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Efficacy of live attenuated influenza vaccine in children: A meta-analysis of nine randomized clinical trials

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ABSTRACT

Nine randomized clinical trials, including approximately 25,000 children aged 6–71 months and 2000 children aged 6–17 years, have evaluated the efficacy of live attenuated influenza vaccine (LAIV) against culture-confirmed influenza as compared to placebo or trivalent inactivated vaccine (TIV). We conducted meta-analyses, based on Mantel–Haenszel relative risks from fixed effect models, to provide an estimate of vaccine efficacy (VE). Relative to placebo, year 1 VE for two doses in vaccine-naïve young children was 77% (95% CI: 72%, 80%; $P < 0.001$) against antigenically similar strains and 72% against strains regardless of antigenic similarity. Efficacy was 85%, 76%, and 73% against antigenically similar A/H1N1, A/H3N2, and B, respectively. Year 1 VE of one dose against antigenically similar strains in vaccine-naive children was 60%; efficacy of one dose in previously vaccinated children in year 2 of the various studies was 87%. In head-to-head trials comparing two doses of TIV and LAIV, vaccine-naïve children who received two doses of LAIV experienced 46% fewer cases of influenza illness caused by antigenically similar strains. Similarly, for studies including older children who had been previously vaccinated, those receiving one LAIV dose experienced 35% fewer cases of influenza illness than those receiving one TIV dose. LAIV showed high VE versus placebo with no evidence of difference by age or by circulating subtype. In these studies, LAIV was more effective than TIV.

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1. Introduction

Influenza virus causes significant morbidity and mortality worldwide [1–4], and annual influenza epidemics confer a heavy burden on health care systems [2,4–6]. Although children are among the most susceptible to influenza infection and are most likely to transmit the illness to others [2,6–10], many children do not receive influenza vaccination [8,11,12]. Moreover, most vaccine-naive children younger than 9 years of age who do receive vaccination receive only one dose rather than the recommended two-dose regimen [8,11,13].

An intranasal cold-adapted, live attenuated influenza virus vaccine [LAIV; FluMist® (Influenza Virus Vaccine Live, Intranasal); MedImmune, Gaithersburg, MD, USA] was first approved for use in the United States in 2003. In September 2007, the US Food and Drug Administration expanded the indication for use in individuals 2–49 years of age, from the previous 5–49-year indication. Several pediatric studies have characterized the safety and efficacy of LAIV in children, and the vaccine was shown to be efficacious in each of these studies [14–23] (Tables 1 and 2). Performing meta-analyses on clinically important subsets of the population of children evaluated in these studies provides more precise estimates of the efficacy of the LAIV vaccine than does reliance on a single study. Previous meta-analyses of LAIV efficacy [24–27] included data from several investigational LAIV formulations and did not include data from several recently published studies. The meta-analyses conducted here focus solely on data for the LAIV that has been approved for use in the United States (FluMist). We summarize data comparing the efficacy of LAIV with either trivalent inactivated influenza vaccine (TIV) or placebo.

2. Materials and methods

2.1. Studies used in the meta-analyses

Wyeth Vaccines Research (Pearl River, NY, USA) and MedImmune have conducted nine randomized, double-blind, controlled trials evaluating the efficacy of LAIV against culture-confirmed

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Table 1
Studies comparing LAIV with placebo included in meta-analyses.

Study period	*Population studied* countries	Age range (months)	Treatment group (doses, *n*)[a]	*n*[b]	Vaccine strains	Circulating strains
AV006[14,15] Year 1: August 1996 to April 1997	*Healthy children, influenza vaccine-naïve (year 1)* United States	≥15 to ≤71	LAIV (2), placebo (2)	881, 433	Year 1: A/Texas/36/91-like (H1N1), A/Wuhan/359/95-like (H3N2), B/Harbin/7/94-like	Year 1: A/Wuhan/359/95-like (H3N2)[c], B/Harbin/7/94-like[c]
Year 2: September 1997 to May 1998			LAIV (1), placebo (1)	189, 99	Year 2: A/Shenzhen/227/95-like (H1N1), A/Wuhan/359/95 (Nanchang-like) (H3N2), B/Harbin/7/94-like	Year 2: A/Sydney/5/97 (H3N2), A/Wuhan/359/95-like (H3N2)[c], B/Harbin/7/94-like[c]
D153-P501[16] Year 1: September 2000 to October 2001	*Healthy children, influenza vaccine-naïve (year 1)* China, Hong Kong, India, Malaysia, Philippines, Singapore, Taiwan, Thailand	≥12 to <36	LAIV (2), placebo (2)	1900, 1274	Year 1: A/New Caledonia/20/99 (H1N1), A/Sydney/05/97 (H3N2), B/Yamanashi/166/98 (Beijing-like)	Year 1: A/Hawaii/15/01-like (H1N1), A/New Caledonia/20/99-like (H1N1)[c], A/Panama/2007/99-like (H3N2)[c], B/Hong Kong/22/01-like, B/Hong Kong/330/01-like[c], B/Hong Kong/1351/02-like[c], B/Sichuan/379/99-like[c], B/Victoria/504/00-like[c]
Year 2: November 2001 to October 2002					Year 2: A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Yamanashi/166/98	Year 2: A/New Caledonia/20/99-like (H1N1)[c], A/Panama/2007/99-like (H3N2)[c], B/Brisbane/32/02-like, B/Hong Kong/330/01-like[c], B/Hong Kong/1351/02-like[c], B/Shizuoka/15/01-like, B/Sichuan/379/99-like[c], B/Victoria/504/00-like[c], B/Yamanshi/166/98-like
D153-P502[17] Year 1: October 2000 to May 2001	*Healthy children attending day care, influenza vaccine-naïve (year 1)* Belgium, Finland, Israel, Spain, United Kingdom	≥6 to <36	LAIV (2), placebo (2)	1059, 725	Year 1: A/New Caledonia/20/99 (H1N1), A/Sydney/05/97 (H3N2), B/Yamanashi/166/98 (Beijing-like)	Year 1: A/New Caledonia/20/99-like (H1N1)[c], A/Panama/2007/99-like (H3N2)[c], B/Sichuan/379/99-like
Year 2: December 2001 to May 2002					Year 2: A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Victoria/504/2000	Year 2: A/New Caledonia/20/99-like (H1N1)[c], A/Panama/2007/99-like (H3N2)[c], B/Hong Kong/330/01-like, B/Hong Kong/1351/02-like, B/Victoria/504/00-like
D153-P504[18] Year 1: April 2001 to November 2001	*Healthy children, influenza vaccine-naïve (year 1)* South Africa, Brazil, Argentina	≥6 to <36	LAIV (2), placebo (1 or 2)[d]	1064, 1069	Year 1: A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Yamanashi/166/98	Year 1: A/New Caledonia/20/99-like (H1N1)[c], A/Panama/2007/99-like (H3N2)[c], B/Victoria/504/00-like[c], B/Yamanashi/166/98-like[c]
Year 2: March 2002 to November 2002			LAIV (1), placebo (1 or 2)[d]	1067, 1069	Year 2: A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Victoria/504/2000	Year 2: A/Moscow/10/99-like (H3N2), A/New Caledonia/20/99-like (H1N1)[c], A/Panama/2007/99-like (H3N2)[c], B/Hong Kong/330/01-like, B/Hong Kong/1351/02-like, B/Shenzhen/654/99-like, B/Sichuan/379/99-like, B/Victoria/504/00-like[c], B/Yamanahashi/166/98-like[c]

D153-P513[19] February 2002 to November 2002	*Healthy children, influenza vaccine-naïve* Philippines, Thailand	≥6 to <36	LAIV 10^5 (2)	546	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/330/01-like, B/Hong Kong/1351/02-like, B/Victoria/504/00-like
			LAIV 10^6 (2)	546		
			LAIV 10^7 (2)	543		
			Placebo (2)	537		
D153-P522[20] October 2002 to May 2003	*Healthy children, influenza vaccine naïve* Bangladesh, Belgium, Finland, Germany, Hong Kong, Korea, Lithuania, Malaysia, Mexico, Philippines, Poland, Singapore, Thailand	≥11 to <24	LAIV+MMR (2)	819	A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Hong Kong/330/2001	A/Fujian/411/2002-like (H3N2), A/New Caledonia/20/99-like (H1N1), A/Panama/2007/99-like (H3N2), B/Victoria/504/00-like, B/Hong Kong/330/01-like, B/Hong Kong/1351/02-like
			Placebo + MMR (2)	413		

MMR = mumps, measles, and rubella vaccine.

[a] All studies used the refrigerated formulation of LAIV except AV006 which used the frozen formulation. Unless otherwise specified, the LAIV dose used was 10^7 median $TCID_{50}$ or 10^7 fluorescent focus units. All meta-analyses included children who received doses of 10^7 median $TCID_{50}$ or fluorescent focus units.

[b] Sample size is the number of subjects randomized in the first year of study.

[c] Same strain circulating both study years.

[d] The placebo groups for one and two doses are combined for the meta-analysis; the same placebo subjects are used in the comparisons with both the one and two-dose LAIV groups.

Table 2
Studies comparing LAIV with TIV included in meta-analyses.

Study period	*Population studied* countries	Age range (months)	Treatment group (doses, *n*)	*n*[a]	Vaccine strains	Circulating strains
D153-P514[21] October 2002 to June 2003	*Children who had experienced two or more practitioner-attended RTIs in the past 12 months, influenza vaccine-naïve* Belgium, Czech Republic, Finland, Germany, Israel, Italy, Poland, Spain, Switzerland, United Kingdom	≥6 to <72	LAIV (2), TIV (2)	1101, 1086	A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Hong Kong/330/01	A/Fujian/411/2002-like (H3N2), A/New Caledonia/20/99-like (H1N1), A/Panama/2007/99-like (H3N2), A/Sydney/5/97-like (H3N2), B/Hong Kong/330/01-like, B/Hong Kong/1351/02-like
D153-P515[22] October 2002 to May 2003	*Children with a diagnosis of asthma (not all influenza vaccine-naïve)* Belgium, Finland, Germany, Greece, Israel, Italy, Netherlands, Norway, Poland, Portugal, Spain, Switzerland, United Kingdom	≥72 to ≤204 (*i.e.*, ≥6 years to ≤17 years)	LAIV (1), TIV (1)	1114, 1115	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 (H3N2)-like, B/Hong Kong/330/01-like, B/Hong Kong/1351/02-like
MI-CP111[23] October 2004 to August 2005	*Healthy children (Two dose group influenza vaccine-naïve)* Asia, Europe, Middle East, United States	≥6 to ≤59	LAIV (2), TIV (2)	4243, 4232	LAIV: A/New Caledonia/20/99 (H1N1), A/Wyoming/03/2003 (H3N2), B/Jilin/20/2003 [B/Shanghai/361/2002-like] TIV: A/New Caledonia/20/99 (H1N1), A/Wyoming/03/2003 (H3N2), B/Jiangsu/10/2003 [B/Shanghai/361/2002-like].	A/New Caledonia/20/99-like (H1N1), A/Wyoming/3/2003-like (H3N2), A/California/7/2004-like (H3N2), B/Yamagata/16/88 lineage, B/Victoria/02/87 lineage

LAIV = live attenuated influenza vaccine; TIV = trivalent inactivated vaccine. All studies comparing LAIV to TIV used the refrigerated formulation of LAIV.

[a] The number of subjects randomized.

influenza in children. Most of the children studied were young. Six trials compared LAIV with placebo [14–20] (Table 1) in children aged between 6 and 71 months. Three trials compared LAIV with TIV [21–23] (Table 2); two of these studied children aged 6–71 months, while one studied children 6–17 years of age. Four studies evaluated children vaccinated for two consecutive influenza seasons. Studies were conducted by both organizations over several years and final patient-level study data was not available to the authors for some of the studies. As a result, primary efficacy analyses from the study data could not be performed. Instead, the authors used the available Clinical Study Reports (CSRs) to abstract the data for the meta-analyses. All studies reported overall rates of influenza for community-acquired influenza antigenically similar to strains in the vaccine as well as overall rates of influenza regardless of antigenic similarity of strain type. For the six studies comparing LAIV with placebo, all included by-strain efficacy for community-acquired subtypes antigenically similar to those in the vaccine as well as subtypes regardless of similarity.

Evaluating the protection LAIV affords against influenza illness caused by a circulating strain that is antigenically similar to a strain in the vaccine provides information about how well the vaccine protects against a targeted strain. To understand whether an influenza vaccine can provide some protection against influenza even when the circulating strains are not similar to those in the vaccine, it is also of interest to evaluate how well the vaccine protects against antigenically dissimilar strains. Many of the primary study analyses from which we abstracted data for these meta-analyses, however, did not include efficacy results for antigenically dissimilar subtypes. Rather, they analyzed results for efficacy against antigenically similar strains and all strains of influenza regardless of antigenic similarity. The meta-analyses conducted here, therefore, only summarize the vaccine efficacy for cases based on subtypes antigenically similar and subtypes without regard to antigenic similarity. Cases caused by antigenically dissimilar subtypes cannot be accurately calculated by subtracting the number of antigenically similar cases from all cases regardless of antigenic similarity as this difference represents a mix of both antigenically dissimilar subtypes and strains of undetermined antigenic similarity.

The studies reported efficacy estimates based on per-protocol and intent-to-treat (ITT) populations. For the analyses based on the first vaccination year, the per-protocol population was defined as those subjects who received the scheduled number of doses to which they were randomized. For those studies evaluating subjects vaccinated for a second influenza season, the per-protocol population was defined for the meta-analyses as those subjects who in year 1 received the two scheduled doses to which they were randomized and received their scheduled year 2 dose. One study re-randomized children to treatment assignment in year 2 [16]. Analyses based on the ITT population in the first vaccination year included children who were scheduled to receive vaccination. For all but two studies [14,15,23], the ITT analyses required the children to have received at least one dose if they were scheduled to receive two doses. In ITT analyses, children were analyzed according to their randomized treatment assignment. For year 2, the ITT population for our meta-analyses included children who received the two scheduled doses in year 1 and were either scheduled to be dosed in year 2 [14–16] or received a dose in year 2 [17,18].

A coding error in one study's [18] assignment of vaccine in year 2 led to approximately half of year 1 placebo children ($n = 347$) receiving an unscheduled first dose of vaccine in year 2. The meta-analyses included these children as "as-treated" subjects.

2.2. Vaccines and placebo

Children vaccinated with LAIV received either one or two doses of approximately 10^7 median tissue culture infectious doses ($TCID_{50}$) or 10^7 fluorescent focus units of each of the three influenza strains (A/H1N1, A/H3N2, and B), administered by the Accuspray™ device (Becton-Dickinson). One study utilized the original 0.5 mL (0.25 mL per nostril) frozen formulation of LAIV [14,15], while the others utilized the current 0.2 mL (0.1 mL per nostril) refrigerated formulation. The two formulations have been demonstrated to have comparable immunogenicity and reactogenicity [28]. The corresponding placebo did not differ noticeably in appearance, taste, or delivery. One study [18] included two different placebos (saline and excipient) which we combined for the meta-analysis. Commercially available TIV approved for use in the corresponding region contained hemagglutinin for each of the three vaccine strains for that season. Subjects aged 6 months to less than 36 months received 0.25 mL per dose (7.5 μg of each hemagglutinin) while subjects aged 36 months to less than 72 months received 0.5 mL per dose (15 μg of each hemagglutinin). In most studies in which children received two doses, the time between doses was approximately 1 month; in one study the dosing interval was 6–10 weeks [14].

2.3. Influenza case definition

The meta-analyses use data based on the endpoint of culture-confirmed symptomatic influenza illness defined by a positive viral culture of a wild-type virus with a subtype that is antigenically similar to one contained in the vaccine. All nine studies used consistent criteria for obtaining a culture except for slight variations in the defining of fever symptoms (across studies, a minimum of ≥100.4 °F rectal, tympanic, or oral; ≥99.5 °F axillary), the beginning of the surveillance period after receiving the first dose (between 11 and 15 days or a specified date, or for the ITT population, some studies started surveillance on the day of dosing), and the time between the onset of symptoms and the time site personnel obtained a culture (between 24 h and 4 days). Cultures were collected if a child had (1) at least one of the following: fever, wheezing, shortness of breath, pulmonary congestion, pneumonia, or acute otitis media, suspected or diagnosed, or (2) at least two of the following symptoms concurrently: rhinorrhea, pharyngitis, cough, muscle aches, chills, headache, irritability, decreased activity, or vomiting.

2.4. Laboratory assessment

For all studies, central laboratories evaluated nasal swabs for presence of influenza virus and for subtype and serotype identification by antigenic methods.

2.5. Data collection

Two individuals from Statistics Collaborative abstracted all data for the meta-analyses from the final Clinical Study Reports for each trial and associated publications (Tables 1 and 2). We analyzed the data using the SAS System for Windows Version 9.1 [29,30] (Cary, NC, USA) and verified the meta-analyses using Stata/SE Version 9.2 for Windows (College Station, TX, USA) [31].

2.6. Statistical analysis

For these meta-analyses, we used relative risk as the measure of vaccine effect. The main outcome of interest was vaccine efficacy, which is calculated as $(1 - R_T/R_C) \times 100$, where R_T and R_C are the influenza rates in the LAIV and control group (either TIV or placebo), respectively, and the corresponding approximate 95% confidence interval (CI) [32,33]. We used a fixed effect model and assumed a general, common treatment effect among the included studies, but we evaluated the heterogeneity among studies. For the summary relative risk from the fixed effects models, we used the pooled Mantel–Haenszel relative risk [32,34,35] and tested the overall

effect of vaccine with the Mantel–Haenszel chi-square statistic assessing the association between vaccination and influenza after adjusting for the different studies. We used the Cochran Q statistic to assess the heterogeneity of the effects across studies [36]. We also performed sensitivity analyses to evaluate whether any single study dominated the results of the meta-analyses by estimating vaccine efficacy and the corresponding 95% confidence interval after sequentially excluding each individual study.

3. Results

3.1. Study subjects

The nine studies included approximately 25,000 children aged 6–71 months and approximately 2000 children aged 6–17 years throughout Asia, Europe, the Middle East, South America, and the United States. Each trial included at least 1000 children. With the exception of two studies evaluating children with a history of recurrent respiratory tract infections or diagnosed with asthma, the children generally did not have significant underlying medical conditions. All but two of the studies [22,23] excluded children who had previously received any influenza virus vaccination, and thus, children randomized to LAIV in year 1 received two doses. In the study of children 6–17 years of age with asthma, all children received a single dose [22]. In one study comparing LAIV and TIV [23], children who were naive to influenza vaccine received two doses of study vaccine and those previously vaccinated received one dose.

3.2. Vaccine efficacy compared with placebo

3.2.1. Efficacy of two doses of LAIV in previously unvaccinated children

Six study reports, including a total of approximately 14,000 healthy children aged 6–71 months, presented estimated vaccine efficacy after either one or two doses of vaccine or placebo. For two doses of LAIV compared with placebo after a single influenza season in the per-protocol population, the estimated vaccine efficacy was 77% ($P < 0.001$, Table 3) against culture-confirmed influenza for antigenically similar subtypes for all strains. Across all studies in this meta-analysis, the percentage of children developing influenza ranged between 1% and 7% (LAIV recipients) and 6% and 20% (placebo recipients). For subtypes regardless of antigenic similarity, the estimated vaccine efficacy was 72% ($P < 0.001$, data not shown) and the percentages of children developing influenza were similar, ranging between 1% and 11% in LAIV recipients and 8% and 21% in placebo recipients (data not shown). Fig. 1 summarizes the corresponding meta-analyses including the relative risk point estimates and approximate 95% CIs for each individual study and the combined efficacy estimate for antigenically similar strains.

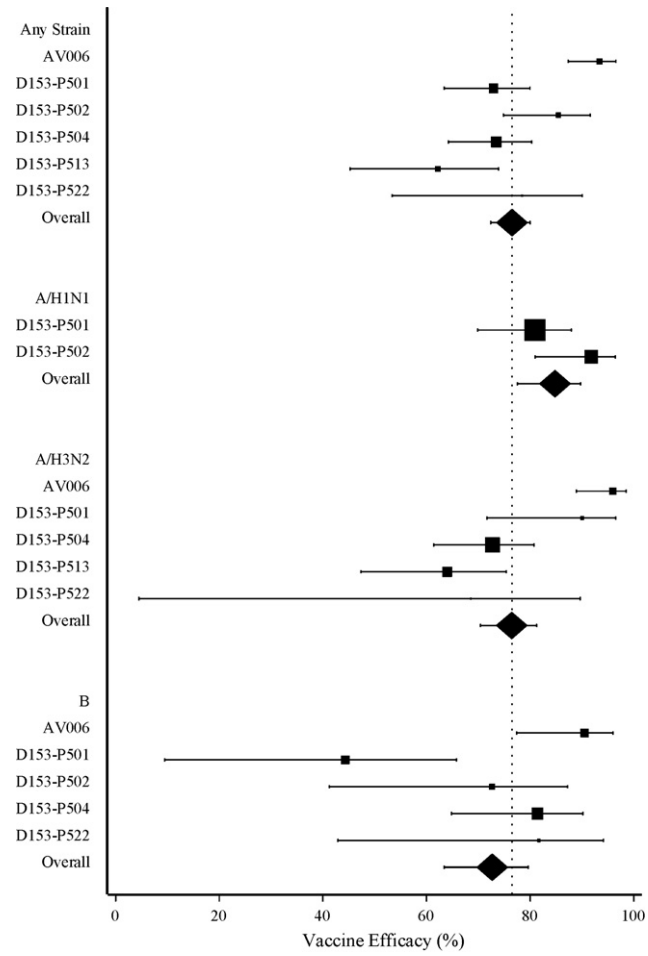

Fig. 1. Meta-analyses of vaccine efficacy for LAIV versus placebo (year 1, two doses) for antigenically similar subtypes. LAIV = live attenuated influenza vaccine; ■ = vaccine efficacy estimate, individual study; ♦ = vaccine efficacy estimate, meta-analysis; Symbol size is relative to size of the individual study.

For the ITT population, the efficacy of two doses of LAIV compared with placebo on culture-confirmed influenza for antigenically similar subtypes and subtypes regardless of antigenic similarity were 75% ($P < 0.001$, Table 4) and 72% ($P < 0.001$, data

Table 3
Vaccine efficacy for two doses versus placebo, overall and for subjects <3 years (antigenically similar subtypes).

Study	Age range (months)	LAIV[a]		Placebo[a]		Vaccine efficacy[b]	Approximate 95% CI (%)	Heterogeneity (Q)	Vaccine effect (MH)
		n/N	(%)	n/N	(%)				
All strains									
AV006	≥15 to ≤71	10/849	1.2	73/410	17.8	93	87, 97		
D153-P501	≥12 to <36	56/1653	3.4	139/1111	12.5	73	63, 80		
D153-P502	≥6 to <36	15/951	1.6	72/665	10.8	85	75, 92		
D153-P504	≥6 to <36	50/944	5.3	188/942	20.0	74	64, 80		
D153-P513	≥6 to <36	35/525	6.7	91/516	17.6	62	45, 74		
D153-P522	≥11 to <24	9/765	1.2	21/385	5.5	78	53, 90		
Total		175/5687	3.1	584/4029	14.5	77	72, 80	$\chi^2 = 25$ (5 d.f.), $p < 0.001$	$\chi^2 = 377$ (1 d.f.), $p < 0.001$
All strains, age <36 months		165/4838	3.4	511/3619	14.1	74	69, 78	$\chi^2 = 8$ (4 d.f.), $p = 0.078$	$\chi^2 = 280$ (1 d.f.), $p < 0.001$

d.f. = degrees of freedom; LAIV = live attenuated influenza vaccine; MH = Mantel–Haenszel.

[a] Culture-confirmed influenza cases.

[b] Vaccine efficacy estimates are based on subjects who received both scheduled doses of vaccine (per-protocol). Vaccine efficacy is based on observed cases (individual studies) or from fixed effects models (total, combined studies).

Table 4
Summary of meta-analyses, by analysis population (antigenically similar subtypes).

Comparison *number of doses* population	Number of studies	Culture-confirmed influenza cases		Relative risk[a]	95% CI (relative risk)	Combined efficacy[a] (%)	95% CI (efficacy)	Studies in meta-analysis[b]
		Vaccine group, *n*/*N* (%)	Comparison group, *n*/*N* (%)					
Placebo								
Two doses								
PP	6	175/5687 (3.1)	584/4029 (14.5)	0.24	0.20, 0.28	77	72, 80	006, 501, 502, 504, 513, 522
ITT	6	204/6266 (3.3)	641/4451 (14.4)	0.25	0.21, 0.29	75	71, 79	006, 501, 502, 504, 513, 522
One dose								
PP/AT	4	111/1961 (5.7)	274/1877 (14.6)	0.40	0.32, 0.49	60	51, 68	006, 501(Y2 PP), 504(Y1 PP, Y2 AT)
ITT	3	117/1852 (6.3)	273/1762 (15.5)	0.42	0.34, 0.51	58	49, 66	006, 501(Y2), 504(Y1)
Year 2								
PP	4	39/2497 (1.6)	207/1648 (12.6)	0.14	0.10, 0.19	87	81, 90	006, 501, 502, 504
ITT	4	51/3029 (1.7)	231/2154 (10.7)	0.17	0.13, 0.22	83	78, 87	006, 501, 502, 504
TIV								
Two doses								
PP	2	91/4966 (1.8)	168/4971 (3.4)	0.54	0.42, 0.70			514, 111
ITT	2	97/5344 (1.8)	179/5318 (3.4)	0.54	0.42, 0.69			514, 111
One dose								
PP	2	69/2038 (3.4)	106/2039 (5.2)	0.65	0.48, 0.87			515, 111
ITT	2	69/2060 (3.3)	106/2068 (5.1)	0.65	0.49, 0.88			515, 111

AT = as-treated population; ITT = intent-to-treat population; PP = per-protocol; Y1 = year 1; Y2 = year 2.
[a] Relative risk and vaccine efficacy estimates are from fixed effects models.
[b] Studies are identified by the last three digits of the study number.

not shown), respectively. The percentage of children developing influenza in the ITT population, for either antigenically similar subtypes or those regardless of similarity, was similar to the per-protocol population.

3.2.2. *Strain-specific efficacy and efficacy in young children*

For the per-protocol population of children who received two doses in year 1, we further investigated efficacy by strain type (A/H1N1, A/H3N2, and B) for all subjects, and we assessed overall efficacy for the subset of subjects younger than 36 months of age. We could not perform this analysis for the intent-to-treat population because we did not have access to patient-level data from some of the studies and some clinical study reports included analyses by strain and age only for the per-protocol populations.

For the by-strain analyses, overall combined efficacy estimates for two doses of LAIV compared to placebo against culture-confirmed influenza in the per-protocol population were, for similar strains (Table 5 and Fig. 1), 85% for A/H1N1, 76% for A/H3N2, and 73% for B. For strains regardless of antigenically similarity, the strain-specific efficacies were 86% for A/H1N1, 75% for A/H3N2, and 62% for B (data not shown). Mantel–Haenszel chi-square statistics were statistically significant for each comparison ($P < 0.001$). Similarly, the combined estimated efficacy for studies that included only children younger than 36 months of age was approximately 74% (Table 3) for subtypes antigenically similar to the vaccine and 69% for strains regardless of antigenic similarity (data not shown).

3.2.3. *Efficacy of one dose of LAIV in previously unvaccinated children*

Although two doses of influenza vaccine are recommended in previously unvaccinated children [13], three studies [14,16,18] also compared one dose of LAIV with placebo in previously unvaccinated young children. In two studies [14,18], children received one dose per-protocol in year 1. Another study that re-randomized subjects for year 2 vaccinated some subjects for the first time in year 2 with 1 dose [16]. Lastly, in the second year of one of the studies that randomized children to a single dose in year 1, a cohort that received placebo in year 1 received one dose of LAIV in year 2 because of an error in vaccine assignment [18]. We combined "as treated" (AT) results from the year 2 cohort with the results for the per-protocol year 1 cohort from this study. A meta-analysis of these four subsets of data yielded an estimated combined efficacy of approximately 60% ($P < 0.001$, Table 4) for antigenically similar strains based on 6% of LAIV children and 15% of placebo children developing influenza. For subtypes regardless of similarity, the combined efficacy is slightly less (59%, $P < 0.001$) with 7% (LAIV) and 17% (placebo) of children developing influenza (data not shown). We evaluated the impact of including and excluding the AT data. Including these additional data in the meta-analysis does not substantially change the estimated efficacy. For the ITT population, the meta-analyses suggested a combined efficacy estimate of 58% for antigenically similar subtypes (Table 4) and 56% for subtypes regardless of similarity (data not shown).

3.2.4. *Efficacy of one dose of LAIV in previously vaccinated children*

Four studies reported data on the incidence of influenza following revaccination in the second year of the study [15–18]. We compared children who received two doses of LAIV in year 1 and an additional dose of LAIV in year 2 to children who received placebo for all three doses (both years) with respect to the proportion of children who contracted influenza during the second influenza season. For the per-protocol populations, the combined estimate of efficacy for year 2 was 87% for antigenically similar subtypes ($P < 0.001$, Table 4 and Fig. 2) with 2% of LAIV recipients and 13% of placebo recipients developing influenza. For subtypes regardless

Table 5
Strain-specific vaccine efficacy for two doses vs. placebo (antigenically similar subtypes).

Strain type study	Age range (months)	LAIV[a]		Placebo[a]		Vaccine efficacy[b]	Approximate 95% CI	Heterogeneity (Q)	Vaccine effect (MH)
		n/*N*	%	*n*/*N*	%				
H1N1									
D153-P501	≥12 to <36	23/1653	1.4	81/1111	7.3	81	70, 88		
D153-P502	≥6 to <36	6/951	0.6	51/665	7.7	92	81, 96		
D153-P504	≥6 to <36	1/944	0.1	0/942	0.0	–[c]	–[c]		
D153-P513	≥6 to <36	0/525	0.0	1/516	0.2	–[c]	–[c]		
D153-P522	≥11 to <24	0/765	0.0	2/385	0.5	–[c]	–[c]		
Total		30/4838	0.6	135/3619	3.7	85	78, 90	$\chi^2 = 3$ (1 d.f.), $p = 0.085$	$\chi^2 = 119$ (1 d.f.), $p < 0.001$
H3N2									
AV006	≥15 to ≤71	4/849	0.5	48/410	11.7	96	89, 99		
D153-P501	≥12 to <36	4/1653	0.2	27/1111	2.4	90	72, 97		
D153-P502	≥6 to <36	0/951	0.0	1/665	0.2	–[c]	–[c]		
D153-P504	≥6 to <36	38/944	4.0	139/942	14.8	73	61, 81		
D153-P513	≥6 to <36	33/525	6.3	90/516	17.4	64	47, 75		
D153-P522	≥11 to <24	5/765	0.7	8/385	2.1	69	4.5, 90		
Total		84/5687	1.5	313/4029	7.8	76	70, 81	$\chi^2 = 19$ (4 d.f.), $p = 0.001$	$\chi^2 = 188$ (1 d.f.), $p < 0.001$
B									
AV006		6/850	0.7	31/417	7.4	91	77, 96		
D153-P501	≥12 to <36	29/1653	1.8	35/1111	3.2	44	9, 66		
D153-P502	≥6 to <36	9/951	0.9	23/665	3.5	73	41, 87		
D153-P504	≥6 to <36	11/944	1.2	59/942	6.3	81	65, 90		
D153-P513	≥6 to <36	2/525	0.4	0/516	0.0	–[c]	–[c]		
D153-P522	≥11 to <24	4/765	0.5	11/385	2.9	82	43, 94		
Total		61/5688	1.1	159/4036	3.9	73	63, 80	$\chi^2 = 16$ (4 d.f.), $p = 0.003$	$\chi^2 = 86$ (1 d.f.), $p < 0.001$

d.f. = degrees of freedom; MH = Mantel–Haenszel.
[a] Culture-confirmed influenza cases.
[b] Vaccine efficacy estimates are based on subjects who received both scheduled doses of vaccine (per-protocol). Vaccine efficacy is based on observed cases (individual studies) or from fixed effects models (total, combined studies).
[c] Study has too few events (<5) to calculate vaccine efficacy or 95% CI or to include it in the heterogeneity test.

of antigenic similarity, the year 2 estimated efficacy was 76% ($P < 0.001$) with 4% of LAIV recipients and 19% of placebo recipients developing influenza (data not shown). For the ITT populations, combined efficacy estimates for year 2 were 83% and 67% for subtypes antigenically similar (Table 4) and regardless of antigenic similarity (data not shown), respectively.

3.3. *Efficacy of LAIV compared with TIV*

Three study reports summarized vaccine efficacy for one or two doses of LAIV or TIV in approximately 13,000 healthy children aged 6 months to 17 years. Two of the studies evaluated efficacy against culture-confirmed influenza in a single influenza season in children younger than 6 years receiving one or two doses, based on previous vaccination status [21,23]. One study evaluated the efficacy of a single dose in children 6–17 years of age with asthma [22]. All showed a lower risk of contracting influenza among children given LAIV than among those given TIV for antigenically similar strains and for strains regardless of antigenic similarity. For children 6–71 months who received two doses of either LAIV or TIV per protocol, there were 53% (95% CI: 22%, 72%) [22] and 45% (95% CI: 25%, 59%) [24] (data not shown) fewer cases of influenza illness based on antigenically similar subtypes in LAIV recipients compared to TIV recipients. For children 6–17 years who received one dose per protocol, there were 35% (95% CI: 4%, 56%) fewer cases of influenza illness based on antigenically similar subtypes in LAIV recipients [23]. In one study, the dominant strain was a mismatched A/H3N2 strain [23]; in the other two studies, the dominant strain was a matched B strain [22,23]. Our meta-analyses showed benefit in both the per-protocol and ITT populations. Across both analysis populations, relative risks for LAIV:TIV ranged from 0.54 after two doses to 0.65 after one dose for antigenically similar strains ($P < 0.001$; Table 4 and Fig. 3) with between 2% and 3% of LAIV recipients and between 3% and 5% of TIV recipients developing influenza. Regardless of antigenic similarity, relative risks for LAIV:TIV across both the per-protocol and ITT populations ranged from 0.50 after two doses to 0.59 after one dose with 5–6% of LAIV recipients and 9–10% of TIV recipients developing influenza ($P < 0.001$; data not shown).

3.4. *Sensitivity analyses*

For each of these meta-analyses, sensitivity analyses suggested that while removing a study alters the efficacy estimate slightly, no individual study has a substantial impact on the overall estimated efficacy. For example, the efficacy for two doses of LAIV compared with placebo for antigenically similar subtypes is approximately 77% while the estimates range between 73% and 79% after removing any single study. Similarly, the efficacy for one dose of LAIV compared with placebo for antigenically similar subtypes is approximately 60% with estimates ranging between 58% and 60%.

4. Discussion

Previous meta-analyses and study summaries that have compared LAIV against TIV or placebo [24–27] have shown that both vaccines are safe and effective for protecting children against influenza; combined estimates of vaccine efficacy have ranged from 63% to 65% for TIV and 79% to 80% for LAIV. However, these previous meta-analyses included data from early investigational LAIV formulations and did not include several recently published

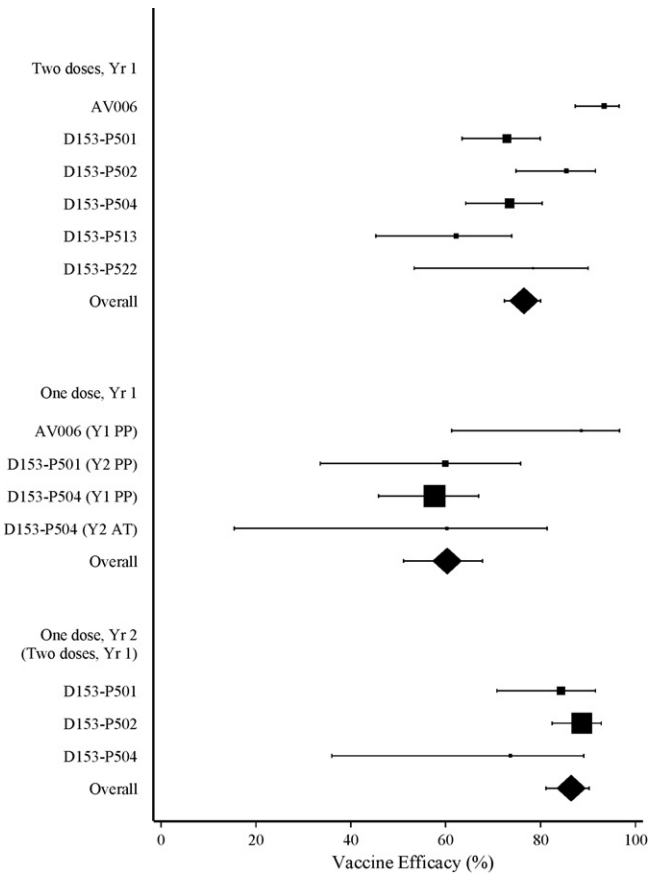

Fig. 2. Meta-analyses of vaccine efficacy for LAIV versus placebo (year 1, one and two doses; year 2, one dose) for antigenically similar subtypes. AT = as-treated population; LAIV = live attenuated influenza vaccine; PP = per-protocol population; ■ = vaccine efficacy estimate, individual study; ♦ = vaccine efficacy estimate, meta-analysis; symbol size is relative to size of the individual study.

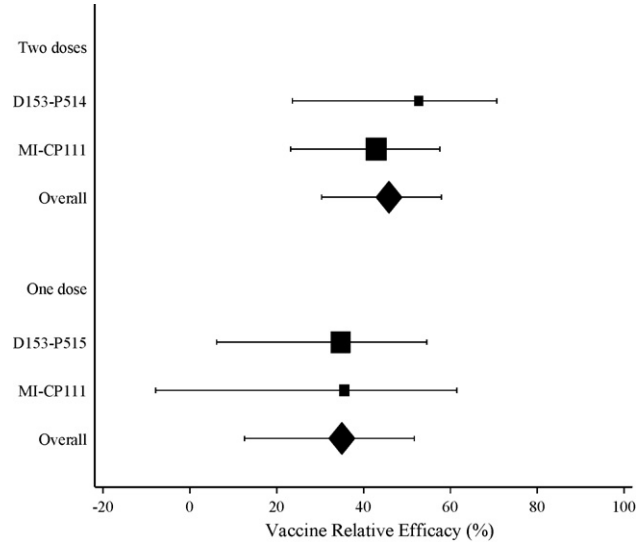

Fig. 3. Meta-analyses of vaccine relative efficacy for LAIV versus TIV (year 1, one and two doses) for antigenically similar subtypes. LAIV = live attenuated influenza vaccine; TIV = trivalent inactivated influenza vaccine; ■ = vaccine efficacy estimate, individual study; ♦ = vaccine efficacy estimate, meta-analysis; symbol size is relative to size of the individual study.

studies. The meta-analyses discussed here are based solely on studies that evaluated LAIV formulations approved for use in the United States and include all studies conducted. Thus, these analyses provide a comprehensive estimate of the efficacy of currently licensed LAIV, confirming that LAIV is highly efficacious against culture-confirmed influenza in children. In the studies analyzed, LAIV was associated with 77–87% efficacy against antigenically similar culture-confirmed influenza, was more efficacious than TIV, and showed no evidence of a difference in efficacy by age or circulating subtype (A/H1N1, A/H3N2, and B).

Although previously unvaccinated children younger than 9 years of age are recommended to receive two doses of vaccine, compliance with the two-dose regimen is low [13]. Our analyses showed that for vaccine-naive children receiving only one dose of vaccine, the vaccine efficacy of LAIV compared with placebo was 60% ($\chi^2 = 82$, $P < 0.001$). The 60% vaccine efficacy of one dose of LAIV was less than the 77% vaccine efficacy provided by the recommended two doses ($\chi^2 = 377$, $P < 0.001$), but one dose still provides clinically significant protection from influenza illness.

The estimated vaccine efficacies for revaccination in year 2 (87% for antigenically similar and 76% for subtypes regardless of antigenic similarity) were higher than the overall vaccine efficacy estimates from year 1 (77% and 72%). This higher observed efficacy in the second year of vaccination may be due to chance. Alternatively, the increase could reflect a priming effect or carry-over protection from the year 1 vaccination; two of the studies reviewed [16,18] demonstrated 56–57% efficacy through a second influenza season for a cohort that received two doses in year 1 and placebo in year 2. An additional explanation could be the increased age of subjects in year 2, although a study in children aged 6–71 months demonstrated similar efficacy regardless of age [14].

For influenza B, vaccine efficacy against subtypes regardless of antigenic similarity was lower than the efficacy against antigenically similar subtypes; however, this was not true for A/H1N1 or A/H3N2. Antigenically dissimilar A/H3N2 strains have circulated in recent years; yet, high levels of efficacy have been seen for LAIV against antigenically dissimilar A/H3N2 strains [14,15,23]. In contrast, antigenically dissimilar A/H1N1 strains did not circulate to a significant degree in the studies analyzed; thus efficacy against similar and all strains are essentially equivalent. For influenza B, although a single B strain is recommended for inclusion in commercial influenza vaccine formulations, two antigenically distinct lineages of influenza B exist (Yamagata and Victoria) and cross-lineage protection has not been demonstrated. As seen in our analyses where alternate lineage B strains circulated to a significant degree, the observed vaccine efficacy against all strains was lower than efficacy against antigenically similar strains.

Meta-analyses on all subsets of the population of children studied provide a more precise estimate of the mean efficacy of the LAIV vaccine than does reliance on a single study. In particular, subjects receiving LAIV had consistently high vaccine efficacy when compared with placebo against antigenically similar strains and regardless of antigenic similarity with no evidence of difference by age. In children receiving LAIV compared with TIV, these studies indicated that LAIV was consistently more effective than TIV. For antigenically similar strains, children receiving two doses of LAIV experienced 46% fewer cases of influenza illness compared with children receiving two doses of TIV. The reduction was 35% for children receiving one dose of LAIV compared with those who received one dose of TIV. Assessing illness caused by all influenza strains regardless of similarity, the reductions in influenza illness associated with LAIV compared with TIV were slightly higher, at 41% and 50%, respectively. This increase reflects higher observed relative efficacy of LAIV compared with TIV against antigenically dissimilar A/H3N2 strains.

4.1. Statistical considerations and limitations of these meta-analyses

For these meta-analyses, we used relative risk as the measure of vaccine effect. The odds ratio is the measure of effect most commonly used in meta-analyses, partly because in epidemiology the odds ratio is invariant to methods of selecting the population and partly because of unfavorable statistical properties of relative risks in certain contexts. A relative risk is bounded between 0 and 1; therefore, use of the relative risk can create impossible risk values if applied to a new comparison group. Also, their asymmetry can cause drastically different results if the coding of the event and non-event are switched. Deeks [37] shows, however, that in many cases relative risks and relative odds give similar inferences, and relative risks are often easier to interpret. In estimating vaccine efficacy, relative risks have satisfactory mathematical properties, straightforward interpretation, and consistency with presentation of results for previous studies.

Fixed effects and random effects models are the two major statistical approaches used in meta-analysis. Random effects models assume that vaccine efficacy truly differs among trials; however, a random effects model with only a small number of trials (six at the most in our case) risks substantially inflating the Type I error rate [38]. A so-called fixed effects model provides a weighted average of the estimates from the individual trials at hand; when the true treatment effect is the same in all the studies, a fixed effect model has statistically optimal properties. In our case, we used a fixed effect model because we were interested in the average vaccine efficacy across the studies. As stated in Section 2, we assumed a general, common treatment effect among the included studies but evaluated the heterogeneity among studies.

Analyzing these data with a meta-analysis does involve limitations associated with combining data across different populations and combining data from within the same study. Combining separate studies together incorporates heterogeneity because of slight variations between studies. For example, different strains circulate in different years, and the distribution of the children's previous exposure to influenza may differ. Even though these slight variations suggest heterogeneity of vaccine efficacy among the studies (Cochran Q statistic: $P < 0.05$ for all strains, Table 3, and H3N2 and B strains, Table 5), the numerical values of the estimates are very similar and the overall estimate of vaccine efficacy clearly indicates that LAIV is highly effective in the prevention of culture-confirmed influenza.

For the meta-analysis of the efficacy of one dose of LAIV compared with placebo, we combined data from the as-treated and per-protocol populations. Assuming that the studies were reasonably homogeneous and that the two populations were quite similar, the estimate obtained from the meta-analysis should provide a reasonably accurate measure of effect. Additionally, the per-protocol (year 1) and as-treated (year 2) populations combined for one study [18] contain many of the same children and are not independent, but the assumption that the efficacy estimates would not be highly correlated supports combining these results together to provide a crude summary of the measure of the efficacy of LAIV compared against placebo for children receiving one dose of vaccine.

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