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BRIEF REPORT

Evaluation of Influenza Vaccine Effectiveness Among Young Children Receiving Consecutive Versus Nonconsecutive Vaccination During Influenza A(H3N2)-Predominant Seasons

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A test-negative case-control analysis of 1478 children aged 6 months to 8 years of age seeking care at an emergency/urgent care setting with influenza like illness during the 2016-17 and 2018-19 (H3N2 predominant) influenza seasons demonstrated that influenza vaccine effectiveness did not vary significantly by the prior seasons' vaccination status.

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Key words. children; H3N2; influenza; season; vaccine effectiveness.

Vaccination remains the best strategy for protection against influenza. However, due to frequent influenza virus antigenic drift and short-lived protective immunity, the composition of seasonal influenza vaccine is regularly updated, requiring annual vaccination. Concerns regarding potential negative effects of repeated influenza vaccination was raised several decades ago [1, 2], and has resurfaced more recently following the 2009 pandemic, with studies reporting lower vaccine effectiveness (VE) in recipients of consecutive years of influenza vaccination compared with the most recent season [3–5], findings that are most evident during influenza A(H3N2)-predominant seasons [3, 4, 6]. However, conflicting studies do not demonstrate differences in VE among consecutive vs nonconsecutive vaccine recipients during the same seasons [5], with less evidence in children. To further explore this observation in children, we aimed to evaluate influenza VE over 2 consecutive years vs only the current season during 2 H3N2-predominant seasons in children.

METHODS

Study Population and Detection Methods

We used data from a prospective cohort study evaluating a new severity classification for influenza infection among children 6 months to 8 years of age with influenza-like illness (ILI) evaluated in an emergency department (ED) or urgent care (UC) setting during the 2016–2017 and 2017–2018 influenza seasons in Colorado. The study methods have been previously described [7].

Influenza Vaccination Status

Vaccination status was defined as shown in Table 1 and verified using the following hierarchy: (1) review of the Colorado Immunization Information System Registry, (2) parent report, and (3) chart review (influenza vaccination status needed to be stipulated specifically).

Statistical Analyses

We conducted descriptive analyses including medians and interquartile ranges for continuous variables and percentages for dichotomous variables, and χ^2 and Wilcoxon tests to compare demographic and clinical characteristics of influenza cases with influenza noncases. Cohen κ and percentage agreement were used to measure concordance between vaccination status by self-report and data obtained in the electronic health record (EHR) including the state immunization registry data. We estimated the odds of influenza infection for children vaccinated over 2 consecutive seasons, the most recent season, and the prior season, and for children unvaccinated over the 2 consecutive seasons. We used a test-negative design [8] to estimate overall and subtype-specific VE using the odds ratio (OR) for testing positive for influenza among vaccinated vs unvaccinated subjects as (1 – OR) × 100. We excluded children with partial influenza vaccination in our primary analyses. We presented 95% confidence intervals (CIs) as 1 – CI_{OR}. VE estimates were adjusted a priori for age, presence of a high-risk medical condition, race, insurance status, and month and year of illness onset using multivariate

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Table 1. Current and Past Year Vaccination Status by Parental Report Versus Chart Review Documentation (Including Immunization Registry Data)

	Vaccination Status by Chart Review/State Immunization Registry	
Vaccination Status	Completely Vaccinated	Unvaccinated
Current vaccination status by parental report		
Completely vaccinated, No. (%)	671 (100)	3 (0)
Unvaccinated, No. (%)	15 (3)	537 (96)
Percentage agreement	98.5%	
Cohen κ (95% CI)	0.97 (.95–.99)	
Past year vaccination status by parental report		
Completely vaccinated, No. (%)	637 (100)	1 (0)
Unvaccinated, No. (%)	28 (8)	324 (92)
Percentage agreement	97.1%	
Cohen κ (95% CI)	0.93 (.90–.97)	

A completely vaccinated individual was defined as a child who received 2 or more influenza vaccines during prior seasons and received 1 vaccine for the current season; or a child who received 2 doses of influenza vaccine at least 4 weeks apart in the current season, according to the 2017–2018 Advisory Committee on Immunization Practices recommendations [9] An unvaccinated individual did not receive any influenza vaccines for a given season.
Kappa is a measure of agreement beyond that of chance with values >0.8 indicating excellent concordance; values 0.61–0.8 indicating strong concordance; values 0.41–0.6 indicating moderate concordance; values 0.21–0.4 indicating fair concordance; and values <0.2 indicating poor concordance.
Abbreviation: CI, confidence interval.

logistic regression. We conducted sensitivity analyses by redefining "vaccinated" as full or partial vaccination during a season and excluded children with symptom onset >7 days prior to testing. To further examine covariate effects on VE, separate stratified analyses were performed for age, year, high-risk medical condition, and influenza subtype. All statistical tests were performed with a level of .05 significance using SAS version 9.4 software.

RESULTS

Study Population

Among 1516 children with ILI enrolled in the study, 38 were excluded after consent (21 met exclusion criteria, 12 families withdrew from the study, and 5 were withdrawn for other reasons). We excluded 47 children with missing vaccination histories. Due to their partial vaccination status, 179 children were excluded from the main analysis cohort. The median duration of symptoms prior to testing was 3 days (interquartile range [IQR], 2–5 days). Of the remaining 1252 eligible children, 356 (28.4%) tested positive for influenza, and of these, 42% were completely vaccinated against influenza for that season. Twenty-nine percent of children were vaccinated in the current and prior seasons, 22% were vaccinated in the prior season only, 42% were not vaccinated either season, and 7% were vaccinated in the current season only (Table 2).

Bivariate Analyses Cases Versus Noncases

The median age of children with influenza was 3.1 years (IQR, 1.6–5.1 years), and 30% were considered at high risk for influenza complications. Compared with children who tested negative for influenza (noncases), influenza positive cases were more likely to be Hispanic/Latino, to receive government insurance, to be unvaccinated against influenza during the season of enrollment, and to attend daycare or school [7].

Vaccination Status Self-Report

We compared vaccination status by self-report vs data obtained in the EHR including state vaccination registry data, and found excellent concordance for both current (κ = 0.97, percentage

Table 2. Influenza Vaccination Status Among Influenza-Positive Cases (Excluding Partial Vaccinations) During the 2016–2017 and 2017–2018 Seasons

Vaccination Status Over 2 Seasons	Influenza Vaccination Year		Influenza Positive		Adjusted VE (95% CI)
2016–2017 influenza season	2015–2016	2016–2017	Total Tested, No.	Influenza Positive, No. (%)	
Neither	No	No	102	46 (45)	Ref
Prior season	Yes	No	61	30 (49)	–17 (–131 to 41)
Current and prior seasons	Yes	Yes	176	44 (25)	55 (21–75)
Current season	No	Yes	21	7 (33)	40 (–73 to 80)
2017–2018 influenza season	2016–2017	2017–2018			
Neither	No	No	211	68 (32)	Ref
Prior season	Yes	No	115	49 (43)	0.0 (–68 to 40)
Current and prior seasons	Yes	Yes	268	59 (22)	53 (26–71)
Current season	No	Yes	110	20 (18)	16 (–55 to 55)
2016–2017 and 2017–2018 seasons	Prior Season	Current Season			
Neither	No	No	313	114 (36)	Ref
Prior season	Yes	No	176	79 (45)	–5 (–58 to 30)
Current and prior seasons	Yes	Yes	444	103 (23)	52 (32–66)
Current season	No	Yes	131	27 (21)	27 (–24 to 57)

Abbreviations: CI, confidence interval; VE, vaccine effectiveness.

agreement = 98.5%) and prior (κ = 0.93, percentage agreement = 97.1%) seasons (Table 1).

Overall VE

Overall adjusted VE was 49% (95% CI, 34%–61%) combined over both enrollment seasons) against any influenza virus. Adjusted VE was 53% (95% CI 27%–70%) in the 2016–2017 season and 45% (95% CI, 22%–61%) in the 2017–2018 season. Estimated VE for children who received influenza vaccine over 2 consecutive seasons (vs neither season) was 52% (95% CI, 32%–66%). Estimated VE for children who received influenza vaccine during the enrollment season but not the prior season (vs neither season) was 27% (95% CI, –24% to 57%), which was not statistically significant. There was no significant difference in VE among children who received vaccination over current and prior seasons vs the current season only.

Sensitivity and Stratified Analyses

In stratified analyses, higher VE was observed for influenza B strains compared with influenza A, younger children aged 6 months to 2 years of age compared with >2 years of age, and children with a high-risk medical condition (Supplementary Figure 1). VE estimates were similar when defining vaccinated as completely or partially vaccinated (Supplementary Figure 2) and after excluding children with symptom duration >7 days prior to testing (Supplementary Figure 3).

DISCUSSION

Utilizing a test-negative design for children presenting to an ED/UC setting with ILI, adjusted VE among children vaccinated over 2 consecutive seasons was comparable to children vaccinated for the current season only. Adjusted VE for children vaccinated during the current season but not prior season was lower but not statistically significant. Our study found no significant difference in VE between children who had received vaccination during current and prior seasons consecutively vs the enrollment season only. Adjusted VE for each enrollment season was lower than VE against medically attended illness reported by the Centers for Disease Control and Prevention (CDC) for this age group [10–12]. These differences may be due to a higher acuity population in our study and different covariates included in the model, as well as different characteristics of our study population from the cohort evaluated by the CDC.

While our findings reflect similar observations for influenza A(H3N2) from studies evaluating influenza VE in children, including a study from the 2017–2018 season [13, 14], several other observational studies show higher VE estimates for those vaccinated during the current season only, compared with 2 consecutive seasons, contrasting our findings. This phenomenon was most pronounced in studies evaluating VE against H3N2 during the 2014–2015 season [3, 4]. During this season, vaccine strains were unchanged from the prior season, and there was significant mismatch between the circulating and vaccine strains, which is consistent with the antigenic distance hypothesis. This theory, first proposed in 1999, posits that VE is influenced by the antigenic similarity between the prior season's vaccine strain and the epidemic strain, as well as the antigenic similarity between the current and prior season vaccine strains. A higher attack rate (decreased VE) is observed in repeat vaccines when the antigenic distance between the prior and current seasons vaccine antigens is small and when the prior antigen is antigenically distant from the circulating strain [15]. A lower attack rate (higher VE rate) is observed in repeat vaccines when the prior vaccine antigen is similar to the circulating antigen. These latter conditions were observed during our study period, since there was no change in the H3N2 component of the vaccine in 2017–2018 (both 2016–2017 and 2017–2018 seasonal vaccines contained the A/Hong Kong/4801/2014 [H3N2]-like virus), which were closely antigenically related to the circulating influenza strain, which may be a potential explanation for the difference in our findings. According to the antigenic distance hypothesis, prior vaccination effects should be minimal when the prior and current season's vaccines are more antigenically distinct, as seen in the 2016–2017 season (there was a change in the H3N2 strain in the 2016–2017 season to the A/Hong Kong/4801/2014 [H3N2]-like virus from the prior A/Switzerland/9715823/2013 [H3N2]-like virus), which we also observed, given the minimal relative difference between the current and prior season VE and the prior season VE.

Several limitations warrant discussion. While the test-negative design is less susceptible to misclassification bias and confounding by health-seeking behavior, there are still inherent limitations using this methodology. If the assumption of equal noninfluenza ILI rates in vaccinated and unvaccinated groups is violated, then VE estimates from a test-negative study may be biased, for which our study in the ED/UC setting may be at risk [8]. A study evaluating influenza VE by test-negative design comparing inpatient and outpatient settings found no differences in VE estimates between settings using this design [16]. Next, our small sample size limits interpretation of stratified analyses by influenza subtype, which would be important to evaluate given that 44% of infections were due to influenza B. The smaller number of patients also prevented us from evaluating other potential confounders that could influence our results. Last, while we relied on state immunization registry data for vaccination status, which is linked with 85% of pediatric primary care practices in Colorado, we also used EHR and parent report during enrollment, which has the potential for misclassification bias. However, self-report of influenza vaccination has generally been shown to be accurate in the ED and hospital setting [17], and concordance was high between our EHR data/immunization registry data and parent interview.

In summary, during the 2016–2017 and 2017–2018 influenza seasons, we did not observe lowered VE among the group vaccinated in consecutive seasons compared with the current vaccination season only, which is in alignment with the antigenic distance hypothesis. These findings support the current recommendations for annual influenza vaccination.

Supplementary Data

Supplementary materials are available at the *Journal of The Pediatric Infectious Diseases Society* online (http://jpids.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Footnote: models adjusted for age, race/ethnicity, high risk medical condition [9], insurance status and month and year of illness onset.

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