Influenza Vaccine Effectiveness Against Pediatric Deaths: 2010–2014

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abstract

BACKGROUND AND OBJECTIVES: Surveillance for laboratory-confirmed influenza-associated pediatric deaths since 2004 has shown that most deaths occur in unvaccinated children. We assessed whether influenza vaccination reduced the risk of influenza-associated death in children and adolescents.

METHODS: We conducted a case–cohort analysis comparing vaccination uptake among laboratory-confirmed influenza-associated pediatric deaths with estimated vaccination coverage among pediatric cohorts in the United States. Case vaccination and high-risk status were determined by case investigation. Influenza vaccination coverage estimates were obtained from national survey data or a national insurance claims database. We estimated odds ratios from logistic regression comparing odds of vaccination among cases with odds of vaccination in comparison cohorts. We used Bayesian methods to compute 95% credible intervals (CIs) for vaccine effectiveness (VE), calculated as (1 − odds ratio) × 100.

RESULTS: From July 2010 through June 2014, 358 laboratory-confirmed influenza-associated pediatric deaths were reported among children aged 6 months through 17 years. Vaccination status was determined for 291 deaths; 75 (26%) received vaccine before illness onset. Average vaccination coverage in survey cohorts was 48%. Overall VE against death was 65% (95% CI, 54% to 74%). Among 153 deaths in children with underlying high-risk medical conditions, 47 (31%) were vaccinated. VE among children with high-risk conditions was 51% (95% CI, 31% to 67%), compared with 65% (95% CI, 47% to 78%) among children without high-risk conditions.

CONCLUSIONS: Influenza vaccination was associated with reduced risk of laboratory-confirmed influenza-associated pediatric death. Increasing influenza vaccination could prevent influenza-associated deaths among children and adolescents.

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WHAT'S KNOWN ON THIS SUBJECT: Annual influenza vaccination beginning at 6 months of age is recommended to prevent influenza and its complications. Most influenza-associated pediatric deaths occur in unvaccinated children. Evidence for the effectiveness of vaccination in preventing influenza-associated deaths is needed.

WHAT THIS STUDY ADDS: Estimated influenza vaccine effectiveness was 65% (95% credible interval, 54% to 74%) against laboratory-confirmed influenza-associated deaths among children. Vaccine effectiveness was lower for children with underlying medical conditions, but protection remained significant. Sensitivity analyses supported the findings.

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In the United States, annual influenza vaccination of children is recommended to reduce adverse health impacts of influenza and prevent severe complications.[1] Though uncommon, influenza-associated deaths among children occur annually, with varying incidence depending on the severity of the influenza season.[2,3] From 1976 to 2007, influenza was estimated to account for >100 deaths annually among children and adolescents.[4,5] Since 2004, when influenza-associated deaths among children aged <18 years became nationally notifiable,[6] reported numbers of deaths have ranged from 37 in the 2011–2012 season to 358 during the 2009 pandemic.[2] Surveillance for pediatric deaths has contributed to identification of groups at high risk of influenza-related mortality, such as children with neurologic conditions,[7] and documented fatal illness among children with and without underlying high-risk medical conditions.[3] Previous reports have indicated low rates of influenza vaccination among pediatric deaths despite a high prevalence of underlying medical conditions that increase risk for influenza complications.[3,8] In this analysis, we used a case–cohort approach comparing influenza vaccination rates among influenza-associated pediatric deaths with vaccination coverage estimates for cohorts of US children to estimate the effectiveness of influenza vaccination against laboratory-confirmed influenza-associated death.

METHODS

Influenza-Associated Pediatric Deaths

To estimate influenza vaccine effectiveness (VE) against death, we used a case–cohort design (or screening method).[9,10] Cases were deaths in US residents aged <18 years with laboratory-confirmed influenza virus infection that were reported to the Influenza-Associated Pediatric Mortality Surveillance System.[3] Data obtained from standardized case report forms included demographic characteristics, state of residence, results of laboratory testing, underlying high-risk medical conditions, and influenza vaccination status. Confirmation of influenza virus infection consisted of clinical diagnostic testing during illness or postmortem examination including antigen detection, viral culture, or nucleic acid amplification. We included children ≥6 months old on November 1 of the influenza season during which death occurred who were eligible to receive ≥1 dose of seasonal influenza vaccine and had complete medical history; 10 deaths among children who turned 6 months old after November 1 were excluded. For cases without illness onset date, we estimated onset as 4 days before death, based on the mean duration of illness among cases with known onset date. We excluded 7 children who received their first dose of current season vaccine <14 days before illness onset because vaccine-induced protection may be incomplete.[11]

Health department personnel determined vaccination status based on a review of available information from the child's medical records, health care provider, state or county immunization information systems, parental report, or coroner's report. Children were considered vaccinated (either fully or partially) if records indicated receipt of ≥1 doses of current season influenza vaccine ≥14 days before onset of illness. Partial vaccination was defined as receipt of 1 dose when health department personnel determined that 2 doses were indicated. Vaccination status was listed as unknown if surveillance personnel could not determine from available records whether the child had received influenza vaccine. If immunization records indicated vaccination for previous seasons but no current season vaccination, children were assumed to be unvaccinated. A sensitivity analysis explored the effects of assuming that children with unknown vaccination status were unvaccinated. Presence of underlying medical conditions was recorded on case report forms according to high-risk conditions for influenza-related complications identified by the Advisory Committee on Immunization Practices (ACIP)[12]: asthma, chronic lung disease, neurologic or neurodevelopmental disorders, heart disease (including congenital heart disease), blood disorders, endocrine disorders, metabolic disorders, kidney disorders, liver disorders, immunosuppression, and pregnancy. For consistency with vaccination coverage estimates, age groups were defined based on child's age on November 1 for influenza season of fatal illness.

Influenza Vaccination Coverage in Cohorts

We used 3 sources of influenza vaccination coverage among comparison cohorts of US children and adolescents: National Immunization Survey–Flu (NIS-Flu),[13] National Health Interview Survey (NHIS),[14] and the MarketScan Commercial Claims and Encounters database (Truven Health Analytics, Ann Arbor, MI). NIS-Flu is a national telephone survey of households with children aged 6 months through 17 years that produces national and state-level estimates (and for some cities, including Chicago and New York City) of influenza vaccine coverage for children. NHIS is an in-person household survey that provides nationally representative estimates of influenza vaccination for children aged 6 months through 17 years with and without specified high-risk medical conditions (cystic fibrosis, sickle cell anemia, diabetes, congenital heart disease or other heart condition, cerebral palsy, muscular dystrophy, or seizures, or an asthma episode in the past 12 months).[15] In NIS-Flu and NHIS, seasonal influenza vaccination coverage is estimated from parental report of child's receipt of ≥1 dose of seasonal influenza vaccine. Data from NIS-Flu and NHIS are weighted by age, sex, race or ethnicity, and geographic area to represent the US population. Monthly coverage estimates and SEs for vaccination received during July or August (depending on survey and season) through May were calculated by Kaplan–Meier survival analysis of data from interviews conducted from August, September, or October through June.[16] Age group was based on the child's age on November 1 of each influenza season.

In the MarketScan Commercial Claims and Encounters database, coverage estimates were based on commercial insurance claims for influenza vaccination; children with no vaccination claim were assumed unvaccinated. We analyzed data from July 2010 through June 2014 among children continuously enrolled in a health plan from January preceding each influenza season. We determined underlying high-risk medical conditions based on International Classification of Diseases, Ninth Revision codes associated with hospitalizations and outpatient visits during a 12-month period.[17] We calculated cumulative vaccination coverage from August through May each season among children aged <18 years with and without underlying high-risk medical conditions. Age categories were based on child's age at vaccination or at the beginning of each calendar year; children in the youngest age category (0–4 years) were ≥10 months old on November 1. For MarketScan comparison cohorts, state-level coverage estimates were used for children without high-risk conditions, and national coverage estimates were used for children in high-risk groups because of their smaller sample sizes.

Analysis

The case–cohort method[9,10] produces an odds ratio (OR), which estimates the relative risk for influenza-associated death among vaccinated versus unvaccinated children. Influenza VE was estimated as (1 − OR). ORs were obtained from logistic regression models where vaccination status of the case was the dependent variable and the log odds of vaccination (proportion vaccinated/1 − proportion vaccinated) in the comparison cohort from NIS-Flu, NHIS, or MarketScan data were entered as an offset. With this offset in the model, the intercept provides an estimate of the log(OR). Cases and corresponding coverage estimates were stratified by influenza season, age, and state of residence (for NIS-Flu and MarketScan) or high-risk condition (for NHIS and MarketScan) for the month ending ≥2 weeks before case illness onset. For average coverage estimates by age group, season, or influenza virus type, we derived confidence limits by averaging the variance of independent, normally distributed coverage estimates. To incorporate uncertainty in coverage estimates from survey data, 10 000 estimates were sampled from normally distributed vaccination coverage estimates for NIS-Flu and NHIS comparison cohorts to calculate 95% credible intervals (CIs) for VE estimates. Because MarketScan estimates were derived from all observations without sampling, confidence limits for VE estimates based on MarketScan data were estimated from logistic regression assuming fixed coverage estimates. We assumed that cases did not contribute uncertainty to VE estimates. Sensitivity analyses were conducted under the assumption that cases with unknown vaccination status were unvaccinated and that coverage estimates based on parental report underestimated coverage by 10% or overestimated coverage by 10% or 20%.[18,19] χ^2 tests were used to evaluate proportions, and 2-sided *P* values <.05 were considered significant. Analyses were conducted in SAS version 9.4 (SAS Institute, Inc, Cary, NC) and R (version 3.1.1; R Core Team, Vienna, Austria).

RESULTS

This analysis included 358 influenza-associated pediatric deaths that occurred during 4 influenza seasons from July 1, 2010 through June 30, 2014 among children aged 6 months through 17 years. Deaths were reported from 43 states, New York City, Chicago, and Washington, DC. Vaccination status was unknown for 67 (19%) children who died. Of 291 deaths in children with known vaccination status, 75 (26%) children had received seasonal influenza vaccination ≥14 days before illness onset and were considered vaccinated. Vaccine type was recorded for 62 cases; 12 (19%) received live-attenuated influenza vaccine and 50 (81%) received inactivated influenza vaccines. Vaccinated proportions were similar for boys and girls and did not differ significantly by age category (Table 1). Black non-Hispanic children who died had significantly lower vaccination rates compared with white non-Hispanic children who died ($P < .05$). Among 31 deaths in vaccinated children aged 6 months through 4 years, 16 (52%) were partially vaccinated.

A total of 153 (53%) of 291 pediatric deaths with known vaccination status occurred among children with ≥1 ACIP underlying high-risk medical conditions. The prevalence of high-risk conditions among pediatric deaths increased from 41% among those aged 6 months to 4 years to 57% and 62% among 5- to 12-year-olds and 13- to 17-year-olds, respectively. Although the proportion of cases vaccinated increased from 20% among those without high-risk conditions to 31% among those with ≥1 high-risk condition and 37% among those with ≥2 high-risk conditions, <50% of cases in all individual high-risk categories were vaccinated (Table 1).

Average influenza vaccination coverage among comparison cohorts in the month preceding case illness onset was higher than vaccinated proportions among pediatric deaths for most months (Fig 1). Among deaths in children with known vaccination status, children who died had lower vaccination uptake for all age categories, seasons, and infecting influenza virus types than the NIS-Flu cohort (Table 2). Overall, average vaccination coverage was 48% among NIS-Flu comparison cohorts. Estimated VE against pediatric death was 65% (95% CI, 54% to 74%). Estimated VE ranged from 40% among 13- to 17-year-olds to 76% among 5- to 12-year-olds. By season, VE ranged from 54% in the 2010 to 2011 season to 80% (with overlapping credible intervals) in the mild 2011 to 2012 season, with the lowest number of pediatric deaths. By virus type, VE point estimates were similar against death associated with influenza A virus (66%) and influenza B virus (62%).

Vaccination uptake among pediatric deaths was also lower than average coverage in the NHIS comparison cohorts with or without high-risk conditions (Table 3). Estimated VE was 51% (95% CI, 31% to 67%) among children with high-risk medical conditions and 65% (95% CI, 47% to 78%) among those without high-risk conditions, similar to VE estimated via NIS-Flu. VE point estimates were lower among children with high-risk conditions compared with those without high-risk conditions in most analyses, but CIs widely overlapped. Among children with high-risk conditions, VE estimates were statistically significant (95% CIs not overlapping 0) only for children aged 5 to 12 years. Estimated VE was statistically significant for 3 of 4 seasons among both children with and without high-risk conditions, for influenza A virus infections among both groups of children, and for influenza B virus infections among children without high-risk conditions.

Table 4 compares the prevalence of high-risk conditions and uptake of influenza vaccination among influenza-associated pediatric deaths and children in the MarketScan database (including an average of >6 million children aged <18 years during the 4 influenza seasons).

TABLE 1 Characteristics of Influenza-Associated Pediatric Deaths With Known Vaccination Status, United States, 2010–2011 to 2013–2014 Influenza Seasons (*N* = 291)

	Total		Vaccinated[a]	
Characteristic	No.	%	No.	% Vaccinated
Overall	291	—	75	26
Sex				
Female	135	46	30	22
Male	156	54	45	29
Age				
6 mo–4 y	93	32	31	33
5–12 y	128	44	26	20
13–17 y	70	24	18	26
Race and ethnicity				
White, non-Hispanic	154	53	42	27
Hispanic or Latino	57	20	12	21
Black, non-Hispanic	39	13	3	8
Asian or Pacific Islander	12	4	8	67
American Indian or Alaskan Native	7	2	2	29
Identified by ≥2 races	1	<1	1	100
Unknown	21	7	7	33
High-risk medical conditions[b]				
No high-risk medical conditions	135	47	27	20
≥1 high-risk medical condition[c]	153	53	47	31
Chronic pulmonary disease (including asthma)	72	25	25	35
Metabolic disorders (including diabetes)	18	6	8	44
Neurologic and neuromuscular disorders	75	26	25	33
Renal disease	3	1	0	0
Cardiac or congenital heart disease	30	10	7	23
Immunosuppressive condition	15	5	7	47
Pregnancy	2	1	0	0
≥2 high-risk medical conditions[c]	46	16	17	37
Other high-risk conditions[d]	37	13	13	35
Location of death[e]				
In hospital	189	66	54	29
Emergency department	54	19	17	31
Outside hospital	45	15	3	7
Influenza virus type or subtype				
Influenza A	173	59	44	25
A(H1N1)pdm09	87	30	24	28
A(H3N2)	68	23	15	22
A, subtype not distinguished				
Influenza B	113	39	31	27
Coinfection (types A and B)	5	2	0	0

Excludes children with unknown vaccination status.
[a] Receipt of ≥1 dose of influenza vaccine ≥14 d before onset of illness for season in which death occurred.
[b] Case investigation form indicates presence of high-risk condition, as defined by ACIP guidance for conditions that increase risk for complications of influenza. High-risk status was not reported for 3 deaths.
[c] >1 medical condition could be reported for each pediatric death.
[d] Includes chromosomal abnormalities, genetic syndromes, and mitochondrial disorders.
[e] Location of death was missing for 3 deaths.

Vaccination coverage in MarketScan among children aged <18 years by high-risk group ranged from 27% among those with no high-risk condition to 45% among children with ≥2 high-risk conditions (Table 4). Prevalence of high-risk conditions was higher among pediatric deaths compared with the MarketScan cohort, and vaccination rates were lower among pediatric deaths for most high-risk groups.

In sensitivity analysis treating deaths with unknown vaccination status as unvaccinated, overall VE increased to 74% for the NIS-Flu cohort, 73% for the NHIS cohort without high-risk conditions, and 50% for the MarketScan cohort without high-risk conditions (Table 5). Alternatively, assuming 10% overestimation of vaccination by parental report in the survey data led to estimates of 56% with NIS-Flu and 58% with the NHIS no high-risk cohort. MarketScan estimates treating deaths with unknown vaccination status as unvaccinated were similar to NHIS estimates assuming 20% overestimation of coverage by parental report. VE estimates among children with high-risk conditions were lower than among those without high-risk conditions for the MarketScan and NHIS cohorts. Estimated VE among children with high-risk conditions remained statistically significant; NHIS coverage estimates were decreased by 10%, whereas that among children without high-risk conditions remained significant when NHIS estimates were decreased by 20%.

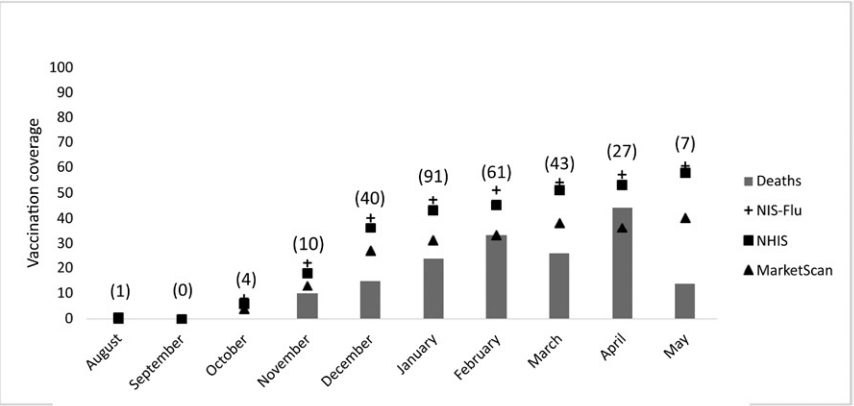

FIGURE 1

Comparison of vaccination coverage among influenza-associated pediatric deaths and comparison cohorts during 4 influenza seasons, according to month of death. Note: Number of deaths shown in parentheses. Coverage estimates for comparison cohorts correspond to month preceding case illness onset.

TABLE 2 Percentage Vaccinated Among Influenza-Associated Pediatric Deaths Compared With NIS-Flu Cohorts, With VE Estimates by Season and Age Group

Stratum	Influenza-Associated Deaths[a]		NIS-Flu[b]		VE[c]	
	No. Vaccinated/Total	% Vaccinated	Average % Vaccinated	(LCL, UCL)	%	95% CI
Overall	75/291	26	48	(42, 55)	65	54 to 74
Age						
6 mo–4 y	31/93	33	55	(47, 62)	61	40 to 76
5–12 y	26/128	20	50	(44, 56)	76	63 to 85
13–17 y	18/70	26	36	(30, 43)	40	0 to 67
Season						
2010–2011	22/73	30	47	(39, 55)	54	22 to 74
2011–2012	4/21	19	51	(44, 59)	80	41 to 95
2012–2013	28/116	24	46	(39, 52)	64	46 to 77
2013–2014	21/81	26	53	(47, 58)	71	52 to 83
Influenza virus						
Influenza A	44/173	25	48	(41 55)	66	53 to 76
Influenza B	31/113	27	49	(42, 55)	62	42 to 75

LCL, lower 95% confidence limit; UCL, upper 95% confidence limit; CI, credible interval.

[a] Excludes cases with unknown vaccination status.

[b] Average influenza vaccine coverage estimates (with lower and upper 95% confidence limits) for NIS-Flu comparison cohorts, paired by season, age category, and state of residence with pediatric deaths, during month ending >14 d before case illness onset.

[c] VE calculated as 100 × (1 − OR) from logistic regression comparing odds of vaccination among influenza-associated deaths to odds of vaccination in NIS-Flu comparison cohorts, with Bayesian 95% CIs.

DISCUSSION

We used national surveillance data on laboratory-confirmed influenza deaths and 3 comparison cohorts over 4 influenza seasons to estimate the effectiveness of influenza vaccination to prevent influenza-associated pediatric deaths. Best estimates based on NHIS survey data suggested that vaccination reduced the risk of influenza-associated death by half among children with high-risk conditions and by nearly two-thirds among children without high-risk conditions. Despite high prevalence (53%) of underlying conditions that increase risk of severe influenza-related complications, only 1 in 4 children who died with laboratory-confirmed influenza had been vaccinated. These results reinforce the need to increase influenza vaccination coverage, especially among children at increased risk of influenza-related complications and death.

To our knowledge, this is the first study to use laboratory-confirmed outcomes to investigate influenza VE against influenza-associated deaths. Observational studies that have used nonspecific outcomes, such as all-cause mortality, have often

TABLE 3 Percentage Vaccinated Among Influenza-Associated Pediatric Deaths Compared With NHIS Sample According to High-Risk Status, With VE Estimates by Season and Age Group

Stratum	Children With High-Risk Medical Conditions						Children Without High-Risk Medical Conditions					
	Influenza-Associated Deaths[a]		NHIS Sample[b]		VE[c]		Influenza-Associated Deaths[a]		NHIS Sample[b]		VE[c]	
	No. Vaccinated/ Total	% Vaccinated	Average % Vaccinated (LCL, UCL)		%	95% CI	No. Vaccinated/ Total	% Vaccinated	Average % Vaccinated (LCL, UCL)		%	95% CI
Overall	47/153	31	47	(37, 57)	51	31 to 67	27/135	20	40	(38, 43)	65	47 to 78
Age												
6 mo–4 y	14/38	37	48	(37, 60)	39	−22 to 71	16/54	30	46	(43, 49)	52	14 to 74
5 –12 y	19/72	26	49	(41, 57)	65	41 to 81	7/55	13	39	(37, 42)	79	57 to 92
13–17 y	14/43	33	41	(31, 51)	33	−28 to 67	4/26	15	30	(27, 33)	60	−5 to 89
Season												
2010–2011	12/29	41	45	(36, 54)	13	−85 to 62	9/43	21	40	(37, 42)	63	24 to 84
2011–2012	3/13	23	48	(39, 56)	73	0 to 94	1/8	13	45	(42, 47)	89	16 to 99
2012–2013	21/64	33	43	(34, 53)	38	0 to 65	7/52	14	37	(34, 39)	76	46 to 90
2013–2014	11/47	23	53	(42, 63)	75	50 to 88	10/32	31	46	(43, 49)	48	−11 to 77
Influenza virus												
Influenza A	26/95	27	46	(36, 56)	59	35 to 74	18/78	23	41	(39, 44)	59	31 to 77
Influenza B	21/55	38	48	(39, 57)	35	−13 to 63	9/55	16	38	(36, 41)	71	43 to 87

LCL, lower 95% confidence limit; UCL, upper 95% confidence limit; CI, credible interval.

[a] Excludes cases with unknown vaccination status.

[b] Average influenza vaccine coverage estimates (with lower and upper 95% confidence limits) for NHIS comparison cohorts, paired by season, age category, and high-risk status with pediatric deaths, during month ending >14 d before case illness onset.

[c] VE estimates and Bayesian 95% CIs estimated from logistic regression.

overestimated effects of influenza vaccination on mortality in older adults.[20–22] Estimates of VE against death from this analysis were similar to VE against medically attended influenza among pediatric patients for the same seasons. For 2011—2012 through 2013—2014 seasons, estimated VE against medically attended influenza ranged from 45% to 57% among young children (ages 6 months–8 years) and from 39% to 58% among older children (ages 9–17 years).[23–26] In addition, estimated VE against severe life-threatening influenza among children admitted to PICUs during the 2010—2011 and 2011—2012 seasons was 74%.[27] VE against medically attended influenza has been used in models to estimate deaths averted by influenza vaccination.[28] Results of this analysis support the use of VE against medically attended influenza to estimate deaths averted by influenza vaccination.

Case–cohort analyses have previously been used to estimate influenza VE against laboratory-confirmed influenza,[29] effectiveness of seasonal influenza vaccine against influenza A(H1N1) pdm09–associated illness,[30] and risk factors for hospitalization and death due to influenza A(H1N1) pdm09 infection.[31] In the main analyses, VE estimates were based

TABLE 4 Prevalence of High-Risk Conditions and Influenza Vaccination Among Children With Influenza-Associated Death and Children in MarketScan Commercial Claims Database, 2010–2014

High-Risk Category[a]	Influenza-Associated Pediatric Deaths (*N* = 291)			MarketScan Commercial Claims Data Set (*N* = 6 543 363)[b]		
	No.	% Total	No. (%) Vaccinated	No.	% Total	No. (%) Vaccinated[c]
No high-risk condition[d]	138	47	28 (20)	5 815 031	89	1 557 855 (27)
Pulmonary conditions, including asthma	39	13	11 (28)	414 868	6	175 528 (42)
Metabolic disorders	6	2	2 (33)	33 248	<1	11 250 (34)
Neurologic disorders	37	13	11 (30)	70 631	1	24 627 (35)
Cardiac and congenital heart diseases	17	6	4 (24)	45 448	<1	16 367 (36)
Immunosuppressive conditions	6	2	2 (33)	58 094	1	18 022 (31)
Pregnancy[e]	2	1	0 (0)	18 523	<1	6316 (34)
≥2 high-risk conditions	46[f]	16	17 (37)	83 146	1	37 114 (45)

[a] Influenza-associated pediatric deaths and children from MarketScan database were classified into mutually exclusive high-risk categories based on groups at increased risk of complications, hospitalizations, or death due to influenza according to the ACIP; children with ≥2 high-risk conditions included those with conditions from ≥2 ACIP high-risk categories.

[b] Numbers and percentages for MarketScan Commercial Claims data set are averages over 4 influenza seasons, 2010–2011 through 2013–2014.

[c] Average over 4 influenza seasons of the number vaccinated by May of each season.

[d] Includes 3 deaths with unknown high-risk status.

[e] Pregnancy restricted to children aged 13–17 y.

[f] Among influenza-associated pediatric deaths, includes children with pulmonary conditions (*n* = 33), metabolic disorders (*n* = 12), neurologic disorders (*n* = 38), cardiac diseases (*n* = 13), and immunosuppressive conditions (*n* = 9).

TABLE 5 Sensitivity Analysis for VE Estimates With Adjustments to Case and Comparison Cohort Vaccination Status

Sensitivity Analysis	No. Flu-Related Deaths	% Cases Vaccinated	Average % Vaccinated (LCL, UCL)	VE	95% CI
NIS-Flu comparison cohort			NIS-Flu cohort[a]		
Excluding deaths with unknown vaccination status	291	26	48 (42, 55)	65	54 to 74
Treating deaths with unknown vaccination status as unvaccinated	358	21	49 (42, 55)	74	66 to 80
Assuming 10% underestimation[b]	291	26	53 (46, 59)	72	64 to 79
Assuming 10% overestimation[b]	291	26	44 (38, 49)	56	44 to 67
Assuming 20% overestimation[b]	291	26	39 (34, 44)	46	29 to 59
NHIS high-risk cohort			NHIS high-risk cohort[c]		
Excluding deaths with unknown vaccination status	153	31	47 (37, 57)	51	31 to 67
Treating deaths with unknown vaccination status as unvaccinated	182	26	47 (37, 56)	62	47 to 73
Assuming 10% underestimation[b]	153	31	52 (41, 62)	61	44 to 73
Assuming 10% overestimation[b]	153	31	42 (34, 51)	41	16 to 59
Assuming 20% overestimation[b]	153	31	37 (30, 45)	27	−4 to 50
NHIS no high-risk cohort			NHIS no high-risk cohort[c]		
Excluding deaths with unknown vaccination status	135	20	40 (38, 43)	65	47 to 78
Treating deaths with unknown vaccination status as unvaccinated	167	16	40 (38, 43)	73	60 to 83
Assuming 10% underestimation[b]	135	20	44 (41,47)	71	56 to 81
Assuming 10% overestimation[b]	135	20	36 (34, 39)	58	35 to 73
Assuming 20% overestimation[b]	135	20	32 (30, 34)	49	24 to 68
MarketScan high-risk cohort			MarketScan high-risk cohort[c]		
Excluding deaths with unknown vaccination status	153	31	35	18	−17 to 42[d]
Treating deaths with unknown vaccination status as unvaccinated	182	26	35	38	12 to 56[d]
MarketScan no high-risk cohort			MarketScan no high-risk cohort[e]		
Excluding deaths with unknown vaccination status	135	20	28	38	4 to 60[d]
Treating deaths with unknown vaccination status as unvaccinated	167	16	27	50	24 to 67[d]

LCL, lower 95% confidence limit; UCL, upper 95% confidence limit; CI, credible interval.
[a] Average coverage estimate for NIS-Flu cohort paired with pediatric death by season, age group, state of residence, and month preceding illness onset.
[b] Survey coverage estimates for each comparison cohort were increased by 10% or reduced by 10% or 20%.
[c] Average national coverage estimate for NHIS and MarketScan comparison cohorts paired with pediatric death by season, age group, high-risk status, and month preceding illness onset.
[d] 95% confidence intervals for VE from logistic regression with odds of vaccination in MarketScan comparison cohort entered as an offset.
[e] For children without high-risk conditions, state-specific coverage estimates were used for MarketScan comparison cohorts paired with pediatric death by season, age group, and month preceding illness onset.

on comparisons with NHIS and NIS-Flu, the 2 surveys used to measure influenza vaccine coverage among US children. NHIS includes coverage estimates among children with high-risk conditions, and NIS-Flu, with its larger sample size, provides state-level vaccination coverage. NHIS has been considered the most representative source for influenza vaccination coverage estimates among children[15] and is used as the data source to track progress toward Healthy People 2020 goals.[32] VE estimates based on NIS-Flu were similar to those based on the NHIS cohort without high-risk conditions.

This study highlights the importance of annual influenza vaccination for children, especially those with underlying high-risk medical conditions. Previous reports have highlighted the high prevalence of underlying high-risk conditions among children who die of influenza-related complications, including neurologic disorders and conditions associated with underlying chromosomal abnormalities and genetic syndromes.[3,7,33] Although children with high-risk conditions in both the NHIS and MarketScan data were more likely than children without high-risk conditions to be vaccinated, vaccination coverage among children at high risk remained below the Healthy People 2020 target of 70% during these seasons.[32] Because of the higher risk of severe complications and influenza-associated death among children with underlying conditions, vaccination is especially important for these children. Previous reports have also highlighted the occurrence of influenza-associated death in previously healthy children with no reported high-risk conditions.[3,34] The current study indicates that although VE estimates tended to be higher among children without underlying high-risk conditions, significant protection was demonstrated for both groups of children for most seasons.

This analysis is subject to several limitations. Coverage estimates from NIS-Flu and NHIS rely on the accuracy of parental report of influenza vaccination, which has been found to overestimate provider report of coverage.[18] Overreporting may be more common for adolescents and children with high-risk conditions.[19] The MarketScan database included only privately insured children, and vaccination rates based on insurance claims of influenza vaccination were lower than those based on reported vaccination for the NHIS cohort. However, MarketScan estimates were also lower than observed vaccination rates (53%–56% among children aged 6 months–8 years and 37%– 43% among those aged 9–17 years) among influenza-negative children enrolled in the outpatient Influenza Vaccine Effectiveness network from 2011—2012 through 2013—2014.[23–25] Sensitivity analysis suggested that vaccination still provided protection against death, assuming 10% to 20% overreporting in NHIS, which resulted in similar estimates to comparisons with MarketScan cohorts. An alternative source of comparison coverage would be immunization information systems, but reporting of influenza vaccination for children is not mandatory in all states.[35] The majority of pediatric deaths with unknown vaccination status had no documentation of influenza vaccination in immunization information systems and were probably unvaccinated; sensitivity analyses treating these deaths as unvaccinated resulted in higher VE estimates. Vaccination coverage in the comparison cohorts was probably intermediate between estimates based on parental report and those based on insurance claims.[18] Finally, our analysis excluded deaths among infants who became eligible for vaccination after November 1 of each season and included partially vaccinated children; partial vaccination provided no protection against severe influenza in a study conducted among children with influenza admitted to PICUs.[27]

Results of this study suggest that vaccination reduced the risk of influenza-associated death among children and adolescents and add to the evidence of benefits of influenza vaccination for children. Annual vaccination is an important strategy to prevent influenza and influenza-associated complications and deaths. These results support current recommendations for annual influenza vaccination for all children ≥6 months of age.

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ABBREVIATIONS

ACIP: Advisory Committee on Immunization Practices
CI: credible interval
NHIS: National Health Interview Survey
NIS-Flu: National Immunization Survey–Flu
OR: odds ratio
VE: vaccine effectiveness

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