Influenza Vaccine Effectiveness Against Pediatric Death in the United States: 2016–2025

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abstract

BACKGROUND AND OBJECTIVES: Seasonal influenza vaccination has been shown to reduce the risk of influenza and severe complications among children aged 6 months and older. Since 2010, reported numbers of influenza-associated pediatric deaths among children younger than 18 years have ranged from 37 during the 2011 to 2012 season to 289 during the 2024 to 2025 season. We estimated influenza vaccine effectiveness (VE) against pediatric death from 2016 to 2017 through 2024 to 2025.

METHODS: We conducted a case-cohort analysis comparing current season influenza vaccination status among reported influenza-associated pediatric deaths with survey estimates of influenza vaccination coverage in pediatric age groups. Underlying medical conditions and current seasonal influenza vaccination were obtained from surveillance case reports. We estimated vaccination odds ratios (OR) and 95% CIs from logistic regression comparing influenza vaccination among children who died with vaccination coverage in comparison cohorts. VE was calculated as $(1 - OR) \times 100$.

RESULTS: From August 2016 through July 2025, 1234 laboratory-confirmed influenza-associated pediatric deaths were reported among children aged 6 months to 17 years. Of 1086 reported deaths with influenza vaccination information, 124 (23%) of 530 children with underlying medical conditions and 70 (13%) of 556 children without known conditions were fully vaccinated against influenza. Average influenza vaccination coverage in survey cohorts was 49%. VE was 80% (95% CI 75–84) overall, 77% (95% CI 71–82) among children with underlying medical conditions and 87% (95% CI 84–89) among children without known conditions.

CONCLUSIONS: Influenza vaccination reduced risk of fatal influenza among children with or without known underlying medical conditions.

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Dr Leonard conceptualized and designed the study, carried out analyses, and drafted the initial manuscript. Drs Reinhart, Lu, Santibanez, Srivastav, and Hung, and Mr Jain, Ms Budd, Ms Huang, Ms Kniss and Ms Price carried out analyses and contributed to and revised the manuscript. Ms Burns critically reviewed and revised the manuscript for important content. Drs Ellington and Flannery conceptualized and designed the study and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

CONFLICT OF INTEREST DISCLOSURES: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the US Centers for Disease Control and Prevention (CDC).

WHAT'S KNOWN ON THIS SUBJECT: Seasonal influenza vaccination reduces the risk of influenza and complications of infection, including influenza-associated death in children and adolescents. During recent influenza seasons, the majority of influenza-associated pediatric deaths have occurred in children who were not fully vaccinated against influenza.

WHAT THIS STUDY ADDS: This study updates national estimates of influenza vaccine effectiveness against influenza-associated deaths among children and adolescents. Influenza vaccination reduced the risk of fatal influenza by 80% among children with or without known underlying medical conditions.

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INTRODUCTION

Seasonal influenza vaccination has been recommended to reduce the risk of influenza and its severe complications, including influenza-associated death in children and adolescents.[1,2] Although rare, influenza-associated pediatric deaths occur annually with varying incidence depending on the influenza season.[3,4] Children younger than 5 years and children and adolescents with certain underlying medical conditions are at increased risk of hospitalization and complications that are attributable to influenza.[5] Neurologic, cardiac, and pulmonary conditions and genetic disorders have been associated with higher risk for influenza-associated pediatric death.[3,6,7] However, children with no underlying conditions still constitute approximately half of influenza-associated pediatric deaths.[4,6–9]

In the United States, deaths in children and adolescents with laboratory-confirmed influenza have been reportable since 2004.[3] From 2005 through 2009, seasonal influenza was estimated to account for more than 100 deaths annually among children and adolescents.[10–12] During the 2009 influenza A(H1N1) pandemic, 288 influenza-associated deaths in children and adolescents were reported.[3,13] Since 2010, reported numbers of influenza-associated deaths among children younger than 18 years have ranged from 37 in the 2011 to 2012 season to 289 in the 2024 to 2025 season (as of January 2026). The number of influenza-associated pediatric deaths reported during the 2024 to 2025 season was the highest since reporting started.[3,4] Since 2021, US influenza vaccination rates have been in decline, leaving more children susceptible to severe complications or death due to influenza.[14] In this analysis of 8 influenza seasons from 2016 through 2025, we estimated influenza vaccine effectiveness against influenza-associated deaths among children and adolescents with and without known underlying medical conditions in the United States.

METHODS

Data Source

We analyzed deaths reported to the US Influenza-Associated Pediatric Mortality Surveillance System during 4 influenza seasons before the start of the COVID-19 pandemic (2016–2017 through 2019–2020) and 4 seasons from 2021–2022 through 2024–2025. During the 2020–2021 season, influenza activity was low, and only 1 influenza-associated pediatric death was reported to the Centers for Disease Control and Prevention (CDC). For this analysis, influenza seasons began on epidemiologic week 40 and ended on week 39 of the following year (approximately October through September). The pediatric mortality surveillance system has been described in detail previously.[6–8,15–17] Briefly, influenza-associated deaths resulting from a clinically compatible illness in US residents younger than 18 years with laboratory-confirmed influenza virus infection, with no period of complete recovery between the illness and death, are reportable.[18] Confirmation of influenza virus infection included clinical diagnostic testing during illness or postmortem examination using antigen detection, viral culture, or nucleic acid amplification.

State and local health departments reported influenza-associated pediatric deaths to CDC using a standard case report form transmitted over a secure, web-based interface. Case reports include sex, birthdate (or age), the child's race and ethnicity as recorded in medical records or coroners' reports, underlying medical conditions, current season influenza vaccination status and date of most recent influenza vaccination (if known), state of residence at time of illness, date of illness onset, date of hospital admission (if hospitalized), clinical information and complications during fatal illness, laboratory tests performed and results (including influenza testing as well as tests for viral and bacterial co-infection), location of death (emergency department, hospital, during transportation to hospital, or out of hospital), and date of death.

State and local health department personnel documented underlying medical conditions from medical records and coroner reports. Underlying medical conditions associated with increased risk for influenza-related complications among children and adolescents were classified based on high-risk groups according to the American Academy of Pediatrics (Supplementary Information).[5] For VE analyses, we stratified pediatric deaths into 2 groups: children with at least 1 underlying medical condition associated with increased risk of complications from influenza and children with no known high-risk condition. Deaths among children with incomplete medical histories or with health conditions not specified as higher risk of influenza complications[5] (history of febrile seizures, skin and soft tissue infections, and other conditions) were grouped with deaths among children with no known underlying medical condition.

To classify current and previous influenza vaccination status, health department personnel determined vaccination status based on review of available information from state or county immunization information systems, case patient medical records, health care providers, parental or coroner reports. Children were considered fully vaccinated if they had received 1 or 2 doses of current season influenza vaccine as recommended by the Advisory Committee on Immunization Practices[1] at least 14 days before onset of illness. Children aged 6 months through 8 years were considered partially vaccinated if they were previously unvaccinated and received 1 dose of current season influenza vaccine at least 14 days before the onset of fatal illness or a second dose fewer than 14 days before illness onset. For case reports without illness onset date, we estimated onset as 5 days before death based on the median duration of illness among cases with recorded date of symptom onset. Children who had been vaccinated in previous

seasons without current season vaccination were considered unvaccinated for the season of fatal infection. In primary analyses, we excluded cases in which health department personnel could not determine the child's current season vaccination status.

For consistency with influenza vaccination coverage estimates, age groups were defined based on the child's age on November 1 of the influenza season when death occurred. Because influenza vaccines are not approved for use in children younger than 6 months, reported deaths among children younger than 6 months on November 1 were excluded.

Influenza Vaccination Coverage in Cohorts

We defined comparison cohorts for each influenza-associated death by age category (6 months-4 years, 5–12 years, and 13–17 years) and state of residence. We obtained estimated mean and SD of influenza vaccination coverage in the calendar month preceding case illness onset for each influenza season from publicly available National Immunization Survey-Flu (NIS-Flu),[19] and National Health Interview Survey (NHIS) (Supplementary Information).[20] To account for differences in vaccination coverage among US children with underlying medical conditions compared with survey averages, we multiplied NIS-Flu comparison cohort influenza vaccination coverage estimates for cases with high-risk conditions by the ratio of cumulative influenza vaccination coverage among children with, vs without underlying medical conditions by age category and season from the annual NHIS survey. Because of changes in collection of high-risk conditions in 2019 and the availability of NHIS data through 2024, average ratios for 2016 through 2020 and from 2023 through 2024 were applied to NIS-Flu comparison coverage estimates for the 2018 through 2019 and 2024 through 2025 seasons, respectively.

Influenza Vaccine Effectiveness

To estimate influenza vaccine effectiveness against influenza-associated death, we adapted the screening method based on a case-cohort analysis as previously described.[2,21,22] The case-cohort method produces an odds ratio (OR), which estimates the relative risk for influenza-associated death in fully-vaccinated children vs those who were not vaccinated against influenza. We included children at least 6 months old on November 1 of the influenza season during which death occurred who were eligible to receive at least 1 dose of seasonal influenza vaccine. We calculated ORs and 95% confidence interval (CI) comparing odds of current season influenza vaccination among cases with odds of vaccination in comparison cohorts by age category, state of residence, and calendar month preceding case illness onset. We used logistic regression with case vaccination status as the dependent variable and the log odds of current season influenza vaccination (proportion vaccinated/1 - proportion vaccinated) in the NIS-Flu comparison cohort entered as an offset. With this offset in the model, the intercept provides an estimate of the log(OR). Influenza VE was estimated as (1 - OR) × 100, expressed as a percentage. For children with high-risk conditions, likelihood of vaccination was based on NHIS-adjusted seasonal influenza vaccination coverage among children aged 6 months to 18 years with underlying medical conditions, by age group, season, and calendar month.

In sensitivity analyses, we evaluated the impact on VE, assuming that cases with undetermined influenza vaccination status were either all vaccinated or all unvaccinated, and evaluated the impact on VE of decreasing vaccination coverage in comparison cohorts by 10% and 20% to account for over-estimation of child and adolescent influenza vaccination in national survey data.[23–26] Analyses were conducted in R (version 4.5.1; R Core Team, Vienna, Austria).

This activity was reviewed by CDC, deemed public health surveillance, and was conducted in accordance with applicable federal law and CDC policy.

RESULTS

Influenza-Associated Pediatric Deaths

From October 2016 through September 2025, excluding the 2020 through 2021 season, 1234 influenza-associated pediatric deaths among children aged 6 months to 17 years were reported by 51 jurisdictions, including 48 states, Washington, DC, the city of Chicago, and New York City. The number of pediatric deaths reported per season among children aged 6 months to 17 years ranged from 37 during 2021 through 2022 to 252 during 2024 through 2025 (Table 1). Overall, 598 (48%) pediatric deaths occurred in children with at least 1 underlying medical conditions and 636 (52%) in those without known conditions. More of the influenza-associated deaths in older children and adolescents had underlying medical conditions (51% among those aged 5–12 years and 56% among 13–17 years) compared with 36% among deaths in children aged 6 months to 4 years. Location of death was reported for 1214 cases: 688 (56%) died during hospitalization, 314 (25%) in the emergency department, and 212 (17%) out of hospital. In all, 868 deaths were associated with influenza A (274 H1N1pdm09, 276 H3N2, and 318 with unknown subtype), 353 deaths were associated with influenza B, and 13 deaths had infection with more than 1 virus type or influenza A subtype. Mean and median number of days from illness onset to death were 9.0 and 5 days among vaccinated children and 8.3 and 5 days among unvaccinated children, respectively.

Influenza Vaccination Among Pediatric Deaths

Among 1117 influenza-associated deaths in children with influenza vaccination information, the percentage of children who were fully vaccinated against influenza ranged from 16% to 19% by age group, sex, and ethnicity, with

TABLE 1 Pediatric influenza-associated deaths and percent with documented influenza vaccination, October 2016-September 2025

	Influenza-Associated Deaths, n (%)	Influenza Vaccination	
		Fully-Vaccinated,[a] n (%)	Not Fully Vaccinated, n (%)
Overall, N	1234	194 (17)	923 (83)
Sex[b]			
Female	649 (53)	94 (16)	498 (84)
Male	579 (47)	99 (19)	422 (81)
Age[c]			
6 months-4 years	459 (37)	65 (16)	348 (84)
5–12 years	554 (45)	92 (18)	411 (82)
13–17 years	221 (18)	37 (18)	164 (82)
Race[d]			
American Indian	23 (2)	4 (17)	19 (83)
Asian	65 (5)	23 (38)	38 (62)
Black	251 (20)	27 (12)	201 (88)
Multiple	20 (2)	3 (17)	15 (83)
Native Hawaiian	13 (1)	1 (11)	8 (89)
White	702 (57)	117 (18)	535 (82)
Not recorded	160 (13)	19 (15)	107 (85)
Ethnicity[d]			
Hispanic or Latino	294 (24)	48 (18)	213 (82)
Not Hispanic or Latino	811 (66)	126 (17)	624 (83)
Not recorded	129 (10)	20 (19)	86 (81)
High-risk medical condition			
No known high-risk condition[e]	636 (52)	70 (12)	569 (88)
≥1 high-risk condition[f]	598 (48)	124 (23)	424 (77)
Asthma	150 (12)	33 (24)	107 (76)
Pulmonary (not including asthma)	88 (7)	29 (35)	53 (65)
Cardiac disease	106 (9)	26 (27)	97 (73)
Neurologic	247 (20)	47 (21)	177 (79)
Neuromuscular	143 (12)	37 (28)	93 (72)
Endocrine (not including diabetes mellitus)	44 (4)	10 (18)	31 (54)
Diabetes mellitus	20 (2)	2 (11)	16 (89)
Renal	25 (2)	5 (23)	17 (77)
Hemoglobinopathy	14 (1)	1 (8)	
Genetic/mitochondrial	136 (11)	38 (29)	91 (71)
Immunocompromizing condition	46 (4)	14 (33)	28 (67)
Obesity	40 (3)	7 (18)	31 (82)
Duration of fatal illness[g]			
Days, mean (SD)	8.5 (8.8)	9.0 (9.1)	8.3 (8.7)
Days, median (IQR)	5 (3–10)	5 (3–11)	5 (3–10)
Location of death[h]			
In hospital	688 (56)	126 (20)	506 (80)
Emergency department	314 (25)	37 (13)	243 (87)
Outside hospital	212 (17)	27 (14)	164 (86)
Influenza season[i]			
2016–2017	98 (8)	20 (22)	71 (78)
2017–2018	168 (14)	31 (20)	125 (80)

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TABLE 1 Pediatric influenza-associated deaths and percent with documented influenza vaccination, October 2016-September 2025 (Continued)

	Influenza-Associated Deaths, n (%)	Influenza Vaccination	
		Fully-Vaccinated,[a] n (%)	Not Fully Vaccinated, n (%)
2018–2019	129 (10)	29 (26)	81 (74)
2019–2020	184 (15)	33 (20)	129 (80)
2021–2022	37 (3)	5 (16)	27 (84)
2022–2023	172 (14)	25 (16)	131 (84)
2023–2024	193 (16)	29 (16)	148 (84)
2024–2025	252 (20)	22 (9)	211 (91)
Influenza virus type/subtype			
Influenza A	868 (70)	139 (18)	645 (82)
A(H1N1)pdm09	274 (22)	49 (20)	200 (80)
A(H3N2)	276 (22)	44 (18)	199 (82)
Influenza B	353 (29)	54 (17)	266 (83)
B(Victoria)	61 (5)	10 (18)	45 (82)
B(Yamagata)	17 (1)	2 (13)	14 (88)
More than 1 influenza virus[j]	13	1 (8)	12 (92)

[a] Denominator is cases in which vaccination status was able to be determined (N = 1117) and excludes unknown vaccination status (N = 117). Not fully vaccinated includes partially vaccinated children who received 1 of 2 recommended doses of current season influenza vaccine.
[b] Sex of child not recorded on case report form for 6 children.
[c] Age on November 1 during the season in which death occurred.
[d] Race and ethnicity were recorded separately.
[e] Presence of high-risk medical conditions was not known for 83 pediatric deaths.
[f] More than 1 high-risk medical condition could be reported for each pediatric death.
[g] Reported onset date of fatal illness was missing for 261 deaths.
[h] Location of death was classified as outside hospital if child was pronounced dead on arrival at health care facility. Location of death was not recorded for 20 deaths.
[i] Influenza seasons are considered from week 40-week 39 of the following year (approximately October 1-September 30).
[j] Deaths with positive laboratory tests for 2 influenza viruses: 2 co-infections with subtype A(H1N1)pdm09 and A(H3N2), and 11 with type A and B viruses.

wider range by race (from 11% to 38%) (Table 1). By influenza season, the percentage of influenza deaths in children with current season influenza vaccination ranged from 26% during 2018 through 2019 to 9% during 2024 through 2025 (Figure 1). Across all seasons, 18% of influenza A-associated deaths and 17% of influenza B-associated deaths occurred among children who were fully vaccinated against influenza. Among deaths in children without known high-risk conditions, 12% were fully vaccinated against influenza compared with 23% among deaths in children with at least 1 underlying medical condition. Among deaths in children with at least 1 high-risk medical condition, the highest percentage of influenza vaccination was found among those with nonasthma pulmonary disorders (35%), followed by immunocompromizing conditions (33%) and genetic and mitochondrial disorders (29%), and lowest among children with hemoglobinopathies (8%), diabetes (11%), and obesity (18%).

Influenza Vaccination Coverage Estimates

During 2016 through 2020, mean survey estimates of current season influenza vaccination coverage in comparison cohorts ranged from 50% to 58% among children with specified underlying medical conditions, vs 51% to 59% among children without known conditions. During 2021 through 2025 after the first waves of COVID-19, mean survey estimates in comparison cohorts decreased, ranging from 42% to 50% among children with high-risk medical conditions, vs 39% to 48% among children without known conditions.

Influenza Vaccine Effectiveness

After excluding deaths among children who were partially vaccinated, 194 (18%) of 1086 influenza-associated deaths occurred in children with current season influenza vaccination and 892 (82%) in unvaccinated children. Overall, VE against influenza-associated pediatric death was 80% (95% CI 75–84) (Figure 2). VE against death was higher among children without known high-risk conditions (87%; 95% CI 84–89) than among children with high-risk medical conditions (77%; 95% CI 71–82). Among children with high-risk medical conditions, VE estimates were higher for those aged 6 months to 4 years (83%; 95% CI 78–88) than those aged 13 to 17 years (66%; 95% CI 57–73). VE against influenza A-associated death was 68% (95% CI 61–74) compared with 77% (95% CI 72–81) against influenza B-associated death, with overlapping CIs. Among children without known underlying medical conditions, VE

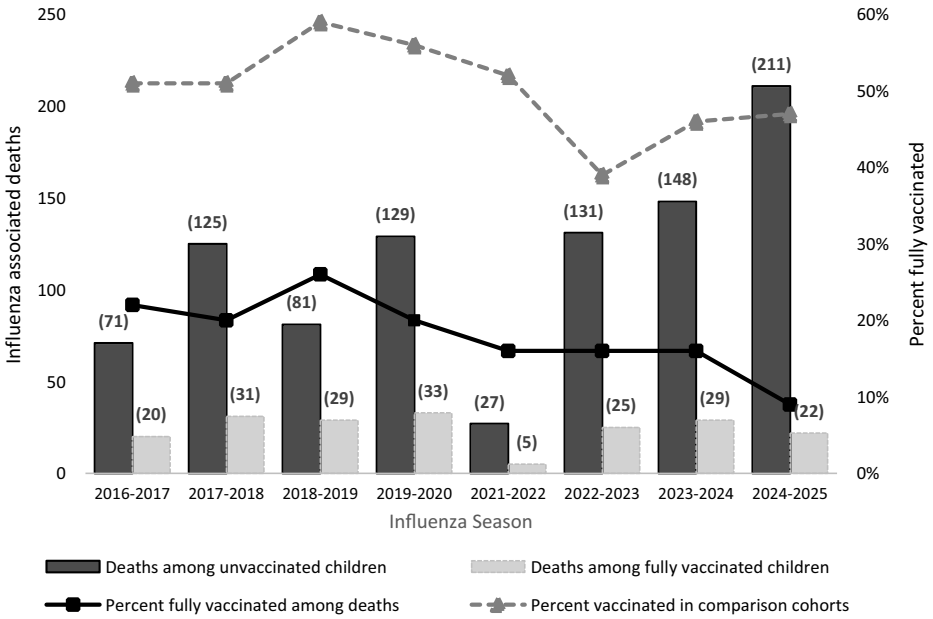

FIGURE 1.

Number and percent of influenza-associated pediatric deaths in influenza vaccinated or unvaccinated US children and adolescents aged 6 months to 17 years compared with influenza vaccination coverage in comparison cohorts (dashed line), 2016–2017 through 2024–2025 (Excluding 2020–2021) influenza seasons. Number of deaths among fully vaccinated and unvaccinated children and adolescents shown in parentheses. Children were considered fully vaccinated if they had received all recommended doses of current season influenza vaccine at least 14 days before onset of illness. The percentage of children who were fully vaccinated before illness onset is indicated by the solid line. Data were reported to the Pediatric Mortality Surveillance System.

estimates were also higher for those aged 6 months to 4 years (89%; 95% CI 86–91) compared with those aged 13 to 17 years (80%; 95% CI 74–84). VE was 87% (95% CI 84–90) against pediatric deaths associated with influenza A and 87% (95% CI 84–89) against deaths associated with influenza B. Among children with high-risk medical conditions, influenza VE against pediatric deaths each season ranged from 66% (95% CI 58–72) in 2019–2020 to 84% (95% CI 81–87) in 2024 through 2025. Among children without known high-risk conditions, VE each season ranged from 77% (95% CI 72–81) in 2022 through 2023 to 95% (95% CI 93–96) in 2024 through 2025.

Sensitivity analyses assuming that all cases with undetermined vaccination status were fully vaccinated resulted in lower but statistically significant estimates of 66% (95% CI 58–73) among children with high-risk medical conditions and 74% (95% CI 68–79) among children without known high-risk conditions (Figure 3). Assuming that cases with unknown vaccination status were not vaccinated had minimal impact on VE estimates. When seasonal influenza vaccination coverage estimates among comparison cohorts were decreased by 10% and 20%, VE against death among children with high-risk conditions was 63% (95% CI 56–69) and 54% (95% CI 46–61), respectively. Among children without known high-risk conditions, decreasing comparison coverage estimates by 10% or 20%, VE against death was 84% (95% CI 80–86) and 79% (95% CI 76–82). VE estimates by age category remained statistically significant in all sensitivity analyses.

DISCUSSION

In this analysis, children and adolescents who died of influenza-associated illness were less likely to have been fully vaccinated against influenza than US children in the same age group and state of residence. Of pediatric deaths in children aged 6 months to 17 years, fewer than 1 in 5 were fully vaccinated against influenza, including fewer than 1 in 4 of those at higher risk of severe influenza or its complications. Approximately half of the pediatric deaths occurred in children without known health conditions, only 12% of whom were fully vaccinated against influenza. In comparison groups of US children and adolescents, influenza vaccination coverage was consistently higher than among children who died with influenza-associated complications. In sensitivity analyses accounting for potential overestimation of influenza vaccination coverage in US survey data, influenza vaccination remained strongly associated with protection. Taken together, results provide additional evidence that seasonal influenza vaccination reduces the risk of influenza-associated deaths in all pediatric age groups.

In addition to protection against influenza-associated deaths,[2] influenza vaccination has been shown to

Characteristic	Vaccinated/Total[a]	(%)	Coverage, % (low-high)[b]	VE (95% CI)[c]
All deaths	194/1086	(18%)	49 (45–54)	80 (75–84)
One or more high-risk medical conditions[d]				
All ages	124/530	(23%)	49 (44–54)	77 (71–82)
6 mos-4 years	35/151	(23%)	55 (50–61)	83 (78–88)
5–12 years	63/264	(24%)	49 (45–53)	75 (70–80)
13–17 years	26/115	(23%)	41 (36-45)	66 (57–73)
Season				
2016–17	13/41	(32%)	54 (49–59)	73 (66–79)
2017–18	20/70	(29%)	50 (45–54)	72 (64–78)
2018–19	20/54	(37%)	59 (55–64)	77 (69–83)
2019–20	20/61	(33%)	55 (51–59)	66 (58–72)
2021–22	4/22	(18%)	48 (43–53)	81 (77–85)
2022–23	13/71	(18%)	43 (38–47)	77 (71–82)
2023–24	17/85	(20%)	46 (42–51)	78 (73–82)
2024–25	17/126	(13%)	45 (40–50)	84 (81–87)
Virus type				
Influenza A	94/386	(24%)	48 (44–53)	68 (61–74)
Influenza B	29/136	(21%)	51 (46–55)	77 (72–81)
No high-risk medical condition				
All ages	70/556	(13%)	49 (45–54)	87 (84–89)
6 mos-4 years	30/232	(13%)	54 (48–59)	89 (86–91)
5–12 years	29/238	(12%)	48 (44–52)	87 (84–89)
13–17 years	11/86	(13%)	40 (35–45)	80 (74–84)
Season				
2016–17	7/49	(14%)	51 (46–56)	86 (82–88)
2017–18	11/82	(13%)	51 (46–56)	87 (84–89)
2018–19	9/51	(18%)	59 (54–63)	87 (84–90)
2019–20	13/91	(14%)	56 (52–61)	88 (86–90)
2021–22	1/9	(11%)	52 (47–57)	89 (87–91)
2022–23	12/83	(14%)	39 (35–43)	77 (72–81)
2023–24	12/89	(13%)	46 (41–50)	83 (80–86)
2024–25	5/102	(5%)	47 (42–52)	95 (93–96)
Virus type				
Influenza A	45/374	(12%)	48 (43–53)	87 (84–90)
Influenza B	25/177	(14%)	53 (48–57)	87 (84–89)

FIGURE 2.

Influenza vaccine effectiveness estimates and percentage vaccinated among influenza-associated pediatric deaths compared with National Immunization Survey-Flu (NIS-Flu) influenza vaccination coverage estimate, by season and age group.

[a]Excludes 31 cases with partial vaccination (receipt of 1 of 2 recommended doses in the season during which death occurred) or documented vaccination 14 days before onset of fatal illness, and 117 cases with vaccination status listed as unknown on the case report form.

[b]Average influenza vaccination coverage among children in NIS-Flu sample by case age category, state, season and reference month. For deaths among children with at least one documented high-risk medical condition, NIS-Flu coverage was multiplied by the ratio of influenza vaccination coverage in the National Health Interview Survey (NHIS) among children with specified high-risk conditions compared with children in the survey sample without high-risk conditions by age category, state influenza vaccination coverage category (low, medium or high) and season (see Methods).

[c]Percent VE = 100 × (1 - vaccination OR), estimated as odds of vaccination (p/[1 - p]) among cases divided by odds of vaccination (coverage/[1 - coverage]) in comparison group, with 95% CIs.

[d]Documentation of at least 1 high-risk medical condition on case report form. Case report forms for 83 pediatric deaths indicated that underlying medical conditions were unknown.

Abbreviations: CI, confidence interval; OR, odds ratio; VE, vaccine effectiveness.

provide protection against laboratory-confirmed influenza-associated hospitalizations and severe outcomes. A meta-analysis of observational case-control studies that used patients with negative molecular influenza test results for comparison reported pooled VE of 67% against influenza-associated hospitalizations among infants and children.[27] In multiple US studies conducted from 2016 to 2017 through 2024 and 2025, influenza vaccination has been associated with prevention of severe outcomes,[28] life-threatening influenza virus infection,[29] influenza-associated hospitalizations, emergency department, urgent care, and health care visits among children with and without high-risk medical conditions.[30–35] Previous analysis of pediatric deaths during 4 seasons from 2010 through 2014 showed low influenza vaccination rates among children and adolescents who died with influenza compared with state and age-specific vaccination coverage.[2] In the current analysis of pediatric deaths over 8 influenza seasons, influenza vaccination rates among influenza-associated pediatric deaths were consistently low despite prevalence of underlying conditions associated with high risk of severe influenza and complications.[2,4,6–8]

Sensitivity analyses supported our main findings. When we decreased comparison cohort vaccination coverage by 10% and 20% to account for over-reporting of children's influenza vaccination by parents and caregivers in NIS-Flu surveys.[24] In a US pediatric hospitalization network, validation of parental report of their child's seasonal influenza vaccination overestimated vaccination rates by 18% to 25%,[25] which is similar to estimates from national immunization surveys in Australia.[26] The resulting lower VE estimates remained statistically significant for all age categories among pediatric deaths in children with and without high-risk medical conditions. Sensitivity analysis that

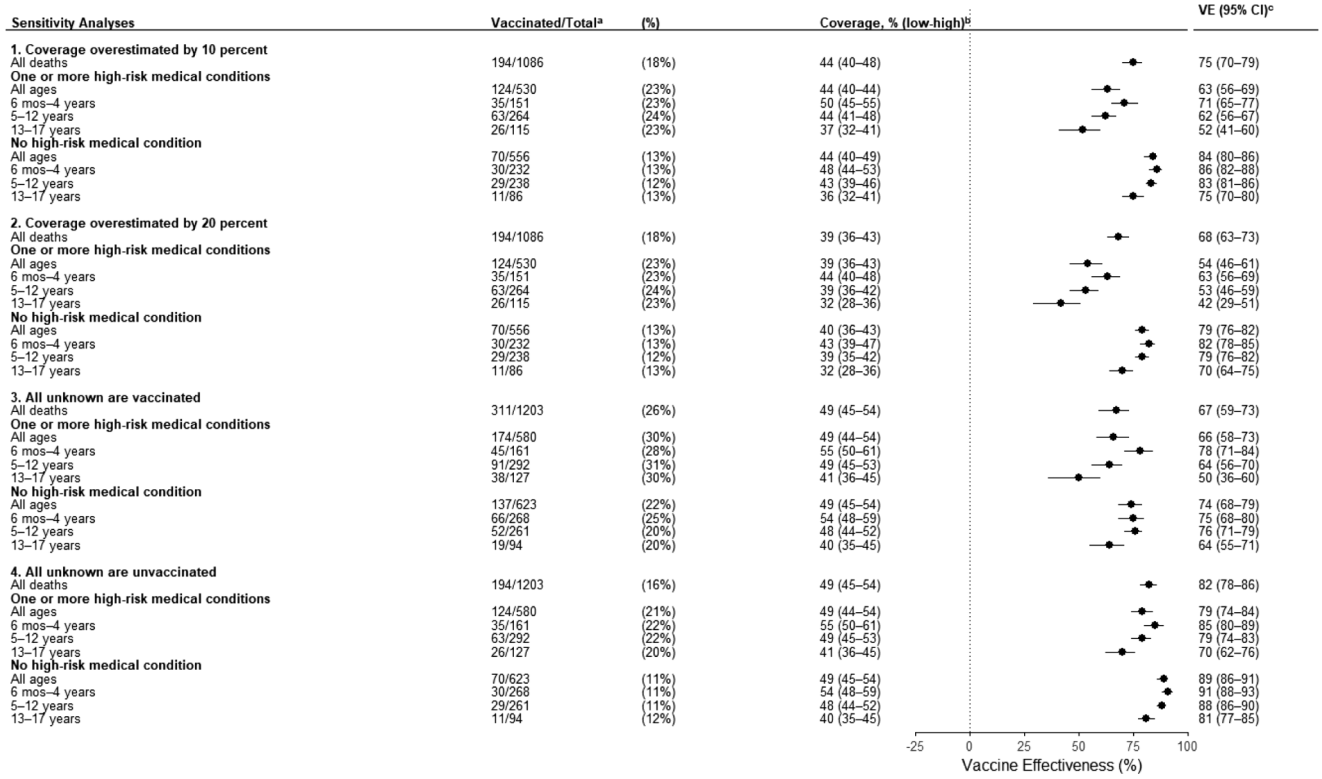

FIGURE 3.

Sensitivity analyses for overestimation of influenza vaccination coverage in National Immunization Survey-Flu (NIS-Flu) Survey and unknown vaccination status among pediatric deaths. [a]Number of deaths among fully vaccinated children (excluding deaths among partially vaccinated children) varies by sensitivity analysis: (1) and (2) exclude deaths among children with vaccination status listed as unknown; (3) reclassified all deaths among those with unknown vaccination status as fully vaccinated; (4) re-classified all deaths among those with unknown vaccination status as unvaccinated.

[b]In sensitivity analysis (1), comparison coverage for every influenza-associated death by case age category, state, season and reference month was decreased by 10%, assuming 10% parental over-report in NIS-Flu sample, and in analysis (2) comparison coverage for each death was decreased by 20%, assuming 20% parental over-report in NIS-Flu. For deaths among children with at least one documented high-risk medical condition, comparison coverage estimates were decreased by 10% or 20% after NIS-Flu coverage was multiplied by the National Health Interview Survey (NHIS) influenza coverage ratio among children with or without specified high-risk conditions by age category, state influenza vaccination coverage category (low, medium or high) and season.

[c]Percent VE and 95% CI were estimated separately for each sensitivity analysis as VE = 100 × (1 - vaccination OR), estimated as odds of vaccination (p/[1 - p]) among cases divided by odds of vaccination (coverage/[1 - coverage]) in comparison group, after applying assumptions to deaths with unknown vaccination status or decreasing comparison coverage estimates to account for potential over-reporting in NIS-Flu.

Abbreviations: OR, odds ratio; VE, vaccine effectiveness.

considered all children for whom vaccination status could not be determined were fully vaccinated resulted in lower but still statistically significant VE estimates. A strength of the current analysis was the ability of state and local health department personnel to link death records to immunization information systems. Since publication in 2017 of influenza vaccine effectiveness against influenza-associated pediatric deaths in the United States,[2] completeness of vaccine data in the Influenza Associated Pediatric Mortality Surveillance System has improved. In the current report, current season influenza vaccination status was unknown for 10% of pediatric deaths compared with 19% of pediatric deaths reported during the 2010 through 2014 seasons.

This analysis is subject to several limitations. Because the surveillance case definition requires laboratory confirmation of influenza virus infection,[18] deaths due to influenza without laboratory confirmation were not reported to state health departments; deaths included in this analysis may not represent all influenza-related deaths. Second, vaccination may not have been recorded in immunization records available to state and local health department personnel who completed case report forms. Misclassification of current season influenza vaccination status among vaccinated children would have overestimated vaccine effectiveness. However, influenza vaccination data and medical records were available from state immunization

information systems for most deaths, including date of influenza vaccination and vaccine type. Third, underlying medical conditions may not have been documented in health records for some children and adolescents. Surveillance officers may not have received complete case medical histories, especially for children who died before hospitalization. Fourth, 2019 to 2024 NHIS survey questions to estimate coverage among children with specified health conditions were limited to asthma episodes and diagnosed diabetes, and the ratio of coverage among children with vs without asthma or diabetes was assumed to be constant throughout the influenza season. If children with asthma or diabetes tend to be vaccinated earlier than other children, coverage among high-risk cohorts may have been greater in September and November, which would have underestimated effectiveness against deaths in children with underlying medical conditions.

Influenza vaccination reduced risk of influenza-associated death among children with or without underlying medical conditions. Together with recent reports on the large number of influenza-associated pediatric deaths during the 2024 through 2025 influenza season[4] and low influenza vaccination among children with influenza-associated necrotizing encephalopathy,[36–38] findings of this analysis highlight the importance of seasonal influenza vaccination to prevent severe illness and complications of influenza in children and adolescents.

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ABBREVIATIONS

CDC: Centers for Disease Control and Prevention
NIS-Flu: National Immunization Survey-Flu
NHIS: National Health Interview Survey
OR: odds ratio
VE: vaccine effectiveness

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