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Association of Prior Vaccination With Influenza Vaccine Effectiveness in Children Receiving Live Attenuated or Inactivated Vaccine

Huong Q. McLean, PhD, MPH; Herve Caspard, MD, ScD; Marie R. Griffin, MD, MPH; Manjusha Gaglani, MD; Timothy R. Peters, MD; Katherine A. Poehling, MD, MPH; Christopher S. Ambrose, MD, MBA; Edward A. Belongia, MD

Abstract

IMPORTANCE Some studies have reported negative effects of prior-season influenza vaccination. Prior-season influenza vaccination effects on vaccine effectiveness (VE) in children are not well understood.

OBJECTIVE To assess the association of prior-season influenza vaccination with subsequent VE in children aged 2 to 17 years.

DESIGN, SETTING, AND PARTICIPANTS This multiseason, test-negative case-control study was conducted in outpatient clinics at 4 US sites among children aged 2 to 17 years with a medically attended febrile acute respiratory illness. Participants were recruited during the 2013-2014, 2014-2015, and 2015-2016 seasons when influenza circulated locally. Cases were children with influenza confirmed by reverse-transcription polymerase chain reaction. Test-negative control individuals were children with negative test results for influenza.

EXPOSURES Vaccination history, including influenza vaccine type received in the enrollment season (live attenuated influenza vaccine [LAIV], inactivated influenza vaccine [IIV], or no vaccine) and season before enrollment (LAIV, IIV, or no vaccine), determined from medical records and immunization registries.

MAIN OUTCOMES AND MEASURES LAIV and IIV effectiveness by influenza type and subtype (influenza A[H1N1]pdm09, influenza A[H3N2], or influenza B), estimated as 100 × (1 − odds ratio) in a logistic regression model with adjustment for potential confounders. Prior season vaccination associations were assessed with an interaction term.

RESULTS Of 3369 children (1749 [52%] male; median age, 6.6 years [range, 2-17 years]) included in the analysis, 772 (23%) had a positive test result for influenza and 1674 (50%) were vaccinated in the enrollment season. Among LAIV recipients, VE against influenza A(H3N2) was higher among children vaccinated in both the enrollment and 1 prior season (50.3% [95% CI, 17.0% to 70.2%]) than among those without 1 prior season vaccination (−82.4% [95% CI, −267.5% to 9.5%], interaction $P < .001$). The effectiveness of LAIV against influenza A(H1N1)pdm09 was not associated with prior season vaccination among those with prior season vaccination (47.5% [95% CI, 11.4% to 68.9%]) and among those without prior season vaccination (7.8% [95% CI, −101.9% to 57.9%]) (interaction $P = .37$). Prior season vaccination was not associated with effectiveness of IIV against influenza A(H3N2) (38.7% [95% CI, 6.8% to 59.6%] among those with prior-season vaccination and 23.2% [95% CI, −38.3% to 57.4%] among those without prior-season vaccination, interaction $P = .16$) or with effectiveness of IIV against influenza A[H1N1]pdm09 (72.4% [95% CI, 56.0% to 82.7%] among

(continued)

Key Points

Question Is prior-season vaccination associated with vaccine effectiveness by type in children aged 2 to 17 years?

Findings In this multiseason, test-negative case-control study, live attenuated influenza vaccine effectiveness was higher in children vaccinated in both the enrollment and prior season compared with those vaccinated only in the enrollment season. Prior-season vaccination was not associated with either inactivated or live attenuated vaccine effectiveness against influenza A(H1N1)pdm09, although there was evidence of residual protection with prior-season vaccination only against influenza B.

Meaning Prior-season vaccination history was not associated with reduced vaccine effectiveness in children, supporting current recommendations for annual influenza vaccination of children.

+ Invited Commentary

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

those with prior season vaccination and 67.5% [95% CI, 32.1% to 84.4%] among those without prior season vaccination, interaction $P = .93$). Residual protection from prior season vaccination only (no vaccination in the enrollment season) was observed for influenza B (LAIV: 60.0% [95% CI, 36.8% to 74.7%]; IIV: 60.0% [36.9% to 74.6%]). Similar results were observed in analyses that included repeated vaccination in 2 and 3 prior seasons.

CONCLUSIONS AND RELEVANCE Influenza VE varied by influenza type and subtype and vaccine type, but prior-season vaccination was not associated with reduced VE. These findings support current recommendations for annual influenza vaccination of children.

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Introduction

The effect of prior influenza vaccination on influenza vaccine effectiveness (VE) has become an area of great interest given expanded recommendations for annual vaccination.[1] An increasing number of influenza VE studies have assessed the association of prior vaccination with vaccine effectiveness in recent years. Data are variable across seasons and across studies during the same seasons, making interpretation of findings challenging.[2,3] Although these studies included children, few studies have specifically assessed prior vaccination in children or have examined the effect of vaccinations received in the prior 2 or 3 seasons.[4-11] Furthermore, little is known about prior vaccination effects in children who receive live attenuated influenza vaccine (LAIV). The mechanism of protection varies by vaccine type and age of the child,[12-15] which may also contribute to the varying effects of prior vaccination.

We conducted a post hoc analysis of data from a VE study conducted over 3 seasons to assess the association of prior-season vaccination with VE and the risk of influenza among vaccinated children aged 2 to 17 years by vaccine type received.

Methods

Study Population and Enrollment

From 2013-2014 through 2015-2016, an observational study was performed using the test-negative design to estimate the seasonal effectiveness of quadrivalent LAIV in children.[5,6,16] The test-negative design has been shown to yield a valid estimate of VE in most scenarios.[17,18] The present study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline, where applicable. The study was reviewed and approved by the institutional review boards at all participating sites: Baylor Scott & White Health (Temple, Texas), Marshfield Clinic Research Institute (Marshfield, Wisconsin), Vanderbilt University Medical Center (Nashville, Tennessee), and Wake Forest School of Medicine (Winston-Salem, North Carolina). Written informed consent was obtained from parents or guardians of all participants; when age-appropriate, assent was obtained from children before enrollment.

Community-dwelling children aged 2 to 17 years who sought outpatient medical care for acute respiratory illness with fever (oral temperature ≥100.0°F at study visit, history of fever reported by parent, or use of antipyretic medication before study visit), with symptom duration of less than 5 days, and without receipt of antiviral medication before enrollment were eligible for study participation each influenza season when influenza circulated locally. Study recruitment occurred at 4 sites across the United States during 2013-2014 and 2014-2015 and at 8 sites (4 previous and 4 additional sites) during 2015-2016. However, because few children were enrolled in the 4 additional sites during 2015-2016 (n = 87) and for consistency in sites across seasons, the analysis was restricted to children enrolled at the 4 sites that recruited children in each of the 3 seasons.

Parents or guardians completed a standardized enrollment survey to ascertain their child's demographic and medical history. A nasal swab sample was collected and tested for influenza using a multiplex reverse-transcription polymerase chain reaction (RT-PCR) assay (eSensor, GenMark Diagnostics).[5,6,16] An influenza case was defined as medically attended febrile acute respiratory illness with laboratory-confirmed influenza by RT-PCR. Control individuals were enrolled children with medically attended febrile acute respiratory illness who tested negative for influenza.

Vaccination History

Influenza vaccination dates and vaccine types were obtained for each participant from 2010-2011 through their enrollment season from medical records or immunization registries. The components included in the vaccine each season are shown in eTable 1 in the Supplement. Vaccination status and vaccine type received were determined for the enrollment season and 1, 2, and 3 prior seasons. During the enrollment season, children were considered to be vaccinated if they had received 1 dose of seasonal vaccine 14 days or more before illness onset. The few children (n = 18) who received 2 doses during their enrollment season were excluded. Prior season vaccination status was determined based on vaccine received during August through July of the season before enrollment. For those eligible for vaccination in the 2 and 3 prior seasons to enrollment, vaccination history was categorized based on the number of influenza seasons in which the child received 1 or more doses of influenza vaccine in the prior 2 seasons (grouped as 0, 1, and 2) and 3 seasons (grouped as 0, 1-2, and 3). For those previously vaccinated, vaccine type received in the 2 and 3 prior seasons was categorized as LAIV only, inactivated influenza vaccine (IIV) only, LAIV and IIV (among those vaccinated in ≥2 seasons), and unknown type. Children with unknown vaccine type in the enrollment season were excluded from all models (n = 2), and children with unknown vaccine type in a prior season were excluded from models assessing vaccine type received in prior seasons (n = 21).

Statistical Analysis

Exclusion criteria for analyses were similar to those previously described[5,6,16]: enrollment outside the period when cases were identified at each site (n = 344), receipt of vaccine less than 14 days before illness onset (n = 43), and conflicting or missing information on vaccination during the enrollment season (including vaccine type, n = 92). In addition, influenza A infection with unknown subtype (n = 1) was excluded because analyses were subtype specific. Statistical analyses were conducted using SAS statistical software, version 9.4 (SAS Institute Inc). A 2-sided *P* value less than .05 was considered statistically significant.

Estimation of Vaccine Effectiveness

To assess the association of prior-season vaccination with VE during the enrollment season, a multivariable logistic regression model was used that included exposure variables for vaccination during the enrollment and prior seasons and an interaction term for vaccination during the enrollment and prior seasons. The effectiveness of LAIV and IIV during the enrollment season were modeled separately but used the same reference group (ie, children who were unvaccinated in both the enrollment and the prior seasons). With use of this model, the vaccine exposure groups, irrespective of vaccine type, were (1) vaccinated in the enrollment season and 1 prior season, (2) vaccinated in the enrollment season only, and (3) vaccinated in the 1 prior season only. Where data permitted, VE was estimated for vaccine type received in the enrollment and 1 prior season.

To assess the association of vaccination received in the 2 and 3 prior seasons with subsequent VE, similar logistic regression models were used that included exposure variables for enrollment season vaccination and 2 or 3 prior season vaccination history and an interaction term for enrollment season and 2 or 3 prior season vaccination history (eTable 2 in the Supplement). The analysis for the 2 prior seasons was restricted to children 30 months or older as of September 1 of the enrollment season because these children were eligible for vaccination (ie, aged ≥6 months) during the entire

2-year period before enrollment. For the same reason, the 3 prior seasons analysis was restricted to children 42 months or older as of September 1 of the enrollment season.

Odds ratios (ORs) comparing vaccinated and unvaccinated children were obtained from the models, and VE was estimated as 100% × (1 − OR). Age (2-4, 5-8, and 9-17 years), site, and season (for models including >1 season) were included in all multivariable models a priori. Other potential confounders, including sex, race/ethnicity (as reported by the child's parents), insurance status (private, public, or other), high-risk conditions, calendar time (measured relative to the peak 4 weeks each season), and number of outpatient visits in the past 6 months (0, 1, or ≥2 visits), were assessed and included in multivariable models if inclusion resulted in more than 10% change in the OR estimate for any of the vaccine exposure categories.

Separate estimates were generated for influenza A(H1N1)pdm09, influenza A(H3N2), influenza B, and each B lineage for each season (if data permitted) and for all seasons combined. For each type and subtype estimate, only seasons with more than 30 cases identified in the study population were included in the all-season estimate. Data from all 3 seasons were used for the influenza B and influenza B/Yamagata lineage estimates, data from the 2013-2014 and 2015-2016 seasons were used for influenza A(H1N1)pdm09, and data from the 2014-2015 and 2015-2016 seasons were used for influenza B/Victoria lineage estimates. Influenza A(H3N2) estimates were reported only for the 2014-2015 season because few influenza A(H3N2) cases (n = 7) were detected during 2013-2014 and 2015-2016.

Risk of Vaccine Failure Among Vaccinated Children

Similar multivariable methods as described above were performed to determine whether prior season vaccination was associated with influenza vaccine failure, except analyses were restricted to children who received vaccine during the enrollment season. The odds of influenza were calculated among vaccinated children who received vaccine (and LAIV or IIV) in a prior season (1, 2, or 3) compared with those who did not receive any vaccine in a prior season (1, 2, or 3).

Results

A total of 3369 children (1749 [52%] male; median age, 6.6 years [range, 2-17 years]) enrolled across 3 influenza seasons were included in the analysis: 970 (29%) were enrolled during 2013-2014, 1509 (45%) during 2014-2015, and 890 (26%) during 2015-2016. In 2013-2014 and 2015-2016, influenza A(H1N1)pdm09 co-circulated with influenza B; in 2014-2015, influenza A(H3N2) co-circulated with influenza B. In the enrollment season, half of the children were unvaccinated, 34% received IIV, and 15% received LAIV. A total of 772 (23%) had a positive test result for influenza. Characteristics of children by vaccination status are shown in **Table 1**. Among 1674 vaccinated children (50%), those who received LAIV were more likely to have private insurance (67% who received LAIV [349 of 522 children] vs 55% who received IIV [630 of 1152 children]) and less likely to have a high-risk condition (6% who received LAIV [32 of 522 children] vs 31% who received IIV [354 of 1152 children]). Prior-season vaccination was associated with vaccination status in the enrollment season (**Table 2**). Children who were vaccinated in the enrollment season were more likely to have been vaccinated in prior seasons (vaccinated: 75% in 1 prior season [1255 of 1674 children], 86% in 2 prior seasons [1224 of 1420 children], and 90% in 3 prior seasons [1106 of 1229 children] vs unvaccinated: 34% in 1 prior season [580 of 1695 children], 51% in 2 prior seasons [793 of 1563 children], and 59% in 3 prior seasons [838 of 1409 children]). LAIV recipients were more likely to have received LAIV in prior seasons (249 of 398 [63%], 299 of 424 [71%], and 289 of 390 [74%] of those vaccinated in the 1, 2, and 3 prior seasons received LAIV, respectively), whereas IIV recipients were more likely to have received IIV (747 of 857 [87%], 701 of 800 [88%], and 647 of 716 [90%] of those vaccinated in the 1, 2, and 3 prior seasons received IIV, respectively). Few vaccinated children younger than 9 years had not received 1 prior season influenza vaccination since the 2010-2011 season (6% of LAIV recipients [24 of 384 children] and 6% of IIV recipients [51 of 820 children]).

Table 1. Characteristics of Children Aged 2 to 17 Years With a Medically Attended Febrile Acute Respiratory Illness by Enrollment Season, 1 Prior Season Influenza Vaccination Status, and VaccineType

Characteristic	Enrollment Season Vaccination Type, No. (%)					
	LAIV		IIV		Not Vaccinated	
	Prior Vaccination (n = 398)	No Prior Vaccination (n = 124)	Prior Vaccination (n = 857)	No Prior Vaccination (n = 295)	Prior Vaccination (n = 580)	No Prior Vaccination (n = 1115)
1 Prior season vaccine type						
LAIV	249 (63)	NA	101 (12)	NA	164 (28)	NA
IIV	146 (37)	NA	747 (87)	NA	407 (70)	NA
Unknown	3 (1)	NA	9 (1)	NA	9 (2)	NA
Age, y						
2-4	148 (37)	33 (27)	395 (46)	75 (25)	226 (39)	246 (22)
5-8	161 (40)	42 (34)	256 (30)	94 (32)	189 (33)	403 (36)
9-17	89 (22)	49 (40)	206 (24)	126 (43)	165 (28)	466 (42)
Sex						
Male	196 (49)	60 (48)	479 (56)	150 (51)	300 (52)	564 (51)
Female	202 (51)	64 (52)	378 (44)	145 (49)	280 (48)	551 (49)
Race/ethnicity[a]						
White	300 (75)	75 (60)	565 (66)	166 (56)	336 (58)	661 (59)
Black	33 (8)	17 (14)	103 (12)	45 (15)	91 (16)	187 (17)
Hispanic	45 (11)	26 (21)	128 (15)	60 (20)	108 (19)	196 (18)
Other	20 (5)	6 (5)	61 (7)	24 (8)	44 (8)	71 (6)
Children in household aged <12 y[a]						
<2	287 (72)	81 (65)	557 (65)	177 (60)	372 (64)	635 (57)
≥2	111 (28)	43 (35)	300 (35)	118 (40)	208 (36)	478 (43)
Outpatient visits in past 6 mo						
0	78 (20)	22 (18)	127 (15)	59 (20)	163 (28)	375 (34)
1	137 (34)	29 (23)	218 (25)	72 (24)	170 (29)	294 (26)
≥2	183 (46)	73 (59)	512 (60)	164 (56)	247 (43)	446 (40)
Insurance						
Public	118 (30)	55 (43)	379 (44)	140 (48)	311 (54)	539 (48)
Private	280 (70)	69 (57)	477 (56)	153 (52)	261 (45)	552 (50)
Neither	0	0	1 (0.1)	2 (0.7)	8 (2)	24 (2)
Interval from symptom onset to enrollment, d						
<2	177 (44)	46 (37)	344 (38)	112 (38)	227 (39)	401 (36)
≥2	221 (56)	78 (63)	513 (62)	183 (62)	353 (61)	714 (64)
Exposure to smoking inside home[a]						
No	368 (92)	100 (81)	781 (91)	250 (86)	498 (86)	947 (85)
Yes	30 (8)	24 (19)	76 (9)	42 (14)	80 (14)	167 (15)
History of ≥2 episodes of wheezing[a]						
No	372 (94)	111 (91)	682 (80)	227 (77)	476 (83)	952 (86)
Yes	25 (6)	11 (9)	169 (20)	66 (23)	98 (17)	161 (14)
High-risk health condition						
No	377 (95)	113 (91)	605 (71)	193 (65)	472 (81)	937 (84)
Yes	21 (5)	11 (9)	252 (29)	102 (35)	108 (19)	178 (16)
Enrollment season						
2013-2014	167 (42)	48 (39)	262 (31)	90 (31)	144 (25)	259 (23)
2014-2015	172 (43)	52 (42)	377 (44)	129 (44)	286 (49)	493 (44)
2015-2016	59 (15)	24 (19)	218 (25)	76 (26)	150 (26)	363 (33)
Influenza period						
Before peak	38 (10)	20 (16)	98 (11)	34 (12)	93 (16)	194 (17)
Peak 4 wk	127 (32)	27 (22)	237 (28)	69 (23)	201 (35)	374 (34)
After peak	233 (59)	77 (62)	522 (61)	192 (65)	286 (49)	547 (49)

(continued)

Table 1. Characteristics of Children Aged 2 to 17 Years With a Medically Attended Febrile Acute Respiratory Illness by Enrollment Season, 1 Prior Season Influenza Vaccination Status, and VaccineType (continued)

Characteristic	Enrollment Season Vaccination Type, No. (%)					
	LAIV		IIV		Not Vaccinated	
	Prior Vaccination (n = 398)	No Prior Vaccination (n = 124)	Prior Vaccination (n = 857)	No Prior Vaccination (n = 295)	Prior Vaccination (n = 580)	No Prior Vaccination (n = 1115)
Site						
A	99 (25)	26 (21)	322 (38)	88 (30)	189 (33)	410 (37)
B	86 (22)	46 (37)	231 (27)	109 (36)	190 (33)	377 (34)
C	125 (31)	27 (22)	194 (23)	52 (17)	113 (19)	118 (11)
D	88 (22)	25 (20)	110 (13)	46 (16)	88 (15)	210 (19)

Abbreviations: IIV, inactivated influenza vaccine; LAIV, live attenuated influenza vaccine; NA, not applicable.

[a] Percentages are among those without missing data.

Table 2. Children Aged 2 to 17 Years With a Medically Attended Febrile Acute Respiratory Illness by Enrollment Season, 2 or 3 Seasons Vaccination History, and Vaccine Type Received

Variable	Enrollment Season Vaccination Type								
	LAIV			IIV			Not Vaccinated		
2 Prior Seasons Vaccination									
No. of prior seasons vaccinated[a]	0	1	2	0	1	2	0	1	2
Children, No.	57	113	311	139	258	542	770	482	311
Vaccine type, No. (%)									
LAIV	NA	65 (58)	132 (42)	NA	47 (18)	32 (6)	NA	154 (32)	48 (15)
IIV	NA	47 (41)	72 (23)	NA	202 (78)	421 (78)	NA	324 (67)	191 (61)
LAIV and IIV	NA	NA	102 (33)	NA	NA	78 (14)	NA	NA	66 (21)
≥1 Unknown	NA	1 (1)	5 (2)	NA	9 (3)	11 (2)	NA	4 (1)	6 (2)
3 Prior Seasons Vaccination									
No. of prior seasons vaccinated[b]	0	1-2	3	0	1-2	3	0	1-2	3
Children, No.	38	171	219	85	344	372	571	669	169
Vaccine type, No. (%)									
LAIV	NA	81 (47)	49 (22)	NA	35 (10)	13 (3)	NA	180 (27)	22 (13)
IIV	NA	58 (34)	35 (16)	NA	259 (75)	253 (68)	NA	416 (62)	80 (47)
LAIV and IIV	NA	30 (18)	129 (59)	NA	38 (11)	97 (26)	NA	65 (10)	57 (34)
≥1 Unknown	NA	2 (1)	6 (3)	NA	12 (3)	9 (2)	NA	8 (1)	10 (6)

Abbreviations: IIV, inactivated influenza vaccine; LAIV, live attenuated influenza vaccine; NA, not applicable.

[a] Among children 2.5 years or older as of September 1 of their enrollment season.

[b] Among children aged 3.5 years or older as of September 1 of their enrollment season.

Vaccine Effectiveness

Influenza A(H1N1)pdm09 Strains

The VE against influenza A(H1N1)pdm09 was 60% or more for IIV recipients for all prior vaccination histories examined, with no significant differences by number of seasons vaccinated or type of vaccine received in prior seasons (**Figure 1** and **Figure 2**; eTables 3 and 4 in the Supplement). Effectiveness of IIV was 72.4% (95% CI, 56.0% to 82.7%) among those with prior season vaccination and 67.5% (95% CI, 32.1% to 84.4%) among those without prior season vaccination (interaction $P = .93$). The effectiveness of LAIV against influenza A(H1N1)pdm09 was not associated with prior season vaccination (47.5% [95% CI, 11.4% to 68.9%]) or among those without prior season vaccination (7.8% [95% CI, −101.9% to 57.9%]) (interaction $P = .37$). Recipients of LAIV in the enrollment season who were vaccinated in each of the 2 or 3 prior seasons had VE estimates of 57.0% (95% CI, 20.4% to 76.7%) and 62.5% (95% CI, 18.2% to 82.8%), respectively. The VE estimates for all other groups were lower. Specifically, VE for LAIV recipients who received IIV in the 1 prior season was 68.0% (95% CI, 19.2% to 87.3%). For those who had received LAIV in the 1 prior season, it was

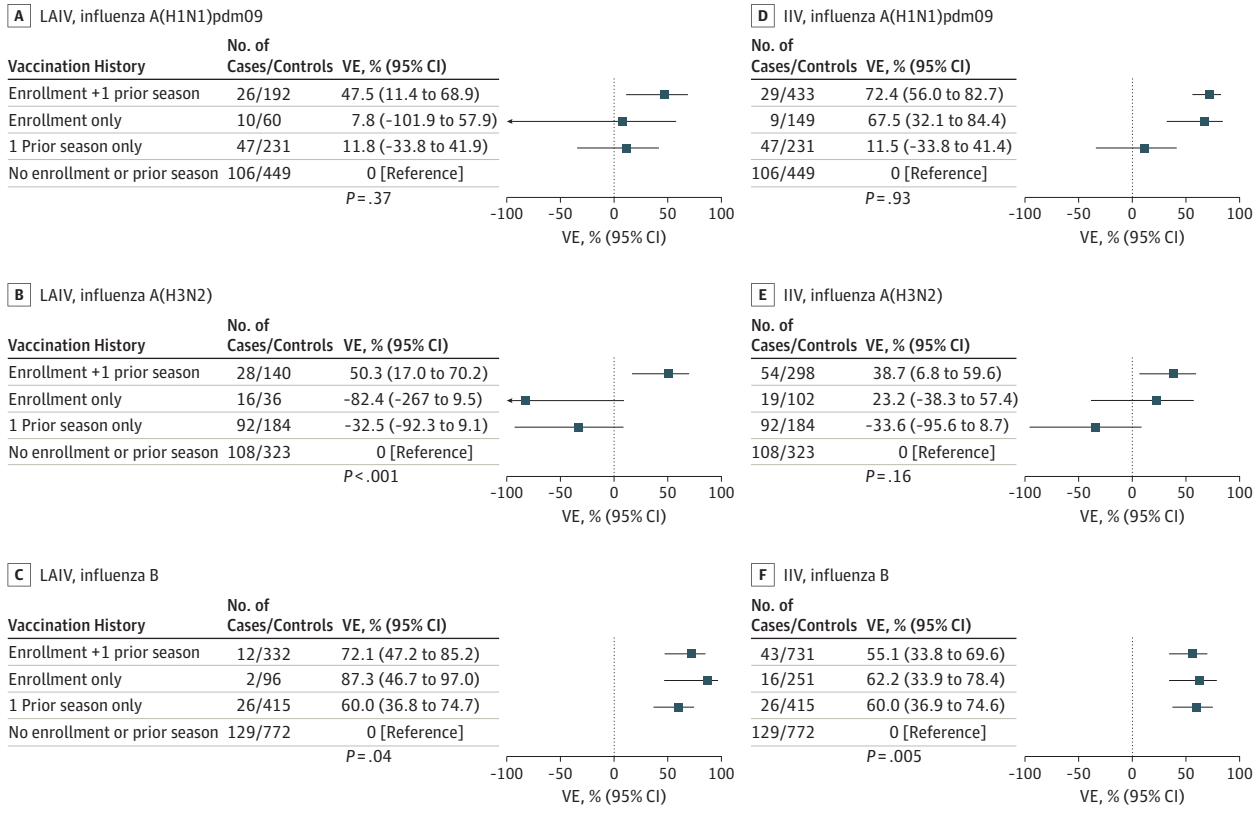
34.5% (95% CI, −17.1% to 63.3%). Residual protection from vaccination in prior seasons only (with no vaccination in the enrollment season) was not observed against A(H1N1)pdm09.

Influenza A(H3N2) Strains

The VE against influenza A(H3N2) did not differ by prior 1-, 2-, or 3-season vaccination history or prior vaccine type for IIV recipients in the enrollment season (Figure 1 and Figure 2; eTables 3 and 4 in the Supplement). Among IIV recipients, VE was 38.7% (95% CI, 6.8% to 59.6%) for those vaccinated in the 1 prior season and 23.2% (95% CI, −38.3% to 57.4%) for those unvaccinated in the 1 prior season (interaction $P = .16$). The VE for recipients who received IIV in the 1 prior season was 39.8% (95% CI, 7.2% to 61.0%) and 20.6% (95% CI, −11.5% to 70.7%) for children who received LAIV in the 1 prior season (interaction $P = .37$)

For LAIV recipients in the enrollment season, VE against influenza A(H3N2) differed by prior season vaccination status. For LAIV recipients in the enrollment season, VE was 50.3% (95% CI, 17.0% to 70.2%) for those vaccinated in the 1 prior season and −82.4% (95% CI, −267.5% to 9.5%) for those unvaccinated in the 1 prior season (interaction $P < .001$). The VE also differed by vaccine type received in the 1 prior season. Recipients of LAIV in the enrollment season who received IIV in the 1 prior season had higher VE compared with those who received LAIV in the 1 prior season (64.7% for LAIV in the enrollment season and IIV in the 1 prior season vs 39.8% for LAIV in the enrollment season and LAIV in the 1 prior season; interaction $P = .001$). Similar results were observed for the 2 and 3 prior seasons vaccination histories, although interaction terms were not significant. No residual

Figure 1. Vaccine Effectiveness (VE) by Enrollment and 1 Prior Season Vaccination History for Live Attenuated Influenza Vaccine (LAIV) and Inactivated Influenza Vaccine (IIV)



A-C, The LAIV effectiveness estimates were obtained from logistic regression models adjusted for age, site, and peak influenza period. The LAIV models for influenza A(H1N1)pdm09 and influenza B also included season and number of outpatient visits in the past year. D-F, The IIV effectiveness estimates were obtained from logistic regression models adjusted for age, site, peak influenza period, and number of outpatient visits in the past year. The IIV models for influenza A(H1N1)pdm09 and influenza B also included season. *P* value is for interaction term for enrollment season vaccination × prior season vaccination.

protection from vaccination in the 1, 2, and 3 prior seasons (with no vaccination in the enrollment season) was observed against influenza A(H3N2).

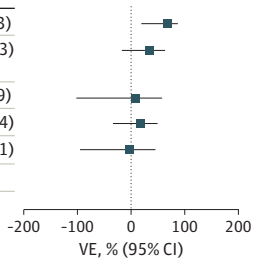
Influenza B Strains

The VE against influenza B was modified by prior vaccination history for both IIV and LAIV recipients in the enrollment season (Figure 1 and Figure 2; eTables 3 and 4 in the Supplement). The VE estimates were high (>50%) among children vaccinated in the enrollment season for all prior season vaccination histories, and residual protection was observed from vaccination received only in the 1, 2, or 3 prior seasons (with no vaccination in the enrollment season) regardless of vaccine type. Similar results were seen by lineage where VE estimates were available.

Figure 2. Vaccine Effectiveness (VE) of Various Types of Influenza Vaccine Received in the Enrollment Season and 1 Prior Season for Live Attenuated Influenza Vaccine (LAIV) and Inactivated Influenza Vaccine (IIV)

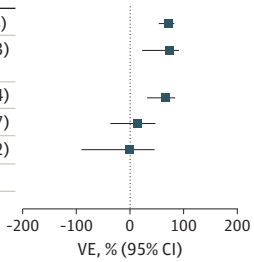
A LAIV, influenza A(H1N1)pdm09

Vaccination History	No. of Cases/Controls	VE, % (95% CI)
Enrollment +1 prior season (IIV)	6/74	68.0 (19.2 to 87.3)
Enrollment +1 prior season (LAIV)	20/116	34.5 (-17.1 to 63.3)
Enrollment only	10/60	7.9 (-102 to 57.9)
1 Prior season only (IIV)	31/157	17.8 (-33.5 to 49.4)
1 Prior season only (LAIV)	16/70	-3.7 (-95.9 to 45.1)
No enrollment or prior season	106/449	0 [Reference]
		P = .39



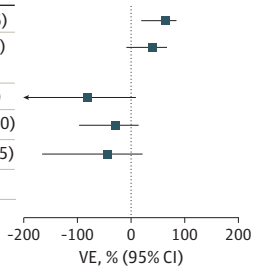
D IIV, influenza A(H1N1)pdm09

No. of Cases/Controls	VE, % (95% CI)
25/374	71.9 (53.9 to 82.8)
4/54	74.0 (22.3 to 91.3)
9/149	67.5 (32.0 to 84.4)
31/157	15.4 (-36.7 to 47.7)
16/70	-1.3 (-90.5 to 46.2)
106/449	0 [Reference]
	P = .93



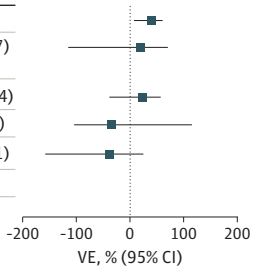
B LAIV, influenza A(H3N2)

Vaccination History	No. of Cases/Controls	VE, % (95% CI)
Enrollment +1 prior season (IIV)	8/56	64.7 (18.9 to 84.6)
Enrollment +1 prior season (LAIV)	20/83	39.8 (-9.3 to 66.8)
Enrollment only	16/36	-81.8 (-266 to 9.7)
1 Prior season only (IIV)	68/132	-30.1 (-96.9 to 14.0)
1 Prior season only (LAIV)	24/48	-44.5 (-166 to 21.5)
No enrollment or prior season	108/323	0 [Reference]
		P = .001



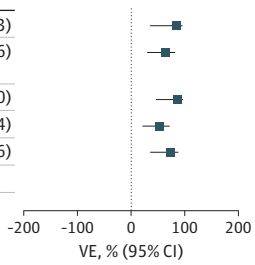
E IIV, influenza A(H3N2)

No. of Cases/Controls	VE, % (95% CI)
48/264	39.8 (7.2 to 61.0)
6/30	20.6 (-115 to 70.7)
19/102	23.2 (-38.3 to 57.4)
68/132	-34.3 (-104 to 116)
24/48	-38.9 (-158 to 25.1)
108/323	0 [Reference]
	P = .37



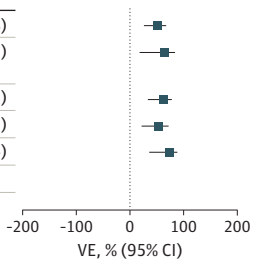
C LAIV, influenza B

Vaccination History	No. of Cases/Controls	VE, % (95% CI)
Enrollment +1 prior season (IIV)	2/130	84.7 (35.7 to 96.3)
Enrollment +1 prior season (LAIV)	10/199	65.0 (29.9 to 82.6)
Enrollment only	2/96	87.4 (46.7 to 97.0)
1 Prior season only (IIV)	19/289	53.4 (21.5 to 72.4)
1 Prior season only (LAIV)	6/118	73.0 (35.8 to 88.6)
No enrollment or prior season	129/772	0 [Reference]
		P = .03



F IIV, influenza B

No. of Cases/Controls	VE, % (95% CI)
36/638	51.2 (26.1 to 67.8)
7/84	64.0 (18.0 to 84.2)
16/251	62.0 (33.5 to 78.3)
19/289	53.4 (21.7 to 72.3)
6/118	73.0 (36.1 to 88.6)
129/772	0 [Reference]
	P = .02



A-C, The LAIV effectiveness estimates were obtained from logistic regression models adjusted for age, site, and peak influenza period. The LAIV models for influenza A(H1N1)pdm09 and influenza B also included season and number of outpatient visits in the past year. D-F, The IIV effectiveness estimates were obtained from logistic regression models adjusted for age, site, peak influenza period, and number of outpatient visits in the past year. The IIV models for influenza A(H1N1)pdm09 and influenza B also included season. *P* value is for interaction term for enrollment season vaccination × prior season vaccination.

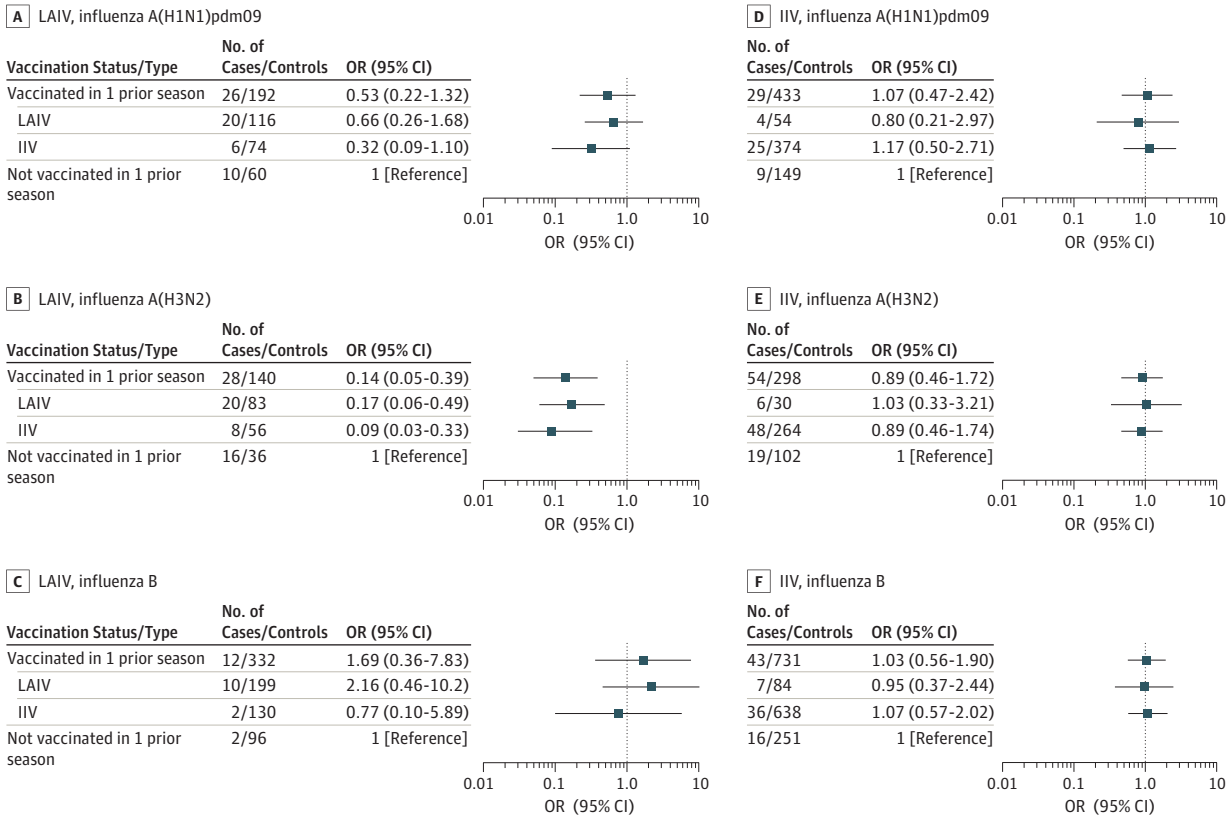
Risk of Vaccine Failure Among Vaccinated Children

Among LAIV recipients in the enrollment season, vaccination (any type) in the 1 prior season was associated with a decreased risk of influenza A(H3N2) compared with those unvaccinated in the 1 prior season (1 prior season ORs: any vaccine type, 0.14 [95% CI, 0.05-0.39]; LAIV, 0.17 [95% CI, 0.06-0.49]; and IIV, 0.09 [95% CI, 0.03-0.33]) (**Figure 3**; eTable 5 in the Supplement). Vaccination in prior seasons was not significantly associated with risk of LAIV failure against influenza A(H1N1)pdm09 or influenza B, although OR estimates for prior vaccination were consistently below 1 for influenza A(H1N1)pdm09. For IIV recipients, there was no evidence that prior season vaccination was associated with risk of IIV failure against influenza A(H1N1)pdm09, influenza A(H3N2), or influenza B.

Discussion

In this multiseason analysis of children aged 2 to 17 years, the association of prior season influenza vaccination with subsequent VE varied by influenza type and subtype, vaccine type received in the enrollment season, and vaccine type received in prior seasons. Among LAIV recipients, protection against influenza A(H3N2) was significantly improved among children who were repeatedly vaccinated despite a substantial antigenic mismatch between the vaccine strain and circulating viruses in 2014-2015. In contrast to previous VE reports for influenza A(H3N2) during the 2014-2015 season, our study found that vaccination in prior seasons was not associated with an increased risk of vaccine failure[19] and that vaccination in both the current and the prior season vaccination was not

Figure 3. Odds Ratios (ORs) of Influenza by Enrollment Season and 1 Prior Season Vaccination History for Live Attenuated Influenza Vaccine (LAIV) and Inactivated Influenza Vaccine (IIV)



A-C, The LAIV models were adjusted for age, site, season, and peak influenza period for the influenza A(H1N1)pdm09 model; age, site, peak influenza period, and insurance status for the influenza A(H3N2) model; and age for the influenza B model. D-F, The IIV models were adjusted for age, site, season, and number of outpatient visits in the past year for influenza A(H1N1)pdm09 model; age, site, and peak influenza period for the influenza A(H3N2) model; and age, site, and season for influenza B models.

associated with lower VE.[7] The LAIV has been shown to boost durable and cross-reactive T-cell responses in children,[20] and this may have contributed to greater protection against the vaccine-mismatched influenza A(H3N2) clade 3C.2a viruses that were predominant during the 2014-2015 season.[6,21] The role of the cross-reactive T-cell response after vaccination deserves further attention. The antigenic distance hypothesis predicts negative interference from repeated vaccination when vaccine strains are identical (vaccine strain 1 is the same as vaccine strain 2) and circulating viruses are drifted, as occurred in the 2014-2015 season. However, the antigenic distance hypothesis was based on simulations of serologic response to inactivated vaccines, and differences in the adaptive immune response to LAIV and IIV might lead to different repeated vaccination effects in children.[12,14,22-24]

Despite recent reports of no or low VE against influenza A(H1N1)pdm09 for LAIV,[5,8,25] we observed 50% VE against influenza A(H1N1)pdm09 among LAIV recipients with 1 prior season vaccination and more than 50% among LAIV recipients with 2 or 3 prior seasons vaccination. The VE against influenza A(H1N1)pdm09 was not significantly associated with 1 prior season vaccination, but the VE estimate was close to 0 for children who received LAIV in the enrollment season (not the prior season). A Finnish study[11] reported higher LAIV effectiveness against influenza A among children with repeated LAIV vaccination (current and prior seasons) during a season dominated by influenza A(H1N1)pdm09 virus. For the current study, the A(H1N1)pdm09 vaccine strain did not change and circulating viruses were antigenically similar to the influenza A/California/7/2009 vaccine component. However, studies conducted by the manufacturer demonstrated reduced replicative fitness of the attenuated influenza A(H1N1) vaccine component compared with older LAIV strains with proven efficacy.[26] The influenza A(H1N1)pdm09 component of LAIV was updated for the 2017-2018 season to address this issue. Few other studies have assessed the association of prior-season vaccination with LAIV protection against influenza A(H1N1)pdm09.

Studies on the duration of protection from influenza vaccination are inconsistent. Some studies have suggested intraseason waning of protection,[27-34] whereas others report residual protection from vaccination in prior seasons.[4,8,21,35-42] Most of these studies reported data for all ages or excluded young children, but recent studies have noted age-related differences in vaccine protection.[4,25,43] In the present study, residual protection against influenza B was observed among children who were unvaccinated during the enrollment season but received either LAIV or IIV in prior seasons. This finding is consistent with prior reports of residual protection against influenza B.[21,35-37] Furthermore, a study conducted during 2012-2013 that examined residual protection by age group found residual protection against influenza B/Yamagata in children aged 9 to 17 years, but not in adults aged 18 to 49 years, when the influenza B/Victoria strain was in the vaccine the prior season.[4] Additional studies are needed to understand age-related differences in residual protection for influenza B.

Vaccination history extending 2 or 3 seasons was not associated with vaccine performance against influenza A(H3N2) or influenza A(H1N1)pdm09 viruses, and results were similar to those from the analysis based on vaccination in the immediate prior season. However, cumulative vaccination history or vaccination in specific seasons may still be important. Most people tend to habitually receive (or not receive) the vaccine every year, and relatively few are vaccinated for the first time or intermittently. It is therefore difficult to separate the effects of single-season vs multiple-season vaccination history. The few studies that have examined vaccination history in more than 1 prior season have varied by season and subtype and are sometimes inconsistent within studies. Nevertheless, several studies have reported lower VE against influenza A(H3N2) or influenza A(H1N1) pdm09 among participants who were vaccinated in the enrollment season and 2[3,19,37,44,45] or 5[21] prior seasons compared with those vaccinated in the enrollment season but not in prior seasons. One study was conducted before our study,[21] whereas the others included the 2014-2015[3,19,37,45] or 2013-2014 and 2015-2016[44] seasons.

It is likely that children vaccinated for the first time differ from adults who are repeatedly vaccinated. Evaluation of prior vaccination effects in children younger than 9 years are complicated by vaccine recommendations based on vaccination history. Children who are receiving influenza

vaccine for the first time are recommended to receive 2 doses. In our study, we excluded the few children who received 2 doses during the enrollment season and, among those vaccinated at younger than 9 years, only 6% who received each vaccine type were previously unvaccinated based on our records. In a study evaluating vaccinations during the 2011-2012 and 2012-2013 seasons, children primed with 2 doses in a single previous season were less likely to have infection caused by influenza A(H3N2) and influenza B viruses than were unprimed children.[46] However, that same study did not find significant differences in VE for fully and partially vaccinated children who received IIV.[46] Studies of VE should continue to evaluate prior vaccination effects, ideally for at least the 2 prior seasons,[47] and examine potential consequences of age cohort–specific or immune-imprinting effects that may shape memory responses in the future.[43,48,49]

Limitations

Limitations in this study include small sample sizes in groups, limiting the ability to distinguish significant or clinically relevant differences when analyses are stratified by type/subtype and age group, with multiple possible combinations of vaccine exposure in different seasons. Estimates derived from small sample sizes are likely biased and should be interpreted with caution. We pooled data across seasons for the influenza A(H1N1)pdm09 and influenza B analyses to increase sample sizes because the vaccine component for influenza A(H1N1) and influenza B/lineage did not change during the study period. However, the influenza B/Yamagata vaccine strain changed during the final season, and vaccination history in the 2 and 3 prior seasons would have included the influenza B/Victoria strain in the early seasons. Also, there is a possibility of residual confounding because children who are repeatedly vaccinated may have a different risk of influenza compared with those who are vaccinated for the first time and those who are consistently not vaccinated.

Conclusions

Influenza VE varied by influenza type and subtype and vaccine type, but prior-season vaccination was not associated with reduced VE. These findings support current recommendations for annual influenza vaccination of children.

ARTICLE INFORMATION

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Corresponding Author: Huong Q. McLean, PhD, MPH, Center for Clinical Epidemiology and Population Health, Marshfield Clinic Research Institute, 1000 N Oak Ave (ML2), Marshfield, WI 54449 (mclean.huong@marshfieldresearch.org).

Author Affiliations: Marshfield Clinic Research Institute, Marshfield, Wisconsin (McLean, Belongia); AstraZeneca, Gaithersburg, Maryland (Caspard, Ambrose); Vanderbilt University Medical Center, Nashville, Tennessee (Griffin); Baylor Scott and White Health, Texas A&M University Health Science Center College of Medicine, Temple (Gaglani); Wake Forest School of Medicine, Winston-Salem, North Carolina (Peters, Poehling).

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Concept and design: McLean, Caspard, Ambrose, Belongia.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: McLean.

Critical revision of the manuscript for important intellectual content: All authors.

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SUPPLEMENT.

eTable 1. Vaccine Strains Included in Influenza Vaccines During 2010-2011 Through 2015-2016 Seasons
eTable 2. Study Population and Vaccine Exposure Groups for Logistic Regression Models for 1, 2, and 3 Prior Seasons
eTable 3. Vaccine Effectiveness of Various Vaccination Histories by Vaccine Type
eTable 4. Vaccine Effectiveness of Various Types of Vaccine Received in Prior Seasons by Vaccine Type
eTable 5. Odds of Influenza by Vaccination History Among Enrollment Season LAIV and IIV Recipients