

Live Attenuated and Inactivated Influenza Vaccine Effectiveness

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abstract

BACKGROUND: Researchers in observational studies of vaccine effectiveness (VE) in which they compared quadrivalent live attenuated vaccine (LAIV4) and inactivated influenza vaccine (IIV) among children and adolescents have shown inconsistent results, and the studies have been limited by small samples.

METHODS: We combined data from 5 US studies from 2013–2014 through 2015–2016 to compare the VE of LAIV4 and IIV against medically attended, laboratory-confirmed influenza among patients aged 2 to 17 years by influenza season, subtype, age group, and prior vaccination status. The VE of IIV or LAIV4 was calculated as $100\% \times (1 - \text{odds ratio})$, comparing the odds of vaccination among patients who were influenza-positive to patients who were influenza-negative from adjusted logistic regression models. Relative effectiveness was defined as the odds of influenza comparing LAIV4 and IIV recipients.

RESULTS: Of 17 173 patients aged 2 to 17 years, 4579 received IIV, 1979 received LAIV4, and 10 615 were unvaccinated. Against influenza A/H1N1pdm09, VE was 67% (95% confidence interval [CI]: 62% to 72%) for IIV and 20% (95% CI: –6% to 39%) for LAIV4. Results were similar when stratified by vaccination in the previous season. LAIV4 recipients had significantly higher odds of influenza A/H1N1pdm09 compared with IIV recipients (odds ratio 2.66; 95% CI: 2.06 to 3.44). LAIV4 and IIV had similar effectiveness against influenza A/H3N2 and B. Our overall findings were consistent when stratified by influenza season and age group.

CONCLUSIONS: From this pooled individual patient–level data analysis, we found reduced effectiveness of LAIV4 against influenza A/H1N1pdm09 compared with IIV, which is consistent with published results from the individual studies included.



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Ms Chung conducted the analyses and drafted the initial manuscript; Drs Flannery and Fry conceptualized and designed the study, contributed to the analyses and interpretation of the results, and critically reviewed and revised the manuscript; Drs Ambrose, Bégué, and Caspard and Ms DeMarcus, Ms Fowlkes, Ms Kersellius, and Ms Steffens coordinated and supervised the study design and data collection for their respective studies and critically reviewed the manuscript; group authors recruited participants for studies, provided feedback for the data analysis methods, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Researchers in individual studies in the United States have reported low effectiveness of quadrivalent live attenuated vaccine (LAIV4) against influenza A/H1N1pdm09 relative to inactivated influenza vaccine (IIV). Estimations by age and prior vaccination status have been limited by small sample sizes.

WHAT THIS STUDY ADDS: In a combined analysis from 5 studies, LAIV4 was less effective than IIV against influenza A/H1N1pdm09 in all pediatric age groups. Differences in prior vaccination did not explain this finding. LAIV4 and IIV had similar effectiveness against A/H3N2 and B.

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Concerns about the effectiveness of the live attenuated influenza vaccine (LAIV) among young children in the 2013–2014 and 2015–2016 influenza seasons prompted the US Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics to recommend against the use of LAIV in the United States during the 2016–2017 and 2017–2018 influenza seasons.^{1,2} Trivalent live attenuated influenza vaccine (LAIV3) was first licensed for use in the United States in 2003; quadrivalent live attenuated vaccine (LAIV4) followed in 2013. In clinical trials conducted before the 2009 influenza pandemic, researchers demonstrated immune responses and efficacy with all LAIV3 components and, in some studies, superiority to trivalent inactivated influenza vaccines (IIVs) among children and adolescents but not among adults.^{3–6} Postlicensure estimates of vaccine effectiveness (VE) of LAIV4 have been obtained from observational studies and may be subject to biases inherent in observational designs. Studies conducted in the United States have heterogeneous findings with LAIV VE estimates against influenza A/H1N1pdm09 ranging from –19% to 50%, although in no study were researchers able to detect statistically significant protection against influenza A/H1N1pdm09 since the 2013–2014 influenza season.^{7–14} In addition, differences between LAIV4 VE determined in United States versus European studies have raised questions about whether prior season vaccination (more common in US studies) may have contributed to the lower VE detected in the United States.¹⁵

Interpreting differences in VE estimates from individual studies is challenging because of small samples when patients are stratified by vaccine type, age group, and/or influenza subtype. In few studies of VE by vaccine type have researchers examined the effect of prior season

vaccination status on current season VE. In this study, we analyzed pooled individual patient-level data from 5 studies that included children and adolescents aged 2 to 17 years in the United States during the 2013–2014 through 2015–2016 influenza seasons, during which all LAIV in the United States were quadrivalent.¹⁶ Our primary aims were to describe the VE of IIV (trivalent or quadrivalent) and LAIV4 in each season by influenza subtype for children aged 2 to 4, 5 to 8, and 9 to 17 years and to examine the association of prior season vaccination on current season VE.

METHODS

We included data from the following 5 studies conducted in outpatient settings in the United States from 2013–2014 through 2015–2016: the US Influenza Vaccine Effectiveness Network (USFLUVE, Centers for Disease Control and Prevention [CDC])^{7,10,11}; a Louisiana State University Health Sciences Center (LSU) study¹³; the Influenza Clinical Investigation for Children (ICICLE, MedImmune)^{8,9,12}; the Department of Defense Global, Laboratory-based, Influenza Surveillance Program (US Air Force School of Aerospace Medicine [USAFSAM])¹⁴; and the Influenza Incidence Surveillance Project (IISP, CDC).¹⁷ Study characteristics are compared in Table 1. In the USFLUVE, ICICLE, USAFSAM, and IISP studies, patients aged 2 to 17 years presenting to outpatient settings (including emergency departments) with acute respiratory infection with fever and/or cough were enrolled, and respiratory specimens were tested with real-time reverse transcription-polymerase chain reaction (RT-PCR) or viral culture. In the LSU study, patients who were clinically tested for influenza were enrolled; patients were first tested by a rapid antigen test and a subsequent polymerase

chain reaction–based respiratory viral panel for patients who were rapid antigen test negative. Current season vaccination status was ascertained by using electronic immunization records (EIRs) including medical records and immunization information systems; in the USAFSAM study, vaccination status including vaccine type was also determined by parental or guardian report of the child’s vaccination. Prior season vaccination was ascertained from EIRs for all studies.

We included patients with conclusive testing results who were enrolled in the United States during the influenza season. Influenza seasons were defined as the period of consecutive weeks with regional or widespread influenza activity¹⁸ and the 3 weeks before and after that period for each state from which patients were enrolled. We excluded patients with unknown vaccination statuses or types, patients who received both IIV and LAIV4 within a season, patients who received a vaccine 0 to 13 days before illness onset, and patients who tested positive for ≥ 1 influenza type and/or subtype.

We used a test-negative, case-control design to calculate the VE of ≥ 1 dose of IIV or LAIV4 as $100\% \times (1 - \text{odds ratio [OR]})$, comparing the odds of vaccination among case patients who were influenza-positive to controls who were influenza-negative. Relative effectiveness estimates are expressed as the odds of influenza among LAIV4 recipients compared with IIV recipients and 95% confidence intervals (CIs). Adjusted models included age group or age in years (for age-stratified models), the calendar time of illness onset (defined as prepeak, peak, or postpeak), and influenza season (for combined-season estimates). Peak period was defined as the week with the most case patients who were influenza-positive by season ± 2 weeks. The study site was included

TABLE 1 Characteristics of Included Studies

Study	No. Patients Included	Study Inclusion	Testing	Current Season Vaccination Status Data Source(s)	Previous Season Vaccination Status Data Source(s)
USFLUVE, CDC	6793	ARI with cough ≤ 7 d duration	RT-PCR	Electronic medical record and immunization registries	Electronic medical record and immunization registries
LSU	3822	Clinical laboratory testing for influenza	Rapid antigen test and respiratory viral panel of rapid antigen test–negatives	Immunization registry	Immunization registry
ICICLE, MedImmune	3521	ARI with fever < 5 d duration	RT-PCR	Electronic medical record and immunization registries	Electronic medical record and immunization registries
Department of Defense Global, Laboratory-based, Influenza Surveillance Program, USAFSAM	1935	ARI with fever and cough and/or sore throat < 72 h duration	Viral culture and RT-PCR	Immunization registry and parent report	Immunization registry
IISP, CDC	1102	ARI with fever and cough and/or sore throat ≤ 7 d duration	RT-PCR	Electronic medical record and immunization registries	Immunization registry

ARI, acute respiratory infection.

as a random effect. VE estimates are not reported if the number of cases in a stratum was < 50 or if the number of vaccinated cases was < 5 . Interaction terms were used to test for differences in VE by age group.

In a subgroup analysis, patients were stratified by prior season vaccination status (categorized as unvaccinated, received IIV, or received LAIV in the previous influenza season). In each stratum, current-season VE was calculated for each vaccine type by using patients who were unvaccinated in the current season as the reference group. Patients were excluded from this subgroup analysis if prior season vaccination records were unavailable, if prior season vaccine type was unknown, if both IIV and LAIV were received within the prior season, or if parent- or guardian-reported current-season vaccination could not be confirmed by EIRs (USAFSAM study only).

Several sensitivity analyses were conducted to examine factors incompletely collected across studies including illness severity (by using

presentations with influenza-like illness [defined as fever plus cough and/or sore throat] and the time from illness onset to enrollment as proxies), high-risk status, and full versus partial vaccination status. Statistical analyses were conducted by using SAS software (SAS Institute, Inc, Cary, NC).

RESULTS

Overall, 17 173 children and adolescents aged 2 to 17 years from 42 states were included in the analysis (Supplemental Table 3). Forty percent of the sample came from USFLUVE, 22% from LSU, 21% from ICICLE, 11% from USAFSAM, and 6% from IISP (Supplemental Table 4). Twenty-three percent of the sample enrolled in the 2013–2014 season, 47% in the 2014–2015 season, and 30% in the 2015–2016 season. The LSU study population was slightly younger (mean 6.4 years) than the average age of 7.4 years, and the IISP and USAFSAM study populations were slightly older (mean 8.0 years). Overall, one-fourth

of patients ($N = 4244$) tested positive for influenza. Among them, 37% ($N = 1582$) were infected with influenza A/H3N2, 25% ($N = 1082$) influenza A/H1N1pdm09, 12% ($N = 519$) unsubtype influenza A, and 25% ($N = 1061$) influenza B. Influenza B lineage was determined for 42% ($N = 447$) of influenza B–positive specimens; 234 (52%) and 213 (48%) were of Victoria and Yamagata lineage, respectively. One-third (38%, $N = 6558$) of patients were vaccinated in the current season, among whom 30% received LAIV4 ($N = 1979$). Among patients who tested negative for influenza, IIV recipients tended to be slightly younger with more high-risk conditions and asthma than LAIV4 recipients (Supplemental Table 5).

In 2013–2014, 19% of specimens tested positive for influenza. Among those, 65% were subtyped as influenza A/H1N1pdm09 virus, and 19% were unsubtype influenza A (Supplemental Table 6). VE against any influenza among those aged 2 to 17 years was 63% (95% CI: 55% to 70%) for IIV and 15% (95% CI: –1%

to 28%) for LAIV4 (Supplemental Table 7). The VE of IIV was similar by age group ($P = .15$). LAIV4 VE estimates increased by age group, but the difference was not statistically significant ($P = .65$). VE against influenza B among those aged 2 to 17 years was 56% (95% CI: 33% to 71%) for IIV and 64% (95% CI: 8% to 86%) for LAIV4, although few influenza B cases were detected in this season.

In the 2014–2015 season, 27% of specimens tested positive for influenza. A majority (68%) were influenza A/H3N2 with an additional 12% untyped influenza A and 20% influenza B (Supplemental Table 6). VE against any influenza among those aged 2 to 17 years was 37% (95% CI: 28% to 44%) for IIV and 25% (95% CI: 10% to 37%) for LAIV4 (Supplemental Table 7). Against influenza A/H3N2, VE was significantly protective only among IIV recipients aged 2 to 4 years. None of the LAIV4 VE estimates against influenza A/H3N2 reached statistical significance. The VE point estimate against influenza B among those aged 2 to 17 years was 49% (95% CI: 32% to 62%) for IIV and 76% (95% CI: 53% to 88%) for LAIV4.

In the 2015–2016 season, 26% of specimens tested positive for influenza, with 44% influenza A/H1N1pdm09, 8% untyped influenza A, and 43% influenza B (Supplemental Table 6). Few influenza A/H3N2 cases were detected ($N = 69$). VE against any influenza among those aged 2 to 17 years was 60% (95% CI: 52% to 67%) for IIV and 39% (95% CI: 16% to 56%) for LAIV4 (Supplemental Table 7). Estimates were similar when stratified by age group. Against influenza A/H1N1pdm09, VE among those aged 2 to 17 years was 66% (95% CI: 59% to 71%) for IIV and 18% (95% CI: –31% to 49%) for LAIV4. Estimates were similar across age groups; none of the LAIV4 VE estimates against influenza

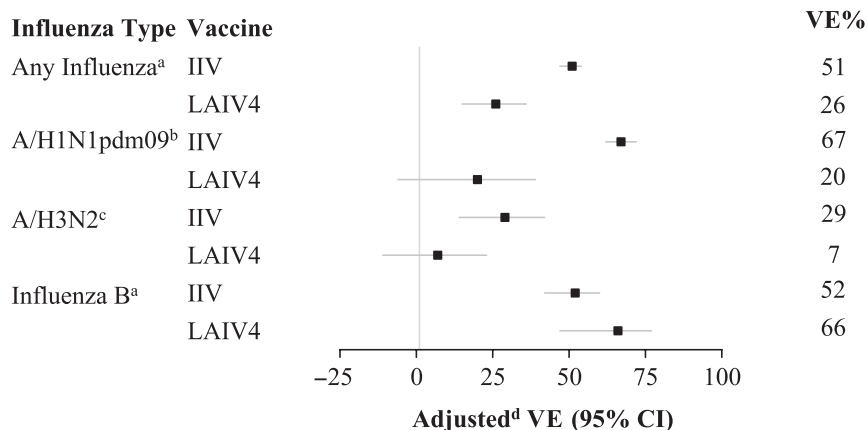


FIGURE 1

Adjusted VE by influenza type and subtype for children aged 2 to 17 years receiving IIV or LAIV4 during 2013 to 2014 through 2015 to 2016. Bars indicate 95% CIs. ^a Includes the 2013–2014 influenza season through the 2015–2016 season. ^b Restricted to the 2013–2014 and 2015–2016 influenza seasons. ^c Restricted to the 2014–2015 influenza season. ^d Models are adjusted for age (group or years for age-stratified models), season, calendar time, and site (as a random effect).

A/H1N1pdm09 reached statistical significance. VE against influenza B was similar for IIV and LAIV4; VE of IIV among those aged 2 to 17 years was 55% (95% CI: 39% to 66%), and it was 54% (95% CI: 35% to 68%) for LAIV4.

Combining data from all seasons, VE against any influenza among those aged 2 to 17 years was 51% (95% CI: 47% to 54%) for IIV and 26% (95% CI: 15% to 36%) for LAIV4 (Fig 1, Supplemental Table 8). VE estimates for LAIV4 increased by age group, but the difference was not statistically significant (P for interaction = .90). Against influenza A/H1N1pdm09, VE was 67% (95% CI: 62% to 72%) for IIV and 20% (95% CI: –6% to 39%) for LAIV4. VE estimates for LAIV4 increased by age group, but the difference was not statistically significant ($P = .71$). VE against influenza B viruses among those aged 2 to 17 years was 52% (95% CI: 42% to 60%) for IIV and 66% (95% CI: 47% to 77%) for LAIV4. There was little heterogeneity in VE estimates by age group.

Overall, LAIV4 recipients were significantly more likely to have any influenza detected compared with IIV recipients (OR = 1.48, 95% CI: 1.28 to 1.70; Fig 2, Supplemental

Table 9). A similar association was observed among those aged 2 to 4 and 5 to 8 years (Supplemental Table 9). There was no significant difference in the odds of influenza infection among those aged 9 to 17 years. LAIV4 recipients had significantly higher odds of influenza A/H1N1pdm09 infection compared with IIV recipients (OR = 2.66, 95% CI: 2.06 to 3.44), and this result was similar for all age groups. LAIV4 recipients aged 2 to 17 and 2 to 4 years had increased odds of influenza A/H3N2 infection compared with IIV recipients (OR = 1.30 [95% CI: 1.06 to 1.58] and OR = 1.99 [95% CI: 1.49 to 2.64], respectively). Estimates for the other age groups suggested higher odds of influenza A/H3N2 infection in LAIV4 recipients but were not statistically significant. The odds of influenza B infection were lower among LAIV4 recipients, but this finding was not statistically significant. No age-stratified relative effectiveness estimates reached statistical significance, but point estimates suggested higher odds of influenza B infection among IIV recipients.

When stratified by prior season vaccination, VE estimates of LAIV4 against influenza A/H1N1pdm09

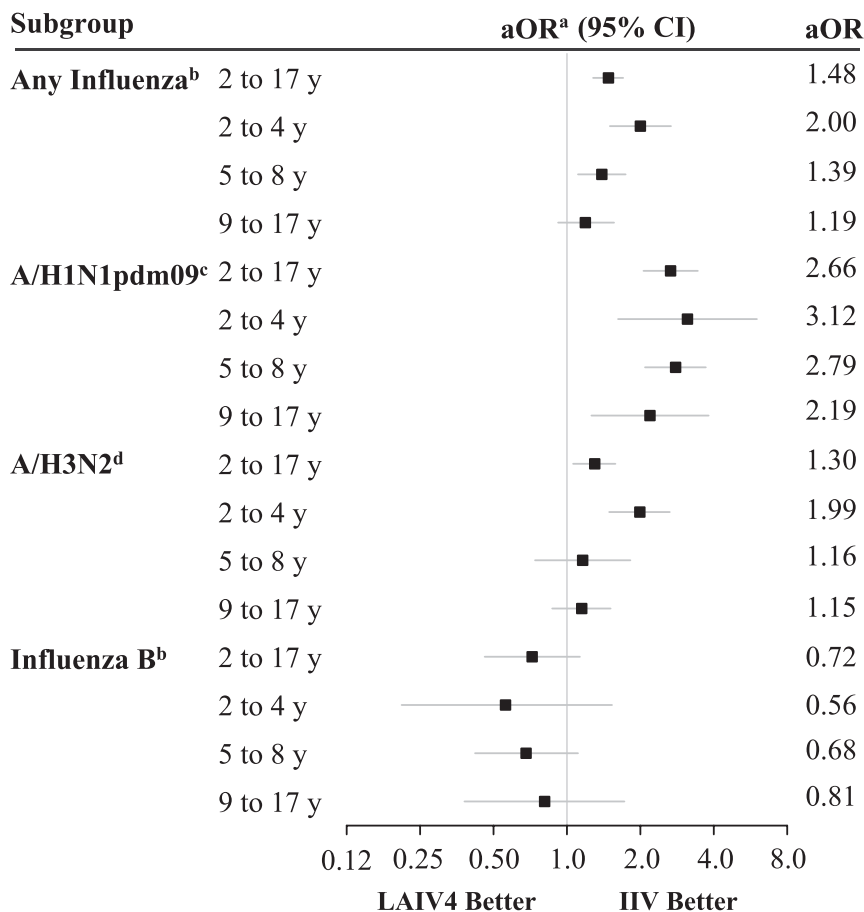


FIGURE 2

Adjusted relative effectiveness of LAIV4 versus IIV by influenza type, subtype, and age group. aOR, adjusted odds ratio. ^a Relative effectiveness estimates are expressed as the odds of influenza among LAIV4 recipients compared with IIV recipients and 95% CIs. An OR of <1 suggests lower odds of influenza in LAIV4 recipients compared with IIV recipients. Models are adjusted for age (group or years for age-stratified models), season, calendar time, and site (as a random effect). ^b Includes the 2013–2014 influenza season through the 2015–2016 season. ^c Restricted to the 2013–2014 and 2015–2016 influenza seasons. ^d Restricted to the 2014–2015 influenza season.

were similar with overlapping CIs that included 0 (Table 2). The current season VE of LAIV4 was 25% (95% CI: –9% to 49%) among patients who were unvaccinated in the prior season, –19% (95% CI: –126% to 38%) among patients who received IIV in the prior season, and 24% (95% CI: –16% to 50%) among patients who received LAIV in the prior season. The difference was not statistically significant (P for interaction = .21). The current season VE of IIV against influenza A/H1N1pdm09 was nonsignificantly ($P = .05$) reduced among those who received IIV in the prior season (46%, 95% CI: 15% to 66%) compared with

patients who were unvaccinated in the prior season (77%, 95% CI: 64% to 85%) and patients who received LAIV in the prior season (73%, 95% CI: 55% to 84%). Against influenza A/H3N2, none of the current season LAIV4 VE estimates were statistically significant regardless of prior season vaccination. Among current season IIV recipients, VE against influenza A/H3N2 was similar among patients who were unvaccinated in the prior season (35%, 95% CI: 16% to 50%) and patients who received IIV in the prior season (36%, 95% CI: 10% to 54%), but VE was lower and not statistically significant among patients who received LAIV

in the prior season (12%, 95% CI: –35% to 43%); however, significant interaction was not detected ($P = .85$). The number of case patients who were influenza-positive in each stratum of prior vaccination exposure was insufficient to examine this association for VE against influenza B (data not shown).

Our findings were not sensitive to the results of individual studies; we removed studies individually and found similar estimates. Results were not sensitive to the definition of the influenza season; similar results were found with the season defined as July 1 to June 30. We also found similar results when analyses were (1) restricted to those with influenza-like illness, (2) restricted to those who presented within 3 days of illness onset, (3) restricted to those without high-risk conditions from USFLUVE and ICICLE, or (4) restricted to those who were fully vaccinated from USFLUVE and ICICLE (data not shown).

DISCUSSION

The results of this pooled individual patient-level data analysis from 3 seasons are consistent with the previously published studies included in the analysis.^{7–14} In 2013–2014 and 2015–2016, low VE of LAIV4 was observed against influenza A/H1N1pdm09. Relative effectiveness estimates favored IIV for all age groups, suggesting a lower risk of influenza A/H1N1pdm09 infection among IIV recipients compared with LAIV4 recipients. Vaccination with either IIV or LAIV in the previous season did not explain the low VE detected for current season LAIV4. Against drifted influenza A/H3N2 virus in 2014–2015, effectiveness was poor for both vaccines regardless of previous season vaccination. These results are consistent with the low overall VE against drifted influenza A/H3N2 observed in the United States during

TABLE 2 VE of Current Season Vaccine Against Influenza A Viruses Stratified by Vaccine Receipt in the Season Before Enrollment

Vaccination	Total	No. Influenza-Positive (%) ^a	No. Influenza-Negative (%) ^a	Adjusted ^b VE, %	95% CI
Influenza A/H1N1pdm09^c					
Prior season unvaccinated					
Current season IIV	567	28 (5)	539 (95)	77	64 to 85
Current season LAIV	213	32 (15)	181 (85)	25	−9 to 49
Current season unvaccinated	3311	542 (16)	2769 (84)	Ref	—
Prior season IIV					
Current season IIV	1412	98 (7)	1314 (93)	46	15 to 66
Current season LAIV	220	29 (13)	191 (87)	−19	−126 to 38
Current season unvaccinated	859	97 (11)	762 (89)	Ref	—
Prior season LAIV					
Current season IIV	217	16 (7)	201 (93)	73	55 to 84
Current season LAIV	329	57 (17)	272 (83)	24	−16 to 50
Current season unvaccinated	292	58 (20)	234 (80)	Ref	—
Influenza A/H3N2^d					
Prior season unvaccinated					
Current season IIV	450	72 (16)	378 (84)	35	16 to 50
Current season LAIV	214	61 (29)	153 (72)	−38	−106 to 7
Current season unvaccinated	2963	605 (20)	2358 (80)	Ref	—
Prior season IIV					
Current season IIV	1226	196 (16)	1030 (84)	36	10 to 54
Current season LAIV	306	55 (18)	251 (82)	28	−12 to 54
Current season unvaccinated	980	198 (20)	782 (80)	Ref	—
Prior season LAIV					
Current season IIV	144	29 (20)	115 (80)	12	−35 to 43
Current season LAIV	402	90 (22)	312 (78)	13	−30 to 42
Current season unvaccinated	285	70 (25)	215 (75)	Ref	—

Analyses exclude $N = 62$ patients for whom parent- or guardian-reported, current season vaccination could not be confirmed by EIRs (USAFSAM), $N = 10$ who received IIV and LAIV in the season before enrollment, $N = 560$ with unavailable records for the season before enrollment, and $N = 53$ with an unknown vaccine type in the season before enrollment. Ref, reference group; —, not applicable.

^a Percent of row total.

^b Adjusted for age (years), season, calendar time, and site (as a random effect).

^c Restricted to the 2013–2014 and 2015–2016 influenza seasons.

^d Restricted to the 2014–2015 influenza season.

that season.^{11,19} Results from a clinical trial of LAIV3 suggested a relative benefit of LAIV3 over trivalent IIV in seasons with drifted influenza A/H3N2 virus circulation in the 2004–2005 influenza season.⁴ Overall in our study, effectiveness against influenza B viruses was moderate for both vaccines.

Our results are consistent with findings of reduced VE of LAIV4 against influenza A/H1N1pdm09 in the 2013–2014 influenza season, which prompted the change in the H1N1pdm09 LAIV4 vaccine virus from A/California/7/2009 to A/Bolivia/559/2013 for the

2015–2016 influenza season.⁷ Notably, we also observed a lower effectiveness of LAIV4 compared with IIV against influenza A/H1N1pdm09 virus in 2015–2016, suggesting the effectiveness remained low despite the change to the A/Bolivia/559/2013 vaccine formulation. Additional efforts have been taken by the manufacturer to identify the cause of the reduced effectiveness of influenza A/H1N1pdm09 LAIV strains. The LAIV H1N1 vaccine virus for the 2017–2018 and 2018–2019 influenza seasons, A/Slovenia/2309/2015, has demonstrated improved replicative fitness in the laboratory

and increased shedding and serum antibody responses among children compared with A/Bolivia/559/2013.^{20,21} Preliminary estimates from the 2017–2018 influenza season in the United Kingdom suggest good effectiveness of the A/Slovenia/2309/2015 LAIV component against influenza A/H1N1pdm09, but additional data are needed.²²

In contrast to findings of reduced LAIV4 effectiveness against influenza A/H1N1pdm09 viruses, our results suggest a possible but nonsignificant benefit of LAIV4 over IIV against influenza B viruses, which has

been described previously.^{3,5} The difference in VE estimates was greatest in the 2013–2014 season, when most IIV used in the United States was trivalent.¹¹ The relative benefit of LAIV4 over IIV may decrease as the proportion of all IIV use that is quadrivalent continues to increase.¹⁶ Because we were unable to distinguish between trivalent and quadrivalent IIV doses for the majority of patients in our study, LAIV4 was compared with a mixture of IIV products, among which VE may differ. In addition, B lineage testing was not available for most studies in this analysis. However, US surveillance data from these 3 seasons indicate circulation of both B lineages,^{23,24} and it is likely that our influenza B cases represent both influenza B lineages.

This analysis was subject to several limitations. Descriptive patient information beyond age, sex, and geographic region of enrollment was not available for all studies. As a result, the estimates from this pooled analysis may be subject to confounding by other, unmeasured factors. In an attempt to control for some of these factors, such as potential differences in disease severity and high-risk status, we conducted several sensitivity analyses on subsets of patients with information on these factors and found results similar to our overall findings. Another limitation of our study was that, for most patients, historical vaccination data were limited to the season immediately before enrollment rather than the complete vaccine priming history. This limited our ability to fully assess the effects of vaccine priming history on current season VE. In a sensitivity analysis restricted to patients with more complete vaccination histories, VE among fully vaccinated children was similar to results of the primary analysis, suggesting that receiving

1 dose of vaccine when 2 are recommended is not confounding our findings.

CONCLUSIONS

Combining data from multiple studies, we estimate VE in subgroups of interest, including narrower age groups and among children vaccinated in the previous season, which was not feasible in the individual studies because of small sample sizes. Our findings are consistent with that of a recently published meta-analysis that included data from outside the United States (including Canada, Finland, Germany, and the United Kingdom); researchers in this study reported suboptimal effectiveness of LAIV4 against influenza A/H1N1pdm09 compared with IIV and similar effectiveness against influenza A/H3N2 in 2014–2015 and influenza B viruses.²⁵ Although LAIV4 containing the updated vaccine virus A/Slovenia/2309/2015 was used in Europe and Canada in 2017–2018, a limited circulation of influenza A/H1N1pdm09 hinders the ability to obtain precise effectiveness estimates.^{26,27} On the basis of evidence for immunogenicity and protection in animal models of the updated influenza A/H1N1pdm09 vaccine virus, ACIP reinstated the recommendation for use of LAIV4 in the United States as licensed for persons aged 2 to 49 years for the 2018–2019 influenza season as a vaccine option alongside age-appropriate IIVs and recombinant influenza vaccines.²⁸

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ABBREVIATIONS

ACIP:	Advisory Committee on Immunization Practices
CDC:	Centers for Disease Control and Prevention
CI:	confidence interval
EIR:	electronic immunization record
ICICLE:	Influenza Clinical Investigation for Children
IISP:	Influenza Incidence Surveillance Project
IIV:	inactivated influenza vaccine
LAIV:	live attenuated influenza vaccine
LAIV3:	trivalent live attenuated influenza vaccine
LAIV4:	quadrivalent live attenuated vaccine
LSU:	Louisiana State University Health Sciences Center
OR:	odds ratio
RT-PCR:	real-time reverse transcription-polymerase chain reaction
USAFSAM:	US Air Force School of Aerospace Medicine
USFLUVE:	US Influenza Vaccine Effectiveness Network
VE:	vaccine effectiveness

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Supplemental Information

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SUPPLEMENTAL TABLE 3 Exclusions From Analyses by Study

	USFLUVE	LSU	ICICLE	USAFSAM	IISP	Total
Total in data set	7310	6747	4095	3575	3168	24 895
Reason for exclusion						
Non-US enrollment	0	0	74	0	0	74
Inpatient	0	697	0	0	0	697
Age <2 y	0	1409	0	0	707	2116
Symptom onset outside period of influenza circulation	394	760	436	794	1051	3435
Unknown patient age	0	0	0	0	8	8
Unknown influenza test result	23	0	7	38	37	105
Unknown vaccination status	0	0	0	491	252	743
Unknown vaccine type	2	0	0	148	6	156
Received IIV and LAIV4 within season	6	0	3	0	0	9
Vaccination 0–13 d before onset	87	59	54	168	4	372
Coinfection with >1 influenza type and/or subtype	5	0	0	1	1	7
Total included in analytic data set	6793	3822	3521	1935	1102	17 173

SUPPLEMENTAL TABLE 4 Comparison of Patients by Study

Characteristic	Total (%) ^a	USFLUVE (%) ^a	LSU (%) ^a	ICICLE (%) ^a	USAFSAM (%) ^a	IISP (%) ^a
All, no.	17 173	6793	3822	3521	1935	1102
Influenza season						
2013–2014	4030 (23.5)	1526 (22.5)	1024 (26.8)	897 (25.5)	378 (19.5)	205 (18.6)
2014–2015	8060 (46.9)	3323 (48.9)	1892 (49.5)	1642 (46.6)	893 (46.1)	310 (28.1)
2015–2016	5083 (29.6)	1944 (28.6)	906 (23.7)	982 (27.9)	664 (34.3)	587 (53.3)
Age at enrollment, y						
Mean, SD	7.4 (4.4)	7.8 (4.6)	6.4 (4.2)	7.0 (4.1)	8.0 (4.5)	8.0 (4.6)
2–4	5846 (34.0)	2146 (31.6)	1655 (43.3)	1187 (33.7)	539 (27.9)	319 (28.9)
5–8	5182 (30.2)	1908 (28.1)	1167 (30.5)	1199 (34.1)	598 (30.9)	310 (28.1)
9–17	6145 (35.8)	2739 (40.3)	1000 (26.2)	1135 (32.2)	798 (41.2)	473 (42.9)
Female	8339 (48.9)	3269 (48.1)	1849 (48.4)	1727 (49.0)	943 (48.7)	551 (50.0)
Race and/or ethnicity ^b						
White, non-Hispanic	7162 (42.3)	4436 (65.3)	NA	2126 (60.4)	NA	600 (54.4)
Black, non-Hispanic	1392 (8.1)	700 (10.3)	NA	566 (16.1)	NA	126 (11.4)
Other race, non-Hispanic	1005 (5.9)	754 (11.1)	NA	215 (6.1)	NA	36 (3.3)
Hispanic, any race	1603 (9.3)	851 (12.5)	NA	601 (17.1)	NA	151 (13.7)
Acute respiratory infection symptoms						
Measured or reported fever ^c	9905 (57.7)	4061 (59.8)	NA	3521 (100.0)	1496 (77.3)	827 (75.0)
Cough ^c	12 213 (71.1)	6793 (100)	NA	3042 (86.4)	1598 (82.6)	780 (70.8)
Sore throat ^c	8115 (47.3)	3941 (58.0)	NA	2350 (66.7)	1138 (58.8)	686 (62.3)
Influenza-like illness ^d	9629 (56.1)	4061 (59.8)	NA	3416 (97.0)	1389 (71.8)	763 (69.2)
≥1 High-risk condition present ^e	2419 (14.1)	1691 (24.9)	NA	728 (20.7)	NA	NA
Asthma present ^e	2036 (11.9)	1443 (21.2)	NA	593 (16.8)	NA	NA
Public health region						
1. CT, ME, MA, NH, RI, and VT	23 (0.1)	0	0	0	23 (1.2)	0
2. NJ and NY	372 (2.2)	0	0	0	226 (11.7)	146 (13.2)
3. DE, DC, MD, PA, VA, and WV	1313 (7.6)	1237 (18.2)	0	0	76 (3.9)	0
4. AL, FL, GA, KY, MS, NC, SC, and TN	1902 (11.1)	0	0	1328 (37.7)	353 (18.2)	221 (20.1)
5. IL, IN, MI, MN, OH, and WI	4718 (27.5)	2890 (42.5)	0	1132 (32.1)	41 (2.1)	655 (59.4)
6. AK, LA, NM, OK, and TX	6733 (39.2)	1425 (21.0)	3822 (100)	1040 (29.5)	446 (23.0)	0
7. IA, KS, MO, and NE	56 (0.3)	0	0	0	56 (2.9)	0
8. CO, MT, ND, SD, UT, and WY	355 (2.1)	0	0	0	275 (14.2)	80 (7.3)
9. AZ, CA, HI, and NV	200 (1.2)	0	0	0	200 (10.3)	0
10. AK, ID, OR, and WA	1501 (8.7)	1241 (18.3)	0	21 (0.6)	239 (12.4)	0
Interval between symptom onset and enrollment, ^f d						
0–2	7599 (44.2)	2550 (37.5)	NA	2528 (71.8)	1935 (100)	586 (53.2)
3–4	3926 (22.9)	2659 (39.1)	NA	993 (28.2)	0	274 (24.9)
>5	1713 (10.0)	1584 (23.3)	NA	0	0	129 (11.7)
Influenza testing result						
Influenza-negative	12 929 (75.3)	5332 (78.5)	3055 (79.9)	2727 (77.4)	1083 (56.0)	732 (66.4)
Influenza-positive	4244 (24.7)	1461 (21.5)	767 (20.1)	794 (22.6)	852 (44.0)	370 (33.6)
Influenza A (no subtype)	519 (3.0)	19 (0.3)	491 (12.8)	1 (<0.1)	5 (0.3)	3 (0.3)
Influenza A/H3N2	1582 (9.2)	694 (10.2)	63 (1.8)	329 (9.3)	375 (19.4)	121 (11.0)
Influenza A/H1N1pdm09	1082 (6.3)	393 (5.8)	70 (1.6)	229 (6.5)	251 (13.0)	139 (12.6)
Influenza B (no lineage)	614 (3.6)	3 (0.0)	143 (3.7)	235 (6.7)	221 (11.4)	12 (1.1)
Influenza B/Yamagata	213 (1.2)	193 (2.3)	NA	NA	NA	20 (1.8)
Influenza B/Victoria	234 (1.4)	159 (2.8)	NA	NA	NA	75 (6.8)
Current season vaccination						
Unvaccinated	10 615 (61.8)	3838 (56.5)	3046 (79.7)	1834 (52.1)	1195 (61.8)	702 (63.7)
Vaccinated	6558 (38.2)	2955 (43.5)	776 (20.3)	1687 (47.9)	740 (38.2)	400 (36.3)
IIV	4579 (26.7)	2153 (31.8)	586 (15.3)	1158 (32.9)	422 (21.8)	260 (23.6)
LAIV4	1979 (11.5)	802 (11.7)	190 (5.0)	529 (15.0)	318 (16.4)	140 (12.7)

AL, Alabama; AK, Alaska; AZ, Arizona; CA, California; CO, Colorado; CT, Connecticut; DC, District of Columbia; DE, Delaware; FL, Florida; GA, Georgia; HI, Hawaii; IA, Iowa; ID, Idaho; IL, Illinois; IN, Indiana; KS, Kansas; KY, Kentucky; LA, Louisiana; MA, Massachusetts; MD, Maryland; ME, Maine; MI, Michigan; MN, Minnesota; MO, Missouri; MS, Mississippi; MT, Montana; NA, data not available; NC, North Carolina; ND, North Dakota; NE, Nebraska; NH, New Hampshire; NJ, New Jersey; NM, New Mexico; NV, Nevada; NY, New York; OH, Ohio; OK, Oklahoma; OR, Oregon; PA, Pennsylvania; RI, Rhode Island; SC, South Carolina; SD, South Dakota; TN, Tennessee; TX, Texas; UT, Utah; VA, Virginia; VT, Vermont; WA, Washington; WI, Wisconsin; WV, West Virginia; WY, Wyoming.

^a Percent of column total.

^b Patients' parents and/or guardians reported the patient's race and/or ethnicity during the enrollment interview. Data were unknown for all patients from the LSU and USAFSAM studies and for 13 patients from ICICLE, 189 from IISP, and 52 from USFLUVE.

^c Symptoms were reported at enrollment. Data were not available from the LSU study.

^d Influenza-like illness is defined as the presence of fever plus cough and/or sore throat. Data were not available from the LSU study and for 5 patients from ICICLE, 7 from IISP, 411 from USAFSAM, and 773 from USFLUVE.

TABLE 4 Continued

^a The presence of a high-risk health condition (including asthma) is defined as the presence of ≥ 1 medical record–documented diagnosis code in the year before enrollment, as defined by the ACIP guidance for conditions that increase the risk for complications due to influenza.²⁹ Data were not available from the IISP, LSU, or USAFSAM studies.

^f The interval between symptom onset and specimen collection was unknown for all patients from the LSU study and 113 patients from IISP.

SUPPLEMENTAL TABLE 5 Comparison of Characteristics by Vaccine Receipt Among Patients Who Tested Negative for Influenza

Characteristic	Unvaccinated (%) ^a	IIV (%) ^a	LAIV4 (%) ^a
All, no.	7574 (59)	3852 (30)	1503 (12)
Influenza season			
2013–2014	1804 (24)	1020 (26)	424 (28)
2014–2015	3517 (46)	1611 (42)	775 (52)
2015–2016	2253 (30)	1221 (32)	304 (20)
Age at enrollment, y			
Mean, SD	7.6 (4.6)	6.5 (4.5)	7.0 (3.9)
2–4	2531 (33)	1751 (45)	504 (34)
5–8	2186 (29)	964 (25)	531 (35)
9–17	2857 (38)	1137 (30)	468 (31)
Female	3680 (49)	1852 (48)	780 (52)
Race and/or ethnicity ^b			
White, non-Hispanic	2801 (62)	1953 (65)	822 (73)
Black, non-Hispanic	640 (14)	315 (10)	74 (7)
Other race, non-Hispanic	345 (8)	315 (10)	85 (8)
Hispanic, any race	713 (16)	425 (14)	151 (13)
Acute respiratory infection symptoms ^c			
Measured or reported fever	3611 (48)	2281 (59)	962 (64)
Cough	4719 (62)	3049 (79)	1141 (76)
Sore throat	3256 (43)	1816 (47)	824 (55)
Influenza-like illness ^d	3501 (46)	2222 (58)	928 (62)
≥1 high-risk condition ^e	912 (22)	974 (34)	108 (10)
Asthma	767 (18)	816 (29)	80 (8)
Public health region			
1. CT, ME, MA, NH, RI, and VT	7 (<1)	2 (<1)	1 (<1)
2. NJ and NY	132 (2)	26 (1)	17 (1)
3. DE, DC, MD, PA, VA, and WV	570 (8)	326 (8)	112 (7)
4. AL, FL, GA, KY, MS, NC, SC, and TN	685 (9)	450 (12)	248 (17)
5. IL, IN, MI, MN, OH, and WI	1800 (24)	1349 (35)	421 (28)
6. AK, LA, NM, OK, and TX	3624 (48)	1225 (32)	414 (28)
7. IA, KS, MO, and NE	16 (<1)	7 (<1)	5 (<1)
8. CO, MT, ND, SD, UT, and WY	87 (1)	66 (2)	41 (3)
9. AZ, CA, HI, and NV	48 (1)	43 (1)	28 (2)
10. AK, ID, OR, and WA	605 (8)	358 (9)	216 (14)
Interval from onset to enrollment, ^f d			
0–2	2185 (42)	1443 (44)	589 (44)
3–4	2229 (43)	1387 (42)	562 (42)
5–7	750 (15)	467 (14)	178 (13)
Study			
USFLUVE	2869 (38)	1849 (48)	614 (41)
LSU	2372 (31)	520 (13)	163 (11)
ICICLE	1311 (17)	988 (26)	428 (28)
USAFSAM	589 (8)	298 (8)	196 (13)
IISP	433 (6)	197 (5)	102 (7)

AL, Alabama; AK, Alaska; AZ, Arizona; CA, California; CO, Colorado; CT, Connecticut; DC, District of Columbia; DE, Delaware; FL, Florida; GA, Georgia; HI, Hawaii; IA, Iowa; ID, Idaho; IL, Illinois; IN, Indiana; KS, Kansas; KY, Kentucky; LA, Louisiana; MA, Massachusetts; MD, Maryland; ME, Maine; MI, Michigan; MN, Minnesota; MO, Missouri; MS, Mississippi; MT, Montana; NC, North Carolina; ND, North Dakota; NE, Nebraska; NH, New Hampshire; NJ, New Jersey; NM, New Mexico; NV, Nevada; NY, New York; OH, Ohio; OK, Oklahoma; OR, Oregon; PA, Pennsylvania; RI, Rhode Island; SC, South Carolina; SD, South Dakota; TN, Tennessee; TX, Texas; UT, Utah; VA, Virginia; VT, Vermont; WA, Washington; WI, Wisconsin; WV, West Virginia; WY, Wyoming.

^a Percent of column total.

^b Patients' parents and/or guardians reported the patient's race and/or ethnicity during the enrollment interview. Data were unknown for 3075 patients who were unvaccinated, 844 who received IIV, and 371 who received LAIV4 and tested negative for influenza.

^c Symptoms were reported at enrollment.

^d Influenza-like illness is defined as the presence of fever plus cough and/or sore throat. Data were not available for 2769 patients who were unvaccinated, 817 who received IIV, and 263 who received LAIV4 and tested negative for influenza.

^e The presence of a high-risk health condition (including asthma) is defined as the presence of ≥1 medical record–documented diagnosis code in the year before enrollment, as defined by the ACIP guidance for conditions that increase the risk for complications due to influenza.²⁹ Data were not available from the IISP, LSU, or USAFSAM studies.

^f The interval between symptom onset and specimen collection was unknown for 2410 patients who were unvaccinated, 555 who received IIV, and 174 who received LAIV4 and tested negative for influenza.

SUPPLEMENTAL TABLE 6 Comparison of Characteristics by Influenza Test Result

Characteristic	Total (%) ^a	Influenza-Negative (%) ^a	Influenza-Positive (%) ^a	Influenza A/H1N1pdm09 (%) ^a	Influenza A/H3N2 (%) ^a	Influenza A, Unsubtyped (%) ^a	Influenza B (%) ^a
All, no.	17 173	12 929	4 244	1 082	1 582	5 19	1 061
Influenza season							
2013–2014	4030 (23.5)	3248 (25.1)	782 (18.4)	507 (46.9)	46 (2.9)	152 (29.3)	77 (7.3)
2014–2015	8060 (46.9)	5903 (45.7)	2157 (50.8)	3 (0.3)	1467 (92.7)	262 (50.5)	425 (40.0)
2015–2016	5083 (29.6)	3778 (29.2)	1305 (30.7)	572 (52.9)	69 (4.4)	105 (20.2)	559 (52.7)
Age at enrollment, y							
Mean (SD)	7.4 (4.4)	7.2 (4.5)	7.9 (4.2)	7.0 (4.0)	8.4 (4.3)	6.4 (3.8)	8.6 (4.2)
2–4	5846 (31.9)	4786 (37.0)	1060 (25.0)	338 (31.2)	336 (21.2)	198 (38.2)	188 (17.7)
5–8	5182 (30.2)	3681 (28.5)	1501 (35.4)	420 (38.8)	530 (33.5)	186 (35.8)	365 (34.4)
9–17	6145 (35.8)	4462 (34.5)	1683 (39.7)	324 (29.9)	716 (45.3)	135 (26)	508 (47.9)
Female	8339 (48.6)	6312 (48.8)	2027 (47.8)	516 (47.7)	780 (49.3)	237 (45.7)	494 (46.6)
Race and/or ethnicity ^b							
White, non-Hispanic	7162 (41.7)	5576 (43.1)	1586 (37.4)	457 (42.2)	743 (47.0)	12 (2.3)	374 (35.2)
Black, non-Hispanic	1392 (8.1)	1029 (8.0)	363 (8.9)	124 (11.5)	135 (8.5)	6 (1.2)	98 (9.2)
Other race, non-Hispanic	1005 (5.9)	745 (5.8)	260 (6.1)	65 (6.0)	110 (7.0)	3 (0.6)	82 (7.7)
Hispanic, any race	1603 (9.3)	1289 (10.0)	314 (7.4)	81 (7.5)	126 (8.0)	2 (0.4)	105 (9.9)
Acute respiratory infection symptoms							
Measured or reported fever ^c	9905 (57.7)	6854 (53.0)	3051 (71.9)	841 (77.7)	1356 (85.7)	24 (4.6)	830 (78.2)
Cough ^e	12 213 (71.1)	8909 (68.9)	3304 (77.9)	955 (88.3)	1454 (91.9)	26 (5)	869 (81.9)
Sore throat ^e	8115 (47.3)	5896 (45.6)	2219 (52.3)	561 (51.8)	1009 (63.8)	16 (3.1)	633 (59.7)
Influenza-like illness ^d	9629 (56.1)	6651 (51.4)	2978 (70.2)	816 (75.4)	1332 (84.2)	23 (4.4)	807 (76.1)
≥ 1 high-risk condition ^e	2419 (14.1)	1994 (15.4)	425 (10.0)	99 (9.1)	214 (13.5)	17 (3.3)	109 (10.3)
Asthma	2036 (11.9)	1663 (12.9)	373 (8.8)	87 (8.0)	186 (11.8)	17 (3.3)	97 (9.1)
Public health region							
1. CT, ME, MA, NH, RI, and VT	23 (0.1)	10 (0.1)	13 (0.3)	2 (0.2)	10 (0.6)	0 (0)	1 (0.1)
2. NJ and NY	372 (2.2)	175 (1.4)	197 (4.6)	55 (5.1)	65 (4.1)	1 (0.2)	76 (7.2)
3. DE, DC, MD, PA, VA, and WV	1313 (7.6)	1008 (7.8)	305 (7.2)	110 (10.2)	128 (8.1)	3 (0.6)	64 (6.0)
4. AL, FL, GA, KY, MS, NC, SC, and TN	1902 (11.1)	1383 (10.7)	519 (12.2)	201 (18.6)	198 (12.5)	1 (0.2)	119 (11.2)
5. IL, IN, MI, MN, OH, and WI	4718 (27.5)	3570 (27.6)	1148 (27.0)	362 (33.5)	561 (35.5)	13 (2.5)	212 (20.0)
6. AK, LA, NM, OK, and TX	6733 (39.2)	5263 (40.7)	1470 (34.6)	196 (18.1)	353 (22.3)	496 (95.6)	425 (40.1)
7. IA, KS, MO, and NE	56 (0.3)	28 (0.2)	28 (0.7)	7 (0.6)	13 (0.8)	2 (0.4)	6 (0.6)
8. CO, MT, ND, SD, UT, and WY	355 (2.1)	194 (1.5)	161 (3.8)	47 (4.3)	83 (5.2)	0 (0)	31 (2.9)
9. AZ, CA, HI, and NV	200 (1.2)	119 (0.9)	81 (1.9)	35 (3.2)	31 (2.0)	0 (0)	15 (1.4)
10. AK, ID, OR, and WA	1501 (8.7)	1179 (9.1)	322 (7.6)	67 (6.2)	140 (8.8)	3 (0.6)	112 (10.6)
Interval from onset to testing, ^{f,d}							
0–2	5663 (33.0)	4217 (32.6)	1446 (34.1)	415 (38.4)	678 (42.9)	7 (1.3)	346 (32.6)
3–4	5861 (34.1)	4178 (32.3)	1683 (39.7)	492 (45.5)	693 (43.8)	13 (2.5)	485 (45.7)
≥ 5	1713 (10.0)	1395 (10.8)	318 (7.5)	97 (9.0)	140 (8.8)	8 (1.5)	73 (6.9)
Study							
USFLUVE	6793 (39.6)	5332 (41.2)	1461 (34.4)	393 (36.3)	694 (43.9)	19 (3.7)	355 (33.5)
LSU	3822 (22.2)	3055 (23.6)	767 (18.1)	70 (6.5)	63 (4.0)	491 (94.6)	143 (13.5)
ICICLE	3521 (20.5)	2727 (21.1)	794 (18.7)	229 (21.2)	329 (20.8)	1 (0.2)	235 (22.1)
USAFSAM	1935 (11.3)	1083 (8.4)	852 (20.0)	251 (23.2)	375 (23.7)	5 (1.0)	221 (20.8)
IISP	1102 (6.4)	732 (5.7)	370 (8.7)	139 (12.8)	121 (7.6)	3 (0.6)	107 (10.1)

AL, Alabama; AK, Alaska; AZ, Arizona; CA, California; CO, Colorado; CT, Connecticut; DC, District of Columbia; DE, Delaware; FL, Florida; GA, Georgia; HI, Hawaii; IA, Iowa; ID, Idaho; IL, Illinois; IN, Indiana; KS, Kansas; KY, Kentucky; LA, Louisiana; MA,

TABLE 6 Continued

Massachusetts; MD, Maryland; ME, Maine; MI, Michigan; MN, Minnesota; MO, Missouri; MS, Mississippi; MT, Montana; NC, North Carolina; ND, North Dakota; NE, Nebraska; NH, New Hampshire; NJ, New Jersey; NM, New Mexico; NV, Nevada; NY, New York; OH, Ohio; OK, Oklahoma; OR, Oregon; PA, Pennsylvania; RI, Rhode Island; SC, South Carolina; SD, South Dakota; TN, Tennessee; TX, Texas; UT, Utah; VA, Virginia; VT, Vermont; WA, Washington; WI, Wisconsin; WV, West Virginia; WY, Wyoming.

^a Percent of column total.

^b Patients' parents and/or guardians reported the patient's race and/or ethnicity during the enrollment interview. Data were unknown for 6011 patients, including 4290 patients who were influenza-negative and 1721 who tested positive for any influenza.

^c Symptoms were reported at enrollment. Data were not available for 3336 patients, including 3139 patients who were influenza-negative and 797 who tested positive for influenza.

^d Influenza-like illness is defined as the presence of fever, plus cough and/or sore throat. Data were not available for 4783 patients, including 3849 patients who were influenza-negative and 934 who tested positive for any influenza.

^e Presence of a high-risk health condition (including asthma) is defined as the presence of ≥ 1 medical record–documented diagnosis code in the year before enrollment, as defined by the ACIP guidance for conditions that increase the risk for complications due to influenza.²⁸ Data were not available from the ISP, LSU, or USAFSAM studies.

^f The interval between symptom onset and specimen collection was unknown for all patients from the LSU study and 113 patients from ISP.

SUPPLEMENTAL TABLE 7 Adjusted VE by Influenza Season for Children Receiving IIV or LAIV4

	Age Group, y	Influenza-Positive		Influenza-Negative		Adjusted ^a VE	
		No. Vaccinated, Total	%	No. Vaccinated, Total	%	VE, %	95% CI
2013–2014 season							
Any influenza							
IIV	2–17	105 of 673	15.6	1020 of 2824	36.1	63	55 to 70
	2–4	34 of 202	16.8	485 of 1088	44.6	71	57 to 81
	5–8	31 of 207	15.0	246 of 764	32.2	59	41 to 71
	9–17	40 of 264	15.2	289 of 972	29.7	56	35 to 71
LAIV4	2–17	109 of 677	16.1	424 of 2228	19.0	15	–1 to 28
	2–4	37 of 205	18.1	139 of 742	18.7	–16	–73 to 22
	5–8	44 of 220	22.1	155 of 673	23.0	13	–12 to 33
	9–17	28 of 252	11.1	130 of 813	16.0	36	–4 to 60
Influenza A/H1N1pdm09 ^b							
IIV	2–17	67 of 426	15.7	1020 of 2824	36.1	68	57 to 76
	2–4	26 of 126	20.6	485 of 1088	44.6	71	49 to 83
	5–8	21 of 136	15.4	246 of 764	32.2	62	41 to 75
	9–17	20 of 164	12.2	289 of 972	29.7	70	47 to 83
LAIV4	2–17	81 of 440	18.4	424 of 2228	19.0	14	–6 to 30
	2–4	26 of 126	20.6	139 of 742	18.7	–22	–106 to 28
	5–8	35 of 150	23.3	155 of 673	23.0	4	–42 to 35
	9–17	20 of 164	12.2	130 of 813	16.0	34	–16 to 63
Influenza B							
IIV	2–17	14 of 71	19.7	1020 of 2824	36.1	56	33 to 71
LAIV4	2–17	6 of 63	9.5	424 of 2228	19.0	64	8 to 86
2014–2015 season							
Any influenza							
IIV	2–17	410 of 1886	21.7	1611 of 5128	31.4	37	28 to 44
	2–4	98 of 401	24.4	755 of 1967	38.4	46	31 to 58
	5–8	139 of 650	21.4	399 of 1402	28.5	36	11 to 54
	9–17	173 of 835	20.7	457 of 1759	26.0	27	13 to 38
LAIV4	2–17	271 of 1747	15.5	775 of 4292	18.1	25	10 to 37
	2–4	63 of 366	17.2	264 of 1476	17.9	16	–13 to 38
	5–8	102 of 613	16.6	267 of 1270	21.0	31	6 to 49
	9–17	106 of 768	13.8	244 of 1546	15.8	28	8 to 43
Influenza A/H3N2 ^b							
IIV	2–17	311 of 1233	25.2	1611 of 5128	31.4	29	14 to 42
	2–4	67 of 265	25.3	755 of 1967	38.4	55	37 to 67
	5–8	107 of 412	26.0	399 of 1402	28.5	25	–14 to 51
	9–17	137 of 556	24.6	457 of 1759	26.0	9	–18 to 29
LAIV4	2–17	234 of 1156	20.2	775 of 4292	18.1	7	–11 to 23
	2–4	56 of 254	22.1	264 of 1476	17.9	12	–27 to 39
	5–8	86 of 391	22.0	267 of 1270	21.0	8	–29 to 34
	9–17	92 of 511	18.0	244 of 1546	15.8	3	–38 to 32
Influenza B							
IIV	2–17	85 of 403	21.1	1611 of 5128	31.4	49	32 to 62
	2–4	24 of 63	38.1	755 of 1967	38.4	13	–64 to 54
	5–8	30 of 142	21.1	399 of 1402	28.5	51	30 to 65
	9–17	31 of 198	15.7	457 of 1759	26.0	59	41 to 71
LAIV4	2–17	22 of 340	6.5	775 of 4292	18.1	76	53 to 88
	2–4	3 of 42	7.1	264 of 1476	17.9	NR	NR
	5–8	8 of 120	6.7	267 of 1270	21.0	81	65 to 90
	9–17	11 of 178	6.2	244 of 1546	15.8	75	32 to 91
2015–2016 season							
Any influenza							
IIV	2–17	212 of 1209	17.5	1221 of 3474	35.2	60	52 to 67
	2–4	67 of 336	19.9	511 of 1227	41.7	61	45 to 72
	5–8	82 of 448	18.3	319 of 984	32.4	57	43 to 67
	9–17	63 of 425	14.8	391 of 1263	31.0	64	48 to 75
LAIV4	2–17	96 of 1093	8.8	304 of 2557	11.9	39	16 to 56
	2–4	21 of 290	7.2	101 of 817	12.4	46	–14 to 75
	5–8	50 of 416	12	109 of 774	14.1	30	–5 to 54
	9–17	25 of 387	6.5	94 of 966	9.7	46	9 to 68
Influenza A/H1N1pdm09 ^b							

TABLE 7 Continued

	Age Group, y	Influenza-Positive		Influenza-Negative		Adjusted ^a VE		
		No. Vaccinated, Total	%	No. Vaccinated, Total	%	VE, %	95% CI	
IIV	2–17	89 of 513	17.4	1221 of 3474	35.2	66	59 to 71	
	2–4	35 of 169	20.7	511 of 1227	41.7	64	46 to 76	
	5–8	35 of 215	16.3	319 of 984	32.4	67	50 to 78	
LAIV4	9–17	19 of 129	14.7	391 of 1263	31.0	65	38 to 80	
	2–17	59 of 483	12.2	304 of 2557	11.9	18	–31 to 49	
	2–4	17 of 151	11.3	101 of 817	12.4	19	–123 to 69	
	5–8	32 of 212	15.1	109 of 774	14.1	11	–40 to 44	
Influenza B	9–17	10 of 120	8.3	94 of 966	9.7	37	–35 to 70	
	IIV	2–17	98 of 529	18.5	1221 of 3474	35.2	55	39 to 66
	2–4	20 of 106	18.9	511 of 1227	41.7	63	35 to 78	
	5–8	43 of 179	24.0	319 of 984	32.4	40	18 to 55	
LAIV4	9–17	35 of 244	14.3	391 of 1263	31.0	63	43 to 76	
	2–17	30 of 461	6.5	304 of 2557	11.9	54	35 to 68	
	2–4	2 of 88	2.3	101 of 817	12.4	NR	NR	
	5–8	14 of 150	9.3	109 of 774	14.1	48	16 to 68	
	9–17	14 of 223	6.3	94 of 966	9.7	46	–2 to 71	

NR, not reported because of insufficient sample size.

^a Models adjusted for age (group or years for age-stratified models), calendar time, and site (as a random effect).

^b Estimates were similar against any influenza A viruses (data not shown).

SUPPLEMENTAL TABLE 8 Adjusted VE by Influenza Type and/or Subtype for Children Receiving IIV or LAIV4 in 2013–2014 and 2015–2016

	Age Group, y	Influenza-Positive		Influenza-Negative		Adjusted ^a VE	
		No. Vaccinated, Total	%	No. Vaccinated, Total	%	VE, %	95% CI
Any influenza ^b							
IIV	2–17	727 of 3768	19.3	3852 of 11 426	33.7	51	47 to 54
	2–4	199 of 939	21.2	1751 of 4282	40.9	58	51 to 64
	5–8	252 of 1305	19.3	964 of 3150	30.6	47	37 to 55
	9–17	276 of 1524	18.1	1137 of 3994	28.5	45	37 to 53
LAIV4	2–17	476 of 3517	13.5	1503 of 9077	16.6	26	15 to 36
	2–4	121 of 861	14.1	504 of 3035	16.6	19	–7 to 38
	5–8	196 of 1249	15.7	531 of 2717	19.5	28	15 to 39
	9–17	159 of 1407	11.3	468 of 3325	14.1	34	17 to 48
Influenza A/H1N1pdm09 ^c							
IIV	2–17	156 of 939	16.6	2241 of 6298	35.6	67	62 to 72
	2–4	61 of 295	20.7	996 of 2315	43.0	68	58 to 76
	5–8	56 of 351	16.0	565 of 1748	32.3	66	56 to 74
	9–17	39 of 293	13.3	680 of 2235	30.4	68	53 to 78
LAIV4	2–17	140 of 923	15.2	728 of 4785	15.2	20	–6 to 39
	2–4	43 of 277	15.5	240 of 1559	15.4	5	–77 to 49
	5–8	67 of 362	18.5	264 of 1447	18.2	15	–12 to 35
	9–17	30 of 284	10.6	224 of 1779	12.6	36	6 to 56
Influenza A/H3N2 ^d							
IIV	2–17	311 of 1233	25.2	1611 of 5128	31.4	29	14 to 42
	2–4	67 of 265	25.3	755 of 1967	38.4	55	37 to 67
	5–8	107 of 412	26.0	399 of 1402	28.5	25	–14 to 51
	9–17	137 of 556	24.6	457 of 1759	26.0	9	–18 to 29
LAIV4	2–17	234 of 1156	20.2	775 of 4292	18.1	7	–11 to 23
	2–4	56 of 254	22.1	264 of 1476	17.9	12	–27 to 39
	5–8	86 of 391	22.0	267 of 1270	21.0	8	–29 to 34
	9–17	92 of 511	18.0	244 of 1546	15.8	3	–38 to 32
Influenza B ^b							
IIV	2–17	197 of 1003	19.6	3852 of 11 426	33.7	52	42 to 60
	2–4	47 of 181	26.0	1751 of 4282	40.9	43	25 to 57
	5–8	75 of 340	22.1	964 of 3150	30.6	46	29 to 58
	9–17	75 of 482	15.6	1137 of 3994	28.5	58	46 to 68
LAIV4	2–17	58 of 864	6.7	1503 of 9077	16.6	66	47 to 77
	2–4	7 of 141	5.0	504 of 3035	16.6	71	34 to 87
	5–8	25 of 290	8.6	531 of 2717	19.5	66	43 to 80
	9–17	26 of 433	6.0	468 of 3325	14.1	66	32 to 85

^a Models adjusted for age (group or years for age-stratified models), season, calendar time, and site (as a random effect).

^b Includes the 2013–2014 influenza season through the 2015–2016 season.

^c Restricted to the 2013–2014 and 2015–2016 influenza seasons.

^d Restricted to the 2014–2015 influenza season.

SUPPLEMENTAL TABLE 9 Adjusted Relative Effectiveness of LAIV4 Versus IIV by Influenza Type and/or Subtype and Age Group

Influenza Type and/or Subtype by Age Group, y	Vaccine Type	Total	Influenza Positive		Adjusted OR ^a	95% CI
			No. Vaccinated	% ^b		
Any influenza ^c						
2–17	LAIV4	1979	476	24	1.48	1.28 to 1.70
	IIV	4579	727	16	Ref	
2–4	LAIV4	625	121	19	2.00	1.50 to 2.67
	IIV	1950	199	10	Ref	
5–8	LAIV4	727	196	27	1.39	1.11 to 1.74
	IIV	1216	252	21	Ref	
9–17	LAIV4	627	159	25	1.19	0.92 to 1.56
	IIV	1413	276	20	Ref	
Influenza A/H1N1pdm09 ^d						
2–17	LAIV4	868	140	16	2.66	2.06 to 3.44
	IIV	2397	156	7	Ref	
2–4	LAIV4	283	43	15	3.12	1.62 to 6.01
	IIV	1057	61	6	Ref	
5–8	LAIV4	331	67	20	2.79	2.09 to 3.71
	IIV	621	56	9	Ref	
9–17	LAIV4	254	30	12	2.19	1.26 to 3.81
	IIV	719	39	5	Ref	
Influenza A/H3N2 ^e						
2–17	LAIV4	1009	234	23	1.30	1.06 to 1.58
	IIV	1922	311	16	Ref	
2–4	LAIV4	320	56	18	1.99	1.49 to 2.64
	IIV	822	67	8	Ref	
5–8	LAIV4	353	86	24	1.16	0.74 to 1.82
	IIV	506	107	21	Ref	
9–17	LAIV4	336	92	27	1.15	0.87 to 1.51
	IIV	594	137	23	Ref	
Influenza B ^c						
2–17	LAIV4	1561	58	4	0.72	0.46 to 1.13
	IIV	4049	197	5	Ref	
2–4	LAIV4	511	7	1	0.56	0.21 to 1.53
	IIV	1798	47	3	Ref	
5–8	LAIV4	556	25	5	0.68	0.42 to 1.11
	IIV	1039	75	7	Ref	
9–17	LAIV4	494	26	5	0.81	0.38 to 1.72
	IIV	1212	75	6	Ref	

Ref, reference group.

^a Relative effectiveness estimates are expressed as the odds of influenza among LAIV4 recipients compared with IIV recipients and 95% CIs. ORs of <1 suggest lower odds of influenza in LAIV4 recipients compared with IIV recipients. Models are adjusted for age (group or years for age-stratified models), season, calendar time, and site (as a random effect).^b Percent of row total.^c Includes the 2013–2014 influenza season through the 2015–2016 season.^d Restricted to the 2013–2014 and 2015–2016 influenza seasons.^e Restricted to the 2014–2015 influenza season.