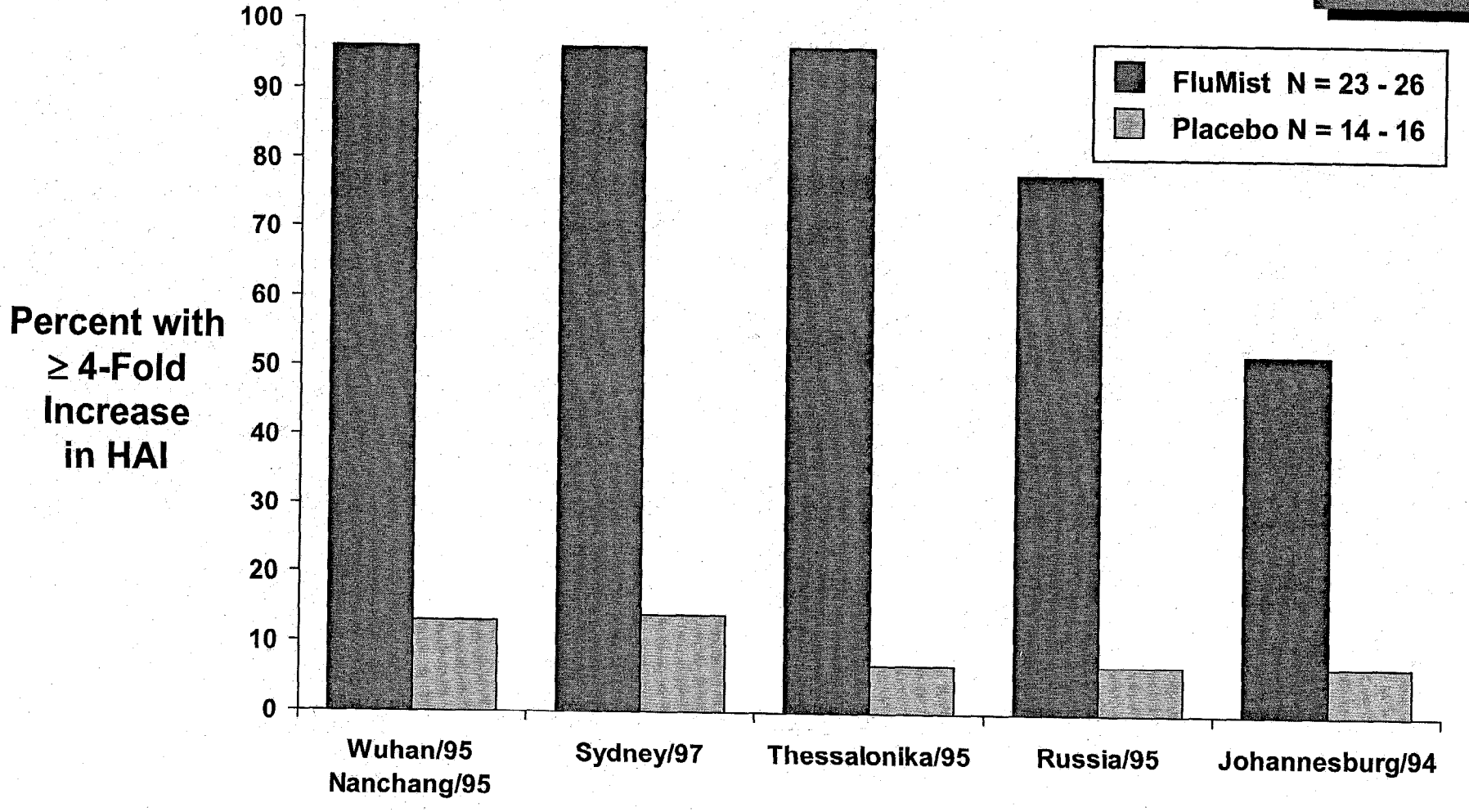
Efficacy of FluMist Preventing Culture-Confirmed Influenza Illness

Healthy Children AV006 Year Two

Circulating Strains	Number of Isolates		Estimated Efficacy %	95% Confidence Interval
	FluMist	Placebo		
A/Sydney (H3N2)	15	51	85.9	(75.3, 91.9)
A/Wuhan (H3N2)	0	4	100	(63.1, 100)
B	0	1		
All	15	56	87.1	(77.7, 92.6)

Heterotypic Responses In Seronegative Children To H3N2 Variants

Healthy Children AV006 Year One



Note: Two Dose Regimen

Natural Infection in Placebo Recipients Protected Against Wild-Type Influenza Illness

Healthy Children AV006 Year Two

Illness in Year One	Illness in Year Two		
	No	Yes	
Yes N = 52	51 (98%)	1 (1.9%)	Efficacy = 86.1% (95% CI: 25.9, 97.6)
No N = 389	335 (86%)	54 (13.9%)	

Efficacy of FluMist Preventing Events Associated with Culture-Confirmed Influenza

Healthy Children AV006 Year Two

Endpoint	FluMist N = 917	Placebo N = 441	% Efficacy (95% CI)
Febrile Illness	12 (1.3%)	54 (12%)	89.3 (80.4, 94.2)
Otitis Media	2 (0.2%)	17 (4%)	94.3 (78.1, 98.5)

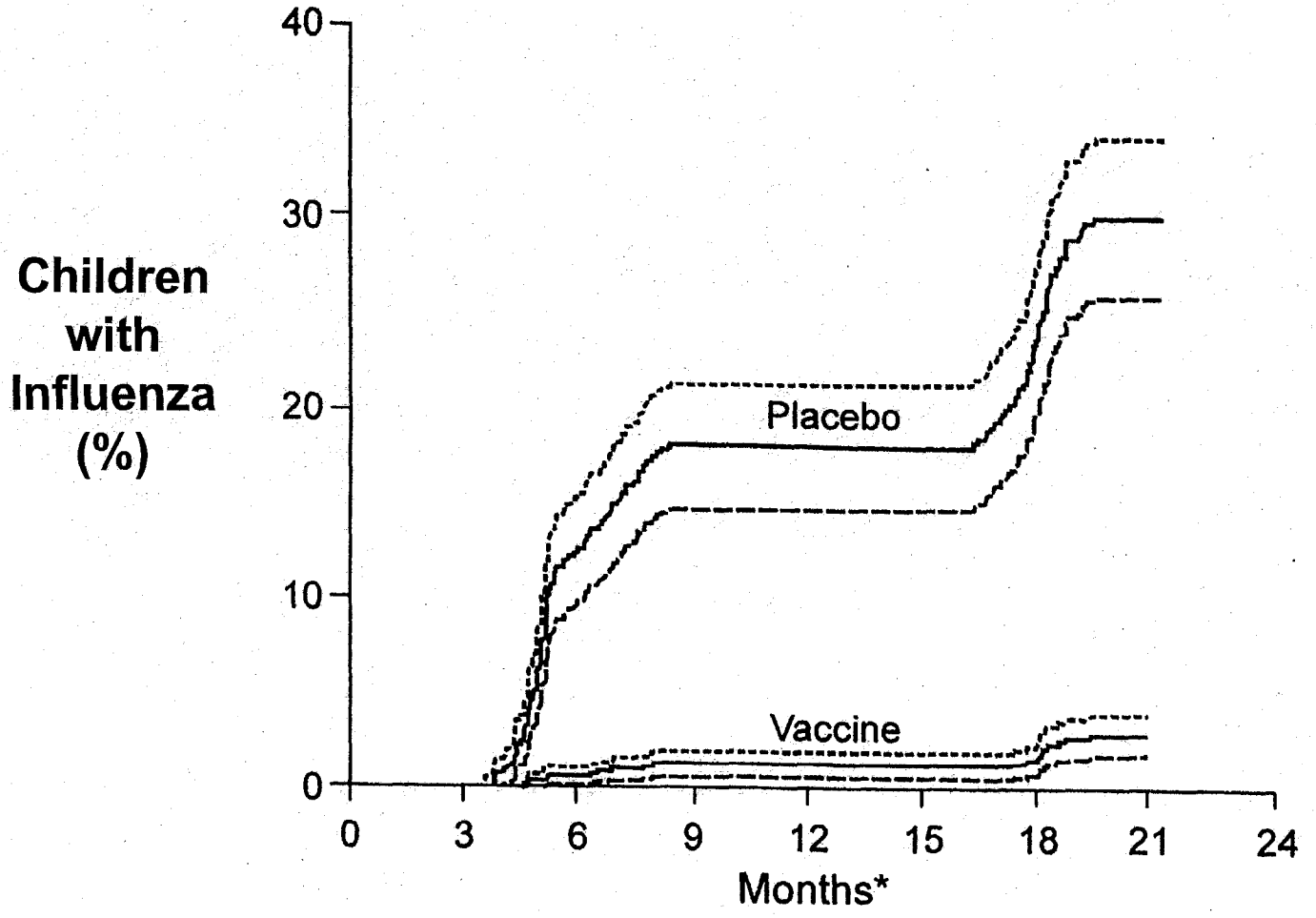
Note: Mean number of days with fever in patients with culture-confirmed influenza.

FluMist 2.1
Placebo 4.9
} P < 0.01

Febrile defined as temperature ≥ 101°F, rectal, or ≥ 101°F, oral, or ≥ 100.4°F, axillary.

Efficacy of FluMist
Two-Year Pediatric Efficacy Trial

Healthy Children AV006



Combined Efficacy of FluMist Preventing Lower Respiratory Illness Associated with Culture-Confirmed Influenza

Healthy Children AV006 Years One & Two

Group Analyzed	Number of Illnesses		Estimated Efficacy %	95% CI	P value
	FluMist	Placebo			
Year One	1	3	83.4	(-15.4, 97.6)	.08
Year Two	0	8	100	(77.0, 100)	<.001
Year One and Year Two Combined	1	11[a]	95.2	(62.2, 99.4)	.004

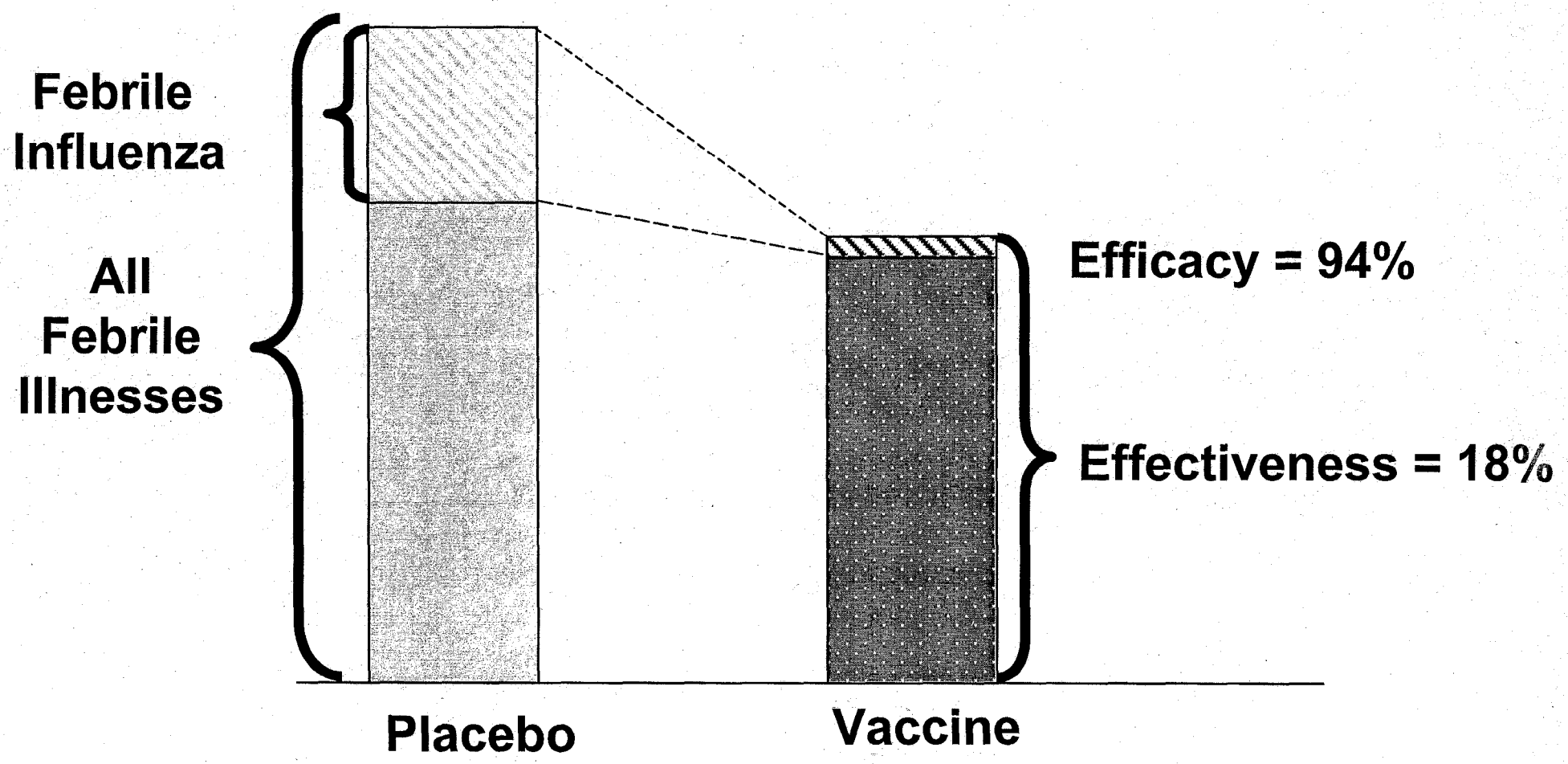
[a]One person had an illness in both years. The analysis considers only the first event.

Note: Lower respiratory illness was defined as physician documented:

Pneumonia	N = 4
Bronchitis	N = 3
Croup	N = 3
Wheezing	N = 2

Efficacy and Effectiveness Of FluMist vs Febrile Illness

Healthy Children AV006 Years One & Two



Combined Effectiveness of FluMist Over Two Study Seasons

Healthy Children AV006 Years One & Two

Endpoint[a]	FluMist	Placebo	Percent Reduction	P value
Febrile illness with antibiotics	0.309	0.403	23.3	.0002
Febrile otitis media with antibiotics	0.126	0.181	30.4	< .0001
Missed Day Care/Preschool/School Days	0.824	0.946	12.8	.07
Parental Lost Work Days	0.263	0.301	12.6	.17
Health Care Provider Visits	1.087	1.223	11.2	.02

[a]Rate per participant computed using Generalized Linear Models.

Febrile defined as temperature ≥ 101°F, rectal, or ≥ 101°F, oral, or ≥ 100.4°F, axillary.

Efficacy Against Influenza A/H1N1 Study Design

Healthy Children AV011

- Challenge with A/H1N1 monovalent vaccine (10^7 $TCID_{50}$)
  - 5-8 months following revaccination in Year Two of Study AV006
- Prior FluMist (N = 144) vs. prior placebo (N = 78) recipients
- Primary endpoint
  - Protection against shedding of type A/H1N1 vaccine virus
- Serum HAI, and nasal IgA measured prior to challenge
- Shedding was assessed on Days 1, 2, 3, and 4 following challenge

Shedding of H1N1 Vaccine Challenge Virus

Healthy Children AV011

Shedding On Any Day	All	
	Prior FluMist N = 142	Prior Placebo N = 77
Yes	6 (4%)	19 (25%)
No	136 (96%)	58 (75%)

Efficacy = 82.9%
(95% CI: 60.2, 92.7)

P < 0.0001

Correlates of Immune Protection in Children

- Any serum HAI antibody (93% reduction in attack rate of viral shedding)
- Any nasal wash IgA antibody (85% reduction in attack rate of viral shedding)
- History of receiving vaccine was correlated with protection from viral shedding among volunteers without HAI or IgA antibody

Conclusions

- FluMist provided a high degree of protection against culture-confirmed influenza in children over two seasons
- FluMist provided a high degree of protection against an antigenically drifted strain of H3N2
- FluMist protected against influenza-associated
  - Otitis Media
  - Febrile Illness
  - Lower Respiratory Infection