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Seasonal Effectiveness of Live Attenuated and Inactivated Influenza Vaccine

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Abstract

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Ms Chung conducted the analyses and drafted the initial manuscript; Drs Flannery, Thompson, and Fry conceptualized and designed the study, contributed to the analyses and interpretation of results, and critically reviewed and revised the manuscript; Drs Gaglani, Jackson, Monto, Nowalk, Talbot, Treanor, Belongia, Murthy, Jackson, Zimmerman, Griffin, and McLean and Mr Petrie coordinated and supervised the data collection at their respective study sites and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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BACKGROUND—Few observational studies have evaluated the relative effectiveness of live attenuated (LAIV) and inactivated (IIV) influenza vaccines against medically attended laboratory-confirmed influenza.

METHODS—We analyzed US Influenza Vaccine Effectiveness Network data from participants aged 2 to 17 years during 4 seasons (2010–2011 through 2013–2014) to compare relative effectiveness of LAIV and IIV against influenza-associated illness. Vaccine receipt was confirmed via provider/electronic medical records or immunization registry. We calculated the ratio (odds) of influenza-positive to influenza-negative participants among those age-appropriately vaccinated with either LAIV or IIV for the corresponding season. We examined relative effectiveness of LAIV and IIV by using adjusted odds ratios (ORs) and 95% confidence intervals (CIs) from logistic regression.

RESULTS—Of 6819 participants aged 2 to 17 years, 2703 were age-appropriately vaccinated with LAIV (n = 637) or IIV (n = 2066). Odds of influenza were similar for LAIV and IIV recipients during 3 seasons (2010–2011 through 2012–2013). In 2013–2014, odds of influenza were significantly higher among LAIV recipients compared with IIV recipients 2 to 8 years old (OR 5.36; 95% CI, 2.37 to 12.13). Participants vaccinated with LAIV or IIV had similar odds of illness associated with influenza A/H3N2 or B. LAIV recipients had greater odds of illness due to influenza A/H1N1pdm09 in 2 seasons: 2010 to 2011 (OR 5.53; 95% CI, 1.35 to 22.76) and 2013–2014 (OR 2.65; 95% CI, 1.34 to 5.27).

CONCLUSIONS—We observed lower effectiveness of LAIV compared with IIV against influenza A/H1N1pdm09 but not A(H3N2) or B among children and adolescents, suggesting poor performance related to the LAIV A/H1N1pdm09 viral construct.

Vaccination is the primary prevention strategy to reduce the morbidity and mortality associated with influenza. The US Advisory Committee on Immunization Practices (ACIP) has recommended annual influenza vaccination for all children aged 6 months and older since 2008.[1] Inactivated influenza vaccines (IIV), administered intramuscularly, are licensed for use among children aged ≥6 months, and live attenuated influenza vaccine (LAIV), administered intranasally, is licensed for use among children aged ≥2 years; both have been demonstrated to be effective against influenza illness in children.[2–5] Several studies conducted before the 2009 influenza A/H1N1pdm09 pandemic demonstrated superior efficacy of LAIV over IIV in children aged 6–71 months, leading ACIP in 2014 to recommend preferential use of LAIV, when immediately available, for healthy children aged 2–8 years.[3–6] However, limited data are available from observational studies after the 2009 pandemic on relative effectiveness of LAIV and IIV in children and adolescents.

The Centers for Disease Control and Prevention has conducted annual studies of influenza vaccine effectiveness (VE) through the US Influenza Vaccine Effectiveness (Flu VE) Network since 2004 to 2005.[7–12] Increasing vaccination coverage and use of LAIV among children and adolescents have allowed VE estimates for LAIV and IIV individually against circulating influenza viruses in each season since the 2009 influenza pandemic.[9–12] These data indicate that both LAIV and IIV provided statistically significant protection against medically attended influenza illness in the outpatient setting during the 3 influenza seasons from 2010 to 2011 to 2012 to 2013. VE point estimates against any influenza among

children or children and adolescents ranged from 45% (2012–2013) to 71% (2010–2011) for LAIV and 48% (2012–2013) to 71% (2010–2011) for IIV.[10,12] However, in 2013 to 2014, Flu VE Network data indicated lower LAIV effectiveness against illness due to A/H1N1pdm09 virus among children, despite effectiveness of IIV (M. Gaglani, unpublished data, 2015). The 2013 to 2014 season was the first time A/H1N1pdm09 viruses predominated in the United States since the 2009 pandemic. In this study, we expand on previous analyses by evaluating VE and relative effectiveness of LAIV and IIV by season and influenza type and subtype among children and adolescents aged 2 to 17 years from 2010 to 2011 through 2013 to 2014.

METHODS

Subject Enrollment and Vaccine Verification

The study design and enrollment criteria of the Flu VE Network have been described previously.[10–13] Participants aged 2 to 17 years were included in this analysis. During the 2010 to 2011 influenza season, patients seeking care for acute respiratory illness with a cough or fever (elevated documented temperature or history of feverishness) ≤7 days in duration were enrolled at participating clinics and hospitals in Wisconsin, Michigan, New York, and Tennessee. During the subsequent 3 seasons, patients seeking care for acute respiratory illness with cough (cough or fever or feverishness in 2011–2012) were enrolled at participating ambulatory clinics in Wisconsin, Michigan, Washington, Pennsylvania, and Texas. Patients were not eligible if enrolled in the previous 14 days; <3% of participants enrolled more than once within a season. Combined nasal and throat swabs were collected by trained study staff and tested for influenza (type and subtype) at network laboratories with reverse transcription polymerase chain reaction (RT-PCR) with methods described previously.[10,11] Influenza-positive cases were participants who were RT-PCR positive for influenza, and test-negative controls were RT-PCR negative. Illness onset and demographic characteristics were assessed during enrollment interview.

Vaccination Status

Documented dates of vaccination, vaccine type, and lot numbers were obtained from provider records, electronic medical record, and registry data. If vaccine type could not be documented from these sources, we relied on parent or guardian report at enrollment of the method of vaccine administration (ie, shot or nasal spray) to assign vaccine type as inactivated or live attenuated. Participants for whom vaccine type could not be determined and participants who received both vaccine types within the same season were excluded. Institutional review boards at each study site approved study procedures.

Participants aged ≥9 years who received ≥1 dose of any current season influenza vaccine ≥14 days before illness onset were considered vaccinated; participants aged 2 to 8 years were considered fully or age-appropriately vaccinated if they received the number of doses recommended by ACIP ≥14 days before illness. Partially vaccinated children who received only 1 of 2 recommended doses were excluded from the main analyses.[14–17] Sensitivity analyses were conducted including partially vaccinated children. Participants vaccinated after illness onset were considered unvaccinated.

Vaccine Components

In each season, an A/H1N1/California/7/2009-like virus was recommended as the A/H1N1 vaccine component.[14–17] Recommended A/H3N2 vaccine components were A/H3N2/Perth/16/2009 for 2010 to 2011 and 2011 to 2012, A/H3N2/Victoria/361/2011 for 2012 to 2013, and A/Texas/50/2012 (an A/Victoria/361/2011-like virus) for 2013 to 2014. For trivalent vaccines, recommended B vaccine components were B/Brisbane/60/2008 (B/Victoria lineage) in 2010 to 2011 and 2011 to 2012, B/Wisconsin/1/2010 in 2012 to 2013, and B/Massachusetts/2/2012 in 2013 to 2014, the latter 2 from the B/Yamagata lineage. Quadrivalent vaccines in 2013 to 2014 also included a B/Brisbane/60/2008-like virus (B/Victoria lineage). All LAIV was quadrivalent in 2013 to 2014 and trivalent in previous seasons.

Estimation of Relative VE

To compare effectiveness of LAIV and IIV, we calculated the odds of influenza (ratio of influenza-positive to influenza-negative participants) among participants who received LAIV or IIV for the corresponding season and examined relative effectiveness using the odds ratio (OR; ie, the ratio of the odds of influenza among those receiving LAIV to the odds among those receiving IIV) and 95% confidence interval (CI). Adjusted ORs <1.0 indicate that the odds of influenza were lower among those who received LAIV, and ORs >1.0 indicate that the odds of influenza among LAIV recipients were higher than among IIV recipients. Statistically significant relative effectiveness estimates were defined as ORs with 95% CIs that excluded 1. Combined-season estimates for influenza A/H1N1pdm09 (2010–2011 and 2013–2014) and A/H3N2 (2011–2012 and 2012–2013) were calculated for seasons in which vaccine components for virus subtypes were antigenically related and there was sufficient virus circulation (defined as 15 vaccinated influenza-positive cases) for a stable estimate from adjusted logistic regression models. For comparison with previously published estimates, we also calculated VE by using a test-negative design, as previously described (Supplemental Tables 4 and 5).[11,12,18–20]

Adjusted logistic models included age at enrollment, gender, race or ethnicity, study site, interval from onset to enrollment, high-risk health conditions, parent- or guardian-rated general health status, and calendar time (dichotomous variables representing 2-week intervals by season). Because LAIV is not recommended for children with high-risk health conditions, we conducted sensitivity analyses excluding patients with any high-risk health condition in the year before enrollment. Models for all ages included age categories (2–4, 5–8, or 9–17 years), and age-stratified models were adjusted for participant's age in years. For combined-season analyses, models also included a term for influenza season. Statistical analyses were conducted in SAS statistical software (version 9.3; SAS Institute, Inc, Cary, NC). *P* values <.05 were considered statistically significant. Figures were generated with the "forestplot" package in R (version 3.1.1; R Core Team, Vienna, Austria).[21,22]

RESULTS

Among 7718 outpatients aged 2 to 17 years enrolled in annual influenza VE studies, 23.1% were enrolled during 2010 to 2011, 25.1% during 2011 to 2012, 30.7% during 2012 to 2013,

and 21.0% during 2013 to 2014. We excluded 899 participants from VE analyses (Table 1). A smaller proportion of the excluded population tested positive for any influenza (15%) compared with the 6819 participants retained for VE analyses (26%) ($P < .001$). Relative effectiveness analyses were restricted to the vaccinated participants ($N = 2703$).

Among 6819 participants included in VE analyses, proportions of influenza-positive cases overall varied from 17.0% (2011–2012) to 41.6% (2012–2013). Furthermore, circulation of influenza types and subtypes varied by season (Table 2). In 2010 to 2011, influenza A/H3N2 cocirculated with influenza A/H1N1pdm09 and influenza B. In 2011 to 2012, influenza A/H3N2 viruses predominated. In 2012 to 2013, influenza A/H3N2 viruses cocirculated with both lineages of influenza B. The 2013 to 2014 season was characterized by predominance of influenza A/H1N1pdm09. In univariate analyses, influenza-positive cases were older than test-negative controls, had better reported general health status, and were less likely to have high-risk health conditions (Supplemental Table 6).

Among the 2703 fully vaccinated participants, 76.4% received IIV and 23.6% received LAIV. The proportion of vaccinated participants receiving LAIV increased from 2010 to 2011 (19.6%) to 2013 to 2014 (25.9%) and varied by study site. Compared with IIV recipients in univariate analyses, LAIV recipients were older, had better reported general health, and had fewer high-risk health conditions (Table 3). LAIV recipients across seasons were similar with respect to age, presence of high-risk health conditions, and gender. For all seasons, receipt of current season vaccine was significantly correlated with influenza vaccination in the previous season. Proportions of participants with previous season vaccination were similar for both vaccinated groups; 79% of LAIV recipients and 77% of IIV recipients had a documented dose of influenza vaccine in the previous season.

Comparison by Season

We compared the relative effectiveness of LAIV and IIV against any influenza by season (Fig 1). Odds of influenza were similar for participants vaccinated with LAIV or IIV from 2010 to 2011 to 2012 to 2013, and ORs were consistent, with no statistically significant difference in VE.[10,13] In 2013 to 2014, 21% of participants vaccinated with LAIV and 8% of those vaccinated with IIV had laboratory-confirmed influenza. The odds of influenza were significantly higher for LAIV recipients compared with IIV recipients aged 2 to 17 years (OR 2.88; 95% CI, 1.62 to 5.12) and 2 to 8 years (OR 5.36; 95% CI, 2.37 to 12.13), whereas OR for participants aged 9 to 17 years was not statistically significant. In all seasons, inclusion of previous season influenza vaccination as a dichotomous variable did not substantially change relative effectiveness estimates (data not shown).

Comparison by Influenza Type

In both 2010 to 2011 and 2013 to 2014, higher proportions of LAIV recipients tested positive for A/H1N1pdm09 compared with IIV recipients (Fig 2). Adjusted odds of A/H1N1pdm09 illness among LAIV recipients aged 2 to 17 years were 5.53 (95% CI, 1.35 to 22.76) times higher in 2010–2011 and 2.65 (95% CI, 1.34 to 5.27) times higher in 2013–2014 compared with IIV recipients. In the combined analysis, odds of A/H1N1pdm09 were significantly higher among LAIV recipients compared with IIV recipients (OR 3.08; 95%

CI, 1.72 to 5.50). In 2010 to 2011, 2011 to 2012, and 2012 to 2013, similar proportions of participants aged 2 to 17 years who received LAIV and IIV tested positive for A/H3N2 viruses, with no statistically significant difference in adjusted odds of A/H3N2 illness in any season or in the combined 2-season analysis. Similarly, proportions of participants who tested positive for influenza B viruses in 2010 to 2011 or 2012 to 2013 did not differ by vaccine type. There was no difference in relative effectiveness for B/Yamagata (OR 1.32; 95% CI, 0.67 to 2.60) or B/Victoria (OR 0.51; 95% CI, 0.21 to 1.19) in 2012 to 2013; B lineage was not determined in 2010 to 2011.

Additional Analyses

Excluding participants with high-risk health conditions resulted in similar relative effectiveness estimates against any influenza in all seasons and age groups (Supplemental Table 7). Including partially vaccinated participants also resulted in similar estimates (Supplemental Table 8). Increased LAIV uptake in 2013 to 2014 allowed us to investigate differences in LAIV recipients. There were no significant differences in positivity by lot of LAIV in 2013 to 2014; 40% of doses were from a single lot (data not shown). None of the 2013 to 2014 participants enrolled within 30 days of LAIV receipt tested positive for vaccine virus.

DISCUSSION

In this analysis of age-appropriately vaccinated children and adolescents over 4 influenza seasons after the 2009 influenza pandemic, we found no statistically significant difference in LAIV effectiveness compared with IIV against medically attended, laboratory-confirmed influenza illness due to A/H3N2 or B viruses. We found significantly higher odds of influenza A/H1N1pdm09 among participants vaccinated with LAIV compared with IIV. Reasons for lower effectiveness of LAIV against the A/H1N1pdm09 virus compared with IIV are not fully understood. However, the finding appears to be specific to the A/H1N1pdm09 vaccine component; we did not detect any statistically significant differences in effectiveness for the other components. Differences in antigenic match between LAIV and IIV vaccine components are unlikely to have contributed because both vaccines included A/California/7/2009 (H1N1pdm09)-like viruses that were antigenically similar to circulating A/H1N1pdm09 viruses in all seasons since 2009.

Lower LAIV effectiveness compared with IIV against A/H1N1pdm09-related illness was unexpected. In 3 randomized IIV-controlled trials of trivalent LAIV among children <8 years of age conducted before 2009, relative efficacy of LAIV was superior to that of IIV against seasonal A/H1N1 viruses.[3–5,23] However, during and after 2009, the prepandemic A/H1N1 components in LAIV were replaced with A/H1N1pdm09 hemagglutinin (HA) and neuraminidase proteins. Evidence for LAIV effectiveness against A/H1N1pdm09 viruses is limited to observational studies. During the 2009 pandemic, we reported that the monovalent A/H1N1pdm09 LAIV was effective against medically attended illness (61% VE; 95% CI, 12 to 82); however, delayed delivery of vaccine until the end of the second phase of the pandemic resulted in very small numbers of influenza-positive cases who received LAIV.[9] Other studies have reported significant VE for LAIV against outpatient and inpatient

medically attended H1N1pdm09-related illness among school-aged children in the United States in 2009 to 2010 and 2010 to 2011.[24–26] However, reduced LAIV effectiveness against A/H1N1pdm09 was observed during 2010 to 2011 among adults in the US military.[27] One Canadian study reported effectiveness of trivalent LAIV against influenza A during the 2013–2014 season; however, the study had few participants who received LAIV.[28] Lack of consistent evidence of superior effectiveness of LAIV after 2009 contributed to ACIP's decision for the 2015 to 2016 season not to renew the preferential recommendation for LAIV for children aged 2 to 8 years; both LAIV and IIV are recommended for children aged ≥2 years.[29]

Properties of the LAIV A/H1N1pdm09 viral construct that affected fitness or stability of the vaccine virus may partially explain the inconsistent results. An amino acid sequence was identified in the HA stalk region of wild-type A/California/7/2009 H1N1pdm09 virus that reduced thermal stability of the LAIV vaccine virus containing the A/H1N1pdm09 HA gene.[30,31] This stalk sequence resulted in lower virus infectivity in ferrets and greater susceptibility to degradation at high temperatures.[30] Even small reductions in infectivity may affect VE; 1 randomized placebo-controlled study in children aged 6 to 35 months conducted before 2009 demonstrated that a 1-log difference in potency of LAIV significantly reduced efficacy.[32] Differences in stability or replication of individual LAIV viruses may result in variation in VE against influenza virus types or subtypes. Substitution of the HA gene in the A/H1N1pdm09 construct for the 2015 to 2016 LAIV vaccine has been proposed to improve stability of the LAIV A/H1N1pdm09 virus.[33] Our finding of lower effectiveness of LAIV against A/H1N1pdm09 in 2 seasons suggests that the lower LAIV effectiveness in 2013–2014 may not be associated with the change from trivalent to quadrivalent LAIV. Additionally, immunologic studies in adults that measured hemagglutination inhibition titers after receipt of quadrivalent LAIV containing prepandemic seasonal A/H1N1 (A/South Dakota/6/2007) vaccine virus compared with trivalent LAIV containing 1 type-B vaccine virus observed no interference by the additional strain.[34] Other shedding and immunogenicity studies showed a response to the LAIV A/H1N1pdm09 vaccine virus.[35,36] Future studies of shedding and immunologic response and effectiveness of LAIV against A/H1N1pdm09-like viruses will be needed after changes are made to the A/H1N1pdm09 vaccine virus.

We did not find superior LAIV effectiveness compared with IIV against illness associated with A/H3N2 or influenza B virus infections over several seasons. However, small sample sizes in some groups may have limited our ability to detect small differences in influenza positivity in the 2 vaccine groups. In contrast, 3 randomized studies conducted in children during the 2002 to 2003 and 2003 to 2004 influenza seasons demonstrated superior efficacy of trivalent LAIV over trivalent IIV against illness caused by circulating influenza viruses including seasonal A/H1N1, A/H3N2, and type B viruses.[3–5] Participants enrolled in our study may have differed in important ways from those enrolled in the randomized controlled trials. Relative effectiveness from observational studies provides a direct comparison of vaccines based on the model of comparative efficacy trials (IIV-controlled LAIV trials), but vaccine type is not randomly allocated. Most children and adolescents enrolled at Flu VE Network sites who received either LAIV or IIV were previously vaccinated, whereas trials enrolled young children with limited previous vaccination. Differences between circulating

influenza viruses during the comparative trials and the 4 seasons included in this analysis may also have contributed, although vaccine efficacy was not calculated in the trials. Notably, 1 randomized trial demonstrated higher relative efficacy of LAIV compared with IIV when the A/H3N2 vaccine component was not well matched to circulating A/H3N2 viruses.[3] Although we observed no statistically significant difference in odds of influenza A/H3N2 or B-associated illness, point estimates suggested lower odds of illness among participants aged 2 to 8 years who received LAIV compared with IIV, but sample size was small.

Our study was subject to several limitations. First, observational studies are more prone to bias than randomized studies, and children and adolescents who received LAIV may differ from those who received IIV in ways that were associated with underlying medical conditions, influenza, or probability of enrollment. However, restriction of analyses to those without high-risk health conditions for whom LAIV would be contraindicated and controlling for potential confounders resulted in similar estimates of relative effectiveness. Furthermore, because we restricted the analysis to the vaccinated population, relative effectiveness estimates are less subject than VE estimates to potential bias due to differences in vaccinated and unvaccinated populations. Finally, enrollment of small numbers of vaccinated children and adolescents limited our ability to estimate relative effectiveness precisely, leading to wide confidence intervals.

CONCLUSIONS

We found that lower LAIV effectiveness in 2013 to 2014 was specific to the A/H1N1pdm09 vaccine component and was consistent with a previously unexamined effect during the 2010 to 2011 influenza season. It will be important to monitor influenza type- and subtype-specific relative effectiveness in the future as vaccination uptake increases and vaccine composition changes or new vaccines are introduced. Influenza vaccine effectiveness can vary with changes in vaccine components or circulating influenza viruses and requires ongoing evaluation to inform vaccine recommendations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
CI	confidence interval
Flu VE	US Influenza Vaccine Effectiveness
HA	hemagglutinin
IIV	inactivated influenza vaccine
LAIV	live attenuated influenza vaccine
OR	odds ratio
RT-PCR	reverse transcription polymerase chain reaction
VE	vaccine effectiveness

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WHAT'S KNOWN ON THIS SUBJECT

Before the 2009 influenza A/H1N1 pandemic, several studies demonstrated superior efficacy of live attenuated influenza vaccine (LAIV) over inactivated vaccines for prevention of influenza in young children.

WHAT THIS STUDY ADDS

In this large observational study conducted over 4 influenza seasons, LAIV was less effective than inactivated vaccines for preventing A/H1N1pdm09 influenza among children and adolescents. No difference was observed in vaccine effectiveness against influenza A/H3N2 or B.

Influenza Season	Age Group, y	Vaccine Type	Total	No. (%) Positive	aOR
2010–2011	2–17	LAIV	116	21 (18)	1.49
		IIV	477	66 (14)	REF
	2–8	LAIV	78	14 (18)	1.34
		IIV	296	35 (12)	REF
	9–17	LAIV	38	7 (18)	1.70
		IIV	181	31 (17)	REF
2011–2012	2–17	LAIV	152	12 (8)	0.67
		IIV	499	51 (10)	REF
	2–8	LAIV	96	6 (6)	0.53
		IIV	325	31 (10)	REF
	9–17	LAIV	56	6 (11)	0.86
		IIV	174	20 (11)	REF
2012–2013	2–17	LAIV	205	61 (30)	0.92
		IIV	622	198 (32)	REF
	2–8	LAIV	128	35 (27)	0.74
		IIV	371	110 (30)	REF
	9–17	LAIV	77	26 (34)	1.19
		IIV	251	88 (35)	REF
2013–2014	2–17	LAIV	164	34 (21)	2.88
		IIV	468	36 (8)	REF
	2–8	LAIV	92	22 (24)	5.36
		IIV	305	21 (7)	REF
	9–17	LAIV	72	12 (17)	1.62
		IIV	163	15 (9)	REF

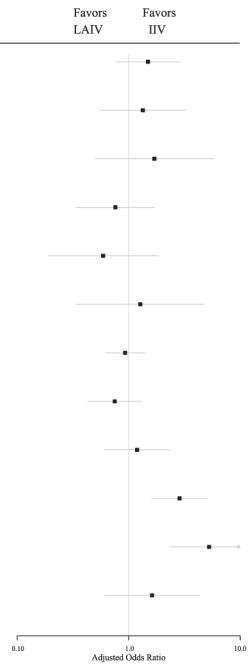

FIGURE 1.

Adjusted odds ratios (aORs) and 95% CIs comparing odds of influenza among LAIV and IIV recipients by influenza season and age group. Adjusted models included age at enrollment (groups for overall estimates or years for age group-specific estimates), gender, study site, race or ethnicity, presence of high-risk health condition, parent- or guardian-rated general health status (not included in 2010–2011 models), interval from onset to enrollment, and calendar time (2-week intervals). REF, reference.

Influenza Type/ Subtype	Influenza Season	Vaccine Type	Total	No. (%) Positive	aOR
A/H1N1pdm09	2010–2011	LAIV	102	7 (9)	5.53
		IIV	420	9 (2)	REF
	2013–2014	LAIV	154	24 (16)	2.65
		IIV	459	27 (6)	REF
	Combined*	LAIV	256	31 (12)	3.08
		IIV	879	36 (4)	REF
A/H3N2	2010–2011	LAIV	103	8 (8)	1.89
		IIV	431	20 (5)	REF
	2011–2012	LAIV	150	10 (7)	0.73
		IIV	490	42 (9)	REF
	2012–2013	LAIV	171	27 (16)	0.77
		IIV	523	99 (19)	REF
	Combined*	LAIV	321	37 (12)	0.69
		IIV	1013	141 (14)	REF
B	2010–2011	LAIV	100	5 (5)	0.46
		IIV	448	37 (8)	REF
	2012–2013	LAIV	174	30 (17)	0.93
		IIV	520	96 (18)	REF

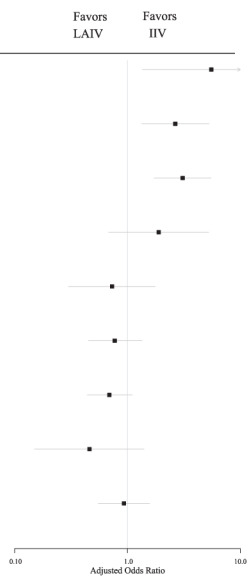

FIGURE 2.

Adjusted odds ratios (aORs) and 95% CIs comparing odds of influenza among LAIV and IIV recipients by influenza type or subtype and season. Adjusted models included age at enrollment (groups), gender, study site, race or ethnicity, presence of high-risk health condition, parent- or guardian-rated general health status (not included in 2010–2011 models), interval from onset to enrollment, season (for combined estimates), and calendar time (2-week intervals defined by season). Estimates were not calculated when the total number of vaccinated cases for the season was <15. *Influenza A/H1N1pdm09 combined estimate includes data from 2010–2011 and 2013–2014. Influenza A/H3N2 combined estimate includes data from 2011–2012 and 2012–2013. REF, reference.

TABLE 1

Number of Subjects Enrolled and Reasons for Exclusion From VE Analyses by Season

	2010–2011[a]	2011–2012	2012–2013	2013–2014
All enrolled outpatients aged 2–17 y	1781	1940	2376	1621
Reason for exclusion				
Unknown vaccine type	32	48	3	1
Partially vaccinated	202	109	115	62
Onset date outside period of influenza circulation	102	41	8	20
Indeterminate vaccination status[b]	21	16	32	25
Enrolled >7 d after illness onset date	15	10	0	1
Inconclusive RT-PCR result	2	0	2	5
Received LAIV and IIV within season	21	2	3	1
Included in VE analysis	1386	1714	2213	1506
Included in relative effectiveness analysis[c]	593	651	827	632

[a] 311 enrollees aged 2–17 y were excluded because of enrollment in an inpatient setting.

[b] Includes those vaccinated <14 d before illness onset and those who received a second dose of vaccine <28 d after the first dose.

[c] Relative effectiveness analyses exclude unvaccinated participants.

TABLE 2

Influenza RT-PCR Results Among Participants Aged 2–17 y by Influenza Season

Season	Total Participants	Test-Negative Controls	Influenza-Positive Cases[a]				
			Any Influenza Positive	A/H3N2 (%)[b]	A/H1N1pdm09 (%)[b]	B/Yamagata (%)[b]	B/Victoria (%)[b]
2010–2011[c]	1386	1050	336	114 (33.9)	70 (20.8)	151 (44.9)	
2011–2012[d]	1714	1438	276	197 (71.4)	28 (10.1)	23 (8.3)	26 (9.4)
2012–2013[e]	2213	1293	920	393 (42.7)	12 (1.3)	307 (33.4)	178 (19.3)
2013–2014[f]	1506	1250	256	25 (9.8)	206 (80.5)	14 (5.5)	3 (1.2)

[a] Includes participants with coinfections; the sum of influenza subtypes may be greater than the number positive for any influenza.

[b] Data are presented as the percentage of all influenza-positive cases.

[c] In 2010–2011, there was 1 influenza A and influenza B coinfection. One influenza A–positive specimen was unsubtypable. Influenza B lineage was not determined.

[d] In 2011–2012, there were 2 influenza B–positive specimens of undetermined lineage.

[e] In 2012–2013, there were 5 influenza A and influenza B coinfections and 2 B/Yamagata and B/Victoria coinfections. Influenza A subtype was not determined for 11 specimens. Influenza B lineage was not determined for 26 specimens.

[f] In 2013–2014, 8 influenza A–positive specimens were unsubtypable.

TABLE 3

Descriptive Characteristics of Participants Aged 2–17 y With Medically Attended Acute Respiratory Infections by Type of Vaccine Received

	IIV[a]	LAIV[b]	P[c]
All, no. (%)[d,e]	2066	637	
Age at enrollment, y			<.001
2–4	827 (40.0)	165 (25.9)	
5–8	470 (22.7)	229 (36.0)	
9–17	769 (37.2)	243 (38.2)	
Female	980 (47.4)	321 (50.4)	.19
Race or ethnicity[f]			.026
White, non-Hispanic	1417 (69.2)	453 (71.7)	
Black, non-Hispanic	154 (7.5)	29 (4.6)	
Other race, non-Hispanic	233 (11.3)	62 (9.8)	
Hispanic, any race	242 (11.7)	88 (13.9)	
High-risk health condition present[g]	653 (31.6)	62 (9.7)	<.001
Vaccinated in previous season[h]	1582 (76.6)	503 (79)	.21
Parent- or guardian-rated general health status[i]			<.001
Good, fair, poor	275 (17.3)	47 (9.0)	
Excellent, very good	1314 (82.7)	474 (91.0)	
Fever or feverishness reported[j]	1367/1830 (74.7)	411/565 (72.7)	.35
Interval between symptom onset and enrollment, d			.69
≤2	883 (42.7)	285 (44.7)	
3–4	769 (37.2)	229 (36.0)	
5–7	414 (20.0)	123 (19.3)	
RT-PCR result			.081
Influenza negative	1715 (82.9)	509 (79.9)	
Influenza positive	351 (17.0)	128 (20.1)	
Influenza season			.043
2010–2011	477 (23.1)	116 (18.2)	
2011–2012	499 (24.1)	152 (23.9)	
2012–2013	622 (30.1)	205 (32.2)	
2013–2014	468 (22.6)	164 (25.8)	
Network site[k]			<.001
Michigan	515 (24.9)	87 (13.7)	
New York	33 (1.6)	24 (3.8)	
Pennsylvania	172 (8.3)	89 (14.0)	
Tennessee	82 (4.0)	26 (4.1)	
Texas	221 (10.7)	116 (18.2)	
Washington	260 (12.6)	91 (14.3)	
Wisconsin	783 (37.9)	204 (32.0)	

[a] In 2010–2011 through 2012–2013, inactivated vaccines were all IIV3 standard dose delivered intramuscularly. In 2013–2014, the IIV group was 81% intramuscular IIV3 standard dose, 18% intramuscular IIV4 standard dose, and 1% shot of unknown type.

[b] In the first 3 seasons included, all LAIV was trivalent. In 2013–2014, the vaccine was a quadrivalent formula.

[c] *P* value for the χ^2 test of difference between IIV and LAIV recipients.

[d] Data are presented as No. (column %).

[e] Those vaccinated after illness onset are considered unvaccinated (84 participants in 2010–2011, 41 participants in 2011–2012, 134 in 2012–2013, and 70 in 2013–2014).

[f] Race or ethnicity was missing for 25 vaccinated participants.

[g] Presence of a high-risk health condition is defined as the presence of ≥1 medical record–documented high-risk code in the year before enrollment, as defined by the ACIP guidance for conditions that increase risk for complications from influenza.[1]

[h] Previous vaccination in 2010–2011 does not include monovalent pandemic influenza vaccine.

[i] Parent- or guardian-rated general health status was not collected in the 2010–2011 season.

[j] Data from all sites in 2010–2011, 2011–2012, and 2012–2013 and from 2 sites (Wisconsin and Pennsylvania) in 2013–2014.

[k] Wisconsin and Michigan contributed to all seasons, Washington, Pennsylvania, and Texas contributed to 2011–2011 through 2013–2014, and New York and Tennessee contributed to the 2010–2011 season.