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Influenza Vaccine Effectiveness for Fully and Partially Vaccinated Children 6 months to 8 Years Old during 2011–2012 and 2012–2013: The Importance of Two Priming Doses

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Abstract

Background—Few studies have examined the effectiveness of full vs. partial vaccination with inactivated trivalent influenza vaccines (IIV3) as defined by the U.S. CDC Advisory Committee on Immunization Practices (ACIP).

Methods—Respiratory swabs were collected from outpatients aged 6 months to 8 years with acute cough for ≤7 days in clinics in 5 states during the 2011–2012 and 2012–2013 influenza seasons. Influenza was confirmed by real-time reverse transcription polymerase chain reaction assay. Receipt of current season IIV3 and up to 4 prior vaccinations was documented from medical records and immunization registries. Using a test-negative design, vaccine effectiveness (VE) was estimated adjusting for age, race/ethnicity, medical conditions, study site, and month of enrollment.

Results—We did not observe higher VE for children fully vs. partially vaccinated with IIV3, as defined by U.S. ACIP, though our sample of partially vaccinated children was relatively small. However, among children aged 2–8 years in both seasons and against A(H3N2) and B influenza illness separately, VE point estimates were consistently higher for children who had received 2 doses in the same prior season compared to those without (VE range of 58–80% vs. 33–44%, respectively). Across seasons, the odds of A(H3N2) illness despite IIV3 vaccination were 2.4-fold

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(95% CI = 1.4–4.3) higher among children who had not received 2 doses in the same prior season. We also noted residual protection among unvaccinated children who were vaccinated the previous season (VE range = 36–40% across outcomes).

Conclusion—Vaccination with IIV3 may provide preventive benefit in subsequent seasons, including possible residual protection if vaccination is missed. Two vaccine doses in the same season may be more effective than alternative priming strategies.

Young children are especially vulnerable to influenza virus infections and along with older adults are the most likely to suffer secondary complications and be hospitalized due to influenza illness [1–5]. However, relatively few studies have examined the effectiveness of inactivated trivalent influenza vaccines (IIV3) in this age group [6, 7]. Over the last decade, the Advisory Committee on Immunization Practices (ACIP) of the CDC in the United States (U.S.) has progressively expanded who should receive annual influenza vaccination. Groups targeted for vaccination expanded from high-risk children only to including all children aged 6–23 months (starting as “encouraged when feasible” in 2002 and recommended since 2004) [8–10], children aged 6–59 months (since 2006) [11], and children aged 6 months to 18 years (since 2008) [12].

ACIP recommends that children aged 6 months to 8 years receive 2 doses of influenza vaccine if they are previously unvaccinated; in 2010, ACIP revised their recommendations to ensure 2 prior doses containing the A(H1N1)pdm09 virus component (Supplemental Figure A). Admittedly, evidence that can inform these recommendations is limited [6, 7, 13]. Improved immunogenicity following 2 doses of IIV3 has been noted, especially among vaccine naïve infants and toddlers, but the findings have not been consistent for children aged ≥2 years or for all vaccine components [14–20].

Findings from observational studies regarding vaccine effectiveness (VE) in preventing laboratory-confirmed influenza outcomes have also been mixed. Some studies have reported significant VE for fully vaccinated children only [21–24], while others have observed similar VE for fully and partially vaccinated children in some age groups [23, 25–28]. Most of these studies have examined VE against all circulating influenza strains [21, 23, 25, 26]; few have been able to consider the importance of full vaccination against a specific influenza type or subtype [19, 24, 27, 29, 30].

Interpreting these findings is difficult because the criteria for full and partial vaccination consist of a variety of potential vaccine exposures. Children who received 2 doses within the same season (4 weeks apart) have consistently been described as fully vaccinated. However, a single dose can also result in full vaccination depending on vaccination history [11, 31–34]. Until 2007, a child with a single current season dose and at least 1 previous seasonal influenza vaccine dose was considered fully vaccinated. After 2007, a single current season dose after 2 or more doses in previous seasons (in specific combinations that have been updated each season by ACIP) constituted full vaccination [11, 31–34]. The definition of “unvaccinated” also varies across studies, with some categorizing partially vaccinated children as unvaccinated [35]. Thus, it is difficult to determine the preventive benefit of particular vaccination schedules from VE studies as typically reported.

The U.S. Influenza Vaccine Effectiveness (Flu VE) Network conducts annual evaluations of VE of seasonal influenza vaccines in preventing outpatient medical care for acute respiratory illness (ARI) with laboratory-confirmed influenza virus infections [21, 36]. In this study, we examine the VE of IIV3 against medically attended influenza ARI among children aged 6 months to 8 years during the relatively mild 2011–2012 influenza season [37] and the moderately severe 2012–2013 season in the U.S. [38].

Specifically, our study has three aims. First, we estimate VE of full and partial IIV3 vaccination using the ACIP criteria for the two seasons. We improve upon our previous VE reports for this age group by limiting our analysis to IIV3 and excluding trivalent live attenuated influenza vaccine (LAIV3) [21, 36], by considering prior doses received during multiple previous seasons [21], and by reporting VE for both fully and partially vaccinated children in both seasons [36]. Second, we estimate VE of IIV3 by the number of current season doses and by alternative definitions of priming that consider doses received in the previous season, doses received across multiple prior seasons, and receipt of 2 doses in at least one prior season. Third, we estimate VE against A(H3N2) and B influenza virus illnesses separately.

MATERIALS & METHODS

Subject Enrollment

Details of the U.S. Flu VE Network's methodology and enrollment during the 2011–2012 [21] and 2012–2013 season [36] have been previously published. Patients seeking outpatient medical care for an ARI (onset ≤7 days) with cough were recruited by study staff in five states (Michigan, Pennsylvania, Texas, Washington, and Wisconsin). Consenting parents completed an enrollment interview to provide patient and household information. Patient's history of high risk medical conditions was confirmed by extraction from medical records. Combined nasal and throat specimens (or nasal specimens only for children aged <2 years) were tested for influenza at network laboratories, using real-time reverse transcription polymerase chain reaction (RT-PCR). The study was reviewed and approved by the institutional review boards at each Network site.

Vaccine Effectiveness

Influenza vaccination status for the study season and for prior seasons was documented from medical records and immunization registries. Participants with indeterminate current season vaccination status (with illness onset <14 days from vaccination or receipt of a second dose of vaccine <28 days from the first dose) and those who received LAIV3 during the study season were excluded. For both seasons, we extracted dates of IIV3 vaccination for the current study season, up to 3 doses of any influenza vaccine from previous seasons, and the earliest recorded influenza vaccination. Thus, up to 4 prior season doses were documented, but this likely underestimated the number of children who received 2 prior doses within the same prior season, especially among repeatedly vaccinated older children.

Because we could not distinguish between seasonal and monovalent A(H1N1)pdm09 vaccines in 2009, we considered doses after October 1, 2009 as monovalent A(H1N1)pdm09

vaccines; monovalent vaccine was introduced and seasonal vaccination declined in early October [39, 40]. Receipt of the monovalent vaccine was considered as it applied to ACIP criteria, but it was not included in the count of prior seasonal vaccinations. There was little change in the percentage of primed children or in our VE results when we used alternative November and December cut-offs for counting monovalent A(H1N1)pdm09 vaccinations.

For the 2012–2013 season only, we were able to confirm whether the child had consistently been enrolled in the site's health system since 6 months of age. For this season, we excluded children aged <2 years who lacked medical records going back at least 1 year and excluded children 2–8 years without records going back at least 2 years.

Vaccine components for the study years and prior seasons are listed in Supplemental Table A; the A(H3N2) and B influenza virus components changed from 2011–2012 to 2012–2013 [37]. The vast majority of tested circulating viruses in the U.S. were antigenically similar to vaccine prototype components during both seasons [37, 38]. However, antigenic differences were noted between circulating viruses and the egg-adapted A(H3N2) strain in the 2012–13 vaccine [41].

Influenza VE is assessed using a test-negative design [42, 43], whereby VE equals 100% × (1-odds ratio [ratio of odds of vaccination among influenza-positive cases to the odds of vaccination among influenza-negative controls]) using logistic regression. Similar to previous VE estimates for this Network [21, 25, 36], adjusted models included values for age [months], race/ethnicity, high-risk medical conditions, days from illness onset to specimen collection, study site, and calendar time [month of enrollment]. Statistically *significant* or non-zero VE is indicated by a 95% confidence interval (CI) that does not overlap with zero.

We define full and partial vaccination using the ACIP criteria for each study season [34, 44] (Supplemental Figure A). We then examine VE using four definitions of vaccine priming: ≥1 doses of any influenza vaccine during the prior season, ≥1 doses recorded across prior seasons, ≥2 doses recorded across prior seasons, and receipt of 2 doses within the same prior season. To test for priming we examine the conditional hypothesis that the effect of current season vaccine varies depending on prior vaccination history; we examine an interaction term for receipt of current season IIV3 by receipt of prior doses after adjusting for both contributing terms [21, 45, 46]. We estimate VE for each combination of current season and prior doses with those unvaccinated in the current season and not meeting the priming criteria as the reference group [21, 45–47]. We also test for differences between VE estimates (e.g., VE of fully vs. partially vaccinated; VE for primed vs. unprimed children) by calculating the odds ratio with one of the two vaccine exposures as the referent.

We estimate that 89 cases are needed to achieve 80% power ($\alpha = .05$) to detect a VE of 50% with an influenza positivity rate of 33% and a vaccination rate of 50% among influenza negative controls. We meet or exceed these criteria in most estimates of VE for fully vaccinated children and those with common prior vaccination exposures (e.g., current season dose plus 1 or more prior doses). However, we have lower power to estimate VE for partially vaccinated children and for those with less common prior vaccination exposures. We

consider as noteworthy consistent patterns of results across models, but there is no adjustment for familywise error. Statistical analyses were conducted using SAS statistical software (version 9.3; SAS Institute, Cary, North Carolina).

RESULTS

Participant Characteristics

During 2011–2012, 1562 children aged 6 months to 8 years were enrolled during weeks with local influenza virus circulation at the 5 Network sites; 30 (2%) with indeterminate vaccination status and 91 (6%) who received LAIV3 were excluded, resulting in an analysis sample of 1,441 children (Supplemental Figure B). During 2012–2013, 1732 children were enrolled; 227 (13%) with incomplete medical records, 30 (2%) with indeterminate vaccination status, and 148 (9%) who received LAIV3 were excluded, resulting in an analysis sample of 1327 children (Supplemental Figure C).

In the 2011–2012 season, influenza circulation began late and peaked in March and April; only 13% (190/1441) of enrolled children were influenza positive (Network site range = 6–17%). In contrast, during the 2012–2013 season, circulation peaked in December and January, and influenza positives made up 38% (499/1327) of enrollees (site range = 8–55%). In both seasons, A(H3N2) viruses were prominent at most sites; influenza positivity increased with age and was higher among Black children (Table 1).

The proportion receiving ≥1 doses of IIV3 was similar in 2011–2012 and 2012–2013 (50% and 45%, respectively). However, the percentage of enrolled children who were vaccinated increased per month in 2012–2013, climbing from 34% in December to 54% in March (Table 1). In both seasons, vaccine coverage declined with age and was lower among Black children.

Potential confounders (associated with both vaccination and influenza positivity) identified in the descriptive analyses were age, race, month of enrollment, and Network site. All of these potential confounders were already included *a priori* in the adjusted models.

VE for Full and Partial Vaccination using ACIP Criteria

The majority of children who received at least 1 dose of IIV3 in 2011–2012 and 2012–13 had sufficient prior doses to meet the definition of fully vaccinated according to ACIP criteria (81%, 591/726 and 79%, 473/596, respectively). Therefore, in analyses that combined children from both seasons, the vast majority of fully vaccinated children (79%, 845/1064) had received a single dose of IIV3; the other 21% (219/1064) received 2 recommended doses, and the vast majority of these were less than 2 years old (88%, 193/219).

We observed significant unadjusted VE for both partial and full vaccination associated with all circulating influenza viruses (both seasons), A(H3N2) viruses (both seasons), and B influenza viruses (2012–2013 season) (Table 2). Adjusted VE point estimates were 11–31 percentage points lower than the crude estimates. VE for full vaccination remained

significant in all models, but VE for partial vaccination was only significant in the 2012–2013 models.

VE estimates for fully vaccinated children were not significantly higher than VE for partially vaccinated children in any of the models. In fact, the only significant difference noted was opposite of the expected direction; in 2012–2013, adjusted VE against A(H3N2) illness was significantly lower among *fully* vaccinated children (Table 2).

VE with Different Prior Vaccination Exposures

Among children aged 2–8 years, we examined four definitions of influenza vaccine priming (Table 3). Because VE estimates associated with 1 versus 2 current season doses of IIV3 were similar (with wide and overlapping CIs) (Supplemental Table B), we defined current season vaccination as receipt of 1 or more doses for the following priming analyses. Without priming, we observed adjusted VE for ≥1 current season dose(s) of IIV3 that ranged from 47% to 53% across the four influenza outcomes (Table 3).

In the first analysis, priming consisted of 1 or more doses of any influenza vaccine in the previous season only. We observed significant effect modification of current season VE by prior season priming in all models (i.e., interaction terms p-values < .1). This cross-season effect is driven by significant residual VE for children who received no current season IIV3 but were vaccinated the previous season; this was noted in all models (VE range = 36–40%).

In the second and third analyses, we expanded the definition of priming to include ≥1 and then ≥2 doses recorded in any prior season (Table 3). However, we did not observe a significant interaction effect for current season IIV3 by prior vaccination history using either of these definitions. Nonetheless, for most of these models the only significant VE was observed for children with current and prior seasonal doses.

In the fourth analysis, only children who had received 2 doses in the same prior season were considered primed. We observed significant interaction terms for current season IIV3 by 2-dose priming history against influenza outcomes in all four models (p-values < .05). Although we observed significant VE for current season IIV3 with or without priming, the VE point estimates were consistently higher for children who had received 2 doses in a prior season compared to those without (VE range of 58–80% vs. 33–42%, respectively) (Table 3). This was statistically significant for VE against A(H3N2) illness; the odds of being A(H3N2) positive were 2.4-fold (95% CI = 1.4–4.3) higher among children who received IIV3 but were unprimed compared to children who received IIV3 after receiving 2 dose priming in a previous season. Although the referent category in this model included unvaccinated children with no record of prior vaccination and those with prior vaccinations but without 2 doses within the same season, we observed similar VE estimates when the referent group was limited to only unvaccinated children with no known prior vaccination (Supplemental Table C).

DISCUSSION

In our study of children aged 6 months to 8 years receiving outpatient medical care for ARI during 2011–2012 and 2012–2013, we found that children aged 2–8 years who received IIV3 after receiving 2 priming doses of any influenza vaccine during the same previous season had significantly higher VE against A(H3N2) illness than children without 2 priming doses. Children with 2-dose priming also had high VE point estimates against ARI associated with all influenza viruses (in both seasons) and B viruses (2012–2013). The effect was most evident when we examined vaccine failure against A(H3N2) illness; among children aged 2–8 years who received IIV3, the odds of A(H3N2) illness despite vaccination were 2.4-fold higher among unprimed children compared to those who received 2 doses of vaccine in a previous season. Our findings are consistent with studies that observed better IIV3 immunogenicity following 2 doses, though this has been demonstrated most consistently among vaccine naïve infants and children younger than those in our analyses [14–20]. Nonetheless, our findings add support to recommendations by multiple international organizations to offer 2 doses of influenza vaccine during a child's first season [34, 44] and suggests the preventive benefits of this initial investment may extend to future seasons.

We did not observe higher VE for children fully vs. partially vaccinated with IIV3 as defined by ACIP in any of our models. The relatively small number of partially vaccinated children combined with the need to adjust for potential confounding (by age, race/ethnicity, geography, and simultaneous changes in vaccine coverage and influenza circulation) made VE estimates for partially vaccinated children imprecise, especially for 2011–2012. Admittedly, the relevance of these observations is limited because during the study period ACIP recommendations for children aged 6 months through 8 years considered doses of vaccine containing the A(H1N1)pdm09 component specifically; yet, we observed few A(H1N1)pdm09 virus infections in our study.

Nonetheless, our finding of significant VE for both full and partial vaccination against ARI associated with all influenza viruses, A(H3N2) viruses, and B influenza viruses in 2012–2013 is consistent with several prior studies [25–27]. In contrast, our observation that partially vaccinated children experienced *higher* VE against A(H3N2) illness than fully vaccinated children was unexpected and is difficult to interpret. Without a much larger sample, it is impossible to disentangle and examine separately the diverse influenza vaccine exposures that constitute partial vs. full vaccination. In the 2012–13 sample, for example, partially vaccinated children, as defined by US ACIP, include those with a single current season dose and at least four kinds of vaccination histories (e.g., no prior vaccination, only 1 prior dose, ≥2 prior doses but without at least 1 dose before and 1 dose after July 2010). These differences in vaccine exposure are also likely interconnected with differences in children's history of natural infections with influenza viruses. Nonetheless, the observed higher VE against A(H3N2) for partially vaccinated children warrants further investigation, especially given recent studies of children aged ≥9 years and adults that reported higher point estimates for VE against influenza A(H3N2) illness among those not vaccinated during the previous season [21, 41, 45, 46, 48, 49] or over the previous 5 seasons [48]. These future investigations should include measures of immune markers, such as pre-season A(H3N2)

antibodies. Indeed, Ohmit et al.'s household cohort study observed lower pre-season A(H3N2) antibody titers which corresponded to lower VE against A(H3N2) illness among those vaccinated in both the current and prior year compared to those vaccinated in the current season only [49].

Children who were vaccinated during the previous season but who missed IIV3 vaccination in the study season appeared to benefit from residual protection. VE point estimates of 36–40% were noted for previously vaccinated children aged 2–8 years in all models; this was noted in both the first study season (2011–2012) when the prior year vaccine components had not changed, as well as in the second study year (2012–2013) when the A(H3N2) and B influenza components had changed [21, 36]. Our findings are consistent with observations of persistent influenza A virus antibodies in children [50] and recent observations of cross-season VE among children [27] and adults [21, 36, 46, 48, 51].

From a methodological standpoint, our findings suggest that reports of VE for children should estimate VE for specific combinations of current and prior season(s)' vaccine exposure, similar to recent recommendations for the presentation of VE estimates for adults [21, 36, 46, 48]. This would also aid in VE comparisons across countries, where definitions of full and partial vaccination vary. In regards to vaccine policy, our findings combined with earlier observations of persistent protection offered by Spring (post-season) doses of IIV3 [17, 52] suggest there may be value in considering alternative vaccine schedules that take advantage of opportunities to vaccinate young children months before influenza season, especially when vaccine components are unchanged. This may be especially relevant in countries and regions with year-round or twice-yearly influenza circulation [53].

Among the strengths of our study is our use of RT-PCR confirmed influenza outcomes with a test-negative design [42, 43, 54] in a multi-site study using a common protocol and procedures that directly recruited children receiving outpatient care for ARI without relying on clinician referral. Our ability to stratify results for A(H3N2) and B influenza virus illnesses improved the specificity of our results. Other study strengths include our ability to examine multiple years of vaccination records from health plan and state registries and the fact that ACIP recommendations for annual seasonal vaccination had consistently applied to all the children in our study.

Our study is limited by several potential sources of information bias. We only documented up to 4 prior vaccination records. While it is reasonable to assume that most children receiving 2 doses in the same season were vaccine naïve prior to that, we cannot confirm this. We also could not examine the cumulative total of all influenza vaccinations. Also, we may have falsely classified some of the children as unprimed due to incomplete vaccination records. Although our Network now documents all influenza vaccination records of enrollees, in the current study we could not verify the completeness of medical records for children during the 2011–2012 season. In an attempt to remove monovalent A(H1N1)pdm09 vaccinations, we likely excluded some seasonal influenza vaccinations administered after October 2009. Taken together, these potential sources of information bias would result in underestimation of VE associated with full vaccination or multi-dose priming, especially among older children for whom more records need to be captured. Thus, although we are

confident in the significant effects we observed, these information biases combined with small sample sizes for some vaccine exposures reduced the precision of our estimates and likely limited our ability to detect true differences in VE.

In addition, our study has at least four other limitations. First, although we excluded children who received LAIV3 during the study season, we could not determine the vaccine types of all previous vaccinations. However, LAIV3 has accounted for a relatively small proportion of vaccinations in our Network to date [21, 25, 36]. Second, unmeasured or residual confounding may have biased our results in unknown ways, since children who consistently receive recommended influenza vaccination doses may differ from those who do not in susceptibility to influenza, access to medical care, and other characteristics. Third, we lack information on past infections and possible immune mechanisms that could explain the differences in clinical protection we observed. Finally, given limitations in our sample size and the number of prior vaccination records we retrieved, we were unable to examine VE associated with other potentially valuable priming histories. For example, future studies should examine whether 2 doses of vaccine in consecutive seasons when A(H3N2) vaccine components were unchanged offer similar priming value in reducing the risk of A(H3N2) illness as the receipt of 2 homologous doses in the same year.

In conclusion, during 2011–12 and 2012–13, vaccination with IIV3 reduced the risk of outpatient medical visits for ARI associated with influenza virus infection by about half. Vaccinations received in previous seasons had preventive value in subsequent seasons in the form of residual protection for those who missed vaccination in and priming which boosted the benefit of IIV. Most notably, children primed with 2 doses of influenza vaccine in the previous same season appeared to enjoy even greater preventive benefit from IIV3 and may have reduced their risk of A(H3N2) illness by two-thirds. Taken together, our findings reinforce the importance of examining influenza VE among children within the context of prior vaccination history and priming. Observational studies (and possibly randomized controlled trials in countries without universal vaccination recommendations for children) are needed to confirm the importance of priming doses to immunogenicity and VE and to inform international vaccine policy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of all subjects under 9 years of age, among those vaccinated with at least one current season dose of inactivated trivalent influenza vaccine (IIV3) and among those influenza virus positive, during 2011–12 and 2012–13 seasons

	Season 2011–12											Season 2012–13										
		IIV3 Vaccinated[a]					Influenza Positive						IIV3 Vaccinated[a]					Influenza Positive				
	Sample	N	(	row %	)	p-value	N	(	row %	)	p-value	Sample	N	(	row %	)	p-value	N	(	row %	)	p-value
Sex						0.89					0.93						0.20					0.11
Female	739	371	(	50	)		98	(	13	)		700	325	(	46	)		250	(	36	)	
Male	702	355	(	51	)		92	(	13	)		627	271	(	43	)		249	(	40	)	
Age						<.0005					<.0005						< .0005					< .0005
6–23 months	350	268	(	77	)		16	(	5	)		279	202	(	72	)		44	(	16	)	
2–4 years	591	296	(	50	)		61	(	10	)		527	231	(	44	)		177	(	34	)	
5–8 years	500	162	(	32	)		113	(	23	)		521	163	(	31	)		278	(	53	)	
Race/Ethnicity						<.0005					0.04						0.01					0.02
White, non-Hispanic	869	470	(	54	)		107	(	12	)		812	372	(	46	)		313	(	39	)	
Black, non-Hispanic	196	71	(	36	)		38	(	19	)		178	60	(	34	)		80	(	45	)	
Other race, non-Hispanic	189	102	(	54	)		20	(	11	)		169	83	(	49	)		54	(	32	)	
Hispanic, any race	187	83	(	44	)		25	(	13	)		168	81	(	48	)		52	(	31	)	
High risk medical condition						0.01					0.11						< .0005					0.25
No high risk	1217	596	(	49	)		168	(	14	)		1014	415	(	41	)		390	(	38	)	
One or more high risk	224	130	(	58	)		22	(	10	)		313	181	(	58	)		109	(	35	)	
Smoker in household[b]						0.05					0.52						0.07					0.54
None	1312	673	(	51	)		171	(	13	)		1203	547	(	45	)		450	(	37	)	
One or more	119	50	(	42	)		18	(	15	)		114	42	(	37	)		46	(	40	)	
Days from onset when enrolled						0.05					0.06						0.55					0.73
≤ 2 days	560	261	(	47	)		87	(	16	)		555	249	(	45	)		212	(	38	)	
3–4 days	570	295	(	52	)		72	(	13	)		500	232	(	46	)		190	(	38	)	
5–7 days	311	170	(	55	)		31	(	10	)		272	115	(	42	)		97	(	36	)	

	Season 2011–12											Season 2012–13										
		IIV3 Vaccinated[a]					Influenza Positive						IIV3 Vaccinated[a]					Influenza Positive				
	Sample	N	(	row %	)	p-value	N	(	row %	)	p-value	Sample	N	(	row %	)	p-value	N	(	row %	)	p-value
Influenza RT-PCR Results						<.0005											< .0005					
Negative	1251	668	(	53	)							828	449	(	54	)						
Positive[c]	190	58	(	31	)							499	147	(	29	)						
A(H3N2) virus	142	46	(	32	)							207	68	(	33	)						
A(H1N1)pdm09 virus	19	5	(	26	)							4	0	(	0	)						
B virus[d]	28	6	(	21	)							289	79	(	27	)						
Month of Enrollment						0.21					< .0005						< .0005					< .0005
December	0	0	(	0	)		0	(	0	)		241	83	(	34	)		107	(	44	)	
January	238	125	(	53	)		6	(	3	)		487	218	(	45	)		229	(	47	)	
February	552	274	(	50	)		42	(	8	)		353	161	(	46	)		118	(	33	)	
March	549	285	(	52	)		122	(	22	)		244	132	(	54	)		45	(	18	)	
April	102	42	(	41	)		20	(	20	)		2	2	(	100	)		0	(	0	)	
Study Site						<.0005					0.0009						< .0005					< .0005
Michigan	437	187	(	43	)		71	(	16	)		396	174	(	44	)		151	(	38	)	
Pennsylvania	154	96	(	62	)		15	(	10	)		125	53	(	42	)		46	(	37	)	
Texas	256	111	(	43	)		16	(	6	)		292	114	(	39	)		82	(	28	)	
Washington	238	128	(	54	)		40	(	17	)		135	87	(	64	)		11	(	8	)	
Wisconsin	356	204	(	57	)		48	(	13	)		379	168	(	44	)		209	(	55	)	

[a] Vaccinated includes participants receiving at least one dose of IIV3 ≥**14** days prior to illness onset. Children in the following categories were excluded: received one or more doses of live attenuated influenza vaccine (LAIV), received 2 doses of IIV3 but with <28 days between doses, or received IIV3 <14 days from illness onset. Those who were vaccinated after illness onset were considered unvaccinated.

[b] Information on household smoking was missing from a small number of children in the 2011–12 season (n = 10) and 2012–13 season (n = 10).

[c] In the 2011–12 season, there was 1 unsubtypable influenza A specimen. In the 2012–13, there were 2 unsubtypable influenza A RT-PCR test results and 3 influenza A and B coinfections.

[d] We identified a mixture of Victoria and Yamagata B virus lineages in 2011–12 (39% and 61%, respectively) and 2012–12 (40% and 60%, respectively).

Table 2

Number and percentage of influenza virus positive (Flu +) illnesses among children under age 9 years old by US Advisory Committee on Immunization Practices' (ACIP) definitions of partial and full vaccination and estimates of influenza vaccine effectiveness (VE) against all influenza A and B viruses, against A(H3N2) viruses only, and against B influenza viruses during 2011–12 season and 2012–13 season

	Season 2011–12									Season 2012–13								
						Unadjusted		Adjusted[a]							Unadjusted		Adjusted[a]	
	Total[b]	Flu +	(	Row %	)	VE	(95% CI)	VE	(95% CI)	Total[b]	Flu +	(	Row %	)	VE	(95% CI)	VE	(95% CI)
Against all A and B influenza viruses																		
Unvaccinated (REF)	715	132	(	18	)	REF		REF		731	352	(	48	)	REF		REF	
Partially Vaccinated	135	15	(	11	)	**45**	**(3–69)**	14	(−60, 54)	123	23	(	19	)	**73**	**(57–83)**	**62**	**(37–77)**
Fully Vaccinated[c]	591	43	(	7	)	**65**	**(50–76)**	**53**	**(29–69)**	473	124	(	26	)	**61**	**(50–70)**	**49**	**(31–62)**
Against all A(H3N2) influenza only																		
Unvaccinated (REF)	679	96	(	14	)	REF		REF		517	138	(	27	)	REF		REF	
Partially Vaccinated	130	10	(	8	)	**49**	**(0–74)**	17	(−80, 62)	106	6	(	6	)	**84**	**(62–93)**	**83**	**(60–93)**
Fully Vaccinated[c]	584	36	(	6	)	**60**	**(41–73)**	**51**	**(22–69)**	409	60	(	15	)	**53**[d]	**(34–66)**	**36**[d]	**(6–56)**
Against all Influenza B viruses only[e]																		
Unvaccinated (REF)										586	207	(	35	)	REF		REF	
Partially Vaccinated										116	16	(	14	)	**71**	**(49–83)**	**52**	**(10–74)**
Fully Vaccinated[c]										412	63	(	15	)	**67**	**(55–76)**	**59**	**(40–72)**

Note: Non-zero VE estimates (with 95% confidence intervals [CI] that do not overlap with zero) are bolded.

[a]Models adjusted for study site, month of enrollment, age (in months), high medical condition, race/ethnicity, and days from illness onset to enrollment.

[b]Totals represent children included in analyses: A[H3N2] totals exclude influenza A[H1N1], A unsubtyped and influenza B cases; influenza B totals exclude influenza A cases. For season 2012–13, there were 3 influenza A(H3N2) and B coinfections that were excluded. Thus, the percentage influenza positive (Flu+) is simply the number of A(H3N2) illnesses divided by the sum of influenza negatives and A(H3N2) positives.

[c]The US Advisory Committee on Immunization Practices (ACIP) makes annual recommendations for fully immunizing children against influenza. ACIP 2011–12 criteria defines full vaccination as 2 current season doses (≥28 days apart) or ≥1 dose in the prior season and 1 dose in the current season; partial vaccination is a single dose of vaccine with no prior dose. ACIP 2012–13 criteria defines full

vaccination as 2 current season doses or 1 dose with full priming (≥2 vaccines since 2010–11; ≥1 doses before and ≥1 after July 2010; ≥2 doses before July 2010, and ≥1 of monovalent 2009[H1N1] pandemic vaccine); partial vaccination is a single dose of vaccine with either no prior dose or incomplete priming.

[d] During the 2012–13 season, using the 2012–13 ACIP criteria, fully vaccinated children had significantly lower estimates of VE against A(H3N2) illness than partially vaccinated in the unadjusted (p = .015) and adjusted models (p = .021). Fully vaccinated children had 2.7-fold (95% CI = 1.2–6.3) higher odds of being influenza positive than partially vaccinated children in the adjusted model.

[e] Due to small numbers of observations we did not make VE estimates against B influenza virus infections in 2011–12 (N = 28) nor against A(H1N1)pdm09 virus infections in 2011–12 (N = 19) or 2012–13 seasons (N = 4).

Table 3

Number and percentage of influenza virus positive (Flu +) illnesses among children aged 2–8 years by vaccine exposure category and estimates of influenza vaccine effectiveness (VE) against all influenza A and B viruses in each season and against A(H3N2) viruses only and against B influenza viruses only during the combined 2011–12 and 2012–13 seasons

	Season 2011–12 - All Viruses							Season 2012–13 - All Viruses							Seasons 2011–12 and 2012–13- A[H3N2] only[a]							Season 2012–13 - B viruses only[b]						
						Adjusted[c]							Adjusted[c]							Adjusted[c]								Adjusted[c]	
	Total	Flu +	(Row %	%	)	VE	(95% CI)	Total	Flu + *c*	(Row %	%	)	VE	(95% CI)	Total[b]	H3 Flu +	(Row %	%	)	VE	(95% CI)	Total[a]	Flu B+	(Row %	%	)	VE	(95% CI)
Current Season Dose of IIV3 Regardless of Priming for Ages 2–8 Years Old																												
Unvaccinated (REF)	633	128	(	20	)	REF		654	332	(	51	)	REF		1051	224	(	21	)	REF		516	194	(	38	)	REF	
One or more doses	458	46	(	10	)	**47**	**(22–65)**	394	123	(	31	)	**49**	**(32–62)**	773	90	(	12	)	**47**	**(28–60)**	338	67	(	20	)	**53**	**(32–68)**
Alternative Definitions of Priming for Ages 2–8 Years Old																												
Priming: ≥1 doses of any influenza vaccine in prior season only[d]																												
Unvaccinated current and prior season (REF)	449	101	(	22	)	REF		471	253	(	54	)	REF		737	171	(	23	)	REF		365	147	(	40	)	REF	
Primed only (with no current season dose)	184	27	(	15	)	**40**	**(1–64)**	183	79	(	43	)	**36**	**(6–56)**	314	53	(	17	)	**39**	**(11–58)**	151	47	(	31	)	**38**	**(2–61)**
Current season dose(s) only (with no prime)	102	14	(	14	)	30	(−35, 64)	95	25	(	26	)	**66**	**(41–80)**	178	20	(	11	)	**58**	**(27–75)**	84	14	(	17	)	**66**	**(33–83)**
Current season and prime dose(s)	356	32	(	9	)	**61**	**(37–76)**	299	98	(	33	)	**52**	**(32–66)**	595	70	(	12	)	**53**	**(34–66)**	254	53	(	21	)	**58**	**(34–73)**
Priming: ≥1 doses of any influenza vaccine in any prior season[e]																												
Unvaccinated in current and prior seasons (REF)	249	51	(	20	)	REF		228	111	(	49	)	REF		396	81	(	20	)	REF		176	59	(	34	)	REF	
Primed only (with no current season dose)	384	77	(	20	)	16	(−30, 46)	426	221	(	52	)	8	(−32 35)	655	143	(	22	)	9	(−28, 36)	340	135	(	40	)	−1	(−57, 35)
Current season dose only (with no prime)	46	7	(	15	)	−12	(−187, 56)	27	10	(	37	)	25	(−81, 69)	64	8	(	13	)	33	(−55, 71)	23	6	(	26	)	6	(−179, 68)
Current season and prime doses	412	39	(	9	)	**58**	**(30–74)**	367	113	(	31	)	**54**	**(32–69)**	709	82	(	12	)	**51**	**(29–66)**	315	61	(	19	)	**55**	**(37, 73)**

	Season 2011–12 - All Viruses							Season 2012–13 - All Viruses							Seasons 2011–12 and 2012–13- A[H3N2] only[a]								Season 2012–13 - B viruses only[b]						
						Adjusted[c]							Adjusted[c]							Adjusted[c]										Adjusted[c]	
	Total	Flu +	(Row %	%	)	VE	(95% CI)	Total	Flu + *c*	(Row %	%	)	VE	(95% CI)	Total[b]	H3 Flu +	(Row %	%	)	VE	(95% CI)		Total[a]	Flu B+	(Row %	%	)	VE	(95% CI)
Priming: ≥2 doses of any influenza vaccine received across prior seasons[f]																													
Unvaccinated current season and unprimed (REF)	378	78	(	21	)	REF		340	165	(	49	)	REF		343	75	(	22	)	REF			166	59	(	36	)	REF	
Primed only (with no current season dose)	255	50	(	20	)	26.2	(−14, 52)	312	165	(	53	)	−10	(−42, 26)	708	149	(	21	)	16	(−19, 41)		350	135	(	39	)	10	(−40, 42)
Current season dose only (with no prime)	162	20	(	12	)	32.7	(−19, 62)	72	23	(	32	)	**44**	**(1–68)**	37	4	(	11	)	42	(−84, 82)		17	5	(	29	)	14	(−184, 74)
Current season and prime doses	296	26	(	9	)	**64.8**	**(42, 79)**	324	102	(	31	)	**47**	**(26–62)**	736	86	(	12	)	53	**(32–68)**		321	62	(	19	)	**59**	**(32–75)**
Priming: 2 doses received in the same prior season[g]																													
Unvaccinated current season **and** unprimed (REF)	511	106	(	21	)	REF		508	248	(	49	)	REF		844	179	(	21	)	REF			398	138	(	35	)	REF	
Primed only (with no current season dose)	122	22	(	18	)	16	(−46, 51)	146	84	(	58	)	−53	(−132, −1)	207	45	(	22	)	−23	(−85, 19)		118	56	(	47	)	−56	(−153, 4)
Current season dose only (with no prime)	318	41	(	13	)	**37**	**(3–59)**	254	95	(	37	)	**37**	**(11–55)**	511	75	(	15	)	**33**	**(7–52)**	*h*	210	51	(	24	)	**42**	**(11–63)**
Current season and prime doses	140	5	(	4	)	**80**	**(49–93)**	140	28	(	20	)	**58**	**(32–75)**	262	15	(	6	)	**70**	**(47–83)**		128	16	(	13	)	68	**(21–77)**

Note: Non-zero VE estimates (with 95% confidence intervals [CI] that do not overlap with zero) are bolded.

[a] Totals exclude children with illnesses associated with influenza B viruses, A(H1N1)pdm09 virus, or unsubtyped A viruses. For season 2012–13, there were 3 influenza A(H3N2) and B coinfections that were excluded. Thus, the percentage influenza positive (Flu+) is simply the number of A(H3N2) illnesses divided by the sum of influenza negatives and A(H3N2) positives. This is presented as an illustration to aid interpreting VE.

[b] Totals exclude children with illnesses associated with influenza A viruses. Thus, the percentage of children who are influenza B virus positive (Flu B+) is simply the number of influenz B virus illnesses divided by the sum of influenza negatives and influenza B positives. This is presented as an illustration to aid interpreting VE.

[c] Models adjusted for study site, month of enrollment, age (in months), high risk status, race/ethnicity, and days from illness onset to enrollment. The model for A(H3N2) illness also included a variable for season and an interaction term for season by month.

[d] For season 2011–12, prior season is 2010–11; for season 2012–13, prior season is 2011–12; the prior vaccine could be inactivated or live attenuated. Receipt of monovalent A(H1N1)pdm09 vaccine was not included. Unvaccinated children received no vaccine in current nor prior season.

[e] Any prior season includes any seasonal vaccination received prior to the current study season (either 2011–12 or 2012–13). Unvaccinated children received no current season IIV3 and have no record of any prior influenza vaccination.

[f]Primed children had records confirmed receipt of 2 or more doses summed across prior seasons; "unvaccinated and unprimed" children did not receive current season IIV3 and did not receive 2 or more previous doses (but may have had 1 dose in one or more seasons).

[g]Primed children received 2 doses in a single season prior to the study season; "unvaccinated and unprimed" children did not receive current season IIV3 and did not have 2 doses of any influenza vaccine in a single prior season (but may have had 2 or more doses across multiple prior seasons).

[h]The odds of being A(H3N2) positive were 2.4-fold (95% CI = 1.4–4.3) higher among children who received IIV3 but were unprimed compared to children who received IIV3 after receiving 2 doses in a previous season.