ORIGINAL ARTICLE

Effect of Previous-Season Influenza Vaccination on Serologic Response in Children During 3 Seasons, 2013– 2014 Through 2015–2016

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Background. The effects of repeated influenza vaccination in children are not well understood. In this study, we evaluated previous vaccination effects on antibody response after vaccination with trivalent inactivated influenza vaccine (IIV) or quadrivalent live-attenuated influenza vaccine (LAIV) among school-aged children (5–17 years) across 3 seasons.

Methods. Children were enrolled in the fall of 2013, 2014, and 2015. The participants received IIV or LAIV according to parent preference (2013–2014) or our randomization scheme (2014–2015). All study children received IIV in 2015–2016. Hemagglutination-inhibition assays measured antibody response to egg-grown vaccine strains from prevaccination and postvaccination serum samples. Geometric mean titers (GMTs) and increases in GMTs from before to after vaccination (geometric mean fold rise [GMFR]) were estimated from repeated-measures linear mixed models.

Results. We enrolled 161 children in 2013–2014, 128 in 2014–2015, and 126 in 2015–2016. Among the IIV recipients, responses to the influenza A(H1N1)pdm09 and B vaccine strains were lowest among children who had received a previous-season IIV. The GMFRs for strains A(H1N1)pdm09 and B were 1.5 to 2.3 for previous-season IIV and 4.3 to 12.9 for previous-season LAIV or no previous vaccine. GMFRs were lower for strain A(H3N2), and differences according to previous-season vaccination history were smaller and not significant in most seasons. Most children had a post-IIV vaccination titer of ≥40 for vaccine strains in all seasons, regardless of previous-season vaccination history. Little to no increase in antibody levels was observed after vaccination with LAIV.

Conclusions. Serologic response to vaccination was greatest for IIV, but previous-season vaccination modified IIV response to A(H1N1)pdm09 and B. Influenza A(H3N2) responses were low in all groups, and LAIV generated minimal serologic response against all strains.

Keywords. children; immune response; influenza; influenza vaccination.

In the United States, annual influenza vaccination of all children aged ≥6 months has been recommended since 2008 [1], although recommendations for young children have been in place since 2003 [2]. Knowledge regarding the effect of repeated annual vaccination has increased significantly in recent years, but data in children have been limited. The few studies that have examined the effect of repeated annual vaccination on influenza vaccine effectiveness (VE) in children found that VE was modified by their previous-season vaccination status [3–5] and that the effect of previous-season vaccination history varied according to the vaccine type received [6–8]. Furthermore, most serologic data on repeated vaccination in children are derived from clinical trials conducted more than a decade ago [9] or from studies that assessed priming doses in young children [10–14]. Two studies compared vaccine serologic responses among children who did and those who did not receive previous-season vaccination. The first study used data from clinical trials of live-attenuated cold-adapted trivalent influenza vaccine over 4 consecutive seasons and found that hemagglutination-inhibition (HI) antibody titers among children vaccinated in each of the previous 4 seasons were lower than those among children vaccinated for the first time [15]. The difference was significant for influenza strains A(H3N2) and B but not for strain A(H1N1). The second study, conducted among school-aged children in Hong Kong during the 2009–2010 season, also found that the effects of previous vaccination on HI antibody response after vaccination with inactivated influenza vaccine (IIV) varied according to influenza type/subtype; antibody

responses against strains A(H3N2) and A(H1N1) were reduced, and responses against the same lineage of influenza B were increased [16, 17]. However, these single-season studies were conducted before the increased uptake of routine annual vaccination in children, and they assessed repeated vaccination with 1 type of influenza vaccine. In this study, we examined the association between previous vaccination history, including vaccine type received, and HI antibody response after vaccination with IIV or live-attenuated influenza vaccine (LAIV) among school-aged children during 3 seasons.

MATERIALS AND METHODS

Study Population and Design

For this analysis, we used data from 3 studies of serologic response to influenza vaccination in children in the 2013–2014 through 2015–2016 influenza seasons. The study design varied according to season, but all participants were aged 5 to 17 years, received influenza vaccine between September and November, and provided a serum sample before (prevaccination) and 21 to 28 days after (postvaccination) vaccination. The studies were observational except for 2014–2015, when the children were randomly assigned to receive IIV or LAIV. Each season, participants were recruited on the basis of influenza vaccination and infection history before enrollment. Vaccination history was obtained using a validated immunization registry that serves the population [18]. Influenza infection history before enrollment in this study was obtained from records of previous participation in annual studies of influenza VE at Marshfield Clinic Research Institute (MCRI) in Marshfield, Wisconsin, from 2011–2012 through 2014–2015 seasons [3, 7, 19] or studies of vaccine response in the 2013–2014 and 2014–2015 seasons [20]. In the fall of 2013, participants received either the 2013–2014 trivalent IIV (Fluzone, Sanofi Pasteur, Bridgewater, New Jersey; 0.5-mL dose) or quadrivalent LAIV (FluMist, MedImmune, Gaithersburg, Maryland; 0.2-mL dose) according to participant preference or contraindication for receipt of LAIV. In the fall of 2014, children aged ≤8 years and without contraindications received the 2014–2015 LAIV according to the then-current US Advisory Committee on Immunization Practices (ACIP) preferential recommendation for LAIV use in that age group [21]; children aged 9 to 17 years were randomly assigned to receive either LAIV or IIV in a 1:1 ratio; and children with a contraindication to LAIV received IIV (ClinicalTrials.gov identifier NCT02250274). In the fall of 2015, all the children received the 2015–2016 trivalent IIV. The differences in study design according to season are summarized in Supplementary Table 1.

During the influenza season, parents/guardians of participants were asked to report the presence or absence of specific acute respiratory illness symptoms weekly by telephone (available all seasons) or through completion of a Web-based application (available in 2014–2015 and 2015–2016). Nasal and oropharyngeal swabs were collected from participants reporting an acute respiratory illness with cough within 7 days of illness onset and the swabs were tested for influenza using reverse transcription polymerase chain reaction (RT-PCR) at MCRI [22, 23].

Written informed consent was obtained from parents/guardians of the children, and assent was obtained from children aged ≥7 years. The MCRI institutional review board approved the study each year.

Serologic Assays

Sera were stored frozen at ≤20°C until tested. HI assays were performed on prevaccination and postvaccination serum samples using standard methods to assess antibody titers to the egg-propagated vaccine reference strains for each season at the Centers for Disease Control and Prevention or a commercial laboratory (Battelle Eastern Science and Technology Center, Aberdeen, Maryland) [23]. The influenza A(H1N1) vaccine component was identical in all 3 seasons, but the influenza A(H3N2) vaccine component was updated for the 2013–2014 and 2015–2016 seasons. The influenza B/Yamagata lineage was included in the trivalent vaccine in all 3 seasons. HI assays were performed using turkey erythrocytes except for the influenza A(H3N2) antigen (A/Switzerland/9715293/2013) in the 2015–2016 season, during which the assays were performed using guinea pig erythrocytes with 20 nM oseltamivir; B antigens were ether treated. Strain-specific HI antibody titers were calculated from the geometric mean of 2 replicate assays per specimen from serial twofold dilutions starting at 1:10. Titers were reported as the reciprocal of the highest dilution that completely inhibited hemagglutination. Titers below the limit of detection (<10) were assigned a value of 5 (or half the threshold of detection).

Statistical Analysis

Separate analyses were conducted for IIV and LAIV receipt during the enrollment season and for each subtype/lineage and season. Participants were categorized into 1 of the following 3 groups on the basis of their vaccination history in the 1 season before enrollment: unvaccinated, IIV, or LAIV. The primary serologic end points were geometric mean titer (GMT), geometric mean fold rise in titer from prevaccination to postvaccination titer (GMFR), and seroprotection (titer ≥40). For children who required a second dose (n = 3 in 2014–2015 and n = 2 in 2015–2016) because they were aged <9 years and their past vaccination history was insufficient according to ACIP recommendations [21, 24], the titer from serum collected approximately 28 days after the second dose (or 56 days after the initial vaccination) was used to determine the postvaccination titer. Serum was not collected for antibody testing after a second dose in 2013–2014. GMTs and GMFRs were estimated using back-transformed model means and differences, respectively,

from repeated-measures linear mixed models with $\log_2$-transformed titers. Differences in seroprotection between groups were compared using the χ^2 or Fisher exact tests.

Subjects with RT-PCR-confirmed influenza in a season before enrollment were excluded from analyses for the subtype/lineage of infection. When data permitted, we examined vaccine response on the basis of vaccination history in the 2 previous seasons according to vaccine type using similar models and among children who were seronegative before vaccination.

All analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Over the 3-year study period, 267 children participated in the vaccine-response studies at MCRI: 161 during 2013–2014, 128 during 2014–2015, and 126 during 2015–2016. Forty percent (n = 107) were eligible and participated in more than 1 consecutive season (67 in 2013–2014 and 2014–2015, 13 in 2014–2015 and 2015–2016, and 27 in all 3 seasons). Characteristics of the study participants according to season of enrollment and vaccine type are shown in Table 1.

Antibody Levels Before and After Vaccination With IIV
Influenza A(H1N1)pdm09
Antibody levels against influenza A(H1N1)pdm09 were generally high (GMT, ≥40) before vaccination except in 2013–2014 among children who were unvaccinated in the previous season (GMT, 21) (Figure 1). After vaccination with IIV, the GMFR was significantly lower in children with previous-season IIV than in previous-season unvaccinated children in 2013–2014 (1.8 vs 8.6, respectively; $P < .0001$) , previous-season LAIV in 2014-2015 (2.3 vs 12.9, respectively; $P = .008$), and both previous-season unvaccinated children and previous-season LAIV in 2015–2016 (1.9 vs 17.2 and 8.7, respectively; $P < .0001$ and

$P = .004$, respectively). In all seasons, >85% of the children had a titer of ≥40 after vaccination regardless of their previous-season vaccination status.

Influenza A(H3N2)
Antibody levels against influenza A(H3N2) strains were generally high before vaccination (GMT, ≥56) except in 2015–2016 among children who were unvaccinated in the previous season (GMT, 26) (Figure 2). After vaccination with IIV, the GMT increased significantly in all previous-season vaccination groups. However, the GMFR was significantly lower in children with previous-season IIV compared to previous-season unvaccinated children (1.4 vs 2.3, respectively; $P = .0008$). In 2014–2015 and 2015–2016, GMFRs were similar across the previous-season vaccination groups. In all seasons, the majority (≥86%) of the children had a titer of ≥40 after vaccination regardless of their previous-season vaccination status.

Influenza B/Yamagata
Prevaccination antibody levels against influenza B/Yamagata strains were highest among children with previous-season IIV in all seasons (Figure 3). After vaccination with IIV (containing a B/Yamagata strain), GMFRs were lower in children with previous-season IIV than in those who were unvaccinated or received LAIV in the previous season. The majority (≥86%) of the children had a titer of ≥40 after vaccination regardless of their previous-season vaccination status.

Influenza B/Victoria
Prevaccination antibody levels against influenza B/Victoria strains were generally lower than levels against B/Yamagata and in 2013-2014 and 2015-2016, lowest among children who were unvaccinated in the previous season (Figures 3 and 4). GMFRs after vaccination were similar among the previous-season vaccination groups in the 2013–2014 and

Table 1. Demographic Characteristics of Study Participants According to Season of Enrollment and Previous Vaccine Type Received

| | IIV Group | | | | | | | | | LAIV Group | | | | | |
| | 2013–2014 | | | 2014–2015 | | | 2015–2016 | | | 2013–2014 | | | 2014–2015 | | |
Characteristic	IIV	LAIV	None	IIV	LAIV	None	IIV	LAIV	None	IIV	LAIV	None	IIV	LAIV	None
No. of children	59	3	37	19	17	8	77	13	36	17	11	34	37	35	12
Age (mean [SD]) (years)ᵃ	10.1 (3.6)	11.0 (4.4)	11.6 (3.6)	12.5 (2.7)	12.2 (2.8)	12.0 (2.0)	11.7 (3.2)	9.8 (2.0)	12.7 (2.6)	8.8 (2.8)	8.3 (3.7)	10.4 (3.4)	10.4 (3.3)	9.3 (3.0)	10.3 (3.5)
5–8 years (n [%])	25 (42)	1 (33)	10 (27)	—	—	—	11 (14)	5 (38)	2 (6)	9 (53)	8 (73)	10 (29)	16 (43)	16 (46)	5 (42)
9–17 years (n [%])	34 (58)	2 (67)	27 (73)	17 (100)	8 (100)	19 (100)	66 (86)	8 (62)	34 (94)	8 (47)	3 (27)	24 (71)	21 (57)	19 (54)	7 (58)
Female sex (n [%])	26 (44)	2 (67)	14 (38)	11 (58)	6 (35)	3 (38)	32 (42)	7 (54)	16 (44)	9 (53)	4 (36)	17 (50)	11 (30)	19 (54)	5 (42)
Race/ethnicity (n [%])															
White, non-Hispanic	53 (90)	3 (100)	35 (95)	17 (89)	16 (94)	8 (100)	70 (91)	10 (77)	32 (89)	16 (94)	11 (100)	30 (88)	36 (97)	31 (89)	11 (92)
Other race, non-Hispanic	2 (3)	—	1 (3)	1 (5)	—	—	2 (3)	2 (15)	3 (8)	1 (6)	—	—	1 (3)	1 (3)	1 (8)
Hispanic	4 (7)	—	1 (3)	1 (5)	1 (6)	—	5 (6)	1 (8)	1 (3)	—	—	4 (6)	—	3 (9)	—
High-risk condition (n [%])	27 (46)	—	7 (19)	4 (21)	3 (18)	—	26 (34)	—	5 (14)	—	2 (18)	4 (12)	10 (27)	1 (3)	3 (25)
Vaccinated ≥4 seasons in past 5 seasons (n [%])	49 (83)	2 (67)	2 (5)	8 (42)	4 (24)	—	50 (65)	11 (85)	—	11 (65)	11 (100)	4 (12)	26 (70)	22 (63)	1 (8)

Abbreviations: IIV, inactivated influenza vaccine; LAIV, live-attenuated influenza vaccine; SD, standard deviation.
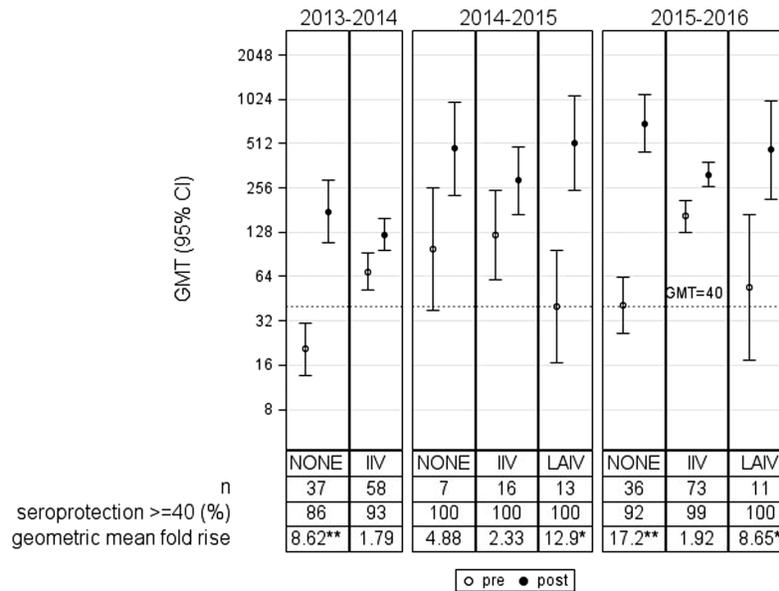ᵃAt the beginning of the season of enrollment.

Figure 1. Prevaccination and postvaccination hemagglutination-inhibition (HI) titers against influenza A(H1N1)pdm09 [A/California/7/2009(H1N1)-like] among participants who received inactivated influenza vaccine (IIV) according to previous-season vaccination status/type. Dotted horizontal line, HI titer of 40; **, $P < .0001$ for the comparison of geometric mean fold rise relative to previous-season IIV receipt; *, $P < .05$ for the comparison of geometric mean fold rise relative to previous-season IIV receipt. Abbreviations: CI, confidence interval; GMT, geometric mean titer.

2014–2015 seasons, but in 2015-2016 GMFRs were lower in children who previously received IIV than in those who were unvaccinated (1.3 vs 2.0, respectively; $P = .01$). Seroprotection with a titer of ≥40 after vaccination varied according to year, between 49% and 58% in 2013–2014, between 71% and 85% in 2014–2015, and between 53% and 100% in 2015–2016, with no consistent trends according to vaccination status in the previous season.
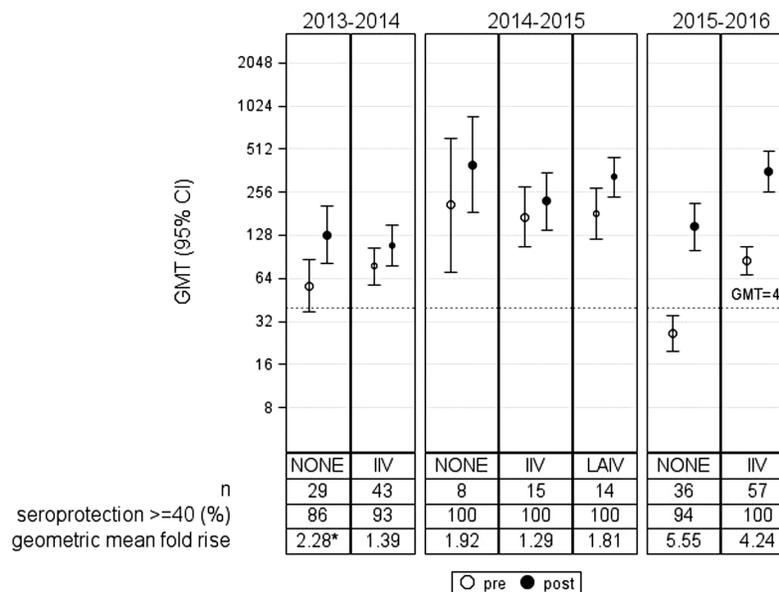

Figure 2. Prevaccination and postvaccination hemagglutination-inhibition (HI) titers against influenza A(H3N2) among participants who received inactivated influenza vaccine (IIV) according to previous-season vaccination status/type. HI antibody titers were assessed against influenza A/Texas/50/2012(H3N2)-like virus in the 2013–2014 and 2014–2015 seasons and influenza A/Switzerland/9715293/2013(H3N2)-like virus in the 2015–2016 season. Dotted horizontal line, HI titer of 40; *, $P < .05$ for the comparison of geometric mean fold rise relative to previous-season IIV receipt. Abbreviations: CI, confidence interval; GMT, geometric mean titer.
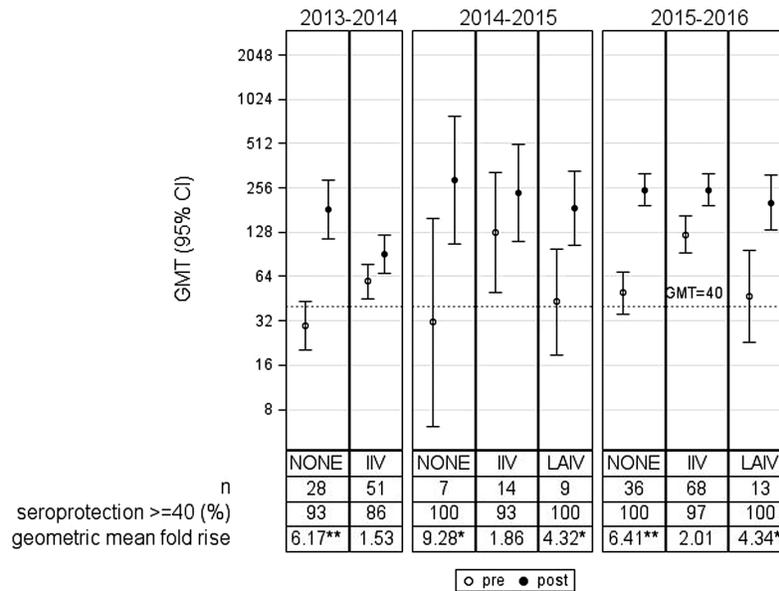
	2013-2014		2014-2015			2015-2016		
	NONE	IIV	NONE	IIV	LAIV	NONE	IIV	LAIV
n	28	51	7	14	9	36	68	13
seroprotection >=40 (%)	93	86	100	93	100	100	97	100
geometric mean fold rise	6.17**	1.53	9.28*	1.86	4.32*	6.41**	2.01	4.34*

○ pre ● post

Figure 3. Prevaccination and postvaccination titers against influenza B/Yamagata among participants who received inactivated influenza vaccine (IIV) according to previous-season vaccination status/type. Hemagglutination-inhibition (HI) antibody titers were assessed against influenza B/Massachusetts/2/2012-like virus in the 2013–2014 and 2014–2015 seasons and influenza B/Phuket/3073/2013-like virus in the 2015–2016 season. Dotted horizontal line, HI titer of 40; **, $P < .0001$ for the comparison of geometric mean fold rise relative to previous-season IIV receipt; *, $P < .05$ for the comparison of geometric mean fold rise relative to previous-season IIV receipt. Abbreviations: CI, confidence interval; GMT, geometric mean titer.

Antibody Levels Before and After Vaccination With LAIV
Influenza A(H1N1)pdm09
Prevaccination antibody levels against influenza A(H1N1) pdm09 were highest among children with previous-season IIV (Supplementary Figure 1). After vaccination with LAIV, there was no significant increase in the GMT (GMFR, 0.7–1.1). Seroprotection with a titer of ≥40 after vaccination varied between 18% and 89%; seroprotection was lower in 2013–2014 than in 2014–2015 and lowest among the children with previous-season LAIV in both of these seasons.
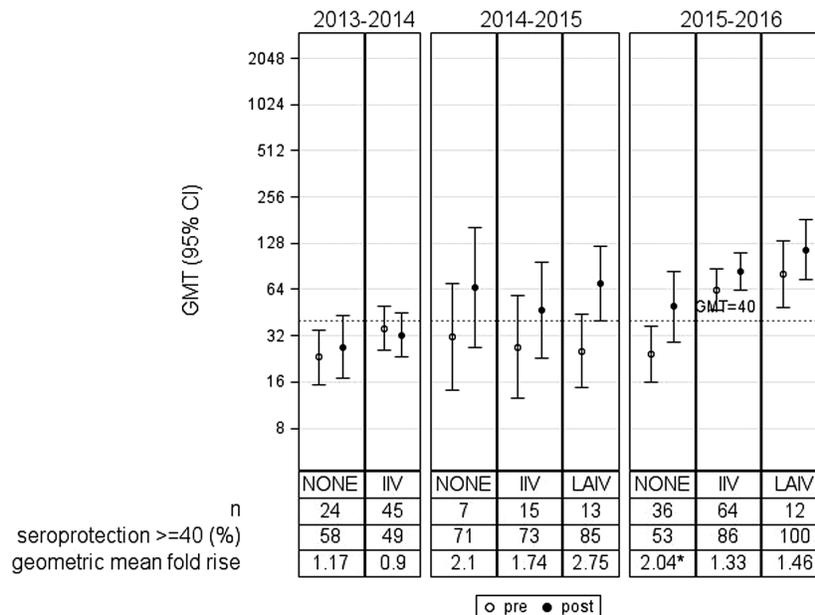
	2013-2014		2014-2015			2015-2016		
	NONE	IIV	NONE	IIV	LAIV	NONE	IIV	LAIV
n	24	45	7	15	13	36	64	12
seroprotection >=40 (%)	58	49	71	73	85	53	86	100
geometric mean fold rise	1.17	0.9	2.1	1.74	2.75	2.04*	1.33	1.46

○ pre ● post

Figure 4. Prevaccination and postvaccination titers against influenza B/Victoria (B/Brisbane/60/2008-like) among participants who received inactivated influenza vaccine (IIV) according to previous-season vaccination status/type. Dotted horizontal line, hemagglutination-inhibition titer of 40; *, $P < .05$ for the comparison of geometric mean fold rise relative to previous-season IIV receipt. Abbreviations: CI, confidence interval; GMT, geometric mean titer.

Influenza A(H3N2)

Prevaccination antibody levels against influenza A(H3N2) strains were similar among the previous-season vaccination groups (Supplementary Figure 2). We found no significant increase in GMTs (GMFR, 0.8–1.1) after vaccination with LAIV. Seroprotection with a titer of ≥40 after vaccination varied between 45% and 93%, depending on season, and we found no consistent trend among the 2 seasons.

Influenza B/Yamagata

Prevaccination antibody levels against influenza B/Yamagata strains were lowest among children who were unvaccinated in the previous season (Supplementary Figure 3). GMTs before and after vaccination in 2013–2014 were similar for all previous-season vaccination groups. After LAIV receipt in 2014–2015, postvaccination GMTs were significantly higher than prevaccination GMTs for previous-season LAIV (GMFR 1.6 [95% confidence interval (CI), 1.3–2.1]) and for those who were unvaccinated in the previous season (GMT ratio, 2.2 [95% CI, 1.2–4.0]) but not for those with previous-season IIV. Seroprotection with a titer of ≥40 after a vaccination varied between 45% and 96% and was highest in children with previous-season IIV, and seroprotection was higher in the 2014–2015 season than in the 2013–2014 season for previous-season unvaccinated or LAIV groups.

Influenza B/Victoria

Prevaccination antibody titers against influenza B/Victoria strains were lowest in children who were unvaccinated in the previous season (Supplementary Figure 4). After vaccination with LAIV, the GMTs were significantly higher than those before vaccination in the 2014–2015 season only in children who were unvaccinated in the previous season (GMFR, 3.0 [95% CI, 1.5–6.1]) and were significantly higher in previous-season unvaccinated children than in those in the previous-season IIV and LAIV groups (P = .04 and .03, respectively). Seroprotection with a titer of ≥40 after vaccination varied between 38% and 90%, and we found no consistent trend according to previous-season vaccination status.

Vaccination History in the Previous 2 Seasons

A similar pattern in antibody responses after vaccination according to previous-season vaccination status was found when vaccine status and type received in the 2 previous seasons were considered for those who received IIV or LAIV and for all viruses tested (Supplementary Figures 5–12).

Response Among Participants Who Were Seronegative at Baseline

Few children were seronegative before vaccination; thus, a comparison between previous vaccination histories was not possible (Supplementary Table 2).

Vaccine Failures

Over the 3-year study period, 34 RT-PCR–confirmed influenza infections after vaccination in the enrollment season. Influenza A(H1N1)pdm09 virus infection was detected in 11 children during the 2013–2014 season and 3 children in the 2015–2016 season. Infection with influenza A(H3N2) was detected in 19 children and with influenza B/Yamagata in 1 child in the 2014–2015 season. We found no differences in the proportion of vaccine failures according to previous-season vaccination group, although the number of cases was small. Children with influenza A(H1N1)pdm09 virus infection during the 2013–2014 season have already been described [20]. Among the children with influenza A(H3N2) infection, 14 (74%) received LAIV during the enrollment season and 10 (53%) received LAIV in the previous season. The majority of these children had a titer of ≥40 against the influenza A(H3N2) vaccine virus (A/Texas/50/2012-like) before (74%) and after (79%) vaccination. The 1 child in whom strain B/Yamagata vaccine failed had a postvaccination titer of 226 against the B/Yamagata vaccine strain (B/Massachusetts/2/2012-like). Titers against the predominant circulating influenza A(H3N2) (A/Switzerland/9715293/2013-like) and B/Yamagata (B/Phuket/3073/2013-like) viruses were not tested that season. Of the 3 children with influenza A(H1N1)pdm09 infection in the 2015–2016 season, 2 had a postvaccination titer of ≥40.

DISCUSSION

In school-aged children, HI antibody response after vaccination in 3 seasons varied according to vaccine type received during the enrollment season and vaccination history, including vaccine type received in the previous season. In general, children with previous-season IIV had the lowest increase in antibody titers (GMFR) after IIV vaccination. Responses to IIV differed according to previous-season vaccination history. In contrast, the effect of previous-season vaccination on LAIV response was less clear, because little to no increase in antibody levels was observed after vaccination.

Among IIV recipients, the effect of previous-season vaccination history varied according to influenza type/subtype. The GMFR was significantly lower in previous-season IIV recipients than in children who were unvaccinated or received LAIV in the previous season for influenza A(H1N1)pdm09 and influenza B. Although similar trends were observed for influenza A(H3N2), differences between the groups were smaller than those observed between influenza A(H1N1)pdm09 and influenza B and were not significant for most seasons. Although the reason for differences in previous vaccination effects according to type/subtype is unclear, the vaccine components each season might be a factor. Vaccine strains remained the same for the influenza A(H1N1)pdm09 and influenza B components in the seasons of enrollment (and in the previous season) for this study. For influenza A(H3N2), there was a new A(H3N2) strain (antigenic cluster change) in 2015–2016 that was antigenically different from the vaccine antigens in the previous 2 seasons.

IIV response was robust (GMFR, >4) in children vaccinated with IIV and in those who were unvaccinated in the previous season (2014–2015). However, in the 2013–2014 and 2014–2015 seasons, a period in which the vaccine strains remained antigenically similar, IIV response was minimal (GMFR, ≤2) and significantly lower among previous-season IIV recipients. In Hong Kong, antibody responses against A(H3N2) and seasonal A(H1N1) were lower among children with previous-season IIV than among those unvaccinated in the previous season, when vaccine strains were the same as those in the previous season, whereas a different (boosting) effect was observed with a change in lineage from Yamagata to Victoria between the first and second season in repeated vaccine recipients who were previously primed with the same lineage (Victoria) [17]. These data contrast with serologic data from adult studies, in which postvaccination titers were significantly lower in previous IIV recipients than in previously unvaccinated participants, regardless of whether a vaccine strain change occurred [25, 26], and clinical data suggest lower VE for influenza A(H3N2) among those with previous-season vaccination (≥1 previous seasons) than among those with no vaccination [27–31].

Although antibody response after IIV among children who received IIV in the previous season was lower than in children who were unvaccinated or received LAIV in the previous season, we found no significant differences according to previous vaccination history in seroprotection with post-IIV vaccination titers of ≥40. With the exception of the B/Victoria strain, which was not in the trivalent IIV during the study enrollment period, ≥85% of the children had a postvaccination titer of ≥40 for all vaccine strains examined. Similar trends with high postvaccination titers regardless of previous-season vaccination status and lowest response to IIV among those with previous-season IIV were seen in school-aged children during the 2009–2010 season in Hong Kong [16, 17]. These data are also consistent with clinical data from a study on IIV in children aged 2 to 17 years conducted during the same seasons as those in our study [8]. Data across 3 seasons, there was no difference in IIV effectiveness against laboratory-confirmed influenza A(H3N2) or A(H1N1) pdm09 among those who received IIV, LAIV, or no vaccine in the previous season, although the sample size was limited [8].

We generally found little increase in GMTs among LAIV recipients regardless of their previous-season vaccination status. Some modest increases in GMTs were observed after LAIV receipt, but the low rate made assessment of the effect of previous-season vaccination on serologic response among LAIV recipients challenging. In adult LAIV recipients, prevaccination HI titers were similar between previous-season vaccinated participants and those who were unvaccinated, but postvaccination HI titers were significantly lower among previous-season LAIV recipients than in those not vaccinated in the previous season [25]. HI antibody response has been correlated with protection after LAIV receipt [32] and has been shown to be similar across

different prime/boost combinations of IIV and LAIV [33] in clinical trials; however, postlicensure studies have found that LAIV does not elicit substantial HI antibody responses, particularly if HI antibodies already exist [20, 34, 35]. Other measures are needed to assess previous vaccination effects of LAIV, because preexisting HI antibody is likely among those with previous vaccination history [33, 36].

This study was subject to several limitations. First, study design varied according to season, and randomization of vaccine type for all age groups was not possible in the seasons examined because of the changing ACIP recommendations. Second, although vaccination history and infection history in previous seasons was known if the participant had a medically attended influenza illness, undocumented influenza exposure was likely, particularly among previous-season unvaccinated participants with a high prevaccination titer. Third, we used only HI antibody titers to assess immune response to vaccination. The limitations of HI assays for LAIV recipients were described earlier, but other measures of immune response, such as anti-neuraminidase antibody levels or cell-mediated immunity, might also be important in assessing immune response. Furthermore, the use of HI assays might be particularly problematic for influenza A(H3N2) because of their changing capacity to agglutinate red blood cells, particularly influenza A(H3N2) group 3C.2a viruses [37]. Last, sample sizes in some groups were limited, particularly for IIV recipients in the 2014–2015 season, who also were aged >8 years, which makes comparisons across seasons challenging.

In this multiseason study of school-aged children, seroprotection with an HI titer of ≥40 was high and did not differ according to previous-season vaccination history after receipt of IIV. However, children with previous-season IIV had a lower response after vaccination than previous-season unvaccinated children or those with previous-season LAIV. The reduced response to vaccination in children with a previous vaccination history was not consistent across vaccine strains and seasons. Previous vaccination effects are complex, and additional studies are needed to understand the variations according to strain and season in addition to any-age cohort effects.

Supplementary Data

Supplementary materials are available at *Journal of the Pediatric Infectious Diseases* Society online.

Notes

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