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Vaccine Effectiveness Against Life-Threatening Influenza Illness in US Children

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Background. Predominance of 2 antigenically drifted influenza viruses during the 2019–2020 season offered an opportunity to assess vaccine effectiveness against life-threatening pediatric influenza disease from vaccine-mismatched viruses in the United States.

Methods. We enrolled children aged <18 years admitted to the intensive care unit with acute respiratory infection across 17 hospitals. Respiratory specimens were tested using reverse-transcription polymerase chain reaction for influenza viruses and sequenced. Using a test-negative design, we estimated vaccine effectiveness comparing odds of vaccination in test-positive case patients vs test-negative controls, stratifying by age, virus type, and severity. Life-threating influenza included death or invasive mechanical ventilation, vasopressors, cardiopulmonary resuscitation, dialysis, or extracorporeal membrane oxygenation.

Results. We enrolled 159 critically ill influenza case-patients (70% ≤8 years; 51% A/H1N1pdm09 and 25% B-Victoria viruses) and 132 controls (69% were aged ≤8 years). Among 56 sequenced A/H1N1pdm09 viruses, 29 (52%) were vaccine-mismatched (A/H1N1pdm09/5A+156K) and 23 (41%) were vaccine-matched (A/H1N1pdm09/5A+187A,189E). Among sequenced B-lineage viruses, majority (30 of 31) were vaccine-mismatched. Effectiveness against critical influenza was 63% (95% confidence interval [CI], 38% to 78%) and similar by age. Effectiveness was 75% (95% CI, 49% to 88%) against life-threatening influenza vs 57% (95% CI, 24% to 76%) against non-life-threating influenza. Effectiveness was 78% (95% CI, 41% to 92%) against matched A(H1N1)pdm09 viruses, 47% (95% CI, –21% to 77%) against mismatched A(H1N1)pdm09 viruses, and 75% (95% CI, 37% to 90%) against mismatched B-Victoria viruses.

Conclusions. During a season when vaccine-mismatched influenza viruses predominated, vaccination was associated with a reduced risk of critical and life-threatening influenza illness in children.

Keywords. influenza; pediatrics; vaccination; severity; case control.

Influenza can cause severe and life-threatening illness in children, accounting for a worldwide estimated 870 000 hospitalizations and 34 800 deaths annually in children aged <5 years [1]. In 2012, the World Health Organization recommended that countries consider children aged 6–59 months as a risk group for influenza vaccination. The US Advisory Committee on Immunization Practices (ACIP) has recommended annual vaccination for all persons aged ≥6 months since 2010 [2]. Despite these recommendations, few countries have adopted childhood influenza vaccination programs, and US influenza vaccination coverage remains between 38% and 62% for children aged <18 years [3].

One barrier to vaccine uptake globally might be the variable and sometimes low effectiveness against mild or moderate

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influenza illness [4]. Similar challenges for other childhood vaccines, such as rotavirus and pertussis, hindered acceptance until recognition increased that these vaccines conferred protection against severe disease [5, 6]. Despite 70 years of experience with influenza vaccines, only 3 randomized trials have examined efficacy against severe vs mild disease in children [7, 8]. Further, the "severe" outcome in these studies was, in most cases, high fever, which is less convincing for decision-making to vaccinate than preventing critical outcomes and death. Studies have shown that vaccination reduces the risk of influenza-associated hospitalization in children [9], but data related to vaccine effects on reducing risk of life-threatening illness or death are scarce [10, 11].

To address these gaps in knowledge of the protective benefits of vaccination against life-threatening influenza infection, the US Centers for Disease Control and Prevention (CDC) funded the national Pediatric Intensive Care Influenza Network [12] to conduct influenza surveillance in critically ill children at the start of the 2019–2020 influenza season. This season was unique in that antigenically drifted B-lineage viruses predominated early, causing the largest national influenza epidemic in children since 1992, and concerns were raised about vaccine failure due to circulation of 2 vaccine-mismatched strains [13, 14]. This provided a unique opportunity to assess vaccine effectiveness (VE) against critical and life-threating outcomes in children infected with antigenically drifted influenza viruses.

METHODS

Study Design

We used the test-negative design to assess VE against critical influenza illness in children aged 6 months to 17 years by comparing the odds of antecedent vaccination in case patients who tested positive vs symptomatic controls who tested negative for influenza.

Enrollment of Case Patients and Controls

To identify case patients and controls, we conducted active surveillance from December 2019 through April 2020 for critical acute respiratory illness (ARI) among children admitted to 17 US hospitals. We defined "critical" ARI as admission to a pediatric intensive care unit or high acuity care unit and having at least 1 sign of systemic illness (temperature of ≥38°C or ≤35°C, leukocytosis, elevated C-reactive protein or procalcitonin, altered mental status) and having at least 1 sign of ARI (cough, shortness of breath, tachypnea or retractions, invasive or noninvasive mechanical ventilation, need for oxygen to maintain saturations of at least 92%, pulmonary infiltrate or hyperinflation on chest imaging). We excluded children who presented >10 days after illness onset, those receiving chronic ventilator support, those awaiting lung transplant, those previously enrolled in the study, those identified as pregnant, and those with no respiratory specimen collection within 72 hours of hospitalization.

Participants were identified based on documented testing of respiratory specimens for influenza viruses using molecular assays. All eligible participants who tested positive for influenza and met the definition for critical ARI were enrolled. For each participant who tested positive by the clinical assay, study staff enrolled 1 control who tested negative and met the definition for critical ARI, matching on hospital and age group (<2 years, 2–8 years, and 9–17 years). At enrollment, study staff also obtained a research mid-turbinate nasal and/or oropharyngeal specimen within 72 hours. All research specimens were tested for influenza viruses at a central laboratory (Vanderbilt University Medical Center) using reverse-transcription polymerase chain reaction (RT-PCR) with CDC primers, probes, and testing protocol to further determine A subtypes (A/H1N1pdm09 and A/H3N2) and B lineages (B-Victoria and B-Yamagata). Participants who tested positive for influenza by either a clinical or research assay were designated as case patients, and those who tested negative by both assays were designated as controls.

Data Collection

Study staff obtained informed consent from the parent or guardian (and assent when applicable) and interviewed them to collect demographic information, symptoms, health status, and influenza vaccination history. Staff conducted standardized medical chart review on underlying conditions, signs and symptoms, vital signs, laboratory values, radiographic findings, and clinical interventions and outcomes.

Influenza Vaccination Status

Study staff verified verbal reports of vaccination from the current and prior seasons through review of the state immunization registries or patient medical records, including contacting the participant's pediatrician. Verbal reports of current season vaccination with dates and location were considered plausible if they could not be verified and were included in the primary analysis. Participants who were vaccinated 0–13 days prior to hospitalization were excluded from the analysis. Participants who reported no vaccination in the current season and who had no vaccination reported in the registry or the medical record were considered unvaccinated.

Vaccinated children were designated as fully vaccinated or partially vaccinated according to the US ACIP 2019–2020 season guidelines [2]. Children aged 6 months to 8 years were considered fully vaccinated if they received 2 doses of influenza vaccine ≥4 weeks apart and ≥14 days before symptom onset in the current season. If the child received only 1 dose ≥14 days before symptom onset in the current season and ≥2 doses in any previous season(s) before 1 July 2019, they were also considered fully vaccinated. If the child received only 1 dose ≥14 days before symptom onset in the current season and had <2

doses in season(s) prior, they were considered partially vaccinated. Children aged >8 years were considered fully vaccinated if they received at least 1 current season dose of influenza vaccine ≥14 days before symptom onset.

2019–2020 Influenza Vaccine Reference Strains

For the 2019–2020 season, reference strains for Northern Hemisphere influenza vaccines included A/Brisbane/02/2018 (H1N1)pdm09 (clade 6B.1A), A/Kansas/14/2017 (H3N2), and B/Colorado/06/2017 (Victoria lineage, clade V1A.1) that contains a 2 amino acid deletion (positions 162–163) in the HA compared to the 2017–2018 B/Brisbane/60/2008 reference strain (clade V1A) [13]. Quadrivalent vaccines also included a B/Phuket/3073/2013-like virus (Yamagata lineage).

Genetic Characterization of Viruses

The CDC conducted whole genome sequencing to obtain full-length hemagglutinin sequences on positive specimens with a RT-PCR cycle threshold value of ≤30 [15]. We used phylogenetic analyses of these sequences to classify viruses into hemagglutinin genetic groups of clades and subclades [15]. Based on antigenic characterization data of A/H1N1pdm09 and B-Victoria lineage subclades during the 2019–2020 season [13], the viruses sequenced in our study were designated as antigenically related (matched) or not (mismatched) to the 2019–2020 Northern Hemisphere vaccine reference strains.

Characterizing the Severity of Influenza Illness

To evaluate vaccine protection against a gradient of disease severity, we distinguished patients with death and life-threatening vs non-life-threatening critical influenza illness. For this analysis, we identified case patients who died within 30 days of hospitalization or had a life-threatening illness defined as receipt of invasive mechanical ventilation, extracorporeal membrane oxygenation, new dialysis, vasopressors, or cardiopulmonary resuscitation.

Statistical Analyses

The primary analysis was effectiveness of full vaccination against critically ill case patients with any influenza virus infection. The secondary analysis was effectiveness against life-threatening vs non-life-threatening influenza virus infection. Preplanned subgroups of the primary analysis included age (≤8 years and 9–17 years), influenza subtype and lineage, and influenza virus subclades identified by sequencing. VE was estimated by comparing the odds of vaccination among case patients and controls, using multivariable logistic regression, expressed as (1 – adjusted odds ratio) × 100%. For all analyses, models were adjusted a priori for consistency with VE studies including sex, race and ethnic group, days from illness onset to hospitalization (0–2, 3–4, 5–7, and 8–10), study site region, age (continuous), and month of hospitalization [16, 17]. We repeated the regression controlling for additional variables including receipt of influenza antivirals before hospitalization and underlying condition groups. The final model retained a priori selected covariates and other covariates that changed the odds ratio by a prespecified threshold of 5%. Firth penalization was applied to subanalyses with 30 or fewer cases.

All data were analyzed in SAS 9.4 (Cary, NC). This activity was determined to meet the definition of research [45 CFR 46.102(l)] involving human subjects [45 CFR 46.102 (e)(1)]. The study protocol was approved by the Boston Children's Hospital Institutional Review Board, which served as the single institutional review board for the enrolling sites.

RESULTS

Participant Characteristics

We enrolled 337 critically ill children with ARI; 8 were excluded (Figure 1). Of the remaining 329 patients, 160 were fully vaccinated, 38 were partially vaccinated, and 131 were unvaccinated. Among the 291 patients included in the primary analysis of full vaccination, 55% (159) tested positive for influenza and 45% (132) tested negative. The median age of case patients was 6 years (interquartile range [IQR], 3–10) and of controls was 4 years (IQR, 2–12; Table 1). The majority of case patients and controls had underlying health conditions, most commonly involving respiratory or neurologic systems. Case patients were more likely to receive influenza antivirals before hospitalization compared with controls. Compared with unvaccinated children, a smaller proportion of fully vaccinated children had asthma and a larger proportion had underlying conditions involving the respiratory, cardiovascular, neurological/neuromuscular, gastrointestinal/hepatic, or endocrine/metabolic systems.

Among all critically ill case patients, the median lengths of intensive care unit and hospital stay were 2 and 5 days, respectively (Table 2). Of the 159 case patients, 57 (36%) had life-threatening illness, with most requiring invasive mechanical ventilation (50 of 57, 88%) or vasopressor-dependent shock (33 of 57, 58%), and 4 died.

Genetic and Antigenic Characterization

Among cases, 80 (50%) infections were A/H1N1pdm09, 2 (1%) were A/H3N2, 13 (8%) were type A viruses with unknown subtype, 61 (38%) were B-lineage viruses (39 B-Victoria, 0 B-Yamagata, and 22 lineage unknown), and 3 (2%) were influenza A and B coinfections. Among 56 A/H1N1pdm09 viruses that were sequenced, most were in the hemagglutinin genetic group 6B.1A subclade 5A (52 of 56). Within this subclade, we identified 2 major phylogenetic groups with additional amino acid substitutions in the hemagglutinin protein: 29 (52%) had amino acid substitutions K130N, N156K, L161I, V250A, and E506D (designated as 5A+156K viruses) and 23 (41%) had amino acid substitutions

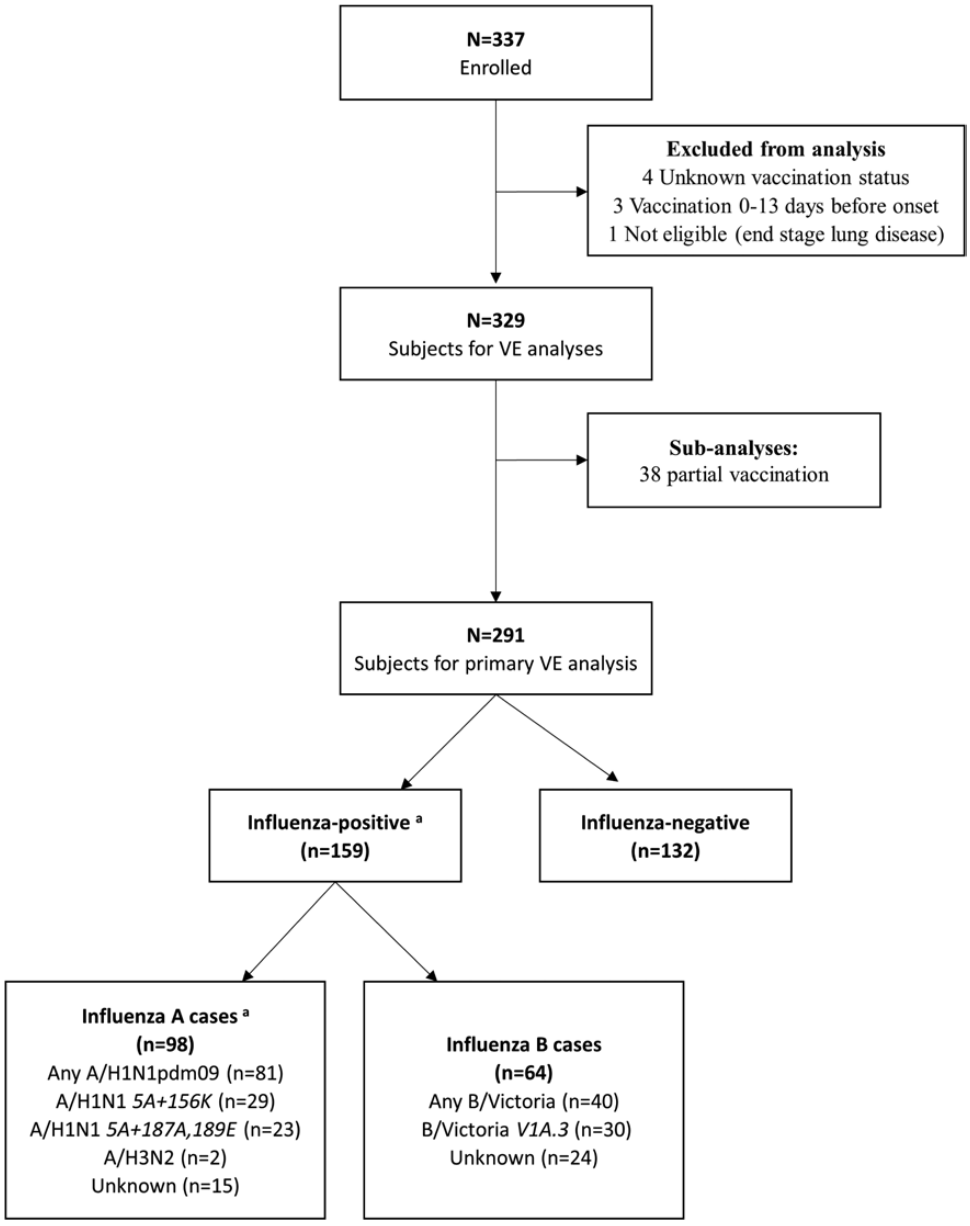

Figure 1. Pediatric Intensive Care Influenza network study enrollment by influenza case status, 2019–2020. [a]Three patients had coinfections (1 with influenza A(H1N1) pdm09 and influenza B, 1 with influenza A and influenza B-Victoria, and 1 with influenza A and influenza B). Reverse-transcription polymerase chain reaction samples with a cycle threshold value ≤30 were shipped to the Centers for Disease Control and Prevention for whole genome sequencing for antigenic and genetic characterization of the viruses. Among those viruses sequenced, there were additionally 4 influenza A/H1N1 5B viruses, 1 A/H3N2 135K+137F virus, and 1 B-Victoria V1A.1 virus. Abbreviation: VE, vaccine effectiveness.

D187A and Q189E (designated as 5A+187A, 189E viruses). Among 31 sequenced B-lineage viruses, almost all (30 of 31) were B-Victoria V1A.3 subclade, which contains 3 amino acid deletions in the hemagglutinin protein at positions 162–164. Among these sequenced viruses, A/H1N1pdm09 5A+187A,187E subclades were antigenically matched to the vaccine reference strain. However, A/H1N1pdm09 5A+156K and the B-Victoria V1A.3 subclades were mismatched to the reference strains included in the 2019–2020 Northern Hemisphere vaccines.

Vaccine Effectiveness

VE against critical illness from any influenza virus was 63% (95% confidence interval [CI], 38% to 78%; Figure 2). Protection did not differ by age group or by full vs partial vaccination. Overall, VE was 64% (95% CI, 34% to 81%) against critical illness from A(H1N1)pdm09 and 68% (95% CI, 34% to 85%) against B-lineage viruses. Among sequenced viruses, vaccination conferred higher protection against matched A/H1N1 5A+187A,187E subclade (78%; 95% CI, 41% to 92%) and mismatched B-Victoria V1A.3 subclade viruses (75%; 95% CI,

Table 1. Characteristics Among Critically Ill Children by Influenza Status and Vaccination Status, 2019–2020

Characteristic	Influenza Status		Vaccination Status	
	Influenza-Positive (N = 159)	Influenza-Negative (N = 132)	Unvaccinated (N = 131)	Fully Vaccinated (N = 160)
Female sex, no. (%)	64 (40.3)	61 (46.2)	54 (41.2)	71 (44.4)
Median age (interquartile range), y	6 (3–10)	4 (2–12)	5 (3–10)	5 (2–12)
Age category, no. (%)				
6–23 m	21 (13.2)	24 (18.2)	19 (14.5)	26 (16.3)
2–8 y	90 (56.6)	67 (50.8)	79 (60.3)	78 (48.8)
9–17 y	48 (30.2)	41 (31.1)	33 (25.2)	56 (35.0)
Race and ethnic group, no. (%)				
White, non-Hispanic	93 (58.5)	85 (64.4)	80 (61.1)	98 (61.3)
Black, non-Hispanic	25 (15.7)	17 (12.9)	22 (16.8)	20 (12.5)
Other, non-Hispanic	6 (3.8)	7 (5.3)	6 (4.6)	7 (4.4)
Hispanic	35 (22.0)	23 (17.4)	23 (17.6)	35 (21.9)
Site location by region, no. (%)				
Northeast	56 (35.2)	41 (31.1)	39 (29.8)	58 (36.3)
Midwest	55 (34.6)	46 (34.9)	48 (36.6)	53 (33.1)
South	26 (16.4)	28 (21.2)	24 (18.3)	30 (18.8)
West	22 (13.8)	17 (12.9)	20 (15.3)	19 (11.9)
Underlying condition, no. (%)[a]				
At least 1 underlying condition	115 (72.3)	101 (76.5)	91 (69.5)	125 (78.1)
Respiratory (including asthma)	66 (41.5)	70 (53.0)	56 (42.8)	80 (50.0)
Asthma	36 (22.6)	30 (22.7)	36 (27.5)	30 (18.8)
Cardiovascular	13 (8.2)	19 (14.4)	9 (6.9)	23 (14.4)
Neurological/neuromuscular	56 (35.2)	69 (52.3)	36 (27.5)	89 (55.6)
Oncologic/immunosuppressive	1 (0.6)	1 (0.8)	1 (0.8)	1 (0.6)
Renal/urologic	6 (3.8)	5 (3.8)	3 (2.3)	8 (5.0)
Gastrointestinal/hepatic	23 (14.5)	37 (28.0)	15 (11.5)	45 (28.1)
Endocrine/metabolic (excluding morbid obesity), no./total no.[b]	32/159 (20.1)	29/130 (22.3)	21/130 (16.2)	40/159 (25.2)
Body mass index–based obesity, no./total no. (%)[c]	24/119 (20.2)	24/92 (26.1)	21/97 (21.7)	27/114 (23.7)
Influenza test results, no. (%)				
Positive	159 (100)	0 (0)	90 (68.7)	69 (43.1)
Negative	0 (0)	132 (100)	41 (31.3)	91 (56.9)
Influenza vaccination, no. (%)				
Full influenza vaccination	69 (43.4)	91 (68.9)	0 (0)	160 (100)
Days from illness onset to hospitalization, no. (%)[d]				
0–2	78 (49.1)	69 (52.3)	63 (48.1)	84 (52.5)
3–4	50 (31.5)	39 (29.6)	43 (32.8)	46 (28.8)
5–7	29 (18.2)	23 (17.4)	25 (19.1)	27 (16.9)
8–10	2 (1.3)	1 (0.8)	0 (0.0)	3 (1.9)
Received influenza antivirals before hospitalization, no. (%)	24 (15.1)	1 (0.8)	10 (7.6)	15 (9.4)

[a]Nine patients responded "yes" to "was the patient on admission otherwise healthy, on no prescription medications, without underlying medical conditions and not dependent on any medical devices prior to initial admission to the hospital for this illness?" These patients were not asked specific questions on underlying conditions. However, based on calculated body mass index (BMI), they were considered obese and were subsequently reclassified as having at least 1 underlying condition.

[b]Among patients with endocrine/metabolic underlying conditions, 4 had diabetes.

[c]The BMI is the weight in kilograms divided by the square of the height in meters. BMI-based obesity was defined on the basis of national reference standards for BMI and was calculated only for patients who were at least 2 years of age. BMI was not calculated for 80 patients because the patient was aged <2 years or was missing a height or weight measurement.

[d]One patient was hospitalized before developing symptoms, and days of illness onset is calculated from onset to admission to intensive care unit.

37% to 90%) compared with mismatched A/H1N1 5A+156K subclade viruses (47%; 95% CI, –21% to 77%), though confidence intervals were overlapping.

We further stratified VE by clinical severity within all critically ill children with influenza. VE was 75% (95% CI, 49% to 88%) against life-threatening illness compared with 57% (95% CI, 24% to 76%) against non-life-threatening illness (Figure 3).

DISCUSSION

In this study of critically ill children with ARI, we estimate that vaccination effectively reduced life-threatening influenza illness by 75% during a season predominated by B/Victoria viruses and A/H1N1pdm09 subclade viruses that were antigenically drifted from vaccine components [13, 14].

Table 2. Clinical Outcomes and Severity Among Critically Ill Children by Influenza Status, 2019–2020

Characteristic	Influenza-Positive (N = 159)	Influenza-Negative (N = 132)
Length of stay, d		
Hospital, median (IQR)[a]	5 (3–11)	6 (3–10)
Intensive care unit, median (IQR)[b]	2 (1–5)	4 (2–7)
Pulmonary infiltrates on chest X-ray, no. (%)[c]	81 (50.9)	70 (53.0)
Bilateral infiltrates, no./total no.(%)	52/81 (64.2)	50/70 (71.4)
Life-threatening illness, no. (%)[d]	57 (35.9)	40 (30.3)
Invasive mechanical ventilation, no. (%)[e]	50 (31.5)	32 (24.2)
Vasopressor-dependent shock, no. (%)[f]	33 (20.8)	21 (15.9)
Cardiopulmonary resuscitation, no. (%)	3 (1.9)	1 (0.8)
Dialysis, no. (%)	3 (1.9)	2 (1.5)
Extracorporeal membrane oxygenation, no. (%)	4 (2.5)	2 (1.5)
In-hospital 30-day mortality, no. (%)	4 (2.5)	1 (0.8)
Other interventions, no. (%)		
Noninvasive mechanical ventilation[g]	67 (42.1)	68 (51.5)

Abbreviation: IQR, interquartile range.

[a]Patients who died during hospitalization (n = 5) were not included.

[b]Fourteen patients were excluded who were only admitted to the high acuity care unit.

[c]Pulmonary infiltrates were identified within the first 24 hours of admission.

[d]Patients with life-threatening illness include those who met any of the following criteria: invasive ventilation, vasopressor use, cardiopulmonary resuscitation for cardiac arrest, dialysis, extracorporeal membrane oxygenation, and in-hospital 30-day mortality.

[e]Invasive ventilation includes endotracheal tube or tracheostomy use throughout intensive care unit (ICU) or high acuity unit stay and for daily ventilation checks at days 1, 2, 3, 4, 5, 6, 7, 14, 21, and 28.

[f]Vasopressor includes use throughout ICU or high acuity unit stay and for pediatric logistic organ dysfunction at days 1, 2, 3, 4, 5, 6, 7, 14, 21, and 28.

[g]Noninvasive ventilation includes bilevel positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP) ≥ 5 cm H_2O use throughout ICU or high acuity unit stay and for daily ventilation checks at days 1, 2, 3, 4, 5, 6, 7, 14, 21, and 28.

Vaccination was estimated to reduce the risk of critical influenza in children by 78% against H1N1pdm09 viruses expressing matched hemagglutinin proteins and 47% against mismatched viruses. Against antigenically drifted B-Victoria viruses, vaccination conferred an estimated 75% protection. The 2019–2020 B-Victoria epidemic was the largest in the United States since 1993–1994 [14]. From these findings, we infer that vaccination prevented a substantial fraction of influenza-associated life-threatening illnesses requiring invasive mechanical ventilation, a strong predictor of death. During a season without circulation of antigenically drifted viruses and higher coverage, we suspect that vaccine impact against life-threatening influenza illness could be more substantial.

Improved understanding and recognition of vaccine protection against life-threatening influenza is an urgent public health issue [12, 18, 19]. If prioritized, this could improve vaccine coverage and vaccine policies worldwide. Several lines of evidence support that vaccination attenuates the severity of influenza infection and is highly effective at preventing

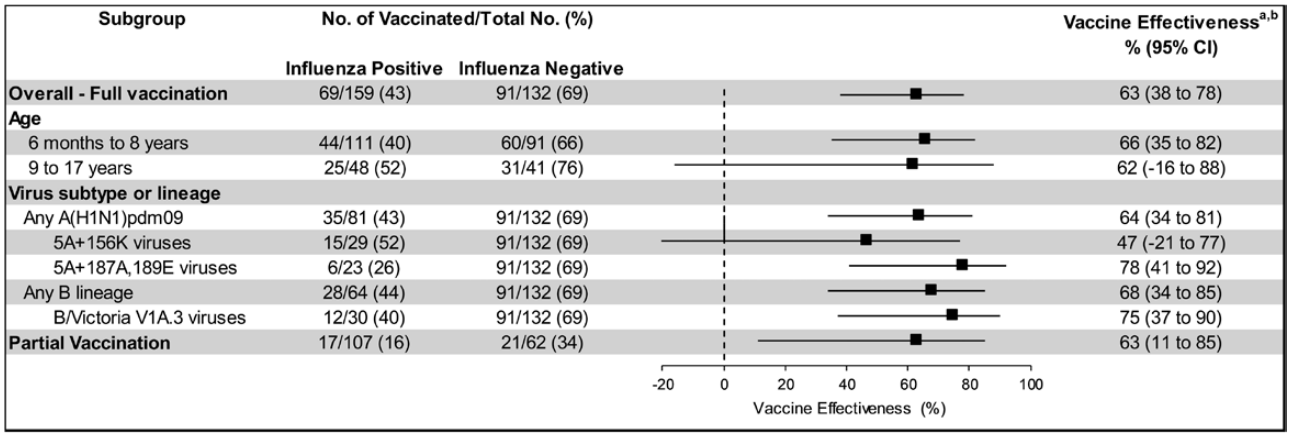

Figure 2. Influenza vaccine effectiveness against critical influenza illness in US children by virus type, 2019–2020. [a]Models are adjusted for age (continuous), sex, race and ethnic group, days from illness onset to hospitalization, calendar time (in months), and region. [b]Firth penalization was applied to adjusted models with 30 or fewer influenza positive cases including the models for 5A+156K, 5A+187A,189E, and V1A.3 viruses. Abbreviation: CI, confidence interval.

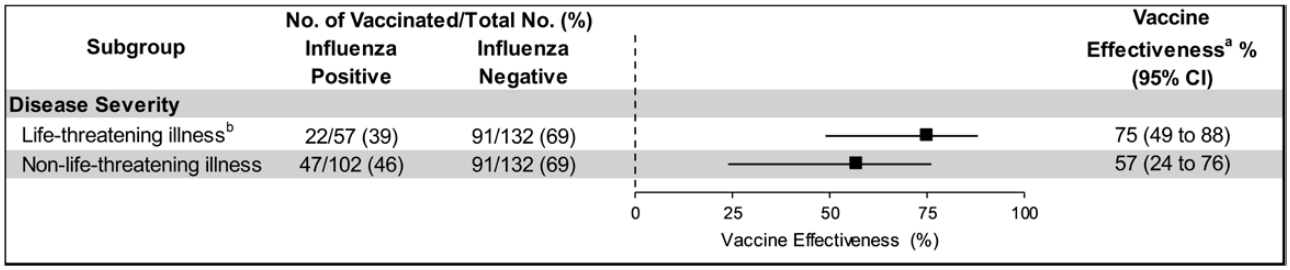

Figure 3. Influenza vaccine effectiveness for life-threatening vs non-life-threatening influenza illness, 2019–2020. [a]Adjusted for age (continuous), sex, race and ethnic group, days from illness onset to hospitalization, calendar time (in months), and region. [b]Patients with life-threatening illness include those who met any of the following criteria: invasive ventilation, vasopressor use, dialysis, cardiopulmonary resuscitation for cardiac arrest, extracorporeal membrane oxygenation, and in-hospital 30-day mortality. Abbreviation: CI, confidence interval.

life-threatening influenza in children [20, 21]. First, compared with critical influenza illness in our study, estimates of protection during the same seasons were lower in US children who developed influenza that required outpatient care (34%–40%), emergency department visits (56%), or hospitalization (62%) [14, 22]. A systematic review and meta-analysis of 37 studies showed that vaccination reduced risk of any influenza hospitalization by 53% [9]. Our VE estimates were also consistent with a smaller US study (74%–82%) of 44 critically ill children with influenza during the 2010–2011 and 2011–2012 seasons [10]. Second, effectiveness against critical influenza illness vs outpatient illness during the same season was higher for matched influenza H1N1pdm09 viruses (79% vs 41%), mismatched B-lineage viruses (75% vs 41%), and mismatched H1N1pdm09 subclades (47% vs 7%) [14]. Third, these findings of higher protection against severe influenza compared with milder illness have biological plausibility. Repeat influenza virus infections occur because of virus drift, waning immunity, or insufficient mucosal immunity in the upper airway [23]. However, with heterologous immunity from prior infection or vaccination [23], recall of antibody and cellular immune responses or presence of mucosal immunity in the lower lungs might attenuate influenza disease by limiting viral replication and spread to the small airways or extrapulmonary organ systems or by accelerating virus clearance [24, 25]. Higher protection against critical vs milder influenza illness aligns with findings from experimental viral challenge studies in animals and adults where preexisting immunity or antiviral treatment halt the progression of respiratory disease through reductions in viral replication and commensurate decreases in cytokines [24, 26, 27]. While findings from observational studies have been mixed, the overall findings support disease attenuation among vaccinated persons who develop infection compared with those who are unvaccinated [21].

The observed protection against critical illness from A/H1N1pdm09 5A+156K subclade viruses in children was perplexing for 2 reasons. First, these circulating viruses were antigenically mismatched to the vaccine component of A/H1N1pdm09. Second, low protection was observed in US adults during the same season [14]. Similarly, during the 2018–2019 season, effectiveness was preserved in children [16, 28] when the A/H3N2 component of the vaccine was mismatched to the circulating A/H3N2 viruses globally, resulting in low or null effectiveness in outpatient and inpatient adults [15, 28]. Most of the cohorts across these studies were vaccinated with an inactivated influenza vaccine; thus, vaccine type was unlikely to explain differences in effectiveness between adults and children. One possibility is that immune responses and correlates of protection in children who are more likely to be immunologically naive are different from those in adults who have a higher probability of being boosted with repeated infections and vaccinations [29, 30].

Antigenic characterization of influenza viruses is largely based on the evolving receptor binding domain on the globular head of the hemagglutinin protein on the surface of the influenza viruses, which is suspected to be one correlate of immune protection [30, 31]. Other components of immunity that contribute to protection may include conserved epitopes on the stalk of the hemagglutinin protein, neuraminidase surface protein, the M protein, or cross-protective T-cell responses [31]. Differential induction of these responses by age is not well studied, and some of these factors may explain broader short-term protection against heterologous strains in children. The possibility also exists that vaccinating young children primes or imprints their immune system to provide durable, and possibly broad, protection against influenza viruses [32]. Our data add to the body of evidence for difficulty in predicting clinical protection based on genetic and antigenic characterization data, thus warranting timely annual studies of effectiveness to inform vaccine strain selection [14, 15]. Other approaches to improve the efficacy of influenza vaccines in children include examination of correlates of protection and longer-term benefits from imprinting through different vaccine types [32].

Our findings must be interpreted with some caveats. Critical influenza illness in children is a relatively rare occurrence that is reflected in the lack of randomized clinical trials evaluating protective efficacy against this outcome. Thus, we used the

observational case-control design, which improves efficiency for rare outcomes but may be subject to selection biases and residual confounding. We reduced information bias by systematic data collection through parent interviews and detailed medical record abstraction by study staff trained to ignore case and control status. Misclassification of vaccination status or case and control status can affect estimates of effectiveness. To reduce misclassification, we invested considerable efforts to verify vaccination history in case patients and controls through medical record review, vaccination registries, and contacting pediatricians. All cases and controls were confirmed using RT-PCR, and enrollment was restricted to 10 days of illness onset to improve assay sensitivity. This pediatric ICU network was specifically designed for collection of detailed patient and clinical characteristics, allowing for evaluation of disease severity among critically ill children. While the study was designed to span 2 influenza seasons to capture diverse influenza viruses, influenza did not circulate during the second season due to the COVID-19 pandemic. Thus, our sample size for subgroup analyses was limited. However, because life-threatening influenza was uncommon, we conducted exploratory secondary analyses and found that the effectiveness estimates were biologically plausible and consistent with estimates in the published literature. Moreover, our sample size of cases was 3-fold larger than the only other published study of effectiveness against influenza in critically ill children [10].

In summary, influenza vaccination was associated with reduced risk of life-threatening influenza in US children during the 2019–2020 season. These data are particularly impressive in the context of circulation of 2 vaccine-mismatched viruses. Our real-world findings suggest that accelerating efforts to bring influenza vaccines to all children could lead to appreciable reductions in critical illness and deaths from influenza worldwide.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC. S. M. O., L. R. F., J. R. B., and M. M. P. are employed by the funding agency and were involved in the study design, collection, analysis, and interpretation of the data; writing the report; and the decision to submit the paper for publication.

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