

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: King JC Jr, Stoddard JJ, Gaglani MJ, et al. Effectiveness of school-based influenza vaccination. *N Engl J Med* 2006;355:2523-32.

**Web-only Supplemental material for King et al.,**

**Effectiveness of a School-Based Influenza Vaccination Intervention.**

**STUDY PERSONNEL RESPONSIBILITIES**

The concept for this study originated from author JCK and the final study design and final protocol evolved from a series of meetings by the investigators from the four clinical study sites in Baltimore, MD, St. Cloud, MN, Seattle, WA, and Killeen, TX, and the sponsor, MedImmune, Inc. (Medical Scientist author JJS). All authors had input into the protocol design and agreed on the final version. Raw data were collected centrally by PPD, Inc. (a contract research organization contracted by MedImmune) and combined into one complete set and forwarded to author LM at the University of Maryland for data cleaning and analyses. All authors were involved in refinement of the analysis and interpretation of the data through a series of analytic discussions. The submitted manuscript was written with the approval and with repeated input of all authors. All four participating clinical sites had a contract with MedImmune that stipulated the freedom to examine the data independently and to submit a manuscript for publication based on the

data with input from all investigators, including author JJS from MedImmune.

MedImmune administrators were invited to review, in a timely manner, the manuscript drafts and make editorial suggestions prior to final manuscript submission.

#### **RATE REDUCTIONS IN THE PRIMARY ANALYSIS**

Unadjusted rate difference calculations (intervention school vs control school) showed relative rate reductions favoring intervention school families, as follows: a 36 percent reduction in the proportion of households reporting fever plus cough or sore throat in children; a 36 percent reduction in the proportion of households reporting fever plus cough or sore throat in adults; a 36 percent lower rate of doctor/clinic visits by children for ILI; a 26 percent lower rate of doctor/clinic visits by adults for ILI; 38 percent lower absentee rates among elementary school students; 14 percent lower absentee rates among middle school students; 40 percent lower absentee rates among high school students; and 25 percent relatively fewer missed workdays among parents. These observed relative reductions were modestly attenuated after adjustment for cluster and state.

## **POST HOC ANALYSIS RESULTS**

Comparison of outcomes among LAIV families compared to non-LAIV families, yielded the results that were generally similar to the comparisons between intervention and control schools with attenuated effect sizes. More hospitalizations for fever or ILI were reported via the anonymous questionnaire in both children and adults in the intervention school compared with control school households ( $P=0.03$ ,  $P=0.05$ , Table 2). However, comparing LAIV families with families who did not receive LAIV revealed no statistically significant difference for rates of hospitalizations of either children or adults (Supplemental Table 1). There were only a small number of hospitalization reports from the family surveys, and the reports occurred mostly in families whose children attended intervention schools but who themselves did not receive LAIV. Hospitalizations were reported in Maryland, Minnesota, and Texas but not in Washington.

For the school and work day absence analyses, the post hoc LAIV vs. no LAIV analysis again showed the same trends although statistical significance was not reached in all cases (Supplemental Table 1).

## **VACCINE -RELATED MEDICAL OUTCOMES**

Parents of children who received LAIV in an intervention school were asked to respond to a survey related to respiratory symptoms and medical use for a 7-day period before vaccination and for the immediate 7 days after vaccination. This survey queried whether the child had any ILI-related symptoms, medication or humidifier use, medically attended visits, days of school missed by the vaccinee, and days of paid work missed by a caretaker for this child's illness. Parents were advised to report serious adverse events that occurred within 42 days of vaccination to study coordinators.

There were significantly elevated rates of illness symptoms (with the exception of wheezing) and nonprescription medicine and humidifier use in the post-vaccination surveys compared with pre-vaccination surveys (Supplemental Table 2). There were no significant increases in prescription medication use, medically attended visits, or days of school or work lost by family members. No hospitalizations were reported among vaccinees in the first seven days after vaccination.

**Supplemental Table 1. Rates from Post hoc Analysis of Reported Health Care Utilization, Medication Utilization, Missed Workdays, and School Absence Due to Fever or ILI During the Peak Influenza Week Referenced by Questionnaire**

<b>Outcome</b>	<b>LAIV</b>	<b>No LAIV</b>	<b>Adjusted Absolute Difference (95% Confidence Interval)*</b>	<b>P Value*</b>
<b>Fever or ILI</b>				
<b>Number (%) households with symptoms per observation week</b>				
Households –no.	1689	6821		
Households reporting children with				
Any fever or ILI	678 (40.1)	3416 (50.1)	4.6 (1.5– 7.6)	0.004
Fever plus cough or sore throat <sup>†</sup>	269 (15.9)	1689 (24.8)	5.6 (3.1–8.1)	<0.001
Households reporting				

adults with

Any fever or ILI	540 (32.0)	2868 (42.0)	4.7 (1.7–7.7)	0.002
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Fever plus cough

or sore throat <sup>†</sup>	186 (11.0)	1019 (14.9)	2.0 (–0.0 to 4.1)	0.05
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**Health care utilization by household members**

**Rate per 100 Individuals per observation week**

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Children –no.	4360	17,549		
Doctor’s	6.8	10.6	3.3 (1.8–4.9)	<0.001
office/clinic				
Emergency room/				
urgent care	0.9	1.3	0.5 (–0.0 to 1.1)	0.06
Hospitalization	0.2	0.1	0.0 (–0.2 to 0.1))	0.82
(no.)	(9)	(26)		
Adults –no.	3423	13,702		

Doctor's				
office/clinic	4.6	6.4	1.4 (0.1–2.6)	0.03
Emergency room/				
urgent care	0.8	1.0	–0.1 (–0.6 to 0.5)	0.80
Hospitalization	0.15	0.15	0.0 (–0.1 to 0.2)	0.77
(no.)	(5)	(21)		

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**Medication utilization by household members to treat fever or ILI**

**Rate per 100 Individuals per observation week**

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Prescription	7.1	10.9	2.6 (1.2– 4.1)	<0.001
Traditional OTC	18.1	23.6	1.8 (–0.2 to 3.9)	0.08
Vitamins or natural/				
herbal remedies	7.3	10.2	1.5 (0.0–3.0)	0.04
Vaporizers or				
humidifiers	4.2	5.6	1.1 (0.1–2.2)	0.03

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**School absence for fever or ILI****Rate of absences per 100 school days**

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**School-age children**

Elementary school	3.8	6.6	2.0 (1.0–2.9)	<0.001
Middle school	4.2	6.2	1.5 (–0.2 to 3.1)	0.08
High school	3.3	5.3	1.7 (–0.1 to 3.6)	0.07

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**Paid workdays missed by adults****Mean number of days of work missed by adults (per household during  
observation week)**

For any fever or ILI

or to care for

children with fever or

ILI	0.298	0.368	0.026 (–0.035 to 0.086)	0.41
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To care for sick

child <sup>‡</sup>	0.233	0.244	–0.007 (–0.068 to 0.054)	0.82
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ILI=influenza-like illness.

Note: Questionnaire was administered during prospectively defined peak influenza week.

\*Based on a mixed-effects model, including random school and cluster effects, and controlling for state differences.

†Number (%) of households reporting one or more children (or adults) with fever and one or more children (or adults) with either cough or sore throat.

‡Based on only those families without an adult who ordinarily stays home during the school day.

**Supplemental Table 2. Seven-Day Recall of Illness Symptoms, Medications, Medical Visits, and School Days or Workdays Missed Before and After Vaccination.**

	<b>Prevaccination</b>	<b>Postvaccination</b>	
	<b>(n=2280)</b>	<b>(n=1329)</b>	<b>P value</b>
<hr/>			
Symptom –no. (%)			
Fever	69 (3)	134 (10)	<.0001
Runny nose	141 (6)	261 (20)	<.0001
Ear ache	13 (1)	22 (2)	<.0022
Cough	146 (6)	164 (12)	<.0001
Sore throat	74 (3)	116 (8)	<.0001
Muscle aches	14 (1)	51 (4)	<.0001
Chills	13 (1)	43 (3)	<.0001
Wheezing	7 (<1)	5 (<1)	.73

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Medication use and medical visits, mean per 100 children

Prescription medications	3.6	4.2	.44
Nonprescription medications	11.8	24.8	<.0001
Vitamins and herbal remedies	2.3	5.6	.0017
Vaporizer/humidifier	0.7	1.8	.0028
Doctors visits	2.1	2.0	.84
Emergency room visits	0.2	0.5	.15
Hospitalizations	0	0	NA
<hr/>			
Absenteeism, mean per 100 children			
School days missed	6.8	8.7	.12
Workdays missed*	4.1	6.4	.19

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\*Only households without a stay-at-home parent were included.

SCHOOLMIST FAMILY SURVEY

Date Survey Completed:  /  /   
 Month Day Year

1. Check the box that indicates the number of people in each of the following age groups who live in your household. Also record the number of people in each group who received a flu vaccine this fall or winter (2004-2005).

Age Group	Number of people in household	Number of people who received FluMist spray	Number of people who received Flu Shot
Infant/toddlers not in school	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input type="checkbox"/> None	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input checked="" type="checkbox"/> None	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input checked="" type="checkbox"/> None
Elementary (PreK-5 <sup>th</sup> grade)	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input type="checkbox"/> None	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input checked="" type="checkbox"/> None	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input checked="" type="checkbox"/> None
Middle School (6 <sup>th</sup> -8 <sup>th</sup> grade)	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input type="checkbox"/> None	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input checked="" type="checkbox"/> None	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input checked="" type="checkbox"/> None
High School (9 <sup>th</sup> -12 <sup>th</sup> grade)	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input type="checkbox"/> None	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input checked="" type="checkbox"/> None	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input checked="" type="checkbox"/> None
Adults (18 or older)	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input checked="" type="checkbox"/> None	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input checked="" type="checkbox"/> None	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input checked="" type="checkbox"/> None


2. How many adults (18 or older) in your household work outside the home?  1  2  3  4  5  6+  None

3. Is there an adult (18 or older) who is usually home during the school day, as caretaker, for the children in the home?  Yes  No

4. Please check the box that indicates the type of health insurance coverage used by the child who brought this form home.  
 Medicaid-based (Medical assistance, public coverage, CHIP)  
 Commercial (private) Insurance (HMO, PPO, POS)  
 Other insurance (Military, CHAMPUS, etc.)  
 No Insurance/Self-pay

5. Please check the box that indicates the race/ethnicity of the child who brought this form home. (If child is of more than one race or race is not listed, check 'Other' and indicate race below)  
 White/Non-Hispanic  Black  Hispanic  Asian  Other (specify): \_\_\_\_\_

6. *During the 7-day period*, have ANY members of your household (including yourself) been sick with fever or flu-like illness (defined as either runny nose, nasal congestion, sinus problems, earache, ear infection, cough, sore throat, muscle aches, chills or wheezing)?

Yes -- Please continue and answer the questions on the following page.   
 No -- Thank you for completing this survey. You do not need to continue.

7. *During the 7-day period*, have ANY household members (including yourself) experienced the following:

Type of Illness	Number of adults (18 or older) with symptoms or check if 'none'.	Number of children with symptoms or check if 'none'.
Fever	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input type="checkbox"/> None	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input type="checkbox"/> None
Runny nose/Congestion/Sinus Problems	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input type="checkbox"/> None	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input type="checkbox"/> None
Earache/Ear infection	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input type="checkbox"/> None	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input type="checkbox"/> None
Cough	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input type="checkbox"/> None	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input type="checkbox"/> None
Sore Throat	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input type="checkbox"/> None	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input type="checkbox"/> None
Muscle Aches/Chills	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input type="checkbox"/> None	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input type="checkbox"/> None
Wheezing	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input type="checkbox"/> None	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input type="checkbox"/> None

8. *During the 7-day period*, have ANY household members (including yourself) made any of the following medical visits for fever or flu-like illness? (Please check 'none' if there were no visits)

Type of Visit	Number of adult (18 or older) visits or check if 'none'.	Number of child visits or check if 'none'.
Doctor office or clinic	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input type="checkbox"/> None	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input type="checkbox"/> None
Emergency Room/Urgent Care	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input type="checkbox"/> None	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input type="checkbox"/> None
Hospital Admission (over 1 day)	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input type="checkbox"/> None	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6+ <input type="checkbox"/> None

9. *During the 7-day period*, how many of the following treatments were used by ANY household members (including yourself) to treat fever or flu-like illness? (Refer to the instructions for assistance answering this question)

Treatment Type	Total number of items used by ALL household members or check if 'none'.
Prescription Medications	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7+ <input type="checkbox"/> None
Traditional Over-the-Counter Medicines	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7+ <input type="checkbox"/> None
Vitamins or Natural/Herbal Remedies	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7+ <input type="checkbox"/> None
Vaporizer or Humidifier	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7+ <input type="checkbox"/> None

10. *During the 7-day period*, how many days of school were missed by children in your household for fever or flu-like illness?

Type of School	Number of days missed or check if 'none'.
Elementary	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7+ <input type="checkbox"/> None
Middle School	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7+ <input type="checkbox"/> None
High School	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7+ <input type="checkbox"/> None

11. *During the 7-day period*, how many days of **paid work** were missed by you or other adults (18 or older) in your household for fever or flu-like illness or to care for any member of your household with fever or flu-like illness? Check the total number of missed work days:  1  2  3  4  5  6  7+  None

12. *Of the total number of missed work days reported in Question 11*, how many work days were missed to care for a sick child(ren) with fever or flu-like illness? Check the total number of missed work days:  1  2  3  4  5  6  7+  None