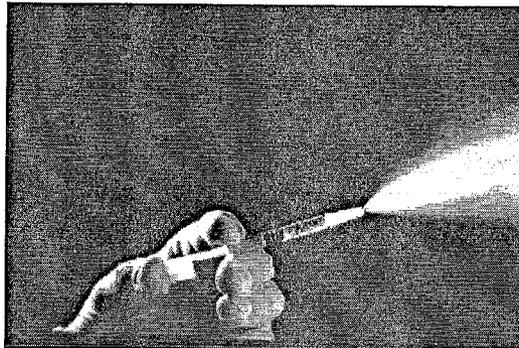


**Aviron**



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**FluMist**

**An Influenza Vaccine  
For Use in Healthy Adults  
Age 18 – 64**

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# **Efficacy and Effectiveness in Healthy Adults**

*Kristin L. Nichol, MD, MPH, MBA*

**University of Minnesota and the Minneapolis VA Medical Center**

# **Clinical Trials: FluMist in Healthy Adults**

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**AV003  
AV009**

***AV003 – Efficacy of the Vaccine in Adults  
Challenge Trial***  
**Treanor J, Vaccine, 2000**

***AV009 – Effectiveness of the Vaccine in Adults  
Field Trial***  
**Nichol KL, JAMA, 1999**

# **Efficacy**

## **Wild Type Influenza Challenge Trial**

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**Healthy  
Adults  
AV003**

### **■ Study design**

- **Double-blind, placebo-controlled trial**
- **18-41 years of age**
- **Serosusceptible ( $HAI \leq 1:8$ ) to H1N1, H3N2, or B strains**
- **Randomization 1:1:1, FluMist: TIV: placebo**
  - **All participants received both intranasal mist and an intramuscular injection**
- **Day 28 challenge with well-matched wild-type virus**

# Primary Endpoint

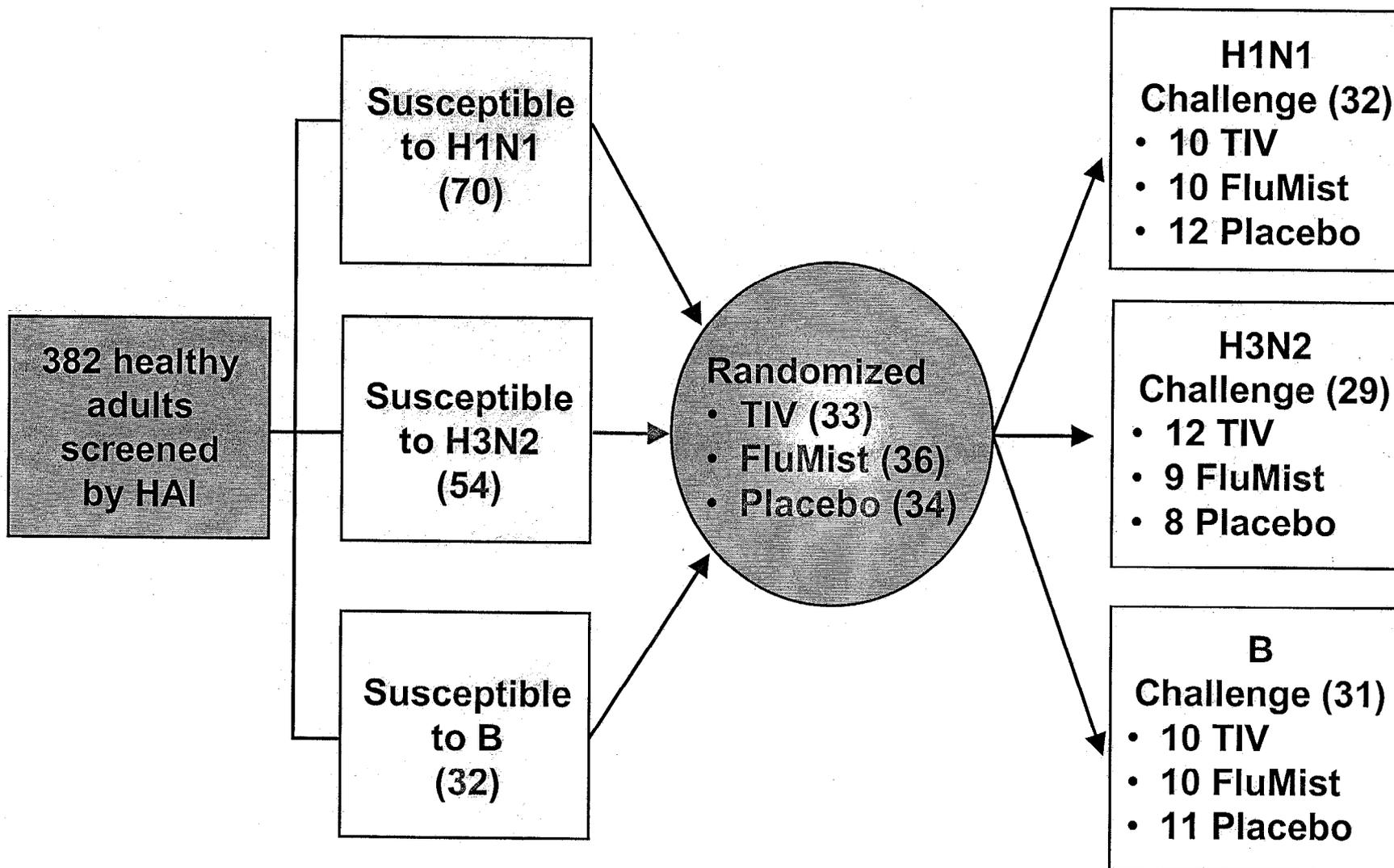
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Healthy  
Adults  
AV003

- **Protection against laboratory-  
documented illness after challenge**
  - **Illness with viral shedding or**
  - **Illness with  $\geq 4$  - fold HAI**

# Dosing Scheme

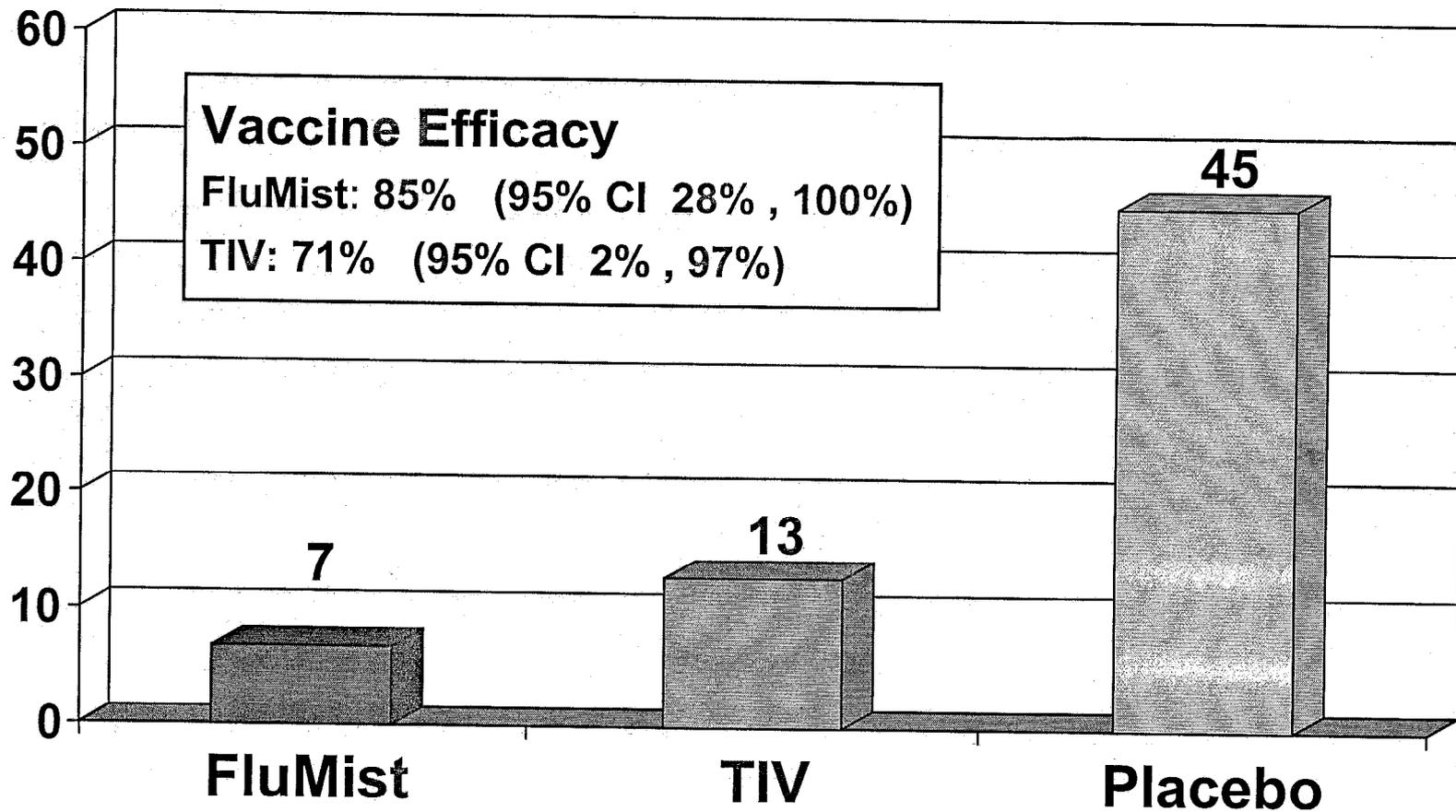
Healthy  
Adults  
AV003



# Primary Endpoint Laboratory-Documented Illness After Challenge

Healthy  
Adults  
AV003

Percent with illness



# Immunogenicity & Efficacy by Strain

Healthy  
Adults  
AV003

**Immunogenicity (Percent with 4- fold serum HAI response 28 days after vaccination)**

Group	A/Texas (H1N1)	A/Shangdong (H3N2)	B/Harbin
FluMist	29%	39%	10%
TIV	96%	94%	92%

**Efficacy (Percent reduction in laboratory confirmed illness)**

Group	A/Texas (H1N1)	A/Shangdong (H3N2)	B/Harbin
FluMist	80%	78%	100%
TIV	60%	64%	100%

**Conclusion: High efficacy was observed despite the low serum HAI response.**

# Efficacy Conclusion

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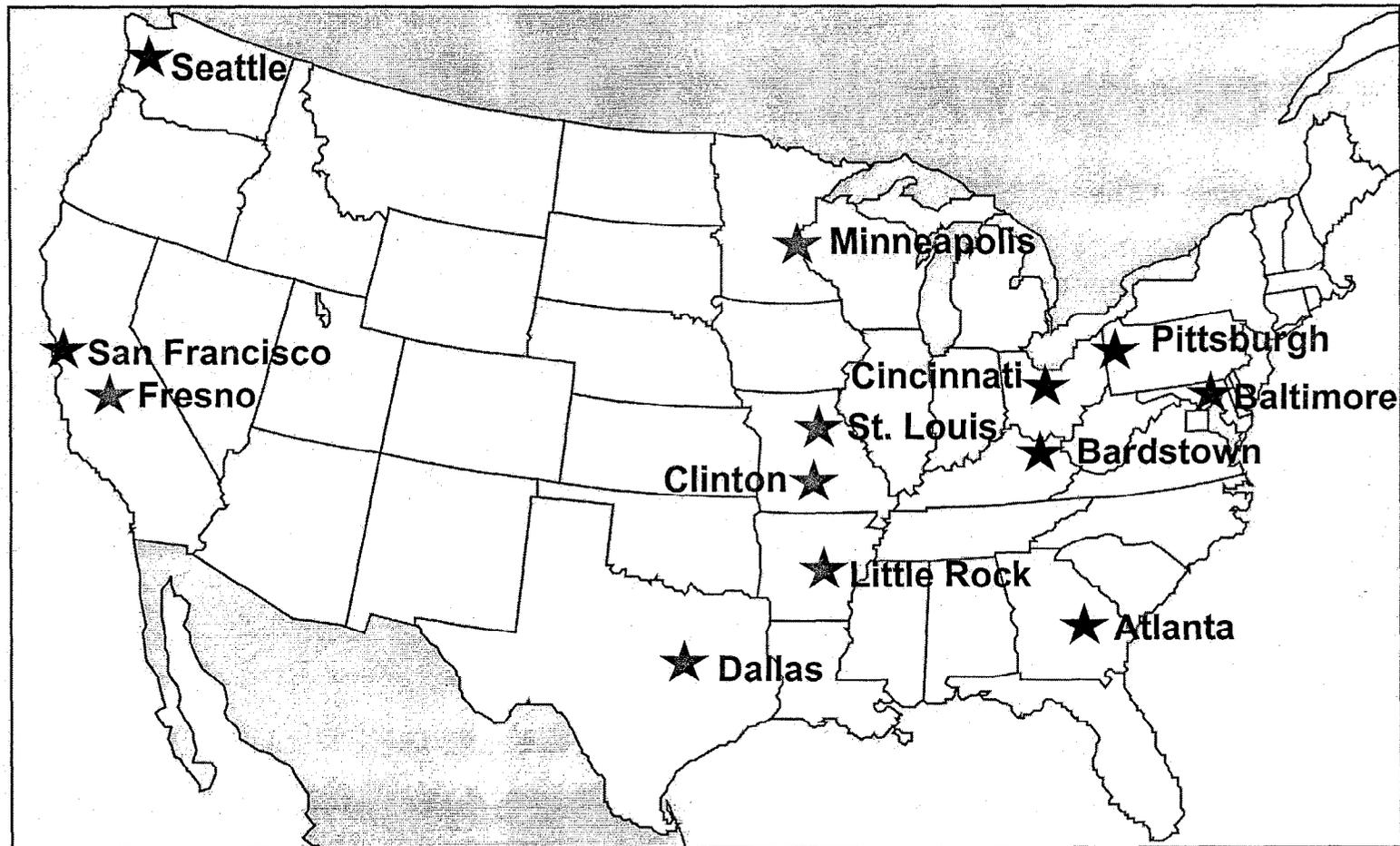
Healthy  
Adults  
AV003

- **FluMist was 85% efficacious in preventing laboratory-documented illness in healthy adults challenged with wild-type influenza**
- **In adults, high efficacy was observed despite the low serum HAI response**

# Effectiveness In Healthy Working Adults

Healthy  
Adults  
AV009

## A Multi-Site Influenza Field Trial



# Effectiveness In Healthy Working Adults

---

Healthy  
Adults  
AV009

## ■ Study design

- Double-blind, placebo-controlled
- 18 – 64 years of age
- Working  $\geq$  30 hours per week
- 4,561 subjects
- Randomization 2:1 – FluMist vs. placebo
- Single season (1997-98)
- A/Sydney/05/97 (H3N2) which circulated in 1997 was not well matched to the vaccine strain, A/Wuhan/359/95

## ■ Regimen: single dose

## ■ Community surveillance for culture-positive influenza

# Effectiveness Outcomes

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- **Febrile illnesses**
  - Percent with illness, number of illnesses, days of illness, work loss, health care use
- **Symptom cards for each month Nov '97 to Mar '98**
  - Biweekly reminder telephone calls
- **Outcome periods based on local and national influenza surveillance**
  - **Site-specific, Peak Outbreak Period**
    - Algorithm to capture 80% of influenza activity around modal week
    - Median duration of 7 weeks
  - **Pooled, 14-week Total Outbreak Period**

# Participant Characteristics

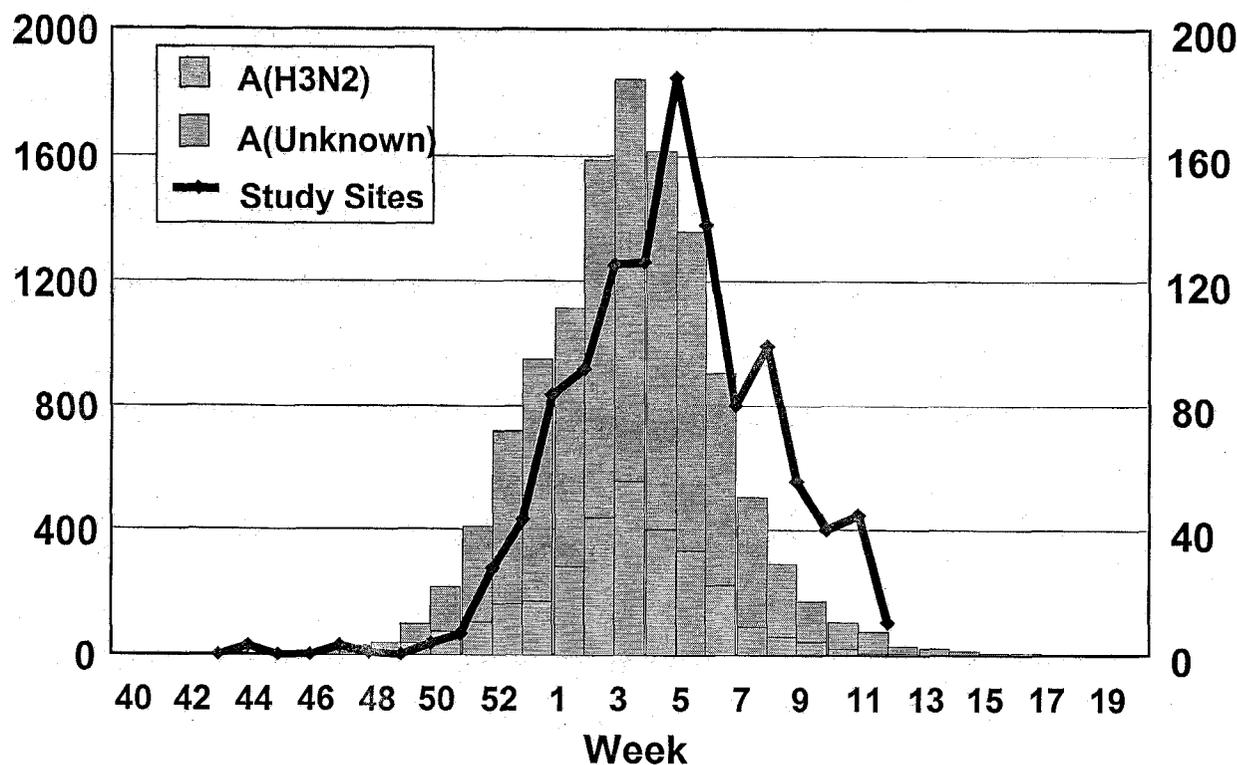
<b>Characteristics</b>	<b>FluMist N = 3041</b>	<b>Placebo N = 1520</b>
<b>Age, Years</b>		
<b>Mean/Median</b>	<b>38</b>	<b>38</b>
<b>(Range)</b>	<b>(18 - 65)</b>	<b>(18 - 65)</b>
<b>Female</b>	<b>55%</b>	<b>54%</b>
<b>Race/Ethnicity</b>		
<b>Caucasian</b>	<b>85%</b>	<b>84%</b>
<b>Black</b>	<b>10%</b>	<b>11%</b>
<b>Any College</b>	<b>81%</b>	<b>78%</b>

# Influenza Activity by Week 1997-98 Season

Healthy  
Adults  
AV009

Number of Isolates (National)

Number of Isolates (Study Sites)



**Peak Outbreak Period: Median 7 Weeks**  
**Total Outbreak Period: 14 Weeks**

# Symptom Card Completion Rates

Group	Nov	Dec	Jan	Feb	Mar
FluMist	90%	91%	89%	89%	88%
Placebo	90%	91%	90%	90%	88%

97% returned at least one of five symptom cards

88% returned 4 or more

# Illness Definitions

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## ■ Pre-Specified

### ● Any Febrile Illness

- At least one day of fever
- At least two consecutive days of symptoms
- At least two symptoms on one day

### ● Severe Febrile Illness

- At least one day of fever
- At least three consecutive days of symptoms
- At least two symptoms on all three days

### ● Febrile URI

- At least one day of fever
- At least two consecutive days of URI symptoms
- At least two URI symptoms for one day

## ■ Not Pre-Specified

### ● CDC Influenza-like Illness

- At least one day of fever
- Plus cough or sore throat on the same or consecutive days

### Symptoms:

#### URI

runny nose  
sore throat  
cough

#### Systemic

fever  
chills  
headache  
muscle aches  
tired/weak

# Prevention of the Occurrence of Illness Peak Outbreak Period

Healthy  
Adults  
AV009

Percent with One or More Illness Events:	FluMist N = 2833	Placebo N = 1420	Reduction	P Value*
Any Febrile Illness (primary endpoint)	13.2	14.6	9.7%	.19
Severe Febrile Illness	10.1	12.2	17.4%	.031
Febrile Upper Respiratory Illness	8.5	10.8	21.9%	.010
CDC-ILI	10.7	13.9	23.2%	.0018

\* Unadjusted for multiple comparisons

# Reduction in the Number of Episodes of Illness Peak Outbreak Period

**Healthy  
Adults  
AV009**

<b>Episodes of:</b>	<b>FluMist N = 2833</b>	<b>Placebo N = 1420</b>	<b>Reduction</b>	<b>P value*</b>
<b>Any Febrile Illness</b>	<b>151.3</b>	<b>168.1</b>	<b>10.0%</b>	<b>.10</b>
<b>Severe Febrile Illness</b>	<b>111.0</b>	<b>136.7</b>	<b>18.8%</b>	<b>.0019</b>
<b>Febrile Upper Respiratory Illness</b>	<b>92.4</b>	<b>121.0</b>	<b>23.6%</b>	<b>&lt; .0001</b>
<b>CDC-ILI</b>	<b>119.2</b>	<b>156.1</b>	<b>23.6%</b>	<b>&lt; .0001</b>

**Note : Number of episodes of illness per 1,000 participants**

**\*\* Unadjusted for multiple comparisons**

# Reduction in the Number of Days of Illness Peak Outbreak Period

Healthy  
Adults  
AV009

Days of Illness	Reduction	P Value*
Any Febrile Illness	22.9%	.0001
Severe Febrile Illness	27.3%	< .0001
Febrile Upper Respiratory Illness	24.8%	<.0001
CDC-ILI	29.6%	<.0001

\* Unadjusted for multiple comparisons

# Effectiveness Against Days of Illness, Work Loss, and Health Care Use Any Febrile Illness

**Healthy  
Adults  
AV009**

<b>Any Febrile Illness</b>	<b>Reduction</b>	<b>P Value</b>
<b>Days of Illness</b>	<b>22.9%</b>	<b>.0001</b>
<b>Illness-associated Days of:</b>		
<b>Missed Work</b>	<b>13.1%</b>	<b>.065</b>
<b>Healthcare Provider Visits</b>	<b>14.7%</b>	<b>.055</b>
<b>Prescription Antibiotics</b>	<b>42.9%</b>	<b>&lt; .0001</b>
<b>OTC Medication Use</b>	<b>23.3%</b>	<b>.0002</b>

**Note: P values unadjusted for multiple comparisons**

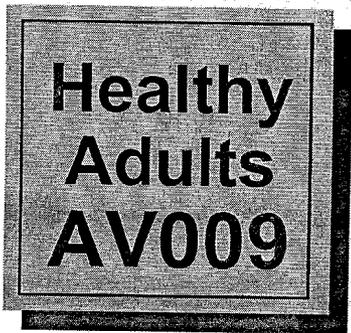
# Effectiveness Against Days of Illness, Work Loss, and Health Care Use Severe Febrile Illness

**Healthy  
Adults  
AV009**

Severe Febrile Illness	Reduction	P Value
Days of Illness	27.3%	< .0001
Illness-associated Days of:		
Missed Work	17.9%	.012
Healthcare Provider Visits	24.8%	.0006
Prescription Antibiotics	47.0%	< .0001
OTC Medication Use	27.6%	< .0001

**Note: P values unadjusted for multiple comparisons**

# Effectiveness Against Days of Illness, Work Loss, and Health Care Use Febrile URI



Febrile URI	Reduction	P Value
Days of Illness	24.8%	< .0001
Illness-associated Days of:		
Missed Work	28.4%	< .0001
Healthcare Provider Visits	40.9%	< .0001
Prescription Antibiotics	45.2%	< .0001
OTC Medication Use	28.0%	< .0001

**Note: P values unadjusted for multiple comparisons**

# Effectiveness Against Days of Illness, Work Loss, and Health Care Use CDC-ILI

**Healthy  
Adults  
AV009**

CDC-ILI	Reduction	P Value
Days of Illness	29.6%	< .0001
Illness-associated Days of:		
Missed Work	19.9%	.0043
Healthcare Provider Visits	20.0%	.0079
Prescription Antibiotics	37.3%	< .0001
OTC Medication Use	27.8%	< .0001

**Note: P values unadjusted for multiple comparisons**

# Effectiveness Conclusions

## Healthy Working Adults

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Healthy  
Adults  
AV009

- **FluMist was highly effective in significantly reducing:**
  - **Illness**
  - **Missed work**
  - **Health-resource utilization**
- **FluMist was highly effective against a drifted circulating strain**