FluMist®

Live, Attenuated Influenza Vaccine

Briefing Document

FDA

Vaccines and Related Biological Products Advisory Committee

Prior Approval Supplemental BLA

Indication Extension to Include Children Less than 5 Years of Age

Table of Contents

List of Abbreviations and Definitions

ACIP	Advisory Committee on Immunization Practices
AE	Adverse event
AOM	Acute otitis media
Any wheezing event	Wheezing captured as RE/AE wheezing or protocol-defined wheezing
ATP	According to protocol
att	Attenuated
BLA	Biologics License Application
ca	Cold-adapted
CAIV-T	Cold-adapted influenza virus vaccine – trivalent liquid (refrigerated FluMist)
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CDC-ILI	CDC-defined influenza-like illness (fever of ≥100°F oral or equivalent plus cough or sore throat on the same or consecutive days)
95% CI	95% confidence interval
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
FDA	United States Food and Drug Administration
FFU	Fluorescent focus units
GMT	Geometric mean titer
HA	Hemagglutinin
HAI	Hemagglutination inhibition
ITT	Intent to treat
LAIV	Live, attenuated influenza vaccine
Matched	Wild-type strains antigenically similar to those contained in the vaccine
MedDRA	Medical Dictionary for Regulatory Activities
Mismatched	Wild-type strains antigenically dissimilar to those contained in the vaccine
MMR	M-M-R®II (trivalent measles, mumps, rubella vaccine)
MMR/VAR	M-M-R®II and VARIVAX®

Modified CDC-ILI	Modified CDC-defined influenza-like illness (fever of ≥100°F oral or equivalent plus cough, sore throat, or runny nose/nasal congestion on the same or consecutive days)
MSW	Medically significant wheezing (see protocol-defined wheeze)
Protocol-defined wheezing	Protocol-defined medically significant wheezing; the presence of wheezing on physical examination that was accompanied by at least one of the following: sign of respiratory distress (tachypnea, retractions, or dyspnea), hypoxemia (O_2 saturation <95%), or a new prescription for daily bronchodilator therapy (not on an "as needed" basis)
RE	Reactogenicity event
RE/AE wheeze	Wheezing captured as a reactogenicity event (i.e., reported by the child's caregiver) or as an adverse event (i.e., reported by a health care provider)
SAE	Serious adverse event
sBLA	Supplemental BLA
SPG	Sucrose, phosphate, glutamate buffer
$TCID_{50}$	Median tissue culture infectious dose
TIV	Trivalent inactivated influenza virus vaccine
ts	Temperature sensitive
U.S.	United States
VAERS	Vaccine Adverse Events Reporting System
VAR	VARIVAX® (varicella vaccine)
WHOART	World Health Organization adverse reaction terminology

1 Overview

Influenza is an important cause of morbidity and mortality in young children. Immunization against influenza is currently recommended in the U.S. for all children 6-59 months of age using injectable trivalent inactivated influenza vaccine (TIV). While TIV is effective, the level of protection in infants and young children has recently been debated. The development of alternative vaccines for prevention of influenza in this population is a high public health priority.

Live, attenuated influenza vaccine (LAIV, FluMist) is currently approved for prevention of influenza in healthy individuals 5-49 years of age. MedImmune has now conducted clinical trials to assess the safety and efficacy of FluMist in children <5 years of age, including a large pivotal trial directly comparing FluMist and TIV. These studies show that FluMist (1) is highly efficacious in prevention of symptomatic influenza, including modified CDC-ILI, (2) has better overall efficacy compared to TIV, and (3) has better cross-protection against mismatched strains of influenza compared to TIV. With regards to safety in the pivotal comparative study, the reactogenicity profile of the vaccines is as expected, with FluMist having a higher rate of runny/stuffy nose and TIV having a higher rate of injection site reactions. Children <24 months of age who received FluMist had statistically significant increase in protocol-defined wheezing, with children <12 months accounting for most but not all of this difference. In post hoc analyses, children 6-11 months of age had a significant increase in all cause hospitalizations, mostly >42 days after vaccination. While the biological plausibility of this latter observation is not certain, further study is needed in this population. Additional post hoc risk-benefit assessment in children 12-23 months of age without a history of wheeze or asthma suggests no increase in hospitalizations, a small but non-significant increase in wheezing post vaccination, and a significant decrease in influenza illness compared to TIV. This same post hoc risk-benefit assessment suggests a highly favorable profile for children ≥24 months of age without a history of wheeze or asthma. Among these children, FluMist recipients had significantly fewer cases of culture-confirmed modified CDC-ILI compared to TIV recipients and no increase in wheezing rates or hospitalizations.

Based on the finding of better overall efficacy compared to TIV that led to the favorable risk-benefit profile of FluMist, MedImmune has proposed an indication for "children 12-59 months of age without a history of wheeze or asthma." For those children 24-59 months of age, significant benefit was observed without wheezing or hospitalization risk. For those children 12-23 months of age, significant benefit was observed with only some residual potential increase in wheezing post vaccination.

FluMist is a highly effective vaccine, with 55% overall better efficacy shown in the pivotal trial compared to TIV. MedImmune believes that the safety and efficacy of FluMist have been established for children 24 months through 59 months of age without a history of wheeze or asthma, and that the risk-benefit profile for children 12-23 months of age without a history of wheeze or asthma warrants use of FluMist in this population as well.

2 Introduction

Background

Influenza is the leading cause of vaccine-preventable morbidity and mortality in the United State (U.S.). Influenza epidemics occur nearly every year and are responsible for an average of approximately 36,000 deaths per year in the U.S. (Thompson 2003). While influenza causes illness in all age groups, rates of infection are highest among children, and otherwise healthy children were recently recognized to be at increased risk for influenza-related hospitalization (Bridges 2003). Among young children, hospitalization rates due to influenza are reported to be comparable to rates in the elderly (Izurieta 2000, Neuzil 2000, Poehling 2006). The majority of influenza-related deaths in children occur in those <5 years of age, and nearly half of the pediatric influenza-related deaths are in children who are otherwise considered healthy (Bhat 2005). Influenza infection is also responsible for excess rates of outpatient clinic visits and emergency room visits in children <5 years of age (Poehling 2006). In addition to the morbidity and mortality in children themselves as a result of influenza infection, children are also the major pathway by which influenza infection is spread within the community (Fox 1982, Neuzil 2002, Weycker 2005).

Vaccination is the primary method for preventing illness and severe complications related to influenza. Annual vaccination is recommended for any person 6 months of age or older who is at increased risk for complications of influenza and for those in close contact with persons at high risk. In 2004 the Advisory Committee on Immunization Practices (ACIP) recommended influenza vaccination of all children 6-23 months of age, as well as their out-of-home caregivers and household contacts (CDC 2004). In February 2006, ACIP updated these recommendations to include children up to 59 months of age and their caregivers and contacts (CDC 2006). Prevention of spread of influenza by vaccination of children is an important part of influenza control.

The only vaccine available for prevention of influenza in children less than 5 years of age is traditional, injectable, trivalent inactivated influenza vaccine (TIV). TIV is composed of split-virus (i.e., subvirion) trivalent formulations that include A/H1N1, A/H3N2, and B antigens, primarily purified hemagglutinin (HA) protein derived from each of the targeted strains. Intramuscular injection of TIV stimulates a serum antibody response against the HA proteins contained in the vaccine, particularly in recipients previously vaccinated or otherwise exposed to influenza.

The magnitude of benefit of TIV in the elderly and in young children has lately come under question (Jackson 2005, Jefferson 2005, Simonsen 2005, Smith 2006). A recent review reported that in children <9 years of age, pooled efficacy for TIV against culture-confirmed

influenza was 63% (Zangwill 2004). In children <5 years of age, efficacy reported in five studies ranged from 12% to 83%; lower than expected efficacy in some studies was attributed to lack of previous influenza exposure in the youngest children or to poor matching of vaccine and circulating strains. For children 6-23 months of age, a randomized, double-blind, placebo-controlled trial reported efficacy against culture-confirmed influenza for TIV of 66% (95% CI 34, 82) in the first study year in which there was a high influenza virus attack rate and –7% (95% CI –247, 67) in the second study year in which there was a lower attack rate (Hoberman 2003). While overall efficacy for TIV is commonly reported to be 70% to 90%, the relatively small number of studies that have specifically evaluated protection in young children indicate efficacy estimates that are lower and more variable. Given the high burden of influenza in children, families, and communities, the development of alternative approaches to vaccination, particularly for young children, is an important medical and public health priority.

Live, attenuated influenza vaccine (LAIV) has been developed as a new approach to influenza vaccination. LAIV replicates in respiratory tract epithelial cells, the normal target tissue of influenza viruses, and LAIV antigens are presented to the immune system in a manner similar to that occurring during natural infection with wild-type viruses. Therefore, the immune response to vaccination with LAIV is expected to mimic that acquired by natural infection with wild-type influenza. In fact, studies have demonstrated that vaccination with LAIV induces influenza-specific serum and nasal antibodies and T-cell responses.

FluMist® (Influenza Virus Vaccine, Trivalent, Types A & B, Live, Cold Adapted) is a live, attenuated intranasally administered vaccine that has been shown to be safe and effective for the prevention of influenza in healthy children and adolescents 5-17 years of age and in healthy adults 18-49 years of age. FluMist is currently approved in the U.S. for use in these individuals.

MedImmune has conducted a series of large clinical trials to assess the efficacy and safety of FluMist in children under the age of 5 years. Based on efficacy and safety data compiled from a pivotal Phase 3 clinical trial and other supportive trials, MedImmune is now seeking to expand the current indication in the U.S. to include children less than 5 years of age. MedImmune believes that FluMist offers young children the potential for better protection against influenza disease (including when the circulating strains are mismatched to the vaccine strains) compared to currently marketed formulations of inactivated influenza vaccines for this pediatric age group. Approval of the expanded age indication would also address the medical need of having an additional manufacturer of influenza vaccine for young children and making available a source of thimerosal-free non-injectable influenza vaccine for this population.

The data from this supplemental BLA (sBLA) are summarized in this briefing document. Primary data as well as post hoc risk-benefit analyses are presented for children 59 months of age and younger. MedImmune believes that these data support the efficacy and safety of FluMist in children 12-59 months of age without a history of wheezing/asthma.

Product Description

Two formulations of FluMist have been studied worldwide, a frozen formulation and a refrigerated formulation. The characteristics of the two formulations are summarized in Table 2-1 below.

Table 2-1 Frozen and Refrigerated Formulations of FluMist

Characteristic	Frozen FluMist	Refrigerated FluMist
Master Donor Virus	A/Ann Arbor/6/60 (H2N2) B/Ann Arbor/1/66	A/Ann Arbor/6/60 (H2N2) B/Ann Arbor/1/66
Valency	Trivalent	Trivalent
Concentration	Approximately 10^7 $TCID_{50}$ per strain per dose	Approximately 10^7 FFU per strain per dose
Excipients	Egg allantoic fluid, SPG	Egg allantoic fluid, SPG, arginine, acid hydrolyzed porcine gelatin
Storage	≤ –15°C (Freezer)	2°C to 8°C (Refrigerator)
Dose Volume	0.5 mL (0.25 mL per nostril)	0.2 mL (0.1 mL per nostril)

FFU = fluorescent focus units; SPG = sucrose, phosphate, glutamate buffer; $TCID_{50}$ = median tissue culture infectious dose.

The frozen formulation was approved at the time of the initial approval for FluMist in June 2003. A refrigerated formulation was developed, and product characterization and clinical data demonstrated comparability of the two formulations. These data were submitted to the FDA in September 2005, and the refrigerated formulation of the vaccine (formerly known as CAIV-T) was approved in January 2007.

The active agents of FluMist consist of two cold-adapted (*ca*), temperature sensitive (*ts*), attenuated (*att*) reassortant influenza strains of type A (i.e., A/H1N1 and A/H3N2), and one *ca/ts/att* reassortant influenza strain of type B. Cold-adapted reassortant vaccine strains are produced in specific pathogen-free chicken eggs and primary chick kidney cells by genetic reassortment between a wild-type influenza virus and a *ca* master donor strain. The vaccine is manufactured in specific pathogen-free eggs using a *ca* reassortant virus containing the six gene segments encoding internal virus proteins from the *ca/ts/att* master donor virus strains

and the two wild-type gene segments encoding the hemagglutinin and neuraminidase surface proteins from wild-type viruses. The resulting *ca/ts/att* strains are referred to as 6:2 reassortants.

For production of refrigerated FluMist, each reassortant virus is further concentrated and purified from egg contaminants by centrifugation on a sucrose gradient prior to formulation. FluMist is stabilized with a sucrose, phosphate, glutamate buffer, as well as arginine and acid hydrolyzed porcine gelatin. The ultracentrifugation step in combination with the new formulation confers the stability of FluMist at 2°C to 8°C. The virus concentration step also permits a lower dosing volume for the refrigerated formulation (0.2 mL) relative to the previously approved frozen formulation (0.5 mL). Each dose of FluMist contains approximately 10^7 FFU (fluorescent focus units) per strain per dose.

3 FluMist Clinical Trial Experience

In 48 completed clinical research trials worldwide, more than 48,000 subjects ranging in age from 6 weeks to >90 years received frozen or refrigerated FluMist. More than 40,000 children and adolescents from 6 weeks to 18 years of age, including >2,000 with conditions such as asthma, recurrent respiratory tract illness, or human immunodeficiency virus infection, have received at least one dose of FluMist in clinical trials.

In addition to this clinical trial experience, more than 45,000 doses of frozen FluMist have been administered in two post-marketing studies and approximately 6 million doses of FluMist have been distributed for commercial use in individuals 5-49 years of age following licensure of the product in 2003 through 2006. During the first two seasons of FluMist commercial use, VAERS (Vaccine Adverse Events Reporting System) did not identify any unexpected serious risk with the vaccine when used according to approved indications (Izurieta 2005). To date, no unexpected serious risks have been identified for FluMist when used according to approved indications.

Studies with FluMist in both children and adults have demonstrated high levels of protection against culture-confirmed influenza (Belshe 1998, Belshe 2000, Treanor 1999, Vesikari 2006, Tam 2007). Additionally, FluMist has demonstrated protection in both children and adults against influenza strains antigenically mismatched to those contained in the vaccine in several studies conducted over multiple seasons (Belshe 2000, Nichol 1999, Gaglani 2005, Piedra 2005, King 2005). Protection against antigenically mismatched strains is especially relevant, because vaccine mismatch appears to be increasingly common, having occurred in the United States to significant degrees in four of the last nine influenza seasons (1997-1998, 2000-2001, 2003-2004, and 2004-2005).

At the time of the initial approval of FluMist in 2003, MedImmune did not seek an indication for children less than 5 years of age because a placebo-controlled safety study in approximately 9500 children 1-17 years of age (Study AV019, Bergen 2004) showed a higher rate of asthma/reactive airways disease in children 18-35 months of age (2.2% frozen FluMist, 0.54% placebo). Post hoc analysis could not rule out an increase in these events in children up to 5 years of age. An important limitation of this study, however, was that it was not designed to prospectively address the risk of asthma.

Subsequently, two open-label, controlled trials were conducted in Europe and Israel during the 2002-2003 influenza season to evaluate the efficacy of FluMist compared to TIV in two pediatric populations. One study randomized 2187 children 6-71 months of age with a history of recurrent respiratory tract infections to receive two doses of refrigerated FluMist or TIV. In this study, children receiving FluMist had 53% (95% CI: 22, 72) fewer cases of influenza illness compared to TIV recipients due to matched strains (Study D153-P514; Ashkenazi 2006). The second study was conducted in 2229 children and adolescents 6-17 years of age with asthma who received a single dose of refrigerated FluMist or TIV. In this study, children receiving FluMist had 35% (95% CI: 4, 56) fewer cases of influenza illness due to matched strains compared to TIV recipients (Study D153-P515; Fleming 2006).

Based on the potential safety signal seen in Study AV019 and the higher efficacy against influenza illness seen in Studies D153-P514 and D153-P515, MedImmune conducted the pivotal study MI-CP111 to evaluate both safety and efficacy of FluMist and TIV in children 6-59 months of age (Belshe 2007). Study MI-CP111 was a randomized, double blind, multinational study that enrolled 8475 children. Children, including those with underlying medical conditions, were eligible to participate, except for those with recent wheezing, severe asthma, or immunocompromise. The primary efficacy endpoint was the relative efficacy of refrigerated FluMist vs. TIV against culture-confirmed modified Centers for Disease Control & Prevention influenza-like illness ("modified CDC-ILI")[1] caused by wild-type strains antigenically similar to those contained in the vaccine. To more effectively understand any risk of wheezing or asthma with FluMist, a prospectively defined case definition was used as the primary assessment of wheezing outcomes. A case (medically

[1] CDC-ILI (Centers for Disease Control and Prevention–defined influenza-like illness), defined as fever (temperature ≥100°F oral or equivalent) plus cough or sore throat on the same or consecutive days, was modified ("modified CDC-ILI") to fever plus cough, sore throat, *or runny nose/nasal congestion* as a means of capturing age-appropriate influenza illness symptoms per discussions with CBER.

significant wheezing, MSW)[2] was defined as a medical diagnosis of wheezing associated with other respiratory findings or with initiation of new bronchodilator therapy. Secondary efficacy endpoints included efficacy against mismatched influenza strains and all circulating strains combined as well as lower respiratory tract infection and otitis media associated with modified CDC-ILI. Other safety outcomes included reactogenicity events, adverse events, serious adverse events, and hospitalizations.

The design of Study MI-CP111 provided the opportunity for a comprehensive evaluation of both benefit and risk of FluMist compared to TIV in the same population over the same influenza season. Pre-specified and exploratory analyses from this trial are provided in this briefing document and (along with supportive data) form the foundation for MedImmune's sBLA submission for US regulatory approval of FluMist in children 12-59 months of age without a history of wheezing or asthma. The studies that provide primary evidence of the efficacy and safety of FluMist that are part of this sBLA (BL 125020/322, filed with the FDA in July 2006) are listed in Table 3-1. Study MI-CP123 provides comparative immunogenicity data, and Study AV018 is also listed and provides data on concurrent vaccination with M-M-R®II and VARIVAX® in infants. A description of the design for each study follows. As requested by the FDA, serious adverse event data from several other studies (see Table 6-1) are summarized in Section 6.4.2 and as part of the safety assessment.

[2] Medically significant wheezing was defined as the presence of wheezing on physical examination that was accompanied by at least one of the following: sign of respiratory distress (tachypnea, retractions, or dyspnea), hypoxemia (O_2 saturation <95%), or a new prescription for daily bronchodilator therapy (not on an "as needed" basis).

Table 3-1 Description of Clinical Efficacy and Safety Studies Included in the sBLA

Study; Year; Location	Design	Population	Treatment; [a] Regimen	Number of Subjects [b]	Endpoints/Objectives
MI-CP111 2004-2005 USA, Europe, Middle East, Asia	Phase 3 Randomized Double blind Active control <u>Follow-Up</u> REs & AEs Days 0-42 Wheezing, protocol defined wheezing (medically significant wheezing, MSW), & SAEs through influenza surveillance period	Children, excluding those with recurrent persistent or severe asthma or immunocompromise 6 to 59 mos of age	CAIV-T + IM Placebo TIV + IN Placebo IN products (CAIV-T and IN Placebo, 0.2 mL) IM products (TIV and IM Placebo, 0.25 or 0.5 mL according to age) Previously vax'd: 1 dose Not previously vax'd: 2 doses, 28-42 days apart	4243 4232 (Note: 241 CAIV-T and 242 TIV with underlying medical conditions)	• Relative efficacy against culture-confirmed modified CDC-ILI due to matched strains (modified CDC-ILI defined as fever plus cough, sore throat, or runny nose/nasal congestion on same or consecutive days) • Safety: rate difference for protocol-defined wheezing (MSW, defined as wheezing on physical exam plus sign of respiratory distress, hypoxemia, or new prescription for daily bronchodilator therapy)
D153-P501 Year 1, 2000-2001 Year 2, 2001-2002 Asia	Phase 3 Randomized Double blind Placebo control Subjects were re-randomized to tx group in Year 2 <u>Follow-Up</u> REs & AEs Days 0-10 SAEs through influenza surveillance period	Healthy children 12 to <36 mos of age Subjects enrolled in Year 2 had to receive both doses in Year 1	<u>Year 1</u> CAIV-T, 0.2 mL IN Placebo, 0.2 mL, IN 2 doses, 28-56 days apart <u>Year 2</u> CAIV-T in Year 1: CAIV-T, 0.2 mL IN Placebo, 0.2 mL IN Placebo in Year 1: CAIV-T, 0.2 mL IN Placebo, 0.2 mL IN 1 dose	1900 1274 881 876 596 594	• Efficacy against culture-confirmed influenza due to matched strains (post Dose 2 in Yr 1; post Dose 1 in Yr 2) • Immunogenicity: strain-specific serum HAI seroconversion post Dose 2, matched strains (subset of subjects)

Table 3-1 Description of Clinical Efficacy and Safety Studies Included in the sBLA (continued)

Study; Year; Location	Design	Population	Treatment; [a] Regimen	Number of Subjects [b]	Endpoints/Objectives
AV006 Year 1: 1996-1997 Year 2: 1997-1998 USA	Phase 3 Randomized Double blind Placebo control Non-randomly assigned to receive 1 or 2 doses in Year 1 <u>Follow-Up</u> REs & AEs Days 0-10 SAEs through influenza surveillance period	Healthy children 15 to 71 mos of age	<u>Year 1</u> FluMist, 0.5 mL IN Placebo, 0.5 mL IN 1 dose or 2 doses, 46-74 days apart <u>Year 2</u> FluMist, 0.5 mL IN Placebo, 0.5 mL IN 1 dose	 1070 532 917 441	• Efficacy against culture-confirmed influenza due to matched strains • Efficacy against influenza-associated AOM • Immunogenicity: strain-specific serum HAI seroconversion, matched strains (subset of subjects) and mismatched strains (subset of subjects)
MI-CP123 2005 USA	Phase 2 Randomized Open label Active control <u>Follow-Up</u> AEs Days 0-42 SAEs through 180 days post final dose	Children 6 to <36 mos of age	CAIV-T, 0.2 mL IN TIV, 0.25 mL IM 2 doses, 28-42 days apart	24 28	• Immunogenicity: strain-specific serum HAI seroconversion post Dose 2, matched strains • Immunogenicity: strain-specific serum HAI seroconversion post Dose 2, mismatched strains

Table 3-1 Description of Clinical Efficacy and Safety Studies Included in the sBLA (continued)

Study; Year; Location	Design	Population	Treatment; [a] Regimen	Number of Subjects [b]	Endpoints/Objectives
AV018 2000-2003 USA, Australia	Phase 3 Randomized Double blind (Group 1 vs. Group 2 only) Placebo control <u>Follow-Up</u> REs & AEs Days 0-41 SAEs through 180 days post final dose	Healthy children 12-15 mos of age	<u>Group 1</u> Dose 1: Placebo+ MMR®II+VARIVAX® Dose 2: FluMist Dose 3: FluMist <u>Group 2</u> Dose 1: FluMist+ MMR®II+VARIVAX® Dose 2: FluMist Dose 3: Placebo* <u>Group 3</u> Dose 1: FluMist Dose 2: FluMist Dose 3: MMR®II + VARIVAX® FluMist and Placebo, 0.5 mL IN MMR®II and VARIVAX®, 0.5 mL SC Dose 1&2, 42 days apart Dose 2&3, 30 days apart	411 422 412	• Immunogenicity: strain-specific serum HAI seroconversion post Dose 2, matched strains (lower limit of 95% CI > -10 for each influenza strain) • Immunogenicity: serum HAI strain-specific GMT ratio post Dose 2, matched strains (lower limit of 95% CI > 0.5 for each influenza strain) • Immunogenicity: post vaccination seropositivity rate (lower limit of 95% CI > -5 for measles, mumps, and rubella, > -10 for varicella) • Immunogenicity: post vaccination antibody titer GMT ratio (lower limit of 95% CI > 0.5 for each antigen)

AE=adverse event; AOM=acute otitis media; CAIV-T=refrigerated FluMist; CDC-ILI=influenza-like illness defined by the Centers for Disease Control and Prevention; CI=confidence interval; FluMist=frozen FluMist; GMT=geometric mean titer; HAI=hemagglutination inhibition; IM=intramuscular; IN=intranasal; MSW=medically significant wheezing; RE=reactogenicity event; SAE=serious adverse event; SC=subcutaneous; TIV=trivalent inactivated influenza virus vaccine

a. Frozen FluMist is formulated to contain approximately 10^7 $TCID_{50}$ of each of the three vaccine strains per dose. CAIV-T is formulated to contain approximately 10^7 FFU of each of the three vaccine strains per dose.

b. Number of subjects in the *Safety Population*.

3.1 Descriptions of Study Designs

AV019

Study AV019 was a randomized, double blind, placebo controlled safety study in healthy children 1 to 17 years of age, conducted during the 2000-2001 influenza season, that evaluated the post vaccination rates of medically attended events for 9689 children enrolled in the Kaiser Health Plan of Northern California. Randomization was 2:1 (frozen FluMist to placebo). A total of 5637 children were 1-8 years of age (3769 FluMist vs. 1868 placebo) and 4052 children were 9-17 years of age (2704 FluMist vs. 1348 placebo). Adverse events (medically attended events, or MAEs) were assessed in this study by extraction from Kaiser Permanente's health care utilization databases associated with hospital, emergency department, or clinic utilization within 42 days of vaccination.

In this study, overall medical utilization was estimated by comparing rates of hospital, emergency department, and clinic usage for all recipients of frozen FluMist with the corresponding rates for all placebo recipients during the safety monitoring period. Four groups of diagnoses representing illness syndromes that could potentially be caused by wild-type influenza infection were prospectively identified, and rates of these pre-specified grouped diagnoses were also used to further assess the safety of FluMist. The four pre-specified grouped diagnoses were acute respiratory tract events, systemic bacterial infections, acute gastrointestinal tract events, and rare events potentially related to influenza.

Prespecified analyses were conducted by age group (all participants, participants 1-8 years of age, 9-17 years of age, 12-17 months of age, and 18-35 months of age), by setting (hospitalization, emergency department, clinic, or all three settings combined), and by dose (after Dose One, after Dose Two, and after all doses combined). The 12-17 and 18-35 month age subsets were selected for post hoc analyses to provide additional information on safety in young children.

MI-CP111

Study MI-CP111 was a pivotal, Phase 3, prospective, randomized, double blind, active-controlled trial in children 6-59 months of age. The primary objective of this study was to estimate the relative efficacy and assess the safety of FluMist compared to TIV. The secondary objectives were to estimate the relative effectiveness of FluMist compared to TIV, and to assess the tolerability of FluMist compared to TIV. The study was conducted during the 2004-2005 influenza season in the U.S. and 15 countries in Europe, the Middle East, and Asia. Children were randomized at a 1:1 ratio to receive either intranasal refrigerated FluMist plus intramuscular placebo (N=4243), or intramuscular TIV plus intranasal placebo

(N=4232). Randomization was stratified by age at first dose (6-23, 24-35, or 36-59 months of age), prior influenza vaccination status, recurrent wheezing history status (defined as the presence or absence of a history of three or more wheezing illnesses requiring medical follow-up or hospitalization), and country. Children who previously received any influenza vaccine, by parent report or chart review, received a single dose of study vaccine plus corresponding placebo (Dose One) on Study Day 0 (ONE DOSE group). Children who never previously received an influenza vaccination (or had an unknown history of influenza vaccination) received two doses of study vaccine plus corresponding placebo: Dose One on Study Day 0, and Dose Two 28-42 days after the first dose (TWO DOSE group).

The primary efficacy endpoint was the incidence of culture-confirmed modified CDC-ILI, occurring during the influenza surveillance period (which ended on 31/May/2005) caused by wild-type strains antigenically similar to those contained in the vaccine (**matched** strains). CDC-ILI (CDC-defined influenza-like illness), defined as fever (temperature ≥100°F oral or equivalent) plus cough or sore throat on the same or consecutive days, was modified ("*modified CDC-ILI*") to fever plus cough, sore throat, *or runny nose/nasal congestion* as a means of capturing age-appropriate influenza illness symptoms per discussions with the Center for Biologics Evaluation and Research (CBER). Culture-confirmed modified CDC-ILI was defined as a positive culture for a wild-type influenza virus associated within ±7 days of modified CDC-ILI symptoms.

The secondary efficacy endpoints of the study included:

- Culture-confirmed modified CDC-ILI caused by wild-type **mismatched** strains;
- Culture-confirmed symptomatic influenza infection caused by wild-type **matched** strains; and
- Culture-confirmed symptomatic influenza infection caused by wild-type **mismatched** strains.

Culture-confirmed symptomatic influenza infection was defined as a positive culture for a wild-type influenza virus associated within ±7 days of one (or more) of the following symptoms: fever (temperature ≥99.8°F oral or equivalent), wheezing, shortness of breath, pulmonary congestion (including bronchitis, bronchiolitis, and croup), pneumonia, or ear infection (acute otitis media [AOM], suspected or diagnosed); or at least two of the following symptoms concurrently: runny/stuffy nose (rhinorrhea), sore throat (pharyngitis), cough, muscle aches, chills, headache, irritability, decreased activity, or vomiting.

The primary analysis included cultures obtained ≥14 days after the final required study vaccination and used the According to Protocol (ATP) Population, defined as randomized

children who had at least one surveillance contact on or after 01/Nov/2004 that was also ≥14 days after the final required vaccination, and who did not experience a major protocol violation during the study. The primary endpoint was also evaluated using cultures obtained at any time after randomization and in the Intent to Treat (ITT) Population, defined as all randomized children.

Nasal swabs for influenza virus culture were to be collected from children within 24 hours of qualifying symptoms or as soon as possible thereafter. Specimens were stabilized in viral transport media within 4 hours of collection and shipped at 2°C to 8°C within 24-72 hours to one of four designated central virology laboratories: Quest Diagnostics Clinical Trials, Van Nuys, California, USA; Department of Microbiology, Prince of Wales Hospital, Hong Kong; Department of Virology, University of Turku, Turku, Finland; ERNVL, RVU Health Protection Agency, London, United Kingdom. Cultures were incubated at 33°C for at least 14 days, and identification of positive samples was performed according to each laboratory's standard procedures. Supernatants from positive cultures were stored at -70°C and shipped to MedImmune for strain-matching by hemagglutination inhibition (HAI) identification assay, and for genotyping and subtyping by PCR. Viruses were characterized as either antigenically similar (matched) or as not well matched (mismatched) to the vaccine strain. Reference antisera provided by the Centers for Disease Control and Prevention (CDC) were used to antigenically characterize isolates and a ≥4-fold difference in HAI titers was considered indicative of antigenic variation between two viruses.

Relative efficacy (percent reduction in cases of influenza illness) was defined as:

Relative efficacy = (1 - [Observed rate in FluMist / Observed rate in TIV]) x 100

As prospectively defined in the Statistical Analysis Plan, non-inferior relative efficacy was demonstrated if the lower bound of the 95% confidence interval (95% CI) was > -30%, and statistically significant superior relative efficacy was demonstrated if the lower bound was > 0%.

Confidence intervals for relative efficacy were constructed using an exact binomial method for multiple strata (age, country, history of prior influenza vaccination, and history of ≥3 wheezing illnesses [recurrent wheezing history]), conditioned upon the total number of cases, with mid-probability adjustment (Guess 1987). These confidence intervals and their corresponding adjusted estimates of relative efficacy, rather than crude estimates, are presented. This procedure is implemented in StatXact 6.0 and Proc STATXACT (Cytel Software).

The pre-specified subgroups for analysis included children 6-23 and 24-59 months of age. Analyses were also conducted by stratification variable, and post hoc assessments were done

by additional age subsets (6-11 and 12-23 months of age) as well as for children with and without a history of wheeze or diagnosis of asthma. History of wheezing (i.e., any wheezing) and history of asthma at baseline were collected prospectively on the case report form, from the parent and/or by chart review.

Safety assessments included reactogenicity events (REs), other adverse events (AEs), serious adverse events (SAEs), and significant new medical conditions (SNMCs). Parents/guardians recorded safety events on study worksheets and submitted the completed worksheets to the clinical site on a monthly basis through the end of the influenza surveillance period (31/May/2005). Qualifying symptoms (those solicited symptoms that were to prompt a study site visit for nasal swab collection) were recorded from administration of Dose One through the end of the influenza surveillance period.

Wheezing outcomes were assessed using a prospectively defined case definition (medically significant wheezing, MSW), defined as the presence of wheezing on physical examination and accompanied by at least one of the following: sign of respiratory distress (tachypnea, retractions, or dyspnea), hypoxemia (O_2 saturation <95%), or a new prescription for daily bronchodilator therapy (not on an "as needed" basis). The incidence and number of episodes of medically significant wheezing were assessed by constructing a 2-sided 95% CI for the rate difference of FluMist minus TIV. The confidence intervals were computed using the asymptotic method of Miettinen and Nurminen (1985) for stratified analyses. This method constructs approximate confidence intervals by inverting a score test for the common rate difference. Constrained estimates of variability are constructed for each stratum and are combined to form a weighted chi-square value. The strata are weighted using an iterative technique to produce weights proportional to the amount of comparative information within each stratum. The strata were the same as those used in the efficacy analyses with the exception of country, due to sparse data issues.

In addition, wheezing reported as an RE or as AE was analyzed as a secondary endpoint ("RE/AE wheezing"). RE/AE wheezing, unlike the case definition of wheezing (MSW), was not a protocol-specified case definition and included wheezing reported by the child's caregiver as well as wheezing reported by a health care provider. RE/AE wheezing and MSW were not mutually exclusive categories. RE/AE wheezing was recorded in the case report form and then coded using MedDRA. Prior to unblinding, the Medical Monitor reviewed all MedDRA terms to identify wheezing illness synonyms (e.g., wheezing, bronchospasm, asthma, bronchiolitis), and those terms were combined for the summary of RE/AE wheezing. Events of RE/AE wheezing and MSW were combined for the analysis of "any wheezing event."

D153-P501, Year 1 and Year 2

Study D153-P501 was a Phase 3, randomized, double blind, placebo-controlled study of FluMist in healthy children 12-35 months of age. The primary objective of this study was to determine the efficacy of FluMist against culture-confirmed influenza illness. Secondary objectives were to investigate the efficacy of FluMist over multiple influenza seasons, the effect of FluMist on AOM, and the possibility of asymptomatic carriage of influenza virus in healthy children during an influenza season.

The study was conducted during the 2000-2001 and 2001-2002 influenza seasons at multiple sites in Asia. In Year 1 of the study, children were randomized at a 3:2 ratio to receive two doses, 28-56 days apart, of refrigerated FluMist (N=1900) or placebo (N=1274). In Year 2 of the study, children who participated in Year 1 were re-randomized at a 1:1 ratio, independently of the Year 1 treatment assignment, to receive a single dose of refrigerated FluMist (total N=1477; 881 who previously received FluMist, 596 who previously received placebo) or placebo (total N=1470; 876 who previously received FluMist, 594 who previously received placebo).

The primary endpoint was the incidence of culture-confirmed symptomatic influenza illness due to wild-type **matched** strains following receipt of the second dose of FluMist or placebo in Year 1 through the day before dosing in Year 2, or 14/Mar/2002 if the child was not dosed for the second year. Efficacy analyses were also performed for Year 2 as a secondary endpoint.

The primary analysis of the primary endpoint was conducted on the ATP Population, defined as children who were aged 12 months to <36 months at enrollment, who were not administered any live viral vaccine within 28 days prior to or post vaccination, who did not receive any therapy or have any medical condition or other occurrence which was likely to materially affect the clinical observations or responses for the child, as determined by the Study Director prior to unblinding, who received all doses of the treatment they were assigned to, and who remained in the study at least 15 days after receiving each dose. Exact, two-sided 95% CIs were constructed using the binomial distribution conditional upon the total number of cases observed. If the lower limit of the 95% CI was > 0%, then the vaccine was statistically significantly superior to placebo. Immunogenicity data obtained from a subset of children from this study are not included as part of this briefing document.

AV006, Year 1 and Year 2

Study AV006 was the pivotal, Phase 3, randomized, double blind, placebo-controlled trial of FluMist, in healthy children 15-71 months of age. The primary objective of this study was to demonstrate efficacy of a two-dose regimen of FluMist against culture-confirmed influenza illness. Secondary objectives included the following: demonstrate efficacy of either a one or

two-dose regimen of FluMist, estimate efficacy of a one-dose regimen of FluMist, and demonstrate efficacy of a single dose of FluMist in the second year of the study in children who received either one or two doses of FluMist in the first year of the study.

The study was conducted during the 1996-1997 and 1997-1998 influenza seasons at multiple sites in the U.S. In Year 1 of the study, children were randomized at a 2:1 ratio to receive frozen FluMist or placebo, with most children receiving two doses of study vaccine, 46-74 days apart. A one-dose regimen was also included in Year 1 of the study, because in any given influenza season a child may only receive a single dose before an influenza outbreak; the one-dose and two-dose regimens were not randomized to compare the regimens. A total of 1070 children received FluMist (N=881 two doses; N=189 one dose) and 532 received placebo (N=433 two doses; N=99 one dose). In Year 2 of the study, children who participated in Year 1 received a single dose of frozen FluMist (N=917) or placebo (N=441) according to the treatment assignment in Year 1.

The primary efficacy endpoint was the incidence of culture-confirmed influenza illness caused by community-acquired subtypes antigenically similar (**matched** strains) to those contained in the vaccine, in children who received two doses of vaccine, for the influenza season directly following vaccination (through 29/Apr/1997). Children were included in the efficacy analyses of the primary endpoint if they had received two doses of study vaccine prior to their first case of influenza, and had not received FluMist or TIV before entry into the trial. Confidence intervals for efficacy were based on Koopman's method for the ratio of binomials. Immunogenicity data obtained from a subset of children from this study are not included as part of this briefing document.

Efficacy and safety data from Study AV006 were previously submitted to CBER in support of the original licensure of FluMist. At the request of CBER, these data from AV006 were included in the sBLA to support the age indication extension to children less than 5 years of age.

MI-CP123

Study MI-CP123 was a Phase 2, prospective, randomized, open-label trial in children 6 to <36 months of age. The objective of this study was to describe the level of serum antibody conferred by FluMist and TIV against influenza virus strains that were antigenically **matched** or antigenically **mismatched** to the vaccine strains. The study was conducted outside of the influenza season in 2005 at multiple sites in the U.S. Children were randomized at a 1:1 ratio to receive two doses of refrigerated FluMist (N=24) by intranasal administration or two doses of TIV (N=28) by intramuscular administration, with Dose Two given 28-42 days after Dose One.

Samples were assayed for serum hemagglutination inhibition (HAI) antibody titer. The reciprocal of the highest dilution of the test serum that completely inhibited hemagglutination was designated the HAI titer. If no inhibition was observed, the titer was reported as <4. Based on a previously performed precision study, a 4-fold or greater difference in titer between two sera was considered significant. The viral antigens used in this assay included whole virus cold adapted (*ca*) A/New Caledonia/20/99 (H1N1), *ca* A/Wyoming/03/2003 (H3N2), and wild-type (*wt*) A/California/07/2004 (H3N2). Wild-type B/Shanghai/361/2002 and *wt* B/Florida/07/2004 antigens were prepared by ether extraction, a technique reported to demonstrate greater sensitivity for detection of influenza B antibodies by HAI when compared to the use of whole virus antigen (Kendal 1983).

Seroconversion/seroresponse rates (the proportions of children achieving ≥4-fold increase in HAI titer) were summarized by baseline serostatus. A two-sided exact 95% CI was constructed on the rate differences using the unconditional exact method proposed by Chan and Zhang (Chan 1999). Geometric mean titers (GMTs) were summarized by treatment group using a percentile-based bootstrap technique stratified by baseline serostatus. Corresponding two-sided 95% CIs based on 10,000 bootstrap data sets constructed by drawing replicates with replacement from each of the four cells (two treatment groups and one strata with two levels) of observed data were performed. The number of replicates drawn from each cell in this fashion was equal to the observed sample size within each cell.

AV018

Study AV018 was a Phase 3, randomized, placebo-controlled trial in healthy children 12 to 15 months of age, conducted outside the influenza seasons in 2000-2002 at multiple sites in the U.S. and Australia. The objective of the study was to evaluate whether concomitant administration of frozen FluMist with other live viral vaccines, M-M-R®II and VARIVAX® (MMR/VAR), would be well tolerated and suitably immunogenic with respect to all antigens contained in the vaccines. Children were randomized at a 1:1:1 ratio to one of three groups (total N=1245), as outlined below. Serum samples were obtained immediately prior to the receipt of study treatment(s) at Visit 1 (Day 0), Visit 2 (Day 42), and Visit 3 (Day 72).

Treatment Group N	Visit 1 Day 0	Visit 2 Day 42	Visit 3 Day 72
MMR/VAR (Group 1)[a] N=411	Placebo + M-M-R®II+Varivax®	FluMist	FluMist
MMR/VAR/FluMist (Group 2)[a] N=422	FluMist + M-M-R®II+Varivax®	FluMist	Placebo
FluMist (Group 3)[b] N=412	FluMist	FluMist	M-M-R®II+Varivax®

a. Randomized, double blind treatment assignment.

b. Randomized, unblinded treatment assignment.

Immunogenicity to mumps, measles, rubella, and varicella antigens was evaluated using antigen-specific enzyme-linked immunosorbent assays (ELISAs) to detect serum antibody (immunoglobulin G) before and after vaccination with MMR and VAR. These assays were performed and validated by Merck Research Laboratories and met FDA acceptance criteria. Seroresponse was defined as a post vaccination assay result of =255 mIU/mL for measles, =10.0 mumps antibody units/mL for mumps, =10 IU/mL for rubella, and =5 gp ELISA units/mL for varicella.

Immunogenicity to influenza viruses was evaluated by measuring serum HAI titers to each of the strains contained in the vaccine, using standard assay procedures. HAI titer was defined as the reciprocal of the highest dilution of the test serum that completely inhibited hemagglutination. A titer of <4 was assigned to serum samples for which no inhibition could be detected, even at the lowest dilution tested (1:4 dilution); titers <4 had a value of 2 imputed to provide a baseline value from which to calculate seroconversion. Seronegativity was defined as HAI titer ≤4. Seroconversion was defined as a ≥4-fold rise in titer from baseline in children who were seronegative at baseline (i.e., those who had a baseline titer of <4 and post vaccination titer of ≥8, and those who had a baseline titer of 4 and post vaccination titer of ≥16).

Determination of equivalent immunogenicity for M-M-R®II and VARIVAX® was based on the lower limit of two-sided exact 90% CIs on the treatment group difference in seropositivity rates (Group 2 minus Group 1) and the ratio of geometric mean titers (GMTs) (Group 2/Group 1). Equivalence based on seropositivity rates was considered established if the lower limit of the two-sided exact 90% CI for the rate difference was greater than the pre-specified equivalence limit of -10 percentage points. Equivalence based on the ratio of GMTs was considered established if the lower limit of the two-sided 90% CI for the ratio was >0.5. In addition, as requested by CBER, two-sided 95% CIs for non-inferiority

evaluations for rate differences and GMT ratios were assessed, and a 5 percentage point margin for measles, mumps, and rubella was applied for the rate difference.

Determination of equivalent immunogenicity for the three influenza strains contained in FluMist study vaccine was based on the lower limit of two-sided exact 90% CIs on treatment group differences in seroconversion rates (Group 2 minus Group 3) and the ratio of GMTs (Group 2/Group 3) after Dose Two. Equivalence based on seroconversion was considered established if the lower limit of the two-sided 90% CI for the rate difference was greater than the pre-specified equivalence limit of -10 percentage points for the A/H3N2 and B strains and -15 percentage points for the A/H1N1 strain. Equivalence based on the ratio of GMTs was considered established if the lower limit of the two-sided 90% CI for the ratio was >0.5. In addition, as requested by CBER, two-sided 95% CIs for non-inferiority evaluations for rate differences and GMT ratios were assessed, and a -10 percentage point non-inferiority margin to the A/H1N1 endpoint was applied for the rate difference.

Confidence intervals for difference in seroresponse rates were constructed using the method of Miettinen and Nurminen (1985). Confidence intervals for all GMTs were based on the percentile-based bootstrap technique and included stratification using Season (1, 2) and country (Australia, U.S.) to control for potential prior exposure to the antigens under study that might vary by these factors.

4 Data Demonstrating Efficacy of FluMist

More than 20,000 children <5 years of age have been evaluated in clinical trials of the efficacy of FluMist. Published data suggest that FluMist has high efficacy in children and higher relative efficacy compared to TIV (Belshe 1998, Belshe 2000, Treanor 1999, Ashkenazi 2006, Vesikari 2006, Belshe 2007, Tam 2007).

In the pediatric studies submitted with the sBLA (Table 4-1), the efficacy of FluMist compared to placebo against matched, culture-positive symptomatic influenza illness has ranged from approximately 73% to 93%, and efficacy has been documented against all three subtypes of influenza: A/H1N1, A/H3N2, and B. In the pivotal trial in children <5 years of age that directly compared the efficacy of FluMist to TIV (Study MI-CP111), FluMist was superior to TIV in protecting against influenza illness caused by matched strains, with 45% fewer cases of influenza illness, and influenza illness caused by all strains, with 55% fewer cases of influenza illness.

Efficacy was not evaluated in Studies MI-CP123 or AV018.

Table 4-1 Efficacy of FluMist against Influenza in Studies Including Children < 5 Years of Age

Protocol	FluMist Formulation	Age Range[a] (mos)	Total No. of Children	Study Season	FluMist Efficacy (95% CI)	
					Matched Strains	All Strains
Active Controlled Trial						
MI-CP111	Refrigerated	6-59	7852	2004-2005	44.5% (22.4, 60.6) fewer cases than TIV	54.9% (45.4, 62.9) fewer cases than TIV
Placebo Controlled Trials						
AV006	Frozen	15-71	1259[b]	1996-1997	93.4% (87.5, 96.5)	93.4% (87.5, 96.5)
			1110[b]	1997-1998	100% (53.7, 100)	87.0% (77.0, 92.6)
D153-P501	Refrigerated	12-35	2764	2000-2001	72.9% (62.8, 80.5)	70.1% (60.9, 77.3)
			1265[c]	2001-2002	84.3% (70.1, 92.4)	64.2% (44.2, 77.3)

a. Age at first vaccination
b. Includes only children who received two doses of study vaccine in Year 1
c. Includes only children who received the same study vaccine in each year of the study

4.1 Efficacy Data from Study MI-CP111

4.1.1 Culture-Confirmed Modified CDC-ILI

The primary efficacy endpoint in Study MI-CP111 was culture-confirmed modified CDC-ILI caused by community-acquired wild-type strains antigenically **matched** to those contained in the vaccines. Culture-confirmed modified CDC-ILI caused by wild-type antigenically **mismatched** strains was a secondary endpoint of the study. Community surveillance in the U.S. (CDC 2005) and Europe (EISS 2005) revealed that strains of influenza circulating during the 2004-2005 (MI-CP111) season were predominantly mismatched to those contained in the 2004-2005 influenza vaccines. Analyses were performed for influenza due to all strains **regardless of antigenic match** (i.e., all symptomatic influenza). Analysis of the primary and secondary endpoints included evaluation of cultures that occurred ≥14 days after the final required study vaccination in the According to Protocol (ATP) Population, and supportive analyses included evaluation of cultures that occurred at any time after randomization in the Intent to Treat (ITT) Population.

In the ATP Population, 146 children had culture-confirmed influenza due to **matched** strains and met the criteria for modified CDC-ILI: 53 children in the FluMist group (Attack Rate =

1.4%), and 93 children in the TIV group (Attack Rate = 2.4%). FluMist recipients had 44.5% fewer cases of influenza illness due to **matched** strains compared to the TIV group, and this difference was statistically significant (Table 4-2). FluMist also demonstrated significantly higher efficacy relative to TIV against **mismatched** strains, with 58.2% fewer cases of influenza illness (Table 4-2). When analyzed by all strains **regardless of antigenic match**, FluMist showed a statistically significant overall reduction of 54.9% fewer cases of influenza illness relative to TIV.

In the ITT Population, 155 children had culture-confirmed influenza due to **matched** strains and met the criteria for modified CDC-ILI: 55 children in the FluMist group (Attack Rate = 1.3%), and 100 children in the TIV group (Attack Rate = 2.4%). As in the ATP Analysis, FluMist statistically superior to TIV against **matched** strains, with 46.0% fewer cases of influenza illness (Table 4-2). FluMist also demonstrated significantly higher efficacy compared to TIV against mismatched strains and strains regardless of antigenic match.

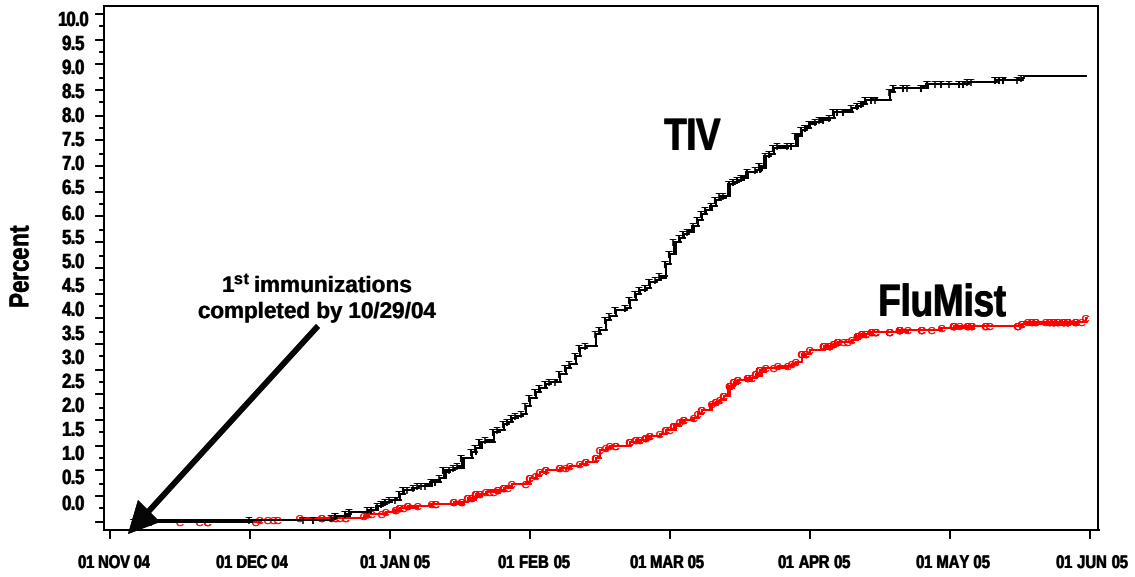
The reduction in influenza illness by FluMist was evident throughout the entire influenza season as shown in Figure 4-2.

Table 4-2 MI-CP111: Efficacy against Culture-Confirmed Modified CDC-ILI Caused by Wild-Type Strains in Children 6-59 Months of Age

	FluMist			TIV			Percent Reduction in Cases of Influenza Illness[a]	95% Exact CI[a]
	N	# of Cases	Crude Attack Rate (cases/N)	N	# of Cases	Crude Attack Rate (cases/N)		
Antigenically Similar								
All strains[b]	3916	53	1.4%	3936	93	2.4%	44.5%	22.4, 60.6
A/H1N1	3916	3	0.1%	3936	27	0.7%	89.2%	67.7, 97.4
A/H3N2	3916	0	0.0%	3936	0	0.0%	---	---
B	3916	50	1.3%	3936	67	1.7%	27.3%	-4.8, 49.9
All strains, ITT[c]	4243	55	1.3%	4232	100	2.4%	46.0%	25.2, 61.4
Antigenically Dissimilar								
All strains	3916	102	2.6%	3936	245	6.2%	58.2%	47.4, 67.0
A/H1N1	3916	0	0.0%	3936	0	0.0%	---	---
A/H3N2	3916	37	0.9%	3936	178	4.5%	79.2%	70.6, 85.7
B	3916	66	1.7%	3936	71	1.8%	6.3%	-31.6, 33.3
All strains, ITT[c]	4243	111	2.6%	4232	255	6.0%	56.6%	45.8, 65.4
Regardless of Antigenic Match								
All strains	3916	153	3.9%	3936	338	8.6%	54.9%	45.4, 62.9
A/H1N1	3916	3	0.1%	3936	27	0.7%	89.2%	67.7, 97.4
A/H3N2	3916	37	0.9%	3936	178	4.5%	79.2%	70.6, 85.7
B	3916	115	2.9%	3936	136	3.5%	16.1%	-7.7, 34.7
All strains, ITT[c]	4243	165	3.9%	4232	355	8.4%	53.9%	44.5, 61.7

ATP Population, except where noted as ITT

a. Adjusted for country, age, prior vaccination status, and recurrent wheezing history status.
b. Primary endpoint.
c. Includes influenza-positive cultures that occurred at any time after randomization in all children.



Culture-confirmed modified CDC-ILI caused by any wild-type strains regardless of antigenic match.

Figure 4-1 MI-CP111: Reported Cases of Influenza Illness

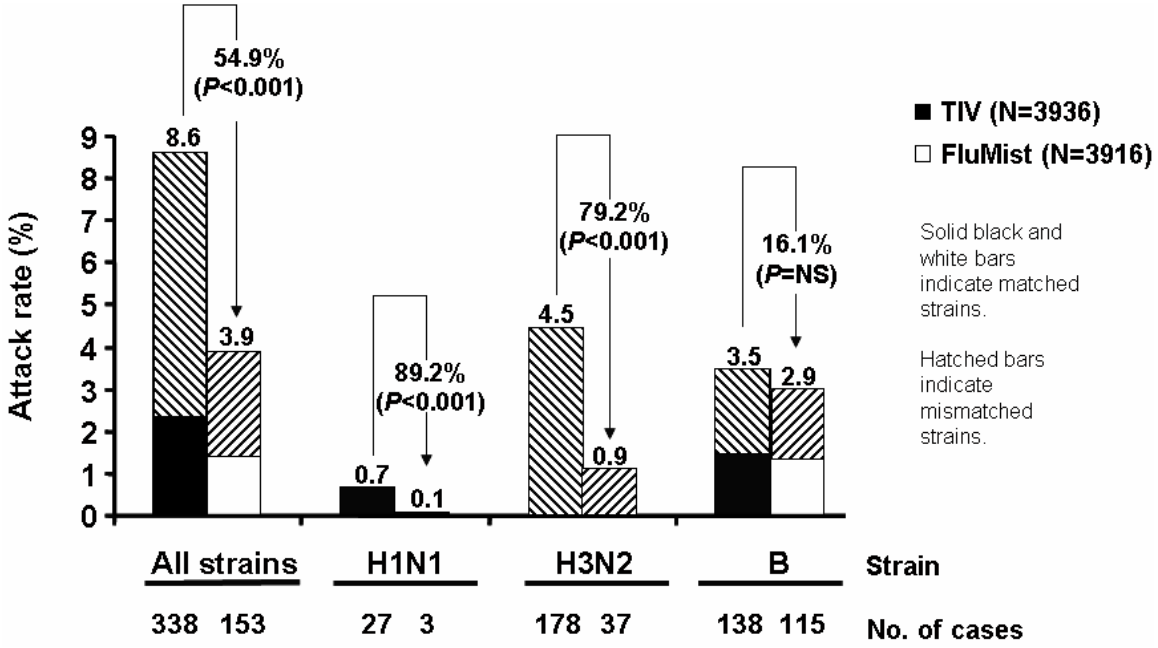


Figure 4-2 MI-CP111: Summary of Relative Efficacy against Culture-Confirmed Modified CDC-ILI

By-Strain Analysis

By-strain analysis of culture-confirmed modified CDC-ILI in the ATP Population demonstrated that FluMist significantly more effective than TIV against **matched** A/H1N1 strains, with 89.2% fewer cases of influenza illness (Table 4-2 and Figure 4-2). No matched A/H3N2 strains were isolated in this study. While there were 27.3% fewer cases of influenza illness caused by matched type B strains in the FluMist group compared to TIV, this difference was not statistically significant.

By-strain analyses demonstrated that FluMist was highly efficacious relative to TIV against **mismatched** A/H3N2 strains, with 79.2% fewer cases of influenza illness, which was statistically significant, as shown previously in Table 4-2 and Figure 4-2. No mismatched A/H1N1 strains were isolated in this study. The 6.3% reduction in cases of influenza illness due to mismatched type B strains for FluMist relative to TIV was not statistically significant.

Other Subpopulation Analyses

Analyses by age subgroup (6-23, 24-59, 24-35, and 36-59 months), history of ≥3 wheezing episodes, prior influenza vaccination status, gender, and race are shown for matched strain analyses in Table 4-3. The point estimates for the percent decrease in influenza illness for FluMist recipients by these variables were generally consistent with the results for the overall study population.

Table 4-3 MI-CP111: Efficacy against Culture-Confirmed Modified CDC-ILI Caused by Wild-Type Matched Strains in Subgroup Analyses

	FluMist N=3893			TIV N=3943			Percent Reduction in Cases of Influenza Illness[a]	95% Exact CI[a]
	N	# of Cases	Crude Attack Rate (cases/N)	N	# of Cases	Crude Attack Rate (cases/N)		
AGE								
6-23 months	1834	23	1.3%	1852	32	1.7%	29.1%	-21.2, 59.1
24-59 months	2082	30	1.4%	2084	61	2.9%	52.5%	26.7, 69.7
24-35 months	1311	17	1.3%	1301	24	1.8%	32.6%	-25.8, 64.5
36-59 months[b]	771	13	1.7%	783	37	4.7%	65.6%	36.3, 82.4
PRIOR INFLUENZA VACCINATION[c]								
Yes	929	18	1.9%	937	29	3.1%	39.3%	-9.2, 66.9
No	2987	35	1.2%	2999	64	2.1%	46.9%	20.0, 65.2
RECURRENT WHEEZING HISTORY[d]								
Yes	246	8	3.3%	216	9	4.2%	24.0%	-104.2, 72.1
No	3670	45	1.2%	3720	84	2.3%	46.9%	23.9, 63.3
GENDER								
Male	2008	24	1.2%	2017	43	2.1%	49.8%	16.5, 70.4
Female	1908	29	1.5%	1919	50	2.6%	44.8%	12.8, 65.6
RACE								
White/Non-Hispanic	3168	49	1.5%	3184	80	2.5%	40.3%	14.9, 58.4
Non-White	748	4	0.5%	752	13	1.7%	64.8%	-4.9, 90.2
Black	156	2	1.3%	140	2	1.4%	-124.7%	-6534, 82.9
Hispanic	225	0	0.0%	243	3	1.2%	100%	-65.1, 100.0
Asian	290	1	0.3%	297	5	1.7%	69.4%	-190.0, 98.8
Other	77	1	1.3%	72	3	4.2%	45.6%	-623.8, 98.2

ATP Population

a. Adjusted for country, age, prior vaccination status, and recurrent wheezing history status.

b. One 60-month-old child was counted in the 36-59 month stratum.

c. Children with an unknown vaccine history were counted as not having received prior influenza vaccination.

d. Positive recurrent wheezing history was defined as a history of ≥3 wheezing illnesses requiring medical follow-up or hospitalization. Children with an unknown wheezing history were counted as having a negative recurrent wheezing history.

As prespecified, analyses of culture-confirmed modified CDC-ILI were performed in children 6-23 months of age (n = 3686, 46.9% of children in the ATP Population). In the **matched** strain analysis for this age subgroup, where the TIV attack rate was lower than the hypothesized 4%, FluMist recipients had 29.1% fewer cases of influenza illness compared to TIV recipients, which was not statistically significant (Table 4-4). FluMist was significantly more effective than TIV for **mismatched** strains (64.0% fewer cases of influenza illness) and all strains **regardless of antigenic match** (55.7% fewer cases), where the TIV attack rate was higher than the hypothesized 4%.

Table 4-4 MI-CP111: Efficacy against Culture-Confirmed Modified CDC-ILI Caused by Wild-Type Strains in Children 6-23 Months of Age

	FluMist			TIV			Percent Reduction in Cases of Influenza Illness[a]	95% Exact CI [a]
	N	# of Cases	Crude Attack Rate (cases/N)	N	# of Cases	Crude Attack Rate (cases/N)		
Antigenically Similar								
All strains	1834	23	1.3%	1852	32	1.7%	29.1%	-21.2, 59.1
A/H1N1	1834	2	0.1%	1852	6	0.3%	67.0%	-56.0, 95.4
A/H3N2	1834	0	0.0%	1852	0	0.0%	---	---
B	1834	21	1.1%	1852	27	1.5%	23.3%	-36.1, 57.2
Antigenically Dissimilar								
All strains	1834	35	1.9%	1852	98	5.3%	64.0%	47.4, 75.8
A/H1N1	1834	0	0.0%	1852	0	0.0%	---	---
A/H3N2	1834	13	0.7%	1852	76	4.1%	82.7%	69.6, 90.8
B	1834	22	1.2%	1852	23	1.2%	4.2%	-73.3, 47.1
Regardless of Antigenic Match								
All strains	1834	59	3.2%	1852	133	7.2%	55.7%	39.9, 67.6
A/H1N1	1834	2	0.1%	1852	6	0.3%	67.0%	-56.0, 95.4
A/H3N2	1834	13	0.7%	1852	76	4.1%	82.7%	69.6, 90.8
B	1834	43	2.3%	1852	50	2.7%	14.5%	-28.7, 43.4

ATP Population

a. Adjusted for country, age, prior vaccination status, and recurrent wheezing history status.

For children 24-59 months of age, results were consistent with those for the overall study population (Table 4-5). FluMist was significantly more effective than TIV against **matched** strains (52.5% fewer cases of influenza illness), **mismatched** strains (54.2% fewer cases), and all strains **regardless of match** (54.4% fewer cases).

Table 4-5 MI-CP111: Efficacy against Culture-Confirmed Modified CDC-ILI Caused by Wild-Type Strains in Children 24-59 Months of Age

	FluMist			TIV			Percent Reduction in Cases of Influenza Illness[a]	95% Exact CI [a]
	N	# of Cases	Crude Attack Rate (cases/N)	N	# of Cases	Crude Attack Rate (cases/N)		
Antigenically Similar								
All strains	2082	30	1.4%	2084	61	2.9%	52.5%	26.7, 69.7
A/H1N1	2082	1	0.0%	2084	21	1.0%	95.4%	75.1, 99.8
A/H3N2	2082	0	0.0%	2084	0	0.0%	---	---
B	2082	29	1.4%	2084	40	1.9%	30.0%	-12.9, 57.0
Antigenically Dissimilar								
All strains	2082	67	3.2%	2084	147	7.1%	54.2%	38.8, 66.0
A/H1N1	2082	0	0.0%	2084	0	0.0%	---	---
A/H3N2	2082	24	1.2%	2084	102	4.9%	76.6%	63.6, 85.4
B	2082	44	2.1%	2084	48	2.3%	7.3%	-40.5, 39.0
Regardless of Antigenic Match								
All strains	2082	94	4.5%	2084	205	9.8%	54.4%	41.8, 64.5
A/H1N1	2082	1	0.0%	2084	21	1.0%	95.4%	75.1, 99.8
A/H3N2	2082	24	1.2%	2084	102	4.9%	76.6%	63.6, 85.4
B	2082	72	3.5%	2084	86	4.1%	17.0%	-13.8, 39.6

ATP Population

a. Adjusted for country, age, prior vaccination status, and recurrent wheezing history status.

4.1.2 Culture-Confirmed Symptomatic Influenza Infection

The percent reduction in cases of culture-confirmed symptomatic influenza infection for FluMist compared to TIV was statistically significant for analyses of **matched** strains (44.5% fewer cases), **mismatched** strains (54.0% fewer cases), and all strains **regardless of match**

(50.6% fewer cases) as shown in Table 4-6. These results, and those for by-strain analyses, were similar to results obtained for the endpoint of modified CDC-ILI.

Table 4-6 MI-CP111: Efficacy against Culture-Confirmed Symptomatic Influenza Infection Caused by Wild-Type Strains in Children 6-59 Months of Age

	FluMist			TIV			Percent Reduction in Cases of Influenza Illness[a]	95% Exact CI [a]
	N	# of Cases	Crude Attack Rate (cases/N)	N	# of Cases	Crude Attack Rate (cases/N)		
Antigenically Similar								
All strains	3916	67	1.7%	3936	118	3.0%	44.5%	25.2, 59.0
A/H1N1	3916	5	0.1%	3936	37	0.9%	86.7%	68.2, 95.4
A/H3N2	3916	0	0.0%	3936	0	0.0%	---	---
B	3916	62	1.6%	3936	82	2.1%	26.1%	-2.8, 47.1
Antigenically Dissimilar								
All strains	3916	128	3.3%	3936	279	7.1%	54.0%	43.3, 62.8
A/H1N1	3916	0	0.0%	3936	0	0.0%	---	---
A/H3N2	3916	49	1.3%	3936	197	5.0%	75.1%	66.0, 82.0
B	3916	80	2.0%	3936	87	2.2%	8.0%	-25.1, 32.3
Regardless of Antigenic Match								
All strains	3916	195	5.0%	3936	393	10.0%	50.6%	41.3, 58.5
A/H1N1	3916	5	0.1%	3936	37	0.9%	86.7%	68.2, 95.4
A/H3N2	3916	49	1.3%	3936	197	5.0%	75.1%	66.0, 82.0
B	3916	141	3.6%	3936	166	4.2%	15.9%	-5.3, 33.0

ATP Population

a. Adjusted for country, age, prior vaccination status, and recurrent wheezing history status.

4.1.3 Acute Otitis Media and Lower Respiratory Illness

Statistically significant relative efficacy of FluMist compared to TIV was also demonstrated in some analyses against acute otitis media (AOM) and lower respiratory illness (LRI) associated with a positive nasal culture. For AOM associated with **mismatched** influenza strains and with all influenza strains **regardless of antigenic match**, the relative efficacy values were 61.4% and 50.6%, respectively, for FluMist compared to TIV. For LRI associated with **mismatched** strains and with all strains **regardless of antigenic match**, the relative efficacy values were 63.4% and 45.9%, respectively.

Table 4-7 MI-CP111: Efficacy against AOM and LRI Associated with Culture-Confirmed Modified CDC-ILI Caused by Wild-Type Strains in Children 6-59 Months of Age

	FluMist			TIV			Percent Reduction in Cases of Influenza Illness[a]	95% Exact CI [a]
	N	# of Cases	Crude Attack Rate (cases/N)	N	# of Cases	Crude Attack Rate (cases/N)		
Acute Otitis Media								
Antigenically Similar	3916	10	0.3%	3936	10	0.3%	0.4%	-146, 59.6
Antigenically Dissimilar	3916	16	0.4%	3936	43	1.1%	61.4%	32.2, 78.8
Regardless of Antigenic Match	3916	26	0.7%	3963	54	1.4%	50.6%	21.5, 69.5
Lower Respiratory Illness								
Antigenically Similar	3916	8	0.2%	3936	11	0.3%	24.5%	-89.8, 71.0
Antigenically Dissimilar	3916	8	0.2%	3936	21	0.5%	63.4%	18.9, 84.7
Regardless of Antigenic Match	3916	18	0.5%	3963	33	0.8%	45.9%	4.4, 70.2

ATP Population

a. Adjusted for country, age, prior vaccination status, and recurrent wheezing history status.

4.2 Efficacy Data from Studies D153-P501 and AV006

Supportive data for efficacy in young children are provided by Study D153-P501 (FluMist vs. placebo in children 12 to 35 months of age) and Study AV006 (FluMist vs. placebo in children 15 to 71 months of age), both of which were 2-year studies. In Study D153-P501 (conducted during the 2000-2001 and 2001-2002 seasons in Asia), statistically significant efficacy of FluMist compared to placebo was observed against culture-confirmed influenza due to **matched** strains (72.9% Year 1, 84.2% Year 2) and all strains **regardless of antigenic match** (70.1% Year 1, 62.4% Year 2) (Table 4-8). Efficacy of FluMist by strain was statistically significant for A/H1N1, A/H3N2, and B in Year 1 and for A/H1N1 and A/H3N2 in Year 2. In Study AV006 (conducted during the 1996-1997 and 1997-1998 seasons in the U.S.), statistically significant efficacy of FluMist compared to placebo was observed against culture-confirmed influenza due to **matched** strains in Year 1 (93.4%) and all strains

regardless of antigenic match in Year 2 (87.0%); all cases of influenza were due to **matched** strains in Year 1, and almost all cases were due to **mismatched** strains in Year 2 (Table 4-9). By-strain analyses for Study AV006 showed statistically significant efficacy against **matched** A/H3N2 and B strains in Year 1 and against **matched** and **mismatched** A/H3N2 strains in Year 2 (no cases due to A/H1N1 strains were observed in either Year 1 or Year 2, and only one case of influenza due to B strains was observed in Year 2).

Table 4-8 D153-P501: Efficacy against Culture-Confirmed Influenza Illness due to Wild-Type Strains in Children Initially 12-35 Months of Age

	FluMist			Placebo			Efficacy	95% CI
	N	# of Cases	Crude Attack Rate (cases/N)	N	# of Cases	Crude Attack Rate (cases/N)		
D153-P501 Yr 1 (2000-2001)								
Antigenically Similar								
All strains	1653	56	3.4%	1111	139	12.5%	72.9%	62.8, 80.5
A/H1N1[a]	1653	23	1.4%	1111	81	7.3%	80.9%	69.4, 88.5
A/H3N2	1653	4	0.2%	1111	27	2.4%	90.0%	71.4, 97.5
B	1653	29	1.8%	1111	35	3.2%	44.3%	6.2, 67.2
Regardless of Antigenic Match								
All strains	1653	81	4.9%	1111	182	16.4%	70.1%	60.9, 77.3
A/H1N1	1653	23	1.4%	1111	82	7.4%	81.1%	69.8, 88.7
A/H3N2	1653	14	0.8%	1111	60	5.4%	84.3%	71.6, 91.9
B	1653	44	2.7%	1111	52	4.7%	43.1%	13.4, 62.8
D153-P501 Yr 2 (2001-2002)[b]								
Antigenically Similar								
All strains	771	12	1.6%	494	49	9.9%	84.3%	70.1, 92.4
A/H1N1	771	0	0.0%	494	4	0.8%	100%	2.9, 100.0
A/H3N2	771	9	1.2%	494	42	8.5%	86.3%	71.4, 94.1
B	771	3	0.4%	494	5	1.0%	61.6%	-97.6, 94.0
Regardless of Antigenic Match								
All strains	771	33	4.3%	494	59	11.9%	64.2%	44.2, 77.3
A/H1N1	771	0	0.0%	494	4	0.8%	100%	2.9, 100.0
A/H3N2	771	10	1.3%	494	43	8.7%	85.1%	69.9, 93.3
B	771	23	3.0%	494	16	3.2%	7.9%	-86.5, 53.4

Per Protocol Efficacy Analysis Population

a. Includes A/H1N1 and A/H1N2 strains. Both were considered antigenically similar to the vaccine.
b. Year 2 data are for children who received the same treatment in each year of the study, i.e., FluMist in each of Years 1 and 2, or placebo in each of Years 1 and 2.

Table 4-9 AV006: Efficacy against Culture-Confirmed Influenza Illness due to Wild-Type Strains in Children Initially 15-71 Months of Age

	FluMist			Placebo			Efficacy	95% CI
	N	# of Cases	Crude Attack Rate (cases/N)	N	# of Cases	Crude Attack Rate (cases/N)		
AV006 Yr 1 (1996-1997) [a]								
Antigenically Similar								
All strains	849	10	1%	410	73	18%	93.4%	87.5, 96.5
A/H1N1	849	0	0%	410	0	0%	---	---
A/H3N2	849	4	0.5%	410	48	12%	96.0%	89.4, 98.5
B	849	6 [b]	0.7%	410	31 [b]	7%	90.5%	78.0, 95.9
Regardless of Antigenic Match								
All strains	849	10	1%	410	73	18%	93.4%	87.5, 96.5
A/H1N1	849	0	0%	410	0	0%	---	---
A/H3N2	849	4	0.5%	410	48	12%	96.0%	89.4, 98.5
B	849	6 [b]	0.7%	410	31 [b]	7%	90.5%	78.0, 95.9
AV006 Yr 2 (1997-1998) [a]								
Antigenically Similar								
All strains	748	0	0%	362	4	1%	100%	53.7, 100
A/H1N1	748	0	0%	362	0	0%	---	---
A/H3N2	748	0	0%	362	3	0.8%	100%	38.2, 100
B	748	0	0%	362	1	0.3%	--- [c]	--- [c]
Regardless of Antigenic Match								
All strains	748	14	2%	362	52	14%	87.0%	77.0, 92.6
A/H1N1	748	0	0%	362	0	0%	---	---
A/H3N2	748	14	2%	362	51	14%	86.7%	76.5, 92.5
B	748	0	0%	362	1	0.3%	--- [c]	--- [c]

Per Protocol Efficacy Analysis Population

a. Year 1 and Year 2 data are for children who received two doses of study vaccine in Year 1; efficacy of FluMist for children in the 1-dose regimen in Year 1 was 88.8% (95% CI: 64.5, 96.5) for any strain.
b. For Year 1 B-strain analysis, N=850 for FluMist and N=417 for placebo due to application of evaluability criteria on a strain-specific basis.
c. Confidence interval not constructed due to the occurrence of only 1 case of influenza due to the B strain.

4.3 Efficacy Conclusions

In the two placebo-controlled efficacy trials that were summarized (Studies AV006 and D153-P501), children who received FluMist experienced statistically significant and medically important reductions in attack rates for symptomatic influenza infection. Efficacy was demonstrated against strains that were matched to the vaccine, against all strains regardless of match, and against individual strains representing each of the three subtypes of influenza (A/H1N1, A/H3N2, and B). Efficacy against all strains regardless of match, which is likely the best indicator of overall, real-world benefit for an individual vaccinee, ranged from 70% to 93% in the initial year of vaccination.

In the pivotal study that compared the efficacy of FluMist to TIV (Study MI-CP111), children who received FluMist experienced statistically significant and medically important reductions in attack rates for symptomatic influenza infection caused by strains matched to the vaccine, mismatched to the vaccine, and all strains regardless of antigenic match. Statistically significant higher efficacy for FluMist relative to TIV was observed across the entire age population in the study (6-59 months). In the overall analyses of efficacy against culture-confirmed modified CDC-ILI, there were 338 cases in 3936 TIV recipients and 153 cases in 3916 FluMist recipients, representing a 55% reduction in influenza cases caused by any matched or mismatched strain in FluMist compared to TIV.

Cross-protection to drifted type A influenza strains has been demonstrated for FluMist in two pediatric trials conducted in different seasons in which different mismatched strains circulated. In Study AV006 Year 2 (1997-1998), when the predominantly circulating strain was the mismatched A/Sydney (H3N2), the overall efficacy for FluMist was 87%. In Study MI-CP111 (2004-2005), when the predominantly circulating H3N2 strain was the mismatched A/California-like, FluMist recipients had 79% fewer cases of influenza illness due to mismatched A/H3N2 strains compared to TIV recipients.

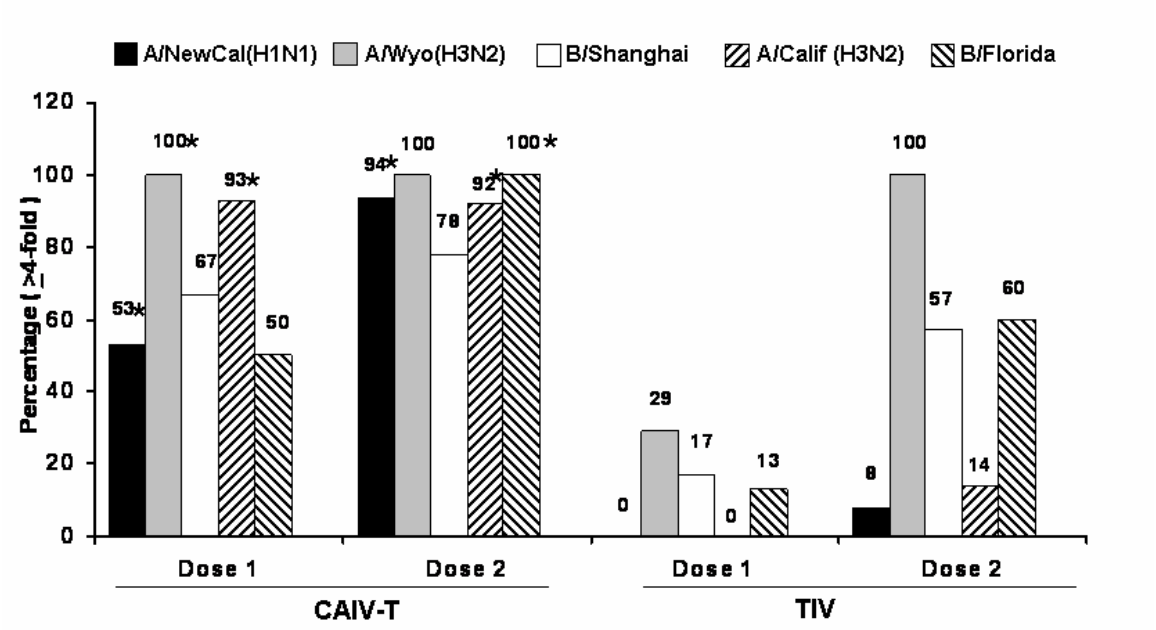
In summary, studies that included children less than 5 years of age demonstrate that:

- FluMist is highly efficacious in the prevention of culture-confirmed influenza illness.
- FluMist has been shown to have better overall efficacy than TIV.
- FluMist resulted in better cross-protection against mismatched influenza A/H3N2 strains compared to TIV.

5 Immunogenicity of FluMist

5.1 Immunogenicity Data from Study MI-CP123

In MI-CP123, children 6-35 months of age were vaccinated with the same FluMist or TIV formulation used in the pivotal efficacy trial MI-CP111; this study was conducted outside of the influenza season. Serum HAI antibody responses to antigenically **matched** and **mismatched** strains that circulated during the 2004-2005 season were higher in seronegative FluMist recipients relative to TIV recipients after each of two doses of vaccine (Figure 5-1). Results were generally similar for all children, which may be accounted for by the study population being largely seronegative at baseline. The results of MI-CP123 indicate that FluMist was generally more immunogenic than TIV in terms of seroconversion and overall GMT of HAI antibody to matched strains and mismatched strains. It should be noted that cold-adapted antigen (not wild-type) was used for HAI testing of both treatment groups for the A/Wyoming (H3N2) and A/New Caledonia (H1N1) strains; however, testing by CDC demonstrated antigenic equivalence (i.e., HAI-ID titers within 4-fold of one another) for the cold-adapted and wild-type strains. Additional testing using wild-type antigen for these two strains is underway. The immunogenicity data for the matched A/H1N1 strain (86% seroconversion rate difference for FluMist relative to TIV following two doses among baseline seronegative subjects) and for the mismatched A/H3N2 (78% seroconversion rate difference for FluMist relative to TIV following two doses among baseline seronegative subjects) are consistent with the efficacy data seen in the MI-CP111 comparative trial, where FluMist was efficacious relative to TIV against matched A/H1N1 strains (89% relative efficacy) and against mismatched A/H3N2 strains (79% relative efficacy).



Vaccine (antigenically matched) strains in solid bars; antigenically mismatched strains in hatched bars. Antigens used in this assay included whole virus cold adapted (*ca*) A/New Caledonia/20/99 (H1N1), *ca* A/Wyoming/03/2003/ (H3N2), and wild-type (*wt*) A/California/07/2004 (H3N2), *wt* B/Shanghai/361/2002 and *wt* B/Florida/07/2004 antigens. CAIV-T refers to refrigerated FluMist.
*Denotes statistically significant difference relative to TIV.

Figure 5-1 MI-CP123: Summary of HAI Seroconversion to Antigenically Matched and Antigenically Mismatched Strains

5.2 Immunogenicity following Concomitant Vaccination with Other Live Viral Vaccines in Study AV018

Immunogenicity data were presented in the sBLA from one further study (Study AV018), in which FluMist was administered concomitantly with other live viral vaccines. This was a Phase 3, randomized, placebo-controlled trial in 1245 healthy children 12-15 months of age.

More than 90% of evaluated children in the MMR/VAR/FluMist and MMR/VAR groups were seronegative for measles, mumps, rubella, and varicella antigens at baseline. Equivalent seroresponse rates were demonstrated in baseline seronegative children for MMR and VAR with and without concomitant FluMist administration (Table 5-1). Antigen-specific GMTs for MMR and VAR with and without concurrent FluMist were within the prespecified equivalence criteria (Table 5-2). The postvaccination rubella GMT was higher in the MMR/VAR group than in the MMR/VAR/FluMist group, but approximately 97% of subjects in both treatment groups exceeded the seropositive threshold of 10 IU.

Table 5-1 AV018: Seroresponse Rates to Measles, Mumps, Rubella, and Varicella Antigens - Baseline Seronegative Children

Antigen	Group 2 n/N (%)	Group 1 n/N (%)	Rate Difference (G2-G1)[a]	90% CI[b]		95% CI[c]	
				CI on Rate Difference	Within Equivalence Criteria?	CI on Rate Difference	Within Equivalence Criteria?
Measles	320/330 (97.0)	329/339 (97.1)	-0.1	-2.4, 2.2	Yes	-2.9, 2.7	Yes
Mumps	326/337 (96.7)	342/346 (98.8)	-2.1	-4.2, -0.3	Yes	-4.7, 0.1	Yes
Rubella	329/338 (97.3)	340/349 (97.4)	-0.1	-2.3, 2.1	Yes	-2.8, 2.6	Yes
Varicella	279/316 (88.3)	263/318 (82.7)	5.6	1.0, 10.3	Yes	0.1, 11.2	Yes

Group 1 (MMR/VAR): Visit 1, placebo mist + M-M-R®II +Varivax®, Visits 2 and 3, FluMist.

Group 2 (MMR/VAR/FluMist): Visit 1, FluMist + M-M-R®II +Varivax®, Visit 2, FluMist, Visit 3, placebo mist.

Seroresponse was defined as a post vaccination assay result of =255 mIU/mL for measles, =10.0 mumps antibody units/mL for mumps, =10 IU/mL for rubella, and =5 gp ELISA units/mL for varicella.

a. Weighted average of the stratum-specific rate differences.

b. Prospectively defined equivalence criteria: lower limit for 90% CI > -10 percentage points.

c. Ad hoc equivalence criteria: lower limit for 95% CI > -5 percentage points for measles, mumps, and rubella, and > -10 percentage points for varicella.

Table 5-2 AV018: GMT Ratios for Measles, Mumps, Rubella, and Varicella Antigens - All Children

Antigen	Group 2 N, GMT	Group 1 N, GMT	Mean GMT Ratio G2/G1	90% CI[a,b]		95% CI[a,c]	
				CI on GMT Ratio	Within Equivalence Criteria?	CI on GMT Ratio	Within Equivalence Criteria?
Measles	344, 3388.4	350, 2813.6	1.21	1.07, 1.36	Yes	1.04, 1.39	Yes
Mumps	347, 82.2	351, 97.4	0.85	0.76, 0.94	Yes	0.74, 0.96	Yes
Rubella	344, 72.6	351, 102.0	0.71	0.64, 0.79	Yes	0.63, 0.81	Yes
Varicella	347, 9.8	352, 9.3	1.06	0.97, 1.16	Yes	0.95, 1.18	Yes

Group 1 (MMR/VAR): Visit 1, placebo mist + M-M-R®II +Varivax®, Visits 2 and 3, FluMist.

Group 2 (MMR/VAR/FluMist): Visit 1, FluMist + M-M-R®II +Varivax®, Visit 2, FluMist, Visit 3, placebo mist.

a. Confidence intervals computed by the percentile-based bootstrap technique.

b. Prospectively defined equivalence criteria: lower limit for 90% CI > 0.5.

c. Ad hoc equivalence criteria: lower limit for 95% CI > 0.5.

Equivalent immunogenicity was also demonstrated against the three influenza strains contained in the vaccine (A/H1N1, A/H3N2, and B) after two doses of FluMist with and without concurrent administration of MMR and VAR in children who were baseline seronegative to influenza on a strain-specific basis[3]. Strain-specific seroconversion rates (=4-fold rise in HAI titer) in children who were seronegative at baseline were similar between the MMR/VAR/FluMist and the FluMist groups for each of the influenza strains (Table 5-3). Strain-specific GMTs after two doses of FluMist were also comparable between the MMR/VAR/FluMist and FluMist groups (Table 5-4).

Table 5-3 AV018: Post Dose Two Seroconversion Rates for Influenza Strains - Baseline Seronegative Children

Strain	Group 2 n/N (%)	Group 3 n/N (%)	Rate Difference (G2-G3)[a]	90% CI[b]		95% CI[c]	
				CI on Rate Difference	Within Equivalence Criteria?	CI on Rate Difference	Within Equivalence Criteria?
A/H1N1	132/310 (42.6)	139/318 (43.7)	-1.0	(-7.5, 5.5)	Yes	(-8.7, 6.7)	Yes
A/H3N2	280/286 (97.9)	294/299 (98.3)	-0.4	(-2.5, 1.5)	Yes	(-3.0, 2.0)	Yes
B	305/319 (95.6)	302/328 (92.1)	3.6	(0.5, 6.8)	Yes	(-0.2, 7.5)	Yes

Group 2 (MMR/VAR/FluMist): Visit 1, FluMist + M-M-R®II +Varivax®, Visit 2, FluMist, Visit 3, placebo mist.

Group 3 (FluMist): Visits 1 and 2, FluMist, Visit 3, M-M-R®II +Varivax®.

Seroconversion was defined as a ≥4-fold rise in titer from baseline in children who were seronegative at baseline.

a. Weighted average of the stratum-specific rate differences.
b. Prospectively defined equivalence criteria: lower limit for 90% CI > -15 percentage points for A/H1N1 strain, and > -10 percentage points for A/H3N2 and B strains.
c. Ad hoc equivalence criteria: lower limit for 95% CI > -10 percentage points for all strains.

[3] Seronegative for influenza strains was defined as HAI titer ≤4. For calculation of 4-fold rise, children with a titer <4 (the lower limit of assay detection) are given a value of 2.

Table 5-4 AV018: Post Dose Two GMT Ratios for Influenza Strains - All Children

Strain	Group 2 N, GMT	Group 3 N, GMT	Mean GMT Ratio G2/G3	90% CI[a,b]		95% CI[a,c]	
				CI on GMT Ratio	Within Equivalence Criteria?	CI on GMT Ratio	Within Equivalence Criteria?
A/H1N1	334, 5.7	339, 5.8	0.98	(0.87, 1.11)	Yes	(0.85, 1.13)	Yes
A/H3N2	334, 102.9	338, 112.3	0.92	(0.82, 1.02)	Yes	(0.81, 1.04)	Yes
B	334, 20.5	338, 17.7	1.16	(1.05, 1.28)	Yes	(1.03, 1.30)	Yes

Group 2 (MMR/VAR/FluMist): Visit 1, FluMist + M-M-R®II +Varivax®, Visit 2, FluMist, Visit 3, placebo mist.
Group 3 (FluMist): Visits 1 and 2, FluMist, Visit 3, M-M-R®II +Varivax®.

a. Confidence intervals computed by the percentile-based bootstrap technique.
b. Prospectively defined equivalence criteria: lower limit for 90% CI > 0.5.
c. Ad hoc equivalence criteria: lower limit for 95% CI > 0.5.

Thus, FluMist and M-M-R®II and VARIVAX® were similarly immunogenic whether given separately or concurrently.

6 Overview of Safety

Comprehensive safety data from five studies of FluMist were presented in the sBLA in support of expansion of the current indication to include children 59 months of age and younger: two active controlled studies (pivotal study MI-CP111 and MI-CP123) and three placebo controlled studies (D153-P501, AV006, and AV018). These studies included 8343 FluMist recipients, 1805 placebo recipients, and 4201 TIV recipients in the Safety Population (6-71 months of age) during the first year of vaccination.

In addition, serious adverse event (SAE) data were integrated for these five studies as well as eight additional studies as outlined in Table 6-1. In the integrated SAE summaries, a total of 30,114 children were included in the Safety Population (6-59 months of age) during the first year of vaccination. This included 18,315 FluMist recipients, 6692 placebo recipients, and 5107 individuals who received TIV. With the exception of SAEs, no pooling of safety data across the studies was done due to differences among the studies in design and duration, as well as differences in safety data collection periods.

A summary of the number of study vaccine doses administered is presented by study and treatment group in Table 6-2. A total of 8343 children received either one dose or two doses

of FluMist in Studies MI-CP111, MI-CP123, D153-P501 (Year 1), AV006 (Year 1), and AV018. A total of 2271 children received FluMist in Year 2 of Studies AV006 and D153-P501. All doses of frozen FluMist contained approximately 10^7 $TCID_{50}$ (median tissue culture infectious dose) and all doses of refrigerated FluMist contained approximately 10^7 FFU (fluorescence focus units) of each of three influenza virus strains: A/H1N1, A/H3N2, and B.

Table 6-1 Tabular Listing of Additional Clinical Studies included in Integrated Assessment of Safety

Study; Year; Location	Design	Population	Treatment; [a] Regimen	Number of Subjects [b]	Endpoints/Objectives [c]
D153-P500 2000 S Africa	Phase 2 Randomized Observer blind Active control <u>Follow-Up</u> REs & AEs Days 0-10 SAEs through 42 days post final dose	Healthy children 12 to <36 mos of age	CAIV-T, 0.2 ml IN FluMist, 0.5 ml IN 2 doses, 28-42 days apart	698 697	• Immunogenicity: strain-specific serum HAI seroconversion post Dose 2, matched strains
D153-P502 Year 1, 2000-2001 Year 2, 2001-2002 Europe, Israel	Phase 3 Randomized Double blind Placebo control Subjects received same tx in Yr 1 and Yr 2 <u>Follow-Up</u> REs & AEs Days 0-10 SAEs through influenza surveillance period	Healthy children 6 to <36 mos of age Subjects enrolled in Year 2 had to receive both doses in Year 1	<u>Year 1</u> CAIV-T, 0.2 ml IN Placebo, 0.2 ml IN 2 doses, 28-42 days apart <u>Year 2</u> CAIV-T, 0.2 ml IN Placebo, 0.2 ml IN 1 dose	1059 725 658 461	• Efficacy against culture-confirmed influenza due to matched strains (post Dose 2 in Yr 1; post Dose 1 in Yr 2) • Efficacy against AOM, febrile AOM, and influenza-associated AOM (post Dose 2 in Yr 1; post Dose 1 in Yr 2) • Efficacy for pharmacoeconomic endpoints: reduction in number of parents taking time off work, number of days paid work missed, number of days missed from day care, ≥1 outpatient or emergency visit, ≥1 antibiotic prescription, number of days treated with an antibiotic, and ≥1 medication for influenza illness (post Dose 2 in Yr 1; post Dose 1 in Yr 2) • Immunogenicity: strain-specific serum HAI seroconversion post Dose 2, matched strains (subset of subjects)

Table 6-1 Tabular Listing of Additional Clinical Studies included in Integrated Assessment of Safety (continued)

Study; Year; Location	Design	Population	Treatment; [a] Regimen	Number of Subjects [b]	Endpoints/Objectives [c]
D153-P504 Year 1, 2001 Year 2, 2002 S Africa, S America	Phase 3 Randomized Double blind Placebo control Subjects randomized to either CAIV-T group in Year 1 received CAIV-T in Year 2 <u>Follow-Up</u> REs & AEs Days 0-10 SAEs through influenza surveillance period	Healthy children 6 to <36 mos of age Subjects enrolled in Year 2 had to receive both doses in Year 1	<u>Year 1</u> CAIV-T/CAIV-T CAIV-T/Placebo Placebo*/Placebo* Placebo**/Placebo** 0.2 ml IN 2 doses, 28-42 days apart <u>Year 2</u> CAIV-T Placebo 0.2 ml IN 1 dose *Vaccine excipients (without virus) **Physiological saline	 1064 1067 543 526 1467 735	• Efficacy against culture-confirmed influenza due to matched strains (1 dose efficacy and 2 dose efficacy) • Immunogenicity: strain-specific serum HAI seroconversion post Dose 2, matched strains (subset of subjects)

Table 6-1 Tabular Listing of Additional Clinical Studies included in Integrated Assessment of Safety (continued)

Study; Year; Location	Design	Population	Treatment; [a] Regimen	Number of Subjects [b]	Endpoints/Objectives [c]
D153-P511 2002 S America, Asia	Phase 3 Randomized Partial blind Placebo control <u>Follow-Up</u> REs & AEs Days 0-10 SAEs through 42 days post final dose	Healthy children 6 to <36 mos of age (must have previously received 3 doses of OPV in 1st yr of life)	Dose 1: CAIV-T+OPV Dose 2: CAIV-T Dose 1: Placebo+OPV Dose 2: Placebo Dose 1: CAIV-T Dose 2: CAIV-T CAIV-T and Placebo, 0.2 ml IN OPV, PO dose per manufacturer	832 836 835	• Immunogenicity: strain-specific serum HAI seroconversion post Dose 2, matched strains, CAIV-T+OPV is non-inferior to CAIV-T alone • Immunogenicity: post vaccination titer ≥1:10 by virus neutralization for each of 3 polio virus types, CAIV-T+OPV is non-inferior to OPV alone

Table 6-1 Tabular Listing of Additional Clinical Studies included in Integrated Assessment of Safety (continued)

Study; Year; Location	Design	Population	Treatment; [a] Regimen	Number of Subjects [b]	Endpoints/Objectives [c]
D153-P513 2002 Asia	Phase 3 Randomized Double blind Placebo control <u>Follow-Up</u> REs & AEs Days 0-10 SAEs through influenza surveillance period	Healthy children 6 to <36 mos of age	CAIV-T 10^5 FFU CAIV-T 10^6 FFU CAIV-T 10^7 FFU Placebo 0.2 ml IN 2 doses, 28-42 days apart	546 546 543 537	• Efficacy against culture-confirmed influenza due to matched strains, post Dose 2 • Immunogenicity: cell-mediated immunity by IFNγ ELISPOT
D153-P514 2002-2003 Europe, Israel	Phase 3 Randomized Open label Active control <u>Follow-Up</u> REs & AEs Days 0-10 SAEs through influenza surveillance period	Children with recurrent respiratory tract illness 6 to <72 mos of age	CAIV-T, 0.2 ml IN TIV, 0.25 or 0.5 ml IM, per age 2 doses, 28-42 days apart	1107 1080 (45% had hx of medically documented wheezing)	• Efficacy against culture-confirmed influenza due to matched strains (non-inferiority and superiority) • Efficacy against culture-confirmed AOM (non-inferiority) • Efficacy against respiratory illness/wheezing (non-inferiority): reduction influenza-like illness associated with wheeze symptoms, use of any medication or antibiotic for RTI, number of unscheduled HCP visits, and number of days school/day care missed For all endpoints, non-inferiority defined as lower bound of CI > -0.5; for efficacy, superiority defined as lower bound of 95% CI >0

Table 6-1 Tabular Listing of Additional Clinical Studies included in Integrated Assessment of Safety (continued)

Study; Year; Location	Design	Population	Treatment; [a] Regimen	Number of Subjects [b]	Endpoints/Objectives [c]
D153-P522 2002-2003 Europe, Asia, Mexico	Phase 3 Randomized Double blind Placebo control <u>Follow-Up</u> REs & AEs Days 0-10 SAEs through influenza surveillance period	Healthy children 11 to <24 mos of age	CAIV-T+MMR Placebo+MMR CAIV-T and Placebo, 0.2 ml IN 2 doses, 28-42 days apart MMR, IM dose per manufacturer (non-US) 1 dose (given at 1st dose of CAIV-T or Placebo)	819 414	• Efficacy against culture-confirmed influenza due to matched strains, post Dose 2 • Immunogenicity: seroconversion for each antigen by IgG specific antibody by ELISA (non-inferiority defined as lower bound of 95% CI > -10 for each antigen)
AV019 2000-2001 USA	Phase 3 Randomized Double blind Placebo control Extraction of MAEs from computerized health care utilization databases for hospitalizations, emergency visits, and clinic visits	Healthy children 1-17 yrs of age (Kaiser Permanente HMO, Northern California)	FluMist, 0.5 ml IN Placebo, 0.5 ml IN <9 yr: 2 doses, 28-42 days apart 9-17 yr: 1 dose	6473 3769 (<9) 2704 (9-17) 3216 1868 (<9) 1348 (9-17)	• Safety: MAEs and SAEs within 42 days of vaccination

Table 6-1 Tabular Listing of Additional Clinical Studies included in Integrated Assessment of Safety (continued)

Study; Year; Location	Design	Population	Treatment; [a] Regimen	Number of Subjects [b]	Endpoints/Objectives [c]

Footnotes for Table 6-1.

AE=adverse event; AOM=acute otitis media; CAIV-T=refrigerated FluMist; CI=confidence interval; ELISA=enzyme-linked immunosorbent assay; ELISPOT=enzyme-linked immunosorbent spot; FFU=fluorescent focus units; FluMist=frozen FluMist; GMT=geometric mean titer; HAI=hemagglutination inhibition; HCP=health care provider; HMO=Health Maintenance Organization; hx=history; IFNγ=interferon gamma; IM=intramuscular; IN=intranasal; LRT=lower respiratory tract; MAE=medically attended event; MMR=trivalent measles, mumps, rubella vaccine; OPV=oral polio vaccine; OTC=over-the-counter; PEFR=peak expiratory flow rate; PO=oral; RE=reactogenicity event; SAE=serious adverse event; SC=subcutaneous; TIV=trivalent inactivated influenza virus vaccine; tx=treatment; URTI=upper respiratory tract infection; wt=wild-type

a. Frozen FluMist is formulated to contain approximately 10^7 $TCID_{50}$ of each of the three vaccine strains per dose. Refrigerated FluMist (CAIV-T) is formulated to contain approximately 10^7 FFU of each of the three vaccine strains per dose.

b. Number of subjects in the *Safety Population*.

Table 6-2 Extent of Exposure - Number of Children who Received at Least One Dose of Study Vaccine

Study Number		Age (mos)[a]	FluMist	Placebo	TIV
MI-CP111		6-59	4179	NA	4173
MI-CP123		6-35	24	NA	28
D153-P501	Year 1	12-35	1901	1273	NA
	Year 2[b]		1354	1341	NA
AV006	Year 1	15-71	1070	532	NA
	Year 2[b]		917	441	NA
AV018		12-15	1169	NA	NA
SAE Studies (Integrated Analysis)[c]		6-59	18315	6692	5107

Safety Population

NA=Not applicable.

a. Age at initial vaccination in Year 1.
b. Children in Year 2 also participated in Year 1.
c. Includes children 6-59 months of age in Studies MI-CP111, MI-CP123, D153-P501, AV006, AV018, AV019, D153-P514, D153-P502, D153-P504, D153-P511, D153-P513, D153-P522, D153-P500.

6.1 Reactogenicity Events

Reactogenicity events (REs) are defined as those events expected to occur as a result of vaccination. The RE terms were predefined and protocol-specific, but those REs that were common among the studies included fever, runny nose/nasal congestion, sore throat, cough, vomiting, muscle ache, headache, chills, decreased activity, and irritability. Data for REs were collected using diary cards. For a protocol-specific time period, the child's parent/legal representative was instructed to take their child's temperature every day and to record in the diary the child's temperature and whether the child had any of the other predefined events.

REs were collected after each dose of study vaccine for Studies MI-CP111, D153-P501, AV006, and AV018 (REs were not collected in Study MI-CP123). The incidence of REs post Dose One and post Dose Two is presented in Table 6-3, Figure 6-1, Figure 6-2, and Figure 6-3 (Study MI-CP111), Table 6-4 (Studies D153-P501 and AV006, Years 1 and 2), and Table 6-5 (Study AV018). Based on these studies, the reactogenicity profile of FluMist in children 6-71 months of age is consistent with the established profile in the currently indicated population including healthy children 5-8 years of age. Study AV018 also demonstrated that concurrent administration of FluMist with M-M-R®II and VARIVAX®

vaccines was associated with acceptable safety and tolerability in children 12-15 months of age.

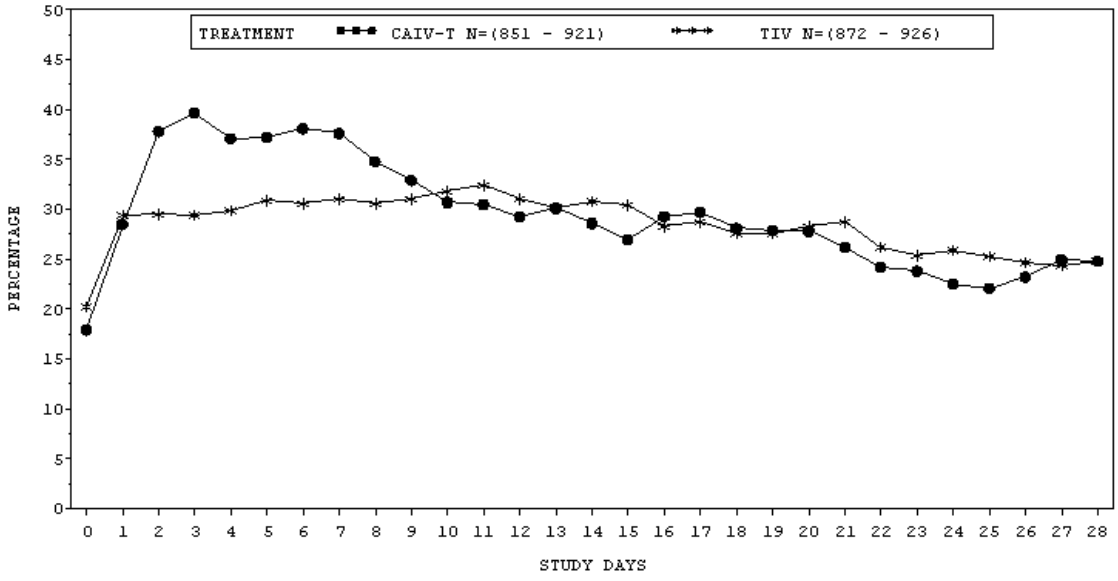
Overall, in children 6-71 months of age in Studies MI-CP111, D153-P501, and AV006, the most frequently reported REs post Dose One and post Dose Two for FluMist were runny nose/stuffy nose/nasal congestion, cough, irritability, decreased appetite, and fever >100°F oral. In the TIV-controlled study (Study MI-CP111), the incidence rate for runny/stuffy nose was higher for FluMist relative to TIV (Table 6-3, Figure 6-1, Figure 6-2, and Figure 6-3), with the other individual REs reported at similar rates between these two treatment groups; the incidence of injection site reactions, however, was higher for TIV relative to FluMist. In healthy children 12-15 months of age in Study AV018, during Days 0-41 post receipt of M-M-R®II and VARIVAX®, runny nose/nasal congestion was the only RE that was statistically significantly increased in those who received concurrent FluMist relative to placebo mist.

Table 6-3 MI-CP111: Reactogenicity Events During Days 0-10 Post Each Dose in Children 6-59 Years of Age

Reactogenicity Event	ONE DOSE Group			TWO DOSE Group					
	Post Dose One			Post Dose One			Post Dose Two		
	FluMist N=929	TIV N=935	Rate Diff	FluMist N=3205	TIV N=3179	Rate Diff	FluMist N=2977	TIV N=3001	Rate Diff
Any RE	641 (69.0%)	597 (63.9%)	5.1	2232 (69.6%)	1998 (62.8%)	6.8	1633 (54.9%)	1537 (51.2%)	3.6
Runny/stuffy nose	528 (56.8%)	428 (45.8%)	11.1	1827 (57.0%)	1472 (46.3%)	10.7	1263 (42.4%)	1140 (38.0%)	4.4
Sore throat	26 (2.8%)	43 (4.6%)	-1.8	141 (4.4%)	152 (4.8%)	-0.4	122 (4.1%)	109 (3.6%)	0.5
Cough	291 (31.3%)	298 (31.9%)	-0.5	934 (29.1%)	943 (29.7%)	-0.5	767 (25.8%)	738 (24.6%)	1.2
Vomiting	66 (7.1%)	66 (7.1%)	0.0	239 (7.5%)	247 (7.8%)	-0.3	194 (6.5%)	195 (6.5%)	0.0
Headache	16 (1.7%)	21 (2.2%)	-0.5	67 (2.1%)	49 (1.5%)	0.5	40 (1.3%)	32 (1.1%)	0.3
Muscle ache	8 (0.9%)	17 (1.8%)	-1.0	43 (1.3%)	34 (1.1%)	0.3	21 (0.7%)	22 (0.7%)	-0.0
Chills	16 (1.7%)	14 (1.5%)	0.2	58 (1.8%)	51 (1.6%)	0.2	23 (0.8%)	34 (1.1%)	-0.4
Decreased activity	61 (6.6%)	56 (6.0%)	0.6	252 (7.9%)	235 (7.4%)	0.5	118 (4.0%)	147 (4.9%)	-0.9
Irritability	156 (16.8%)	161 (17.2%)	-0.4	594 (18.5%)	565 (17.8%)	0.8	266 (8.9%)	262 (8.7%)	0.2
Abdominal pain	37 (4.0%)	37 (4.0%)	0.0	117 (3.7%)	130 (4.1%)	-0.4	73 (2.5%)	71 (2.4%)	0.1
Decreased appetite	128 (13.8%)	131 (14.0%)	-0.2	464 (14.5%)	428 (13.5%)	1.0	234 (7.9%)	262 (8.7%)	-0.9
Fever									
>100°F oral or equivalent	101 (10.9%)	91 (9.7%)	1.1	492 (15.4%)	371 (11.7%)	3.7	323 (10.8%)	355 (11.8%)	-1.0
>101°F oral or equivalent	57 (6.1%)	60 (6.4%)	-0.3	246 (7.7%)	213 (6.7%)	1.0	172 (5.8%)	205 (6.8%)	-1.1
>102°F oral or equivalent	27 (2.9%)	29 (3.1%)	-0.2	113 (3.5%)	120 (3.8%)	-0.2	89 (3.0%)	114 (3.8%)	-0.8
>103°F oral or equivalent	9 (1.0%)	10 (1.1%)	-0.1	39 (1.2%)	46 (1.4%)	-0.2	29 (1.0%)	38 (1.3%)	-0.3
>104°F oral or equivalent	4 (0.4%)	1 (0.1%)	0.3	9 (0.3%)	11 (0.3%)	-0.1	5 (0.2%)	12 (0.4%)	-0.2

Rate difference is FluMist minus TIV.
Excludes injection site reactions.

Any Reactogenicity Event



Runny Nose/Nasal Congestion

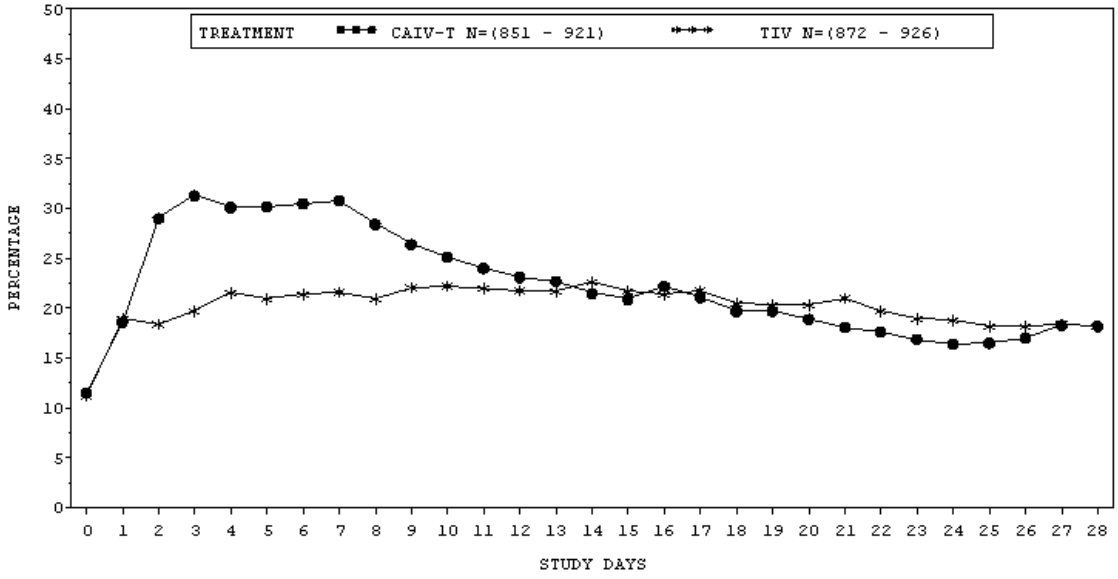
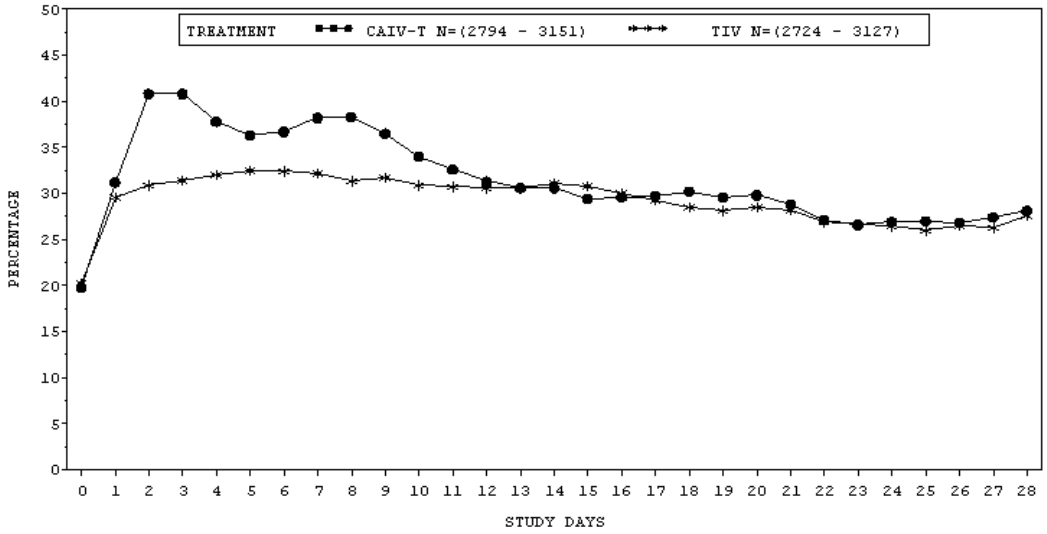


Figure 6-1 **MI-CP111: Reactogenicity Events Days 0-28 Post Dosing, by Study Day, in the ONE DOSE Group in Children 6-59 Months of Age**

Any Reactogenicity Event



Runny Nose/Nasal Congestion

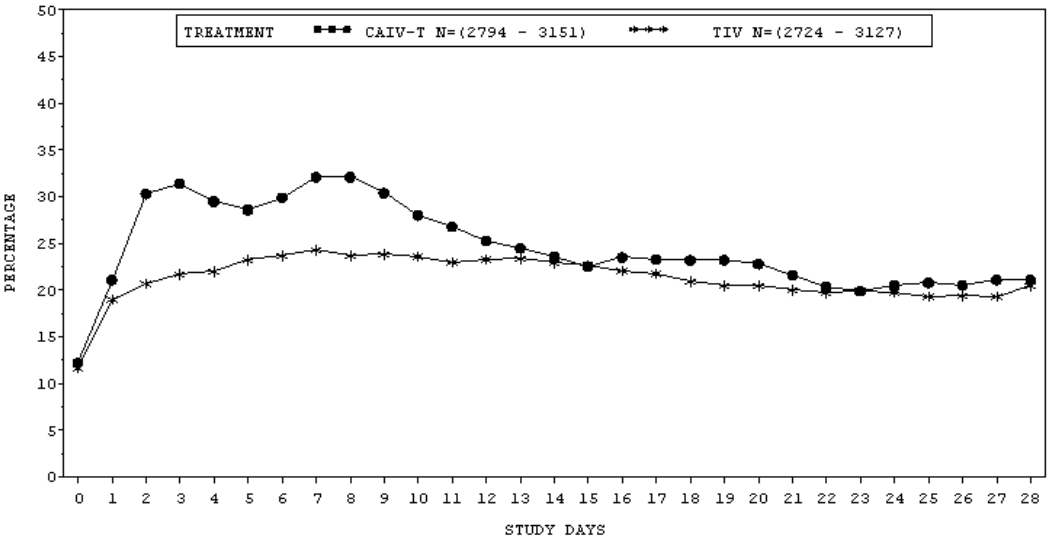
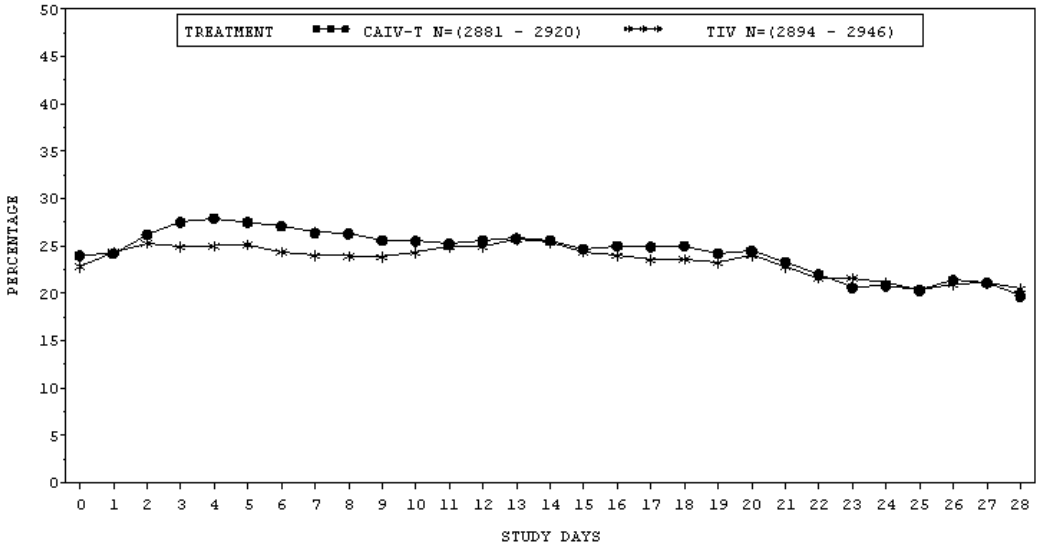


Figure 6-2 **MI-CP111: Reactogenicity Events Days 0-28 Post Dosing, by Study Day, in the TWO DOSE Group Post Dose One in Children 6-59 Months of Age**

Any Reactogenicity Event



Runny Nose/Nasal Congestion

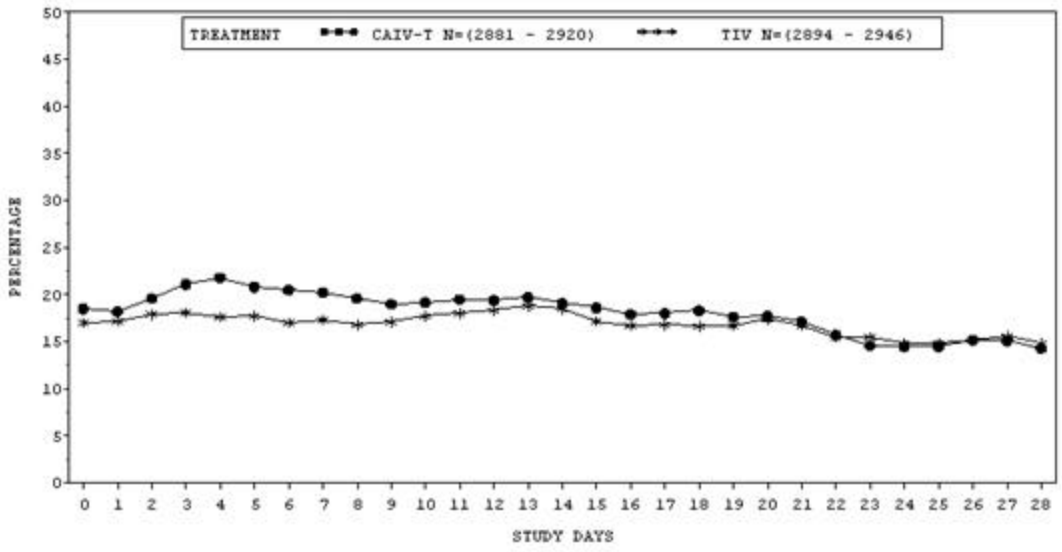


Figure 6-3 **MI-CP111: Reactogenicity Events Days 0-28 Post Dosing, by Study Day, in the TWO DOSE Group Post Dose Two in Children 6-59 Months of Age**

Table 6-4 D153-P501 and AV006, Years 1 & 2: Reactogenicity Events During Days 0-10 Post Each Dose in Children Initially 12-35 Months of Age (D153-P501) and Initially 15-71 Months of Age (AV006)

Reactogenicity Event	D153-P501 Year 1				D153-P501 Year 2		AV006 Year 1				AV006 Year 2	
	Post Dose One		Post Dose Two		Post Dosing		Post Dose One		Post Dose Two		Post Dosing	
	FluMist N=1764-1857	Placebo N=1182-1246	FluMist N=1579-1661	Placebo N=1088-1119	FluMist N=1345-1352	Placebo N=1327-1340	FluMist N=1056	Placebo N=530	FluMist N=850	Placebo N=415	FluMist N=912	Placebo N=441
Any RE	**1397 (76.0)**	**851 (69.5)**	**1030 (63.5)**	**657 (59.2)**	**999 (73.9)**	**936 (70.1)**	**783 (74)**	**351 (66)**	**584 (69)**	**257 (62)**	527 (58)	254 (58)
Cough	**630 (34.1)**	**481 (38.6)**	568 (34.3)	374 (33.5)	567 (42.0)	543 (40.6)	296 (28)	154 (29)	305 (36)	138 (33)	219 (24)	112 (25)
Runny nose/ Nasal congestion	**1151 (62.0)**	**647 (52.0)**	**827 (49.8)**	**510 (45.6)**	**838 (62.0)**	**743 (55.4)**	**621 (59)**	**256 (48)**	438 (51)	191 (46)	384 (42)	186 (42)
Irritability	445 (24.1)	265 (21.3)	260 (15.7)	167 (15.0)	228 (16.9)	208 (15.6)	276 (26)	137 (26)	142 (17)	77 (19)	132 (14)	70 (16)
Vomiting	282 (15.3)	212 (17.1)	195 (11.8)	127 (11.4)	210 (15.6)	187 (14.0)	**64 (6)**	**19 (4)**	61 (7)	20 (5)	44 (5)	18 (4)
Decreased activity	**248 (13.4)**	**133 (10.7)**	133 (8.0)	96 (8.6)	134 (9.9)	120 (9.0)	170 (16)	68 (13)	109 (13)	52 (13)	104 (11)	56 (13)
Decreased appetite	**448 (24.2)**	**245 (19.7)**	275 (16.6)	214 (19.1)	295 (21.9)	268 (20.0)	NC	NC	NC	NC	NC	NC
Stomach ache	NC	NC	NC	NC	146 (10.8)	142 (10.6)	NC	NC	NC	NC	NC	NC
Sore throat	NC	NC	NC	NC	NC	NC	104 (10)	42 (8)	48 (6)	28 (7)	92 (10)	37 (8)
Headache	NC	NC	NC	NC	NC	NC	84 (8)	34 (6)	41 (5)	23 (6)	84 (9)	31 (7)
Chills	NC	NC	NC	NC	NC	NC	42 (4)	18 (3)	27 (3)	12 (3)	31 (3)	13 (3)
Muscle aches	NC	NC	NC	NC	NC	NC	**55 (5)**	**14 (3)**	23 (3)	7 (2)	26 (3)	16 (4)

Reactogenicity Event	D153-P501 Year 1				D153-P501 Year 2		AV006 Year 1				AV006 Year 2	
	Post Dose One		Post Dose Two		Post Dosing		Post Dose One		Post Dose Two		Post Dosing	
	FluMist N=1764-1857	**Placebo N=1182-1246**	**FluMist N=1579-1661**	**Placebo N=1088-1119**	**FluMist N=1345-1352**	**Placebo N=1327-1340**	**FluMist N=1056**	**Placebo N=530**	**FluMist N=850**	**Placebo N=415**	**FluMist N=912**	**Placebo N=441**
Fever:												
≥37.5°C axillary	**393 (22.0)**	**209 (17.6)**	241 (15.2)	164 (15.0)	242 (18.0)	218 (16.4)	---	---	---	---	---	---
≥38.6°C axillary	87 (4.9)	48 (4.1)	64 (4.0)	41 (3.8)	62 (4.6)	67 (5.0)	---	---	---	---	---	---
≥40.0°C axillary	5 (0.3)	2 (0.2)	5 (0.3)	4 (0.4)	4 (0.3)	6 (0.5)	---	---	---	---	---	---
>100°F oral	---	---	---	---	---	---	**174 (16)**	**64 (12)**	94 (11)	45 (11)	99 (11)	42 (10)
>101°F oral	---	---	---	---	---	---	73 (7)	31 (6)	42 (5)	25 (6)	51 (6)	15 (3)
>102°F oral	---	---	---	---	---	---	26 (2)	19 (4)	19 (2)	16 (4)	26 (3)	8 (2)
>103°F oral	---	---	---	---	---	---	9 (0.9)	7 (1)	6 (0.7)	5 (1)	11 (1)	1 (0.2)
>104°F oral	---	---	---	---	---	---	1 (0.1)	1 (0.2)	1 (0.1)	2 (0.5)	2 (0.2)	0 (0)

NC = not collected.

Bolded values are significantly different between treatment groups ($p < 0.05$, Fisher's exact test).

Table 6-5 AV018: Reactogenicity Events Days 0-41 Post Dosing in Children 12-15 Months of Age

Reactogenicity Event	Days 0-41 Post Visit 1	
	Group 2 (MMR/VAR/FluMist) N=412	**Group 1 (MMR/VAR) N=393**
Any RE	389 (94.4)	366 (93.1)
Cough	211 (51.2)	204 (51.9)
Runny nose/Nasal congestion	**346 (84.0)**	**305 (77.6)**
Sore throat	62 (15.0)	50 (12.7)
Irritability	296 (71.8)	276 (70.2)
Headache	18 (4.4)	15 (3.8)
Chills	15 (3.6)	8 (2.0)
Vomiting	97 (23.5)	89 (22.6)
Muscle aches	11 (2.7)	9 (2.3)
Decreased activity	113 (27.4)	97 (24.7)
Fever:		
>100°F oral or equivalent	270 (65.5)	238 (60.6)
>101°F oral or equivalent	165 (40.0)	153 (38.9)
>102°F oral or equivalent	96 (23.3)	83 (21.1)
>103°F oral or equivalent	30 (7.3)	34 (8.7)
>104°F oral or equivalent	6 (1.5)	8 (2.0)

Bolded values are significantly different between treatment groups (90% and 95% exact unconditional CIs for the rate difference).
Excludes injection site reactions.

6.2 Adverse Events

Adverse events (AEs) reported at an incidence of ≥1% in any treatment group post Dose One and post Dose Two are presented in the Table 6-6 (Study MI-CP111), Table 6-7 (Study D153-P501), Table 6-8 (Study AV006), and Table 6-9 (Study AV018). In the studies for which AE data were included in the sBLA, the individual AEs reported were those commonly expected to occur in a pediatric population. In Studies MI-CP111, D153-P501, AV006, and MI-CP123, as expected, the rates of any event post Dose Two were lower than those post Dose One among children receiving FluMist.

In Study MI-CP111, for all children, approximately one third of children in each treatment group reported at least one AE within 28 days of vaccination (Table 6-6). No individual event was reported at the MedDRA preferred term level at an incidence of >8% in the FluMist group or >9% in the TIV group. The event associated with the greatest increase in FluMist vs. TIV in any comparison was sneezing (rate difference of 1.1 percentage points) and was only associated with the ONE DOSE group. The events associated with the greatest increase in TIV vs. FluMist in any comparison were diarrhea, acute otitis media, and rash (rate differences from 1.1-1.5 percentage points).

Approximately one-third of children in the FluMist and placebo groups reported at least one AE during Days 0-10 after receipt of study vaccine in Study D153-P501 (Year 1). Individual events were reported at similar rates between the two treatment groups, with the exception of fever[4] (15.4% FluMist vs. 11.7% placebo after Dose One). Following re-vaccination with a single dose of FluMist or placebo in Year 2, the proportions of children who reported at least one AE and each individual AE were similar to those for Year 1: coughing, rhinitis, upper respiratory tract infection, and fever accounted for the majority of events; the rate of fever, although lower than Year 1, remained statistically significantly higher for FluMist (12.7% vs. 9.8% placebo) (Table 6-7).

Fewer than one-fifth of children in the FluMist and placebo groups reported at least one AE during Days 0-10 after receipt of study vaccine in Study AV006 (Year 1). Individual events were reported at similar rates between the two treatment groups, with the exceptions of abdominal pain (2% FluMist vs. 0.2% placebo) and rash (0.4% FluMist vs. 2.1% placebo). Following re-vaccination with a single dose of FluMist or placebo in Year 2, the proportions of children who reported at least one AE were lower than those reported for Year 1.

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[4] In Study D153-P501, fever was defined as a temperature of ≥38°C rectal or oral, or ≥37.5°C axillary. In general, an RE was also reported as an AE if the event required any prescription or non-prescription medication during Days 0-10 post vaccination, required an unscheduled health care provider visit and/or health care provider consultation during Days 0-10 post vaccination, or resulted in study termination.

Individual events were reported at similar rates between the two treatment groups, with the exception of conjunctivitis (0.1% FluMist vs. 1% placebo). The majority of events reported in both treatment groups in Year 2 were accounted for by allergic reaction, accident injury, and diarrhea (Table 6-8).

Approximately one half of MMR/VAR/FluMist or MMR/VAR recipients reported at least one AE during Days 0-41 after receipt of study vaccines in Study AV018 (Table 6-9). Individual events were reported at similar rates between the two treatment groups, with the exceptions of a higher rate in the concomitant FluMist group for diarrhea (17.1% MMR/VAR/FluMist vs. 15.0% MMR/VAR) injection site bruise (1.2% MMR/VAR/FluMist vs. 0.3% MMR/VAR), and undifferentiated ear infection (1.7% MMR/VAR/FluMist vs. 0.8% MMR/VAR). Of note, rates of wheezing during Days 0-41 were lower in those who received concurrent FluMist vs. placebo (1.2% MMR/VAR/FluMist vs. 2.5% MMR/VAR).

In Study MI-CP123, the percentage of children reporting any AEs was similar between the two treatment groups: 67% to 75% in the FluMist group, and 71% to 79% in the TIV group. Individual events were reported at similar rates between the treatment groups, and the majority of events were assessed as mild in severity.

Table 6-6 MI-CP111: Adverse Events Reported During Days 0-28 Post Each Dose in ³1% of Children in Any Group in Children 6-59 Months of Age

MedDRA Preferred Term	ONE DOSE Group			TWO DOSE Group					
	Post Dose One			Post Dose One			Post Dose Two		
	FluMist N=933	TIV N=947	Rate Diff	FluMist N=3246	TIV N=3226	Rate Diff	FluMist N=3002	TIV N=3034	Rate Diff
N of Events	494	453		1713	1724		1236	1242	
N of Subjects Reporting ≥1 Event	311 (33.3%)	301 (31.8%)	1.5	1105 (34.0%)	1109 (34.4%)	-0.3	813 (27.1%)	824 (27.2%)	-0.1
Conjunctivitis	12 (1.3%)	8 (0.8%)	0.4	58 (1.8%)	64 (2.0%)	-0.2	50 (1.7%)	49 (1.6%)	0.1
Diarrhoea	63 (6.8%)	58 (6.1%)	0.6	209 (6.4%)	242 (7.5%)	-1.1	151 (5.0%)	147 (4.8%)	0.2
Teething	21 (2.3%)	27 (2.9%)	-0.6	144 (4.4%)	154 (4.8%)	-0.3	70 (2.3%)	79 (2.6%)	-0.3
Bronchitis	10 (1.1%)	15 (1.6%)	-0.5	52 (1.6%)	42 (1.3%)	0.3	59 (2.0%)	51 (1.7%)	0.3
Croup infectious	15 (1.6%)	7 (0.7%)	0.9	33 (1.0%)	39 (1.2%)	-0.2	33 (1.1%)	27 (0.9%)	0.2
Gastroenteritis	13 (1.4%)	8 (0.8%)	0.5	27 (0.8%)	22 (0.7%)	0.1	31 (1.0%)	32 (1.1%)	-0.0
Otitis media acute	63 (6.8%)	64 (6.8%)	-0.0	253 (7.8%)	248 (7.7%)	0.1	213 (7.1%)	262 (8.6%)	-1.5
Sinusitis	16 (1.7%)	14 (1.5%)	0.2	28 (0.9%)	18 (0.6%)	0.3	12 (0.4%)	7 (0.2%)	0.2
Sneezing	18 (1.9%)	8 (0.8%)	1.1	24 (0.7%)	27 (0.8%)	-0.1	10 (0.3%)	11 (0.4%)	-0.0
Wheezing	22 (2.4%)	18 (1.9%)	0.5	84 (2.6%)	82 (2.5%)	0.0	63 (2.1%)	70 (2.3%)	-0.2
Dermatitis diaper	4 (0.4%)	6 (0.6%)	-0.2	32 (1.0%)	34 (1.1%)	-0.1	23 (0.8%)	24 (0.8%)	-0.0
Rash	23 (2.5%)	23 (2.4%)	0.0	41 (1.3%)	83 (2.6%)	-1.3	26 (0.9%)	25 (0.8%)	0.0

Rate difference is FluMist minus TIV.

Statistical significance for AEs was not calculated in this study.

Table 6-7 D153-P501 Years 1 and 2: Adverse Events Reported During Days 0-10 Post Each Dose in ³1% of Children in Any Group in Children Initially 12-35 Months of Age

Body System Event	Year 1, Post Dose One		Year 1, Post Dose Two		Year 2, Post Dosing	
	FluMist N=1901	**Placebo N=1273**	**FluMist N=1671**	**Placebo N=1127**	**FluMist N=1354**	**Placebo N=1341**
Number of Events	955	591	572	388	803	660
Total N of Subjects Reporting ≥1 Event	**640 (33.7)**	**387 (30.4)**	391 (23.4)	254 (22.5)	**468 (34.6)**	**412 (30.7)**
Gastrointestinal						
Abdominal pain	1 (0.1)	2 (0.2)	1 (0.1)	0 (0.0)	20 (1.5)	12 (0.9)
Diarrhea	39 (2.1)	16 (1.3)	19 (1.1)	14 (1.2)	10 (0.7)	11 (0.8)
Vomiting	23 (1.2)	23 (1.8)	13 (0.8)	10 (0.9)	24 (1.8)	21 (1.6)
Respiratory						
Coughing	148 (7.8)	123 (9.7)	120 (7.2)	83 (7.4)	166 (12.3)	147 (11.0)
Rhinitis	227 (11.9)	125 (9.8)	105 (6.3)	86 (7.6)	187 (13.8)	160 (11.9)
Upper resp tract infection	98 (5.2)	62 (4.9)	86 (5.1)	51 (4.5)	86 (6.4)	77 (5.7)
Body As A Whole						
Fever	**292 (15.4)**	**149 (11.7)**	144 (8.6)	91 (8.1)	**172 (12.7)**	**131 (9.8)**
Bodily discomfort	14 (0.7)	7 (0.5)	2 (0.1)	1 (0.1)	13 (1.0)	8 (0.6)
Anorexia	11 (0.6)	7 (0.5)	11 (0.7)	3 (0.3)	20 (1.5)	15 (1.1)

Bolded values are significantly diffe rent between FluMist and placebo ($p < 0.05$, Fisher's exact test). Two additional AEs met statistical significance but the incidence rates were <1.0% and are therefore not represented in this table:

Bronchitis, Year 1, post Dose Two: FluMist (1, 0.1%) vs. placebo (7, 0.6%), $p < 0.05$
Pharyngitis, Year 1, post Dose Two: FluMist (13, 0.8%) vs. placebo (2, 0.2%), $p < 0.05$.

Table 6-8 AV006 Years 1 and 2: Adverse Events Reported During Days 0-10 Post Each Dose in ³1% of Children in Any Group in Children Initially 15-71 Months of Age

Body System Event	Year 1, Post Dose One		Year 1, Post Dose Two		Year 2, Post Dosing	
	FluMist N=1070	**Placebo N=532**	**FluMist N=854**	**Placebo N=418**	**FluMist N=917**	**Placebo N=441**
Total N of Subjects Reporting ≥1 Event	191 (18)	78 (15)	119 (14)	62 (15)	116 (13)	60 (14)
Body As A Whole						
Allergic reaction	12 (1)	3 (0.6)	0 (0)	0 (0)	9 (1)	7 (2)
Infection	12 (1)	6 (1)	16 (2)	7 (2)	5 (0.5)	6 (1)
Injury accident	15 (1)	4 (0.8)	4 (0.5)	1 (0.2)	14 (2)	4 (0.9)
Pain	23 (2)	13 (2)	3 (0.4)	4 (1)	8 (0.9)	6 (1)
Pain abdominal	**19 (2)**	**1 (0.2)**	7 (0.8)	2 (0.5)	10 (1)	3 (0.7)
Digestive System						
Anorexia	11 (1.0)	3 (0.6)	8 (0.9)	3 (0.7)	2 (0.2)	2 (0.5)
Diarrhea	38 (4)	17 (3.2)	21 (2)	10 (2)	12 (1)	11 (3)
Skin/Appendages						
Rash	**4 (0.4)**	**11 (2.1)**	6 (0.7)	2 (0.5)	9 (1)	4 (0.9)
Special Senses						
Conjunctivitis	5 (0.5)	2 (0.4)	5 (0.6)	3 (0.7)	**1 (0.1)**	**6 (1)**
Otitis media	20 (2)	6 (1)	27 (3)	8 (2)	12 (1)	6 (1)

Bolded values are significantly diffe rent between FluMist and placebo ($p < 0.05$, Fisher's exact test).

Table 6-9 AV018: Adverse Events Reported During Days 0-41 Post Dosing in ³1% of Children in Any Group in Children 12-15 Months of Age

Body System Preferred Term	Days 0-41 Post Visit 1	
	Group 2 (MMR/VAR/FluMist) N=410	Group 1 (MMR/VAR) N=394
N Reporting ≥1 AE	191 (46.6)	191 (48.5)
Body as a Whole		
Infection	6 (1.5)	6 (1.5)
Infection fungal	6 (1.5)	5 (1.3)
Infection viral	7 (1.7)	10 (2.5)
Injection site bruise	5 (1.2)	1 (0.3)
Injury accidental	23 (5.6)	19 (4.8)
Digestive		
Anorexia	13 (3.2)	15 (3.8)
Diarrhea	70 (17.1)	59 (15.0)
Gastroenteritis	6 (1.5)	4 (1.0)
Nervous		
Sleep disorder	9 (2.2)	5 (1.3)
Respiratory		
Bronchiolitis	0 (0.0)	4 (1.0)
Bronchitis	0 (0.0)	7 (1.8)
Croup	6 (1.5)	7 (1.8)
Epistaxis	2 (0.5)	4 (1.0)
Pharyngitis	8 (2.0)	12 (3.0)
Sinusitis	5 (1.2)	4 (1.0)
Sneezing	8 (2.0)	8 (2.0)
Wheezing	5 (1.2)	10 (2.5)
Skin		
Eczema	4 (1.0)	6 (1.5)
Rash	8 (2.0)	8 (2.0)
Special Senses		
Conjunctivitis	12 (2.9)	13 (3.3)
Ear infection, undifferentiated	7 (1.7)	3 (0.8)
Otitis media	33 (8.0)	43 (10.9)
Pain ear	4 (1.0)	3 (0.8)

Statistical significance for AEs was not calculated in this study.

6.3 Wheezing

6.3.1 Medically Attended Asthma/Reactive Airways Disease in Study AV019

Prior to the licensure of FluMist in 2003, the Phase 3 placebo controlled safety study AV019 was conducted in 9689 children 1-17 years of age in conjunction with the Kaiser Permanente Health Maintenance Organization (HMO). In prespecified safety analyses, a signal for asthma/reactive airways disease (a coded diagnostic term in the HMO database) was initially found in children 18-35 months of age within 42 days of vaccination: 2.2% who received FluMist vs. 0.54% who received placebo. In post hoc analyses, a statistically significant increased risk could not be ruled out in children up to 59 months of age: for children 12-59 months of age, the rates of asthma/reactive airways disease were 0.69% for FluMist recipients vs. 0.20% for placebo recipients. Medical visits for asthma/reactive airways disease were not temporally clustered within the 42-day post-vaccination period, there were no hospitalizations, and most of the visits were associated with standard medication use. There was no increased risk found in children 5 years of age and older; rates of asthma/reactive airways disease were significantly decreased in some analyses of older children who received FluMist vs. placebo (Belshe, 2004). In analyses that evaluated combined rates of asthma/reactive airways disease or wheezing/shortness of breath (both of which were coded diagnoses in the HMO database), no statistical increase was seen for FluMist recipients in any age group.

6.3.2 Protocol-Defined Wheezing in Study MI-CP111

A case definition ("medically significant wheezing [MSW]") was used in the protocol to establish a basis for prospective comparison between the two treatment groups in this study based on the presence of clinical features used to classify asthma exacerbations in a standardized Pediatric Assessment Score (Kelly 2000). Protocol-defined wheezing (MSW) was defined as the presence of wheezing on physical examination accompanied by at least one of the following: sign of respiratory distress (tachypnea, retractions, or dyspnea), hypoxemia (O_2 saturation <95%), or a new prescription for daily bronchodilator therapy (not on an "as needed" basis). This was chosen to assure that wheezing was documented to be present by a health care provider (rather than a report only by the caregiver) and that the wheezing was either accompanied by clinical signs or associated with the necessity to implement treatment.

When analyzed by dose in all children 6-59 months of age, the rate difference for incidence of protocol-defined wheezing (MSW) was statistically significant after Dose One in children receiving two doses of vaccine (2.3% FluMist vs. 1.5% TIV) (Table 6-10). When analyzed by pre-specified age group (6-23 months vs. 24-59 months of age) and by dose, children 6-

23 months of age generally had higher rates of protocol-defined wheezing (MSW) in both treatment groups than children 24-59 months of age. For children 24-59 months of age, no significant increases in protocol-defined wheezing (MSW) between treatment groups were observed, with the point estimates generally being higher for TIV compared to FluMist. For children 6-23 months of age, rate differences for FluMist were higher relative to TIV. Similar to the "all subjects" analysis, protocol-defined wheezing (MSW) was significantly increased post Dose One in children 6-23 months of age receiving two doses of vaccine (3.2% vs. 2.0%). Higher rates of protocol-defined wheezing (MSW) for FluMist relative to TIV were observed during Weeks 2, 3, and 4 post Dose One in children 6-23 months of age receiving two doses of vaccine. In addition, the rate from Day 0 through 42 days after receipt of last dose for children 6-23 months of age was statistically significantly higher in FluMist vs. TIV recipients (5.9% vs. 3.8%) (Table 6-10). Based on these pre-specified analyses, the subgroup that most contributed to the increase in protocol-defined wheezing (MSW) for all children 6-59 months of age was children 6-23 months of age.

Table 6-10 MI-CP111: Protocol-Defined Wheezing (MSW) Within 42 Days After Each Study Vaccination in Children 6-59 Months of Age

Age Group and Previous Vaccination Status	Timepoint	FluMist N=4179			TIV N=4173			Rate Difference[a]	95% CI for Rate Difference[a]
		N	# of Cases	Crude Rate cases/N	N	# of Cases	Crude Rate cases/N		
All Children 6-59 Months	Post Last Dose[b]	4179	164	3.9%	4173	131	3.1%	0.70	-0.08, 1.50
Previously Vaccinated	Post Dose One	933	19	2.0%	947	17	1.8%	0.03	-1.24, 1.38
Not Previously Vaccinated	**Post Dose One**	**3246**	**74**	**2.3%**	**3226**	**48**	**1.5%**	**0.77**	**0.12, 1.46**
	Post Dose Two[c]	3002	73	2.4%	3034	67	2.2%	0.20	-0.56, 0.97
All Children 6-23 Months	**Post Last Dose[b]**	**1992**	**117**	**5.9%**	**1975**	**75**	**3.8%**	**2.03**	**0.72, 3.38**
Previously Vaccinated	Post Dose One	267	7	2.6%	269	3	1.1%	1.34	-1.11, 4.30
Not Previously Vaccinated	**Post Dose One**	**1725**	**55**	**3.2%**	**1706**	**34**	**2.0%**	**1.18**	**0.13, 2.29**
	Post Dose Two[c]	1578	57	3.6%	1595	39	2.4%	1.15	-0.04, 2.38
All Children 24-59 Months	Post Last Dose[b]	2187	47	2.1%	2198	56	2.5%	-0.50	-1.42, 0.39
Previously Vaccinated	Post Dose One	666	12	1.8%	678	14	2.1%	-0.49	-2.07, 1.10
Not Previously Vaccinated	Post Dose One	1521	19	1.2%	1520	14	0.9%	0.30	-0.46, 1.09
	Post Dose Two[c]	1424	16	1.1%	1439	28	1.9%	-0.85	-1.83, 0.05

Bold type indicate statistically significant difference between FluMist and TIV.

a. Rate difference was adjusted for age, recurrent wheezing history status, and prior vaccination status for "all children;" and for age and recurrent wheezing history status for previously vaccinated and not previously vaccinated children.

b. Includes time immediately after receiving vaccine at Dose One through 42 days after last dose (either Dose One or Dose Two, depending upon prior vaccination status).

c. Includes time immediately after receiving study vaccine at Dose One through 42 days after Dose One, or until immediately prior to receipt of Dose Two (if <42 days between doses).

A total of 18 children (11/4179 [0.3%] FluMist; 7/4173 [0.2%] TIV) were hospitalized in association with an adverse event that met the definition of protocol-defined wheezing (MSW) within 42 days of dosing (see Appendix A and Appendix B for details on these children). No deaths resulted from these 18 events, and none of the hospitalized children required mechanical ventilation or admission to an intensive care unit. Two thirds (12 of 18) of the hospitalized children were 6-23 months of age: 9/1992 [0.5%] in the FluMist group and 3/1975 [0.2%] in the TIV group. Of the 9 children in the FluMist group, 2 had a past history of wheezing or asthma, 1 had RSV infection, and 2 children had both a past history of wheezing or asthma and RSV infection. Of the 3 children in the TIV group, 1 had RSV infection, 1 had a past history of wheezing or asthma and RSV infection, and 1 had a past history of wheezing or asthma and mycoplasma infection.

Most of the hospitalized children received standard therapy including bronchodilators and steroids. The median duration of hospitalization in children 6-23 months of age was 4.5 days in the FluMist group (including one child with Down Syndrome who was hospitalized for 21 days) and 4 days in the TIV group. Thus, there was no evidence that the severity of hospitalized protocol-defined wheezing (MSW) cases differed between the FluMist and TIV treatment groups.

There was also no evidence that the severity of protocol-defined wheezing (MSW) was different between FluMist and TIV recipients as assessed by the distribution of defining criteria (presence of wheezing on physical examination with hypoxemia, respiratory distress, or new prescription for daily bronchodilator therapy) (Table 6-11). For example, the proportion of children 6-23 months of age with protocol-defined wheezing (MSW) who met the case definition on the basis of receiving a new prescription for daily bronchodilator therapy only (i.e., did not have respiratory distress or hypoxemia) was similar: 75% for FluMist vs. 69% for TIV from administration through 42 days after the last vaccination. Likewise, the proportion of children with protocol-defined wheezing (MSW) in this age group who had respiratory distress or hypoxemia was also similar: 25% for FluMist vs. 31% for TIV.

Table 6-11 MI-CP111: Measures of Severity of Protocol-Defined Wheezing (MSW) in Children 6-23 Months of Age

Age Subgroup (months) Outcome	FluMist			TIV		
	6-11 N=684	12-23 N=1308	6-23 N=1992	6-11 N=683	12-23 N=1292	6-23 N=1975
Number of children with protocol-defined wheezing from Day 0 through 42 days after last vaccination	47	70	117	29	46	75
Number of these children with outcome of:						
Hospitalization	4 (9%)	5 (7%)	9 (8%)	2 (7%)	1 (2%)	3 (4%)
Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
ICU or mechanical ventilation	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
New bronchodilator prescription and not hypoxemia or respiratory distress	38 (81%)	50 (71%)	88 (75%)	20 (69%)	32 (70%)	52 (69%)
Any respiratory distress or hypoxemia	9 (19%)	20 (29%)	29 (25%)	9 (31%)	14 (30%)	23 (31%)
≥1 additional MSW episode through 180 days post final dose	18 (38%)	20 (29%)	38 (32%)	7 (24%)	14 (30%)	21 (28%)
≥2 additional MSW episodes through 180 days post final dose	2 (4%)	3 (4%)	5 (4%)	2 (31%)	2 (4%)	4 (5%)

Rates of recurrent protocol-defined wheezing (MSW) over the approximate 7 months of follow-up on the study were also analyzed (Table 6-11). Among children 6-23 months of age who had an episode of protocol-defined wheezing (MSW) from administration through 42 days after the last vaccination, the rates of at least one additional episode (32% FluMist vs. 28% TIV) and the rates of at least two additional episodes (4% FluMist vs. 5% TIV) were similar. Thus, there was no evidence in this study that children with protocol-defined wheezing (MSW) post vaccination with FluMist were predisposed to subsequent episodes of protocol-defined wheezing compared to children who wheezed post vaccination with TIV.

Rates of protocol defined wheezing (MSW) were also analyzed for the 6-11 month and 12-23 month subsets of children within 42 days after vaccination (Table 6-12). Wheezing rates for all children 12-23 months of age were statistically significantly increased in FluMist vs. TIV (rate difference = 1.83). Rates for all children 6-11 months of age were also increased in FluMist vs. TIV recipients (rate difference = 2.39) but this did not reach statistical significance.

Table 6-12 MI-CP111: Protocol-Defined Wheezing (MSW) Within 42 Days After Each Study Vaccination in Children 6-23 Months of Age

Age Group and Previous Vaccination Status	Timepoint	FluMist N=4179			TIV N=4173			Rate Difference[a]	95% CI for Rate Difference[a]
		N	# of Cases	Crude Rate cases/N	N	# of Cases	Crude Rate cases/N		
All Children 6-23 Months	**Post Last Dose[b]**	**1992**	**117**	**5.9%**	**1975**	**75**	**3.8%**	**2.03**	**0.72, 3.38**
Previously Vaccinated	Post Dose One	267	7	2.6%	269	3	1.1%	1.34	-1.11, 4.30
Not Previously Vaccinated	**Post Dose One**	**1725**	**55**	**3.2%**	**1706**	**34**	**2.0%**	**1.18**	**0.13, 2.29**
	Post Dose Two[c]	1578	57	3.6%	1595	39	2.4%	1.15	-0.04, 2.38
All Children 6-11 Months	Post Last Dose[b]	684	47	6.9%	683	29	4.2%	2.39	-0.02, 4.94
Previously Vaccinated	Post Dose One	2	0	0.0%	1	0	0.0%	0.00	-85.21, 74.23
Not Previously Vaccinated	Post Dose One	682	26	3.8%	682	14	2.1%	1.61	-0.18, 3.53
	Post Dose Two[c]	625	21	3.4%	642	15	2.3%	0.91	-0.96, 2.94
All Children 12-23 Months	Post Last Dose[b]	**1308**	**70**	**5.4%**	**1292**	**46**	**3.6%**	**1.83**	**0.28, 3.45**
Previously Vaccinated	Post Dose One	265	7	2.6%	268	3	1.1%	1.36	-1.11, 4.34
Not Previously Vaccinated	Post Dose One	1043	29	2.8%	1024	20	2.0%	0.90	-0.42, 2.27
	Post Dose Two[c]	953	36	3.8%	953	24	2.5%	1.31	-0.25, 2.95

Bold type indicate statistically significant difference between FluMist and TIV.

a. Rate difference was adjusted for age, recurrent wheezing history status, and prior vaccination status for "all children;" and for age and recurrent wheezing history status for previously vaccinated and not previously vaccinated children.

b. Includes time immediately after receiving vaccine at Dose One through 42 days after last dose (either Dose One or Dose Two, depending upon prior vaccination status).

c. Includes time immediately after receiving study vaccine at Dose One through 42 days after Dose One, or until immediately prior to receipt of Dose Two (if <42 days between doses).

6.3.3 Any Wheezing Event in Study MI-CP111

In addition to protocol-defined wheezing (MSW) in Study MI-CP111, wheezing captured as a reactogenicity event (RE) or as an adverse event (AE) was analyzed as a secondary endpoint ("RE/AE wheezing"). RE/AE wheezing, unlike protocol-defined wheezing, was not a prespecified case definition and included wheezing reported by the child's caregiver as well as wheezing reported by a health care provider. For purposes of post hoc analysis, RE/AE wheezing events were combined with protocol-defined wheezing (MSW) events in a category described as "any wheeze."

When rates of any wheezing event were analyzed through 42 days following last vaccination in all children 6-59 months of age, the rate was significantly higher for FluMist recipients compared to TIV recipients (7.8% FluMist, 6.6% TIV) (Table 6-13). This rate difference was primarily driven by children 6-23 months of age, where the rate was also significantly higher for FluMist recipients compared to TIV recipients. In children 24-59 months of age, rates were similar between treatment groups (4.9% FluMist, 5.3% TIV).

Table 6-13 MI-CP111: Any Wheezing Event in Children 6-59 Months of Age

Age Group (mos)	Through 42 Days After Last Dose			Through 180 Days After Last Dose		
	FluMist n/N (%)	TIV n/N (%)	Rate Diff	FluMist n/N (%)	TIV n/N (%)	Rate Diff
6-59	**324/4179 (7.8%)**	**275/4173 (6.6%)**	**1.2**	619/4179 (14.8%)	597/4173 (14.3%)	0.5
6-23	**216/1992 (10.8%)**	**158/1975 (8.0%)**	**2.8**	367/1992 (18.4%)	334/1975 (16.9%)	1.5
6-11	80/684 (11.7%)	67/683 (9.8%)	1.9	143/684 (20.9%)	139/683 (20.4%)	0.6
12-23	**136/1308 (10.4%)**	**91/1292 (7.0%)**	**3.4**	224/1308 (17.1%)	195/1292 (15.1%)	2.0
24-59	108/2187 (4.9%)	117/2198 (5.3%)	-0.4	252/2187 (11.5%)	263/2198 (12.0%)	-0.4

Rate difference is FluMist minus TIV. **Bold type** indicates statistically significant difference between treatment groups.

Rates of any wheezing event were also analyzed through 180 days following last vaccination (Table 6-13). In children 24-59 months rates were similar (11.5% FluMist, 12.0% TIV). In the younger children, the rate differences were lower between FluMist and TIV compared to analyses through 42 days.

6.3.4 Wheezing Events in Studies MI-CP123, D153-P501, AV006, and AV018

Post vaccination wheezing AEs (coded as preferred terms of bronchospasm, bronchiolitis, asthma, and wheezing) were collected in the other studies and are summarized as follows.

- In Study MI-CP123 (N=52 children 6-35 months of age), no AEs of wheezing, asthma, bronchospasm, or bronchiolitis were reported.
- In Study D153-P501 (N=3174 children 12-35 months of age), reported synonyms for wheezing illnesses included the WHOART terms of bronchospasm and bronchiolitis. During Days 0-10 after receipt of study vaccine in both years of this study, rates of bronchospasm ranged from 0.1-0.5% for FluMist and from 0.4-0.8% for placebo; rates of bronchiolitis were 0% for FluMist and 0.1-0.2% for placebo.
- In Study AV006 (N=1602 children 15-71 months of age), reported synonyms for wheezing illnesses included the COSTART term of asthma. During Days 0-10 after receipt of study vaccine, rates of asthma ranged from 0.3-0.6% for FluMist and 0.4-0.5% for placebo.
- In Study AV018 (N=1245 children 12-15 months of age), reported synonyms for wheezing illnesses included the modified COSTART terms of bronchiolitis and wheezing. In this study, rates of wheezing from Days 0-41 post receipt of M-M-R®II, VARIVAX®, and either FluMist or placebo mist were lower in the group that received concomitant FluMist (MMR/VAR/FluMist, 1.2%) than in the group that received concomitant placebo mist (MMR/VAR, 2.5%); rates of bronchiolitis were 0% and 1.0%, respectively.

6.4 Deaths and Serious and Significant Adverse Events

6.4.1 Deaths

In the 13 studies for which SAE data were integrated, there were 11 (<0.1%) deaths overall (7/18,315 children [<0.1%] in the FluMist group, 3/6692 children [<0.1%] in the placebo group, and 1/5107 children [<0.1%] in the TIV group) that occurred during the first year of the study. Two deaths (1/2587 children [<0.1%] in the FluMist group and 1/1720 children [0.1%] in the placebo group) occurred during the second year of vaccination. Overall, none of these deaths was judged by the investigator as related to FluMist.

6.4.2 Other Serious Adverse Events in the Integrated Analysis of Safety

All Children 6-59 Months of Age

Serious adverse events with ≥0.2% incidence in any treatment group reported within Days 0-42 post dosing and from Day 0 through 180 post final dose are shown in Table 6-14 and Table 6-15, respectively, for Year 1 and in Table 6-16 and Table 6-17, respectively, for Year 2.

In the first year of vaccination, the proportions of all children 6-59 months of age reporting at least one SAE within Days 0-42 post Dose One and post Dose Two were similar between the FluMist, placebo, and TIV groups (0.8%, 1.0%, and 0.6%, respectively, for post Dose One and 0.8%, 0.8%, and 1.0%, respectively, for post Dose Two). A higher frequency of SAEs was reported during the longer SAE reporting period (i.e., Day 0 through 180 days after the last dose of study vaccine), but the proportions of all children 6-59 months of age reporting at least one SAE were similar between the three treatment groups (3.6%, 4.1%, and 3.4%, respectively). Gastroenteritis and pneumonia were the most commonly reported SAEs across the three treatment groups in the first year of vaccination. The types and relative frequencies of the other SAEs were similar between the three treatment groups, including SAEs associated with reactogenicity events (e.g., pyrexia, vomiting) and any wheezing illness (a combined term of the MedDRA preferred terms asthma, bronchospasm, wheezing, and bronchiolitis). No individual related SAE occurred in > 0.1% of subjects.

In the second year of vaccination, the proportions of children 6-59 months of age reporting at least one SAE within Days 0-42 after dosing were similar between the FluMist and placebo groups (0.5% and 0.7%, respectively). A higher frequency of SAEs was reported during the longer SAE reporting period (i.e., Day 0 through 180 days after the last dose of study vaccine), but the proportions of all children 6-59 months of age reporting at least one SAE were similar between the two treatment groups (2.3% and 1.8%, respectively). Pyrexia and gastroenteritis were the most common SAEs in the placebo-controlled studies during the second year of vaccination. The types and relative frequencies of these and the other SAEs were generally similar between the two treatment groups, including SAEs associated with other reactogenicity events and any wheezing illness.

Table 6-14 Serious Adverse Events Reported Within Days 0-42 After Each Dose in ³ 0.2% of All Children 6-59 Months of Age in Year 1

System Organ Class/ MedDRA 8.0 Preferred Term	Post Dose One			Post Dose Two		
	FluMist/ N=18315	Placebo N=6692	TIV N=5107	FluMist/ N=14080	Placebo N=5650	TIV N=3944
Total Number of Events	217	109	44	153	72	47
Total N of Children Reporting ≥ 1 Event	149 (0.8%)	64 (1.0%)	33 (0.6%)	111 (0.8%)	48 (0.8%)	38 (1.0%)
General Disorders & Administration Site Conditions						
Pyrexia	13 (0.1%)	11 (0.2%)	1 (0.0%)	8 (0.1%)	6 (0.1%)	3 (0.1%)
Infections & Infestations						
Gastroenteritis	26 (0.1%)	14 (0.2%)	6 (0.1%)	18 (0.1%)	8 (0.1%)	6 (0.2%)
Pneumonia	22 (0.1%)	5 (0.1%)	8 (0.2%)	14 (0.1%)	7 (0.1%)	4 (0.1%)
Metabolism & Nutrition Disorders						
Dehydration	10 (0.1%)	11 (0.2%)	0 (0.0%)	7 (0.0%)	3 (0.1%)	0 (0.0%)

Includes children 6-59 months of age at time of initial vaccination in Studies MI-CP111, MI-CP123, D153-P501, AV006, AV018, AV019, D153-P514, D153-P502, D153-P504, D153-P511, D153-P513, D153-P522, and D153-P500.

Table 6-15 Serious Adverse Events Reported from Day 0 through 180 Days Post Last Dose in [3] 0.2% of All Children 6-59 Months of Age in Year 1

System Organ Class/ MedDRA 8.0 Preferred Term	Through 180 Days Post Last Dose		
	FluMist/ (N=14058)	Placebo (N=5244)	TIV (N=5107)
Total Number of Events	788	355	222
Total N of Children Reporting ≥ 1 Event	505 (3.6%)	213 (4.1%)	173 (3.4%)
Gastrointestinal Disorders			
Vomiting	22 (0.2%)	9 (0.2%)	2 (0.0%)
Diarrhoea	18 (0.1%)	20 (0.4%)	0 (0.0%)
General Disorders & Administration Site Conditions			
Pyrexia	46 (0.3%)	29 (0.6%)	7 (0.1%)
Infections & Infestations			
Gastroenteritis	85 (0.6%)	39 (0.7%)	31 (0.6%)
Pneumonia	73 (0.5%)	29 (0.6%)	29 (0.6%)
Bronchopneumonia	32 (0.2%)	7 (0.1%)	4 (0.1%)
Otitis Media	24 (0.2%)	3 (0.1%)	4 (0.1%)
Upper Respiratory Tract Infection	23 (0.2%)	13 (0.2%)	9 (0.2%)
Bronchiolitis	21 (0.1%)	8 (0.2%)	6 (0.1%)
Bronchitis	20 (0.1%)	13 (0.2%)	4 (0.1%)
Gastroenteritis Rotavirus	12 (0.1%)	3 (0.1%)	8 (0.2%)
Metabolism & Nutrition Disorders			
Dehydration	39 (0.3%)	19 (0.4%)	5 (0.1%)
Nervous System Disorders			
Febrile Convulsion	29 (0.2%)	18 (0.3%)	10 (0.2%)
Respiratory, Thoracic & Mediastinal Disorders			
Asthma	18 (0.1%)	9 (0.2%)	3 (0.1%)

Includes children 6-59 months of age at time of initial vaccination in Studies MI-CP111, MI-CP123, D153-P501, AV006, AV018, AV019, D153-P514, D153-P502, D153-P504, D153-P511, D153-P513, D153-P522, and D153-P500.

Table 6-16 Serious Adverse Events Reported Within Days 0-42 After Dosing in ³0.2% of All Children 6-59 Months of Age in Year 2

System Organ Class/ MedDRA 8.0 Preferred Term	Day 0-42 Post Dose	
	FluMist (N=2587)	Placebo (N=1720)
Total Number of Events	20	20
Total Number of Subjects Reporting ≥ 1 Event	13 (0.5%)	12 (0.7%)
General Disorders & Administration Site Conditions		
Pyrexia	3 (0.1%)	3 (0.2%)

Includes children 6-59 months of age at time of initial vaccination in Studies AV006, D153-P501, D153-P502 and D153-P504.

Table 6-17 Serious Adverse Events Reported from Day 0 through 180 Days Post Dose in ³0.2% of All Children 6-59 Months of Age in Year 2

System Organ Class/ MedDRA 8.0 Preferred Term	Through 180 Days Post Dose	
	FluMist (N=1859)	Placebo (N=1356)
Total Number of Events	70	44
Total Number of Subjects Reporting ≥ 1 Event	43 (2.3%)	25 (1.8%)
General Disorders and Administration Site Conditions		
Pyrexia	8 (0.4%)	5 (0.4%)
Infections and Infestations		
Gastroenteritis	6 (0.3%)	3 (0.2%)
Pneumonia	4 (0.2%)	1 (0.1%)
Upper Respiratory Tract Infection	4 (0.2%)	1 (0.1%)
Bronchitis	0 (0.0%)	3 (0.2%)
Injury, Poisoning and Procedural Complications		
Head Injury	3 (0.2%)	1 (0.1%)
Metabolism and Nutrition Disorders		
Dehydration	4 (0.2%)	0 (0.0%)
Nervous System Disorders		
Febrile Convulsion	3 (0.2%)	1 (0.1%)

Includes children 6-59 months of age at time of initial vaccination in Studies AV006, D153-P501, D153-P502 and D153-P504.

By Age Subgroup and Category of Serious Adverse Event, FluMist vs. Placebo

In the first year of vaccination for the nine placebo controlled studies, the proportions of all children 6-59 months of age reporting at least one SAE within Days 0-42 post Dose One and post Dose Two were similar between the FluMist and placebo groups (0.9% and 1.0%, respectively, for post Dose One and 0.7% and 0.8%, respectively, for post Dose Two) as shown in Table 6-18. Higher frequencies of SAEs were reported during the longer SAE reporting period (i.e., Day 0 through 180 days post final dose) (Table 6-19). The proportions of all children 6-59 months of age reporting at least one SAE were lower in the FluMist group than in the placebo group (3.5% and 4.1%, respectively). There was a higher frequency of SAEs in both the FluMist and placebo groups for children 6-23 months of age than for children 24-59 months of age. This difference was most evident for children 6-11 months of age. For children 12-23 months of age, the frequency of SAEs in both treatment groups decreased.

Gastroenteritis was the most common SAE in the placebo-controlled studies during the first year of vaccination (Figure 6-4). For children 6-11 months of age, the frequency of any gastroenteritis SAE was similar between FluMist and placebo recipients but occurred at a higher rate than in the other age categories. The types and relative frequencies of the other SAEs were similar between the two treatment groups, including SAEs associated with any wheezing illness.

Table 6-18 Serious Adverse Events (Overall and Selected) Reported Within Days 0-42 After Each Dose by Age Subgroup

SAE Age Subgroup	Number of Children (%) Reporting [3] 1 SAE, Days 0-42			
	Post Dose One		Post Dose Two	
	FluMist	Placebo	FluMist	Placebo
Any SAE				
All Children, 6-59 mos	102/11783 (0.9%)	64/6692 (1.0%)	63/8842 (0.7%)	48/5650 (0.8%)
6-23 months	83/6320 (1.3%)	51/3664 (1.4%)	46/4351 (1.1%)	36/2966 (1.2%)
24-59 months	19/5463 (0.3%)	13/3028 (0.4%)	17/4491 (0.4%)	12/2684 (0.4%)
6-11 months	18/1003 (1.8%)	12/573 (2.1%)	14/695 (2.0%)	11/516 (2.1%)
12-23 months	65/5317 (1.2%)	39/3091 (1.3%)	32/3656 (0.9%)	25/2450 (1.0%)
Any Gastroenteritis SAE				
All Children, 6-59 mos	24/11783 (0.2%)	32/6692 (0.5%)	21/8842 (0.2%)	17/5650 (0.3%)
6-23 months	21/6320 (0.3%)	23/3664 (0.6%)	15/4351 (0.3%)	15/2966 (0.5%)
24-59 months	3/5463 (0.1%)	9/3028 (0.3%)	6/4491 (0.1%)	2/2684 (0.1%)
6-11 months	6/1003 (0.6%)	9/573 (1.6%)	5/695 (0.7%)	3/516 (0.6%)
12-23 months	15/5317 (0.3%)	14/3091 (0.5%)	10/3656 (0.3%)	12/2450 (0.5%)
Any Pneumonia SAE				
All Children, 6-59 mos	27/11783 (0.2%)	6/6692 (0.1%)	9/8842 (0.1%)	12/5650 (0.2%)
6-23 months	23/6320 (0.4%)	6/3664 (0.2%)	7/4351 (0.2%)	11/2966 (0.4%)
24-59 months	4/5463 (0.1%)	0/3028 (0.0%)	2/4491 (<0.1%)	1/2684 (<0.1%)
6-11 months	6/1003 (0.6%)	0/573 (0.0%)	2/695 (0.3%)	5/516 (1.0%)
12-23 months	17/5317 (0.3%)	6/3091 (0.2%)	5/3656 (0.1%)	6/2450 (0.2%)
Any Wheezing SAE				
All Children, 6-59 mos	14/11783 (0.1%)	5/6692 (0.1%)	5/8842 (0.1%)	5/5650 (0.1%)
6-23 months	8/6320 (0.1%)	4/3664 (0.1%)	4/4351 (0.1%)	3/2966 (0.1%)
24-59 months	6/5463 (0.1%)	1/3028 (<0.1%)	1/4491 (<0.1%)	2/2684 (0.1%)
6-11 months	1/1003 (0.1%)	1/573 (0.2%)	0/695 (0.0%)	0/516 (0.0%)
12-23 months	7/5317 (0.1%)	3/3091 (0.1%)	4/3656 (0.1%)	3/2450 (0.1%)

Includes children in the indicated age subgroups at time of initial vaccination in Studies AV006, AV018, AV019, D153-P501, D153-P502, D153-P504, D153-P511, D153-P513, and D153-P522.

Gastroenteritis includes the MedDRA terms abdominal pain, diarrhea, duodenitis , enteritis, enterocolitis, gastritis, vomiting, diarrhea infectious, dysentery, gastritis viral, gastroenteritis, viral stool test positive.

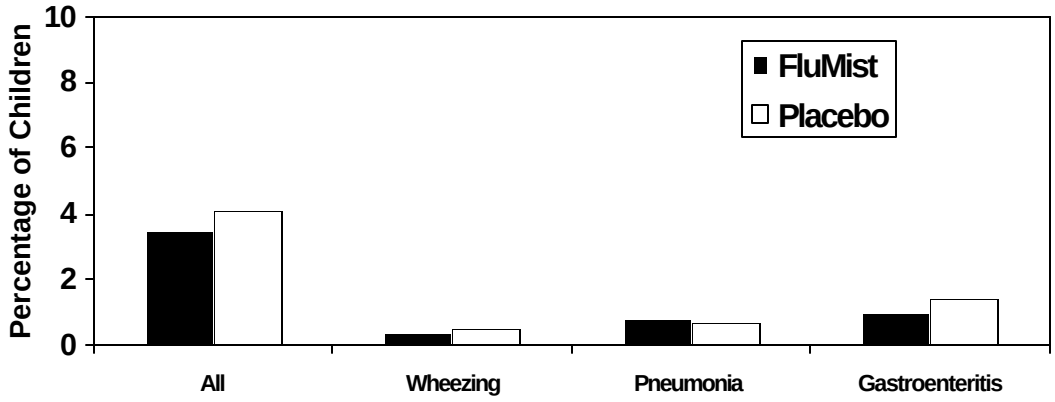
Pneumonia includes the MedDRA terms bronchopneumonia, lobar pneumonia, lower respiratory tract infection, pneumonia, pneumonia adenoviral, pneumonia bacterial, pneumonia mycoplasmal, pneumonia parainfluenza viral, pneumonia respiratory syncytial viral, pneumonia streptococcal, pneumonia viral, and pneumonitis. **Wheezing** includes the MedDRA terms wheeze, asthma, bronchospasm, bronchiolitis.

Table 6-19 Serious Adverse Events (Overall and Selected) Reported from Day 0 through 180 Days After the Last Dose by Age Subgroup

SAE Age Subgroup	Number of Children (%) Reporting [3] 1 Selected SAE, through 180 Days Post Last Dose	
	FluMist	Placebo
Any SAE		
All Children, 6-59 months	311/8911 (3.5%)	213/5244 (4.1%)
6-23 months	234/5768 (4.1%)	165/3357 (4.9%)
24-59 months	77/3143 (2.4%)	48/1887 (2.5%)
6-11 months	64/1003 (6.4%)	49/573 (8.6%)
12-23 months	170/4765 (3.6%)	116/2784 (4.2%)
Any Gastroenteritis SAE		
All Children, 6-59 months	91/8911 (1.0%)	74/5244 (1.4%)
6-23 months	71/5768 (1.2%)	56/3357 (1.7%)
24-59 months	20/3143 (0.6%)	18/1887 (1.0%)
6-11 months	24/1003 (2.4%)	22/573 (3.8%)
12-23 months	47/4765 (1.0%)	34/2784 (1.2%)
Any Pneumonia SAE		
All Children, 6-59 months	75/8911 (0.8%)	39/5244 (0.7%)
6-23 months	56/5768 (1.0%)	32/3357 (1.0%)
24-59 months	19/3143 (0.6%)	7/1887 (0.4%)
6-11 months	17/1003 (1.7%)	9/573 (1.6%)
12-23 months	39/4765 (0.8%)	23/2784 (0.8%)
Any Wheezing SAE		
All Children, 6-59 months	33/8911 (0.4%)	25/5244 (0.5%)
6-23 months	24/5768 (0.4%)	19/3357 (0.6%)
24-59 months	9/3143 (0.3%)	6/1887 (0.3%)
6-11 months	4/1003 (0.4%)	5/573 (0.9%)
12-23 months	20/4765 (0.4%)	14/2784 (0.5%)

Includes children in the indicated age subgroups at time of initial vaccination in Studies AV006, AV018, AV019, D153-P501, D153-P502, D153-P504, D153-P511, D153-P513, and D153-P522.

Gastroenteritis includes the MedDRA terms abdominal pain, diarrhea, duodenitis, enteritis, enterocolitis, gastritis, vomiting, diarrhea infectious, dysentery, gastritis viral, gastroenteritis, viral stool test positive. **Pneumonia** includes the MedDRA terms bronchopneumonia, lobar pneumonia, lower respiratory tract infection, pneumonia, pneumonia adenoviral, pneumonia bacterial, pneumonia mycoplasmal, pneumonia parainfluenza viral, pneumonia respiratory syncytial viral, pneumonia streptococcal, pneumonia viral, and pneumonitis. **Wheezing** includes the MedDRA terms wheeze, asthma, bronchospasm, bronchiolitis.



N=14,155 children 6-59 months of age.

Includes children in the indicated age subgroups at time of initial vaccination in Studies AV006, AV018, AV019, D153-P501, D153-P502, D153-P504, D153-P511, D153-P513, and D153-P522.

Wheezing includes the MedDRA terms wheeze, asthma, bronchospasm, bronchiolitis. **Pneumonia** includes the MedDRA terms bronchopneumonia, lobar pneumonia, lower respiratory tract infection, pneumonia, pneumonia adenoviral, pneumonia bacterial, pneumonia mycoplasmal, pneumonia parainfluenza viral, pneumonia respiratory syncytial viral, pneumonia streptococcal, pneumonia viral, and pneumonitis. **Gastroenteritis** includes the MedDRA terms abdominal pain, diarrhea, duodenitis, enteritis, enterocolitis, gastritis, vomiting, diarrhea infectious, dysentery, gastritis viral, gastroenteritis, viral stool test positive.

Figure 6-4 Serious Adverse Events from Day 0 through 180 Days Post Final Dose in Placebo Controlled Trials for Children 6-59 Months of Age

6.4.3 Other Serious Adverse Events in Study MI-CP111

The majority of SAEs in Study MI-CP111 reported from Days 0-42 post dosing (Table 6-20) and from Day 0 through 180 days post last dose (Table 6-21) were in-patient hospitalizations.

Table 6-20 MI-CP111: All-Cause Hospitalizations from Days 0-42 Post Dose in Children 6-59 Months of Age

Days 0-42	ONE DOSE Group		TWO DOSE Group			
	Post Dose 1		Post Dose 1		Post Dose 2	
	FluMist N=933	TIV N=947	FluMist N=3246	TIV N=3226	FluMist N=3002	TIV N=3034
All SAEs	3 (0.3%)	7 (0.7%)	22 (0.7%)	16 (0.5%)	22 (0.7%)	25 (0.8%)
All-Cause Hospitalizations	3 (0.3%)	7 (0.7%)	22 (0.7%)	16 (0.5%)	20 (0.7%)	24 (0.8%)

Table 6-21 MI-CP111: All-Cause Hospitalizations through 180 Days Post Final Dose in Children 6-59 Months of Age

Day 0 through 180 Days Post Final Dose	ONE DOSE Group		TWO DOSE Group		Total	
	FluMist N=933	TIV N=947	FluMist N=3246	TIV N=3226	FluMist N=4179	TIV N=4173
All SAEs	16 (1.7%)	24 (2.5%)	120 (3.7%)	104 (3.2%)	136 (3.3%)	128 (3.1%)
All-Cause Hospitalizations	14 (1.5%)	23 (2.4%)	116 (3.6%)	96 (3.0%)	130 (3.1%)	119 (2.9%)

Hospitalizations

Additional analyses were performed to specifically evaluate the rates of hospitalization through 180 days post final dose by age subgroup. All-cause hospitalizations were analyzed by age subgroup and time of first occurrence (within 42 days or >42 days after final dose) (Figure 6-5). An increased rate of hospitalization was observed for FluMist recipients 6-11 months of age for both time periods. The majority of excess hospitalizations in this subset of younger children were late events, occurring >42 days after receipt of final study vaccination, were not temporally clustered, and were accounted for by events commonly expected to occur in a young pediatric population, i.e., gastrointestinal and lower respiratory tract infections. A biological rationale for the association between receipt of FluMist and these late occurring hospitalizations cannot readily be explained.

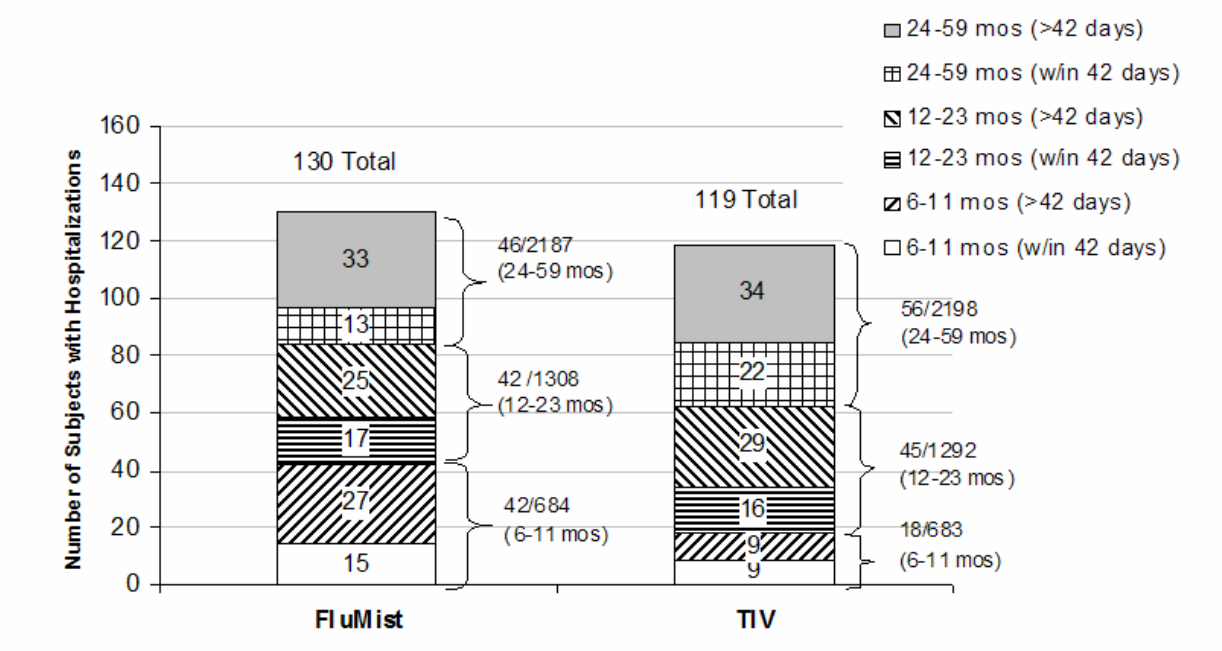


Figure 6-5 **MI-CP111: All-Cause Hospitalizations by Age and Time of First Incidence**

Based on the excess of late hospitalizations in young children, all-cause hospitalizations and respiratory hospitalizations (defined post hoc by manual review at the MedDRA preferred term level) were summarized through 42 days and 180 days post last dose. For analyses through 42 days post last dose, rates were similar (<1 percentage point difference) between treatment groups for all age subgroups (Table 6-22). For analyses through 180 days post last dose, however, statistically significantly higher rates of both all-cause and respiratory hospitalizations were observed for FluMist recipients 6-11 months of age (Table 6-23). In older subgroups of children 12-23 and 24-59 months of age, hospitalization rates were not observed to be increased in FluMist vs. TIV recipients overall.

Table 6-22 MI-CP111: Hospitalizations through 42 Days Post Final Dose

Age (mos)	Type of Hospitalization	FluMist	TIV	Rate Difference
6-59	All-Cause	45/4179 (1.1%)	47/4173 (1.1%)	-0.0
	Respiratory	27/4179 (0.6%)	26/4173 (0.6%)	0.0
6-23	All-Cause	32/1992 (1.6%)	25/1975 (1.3%)	0.3
	Respiratory	21/1992 (1.1%)	15/1975 (0.8%)	0.3
6-11	All-Cause	15/684 (2.2%)	9/683 (1.3%)	0.9
	Respiratory	10.684 (1.5%)	4/683 (0.6%)	0.9
12-23	All-Cause	17/1308 (1.3%)	16/1292 (1.2%)	0.1
	Respiratory	11/1308 (0.8%)	11/1292 (0.9%)	-0.0
24-59	All-Cause	13/2187 (0.6%)	22/2198 (1.0%)	-0.4
	Respiratory	6/2187 (0.3%)	11/2198 (0.5%)	-0.2

Safety Population

Rate difference is FluMist minus TIV. No statistically significant differences between treatment groups were observed.

Respiratory hospitalizations include MedDRA preferred terms of acute sinusitis, acute tonsillitis, bronchiolitis, bronchitis, bronchopneumonia, croup infectious, influenza, laryngitis, mastoiditis, otitis media acute, pharyngitis, pharyngotonsillitis, pneumonia, sinusitis, upper respiratory tract infection, viral infection, asthma, bronchospasm, tonsillar hypertrophy, wheezing, adenoidal disorder, pulmonary congestion, tonsillitis, and viral upper respiratory tract infection.

Table 6-23 MI-CP111: Hospitalizations through 180 Days Post Final Dose

Age (mos)	Type of Hospitalization	FluMist	TIV	Rate Difference
6-59	All-Cause	130/4179 (3.1%)	119/4173 (2.9%)	0.3
	Respiratory	66/4179 (1.6%)	54/4173 (1.3%)	0.3
6-23	All-Cause	84/1992 (4.2%)	63/1975 (3.2%)	1.0
	Respiratory	45/1992 (2.3%)	29/1975 (1.5%)	0.8
6-11	All-Cause	**42/684 (6.1%)**	**18/683 (2.6%)**	**3.5**
	Respiratory	**22/684 (3.2%)**	**8/683 (1.2%)**	**2.0**
12-23	All-Cause	42/1308 (3.2%)	45/1292 (3.5%)	-0.3
	Respiratory	23/1308 (1.8%)	21/1292 (1.6%)	0.1
24-59	All-Cause	46/2187 (2.1%)	56/2198 (2.5%)	-0.4
	Respiratory	21/2187 (1.0%)	25/2198 (1.1%)	-0.2

Safety Population

Rate difference is FluMist minus TIV. **Bold type** indicates statistically significant difference.

Respiratory hospitalizations include MedDRA preferred terms of acute sinusitis, acute tonsillitis, bronchiolitis, bronchitis, bronchopneumonia, croup infectious, influenza, laryngitis, mastoiditis, otitis media acute, pharyngitis, pharyngotonsillitis, pneumonia, sinusitis, upper respiratory tract infection, viral infection, asthma, bronchospasm, tonsillar hypertrophy, wheezing, adenoidal disorder, pulmonary congestion, tonsillitis, and viral upper respiratory tract infection.

Within the respiratory hospitalization subgroup, an additional exploratory analysis was performed to specifically evaluate the rates of lower respiratory hospitalization as a reflection of more serious respiratory disease. This analysis demonstrates that in children 12-23 months and 24-59 months of age the rates are the same, but in the 6-11 month subgroup the rates for FluMist are higher than TIV, as was seen for all cause and respiratory hospitalizations (Table 6-24).

Table 6-24 MI-CP111: Lower Respiratory Hospitalizations through 42 Days and through 180 Days Post Final Dose

Age (mos)	Through 42 Days Post Final Dose			Through 180 days Post Final Dose		
	FluMist	TIV	Rate Diff	FluMist	TIV	Rate Diff
6-11	8/684 (1.2%)	3/683 (0.4%)	0.7	**17/684 (2.5%)**	**6/683 (0.9%)**	**1.6**
12-23	8/1308 (0.6%)	6/1292 (0.5%)	0.1	14/1308 (1.1%)	11/1292 (0.9%)	0.2
24-59	5/2187 (0.2%)	8/2198 (0.4%)	-0.1	17/2187 (0.8%)	17/2198 (0.8%)	0.0

Rate difference is FluMist minus TIV. **Bold type** indicates statistically significant difference between treatment groups.

Lower respiratory hospitalizations include MedDRA preferred terms of pneumonia, pneumonia respiratory syncytial virus, bronchopneumonia, asthma, wheezing, bronchospasm, bronchitis, and bronchiolitis.

Based on the increase in hospitalizations for the 6-11 month age group, MedImmune is not currently seeking an indication in children under 12 months of age.

6.5 Safety Conclusions

Comprehensive safety data from five clinical trials of FluMist in young children were summarized in the sBLA (active-controlled studies MI-CP111 and MI-CP123; and placebo-controlled studies D153-P501, AV006, AV018). These studies evaluated safety in over 14,000 children, more than 8,000 of whom received FluMist. In aggregate, these studies showed that the safety profile in young children was similar to that already established in older children with respect to the occurrence of expected minor adverse events and reactogenicity events, i.e., mostly mild and transient upper respiratory and systemic symptoms. In the pivotal TIV-controlled study of FluMist (Study MI-CP111), higher rates of all cause hospitalizations were seen in FluMist vs. TIV recipients 6-11 months of age and higher rates of wheezing were seen in FluMist vs. TIV recipients 6-23 months of age.

Serious adverse event data in children <5 years of age from 13 clinical studies of FluMist were analyzed through 42 days and through 180 days following vaccination. These studies included a combined total of >18,000 FluMist recipients, >6600 placebo recipients, and >5000 TIV recipients. Integration across the placebo-controlled, TIV-controlled, and uncontrolled trials demonstrated a similar incidence of SAEs for FluMist, TIV, and placebo recipients. Nearly all of the SAEs were hospitalizations, and the most

common were gastrointestinal and lower respiratory disorders. The relative frequencies of these and other SAEs of special interest, i.e., SAEs associated with reactogenicity events or with wheezing, were also similar for FluMist, TIV, and placebo recipients. Thus, on the basis of these integrated SAE analyses there was no evidence of a new safety concern in young children.

Based on clinical studies of FluMist compared to placebo and to TIV:

- Integration of safety data demonstrated a similar incidence of SAEs for FluMist, TIV, and placebo recipients.
- Across the five clinical trials of FluMist in young children summarized in the sBLA, the safety profile was similar to that already established in older children with respect to minor adverse event and reactogenicity events.
- In Study MI-CP111 that compared FluMist to TIV, all-cause hospitalization rates were significantly increased in FluMist recipients compared to TIV recipients 6-11 months of age, and wheezing rates were significantly increased in FluMist recipients compared to TIV recipients 6-23 months of age.

7 Post Hoc Risk-Benefit Analysis

FluMist has been shown to have superior efficacy versus TIV in children 59 months of age and younger. However, among children 6-23 months of age, FluMist was associated with a higher risk of protocol-defined wheeze (MSW) in the 42-day post-vaccination period, and all-cause hospitalizations were increased in children 6-11 months of age. To assess the overall benefits and risks of FluMist relative to TIV in young children, MedImmune undertook post hoc analyses of efficacy and safety data from the MI-CP111 trial. In these analyses, multiple comparisons are made and subset analyses are based on non-randomized groups of children in MI-CP111.

These analyses were based on rate differences and evaluated safety endpoints including wheezing and hospitalization through 42 days and 180 days post final vaccination, and the efficacy endpoint of culture confirmed modified CDC-ILI regardless of antigenic match. These analyses were performed separately for age subgroups and for children with and without a history of wheezing or asthma.

7.1 Wheezing by Age and History

As previously discussed, in addition to the protocol-defined case definition of wheezing in Study MI-CP111, wheezing events were captured during the study by parent reporting

of reactogenicity events (REs) and investigator reporting of adverse events (AEs); these non-MSW wheezing events were combined with MSW events in a category described as "any wheeze."

Stratification by past history of wheeze or asthma demonstrated that rates of any wheezing and protocol-defined wheezing (MSW) through 42 days following last vaccination were higher in children less than 24 months of age *with* a past history of wheeze or asthma compared to children *without* a past history of wheeze or asthma (Table 7-1 and Table 7-2).

Table 7-1 MI-CP111: Protocol-Defined Wheezing (MSW) by Age and Past History of Wheeze or Asthma through 42 Days after Last Vaccination

Age Group (mos)	With a History			Without a History		
	FluMist n/N (%)	TIV n/N (%)	Rate Diff	FluMist n/N (%)	TIV n/N (%)	Rate Diff
6-11	**16/77 (20.8%)**	**5/63 (7.9%)**	**12.8%**	31/607 (5.1%)	24/620 (3.9%)	1.2%
12-23	35/25 (13.7%)	23/232 (9.9%)	3.8%	35/1053 (3.3%)	23/1060 (2.2%)	1.2%
24-35	16/323 (5.0%)	19/337 (5.6%)	-0.7%	18/1049 (1.7%)	13/1042 (1.2%)	0.5%
36-47	6/137 (4.4%)	9/129 (7.0%)	-2.6%	2/296 (0.7%)	6/331 (1.8%)	-1.1%
48-59	2/112 (1.8%)	7/107 (6.5%)	-4.8%	3/270 (1.1%)	2/252 (0.8%)	0.3%

Rate difference is FluMist minus TIV. **Bold type** indicates statistically significant difference between treatment groups.

Table 7-2 MI-CP111: Any Wheezing Events by Age and Past History of Wheeze or Asthma through 42 Days after Last Vaccination

Age Group (mos)	With a History			Without a History		
	FluMist n/N (%)	TIV n/N (%)	Rate Diff	FluMist n/N (%)	TIV n/N (%)	Rate Diff
6-11	**24/77 (31.2%)**	**9/63 (14.3%)**	**16.9%**	56/607 (9.2%)	58/620 (9.4%)	-0.1%
12-23	**67/255 (26.3%)**	**41/232 (17.7%)**	**8.6%**	69/1053 (6.6%)	50/1060 (4.7%)	1.8%
24-35	40/323 (12.4%)	39/337 (11.6%)	0.8%	38/1049 (3.6%)	38/1042 (3.6%)	0.0%
36-47	14/137 (10.2%)	13/129 (10.1%)	0.1%	6/296 (2.0%)	11/331 (3.3%)	-1.3%
48-59	6/112 (5.4%)	12/107 (11.2%)	-5.9%	4/270 (1.5%)	4/252 (1.6%)	-0.1%

Rate difference is FluMist minus TIV. **Bold type** indicates statistically significant difference between treatment groups.

For children less than 24 months of age, rates of wheezing events through 180 days following last vaccination followed a pattern similar to that seen through 42 days (Table 7-3 and Table 7-4).

Table 7-3 MI-CP111: Protocol-Defined Wheezing (MSW) by Age and Past History of Wheeze or Asthma through 180 Days after Last Vaccination

Age Group (mos)	With a History			Without a History		
	FluMist n/N (%)	TIV n/N (%)	Rate Diff	FluMist n/N (%)	TIV n/N (%)	Rate Diff
6-11	22/77 (28.6%)	10/63 (15.9%)	12.7%	71/607 (11.7%)	61/620 (9.8%)	1.9%
12-23	60/255 (23.5%)	48/232 (20.7%)	2.8%	70/1053 (6.6%)	66/1060 (6.2%)	0.4%
24-35	53/323 (16.4%)	46/337 (13.6%)	2.8%	42/1049 (4.0%)	50/1042 (4.8%)	-0.8%
36-47	21/137 (15.3%)	16/129 (12.4%)	2.9%	8/296 (2.7%)	9/331 (2.7%)	0.0%
48-59	13/112 (11.6%)	14/107 (13.1%)	-1.5%	5/270 (1.9%)	6/252 (2.4%)	-0.5%

Rate difference is FluMist minus TIV. None of the differences between treatment groups were statistically significant.

Table 7-4 MI-CP111: Any Wheezing Events by Age and Past History of Wheeze or Asthma through 180 Days after Last Vaccination

Age Group (mos)	With a History			Without a History		
	FluMist n/N (%)	TIV n/N (%)	Rate Diff	FluMist n/N (%)	TIV n/N (%)	Rate Diff
6-11	33/77 (42.9%)	17/63 (27.0%)	15.9%	110/607 (18.1%)	122/620 (19.7%)	-1.6%
12-23	94/255 (36.9%)	72/232 (31.0%)	5.8%	130/1053 (12.3%)	123/1060 (11.6%)	0.7%
24-35	91/323 (28.2%)	92/337 (27.3%)	0.9%	85/1049 (8.1%)	94/1042 (9.0%)	-0.9%
36-47	32/137 (23.4%)	24/129 (18.6%)	4.8%	16/296 (5.4%)	18/331 (5.4%)	0.0%
48-59	20/112 (17.9%)	24/107 (22.4%)	-4.6%	8/270 (3.0%)	11/252 (4.4%)	-1.4%

Rate difference is FluMist minus TIV. None of the rate differences were statistically significant.

7.2 Hospitalization Rates by Age and History

Overall, the rates of inpatient hospitalization were similar for the two treatment groups through 42 days after last vaccination (1.1% FluMist, 1.1% TIV). When analyzed by age and history of wheeze or asthma, rates of hospitalization were statistically significantly higher in FluMist recipients compared to TIV recipients among children 24-35 months of age *with* a history of wheeze or asthma and statistically significantly lower in FluMist recipients compared to TIV recipients among children 36-47 months of age *without* a history of wheeze or asthma (Table 7-5).

Table 7-5 MI-CP111: All-Cause Hospitalization Rates by Age and Past History of Wheeze or Asthma, through 42 Days After Last Vaccination

Age Group (mos)	With a History			Without a History		
	FluMist n/N (%)	TIV n/N (%)	Rate Diff	FluMist n/N (%)	TIV n/N (%)	Rate Diff
6-11	2/77 (2.6%)	1/63 (1.6%)	1.0%	13/607 (2.1%)	8/620 (1.3%)	0.9%
12-23	6/255 (2.4%)	2/232 (0.9%)	1.5%	11/1053 (1.0%)	14/1060 (1.3%)	-0.3%
24-35	**4/323 (1.2%)**	**0/337 (0.0%)**	**1.2%**	8/1049 (0.8%)	13/1042 (1.2%)	-0.5%
36-47	0/137 (0.0%)	1/129 (0.8%)	-0.8%	**0/296 (0.0%)**	**6/331 (1.8%)**	**-1.8%**
48-59	0/112 (0.0%)	2/107 (1.9%)	-1.9%	1/270 (0.4%)	0/252 (0.0%)	0.4%

Rate difference is FluMist minus TIV. **Bold type** indicates statistically significant difference between treatment groups.

When assessed through 180 days after last vaccination, the overall rates of inpatient hospitalization were similar for the two treatment groups (3.1% FluMist, 2.9% TIV).

However, when analyzed by age subgroup, a statistically significant difference in the rate of all-cause hospitalization was observed for children 6-11 months of age through 180 days following last vaccination (6.1% FluMist, 2.6% TIV). The majority of excess hospitalizations in this subset of younger children occurred late (occurred >42 through 180 days after receipt of final study vaccination), were not temporally clustered, and were events commonly expected to occur in a young pediatric population, i.e., gastrointestinal and lower respiratory tract infections. A biological rationale for an association between receipt of FluMist and these late occurring hospitalizations cannot be readily explained.

Based on the observation of increase in hospitalizations for children 6-11 months of age, MedImmune is currently not seeking an indication in this age group. Further study in this age group is needed.

In older subgroups of children 12-23 and 24-59 months of age, hospitalization rates were not increased in FluMist vs. TIV recipients overall. Stratification of these older age subgroups by prior history of any wheeze or asthma showed increased hospitalization rates for FluMist compared to TIV in children 12-47 months of age *with* a prior history and no increase in hospitalization rates in children 12-47 months of age *without* a prior history. Additionally, there was no increase in children 48-59 months of age *with or without* a prior history (Table 7-6). In the study, 77% of children 12-59 months of age did not have a prior history of wheeze or asthma.

Table 7-6 MI-CP111: All-Cause Hospitalization Rates by Age and Past History of Wheeze or Asthma, through 180 Days After Last Vaccination

Age Group (mos)	With a History			Without a History		
	FluMist n/N (%)	TIV n/N (%)	Rate Diff	FluMist n/N (%)	TIV n/N (%)	Rate Diff
6-11	5/77 (6.5%)	1/63 (1.6%)	4.9%	**37/607 (6.1%)**	**17/620 (2.7%)**	**3.4%**
12-23	12/255 (4.7%)	6/232 (2.6%)	2.1%	30/1053 (2.8%)	39/1060 (3.7%)	-0.8%
24-35	10/323 (3.1%)	5/337 (1.5%)	1.6%	24/1049 (2.3%)	30/1042 (2.9%)	-0.6%
36-47	4/137 (2.9%)	2/129 (1.6%)	1.4%	4/296 (1.4%)	10/331 (3.0%)	-1.7%
48-59	**0/112 (0.0%)**	**4/107 (3.7%)**	**-3.7%**	4/270 (1.5%)	5/252 (2.0%)	-0.5%

Rate difference is FluMist minus TIV. **Bold type** indicates statistically significant difference between treatment groups.

7.3 Efficacy by Age and History

Analyses of the efficacy outcome of culture confirmed modified CDC-ILI by age subgroup and wheezing history are presented in (Table 7-7). For children *with* a past history of wheezing or asthma, rates of culture confirmed illness were statistically significantly lower in children 12-23 months and 24-35 months of age who received FluMist vs. TIV. In the other age subsets analyzed, rates of illness were consistently lower in FluMist vs. TIV, but not statistically significantly different. For children *without* a past history of wheezing or asthma, rates of culture confirmed illness were statistically significantly lower in FluMist vs. TIV recipients for each of the five age subsets analyzed.

Table 7-7 MI-CP111: Culture Confirmed Modified CDC-ILI Rates by Age and Past History of Wheeze or Asthma, through 180 Days After Last Vaccination

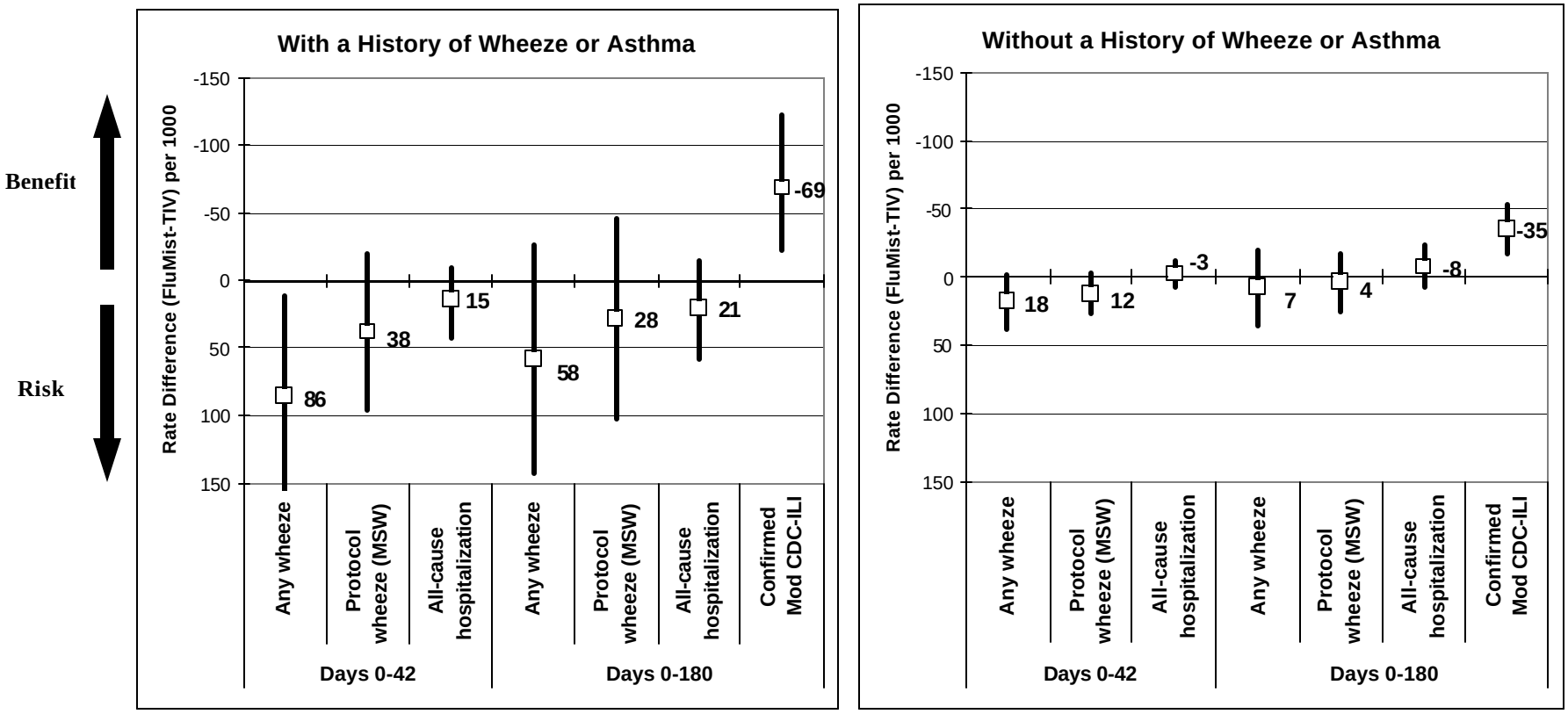
Age Group (mos)	With a History			Without a History		
	FluMist n/N (%)	TIV n/N (%)	Rate Diff	FluMist n/N (%)	TIV n/N (%)	Rate Diff
6-11	4/77 (5.2%)	9/63 (14.3%)	-9.1%	**13/607 (2.1%)**	**31/620 (5.0%)**	**-2.9%**
12-23	**12/255 (4.7%)**	**27/232 (11.6%)**	**-6.9%**	**32/1053 (3.0%)**	**69/1060 (6.5%)**	**-3.5%**
24-35	**18/323 (5.6%)**	**40/337 (11.9%)**	**-6.3%**	**35/1049 (3.3%)**	**77/1042 (7.4%)**	**-4.1%**
36-47	10/137 (7.3%)	15/129 (11.6%)	-4.3%	**10/296 (5.1%)**	**33/331 (3.0%)**	**-4.9%**
48-59	10/112 (8.9%)	17/107 (15.9%)	-7.0%	**12/270 (4.4%)**	**32/252 (12.7%)**	**-8.3%**

Rate difference is FluMist minus TIV. **Bold type** indicates statistically significant difference between treatment groups.

7.4 Summary of Efficacy and Safety by Age and History

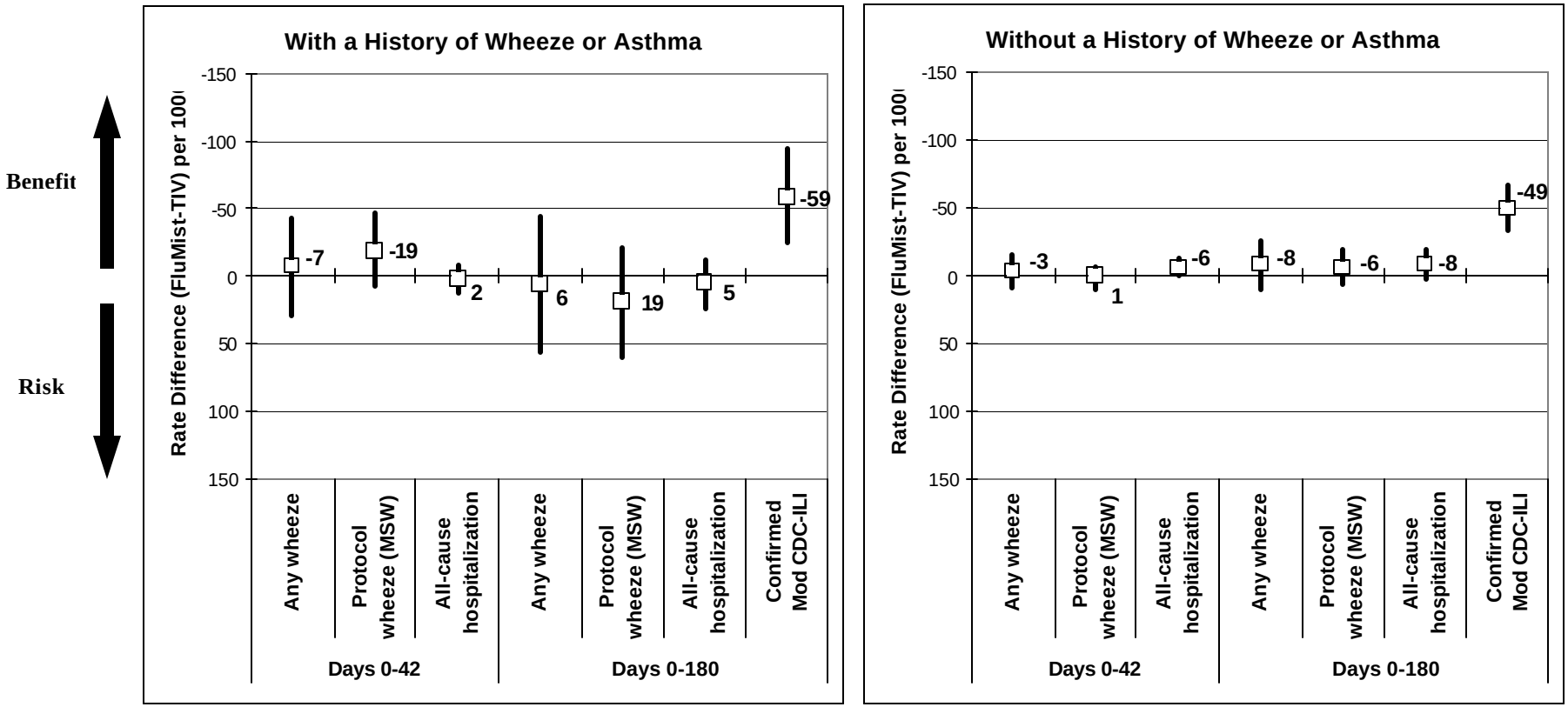
In Study MI-CP111, FluMist demonstrated statistically superior and medically meaningful greater efficacy compared to TIV against matched and mismatched strains. The rate of wheezing within 42 days after dosing was significantly increased in FluMist recipients <24 months of age compared to TIV. All-cause hospitalization was increased through 180 days after last vaccination in children 6-11 months of age and in children 12-47 months of age with a history of wheeze or asthma. The profile for FluMist in MI-CP111 was favorable for children 12-59 months of age without a past history of wheezing or asthma, which is the group for whom MedImmune is currently seeking approval by the U.S. FDA.

A summary of the safety and efficacy of FluMist compared to TIV is shown for children 12-23 and 24-59 months of age is presented in Figure 7-1 and Figure 7-2. Safety endpoints (any wheeze, protocol wheeze, and all-cause hospitalization) are presented through 42 days and 180 days after final vaccination. Efficacy (culture-confirmed modified CDC-ILI) is presented through 180 days after final vaccination. All endpoints are calculated using the study's safety population and presented as rate differences per 1000 children (FluMist minus TIV) with 95% confidence intervals.



Days 0-42 is from Day 0 through 42 days after final vaccination. Days 0-180 is from Day 0 through 180 days after final vaccination.

Figure 7-1 **MI-CP111: Event Rate Differences (FluMist minus TIV) per 1000 Children for Children 12-23 Months of Age, with 95% Confidence Intervals**



Days 0-42 is from Day 0 through 42 days after final vaccination. Days 0-180 is from Day 0 through 180 days after final vaccination.

Figure 7-2 **MI-CP111: Event Rate Differences (FluMist minus TIV) per 1000 Children for Children 24-59 Months of Age, with 95% Confidence Intervals**

Among children 12-59 months of age *with* a history of wheeze or asthma, rates of all-cause hospitalization were increased in FluMist recipients through 180 days after vaccination: children 12-23 months of age with a history of wheeze or asthma had a rate increase of 21 per 1000 (not statistically significant) and children 24-59 months of age had a rate increase 5 per 1000 (not statistically significant). Additionally, among children 12-23 months of age with a history of wheeze or asthma, the rates of protocol-defined wheeze (MSW) and any wheeze were increased by 38 (not statistically significant) and 86 (statistically significant) per 1000, respectively, through 42 days; through 180 days, the rates were increased by 28 per 1000 (not statistically significant) and 58 per 1000 (not statistically significant), respectively. In children 12-23 and 24-59 months of age with a history of wheeze or asthma, there were statistically significant decreases in influenza illness of 69 and 59 per 1000, respectively, through 180 days.

In children 12-23 months *without* a history of wheeze or asthma, the rate of all-cause hospitalization through 180 days was not increased. The rates of protocol-defined wheeze (MSW) and any wheeze through 42 days were increased by 12 and 18 per 1000 respectively in FluMist recipients; through 180 days, the rate was increased by 4 and 7 per 1000 respectively in FluMist recipients. None of the rates differences for wheezing were statistically significant. The rate of influenza illness through 180 days was decreased by 35 per 1000 (statistically significant) in FluMist recipients in this population.

In children 24-59 months of age *without* a history of wheeze or asthma, rates of wheezing and hospitalization were not increased in FluMist recipients; the rate of influenza illness was decreased by 49 per 1000.

Based on all of the findings above, MedImmune is seeking an expanded indication for FluMist in the U.S. for children 12-59 months of age without a history of wheezing or asthma.

7.5 Summary of Data in Children Less than 5 Years of Age

In Study MI-CP111, the benefit-risk profile of FluMist compared to TIV, based on rates of wheezing, hospitalization, and influenza illness, was favorable for the 77% of children in this study who were 12-59 months of age *without* a history of wheeze or asthma.

8 Screening Children 12-59 Months of Age for Receipt of FluMist

For clinical use in children 12-59 months of age without a history of wheeze or asthma, healthcare providers will need simple screening tools that will enable them to identify the appropriate patient population for FluMist. The goal this effort would be to identify the same groups identified in MI-CP111.

In Study MI-CP111, 23% of children 12-59 months of age had a history of wheezing or asthma.[5] In the study, the source of the wheezing history was documented either through parental reporting or chart review. Of the children 12-59 months with a history of wheeze or asthma, 85% had past wheezing reported by parents, while 70% had wheezing detected on chart review. Analysis of the overlap showed that 30% of children had wheezing reported by the parent alone, and 15% of children had wheezing reported by chart alone. The potential hospitalization risk associated with FluMist was similar regardless of the source of the wheezing history (parent versus chart).

Based on these data from MI-CP111, it is anticipated that primary screening efforts should focus on health care provider questioning of parents or guardians. The parent report of wheezing history would be supplemented by the health care provider's standard review or pre-existing knowledge of the patient's medical history. Based on MI-CP111, it would be expected that the answer to the question *"Has a parent or healthcare provider ever noted wheezing or asthma in this child?"* would segregate children in a manner similar to the segregation achieved in the trial. This could also be facilitated by adding appropriate language to the FluMist Vaccine Information Statement (VIS), a form that is already required by The National Childhood Vaccine Injury Act to be given to the parent/guardian prior to each vaccination.

[5] The specific questions asked by site staff were "Does subject have a past medical history of wheeze?" and "Has a diagnosis of asthma ever been made?"

9 Overall Summary and Conclusions

Based on the finding of better overall efficacy compared to TIV that led to the favorable risk-benefit profile of FluMist, MedImmune has proposed an indication for "children 12-59 months of age without a history of wheeze or asthma." For those children 24-59 months of age, significant benefit was observed without wheezing or hospitalization risk. For those children 12-23 months of age, significant benefit was observed with only some residual potential increase in wheezing post vaccination.

FluMist is a highly effective vaccine, with 55% overall better efficacy shown in the pivotal trial compared to TIV. MedImmune believes that the safety and efficacy of FluMist have been established for children 24 months through 59 months of age without a history of wheeze or asthma, and that the risk-benefit profile for children 12-23 months of age without a history of wheeze or asthma warrants use of FluMist in this population as well.

10 Pharmacovigilance Plan

MedImmune's pharmacovigilance plan to support the requested age indication extension is included (Table 10-1) along with a summary of actions (Table 10-2). The Risk Minimization Action Plan has also been included to identify and describe actions, including metrics for measuring the success of these actions, to address and minimize the identified risk issues associated with administration of FluMist in non-indicated populations (Table 10-3).

Table 10-1 Pharmacovigilance Plan for FluMist

Issues	Objectives	Actions	Rationale	Monitoring	Milestones
Identified Risk: Respiratory Disorders					
Increased incidence of medically significant wheezing has been observed in individuals less than 2 yr of age administered FluMist compared to infants receiving TIV. The short and long-term clinical significance of this observation is not yet fully characterized. **MI-CP111**: In the subset of children under 2 yr of age who had not previously been vaccinated against influenza and who received 2 doses, post-dose 1 medically significant wheezing rates were statistically increased in FluMist recipients compared to TIV recipients.	To detect, estimate and characterize cases of asthma, wheezing, bronchiolitis, bronchospasm, and reactive airway disease including exacerbations of pre-existing respiratory conditions.	**Passive Surveillance: Spontaneous Reports**			
		Active query of asthma, wheezing, bronchiolitis, bronchospasm, and reactive airway disease reports with standardized event specific questionnaire.	High quality case reports will enhance case series assessment and ability to efficiently identify signals.	Achievement of complete data set for each case report.	Ongoing
		Passive Surveillance: Accelerated ADR Reporting			
		All postmarketing reports of events involving the respiratory system that are included in the accelerated terms list (see attached), regardless of seriousness and labeledness, will be aggregated and reported to the agency every month as case listings with respective individual case safety reports. This will be continued for the initial 2-year period of postmarketing experience.	Accelerated reporting will enable the agency to closely monitor all reported respiratory disorders of interest on an ongoing basis.	Occurrences of suspected life threatening asthma attacks or asthma deaths.	Completion at 2 years postmarketing

Table 10-1 Pharmacovigilance Plan for FluMist (continued)

Issues	Objectives	Actions	Rationale	Monitoring	Milestones
Identified Risk: Respiratory Disorders (continued)					
		Passive Surveillance: Periodic ADR Reporting			
		A comprehensive evaluation of asthma, wheezing, SOB and RAD will be presented in the PSUR during the initial 2 years of postmarketing experience.	The PSUR provides a comprehensive safety evaluation including information on patient exposure and planned or ongoing clinical trials.	Reporting rates, severity and outcomes between different time intervals.	Annually
		Observational Study: Cohort Study			
		Post Marketing Safety Study in Children less than 5 Years of Age	A population-based study enhances detection of AEs (numerator) and provides patient exposure (denominator) for estimation of incidence.	Incidence rates compared to controls and background rates.	Anticipated start date: Fall 2007 or during the first influenza season following approval of the product. Final report date will be written when approximately 20,000 FluMist recipients are cumulatively vaccinated in each age cohort, and follow-up has been completed after the last dose in the age cohort.

Table 10-1 Pharmacovigilance Plan for FluMist (continued)

Issues	Objectives	Actions	Rationale	Monitoring	Milestones
Identified Risk: Increased hospitalization rates in children 6-59 months of age					
Increased hospitalization rates were observed in FluMist recipients of certain pediatric subgroups An increased hospitalization rate was observed in FluMist recipients <12 months of age regardless of medical history. These hospitalizations were accounted for mainly by gastroenteritis and pneumonia. In the subgroup of children 12-59 months of age, FluMist recipients with prior history of wheezing/asthma showed higher hospitalization rates compared to TIV subjects.	To detect, estimate and characterize hospitalization rates, with particular emphasis on hospitalizations due to gastrointestinal or respiratory disorders.	**Passive Surveillance: Periodic ADR Reporting**			
		A comprehensive evaluation of hospitalizations, especially those due to gastrointestinal and respiratory disorders (particularly gastroenteritis and pneumonia), will be presented in the PSUR during the initial 2 years of postmarketing experience.	The PSUR provides a comprehensive safety evaluation including information on patient exposure, and planned or ongoing clinical trials.	Reporting rates, severity and outcomes between different time intervals.	Annually
		Observational Study: Cohort Study			
		Post Marketing Safety Study in Children less than 5 Years of Age	A population-based study enhances detection of AEs (numerator) and provides patient exposure (denominator) for estimation of incidence.	Incidence rates compared to controls and background rates.	Anticipated start date: Fall 2007 or during the first influenza season following approval of the product. Final report date will be written when approximately 20,000 FluMist recipients are cumulatively vaccinated in each age cohort, and follow-up has been completed after the last dose in the age cohort.

Table 10-1 Pharmacovigilance Plan for FluMist (continued)

Issues	Objectives	Actions	Rationale	Monitoring	Milestones
Identified Risk: Increased hospitalization rates in children 6-59 months of age (continued)					
		Observational Study: Cohort Study (continued)			
		FM025: Post-Marketing Evaluation of the Safety of Influenza Virus Vaccine Live, Intranasal (FluMist™) in Healthy Children and Healthy Adults 5 through 49 Years of Age	A population-based study enhances detection of AEs (numerator) and provides patient exposure (denominator) for estimation of incidence.	Incidence rates compared to controls and background rates.	Start date: Oct.-2003 Interim analyses: annually for cumulative data Final report: Dec.-2011
Potential Risk: Immune System Disorders					
Acute severe hypersensitivity disorders may be observed after administration of vaccines. Reactions may be associated with allergy to egg or other excipients of vaccines. These reactions include anaphylaxis, urticaria, angioedema and skin rashes. Delayed hypersensitivity reactions may also occur and include erythema multiforme, serum sickness and arthralgias.	To detect, estimate and characterize hypersensitivity disorders.	**Passive Surveillance: Spontaneous Reports**			
		Active query of all reports with standardized event specific questionnaires.	High quality case reports will enhance case series assessment and ability to efficiently identify signals.	Achievement of complete data set for each case report.	Ongoing
		Passive Surveillance: Accelerated ADR Reporting			
		All postmarketing reports of events suggesting a hypersensitivity reaction, which are included in the accelerated terms list (see attached), regardless of seriousness and labeledness, will be aggregated and reported to the agency every month as case listings with respective individual case safety reports. This will be continued for the initial 2-year period of postmarketing experience.	Accelerated reporting of acute hypersensitivity events will enable the FDA to have timely awareness of all such events reported to the company on an ongoing basis.	Occurrences of life threatening reactions or deaths.	Completion at 2 years postmarketing

Table 10-1 Pharmacovigilance Plan for FluMist (continued)

Issues	Objectives	Actions	Rationale	Monitoring	Milestones
Potential Risk: Immune System Disorders (continued)					
		Observational Study: Cohort Study			
		FM025: Post-Marketing Evaluation of the Safety of Influenza Virus Vaccine Live, Intranasal (FluMist™) in Healthy Children and Healthy Adults 5 through 49 Years of Age	A population-based study enhances detection of AEs (numerator) and provides patient exposure (denominator) for estimation of incidence.	Incidence rates compared to controls and background rates.	Start date: Oct.-2003 Interim analyses: annually for cumulative data Final report: Dec.-2011
		Post Marketing Safety Study in Children less than 5 Years of Age	A population-based study enhances detection of AEs (numerator) and provides patient exposure (denominator) for estimation of incidence.	Incidence rates compared to controls and background rates.	Anticipated start date: Fall 2007 or during the first influenza season following approval of the product. Final report date will be written when approximately 20,000 FluMist recipients are cumulatively vaccinated in each age cohort, and follow-up has been completed after the last dose in the age cohort.

Table 10-1 Pharmacovigilance Plan for FluMist (continued)

Issues	Objectives	Actions	Rationale	Monitoring	Milestones
Potential Risk: Nervous System Disorders					
Bell's palsy, GBS, encephalitis, and convulsions are nervous system adverse events that have been reported in persons after vaccination. Evidence for a definite causal association is lacking in majority of cases. Bell's palsy was linked to vaccination with NasalFlu, and was thought to be due to absorption of enterotoxin used as adjuvant in the vaccine. FluMist is live attenuated vaccine, and does not include enterotoxin or other adjuvants in its formulation.	To detect, estimate and characterize nervous system disorders.	**Passive Surveillance: Spontaneous Reports**			
		Active query of all reports of Bell's palsy, GBS, convulsions and encephalitis with standardized event specific questionnaires	High quality case reports will enhance case series assessment and ability to efficiently identify signals.	Achievement of complete data set for each case report.	Ongoing
		Passive Surveillance: Accelerated ADR Reporting			
		All postmarketing reports of events involving the nervous system that are included in the accelerated terms list (see attached), regardless of seriousness and labeledness, will be aggregated and reported to the agency every month as case listings with respective individual case safety reports. This will be continued for the initial 2-year period of postmarketing experience.	Accelerated reporting of events involving the nervous system that are included in the accelerated terms list will enable the FDA timely awareness basis of all such events reported to the company on an on-going basis	Occurrences of life threatening reactions or deaths.	Completion at 2 years postmarketing
		Passive Surveillance: Periodic ADR Reporting			
		A comprehensive evaluation of nervous system disorders will be presented in the PSUR during the initial 2 years of postmarketing experience.	The PSUR provides a comprehensive safety evaluation including information on patient exposure and planned or ongoing clinical trials.	Reporting rates, severity and outcomes between different time intervals.	Annually

Table 10-1 Pharmacovigilance Plan for FluMist (continued)

Issues	Objectives	Actions	Rationale	Monitoring	Milestones
Potential Risk: Nervous System Disorders (continued)					
		Observational Study: Cohort Study			
		FM025: Post-Marketing Evaluation of the Safety of Influenza Virus Vaccine Live, Intranasal (FluMist™) in Healthy Children and Healthy Adults 5 through 49 Years of Age	A population-based study enhances detection of AEs (numerator) and provides patient exposure (denominator) for estimation of incidence.	Incidence rates compared to controls and background rates. Threshold for Bell's Palsy, Encephalitis, GBS, MS: 1 case. Threshold for Autism: 1 per 2,000 (lower bound of rate estimate) during course of proposed study.	Start date: Oct.-2003 Interim analyses: annually for cumulative data Final report: Dec.-2011
		Post Marketing Safety Study in Children less than 5 Years of Age	A population-based study enhances detection of AEs (numerator) and provides patient exposure (denominator) for estimation of incidence.	Incidence rates compared to controls and background rates.	Anticipated start date: Fall 2007 or during the first influenza season following approval of the product. Final report date will be written when approximately 20,000 FluMist recipients are cumulatively vaccinated in each age cohort, and follow-up has been completed after the last dose in the age cohort.

Table 10-1 Pharmacovigilance Plan for FluMist (continued)

Issues	Objectives	Actions	Rationale	Monitoring	Milestones
Potential Risk: Infections (secondary transmission)					
Shedding of FluMist virus leading to secondary transmission is possible with potential safety risks for immunocompromised patients, including bone marrow transplant recipients, and patients with cancer, HIV/AIDS, or receiving immunosuppressive drug therapy. A randomized, double-blind, placebo-controlled study was conducted in a daycare setting in children less than 3 years of age to assess the probability that vaccine viruses will be transmitted from a vaccinated individual to a non-vaccinated individual (study D145-P500, Vesikari 2006). With documented transmission of one Type B in 1 placebo subject who had no clinical symptoms, and possible transmission of Type A viruses in 4 placebo subjects, the probability of acquiring a transmitted vaccine virus was estimated to be 2.4%.	To detect and estimate FluMist secondary transmission, and characterize the adverse events that may result from this risk.	**Clinical Trials**			
		MI-CP114: A phase I randomized, double-blind trial of the safety and immunogenicity of FLUMIST® vs. placebo in immunocompromised children ages 5 through 17 years of age	This trial aims to describe the safety of FluMist compared with placebo in mild to moderately immunocompromised children with cancer	Incidence of reactogenicity events and serious adverse events during the study	Start date: 08-Aug-2005 Final report: 01-Aug-2007
		Passive Surveillance: Periodic ADR Reporting			
		A comprehensive evaluation of events suggestive of infections and infestations will be presented in the PSUR during the initial 2 years of postmarketing experience.	The PSUR provides a comprehensive safety evaluation including information on patient exposure and planned or ongoing clinical trials.	Reporting rates, severity and outcomes between different time intervals.	Annually

Table 10-1 Pharmacovigilance Plan for FluMist (continued)

Issues	Objectives	Actions	Rationale	Monitoring	Milestones
Potential Risk: Infections due to Medication Error					
There is the potential for safety risks following vaccination of immunocompromised persons, including bone marrow transplant recipients, and patients with cancer, HIV/AIDS, or receiving immunosuppressive drug therapy. **PACTG-P1057**: There were no unexpected toxicities associated with administration of FluMist in HIV+ children in this study. Administration of FluMist and TIV is safe in HIV infected children ages 5-<18 years, receiving anti-retroviral therapy, and with CD4 >15%	To characterize the adverse events that may result from vaccinating immuno-compromised persons.	**Clinical Trials**			
		MI-CP114: A phase I randomized, double-blind trial of the safety and immunogenicity of FLUMIST® vs. placebo in immunocompromised children ages 5 through 17 years of age	This trial aims to describe the safety of FluMist compared with placebo in mild to moderately immunocompromised children with cancer	Incidence of reactogenicity events and serious adverse events during the study	Start date: 08-Aug-2005 Final report: 01-Aug-2007
		Passive Surveillance: Periodic ADR Reporting			
		A comprehensive evaluation of events suggestive of infections and infestations will be presented in the PSUR during the initial 2 years of postmarketing experience.	The PSUR provides a comprehensive safety evaluation including information on patient exposure and planned or ongoing clinical trials.	Reporting rates, severity and outcomes between different time intervals.	Annually
		Observational Study: Cohort Study			
		FM025: Post-Marketing Evaluation of the Safety of Influenza Virus Vaccine Live, Intranasal (FluMist™) in Healthy Children and Healthy Adults 5 through 49 Years of Age	A population-based study enhances detection of AEs (numerator) and provides patient exposure (denominator) for estimation of incidence.	Incidence rates compared to controls and background rates.	Start date: Oct.-2003 Interim analyses: annually for cumulative data Final report: Dec.-2011

Table 10-1 Pharmacovigilance Plan for FluMist (continued)

Issues	Objectives	Actions	Rationale	Monitoring	Milestones
Potential Risk: Infections					
Pregnancy exposure via accidental administration or secondary transmission to vaccine virus strain involves potential risks for fetus from exposure to a live attenuated virus.	To detect, estimate and characterize pregnancy exposures to FluMist.	**Passive Surveillance: Spontaneous Reports**			
		Active query and follow-up of all cases with a pregnancy exposure questionnaire.	High quality case reports and systematic monitoring of pregnancy exposures will help determine risks of FluMist during pregnancy.	Achievement of complete data set for each case report.	Ongoing
		Passive Surveillance: Periodic ADR Reporting			
		A comprehensive evaluation of pregnancy exposures and outcomes will be presented in the PSUR during the initial 2 years of postmarketing experience.	The PSUR provides a comprehensive safety evaluation including information on patient exposure and planned or ongoing clinical trials.	Reporting rates, severity and outcomes between different time intervals.	Annually
		Observational Study: Cohort Study			
		FM025: Post-Marketing Evaluation of the Safety of Influenza Virus Vaccine Live, Intranasal (FluMist™) in Healthy Children and Healthy Adults 5 through 49 Years of Age	A population-based study enhances detection of AEs (numerator) and provides patient exposure (denominator) for estimation of incidence.	Incidence rates compared to controls and background rates.	Start date: Oct.-2003 Interim analyses: annually for cumulative data Final report: Dec.-2011

Table 10-2 Summary of Pharmacovigilance Actions for FluMist

Actions	Objectives	Milestones
Clinical Trials		
MI-CP114 A phase I randomized, double-blind trial of the safety and immunogenicity of FLUMIST vs. placebo in immunocompromised children ages 5 through 17 years of age	This trial aims to describe the safety of FluMist compared with placebo in mild to moderately immunocompromised children with cancer • Viral shedding and secondary transmission in immunocompromised patients, including bone marrow transplant recipients, and patients with cancer, HIV/AIDS, or receiving immunosuppressive drug therapy. • Medication errors in immunocompromised patients, including bone marrow transplant recipients, and patients with cancer, HIV/AIDS, or receiving immunosuppressive drug therapy.	Start date: 08-Aug-2005 Final report: 01-Aug-2007
Passive Surveillance		
Spontaneous Reports Active query with standardized event specific questionnaires.	High quality case reports will enhance case series assessment and ability to efficiently identify signals. • Asthma, wheezing, bronchiolitis, bronchospasm, and reactive airway disease • Acute severe hypersensitivity disorders • Nervous system disorders (Bell's palsy, GBS, encephalitis, and convulsions) • Pregnancy exposures	Ongoing
Accelerated ADR Reporting All postmarketing reports of events that are included in the accelerated terms list (see attached), regardless of seriousness and labeledness, will be aggregated and reported to the agency every month as case listings with respective individual case safety reports. This will be continued for the initial 2-year period of postmarketing experience.	Accelerated reporting will enable the agency to closely monitor all reported respiratory disorders of interest on an ongoing basis. • Asthma, wheezing, SOB and RAD • Acute severe hypersensitivity disorders • Bell's palsy, GBS, seizures, encephalitis	Completion at 2 years postmarketing

Table 10-2 Summary of Pharmacovigilance Actions for FluMist (continued)

Actions	Objectives	Milestones
Passive Surveillance (continued)		
Periodic ADR Reporting A comprehensive evaluation of events associated with the identified and potential risks will be presented in the PSUR during the initial 2 years of postmarketing experience.	The PSUR provides a comprehensive safety evaluation including information on patient exposure and planned or ongoing clinical trials. • Asthma, wheezing, bronchiolitis, bronchospasm, and reactive airway disease • Increased rate of hospitalization in FluMist recipients of certain pediatric subgroups • Acute severe hypersensitivity disorders • Nervous system disorders (Bell's palsy, GBS, encephalitis, and convulsions) • Viral shedding and secondary transmission in immunocompromised patients, including bone marrow transplant recipients, and patients with cancer, HIV/AIDS, or receiving immunosuppressive drug therapy. • Medication errors in immunocompromised patients, including bone marrow transplant recipients, and patients with cancer, HIV/AIDS, or receiving immunosuppressive drug therapy. • Pregnancy exposures	Annually

Table 10-2 Summary of Pharmacovigilance Actions for FluMist (continued)

Actions	Objectives	Milestones
Observational Studies		
Cohort Study Population based study utilizing healthcare database system. **FM025**: Post-Marketing Evaluation of the Safety of Influenza Virus Vaccine Live, Intranasal (FluMist™) in Healthy Children and Healthy Adults 5 through 49 Years of Age	A population-based study enhances detection of AEs (numerator) and provides patient exposure (denominator) for estimation of incidence. • Acute severe hypersensitivity disorders • Increased rate of hospitalization in FluMist recipients in certain pediatric subgroups • Nervous system disorders (Bell's palsy, GBS, encephalitis, and convulsions) • Medication errors in immunocompromised patients, including bone marrow transplant recipients, and patients with cancer, HIV/AIDS, or receiving immunosuppressive drug therapy. • Pregnancy exposures	Start date: Oct.-2003 Interim analyses: annually for cumulative data Final report: Dec.-2011
Post Marketing Safety Study in Children less than 5 Years of Age	A population-based study enhances detection of AEs (numerator) and provides patient exposure (denominator) for estimation of incidence. • Asthma, wheezing, bronchiolitis, bronchospasm, and reactive airway disease including exacerbations of pre-existing respiratory conditions • Increased rate of hospitalization in FluMist recipients in certain pediatric subgroups • Acute severe hypersensitivity disorders • Nervous system disorders (Bell's palsy, GBS, encephalitis, and convulsions)	Anticipated start date: Fall 2007 or during the first influenza season following approval of the product. Final report date will be written when approximately 20,000 FluMist recipients are cumulatively vaccinated in each age cohort, and follow-up has been completed after the last dose in the age cohort.

Table 10-3 Risk Minimization Management Plan for FluMist

<table>
<tr><th>Risk</th><th>Population at Risk</th><th>Magnitude and Severity of Risk*</th><th>Risk Characteristics</th></tr>
<tr><td>Vaccination errors</td><td>• Infants <12 months age group
• Increased hospitalization among children 12-59 months with a history of wheezing/asthma</td><td>• Medically significant wheezing and increased hospitalization:
  • 6-11 mo: 13.6% FluMist vs. 10.4% TIV
• Increased rate of hospitalization
  • 12-23 months with history of wheezing/asthma: 4.7% FluMist vs. 2.6% TIV
  • 24-59 months with history of wheezing/asthma: 2.4% FluMist vs. 1.9% TIV</td><td>In children 12-23 and 24-59 months of age, hospitalization rates were not observed to be increased in FluMist recipients overall. Stratification of these older age subgroups by prior history of wheezing/asthma showed higher hospitalization rates for FluMist in subjects with a prior history, and lower hospitalization rates for FluMist subjects without a prior history.</td></tr>
<tr><td colspan="4">Risk: Vaccination errors</td></tr>
<tr><td colspan="2">Routine risk minimization activities
• US Package Insert – Include this risk under the warnings and precautions section of the proposed package insert.</td><td colspan="2">Warnings/precautions
• Enhance information regarding medically significant wheezing in children < 24 months, and increased hospitalization in children 12-59 months with a history of wheezing/asthma</td></tr>
<tr><td colspan="2" rowspan="3">Additional Risk Minimization Tool 1
• Targeted Education & Outreach to Healthcare Practitioners</td><td colspan="2">Goal
• No reports of administration of FluMist among infants less than 12 months of age and among children aged 12-59 months with a history of wheezing/asthma (vaccination errors).</td></tr>
<tr><td colspan="2">Objective
• To make HCPs aware of target population and risks associated with FluMist in certain subgroups (i.e., infants less than 12 months of age and among children aged 12-59 months with a history of wheezing/asthma)</td></tr>
<tr><td colspan="2">Proposed Actions
• Provide safety information via continuing medical education (CME) programs
  • Create an educational slide deck for HCPs
• Create a detail aid for use by sales specialists
• Revise current FluMist website with updated safety information</td></tr>
</table>

Table 10-3 Risk Minimization Management Plan for FluMist (continued)

Risk	Population at Risk	Magnitude and Severity of Risk*	Risk Characteristics
Risk: Vaccination errors (continued)			

Additional Risk Minimization Tool 1 (continued)		***Evaluation Plan for Measurement of Goal***
		• Passive surveillance of spontaneous adverse event reports for assessing vaccination errors among non-indicated pediatric populations following FluMist exposure
		• Large, post-marketing cohort study to estimate the rate of vaccination errors among pediatric patients associated with FluMist
		• Time interval for review of plan:
		  • Quarterly review at the Signaling Committee and summarized at least annually at meeting of Product Safety Review Board
		  • Ad hoc meetings, whenever goal is not met	

Additional risk minimization activity 2 • Targeted Education & Outreach to Parents or Guardians of Children Vaccinated with FluMist		***Goal*** • No reports of administration of FluMist among infants less than 12 months of age and among children aged 12-59 months with a history of wheezing/asthma (vaccination errors)	
		Objective • To make parents or guardians of children vaccinated with FluMist aware of target population and risks associated with FluMist in certain subgroups (i.e., infants less than 12 months of age and among children aged 12-59 months with a history of wheezing/asthma)	
		Proposed Actions • Provide safety information via educational pamphlets for parents or guardians of children vaccinated with FluMist • Screening questions will be included in the educational pamphlets • Revise current FluMist website with updated safety information written in lay term for consumers	

		Evaluation Plan for Measurement of Goal
		• Passive surveillance of spontaneous adverse event reports for assessing vaccination errors among non-indicated pediatric populations following FluMist exposure
		• Large, post-marketing cohort study to estimate the rate of vaccination errors among pediatric patients associated with FluMist
		• Time interval for review of plan:
		  • Quarterly review at the Signaling Committee and summarized at least annually at meeting of Product Safety Review Board
		  • Ad hoc meetings, whenever goal is not met	

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12 Appendices

Appendix A SAEs of Hospitalization Associated with Medically Significant Wheezing – Subjects 6-23 Months of Age

Appendix B SAEs of Hospitalization Associated with Medically Significant Wheezing – Subjects 24-59 Months of Age

Appendix C Selected References

Appendix A SAEs of Hospitalization Associated with Medically Significant Wheezing - Subjects 6-23 Months of Age

PID# Country	Age (mos) Gender	Past Medical History	MSW Preferred Term	# Days from Previous Dose to AE Onset	# Days from Previous Dose to Hosp Onset	Duration (dy) of Hosp	Duration (dy) of AE	Chest X-ray Findings	Lab Results	Treatment Received	AE Severity/ Outcome	Relation of AE to Study Product[a]
FluMist TWO DOSE GROUP												
43830056 Israel	9 M	None	Wheezing	13 PD1	14 PD1	3	21	Bilateral infiltrates, hyperinflation		Inhaled bronchodilators, inhaled/systemic steroids	Severe Recovered	Probably
			Wheezing Pneumonia	37 PD1	41 PD1	5	13	Bilateral infiltrates		Inhaled bronchodilators, inhaled steroids	Severe Recovered Moderate Recovered	Probably not
45280054 Hong Kong	20 M	Wheeze history noted by parent/ guardian	Broncho-spasm	36 PD1	37 PD1	6	7	No consolidation	NPA negative for influenza and RSV	Inhaled bronchodilators, oral steroids, antihistamines, O_2	Severe Resolved w/resid	Possibly
42590093 US	21 F	None	Wheezing	32 PD1	32 PD1	4	20	Hyperinflation	RSV negative	Inhaled bronchodilators, parenteral steroids, IV fluids	Moderate Recovered	Probably not
40760014 Germany	23 F	Pre-term; ≥3 wheezing illnesses	Pneumonia	12 PD1	14 PD1	7	9	Atypical obstructive pneumonia	NP swab positive for rhinovirus	Inhaled bronchodilators, inhaled steroids, antibiotics	Moderate Recovered	Probably not
42590045 US	6 M	Down Syndrome	Pneumonia	37 PD2	41 PD2	21	25	Right sided pneumonia	Respiratory panel negative	Inhaled bronchodilators, antibiotics, O_2	Severe Resolved w/resid	Probably not (IN) Definitely not (IM)
43550076 Finland	8 F	Nocturnal cough	Pneumonia	38 PD2	39 PD2	2	9	Bilateral alveolar infiltrates		Inhaled bronchodilators, steroids, antibiotics	Severe Recovered	Definitely not

Appendix A SAEs of Hospitalization Associated with Medically Significant Wheezing - Subjects 6-23 Months of Age (cont)

PID# Country	Age (mos) Gender	Past Medical History	MSW Preferred Term	# Days from Previous Dose to AE Onset	# Days from Previous Dose to Hosp Onset	Duration (dy) of Hosp	Duration (dy) of AE	Chest X-ray Findings	Lab Results	Treatment Received	AE Severity/ Outcome	Relation of AE to Study Product[a]
FluMist TWO DOSE GROUP (continued)												
43480013 Belgium	11 F	GE reflux; Wheeze in past 12 mos	Bronchitis	35 PD2	36 PD2	13	14	No infiltrates	NPA negative for influenza, parainfluenza, RSV, rhinovirus, adenovirus, metapneumo-virus, coronavirus	Inhaled bronchodilators, inhaled steroids, decongestants	Mild Recovered	Definitely not
43480006 Belgium	21 M	RSV; ≥3 wheezing illnesses	Pneumonia	1 PD2	3 PD2	4	6	Broncho-pneumonia	NPA positive for RSV	IV fluids, antipyretics, O_2	Severe Recovered	Probably not
43400007 US	22 F	None	Bronchiolitis	24 PD2	24 PD2	2	5	Atelectasis, peribronchial thickening	RSV positive	Inhaled bronchodilators	Moderate Recovered	Probably not
TIV TWO DOSE GROUP												
80100037 Belgium	8 F	RSV bronchiolitis	Bronchiolitis	8 PD2	12 PD2	5	13	No infiltrates; bronchial and peribronchial blurring	NPA positive for RSV	Inhaled bronchodilators, inhaled steroids, O_2	Severe Recovered	Probably not
43790012 Israel	9 M	Wheeze in past 12 mos	Pneumonia	25 PD2	30 PD2	3	8	Bilateral infiltrates, hyperinflation	Mycoplasma pneumoniae titer 1:160	Oral steroids, antibiotics	Moderate Recovered	Probably not
45300006 Hong Kong	13 F	None	Bronchiolitis	0 PD2	3 PD2	4	11	Normal	NPA positive for RSV	Inhaled bronchodilators, antihistamines, antipyretics	Resolved w/resid	Definitely not

AE = adverse event; Hosp = hospitalization; IM = intramuscular; IN = intranasal; IV = intravenous; MSW = medically significant wheezing; NP = nasopharyngeal; NPA = nasopharyngeal aspirate; PD1 = post Dose One; PD2 = post Dose Two; Resolved w/resid = resolved with residual effects; RSV = respiratory syncytial virus.
The information in this table is derived from the SAE narratives produced by MedImmune Product Safety and may or may not be contained in the data listings.

a. Relationship applies to both IN and IM products unless otherwise indicated.

Appendix B SAEs of Hospitalization Associated with Medically Significant Wheezing - Subjects 24-59 Months of Age

PID# Country	Age (mos) Gender	Past Medical History	MSW Preferred Term	# Days from Previous Dose to AE Onset	# Days from Previous Dose to Hosp Onset	Duration (dy) of Hosp	Duration (dy) of AE	Chest X-ray Findings	Lab Results	Treatment Received	AE Severity/ Outcome	Relation of AE to Study Product[a]
FluMist TWO DOSE GROUP												
45350018 Korea	31 M	None	Pneumonia	11 PD1	14 PD1	6	13	Unremarkable	NPA positive for RSV, negative for influenza, parainfluenza, & adenovirus	Ambroxol, letosteine, streptokinase, IV fluids	Moderate Recovered	Definitely not
80090086 Belgium	56 M	Laryngitis stridulosa	Bronchiolitis	8 PD1	8 PD1	3	3	Bronchial accentuation/ enlargement	Increased WBC, total eosinophils, serum IgE	Bronchodilators, steroids, IV fluids, O_2	Severe Recovered	Possibly
TIV ONE DOSE GROUP												
45350003 Korea	25 M	None	Broncho-pneumonia	33 PD1	39 PD1	4	29	Unremarkable	NPA positive for RSV, negative for influenza, parainfluenza, & adenovirus	Inhaled bronchodilators, decongestants/ antihistamines, IV fluids	Moderate Recovered	Definitely not
44170003 Spain	51 M	≥3 wheezing illnesses; diagnosed with asthma at 21 mos of age	Wheezing	4 PD1	4 PD1	4	6	Not done	Not done	Inhaled bronchodilators, oral steroids, O_2	Moderate Recovered	Probably not

Appendix B SAEs of Hospitalization Associated with Medically Significant Wheezing - Subjects 24-59 Months of Age (cont)

PID# Country	Age (mos) Gender	Past Medical History	MSW Preferred Term	# Days from Previous Dose to AE Onset	# Days from Previous Dose to Hosp Onset	Duration (dy) of Hosp	Duration (dy) of AE	Chest X-ray Findings	Lab Results	Treatment Received	AE Severity/ Outcome	Relation of AE to Study Product[a]
TIV TWO DOSE GROUP												
43660049 Finland	29 F	None	Wheezing	6 PD1	20 PD1	2	23	Atelectasis	Not done	Bronchodilators, steroids, antibiotics	Moderate Recovered	Possibly (IN) Probably not (IM)
43950107 Italy	38 M	None	Pneumonia	33 PD2	37 PD2	4	9	Diffuse vascular enhancement, no consolidation		Bronchodilators, inhaled steroids, antibiotics	Moderate Recovered	Probably not

AE = adverse event; Hosp = hospitalization; IM = intramuscular; IN = intranasal; IV = intravenous; MSW = medically significant wheezing; NPA = nasopharyngeal aspirate; PD1 = post Dose One; PD2 = post Dose Two; Resolved w/resid = resolved with residual effects; RSV = respiratory syncytial virus; WBC = white blood cell.

The information in this table is derived from the SAE narratives produced by MedImmune Product Safety and may or may not be contained in the data listings.

b. Relationship applies to both IN and IM products unless otherwise indicated.

Source: SAE Narratives, Appendix 11.3

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Superior Relative Efficacy of Live Attenuated Influenza Vaccine Compared With Inactivated Influenza Vaccine in Young Children With Recurrent Respiratory Tract Infections

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Background: Young children have a high incidence of influenza and influenza-related complications. This study compared the efficacy and safety of cold-adapted influenza vaccine, trivalent (CAIV-T) with trivalent inactivated influenza vaccine (TIV) in young children with a history of recurrent respiratory tract infections (RTIs).

Methods: Children 6 to 71 months of age were randomized to receive 2 doses of CAIV-T (n = 1101) or TIV (n = 1086), 35 ± 7 days apart before the start of the 2002–2003 influenza season and were followed up for culture-confirmed influenza, effectiveness outcomes, reactogenicity, and adverse events.

Results: Overall, 52.7% (95% confidence interval [CI] = 21.6%–72.2%) fewer cases of influenza caused by virus strains antigenically similar to vaccine were observed in CAIV-T than in TIV recipients. Greater relative efficacy for CAIV-T was observed for the antigenically similar A/H1N1 (100.0%; 95% CI = 42.3%–100.0%) and B (68.0%; 95% CI = 37.3%–84.8%) strains but not for the antigenically similar A/H3N2 strains (−97.1%; 95% CI = −540.2% to 31.5%). Relative to TIV, CAIV-T reduced the number of RTI-related healthcare provider visits by 8.9% (90% CI = 1.5%–15.8%) and missed days of school, kindergarten, or day care by 16.2% (90% CI = 10.4%–21.6%). Rhinitis and rhinorrhea, otitis media, and decreased appetite were the only events that were reported more frequently in CAIV-T subjects. There was no difference between groups in the incidence of wheezing after vaccination.

Conclusions: CAIV-T was well tolerated in these children with RTIs and demonstrated superior relative efficacy compared with TIV in preventing influenza illness.

Key Words: influenza, respiratory tract infection, cold-adapted influenza vaccine, trivalent, children

(*Pediatr Infect Dis J* 2006;25: 870–879)

Influenza is common in children and adolescents and is associated with a high incidence of complications,[1,2] particularly among young children.[3–5] Injectable trivalent inactivated influenza vaccine (TIV) is currently approved in the United States for use in children 6 months of age and older.[6] Efficacy rates for TIV in children younger than 5 years of age have been reported to range from 12% to 83%.[6–8]

Live attenuated influenza vaccine (LAIV; FluMist; MedImmune, Gaithersburg, MD) is a frozen, cold-adapted, temperature-sensitive, trivalent influenza vaccine approved in the United States for prevention of influenza in healthy children and adolescents 5 to 17 years of age and in healthy adults 18 to 49 years of age.[9] In healthy children 15 to 85 months of age, LAIV has been shown to reduce the rate of culture-confirmed influenza by 94% and to reduce episodes of febrile acute otitis media (AOM) by 30% compared with placebo.[10,11] To date, there is a single published report of the safety of LAIV in children with asthma or wheezing,[12] and a single study has reported an increased risk of asthma in young children after LAIV.[13] Children with recurrent respiratory infections often have a history of wheezing illness. Such a population might be expected to benefit significantly from a more effective vaccine against influenza but also might be particularly susceptible to wheezing associated with an attenuated live virus vaccine.

The objective of this study was to compare the efficacy and safety of cold-adapted influenza vaccine, trivalent (CAIV-T), an investigational refrigerator-stable formulation of LAIV, with TIV in preventing culture-confirmed influenza during the 2002–2003 influenza season in children aged 6 to 71 months with a history of recurrent respiratory tract infections (RTIs).

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MATERIALS AND METHODS

Vaccines. CAIV-T was supplied by Wyeth Pharmaceuticals (Marietta, PA) and was formulated to contain approximately 10^7 fluorescent focus units of 3 influenza reassortant virus strains representing the hemagglutinin (HA) and neuraminidase (NA) antigens of the A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), and B/Hong Kong/330/01 influenza strains. The HA and NA antigens of the wild-type influenza strains used to generate the CAIV-T reassortants were antigenically representative of vaccine strains recommended by the World Health Organization (WHO) for the 2002–2003 influenza season: A/New Caledonia/20/99-like, A/Moscow/10/99-like (A/Panama/2007/99), and B/Hong Kong/330/01-like. After manufacture, the vaccine was filled into spray applicators and shipped to the study sites, where it was stored at 2°C to 8°C until just before intranasal administration (0.1 mL into each nostril).

Licensed TIV, types A and B, split virion, was obtained from Aventis Pasteur (Lyon, France) and contained antigens identical to or antigenically representative of the WHO recommendations for the 2002–2003 influenza season, specifically the HA and NA antigens of the A/Moscow/10/99 (H3N2)-like strain (A/Panama/2007/99), A/New Caledonia/20/99 (H1N1)-like strain (A/New Caledonia/20/99), and B/Hong Kong/330/2001-like strain (B/Shangdong/7/97). TIV was administered by intramuscular injection according to the manufacturer's dosing instructions. Children aged 6 to <36 months received 0.25 mL per dose (7.5 μg of each HA), whereas children 36 to <72 months of age received 0.5 mL per dose (15 μg of each HA).

Subjects. Children 6 to 71 months of age with a history of recurrent RTIs were eligible for enrollment. RTIs included, but were not limited to, common colds, AOM, bronchitis, pneumonia, and bronchiolitis. Recurrence was defined as 2 or more practitioner-attended RTIs in the previous 12 months or since birth for participants younger than 12 months.

Exclusion criteria included serious chronic disease (including progressive neurologic disease), Down syndrome or other known cytogenetic disorders, known or suspected disease of the immune system or current receipt of immunosuppressive therapy, including systemic corticosteroids, receipt of any blood products (including immunoglobulin) within the previous 6 months, an immunosuppressed or immunocompromised individual living in the same household, previous receipt of any influenza vaccine, documented history of hypersensitivity to egg or to egg protein or any other component of CAIV-T or TIV, receipt of aspirin or aspirin-containing products within the previous 2 weeks, and receipt of any investigational vaccine from 1 month before enrollment to the conclusion of the study.

Study Design. This phase III, randomized, open-label study was conducted at 114 study sites in 9 European countries (Belgium, Czech Republic, Finland, Germany, Italy, Poland, Spain, Switzerland, and the United Kingdom) and Israel between October 4, 2002, and June 2, 2003. The study was conducted in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice, the Declaration of Helsinki, and national and local laws. The protocol was approved by the independent ethics committee for each study site, and written informed consent was obtained from the parents or legal guardians of all study participants. Enrollment took place over a period of approximately 2 weeks, beginning in October 2002.

Study participants were prospectively randomized in a 1:1 ratio to receive 2 doses of CAIV-T or TIV, 35 ± 7 days apart. Randomization was accomplished using an automated, telephone-based, interactive, voice response system. Trial personnel telephoned the interactive voice response system, entered site- and subject-specific information, and shortly thereafter received a fax confirming treatment (CAIV-T or TIV) and subsequent number assignment.

Study Evaluations. Surveillance for influenza-like illness began on the 11th day after receipt of the first vaccine dose and consisted of weekly telephone contacts, clinic visits, or home visits, as applicable, and continued to the end of the study (approximately May 31, 2003). Nasal swab viral culture was required if subjects exhibited 1 or more of the following: fever (≥38°C rectal or ≥37.5°C axillary), shortness of breath, pulmonary congestion, pneumonia, ear infection (AOM, suspected or diagnosed) or wheezing. Nasal swab viral cultures were also required if subjects showed 2 or more of the following: runny nose or nasal congestion (rhinorrhea), sore throat (pharyngitis), cough, muscle aches, chills, headache, irritability, decreased activity or vomiting. Cultures could also be obtained at the investigators' clinical discretion. Specimens were cultured, typed, and subtyped by central laboratories throughout Europe. Specimens were cultured on Madin-Darby canine kidney monolayer cultures and typed by immunostaining using type A– and type B–specific antisera. In some instances, typing was determined by serologic methods. Identification of isolates was conducted by Wyeth Research Laboratories (Pearl River, NY) using HA inhibition assay and polymerase chain reaction (PCR) sequencing methods similar to those previously described for influenza H3N2 and B viruses.[14,15] If the 2 methods gave different results, the determination of strain matching to the vaccine was based on the PCR sequencing test.

Effectiveness data relating to AOM, wheezing, respiratory illness, school attendance, healthcare provider visits, and use of medications or antibiotics were recorded on a case report form (CRF) and/or documented at each clinic or home visit during the surveillance phase of the study.

Reactogenicity events were monitored by subjects' parents or guardians for 11 consecutive days after each study vaccination. Events to be recorded on the diary card were fever (≥38°C rectal or ≥37.5°C axillary), runny nose/nasal congestion, sore throat, cough, wheeze, vomiting, decreased activity level, decreased appetite, irritability, abdominal pain/stomachache, headache, chills, muscle aches and use of antipyretics. Reactogenicity events that required a medical visit were also recorded as adverse events (AEs), as defined below. For subjects receiving TIV, the presence or absence of redness, swelling, and/or pain around the injection site was also recorded.

Episodes of wheezing occurring during the 42 days after vaccination were recorded as follows: episodes of wheezing were recorded on diary cards by parents/guardians between days 0 and 10 and were not necessarily associated

with a visit to a medical practitioner; episodes of wheezing associated with influenza-like illness were recorded on the CRF on days 11 through 41 during the surveillance period; wheezing episodes that were observed by a medical practitioner were recorded as a subset of the surveillance phase wheezing episodes.

AEs were also recorded on the CRF and were defined as any clinically significant untoward, undesired, or unexpected event, including those that required prescription or nonprescription medication within 11 days postvaccination (days 0–10), required an unscheduled healthcare provider visit or consultation within 28 days of vaccination, or resulted in study termination or a clinically significant event at any point during the study period. Serious AEs (SAEs), including hospitalizations, were monitored from enrollment through completion of the study.

Study End Points. The primary efficacy end point was the first episode in a study child of a culture-confirmed influenza illness caused by a community-acquired subtype antigenically similar to those contained in the vaccine. PCR and sequencing were employed to unambiguously assign serotype based on comparisons with specific HA1 sequences of appropriate reference strains.

Secondary efficacy end points were (1) the incidence of culture-confirmed influenza illness caused by any influenza virus subtype (2); the incidence of AOM (first and all episodes) associated with culture-confirmed influenza antigenically similar to the vaccine, all episodes of AOM regardless of culture, and febrile AOM (first and all episodes) regardless of culture; and (3) the incidence of respiratory illness and other effectiveness outcomes associated with influenza-like illness, including wheeze, medication/antibiotics used for RTIs, number of healthcare provider visits for RTIs, rates of overnight hospitalizations associated with current illness, and days of school, kindergarten, or day care missed.

An episode of AOM was defined as a visually abnormal tympanic membrane (in regard to color, position, and/or mobility) suggestive of middle ear effusion with at least 1 of the following: fever (≥38°C rectal or ≥37.5°C axillary), earache, irritability, diarrhea, vomiting, acute otorrhea not caused by external otitis, or other symptoms of respiratory infection. Febrile AOM was defined as AOM plus fever (≥38°C rectal or ≥37.5°C axillary), and influenza-associated AOM was defined as AOM in a child with a positive culture for influenza virus antigenically similar to a strain in the vaccine. An episode of AOM was defined as one in which at least 30 days had elapsed since the onset of the previous episode.

The primary safety variables evaluated were reactogenicity events, wheeze reports from the CRF and AEs.

Statistical Analysis. The study, with a planned evaluable sample size of 1760 subjects (880 per study group), was designed to have at least 90% power to demonstrate noninferiority for efficacy between CAIV-T and TIV and at least 80% power to detect frequency differences between the CAIV-T and TIV groups. The standard for noninferiority was that the lower bound of the 90% confidence interval (CI) for efficacy was greater than −0.5. The standard for superiority was a lower bound of the 95% CI of >0.

For efficacy analysis, 2 populations were defined: intent to treat (all subjects who received at least 1 dose of study vaccine) and per protocol (PP; all subjects who received 2 doses of vaccine with no major protocol violations). Efficacy estimates against influenza for the intent-to-treat population were based on illness episodes occurring from the day of first vaccination through the end of the surveillance period (approximately May 31, 2003). For the PP population, efficacy estimates were based on illness episodes occurring from 15 days after the second vaccination or from the onset of the influenza season, whichever occurred later, through the end of the surveillance period. Efficacy was assessed for all countries combined, for any strain and for each strain separately. Efficacy of CAIV-T relative to TIV was defined in terms of relative incidence rates as $1\text{-}I_C/I_T$, where I_C refers to the incidence rate in the CAIV-T group and I_T is similarly defined for the TIV group. Two-sided 90% and 95% CIs were constructed using the exact binomial distribution conditioned on the total number of cases observed.

Analyses of AOM effectiveness variables included only those episodes that started during the country-specific influenza season. For the first episode of AOM, vaccine efficacy and 2-sided 90% CIs were computed conditional on the total number of cases. Analyses involving recurrent episodes of AOM with at least 5 TIV cases used the Andersen-Gill model for multiplicative hazards of recurrent events, with treatment as the only effect. However, when there were too few TIV events to perform the Andersen-Gill analysis (defined as fewer than 5 events), a crude estimate of effectiveness based on the observed percentages was computed without the corresponding CIs. Statistical analysis involving multiple events per subject was planned to be performed using the Andersen-Gill model.

For respiratory and other effectiveness outcomes, relative effectiveness was defined in the same manner as for efficacy against influenza, with CIs at the 95% level for superiority and the 90% level for noninferiority.

The safety populations consisted of all subjects who received the first dose of study vaccine (dose 1 safety analysis population) and all subjects who received the second dose of study vaccine (dose 2 safety analysis population). The incidence of AEs and reactogenicity events was analyzed using a 2-sided Fisher exact test. Two-sided 90% CIs were calculated for the difference in incidence of wheezing between the 2 treatment groups.

RESULTS

Patient Population and Demographics. A total of 2187 subjects were randomized to receive either CAIV-T (n = 1101) or TIV (n = 1086). A summary of patient flow with reasons for exclusion from the efficacy analysis is presented in Figure 1. The PP population consisted of 2085 subjects (1050 CAIV-T, 1035 TIV) who received treatment as randomized without significant protocol violations. Baseline demographics for this population are presented in Table 1. The treatment groups were well matched with regard to age, sex, ethnic origin, and medical history. More than 40% of subjects in

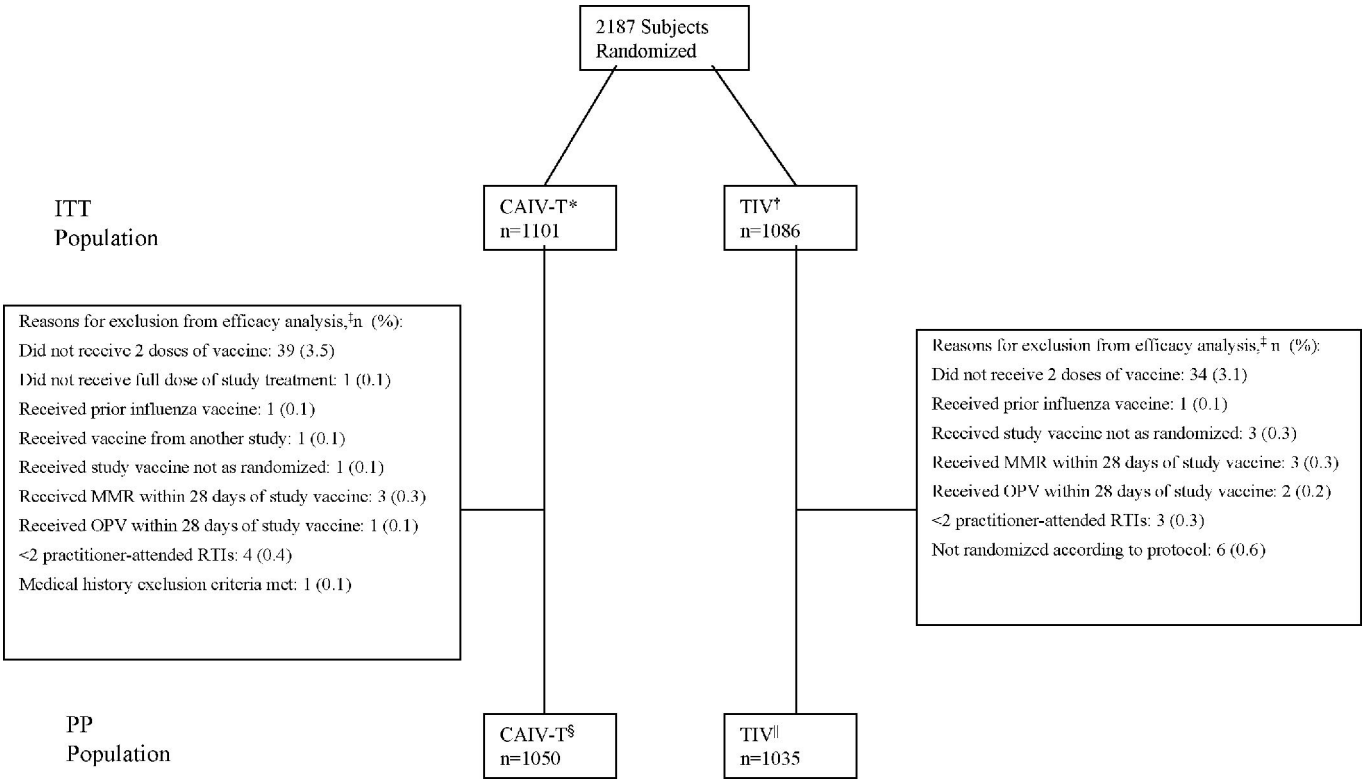

FIGURE 1. Patient flow and efficacy populations. CAIV-T indicates cold-adapted influenza vaccine, trivalent; ITT, intent to treat; MMR, measles-mumps-rubella; OPV, oral polio vaccine; PP, per protocol; RTIs, respiratory tract infections; and TIV, trivalent inactivated influenza vaccine. *Includes 1 subject who received TIV. †Includes 7 subjects who received CAIV-T. ‡Subjects may have been excluded for more than 1 reason. §Includes 1 subject who received TIV. ‖Includes 7 subjects who received CAIV-T.

each group had a history of wheezing (>30% within the previous 12 months), and approximately 23% of all subjects had been previously diagnosed with asthma. Four of the 10 participating countries (Israel, United Kingdom, Belgium, and Poland) contributed almost two thirds (65%) of enrolled subjects.

TABLE 1. Baseline Characteristics (Per-Protocol Efficacy Population)

Characteristic	Treatment Group	
	CAIV-T n = 1050	TIV n = 1035
Gender, n (%)		
Girls	490 (46.7)	475 (45.9)
Boys	560 (53.3)	560 (54.1)
Age at first vaccination, mo		
Mean (SD)	38.1 (17.4)	39.9 (17.2)
Range	6.0–71.9	6.0–71.9
Ethnic origin, n (%)		
White	1022 (97.3)	1000 (96.6)
Black	15 (1.4)	13 (1.3)
Asian	3 (0.3)	3 (0.3)
Indian	5 (0.5)	11 (1.1)
Other	5 (0.5)	8 (0.8)
Medical history		
History of wheezing	495 (47.1)	461 (44.5)
History of wheezing in past 12 mo	377 (35.9)	350 (33.8)
History of diagnosis of asthma	236 (22.5)	236 (22.8)

SD, standard deviation.

Influenza Illness. There were 4497 illness visits (2305 in CAIV-T recipients and 2192 in TIV recipients), during which 4112 nasal swabs (2106 CAIV-T, 2006 TIV) were collected, representing 91.4% and 91.5% of illness visits in each group, respectively. Conclusive culture results were available for 4090 (99.5%) swabs, 113 (2.8%) of which were positive for influenza virus. The distribution of culture-confirmed influenza by week and treatment is summarized in Figure 2.

The incidence of influenza illness caused by subtypes antigenically similar to those in the vaccine was 2.3% and 4.8% in the CAIV-T and TIV groups, respectively (Table 2). Strains identified during surveillance included A/New Caledonia/20/99-like (H1), A/Panama/2007/99-like (H3), A/Sydney/5/97-like (H3), B/Hong Kong/330/01-like, and B/Hong Kong/1351/02-like—all of which were considered antigenically similar to the vaccine strains—plus A/Fujian/411/2002-like (H3), which is considered to be antigenically distinct from the H3N2 vaccine strains. According to WHO data, there is a 16-fold difference in titer between A/Panama/2007/99 and A/Fujian/411/2002 when tested with anti-Panama reference serum, which determines that these 2 strains are not related.[16] However, the 4-fold difference in titers between A/Panama/2007/99 and A/Sydney/5/97 is consid-

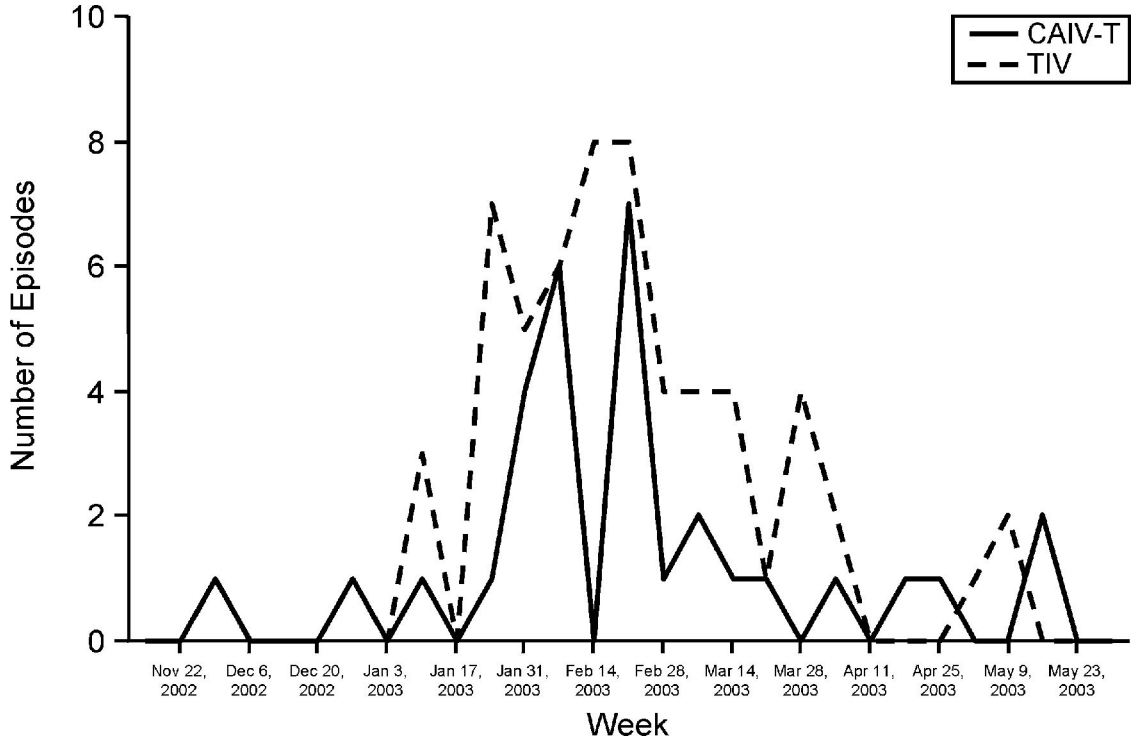

FIGURE 2. Episodes of any culture-confirmed illness by week and treatment group (per-protocol efficacy population). CAIV-T indicates cold-adapted influenza vaccine, trivalent; TIV, trivalent inactivated influenza vaccine.

ered to be borderline.[17] Differences in titers of <4-fold would indicate antigenic equivalence between strains.[18]

Overall, in the PP analysis, there were significantly fewer episodes of culture-confirmed influenza caused by subtypes antigenically similar to those in the vaccine in CAIV-T compared with TIV recipients. Individually, greater relative efficacy for CAIV-T compared with TIV was observed for the A/H1N1 and B strains but not for the A/H3N2 strains. Similar results were seen for efficacy against any influenza subtype.

Although this study was not powered to demonstrate efficacy in individual participating countries, significant efficacy for CAIV-T relative to TIV against viral strains anti-

TABLE 2. Relative Efficacy Against Community-Acquired Culture-Confirmed Influenza Illness

Influenza Subtype	Treatment Group				Relative Efficacy	
	CAIV-T		TIV		% (90% CI)‡	(95% CI)‡
	N*	n (%)†	N*	n (%)†		
Community-acquired subtypes antigenically similar to those in the vaccine						
Per-protocol population						
Any strain	1050	24 (2.3)	1035	50 (4.8)	52.7 (27.2–69.8)	(21.6–72.2)
A/H1	1050	0 (0.0)	1035	8 (0.8)	100.0 (55.2–100.0)	(42.3–100.0)
A/H3	1050	12 (1.1)	1035	6 (0.6)	−97.1 (−431.9 to 20.7)	(−540.2 to 31.5)
B	1050	12 (1.1)	1035	37 (3.6)	68.0 (43.0–82.9)	(37.3–84.8)
Intent-to-treat population						
Any strain	1101	25 (2.3)	1086	52 (4.8)	52.6 (27.7–69.4)	(22.2–71.8)
Any community-acquired subtypes						
Per-protocol population						
Any strain	1050	29 (2.8)	1035	60 (5.8)	52.4 (29.6–68.2)	(24.6–70.5)
A/H1	1050	0 (0.0)	1035	10 (1.0)	100.0 (65.6–100.0)	(56.0–100.0)
A/H3	1050	18 (1.7)	1035	12 (1.2)	−47.9 (−196.5 to 24.4)	(−236.5 to 32.6)
B	1050	12 (1.1)	1035	38 (3.7)	68.9 (44.6–83.3)	(39.2–85.2)
Intent-to-treat population						
Any strain	1101	30 (2.7)	1086	63 (5.8)	53.0 (31.1–68.4)	(26.3–70.6)

*Number of subjects in the analysis.
†Number of subjects with culture-confirmed influenza.
‡Exact CI conditioned on the total number of cases.

genically similar to those in the vaccine was observed in Belgium (relative efficacy, 100%; 95% CI = 72.9%–100%), and a positive trend toward protection was also observed in the Czech Republic, Finland, Israel, Italy, Spain and the United Kingdom. The numbers of cases of illness caused by virus strains antigenically similar to the vaccine were too small (≤3) to allow an evaluation of relative efficacy in Germany, Poland and Switzerland.

The highest incidence of culture-confirmed influenza occurred in children 30 to <36 months of age in the CAIV-T group (5.9%) and in children 60 to <66 months of age in the TIV group (13.1%). Although the study was not powered to demonstrate relative efficacy in different age groups, the incidence of culture-confirmed influenza was observed to be higher in TIV compared with CAIV-T recipients for 7 of the 11 age groups evaluated, with the greatest difference seen in children 60 to <66 months of age (13.1% versus 1.2%).

AOM. Very few cases of influenza-associated AOM (2 CAIV-T; 6 TIV) were reported during the study, preventing an evaluation of differences in incidence between treatment groups. There was no significant difference between treatment groups in the incidence of all episodes of AOM.

Respiratory and Other Effectiveness Outcomes. Compared with TIV, CAIV-T significantly reduced the number of healthcare provider visits for RTIs and the number of days of school, kindergarten, or day care missed (Table 3). There were no significant differences between groups in wheezing symptoms associated with influenza-like illness, use of medications or antibiotics for treatment of respiratory illness, or occurrence of overnight hospitalizations.

Reactogenicity and AEs. In the 11 days after dose 1, the percentage of subjects experiencing at least 1 reactogenicity event was higher in the CAIV-T group (87.2%) than in the TIV group (83.7%, $P = 0.033$), principally owing to a higher incidence of runny nose/nasal congestion among CAIV-T recipients (68.3% versus 55.1%; $P < 0.001$) (Table 4). In the 11 days after dose 2, there was no significant difference between groups in the overall incidence of reactogenicity events, although CAIV-T recipients had significantly higher rates of runny nose/nasal congestion (52.1% versus 44.4%, $P = 0.0001$) and decreased appetite (23.9% versus 19.8%, $P = 0.031$) than subjects treated with TIV.

Almost one third (31.6%) of TIV recipients experienced some type of local reaction at the injection site after dose 1, and 28.9% exhibited local reactions after dose 2. Pain was reported by 24.2% and 23.3% of subjects after doses 1 and 2, respectively.

Fifteen subjects had nasal swabs that were positive for CAIV-T during episodes of symptomatic influenza illness. Fourteen subjects were CAIV-T recipients and 1 received TIV. Reported symptoms in CAIV-T recipients included runny nose (12 subjects), cough (10 subjects), wheezing (3 subjects), fever (3 subjects) and sore throat (2 subjects); pneumonia, pulmonary congestion, and ear infection were reported by 1 subject each. Three of these CAIV-T recipients reported wheezing. However, it is important to note that the overall incidence of wheezing episodes was similar in both treatment groups. Illness was observed after the first dose in 10 subjects and after the second dose in 4 subjects, with onset of symptoms ranging from the day before vaccination to 20 days after vaccination. The TIV recipient was a 5-year-old boy who developed a sore throat, cough, and wheezing 13 days after the first dose of vaccine, associated with a positive nasal swab for B/Hong Kong/330/01 vaccine-like virus. The child remained afebrile, and the illness resolved within 1 day. A 2-year-old female sibling of this child (who received CAIV-T on the same day as her brother received TIV) also developed a sore throat and cough (not associated with wheezing) with fever 13 days after the first dose of vaccine and had a positive swab for B/Hong Kong/330/01 vaccine-like virus. The illness in this child resolved within 5 days. Neither sibling had a history of wheezing. This study was not designed to evaluate risk of CAIV-T in a household setting. The event could represent a true transmission episode; alternatively, because specimens were obtained and cultured at the same visit, this could represent an inadvertent cross-contamination event.

The incidence of AEs within 11 days of the first vaccine dose was higher in the CAIV-T than the TIV group, (33.8% versus 29.6%; $P = 0.039$), principally owing to a higher incidence of rhinitis (8.7% versus 5.3%; $P = 0.002$). After dose 2, a trend toward a higher incidence of AEs within 11 days was evident in the CAIV-T group (32.4% versus 28.6%; $P = 0.059$), principally owing to a higher incidence of rhinitis

TABLE 3. Relative Efficacy Against Respiratory Illness and Other Effectiveness Outcomes Associated With Influenza-like Illness

End Point	Treatment Group				% Relative Efficacy (90% CI)‡
	CAIV-T		TIV		
	N*	n (%)†	N*	n (%)†	
Use of medications or antibiotics for treatment of RTI	1048	368 (35.1)	1034	354 (34.2)	−2.6 (−16.3 to 9.5)
Unscheduled healthcare provider visits	72,476	878 (1.2)	71,337	949 (1.3)	8.9 (1.5–15.8)
Overnight hospitalizations	1048	12 (1.1)	1034	11 (1.1)	−7.6 (−134.6 to 50.3)
Days off school/kindergarten/day care§	55,892	1145 (2.0)	55,490	1357 (2.4)	16.2 (10.4–21.6)
Wheezing symptoms associated with influenza-like illness	1048	77 (7.3)	1034	71 (6.9)	−7.0 (−42.2 to 19.4)

*Number of subjects or surveillance days in the calculation.
†Number of incidents or number of days with the event.
‡Exact CI conditioned on the total number of incidents or number of days.
§Subjects were included in the analysis if the child was ever in school, kindergarten, or daycare or they missed any days of school.

TABLE 4. Reactogenicity Events Reported in >1% of Subjects Within 11 Days of Vaccination

Event	Incidence, n (%)					
	After Dose 1			After Dose 2		
	CAIV-T n = 630–1067†	TIV n = 684–1050†	*P* Value*	CAIV-T n = 625–1029†	TIV n = 679–1012†	*P* Value*
Any event‡	863 (87.2)	791 (83.7)	0.033	694 (76.2)	648 (73.6)	0.210
Runny nose or nasal congestion	729 (68.3)	579 (55.1)	0.000	536 (52.1)	449 (44.4)	0.001
Fever ≥37.5°C	231 (23.5)	208 (21.4)	0.279	191 (19.8)	172 (18.5)	0.484
Fever ≥38.6°C	49 (5.1)	62 (6.5)	0.204	53 (5.6)	47 (5.1)	0.682
Cough	467 (44.2)	457 (44.1)	0.965	417 (40.8)	378 (37.8)	0.158
Medication to treat a fever	202 (20.5)	184 (18.5)	0.307	177 (18.3)	152 (15.7)	0.146
Medication to prevent a fever	156 (15.4)	143 (14.3)	0.491	126 (12.9)	116 (11.9)	0.537
Decreased appetite	309 (29.5)	277 (26.8)	0.188	241 (23.9)	198 (19.8)	0.031
Irritability	265 (25.5)	231 (22.9)	0.180	181 (18.4)	157 (16.1)	0.188
Decreased activity	224 (21.4)	195 (19.1)	0.190	171 (17.2)	142 (14.3)	0.085
Abdominal pain§	136 (21.1)	131 (18.5)	0.219	86 (13.6)	88 (12.7)	0.684
Vomiting	119 (11.5)	124 (12.0)	0.733	105 (10.6)	97 (9.8)	0.603
Sore throat	115 (11.3)	120 (12.0)	0.628	128 (13.0)	100 (10.2)	0.057
Wheeze	96 (9.3)	101 (9.9)	0.708	77 (7.8)	71 (7.2)	0.670
Headache§	90 (14.2)	89 (12.8)	0.470	75 (11.9)	74 (10.6)	0.487
Chills§	37 (5.8)	53 (7.7)	0.192	28 (4.5)	26 (3.8)	0.579
Muscle ache§	36 (5.7)	50 (7.3)	0.265	33 (5.3)	37 (5.4)	0.903

*Fisher exact test, 2-sided, for percentage of subjects.
†Number of subjects with known values.
‡Any event does not include the administration of fever medication.
§Not all children were old enough to verbalize this symptom.

(6.1% versus 3.8%; $P = 0.021$) and otitis media (3.7% versus 1.8%; $P = 0.011$). Only 1 AE-related discontinuation was reported: a 4-year-old TIV recipient withdrew from the study 26 days after the first vaccination after developing a pertussis infection that was judged by the investigator to be unrelated to vaccine administration.

The incidence of wheezing was similar in both treatment groups, regardless of the method used to record wheezing episodes (Table 5). There was no significant difference in the first incidence of wheeze reported as a reactogenicity event. In addition, there was no difference in the incidence of bronchitis, bronchospasm, cough, dyspnea, pneumonia, bronchiolitis, or lower RTI captured as an AE after either dose. Overall, a first episode of wheeze was reported by 12.5% of CAIV-T recipients and 13.2% of TIV recipients during the 42 days after the first vaccine dose and by 13.8% of CAIV-T recipients and 12.3% of TIV recipients in the 42 days after dose 2. After dose 1, 55 (5.0%) CAIV-T recipients and 49 (4.5%) TIV recipients reported a single episode of wheeze between days 11 and 41; 44 CAIV-T subjects and 32 TIV subjects experienced a single episode of wheeze that was observed by a medical practitioner; only 1 subject in the CAIV-T group experienced 2 episodes of wheeze that were observed by a medical practitioner; and 4 TIV recipients reported 2 wheezing episodes, also observed by a medical practitioner. After the second study dose, 64 (6.0%) CAIV-T recipients and 58 (5.5%) TIV recipients experienced a single episode of wheeze between days 11 and 41. A single medical practitioner–observed wheezing episode was reported in 52 CAIV-T and 51 TIV subjects; 2 CAIV-T subjects reported 2 wheezing episodes and 1 CAIV-T recipient experi-

TABLE 5. Incidence of First Episode of Wheeze

Vaccination	Source of Episodes		Treatment Group				Difference (90% CI)‖
			CAIV-T		TIV		
	Period, (days)*	Method†	N‡	n (%)§	N‡	n (%)§	
Dose 1	0–41	Any	1107	138 (12.5)	1080	143 (13.2)	−0.8 (−3.1 to 1.6)
	0–10	Diary cards	1107	96 (8.7)	1080	101 (9.4)	−0.7 (−2.7 to 1.3)
	11–41	Surveillance	1107	56 (5.1)	1080	53 (4.9)	0.2 (−1.4 to 1.7)
	11–41	Practitioner	1107	45 (4.1)	1080	36 (3.3)	0.7 (−0.6 to 2.1)
Dose 2	0–41	Any	1068	147 (13.8)	1046	129 (12.3)	1.4 (−1.0 to 3.8)
	0–10	Diary cards	1068	77 (7.2)	1046	71 (6.8)	0.4 (−1.4 to 2.3)
	11–41	Surveillance	1068	67 (6.3)	1046	62 (5.9)	0.3 (−1.4 to 2.1)
	11–41	Practitioner	1068	54 (5.1)	1046	53 (5.1)	0.0 (−1.6 to 1.6)

*For vaccination 1, wheeze data were collected up to day 41 or the second vaccination, whichever occurred earlier.
†Diary card wheeze data were reported by parents/guardians. Episodes of wheeze associated with influenza-like illness during the surveillance phase were reported on the case report form. Practitioner-reported wheeze during the surveillance phase was further described as "observed by a medical practitioner."
‡Number of subjects participating during the collection period.
§Number of subjects with at least 1 episode of wheeze in the indicated period and method of collection.
‖Exact confidence limits for the difference in percentages.

enced 3 wheezing episodes; 4 TIV subjects reported 2 episodes of wheeze.

Overall, 104 SAEs were reported in 64 (5.8%) CAIV-T subjects and 76 SAEs were reported in 51 (4.7%) TIV subjects; 2 (0.2%) CAIV-T recipients and 4 (0.4%) TIV recipients experienced SAEs that were judged by the investigator to be at least possibly related to vaccine. There were no significant differences between groups overall or within any of the body system categories, including the respiratory system. No deaths were reported during the study.

DISCUSSION

In the present trial, CAIV-T demonstrated superior protection against influenza strains similar to those in the vaccine compared with TIV, with an overall relative efficacy of 52.7% (95% CI = 21.6%–72.2%), and relative efficacy for individual vaccine strains of 100% against A/New Caledonia/20/99-like (H1N1) viruses and of 68% against B/Hong Kong/330/01-like viruses. CAIV-T appeared to have similar efficacy to TIV against A/Panama/2007/99-like (A/H3) viruses in this trial. The latter observation could be explained by low H3N2 attack rates, which may have reduced the ability to discriminate differences in efficacy between CAIV-T and TIV. However, CAIV-T was shown to have higher relative efficacy against H1N1 compared with TIV despite relatively few culture-positive illnesses. The H3N2 attack rate in the previous 2001–2002 influenza season is unknown for this population of children. However, a placebo-controlled trial of CAIV-T was conducted in a similar population of children 6 to 36 months of age during the 2001–2002 season in Europe and Israel. An A/Panama/2007/99-like (A/H3) virus was the predominant influenza isolate during that season; culture-confirmed H3N2 infection was documented in more than 20% of children.[19] It is reasonable to assume that the H3N2 attack rate for the European and Israeli population of children in the current study was also high in the same influenza season. For these children, the "priming" effect of previous natural H3N2 exposure may have been boosted by TIV and reduced the ability to distinguish differences in efficacy between live attenuated and inactivated vaccine. High efficacy of 86% to 95% against A/H3 strains has been observed in earlier trials of both frozen and liquid forms of LAIV in young children.[10,11,19,20]

In a previous study in healthy children 1 to 17 years of age, a post hoc analysis revealed an association between LAIV treatment and an increased risk of asthma in children younger than 3 years.[13] In contrast, in the present study in which data were prospectively collected and analyses were prespecified, no statistically significant differences were observed between CAIV-T and TIV in the incidence of wheezing after either dose of vaccine, regardless of the evaluation method used. In addition, there were no significant differences in the rates of respiratory SAEs between treatment groups. These data differ from the post hoc analysis reported by Bergen et al[13] in demonstrating no increased risk of asthma or reactive airways disease after immunization with CAIV-T in children younger than 5 years. It is also important to note that the 2 treatment groups in this study were similar with respect to history of asthma and wheezing episodes, with more than 40% of subjects in each treatment group reporting a history of wheezing. In a large, open-label, community-based study of more than 11,000 children aged 18 months to 18 years (10% of whom had a history of mild intermittent asthma, reactive airway disease, or wheezing illness), LAIV was well tolerated by all age groups.[21] In this study, in which 190 comparisons were made without adjustment for multiple comparisons, there was no increased relative risk of asthma in the period 0 to 14 days after LAIV vaccination in any age group. Although an increased relative risk for asthma events (compared with a prevaccination reference period) was reported 15 to 42 days postvaccination in year 1 in children 18 months to 4 years of age (relative risk, 2.85; 95% CI = 1.01–8.03), no increase was observed in asthma relative risk in children 18 months to 4 years of age in the subsequent 3 vaccine years. Further such studies should be performed in healthy children to clarify these findings.

A recent study of influenza and influenza-related claims from a large US health insurance database found that 24.9% of all cases of influenza-like illness occurred in children aged 4 years or younger.[1] During influenza seasons, influenza accounts for approximately one quarter of excess outpatient visits in children younger than 3 years,[22] and analysis of effectiveness data gathered during this trial showed that, compared with TIV, CAIV-T significantly reduced the number of healthcare provider visits by 8.9% (90% CI = 1.5%–15.8%) and the number of days missed from school, kindergarten, or day care missed by 16.2% (90% CI = 10.4%–21.6%). These findings are consistent with those of another recent study, which showed that CAIV-T significantly reduced the need for parental time off work, medical visits for influenza, and antibiotic use, compared with placebo in children aged 6 to <36 months of age and attending day care.[19] CAIV-T has the potential, therefore, to reduce the substantial impact associated with influenza infection in young children.[23]

The profile of reactogenicity events and AEs in this study was similar in both treatment groups, except that CAIV-T recipients had a higher incidence of runny nose/nasal congestion within 11 days after both doses, consistent with the findings of previous trials with the frozen formulation,[24] and a higher incidence of decreased appetite and otitis media after dose 2. In contrast, injection site reactions and/or pain at the injection site were reported by approximately one quarter of TIV recipients. SAEs were infrequent in both treatment groups.

The findings from this study indicate that CAIV-T has a comparable safety and tolerability profile to TIV in young children with a history of recurrent respiratory illness, with superior efficacy demonstrated against culture-confirmed influenza illness. According to this evidence, CAIV-T is preferable to TIV in this population. Additional studies are in progress to further evaluate the comparative efficacy of CAIV-T and TIV in young children.

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ORIGINAL ARTICLE

Live Attenuated versus Inactivated Influenza Vaccine in Infants and Young Children

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ABSTRACT

BACKGROUND

Universal vaccination of children 6 to 59 months of age with trivalent inactivated influenza vaccine has recently been recommended by U.S. advisory bodies. To evaluate alternative vaccine approaches, we compared the safety and efficacy of intranasally administered live attenuated influenza vaccine with those of inactivated vaccine in infants and young children.

METHODS

Children 6 to 59 months of age, without a recent episode of wheezing illness or severe asthma, were randomly assigned in a 1:1 ratio to receive either cold-adapted trivalent live attenuated influenza vaccine (a refrigeration-stable formulation of live attenuated intranasally administered influenza vaccine) or trivalent inactivated vaccine in a double-blind manner. Influenza-like illness was monitored with cultures throughout the 2004–2005 influenza season.

RESULTS

Safety data were available for 8352 children, and 7852 children completed the study according to the protocol. There were 54.9% fewer cases of cultured-confirmed influenza in the group that received live attenuated vaccine than in the group that received inactivated vaccine (153 vs. 338 cases, P<0.001). The superior efficacy of live attenuated vaccine, as compared with inactivated vaccine, was observed for both antigenically well-matched and drifted viruses. Among previously unvaccinated children, wheezing within 42 days after the administration of dose 1 was more common with live attenuated vaccine than with inactivated vaccine, primarily among children 6 to 11 months of age; in this age group, 12 more episodes of wheezing were noted within 42 days after receipt of dose 1 among recipients of live attenuated vaccine (3.8%) than among recipients of inactivated vaccine (2.1%, P=0.076). Rates of hospitalization for any cause during the 180 days after vaccination were higher among the recipients of live attenuated vaccine who were 6 to 11 months of age (6.1%) than among the recipients of inactivated vaccine in this age group (2.6%, P=0.002).

CONCLUSIONS

Among young children, live attenuated vaccine had significantly better efficacy than inactivated vaccine. An evaluation of the risks and benefits indicates that live attenuated vaccine should be a highly effective, safe vaccine for children 12 to 59 months of age who do not have a history of asthma or wheezing. (ClinicalTrials.gov number, NCT00128167.)

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Hospitalization rates for culture-confirmed influenza among young children are similar to those among the elderly, and outpatient visits for confirmed influenza are more frequent among infants and young children than in any other age group.[1] For these reasons, U.S. advisory bodies have recently recommended the routine vaccination of all children 6 to 59 months of age with the licensed trivalent inactivated influenza vaccine.[2] The implementation of this recommendation will be challenging because of the limited supplies of inactivated vaccine during many influenza seasons,[3-5] the modest efficacy of inactivated vaccine in young children,[6] and the frequent need to administer the inactivated vaccine by injection concurrent with multiple other parenteral vaccines.

Previous clinical trials of live attenuated trivalent influenza vaccine in young children have shown it to be highly effective.[7-9] Live attenuated influenza vaccine showed high efficacy when epidemic influenza viruses were not well matched to the recommended vaccine antigens.[7] Initial studies comparing the efficacy of cold-adapted trivalent live attenuated influenza vaccine with trivalent inactivated vaccine have shown the former to be more effective (35 to 53% reduction in the influenza attack rate with live attenuated vaccine, as compared with inactivated vaccine).[10,11] Although the safety of live attenuated influenza vaccine was assessed in children in both prospective and database studies,[12-15] additional prospective studies of both inactivated vaccine and live attenuated vaccine were needed. In one study,[15] but not in others,[10,11,16] wheezing events were more frequent among young children given formulations of live attenuated vaccine. The present trial was designed to assess the safety and relative efficacy of live attenuated intranasal influenza vaccine and inactivated vaccine in children 6 to 59 months of age.

METHODS

STUDY DESIGN

The study was proposed by a subgroup of the authors, and the protocol was developed by all the authors in collaboration with an advisory committee. Data were gathered at each study site by the local principal investigator and the local staff. The data were monitored by PPD in the United States and Europe and by Quintiles at the Asian sites. A data and safety monitoring board oversaw the study. The analysis was performed by biostatisticians employed by the sponsor. All authors had complete access to all data and all individual case-report forms, including data on all serious adverse events. All the authors vouch for the accuracy and completeness of the reported data.

The study was conducted at 249 sites (physicians' offices and primary care clinics) in 16 countries: the United States (49% of subjects), 12 countries in Europe and the Middle East (45% of subjects), and 3 countries in Asia (6% of subjects). The protocol and the informed consent forms were approved by the institutional review board at each participating center, and the study was conducted in accordance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice.

After written informed consent had been obtained from a parent or guardian, children 6 to 59 months of age were randomly assigned on a 1:1 basis to receive either live attenuated vaccine or inactivated vaccine with the use of a centrally managed computer-generated randomization schedule. Subjects were stratified according to age on receipt of the first dose, the presence or absence of previous influenza vaccination, the presence or absence of a history of recurrent wheezing (defined as three or more wheezing episodes, each requiring medical follow-up or hospitalization, according to the parent's report or chart review), and country of residence. Children with a history of hypersensitivity to any component of the live attenuated vaccine or the inactivated vaccine were excluded; other exclusion criteria were a known immunosuppressive condition, medically diagnosed or treated wheezing within 42 days before enrollment, a history of severe asthma (as judged by the investigator), body temperature higher than 37.8°C (100°F) measured orally or the equivalent within 3 days before enrollment, and the use of aspirin or salicylate-containing products within 30 days before enrollment. Children with mild or moderate asthma or a history of wheezing (i.e., more than 42 days before enrollment) were included in the trial.

Children who had not previously been vaccinated against influenza were given two doses of

the assigned study vaccine; the first dose (dose 1) was administered on day 0 of the trial, and the second dose was administered 28 to 42 days later. Those who had previously been vaccinated against influenza were given only one dose. Subjects who were assigned to receive live attenuated vaccine, which was administered intranasally, also received a concurrent injection of intramuscular saline, and those assigned to receive inactivated vaccine, which was administered intramuscularly, also received a concurrent intranasal mist of saline.

VACCINES AND PLACEBO

The live attenuated intranasal vaccine was a refrigeration-stable (2 to 8°C) formulation of the currently licensed frozen FluMist (LAIV, MedImmune). This vaccine consisted of three cold-adapted reassortant influenza viruses grown in specific pathogen-free chicken eggs. Each dose of vaccine contained approximately 10^7 fluorescence focus assay units of each of the three strains of the 2004–2005 influenza season, as recommended by the Food and Drug Administration (A/New Caledonia/20/99 [H1N1], A/Wyoming/3/2003 [an A/Fujian/411/2002 (H3N2)–like virus], and B/Jilin/20/2003 [a B/Shanghai/361/2002-like virus]). A total of 0.2 ml of vaccine was administered (0.1 ml into each nostril with the use of an intranasal-spray device).

The licensed inactivated vaccine consisted of the recommended 2004–2005 influenza strains (A/New Caledonia/20/99 [H1N1], A/Wyoming/3/2003 [an A/Fujian/411/2002 (H3N2)–like virus], and B/Jiangsu/10/2003 [a B/Shanghai/361/2002-like virus]), and the vaccine was administered by intramuscular injection, according to the manufacturer's dosing instructions. In the United States and Asia, Fluzone (Aventis Pasteur) was used, and in Europe and the Middle East, Vaxigrip (Aventis Pasteur) was used. Children 6 to 35 months of age received 0.25 ml of intramuscular inactivated vaccine, and those 36 to 59 months of age received 0.5 ml of intramuscular inactivated vaccine.

Intranasal and intramuscular placebos were composed of physiologic saline and were given in a manner identical to the administration of the corresponding study vaccine. The subject, the subject's parent or guardian, the staff at the clinical site who were evaluating the subjects (including the investigators, study nurses, and coordinators), and the clinical, biostatistical, and data-management staff employed by the sponsor were unaware of the treatment assignments. The vaccines and placebos were maintained at 2 to 8°C and were shipped by express courier to the study sites.

SURVEILLANCE FOR OUTCOMES AND SYMPTOMS OF INFLUENZA

Parents or guardians recorded local reactions, daily temperatures (oral, axillary, or rectal), systemic adverse events, and concomitant medications on worksheets from the time that dose 1 was administered until 42 days after the administration of the second dose, or until 42 days after dose 1 among subjects who received only one dose. Data on medically significant wheezing and serious adverse events (defined as events that were life-threatening or that resulted in death, hospitalization or prolonged hospitalization, significant disability or incapacity, or another important medical event requiring intervention to prevent one of these outcomes) were collected from the day of dose 1 until the end of the influenza surveillance period, extending through May 31, 2005. Medically significant wheezing was prospectively defined as the presence of wheezing on a physical examination conducted by a health care provider, with a prescription for a daily bronchodilator; respiratory distress; or hypoxemia. Study staff contacted the children's parents or guardians every 7 to 10 days throughout the influenza surveillance period, and if symptoms defined in the study protocol as suggestive of influenza were reported, nasal swabs for viral cultures were obtained either at the study site or at the child's home. Virologic methods are summarized in the Supplementary Appendix (available with the full text of this article at www.nejm.org).

STATISTICAL ANALYSIS

Assuming a 3.0% attack rate in the group that received inactivated vaccine and a 1.8% attack rate in the group that received live attenuated vaccine (relative efficacy rate, 40%) and assuming that sufficient data would be collected for 90% of the children to be included in the according-to-protocol population, we calculated that a sample of 8500 children would provide more than 90% power to demonstrate the superiority of live attenuated vaccine to inactivated vaccine (see the Statistics

section in the Supplementary Appendix). The primary end point was the efficacy of live attenuated vaccine, as compared with that of inactivated vaccine, in preventing culture-confirmed influenza-like illness as defined by the Centers for Disease Control and Prevention (CDC), modified to account for the subject's age, caused by well-matched influenza strains. The modified CDC definition of influenza-like illness was an oral temperature of 37.8°C or higher or the equivalent in the presence of cough, sore throat, or runny nose or nasal congestion occurring on the same or consecutive days; the addition of runny nose or nasal congestion to the case definition accounts for the age modification. Culture-positive influenza strains were assessed according to whether the isolated virus was well matched or significantly drifted to the vaccine strains. For detailed information on the statistical methods, see the Supplementary Appendix.

Secondary efficacy end points included the efficacy of live attenuated vaccine, as compared with that of inactivated vaccine, in preventing culture-confirmed influenza-like illness (according to the modified CDC definition) caused by antigenically mismatched influenza viruses and by all influenza viruses. Other efficacy end points included any culture-confirmed symptomatic influenza infection (as distinguished from influenza-like illness that met the modified CDC definition), medically diagnosed acute otitis media with fever and antibiotic use, and medically diagnosed lower respiratory illness, all associated with a positive nasal-swab culture for influenza virus at any time during the interval between the seventh day before the onset of the illness and the seventh day after the end of the illness.

RESULTS

STUDY POPULATION AND FOLLOW-UP

From October 20 to October 29, 2004, a total of 8475 children were enrolled (for details on the study populations, see Fig. 1 in the Supplementary Appendix). On average, 34 children (range, 1 to 270; median, 26) underwent randomization at each study site. Safety data were available for 8352 children, 7852 of whom were included in the analysis of the according-to-protocol population. Demographic and other characteristics, including number of days of follow-up, were well balanced between the group that received live attenuated vaccine and the group that received inactivated vaccine (Table 1). A total of 1880 of the children had previously received an influenza vaccine, and 6472 had not previously been vaccinated. Of those who received dose 1 of the vaccine and were assigned to receive a second dose, 3002 (92.4%) in the live-attenuated-vaccine group and 3034 (94.0%) in the inactivated-vaccine group received both doses. Overall on entry into the trial, 5.7% of the children in each group had underlying medical conditions, 21% had a history of any wheezing (as reported by a parent, guardian, or health care provider), and 6% had recurrent wheezing. More than 20,000 nasal specimens were cultured during the surveillance period (2.4 cultures per child).

EFFICACY

Kaplan–Meier curves for the time of the acquisition of a culture-confirmed influenza-like illness (according to the modified CDC definition) in the two groups are shown in Figure 1, and the attack rates are summarized in Table 2. There were 185 (54.9%) fewer cases of influenza in the live-attenuated-vaccine group (153 cases; attack rate, 3.9%) than in the inactivated-vaccine group (338 cases; attack rate, 8.6%) ($P<0.001$). According to the virus subtype, vaccination with live attenuated vaccine resulted in 89.2% fewer cases of influenza A/H1N1 ($P<0.001$), 79.2% fewer cases of influenza A/H3N2 ($P<0.001$), and 16.1% fewer cases of influenza B ($P=0.19$). The live attenuated vaccine was significantly more protective against both well-matched and mismatched influenza A viruses (Table 2). All isolates of H1N1 virus were regarded as antigenically matched. All isolates of H3N2 virus were antigenically mismatched. In contrast, the circulating B strains were divided into two lineages, Yamagata-like (strains that were antigenically matched and mismatched to vaccine) and Victoria-like (antigenically mismatched to vaccine). Although the difference was not significant, live attenuated vaccine showed a relative efficacy of 27%, as compared with inactivated vaccine, against the matched B strains, but there was no significant difference in efficacy against mismatched B strains.

For all culture-confirmed symptomatic influenza, the overall attack rates were 5.0% in the group

that received live attenuated vaccine and 10.0% in the group that received inactivated vaccine, with a 50.6% reduction in the live-attenuated-vaccine group, as compared with the inactivated-vaccine group (P<0.001). Significant reductions were also seen in the overall attack rates of acute otitis media and lower respiratory illness associated with positive influenza cultures, as diagnosed by a health care provider, with a relative efficacy in the live-attenuated-vaccine group of 50.6% (P=0.004) and 45.9% (P=0.046), respectively (see Table 1 in the Supplementary Appendix).

ADVERSE EVENTS

The incidence of pain, redness, and swelling at the injection site, with most instances reported as mild to moderate in severity, was higher in the group that received inactivated vaccine than in the group that received intramuscular placebo. Among subjects being vaccinated for the first time, 57.0% of those receiving intramuscular placebo and 46.3% of those receiving intranasal placebo had a runny or stuffy nose within 10 days after vaccination. With fever defined as a temperature of more than 37.8°C, fever occurred in 5.4%

Table 1. Characteristics and Follow-up of Subjects Included in the Safety Population.*

Variable	Live Attenuated Vaccine	Inactivated Vaccine	Total
No. of subjects	4179	4173	8352
History of influenza vaccination — no. (%)	933 (22.3)	947 (22.7)	1880 (22.6)
Mean age at first vaccination — mo	25.7	25.6	25.6
Age distribution — no. (%)			
6–23 mo	1992 (47.7)	1975 (47.3)	3967 (47.5)
6–11 mo	684 (16.4)	683 (16.4)	1367 (16.4)
12–23 mo	1308 (31.3)	1292 (31.0)	2600 (31.1)
24–35 mo	1372 (32.8)	1379 (33.0)	2751 (32.9)
36–59 mo	815 (19.5)	818 (19.6)	1633 (19.6)
60 mo	0	1 (<0.1)	1 (<0.1)
Sex — no. (%)			
Male	2142 (51.3)	2147 (51.4)	4289 (51.4)
Female	2037 (48.7)	2026 (48.6)	4063 (48.6)
Race or ethnic group — no. (%)†			
White and non-Hispanic	3351 (80.2)	3356 (80.4)	6707 (80.3)
Black	171 (4.1)	156 (3.7)	327 (3.9)
Hispanic	267 (6.4)	272 (6.5)	539 (6.5)
Asian	309 (7.4)	307 (7.4)	616 (7.4)
Other	81 (1.9)	82 (2.0)	163 (2.0)
History of any wheezing — no. (%)	899 (21.5)	863 (20.7)	1762 (21.1)
History of recurrent wheezing — no. (%)	271 (6.5)	239 (5.7)	510 (6.1)
History of asthma — no. (%)	164 (3.9)	169 (4.0)	333 (4.0)
Duration of follow-up — days			
Median	219	219	219
Range	0–224	0–224	0–224

* The categories of any wheezing, recurrent wheezing, and asthma were not mutually exclusive.
† Race or ethnic group was reported by the child's parent or guardian.

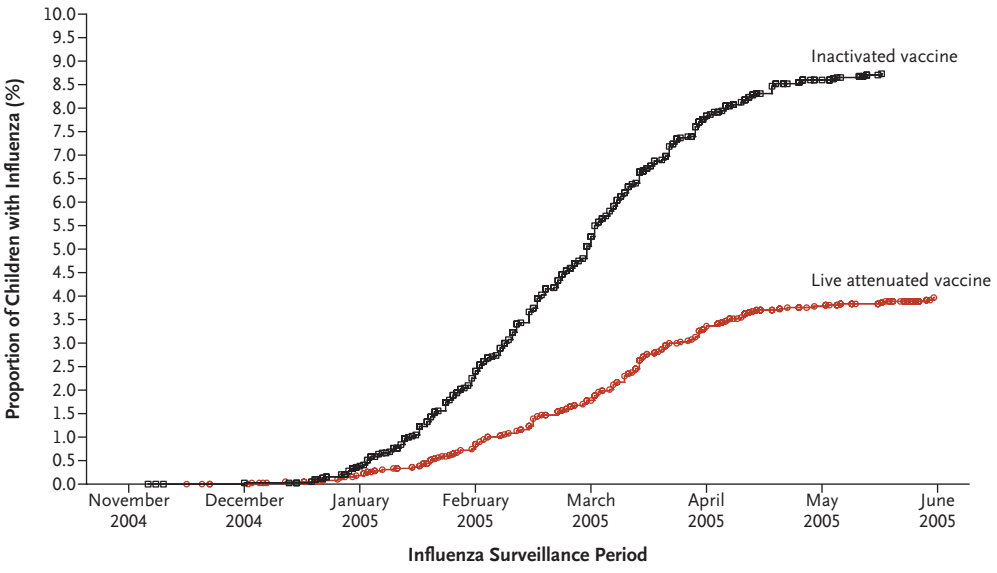

Figure 1. Kaplan–Meier Curves for the Time to the First Culture-Confirmed Report of Influenza in the Two Vaccine Groups.

Culture-confirmed influenza was caused by any wild-type influenza strain (regardless of antigenic match or mismatch to vaccine) in children who received a study vaccine according to the study protocol (P<0.001 by the log-rank test). Of 3936 children given inactivated vaccine, 338 had influenza, and of 3916 children given live attenuated vaccine, 153 had influenza. Each square denotes one infected child in the inactivated-vaccine group, and each circle one infected child in the live-attenuated-vaccine group.

of the live-attenuated-vaccine group and 2.0% of the inactivated-vaccine group on day 2 after receipt of dose 1 of vaccine (P<0.001). With the use of a higher temperature cutoff (fever defined as 38.9°C [>102°F]), the incidence of fever was low (<1% on day 2, after receipt of dose 1) in both vaccine groups. No significant differences in fever were found between the two groups after the second dose (see Fig. 2 in the Supplementary Appendix).

The rates of medically significant wheezing during the 42-day period after each dose of vaccine are shown in Table 3. Overall, there was no significant difference in medically significant wheezing between the two groups. In previously unvaccinated children, after dose 1, there were 74 cases of medically significant wheezing (2.3%) among children given live attenuated vaccine, as compared with 48 cases (1.5%) among those given inactivated vaccine, with a significant adjusted rate difference of 0.77% (95% confidence interval [CI], 0.12 to 1.46). The increase in medically significant wheezing was seen primarily during the second, third, and fourth weeks after vaccination (Fig. 3 in the Supplementary Appendix). Among previously unvaccinated children 24 months of age or older, there was no significant difference in the rates of medically significant wheezing between the two groups. Among those younger than 24 months of age, 55 children (3.2%) in the live-attenuated-vaccine group and 34 children (2.0%) in the inactivated-vaccine group had medically significant wheezing after receipt of dose 1, with an adjusted difference of 1.18 (95% CI, 0.13 to 2.29). The difference in the incidence of medically significant wheezing was seen primarily in children less than 12 months of age (see Fig. 4 in the Supplementary Appendix), with 12 more episodes of wheezing after dose 1 in children in this age group who received live attenuated vaccine than in those who received inactivated vaccine (3.8% vs. 2.1%, P=0.08).

A review of hospital records for children less than 24 months of age who were hospitalized with medically significant wheezing indicated a

Table 2. Influenza Attack Rates in the According-to-Protocol Population.*

Variable	Similarity to Vaccine†	Live Attenuated Vaccine (N=3916)‡		Inactivated Vaccine (N=3936)§		Reduction in Attack Rate with Live Vaccine¶
		Cases	Attack Rate	Cases	Attack Rate	
		no.	%	*no.*	%	% *(95% CI)*
Virus	Well matched	53	1.4	93	2.4	44.5 (22.4 to 60.6)
A/H1N1		3	0.1	27	0.7	89.2 (67.7 to 97.4)
A/H3N2		0	0	0	0	—
B		50	1.3	67	1.7	27.3 (–4.8 to 49.9)
Age at first vaccination (any influenza virus)	Well matched					
6–23 mo		23	1.3	32	1.7	29.1 (–21.2 to 59.1)
24–35 mo		17	1.3	24	1.8	32.6 (–25.8 to 64.5)
36–59 mo		13	1.7	37	4.7	65.6 (36.3 to 82.4)
Previous vaccination (any influenza virus)	Well matched					
Yes		18	1.9	29	3.1	39.3 (–9.2 to 66.9)
No		35	1.2	64	2.1	46.9 (20.0 to 65.2)
Virus	Not well matched	102	2.6	245	6.2	58.2 (47.4 to 67.0)
A/H1N1		0	0	0	0	—
A/H3N2		37	0.9	178	4.5	79.2 (70.6 to 85.7)
B		66	1.7	71	1.8	6.3 (–31.6 to 33.3)
Virus	Regardless of match	153	3.9	338	8.6	54.9 (45.4 to 62.9)
A/H1N1		3	0.1	27	0.7	89.2 (67.7 to 97.4)
A/H3N2		37	0.9	178	4.5	79.2 (70.6 to 85.7)
B		115	2.9	136	3.5	16.1 (–7.7 to 34.7)

* Children had influenza-like illness and culture-positive infection. Modified CDC influenza-like illness was defined as the presence of an increased oral temperature (>100°F [37.8°C] or the equivalent) in the presence of cough, sore throat, runny nose, or nasal congestion occurring on the same or consecutive days. The analysis of the primary end point in subgroups (stratified according to age, vaccination status, and presence or absence of a history of recurrent wheezing) provided estimates of the relative efficacy of live attenuated vaccine of 24.0 to 65.6%, a finding consistent with the relative efficacy of 44.5% observed in the overall according-to-protocol population. Higher estimates of the relative efficacy of live attenuated vaccine, as compared with inactivated vaccine, against matched influenza strains were seen in 13 of the 15 countries in which matched strains were isolated.

† Viruses were characterized as antigenically similar to vaccine or not well matched to vaccine. Reference antiserum provided by the CDC was used to characterize isolates antigenically and a difference by a factor of 4 or more in the hemagglutination-inhibition titers was considered indicative of antigenic variation between two viruses.

‡ Four subjects had both influenza A/H3N2 and influenza B virus infections; two isolates could not be characterized as antigenically well matched or not well matched to vaccine virus antigen.

§ Two subjects had both influenza A/H1N1 and influenza B virus infections; six subjects had both influenza A/H3N2 and influenza B virus infections; five isolates could not be characterized as antigenically well matched or not well matched to vaccine virus antigen.

¶ The analysis of subjects in the intention-to-treat population confirmed the results in the according-to-protocol population. The observations were robust in all subgroups (stratified according to age, vaccination status, presence or absence of a history of recurrent wheezing, and country of residence). Among children 6 to 23 months of age, in whom the overall attack rates of influenza were 3.2% in the live-attenuated-vaccine group and 7.2% in the inactivated-vaccine group, the relative efficacy of live attenuated vaccine of 55.7% was significant.

Table 3. Incidence in the Safety Population of Medically Significant Wheezing within 42 Days after Receiving Vaccine.*

Variable	Live Attenuated Vaccine	Inactivated Vaccine	Adjusted Rate Difference (95% CI)†
	no./total no. of cases (%)		
All children (6–59 mo of age)			
Previously vaccinated			
After dose 1	19/933 (2.0)	17/947 (1.8)	0.03 (–1.24 to 1.38)
Not previously vaccinated			
After dose 1	74/3246 (2.3)	48/3226 (1.5)	0.77 (0.12 to 1.46)
After dose 2	73/3002 (2.4)	67/3034 (2.2)	0.20 (–0.56 to 0.97)
Children <24 mo‡			
Previously vaccinated			
After dose 1	7/267 (2.6)	3/269 (1.1)	1.34 (–1.11 to 4.30)
Not previously vaccinated			
After dose 1	55/1725 (3.2)	34/1706 (2.0)	1.18 (0.13 to 2.29)
After dose 2	57/1578 (3.6)	39/1595 (2.4)	1.15 (–0.04 to 2.38)
Children ≥24 mo‡			
Previously vaccinated			
After dose 1	12/666 (1.8)	14/678 (2.1)	–0.49 (–2.07 to 1.10)
Not previously vaccinated			
After dose 1	19/1521 (1.2)	14/1520 (0.9)	0.30 (–0.46 to 1.09)
After dose 2	16/1424 (1.1)	28/1439 (1.9)	–0.85 (–1.83 to 0.05)
Children with a history of recurrent wheezing (6–59 mo of age)			
Previously vaccinated			
After dose 1	10/98 (10.2)	7/78 (9.0)	1.08 (–8.52 to 10.26)
Not previously vaccinated			
After dose 1	12/173 (6.9)	12/161 (7.5)	–0.43 (–6.31 to 5.38)
After dose 2	10/148 (6.8)	14/140 (10.0)	–3.26 (–10.10 to 3.33)
Children without a history of recurrent wheezing (6–59 mo of age)			
Previously vaccinated			
After dose 1	9/835 (1.1)	10/869 (1.2)	–0.07 (–1.14 to 1.02)
Not previously vaccinated			
After dose 1	62/3073 (2.0)	36/3065 (1.2)	0.84 (0.21 to 1.50)
After dose 2	63/2854 (2.2)	53/2894 (1.8)	0.37 (–0.35 to 1.13)

* The health care provider documented the wheezing as accompanied by tachypnea, retractions, or dyspnea, an oxygen saturation of less than 95%, while breathing ambient air, or receipt of a new prescription for daily bronchodilators.

† Differences in rates were adjusted for the subject's age and the presence or absence of a history of recurrent wheezing.

‡ The proportion of subjects with medically significant wheezing who were younger than 24 months of age in the two study groups who had tachypnea, dyspnea, retractions, or hypoxemia after dose 1 was similar (27% in the live-attenuated-vaccine group and 26% in the inactivated-vaccine group). A total of 12 subjects younger than 24 months of age (9 [0.5%] and 3 [0.2%], respectively) were hospitalized in association with medically significant wheezing within 42 days after receiving a dose of vaccine. No child was treated in an intensive care unit, received mechanical ventilation, or died because of medically significant wheezing. The difference in the rate of medically significant wheezing after dose 1 among previously unvaccinated children 6 to 23 months of age occurred primarily among those who were 6 to 11 months of age (3.8% in the live-attenuated-vaccine group vs. 2.1% in the inactivated-vaccine group; adjusted rate difference, 1.61% [95% CI, –0.18 to 3.53]); among children 12 to 23 months of age who had medically significant wheezing (2.8% in the live-attenuated-vaccine group vs. 2.0% in the inactivated-vaccine group), the adjusted rate difference (0.9% [95% CI, –0.42 to 2.27]) was not significant.

Table 4. Medically Significant Wheezing, Serious Adverse Events, and Rates of Hospitalization According to Age Group, through 180 Days after the Last Dose of Vaccine.*

Age	Event	Live Attenuated Vaccine	Inactivated Vaccine
		no./total no. (%)	
6–11 mo	Medically significant wheezing	93/684 (13.6)	71/683 (10.4)
	Any serious adverse event	44/684 (6.4)	23/683 (3.4)
	Hospitalization for any cause	42/684 (6.1)	18/683 (2.6)
12–59 mo	Medically significant wheezing	272/3495 (7.8)	255/3490 (7.3)
	Any serious adverse event	92/3495 (2.6)	105/3490 (3.0)
	Hospitalization for any cause	88/3495 (2.5)	101/3490 (2.9)
6–59 mo	Medically significant wheezing	365/4179 (8.7)	326/4173 (7.8)
	Any serious adverse event	136/4179 (3.3)	128/4173 (3.1)
	Hospitalization for any cause	130/4179 (3.1)	119/4173 (2.9)

* Medically significant wheezing, serious adverse events, and hospitalizations were analyzed from the day of the first dose through 180 days after the last dose of vaccine (for a breakdown according to causes of hospitalization and diagnostic category, see Table 4 in the Supplementary Appendix).

similar severity of illness among those receiving live attenuated vaccine and those receiving inactivated vaccine and in the duration of stay in the hospital, associated diagnoses, and treatment (Table 2 and Table 3 in the Supplementary Appendix). Beyond 42 days after vaccination, the rates of medically significant wheezing did not differ significantly between the two groups among children less than 24 months of age (7.6% in the live-attenuated-vaccine group and 7.1% in the inactivated-vaccine group). The proportion of those less than 24 months of age who had medically significant wheezing within 42 days after vaccination and who had at least one additional medically significant wheezing episode during the study period was similar in the two groups (32% in the live-attenuated-vaccine group and 28% in the inactivated-vaccine group); the proportion of these children who had two or more additional medically significant wheezing episodes was 4.3% and 5.3%, respectively.

The incidence of serious adverse events in the two groups was similar (136 in the live-attenuated-vaccine group and 128 in the inactivated-vaccine group) (Table 4). Six serious adverse events in the live-attenuated-vaccine group (bronchiolitis in two children, and asthma exacerbation, wheezing, acute gastroenteritis, and reactive airway disease in one child each) and five in the inactivated-vaccine group (pneumonia, wheezing, febrile convulsion, febrile convulsion and pneumonia, and viral gastroenteritis in one child each) were considered by the investigator, who was unaware of the treatment assignments, to be potentially related to the study vaccine. One death occurred in each vaccine group — one because of aspiration of a foreign body and one because of a house fire. New diagnoses of chronic diseases assessed within 180 days after the last dose of vaccine were infrequent in the two groups, with overall incidence rates of 1.7% in the live-attenuated-vaccine group and 1.3% in the inactivated-vaccine group.

A post hoc analysis for the study period through 180 days after the last dose of vaccine showed that children 6 to 11 months of age were hospitalized for any cause at a higher rate in the live-attenuated-vaccine group than in the inactivated-vaccine group (6.1% vs. 2.6%; difference in rate, 3.5% [95% CI, 1.4 to 5.8]) (Fig. 2 and Table 4, and Table 4 in the Supplementary Appendix). The rate of hospitalization for respiratory diagnoses in this age group was 3.2%, as compared with 1.2% in the two groups, respectively (absolute difference, 2.0% [95% CI, 0.5 to 3.8]). The differences in hospitalization rates among children 12 to 23 months of age (3.2% in the live-attenuated-vaccine group and 3.5% in the inactivated-vaccine group) and among children 24 to 59 months of age were not significant. Although not statistically significant, there was a trend toward a higher rate of hospitalization for any cause among children receiving live attenuated vaccine who were 6 to 47 months of age and had a history

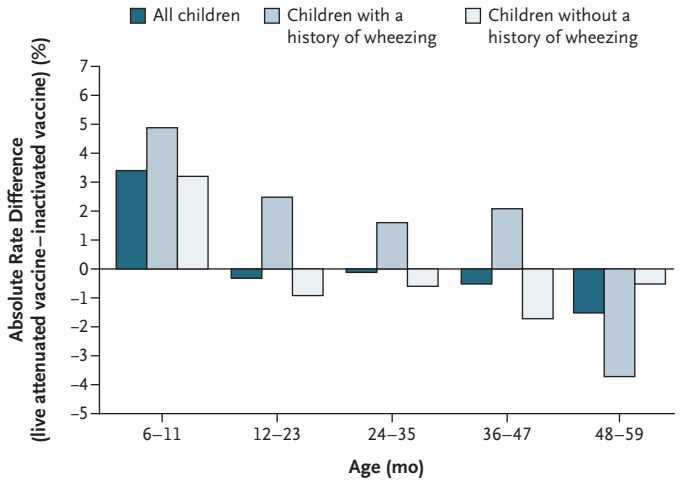

Figure 2. Difference in Rates of Hospitalization between the Two Vaccine Groups, According to Age and the Presence or Absence of a History of Wheezing Illness before Vaccination.

Among children 6 to 11 months of age, for the comparison between live attenuated vaccine and inactivated vaccine among all children regardless of whether there was a history of wheezing illness, P=0.002, and for the comparison between live attenuated vaccine and inactivated vaccine among children with a history of wheezing illness, P=0.004. Among children 48 to 59 months of age, for the comparison between live attenuated vaccine and inactivated vaccine among children without a history of wheezing, P=0.039. For all other comparisons, P>0.05. P values were calculated by inverting two one-sided tests on the basis of asymptotic methods and with the use of StatXact software, version 6.2 (Statistical Solutions).

of wheezing than among those receiving inactivated vaccine who were in the same age group and had a history of wheezing. Among children 12 to 59 months of age who did not have a history of wheezing, the rates of hospitalization for any cause were lower in the live-attenuated-vaccine group than in the inactivated-vaccine group (P=0.07).

DISCUSSION

Many believe that the successful control of annual influenza epidemics depends on vaccinating a high proportion of children.[16-18] As U.S. public health authorities move toward this goal, highly effective vaccines are needed, including vaccines with efficacy against antigenically drifted influenza strains. The live attenuated influenza vaccine we used has many of the characteristics that are desirable for the control of epidemic influenza. In addition to its high acceptability because of the mode of administration, the significantly higher efficacy of this live attenuated vaccine than of the licensed inactivated vaccine suggests that it can play an important role in the control of influenza. This higher efficacy was seen not only for well-matched strains but also for viruses that were antigenically drifted from the antigen in the vaccine.

Some earlier studies have suggested the potential for wheezing in young children after receipt of live attenuated influenza vaccine,[15] whereas others have not.[10,16] Our comprehensive, prospective safety study showed an increased risk of medically significant wheezing (within 42 days after vaccination) among recipients of live attenuated vaccine who were younger than 12 months of age. The pathogenesis of wheezing in some children given live attenuated vaccine remains unknown, although in our study, the wheezing developed after the peak of viral replication and at the time when immune responses to the viruses are expected — that is, during weeks 2, 3, and 4 after vaccination.

The incidence of serious adverse events did not differ significantly between the two groups. However, in post hoc analyses, rates of hospitalization for any cause among infants 6 to 11 months of age were significantly higher in the live-attenuated-vaccine group than in the inactivated-vaccine group. In addition, higher, but not significantly higher, rates of hospitalization were observed among children in the age groups of 12 to 23 months, 24 to 35 months, and 36 to 47 months who had a history of wheezing illness before entering the study. These observations require further study. Children 12 months of age or older who had no history of wheezing illness before vaccination and who received live attenuated vaccine had lower rates of hospitalization for any cause during the study than those who received inactivated vaccine. On the basis of our results, the risk–benefit ratio for live attenuated vaccine appears favorable among children 12 to 47 months of age who have no history of wheezing.

Until additional data are available, the observations related to medically significant wheezing and rates of hospitalization will restrict the use of live attenuated vaccine in children younger than 1 year and in children 12 to 47 months of age who have a history of asthma or wheezing. Additional studies to determine the optimal use of both vaccines in infants and young children are warranted.

The high influenza attack rate among children in the inactivated-vaccine group who were less than 12 months of age and had a history of wheezing (14%) suggests that inactivated vaccine has low efficacy in this group. Further studies might show whether an initial dose of inactivated vaccine followed by live attenuated vaccine would provide optimal protection for children younger than 1 year of age while also ensuring maximum vaccine safety.

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APPENDIX

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Safety of cold-adapted live attenuated influenza vaccine in a large cohort of children and adolescents

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Objective. **To determine the safety of cold-adapted trivalent intranasal influenza virus vaccine (CAIV) in children and adolescents.**

Study design. **A randomized, double blind, placebo-controlled safety trial in healthy children age 12 months to 17 years given CAIV (FluMist; MedImmune Vaccines, Inc.) or placebo (randomization, 2:1). Children <9 years of age received a second dose of CAIV or placebo 28 to 42 days after the first dose. Enrolled children were then followed for 42 days after each vaccination for all medically attended events. Prespecified outcomes included 4 prespecified diagnostic groups and 170 observed individual diagnostic categories. The relative risk and the 2-sided 90% confidence interval were calculated for each diagnostic group and individual category by clinical setting, dose and age. More than 1500 relative risk analyses were performed.**

Results. **A total of 9689 evaluable children were enrolled in the study. Of the 4 prespecified diagnostic categories (acute respiratory tract events, systemic bacterial infection, acute gastrointestinal tract events and rare events potentially associated with wild-type influenza), none was associated with vaccine. Of the biologically plausible individual diagnostic categories, 3, acute gastrointestinal events, acute respiratory events and abdominal pain, had different analyses that demonstrated increased and decreased relative risks, making their association with the vaccine unlikely. For reactive airway disease a significant increased relative risk was observed in children 18 to 35 months of age with a relative risk of 4.06 (90% confidence interval, 1.29 to 17.86) in this age group. The individual diagnostic categories of upper respiratory infection, musculoskeletal pain, otitis media with effusion and adenitis/adenopathy had at least one analysis that achieved a significant increased risk ratio. All of these events were infrequent.**

Conclusion. **CAIV was generally safe in children and adolescents. The observation of an increased risk of asthma/reactive airway disease in children <36 months of age is of potential concern. Further studies are planned to evaluate the risk of asthma/reactive airway disease after vaccine.**

INTRODUCTION

Influenza A and B viruses are a major cause of respiratory tract illnesses in children.[1] Recent studies have demonstrated increased risk of hospitalizations because of influenza in young children.[2, 3] Children can also act as a reservoir for transmission of virus to other household members and to the general population.[4–6] For 2002 to 2003 the ACIP encouraged the use of the influenza vaccine in children 6 to 23 months of age.[7] The lack of a rapid and easy means of administering influenza vaccine on an annual basis to children may slow down the implementation of this more widespread vaccination program. Live attenuated, cold-adapted, trivalent intranasal influenza virus vaccine (CAIV) could represent an alternative approach to influenza vaccination in children and adults.

CAIV is produced by genetic reassortment between a wild-type influenza virus and an attenuated master donor virus for each 6:2 reassortant strain to be included in the vaccine. Each vaccine virus derives two gene segments encoding the hemagglutinin and neuraminidase from a wild-type influenza virus, and the remaining six gene segments encoding proteins are responsible for cold adaptation, temperature sensitivity and attenuation from the master donor virus. The vaccine is grown in the allantoic cavity of pathogen-free eggs and is a combination of two influenza A strains and one influenza B strain.[8–11] Prior studies have shown that CAIV was effective in preventing influenza

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and influenza-related otitis media in children.[12, 13] It was the purpose of this study to evaluate the safety of CAIV containing influenza A and influenza B strains in a study population of ~10 000 children with medical utilization in the hospital, clinic and emergency department as outcomes.

METHODS

Vaccine and placebo. MedImmune Vaccines, Inc., supplied CAIV in frozen single dose intranasal applicators. Each 0.5-ml dose was delivered as an intranasal spray. Each applicator had a dose divider that was to allow for the delivery of approximately one-half the contents to each nostril. Each dose of CAIV contained 10^7 median tissue culture infectious dose of each of the three 6:2 reassortant strains of influenza recommended by the Food and Drug Administration for the 1999 to 2000 influenza season: A/Beijing/262/95 (H1N1); A/Sydney/05/97 (H3N2); and B/Yamanashi/166/98 influenza strains. Vaccine and placebo contained allantoic fluid containing sucrose-phosphate-glutamate.[14–16]

Subjects. The protocol was reviewed and approved by the Kaiser Permanente Institutional Review Board. Healthy children and adolescents 1 through 17 years of age were eligible to enroll in the study. To be eligible children must not have received the 2000 to 2001 formulation of trivalent influenza vaccine. Children also could not have received any live virus vaccine within 1 month of enrollment or any inactivated vaccine within 2 weeks of enrollment in this study. Children were excluded from the study if they had a history of egg allergy, a history of asthma (by parent report), a fever (>100.0°F oral) or respiratory illness within 72 h of enrollment. In addition children with immunodeficiency or children taking immunosuppressive agents were excluded.

Study design. This was a randomized, double blind, placebo-controlled study. The randomization ratio was 2:1 (CAIV to placebo). Children <9 years of age received a second dose of the same agent 28 to 42 days after the first dose. Enrollment began in October 2000 and was completed at the end of December 2000. Enrolled children were then followed for 42 days after each vaccination for any medically attended event or serious adverse event (SAE).

Data collection and statistical analysis. Within Kaiser Permanente (KP) children are assigned a unique medical record number that identifies them for life. Kaiser Permanente maintains automated clinical information system databases that contain diagnoses for all clinic, emergency and hospital visits. In addition, because KP is self-insured, claims for utilization outside of KP are also available from computerized data. For the purposes of this study, a study population database was created from the vaccination logs submitted by study nurses at the 31 participating sites. On a weekly basis this database was linked with utilization databases to identify any hospitalizations, emergency visits or clinic visits within 42 days of receipt of a dose of vaccine. The investigators reviewed each utilization to confirm the diagnosis and assess severity and possible relationship to vaccine. For serious adverse events (SAEs), additional follow-up was obtained through contact with the patient's personal physician, with their parents and through medical record review.

Outcomes in this study included four prespecified diagnostic groupings and an analysis that included all observed diagnostic categories. Rates of events were compared for each diagnostic group and individual diagnostic category, and a rate ratio was calculated. The first event for each diagnosis for each child in each observation window was used. The relative risk (RR) and its two-sided 90% confidence interval (CI) were calculated according to the midprobability exact binomial method adjusted for follow-up time.[17] The four prespecified diagnostic groups included acute respiratory tract events (mastoiditis, sinusitis, laryngitis, tracheitis, laryngotracheitis, epiglottitis, croup, bronchitis, bronchiolitis, viral pneumonia, bronchopneumonia with unspecified organism, pneumonia with unspecified organism, influenza with pneumonia, influenza with other respiratory manifestations, extrinsic asthma, intrinsic asthma, unspecified asthma, wheezing, pulmonary congestion, shortness of breath), systemic bacterial infection, acute gastrointestinal tract events and rare events potentially associated with wild-type influenza (encephalitis, Reye syndrome, myocarditis and pericarditis, Guillain-Barré syndrome, polymyositis and seizures).

Comparisons were made for each setting separately and for all three settings combined, for each dose separately and for both doses combined, as well as for each of four age groups: 1 to 8 years of age, 9 to 17 years of age, 12 to 17 months of age and 18 to 35 months of age and all ages combined. No adjustment was made for these multiple comparisons in the statistical analysis. A statistically significant increase in the CAIV group was declared if the lower bound of the 90% CI for the rate ratio exceeded 1. Detecting significant decreases in the CAIV group was not a goal of the trial. Such results are presented for contextual purposes.

RESULTS

Between October 2, 2000 and December 22, 2000, 9689 evaluable children were enrolled. Of these, 3769 children 1 to 8 years of age received CAIV and 1868 received placebo, whereas in children 9 to 18 years of age, 2704 children received CAIV and 1348 received placebo. Overall 86.6% of the younger children received both a first and second dose. CAIV participants were 51% female compared with 50% in controls. The popu-

TABLE 1. Participants who experienced a medical adverse event, by utilization setting and treatment group

Utilization Setting	CAIV (N = 6473)	Placebo (N = 3216)
Hospital*	31 (0.5)†	19 (0.6)
Emergency Department	186 (2.9)	104 (3.2)
Clinic	2305 (35.6)	1191 (37.0)

* Hospitalizations <24 h in duration were not necessarily reported as SAEs.
† Numbers in parentheses, percent.

lation was 6% African-American, 55% White, 20% Hispanic, 10% Asian and 9% other.

Overall utilization rates by setting (emergency room, clinic, hospital) are summarized in Table 1. In comparing overall numbers of events, it is important to note that because of the 2:1 randomization, twice the number of events is expected in the CAIV group than in the placebo group. The percentages of children with utilization in the hospital, emergency room and clinics are almost identical in the two groups.

The rates of utilization for the prespecified diagnostic groups are shown in Table 2 for all utilization settings combined. There were no significant increases for these outcomes in vaccinees when utilization at all settings was combined; however, significantly elevated rates were observed in some analyses in the CAIV group for acute respiratory tract events and for acute gastrointestinal events when analyzed for individual utilization settings as shown in Table 3. Of note, but not shown, is that significantly decreased rates were observed in 16 comparisons for these prespecified outcomes by individual utilization setting, including 8 analyses for acute respiratory events and 8 analyses for acute gastrointestinal events.

Medical utilization occurred for 170 unique individual diagnostic categories. When accounting for the comparisons by dose, age and setting, >1500 statistical comparisons were made in this study. The comparisons for which we observed a statistically elevated risk ratio are shown in Table 4. During the 42-day observation period, significantly elevated risks were observed in one or more comparisons for asthma, abdominal pain, upper respiratory infection (URI), musculoskeletal pain, otitis media with effusion and adenitis/adenopathy as well as for several diagnostic categories not thought to have biologic likelihood. Further evaluation was conducted for events thought to have a biologically plausible association.

Overall asthma diagnoses were observed in 0.9% of CAIV recipients and 0.9% of controls. Elevated risk ratios were observed in 4 of the 31 separate comparisons, all of these in children 18 to 35 months of age. In this age group there were 16 asthma events (all settings and doses combined) in CAIV recipients and 2 in placebo recipients (RR 4.06; 90% CI 1.29 to 17.86). When the time association for asthma was evaluated (Fig. 1), no consistent time association of these events with receipt of vaccine was noted. All of these events occurred in the clinic except for one in the emergency department. No child required hospitalization. Treatment consisted of beta-2 agonist for 94% (17 of 18), antibiotics for 56% (10 of 18), systemic corticosteroids for 33% (6 of 18) and inhaled corticosteroids for 17% (3 of 18). The data were subsequently also evaluated by combining the diagnoses of asthma, shortness of breath and wheezing. The relative risks were no longer significant using this combined diagnostic category, peaking at RR = 2.19; 90% CI 0.90 to 6.00 after the first dose of vaccine in children 12 to 35 months (17 of 904 for the vaccine group and 4 of 465 for the placebo group).

Although history of asthma or possible asthma according to the parent was an exclusion criteria for participation in the trial, 7 of the 16 (44%) CAIV participants 18 to 35 months of age with the diagnosis of asthma had a prior visit for asthma in their medical record. To further evaluate a possible increased risk of asthma in CAIV recipients with a prior history of asthma, the electronic medical record for all participants was reviewed to identify children with a visit before the study for asthma/reactive airway disease. This review revealed 8.8% of study participants with a history of asthma/reactive airway disease. In these children receipt of CAIV was not associated with an increased risk of an asthma diagnosis in the 42 days after vaccine with a RR of 1.11; 90% CI 0.59 to 2.14.

In all settings combined, abdominal pain occurred in

TABLE 2. Rates and relative risks for the prespecified grouped diagnoses: all ages, all doses and all utilization settings combined*

Prespecified Grouped Diagnosis	No. of Participants		Rate/1000 Person-mo† (CAIV/Placebo)	Binomial Relative Risks†
	CAIV (N = 6473)	Placebo (N = 3216)		
Acute respiratory tract events	1042	577	82.24/91.81	0.90 (0.82, 0.98)‡
Systemic bacterial infections	0	0	0/0	NE
Acute gastrointestinal tract events	161	95	12.71/15.12	0.84 (0.68, 1.04)
Rare events potentially related to influenza§	8	3	0.63/0.48	1.32 (0.44, 4.62)

* A significantly increased risk is defined by a lower bound of the 90% CI >1, and a significantly decreased risk is defined by an upper bound of the 90% CI <1.
† Based on first event.
‡ Numbers in parentheses, 90% CI.
§ Events that occurred in this category included seizure(s) (1 in CAIV, 0 in placebo), febrile seizure (5 in CAIV, 1 in placebo), and epilepsy (2 in CAIV, 2 in placebo).
NE, not estimable because of zero events.

TABLE 3. Prespecified grouped diagnoses associated with significantly increased risk for CAIV recipients when analyzed by age group, utilization setting, and dose*

Prespecified Grouped Diagnosis	Age (yr)	Utilization Setting†	Dose‡	No. of Participants		Rate/1000 Person-mo§ (CAIV/Placebo)	Binomial Relative Risks§
				CAIV (n/N)	Placebo (n/N)		
Acute respiratory tract events	9–17	ED	1¶	10/2704	0/1347	2.66/0	NE (1.92, NE)‖
Acute gastrointestinal tract events	9–17	ED	1¶	10/2704	0/1347	2.66/0	NE (1.92, NE)

* A significantly increased risk is defined by a lower bound of the 90% CI >1.
† Analyses were performed separately by setting (clinic, ED or hospital) and combined across the three settings.
‡ Analyses were performed separately by dose (one or two) and combined across doses.
§ Based on participant incidence.
¶ Participants 9 to 17 years of age received a one dose regimen.
‖ Numbers in parentheses, 90% CI.
NE, not estimable because of D events occurring in the placebo group, ED, Emergency Department.

TABLE 4. Medical adverse events associated with statistically significantly increased risk in CAIV recipients*

Medical Adverse Events	Age	Utilization Setting†	Dose‡	No. of Participants		Rate per 1000-Person mo§ (CAIV/Placebo)	Binomial Relative Risks§
				CAIV (n/N)	Placebo (n/N)		
URI	1–17 yr	ED	1	11/6473	0/3216	1.35/0	NE (2.14, NE)¶
URI	1–8 yr	ED	1	9/3769	0/1869	2.05/0	NE (1.70, NE)
URI	18–35 mo	Combined	Combined	153/728	60/369	88.90/68.64	1.30 (1.01, 1.67)
Asthma	18–35 mo	Clinic	Combined	15/728	2/369	8.72/2.29	3.81 (1.20, 16.82)
Asthma	18–35 mo	Clinic	1	9/728	0/369	10.54/0	NE (1.74, NE)
Asthma	18–35 mo	Combined	Combined	16/728	2/369	9.30/2.29	4.06 (1.29, 17.86)
Asthma	18–35 mo	Combined	1	10/728	0/369	11.71/0	NE (1.95, NE)
Musculoskeletal pain	18–35 mo	Clinic	Combined	7/728	0/339	4.07/0	NE (1.30, NE)
Musculoskeletal pain	18–35 mo	Clinic	1	7/728	0/369	8.20/0	NE (1.30, NE)
Abdominal pain	1–17 yr	ED	Combined	14/6473	1/3216	1.11/0.16	6.94 (1.52, 73.81)
Abdominal pain	9–17 yr	ED	1‖	7/2704	0/1347	1.86/0	NE (1.28, NE)
Otitis media with effusion	1–8 yr	Clinic	2	49/3242	15/1600	10.86/6.73	1.61 (1.001, 2.67)
Adenitis/adenopathy	9–17 yr	Clinic	1‖	8/2704	0/1347	2.13/0	NE (1.49, NE)
Benign lesion	1–8 yr	Clinic	1	14/3769	2/1869	3.19/0.92	3.48 (1.08, 15.42)
Elective procedure	1–8 yr	Clinic	2	27/3242	6/1600	5.99/2.69	2.22 (1.08, 4.95)
Enuresis	1–17 yr	Clinic	Combined	15/6473	2/3216	1.18/0.32	3.72 (1.17, 16.42)
Enuresis	1–8 yr	Clinic	Combined	10/3769	1/1869	1.12/0.23	4.95 (1.04, 53.92)
Enuresis	1–8 yr	Clinic	2	7/3242	0/1600	1.55/0	NE (1.27, NE)
Speech delay	1–17 yr	Clinic	1	8/6473	0/3216	0.98/0	NE (1.49, NE)
Speech delay	1–8 yr	Clinic	1	7/3769	0/1869	1.59/0	NE (1.28, NE)
UTI	9–17 yr	Clinic	1‖	15/2704	1/1347	3.98/0.53	7.47 (1.65, 79.06)
Seborrhea	1–17 yr	Clinic	Combined	6/6473	0/3216	0.47/0	NE (1.06, NE)
Otitis externa	1–8 yr	Clinic	1	6/3769	0/1869	1.37/0	NE (1.06, NE)
Warts	1–17 yr	Clinic	Combined	57/6473	17/3216	4.50/2.71	1.66 (1.06, 2.66)

* A significantly increased risk is defined by a lower bound of the 90% CI >1.
† Analyses were performed separately by setting (clinic, ED or hospital) for all listed medical adverse events and combined across the three settings (Combined) for URI, asthma and abdominal pain.
‡ Analyses were performed separately by dose (1 or 2) and combined across doses (combined).
§ Based on participant incidence.
¶ Numbers in parentheses, 90% CI.
‖ Participants 9 to 17 years of age received a 1 dose regimen.
NE, not estimable because of 0 events occurring in the placebo group; ED, Emergency Department; UTI, urinary tract infection.

0.7% (47 of 6473) of the vaccine group and 0.8% (26 of 3216) of placebo recipients. However, in 2 of 26 analyses, there was an elevated risk ratio for abdominal pain, both events in the emergency department (Table 4). There were 14 children with abdominal pain in the emergency department in the CAIV group compared with one in the placebo group. No consistent time association was observed for abdominal pain in the emergency department setting. To evaluate a possible increased risk of potentially severe medical events that can present with abdominal pain, medical utilization for the following diagnostic categories was identified: appendicitis; gastroenteritis; intestinal obstruction; mesenteric adenitis; pancreatitis; intestinal perforation; ulcer; volvulus; and intussusception. Apart from gastroenteritis, where a relative risk of 0.87 was observed (90% CI 0.60, 1.11), 1 event each was observed for appendicitis and "rule-out" appendicitis. Review of the medical record for the child with appendicitis revealed onset of abdominal pain before receipt of CAIV.

The diagnostic category of URI was significant for increased risk in 3 of 41 comparisons. The comparison containing the greatest number of events was 18 to35 month olds in the combined setting. The RR was 1.30, and the 90% CI was 1.01 to 1.67. Over the 42-day observation period, there was no temporal relationship with vaccination.

There was at least one analysis demonstrating increased risk for the diagnostic categories of musculo-

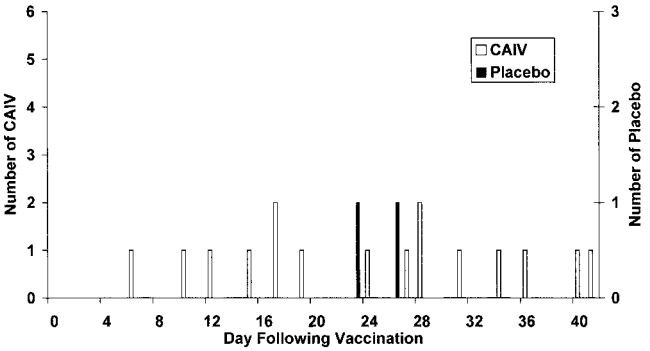

FIG. 1. Asthma in all settings combined by day after vaccination for participants 18 to 35 months of age, all doses combined. Note different scale for the Y axis (number of events) used to account for 2:1 randomization ratio.

skeletal pain, otitis media with effusion and adenitis/adenopathy. In each of these categories, the number of events was small. When these diagnostic categories were evaluated for a temporal relationship with vaccination, no consistent time association was observed. However, because otitis media with effusion is a chronic disorder without an acute onset, evaluating time association therefore is difficult.

When the children with enuresis, speech delay and seborrhea were reviewed, each of these children had a history of these conditions before receipt of vaccine. The majority of children with otitis externa and urinary tract infection had an etiologic agent identified. The children hospitalized for elective procedures were each receiving treatment for conditions identified before trial participation.

The diagnostic categories with observed decreased risk ratios are shown in Table 5. As can be seen, decreased relative risks were observed for 51 comparisons compared with 24 with elevated risk ratios. Some of the comparisons with significantly decreased relative risks included the same diagnostic categories for which elevated risks were observed in other comparisons tending to decrease the likelihood of a true causal relationship with vaccination.

The rate of SAE was 0.2% and equally distributed between vaccine (13 of 6473) and placebo (7 of 3216). No SAE in vaccine recipients was judged related to CAIV.

DISCUSSION

Several studies have evaluated the efficacy of cold-adapted intranasal influenza vaccines in children.[12, 13, 18–22] A recent study also reported on the safety of the CAIV in children.[22] Our study was designed exclusively to evaluate the safety of this vaccine in children and adolescents. In this study there was utilization for 170 unique diagnoses resulting in >1500 statistical analyses (Tables 4 and 5). Therefore one would expect some observations to achieve statistical significance by chance alone. Many of the diagnoses that achieved significance were not thought to be biologically plausible by the investigators.

There were six individual diagnoses that were associated with increased risk and were believed to be biologically plausible: asthma; URI; abdominal pain; musculoskeletal pain; adenitis/adenopathy; and otitis media with effusion.

We observed an increased risk of asthma in young children 18 to 35 months of age after receipt of CAIV. It is possible that the long period of replication, up to 21 days, observed by Vesikari et al.[23] could also be associated with an increased risk of reactive airway disease in this age group. This increased risk of asthma with CAIV has potential significance for the use of vaccine in young children with a history of or who are predisposed to asthma. It is possible that use of vaccine in children <3 years of age, who are more likely to be influenza-naive, could be associated with induction of wheezing. Additional studies in asthmatics and in young children to evaluate a possible risk of reactive airway disease are warranted. The CAIV vaccine has been licensed and is now available for healthy individuals 5 to 49 years of age for the 2003 to 2004 influenza virus season. Because of the increased risk for medically attended asthma visits observed in this study in young children, the manufacturer did not seek an initial indication in children <5 years of age.

There was an increased risk of abdominal pain in the vaccine group in the emergency department setting but a decreased risk in the clinic and in the combined settings. The lack of close temporal relationship between abdominal pain and vaccination also makes it unlikely that the vaccine is a cause of abdominal pain.

The increased risk observed in the vaccine group for musculoskeletal pain, adenitis/adenopathy and otitis media with effusion were thought to be biologically plausible. However, in each case it was reported in only a small number of the total analyses for each diagnosis, and the incidence of each diagnosis was low (2.13 visits/1000 person-months for adenitis/adenopathy, 8.20 visits/1000 person-months for musculoskeletal pain and 10.86 visits/1000 person-months for otitis media with effusion in the vaccine group for the analysis identified as at increased risk). The CAIV may be associated with these diagnoses, but its impact appears small.

Conjunctivitis did not appear to be at increased risk during the 42-day observation period (RR 0.65; 90% CI 0.44 to 0.96), but on evaluation of the first 14 days postvaccination it did appear to have an increased risk. This evaluation was conducted because of the close proximity of the eye to the administration site. This risk occurred for both vaccine doses and was most significant for younger children. The overall number of conjunctivitis events was small: 15 of 2716 vaccine

TABLE 5. Medical adverse events associated with statistically significantly decreased risk in CAIV recipients*

Medical Adverse Events	Age	Utilization Setting†	Dose‡	No. of Participants		Rate/1000 Person-mo§ (CAIV/ Placebo)	Binomial Relative Risks§
				CAIV (*n*/*N*)	Placebo (*n*/*N*)		
ADD	1–8 yr	Clinic	2	5/3242	7/1600	1.11/3.14	0.35 (0.13, 0.94)¶
Abdominal pain	1–8 yr	Clinic	1	8/3769	11/1869	1.82/5.04	0.36 (0.16, 0.78)
Abdominal pain	1–8 yr	Combined	1	10/3769	12/1869	2.28/5.50	0.41 (0.20, 0.85)
Acute gastroenteritis	1–17 yr	Clinic	1	37/6473	28/3216	4.54/6.90	0.66 (0.44, 0.997)
Acute gastroenteritis	12–17 mo	Clinic	1	0/171	3/90	0/28.29	0 (0, 0.61)
Acute gastroenteritis	12–17 mo	Combined	1	0/171	3/90	0/28.29	0 (0, 0.61)
Behavioral disorder	1–8 yr	Clinic	2	2/3242	5/1600	0.44/2.24	0.20 (0.04, 0.78)
Conjunctivitis	1–8 yr	Clinic	2	42/3242	32/1600	9.31/14.36	0.65 (0.44, 0.96)
Conjunctivitis	1–8 yr	Combined	2	42/3242	32/1600	9.31/14.36	0.65 (0.44, 0.96)
Constipation	1–17 yr	Clinic	1	15/6473	15/3216	1.84/3.70	0.50 (0.27, 0.92)
Constipation	1–17 yr	Combined	1	15/6473	15/3216	1.84/3.70	0.50 (0.27, 0.92)
Constipation	9–17 yr	Clinic	1‖	1/2704	6/1347	0.27/3.20	0.08 (0.01, 0.44)
Constipation	9–17 yr	Combined	1‖	1/2704	6/1347	0.27/3.20	0.08 (0.01, 0.44)
Contact dermatitis	1–8 yr	Clinic	Combined	16/3769	15/1869	1.80/3.40	0.53 (0.29, 0.96)
Cough	1–17 yr	Clinic	Combined	30/6473	24/3216	2.37/3.82	0.62 (0.39, 0.98)
Cough	1–17 yr	Combined	Combined	30/6473	24/3216	2.37/3.82	0.62 (0.39, 0.98)
Diarrhea	1–17 yr	Clinic	1	6/6473	8/3216	0.74/1.97	0.37 (0.15, 0.92)
Diarrhea	1–8 yr	Clinic	1	5/3769	7/1869	1.14/3.21	0.35 (0.13, 0.95)
Eczema	12–17 mo	Clinic	Combined	0/171	3/90	0/14.43	0 (0, 0.60)
Febrile Illness	1–17 yr	Clinic	Combined	9/6473	13/3216	0.71/2.07	0.34 (0.16, 0.70)
Febrile Illness	1–8 yr	Clinic	Combined	8/3769	12/1869	0.90/2.72	0.33 (0.15, 0.70)
Febrile Illness	1–8 yr	Clinic	2	2/3242	6/1600	0.44/2.69	0.16 (0.03, 0.62)
Gingivitis	1–17 yr	Clinic	1	5/6473	7/3216	0.61/1.73	0.36 (0.13, 0.95)
Gingivitis	1–17 yr	Clinic	Combined	6/6473	9/3216	0.47/1.43	0.33 (0.13, 0.80)
Gingivitis	1–8 yr	Clinic	Combined	6/3769	8/1869	0.67/1.81	0.37 (0.15, 0.92)
Gynecologic disorder	9–17 yr	Clinic	1	6/2704	9/1347	1.59/4.80	0.33 (0.13, 0.80)
Migraine	9–17 yr	Clinic	1	4/2704	6/1347	1.06/3.220	0.33 (0.11, 0.98)
Otitis media	1–8 yr	ED	2	9/3242	10/1600	2.00/4.49	0.44 (0.20, 0.96)
Pharyngitis	1–8 yr	Clinic	2	60/3242	43/1600	13.30/19.30	0.69 (0.50, 0.99)
Pharyngitis	1–8 yr	Combined	2	62/3242	43/1600	13.74/19.30	0.71 (0.51, 0.99)
Pharyngitis	1–8 yr	Clinic	Combined	123/3769	78/1869	13.81/17.69	0.78 (0.62, 0.99)
Pharyngitis	1–8 yr	Combined	Combined	125/3769	79/1869	14.04/17.91	0.78 (0.62, 0.99)
Thrush	1–8 yr	Clinic	2	3/3242	7/1600	0.67/3.14	0.21 (0.06, 0.66)
Thrush	1–8 yr	Clinic	Combined	8/3769	9/1869	0.90/2.04	0.44 (0.19, 0.997)
Tonsillitis	1–17 yr	Clinic	1	1/6473	6/3216	0.12/1.48	0.08 (0.01, 0.43)
Tonsillitis	1–17 yr	Combined	1	2/6473	6/3216	0.25/1.48	0.17 (0.03, 0.62)
Tonsillitis	1–17 yr	Clinic	Combined	2/6473	6/3216	0.16/0.95	0.17 (0.03, 0.62)
Tonsillitis	1–17 yr	Combined	Combined	3/6473	6/3216	0.24/0.95	0.25 (0.07, 0.80)
Tonsillitis	1–8 yr	Clinic	1	1/3769	6/1869	0.23/2.75	0.08 (0.01, 0.43)
Tonsillitis	1–8 yr	Combined	1	1/3769	6/1869	0.23/2.75	0.08 (0.01, 0.43)
Tonsillitis	1–8 yr	Clinic	Combined	2/3769	6/1869	0.22/1.36	0.17 (0.03, 0.62)
Tonsillitis	1–8 yr	Combined	Combined	2/3769	6/1869	0.22/1.36	0.17 (0.03, 0.62)
Trauma	1–17 yr	ED	Combined	73/6473	51/3216	5.76/8.12	0.71 (0.53, 0.96)
Trauma	1–17 yr	ED	1	49/6473	36/3216	6.01/8.87	0.50 (0.28, 0.87)
Trauma	1–8 yr	ED	1	18/3769	18/1869	4.10/8.25	0.63 (0.43, 0.93)
Trauma	1–8 yr	ED	Combined	42/3769	33/1869	4.72/7.48	0.73 (0.60, 0.91)
Viral syndrome	1–17 yr	Clinic	Combined	154/6473	104/3216	12.16/16.55	0.56 (0.40, 0.77)
Viral syndrome	1–8 yr	Clinic	2	54/3242	48/1600	11.97/21.54	0.56 (0.40, 0.77)
Viral syndrome	1–8 yr	Clinic	Combined	115/3769	81/1869	12.91/18.37	0.70 (0.55, 0.89)
Viral syndrome	18–35 mo	Clinic	2	12/622	13/317	13.84/29.42	0.47 (0.24, 0.92)
Well care/reassurance/FU	1–8 yr	ED	1	4/3769	7/1869	0.91/3.21	0.28 (0.09, 0.81)

* A significantly decreased risk is defined by an upper bound of the 90% CI <1.

† Analyses were performed separately by setting (clinic, ED or hospital) for all listed medical adverse events and combined across the three settings (Combined) for URI, asthma and abdominal pain.

‡ Analyses were performed separately by dose (1 or 2) and combined across doses (Combined).

§ Based on participant incidence.

¶ Numbers in parentheses, 90% CI.

‖ Participants 9 to 17 years of age received a 1-dose regimen.

ADD, attention deficit disorder; ED, Emergency Department; NE, not estimable because of 0 events occurring in the placebo group.

recipients (0.55%) after the first dose in children 12 to 77 months of age; and 13 of 1244 vaccine recipients (1.0%) after the second dose in children 12 to 47 months. All cases of conjunctivitis were mild. Further virologic studies of this outcome would seem warranted.

Increased rates of runny nose/nasal congestion have been reported in other CAIV trials.[24] In our study of medically attended events, there was an increased risk of URI in only 3 of 41 analyses. URI was most frequent for 18 to 35 month olds in the combined setting for an incidence rate of 88.9 visits/1000 person-months in the vaccine group *vs.* 68.6 visits/1000 person-months in the placebo group. This observation in this age group is consistent with reports by Vesikari et al.[23] which demonstrated that in contrast to the very short lived replication of CAIV in older individuals and adults, viral replication may continue for 1 week or more in young children. We hypothesize that this longer replication could be associated with the URI symptoms observed.

Large studies such as this one, where medical visits recorded in health care utilization databases are the outcomes of interest, can be a very effective means of evaluating vaccine safety. The clinical significance of medical events with increased risk and biologic plausibility for association with vaccination, however, is most appropriately considered in the context of an assessment of overall risk and benefit. In addition large studies of this type serve to generate hypotheses for evaluation in subsequent follow-up studies. Influenza vaccine is the most effective strategy presently available to prevent influenza. As we try to improve our vaccine coverage of already identified high risk groups, target additional high risk groups and promote vaccination in all segments of the population, an intranasal, even potentially self-administered influenza vaccine would be of great benefit. The CAIV appears to be safe in children >3 years of age and in adolescents. The significance of a possible increased risk of reactive airway disease observed in our study awaits further investigation.

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Comparison of the Efficacy and Safety of Live Attenuated Cold-Adapted Influenza Vaccine, Trivalent, With Trivalent Inactivated Influenza Virus Vaccine in Children and Adolescents With Asthma

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Background: Despite their potential for increased morbidity, 75% to 90% of asthmatic children do not receive influenza vaccination. Live attenuated influenza vaccine (LAIV), a cold-adapted, temperature-sensitive, trivalent influenza vaccine, is approved for prevention of influenza in healthy children 5 to 19 years of age. LAIV has been studied in only a small number of children with asthma.

Methods: Children 6 to 17 years of age, with a clinical diagnosis of asthma, received a single dose of either intranasal CAIV-T (an investigational refrigerator-stable formulation of LAIV; n = 1114) or injectable trivalent inactivated influenza vaccine (TIV; n = 1115) in this randomized, open-label study during the 2002–2003 influenza season. Participants were followed up for culture-confirmed influenza illness, respiratory outcome, and safety.

Results: The incidence of community-acquired culture-confirmed influenza illness was 4.1% (CAIV-T) versus 6.2% (TIV), demonstrating a significantly greater relative efficacy of CAIV-T versus TIV of 34.7% (90% confidence interval [CI] 9.4%–53.2%; 95% CI = 3.9%–56.0%). There were no significant differences between treatment groups in the incidence of asthma exacerbations, mean peak expiratory flow rate findings, asthma symptom scores, or nighttime awakening scores. The incidence of runny nose/nasal congestion was higher for CAIV-T (66.2%) than TIV (52.5%) recipients. Approximately 70% of TIV recipients reported injection site reactions.

Conclusions: CAIV-T was well tolerated in children and adolescents with asthma. There was no evidence of a significant increase in adverse pulmonary outcomes for CAIV-T compared with TIV. CAIV-T had a significantly greater relative efficacy of 35% compared with TIV in this high-risk population.

Key Words: influenza, asthma, cold-adapted influenza vaccine, trivalent, children

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Children with asthma are at increased risk of complications when infected with respiratory pathogens, including influenza, and experience excess morbidity and mortality during influenza outbreaks.[1,2] Asthmatic children are also more likely to require hospitalization for influenza[3–5] and to experience asthma exacerbations after influenza illness.[6] Although routine influenza vaccination is recommended in all high-risk children,[7] 75% to 90% of children with asthma remain unvaccinated.[8,9]

Injectable trivalent inactivated influenza vaccine (TIV) is the only vaccine currently approved for use in high-risk children and adolescents. Few trials have specifically evaluated the efficacy of TIV in children with asthma. Reported efficacy rates for TIV in children younger than 5 years range from 12% to 83%.[10] In an efficacy trial of TIV in children between 2 and 14 years of age with asthma, efficacy rates of 67.5% for influenza A (H3N2) and 43.7% for influenza B were demonstrated.[11] Results of studies evaluating the effect of TIV administration on symptoms and pulmonary function in children with asthma have been mixed.[12–18]

Live attenuated influenza vaccine (LAIV, FluMist; MedImmune, Gaithersburg, MD) is a cold-adapted, temper-

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ature-sensitive, trivalent influenza vaccine currently approved for prevention of influenza in healthy children between 5 and 19 years of age.[19–21] To date, the safety of LAIV has been studied in only a small number of children with asthma.[22] A potential association between LAIV administration and increased risk of asthma has been observed.[23,24]

The objective of the present study was to compare the safety and efficacy of a single dose of CAIV-T, an investigational refrigerator-stable formulation of LAIV, with TIV during a single influenza season in children and adolescents aged 6 to 17 years with asthma.

MATERIALS AND METHODS

Vaccines. CAIV-T (lot no. 7-6169-003A) was supplied by Wyeth (Marietta, PA) and consisted of 3 cold-adapted attenuated reassortant strains, representing the hemagglutinin (HA) and neuraminidase antigens of the A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), and B/Hong Kong/330/01 influenza strains. The HA and neuraminidase antigens of the wild-type influenza strains used to generate the CAIV-T reassortants were antigenically representative of viruses recommended by the World Health Organization for the 2002–2003 influenza season: A/New Caledonia/20/99-like, A/Moscow/10/99-like (A/Panama/2007/99), and B/Hong Kong/330/01-like strains. Each dose was formulated to contain approximately 10^7 fluorescent focus units of the three 6:2 influenza reassortant virus strains in 0.2 mL. After manufacture, the vaccine was stored frozen and shipped to the study sites at 2°C to 8°C, where it was stored at that temperature until just before intranasal administration using a spray applicator (0.1 mL into each nostril).

Licensed TIV, types A and B, split virion (lot no. W06431), was obtained from Aventis Pasteur (Lyon, France) and contained antigens identical to or antigenically representative of the World Health Organization recommendations for the 2002–2003 influenza season, specifically A/New Caledonia/20/99–IVR-116, 15 μg HA per one 0.5-mL dose; A/Panama/2007/99–RESVIR-17, 15 μg HA per 1 0.5-mL dose; and B/Shangdong/7/97 (B/Hong Kong/330/01-like strain), 15 μg HA per 1 0.5-mL dose. TIV was administered by intramuscular injection according to the manufacturer's dosing instructions.

Subjects. Children 6 to 17 years of age with a clinical diagnosis of asthma were eligible for enrollment. Asthma was defined as an *International Classification of Diseases*, *Ninth Revision* diagnosis code of 493 plus 1 or more prescriptions for asthma medication that were administered within the previous 12 months. Asthma medication was defined as inhaled and oral β agonists; theophylline; inhaled, oral, and injected steroids; cromolyn; other unclassified asthma medications; and antibiotics used for treatment of respiratory illness associated with a wheezing episode.

Exclusion criteria included serious chronic disease (including progressive neurologic disease) and known or suspected disease of the immune system or current receipt of immunosuppressive therapy, including high-dose systemic corticosteroids. Subjects receiving high doses of systemic corticosteroids given daily or on alternate days, for 14 days or more, were excluded from vaccination until corticosteroid therapy was discontinued for at least 1 month. High doses were defined as 2 mg/kg per day or more of prednisolone or its equivalent, or 20 mg or more daily if the subject weighed more than 10 kg.

Study Design. This phase III, randomized, open-label, active-controlled study was conducted at 145 study sites in Belgium, Finland, Germany, Greece, Israel, Italy, the Netherlands, Norway, Poland, Portugal, Spain, Switzerland, and the United Kingdom from October 4, 2002, to May 31, 2003. The study was conducted in accordance with the International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice, the Declaration of Helsinki, and national and local laws. The protocol was approved by the independent ethics committee at each site, and written informed consent was obtained from each subject or his or her parent or guardian. Enrollment took place over a period of 6 weeks, commencing on October 4, 2002.

All subjects underwent a screening period of at least 7 days, during which baseline asthma parameters were assessed (Fig. 1). Subjects were then randomized 1:1 to receive a single intranasal dose of CAIV-T or an intramuscular injection of licensed TIV. Randomization was accomplished using an automated interactive voice response system.

During the screening period and for 15 days postvaccination, subjects were monitored daily by their parents or guardians, and information was recorded using diary cards as follows: peak expiratory flow rate (PEFR) was measured 3 times each morning, before any asthma medication was received. Daily asthma symptom scores were assessed in the evening before the subject went to sleep and were based on a 4-point scale on which 0 = no symptoms, 1 = occasional symptoms, 2 = frequent symptoms, and 3 = continuous symptoms. Nighttime awakening scores were assessed each morning. The subject, parents, or guardians described the frequency of asthma-related nighttime awakenings using the following 4-point scale: 0 = fine; 1 = slept well, slight wheeze or cough; 2 = awake 2 to 3 times, wheeze or cough; 3 = bad night, awake most of the time. Any asthma medications used were also recorded. In addition, symptoms of asthma exacerbations were collected during surveillance for influenza-like symptoms.

During the surveillance phase, from day 14 after vaccination until approximately May 31, 2003, subject(s)/parent(s)/legal guardian(s) were contacted weekly to determine whether the subject met the criteria for an illness visit and nasal swab as defined in the protocol. Surveillance for influenza-like symptoms consisted of telephone contacts, clinic visits, or home visits, as applicable. Nasal swab viral culture was required if subjects exhibited fever (≥38°C oral temperature), pulmonary congestion, pneumonia, or ear infection (acute otitis media, suspected or diagnosed). Nasal swab viral cultures were also required if subjects showed 2 or more of the following: shortness of breath, runny nose or nasal congestion (rhinorrhea), sore throat (pharyngitis), cough, muscle aches, chills, headache, irritability, decreased activity, vomiting, increase in wheezing or increased use of medication to treat wheezing. Cultures could also be obtained at the investigators' clinical discretion. Subjects who met the criteria for nasal swab viral culture were to have a clinic or home visit within 4 days after the onset of the illness. Specimens were

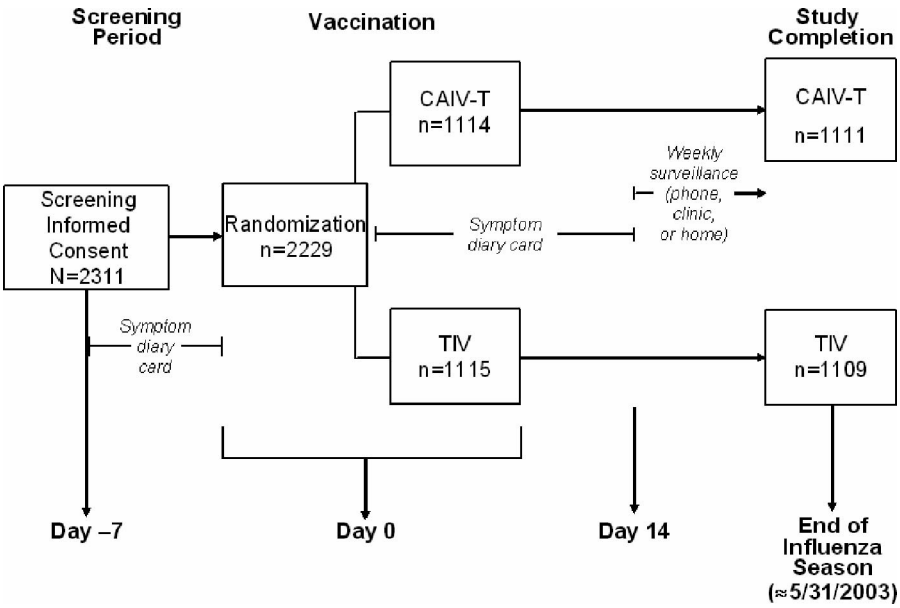

FIGURE 1. Study design. CAIV-T indicates cold-adapted influenza vaccine, trivalent; TIV, trivalent inactivated influenza vaccine.

cultured, typed, and subtyped by specific primary testing laboratories throughout Europe. Virus-positive specimens were shipped to the sponsor (Wyeth Vaccines Research, Pearl River, NY) for further identification. Influenza isolates were identified using HA inhibition assay and polymerase chain reaction (PCR) sequencing methods similar to those previously described for influenza H3N2 and B viruses.[25,26] If the 2 methods yielded different results, the PCR sequence was used to determine antigenic similarity to the vaccine.

Adverse events (AEs) were recorded on the diary card and were defined for this study as any clinically significant event (following administration of the vaccine dose), including but not limited to the following events: (1) those that required prescription or nonprescription medication within 15 days postvaccination (days 0–14), (2) those that required an unscheduled healthcare provider visit or consultation within 28 days of vaccination, (3) those that resulted in study termination, or (4) any other clinically significant event occurring at any point during the study period. Serious AEs (SAEs) were monitored through completion of the surveillance phase (May 31, 2003) and included events that resulted in death, were life threatening, resulted in subject hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, resulted in cancer, or resulted in congenital anomaly or birth defect (in the offspring of a vaccine recipient). Additionally, important medical events that may not have resulted in death, were not life threatening, or did not require hospitalization could have been considered SAEs when, according to appropriate medical judgment, they jeopardized the patient or subject and required medical or surgical intervention to prevent one of the outcomes listed above.

Reactogenicity events—predefined events that could occur after vaccine administration—were recorded for 15 consecutive days after study vaccination. Events to be recorded were fever (oral temperature ≥38°C), runny nose/nasal congestion, sore throat, cough, wheeze, vomiting, change in activity level, appetite change, irritability, abdominal pain/stomachache, headache, chills, and muscle aches. For subjects receiving TIV, the presence or absence of redness, swelling, and/or pain around the injection site was also recorded. Reactogenicity events that met the criteria for an AE or SAE as described above were also recorded as such.

Study End Points. The primary efficacy end point was the incidence of culture-confirmed influenza illness caused by a community-acquired subtype antigenically similar (as determined by serologic methods and/or PCR sequencing) to that in the vaccine. Secondary end points were the incidence of culture-confirmed influenza illness caused by any influenza virus subtype, the use of any prescribed medication or antibiotics, incidence of unscheduled healthcare provider visits, incidence of hospitalizations, and number of days missed from school or work.

The primary safety end point was the incidence of asthma exacerbation, defined as acute wheezing illness associated with hospitalization, any unscheduled clinical visit, or any new prescription (including rescue medication). This information was collected on the diary card and/or from telephone contacts during the surveillance phase. Secondary safety end points were (1) recurrent episodes during the surveillance period of acute wheezing illness associated with hospitalization, unscheduled clinical visit, or increased or new asthma medication use (medically required increase in daily dosage of currently prescribed asthma medication or newly prescribed asthma medication); (2) the first asthma exacerbation episode within 42 days; (3) PEFR scores; (4) nighttime awakenings (or sleep scores); and (5) asthma symptom scores. The PEFR values, sleep scores, and asthma scores were recorded on the diary card for at least 7 consecutive days before vaccination and for 15 days after vaccination. Asthma exacerbations were defined as acute wheezing illness associated with hospitalization, unscheduled clinic

visits, or new prescriptions. New prescriptions were defined as medically required increases in daily dosage of currently prescribed asthma medication or medically required newly prescribed asthma medications.

Statistical Analysis. The study, with a sample size of 1760 subjects (880 per study group), was designed to have at least 80% power to reject a hypothesis of clinical nonequivalence for the incidence of asthma exacerbation during the surveillance period and 90% power to demonstrate noninferiority for the primary efficacy end point of the noninferiority test (CAIV-T versus TIV). The standards for noninferiority were that the lower bound of a 90% confidence interval (CI) for efficacy was higher than −0.5, and the bounds for a 90% CI for the rate difference for safety were within ±5%. For superiority, a 95% CI was used.

For efficacy analysis, 2 populations were defined: intent to treat (all subjects who received a vaccination) and per protocol (subjects who received vaccination as randomized, with no major protocol violations). Efficacy estimates for influenza were based on illness episodes that occurred from 15 days after vaccination until the end of the surveillance period (approximately May 31, 2003). Efficacy of CAIV-T relative to TIV was defined in terms of incidence rates as $1 - I_C/I_T$, where I_C is the case incidence rate for the CAIV-T group and I_T is similarly defined for the TIV group. Exact, 2-sided 90% (for noninferiority) and 95% (for superiority) CIs were constructed using the binomial distribution conditional on the total number of cases observed. Efficacy against the pharmacoeconomic end points was assessed by similar methods for noninferiority.

The safety population consisted of all subjects who received at least 1 dose of study vaccine and was divided by treatment group (CAIV-T versus TIV) according to vaccine actually received. For safety, the noninferiority of CAIV-T relative to TIV was assessed using 2 analyses of incidence of asthma exacerbation.

The first analysis determined the difference in incidence of asthma exacerbation between treatment groups using 2-sided 90% CIs. CIs at the 95% level for assessing superiority of 1 treatment over the other were calculated as exploratory analyses. If the bounds of the 2-sided 90% CI were within the equivalence criterion of ±5%, the effects of the 2 vaccines on asthma exacerbation were judged equivalent. If the bounds of the 2-sided 95% CI did not include 0, the effects were considered different. Assessments of incidence of asthma exacerbation within a limited period of 42 days after vaccination were exploratory and were performed to allow comparison with other studies.

The second analysis was an exploratory analysis of incidence of asthma exacerbation using the proportional hazard model of survival analysis to account for the duration from the start of surveillance until the first episode of asthma exacerbation. This was calculated for CAIV-T relative to TIV as 1 minus relative risk.

The difference in incidence rates of asthma exacerbation for the 2 treatment groups was estimated by exact methods, using Chen's method in StatXact (Cytel, Inc., Cambridge, MA). Other analyses used the proportional hazard model of survival analysis to take into account the duration from the start of surveillance until the first episode or between episodes. If the bounds of a 2-sided 90% CI were within the equivalence criterion of ±5%, the effects of the vaccines on asthma exacerbation were judged equivalent. If the bounds of a 2-sided 95% CI did not include 0, the effects were considered different. The result of the analysis of all episodes of asthma exacerbation was expressed similarly for CAIV-T relative to TIV as 1 minus relative risk, using the Andersen-Gill model for multiplicative hazards of recurrent events.

Several summary measures of PEFR were compared, with adjustment for baseline for the 2 treatment groups. Ninety percent CIs were computed by either Student *t* test or Chen's method. For nighttime awakenings, the frequencies of scores by day and treatment were tabulated. The incidences of subjects with at least 1 bad night in the 2 treatment groups were compared by Chen's method. For daily asthma scores, the frequencies of scores by day and treatment were tabulated. The incidences of subjects with at least 1 day of continuous asthma symptoms in the 2 treatment groups were compared by Chen's method. The incidence of fever, systemic reactions, and AEs was analyzed using a Fisher exact test.

RESULTS

A total of 2311 subjects were screened, 2229 of whom were randomized to treatment and make up the intent-to-treat population (CAIV-T, n = 1114; TIV, n = 1115; Fig. 1). Baseline characteristics for the intent-to-treat population, including asthma history, are summarized in Table 1. The groups were balanced for demographic variables (sex, age, and ethnic origin) and asthma history (age at diagnosis, hospitalizations for asthma, previous use of corticosteroids for asthma, and current asthma medications). The per-protocol efficacy population consisted of 2211 subjects (99.2%) who received treatment as randomized without major protocol violations: 1109 in the CAIV-T group and 1102 in the TIV group.

Influenza Illness and Pharmacoeconomic End Points. There were 2450 illness visits documented during the study period: 1255 in CAIV-T recipients and 1195 in TIV recipients. During these visits, 2353 nasal swabs were collected (1201 from CAIV-T recipients, 1152 from TIV recipients, representing 95.7% and 96.4% of illness visits in each group, respectively); 99.2% of these yielded conclusive results for each group. Overall, 129 positive cultures were obtained from 128 swabs; 1 swab from a TIV recipient was positive for both influenza AH3N2 and B virus. Serotype could be identified by PCR for 95.3% of positive cultures and by serology for 63.6% of positive cultures. Distribution of culture-confirmed influenza by week and treatment is summarized in Figure 2. The surveillance period for influenza infection began 14 days after vaccine administration (per protocol). However, 4 subjects presenting with respiratory symptoms within 14 days of vaccination were cultured. No wild-type influenza virus was recovered. H1N1 and B vaccine virus was recovered from 1 subject each; both of these were CAIV-T recipients.

The incidence of influenza caused by strains antigenically similar to vaccine strains in the per-protocol population

TABLE 1. Baseline Characteristics (All Randomized Subjects)

Characteristic	Treatment Group	
	CAIV-T, n = 1114	TIV, n = 1115
Sex, n (%)		
Girls	420 (37.7)	392 (35.2)
Boys	694 (62.3)	723 (64.8)
Age at vaccination, yr		
Mean (SD)	11.1 (2.9)	10.9 (3.0)
Range	6.0–17.8	6.0–17.9
Ethnic origin, n (%)		
White	1091 (97.9)	1089 (97.7)
Black	9 (0.8)	8 (0.7)
Asian	3 (0.3)	4 (0.4)
Indian subcontinent	7 (0.6)	2 (0.2)
Other	4 (0.4)	12 (1.1)
Asthma history		
Age at diagnosis, yr		
Mean (SD)	4.7 (3.2)	4.8 (3.2)
Range	0.0–16.0	0.0–16.0
Subjects ever hospitalized for asthma, n (%)	340 (31)	349 (31)
Subjects ever using corticosteroids for asthma, n (%)	485 (44)	481 (43)
Subjects currently taking medications for asthma, n (%)		
Inhaled or oral β agonist (short acting)	793 (71.2)	790 (70.9)
Inhaled or oral β agonist (long acting)	356 (32.0)	361 (32.4)
Theophylline	14 (1.3)	10 (0.9)
Inhaled corticosteroids	772 (69.3)	767 (68.8)
With an inhaled or oral β agonist (long acting) or theophylline or a leukotriene receptor antagonist	394 (35.4)	401 (36.0)
Leukotriene receptor antagonist	157 (14.1)	179 (16.1)
Systemic corticosteroids	21 (1.9)	14 (1.3)
Cromoglycate and related products	98 (8.8)	102 (9.1)
Unclassified asthma medication	48 (4.3)	58 (5.2)
Antibiotics used for treatment of respiratory illness*	16 (1.4)	16 (1.4)

SD, standard deviation.
*Associated with a wheezing episode.

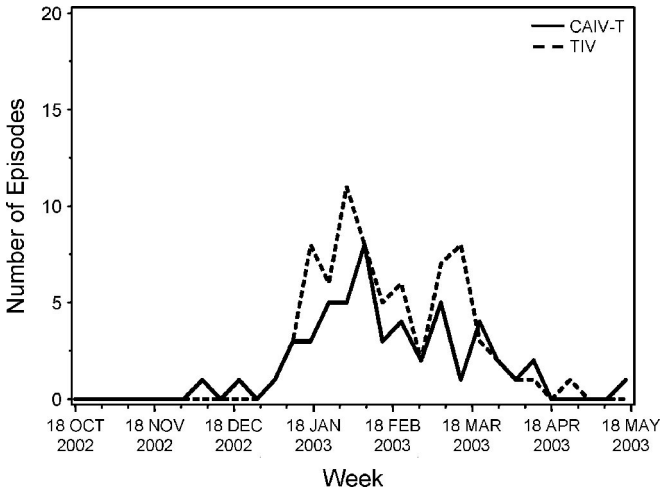

FIGURE 2. Number of episodes of culture-confirmed influenza (per-protocol population). CAIV-T indicates cold-adapted influenza vaccine, trivalent; TIV, trivalent inactivated influenza vaccine.

was 46 (4.1%) of 1109 subjects in the CAIV-T group and 70 (6.4%) of 1102 subjects in the TIV group (Table 2). Strains isolated during surveillance included A/New Caledonia/20/99-like (H1N1), A/Panama/2007/99-like (H3N2), B/Hong Kong/1351/02-like, and B/Hong Kong/330/01-like, all of which were considered identical to or antigenically similar to the vaccine strains and A/Fujian/411/2002-like (H3N2). The overall relative efficacy of CAIV-T versus TIV was 34.7% (90% CI = 9.4%–53.2%; 95% CI = 3.9%–56.0%), indicating that CAIV-T was significantly more effective than TIV. Type B virus predominated during this study. Individually, greater efficacy for CAIV-T compared with TIV was suggested for the A/H1 and B strains but not for the A/H3 strains; there was a similar incidence of A/H3 in both treatment groups. Similar results were seen for efficacy against any influenza subtype; overall efficacy of CAIV-T was 31.9% greater than TIV (90% CI = 6.6%–50.6%) (Table 2).

CAIV-T and TIV showed no demonstrable difference in efficacy against pharmacoeconomic end points related to respiratory illness, as summarized in Table 3. The small number of subjects who required hospitalization precludes an assessment of efficacy using number of hospitalizations as an end point.

Asthma Events. No significant difference between the CAIV-T and TIV groups was observed in the incidence of asthma exacerbations after vaccination. The observed incidence of asthma exacerbation during the entire study period was 31.2% for CAIV-T and 29.6% for TIV (90% CI = −1.6 to 4.8; 95% CI = −2.2 to 5.4). The incidence of asthma exacerbation occurring within 42 days after vaccination was also comparable for both treatment groups, with an estimate of the percentage point difference in incidence of −0.1 (90% CI = −2.4 to 2.2; 95% CI = −2.8 to 2.6). Similar results were observed for all episodes of asthma exacerbation, with a difference in rate per 100 subjects of −11.7 (90% CI = −27.2 to 1.9; 95% CI −30.4 to 4.3). In the majority of subjects, asthma exacerbation episodes were associated with unscheduled clinic visits and new prescriptions rather than hospitalizations (Fig. 3).

No significant differences were observed between treatment groups in mean PEFR findings, asthma symptom scores, or nighttime awakening scores. The majority of subjects in both groups reported no asthma symptoms (score 0) during screening and through 15 days postvaccination, with similar proportions of subjects in each group having a score of 0.

Reactogenicity Events and AEs. The incidence of reactogenicity events for CAIV-T and TIV is shown in Table 4. Overall, 84.2% of CAIV-T recipients and 78.9% of TIV recipients reported at least 1 reactogenicity event within 15 days after vaccination. The percentage of subjects experiencing each event was similar between treatment groups, except for runny nose/nasal congestion (66.2% CAIV-T versus 52.5% TIV; $P < 0.001$) and wheeze (19.5% CAIV-T versus 23.8% TIV; $P = 0.020$) (Table 4). A total of 70.8% of TIV recipients experienced some type of local reaction at the injection site within 15 days after vaccination; 59.8% of TIV recipients experienced injection site pain.

TABLE 2. Efficacy Against Community-Acquired Culture-Confirmed Influenza Illness

Influenza Subtype	Subjects With Culture-Confirmed Illness, n (%)		Efficacy	
	CAIV-T	TIV	% (90% CI)*	(95% CI)*
Antigenically similar to those in the vaccine				
Per-protocol population				
Any strain	46 (4.1)	70 (6.4)	34.7 (9.4–53.2)	(3.9–56.0)
A/H1	0 (0.0)	5 (0.5)	100.0 (18.5–100.0)	(−8.4 to 100.0)
A/H3	12 (1.1)	12 (1.1)	0.6 (−111.7 to 53.4)	(−141.8 to 59.2)
B	34 (3.1)	53 (4.8)	36.3 (6.6–56.8)	(0.1–59.8)
Intent-to-treat population				
Any strain	46 (4.1)	70 (6.3)	34.2 (8.7–52.9)	(3.2–55.7)
Any community-acquired subtypes				
Per-protocol population				
Any strain	50 (4.5)	73 (6.6)	31.9 (6.6–50.6)	(1.1–53.5)
A/H1	0 (0.0)	6 (0.5)	100.0 (35.7–100.0)	(15.6–100.0)
A/H3	17 (1.5)	13 (1.2)	−29.9 (−157.2 to 33.3)	(−190.9 to 40.6)
B	35 (3.2)	55 (5.0)	36.8 (8.0–56.9)	(1.6–59.8)
Intent-to-treat population				
Any strain	50 (4.5)	74 (6.6)	32.4 (7.3–50.9)	(1.9–53.7)

*Exact CI conditioned on the total number of cases.

The difference between treatment groups for the incidence of AEs through 15 days and 28 days postvaccination was less than 1 percentage point, except for rhinitis and headache. Both of these events had a higher incidence among CAIV-T recipients than among TIV recipients through 15 days postvaccination (7.4% versus 3.9% for rhinitis; 6.5% versus 4.2% for headache), with similar trends noted for both events through 28 days postvaccination (Table 5). The incidence of central nervous system AEs other than headache was low (<0.3% in either group) through both 15 and 28 days postvaccination.

Only 1.8% of CAIV-T recipients and 1.7% of TIV recipients experienced SAEs. The most common SAEs reported were respiratory, with a 0.9% incidence in both treatment groups. A total of 4 SAEs were reported as probably related to study vaccine by a study investigator or medical monitor. These included 3 events in CAIV-T recipients: pneumonia associated with a severe asthma attack (2 days postvaccination), acute pansinusitis (93 days postvaccination), and a painful gland behind the left ear (43 days postvaccination). The other related SAE was hyperglycemia with nausea, which occurred in a TIV recipient 3 hours after vaccination.

TABLE 3. Vaccine Efficacy Against Pharmacoeconomic End Points Related to Respiratory Illness

End Point	Treatment Group		% Efficacy (90% CI)†
	CAIV-T, n (%)*	TIV, n (%)*	
Use of any medications or antibiotics	303 (27.3)	297 (27.0)	−1.3 (−16.2 to 11.7)
Unscheduled healthcare provider visits	607 (0.7)	599 (0.7)	−0.6 (−10.8 to 8.6)
Hospitalizations	0 (0.0)	2 (0.2)	100.0 (−244.7 to 100.0)
Days off school/work	1178 (1.4)	1075 (1.3)	−9.2 (−17.2 to −0.8)

*Number of incidents or number of days with the event. Correspondingly, percentages are based on the number of subjects or total surveillance days.

†Exact CI conditional on the total number of incidents or number of days.

DISCUSSION

This is the first study to compare directly a single dose of inactivated injectable (TIV) and an investigational formulation of live intranasal (CAIV-T) vaccination in preventing culture-confirmed influenza among asthmatic children. In this study, the relative efficacy of CAIV-T was significantly greater compared with TIV: 35% for influenza strains antigenically similar to those in the vaccine and 32% for all influenza strains. These results are consistent with data from a study comparing CAIV-T and TIV in a younger population

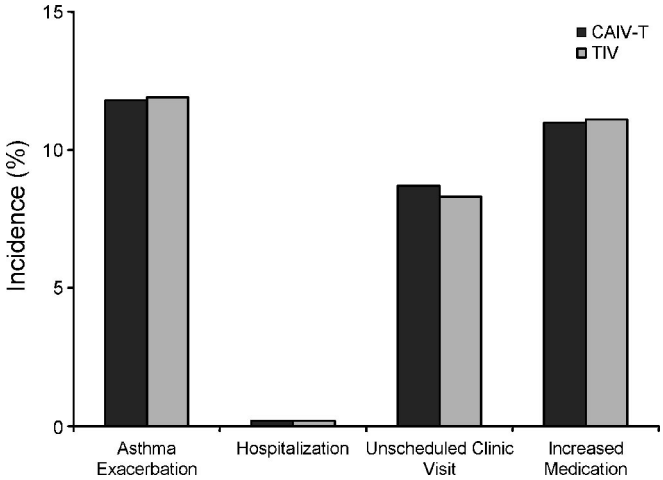

FIGURE 3. Asthma exacerbations occurring within 42 days of vaccination. CAIV-T indicates cold-adapted influenza vaccine, trivalent; TIV, trivalent inactivated influenza vaccine.

TABLE 4. Number (%) of Subjects Reporting Systemic Reactogenicity Events Within 15 Days After Vaccination

Reactogenicity Event	Treatment Group		*P* Value†
	CAIV-T (n = 940–1086), n (%)*	TIV (n = 936–1071), n (%)*	
Fever‡ ≥38°C	60 (6.3)	55 (5.8)	0.701
Fever‡ ≥39.1°C	7 (0.7)	10 (1.1)	0.477
Fever‡ ≥40.0°C	1 (0.1)	0 (0.0)	1.000
Runny nose or nasal congestion	719 (66.2)	562 (52.5)	0.000
Sore throat	322 (30.4)	285 (27.3)	0.124
Cough	474 (44.3)	497 (46.9)	0.240
Vomiting	72 (6.9)	63 (6.1)	0.533
Decreased activity	247 (23.1)	228 (21.8)	0.498
Decreased appetite	178 (16.8)	180 (17.3)	0.817
Wheeze	206 (19.5)	249 (23.8)	0.020
Irritability	158 (14.9)	131 (12.7)	0.145
Headache	429 (40.1)	391 (37.0)	0.154
Stomachache	266 (25.3)	230 (22.2)	0.100
Chills	158 (14.9)	134 (13.0)	0.207
Muscle ache	184 (17.4)	202 (19.7)	0.176
Medication to prevent fever	76 (7.5)	83 (8.3)	0.563
Medication to treat fever	78 (7.7)	71 (7.1)	0.671
Any event§	904 (84.2)	828 (78.9)	0.002

*n, Number of subjects with known values.
†Two-sided Fisher exact test.
‡Oral temperature.
§Does not include the administration of fever medication.

TABLE 5. Adverse Events Reported in ≥1% of Vaccine Recipients (All Randomized Subjects)

AE	Incidence, n (%)		*P* Value*
	CAIV-T (n = 1115)	TIV (n = 1114)	
≤15 d after vaccination			
Any AE	283 (25.4)	222 (19.9)	0.002
Respiratory AEs			
Any	189 (17.0)	146 (13.1)	0.013
Rhinitis	82 (7.4)	43 (3.9)	0.000
Coughing	40 (3.6)	40 (3.6)	1.000
URTI	39 (3.5)	31 (2.8)	0.395
Pharyngitis	37 (3.3)	34 (3.1)	0.810
Bronchospasm	31 (2.8)	30 (2.7)	1.000
AEs × 2			
Fever	26 (2.3)	27 (2.4)	0.891
Headache	72 (6.5)	47 (4.2)	0.023
Abdominal pain	19 (1.7)	14 (1.3)	0.484
≤28 d after vaccination			
Any event	369 (33.1)	307 (27.6)	0.005
Respiratory AEs			
Any	253 (22.7)	211 (18.9)	0.032
Rhinitis	103 (9.2)	61 (5.5)	0.001
URTI	63 (5.7)	56 (5.0)	0.572
Coughing	62 (5.6)	57 (5.1)	0.706
Pharyngitis	49 (4.4)	47 (4.2)	0.917
Bronchospasm	44 (3.9)	48 (4.3)	0.672
Bronchitis	11 (1.0)	8 (0.7)	0.646
Nonrespiratory Aes			
Abdominal pain	20 (1.8)	15 (1.3)	0.496
Gastroenteritis	12 (1.1)	4 (0.4)	0.076
Headache	80 (7.2)	55 (4.9)	0.033
Vomiting	14 (1.3)	6 (0.5)	0.114
Fever	35 (3.1)	37 (3.3)	0.812
Otitis media	12 (1.1)	5 (0.4)	0.142

URTI, upper respiratory tract infection.
*Two-sided Fisher exact test.

of children (aged 6–71 months) with a history of recurrent respiratory tract illnesses, in which a statistically significant relative efficacy of 53% was observed for CAIV-T over TIV.[27] Although the reasons for higher observed relative efficacy for CAIV-T were not evaluated in these trials, induction of innate and specific mucosal immunity, as well as other factors, may play a role.

Because there was no placebo group in the current study, the absolute efficacy of each vaccine cannot be calculated. Absolute rates have been reported in previous placebo-controlled trials of TIV,[10,11,28,29] live intranasal vaccine (LAIV, FluMist),[30,31] and the investigational refrigerator-stable formulation CAIV-T[32,33] in various populations. A relative efficacy advantage for CAIV-T and LAIV compared with placebo was observed both for influenza strains matched to the vaccine and for all community-acquired strains. In the current trial, the majority of influenza cases were caused by type B viruses, and thus relative efficacy against these viruses predominated.

Overall, both vaccines appeared safe and well tolerated in the study population. Reactogenicity events and AEs reported in the current study were as expected, according to previous LAIV and TIV data in children[10,34]: there was an increase in runny nose/nasal congestion noted for LAIV recipients (66% versus 53%), and injection site reactions were noted for the majority (71%) of TIV recipients.

Children with asthma have a high rate of complications associated with influenza infection, including hospitalization and exacerbation of their underlying disease.[1–6] Although the risk of asthma exacerbations after inactivated influenza vaccination has been studied in several large trials,[12–18] little is known about the risk after vaccination with live attenuated vaccine. In a large-scale safety trial in healthy children and adolescents, administration of the frozen formulation of LAIV was reportedly associated with an increased risk of asthma/reactive airways disease in children aged 18 to 35 months and with a significantly reduced risk in children 5 years of age and older.[23,24] The study was designed initially to include only healthy children and was not prospectively designed to address the issue of asthma/wheezing exacerbation; a number of questions about the issue thus remained. A small, randomized, double-blind, placebo-controlled trial in children with moderate to severe asthma (N = 48) found no significant difference in asthma measures (eg, forced expiratory volume in 1 second, PEFR, use of medications, and clinical scores) with CAIV-T compared with placebo.[22] In a large, open-label, community-based study in which almost 19,000 doses of LAIV were administered to more than 11,000 children 18 months to 18 years of age, 10% of whom had a history of mild intermittent asthma, reactive airway disease, or wheezing illness, LAIV was found to be well tolerated by all age groups.[35] In this study, 190 comparisons were made without adjustment for multiple comparisons. No increased relative risk of asthma was observed in any age group in the period 0 to 14 days after LAIV vaccination. An increased relative risk for asthma events compared with a prevaccination reference period was reported in year 1 in children 18 months to 4 years of age 15 to 42 days postvaccination (relative risk, 2.85; 95% CI = 1.01–8.03). No increase was

observed in asthma relative risk in children 18 months to 4 years of age in the subsequent 3 vaccine years.

The current study described in this paper was large and included only children with asthma (aged 6–18 years). Approximately 70% of study participants were taking inhaled steroids, more than 40% had a history of systemic steroid treatment, and 31% previously required hospitalization for asthma. A major finding was that no significant differences were observed in asthma exacerbations, mean PEFR, asthma symptom scores, or nighttime awakening scores between CAIV-T and TIV. Although the forced expiratory volume in 1 second is considered a more reliable measure than PEFR, the PEFR results in this study were consistent with other clinical outcome measures and with an earlier safety study of CAIV-T in children and adolescents with moderate to severe asthma.[22] Because certain upper respiratory tract infections such as rhinovirus infections are a known cause of asthma exacerbations,[36] evaluation of the risk of LAIV and asthma exacerbation is an important aspect of the risk/benefit of the vaccine. Although the sample size of the current trial cannot exclude any risk of asthma/wheezing exacerbation after CAIV-T in children with asthma, exacerbations are likely to be no more frequent than those after TIV, which is currently recommended for influenza immunization of children with asthma. Findings are also consistent with the above mentioned study comparing CAIV-T and TIV in a younger population of children (aged 6–71 months) with a history of recurrent respiratory tract illnesses; no differences were observed in wheezing illness between vaccine groups in this population of younger children.[27] In conclusion, this study demonstrated that CAIV-T was well tolerated in children with asthma. There was no evidence of significant increase in pulmonary outcomes for CAIV-T compared with TIV. CAIV-T had a significantly greater relative efficacy of 35% compared with TIV in this high-risk population.

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Effectiveness of Inactivated Influenza Vaccine in Preventing Acute Otitis Media in Young Children

A Randomized Controlled Trial

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Context Acute otitis media (AOM) frequently complicates influenza infection. Previous studies have found influenza vaccine effective in reducing the occurrence of AOM in children mainly older than 2 years.

Objective To evaluate the effectiveness of inactivated influenza vaccine in preventing AOM in children aged 6 to 24 months.

Design, Setting, and Patients Randomized, double-blind, placebo-controlled trial of 786 children aged 6 to 24 months enrolled at Children's Hospital of Pittsburgh before the 1999-2000 (411 children) and 2000-2001 (375 children) respiratory seasons (defined as December 1 through March 31 of the respective following year). Children received influenza vaccine or placebo in a 2:1 ratio. The first cohort was observed for 1 year and the second cohort until the end of the ensuing respiratory season.

Intervention Two doses (0.25 mL each) of inactivated trivalent subvirion influenza vaccine or placebo were administered intramuscularly approximately 4 weeks apart.

Main Outcome Measures Proportion of children who developed AOM, monthly occurrence rate of AOM, estimated proportion of time with middle ear effusion, and utilization of selected health care and related resources.

Results Of the 66 children in the vaccine group from whom serum samples were collected, seroconversion against strains in the vaccine formulations developed in 88.6% to 96.8%, depending on the specific strain. The efficacy of the vaccine against culture-confirmed influenza was 66% (95% confidence interval [CI], 34%-82%) in 1999-2000 and −7% (95% CI, −247% to 67%) in 2000-2001; however, influenza attack rates differed between these 2 periods (in the placebo group, 15.9% and 3.3%, respectively). Compared with placebo, influenza vaccine did not reduce the proportion of children who had at least 1 episode of AOM during the respiratory season (in the first cohort: vaccine, 49.2% vs placebo, 52.2%; $P=.56$]; in the second cohort: vaccine, 55.8% vs placebo, 48.3%; $P=.17$). The vaccine also did not reduce the monthly rate of AOM; the estimated proportion of time with middle ear effusion; or the utilization of selected health care and related resources. There were also no differences between the vaccine and placebo groups regarding any of these outcomes during peak influenza periods. The vaccines administered to both cohorts of children were well tolerated.

Conclusion Administration of inactivated trivalent influenza vaccine to children aged 6 to 24 months did not reduce their burden of AOM or their utilization of selected health care and related resources.

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VIRUSES THAT CAUSE RESPIRATORY tract infections are often present in the middle ear exudate of children with acute otitis media (AOM).[1] These viruses may play an important role in the pathogenesis of AOM and may slow the response to antimicrobial therapy.[2,3] Accordingly, it seems reasonable to expect that the administration of vaccines effective against viral infections might also serve to lessen morbidity from AOM.

Influenza vaccines (inactivated trivalent administered intramuscularly or intranasally or live attenuated trivalent administered intranasally) have been found effective in preventing AOM in 4 previous studies involving children mainly

See also p 1633 and Patient Page.

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older than 2 years; reductions of 30% to 44% in the occurrence of AOM episodes were reported.[4-7] However, certain important limitations of those studies may preclude generalizability of their results, particularly to children aged 6 to 24 months. These limitations include small sample size, enrollment only of otitis-prone children or day-care attendees, nonrandomized allocation of participants, single or incomplete blinding, dependence on parental reporting of episodes rather than active surveillance, and lack of standardized criteria for the diagnosis of AOM.

We undertook our study to determine whether inactivated trivalent influenza vaccine administered intramuscularly is effective in reducing the occurrence of AOM and other forms of otitis media in the children most vulnerable to the disease, namely, those aged 6 to 24 months. The study was designed to evaluate the effect of the vaccine during the influenza season, the broader respiratory season, and the 1-year period following vaccination. Although the vaccine does not protect against infections other than influenza, we hypothesized that preventing episodes of AOM associated with influenza might, by preserving normal middle ear status, reduce the occurrence of subsequent episodes of AOM associated with other respiratory viral infections. Secondary objectives of the study were to evaluate the vaccine's safety, immunogenicity, and efficacy against culture-proven influenza in these young children, as well as the effects of vaccination on the children's utilization of selected health care and related resources.

METHODS

Participants

The study was approved by the Children's Hospital of Pittsburgh Human Rights Committee. We recruited healthy children aged 6 to 24 months from the hospital's primary care center and from the community at large. Research personnel informed parents in the primary care center about the study, and advertisements were placed on the radio and in the regional newspaper. Written informed consent was obtained from the parent(s) of each enrolled child. We excluded children who had been born prematurely or had a craniofacial abnormality; or who had or were living with persons who had any medical condition placing them at high risk of complications of influenza[8]; or who had a neurologic disorder, a history of tympanostomy tube insertion, hypersensitivity to egg protein or thimerosal, or a febrile illness or severe respiratory illness within the preceding 48 hours.

Procedures

We enrolled 2 cohorts of children: during the periods October 4, 1999, to November 30, 1999, and September 5, 2000, to December 8, 2000. We stratified the children according to whether they were prone to otitis (ie, had a history of at least 3 episodes of AOM in the preceding 6 months or 4 episodes in the preceding 12 months) and whether they were attending day care (defined as exposed to 3 or more nonfamily children for at least 10 hours per week). We also stratified children in the second cohort according to whether they had received at least 1 dose of the then newly available pneumococcal conjugate vaccine. Within each stratum, we randomly assigned the children in blocks of 9, using a computer-generated list, to either the vaccine group or the placebo group in a 2:1 ratio. To each child we administered 2 doses, approximately 4 weeks apart, of either vaccine or placebo (0.25 mL each) intramuscularly. Administration was performed by nonblinded research nurses who were not involved in subsequent clinical follow-up of the children. Assignments to treatment groups were not revealed to parents, investigators, research personnel conducting clinical follow-up, or nonstudy health care providers, all of whom remained blinded throughout the study. Randomization lists were kept in locked files not accessible to blinded personnel.

Vaccine

Inactivated trivalent subvirion influenza vaccine (Fluzone) was supplied by Aventis Pasteur (Swiftwater, Pa). Strains in the 1999-2000 formulation were A/Beijing/262/95 (H1N1), A/Sydney/15/97 (H3N2), and B/Yamanashi/166/98; and in the 2000–2001 formulation, A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), and B/Yamanashi/166/98. The placebo, also supplied by Aventis Pasteur, consisted only of a standard diluent.

Surveillance for Otitis Media

Surveillance for the occurrence of otitis media following administration of the second dose of vaccine or placebo was maintained in the first cohort of children through biweekly visits until the end of the ensuing respiratory season, ie, March 31, 2000, and through monthly visits thereafter until November 15, 2000. Surveillance in the second cohort was maintained through biweekly visits until March 31, 2001. Parents were instructed to contact study staff if any sign or symptom of either an upper respiratory tract infection or AOM developed so that an interim visit could be arranged. Acute care visits were defined as those that resulted from the presence of fever (at least 38°C) within 72 hours or the occurrence of otalgia or that substituted for an illness-related visit to the children's primary care clinicians. All examinations were conducted by study clinicians using pneumatic otoscopy, supplemented by tympanometry and spectral gradient acoustic reflectometry. The diagnosis of middle ear effusion was based on the presence of 2 of 4 elements: decreased or absent tympanic membrane mobility, yellow or white discoloration of the tympanic membrane, opacification of the tympanic membrane not due to scarring, and visible bubbles or air-fluid levels. The diagnosis of AOM was based on the presence of purulent otorrhea of recent onset not due to otitis externa or of middle ear effusion accompanied by 1 or more of the following: ear pain, marked redness of the tympanic membrane, and substantial bulging of the tympanic membrane. We prescribed treatment for AOM according to published guidelines.[9] Decisions regarding myrin-

gotomy and tympanostomy tube insertion were not part of the study protocol and were made by the children's primary care clinicians.

Influenza Surveillance

To diagnose influenza, we performed throat cultures during visits at which patients had symptoms or signs of an upper respiratory tract infection accompanied by fever (at least 38°C), AOM, or both. The culture swabs were placed into viral transport media and immediately refrigerated. Within 4 hours, monkey kidney cell culture tubes were inoculated with processed throat specimens. On weekends and after routine hours, throat swabs were stored in viral transport media at 4°C until the next business day. Cultures were maintained at between 33°C and 35°C, examined daily for cytopathic effect, and tested for hemadsorption at 4, 7, and 14 days after inoculation and anytime cytopathic effect was observed. Typing and subtyping of influenza strains were performed using standard techniques.[10] No attempt was made to culture other viral pathogens.

Immunogenicity

At the beginning of the enrollment period each year, research personnel asked consecutive parents for additional permission to obtain blood samples from their children. Samples were collected from 53 children in the first cohort and 40 children in the second cohort immediately before administering the first dose of vaccine or placebo and again 4 weeks after the second dose. Serum samples were tested by blinded personnel in a laboratory at East Virginia Medical School, Norfolk, Va, for the presence of antibody to the 3 influenza serotypes using a standardized hemagglutination-inhibition assay.[11] Seroconversion was defined as a 4-fold increase in antibody titers and/or a postimmunization antibody titer greater than 1:40.

Safety Evaluation

Monitoring of unexpected adverse events was conducted at each visit by review of the child's medical record and interview with the parent. The occurrence of minor adverse reactions (eg, injection site reactions, low-grade fever, crying) was not systematically recorded.

Health Care Utilization

At each visit, parents were asked about any illnesses their child had since the preceding visit, visits to primary care clinicians and emergency departments, hospitalizations, use of antibiotics, and whether the study visit substituted for a clinician visit. Parents were also asked about illnesses in other family members, time lost from work, or a need for alternative child-care arrangements because of the child's illness.

Statistical Analysis

The study's primary outcome measure was the proportion of children who had at least 1 episode of AOM during the ensuing respiratory season. To detect a 33% reduction in the proportion of such children (eg, 30% of control children vs 20% of immunized children), with 2-tailed α level of .05 and β level of .20, we calculated that 466 evaluable children in the vaccine group and 232 evaluable children in the placebo group were needed during the 2-year study period. To determine the efficacy of the vaccine against influenza, the analysis was conducted for cases that occurred at any time following administration of the first dose and were based on person-months at risk; confidence intervals (CIs) for vaccine efficacy were based on an assumption of asymptotic normality of the log of the ratio of Poisson rates.[12] Otitis media–related outcomes were included in analyses if they occurred at least 2 weeks following administration of the second dose.

We based results on an intention-to-treat analysis that included all available data from all participants. The number of episodes of AOM for each child was calculated by totaling episodes that presented acutely and episodes defined as new because evidence of AOM persisted for more than 28 days, or supervened in the course of otitis media with effusion, or recurred after documented resolution of an episode. We estimated the proportion of days with middle ear effusion based on the diagnosis at each visit and on interpolations for intervals between visits, provided that the intervals did not exceed 60 days. If an interval between 2 visits exceeded 60 days, we assumed the status at the first visit to have continued for 30 additional days and the status at the second visit to have prevailed for 30 days preceding that visit. Middle ear status for the remaining days in the interval was considered indeterminate.

We used a logistic regression model that included adjustment for the stratification variables to compare by treatment groups the proportion of children who had at least 1 episode of AOM. We assessed differences between monthly rates of episodes of AOM and of febrile respiratory tract infections using a Poisson regression model in which the stratification variables were included as independent variables. We used a weighted regression model to compare mean proportions of days with middle ear effusion, with weights equal to the lengths of observed time, after first applying an arcsine transformation to obtain a distribution that better approximated a normal distribution.

For health care resource utilization outcomes, we compared treatment groups applying the method of generalized estimated equations.[13] Analyses were performed with SAS version 8.2 (SAS Institute Inc, Cary, NC).

The level of significance for all outcomes was .05.

RESULTS

Study Population

The first cohort of the study included 411 children and the second cohort included 375 children. Of these, 373 (91%) and 346 (92%) completed the study, defined as having a final visit after August 2000 for the first cohort and during March 2001 for the second cohort (FIGURE). Selected demographic and clinical characteristics of the children are summarized in TABLE 1. Approximately half were aged 6 to 12 months at enrollment. There were no significant differences in characteris-

tics between the vaccine and placebo groups in either of the 2 cohorts.

Immunogenicity of Vaccine

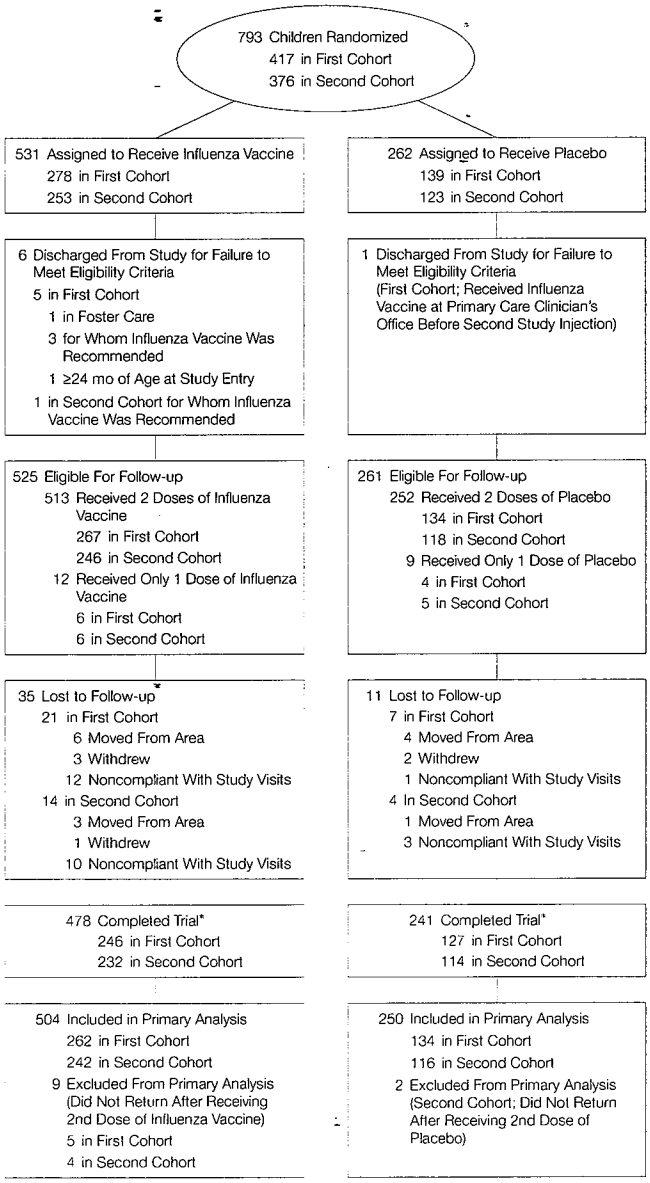
Of the 66 children in the vaccine group from whom serum samples were collected, seroconversion (defined as a hemagglutination-inhibition titer of ≥1:40, a 4-fold or greater increase in antibody titer, or both) against strains in the vaccine formulations developed in 88.6% to 96.8%, depending on the strain (TABLE 2).

Efficacy

Influenza. Throat cultures for influenza virus were obtained in 1113 (88%) of 1260 episodes of illness in which fever, AOM, or both were present. During the first year of the study, influenza was epidemic in the community. The influenza season was defined as the 6-week period (January 3 to February 15, 2000) during which 25 (67%) of the 37 culture-proven cases of influenza occurred; the other 12 cases occurred during the remaining 25 weeks of surveillance. During the second year, influenza occurred infrequently and there was no clustering of cases. The influenza season was defined as the 13-week period (January 4 to March 30, 2001) during which 11 (85%) of the 13 culture-proven cases occurred; the other 2 cases occurred during the remaining 16 weeks of surveillance. In the first cohort, culture-proven influenza was identified in 15 (5.5%) of 273 children in the vaccine group and 22 (15.9%) of 138 children in the placebo group. In the second cohort, corresponding values were 9 (3.6%) of 252 children in the vaccine group and 4 (3.3%) of 123 children in the placebo group. Accordingly, efficacy rates against influenza were 66% (95% confidence interval [CI], 34%-82%) in the first cohort and −7% (95% CI, −247% to 67%) in the second cohort. In the first cohort, efficacy rates against influenza in children aged 6 to 12 months, 13 to 18 months, and 19 to 24 months were 63%, 66%, and 69%, respectively. Of the 37 cases that occurred in the first cohort, 14 were caused by A/Beijing, 18 by A/Sydney, and 5 were not typed. Of the 13 cases that occurred in the second cohort, 5 were caused by A/New Caledonia, 5 by B/Yamanashi, 1 by A/Panama, and 2 were not typed. Circulating influenza strains were well matched with vaccine strains in the 2 respiratory seasons during which the study was conducted. All of the 24 cases in the vaccine group and 24 of the 26 cases in the placebo group occurred 2 weeks or longer after the second dose of vaccine or placebo.

Respiratory Tract Infections. In the first cohort, no differences in rates of febrile respiratory tract infections were noted between the influenza vaccine and placebo groups during the influenza sea-

Figure. Flow of Patients Through the Trial



Asterisk indicates defined as having a final visit after August 2000 for the first cohort and during March 2001 for the second cohort.

Table 1. Characteristics of Children Eligible for Follow-up in in Both Cohorts

Characteristic	No. (%) of Children					
	Cohort 1 (n = 411)		Cohort 2 (n = 375)		Total (N = 786)	
	Vaccine (n = 273)	Placebo (n = 138)	Vaccine (n = 252)	Placebo (n = 123)	Vaccine (n = 525)	Placebo (n = 261)
Demographics						
Age at entry, mo						
6-12	119 (43.6)	57 (41.3)	150 (59.5)	62 (50.4)	269 (51.2)	119 (45.6)
13-18	83 (30.4)	45 (32.6)	61 (24.2)	38 (30.9)	144 (27.4)	83 (31.8)
19-24	71 (26.0)	36 (26.1)	41 (16.3)	23 (18.7)	112 (21.3)	59 (22.6)
Male	128 (46.9)	75 (54.3)	139 (55.2)	70 (56.9)	267 (50.9)	145 (55.6)
Female	145 (53.1)	63 (45.7)	113 (44.8)	53 (43.1)	258 (49.1)	116 (44.4)
Race						
White	140 (51.3)	77 (55.8)	128 (50.8)	56 (45.5)	268 (51.1)	133 (51.0)
Black	116 (42.5)	52 (37.7)	102 (40.5)	58 (47.2)	218 (41.5)	110 (42.1)
Other	17 (6.2)	9 (6.5)	22 (8.7)	9 (7.3)	39 (7.4)	18 (6.9)
Maternal education						
Less than high school	25 (9.2)	11 (8.0)	31 (12.3)	15 (12.2)	56 (10.7)	26 (10.0)
High school graduate with or without technical or other training	173 (63.4)	90 (65.2)	147 (58.3)	74 (60.2)	320 (61.0)	164 (62.8)
College graduate	74 (27.1)	37 (26.8)	74 (29.4)	34 (27.6)	148 (28.2)	71 (27.2)
Unknown	1 (0.4)	0	0	0	1 (0.2)	0
Health insurance status						
Private	121 (44.3)	69 (50.0)	121 (48.0)	65 (52.9)	242 (46.1)	134 (51.3)
Medicaid	140 (51.3)	60 (43.5)	127 (50.4)	56 (45.5)	267 (50.9)	116 (44.4)
None	12 (4.4)	9 (6.5)	4 (1.6)	2 (1.6)	16 (3.0)	11 (4.2)
Health care provider						
Children's Hospital of Pittsburgh clinics	143 (52.4)	61 (44.2)	120 (47.6)	62 (50.4)	263 (50.1)	123 (47.1)
Private practitioner	130 (47.6)	77 (55.8)	132 (52.4)	61 (49.6)	262 (49.9)	138 (52.9)
Exposure to household cigarette smoke						
Yes	95 (34.8)	56 (40.6)	87 (34.5)	48 (39.0)	182 (34.7)	104 (39.8)
No	178 (65.2)	82 (59.4)	165 (65.5)	75 (61.0)	343 (65.3)	157 (60.2)
Other children in household						
Yes	186 (68.1)	91 (65.9)	145 (57.5)	75 (61.0)	331 (63.0)	166 (63.6)
No	87 (31.9)	47 (34.1)	107 (42.5)	48 (39.0)	194 (37.0)	95 (36.4)
Recurrent AOM*						
Yes	66 (24.2)	33 (23.9)	40 (15.9)	21 (17.1)	106 (20.2)	54 (20.7)
No	207 (75.8)	105 (76.1)	212 (84.1)	102 (82.9)	419 (79.8)	207 (79.3)
Day care†						
Yes	75 (27.5)	39 (28.3)	68 (27.0)	34 (27.6)	143 (27.2)	73 (28.0)
No	198 (72.5)	99 (71.7)	184 (73.0)	89 (72.4)	382 (72.8)	188 (72.0)
Had received ≥1 dose of pneumococcal conjugate vaccine						
Yes	NA	NA	179 (71.0)	83 (67.5)	179 (71.0)	83 (67.5)
No	NA	NA	73 (29.0)	40 (32.5)	73 (29.0)	40 (32.5)
Middle ear status at the time of the second dose of vaccine or placebo‡						
AOM	40 (15.0)	19 (14.3)	31 (12.6)	10 (8.5)	71 (13.8)	29 (11.6)
Otitis media with effusion	42 (15.7)	24 (18.0)	46 (18.7)	17 (14.4)	88 (17.2)	41 (16.3)
Normal	185 (69.3)	90 (67.7)	169 (68.7)	91 (77.1)	354 (69.0)	181 (72.1)

Abbreviations: AOM, acute otitis media; NA, not applicable.
*Defined as ≥3 AOM episodes in the preceding 6 months or 4 episodes in the preceding 1 year.
†Defined as ≥10 h/wk with ≥3 other children.
‡Data are not available for children withdrawn from the study before receiving the second dose of vaccine or placebo.

son (0.23 vs 0.25 episodes per person-month, respectively, $P=.71$) or during the respiratory season (0.21 vs 0.22 episodes per person-month, respectively, $P=.66$). However, in the second cohort, rates were actually higher in the vaccine group than in the placebo group during the influenza season (0.23 vs 0.17 episodes per person-month, respectively, $P=.03$) and during the respiratory season (0.22 vs 0.17 episodes per person-month, respectively, $P=.10$).

Episodes of AOM. TABLE 3 shows that in the first cohort, there were no differences overall between the vaccine group and the placebo group in the proportions of children who had at least 1 episode of AOM during the ensuing influenza season (30.5% vs 29.9%, $P=.89$), during the respiratory season (49.2% vs 52.2%, $P=.56$), or during the entire 1-year follow-up period (57.3% vs 61.9%, $P=.35$).

The difference between the vaccine and placebo groups in the proportion of children with AOM during the respiratory season was 3.0% (95% CI, −13.4% to 7.4%). Within the subgroup of children in the first cohort aged 19 to 24 months, the proportions who had at least 1 episode of AOM during the ensuing influenza and respiratory seasons were suggestively lower in the vaccine group than in the placebo group (19.4% vs 34.3%, $P=.10$; and 36.8% vs 54.3%, $P=.09$, respectively), and during the 1-year follow-up period, significantly lower (44.1% vs 65.7%, $P=.04$). Nevertheless, tests for interaction between vaccine effectiveness and age group produced nonsignificant results. In the second cohort there were no significant differences between the vaccine and placebo groups in the proportions who had at least 1 episode of AOM.

TABLE 4 shows data from both cohorts concerning the distribution of observed episodes of AOM and the mean monthly rates of occurrence of episodes of AOM during the influenza and respiratory seasons, and from the first cohort, values for the entire follow-up year. None of the differences between the vaccine and placebo groups was statistically significant.

Table 2. Geometric Means of Reciprocals of Serum Antibody Titers to Influenza and Children Who Were Seroprotected According to Cohort and Treatment Group

Treatment Group, Timing, and Outcome Measure*	Vaccine Type/Serotype					
	A/H1N1	A/H3N2	B	A/H1N1	A/H3N2	B
Vaccine		**First Cohort (n = 35)**			**Second Cohort (n = 31)**	
Prevaccination						
Mean of reciprocals of titers	5.0	18.5	9.8	5.0	9.5	5.0
Seropositive, No. (%)	0	4 (11.4)	6 (17.1)	0	7 (22.6)	0
Postvaccination						
Mean of reciprocals of titers	46.8	68.3	130	44.3	69.2	42.8
Seroprotected, No. (%)	32 (91.4)	31 (88.6)	32 (91.4)	28 (90.3)	30 (96.8)	28 (90.3)
Placebo		**First Cohort (n = 18)**			**Second Cohort (n = 9)**	
Prevaccination						
Mean of reciprocals of titers	5.0	22.4	12.8	5.0	9.3	5.4
Seropositive, No. (%)	0	4 (22.2)	4 (22.2)	0	2 (22.2)	0
Postvaccination						
Mean of reciprocals of titers	5.0	23.8	13.6	5.0	7.9	5.4
Seroprotected, No. (%)	0	4 (22.2)	6 (33.3)	0	1 (11.1)	0

*Prevaccination seroprotection was defined as the presence of a titer of 1:40 or higher; postvaccination seroprotection was defined as the presence of a titer of 1:40 or higher or a 4-fold increase in antibody titer.

The proportions of children who had an episode of AOM within 1 week of having a positive throat culture for influenza were similar between groups with 13 (54.2%) of 24 in the vaccine and 12 (48.0%) of 25 in the placebo groups ($P=.88$). Acute otitis media was diagnosed at 465 (36.8%) of 1262 acute care visits vs 468 (9.6%) of 4881 routine visits ($P<.001$). That fact notwithstanding, to test the possibility that a vaccine-vs-placebo difference might have been obscured by the inclusion, in the overall analysis, of more or less subclinical cases of AOM diagnosed at other than acute care visits, we further considered the effectiveness of the vaccine in an analysis limited to acute care visits during the influenza and respiratory seasons of each year of the study. Again, there were no differences between the vaccine group and the placebo group in the proportions of children who experienced at least 1 episode of AOM during the 2 influenza seasons (35.6% vs 37.1% and 42.9% vs 31.0%, respectively) or during the 2 respiratory seasons (45.9% vs 41.8% and 44.8% vs 34.2%, respectively).

TABLE 5 shows that there were no significant differences between the vaccine group and the placebo group in the proportions of days with middle ear effusion during the influenza and respiratory seasons.

Table 3. Children Who Experienced at Least 1 Episode of AOM According to Age at Enrollment, by Follow-up Period, and Treatment Group

Cohort, Follow-up Period, and Age Group	No./Total (%) of Children With >1 Episode of AOM		*P* Value
	Vaccine	Placebo	
	First Cohort		
Influenza season*			
All children	79/259 (30.5)	40/134 (29.9)	.89
6-12 mo	35/117 (29.9)	17/54 (31.5)	.84
13-18 mo	31/75 (41.3)	11/45 (24.4)	.06
19-24 mo	13/67 (19.4)	12/35 (34.3)	.10
Respiratory season†			
All children	129/262 (49.2)	70/134 (52.2)	.56
6-12 mo	61/117 (52.1)	27/54 (50.0)	.79
13-18 mo	43/77 (55.8)	24/45 (53.3)	.79
19-24 mo	25/68 (36.8)	19/35 (54.3)	.09
1-Year follow-up period			
All children	150/262 (57.3)	83/134 (61.9)	.35
6-12 mo	72/117 (61.5)	32/54 (59.3)	.78
13-18 mo	48/77 (62.3)	28/45 (62.2)	.99
19-24 mo	30/68 (44.1)	23/35 (65.7)	.04
	Second Cohort		
Influenza season*			
All children	125/239 (52.3)	49/116 (42.2)	.07
6-12 mo	78/142 (54.9)	27/56 (48.2)	.39
13-18 mo	27/59 (45.8)	14/38 (36.8)	.39
19-24 mo	20/38 (52.6)	8/22 (36.4)	.23
Respiratory season†			
All children	135/242 (55.8)	56/116 (48.3)	.17
6-12 mo	83/142 (58.5)	32/56 (57.1)	.87
13-18 mo	31/61 (50.8)	14/38 (36.8)	.18
19-24 mo	21/39 (53.8)	10/22 (45.5)	.53

Abbreviation: AOM, acute otitis media.
*Influenza season was defined as January 3 to February 15, 2000, for the first cohort and as January 4 to March 30, 2001, for the second cohort.
†For each cohort, the respiratory season was defined as the period from December 1 through March 31 of the respective following year.

Health Care Utilization

TABLE 6 shows that in neither cohort were there any statistically significant differences between the vaccine group and the placebo group during ensuing respiratory seasons regarding utilization of selected health care resources. During the second year of the study the rate of hospitalization was actually higher in the vaccine group than in the placebo group.

Table 4. Observed Episodes of AOM by Follow-up Period, Cohort, and Treatment Group

Observations of AOM	Vaccine	Placebo	*P* Value
First Cohort			
Influenza season*			
No. of children	259	134	
Episodes, No. (%) of children			
0	180 (69.5)	94 (70.1)	
1	65 (25.1)	32 (23.9)	
2	14 (5.4)	8 (6.0)	
≥3	0	0	
Total No. of episodes	93	48	
Mean monthly rate of AOM episodes	0.25	0.25	>.99
Respiratory season†			
No. of children	262	134	
Episodes, No. (%) of children			
0	133 (50.8)	64 (47.8)	
1	62 (23.7)	41 (30.6)	
2	40 (15.3)	16 (11.9)	
≥3	27 (10.3)	13 (9.7)	
Total No. of episodes	231	113	
Mean monthly rate of AOM episodes	0.24	0.23	.65
1-Year follow-up			
No. of children	262	134	
Episodes, No. (%) of children			
0	112 (42.7)	51 (38.1)	
1	48 (18.3)	35 (26.1)	
2	45 (17.2)	23 (17.2)	
≥3	57 (21.8)	25 (18.7)	
Total No. of episodes	370	175	
Mean monthly rate of AOM episodes	0.14	0.13	.37
Second Cohort			
Influenza season*			
No. of children	239	116	
Episodes, No. (%) of children			
0	114 (47.7)	67 (57.8)	
1	84 (35.1)	31 (26.7)	
2	37 (15.5)	16 (13.8)	
≥3	4 (1.7)	2 (1.7)	
Total No. of episodes	170	69	
Mean monthly rate of AOM episodes	0.28	0.23	.19
Respiratory season†			
No. of children	242	116	
Episodes, No. (%) of children			
0	107 (44.2)	60 (51.7)	
1	75 (31.0)	30 (25.9)	
2	41 (16.9)	21 (18.1)	
≥3	19 (7.9)	5 (4.3)	
Total No. of episodes	216	87	
Mean monthly rate of AOM episodes	0.27	0.23	.15

Abbreviation: AOM, acute otitis media.
*Influenza season was defined as January 3 to February 15, 2000, for the first cohort and as January 4 to March 30, 2001, for the second cohort.
†For each cohort, the respiratory season was defined as the period from December 1 through March 31 of the respective following year.

Safety

During the 2 years of the study, 39 children in the vaccine group and 12 children in the placebo group underwent insertion of tympanostomy tubes, and 27 and 12 children, respectively, were hospitalized for other reasons. Three adverse events occurred that were considered serious and possibly related to receipt of influenza vaccine: 1 child had 2 brief episodes of unexplained staring on the day of the first vaccination; 1 child had mild intercostal retractions and wheezing 1 day after the second vaccination, and 1 child developed acute gastroenteritis 3 days after the first vaccination.

COMMENT

In our study, influenza vaccination in a group of healthy children aged 6 to 24 months failed to affect the overall occurrence of AOM, although during an epidemic season the vaccine might have provided a measure of protection against AOM to children aged 19 to 24 months and provided some measure of protection against influenza across the age spectrum studied. The results in our study of whether influenza vaccination affects AOM are thus at variance with the results of previous studies in which use of the vaccine reportedly provided an approximate one-third reduction in AOM occurrence.[4-6] The discordant results may be attributable to some of the methodological differences between studies, the most important of which may involve age. More than 75% of the children we enrolled were aged 18 months or younger (mean age, 14 months) compared with mean ages ranging from 20 to 43 months in 3 of the earlier studies.[4-6] Two age-related factors may have been operative. First, the proportion of viral respiratory infections due to influenza virus may be lower in younger children than in older children, so that in younger children the consequences of noninfluenza viral infections may have obscured any effect of influenza vaccination. Evidence that most episodes of respiratory tract infection in the children in our study were caused by viruses other than influenza consists of the facts that during the respiratory sea-

sons, more than 90% of the children with febrile illnesses whom we tested were culture-negative for influenza virus and that during the second year of our study, the incidence of influenza never reached epidemic proportions. Differences between our results and those of a recently reported study that evaluated the efficacy of an intranasally administered, inactivated, virosomal influenza vaccine[7] may be attributable to the generally younger age of our participants; the inclusion in that study only of otitis-prone children who had had an episode of AOM within 2 to 8 weeks; and differences in the manufacture, contents, and route of administration of the vaccines.

A second age-related factor could be that, although satisfactorily immunogenic in young children, influenza vaccine may for other reasons be less effective in preventing influenza—and accordingly, influenza-related otitis media—in younger children than in older children. In a recent study by Hurwitz et al,[14] children aged 24 to 60 months were randomized to receive either inactivated influenza vaccine or placebo and were observed during the ensuing winter for influenza infection, using serologic criteria for the diagnosis. The investigators found no reductions in vaccinated children in respiratory-related events, including ear infections, physician visits, antibiotics prescribed, or missed day-care attendance by children or work attendance by parents. Children with prevaccination titers of 1:5 or lower were less likely to achieve a 4-fold increase in antibody titer after vaccination than children with prevaccination titers of 1:10 or more. In addition, children aged 36 months or older were more likely to respond to vaccination than were younger children. Overall, efficacy of the inactivated vaccine against serologically confirmed influenza was only 31% to 45%, and efficacy was greater in children with prevaccination titers of 1:10 or higher than in those with titers of 1:5 or less.

Table 5. Estimated Proportion of Days With Middle Ear Effusion by Follow-up Period, Cohort, and Treatment Group*

	Influenza Season†				Respiratory Season‡				1-Year Follow-up	
	First Cohort		Second Cohort		First Cohort		Second Cohort		First Cohort	
Days With Middle Ear Effusion	Vaccine (n = 258)	Placebo (n = 133)	Vaccine (n = 239)	Placebo (n = 116)	Vaccine (n = 262)	Placebo (n = 134)	Vaccine (n = 241)	Placebo (n = 116)	Vaccine (n = 262)	Placebo (n = 134)
Days classified as effusion present, No. (%) of children										
0	112 (43.4)	50 (37.6)	65 (27.2)	32 (27.6)	76 (29.0)	28 (20.9)	59 (24.5)	29 (25.0)	59 (22.5)	21 (15.7)
1-25	24 (9.3)	19 (14.3)	42 (17.6)	21 (18.1)	47 (17.9)	46 (34.3)	48 (19.9)	29 (25.0)	98 (37.4)	67 (50.0)
26-50	40 (15.5)	19 (14.3)	50 (20.9)	33 (28.4)	54 (20.6)	22 (16.4)	59 (24.5)	31 (26.7)	56 (21.4)	26 (19.4)
51-75	31 (12.0)	14 (10.5)	39 (16.3)	17 (14.7)	47 (17.9)	15 (11.2)	32 (13.3)	18 (15.5)	30 (11.5)	12 (9.0)
≥76	51 (19.8)	31 (23.3)	43 (18.0)	13 (11.2)	38 (14.5)	23 (17.2)	43 (17.8)	9 (7.8)	19 (7.3)	8 (6.0)
Total days per follow-up period classified as effusion present, mean (SD), %	34.0 (38.4)	36.6 (38.6)	37.1 (33.4)	31.7 (29.3)	34.8 (32.5)	33.3 (31.9)	36.2 (32.1)	30.9 (27.7)	26.5 (26.1)	24.6 (23.6)
P value§	.49		.14		.85		.14		.92	

*Percentages may not sum to 100 due to rounding.
†Influenza season was defined as January 3 to February 15, 2000, for the first cohort and as January 4 to March 30, 2001, for the second cohort.
‡For each cohort, the respiratory season was defined as the period from December 1 through March 31 of the respective following year.

Table 6. Selected Measures of the Potential Economic Impact of Influenza Vaccine During the Ensuing Respiratory Season*

	First Cohort		Second Cohort		Total	
Measure	Vaccine (n = 267)	Placebo (n = 134)	Vaccine (n = 246)	Placebo (n = 118)	Vaccine (n = 513)	Placebo (n = 252)
Visits to primary care physicians, mean (SD)†	1.97 (1.69)	2.07 (1.52)	2.2 (1.75)	2.12 (1.77)	2.08 (1.72)	2.10 (1.64)
Visits to emergency departments, mean (SD)	0.19 (0.48)	0.18 (0.49)	0.3 (0.58)	0.31 (0.56)	0.25 (0.54)	0.24 (0.53)
Children hospitalized, No. (%)‡	33 (12.4)	17 (12.7)	33 (13.4)	7 (5.9)§	66 (12.9)	24 (9.5)
Courses of antibiotics, mean (SD)	1.79 (2.36)	1.92 (2.37)	2.04 (2.57)	1.66 (1.76)	1.91 (2.46)	1.80 (2.11)
Instances of illness in any family member other than the child, mean (SD)	2.74 (1.95)	2.59 (1.73)	2.86 (1.98)	2.73 (1.90)	2.80 (1.96)	2.65 (1.81)
Visits at which parents reported missing work, No./Total (%)‖	105/2004 (5.2)	58/1056 (5.5)	166/1767 (9.4)	57/878 (6.5)	271/3771 (7.2)	115/1934 (5.9)
Visits at which parents reported making other than usual day-care arrangements, No./Total (%)	50/2004 (2.5)	31/1056 (2.9)	71/1767 (4.0)	33/878 (3.8)	121/3771 (3.2)	64/1934 (3.3)

*Treatment groups were compared applying the method of generalized estimating equations.[13] For each cohort, the respiratory season was defined as the period from December 1 through March 31 of the respective following year.
†Includes study visits that were substituted for primary care physician visits.
‡Reasons for hospitalization include bilateral myringotomy and placement of tympanostomy tubes.
§Vaccine vs placebo (second cohort), $P = .05$.
‖Limited to working families.

By comparison, in both cohorts in our study, the seroconversion rate to each vaccine serotype was approximately 90%, and the vaccine was not more likely to induce significant antibody responses in older than in younger children. Nonetheless, among the few children in our study whom we tested, those who had prevaccination hemagglutination-inhibition titers of 1:10 or higher (36% in the first cohort and 8% in the second cohort) also had the highest postvaccination titers. It seems possible that lack of previous exposure to influenza viruses on the part of our study population contributed, in the second year of the study, to the vaccine's inability to prevent influenza, and in both years, to its inability to reduce the incidence of AOM. Finally, it is possible, although not likely, that the vaccines formulated for the 1999-2000 and 2000-2001 seasons were not as effective overall in preventing influenza as vaccines formulated in previous years.

Given that our study did not find a significant difference between vaccine and placebo, it is important to consider the magnitude of difference we were able to detect. The 95% CIs for detecting a difference between the vaccine and placebo groups in the proportion of children with AOM during the respiratory season were −13.4% to 7.4% for the first cohort, −3.5% to 18.5% for the second cohort, and −5.7% to 9.5% for the combined cohorts. Accordingly, our study cannot statistically eliminate the possibility of a decrease in the proportion of children with AOM of 13.4% for the first, 3.3% for the second, and 5.7% for the combined cohorts. An additional consideration is that only 15.9% of children in the placebo group in the first cohort and 3.6% in the second cohort had influenza, and therefore, only a small reduction of AOM could be expected in the vaccine group.

Our study had a number of limitations beyond the fact that, during its second year, the incidence of influenza in the community never reached epidemic proportions. First, we performed cultures for influenza using throat swabs, a method chosen as less invasive than using nasopharyngeal swabs, which may have resulted in underidentification of the virus. Second, because our surveillance, although relatively intensive, relied to some extent on parents' initiating visits for illness, episodes of either influenza or AOM might have been missed. And third, our study was not powered to rule out the possibility of differences in efficacy within specific age subgroups.

Recently, the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention and the American Academy of Pediatrics issued statements encouraging the vaccination of children aged 6 to 23 months against influenza,[8] based on reports that hospitalization rates in such children increase during periods of influenza activity.[15-17] Our study was not designed or powered to detect differences in hospitalization rates. Although influenza vaccination did not reduce the occurrence of AOM in the children we studied, the limited protection we found against the occurrence of influenza itself may be viewed as lending support to immunize healthy infants and young children.

Author Contributions: Dr Hoberman, as principal investigator, had full access to all of the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Administrative, technical, or material support: Hoberman, Lave, Kearney, Haralam, Byers, Zoffel, Fabian, Bernard, Kerr.
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Efficacy and Safety of a Live Attenuated, Cold-Adapted Influenza Vaccine, Trivalent Against Culture-Confirmed Influenza in Young Children in Asia

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ABSTRACT

Background: This study was designed to evaluate the efficacy and safety of cold-adapted influenza vaccine, trivalent (CAIV-T) against culture-confirmed influenza in children 12 to <36 months of age during 2 consecutive influenza seasons at multiple sites in Asia.

Methods: In year one, 3174 children 12 to <36 months of age were randomized to receive 2 doses of CAIV-T (n=1900) or placebo (n=1274) intranasally ≥28 days apart. In year two, 2947 subjects were re-randomized to receive 1 dose of CAIV-T or placebo.

Results: Mean age at enrollment was 23.5±7.4 months. In year 1, efficacy of CAIV-T compared with placebo was 72.9% (95% confidence interval [CI]: 62.8%, 80.5%) against antigenically similar influenza subtypes, and 70.1% (95% CI: 60.9%, 77.3%) against any strain. In year 2, revaccination with CAIV-T demonstrated significant efficacy against antigenically similar (84.3%; 95% CI: 70.1%, 92.4%) and any (64.2%; 95% CI: 44.2%, 77.3%) influenza strains. In year 1, fever, runny nose/nasal congestion, decreased activity and appetite, and use of fever medication were more frequent with CAIV-T after dose 1. Runny nose/nasal congestion after dose 2 (year 1) and dose 3 (year 2) and use of fever medication after dose 3 (year 2) were the only other events reported significantly more frequently in CAIV-T recipients.

Conclusions: CAIV-T was well tolerated and effective in preventing culture-confirmed influenza illness over multiple and complex influenza seasons in young children in Asia.

INTRODUCTION

Young children are a very high-risk group for influenza infection and related complications as well as being a viral reservoir during an influenza season.[1-6] Despite the variable efficacy of trivalent, inactivated influenza vaccine (TIV) observed in children,[7-9] especially younger, immunologically naïve children,[10] the Advisory Committee on Immunization Practices of the United States Centers for Disease Control and Prevention has recommended that children 6 months to 5 years of age be routinely vaccinated against influenza.[11]

While the burden of influenza among children in tropical Asia appears similar to that elsewhere,[12-14] a recent report on influenza-related hospitalization rates in children in Hong Kong demonstrated higher disease rates, exceeding those for temperate regions.[15] Other unique characteristics in the region present considerable challenges to the development and effective implementation of an influenza vaccination policy in children.[16] These include significant annual variability in both influenza seasonality and circulating influenza viruses. In addition, influenza appears to be endemic in some Asian areas with year-round infections as compared to temperate regions where the disease occurs as distinct seasonal outbreaks.[17,18] With 2 of the past 3 pandemics originating in the region, the need to reduce the burden of circulating influenza is of major global public health significance.[19] However, even among adults, TIV has not demonstrated significant protection against antigenically drifted influenza viruses.[20] This represents a significant challenge to the use of TIV in an environment of diverse circulating strains and potentially limits its effectiveness as a public health intervention among children in this region. Currently, the World Health Organization (WHO) makes no specific recommendations for strain composition of TIV for use in tropical Asia.[21]

Live attenuated intranasal influenza vaccines have been shown to elicit broad protective immune responses to influenza virus strains, including both systemic and specific mucosal antibodies.[22] A frozen formulation of live attenuated influenza virus vaccine (LAIV; FluMist®, MedImmune, Gaithersburg, MD) has demonstrated protection against antigenically-drifted influenza in young children,[23,24] and may offer in this region a more appropriate alternative for this age group. Therefore, the purpose of the trial reported here was to evaluate the efficacy of the refrigerated formulation of LAIV (cold-adapted influenza vaccine, trivalent; CAIV-T) against culture-confirmed influenza in young children residing in South, Southeast, and East Asia during multiple influenza seasons over 2 years and to determine the durability and breadth of that protection**.**

MATERIALS AND METHODS

Design

This prospective, randomized, double-blind, placebo-controlled, multicenter, crossover trial was conducted during 2 consecutive years at 16 sites in 8 countries (China, Hong Kong, India, Malaysia, the Philippines, Singapore, Taiwan, and Thailand) between September 30, 2000, and May 31, 2003. The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. Approvals for the original study protocol and all subsequent amendments were obtained from all Human Ethics Committees, Institutional Review Boards, and any regional or national Ethics Committees at participating centers as applicable, before the commencement of any protocol-related activities. Written informed consent was obtained from the parents or legal guardians of all infants prior to enrollment into the study.

Participants

Children aged 12 to <36 months at enrollment who were in good health as determined by medical history, physical examination, and clinical judgment were eligible. Subjects with serious chronic disease, including progressive neurologic disease, Down's syndrome or other cytogenetic disorder, or known or suspected disease of the immune system, and those with documented history of hypersensitivity to egg or egg protein were excluded. All subjects who completed the primary series of CAIV-T or placebo in year 1 and who continued to be free of exclusion criteria were eligible for re-randomization in year 2.

Vaccine and Placebo

CAIV-T reassortant vaccine strains were supplied by MedImmune Vaccines (Mountain View, CA). The refrigerated formulation of CAIV-T vaccine was manufactured and released by Wyeth (Marietta, PA). Each 0.2-mL dose contained approximately 10^7 median tissue culture infectious doses or equivalent fluorescent focus units of each 6:2 reassortant virus strain. The vaccine viruses were grown in specific pathogen-free eggs, purified, and formulated with sucrose-phosphate-glutamate, acid-hydrolyzed porcine gelatin, and arginine as stabilizers. The vaccine contained no preservatives. Placebo consisted of sterile physiological saline manufactured by Wyeth (Marietta, PA). Vaccine and placebo were frozen and shipped to the study sites, where they were stored at 2ºC to 8ºC until just before intranasal administration using a spray applicator (approximately 0.1 mL in each nostril). Both CAIV-T and placebo were supplied in identically packaged sprayers; neither the study subjects, their parent(s)/guardian(s), or the clinical personnel were aware of the treatment being administered.

Vaccine composition was planned to be antigenically representative of the WHO recommendations for the Northern Hemisphere for each year. However, in year 1, due to industry-wide technical problems in the production of the A/H3N2/Moscow/10/99-like virus, A/H3N2/Panama/2007/99 vaccine virus, the recommended strain was replaced with A/H3N2/Sydney/05/97.[25] This decision was based on the antigenic similarity of the hemagglutinin (HA) antigens, a WHO report indicating that A/H3N2/Sydney/05/97-like viruses were circulating prior to the 2000–2001 season,[26] and previous clinical trials with the frozen formulation of LAIV that had demonstrated efficacy against mismatched influenza A/H3N2 virus.[23]

In year 2, because of delays in manufacture, the recommended B vaccine component, B/Victoria/504/2000 (B/Sichuan/379/99-like, Yamagata lineage), was replaced with B/Yamanashi/166/98 (Victoria lineage). Therefore, the B component of the second-year vaccine formulation was not antigenically representative of the B/Victoria/504/2000 (B/Sichuan/379/99-like) virus recommended by the WHO for the upcoming influenza season.

In year 1, subjects were randomized 3:2 (CAIV-T:placebo) to receive 2 doses of CAIV-T or 2 doses of placebo at least 28 days apart using a randomization schedule generated by Wyeth. In year 2, subjects were re-randomized in a 1:1 ratio to receive a single dose of CAIV-T or placebo without consideration of their group assignment in the first year. A schematic representation of the study design (Figure S1) is presented in the web-only supplementary materials available at the journal's web site.

Surveillance for Influenza Illness

Surveillance for influenza-like illness was based on weekly telephone contacts, clinic visits, or home visits, beginning on the eleventh day after receipt of the first dose of study treatment and continued for 2 years until the end of the study. A nasal swab sample was obtained if subjects exhibited any predefined symptoms considered associated with an influenza-like illness.[27] Influenza seasons were defined by (1) the first and last positive cultures of the influenza season if there were sufficient number of cases of culture-confirmed influenza in a given country to identify a seasonal pattern, with random isolates occurring outside of this window being excluded, or (2) if no pattern was evident using influenza cultures, country-specific data from government sources or WHO surveillance data were used.

Influenza-positive specimens obtained by culture were identified by the Centers for Disease Control and Prevention (Atlanta, GA). Additional strain and serotype identification was performed by Wyeth (Pearl River, NY) using virus genotype (years 1 and 2) and virus sequence (year 2) methods.[28,29]

Efficacy estimates were based on illness episodes occurring during the influenza seasons as defined for each country during blind review and based on the weekly number of episodes of culture-confirmed influenza.

Immunogenicity

A subset of 111 subjects at 5 sites participated in an immunogenicity evaluation. The same subjects did not necessarily participate in the cohort in both years. Blood samples were obtained before and after the second vaccination in year 1, and before and after vaccination in year 2.

Samples were assayed for antibodies to influenza A/H1N1, A/H3N2, and B strains by hemagglutination inhibition assay (HAI). Reference viruses used for year 1 samples were A/New Caledonia/20/99 (H1), A/Sydney/5/97 (H3), and B/Yamanashi/166/98 and for year 2 samples were A/New Caledonia/20/99 (H1), A/Sydney/5/97 (H3), and B/Victoria/2/87. Seroconversion was defined as a ≥4-fold increase in antibody titer.[30,31]

Safety Assessment

Following administration of CAIV-T or placebo, parent(s)/legal guardian(s) recorded prompted postvaccination daily symptom information for 11 consecutive days including the day of administration. Other adverse events (AEs) occurring within 11 days following any study dose administration were also collected.

An AE was defined as any clinically significant event, including but not limited to (1) events requiring prescription or nonprescription medication within 11 days of vaccination, (2) any event requiring an unscheduled healthcare provider visit and/or consultation within 11 days of vaccination, (3) events resulting in study termination, and (4) any other clinically significant event occurring at any time during the course of the study. Serious adverse events (SAEs), including hospitalizations, were monitored from enrollment until the end of the study.

Statistical Analysis

The sample size calculation assumed rates of culture-confirmed influenza in the placebo and CAIV-T groups (12% and 3% respectively) as previously reported,[23] and a subject discontinuation rate of 60% or less over 2 years. A sample size of 3000 subjects (1800 in the

CAIV-T group and 1200 in the placebo group) permitted at least 90% power to demonstrate 45% efficacy at the 0.05 significance level.

The randomization schedule for each year was generated by Wyeth Vaccines Research. In year 1, vaccine and placebo were labeled with 1 of 5 treatment codes, 3 of which corresponded to CAIV-T treatment and 2 to placebo, to ensure blinding with a 3:2 ratio. At enrollment, each subject was assigned the next sequential subject number and received study product of the treatment code assigned to that subject number according to a preprinted randomization allocation list. In year 2, randomization at each site was accomplished using an interactive voice response system (IVRS). Trial personnel telephoned the IVRS system to obtain a 6-digit vaccine identification number corresponding to nasal sprays mailed to that site and numbered according to a predetermined randomization list.

The per protocol (PP) population in year 1 included all randomized subjects who received all doses of assigned treatment and who remained in the study for at least 15 days after receiving the second dose of CAIV-T or placebo. The PP population in year 2 included all re-randomized subjects who received their assigned treatment and remained in the study for at least 15 days after vaccination in year 2. The intent-to-treat (ITT) population in year 1 included all subjects who were enrolled in the study and received at least 1 dose of study treatment. The year 2 ITT population included all subjects re-randomized in year 2.

The primary efficacy end point was the first episode of culture-confirmed influenza illness caused by a subtype antigenically similar to that in the vaccine after receipt of the second dose of study vaccine or placebo during year 1 in the PP population. Secondary efficacy end points included the first episode of culture-confirmed influenza illness caused by any influenza virus

subtype after receipt of the second dose of study vaccine or placebo during year 1 and the first episode of culture-confirmed influenza caused by subtypes antigenically similar to vaccine components after completion of a primary series in year 1 and a single dose in year 2. An additional proposed secondary end point was to evaluate all episodes of clinically defined AOM, febrile AOM, and influenza-associated AOM. However, there were too few cases to provide adequate analysis. Immunologic seroconversion as measured by serum HAI was also evaluated. Geometric mean fold rise (GMFR) is defined as the relative increase in geometric antibody titers after vaccination over corresponding prevaccination titers.

Vaccine efficacy against culture-confirmed influenza was defined as $1 - I_V/I_C$, where I_V is the case incidence for the CAIV-T group, and I_C is similarly defined for the placebo group. For each estimate of vaccine efficacy, 95% confidence intervals (CI) were determined using the binomial distribution conditional on the total number of cases observed.

All subjects who received ≥1 dose of study vaccine were evaluated for safety. Reactogenicity events were summarized for each dose and compared using a 2-sided Fisher exact test without adjustment for multiple comparisons. AEs within 11 days after dose administration were summarized.

RESULTS

Study Participants

Enrollment occurred during a 10-week period beginning September 30, 2000; 3174 subjects (CAIV-T, n=1900; placebo, n=1274) were randomized. Participant flow is summarized in

Figure 1. The year 1 PP efficacy population consisted of 2764 subjects (1653 CAIV-T, 1111 placebo). Demographic characteristics of this population are presented in **Table 1**.

In year two, 2947 subjects were re-randomized to receive either a single dose of CAIV-T or placebo **(Figure 1)**, administered during a 4- to 6-week period beginning November 9, 2001. The year 2 PP efficacy population consisted of 2527 subjects. An additional 69 subjects from year 1 were not randomized in year 2 but were followed-up for safety and influenza surveillance throughout year 2. A more detailed summary of participant flow, including reasons for exclusion from the PP analysis in years 1 and 2 is presented in the web-only supplementary materials (Figure S2) available at the journal's web site.

Culture-Confirmed Influenza

The pattern of influenza seasons in participating countries during the 2-year period from October 2000 through October 2002 is summarized in **Figure 2**.

Circulating Strain Variants

A high percentage (29.2%) of year 1 influenza B viruses were considered antigenically distinct from the vaccine, while 99.2% of circulating influenza A/H1N1 viruses were antigenically similar to those in the vaccine. All B cultures in year 1 that were classified as antigenically similar were identified by the Centers for Disease Control and Prevention as being similar to B/Sichuan/379/99, a strain that is related but antigenically distinguishable from the year 1 vaccine strain, B/Yamanashi. Over 77% of year 2 influenza B viruses were antigenically distinct from those of the vaccine. Circulating strains isolated from participating subjects at all sites by month are summarized in the lower panel of **Figure 2.**

Vaccine Efficacy: Year 1

Per-protocol vaccine efficacy against culture-confirmed influenza in year 1 is summarized in **Table 2**. The incidence of influenza caused by strains antigenically similar to vaccine was 3.4% and 12.5% in the CAIV-T and placebo groups, respectively. Overall efficacy of CAIV-T against influenza viruses antigenically similar to those in the vaccine was 72.9% (95% CI: 62.8%, 80.5%). Statistically significant vaccine efficacy was observed against all 3 circulating viruses antigenically similar to the vaccine, influenza A/H1N1 (80.9%) and AH3N2 (90.0%), and B (44.3%). Overall, vaccine efficacy against any influenza strain was 70.1% (95% CI: 60.9%, 77.3%), with vaccine efficacy against any A/H1N1, A/H3N2, or B strain being similar to that against viruses antigenically similar to the vaccine (81.1%, 84.3% and 43.1% respectively). Only 0.8% of CAIV-T recipients had confirmed cases of influenza caused by drifted strains (n=14 cases, all influenza B) and 1.6% of placebo recipients (n=18 cases, 17 B and 1 A/H1). Although it did not achieve statistical significance, vaccine efficacy against all influenza strains that were confirmed to be antigenically dissimilar to the vaccine was 47.7% (95% CI: –11.2%, 75.9%).

Durability of Protection

Malaysia and the Philippines experienced late influenza outbreaks in year 1. Malaysia experienced an initial influenza outbreak of primarily A/H3N2 and B strains between October 26, 2000 and March 1, 2001; this outbreak was then followed by an outbreak of A/H1N1 between August 7, 2001 and November 16, 2001. This second outbreak occurred 7.5 to 12.5 months after the second vaccine dose in year 1 and vaccine efficacy was 85.1% (95% CI: 28.2, 98.4) against antigenically similar strains. In the Philippines, there was 1 week between November 13, 2000 and November 20, 2000 in which there were no cases of influenza in the PP

population. Subsequently, an A/H1N1, A/H3N2, and B outbreak occurred between June 7, 2001 and November 26, 2001. This outbreak occurred 5.5 to 13 months following the second dose and vaccine efficacy was 69.4% (95% CI: 42.4, 84.5) against antigenically similar strains. A combined analysis of these 2 seasons in Malaysia and the Philippines yielded a vaccine efficacy of 72.9% (95% CI: 51.5, 85.5).

Vaccine Efficacy: Year 2

Pair-wise comparisons of the 4 study groups were performed to highlight the effects of different vaccination regimens on vaccine efficacy against antigenically similar and any influenza viruses in year 2 **(Table 3)**.

Efficacy of 2 Doses

In the United States, a 2-dose regimen of the frozen formulation of CAIV-T (FluMist®, MedImmune) is indicated for previously-unvaccinated children 5 through 8 years of age, and a single dose is indicated in subsequent years. In the current study of Asian children 12 to <36 months of age at enrollment, annual vaccination during 2 successive years (2 doses of CAIV-T in year 1 and 1 dose of CAIV-T in year 2) provided significant efficacy against both antigenically similar (84.3%; 95% CI: 70.1%, 92.4%) and any (64.2%; 95% CI: 44.2%, 77.3%) influenza strain compared with no vaccination (2 doses of placebo in year 1 and 1 dose of placebo in year 2). Efficacy against antigenically similar A/H3N2 influenza strains was 86.3% (95% CI: 71.4%, 94.1%). There were insufficient cases to accurately assess and draw conclusions for efficacy against antigenically similar or any A/H1 and B subtypes.

Revaccination in the second year (CAIV-T/CAIV-T) yielded greater efficacy against antigenically similar influenza strains than vaccination in the first year only (CAIV-T/placebo). The estimated efficacy benefit of a second year revaccination against antigenically similar strains compared with vaccination in the first year only was 64.2% (95% CI: 28.9%, 83.2%).

Durability of Protection

The persistence of protection afforded by 2 doses of CAIV-T was demonstrated comparing the CAIV-T /placebo and placebo/placebo groups. The overall efficacy of 56.2% (95% CI: 30.5%, 72.7%) against antigenically similar strains indicates that a primary series of 2 doses of CAIV-T elicits an immune response capable of protecting against influenza for 2 years in many but not all children.

Efficacy of a Single Dose

A full series of vaccinations over 2 years (CAIV-T/CAIV-T) was more protective than a single dose of CAIV-T in year 2 (placebo/CAIV-T). Relative efficacy against culture-confirmed influenza subtypes antigenically similar to the vaccine was 60.9% (95% CI: 15.9%, 82.6%). However, a single dose of CAIV-T in year 2 (placebo/CAIV-T) was superior to no vaccination at all (placebo/placebo) with an efficacy of 59.9% (95% CI: 31.3%, 77.4%) against antigenically similar strains.

Immunogenicity Assessment

The immunogenicity results are presented in **Table 4**. After 2 doses in year 1, CAIV-T elicited significant anti-influenza antibody responses compared with placebo. Seroconversion rates were higher among seronegative subjects for all influenza strains.

For year 2, the seroconversion rates and fold-increases in geometric mean titers (GMTs) were statistically significant only for treatment groups that received CAIV-T in year 2 **(Table 5)**, irrespective of serologic status before vaccination or the vaccination received in year 1. Seronegative subjects receiving CAIV-T and tested for antibody in year 2 had statistically significant fold-increases in GMTs for all virus subtypes.

Safety Evaluation

Reactogenicity events are summarized in **Table 6**. There was a significantly higher frequency of fever ≥37.5°C (22.0% vs 17.6%; *P*=0.004), runny nose/nasal congestion (62.0% vs 52.0%; *P*<0.001), decreased activity (13.4% vs 10.7%; *P*=0.026), decreased appetite (24.2% vs 19.7%; *P*=0.003), and use of fever medication (21.3% vs 18.4%; *P*=0.044) following the first dose of CAIV-T in year 1, when compared with placebo. There was no significant difference between treatment groups for fever ≥38.6%. Following dose 2 in year 1, runny nose/nasal congestion was the only event that was reported by a significantly higher (*P*=0.030) proportion of CAIV-T (49.8%) than placebo recipients (45.6%).

Similar results were observed after vaccination in year 2, with a higher incidence of runny nose/nasal congestion (62.0% vs 55.4%, *P*=0.001) and use of fever medication (*P*=0.019) in CAIV-T recipients.

Among AEs occurring within 11 days after vaccination, only fever was reported more frequently (*P*=0.003) in year 1 after the first dose of CAIV-T than placebo (15.4% vs 11.7%). There were no differences in AEs reported after the second dose. After dose 1 in year 2, fever was again the only event more common in CAIV-T recipients (12.7% vs 9.8%, *P*=0.017).

In year 1, SAEs were uncommon in both treatment groups, with no significant differences between the CAIV-T and placebo groups (P=0.516). The most frequently reported year 1 SAEs were bronchospasm (7 CAIV-T, 3 placebo), bronchitis (3 CAIV-T, 2 placebo), and rhinitis (3 CAIV-T, 0 placebo). There was only 1 reported SAE in year 2 in a child who was hospitalized with pneumonia 6 days after receiving CAIV-T. Only 1 subject discontinued because of a safety-related event: a 20-month-old female developed fever that persisted for 3 days and was judged to be possibly related to study medication, 2 days after receiving the first dose of CAIV-T in year 1. There were 2 deaths in the study, both in year 1. One child died of an unknown cause after a brief illness approximately 4 months after receiving the second dose of placebo. The second child died from an accidental drowning 15 days after receipt of the first dose of CAIV-T. Neither death was considered related to study vaccine.

DISCUSSION

This clinical trial is a comprehensive evaluation of the efficacy of live attenuated influenza vaccine in young children. The trial has established that the rates of culture-confirmed influenza in young children across the region are similar to those reported in the United States using the same illness criteria,[23,27] and is the first demonstration for any influenza vaccine of efficacy against all 3 influenza virus subtypes (A/H1N1, A/H3N2, and B) circulating during the same influenza season. Further, in 2 countries, 2 doses of CAIV-T administered in year 1 conferred protection against antigenically similar A/H1N1, A/H3N2, and B strains that was comparable to the efficacy seen in the overall study, despite the fact that the outbreaks occurred 5.5 to 13 months after the second vaccine dose. Additionally, significant protection was demonstrated against antigenically similar influenza A/H3N2 virus over a second year of the trial (up to 23

months after the second dose). However, the decline in the level of protection over time, and the beneficial effect of another dose in the second year, clearly supports the value of annual vaccination.

Although CAIV-T demonstrated efficacy against all community-acquired influenza strains, this study was not designed to specifically evaluate efficacy against antigenically drifted strains. Indeed, statistical significance was not achieved for efficacy against influenza caused by viral strains that were confirmed to be dissimilar to the vaccine perhaps because of the small number of cases in this study. However, other studies have shown efficacy against mismatched influenza strains.[23,32]

As observed with the frozen formulation of CAIV-T in older children, the refrigerated formulation of CAIV-T was highly effective in eliciting serum antibody responses as measured by HAI, with the strongest responses detected in children considered seronegative for influenza. After vaccination in year 2, increased seroconversion and HA titers to A/H1N1 and B strains were observed only in CAIV-T recipients. Increases observed in subjects who were seropositive in year 2 before vaccination, illustrate the ability of CAIV-T to provide an immune boost on subsequent immunization and confirm that the ability to develop an immune response is not adversely affected by prior vaccination with that strain.

Administration of multiple doses of CAIV-T to children 12 to <36 months of age was safe and well tolerated. After the first dose in year 1, the incidence of reactogenicity events such as runny nose/nasal congestion, decreased appetite, decreased activity, and the use of fever medications were statistically greater in CAIV-T recipients than the background rates reported by placebo recipients. However, the relative differences in incidence were low, ranging from 10% for nasal

congestion to 2.7% for decreased activity. SAEs were infrequent and similar between CAIV-T and placebo recipients.

Our findings are consistent with other reports of the efficacy and safety of CAIV-T in young children.[33-35] In a placebo-controlled trial of healthy children 6 to <36 months of age attending day care at sites throughout Europe and Israel, CAIV-T reduced the incidence of influenza caused by antigenically similar influenza strains by 85% after 2 doses of vaccine in year 1 and by 89% after a single dose of vaccine in year 2.[33] In a comparative study with TIV in children 6 to 71 months of age with a history of recurrent respiratory tract infections, CAIV-T resulted in 52.7% fewer cases of influenza caused by strains antigenically similar to the vaccine than did TIV.[35] CAIV-T was well tolerated in both of these studies and runny nose/nasal discharge was the only reactogenicity event that occurred significantly more frequently with CAIV-T than placebo. In large studies in young children, CAIV-T was associated with statistically increased rates of wheezing and, in certain subsets, with increased rates of all-cause hospitalization.[36,37] In the present study the incidence of wheezing and of serious adverse events including hospitalization was rare and similar among recipients of CAIV-T or placebo. In other studies specifically conducted in children with asthma or a history of respiratory tract infections, no significant increase in wheezing or other serious adverse outcomes was observed.[34,35]

The diversity of seasonality and circulating strains in Asia, the absence of clear guidance on vaccine composition for the region, and the variable efficacy of TIV in this age group suggests the need for an influenza vaccine that can be easily administered and provide broad protection against circulating influenza viruses over more than 1 year. CAIV-T was demonstrated to be a versatile, durable, and highly efficacious intervention in the control of influenza among young children in tropical and temperate regions in Asia.

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Legends to Figures

Figure 1. Summary of study design and patient distribution.

Figure 2. Seasonality of influenza in Asian countries during a 2-year period. Bars represent periods of high influenza activity in countries where the study was conducted with the number of positive nasal swabs for each subtype (H1, H3, B) during that interval shown within the bar. The lower panel lists the virus strains identified during the study and their temporal distribution by month. Virus strains in the lower panel represented with shaded text are antigenically distinct from vaccine strains.

Figure S1. Study design. Subjects were randomized 3:2 (CAIV-T:placebo) to receive 2 doses of CAIV-T or 2 doses of placebo in year 1. In year 2, subjects were re-randomized in a 1:1 ratio to receive a single dose of CAIV-T or placebo without consideration of their group assignment in the first year.

Figure S2. Participant flow, including reasons for exclusion from the per protocol analysis.

Tables

Table 1. Demographic Characteristics of the Year 1 Per-Protocol Population

	Treatment Group		
Characteristic	**CAIV-T n=1653**	**Placebo n=1111**	**Total N=2764**
Sex, n (%)			
Girls	773 (46.8)	523 (47.1)	1296 (46.9)
Boys	880 (53.2)	588 (52.9)	1468 (53.1)
Ethnic origin, n (%)			
Indian subcontinent	112 (6.8)	83 (7.5)	195 (7.1)
Chinese	602 (36.4)	396 (35.6)	998 (36.1)
Filipino	433 (26.2)	300 (27.0)	733 (26.5)
Thai	492 (29.8)	321 (28.9)	813 (29.4)
Malay	1 (0.1)	1 (0.1)	2 (0.1)
European	1 (0.1)	1 (0.1)	2 (0.1)
Other	12 (0.7)	9 (0.8)	21 (0.8)
Age at first vaccination (mo)			
Mean (SD)	23.6 (7.4)	23.4 (7.3)	23.5 (7.4)
Median	23.3	23.4	23.3

Characteristic	Treatment Group		
	CAIV-T	**Placebo**	**Total**
	n=1653	**n=1111**	**N=2764**
Range	12.0–35.9	12.0–35.9	12.0–35.9
Age group (mo), n (%)			
12 to <18	469 (28.4)	343 (30.9)	812 (29.4)
18 to <24	402 (24.3)	233 (21.0)	635 (23.0)
24 to <30	357 (21.6)	266 (23.9)	623 (22.5)
30 to <36	425 (25.7)	269 (24.2)	694 (25.1)

CAIV-T=cold-adapted influenza vaccine, trivalent; SD=standard deviation.

Table 2. Efficacy of CAIV-T Against Culture-Confirmed Influenza in Year 1

Influenza Subtype	Treatment Group				
	CAIV-T		Placebo		
	No. of Subjects in Population	No. (%) With Culture-Confirmed Influenza	No. of Subjects in Population	No. (%) With Culture-Confirmed Influenza	Efficacy, % (95% CI)
Subtypes antigenically similar to the vaccine					
Per protocol population					
Any antigenically similar strain	1653	56 (3.4)	1111	139 (12.5)	72.9 (62.8, 80.5)
A/H1N1	1653	23 (1.4)	1111	81 (7.3)	80.9 (69.4, 88.5)
A/H3N2	1653	4 (0.2)	1111	27 (2.4)	90.0 (71.4, 97.5)
B	1653	29 (1.8)	1111	35 (3.2)	44.3 (6.2, 67.2)
Intent-to-treat population					

Influenza Subtype	Treatment Group				Efficacy, % (95% CI)
	CAIV-T		Placebo		
	No. of Subjects in Population	No. (%) With Culture-Confirmed Influenza	No. of Subjects in Population	No. (%) With Culture-Confirmed Influenza	
Any antigenically similar strain	1900	70 (3.7)	1274	157 (12.3)	70.1 (60.1, 77.8)
Any subtypes					
Per protocol population					
Any strain	1653	81 (4.9)	1111	182 (16.4)	70.1 (60.9, 77.3)
A/H1N1	1653	23 (1.4)	1111	82 (7.4)	81.1 (69.8, 88.7)
A/H3N2	1653	14 (0.8)	1111	60 (5.4)	84.3 (71.6, 91.9)
B	1653	44 (2.7)	1111	52 (4.7)	43.1 (13.4, 62.8)
Intent-to-treat population					

Influenza Subtype	Treatment Group				
	CAIV-T		Placebo		
	No. of Subjects in Population	No. (%) With Culture-Confirmed Influenza	No. of Subjects in Population	No. (%) With Culture-Confirmed Influenza	Efficacy, % (95% CI)
Any strain	1900	98 (5.2)	1274	204 (16.0)	67.8 (58.8, 74.9)

CAIV-T=cold-adapted influenza vaccine, trivalent; CI=confidence interval.

Table 3. Efficacy of CAIV-T Against Culture-Confirmed Influenza in Year 2: Comparison of Treatment Groups (Per-Protocol Efficacy Population)

	Antigenically Similar Strain		Any Strain	
Treatment Comparison* (Year 1 Treatment/Year 2 Treatment)	**Influenza Cases/ Comparison Populations**	**Efficacy, % (95% CI)**	**Influenza Cases/ Comparison Populations**	**Efficacy, % (95% CI)**
CAIV-T/CAIV-T vs placebo/placebo	12/771 vs 49/494	84.3 (70.1, 92.4)	33/771 vs 59/494	64.2 (44.2, 77.3)
CAIV-T/placebo vs placebo/placebo	33/759 vs 49/494	56.2 (30.5, 72.7)	70/759 vs 59/494	44.8 (18.2, 62.9)
CAIV-T/CAIV-T vs CAIV-T/placebo	12/771 vs 33/759	64.2 (28.9, 83.2)	33/771 vs 50/759	35.0 (–2.9, 59.5)
CAIV-T/CAIV-T vs placebo/CAIV-T	12/771 vs 20/503	60.9 (15.9, 82.6)	33/771 vs 26/503	17.2 (–44.2, 52.0)
placebo/CAIV-T vs placebo/placebo	20/503 vs 49/494	59.9 (31.3, 77.4)	26/503 vs 59/494	56.7 (30.3, 73.8)

CAIV-T=cold-adapted influenza vaccine, trivalent; CI=confidence interval.

*Subjects randomized to CAIV-T in year 1 received 2 doses of CAIV-T in year 1. Subjects re-randomized to CAIV-T in year 2 received a single dose of CAIV-T.

Table 4. Serum HAI Assay Seroconversion Rate and Geometric Mean Antibody Titer Fold-Rise Following 2 Doses in Year 1

			HAI Assay			
Virus Type/ Subtype	**Serologic Status Before Vaccination**	**Treatment Group**	**n**	**Seroconversion Rate, n (%)***	**GMFR[†] (95% CI[‡])**	**P Value[§]**
A/H1N1	All	CAIV-T	111	67 (60.4)	5.0 (3.9, 6.5)	<0.001
		Placebo	75	8 (10.7)	1.2 (1.0, 1.5)	0.045
	Seronegative[‖]	CAIV-T	71	60 (84.5)	9.6 (7.2, 12.8)	<0.001
		Placebo	52	7 (13.5)	1.4 (1.1, 1.8)	0.015
A/H3N2	All	CAIV-T	111	68 (61.3)	17.0 (11.0, 26.4)	<0.001
		Placebo	75	3 (4.0)	1.1 (1.0, 1.4)	0.141
	Seronegative[‖]	CAIV-T	61	58 (95.1)	91.0 (64.0, 129.6)	<0.001
		Placebo	47	1 (2.1)	1.2 (0.9, 1.5)	0.229
B	All	CAIV-T	111	63 (56.8)	6.8 (4.9, 9.4)	<0.001

	Placebo	75	3 (4.0)	1.0 (0.9, 1.2)	0.526
Seronegative[‖]	CAIV-T	82	61 (74.4)	11.7 (8.1, 16.8)	<0.001
	Placebo	63	3 (4.8)	1.1 (0.9, 1.3)	0.349

CAIV-T=cold-adapted influenza vaccine, trivalent; CI=confidence interval; GMFR=geometric mean fold-rise; HAI=hemagglutination inhibition.

*$P<0.001$ for all serologic status comparisons. No adjustment was made for multiple comparisons.

[†]Calculated for those subjects with pre- and postvaccination HAI assay values for that particular strain. The starting dilution was 1:4.

[‡]Confidence limits are back transforms of a CI based on Student *t* distribution for the mean logarithm of the titers.

[§]*P* value for the null hypothesis that the mean logarithm of the fold-rise within subject was 0 and was derived by a 2-sided, 1-sample Student *t* test on the logarithms. No adjustment was made for multiple comparisons.

[‖]Subjects with a baseline HAI antibody titer ≤1:4 to that particular influenza virus strain.

Table 5. Serum Seroconversion Rate and Geometric Mean Antibody Titer Fold-Rise Following 1 Dose in Year 2

				HAI Assay		
Virus Type/ Subtype	**Serologic Status Before Vaccination**	**Treatment Group**	**n**	**Seroconversion Rate n (%)***	**GMFR† (95% CI‡)**	***P* Value§**
A/H1N1	All	Group 1 (C/C;C)	50	14 (28.0)	2.1 (1.5, 2.8)	<0.001
		Group 2 (C/C;P)	50	2 (4.0)	1.1 (0.9, 1.2)	0.280
		Group 3 (P/P;C)	45	9 (20)	1.5 (1.0, 2.2)	0.033
		Group 4 (P/P;P)	26	1 (3.8)	1.3 (0.8, 1.9)	0.249
	Seronegative‖	Group 1 (C/C;C)	11	9 (81.8)	9.7 (4.5, 20.5)	<0.001
		Group 2 (C/C;P)	11	1 (9.1)	1.1 (0.8, 1.5)	0.676
		Group 3 (P/P;C)	22	7 (31.8)	2.4 (1.4, 4.1)	0.003
		Group 4 (P/P;P)	15	1 (6.7)	1.5 (0.8, 3.0)	0.219
A/H3N2	All	Group 1 (C/C;C)	50	16 (32.0)	1.9 (1.3, 2.8)	<0.001
		Group 2 (C/C;P)	50	0 (0.0)	0.9 (0.7, 1.1)	0.151

		Group 3 (P/P;C)	45	17 (37.8)	3.0 (2.0, 4.6)	<0.001
		Group 4 (P/P;P)	26	3 (11.5)	1.1 (0.7, 1.7)	0.733
	Seronegative[‖]	Group 1 (C/C;C)	4	3 (75.0)	8.0 (1.1, 59.9)	0.046
		Group 2 (C/C;P)	6	0 (0.0)	1.3 (0.9, 1.8)	0.175
		Group 3 (P/P;C)	16	12 (75.0)	8.0 (3.6, 17.8)	<0.001
		Group 4 (P/P;P)	11	2 (18.2)	1.8 (0.8, 3.7)	0.121
B	All	Group 1 (C/C;C)	50	13 (26.0)	1.8 (1.2, 2.7)	0.005
		Group 2 (C/C;P)	50	1 (2.0)	0.9 (0.7, 1.0)	0.105
		Group 3 (P/P;C)	45	14 (31.1)	2.6 (1.7, 3.9)	<0.001
		Group 4 (P/P;P)	26	3 (11.5)	1.3 (0.9, 2.0)	0.195
	Seronegative[‖]	Group 1 (C/C;C)	21	11 (52.4)	4.1 (2.2, 7.7)	<0.001
		Group 2 (C/C;P)	24	1 (4.2)	1.0 (0.8, 1.1)	0.714
		Group 3 (P/P;C)	32	13 (40.6)	3.4 (1.9, 6.0)	<0.001
		Group 4 (P/P;P)	21	2 (9.5)	1.3 (0.9, 1.8)	0.119

C=Cold-adapted influenza vaccine, trivalent; CI=confidence interval; GMFR=geometric mean fold-rise; HAI=hemagglutination inhibition; P=placebo.

*For GMFR calculations, n was derived from only those subjects who had known HAI assay values for both pre- and postvaccination blood draws for that particular strain.

†*P* value between treatment groups in each serologic status comparison was <0.001. No adjustment was made for multiple comparisons.

‡Confidence limits are back transforms of a CI based on Student *t* distribution for the mean logarithm of the titers.

§*P*-value for the null hypothesis that the mean logarithm of the fold-rise within subject was 0 and was derived by a 2-sided, 1-sample Student *t* test on the logarithms. No adjustment was made for multiple comparisons.

‖Serologic status before vaccination. Seronegative subjects were defined as those with a baseline HAI antibody titer ≤1:4 to that particular influenza virus strain.

Table 6. Reactogenicity Events Reported on Subject Diary Cards Occurring in the First 11 Days Following Each Dose of CAIV-T or Placebo

	Year 1						Year 2		
	Dose 1			Dose 2			Dose 1*		
Event	CAIV-T n=1764–1857[†] No. (%)	Placebo n=1182–1246[†] No. (%)	[‡]P Value	CAIV-T n=1579–1661[†] No. (%)	Placebo n=1088–1119[†] No. (%)	[‡]P Value	CAIV-T n=1345–1352[†] No. (%)	Placebo n=1327–1340[†] No. (%)	[‡]P Value
[§]Fever 37.5°C	393 (22.0)	209 (17.6)	0.004	241 (15.2)	164 (15.0)	0.956	242 (18.0)	218 (16.4)	0.305
[§]Fever 38.6°C	87 (4.9)	48 (4.1)	0.323	64 (4.0)	41 (3.8)	0.762	62 (4.6)	67 (5.0)	0.652
[§]Fever 40.0°C	5 (0.3)	2 (0.2)	0.709	5 (0.3)	4 (0.4)	>0.99	4 (0.3)	6 (0.5)	0.545
Runny nose or nasal discharge	1151 (62.0)	647 (52.0)	<0.001	827 (49.8)	510 (45.6)	0.030	838 (62.0)	743 (55.4)	0.001
Cough	630 (34.1)	481 (38.6)	0.010	568 (34.3)	374 (33.5)	0.683	567 (42.0)	543 (40.6)	0.481
Vomiting	282 (15.3)	212 (17.1)	0.193	195 (11.8)	127 (11.4)	0.763	210 (15.6)	187 (14.0)	0.254
Decreased activity	248 (13.4)	133 (10.7)	0.026	133 (8.0)	96 (8.6)	0.623	134 (9.9)	120 (9.0)	0.429
Decreased appetite	448 (24.2)	245 (19.7)	0.003	275 (16.6)	214 (19.1)	0.094	295 (21.9)	268 (20.0)	0.255

Irritability	445 (24.1)	265 (21.3)	0.081	260 (15.7)	167 (15.0)	0.629	228 (16.9)	208 (15.6)	0.374
Stomach ache	NC	NC	—	NC	NC	—	146 (10.8)	142 (10.6)	0.901
Use of fever medication	395 (21.3)	228 (18.4)	0.044	231 (14.0)	163 (14.6)	0.658	246 (18.2)	198 (14.8)	0.019
‖Any event	1397 (76.0)	851 (69.5)	<0.001	1030 (63.5)	657 (59.2)	0.025	999 (73.9)	936 (70.1)	0.032

CAIV-T=cold-adapted influenza vaccine, trivalent; NC=not collected in year 1 because not all children were old enough to verbalize this symptom.

*Subjects who received CAIV-T in year 2 only were not analyzed separately from those who received CAIV-T in both years.

†n represents the number of subjects with known values.

‡Two-sided Fisher exact test. No adjustment was made for multiple comparisons.

§Axillary temperature (equivalent fever cut off points are used for temperatures obtained orally or rectally).

‖Any event does not include the administration of fever medication.

Figures

Figure 1.

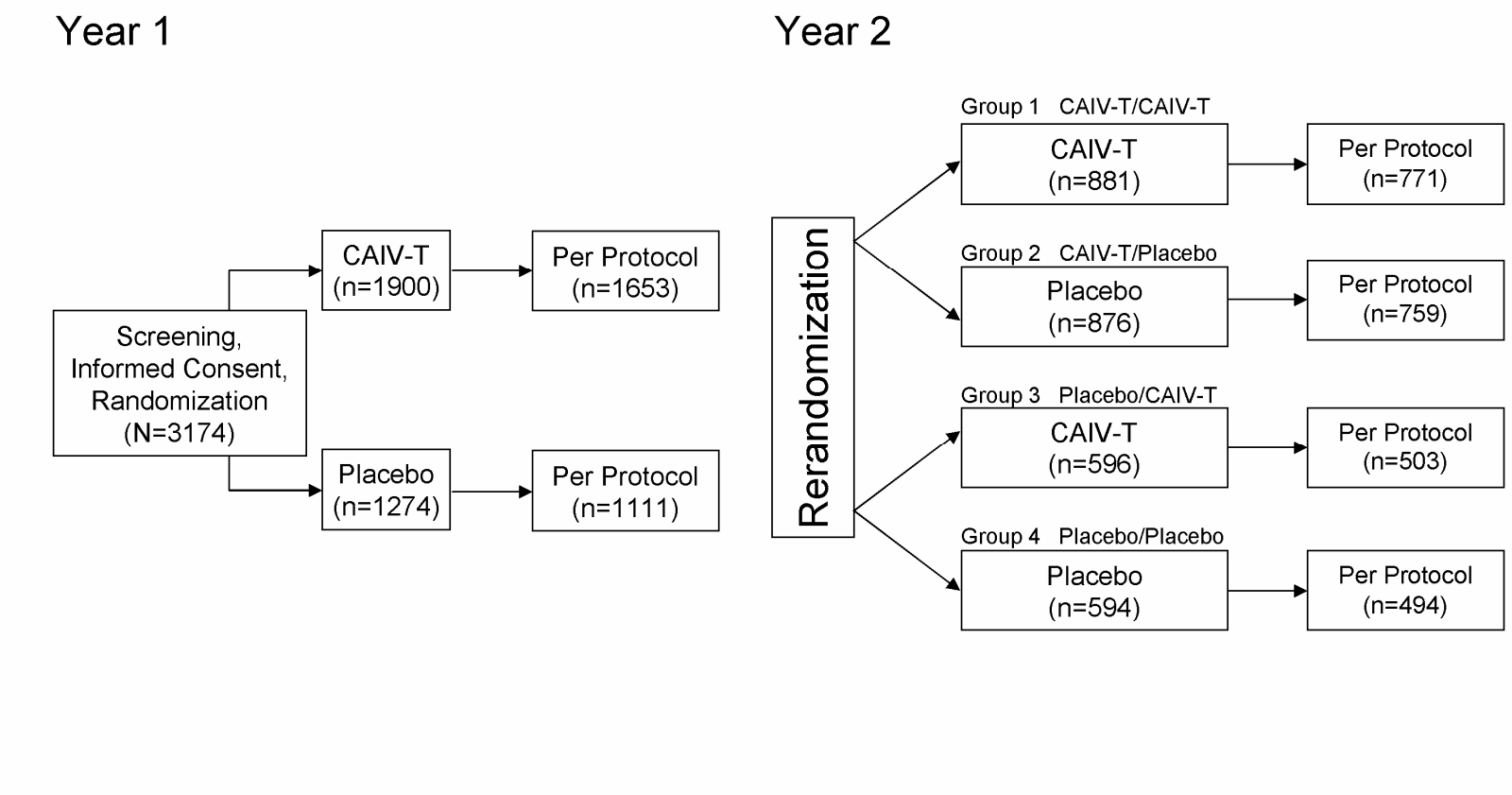
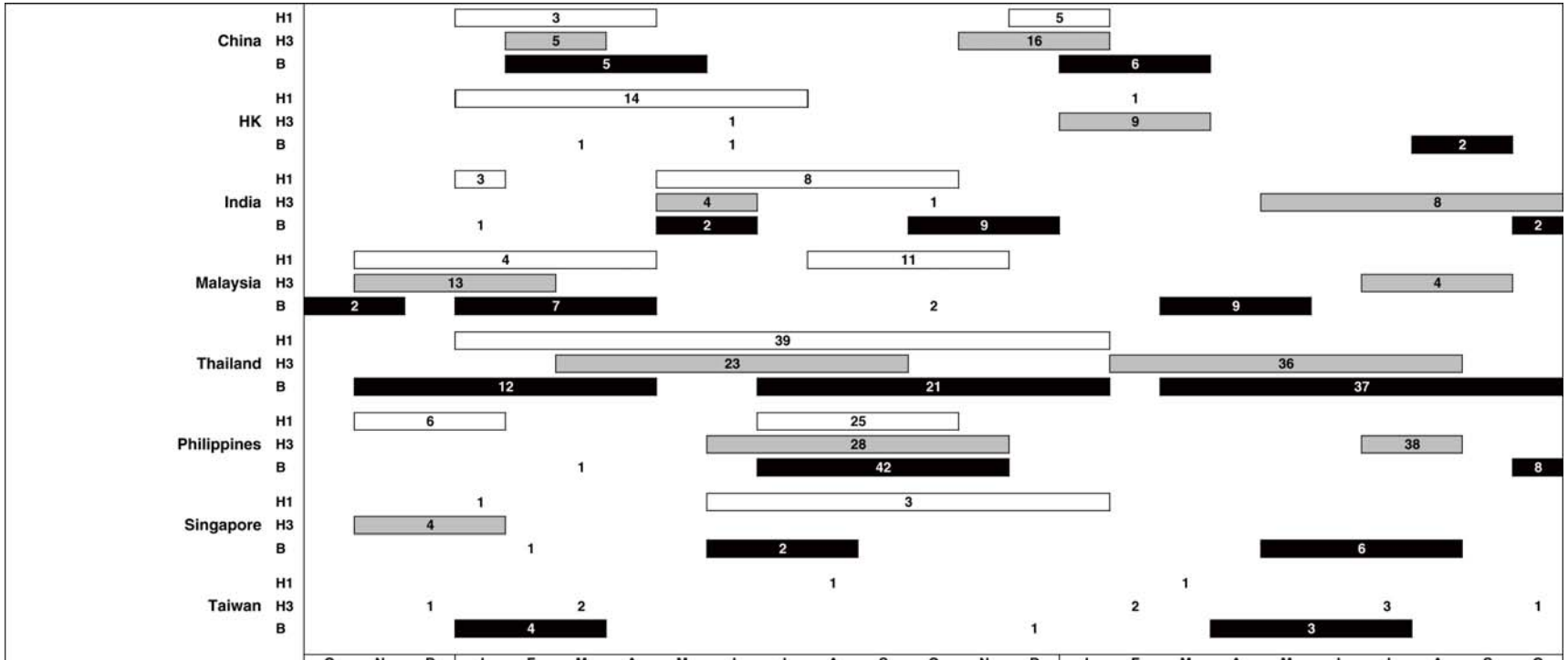


Figure 2.



	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O
	2000			2001												2002									
A/New Calidonia/20/99-Like (H1)		1		2			1	1		1		1	1	3	3	3	1	1							
A/New Calidonia/20/99-Like (H1N1)		4	2	20	3	3	4	6	3	13	13	16	9	3											
A/New Calidonia/20/99-Like (H1N2)								1			1	1	3												
A/Hawaii/15/01-Like(H1)				1																					
A/Panama/2007/99-Like(H3)														1	3	3	2	3	1	4	7	38	8	3	3
A/Panama/2007/99-Like(H3N2)		1	2	4	2	6			3	10	1	2	1	1	8	3	4	4				14			
B/Brisbane/32/02-Like																								1	4
B/Hong Kong/1351/02-Like																			7	7	4	17	4		4
B/Hong Kong/22/01-Like						1																			
B/Hong Kong/330/01-Like													21	11	2			2	1	1	1	3			2
B/Shizuoka/15/01-Like																	2		2						
B/Sichuan/379/99-Like	1	4		8	10	7	2	2	3	6	4	7	20	5	3	1							1	2	
B/Victoria/504/00-Like																	1								1
B/Yamanashi/166/98-Like																2		2				1			
H3 (Not Done)		2	4	3	3	1	2	8	7	10	6	3													
H3 (Indeterminate)																			1			2	5		
B (Not Done)										1															
B (Indeterminate)																						1	1		

Figures for web-only supplement.

Figure S1.

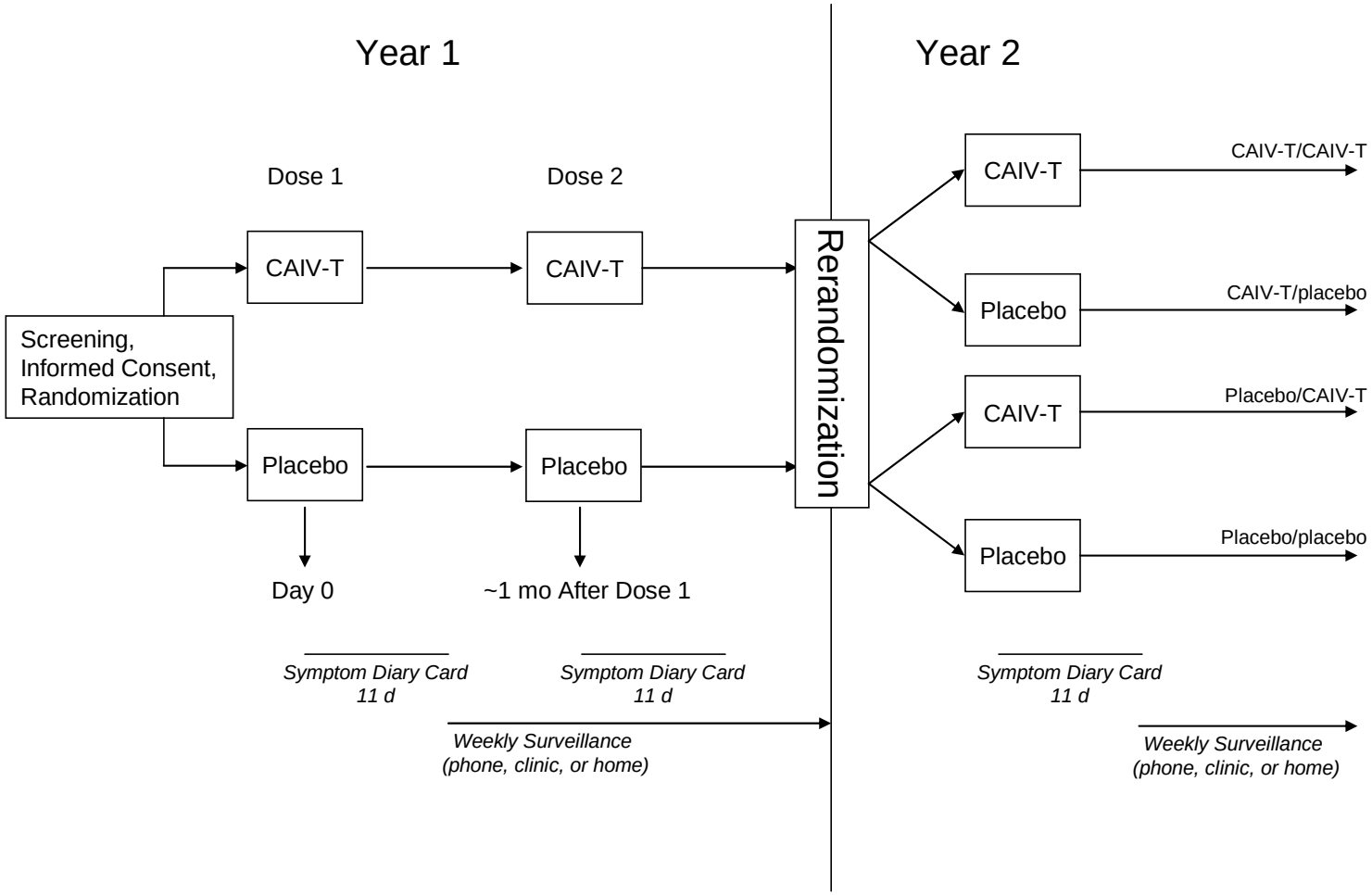
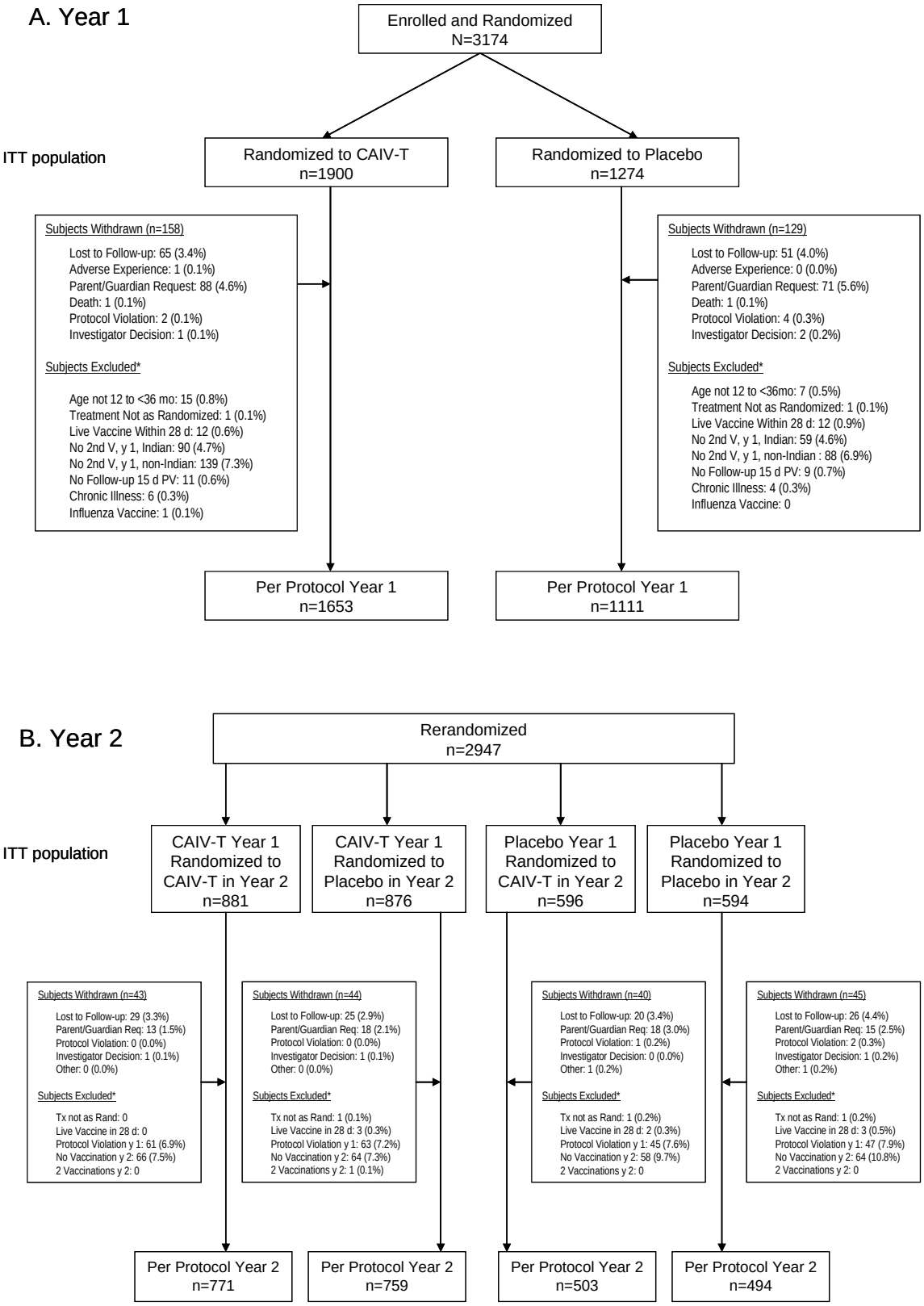


Figure S2.


A. Year 1
Enrolled and Randomized
N=3174
ITT population
Randomized to CAIV-T
n=1900
Randomized to Placebo
n=1274
Subjects Withdrawn (n=158)
Lost to Follow-up: 65 (3.4%)
Adverse Experience: 1 (0.1%)
Parent/Guardian Request: 88 (4.6%)
Death: 1 (0.1%)
Protocol Violation: 2 (0.1%)
Investigator Decision: 1 (0.1%)
Subjects Excluded*
Age not 12 to <36 mo: 15 (0.8%)
Treatment Not as Randomized: 1 (0.1%)
Live Vaccine Within 28 d: 12 (0.6%)
No 2nd V, y 1, Indian: 90 (4.7%)
No 2nd V, y 1, non-Indian: 139 (7.3%)
No Follow-up 15 d PV: 11 (0.6%)
Chronic Illness: 6 (0.3%)
Influenza Vaccine: 1 (0.1%)
Subjects Withdrawn (n=129)
Lost to Follow-up: 51 (4.0%)
Adverse Experience: 0 (0.0%)
Parent/Guardian Request: 71 (5.6%)
Death: 1 (0.1%)
Protocol Violation: 4 (0.3%)
Investigator Decision: 2 (0.2%)
Subjects Excluded*
Age not 12 to <36mo: 7 (0.5%)
Treatment Not as Randomized: 1 (0.1%)
Live Vaccine Within 28 d: 12 (0.9%)
No 2nd V, y 1, Indian: 59 (4.6%)
No 2nd V, y 1, non-Indian : 88 (6.9%)
No Follow-up 15 d PV: 9 (0.7%)
Chronic Illness: 4 (0.3%)
Influenza Vaccine: 0
Per Protocol Year 1
n=1653
Per Protocol Year 1
n=1111
B. Year 2
Rerandomized
n=2947
ITT population
CAIV-T Year 1
Randomized to
CAIV-T in Year 2
n=881
CAIV-T Year 1
Randomized to
Placebo in Year 2
n=876
Placebo Year 1
Randomized to
CAIV-T in Year 2
n=596
Placebo Year 1
Randomized to
Placebo in Year 2
n=594
Subjects Withdrawn (n=43)
Lost to Follow-up: 29 (3.3%)
Parent/Guardian Req: 13 (1.5%)
Protocol Violation: 0 (0.0%)
Investigator Decision: 1 (0.1%)
Other: 0 (0.0%)
Subjects Excluded*
Tx not as Rand: 0
Live Vaccine in 28 d: 0
Protocol Violation y 1: 61 (6.9%)
No Vaccination y 2: 66 (7.5%)
2 Vaccinations y 2: 0
Subjects Withdrawn (n=44)
Lost to Follow-up: 25 (2.9%)
Parent/Guardian Req: 18 (2.1%)
Protocol Violation: 0 (0.0%)
Investigator Decision: 1 (0.1%)
Other: 0 (0.0%)
Subjects Excluded*
Tx not as Rand: 1 (0.1%)
Live Vaccine in 28 d: 3 (0.3%)
Protocol Violation y 1: 63 (7.2%)
No Vaccination y 2: 64 (7.3%)
2 Vaccinations y 2: 1 (0.1%)
Subjects Withdrawn (n=40)
Lost to Follow-up: 20 (3.4%)
Parent/Guardian Req: 18 (3.0%)
Protocol Violation: 1 (0.2%)
Investigator Decision: 0 (0.0%)
Other: 1 (0.2%)
Subjects Excluded*
Tx not as Rand: 1 (0.2%)
Live Vaccine in 28 d: 2 (0.3%)
Protocol Violation y 1: 45 (7.6%)
No Vaccination y 2: 58 (9.7%)
2 Vaccinations y 2: 0
Subjects Withdrawn (n=45)
Lost to Follow-up: 26 (4.4%)
Parent/Guardian Req: 15 (2.5%)
Protocol Violation: 2 (0.3%)
Investigator Decision: 1 (0.2%)
Other: 1 (0.2%)
Subjects Excluded*
Tx not as Rand: 1 (0.2%)
Live Vaccine in 28 d: 3 (0.5%)
Protocol Violation y 1: 47 (7.9%)
No Vaccination y 2: 64 (10.8%)
2 Vaccinations y 2: 0
Per Protocol Year 2
n=771
Per Protocol Year 2
n=759
Per Protocol Year 2
n=503
Per Protocol Year 2
n=494

ARTICLE

Safety, Efficacy, and Effectiveness of Cold-Adapted Influenza Vaccine-Trivalent Against Community-Acquired, Culture-Confirmed Influenza in Young Children Attending Day Care

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ABSTRACT

OBJECTIVE. The goal was to evaluate the safety, tolerability, and efficacy of an investigational, refrigerator-stable formulation of live attenuated influenza vaccine (cold-adapted influenza vaccine-trivalent) against culture-confirmed influenza, acute otitis media, and effectiveness outcomes in young children in day care over 2 consecutive influenza seasons.

METHODS. Children 6 to <36 months of age who were attending day care were assigned randomly in year 1 to receive 2 doses of vaccine or placebo intranasally, 35 ± 7 days apart. In year 2, subjects received 1 dose of the same treatment as in year 1.

RESULTS. A total of 1616 subjects (vaccine: 951 subjects; placebo: 665 subjects) in year 1 and 1090 subjects (vaccine: 640 subjects; placebo: 450 subjects) in year 2 were able to be evaluated for efficacy. The mean age at first vaccination was 23.4 ± 7.9 months. In year 1, the overall efficacy of the vaccine against influenza subtypes similar to the vaccine was 85.4%; efficacy was 91.8% against A/H1N1 and 72.6% against B. In year 2, the overall efficacy was 88.7%; efficacy was 90.0% against H1N1, 90.3% against A/H3N2, and 81.7% against B. Efficacy against all episodes of acute otitis media associated with culture-confirmed influenza was 90.6% in year 1 and 97.0% in year 2. Runny nose or nasal discharge after dose 1 in year 1 was the only reactogenicity event that was significantly more frequent with cold-adapted influenza vaccine-trivalent (82.3%) than placebo (75.4%).

CONCLUSIONS. Cold-adapted influenza vaccine-trivalent was well tolerated and effective in preventing culture-confirmed influenza illness in children as young as 6 months of age who attended day care.

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doi:10.1542/peds.2006-0725

Key Words
influenza, cold-adapted influenza vaccine-trivalent, children

Abbreviations
AE—adverse event
AOM—acute otitis media
CAIV-T—cold-adapted influenza vaccine-trivalent
CI—confidence interval
LAIV—live attenuated influenza vaccine
PCR—polymerase chain reaction
PP—per protocol
TIV—trivalent influenza vaccine

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INFLUENZA IS A major cause of serious respiratory illness and acute otitis media (AOM) in young children and is associated with significant public health and socioeconomic burdens through excess hospitalizations, clinic and outpatient visits, antibiotic prescriptions, and lost parental workdays.[1–6] Influenza-associated hospitalization rates for children <2 years of age are comparable to those seen for elderly persons and adults at high risk for complications of influenza.[7–13] During an influenza season, up to 33% of emergency department visits for children <12 months of age[8] and 20% of excess hospitalizations for children <3 years of age[12] have been attributed to influenza infection.

High influenza attack rates and the propensity to shed larger amounts of influenza virus for longer periods than older children and adults indicate that young children are significant reservoirs of influenza in the community.[14–17] Children attending day care frequently experience the highest influenza attack rates[2,18]; however, influenza is underdiagnosed frequently in this age group.[19] Routine immunization of young children may provide communitywide benefits by reducing the transmission of influenza to susceptible populations, decreasing the overall community disease burden, and reducing the overall economic burden of influenza.[20,21]

Inactivated trivalent influenza vaccine (TIV) is recommended in the United States for use in children 6 months to <5 years of age.[22] Few efficacy studies using TIV in young children have been published. Estimates of TIV efficacy against influenza illness range from 12% to 83% and vary according to age, circulating influenza virus strains, level of disease burden, and other variables.[23] Variability in TIV efficacy and effectiveness against AOM has also been observed.[23–27]

The frozen formulation of live attenuated influenza vaccine (LAIV) (FluMist; MedImmune, Gaithersburg, MD) was approved in the United States in 2003 for healthy persons 5 to 49 years of age. A new, refrigerator-stable formulation of LAIV, referred to as cold-adapted influenza vaccine-trivalent (CAIV-T), is currently in development. The clinical trial described here evaluated the safety, tolerability, and efficacy of CAIV-T against culture-confirmed influenza, during 2 consecutive influenza seasons, in children 6 to <36 months of age who were attending day care. Vaccine efficacy against AOM and certain effectiveness outcomes were also determined.

METHODS

Design

This prospective, randomized, double-blind, placebo-controlled, multicenter trial was conducted over 2 consecutive influenza seasons at 70 clinical centers located in Belgium, Finland, Israel, Spain, and the United Kingdom, between October 2, 2000, and May 31, 2002. The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The study protocol and all subsequent amendments were approved by the human ethics committees, institutional review boards, and any regional or national ethics committees at participating centers.

Participants

Eligible subjects were children who were 6 to <36 months of age at the time of enrollment and who were in good health, as determined by medical history and physical examination. Children were required to be attending day care for a minimum of 12 hours/week. Eligibility to participate in the second year of the trial required continued good health and completion of the primary dosing series and surveillance in year 1. Written informed consent was obtained from the parent or guardian of each child. Exclusion criteria for both years included any serious chronic disease, Down syndrome or other cytogenetic disorders, immunosuppression or a household member with immunosuppression, receipt of immunoglobulin in the previous 6-month period, receipt of any investigational vaccine or agent 1 month before enrollment or any influenza treatment within the 2 weeks before enrollment, documented history of hypersensitivity to egg or egg protein, clinically confirmed respiratory illness with wheezing within 2 weeks before enrollment, receipt of aspirin within 2 weeks before enrollment, receipt of any live virus vaccine within 1 month before enrollment, and previous influenza vaccination (year 1) or off-protocol influenza vaccination (year 2).

Vaccine and Placebo

CAIV-T was manufactured and release-tested by Wyeth Vaccines Research (Marietta, PA) and consisted of 3 cold-adapted, attenuated, reassortant strains, representing the hemagglutinin and neuraminidase antigens of the A/New Caledonia/20/99 (H1N1), A/Sydney/05/97 (H3N2), and B/Yamanashi/166/98 influenza strains for the first year of the study and the hemagglutinin and neuraminidase antigens of the A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), and B/Victoria/504/2000 influenza strains for the second year of the study. Each 0.2-mL dose of CAIV-T was formulated to contain $\sim 10^7$ median tissue culture dose (or equivalent fluorescent units in year 2) of each of the 6:2 influenza reassortant virus strains. After manufacture, the vaccine was stored frozen and then shipped to the study sites at 2°C to 8°C, at which temperature it was stored until just before administration.

The hemagglutinin and neuraminidase antigens of the wild-type influenza strains used to generate the type A/H1N1 and type B vaccine reassortants for the year 1 CAIV-T formulation were antigenically representative of virus recommended by the World Health Organization

for the 2000/2001 influenza season in the Northern Hemisphere. Because of industrywide technical problems encountered in the production of the recommended H3N2 A/Panama/2007/99 (A/Moscow/10/99-like) vaccine strain,[28] a decision was made to use the H3N2 vaccine strain (A/Sydney/05/97) recommended for the previous 1999/2000 season in the year 1 CAIV-T formulation. This decision was based on the antigenic similarity of the hemagglutinin antigen with that of A/Panama/2007/99, the circulation of A/Sydney/05/97-like viruses before the 2000/2001 season,[29] and previous clinical trials with a frozen formulation of CAIV-T that demonstrated both cross-reactive antibody development (as measured with a hemagglutinin-inhibiting antibody assay) and efficacy against mismatched influenza A/H3N2 virus.[30] The A/Sydney/05/97 antigens matched the antigens used in commercial TIV for that season. The vaccine composition for year 2 consisted of vaccine strains that were antigenically representative of the World Health Organization 2001/2002 Northern Hemisphere composition recommendations.[31] Placebo consisted of sterile physiologic saline solution manufactured by Wyeth Vaccines Research.

In year 1, subjects were assigned randomly to receive a primary series of 2 doses of either CAIV-T or placebo, in a 3:2 ratio, 35 ± 7 days apart. In year 2, all subjects received a single dose of either CAIV-T or placebo according to their year 1 treatment assignments. In both years, study subjects, their parents or guardians, and the clinical personnel were unaware of the treatment being administered. CAIV-T and placebo were supplied in single-dose, identically packaged sprayers labeled with the codes to which subjects were assigned. The total single-dose volume of 0.2 mL (~0.1 mL into each nostril) of vaccine or placebo was administered intranasally with the spray applicator intended for commercial use. The first dose of the primary series was administered on study day 0, after informed consent had been obtained.

Surveillance for Influenza Illness

Surveillance for influenza-like illness was based on regular telephone contacts, clinic visits, or home visits (as applicable). In both years, contact started 11 days after receipt of the first study dose (day 0) and continued weekly through completion of the first (May 31, 2001) or second (May 31, 2002) season surveillance period.

A nasal swab sample was required if subjects exhibited fever (rectal temperature of ≥38°C or axillary temperature of ≥37.5°C), wheezing, shortness of breath, pulmonary congestion, pneumonia, or ear infection (suspected or diagnosed AOM). A nasal swab sample was also required if subjects showed ≥2 of the following: runny nose or nasal congestion (rhinorrhea), sore throat (pharyngitis), cough, muscle aches, chills, headache, irritability, decreased activity, or vomiting. A viral culture was also obtained at the investigators' discretion.

Nasal specimens were cultured in Madin-Darby canine kidney monolayer cultures, and typing was determined by immunostaining positive cultures with influenza type A-specific and type B-specific monoclonal antibodies. Nasal specimens were cultured and typed in the Department of Virology at the University of Turku (Turku, Finland). Positive specimens were shipped to Wyeth Vaccines Research (Pearl River, NY) for additional identification. Subtype identification and antigenic characterization were performed for 78.3% of all influenza-positive isolates in year 1, by the Centers for Disease Control and Prevention (Atlanta, GA), with serologic techniques. In year 2, identification assays, including polymerase chain reaction (PCR) assays and sequencing of *HA1* gene fragments, were performed by Wyeth Vaccines Research with methods similar to those described previously for H3N2 and B viruses.[32,33] In the second season, wild-type B/Hong Kong/1351/02 strain cocirculated[32,34] and was associated with difficulties in serotyping. PCR analyses and *HA1* sequencing methods were used for subtype identification and antigenic characterization of 99.0% of all influenza-positive isolates in year 2, whereas only 87.6% of isolates were identifiable with serologic testing. All strain-specific efficacy analyses in year 2 were based on PCR analyses, with serotyping confirmation when possible. Influenza-positive specimens obtained within 28 days after any vaccine dose were tested to determine whether they were CAIV-T-like or wild-type (community acquired).

AOM

An ear examination was performed if the subject developed symptoms suggesting AOM. AOM was defined as a visually abnormal tympanic membrane (with regard to color, position, and/or mobility) suggesting an effusion in the middle ear cavity, concomitant with ≥1 of the following signs and/or symptoms of acute infection: fever (rectal temperature of ≥38°C or axillary temperature of ≥37.5°C), earache, irritability, diarrhea, vomiting, acute otorrhea not caused by external otitis, or other symptoms of respiratory infection.[35,36] An episode of febrile otitis media was defined as an episode of AOM in a child with a documented fever (rectal temperature of ≥38°C or axillary temperature of ≥37.5°C), and an episode of influenza-associated AOM was defined as an episode of AOM in a child with a positive culture for influenza virus. An episode of AOM in a study participant was included in the efficacy analysis if it complied with the definition of AOM given above, occurred ≥15 days after receipt of the first dose of vaccine or placebo, and occurred during the period in which influenza virus was isolated in each country.

Effectiveness Outcomes

The ability of CAIV-T, relative to placebo, to reduce the burden of respiratory illness in children attending day

care was determined by evaluating the reduction in the following predefined end points during the influenza season: (1) the incidence of a parent or guardian taking time off from paid work at least once to care for the child during the current influenza-like illness, (2) the total number of days of paid work missed for parents or guardians, (3) the total number of days missed from day care as a result of influenza-like illness, (4) the incidence of ≥1 outpatient or emergency department visit because of acute febrile and/or respiratory illness, (5) the incidence of ≥1 prescription of antibiotics as a result of influenza-like illness, and (6) the number of days of treatment with an antibiotic prescribed as a result of the influenza-like illness.

Safety Assessment

After each study vaccination, parents and legal guardians were asked to record information on a diary card regarding axillary or rectal temperature, runny nose/nasal congestion, sore throat, cough, vomiting, activity level, appetite, irritability, headache, chills, muscle pain, and the use of antipyretic medications (for prophylaxis or treatment), as well as any unscheduled physician visits and medications, for 11 consecutive days, including the day of vaccination (day 0). An adverse event (AE) was defined as any clinically significant event, including but not limited to (1) events that required any prescription or nonprescription medication within 11 days after vaccination, (2) events that required an unscheduled health care provider visit and/or health care provider consultation within 11 days after vaccination, (3) events that resulted in study termination, or (4) any other clinically significant event that occurred at any time during the course of the study. Serious AEs, including hospitalizations, were monitored and collected through the end of the influenza season in each year of the study.

Statistical Analyses

Sample size estimates were based on assumed attack rates of culture-confirmed influenza in the placebo and CAIV-T groups of 12% and 3%, respectively (as observed in a previous trial of LAIV in older children[30]) and a subject discontinuation rate of ≤25%. A sample size of 1100 children that were able to be evaluated (with 3:2 randomization) permitted ≥90% power that the lower limit of the 95% confidence interval (CI) of efficacy over the first season would be ≥45%. The planned sample size for this study provided ≥80% power to detect frequency differences between the CAIV-T and placebo groups ranging from 4.3% to 8.2%.

The randomization schedule was generated by Wyeth Vaccines Research. Study product for year 1 was labeled with 1 of 5 letter codes, namely, A, H, or M (CAIV-T) or B or K (placebo). Each subject was assigned the next sequential number by the study site investigator and received study product for the treatment assigned to that subject number, according to a preprinted randomization allocation list provided to the study site by Wyeth Vaccines Research. The number sequence was concealed until interventions were assigned. Two efficacy populations were defined for both seasons, that is, the intent-to-treat population (all subjects who received ≥1 dose of study vaccine or placebo in year 1 or who received a single dose of study vaccine or placebo at the start of year 2) and the per-protocol (PP) population (subjects who received both vaccinations, or a single vaccination in year 2, to which they were assigned; who received no live viral vaccine within 28 days of any study vaccination; and who had no major protocol violations).

The primary efficacy end point was the efficacy of a primary series of 2 doses of CAIV-T, relative to placebo, against culture-confirmed influenza caused by subtypes antigenically similar to those contained in the vaccine in the first season. Secondary efficacy end points included the efficacy of 2 doses of CAIV-T against culture-confirmed influenza caused by any community-acquired subtypes in season 1; efficacy of CAIV-T against culture-confirmed influenza caused by subtypes antigenically similar to those contained in the vaccine and against any subtype in year 2; efficacy against all episodes of AOM, febrile AOM (first and all episodes), and influenza-associated AOM (first and all episodes) in both years; and improvement in effectiveness outcomes.

Vaccine efficacy was estimated as vaccine efficacy = $1 - (C/N_C)/(P/N_P)$, where N_C is the number of subjects who received CAIV-T, C is the number of CAIV-T subjects who were case subjects, N_P =is the number of subjects who received placebo, and P is the number of placebo subjects who were case subjects. For these estimates, conditional on the total number of cases, 95% CIs were obtained from the binomial distribution. For the purpose of estimating efficacy, only the first episode of each kind of illness for each subject was taken into account, unless otherwise indicated.

An episode of AOM was defined as one in which ≥30 days had passed since the onset of the previous episode. Estimates of efficacy (with 95% CIs) of CAIV-T, relative to placebo, against first episodes of AOM associated with a positive culture for influenza virus antigenically similar to virus contained in the vaccine and AOM associated with fever were calculated for the PP population. Estimates of efficacy of CAIV-T, relative to placebo, against all episodes of AOM, all febrile AOM, and all influenza-associated AOM were based on the hazard ratio estimated from the Andersen-Gill model for multiplicative hazards of recurrent events, with treatment as the only effect.

For effectiveness end points, relative effectiveness was defined in the same manner as for vaccine efficacy against influenza, that is, relative effectiveness = $1 - I_C/I_P$, where I_C and I_P are incidence rates for CAIV-T and

placebo, respectively, in the PP population. For the variables that were not defined as incidence variables, the rates I_C and I_P were defined as the quotient of the total number of days of missed work or days of antibiotic treatment, as appropriate, divided by the total number of days of surveillance. CIs at the 95% level for relative effectiveness were computed from the binomial distribution, as for vaccine efficacy.

Because the circulation of influenza and its resulting impact on the community vary according to region, the analyses of efficacy for effectiveness end points were conducted with events that occurred during the influenza season of each country, for more accurate assessment of the true impact of the vaccine on these end points. The influenza season within each country was defined as the period from the time of isolation of the first wild-type influenza-positive culture among study participants after vaccination through the time of the last identification of an influenza-positive culture in that country.

All subjects who received any dose of study vaccine were included in the analysis of safety. For the analysis of safety according to dose, subjects were analyzed according to the vaccine that they actually received (as treated), CAIV-T or placebo. For analyses of the safety population that included >1 dose, subjects who received ≥1 dose of CAIV-T were classified as "CAIV-T" and subjects who received only placebo were classified as "placebo." For AEs within 11 days after vaccination, the incidence rates for each body system and for each event for the 2 treatment groups were compared by using Fisher's exact test (2-sided). For the summary of reactogenicity events, *P* values were obtained by using Fisher's exact test. Mild, moderate, and severe fevers were defined with axillary temperatures of ≥37.5°C, ≥38.6°C, and ≥40.0°C, respectively. These cutoff points were considered equivalent to rectal temperatures of ≥38.0°C, ≥39.1°C, and ≥40.0°C, respectively. Subjects whose temperature was measured orally were analyzed with the same fever cutoff points as for rectal temperature measurements. Subjects whose temperature was measured aurally or whose method of measurement was unknown were analyzed with the most conservative fever cutoff points (ie, those for axillary temperature measurements). These conversions were similar to those used in a previously published efficacy trial of LAIV.[37]

RESULTS

Subjects

Enrollment began on October 2, 2000, before the start of the first influenza season, and was completed on November 18, 2000. A total of 1784 subjects, at 70 sites, prospectively underwent random assignment to 1 of 2 study groups, in a 3:2 ratio (CAIV-T/placebo). All doses of CAIV-T or placebo in the primary series were administered by December 29, 2000. Participant flow, including withdrawals and reasons for exclusion from the efficacy analysis during year 1, is summarized in Fig 1.

A total of 1735 subjects (97.3%) completed year 1; of the 49 subjects (2.7%) who withdrew during year 1, most did so at parental request (1.2%) or were lost to

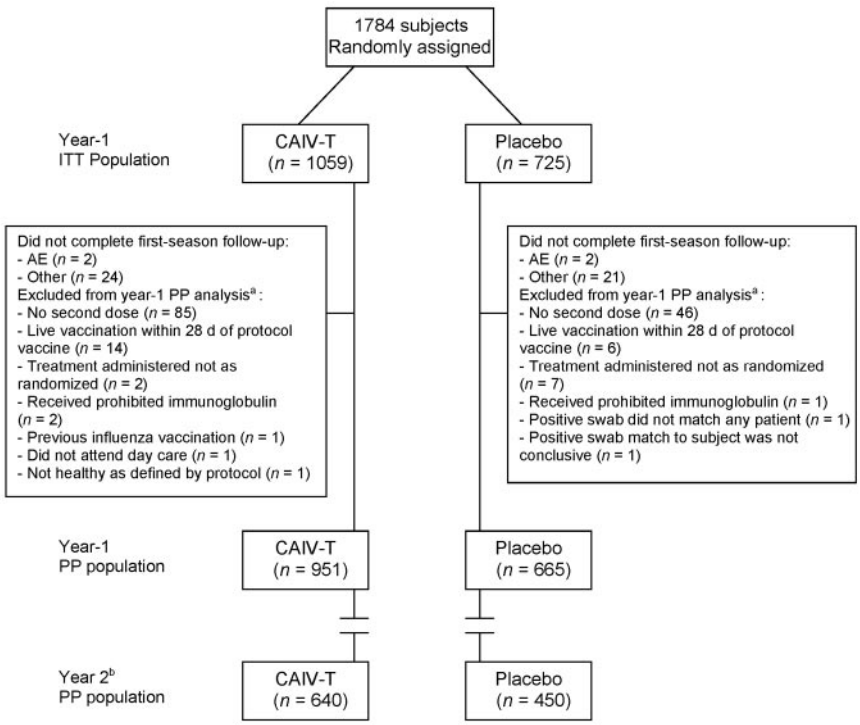

FIGURE 1
Participant flow, including reasons for withdrawal and exclusion from the PP analysis in year 1. ITT indicates intent to treat. [a] Subjects might have been excluded for >1 reason. [b] In year 2, 1119 subjects who had received both doses of study vaccine or placebo received a single dose of the same treatment they had received in year 1.

follow-up monitoring (1.0%). Four subjects (2 in the CAIV-T group and 2 in the placebo group) withdrew during year 1 because of AEs; 3 of these AEs were judged to be not related to study medication, and 1 (idiopathic thrombocytopenic purpura in a placebo recipient) was judged to be probably not related to study medication.

In year 2, 1119 subjects, at 62 sites, who completed year 1 successfully (ie, received both doses of study vaccine according to the protocol) received a single dose of the same treatment they had received in year 1. Clinical supply of CAIV-T for year 2 was not available until the end of November in 2001; all vaccine doses in year 2 were administered between December 3 and December 21, 2001. A total of 1112 subjects (99.4%) completed the study; 7 subjects (1 in the CAIV-T group and 6 in the placebo group) were lost to follow-up monitoring during year 2. No subjects withdrew from the study in year 2 because of AEs. An additional 22 subjects (17 in the CAIV-T group and 5 in the placebo group) were excluded from the PP efficacy analysis in year 2 because of major protocol violations.

A total of 1616 subjects (90.6%), including 951 CAIV-T recipients (89.8%) and 665 placebo recipients (91.7%), were included in the primary analysis of efficacy in season 1 (2000/2001). Baseline demographic characteristics for the PP efficacy population are presented in Table 1. A total of 4210 nasal swabs were collected during 4717 illness visits in season 1, and conclusive culture results (whether positive or negative for influenza) were obtained for 98.7% of the swabs. Fifty-six samples failed to yield results, primarily because of culture contamination by fungus or other agents. During the first season, an average of 2.34 and 2.38 swabs per subject were collected from CAIV-T and placebo recipients, respectively. In season 2, 1537 nasal swabs were collected during 1651 illness visits; conclusive results were obtained for 98.4% of swabs, of which 12.8% were determined to be positive for influenza. Swab rates in season 2 were 1.33 and 1.44 swabs per subject for CAIV-T and placebo recipients, respectively.

Culture-Confirmed Influenza

Influenza strains that were circulating in the community during the 2 seasons are summarized in Table 2. During the first season, all circulating influenza strains matched the vaccine strains, and most illnesses were caused by influenza A/H1N1 and influenza B strains. During the second season (2001/2002), a variety of influenza strains were circulating in the community, with clinical disease being caused by all 3 of the vaccine-like strains of influenza (A/H1N1, A/H3N2, and B). In addition, illness was caused by 2 influenza B strains that emerged from a different influenza B lineage and were antigenically distinct from the influenza B vaccine virus.

Vaccine efficacy against culture-confirmed influenza is summarized in Table 3. In year 1, the overall efficacy of CAIV-T against community-acquired subtypes of influenza virus antigenically similar to those in the vaccine was 85.4% (95% CI: 74.3%–92.2%), with efficacy for individual vaccine strains of 91.8% (95% CI: 80.8%–97.1%) against A/New Caledonia/20/99-like (H1N1) viruses and 72.6% (95% CI: 38.6%–88.9%) against B/Sichuan/379/99-like viruses. In year 1, only 1 case of A/Panama/2007/99-like (H3N2) virus was detected in a placebo recipient; therefore, efficacy could not be assessed. The vaccine also provided similar protection in year 1 against all wild-type influenza strains, regardless of antigenic similarity to the vaccine, with efficacy of 85.9% (95% CI: 76.4%–92.0%). In a posthoc analysis, efficacy against any antigenically similar strain was 90.8% (95% CI: 69.6%–98.2%) and 83.6% (95% CI: 66.9%–92.6%) for subjects 12 to 23 months and ≥24

TABLE 1 **Demographic Characteristics of Subjects in Years 1 and 2 (PP Efficacy Population)**

	Year 1			Year 2		
	CAIV-T ($n = 951$)	Placebo ($n = 665$)	Total ($n = 1616$)	CAIV-T ($n = 640$)	Placebo ($n = 450$)	Total ($n = 1090$)
Gender, *n* (%)						
Girls	455 (47.8)	328 (49.3)	783 (48.5)	299 (46.7)	231 (51.3)	530 (48.6)
Boys	496 (52.2)	337 (50.7)	833 (51.5)	341 (53.3)	219 (48.7)	560 (51.4)
Ethnic origin, *n* (%)						
White	918 (96.5)	644 (96.8)	1562 (96.7)	623 (97.3)	440 (97.8)	1063 (97.5)
Black	8 (0.8)	4 (0.6)	12 (0.7)	7 (1.1)	2 (0.4)	9 (0.8)
Other	25 (2.6)	17 (2.6)	42 (2.6)	10 (1.6)	8 (1.8)	18 (1.7)
Age at first vaccination in year 1, mo						
Mean ± SD	23.3 ± 8.0	23.5 ± 7.8	23.4 ± 7.9	23.5 ± 7.9	23.7 ± 7.8	23.6 ± 7.9
Median	24.3	24.7	24.5	24.6	25.1	24.7
Range	6.0–35.9	6.0–35.9	6.0–35.9	6.0–35.9	6.0–35.9	6.0–35.9
Age according to subgroup, *n* (%)						
6 to <12 mo	110 (11.6)	64 (9.6)	174 (10.8)	ND	ND	ND
12 to 23 mo	351 (36.9)	247 (37.1)	598 (37.0)	ND	ND	ND
≥24 mo	490 (52.5)	354 (53.2)	844 (52.2)	ND	ND	ND

ND indicates not determined.

TABLE 2 **Strains of Community-Acquired Influenza Virus**

Circulating Wild-Type Influenza Strains	Antigenically Matched to Vaccine Strains
Year 1 (2000/2001)	
A/New Caledonia/20/99-like (H1N1)	Yes
A/Panama/2007/99-like (H3N2)	Yes
B/Sichuan/379/99-like[a]	Yes
Year 2 (2001/2002)	
A/New Caledonia/20/99-like (H1N1)	Yes
A/Panama/2007/99-like (H3N2)	Yes
B/Hong Kong/330/01-like	No[b]
B/Hong Kong/1351/02-like	No[b]
B/Victoria/504/00-like	Yes

[a] The Centers for Disease Control and Prevention reported that the B/Yamanashi/168/99 vaccine strain used in the year 1 CAIV-T formulation produced high titers of cross-reacting antibody for the World Health Organization-recommended B/Sichuan/379/99-like virus.[49]

[b] The B/Hong Kong/330/01-like and B/Hong Kong/1351/02-like isolates were members of the B/Victoria/2/87 lineage, a virus lineage that is antigenically distinct from the B/Yamagata/16/88 lineage, of which the B/Victoria/504/00 vaccine strain is a member.

months of age, respectively. For subjects 6 to <12 months of age, the numbers of influenza cases were too small (2 CAIV-T recipients and 5 placebo recipients) to allow reliable evaluation of efficacy against antigenically similar strains; however, significant efficacy was demonstrated against any influenza strain in this age group (83.4%; 95% CI: 12.7%–98.3%).

In year 2, CAIV-T demonstrated protective efficacy similar to that in year 1, including against the A/New Caledonia/20/99-like virus, against which subjects had received 2 doses in year 1. In year 2, efficacy against influenza illness caused by influenza strains antigenically similar to those in the vaccine was 88.7% (95% CI: 82.0%–93.2%). In contrast to year 1, circulation of wild-type A/H3N2 influenza virus was more prevalent in year 2, as evidenced by the high attack rate among placebo recipients. In year 2, efficacy of CAIV-T against each of the individual vaccine strains was found to be 90.0% (95% CI: 56.3%–98.9%), 90.3% (95% CI: 82.9%–94.9%), and 81.7% (95% CI: 53.7%–93.9%) for the H1N1 A/New Caledonia/20/99-like viruses, H3N2 A/Panama/2007/99-like viruses, and B/Victoria/504/00-like viruses, respectively.

Influenza seasons according to country began as early as December 1, 2000 (Israel), and ended as late as May 31, 2001 (Spain), in year 1. In year 2, influenza seasons began on December 14, 2001 (Spain), and ended on April 18, 2002 (Finland and Israel). Table 4 summarizes efficacy against culture-confirmed influenza in both seasons according to country. In year 1, statistically significant efficacy against influenza strains antigenically similar to those in the vaccine was observed on a country basis in Israel, Finland, and the United Kingdom. Each of these countries had a placebo attack rate of ~16%. In Belgium and Spain, much lower attack rates were observed, and vaccine efficacy could not be determined.

In the second season (2001/2002), a much more significant influenza epidemic occurred, with high placebo attack rates of ≥30% being seen in Belgium, Israel, and Spain and with substantial attack rates also being observed in Finland (16.3%) and the United Kingdom (18.6%). Statistically significant efficacy was observed in all countries in year 2. Overall, strain-specific attack rates were 3.1% (A/H1N1), 22.4% (A/H3N2), and 7.3% (B). In year 2, all A/H1N1 and A/H3N2 virus isolates were identified as antigenically similar to the vaccine. However, only 29 (62%) of 47 influenza B isolates were identified as antigenically similar to the vaccine; 17 (36%) were identified as antigenically not similar to the vaccine, and the antigenic relatedness of 1 remaining isolate (from a CAIV-T recipient) could not be determined. Twelve (67%) of these 18 isolates came from children in Israel, and most were B/Hong Kong/1351/02-like. The emergence of these divergent strains was reflected in a lower efficacy estimate against any community-acquired strains, particularly in Israel. The attack rates for these 17 identified divergent strains were 1.1% and 2.2% in CAIV-T and placebo recipients, respectively; however, efficacy did not achieve statistical significance (50.8%; 95% CI: −43.0% to 84.1%).

AOM

Efficacy of CAIV-T against all AOM end points is summarized in Table 5. The efficacy of CAIV-T against all episodes of influenza-associated AOM was high (90.6% and 97.0% reduction in incidence in years 1 and 2, respectively). However, no difference between groups in the incidence of all episodes of AOM, first episode of febrile AOM, or all episodes of febrile AOM in either year was seen.

Effectiveness Outcomes

Effectiveness of CAIV-T against socioeconomic end points was most apparent in year 2, when the overall placebo attack rate for influenza was 30.9%. CAIV-T was effective against all socioeconomic end points in year 2 and effective against some in year 1, despite the lower influenza attack rate in placebo recipients (Table 6). During season 2 (2001/2002), CAIV-T reduced significantly the need for a parent or guardian to take time off from work by 45.1%, days of work lost by 47.5%, days of missed day care by 36.3%, and days of antibiotic use for influenza illness by 24.0%. Furthermore, the results demonstrated the substantial effect of vaccination with CAIV-T on severe disease, as reflected by a 35.1% reduction in the number of subjects with ≥1 emergency department visit during the second season.

Safety Evaluation

Reactogenicity events are summarized in Table 7. Runny nose or nasal discharge was observed in a marginally but statistically significantly greater proportion of CAIV-T recipients (82.3%), compared with placebo recipients (75.4%), after the first dose in year 1 ($P = 0.001$). No

TABLE 3 Efficacy of CAIV-T Against Culture-Confirmed Influenza Illness According to Influenza Strain

	Year 1					Year 2				
	CAIV-T		Placebo		Efficacy, % (95% CI)[c]	CAIV-T		Placebo		Efficacy, % (95% CI)
	No. of Subjects[a]	No. With Influenza Illness (%)[b]	No. of Subjects	No. With Influenza Illness (%)		No. of Subjects	No. With Influenza Illness (%)	No. of Subjects	No. With Influenza Illness (%)	
Community-acquired subtypes antigenically similar to vaccine[d]										
ITT population										
Any strain[e]	1059	19 (1.8)	725	79 (10.9)	83.5 (72.6–90.6)	658	22 (3.3)	461	140 (30.4)	89.0 (82.7–93.3)
PP population										
Any strain[f]	951	15 (1.6)	665	72 (10.8)	85.4 (74.3–92.2)	640	21 (3.3)	450	131 (29.1)	88.7 (82.0–93.2)
A/H1N1	951	6 (0.6)	665	51 (7.7)	91.8 (80.8–97.1)	640	2 (0.3)	450	14 (3.1)	90.0 (56.3–98.9)
A/H3N2	951	0 (0)	665	1 (0.2)	ND	640	14 (2.2)	450	101 (22.4)	90.3 (82.9–94.9)
B	951	9 (0.9)	665	23 (3.5)	72.6 (38.6–88.9)	640	6 (0.9)[f]	450	23 (5.1)	81.7 (53.7–93.9)
Any community-acquired subtypes										
ITT population										
Any strain	1059	23 (2.2)	725	97 (13.4)	83.8 (74.2–90.2)	658	31 (4.7)	461	148 (32.1)	85.3 (78.3–90.4)
PP population										
Any strain[f]	951	18 (1.9)	665	89 (13.4)	85.9 (76.3–92.0)	640	28 (4.4)	450	139 (30.9)	85.8 (78.6–90.9)
A/H1N1	951	6 (0.6)	665	60 (9.0)	93.0 (83.9–97.5)	640	2 (0.3)	450	14 (3.1)	90.0 (56.3–98.9)
A/H3N2	951	1 (0.1)	665	5 (0.8)	ND	640	14 (2.2)	450	101 (22.4)	90.3 (82.9–94.9)
Any other A type[g]	951	1 (0.1)	665	3 (0.5)	ND	640	0 (0.0)	450	0 (0.0)	ND
B	951	10 (1.1)	665	25 (3.8)	72.0 (39.7–88.0)	640	14 (2.2)[h]	450	33 (7.3)	70.2 (42.7–85.3)

ITT indicates intent to treat; ND, not determined.

[a] Number of subjects in analysis.

[b] Number of subjects with culture-confirmed influenza illness.

[c] Exact CI, conditioned on the total number of cases.

[d] The following strains isolated in this study were considered antigenically similar to those in the vaccine: year 1: A/New Caledonia/20/99-like (H1N1), A/Panama/2007/99-like (H3N2), and B/Sichuan/379/99-like; year 2: A/New Caledonia/20/99-like (H1N1), A/Panama/2007/99-like (H3N2), and B/Victoria/504/00-like.

[e] Primary efficacy end point.

[f] Overall efficacy was determined on the basis of the first occurrence of culture-confirmed influenza in an individual. Multiple episodes of influenza in the same individual were captured as separate illnesses in the evaluation of efficacy against individual strains.

[g] Influenza A isolates that could not be typed more specifically.

[h] Of 14 B isolates obtained from CAIV-T recipients in year 2, 6 were identified as antigenically similar to vaccine, 7 were identified as antigenically not similar to vaccine, and the antigenic relatedness of 1 isolate could not be determined.

TABLE 4 **Efficacy of CAIV-T Against Culture-Confirmed Influenza Illness According to Country (PP Efficacy Population)**

	Year 1					Year 2				
	CAIV-T		Placebo		Efficacy, % (95% CI)[c]	CAIV-T		Placebo		Efficacy, % (95% CI)
	No. of Subjects[a]	No. With Influenza Illness (%)[b]	No. of Subjects	No. With Influenza Illness (%)		No. of Subjects	No. With Influenza Illness (%)	No. of Subjects	No. With Influenza Illness (%)	
Subtypes antigenically similar to vaccine[d]										
Belgium	170	1 (0.6)	121	5 (4.1)	85.8 (−27.2 to 99.7)	119	3 (2.5)	91	32 (35.2)	92.8 (77.1 to 98.6)
Finland	257	4 (1.6)	173	24 (13.9)	88.8 (67.3 to 97.2)	136	0 (0.0)	86	14 (16.3)	100.0 (80.9 to 100.0)
Israel	220	6 (2.7)	158	22 (13.9)	80.4 (50.2 to 93.5)	184	8 (4.3)	130	36 (27.7)	84.3 (65.6 to 93.7)
Spain	167	2 (1.2)	117	6 (5.1)	76.6 (−30.6 to 97.7)	136	8 (5.9)	100	41 (41.0)	85.7 (69.0 to 94.2)
United Kingdom	137	2 (1.5)	96	15 (15.6)	90.7 (59.8 to 99.0)	65	2 (3.1)	43	8 (18.6)	83.5 (17.1 to 98.3)
Any subtypes										
Belgium	170	2 (1.2)	121	6 (5.0)	76.3 (−32.7 to 97.7)	119	3 (2.5)	91	34 (37.4)	93.3 (78.5 to 98.7)
Finland	257	4 (1.6)	173	28 (16.2)	90.4 (72.5 to 97.5)	136	0 (0.0)	86	14 (16.3)	100.0 (80.9 to 100.0)
Israel	220	6 (2.7)	158	25 (15.8)	82.8 (57.0 to 94.2)	184	15 (8.2)	130	41 (31.5)	74.2 (52.3 to 86.7)
Spain	167	4 (2.4)	117	13 (11.1)	78.4 (30.2 to 94.9)	136	8 (5.9)	100	42 (42.0)	86.0 (69.8 to 94.3)
United Kingdom	137	2 (1.5)	96	17 (17.7)	91.8 (65.3 to 99.1)	65	2 (3.1)	43	8 (18.6)	83.5 (17.1 to 98.3)

[a] Number of subjects in analysis.

[b] Number of subjects with culture-confirmed influenza illness.

[c] Exact CI, conditioned on the total number of cases.

[d] The following strains isolated in this study were considered antigenically similar to those in the vaccine: year 1: A/New Caledonia/20/99-like (H1N1), A/Panama/2007/99-like (H3N2), and B/Sichuan/379/99-like; year 2: A/New Caledonia/20/99-like (H1N1), A/Panama/2007/99-like (H3N2), and B/Victoria/504/00-like.

TABLE 5 **Efficacy of CAIV-T Against AOM, Febrile AOM, and AOM Associated With Influenza Illness Antigenically Similar to the Vaccine (PP Efficacy Population)**

	Year 1					Year 2				
	CAIV-T		Placebo		Efficacy, % (95% CI)[c]	CAIV-T		Placebo		Efficacy, % (95% CI)
	No. of Subjects[a]	No. of Episodes (%)[b]	No. of Subjects	No. of Episodes (%)		No. of Subjects	No. of Episodes (%)	No. of Subjects	No. of Episodes (%)	
AOM (all episodes)	951	274 (28.8)	664	199 (30.0)	4.8 (−15.7 to 21.7)	639	90 (14.1)	450	60 (13.3)	−6.4 (−52.0 to 25.5)
Febrile AOM (first episode)	951	159 (16.7)	664	116 (17.5)	4.3 (−22.7 to 25.1)	639	41 (6.4)	450	38 (8.4)	24.0 (−21.4 to 52.3)
Febrile AOM (all episodes)	951	184 (19.3)	664	129 (19.4)	1.1 (−25.9 to 22.3)	639	45 (7.0)	450	41 (9.1)	22.8 (−20.9 to 50.7)
Influenza-associated AOM (first episode)	951	3 (0.3)	664	22 (3.3)	90.5 (68.3 to 98.2)	639	1 (0.2)	450	23 (5.1)	96.9 (81.1 to 99.9)
Influenza-associated AOM (all episodes)	951	3 (0.3)	664	22 (3.3)	90.6 (68.7 to 97.2)	639	1 (0.2)	450	23 (5.1)	97.0 (77.6 to 99.6)

[a] Number of subjects in the calculation.

[b] Number of episodes of the indicated illness.

[c] For all episodes, the estimate and CI were computed from the Andersen-Gill model with treatment as the only effect. For first episodes, the estimate and CI were computed from the proportions of cases, as for influenza.

TABLE 6 **Effectiveness of CAIV-T for Socioeconomic End Points (PP Efficacy Population)**

	Year 1					Year 2				
	CAIV-T		Placebo		Efficacy, % (95% CI)[c]	CAIV-T		Placebo		Efficacy, % (95% CI)
	No. of Subjects or Total d[a]	No. of Incidents or Event d (%)[b]	No. of Subjects or Total d	No. of Incidents or Event d (%)		No. of Subjects or Total d	No. of Incidents or Event d (%)	No. of Subjects or Total d	No. of Incidents or Event d (%)	
Parent or guardian taking time off work	951	247 (26.0)	664	203 (30.6)	15.0 (−2.8 to 29.7)	640	82 (12.8)	450	105 (23.3)	45.1 (26.0 to 59.4)
Paid work missed, d	105 024	805 (0.8)	73 093	695 (1.0)	19.4 (10.6 to 27.3)	61 992	235 (0.4)	43 933	317 (0.7)	47.5 (37.6 to 55.8)
Day care missed, d	104 884	1749 (1.7)	73 023	1435 (2.0)	15.1 (8.9 to 20.9)	61 768	883 (1.4)	43 842	984 (2.2)	36.3 (30.2 to 41.9)
Having ≥1 outpatient or emergency department visit	951	361 (38.0)	664	292 (44.0)	13.7 (−1.1 to 26.2)	640	84 (13.1)	450	91 (20.2)	35.1 (11.7 to 52.3)
Having ≥1 antibiotic prescription	951	376 (39.5)	664	261 (39.3)	−0.6 (−18.2 to 14.3)	640	148 (23.1)	450	145 (32.2)	28.2 (9.1 to 43.3)
Duration of treatment with antibiotic, d	104 375	3739 (3.6)	73 112	2711 (3.7)	3.4 (−1.5 to 8.1)	61 915	1428 (2.3)	43 933	1333 (3.0)	24.0 (18.0 to 29.5)
≥1 medication taken for "flu" illness	951	482 (50.7)	664	361 (54.4)	6.8 (−7.1 to 18.8)	640	264 (41.3)	450	247 (54.9)	24.8 (10.2 to 37.1)

[a] Number of subjects or total number of surveillance days in calculation.

[b] Number of incidents or number of days with event.

[c] Exact CI, conditioned on the total number of incidents or number of days.

TABLE 7 **Reactogenicity Events Reported Within the First 11 Days After Each Dose of CAIV-T or Placebo**

	Year 1						Year 2 Dose		
	Dose 1			Dose 2					
	No. (%)		P^b	No. (%)		P^b	No. (%)		P^b
	CAIV-T (n = 222–1021)[a]	Placebo (n = 163–682)		CAIV-T (n = 242–905)	Placebo (n = 162–608)		CAIV-T (n = 569–631)	Placebo (n = 387–437)	
Fever of ≥37.5°C[c]	294 (32.0)	167 (27.8)	.098	257 (31.2)	180 (32.5)	.637	133 (22.6)	86 (21.8)	.815
Fever of ≥38.6°C[c]	65 (7.3)	42 (7.3)	1.000	89 (11.0)	58 (10.8)	.929	48 (8.4)	29 (7.5)	.631
Fever of ≥40.0°C[c]	8 (0.9)	2 (0.4)	.332	4 (0.5)	3 (0.6)	1.000	2 (0.3)	5 (1.3)	.125
Runny nose or nasal discharge	840 (82.3)	514 (75.4)	.001	659 (72.8)	428 (70.4)	.322	423 (67.0)	268 (61.3)	.059
Sore throat[d]	98 (11.2)	72 (11.8)	.741	92 (11.4)	65 (11.9)	.796	72 (12.0)	56 (13.2)	.566
Cough	541 (56.1)	373 (56.9)	.759	498 (56.7)	334 (55.9)	.789	306 (48.6)	196 (45.3)	.288
Vomiting	153 (16.6)	109 (17.2)	.731	112 (13.6)	77 (13.6)	1.000	65 (10.6)	47 (11.1)	.839
Decreased activity	224 (24.1)	132 (20.6)	.111	202 (24.0)	140 (24.6)	.849	124 (20.4)	80 (18.8)	.579
Decreased appetite	358 (37.7)	234 (36.4)	.598	293 (34.2)	196 (33.7)	.865	174 (28.3)	117 (27.5)	.779
Irritability	371 (40.1)	242 (38.1)	.460	266 (31.5)	178 (31.5)	1.000	139 (23.1)	100 (24.1)	.708
Headache[d]	36 (15.0)	15 (8.9)	.070	28 (11.2)	20 (11.9)	.876	NR	NR	NR
Chills	16 (7.0)	19 (11.2)	.155	23 (9.3)	15 (8.9)	1.000	NR	NR	NR
Muscle pain	22 (9.9)	12 (7.4)	.468	19 (7.9)	11 (6.8)	.847	NR	NR	NR
Prophylactic antipyretic therapy	146 (17.8)	105 (18.4)	.832	138 (17.6)	99 (19.1)	.509	91 (15.8)	49 (12.3)	.137
Antipyretic treatment	224 (26.7)	134 (23.5)	.191	213 (26.8)	147 (28.5)	.486	112 (19.7)	69 (17.6)	.450
Any event[e]	933 (97.1)	596 (96.8)	.764	764 (95.5)	504 (95.3)	.894	500 (80.5)	338 (79.0)	.583

NR indicates not recorded.

[a] n represents the number of subjects with known values.

[b] Two-sided Fisher exact test.

[c] Axillary temperature (equivalent fever cutoff points were used for temperatures obtained orally or rectally).

[d] Not all children were old enough to verbalize this symptom.

[e] Does not include the administration of fever medication.

other significant differences in reactogenicity events after any dose in either year were observed, although the CAIV-T group had greater incidence of headache (15.0% vs 8.9%; P = .070) and fever of >37.5°C (32.0% vs 27.8%; P = .098) after the first dose in year 1. For children <24 months of age, chills were reported less frequently by CAIV-T recipients than placebo recipients after dose 1 in year 1 (0% vs 16.7%; P = .029), and runny nose or nasal discharge was more frequent in CAIV-T recipients after dose 2 (81.3% vs 74.6%; P = .035). No other significant differences in reactogenicity events in children <24 months of age were observed.

Similar proportions of subjects in the CAIV-T (36.4%) and placebo (35.4%) groups (P = .688) reported ≥1 AE within 11 days after the first vaccination in year 1, and the proportions reporting AEs within each body system were also similar. AEs reported most frequently among CAIV-T and placebo recipients after the first study dose included fever (8.7% and 7.2%, respectively), rhinitis (8.2% and 8.0%), cough (6.4% and 7.9%), otitis media (5.8% and 4.0%), and upper respiratory tract infection (4.3% and 4.6%). The AEs reported most frequently after dose 1 among CAIV-T and placebo recipients 6 to <12 months of age were diarrhea (5.6% and 2.9%, respectively), bronchospasm (0% and 5.7%), cough (5.6% and 4.3%), rhinitis (9.6% and 4.3%), upper respiratory tract infection (9.6% and 7.1%), fever (15.2% and 11.4%), and otitis media (9.6% and 5.7%). Similar AE profiles were observed within 11 days after the second vaccination in year 1 and the single vaccination in year 2. With the exception of bronchospasm after the second vaccination (P = .016), there were no statistically significant differences in the proportions of subjects in each treatment group who experienced each of these events (all P > .10). Lower respiratory tract illnesses reported as AEs were infrequent and were similar between treatment groups after the first (pneumonia: 3 CAIV-T recipients and 2 placebo recipients; bronchitis: 5 CAIV-T recipients and 5 placebo recipients; bronchiolitis: 4 CAIV-T recipients and 2 placebo recipients; bronchospasm: 7 CAIV-T recipients and 11 placebo recipients) and second (pneumonia: 6 CAIV-T recipients and 4 placebo recipients; bronchitis: 13 CAIV-T recipients and 15 placebo recipients; bronchiolitis: 2 CAIV-T recipients and 4 placebo recipients; bronchospasm: 8 CAIV-T recipients and 7 placebo recipients; LRI: 1 CAIV-T recipient and 0 placebo recipients) vaccine doses.

Lower respiratory tract illnesses reported as serious AEs from receipt of the first dose of study medication through the end of the first influenza surveillance period were also similar between treatment groups (pneumonia: 11 CAIV-T recipients and 9 placebo recipients; bronchitis: 3 CAIV-T recipients and 1 placebo recipient; bronchospasm: 2 CAIV-T recipients and 2 placebo recipients; bronchiolitis: 1 CAIV-T recipient and 2 placebo recipients). In subjects 6 to <12 months of age, lower respiratory tract infections reported as serious AEs were pneumonia (2 CAIV-T recipients and 1 placebo recipi-

ent), bronchitis (2 CAIV-T recipients and 0 placebo recipients), and bronchospasm (1 CAIV-T recipient and 0 placebo recipients). Serious AEs judged to be possibly, probably, or definitely related to study vaccination were reported for 9 CAIV-T recipients (pneumonia and AOM, 2 recipients; bronchopneumonia, 2 recipients; pneumonia, 1 recipient; bronchiolitis, 1 recipient; bronchitis and AOM, 1 recipient; idiopathic thrombocytopenic purpura, 1 recipient; and fever, acute respiratory tract infection, dehydration, and AOM, 1 recipient) and 5 placebo recipients (1 each for pneumonia and constipation; cough, wheeze, and lung consolidation; pneumonia; idiopathic thrombocytopenic purpura; and hypersensitivity, erythema, and periorbital edema). There were no statistically significant differences in serious AEs between treatment groups during the second influenza surveillance period. Six lower respiratory tract illnesses were reported, all among CAIV-T recipients (5 cases of pneumonia and 1 of bronchospasm). Two cases of pneumonia were judged to be possibly, probably, or definitely related to study vaccination. A total of 4 subjects (2 CAIV-T recipients and 2 placebo recipients) were withdrawn from the study because of AEs. No deaths occurred during the study period.

DISCUSSION

In the current trial, vaccination of children 6 to <36 months of age (mean age: 23 months) with CAIV-T over 2 consecutive influenza seasons was safe, well tolerated, and highly efficacious against culture-confirmed influenza illness. The frozen formulation of LAIV was studied previously over 2 seasons by using similar nasal swab criteria and was shown to be highly effective in year 1 against vaccine-matched A/H3N2 virus (95%; 95% CI: 88%–97%) and B virus (91%; 95% CI: 79%–96%) and in year 2 against a mismatched A/H3N2 virus (86%; 95% CI: 75%–92%).[30,37] Children in that study had a mean age of >40 months, and few children <2 years of age were enrolled. Data from the current trial demonstrated high efficacy rates in children with a mean age of 23 months.

This study demonstrated the efficacy of CAIV-T against all 3 A/H1, A/H3, and B strains circulating in the same season. Because Centers for Disease Control and Prevention subtyping and full antigenic characterization of isolates were unsuccessful for 22% of isolates in year 1, influenza viruses that could not be matched to vaccine antigen in that year might have been a mixture of vaccine-like and unmatched viruses. PCR assays in year 2 allowed subtyping and antigenic characterization of 99% of isolates and therefore dramatically improved the ability to distinguish isolates as vaccine-like or unmatched. The efficacy against a related but drifted influenza B virus in the second season was not surprising, given previous observations with the frozen formulation of CAIV-T among older children,[30] which demonstrated protection between strains of considerably less antigenic similarity. In the current trial, the point estimates of efficacy against antigenically similar influenza B strains in years 1 and 2 were lower than those for influenza A strains. However, because the CIs for these point estimates overlapped, conclusions regarding relative efficacy against matched A or B strains could not be drawn. In the current trial, 36% of influenza B isolates in year 2 were not antigenically similar to the vaccine strain; although the point estimate of efficacy against these unmatched B viruses was 50.8%, this did not achieve statistical significance.

In previous trials, the 2-dose primary series of LAIV was administered at intervals of 60 ± 14 days.[37] In the current study, doses were planned to be given at a reduced interval of 35 ± 7 days. Despite an actual mean dosing interval of 33 days in a much younger population, vaccine efficacy was high and comparable to that reported among older children.

In this trial, CAIV-T demonstrated a high level of efficacy against episodes of AOM that were associated with a positive influenza nasal swab. This was not surprising, given the high efficacy against culture-confirmed influenza. For this trial, a case definition for AOM that had been published previously and was used in previous trials involving other pediatric vaccines in this age range[35,36] was used. As also seen in clinical trials with pneumococcal conjugate vaccine[35] and TIV,[26] CAIV-T was not able to reduce significantly all episodes of AOM from any cause during the influenza season. TIV was shown to reduce AOM rates for children attending day care,[24,38] but a study conducted in younger children did not support those findings.[26] Influenza viruses might represent a smaller fraction of the pathogens associated with AOM in younger children, limiting the impact of influenza vaccine in preventing this illness.

The impact of CAIV-T vaccination on effectiveness outcomes was most apparent when influenza attack rates for children were high. Vaccine effectiveness was statistically significant for all parameters measured in the second year of the trial. In that year, CAIV-T reduced significantly the proportion of households with a parent taking time off from work to care for a child, the number of days lost from day care, the number of days of parental work loss, the number of antibiotic prescriptions written, the number of days of antibiotic use, the use of outpatient clinics and emergency departments, and the use of nonprescription medications for respiratory illness. Vaccinating children had effects on equivalent parameters that were comparable to those of directly immunizing healthy adults with CAIV-T.[39] Although this study was not designed to address the community impact of vaccinating children, other studies showed that vaccinating school-aged children decreases significantly health care utilization and school and work days missed.[40–43] In addition, an economic analysis of LAIV

vaccination of children 15 to 71 months of age demonstrated that vaccination is cost-effective from societal and third-party payer perspectives and that the greatest benefits occur when children are vaccinated in a group setting and when only 1 dose is required for protection.[44]

With respect to safety and tolerability events reported by parents or legal guardians that occurred in the first 11 days after each dose, CAIV-T, when administered to this much-younger pediatric population, had fewer significant reactogenicity and tolerability findings than reported for older children.[30,37] Although previous reports indicated statistically significant increases of fever, runny nose or nasal congestion, abdominal pain, and vomiting among CAIV-T recipients, only runny nose or nasal congestion achieved statistical significance in this trial of younger children and only in the first year, after the first dose. No statistically significant increases in rates of fever were observed for placebo or CAIV-T recipients after any dose in either year.

Furthermore, no significant safety events were observed in the 2 study groups during the influenza season. A large-scale clinical trial showed an increase in asthma episodes in children 18 to 35 months of age who were given the frozen formulation of CAIV-T.[45] No such observations were found in this clinical trial; however, this trial was not powered to detect small differences in such events among CAIV-T versus placebo recipients. In a large study of children 6 to 59 months of age who were assigned randomly to receive CAIV-T or TIV, there was a small but significant increase in medically significant wheezing in previously unvaccinated children 6 to 23 months of age who received CAIV-T.[46] However, in a similar study in children 6 to 71 months of age with a history of recurrent respiratory tract infections, there was no difference between treatment groups in the incidence of wheezing.[47] Similar findings were seen in a trial comparing TIV and CAIV-T in children and adolescents 6 to 17 years of age with asthma; there was no difference between treatment groups in pulmonary outcomes, including asthma exacerbations.[48]

This clinical trial of an intranasally delivered liquid formulation of LAIV in children 6 to <36 months of age demonstrated conclusively efficacy against culture-confirmed influenza illness over 2 consecutive seasons, including efficacy against all 3 vaccine-like influenza viruses. Significant vaccine effectiveness was also observed. Other than a previously observed increase in runny nose or nasal congestion, no significant tolerability or safety findings were observed. CAIV-T represents a valuable public health intervention for reducing influenza illness in young children.

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Safety, Efficacy, and Effectiveness of Cold-Adapted Influenza Vaccine-Trivalent Against Community-Acquired, Culture-Confirmed Influenza in Young Children Attending Day Care

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CME REVIEW ARTICLE

CHIEF EDITORS' NOTE: This is the second of four articles to be published in 2004 for which a total of up to 4 Category 1 CME credit hours can be earned. Instructions for how credit hours can be earned appear at the end of the Table of Contents. The CME activity contained within this series is supported by an unrestricted educational grant from Roche Laboratories. Honoraria are provided to authors of all articles.

Safety and efficacy of trivalent inactivated influenza vaccine in young children: a summary for the new era of routine vaccination

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Increasing use of influenza vaccine in children is expected as this important virus becomes more widely recognized as a major cause of morbidity in young children. Clinicians and third party payers must consider the implications of national vaccine use recommendations, with their current focus on young children, on their practices and on the community at large. Two influenza vaccines are available in the United States, an inactivated, trivalent intramuscular formulation (TIV) which is approved for use among children ≥6 months of age; and a live, attenuated intranasal trivalent preparation (LAIV) indicated for healthy persons 5 to 49 years of age. This review summarizes available data regarding the safety and efficacy of TIV, in comparison with LAIV, with particular attention to children <9 years of age, the population for whom two doses of vaccine are recommended for first time vaccination. It is apparent that relatively few data are available on the safety of TIV in young children, that important age-specific differences in TIV vaccine efficacy exist and that LAIV appears similar to TIV with regard to safety and efficacy in younger children, but no head-to-head comparison of these two licensed products is available.

LEARNING OBJECTIVES

1. *To describe the relatively few available data on the safety and efficacy of contemporary formulations of trivalent inactivated influenza vaccine (TIV) in healthy young children, particularly those 6 to 23 months of age for whom vaccine is now recommended.*
2. *To explain that use of TIV does not frequently result in serious adverse events and that vaccine efficacy appears to increase with age.*
3. *To compare published/presented data on the safety and efficacy of TIV with the live, attenuated influenza vaccine (LAIV).*
4. *To cite specific areas of ongoing clinical research regarding influenza vaccination of children.*

Influenza virus continues to be an important global cause of morbidity and mortality. In the United States ~10 to 20% of adults and 15 to 40% of children experience symptomatic influenza each year resulting in 30 000 to 70 000 excess deaths, 100 000 to 150 000 hospitalizations and up to 3 billion dollars in direct medical costs including diagnostic evaluation and antimicrobial therapy.[1, 2] Among children <5 years old, influenza-related hospitalization rates are highest in those <1 year of age and comparable with rates for

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adults ≥65 years of age.[3, 4] Illness in pediatric populations also results in substantial lost productive work time among adult contacts who care for ill children and may lead to secondary illnesses such as otitis media or bacterial pneumonia among others. In addition school age children are particularly important for the dissemination and maintenance of influenza virus in households and communities.[5] Because vaccination remains the most efficient means for influenza prevention and control, efforts to vaccinate young children therefore might not only provide individual protection but also be expected to impact on community spread.[6, 7]

INFLUENZA VACCINE RECOMMENDATION

Inactivated influenza vaccine was first shown to be potentially efficacious in preventing human disease during World War II[8] and has been recommended since at least 1960[9] for individuals at high risk of morbidity and death after infection. A trivalent preparation is currently produced by Evans Vaccines, Ltd. (Liverpool, UK) and Aventis Pasteur, Inc. (Swiftwater, PA). In June 2003 a live, attenuated influenza vaccine (LAIV; MedImmune, Inc., Gaithersburg, MD) was licensed for use in healthy persons 5 to 49 years of age by the US Food and Drug Administration. The US Public Health Service Advisory Committee on Immunization Practices (ACIP) guidelines for its use published in September 2003.[10] In anticipation of licensure of this vaccine and beginning with the 2002 to 2003 influenza season, ACIP "encouraged" routine vaccination of all healthy children 6 to 23 months of age.[1] This was updated in October 2003 with a full recommendation for vaccination of all children 6 to 23 months of age.[11] Questions remain, however, regarding (1) the limited nature of the data on the safety and efficacy of trivalent inactivated influenza vaccine (TIV) in the youngest age groups and (2) various logistic implications for individual clinical practices to implement seasonal vaccination of large numbers of children. To this end more data will be collected in coming years, which is necessary to critically evaluate current policies for influenza vaccination of young children.

Clinicians and third party payers continue discussions as to how and whether to apply the ACIP's recommendation for vaccination of young children; it is important for these groups to be apprised of available data to assist in their decision-making. This review attempts to summarize these data regarding the safety and efficacy of TIV with attention to healthy children under the age of 9 years, the group for whom two doses of vaccine are recommended if the child has not previously received vaccine. We reviewed the English literature for published studies of TIV that included 15-μg/ml amounts of each hemagglutinin antigen (as in the current formulations) and LAIV for comparison purposes. We have included selected data that have been presented in public scientific or advisory meetings and made note of monovalent and bivalent preparations of these vaccines when appropriate.

SAFETY OF TIV IN YOUNG CHILDREN

It is generally known that TIV vaccination of adults can result in predictable local reactions such as those associated with all injectable vaccines, including soreness, redness or swelling at the injection site, usually within 24 h of vaccination. The occurrence of systemic signs and symptoms such as fever, malaise, headache and lethargy, however, although not likely to occur with greater frequency among vaccinees than among randomized adult controls, has led many parents/caregivers and clinicians to avoid vaccination of young children.[12, 13] In some cases these clinical findings, rather than being caused by the vaccine, may be the result of an incubating viral infection already present before vaccination. This is not unexpected given that influenza vaccination is usually performed just before or during the peak of winter respiratory virus activity. Other serious complications after influenza vaccination, such as neuritis and cranial nerve palsies, have been reported on rare occasions, but only Guillain-Barré syndrome has been shown to be clearly associated with vaccination, and then only among adults who received the 1976 formulation.[14]

A paucity of prospective data is available to precisely quantify the likelihood of adverse reactions in pediatric patients who receive contemporary formulations of TIV. TIV was recommended for use in children based primarily on studies of monovalent (subtype A) vaccine performed in the 1960s and 1970s, and mainly among older children.[15–18] These studies noted that: (1) reactions in children were greater than noted in adults without significant differences noted by age among children between 3 and 12 years of age; (2) reactions associated with whole virus vaccines (as low as 3 to 6 μg of antigen per dose) were more common than those seen with split virus vaccines (up to 60 μg of antigen per dose); (3) systemic reactions diminished in frequency with the second dose, as did overall differences between split virus and whole virus vaccine preparations in the likelihood of reactions; and (4) local reactions with the bivalent vaccine preparations did not substantially vary between high risk and "normal" vaccine recipients. These studies included >1300 high risk children and 2600 healthy children and led to the general belief that influenza vaccine would likely be safe when given to large numbers of children. None of these studies included formulations currently in use.

Prospectively collected data on the safety of TIV among healthy children <9 years of age are sparse and often uncontrolled. We identified only 5 such studies that used formulations with the same antigenic con-

tent as that in use today, 4 of which evaluated local reactions (Table 1).[19–24] All 4 of these studies were randomized, were blinded and included a control group, although one study provided a monovalent influenza vaccine control rather than placebo. Overall only 231 vaccinations of children <6 years of age and <900 children <18 years of age were evaluated. No study reported serious reactions after vaccination. The largest trial included 635 vaccinees, 200 of whom were <6 years of age; this was also the only trial that reported age-specific reaction rates.[22] In this study 3 to 6% of vaccinated children reported a local reaction, and systemic signs/symptoms occurred in 4 to 16%, with coryza and fever being the most common. Fever was 2-fold more likely in children <6 years of age than among older groups. Only one trial specifically evaluated local reactions among children <24 months of age; it included only 12 vaccinees.[20] No raw data were reported to assess reactogenicity among individual children who received repeated dosing in successive years, although one study noted that subsequent dosing was not associated with an increase in reactogenicity.[22] In view of the limited number of studies and the small number of children evaluated, we believe the collection of additional prospective data is necessary to more completely describe the spectrum and severity of adverse events associated with TIV use in young children.

Although not the focus of this review, TIV safety has been evaluated in a small number of children with high risk conditions including asthma, bronchopulmonary dysplasia and congenital heart disease, all of which reported safety profiles similar to those seen in healthy children as noted above.[25, 26]

We were not able to identify any published postlicensure studies of the safety of TIV in healthy children. A large, health maintenance organization- and population-based retrospective cohort screening study was presented to the ACIP in 2002.[27] This study utilized data from the Vaccine Safety Datalink Project[28] to evaluate the safety of TIV among >250 000 children <18 years of age who had received >430 000 doses of TIV. It included nearly 9000 children 6 to 23 months of age; 23% of all enrolled children were in the high risk category targeted for TIV.

This study did not identify any serious adverse events after TIV vaccination compared with predefined control periods before and after immunization. These data are reassuring in that if a child had a serious adverse event after TIV, s/he would likely have come to care in the study health maintenance organizations with a population of prepaid health care subscribers. Data were not prospectively collected at the time of vaccination, however, and common but relatively minor adverse events may therefore not have been detected. A follow-up study to collect more data for children 6 to <24 months of age is in progress.

SAFETY OF LAIV IN YOUNG CHILDREN

Previous work regarding the safety of LAIV in children is briefly summarized for comparison to TIV. LAIV has been administered to >20 000 children and adults in prelicensure studies and appears to be generally safe and well-tolerated.[10] In individual studies

TABLE 1. Published, prospective studies that reported safety of TIV in healthy US children <9 years of age

Study/yr	Design	*N* (TIV/Placebo Recipients), Age	HA Dose (μg/Strain)	Vaccine Type	Results
Gruber et al.,[19] 1990	Randomized, double blinded, placebo-controlled	19/27, 3–5 yr 26/28, 6–9 yr 9/22, 10–18 yr	15	Subvirion	Local reactions noted in 20% of vaccines and 19% of controls. No age-specific data available
Piedra et al.,[20] 1993	Randomized, blinded, placebo-controlled	12/6, 6–32 mo	15	Split	One vaccinee with fever to 38.2°C
Khan et al.,[21] 1996	Randomized, blinded, placebo-controlled	168/87, 9–12 yr	15	Split	Fever up to 37.4°C in 9% of vaccines (some with sc vaccination), 1.1% controls; local reactions in 27% of vaccines (93%, erythema at the site)
Neuzil et al.,[22] 2001, and Edwards et al.,[23] 1994	Randomized, double blinded, controlled	200, 1–<6 yr* 259, 6–<11 yr 176, 11–15 yr	15	Split	3–7% with redness or induration; 4–16% with fever, cough, coryza or sore throat. Reaction rates not worse with repeated dosing
Hoberman et al.,[24] 2003	Randomized, double blinded, placebo-controlled	525/262, 6–24 mo	15	Split	Local reactions not assessed. No serious adverse events likely caused by vaccine; no difference in all cause hospitalization between groups

* This study was a multiyear study, and children were enrolled and followed for up to 4 years. A total of 277 children <16 years of age received TIV during the study, and children were multiply vaccinated over time. Therefore, the number of children represents all those who ever received TIV, in the age group noted.

certain signs and symptoms occurred significantly more often among immunized children than among controls, including nasal congestion, fever >37.8°C and, much less commonly, vomiting, abdominal pain or muscle aches. In young children the absolute difference in the rate of these events between immunized children and placebo recipients was <12% (Table 2).[29] In the majority of studies, no statistically significant differences were noted between vaccine and placebo recipients.[30] As with TIV reactogenicity of LAIV is usually self-limited and often noted only with the first dose. No published data specifically addressed the issue of age-related differences in reactogenicity, although one study evaluating children as young as 12 months of age demonstrated that the type and likelihood of reactions in this age group did not differ from those seen in studies of older children.[31]

Safety data from a large, prospective, randomized, double blind, placebo-controlled trial of LAIV has been presented.[32, 33] This study enrolled 9689 children 1 to 17 years of age who were members of the Northern California Kaiser Permanente Health Care Plan. The primary endpoint was medically attended events in the clinic, hospital or emergency department ascertained through automated data. The authors noted many events to be either at increased or at decreased risk of occurrence in the LAIV group compared with placebo. The most important adverse event noted was a discharge diagnosis of asthma, which was statistically more common among LAIV vaccinees than among placebo recipients for children 18 to 35 months of age only (relative risk, 4; $P = 0.02$). Although it is biologically plausible that LAIV may precipitate reactive airway symptoms resulting in a visit to a health care provider, its significance in this study is unclear. The analysis included >1500 statistical comparisons without adjustment for multiplicity, utilized a conservative P value definition of 0.10 and included visits that were not clustered in a consistent time period postvaccination. No serious adverse events were noted with LAIV vaccination. Reductions in acute gastrointestinal events, cough, febrile illness, pharyngitis, tonsillitis and viral syndrome were noted in the vaccine group. These data ultimately led the manufacturer to not seek an indication in children <5 years of age. Clearly, adverse events noted in this study should be carefully monitored in LAIV postlicensure studies.

Because LAIV is a live (albeit attenuated) vaccine, it can theoretically be transmitted from a vaccinee to a close contact. With the exception of one event in an unpublished Finnish study, however, transmission of virus to susceptible contacts has not been documented. The Finnish study evaluated 98 vaccinated and 99 unvaccinated children 8 to 36 months of age in a day care setting. Eight percent of LAIV recipients shed vaccine virus, and the mean duration of shedding was 7.6 days. One placebo recipient acquired LAIV virus from a vaccine recipient, and this child shed virus for 1 day.[34]

The genetic composition of LAIV strains have been extensively studied by the manufacturer and CDC using laboratory and clinical trial isolates, and no reversion to wild-type or more virulent phenotypes has been demonstrated to date.[35] It is considered highly unlikely that such an event will be seen in the future; several genetic mutations must take place simultaneously for viral reversion to occur. Clearly this issue will need to be reconsidered as LAIV use begins postlicensure and the potential for recombination with wild-type influenza viruses becomes increasingly prominent.

EFFICACY OF TIV IN YOUNG CHILDREN

We identified 7 randomized, controlled trials that reported efficacy data for children <9 years of age (Table 3).[19, 21–24, 36–40] Only 1 study, designed to evaluate the impact of TIV on prevention of acute otitis media, specifically assessed children 6 to 24 months of age, the age for which vaccination is now "recommended."[24] The published data include <1020 TIV

TABLE 2. Symptoms associated with LAIV between Day 0 and Day 10 after vaccination among children 15 to 71 months of age enrolled in a prospective trial

Symptom/Sign	% with Symptom or Sign, Any Occurrence from Day 0–10 Postvaccination		
	Yr 1, Dose 1 (N = 1070 LAIV/532 placebo)	Yr 1, Dose 2 (N = 881 LAIV/433 placebo)	Yr 2 (N = 917 LAIV/441 placebo)
Runny nose/congestion	59, 48*†	36, 33	24, 25
Sore throat	10, 8	6, 7	10, 8
Cough	28, 29	36, 33	24, 25
Vomiting	6, 4*	7, 5	5, 4
Muscle ache	5, 3*	3, 2	3, 4
Headache	8, 6	5, 6	9, 7
Chills	4, 3	3, 3	3, 3
Decreased activity	16, 13	13, 13	11, 13
Irritability	26, 26	17, 19	14, 16
Fever >38.3°C orally	7, 6	5, 6	6, 3

* $P < 0.05$ for Fisher's exact test.
† As reported in Reference 29, significant only on Days 2, 3, 8 and 9 after adjustment for age of child, month of vaccination, and child care attendance.

TABLE 3. Published studies that report protective efficacy of TIV in healthy US children <9 years of age against influenza infection or illness*

Study Design/Reference	*N* (TIV/Placebo Recipients), Age	Endpoint	% with Infection or Illness among Vaccine/Placebo Groups	VE (%)	Comments
Randomized, double blinded, placebo-controlled: Gruber et al.,[19] 1990	19/27, 3–5 yr	Influenza illness by serology or culture	16/30 (drifted B strain)	47	Overall VE 76% for children 3–18 yr against febrile or complicated illness. No protection among household contacts noted
	26/28, 6–9 yr		15/36	56	
	9/22, 10–18 yr		11/41	74	
Randomized, double blinded, placebo-controlled: Clover et al.,[36] 1991	30/33, 3–9 yr†	Influenza illness by serology or culture	13/30 (drifted A strain)	56	Protection against infection in children 3–9 yr 35%. No protection among household contacts of vaccines
	19/31, 10–18 yr		0/not known	100	
Randomized, double blinded, placebo-controlled: Piedra et al.,[37] 1991	13/19, 3–5 yr	Influenza illness by serology or culture	23/26 (drifted A strain)	12	Overall VE 76% for children 3–18 yr against any illness
	33/31, 6–10 yr		0/23	100	
	16/19, 11–18 yr		0/11	100	
Randomization by day care, unblinded, controlled: Heikkinen et al.,[38] 1991	187/187, 1–4 yr	Influenza illness by rapid antigen detection of NP sample	3/16 (type A)	83	
Randomized, controlled: Hurwitz et al.,[39,40] 2000	46/51, 2–5 yr	Infection by serology	11/16 (A/H3N2)	31 (−0.95, 73)‡	All children received 2 doses of vaccine. Household contacts of vaccinated children with significantly less respiratory illness, missed school and medications prescribed
			24/43 (B)	45 (−2, 69)	
Randomized, double blinded controlled, multiyear study: Neuzil et al.,[22] 2001 and Edwards et al.,[23] 1994	200,§ 1–<6 yr	Infection by serology or culture	Not available	44 (−3.5, 69) for A/H1 yr	Heterotypic strains circulated in 2 of 4 yr. Overall VE 91% (A/H1) and 77% (A/H3) against symptomatic, culture-confirmed disease among all children <16 yr
				49 (−39, 81) for H3 yr	
	259, 6–10 yr			76 (53, 88) for H1 yr	
				74 (37, 89) for H3 yr	
	176, 11–15 yr			81 (47, 93) for H1 yr	
				70 (−1.2, 91) for H3 yr	
Randomized, blinded, placebo-controlled: Khan et al.,[21] 1996	168/87, 9–12 yr	School absence caused by ILI or illness by serology	4/10 (school absence)	56	Study performed in Russia
			1/23 (serology)	94 for A/H3N2	
Randomized, double blinded, placebo-controlled: Hoberman et al.,[24] 2003	525/261, 6–24 mo	Illness by culture	6/16	66 (34, 82) in Yr 1	Study primarily designed to evaluate prevention of otitis media, not influenza vaccine efficacy
			4/3	−7 (−247, 67) in Yr 2	

* Pooled analysis of studies that only included children <9 years of age, received two doses of vaccine in the first year of vaccination, and utilized only culture positivity or antigen detection was 63% (95% CI 45–75) using a fixed effects model.

† All received two doses annual doses of vaccine or placebo.

‡ Numbers in parentheses, 95% CI.

§ This study was a multiyear study, and children were enrolled and followed for up to 4 years. A total of 277 children <16 years of age received TIV during the study, and children were multiply vaccinated over time. Therefore, the number of children represents all those who ever received TIV, in the age group noted.

VE, vaccine efficacy; NP, nasopharyngeal; ILI, influenza-like illness.

vaccinees <5 years of age; 5 of 7 studies included <50 children and only 1 presented reliable data for more than 1 influenza season. No study is available that provides efficacy estimates against homotypic (nondrifted) influenza strains over a range of age groups. In addition methodologic differences make direct comparisons of vaccine efficacy results between studies problematic. The most important of these include: the endpoint under study (infection *vs.* illness); the manner in which the endpoint was ascertained (seroconversion, culture, other surveillance method); the possibility that the circulating strain is the same (homotypic) or different (heterotypic) from that which is included in the study vaccine; and the number of doses received/child (1 *vs.* 2).

To more fully clarify TIV vaccine efficacy, we pooled results from five studies that included only children <9 years of age who received two doses of vaccine in the first year of vaccination and clearly reported culture positivity or antigen detection as the clinical endpoint.[19, 24, 36,38] Determination of vaccine efficacy is most reliable when direct evidence of viral illness during an acute clinical illness is the clinical standard. Use of seroconversion (only) may overestimate efficacy because such studies usually obtain serologies only before and after a given influenza season, potentially including those who were not overtly symptomatic. Culture-based studies include prospectively identified ill children with known concurrent influenza infection. A test for heterogeneity (based on Cochran's Q statistic) of these studies was found to be not significant (indicating a lack of statistical heterogeneity), and the pooled vaccine efficacy was 63% [95% confidence interval (95% CI), 45, 70] with a fixed effects model. Although this estimate includes data from all English language published studies of young children given TIV as recommended by the ACIP, it is not a formal metaanalysis. We did not attempt to identify unpublished data or select those patients from serology-based studies who may have also had cultures obtained.

Despite limitations in the data noted above, some general conclusions can be made. (1) Studies with age-specific data suggest that protective efficacy increases with age in children. This may result from acquisition of preexisting functional antibody over time and/or immunologic priming or other biologic differences. Age specificity is also noted in adult populations among whom TIV protective efficacy against illness and hospitalization appear to decrease with age, particularly those >65 years among whom immune senescence may play a role. (2) The range of efficacy among children <5 years of age is quite broad (12 to 83%) and limited by the small number of studies. Only one study specifically evaluated and reported data for children 6 to 23 months of age; efficacy was 66% (95% CI 34, 82) in the first study year in which the influenza virus attack rate was high and –7% (95% CI –247, 67) in the second study year in which a low attack rate was noted.[24] Another study included children 1 to <6 years of age and demonstrated efficacy of 44 to 49% depending on viral strain.[22] 3) Three studies explicitly document only poor to moderate heterotypic protection from inactivated vaccine.[19, 36, 37] In a fourth trial, in which two of the four study years included heterotypic circulating strains, protection by year was not described.[22] (4) Overall vaccine efficacy in children, reported in many textbooks to be 70 to 90%, seems overly optimistic and needs to be considered more specifically by age group, particularly in the context of the ACIP recommendation for general usage in healthy young infants and children ≥6 months of age.

EFFICACY OF LAIV IN YOUNG CHILDREN

The protective efficacy of LAIV in children against serologic and/or culture-confirmed influenza infection has been extensively reviewed elsewhere.[30, 41] Table 4 lists selected placebo-controlled trials which include a mix of spray and drop delivery systems and bi- and trivalent formulations.[23, 36, 37, 42] The largest trial evaluated the licensed formulation and reported 95 and 91% efficacy against homotypic type A/H3N2 and B strains, respectively, among 1070 vaccinated children 15 to 71 months of age.[42] In the second year of the study, 86% protection against a heterotypic A/H3N2 strain was noted.[43] Field data for H1N1 were not available in this trial, but the rate of protection after subsequent nasal challenge with A/H1N1 vaccine was 83% against viral shedding.[44]

No head-to-head comparison of TIV and LAIV using the US-licensed spray formulation has been published. Studies from Texas and Tennessee compared TIV and bivalent LAIV in the same pediatric population during the same years, and no significant differences between vaccines were noted.[22, 23, 36, 37] The only published trial that compared trivalent LAIV and TIV was conducted by CDC investigators in Russia using a trivalent LAIV manufactured in Russia and TIV produced in this country by Wyeth-Ayerst.[21] This trial included children 9 to 12 years of age; TIV efficacy against infection demonstrated by seroconversion was 72% for LAIV and 94% for TIV. The master strain to create the Russian LAIV is different from the licensed US product, and the validity of comparison of these two vaccines is therefore unclear.

EFFECTIVENESS OF INFLUENZA VACCINES

The effectiveness of both TIV and LAIV against various clinical endpoints has been clearly demonstrated in healthy children and adults. These studies generally show a significant impact of influenza vaccine on influenza-like illnesses, hospitalization because of cardiopulmonary conditions, visits to health care

TABLE 4. Selected studies of the efficacy of LAIV in healthy children

Study Design, Reference	LAIV Formulation	*N* (LAIV/Placebo Recipients), Age	Vaccine/Placebo (% with Infection/Illness)	Vaccine Efficacy (%)	Comment
Randomized, double blinded, placebo-controlled: Belshe et al.,[42] 1998	Trivalent spray	1070/532, 15–71 mo	0.7/12	95 (88, 97)*	In second year of study, vaccine efficacy against drifted nonvaccine-containing A/H3N2 strain was 86%
			0.7/7	91 (79–96)	
Randomized, double blinded, placebo-controlled: Neuzil et al.,[22] 2001 and Edwards et al.[23] 1994	Bivalent drop	200,† 1–<6 yr	Not available	57 (10, 79) for H1 yr	Overall vaccine efficacy was 96% (A/H1) and 68% (A/H3) against symptomatic, culture-confirmed disease among all children <16 yr
				41 (−66–79) for H1 yr	
		259, 6–10 yr		89 (70–96) for H1 yr	
				67 (26–86) for H3 yr	
		176, 11–15 yr		80 (49–92) for H1 yr	
				−55 (−202–20) for H3 yr	
Randomized, double blinded, placebo-controlled: Clover et al.,[36] 1991	Bivalent drop	17/33, 3–9 yr	6/30	81	
		29/31, 10–18 yr	24/52	51	The epidemic strain was a drifted A strain
Randomized, double blinded, placebo-controlled: Piedra et al.,[37] 1991	Bivalent drop	12/19, 3–5 yr	17/26	35	Vaccine efficacy 57% for 3–18 yr combined
		22/31, 6–10 yr	9/23	61	
		27/19, 10–18 yr	4/11	61	

* Numbers in parentheses, 95% CI.

† This study was a multiyear study, and children were enrolled and followed for up to 4 years. A total of 277 children <16 years of age received TIV during the study, and children were multiply vaccinated over time. Therefore, the number of children represents all those who ever received TIV, in the age group noted.

providers, utilization of healthcare resources, incidence of concomitant otitis media, work productivity and school and work absenteeism.[45–48] Population-based studies in Japan and the US have also convincingly shown that use of TIV in young children can have a beneficial impact on the community at large across all age groups despite targeting vaccination to young children only, highlighting the impact of this age group on maintenance and spread of influenza to household and community contacts.[6, 7] Lastly the potential cost effectiveness of influenza vaccination of children has been shown to be comparable with or better than several currently recommended pediatric vaccinations, although this is dependent in large part on the cost of the vaccine.[49]

IMPLICATIONS

We have attempted to concisely summarize the available controlled data regarding the safety and efficacy of TIV in comparison with LAIV with specific attention to young children, the group for which the ACIP now recommend vaccination. Our review indicates that: (1) relatively few data are available to completely assess the safety and efficacy of contemporary TIV formulations in young children; (2) no alarming serious adverse events appear to frequently occur in young children after TIV; (3) important age-specific differences in TIV efficacy are apparent, with older children benefiting the most from vaccination; and (4) LAIV appears similar to TIV with regard to safety and efficacy in younger children. This review also highlights some important questions and areas of research that remain. These include: (1) safety of TIV in the youngest children for whom it is currently being considered as a routine vaccination (<24 months of age); (2) a need for continued study of increased respiratory events after LAIV administration in children <5 years of age; (3) direct comparison of the efficacy of trivalent LAIV and TIV; and (4) a clear need for systematic assessment of the emergence of rare adverse events potentially associated with TIV and/or LAIV after each is used with greater efficiency in coming years.

Implementation of the ACIP recommendation to vaccinate all children 6 to 23 months of age remains difficult for clinicians, given the practical realities of office-based vaccination of a large number of children in a relatively short (seasonal) time frame.[50] Many practices are not equipped to handle such campaigns as compared with provider or health maintenance organizations, which may have a built-in infrastructure for such programs. The potential benefit of influenza vaccination to individuals and communities, however, is clear, and it remains our most timely and effective intervention against this disease. No population-based data are available on vaccine coverage among healthy children, but coverage is only 9 to 25% among children

with asthma, the largest at risk pediatric group.[51] Weighing the relative risks and benefits of vaccination with TIV for children ≥6 months of age and LAIV for children >5 years of age remains the responsibility of all who provide health care to children.

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Multiple Choice Questions

1. Young children are at low risk of infection with influenza virus in any given year; as such, population-based rates of influenza-related hospitalizations are not as high as those seen in adults >65 years of age. TRUE or FALSE
2. All of the following are false statements regarding the safety of trivalent inactivated influenza vaccine (TIV) except:
   a. The safety of TIV has been prospectively evaluated in >10 000 children, a large percentage of whom were <2 years of age
   b. Published, postlicensure studies of influenza vaccine safety in young children have confirmed its safety
   c. Local reactions, moderate in severity, occur in >50% of vaccinated children
   d. Despite relatively few data, it does not appear that the risk of serious adverse events after vaccination is significant
3. All of the following are false statements regarding TIV, except:
   a. In children the protective efficacy appear to increase with age
   b. A high level of protection can be expected to occur even if the circulating strain is not included in the TIV
   c. Head-to-head comparisons of the two available vaccines (TIV and live, attenuated) have determined them to have equivalent protective efficacy
   d. Even with widespread use of influenza vaccines in communities, a positive impact on school absenteeism, antimicrobial use and other utilization of health care resources has not been demonstrated
4. Either the inactivated influenza vaccine or the live, attenuated, intranasal vaccine may be used to vaccinate a 6-year-old child with HIV infection. TRUE or FALSE
5. Vaccine coverage among children with asthma is approximately:
   a. <5%
   b. 9 to 25%
   c. 30 to 60%
   d. >75%

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Address: _____

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1. TRUE or FALSE
2. ⓐ ⓑ ⓒ ⓓ
3. ⓐ ⓑ ⓒ ⓓ
4. TRUE or FALSE
5. ⓐ ⓑ ⓒ ⓓ

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