MAJOR ARTICLE

Effectiveness of Influenza Vaccine Against Life-threatening RT-PCR-confirmed Influenza Illness in US Children, 2010–2012

Jill M. Ferdinands,[1,2] Lauren E. W. Olsho,[3] Anna A. Agan,[4] Niranjan Bhat,[5] Ryan M. Sullivan,[4] Mark Hall,[6] Peter M. Mourani,[7] Mark Thompson,[1] and Adrienne G. Randolph[4] on behalf of the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network

[1]Influenza Division, US Centers for Disease Control and Prevention, and [2]Battelle Memorial Institute, Atlanta, Georgia; [3]Abt Associates, Inc., Cambridge, and [4]Department of Anesthesia, Perioperative and Pain Medicine (Critical Care), Boston Children's Hospital, Massachusetts; [5]Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; [6]Division of Critical Care Medicine, Nationwide Children's Hospital, Columbus, Ohio and [7]Section of Critical Care Medicine, Department of Pediatrics, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora

(See the editorial commentary by Peters and Poehling on pages 671–3.)

Background. No studies have examined the effectiveness of influenza vaccine against intensive care unit (ICU) admission associated with influenza virus infection among children.

Methods. In 2010–2011 and 2011–2012, children aged 6 months to 17 years admitted to 21 US pediatric intensive care units (PICUs) with acute severe respiratory illness and testing positive for influenza were enrolled as cases; children who tested negative were PICU controls. Community controls were children without an influenza-related hospitalization, matched to cases by comorbidities and geographic region. Vaccine effectiveness was estimated with logistic regression models.

Results. We analyzed data from 44 cases, 172 PICU controls, and 93 community controls. Eighteen percent of cases, 31% of PICU controls, and 51% of community controls were fully vaccinated. Compared to unvaccinated children, children who were fully vaccinated were 74% (95% CI, 19% to 91%) or 82% (95% CI, 23% to 96%) less likely to be admitted to a PICU for influenza compared to PICU controls or community controls, respectively. Receipt of 1 dose of vaccine among children for whom 2 doses were recommended was not protective.

Conclusions. During the 2010–2011 and 2011–2012 US influenza seasons, influenza vaccination was associated with a three-quarters reduction in the risk of life-threatening influenza illness in children.

Keywords. case-control studies; child; influenza vaccines; intensive care; respiratory failure; influenza infection.

One to 7 per 10 000 US children under the age of 18 years are hospitalized with laboratory-confirmed influenza each year [1–6]. Although most of these children require only standard care, 4%–24% of children hospitalized with influenza-related illness are admitted to an intensive care unit (ICU) for life-threatening complications [1, 2, 4, 7–9]. Fifty to 60% of these children have preexisting chronic medical conditions [10, 11].

Vaccination is the primary influenza prevention strategy. Many studies have shown effectiveness of influenza vaccine against laboratory-confirmed symptomatic and medically attended outpatient influenza illness among children [12–27], although estimates of vaccine effectiveness (VE) vary by study and season, and fewer data are available on effectiveness of inactivated vaccine in children aged 6–23 months [28]. Hadler et al observed an 82% reduction in influenza hospitalization among children aged 3–9 years, but no reduction in influenza hospitalization among children <3 years old from a single dose of monovalent H1N1pdm influenza vaccine during the 2009 pandemic

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Correspondence: Jill M. Ferdinands, PhD, US Centers for Disease Control and Prevention, 1600 Clifton Rd NE, MS A-20, Atlanta, GA 30333 (jferdinands@cdc.gov).

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[29]. No studies to our knowledge have examined the protection conferred by influenza vaccine against ICU admission or death from influenza infection among children.

Since 2008, when the US Advisory Committee on Immunization Practices (ACIP) recommended that all children aged ≥6 months receive influenza vaccine annually [30], assessments of influenza VE in US children have relied upon observational studies, typically using a case-control design. These studies are at substantial risk for confounding because characteristics such as age, underlying health status, and geographic location can affect both the likelihood of vaccination and the risk of developing disease. The aim of this study was to estimate the effect of influenza vaccine in preventing life-threatening influenza illness in children using methods designed to minimize this potential confounding.

METHODS

We enrolled children aged 6 months through 17 years during the 2010–2011 and 2011–2012 influenza seasons from 21 US pediatric intensive care units (PICUs) participating in the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network [31]. Children admitted with acute severe respiratory illness of ≤7 days duration who tested positive for influenza by real-time reverse-transcription polymerase chain reaction (RT-PCR) were classified as cases; admitted children who tested negative for influenza were classified as PICU controls [32, 33]. A secondary group of community controls was created from a matched sample of children who resided in the same geographic area and had not experienced an influenza-associated hospitalization between September of the study year and the matched case's PICU admission date. The study was approved by institutional review boards at Abt Associates, Inc (Cambridge, MA), the Centers for Disease Control and Prevention (CDC), and each participating site.

Influenza Surveillance and Season Definition

Active recruitment began at each site when ≥1 PICU patient with laboratory-confirmed influenza infection was admitted and there was evidence of widespread and increasing local influenza activity from state or local laboratories. Study enrollment ceased when local influenza activity had declined and the proportion of study specimens testing positive for influenza at the reference laboratory fell below 15%. Initiation of enrollment ranged from week 2 to week 10 in 2011 (mean, week 7) and from week 1 to week 13 in 2012 (mean, week 8). Outside active recruitment periods, only patients testing positive for influenza from routine clinical testing were approached for enrollment.

Enrollment of Cases and PICU Controls

During active recruitment, patients admitted for intensive care were screened using criteria in Table 1. Children admitted to the ICU for <24 hours (during the week) or <48 hours (on weekends) were not enrolled. Patients with rare respiratory conditions for whom it would be difficult to find a matched community control were excluded.

After consent was obtained, the parent/guardian provided the patient's influenza vaccination history, demographic characteristics, and date of illness onset. Samples were collected for influenza testing with flocked nasopharyngeal swabs (Copan Diagnostics, Murietta, CA) using a standardized technique. Endotracheal and nasopharyngeal aspirates (using the N-Pak Syringe Aspiration Kit; M-Pro, Annandale, MN) were collected from intubated and nonintubated patients, respectively. Hospital course, laboratory results, and outcomes were obtained from manual medical record abstraction.

Respiratory samples were placed in viral transport medium, frozen at −80°C, and shipped on dry ice to the reference laboratory. Specimens were tested for influenza virus using RT-PCR performed by the Marshfield Clinic Research Foundation (Marshfield, WI) using primers, probes, and reagents supplied by CDC and methods described elsewhere [34]. RT-PCR results were not used for clinical decisions.

Enrollment of Community Controls

Our goal in selecting community controls was to identify children similar to cases in terms of influenza exposure risk and underlying risk for developing influenza-related critical illness. To approximate exposure risk, community controls were matched by geographic region and enrolled as possible within 30 days of enrollment of the matched case.

Matching by underlying risk for developing severe influenza was based on the presence of chronic medical conditions (classified into three influenza risk categories as described in the Supplement) and five age categories: infant (180–364 days), toddler (1 year to <3 years), preschool (3–5 years), school age child (6–12 years), and adolescent (13–17 years). Potential control subjects were drawn from the population of children who received inpatient or outpatient care at facilities affiliated with each site during the preceding two years. Letters were sent to families with study information and an opportunity to opt out of the pool of candidate controls. After identification of a case, 8 potential controls from the case's corresponding age and influenza risk categories were randomly selected and sequentially contacted by telephone until 2 controls were enrolled. At 5 sites, modified community control recruitment methods were used as described in the Supplement. A structured interview assessed demographic, medical, and influenza vaccination information from consented parents/guardians.

Influenza Vaccination Status

We classified children as fully or partially vaccinated based on contemporaneous ACIP recommendations. For 2010–2011, the number of doses required to be fully vaccinated was

Table 1. Study Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
ICU Enrollees	
1. Age 6 mo through 17 y 2. Residence within site's geographic catchment area 3. Admission to an ICU with the capability to provide mechanical ventilator support 4. Symptomatic for acute severe viral infection by at least one of the following: • Lower respiratory tract infection as evidenced by any of the following: hypoxia, hypercarbia, infiltrates on chest radiograph, respiratory failure, respiratory insufficiency or severe distress, tachypnea, or retractions • Shock requiring vasoactive agents (dopamine, dobutamine, epinephrine, norepinephrine, phenylephrine) and receiving antibiotics due to clinical suspicion of infection • Central nervous system dysfunction (altered mental status or clinical suspicion of meningitis, encephalitis, or encephalopathy) plus fever (temperature ≥38°C) and cough or sore throat • Acute increase in respiratory support, including any of the following: ◦ Continuous intravenous (IV) or inhaled beta-agonist therapy for severe bronchospasm ◦ Mechanical ventilator support via a mask, endotracheal tube or tracheostomy tube ◦ High-flow nasal cannula oxygen support 5. Parent or legal guardian able and willing to provide permission 6. Parent or legal guardian can complete interview and consent process in English or Spanish	1. Inability to consent parent/guardian and collect respiratory specimen for RT-PCR testing within 7 d of illness onset 2. In ICU for <24 h, or if admitted on the weekend, patient was discharged from ICU before Monday morning 3. Nosocomial-acquired infection as determined at the study site by infection control group 4. Neuromuscular disease requiring chronic mechanical ventilator support through a mask or tracheostomy for neuromuscular weakness 5. Chronic mechanical ventilator support through a tracheostomy for chronic respiratory failure 6. End-stage lung disease being evaluated or awaiting lung transplant 7. Evidence of current pregnancy from clinical management or other documentation
Community Controls	
1. Age 6 mo through 17 y 2. Reside within site's geographic catchment area 3. Parent or legal guardian able and willing to provide permission 4. Parent or legal guardian can complete interview and consent process in English or Spanish 5. Received medical services at the PALISI site or an affiliated clinic within past 24 mo	1. Overnight hospital stay or hospital admission for confirmed or probable influenza between 1 September 2010 (year 1) or 1 September 2011 (year 2) and admission date for the reference case 2. Underlying medical condition requiring chronic mechanical ventilator support 3. End-stage lung disease being evaluated for or awaiting lung transplant 4. Pregnancy (parent-reported) 5. Child is in custody of the State

Abbreviations: ICU, intensive care unit; PALISI, pediatric acute lung injury and sepsis investigators; RT-PCR, reverse-transcription polymerase chain reaction.

determined by the algorithm in Supplementary Figure 1 [35]. For 2011–2012, a child ≥9 years old was considered fully vaccinated if the child received 1 dose of vaccine >14 days prior to onset. A child <9 years old was considered fully vaccinated if the child (a) received 2 doses ≥28 days apart and >14 days prior to onset or (b) received at least 1 dose >14 days prior to onset and ≥1 dose of seasonal vaccine in the previous season [36]. A child who received 2 doses <28 days apart with at least 1 dose >14 days prior to onset was considered partially vaccinated. Vaccination status in community controls was ascertained in relation to the matched case's date of illness onset. We contacted each vaccine provider that had administered influenza vaccine to the child to obtain and manually review medical records for vaccine verification. Vaccination status was also obtained by manual review of state/local immunization registries. Due to incomplete access to medical records for community controls, parental report of vaccination was used for the comparison of cases to community controls. Although an alternative would have been to limit community controls to those with verified vaccine status, those controls differed from controls without verified vaccine status, and using this subset would tend to bias VE upwards.

Statistical Analysis

Cases were compared with PICU controls using an unconditional logistic regression model. Cases were compared with community controls using conditional logistic regression with strata defined by matched cases and controls. Models included as few covariates as possible to preserve statistical power while controlling confounding. A variable whose exclusion resulted in ≥10% change in adjusted VE was considered a confounder. If several similar variables were available, the most parsimonious variable that maintained control of confounding was used.

The regression model used to compare cases to PICU controls included the natural log of age in months, gender, time of illness onset (pre-, peak, or post-peak influenza period), reported contact with a person with suspected or confirmed influenza, history of moderate to severe respiratory disorders (excluding mild asthma), history of cardiac disorders, illness severity on admission (PRISM Score [37]), days between illness onset and influenza testing, and a dichotomous variable indicating if enrollment occurred outside active recruitment. We adjusted for geographic area by including site as a random effect. Peak influenza period was defined as ranging from the 25th to 75th percentiles of case onset date. Pre- and post-influenza periods were defined as earlier than the 25th or later than the 75th percentile of case onset date, respectively. The Pediatric Risk of Mortality III (PRISM III) is a validated pediatric physiology score used to describe patient illness severity in the first 24 hours of admission to an intensive care unit and is calculated using the most abnormal values from 17 physiologic variables.

The conditional logistic regression analysis used to compare cases to community controls was matched by age, influenza risk category, and geographic area. Covariates included gender, race, and presence of ≥3 chronic health conditions. Although we aimed for consistency between the PICU and community control analyses, the models differed because the control groups differed. Unlike PICU controls, community controls were much less likely than cases to have multiple underlying conditions, and it was necessary to control for multiplicity of conditions in that model. Race was not a confounder in the PICU analysis and was eliminated from that model. Season was not a significant confounder in either analysis. VE was calculated as (1 minus the adjusted odds ratio) × 100%. Analyses were conducted in SAS v9.3 (Cary, NC, USA).

RESULTS

Over 8000 PICU admissions from 21 participating PICUs (Figure 1) were screened for eligibility. Of 428 eligible patients, 223 (52%) were enrolled. Of these, 7 observations were excluded: 6 due to unverified vaccine status and 1 due to indeterminate RT-PCR results, leaving 216 observations. Of these, 44 were influenza-positive cases and 172 were influenza-negative controls. Of eligible PICU patients not enrolled, 84% did not enroll because of refusal by the parent/guardian, child or physician, and 16% for other reasons. Of 5261 individuals identified as potential community controls, 232 (4%) chose to opt out of the pool of candidate controls after receiving introductory letters. Of 310 candidate community controls matched to a case and successfully contacted, 63 were ineligible, 144 had parents/guardians who refused to participate or withdrew before interview completion, and 103 (33%) were enrolled. We excluded 8 community controls with unknown vaccination status and 2 community controls without matched cases, leaving 44 cases, 172 PICU controls, and 93 community controls in the final analyses.

The median age of cases and PICU controls was 4.3 and 3.0 years, respectively ($P = .07$). Compared with PICU controls, cases were more likely to be male ($P = .03$; Table 2). Fifty-five percent of cases and 69% of PICU controls had at least 1 underlying chronic medical condition, with respiratory and neuromuscular disorders the most common. PICU controls were more likely than cases to have moderate or severe respiratory conditions ($P = .02$) and disorders involving an aspiration risk ($P = .04$). PICU controls were less likely than cases to have chronic cardiac conditions ($P = .03$).

Compared with cases, community controls were less likely to be white ($P = .04$). Despite matching by influenza risk category,

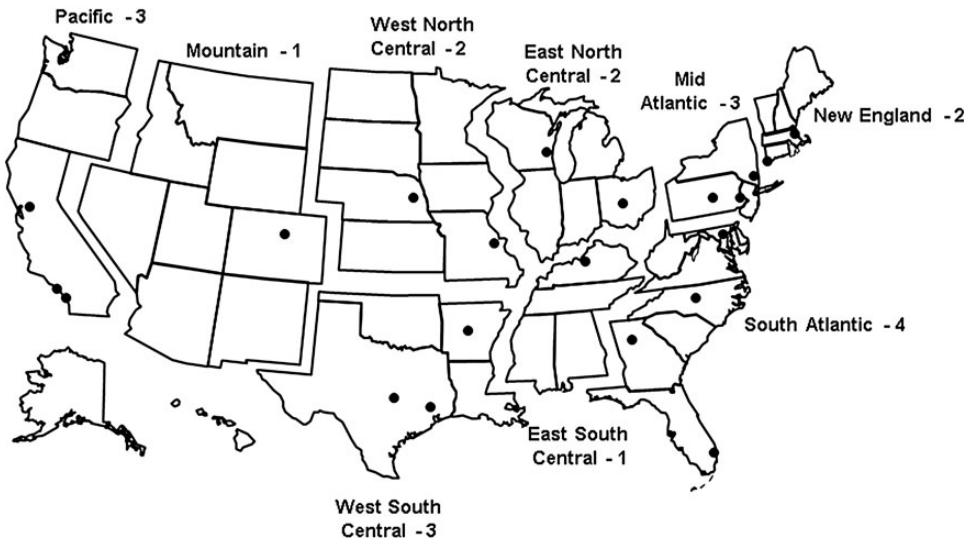

Figure 1. Map of participating pediatric intensive care units.

Table 2. Characteristics of the Pediatric Intensive Care Unit (PICU) Influenza Positive Cases, PICU Influenza Negative Controls, and Community Controls

	PICU Cases (n = 44)	PICU Controls (n = 172)	Community Controls (n = 93)
Female, N (%)	14 (32)	87 (51)**	40 (43)
Age, median (IQR), mo	51 (33–92)	36 (15–79)*	54 (22–113)
Age group, N (%)			
6 to <24 mo	10 (23)	65 (38)	25 (27)
24 to <60 mo	14 (32)	49 (28)	25 (27)
5 to <9 yr	11 (25)	27 (16)	17 (18)
≥9 yr	9 (20)	31 (18)	26 (28)
Hispanic ethnicity, N (%)	9 (20)	53 (31)	26 (28)
White race, N (%)	31 (70)	119 (69)	50 (54)**
Season, N (%)			
2010–2011	30 (68)	87 (51)**	71 (76)
2011–2012	14 (32)	85 (49)	22 (23)
Preexisting risk for complications of influenza infection, N (%)[a]			
Low to average risk	20 (45)	58 (34)	43 (46)
Moderate risk	9 (20)	26 (15)	17 (18)
High risk	15 (34)	88 (51)	33 (35)
Chronic underlying health conditions, N (%)			
Any respiratory	17 (39)	93 (54)*	27 (29)
Any asthma	12 (27)	58 (34)	16 (17)
Mild asthma only	5 (11)	15 (9)	4 (4)
Moderate or severe respiratory	10 (23)	71 (41)**	21 (23)
Cardiac	6 (14)	8 (5)**	7 (8)
Neuromuscular	16 (36)	60 (35)	8 (9)***
Metabolic/genetic	6 (16)	23 (13)	4 (4)**
Renal	1 (2)	1 (1)	2 (2)
Immunologic	0 (0)	4 (2)	5 (5)
Diabetes	0 (0)	3 (2)	4 (4)
Aspiration risk	4 (9)	39 (23)**	NA
≥2 conditions	13 (30)	61 (35)	11 (12)***
≥3 conditions	8 (20)	37 (22)	3 (3)***
Influenza vaccination status by parental report, N (%)			
Full	11 (25)	79 (46)**	47 (51)**
Partial	12 (28)	24 (14)	15 (16)
None	20 (45)	61 (35)	31 (33)
Don't know/missing	1 (2)	8 (5)	0 (0)
Verified influenza vaccination status, N (%)			
Full	8 (18)	54 (31)	NA
Partial	6 (14)	28 (16)	NA
None	30 (68)	90 (52)	NA

Abbreviations: IQR, interquartile range; SE, standard error.

*P < .10, **P < .05, ***P < .01 for test of difference between cases and controls using chi-square test of heterogeneity for R × 2 contingency table for categorical variables or ANOVA F test for continuous variables, transformed as needed; Fisher's exact test was used for comparisons with cell counts <5.

[a] As defined by the authors' risk categorization scheme described in Supplementary Section 1.

community controls were less likely than cases to have neuromuscular (P < .001) or metabolic/genetic disorders (P = .02) and far less likely to have more than 1 underlying chronic condition (12% vs 30%, P = .005). Median duration between case and matched community control enrollment was 21 days (range, 0–146 days).

Regarding overall vaccination coverage among study enrollees, 62 (29%) of PICU enrollees and 47 (51%) of community controls were fully vaccinated. Rates of full vaccination among study enrollees with ≥1 chronic condition known to elevate risk of serious influenza complications were 37% and 61% for PICU enrollees and community controls, respectively. Among the 34 PICU enrollees categorized as partially vaccinated, 29 (85%) received 1 of 2 recommended doses of vaccine and 5 (15%) received 2 doses <28 days apart.

Parents of PICU enrollees reported greater levels of full vaccination than were verified: 27% of cases and 32% of PICU controls with parental report of full vaccination did not have evidence of full vaccination in medical records or state immunization registries. Due to incomplete access to medical records for community controls, the analogous rates among community controls are unknown.

A summary of clinical course and outcomes is shown in Table 3. A noninfluenza pathogen was identified in 61% of PICU controls; 76 PICU enrollees had RT-PCR-confirmed respiratory syncytial virus (RSV) infection. Compared with PICU controls, cases had greater illness severity on admission (PRISM scores) and greater frequency of acute lung injury, respiratory failure requiring invasive mechanical ventilator support, septic shock requiring vasopressors, use of most rescue therapies, and mortality (9.1% of cases vs 1.9% of PICU controls, P = .03).

Circulating and Vaccine Influenza Strains

In both study years, the Northern Hemisphere influenza vaccine included A/California/7/2009(H1N1)-like virus, A/Perth/16/2009(H3N2)-like virus, and B/Brisbane/60/2008-like virus strains [38]. In 2010–2011, circulating influenza strains were antigenically similar to vaccine strains [39]; in 2011–2012, there was minor antigenic drift in circulating A(H3N2) viruses [40]. Of our cases, 72% and 28% had influenza A and B infection, respectively. Of influenza A infections, approximately half were influenza A(H3N2), consistent with national patterns.

Vaccine Effectiveness

In the comparison of cases to PICU controls, estimated adjusted effectiveness of full influenza vaccination was 74% (95% CI, 19% to 91%) in preventing PICU admission for RT-PCR-confirmed influenza illness (Table 4). We found no protective benefit from partial vaccination (VE = −6% [95% CI, −243% to 67%]). We observed no interaction between vaccination status and age, although statistical power to find an interaction was limited. Comparing cases to community controls, we found an

Table 3. Pediatric Intensive Care Unit (PICU) Course and Clinical Outcomes of Influenza Cases and PICU Controls

	PICU Cases (n = 44)	PICU Controls (n = 172)	*P* Value[a]
Reported contact with a person with suspected or confirmed influenza, N (%)	22 (50)	50 (29)	.01
Days from symptom onset to enrollment, mean (SE)	4.3 (0.25)	3.7 (0.13)	.04
Admission illness severity (PRISM III), mean (med)	17.2 (15)	14.7 (15)	.02
Noninfluenza bacterial or viral pathogenic organism identified in first 72 h	16 (36.4)	106 (61.6)	.004
Severe complications, N (%)			
Pneumothorax, effusion, or requiring a chest tube	13 (29.5)	24 (14)	.02
Severe bronchospasm	6 (13.6)	40 (23.3)	.22
Acute Lung Injury/ARDS	10 (22.7)	10 (5.8)	.002
Shock requiring vasopressors[b]	10 (22.7)	13 (7.6)	.01
Treatments, N (%)			
Received any antiviral agents	39 (88.6)	42 (24.4)	<.001
Received anti-influenza antiviral agents[c]	39 (88.6)	39 (22.7)	<.001
Mechanical ventilator support	32 (72.7)	115 (66.9)	.59
Noninvasive mechanical ventilator support only	6 (18.8)	49 (42.6)	.01
Invasive mechanical ventilator support	26 (81.3)	66 (57.4)	.01
High frequency ventilation	3 (11.5)	3 (4.5)	.36
Steroids for any reason	32 (72.7)	101 (58.7)	.12
Stress dose (hypotension/adrenal suppression)	4 (12.5)	6 (5.9)	.25
Daily for pulmonary inflammation	21 (65.6)	83 (82.2)	.08
Rescue therapies, N (%)			
Nitric oxide	5 (11.4)	2 (1.2)	.004
Endotracheal surfactant	2 (4.5)	1 (0.6)	.11
Dialysis or hemofiltration	3 (6.8)	1 (0.6)	.03
Extracorporeal membrane oxygenation (ECMO)	3 (6.8)	1 (0.6)	.03
Discharge disposition, N (%)			
Died	4 (9.1)	3 (1.7)	.03
Survived	40 (90.9)	169 (98.3)	
Discharged to home	37 (92.5)	159 (94.1)	
Transferred to other acute care facility	0 (0)	5 (3)	
Transferred to rehab/chronic care facility	2 (5)	4 (2.4)	
Hospitalized at the end of data collection	1 (2.5)	1 (0.6)	

[a] Fisher exact test (2-sided).

[b] 22.7% of cases and 6.4% of PICU controls received vasoactive infusions on admission day.

[c] 97.4% of cases and 100% of PICU controls who received anti- influenza antiviral agents received oseltamivir (Tamiflu).

estimated adjusted vaccine effectiveness for full vaccination (compared to none) of 82% (95% CI, 23% to 96%) and no benefit from partial vaccination (VE = −79% [95% CI, −541% to 50%]) (Table 5).

Sensitivity Analyses

For the comparison of cases to PICU controls, we explored various health-related variables to control for underlying health conditions; results were similar to those above. In a model that did not adjust for any underlying health conditions, VE was 69% (95% CI, 12% to 89%). In a model that excluded the 5 subjects enrolled outside the period of active recruitment, VE for full vaccination was 76% (95% CI, 20% to 92%).

For the comparison of cases to community controls, when restricting the case-control pairs to those in which controls were enrolled within 45 days after the case, adjusted VE was 88% (95% CI, 12% to 98%). Community controls were much less likely than cases to have multiple underlying conditions. In a model that did not adjust for multiple chronic conditions, adjusted VE for full vaccination was 62% despite matching controls to cases on influenza risk category (Supplementary Table 3).

We examined effectiveness of influenza vaccine against RSV infection as an indicator of potential bias in our VE estimates. We observed no significant association between full (OR=1.4; 95% CI, .61 to 3.20, $P = .42$) or partial (OR= 1.33, 95% CI, .52 to 3.42; $P = .55$) influenza vaccination and RSV infection.

Table 4. Regression Model Results and Vaccine Effectiveness Based on Comparison of Cases and PICU Controls (n = 44 Cases, 172 PICU Controls)

	Odds Ratio (95% CI)	*P* Value	Vaccine Effectiveness (95% CI)
Full vaccination	0.26 (.09 to .81)	.02	74% (19% to 91%)
Partial vaccination	1.06 (.33 to 3.43)	.93	−6% (−243 to 67%)
No vaccination	Ref		
Female	0.31 (.13 to .75)	.01	
Log of age (mo)	1.76 (1.13 to 2.74)	.01	
History of moderate to severe chronic respiratory disorder	0.25 (.09 to .70)	.01	
History of cardiac disorder	8.64 (1.72 to 43.5)	.01	
Pre-influenza peak	0.79 (.26 to 2.42)	.68	
Peak influenza period	Ref		
Post-influenza peak	0.69 (.24 to 11.4)	.50	
Enrollment outside active recruitment period	3.09 (.32 to 30.3)	.33	
Days between onset and RT-PCR influenza testing	1.37 (1.07 to 1.77)	.01	
PRISM score (severity of illness at PICU admission)	1.08 (1.01 to 1.15)	.02	
Contact with a person with confirmed or suspected influenza	4.48 (1.76 to 11.4)	.002	

Season and race were not independent predictors of influenza positivity or confounders of the relationship between vaccination and influenza positivity and therefore were eliminated from the final model. Vaccination status was confirmed by medical record or immunization registry for cases and PICU controls.

Abbreviations: CI, confidence interval; PICU, pediatric intensive care unit; Ref, reference group; RT-PCR, reverse-transcription polymerase chain reaction.

DISCUSSION

We assessed the effectiveness of influenza vaccination during the 2010–2011 and 2011–2012 US influenza seasons using a case-control study with 2 control groups. This study found that influenza vaccination was associated with a three-quarters reduction in the risk of life-threatening influenza illness in children. Our study also showed low influenza vaccine coverage; although 34% of children admitted to the PICU in our study had underlying conditions known to increase the risk of serious influenza complications, only 37% of these children (18% of cases and 39% of PICU controls) were fully vaccinated against influenza.

To our knowledge, this study is the first to specifically estimate VE against life-threatening outcomes of influenza infection in children. Two previous studies in children have assessed VE against seasonal influenza hospitalization or emergency department visits: In a 2005–2006 test-negative case-control study, Staat et al [16] reported VE of 67% (95% CI, −48% to 92%) against hospitalization with laboratory-confirmed influenza among US children aged 6 to 59 months. Using a similar design, Kelly et al [26] reported VE of 51% (95% CI, −21% to 80%) against laboratory-confirmed influenza-associated emergency department visits among Australian children in 2008. In addition, Castilla et al [41] recently reported VE of 89% against severe influenza illness in a study that included 125 children and 566 adults hospitalized with RT-PCR-confirmed influenza; however, they did not present a VE estimate for the pediatric subsample. Our observed VE is similar to that

Table 5. Regression Model Results and Vaccine Effectiveness Based on Comparison of Cases and Community Controls (n = 44 Cases, 93 Community Controls)

	Odds Ratio (95% CI)	*P* Value	Vaccine Effectiveness (95% CI)
Full vaccination	0.18 (.04 to .77)	.02	82% (23% to 96%)
Partial vaccination	1.79 (.50 to 6.41)	.37	−79% (−541% to 50%)
No vaccination	Ref		
Female	0.33 (.12 to .90)	.03	
White race	4.27 (1.22 to 15.0)	.02	
≥3 chronic health conditions	24.6 (3.81 to 158.7)	.0008	

From a conditional logistic regression model with cases and controls matched by age group, geographic area, and influenza risk category. Vaccination status was based on parental report for both cases and controls.

Abbreviations: CI, confidence interval; Ref, reference group.

observed against influenza-associated hospitalization in US children aged 3 to 9 years during the 2009 influenza pandemic [29] , and our finding that partial influenza vaccination was not protective is consistent with many studies of influenza VE in children [14–18].

Children with underlying health conditions are both more likely to be vaccinated and more likely to have severe complications of influenza. Unless adequately controlled for, this 'unhealthy vaccinee' bias tends to falsely lower VE. We confronted this problem by using two sets of controls: PICU controls, who presumably are more similar to cases regarding unmeasured potential confounders that increase the likelihood of ICU admission given a severe lower respiratory tract infection, and community controls matched to cases based on underlying risk of influenza-related illness. Although the comparison of cases to community controls was designed to reduce confounding by matching on risk of severe illness, the large difference in our VE estimates after controlling for the presence of multiple underlying health conditions (62% before controlling for this factor compared to 82% after controlling for this factor) suggests that there remained residual confounding by health status. Cases were more similar to PICU controls than to community controls in terms of the prevalence of multiple underlying conditions, and confounding of the VE estimate by the presence of underlying conditions was less pronounced in the comparison of cases and PICU controls (69% and 74% before and after controlling for this factor, respectively). Future studies of influenza VE in this population should consider additional methods, such as the use of propensity score matching, to control for confounding by health status.

Although parental report is a simple and widely used method for ascertaining immunization status, it is susceptible to social-desirability and recall biases [42], perhaps particularly when subjects are recruited in an ICU setting. In our study, parents of cases and PICU controls reported greater levels of full vaccination than were subsequently verified, similar to patterns reported in the literature [43, 44]. A strength of our study was the use of detailed medical record review and interrogation of immunization registries to confirm vaccination status for cases and PICU controls. Our comparison of cases to community controls, however, relied upon parental report. Misclassification of vaccination status based on parental report may bias our VE estimate downward. If parental over-report of vaccination was more pronounced among cases than community controls, this, too, would cause our VE estimate to be biased downward.

Our study began during a period of heightened awareness of influenza vaccination, 1 year following the 2009 influenza pandemic, and 2 years following the expansion of the ACIP recommendations to include annual vaccination for all children aged ≥6 months. Nevertheless, less than a third of cases and PICU controls were fully vaccinated, even though almost half of these had at least one high-risk condition. Among the cases and PICU controls with at least 1 high-risk condition, only 37% were fully vaccinated (similar to prior reports [35]). It is essential to investigate care patterns and missed opportunities for vaccination in children such as these.

Our study has several limitations. We enrolled a relatively small number of cases despite conducting enrollment at 21 PICUs. This was due in part to the rarity of life-threatening influenza among children in general and an unusually mild influenza season in the second year of the study. Thus, we could not stratify our analysis by season, age, vaccine type, or influenza flu type/subtype. We did not perform antigenic characterization of influenza viruses recovered from study participants to evaluate match of strain with the vaccine. However, national testing performed by the CDC showed that circulating influenza strains were similar to vaccine strains. Overall, 52% of eligible PICU patients enrolled in our study. Although this rate is lower than anticipated, it is similar to that achieved in other hospital-based observational studies in which invasive biologic specimens are required [45]. There may have been differences between patients who enrolled compared with those who did not; however, among PICU controls with high-risk conditions, we observed an influenza vaccination rate (37%) similar to that reported previously in a nationally representative sample (33%–36%; [35]). Finally, for our analysis using community controls, we relied on parental report of vaccination status due to insufficient return of authorizations for vaccine verification and evidence of differential returns by vaccine status, which can bias estimates of VE.

CONCLUSIONS

In this study, influenza vaccination was associated with about a three-quarters reduction in risk of influenza-related critical illness in children. Vaccine coverage was low, even among children with comorbid conditions that increase the risk of severe influenza complications. Our results highlight the value of increasing the use of influenza vaccines among children.

Supplementary Data

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

Notes

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Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) PICFlu Members Participating: Arkansas Children's Hospital, Little Rock, AR (Ronald C. Sanders, MD, Glenda Hefley, RN, MNsc); Children's Hospital of Los Angeles, Los Angeles, CA (Barry Markovitz, MD, Jeff Terry, MBA, Rica Sharon P. Morzov, RN, BSN, CPN, Karen Waters, RN, BSN); Children's Hospital and Research Center, Oakland, CA (Heidi Flori, MD, Julie Simon, RN); Children's Hospital of Orange County, Orange, CA (Nick Anas, MD, Adam Schwarz, MD, Chisom Onwunyi, RN, BSN, MPH, CCRP, Stephanie Osborne, RN, CCRC, Tiffany Patterson, BS, CRC, Ofelia Vargas-Shiraishi, BS, CCRC); Children's Hospital Colorado, Aurora, CO (Peter Mourani, MD, Valeri Batara Aymami, RN, MSN-CNS, Susanna Burr, CRC, Stephanie Huston, BS, RPSGT, CRC, Emily Jewett, Danielle Loyola, RN, BSN, MBA); Yale-New Haven Children's Hospital, New Haven, CT (John S. Giuliano Jr, MD, Chi Ngo, Elyor Vidal); Holtz Children's Hospital, Miami, FL (Gwenn McLaughlin, MD); Children's Healthcare of Atlanta at Egleston, Atlanta, GA (Matthew Paden, MD, Rich Toney, RN, Chee-Chee Manghram, Stephanie Meisner, RN, BSN, CCRP, Cheryl L. Stone, RN); Kosair Children's Hospital, Louisville, KY (Vicki Montgomery, MD, FCCM, Janice Sullivan, MD, Tracy Evans, RN, Kara Richardson, RN); Boston Children's Hospital, Boston, MA (Adrienne Randolph, MD, MSc, Anna Agan, BA, Ellen Smith, BS, Ryan M. Sullivan, RN, BSN, CCRN); Johns Hopkins Children's Center, Baltimore, MD (Melania Bembea, MD, MPH, Elizabeth White, RN, CCRP); St. Louis Children's Hospital, St. Louis, MO (Allan Doctor, MD, Mary Hartman, MD, Bert Hicks, RN, Rachel Jacobs, BA); Duke University Children's Hospital, Durham, NC (Ira Cheifetz, MD, Kyle Rehder, MD, Samantha Tate); Children's Hospital of Nebraska, Omaha, NE (Edward Truemper, MD, Machelle Zink, RN, BSN, MEd, CCRC); Maria Fareri Children's Hospital at Westchester Medical Center, Valhalla, NY (Simon Li, MD, Aalok R. Singh, MD, Yuliya Anikanova, MD); Nationwide Children's Hospital, Columbus, OH (Mark W. Hall, MD, Lisa Steele, RN, BSN, CCRN); Penn State Children's Hospital, Hershey, PA (Neal Thomas, MD, Jill Raymond, RN, MSN, Debra Spear, RN); Children's Hospital of Philadelphia, Philadelphia, PA (Julie Fitzgerald, MD, Mark Helfaer, MD, Scott Weiss, MD, Mary Ann Diliberto, RN, Ruth Lathe, Brooke B. Park, RN, BSN, Martha Sisko, RN, BSN, CCRC); Dell Children's Medical Center of Central Texas, Austin, TX (Renee Higgerson, MD, LeeAnn Christie, RN); Texas Children's Hospital, Houston, TX (Laura L. Loftis, MD, Nancy Jaimon, RN, MSN-Ed, Ursula Kyle, MS); Children's Hospital of Wisconsin, Milwaukee, WI (Rainer Gedeit, MD, Briana E. Horn, Kate Luther, MPH, Kathy Murkowski, RRT, CCRC).

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