

# 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,<sup>1,2</sup> particularly among young children.<sup>3–5</sup> Injectable trivalent inactivated influenza vaccine (TIV) is currently approved in the United States for use in children 6 months of age and older.<sup>6</sup> Efficacy rates for TIV in children younger than 5 years of age have been reported to range from 12% to 83%.<sup>6–8</sup>

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.<sup>9</sup> 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.<sup>10,11</sup> To date, there is a single published report of the safety of LAIV in children with asthma or wheezing,<sup>12</sup> and a single study has reported an increased risk of asthma in young children after LAIV.<sup>13</sup> 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).

Accepted for publication July 14, 2006.

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ISSN: 0891-3668/06/2510-0870

DOI: 10.1097/01.inf.0000237829.66310.85

## 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  $\mu$ g of each HA), whereas children 36 to <72 months of age received 0.5 mL per dose (15  $\mu$ g 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  $\pm$  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 ( $\geq 38^\circ\text{C}$  rectal or  $\geq 37.5^\circ\text{C}$  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.<sup>14,15</sup> 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 ( $\geq 38^\circ\text{C}$  rectal or  $\geq 37.5^\circ\text{C}$  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 ( $\geq 38^{\circ}\text{C}$  rectal or  $\geq 37.5^{\circ}\text{C}$  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 ( $\geq 38^{\circ}\text{C}$  rectal or  $\geq 37.5^{\circ}\text{C}$  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  $I_C/I_T$ , 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.

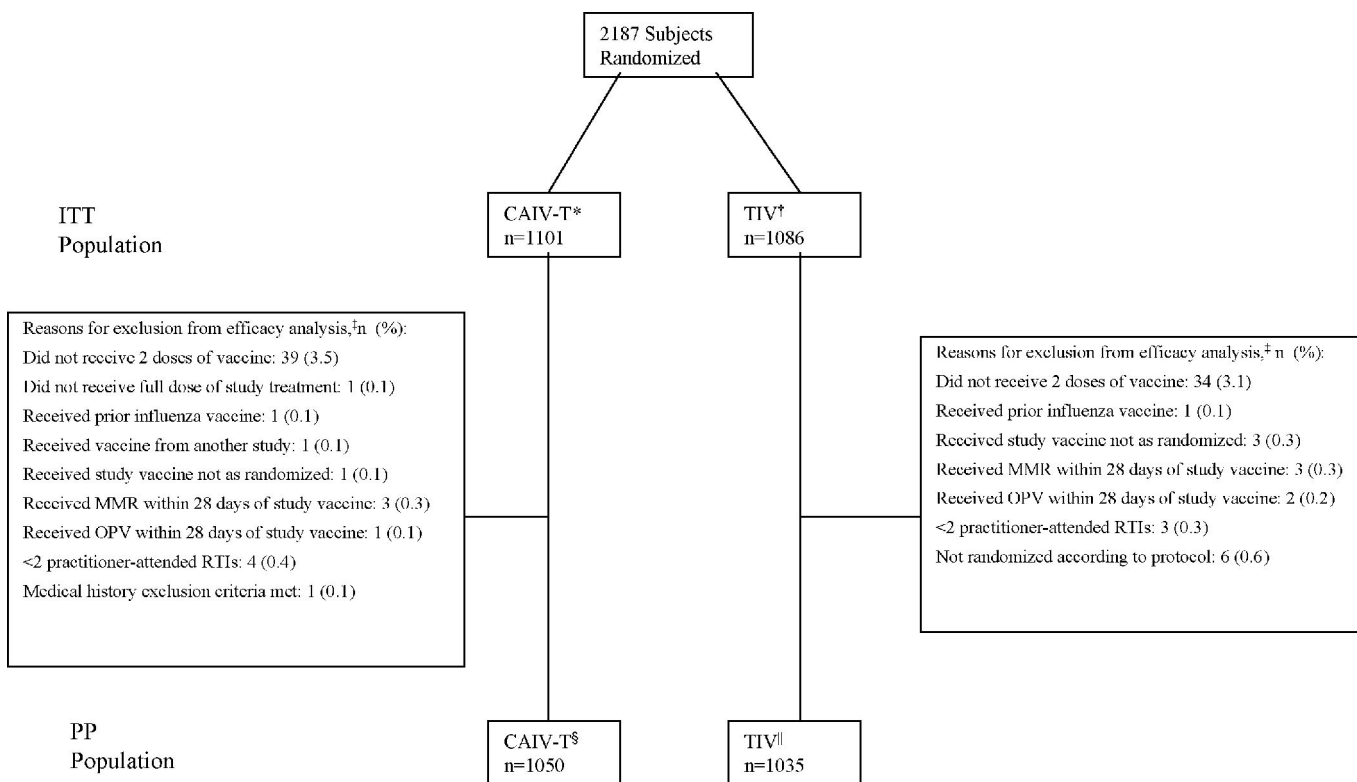
Analyses of AOM effectiveness variables included only those episodes that started during the country-specific influenza season. For the first episode of AOM, vaccine efficacy and 2-sided 90% CIs were computed conditional on the total number of cases. Analyses involving recurrent episodes of AOM with 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

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

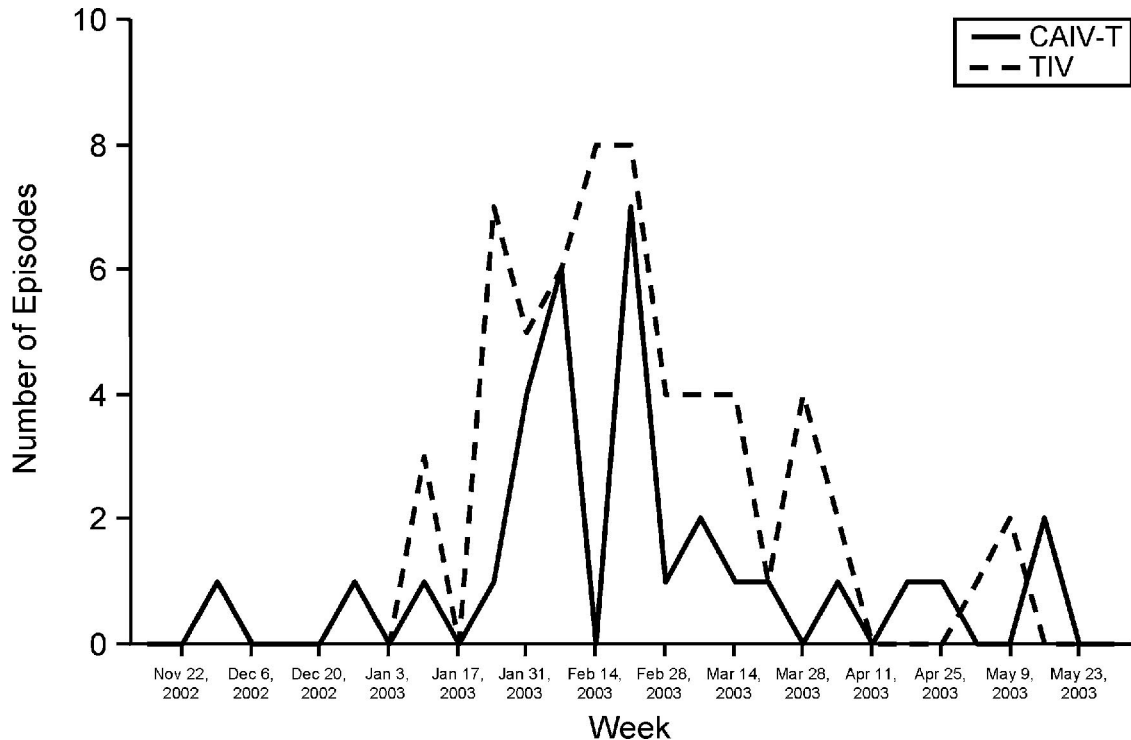
Characteristic	Treatment Group	
	CAIV-T n = 1050	TIV n = 1035
Gender, n (%)		
Girls	490 (46.7)	475 (45.9)
Boys	560 (53.3)	560 (54.1)
Age at first vaccination, mo		
Mean (SD)	38.1 (17.4)	39.9 (17.2)
Range	6.0–71.9	6.0–71.9
Ethnic origin, n (%)		
White	1022 (97.3)	1000 (96.6)
Black	15 (1.4)	13 (1.3)
Asian	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.

participating countries (Israel, United Kingdom, Belgium, and Poland) contributed almost two thirds (65%) of enrolled subjects.

**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.<sup>16</sup> 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.<sup>17</sup> Differences in titers of <4-fold would indicate antigenic equivalence between strains.<sup>18</sup>

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) <sup>‡</sup>	(95% CI) <sup>‡</sup>
	N*	n (%) <sup>†</sup>	N*	n (%) <sup>†</sup>		
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.

<sup>†</sup>Number of subjects with culture-confirmed influenza.

<sup>‡</sup>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 ( $\leq 3$ ) 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) <sup>‡</sup>
	CAIV-T		TIV		
	N*	n (%) <sup>†</sup>	N*	n (%) <sup>†</sup>	
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 <sup>§</sup>	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.

<sup>†</sup>Number of incidents or number of days with the event.

<sup>‡</sup>Exact CI conditioned on the total number of incidents or number of days.

<sup>§</sup>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 <sup>†</sup>	TIV n = 684–1050 <sup>†</sup>	P Value*	CAIV-T n = 625–1029 <sup>†</sup>	TIV n = 679–1012 <sup>†</sup>	P Value*
Any event <sup>‡</sup>	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 <sup>§</sup>	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 <sup>§</sup>	90 (14.2)	89 (12.8)	0.470	75 (11.9)	74 (10.6)	0.487
Chills <sup>§</sup>	37 (5.8)	53 (7.7)	0.192	28 (4.5)	26 (3.8)	0.579
Muscle ache <sup>§</sup>	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.

<sup>†</sup>Number of subjects with known values.

<sup>‡</sup>Any event does not include the administration of fever medication.

<sup>§</sup>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) <sup>  </sup>
			CAIV-T		TIV		
	Period, (days)*	Method <sup>†</sup>	N <sup>‡</sup>	n (%) <sup>§</sup>	N <sup>‡</sup>	n (%) <sup>§</sup>	
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.

<sup>†</sup>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.”

<sup>‡</sup>Number of subjects participating during the collection period.

<sup>§</sup>Number of subjects with at least 1 episode of wheeze in the indicated period and method of collection.

<sup>||</sup>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.<sup>19</sup> 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.<sup>10,11,19,20</sup>

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.<sup>13</sup> 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<sup>13</sup> 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.<sup>21</sup> 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.<sup>1</sup> During influenza seasons, influenza accounts for approximately one quarter of excess outpatient visits in children younger than 3 years,<sup>22</sup> 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.<sup>19</sup> CAIV-T has the potential, therefore, to reduce the substantial impact associated with influenza infection in young children.<sup>23</sup>

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,<sup>24</sup> 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.

## ACKNOWLEDGMENTS

*The authors thank the participating children and their parents, the study nurses and coordinators, the clinical testing*

laboratory staff, and the clinical research associates and scientists at Wyeth and MedImmune. The authors thank Fabrizio Pregliasco, MD, Rolf Heckler, PhD, J. C. Manuguerra, PhD, Raija Vainionpää, PhD, William F. Carman, PhD, Lidia B. Brydak, PhD, Frank H. M. Pistor, PhD, Pietro Crovari, MD, and Maria C. Zambon, PhD, and their staff for culture confirmation and subtyping of influenza. The authors also thank Iksung Cho, MS, Robert Walker, MD, and Edward M. Connor, MD, for their critical review of the manuscript and Catherine Grillo, MS, and Janet Stead, BM, BS, who provided medical writing and editorial assistance. This work was supported by MedImmune and Wyeth Research.

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