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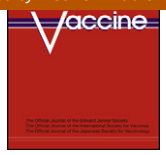

The efficacy of intranasal live attenuated influenza vaccine in children 2 through 17 years of age: A meta-analysis of 8 randomized controlled studies

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ABSTRACT

Background: Nine randomized controlled clinical trials, including approximately 26,000 children aged 6 months to 17 years, have evaluated the efficacy of live attenuated influenza vaccine (LAIV) against culture-confirmed influenza illness compared with placebo or trivalent inactivated influenza vaccine (TIV). The objective of the current analysis was to integrate available LAIV efficacy data in children aged 2–17 years, the group for whom LAIV is approved for use.
Methods: A meta-analysis was conducted using all available randomized controlled trials and a fixed-effects model. Cases caused by drifted influenza B were analyzed as originally classified and with all antigenic variants classified as dissimilar.
Results: Five placebo-controlled trials (4 were 2-season trials) and 3 single-season TIV-controlled trials were analyzed. Compared with placebo, year 1 efficacy of 2 doses of LAIV was 83% (95% CI: 78, 87) against antigenically similar strains; efficacy was 87% (95% CI: 78, 93), 86% (95% CI: 79, 91), and 76% (95% CI: 63, 84) for A/H1N1, A/H3N2, and B, respectively. Classifying B variants as dissimilar, efficacy against all similar strains was 87% (95% CI: 83, 91) and 93% (95% CI: 83, 97) against similar B strains. Year 2 efficacy was 87% (95% CI: 82, 91) against similar strains. Compared with TIV, LAIV recipients experienced 44% (95% CI: 28, 56) and 48% (95% CI: 38, 57) fewer cases of influenza illness caused by similar strains and all strains, respectively. LAIV efficacy estimates for children from Europe, the United States, and Middle East were robust and were similar to or higher than those for the overall population.
Conclusions: In children aged 2–17 years, LAIV demonstrated high efficacy after 2 doses in year 1 and revaccination in year 2, and greater efficacy compared with TIV. This meta-analysis provides precise estimates of LAIV efficacy among the approved pediatric age group.

1. Introduction

Influenza affects an estimated 1 billion people annually worldwide [1], with up to 5 million cases of severe illness and 500,000 deaths attributable to infection with influenza each year [2]. For epidemiologic and immunologic reasons, children are among the most susceptible to influenza infection and are primarily responsible for transmitting the illness to others [3–8]. Annual influenza vaccination is the principal measure for preventing influenza disease [2]; however, in many countries, influenza vaccination is not currently recommended for the vast majority of children.

A live attenuated influenza vaccine (LAIV, MedImmune, Gaithersburg, MD, USA) has been approved for use in many countries in eligible children and adolescents 2 years of age and older. The vaccine was originally derived at the University of Michigan by cold adaptation of an influenza type A strain (A/Ann Arbor/6/60 H2N2) and a type B strain (B/Ann Arbor/1/66) through serial passage at sequentially lower temperatures. During this process, the Ann Arbor strains acquired multiple mutations in genes encoding internal nonglycosylated proteins, resulting in master donor viruses with a cold-adapted, temperature-sensitive, and attenuated phenotype. These vaccine strains are updated annually to produce a trivalent vaccine with A/H1N1, A/H3N2, and type B influenza strains with hemagglutinin (HA) and neuraminidase (NA)

Abbreviations: AOM, acute otitis media; LAIV, live attenuated influenza vaccine; RR, relative risk; TIV, trivalent inactivated influenza vaccine.

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proteins that match those of the strains selected for the specific annual formulation. The vaccine is administered as a nasal spray using the Accuspray device (Becton Dickinson, Franklin Lakes, NJ, USA).

Nine randomized, controlled clinical trials have evaluated the efficacy of LAIV against culture-confirmed influenza illness compared with placebo or trivalent inactivated influenza vaccine (TIV) [9–18]. A previous meta-analysis of these trials by Rhorer et al. [19] evaluated the efficacy of LAIV in children in all subjects enrolled, many of whom were 6–23 months of age. Additionally, the meta-analysis by Rhorer et al. relied on summary statistics from each trial instead of subject-level data and thus the effects of subject characteristics such as gender and geographic region could not be explored. Lastly, results of TIV-controlled studies by influenza type and subtype were not explored by Rhorer et al. The objective of this analysis was to evaluate the efficacy of LAIV in children 2–17 years of age overall and by type/subtype, including the effects of various subject characteristics, using data from all available randomized controlled trials. This is the first meta-analysis conducted for children 2–17 years of age, the age group for whom LAIV is approved for use.

2. Methods

2.1. Trials used in meta-analysis

Of the 9 randomized, controlled trials evaluating the efficacy of LAIV against culture-confirmed influenza in children, one was conducted exclusively in children younger than 24 months and was excluded from analysis. Of the remaining 8 trials that enrolled children 2–17 years of age, 5 compared LAIV with placebo, of which 4 evaluated children vaccinated for 2 consecutive influenza seasons (Table 1) [9,11–15]. Placebo-controlled trials enrolled children in year 1 who had not been previously vaccinated against influenza. Three trials compared LAIV with TIV (Table 1) [16–18] over a single influenza season. These trials enrolled children regardless of previous influenza vaccination. In the Ashkenazi et al. study, all subjects received 2 doses of vaccine, while in the Fleming et al. study, all subjects received a single dose of vaccine [16,18]. In the study by Belshe et al., previously unvaccinated children received 2 doses of vaccine, while previously vaccinated children were administered a single dose of vaccine [17].

2.2. Planned analysis

All previous analyses of the studies in question have shown that efficacy results were similar for the per-protocol and intent-to-treat populations. Accordingly, the current analysis was limited to the per-protocol population of children ≥24 months of age at vaccination. Efficacy in year 1 was measured for children ≥24 months of age at enrollment; efficacy in year 2 was measured for children ≥24 months of age at year 2 vaccination. The prespecified endpoints of interest were efficacy relative to placebo and TIV against culture-confirmed influenza illness caused by antigenically similar strains and all strains regardless of antigenic match. Dosing regimens inconsistent with the recommended use of LAIV (e.g. low titer formulations or use of a single dose in previously unvaccinated children) were not examined. Predefined subgroup analyses included efficacy by influenza type/subtype (A/H3N2, AH1N1, B), by gender, and by region.

Classification of drifted, antigenic variant influenza B viruses varied across trials, with some classifying them as antigenically similar and others classifying them as antigenically dissimilar [20]. In the current analysis, illnesses caused by drifted influenza B viruses were analyzed as originally classified by the trials and secondarily by classifying all antigenic variants of B viruses as dissimilar.

2.3. Vaccines and placebo

In all trials, LAIV consisted of $10^{6.5–7.5}$ median tissue culture infectious doses ($TCID_{50}$) or fluorescent focus units of each of the 3 influenza strains (A/H1N1, A/H3N2, and B). Placebo did not differ in appearance, delivery, or taste. In one study, 2 different placebo formulations (saline and excipient) were investigated; for this meta-analysis, as in the original study, data from these 2 groups were combined [12]. TIV-controlled trials used commercially-available TIV approved for use in the corresponding region; children 6 months to younger than 36 months received 0.25 mL per dose (7.5 μg of each hemagglutinin) while children 36 months and older received 0.5 mL per dose (15 μg of each hemagglutinin). For the trials in which children received 2 doses, the time between doses was approximately 1 month, with the exception of one study in which the interval was 6–10 weeks [9,11].

2.4. Influenza case definition

Culture-confirmed symptomatic influenza illness was defined by a positive viral culture of a wild-type influenza virus. Nasal swab cultures were collected if a child had (1) ≥1 of the following: acute otitis media (suspected or diagnosed), fever, pneumonia, pulmonary congestion, shortness of breath, or wheezing or (2) ≥2 of the following symptoms concurrently: chills, cough, decreased activity, headache, irritability, muscle aches, pharyngitis, rhinorrhea, or vomiting. Criteria for obtaining a culture were generally consistent across trials, with the exception of slight variations in the definition of fever (minimum of ≥37.5 °C axillary, ≥38 °C oral, rectal, or tympanic), the start of surveillance after receiving the first dose (from 11 to 15 days or a specified date), and the recommended time between the onset of symptoms and collection of culture (from 24 h to 4 days) [19]. In all trials, central laboratories evaluated nasal swabs for the presence of influenza virus and subtypes, and serotypes were identified through antigenic methods.

2.5. Statistical analysis

Subject-level data were extracted for eligible children from the clinical trial databases for each relevant study (Table 1). The data were analyzed using the SAS System for Windows version 8.2 (Cary, NC, USA). The meta-analysis was conducted on the per-protocol population using the fixed-effects model [21]. A log binomial model was used to calculate LAIV relative risk adjusting for study variation. LAIV efficacy relative to placebo and TIV was calculated as 1 minus the adjusted relative risk (RR) of culture-confirmed influenza in LAIV recipients relative to placebo or TIV recipients, respectively. The 95% CI of LAIV efficacy was constructed from the 95% CI of the adjusted RR. The Cochran Q statistic was used to assess the heterogeneity of the effects across trials [22]. Studies with no influenza cases for a particular subtype were excluded from the corresponding analysis.

3. Results

The 8 trials included 4288 children 24–71 months of age in placebo-controlled trials and 7986 children 24 months to 17 years of age in TIV-controlled trials (Table 1). Demographics were similar among LAIV recipients and TIV and placebo controls. Children in TIV-controlled studies were older than those in placebo-controlled trials due to the inclusion of the TIV-controlled study in children 6–17 years of age.

Table 1
Trials comparing LAIV with placebo and TIV in children 2–17 years of age.

Study, period	Population, geography	Age range (mo)	Treatment group (doses, *n*)	*N*	Vaccine strains	Predominant circulating strain(s)
Trials comparing LAIV with placebo						
Belshe (1998) [11] Year 1: Aug 1996–Apr 1997	United States	24–71	LAIV (2) Placebo (2)	717 342	A/Texas/36/91-like (H1N1), A/Wuhan/359/95-like (H3N2), B/Harbin/7/94-like	A/Wuhan/359/95-like (H3N2), B/Harbin/7/94-like
Belshe (2000) [9] Year 2: Sep 1997–May 1998	United States	24–83	LAIV (1) Placebo (1)	748 362	A/Shenzhen/227/95-like (H1N1), A/Wuhan/359/95 (Nanchang-like) (H3N2), B/Harbin/7/94-like	A/Sydney/5/97 (H3N2) (antigenic variant)
Tam (2007) [14] Year 1: Sep 2000–Oct 2001	Asia	24–35	LAIV (2) Placebo (2)	782 534	A/New Caledonia/20/99 (H1N1), A/Sydney/05/97 (H3N2), B/Yamanashi/166/98 (Beijing-like)	A/New Caledonia/20/99-like (H1N1), A/Panama/2007/99-like (H3N2), B/Sichuan/379/99-like (antigenic variant), B/Hong Kong/330/01-like (opposite lineage)
Tam (2007) [14] Year 2: Nov 2001–Oct 2002	Asia	24–47	LAIV (1) Placebo (1)	771 494	A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Yamanashi/166/98	A/New Caledonia/20/99-like (H1N1), A/Panama/2007/99-like (H3N2), B/Sichuan/379/99-like (antigenic variant), B/Hong Kong/1351/02-like (opposite lineage)
Vesikari (2006) [15] Year 1: Oct 2000–May 2001	Children attending day care Europe, Israel	24–35	LAIV (2) Placebo (2)	490 356	A/New Caledonia/20/99 (H1N1), A/Sydney/05/97 (H3N2), B/Yamanashi/166/98 (Beijing-like)	A/New Caledonia/20/99-like (H1N1), B/Sichuan/379/99-like (antigenic variant)
Vesikari (2006) [15] Year 2: Dec 2001–May 2002	Children attending day care Europe, Israel	24–47	LAIV (1) Placebo (1)	570 403	A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Victoria/504/2000	A/New Caledonia/20/99-like (H1N1), A/Panama/2007/99-like (H3N2), B/Victoria/504/00-like, B/Hong Kong/1351/02-like (opposite lineage)
Bracco Neto (2009) [12] Year 1: Apr 2001–Nov 2001	South Africa, South America	24–35	LAIV (2) Placebo (2)	344 332	A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Yamanashi/166/98	A/Panama/2007/99-like (H3N2), B/Yamanashi/166/98-like
Bracco Neto (2009) [12] Year 2: Mar 2002–Nov 2002	South Africa, South America	24–47	LAIV (1) Placebo (1)	265 276	A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Victoria/504/2000	A/New Caledonia/20/99-like (H1N1), A/Panama/2007/99-like (H3N2), B/Hong Kong/1351/02-like (opposite lineage)
Forrest (2008) [13] Feb 2002–Nov 2002	Asia	24–35	LAIV (2) Placebo (2)	209 182	A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Victoria 504/2000	A/Panama/2007/99-like (H3N2), B/Hong Kong/330/01-like (opposite-lineage), B/Hong Kong/1351/02-like (opposite-lineage)
Trials comparing LAIV with TIV						
Ashkenazi (2006) [16] Oct 2002–June 2003	Children with 2 or more RTIs in the past 12 months Europe, Israel	24–71	LAIV (2) TIV (2)	790 819	A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Hong Kong/330/01	A/New Caledonia/20/99-like (H1N1), A/Panama/2007/99-like (H3N2), A/Fujian/411/2002-like (H3N2) (antigenic variant), B/Hong Kong/1351/02-like
Fleming (2006) [18] Oct 2002–May 2003	Children with a diagnosis of asthma Europe, Israel	6–17 years	LAIV (1) TIV (1)	1109 1102	A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Hong Kong/330/01	A/New Caledonia/20/99-like (H1N1), A/Panama/2007/99-like (H3N2), B/Hong Kong/1351/02-like
Belshe (2007) [17] Oct 2004–Aug 2005	Europe, Middle East, Asia, United States	24–59	LAIV (1/2)[a] TIV (1/2)[a]	2083 2083	LAIV: A/New Caledonia/20/99 (H1N1), A/Wyoming/3/2003 (H3N2), B/Jilin/20/2003 [B/Shanghai/361/2002-like] TIV: A/New Caledonia/20/99 (H1N1), A/Wyoming/3/2003 (H3N2), B/Jiangsu/10/2003 [B/Shanghai/361/2002-like]	A/New Caledonia/20/99-like (H1N1), A/California/7/2004-like (H3N2), B/Shanghai/361/2002-like, B/Florida/7/2004-like (antigenic variant), B/Hong Kong/330/01-like (opposite lineage)

LAIV, live attenuated influenza vaccine; RTI, respiratory tract infection; TIV, trivalent inactivated influenza vaccine.

[a] Depending on previous influenza vaccinations; 2 doses were administered to those previously unvaccinated, 1 dose was administered to those previously vaccinated.

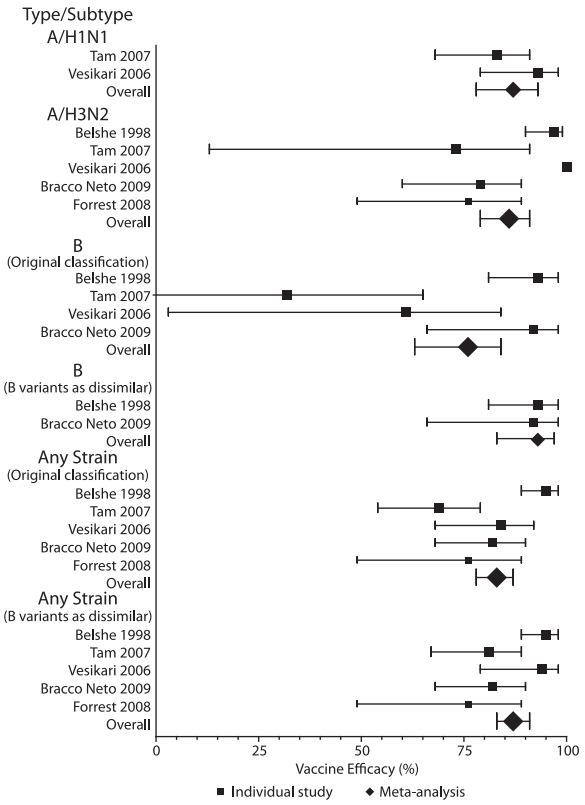

Fig. 1. LAIV efficacy versus placebo (year 1; 2 doses) for antigenically similar strains by type/subtype and study. LAIV, live attenuated influenza vaccine. Symbol sizes are relative to the study population sizes. See Table 1 for details of each study.

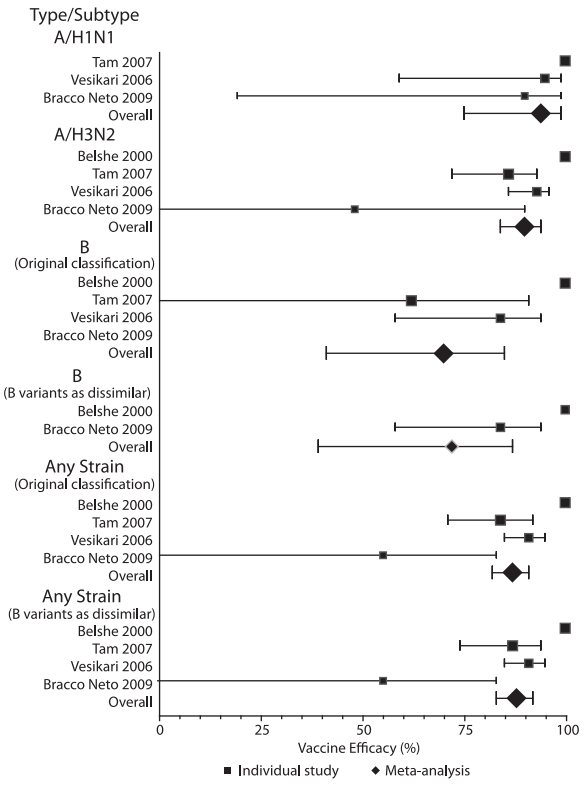

Fig. 2. Live attenuated influenza vaccine efficacy versus placebo (year 2; 1 revaccination dose) for antigenically similar strains by type/subtype and study. Symbol sizes are relative to the study population sizes. See Table 1 for details of each study.

3.1. Efficacy of LAIV compared with placebo

For the per-protocol population receiving 2 doses of LAIV compared with placebo after year 1, the estimated vaccine efficacy was 83% (95% CI: 78, 87; Table 2 and Fig. 1) against culture-confirmed influenza for antigenically similar strains (3% of LAIV versus 16% of placebo recipients developed influenza). By individual type/subtype, efficacy estimates were 87% (95% CI: 78, 93) for A/H1N1, 86% (95% CI: 79, 91) for A/H3N2, and 76% (95% CI: 63, 84) for B. With antigenically drifted B strains classified as dissimilar, efficacy against similar B strains increased to 93% (95% CI: 83, 97) and overall efficacy against all similar strains increased to 87% (95% CI: 83, 91). Vaccine efficacy was 79% (95% CI: 73, 83) for all strains regardless of antigenic match to the vaccine (4% of LAIV versus 18% of placebo recipients developed influenza).

After revaccination in year 2, the estimated vaccine efficacy compared with placebo was 87% (95% CI: 82, 91; Table 3 and Fig. 2) against culture-confirmed influenza caused by antigenically similar strains (1% of LAIV and 12% of placebo recipients developed influenza). As in year 1, efficacy was high against A/H1N1, A/H3N2, and B. Vaccine efficacy was 78% (95% CI: 72, 82) for all strains regardless of antigenic match (4% of LAIV and 18% of placebo recipients developed influenza).

3.2. Relative efficacy of LAIV compared with TIV

Compared with TIV, LAIV recipients overall experienced 44% (95% CI: 28, 56) and 48% (95% CI: 38, 57) fewer cases of influenza illness caused by similar strains and all strains regardless of match, respectively (Table 3 and Fig. 3). For similar strains by individual type/subtype, LAIV recipients experienced 97% (95% CI: 77, 100) fewer illnesses caused by A/H1N1 and 41% (95% CI: 21, 56) fewer illnesses caused by B strains; no difference was seen for antigenically similar A/H3N2 strains (relative efficacy, −31% [95% CI: −145, 30]). With antigenically drifted B strains classified as dissimilar, relative efficacy against similar B strains increased to 49% (95% CI: 27, 64) and overall relative efficacy against all similar strains increased to 50% (95% CI: 33, 62). For strains regardless of antigenic match, LAIV recipients experienced 97% (95% CI: 78, 100) fewer illnesses

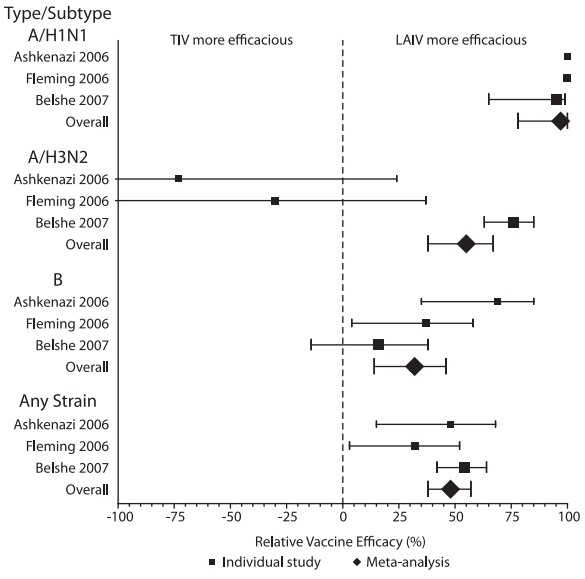

Fig. 3. LAIV efficacy versus TIV (year 1; 1 and 2 doses) for all strains regardless of antigenic similarity by type/subtype and study. LAIV, live attenuated influenza vaccine; TIV, trivalent inactivated influenza vaccine. Symbol sizes are relative to the study population sizes. See Table 1 for details of each study.

Table 2
Efficacy of LAIV versus placebo in years 1 and 2.

Influenza strain	LAIV *n*/*N* (%)	Placebo *n*/*N* (%)	Vaccine efficacy (95% CI)	Heterogeneity (*Q*)
Following year 1 vaccination, antigenically similar strains				
A/H1N1	14/1272 (1.1)	78/890 (8.8)	87 (78, 93)	0.1495
A/H3N2	26/2542 (1.0)	135/1746 (7.7)	86 (79, 91)	0.0025
B (original classification)	30/2333 (1.3)	82/1564 (5.2)	76 (63, 84)	0.0001
B (variants as dissimilar)	6/1061 (0.6)	52/674 (7.7)	93 (83, 97)	0.8557
Any strain (original classification)	70/2542 (2.8)	281/1746 (16.1)	83 (78, 87)	0.0002
Any strain (B variants as dissimilar)	46/2542 (1.8)	260/1764 (14.5)	87 (83, 91)	0.0056
Following year 1 vaccination, all strains regardless of antigenic similarity				
A/H1N1	14/1272 (1.1)	85/890 (9.6)	88 (80, 93)	0.0764
A/H3N2	32/2542 (1.3)	143/1746 (8.2)	84 (77, 89)	0.0003
B	47/2542 (1.8)	102/1746 (5.8)	68 (55, 77)	<0.0001
Any strain	94/2542 (3.7)	311/1746 (17.8)	79 (73, 83)	<0.0001
Following year 2 revaccination, antigenically similar strains				
A/H1N1	2/1606 (0.1)	27/1173 (2.3)	94 (75, 99)	0.6610
A/H3N2	20/2354 (0.8)	137/1535 (8.9)	90 (84, 94)	0.1040
B (original classification)	12/2354 (0.5)	28/1535 (1.8)	70 (41, 85)	0.3280
B (variants as dissimilar)	9/1583 (0.6)	23/1041 (2.2)	72 (39, 87)	NE
Any strain (original classification)	33/2354 (1.4)	183/1535 (11.9)	87 (82, 91)	0.0222
Any strain (B variants as dissimilar)	30/2354 (1.3)	179/1535 (11.7)	88 (83, 92)	0.0283
Following Year 2 Revaccination, All Strains Regardless of Antigenic Similarity				
A/H1N1	2/1606 (0.1)	27/1173 (2.3)	94 (75, 99)	0.6610
A/H3N2	35/2354 (1.5)	186/1535 (12.1)	88 (84, 92)	0.1514
B	55/2354 (2.3)	76/1535 (5.0)	43 (19, 59)	0.0107
Any strain	91/2354 (3.9)	275/1535 (17.9)	78 (72, 82)	<0.0001

LAIV, live attenuated influenza vaccine; NE, not estimable.

caused by A/H1N1, 55% (95% CI: 38, 67) fewer illnesses caused by A/H3N2, and 32% (95% CI: 14, 46) illnesses caused by B strains.

3.3. *Efficacy of LAIV by gender and region*

When analyzed by gender, LAIV efficacy versus placebo in year 1 was higher among females. Efficacy against antigenically similar strains was 89% (95% CI: 84, 93) among females compared with 75% (95% CI: 66, 82) among males. However, efficacy after revaccination in year 2 was similar by gender, with efficacy of 90% (95% CI: 82, 94) among females and 86% (95% CI: 77, 91) among males. Additionally, LAIV efficacy relative to TIV was comparable in males (40% [95% CI: 24, 52] fewer cases for all strains regardless of antigenic match) and females (59% [95% CI: 45, 69] fewer cases). By region, LAIV efficacy estimates relative to placebo and TIV for children from Europe, the United States, and Middle East were robust and were similar to or higher than those observed in the overall population. LAIV efficacy in year 1 relative to placebo against all strains was similar across all regions. LAIV efficacy against similar strains relative to placebo in year 1 for children from Asia (71% [95% CI: 59, 80]) was lower than the efficacy observed in the overall population. However, this difference was due to the disproportionate circulation of drifted B viruses in Asia; LAIV efficacy in children from Asia was 81% (95% CI: 67, 89) in year 1 against similar strains when drifted B viruses were classified as dissimilar. For placebo-controlled and TIV-controlled studies, most regions had data from only a single study. Few data were available regarding LAIV efficacy in year 2 relative to placebo in South America and Africa, and few to no data were available regarding LAIV efficacy relative to TIV in Asia, South America, and Africa.

4. Discussion

This meta-analysis is the first to provide a precise estimate of the efficacy of LAIV compared with placebo and TIV for children and adolescents 2–17 years of age, the age group for whom LAIV is approved for use. LAIV exhibited consistently high efficacy versus placebo and TIV against antigenically similar strains and all strains regardless of antigenic match. Not surprisingly, efficacy relative to placebo was lower when measured against all strains regardless of match. This difference is largely attributable to the recent cocirculation of 2 distinct lineages of influenza B strains, only 1 of which is contained in the trivalent vaccine each year [23]. Because of antigenic differences between the 2 influenza B lineages, efficacy against opposite-lineage influenza B strains is reduced for all influenza vaccines; efficacy of LAIV in children against opposite-lineage B strains has been estimated to be approximately 30% [24].

LAIV efficacy relative to TIV was high when measured against similar strains (44%–50% fewer cases of influenza illness among LAIV recipients) and all strains regardless of antigenic match (48% fewer cases). LAIV efficacy was consistently higher than TIV in all studies and across types/subtypes. The only exception was that the available sample was unable to demonstrate a statistically significant difference between LAIV and TIV for antigenically similar A/H3N2 strains; this is in part due to the limited circulation of antigenically similar A/H3N2 strains during the 3 TIV-controlled studies. However, the efficacy of LAIV relative to TIV against all A/H3N2 strains was high at 55% (95% CI: 38, 67), due to the high efficacy of LAIV and lower efficacy of TIV against antigenically dissimilar A/H3N2 strains. Placebo-controlled studies have also demonstrated that LAIV efficacy against antigenically dissimilar A/H3N2 strains can be high [9]. However, when the antigenic difference between the vaccine and circulating A/H3N2 strains is considerable, as occurred with emergence of the A/Fujian variant in 2003, LAIV efficacy may be reduced [10,25].

LAIV efficacy after revaccination in year 2 with a single dose was consistently higher compared with the efficacy of 2 doses in year 1, which is likely due to continuing immunity from the first season vaccination [26]. The sustained duration of LAIV protection in children has been described previously. In 1 study in Asia in which influenza circulated through 13 months after vaccination, LAIV efficacy was 74% (95% CI: 40, 89) during late-season outbreaks that occurred 5.5–13 months after vaccination, which was similar to the 69% (95% CI: 53, 80) efficacy observed for the season overall [27].

Table 3
Relative efficacy of LAIV versus TIV.

Influenza strain	Study	LAIV *n*/*N* (%)	TIV *n*/*N* (%)	Relative vaccine efficacy (95% CI)	Heterogeneity (*Q*)
Antigenically similar strains					
A/H1N1	Ashkenazi (2006)	0/790 (0.0)	6/819 (0.7)	100 (NE, 100)	
	Fleming (2006)	0/1109 (0.0)	5/1102 (0.5)	100 (NE, 100)	
	Belshe (2007)	1/2083 (0.0)	21/2083 (1.0)	95 (65, 99)	
	Meta-analysis	1/3982 (0.0)	32/4004 (0.8)	97 (77, 100)	NE
A/H3N2	Ashkenazi (2006)	10/790 (1.3)	5/819 (0.6)	−107 (−504, 29)	
	Fleming (2006)	12/1109 (1.1)	12/1102 (1.1)	1 (−120, 55)	
	Meta-analysis	22/1899 (1.2)	17/1921 (0.9)	−31 (−145, 30)	0.2729
B (original classification)	Ashkenazi (2006)	9/790 (1.1)	29/819 (3.5)	68 (32, 85)	
	Fleming (2006)	34/1109 (3.1)	53/1102 (4.8)	36 (3, 58)	
	Belshe (2007)	29/2083 (1.4)	40/2083 (1.9)	27 (−16, 55)	
	Meta-analysis	72/3982 (1.8)	122/4004 (3.0)	41 (21, 56)	0.1586
B (variants as dissimilar)	Ashkenazi (2006)	9/790 (1.1)	29/819 (3.5)	68 (32, 85)	
	Fleming (2006)	34/1109 (3.1)	53/1102 (4.8)	36 (3, 58)	
	Belshe (2007)	1/2083 (0.0)	5/2083 (0.2)	80 (−71, 98)	
	Meta-analysis	44/3982 (1.1)	87/4004 (2.2)	49 (27, 64)	0.1704
Any strain (original classification)	Ashkenazi (2006)	19/790 (2.4)	39/819 (4.8)	49 (13, 71)	
	Fleming (2006)	46/1109 (4.1)	70/1102 (6.4)	35 (6, 55)	
	Belshe (2007)	30/2083 (1.4)	61/2083 (2.9)	51 (24, 68)	
	Meta-analysis	95/3982 (2.4)	170/4004 (4.2)	44 (28, 56)	0.5563
Any strain (B variants as dissimilar)	Ashkenazi (2006)	19/790 (2.4)	39/819 (4.8)	49 (13, 71)	
	Fleming (2006)	46/1109 (4.1)	70/1102 (6.4)	35 (6, 55)	
	Belshe (2007)	2/2083 (0.1)	26/2083 (1.2)	92 (68, 98)	
	Meta-analysis	67/3982 (1.7)	135/4004 (3.4)	50 (33, 62)	0.0014
All strains regardless of antigenic similarity					
A/H1N1	Ashkenazi (2006)	0/790 (0.0)	7/819 (0.9)	100 (NE, 100)	
	Fleming (2006)	0/1109 (0.0)	6/1102 (0.5)	100 (NE, 100)	
	Belshe (2007)	1/2083 (0.0)	21/2083 (1.0)	95 (65, 99)	
	Meta-analysis	1/3982 (0.0)	34/4004 (0.8)	97 (78, 100)	NE
A/H3N2	Ashkenazi (2006)	15/790 (1.9)	9/819 (1.1)	−73 (−293, 24)	
	Fleming (2006)	17/1109 (1.5)	13/1102 (1.2)	−30 (−166, 37)	
	Belshe (2007)	24/2083 (1.2)	102/2083 (4.9)	76 (63, 85)	
	Meta-analysis	56/3982 (1.4)	124/4004 (3.1)	55 (38, 67)	<0.0001
B	Ashkenazi (2006)	9/790 (1.1)	30/819 (3.7)	69 (35, 85)	
	Fleming (2006)	35/1109 (3.2)	55/1102 (5.0)	37 (4, 58)	
	Belshe (2007)	72/2083 (3.5)	86/2083 (4.1)	16 (−14, 38)	
	Meta-analysis	116/3982 (2.9)	171/4004 (4.3)	32 (14, 46)	0.0340
Any	Ashkenazi (2006)	23/790 (2.9)	46/819 (5.6)	48 (15, 68)	
	Fleming (2006)	50/1109 (4.5)	73/1102 (6.6)	32 (3, 52)	
	Belshe (2007)	94/2083 (4.5)	205/2083 (9.8)	54 (42, 64)	
	Meta-analysis	167/3982 (4.2)	324/4004 (8.1)	48 (38, 57)	0.1898

LAIV, live attenuated influenza vaccine; NE, not estimable, TIV, trivalent inactivated influenza vaccine.

Analyses of LAIV efficacy by various subject characteristics demonstrated LAIV is highly efficacious in male and female children as well as across multiple geographic regions. The finding of higher efficacy in female subjects in year 1 of placebo-controlled studies is not readily explained; the lack of a difference in year 2 of placebo-controlled studies suggests that the difference could be due to chance alone and not a true biologic difference. Even if true, the difference would have no clinical relevance given that LAIV provided greater efficacy compared with TIV in both male and female subjects. The impact of subject age on LAIV efficacy was not evaluated in the current analysis. Additionally, data for children and adolescents 7 through 17 years of age is limited to one single-season study that compared LAIV and TIV. However, a previous analysis of LAIV efficacy by age in studies with broad enrollment age ranges demonstrated that LAIV efficacy does not decline with increasing age or repeated exposure to influenza in children up to 17 years of age [28].

In addition to the incidence of culture-confirmed influenza illness, all of the studies in the current analysis that were conducted in children 6 years of age and younger prospectively evaluated the incidence of acute otitis media (AOM). Among children 24–71 months of age, LAIV reduced the incidence of influenza-associated AOM by 91% (95% CI: 84, 96) relative to placebo and 62% (95% CI: 21, 83) relative to TIV. Additionally, LAIV reduced the severity of influenza illness among breakthrough cases in children 24–71 months of age, as the rate of AOM among subjects with influenza was 57% (95% CI: 19, 79) lower among LAIV recipients relative to placebo recipients [29].

4.1. Limitations

As expected, significant heterogeneity was demonstrated in some comparisons. This can be explained by slight variations in the trials with regard to circulating strains during different influenza seasons, previous exposure of participants to influenza vaccination or disease, and other factors. However, the numerical values of the efficacy estimates across studies were similar. Certain subgroup analyses, especially those examining regional differences, consisted of only 1 study in each region and thus should be interpreted with caution. The majority of study participants were younger than 7 years of age; only one single-season study presented data for children and adolescents 7–17 years of age. However, LAIV efficacy in children and adolescents has not been shown to vary as a function of age or pre-existing immunity to influenza [28].

Consistent with the previous meta-analysis by Rhorer et al., the present analysis used a fixed effects rather than a random effects model. A random effects model would be more appropriate if vaccine efficacy was assumed to differ among trials. However, the small number of trials available could result in a substantial Type I error rate [30]. Because the objective of the current analysis was to provide a weighted average of vaccine efficacy estimates across multiple studies, a fixed effects model is more appropriate.

5. Conclusions

In children 2 through 17 years of age, LAIV has demonstrated high efficacy after 2 doses in year 1 and after revaccination with a single dose in year 2. Efficacy was similar for A/H1N1, A/H3N2, and B strains. LAIV demonstrated greater efficacy compared with TIV in all 3 studies comparing the 2 vaccines. LAIV efficacy estimates relative to placebo and TIV for children from Europe, the United States, and Middle East were robust and were similar to or higher than those observed in the overall population. This meta-analysis provides more precise estimates of LAIV efficacy among the approved pediatric age group and should provide reassurance regarding the routine use of LAIV in eligible children 2 years of age and older.

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