Influenza clinical testing and oseltamivir treatment in hospitalized children with acute respiratory illness, 2015–2016

Lubna Hamdan | Varvara Probst | Zaid Haddadin | Herdi Rahman | Andrew J. Spieker | Simon Vandekar | Laura S. Stewart | John V. Williams | Julie A. Boom | Flor Munoz | Janet A. Englund | Rangaraj Selvarangan | Mary A. Staat | Geoffrey A. Weinberg | Parvin H. Azimi | Eileen J. Klein | Monica McNeal | Leila C. Sahni | Monica N. Singer | Peter G. Szilagyi | Christopher J. Harrison | Manish Patel | Angela P. Campbell | Natasha B. Halasa

1Department of Pediatrics, Division of Infectious Diseases, Vanderbilt University Medical Center, Nashville, Tennessee, USA
2Department of Biostatistics, Vanderbilt University Medical Center, Nashville, Tennessee, USA
3Pediatric Infectious Diseases, Institute for Infection, Inflammation, and Immunity in Children, University of Pittsburgh School of Medicine, UPMC Children’s Hospital of Pittsburgh, Pittsburgh, Pennsylvania, USA
4Primary Care Practice at Palm Center, Immunization Project, Baylor College of Medicine, Texas Children’s Hospital, Houston, Texas, USA
5Pediatrics and Molecular Virology and Microbiology, Baylor College of Medicine, Texas Children’s Hospital, Houston, Texas, USA
6Department of Pediatrics, Division of Infectious Diseases, Seattle Children’s Hospital, Seattle, Washington, USA
7Pathology & Laboratory Medicine, Children’s Mercy Hospital, Kansas City, Missouri, USA
8Pediatric Infectious Diseases, University of Cincinnati College of Medicine, Cincinnati Children’s Hospital and Medical Center, Cincinnati, Ohio, USA
9Pediatric Infectious Diseases, University of Rochester Medical Center, Rochester, New York, USA
10Pediatric Infectious Diseases, Children’s Hospital and Research Center, Oakland, California, USA
11Department of Pediatrics, Division of Emergency Medicine, Seattle Children’s Hospital, Seattle, Washington, USA
12Department of Pediatrics, Section of Hematology-Oncology, Baylor College of Medicine, Texas Children’s Hospital, Houston, Texas, USA
13Department of Pediatrics, University of California at Los Angeles Mattel Children’s Hospital, Los Angeles, California, USA
14Pediatric Infectious Diseases, Children’s Mercy Hospital, Kansas City, Missouri, USA
15National Center for Immunization and Respiratory Diseases, Division of Viral Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA
16Epidemiology and Prevention Branch, Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Correspondence
Natasha B. Halasa, MD MPH, Craig Weaver Professor of Pediatrics, Pediatric Infectious Diseases, 1161 21st Ave South, D7232 MCN, Nashville, TN 37232, USA.
Email: natasha.halasa@vumc.org

Funding information
REDCap, Grant/Award Number: UL1 TR000445 from NCATS/NIH; Centers for Disease Control and Prevention Cooperative New Vaccine Surveillance Network

Abstract
Background: Antiviral treatment is recommended for all hospitalized children with suspected or confirmed influenza, regardless of their risk profile. Few data exist on adherence to these recommendations, so we sought to determine factors associated with influenza testing and antiviral treatment in children.
Methods: Hospitalized children <18 years of age with acute respiratory illness (ARI) were enrolled through active surveillance at pediatric medical centers in seven cities between 11/1/2015 and 6/30/2016; clinical information was obtained from parent

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.
© 2021 The Authors. Influenza and Other Respiratory Viruses published by John Wiley & Sons Ltd.
interview and chart review. We used generalized linear mixed-effects models to identify factors associated with influenza testing and antiviral treatment.

**Results:** Of the 2299 hospitalized children with ARI enrolled during one influenza season, 51% \((n = 1183)\) were tested clinically for influenza. Clinicians provided antiviral treatment for 61 of 117 (52%) patients with a positive influenza test versus 66 of 1066 (6%) with a negative or unknown test result. In multivariable analyses, factors associated with testing included neuromuscular disease \((aOR = 5.35, 95\% CI [3.58–8.01])\), immunocompromised status \((aOR = 2.88, 95\% CI [1.66–5.01])\), age \((aOR = 0.93, 95\% CI [0.91–0.96])\), private only versus public only insurance \((aOR = 0.78, 95\% CI [0.63–0.98])\), and chronic lung disease \((aOR = 0.64, 95\% CI [0.51–0.81])\). Factors associated with antiviral treatment included neuromuscular disease \((aOR = 1.86, 95\% CI [1.04, 3.31])\), immunocompromised state \((aOR = 2.63, 95\% CI [1.38, 4.99])\), duration of illness \((aOR = 0.92, 95\% CI [0.84, 0.99])\), and chronic lung disease \((aOR = 0.60, 95\% CI [0.38, 0.95])\).

**Conclusion:** Approximately half of children hospitalized with influenza during the 2015–2016 influenza season were treated with antivirals. Because antiviral treatment for influenza is associated with better health outcomes, further studies of subsequent seasons would help evaluate current use of antivirals among children and better understand barriers for treatment.

**KEYWORDS**
clinical testing, hospitalization, influenza, nucleic acid amplification tests (NAAT), oseltamivir, rapid influenza testing

---

**INTRODUCTION**

Influenza is an important cause of acute respiratory illnesses (ARI), with an estimated 4.3–21 million clinical outpatient visits, 140,000–810,000 hospitalizations, and 12,000–81,000 deaths annually over the past decade in the United States (U.S.).\(^1\)–\(^4\) Influenza has a high attack rate in children with an estimated incidence of 19/1000 per year and an overall mortality rate of 15 deaths per 1000 influenza-positive children.\(^5\) Children less than 5 years of age, and especially children less than 2 years of age, American Indians or Alaska Natives and those with underlying comorbidities are at higher risk for developing influenza-associated complications.\(^6\) However, nearly 50% of hospitalized children with influenza do not have an underlying medical condition.\(^7\)

Influenza vaccination is the mainstay of prevention against influenza disease and can prevent influenza-associated complications in children 6 months of age and older.\(^8\) If an infection is acquired, antiviral treatment for influenza disease has been shown to reduce complications, shorten the length of hospitalization, and reduce mortality; these benefits are more pronounced when treatment is initiated within 48 h of symptom onset.\(^9\)–\(^11\) However, variation in the prescribing patterns among clinicians exist, possibly due to concerns about effectiveness and reporting biases in industry funded trials.\(^12\)–\(^13\) Detailed recommendations by the Infectious Diseases Society of America (IDSA) for antiviral treatment for influenza disease were published in response to the 2009 pandemic and has been updated periodically.\(^14\) The recommendations include antiviral treatment for all hospitalized individuals with confirmed or suspected influenza, regardless of underlying illness or vaccination status, and recommend initiation of treatment within 48 h of symptom onset.\(^15\) In addition, the recommendations advise that persons hospitalized for confirmed influenza may also benefit from treatment even if initiated more than 48 h after the onset of illness.\(^14\) The American Academy of Pediatrics (AAP) recommends treatment as soon as possible for children hospitalized with suspected influenza, hospitalized for severe, complicated, or progressive illness attributable to influenza regardless of duration of symptoms, and to children with suspected influenza and at increased risk of complications. It also recommends considering treatment for any healthy child with suspected influenza, and to healthy children with suspected influenza who live with a household contact who is <6 months old or has a medical condition that predisposes them to complications.\(^15\) Despite these recommendations, controversy among physicians exists and suboptimal antiviral use has been reported in recent studies.\(^16\)–\(^17\)

Clinical testing for influenza illness may influence antiviral treatment; however, based on updated 2018 IDSA recommendations, antiviral treatment decisions should not be delayed until laboratory confirmation of influenza.\(^6\) Data are limited on factors associated with
making clinical decisions whether to test for and/or to treat influenza. This study describes influenza testing and antiviral treatment practices in children admitted with a diagnosis of ARI during the 2015–2016 influenza season and identifies factors associated with decisions for influenza testing and antiviral treatment.

2 | METHODS

2.1 | Study description

As part of the Centers for Disease Control and Prevention (CDC) New Vaccine Surveillance Network (NVSN), active population-based ARI surveillance was conducted from November 1, 2015, through June 30, 2016, at pediatric medical centers in seven cities: Rochester, New York; Cincinnati, Ohio; Nashville, Tennessee; Kansas City, Missouri; Houston, Texas; Seattle, Washington; and Oakland, California.

2.2 | Study population

Children <18 years old were eligible for enrollment if they were admitted to a participating hospital, resided within each hospital’s surveillance area, had illness duration <14 days, were enrolled in the study within 48 h of admission, and had one or more of the following admission diagnoses: acute respiratory illness, apnea, asthma exacerbation, reactive airways disease, bronchiolitis, croup, cystic fibrosis exacerbation, respiratory syncytial virus infection, febrile neonate, febrile seizure, hypothermia, paroxysmal cough, wheezing, influenza, fever without localizing signs, respiratory distress, otitis media, pharyngitis, pneumonia, pneumonitis, rule-out sepsis, sinusitis, tonsillitis, streptococcal pharyngitis, upper respiratory infection, other respiratory infection, bronchiectasis, tracheitis, and/or pleural effusion.

Children were excluded if they had a known nonrespiratory cause for hospitalization, had fever and neutropenia with malignancy, were discharged from a hospital in the prior 4 days, were transferred after admission at another hospital for 48 h, had never been discharged home after birth, or had previously enrolled in this study <14 days prior to their current admission.

For this study, we included children who were hospitalized during each site’s influenza season defined as the date of first through the last influenza positive case for each site based on research testing results (Figure 1A). We excluded 24 children who received influenza antiviral treatment prior to hospitalization (Figure 1A).

2.3 | Study design

Following written informed consent from a parent or guardian and assent when applicable, demographic data, history of current illness, social history and treatment received before presentation were collected through parent/guardian interviews. Standardized medical chart reviews were performed, and clinical interventions and outcome data were collected including chronic comorbid conditions, types and results of clinical influenza diagnostic studies performed, antiviral treatment, intensive care unit (ICU) admissions, and oxygen requirement.

Institutional Review Board approval was obtained from the CDC and at each individual site.

2.4 | Definitions

2.4.1 | Influenza season

Influenza season was defined as the period between the dates of the first through last influenza positive case for each specific site, based upon research laboratory testing. Research laboratory diagnostic influenza assays varied by site, but all were nucleic acid amplification tests (NAATs) for which CDC-generated influenza proficiency panels were successfully completed.

Influenza clinical testing was defined as any influenza testing that was ordered by providers. Clinical testing was available for those subjects whose treating provider ordered testing from the clinical laboratory of their respective hospital as part of standard care; the method of clinical laboratory testing was either rapid influenza diagnostic testing (RIDT) or NAATs. Positive test results were defined according to results documented in medical charts for influenza A, influenza A/(H1N1)pdm09, influenza A(H3N2), and influenza B lineage viruses.

2.4.2 | Antiviral use

Influenza antiviral use was defined as in-hospital receipt of a neuraminidase inhibitor (oseltamivir or zanamivir) or adamantane (amantadine or rimantadine) documented by chart review.

2.4.3 | Underlying medical condition

Underlying medical conditions included chronic pulmonary/airway, cardiac, gastrointestinal, liver, kidney, endocrine, neurologic/neuromuscular, hematologic/oncologic, genetic/metabolic, or immunocompromised conditions. Chronic lung disease included asthma, cystic fibrosis, bronchopulmonary dysplasia, and other lung disorders recorded in the chart. Neuroromuscular disease included cerebral palsy, seizures, and other neuromuscular diseases recorded in the chart. Immunocompromised included children with a history of immunodeficiency/immunosuppressive condition, transplant (peripheral blood stem cells, bone marrow, cord blood, or solid organ), cancer diagnosis within the prior 5 years, and sickle cell anemia.
2.4.4 | Influenza vaccine reporting

Receipt of influenza vaccine was determined by parental report of receiving influenza vaccination for the current season for children who were 6 months or older.

2.5 | Data analysis

All analyses were performed using Stata IC 15.0 (StatCorp LLC, College Station, TX) or R version 4.0.3. Data were collected and managed by the CDC’s Secure Access Management Services (SAMS).

Demographic and clinical characteristics were evaluated using descriptive statistics (frequency and percentage for categorical variables, or mean and standard deviation for continuous variables). Between-group comparisons were performed using Pearson’s chi-squared test for categorical variables and two-sample t tests of mean differences for continuous variables.

We used a generalized linear mixed-effects model on the log-odds scale to evaluate factors associated with influenza testing and antiviral treatment, separately. To address missing data, we used multiple imputation via chained equations with \( M = 500 \) iterations, aggregating results using Rubin’s rules. The following predictors were included a priori in each of the two models: continuous age (years), sex, race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and other), fever, cough, fever & cough, duration of illness prior to admission, chronic lung disease, neuromuscular disease, immunocompromised status, congenital heart disease, influenza vaccination, and insurance status (public, private, both, and self-pay). We included a random intercept for each study site. From these models, we estimated adjusted odds ratios for each predictor and derived corresponding Wald-based 95% confidence intervals.

(Figure 1) A study cohort including total admissions due to acute respiratory illnesses and excluded subjects. (B) Acute respiratory illness admissions: total and during influenza season.
intervals and p-values. Statistical significance was determined at the nominal α = 0.05 level (two-sided).

3 | RESULTS

3.1 | Patient characteristics

Among the 3926 enrolled children who were hospitalized with ARI or febrile illness between July 2015 and June 2016, 2299 (58%) met eligibility criteria for this analysis (Figure 1A). The total duration of influenza season by each site is represented in Figure 1B. The Houston and Oakland sites had the highest numbers of enrollments representing half of the cohort, and Seattle had the longest influenza season (Figure 1B).

For children who were enrolled and eligible, the mean age was 2.8 years (median 1 year, IQR [0–4]), 56% were under 2 years, 58% male, and 44% had at least one underlying medical condition. The mean duration from symptom onset to admission was 3.3 days; 43% had symptoms for ≤2 days prior to hospitalization.

3.2 | Clinical influenza testing

Among our population, 1183 (51%) were tested for influenza (Table 1): 24% RIDT, 71% NAATs, and 6% both. Factors with significant positive association with testing included neuromuscular disease (aOR = 5.35, 95% CI [3.58–8.01]), congenital heart disease (aOR = 2.52, 95% CI [1.59–3.99]), and immunocompromised status (aOR = 2.88, 95% CI [1.66–5.01]), while those negatively associated with testing included age (aOR = 0.93, 95% CI [0.91–0.96]), private vs. public insurance (aOR = 0.78, 95% CI [0.63–0.98]) and chronic lung disease (aOR = 0.64, 95% CI [0.51–0.81]) (Table 2).

Of the 1183 tested, 117 (10%) were influenza positive. Compared to influenza-negative children, children with influenza were older (mean age, 3.6 vs. 2.3 years), more likely to have neuromuscular disease (14% vs. 4%), have congenital heart disease (7% vs. 3%), be immunocompromised (5% vs. 2%), receive oseltamivir (11% vs. 2%), require oxygen support (65% vs. 55%), be admitted to the ICU (24% vs. 8%), and be intubated (5% vs. 1%), all p < 0.001. Influenza positive patients were less likely than influenza negative patients to have chronic lung disease (24% vs. 36%, p < 0.001).

3.3 | Antiviral treatment

All treated patients received oseltamivir. Antiviral treatment was positively associated with neuromuscular disease (aOR = 1.86, 95% CI [1.04, 3.31]), and immunocompromised state (aOR = 2.63, 95% CI [1.38, 4.99]) and was negatively associated with duration of illness (aOR = 0.92, 95% CI [0.84, 0.99]) and chronic lung disease (aOR = 0.60, 95% CI [0.38, 0.95]) (Table 3).

Moreover, children who were tested for influenza were more likely to receive antiviral treatment (tested vs. not tested: 127/1183 (11%) vs. 22/1183 (2%), p < 0.001). Additionally, children who tested positive were more likely to be treated (positive vs. nonpositive 61/117 (52%) vs. 66/1066 (6%), p < 0.001).

4 | DISCUSSION

In our study of children hospitalized with ARI during the 2015-2016 influenza season across multiple pediatric medical centers, influenza testing during the influenza season was infrequent and antiviral treatment among influenza positive children was low. Additionally, only half of the children with laboratory-confirmed influenza during standard care received antiviral treatment despite the IDSA and AAP recommendations of empiric antiviral treatment for hospitalized patients with confirmed or suspected influenza without the need for testing.

Shorter duration of illness was associated with higher odds of antiviral treatment. The 2009 IDSA guidelines recommended empiric antiviral treatment for hospitalized patients with confirmed or suspected influenza if treatment can be commenced within 48 h of symptom onset. The updated guidelines in 2018 included antiviral treatment for all hospitalized individuals with confirmed or suspected influenza, regardless of the illness duration prior to hospitalization. Supportive evidence mainly depended on adult studies. Among the few studies investigating antiviral effects in children, early treatment was found to shorten the duration of symptoms, decrease hospital admissions, and reduce the risk for developing otitis media. In hospitalized children, early antiviral treatment with oseltamivir also shortened the duration of hospitalization. Therefore, further investigation to understand barriers for antiviral treatment and physicians’ perceptions of antiviral may be useful.

Suboptimal antiviral use among hospitalized patients has been reported previously, especially in the pre-H1N1-2009 pandemic era. A prior NIVS study with three clinical sites between 2004 and 2009 reported that only 1.5% of hospitalized children under 5 years of age with research-confirmed influenza received antiviral treatment. Other data from 2003 to 2008 from children ≤1 year who had a positive clinical influenza test within 48 h of symptom onset, 37%-48% were treated with an antiviral. In contrast, during the 2009-H1N1 pandemic, a study noted that 77% of children hospitalized with influenza received an antiviral but a 27% decline was reported the following year. The FluSurv-NET subsequently reported that 72% of 6469 hospitalized children with confirmed influenza received antivirals between 2010 and 2015. Only evaluating populations with positive clinical testing compared to broader populations that might be eligible for antiviral treatment may overestimate the antiviral coverage. Our findings indicate that additional efforts are needed to increase awareness of antiviral effectiveness and current empiric influenza treatment recommendations in hospitalized children with suspected influenza without delay for testing results.

Approximately half of the enrolled children had a provider-initiated influenza test with the majority having a NAAT performed.
which is the recommended test for this population. Also our study showed an association between testing, testing results, and receiving treatment. Historically, RIDT was the most commonly used diagnostic test. While RIDT sensitivity is higher in children than adults, sensitivity in children is estimated to be 67%. During the 2009 H1N1 pandemic, RIDT was associated with a higher false negative rate and clinicians were directed to start antiviral treatment if influenza was highly suspected despite a negative result. Despite the limited sensitivity of RIDT, a study among children seeking care in the Emergency Department showed that a positive RIDT was associated with increased antiviral use. A recent study documented use of rapid influenza NAAT in acute care settings improved

| TABLE 1 Demographics and clinical characteristics of children hospitalized with ARI during 2015–2016 influenza season |
|-------------------------------------------------------------|
| Treated                                                     | Tested                                      |
| 149/2299 (6.5%)                                             | 1183/2299 (51.5%)                           |
| n (%)                                                       | n (%)                                       |
| Mean ± SD                                                  | Mean ± SD                                   |
| Median [IQR]                                               | Median [IQR]                                |

Demographics

| Age (years), mean | 3.2 ± 4.2 | 24 ± 3.6 |
| Age (years), median | 1 [0–5] | 1 [0–3] |
| Sex, Male | 92/1337 (6.9%) | 680/1337 (50.9%) |
| Race | Race |
| Non-Hispanic White | 34/735 (4.6%) | 377/735 (51.3%) |
| Non-Hispanic Black | 37/478 (7.7%) | 198/478 (41.4%) |
| Hispanic | 69/798 (8.7%) | 448/798 (56.14%) |
| Other | 7/274 (2.6%) | 152/274 (55.5%) |

Insurance status

| Private | 35/746 (4.7%) | 35/746 (4.7%) |
| Public | 107/1375 (7.8%) | 107/1375 (7.8%) |
| Both | 4/112 (3.6%) | 4/112 (3.6%) |
| Self-pay | 2/59 (3.4%) | 2/59 (3.4%) |

Clinical characteristics

| Chronic lung diseases | 33/690 (4.9%) | 287/690 (41.6%) |
| Neuromuscular diseases | 21/201 (14.1%) | 160/201 (79.6%) |
| Congenital heart disease | 11/115 (9.6%) | 84/115 (73%) |
| Immunocompromised | 16/80 (20%) | 59/80 (73.8%) |
| Influenza vaccination ≥6 months | 68/1085 (6.3%) | 555/1085 (51.2%) |
| Antiviral treatment | 149/149 (100%) | 127/149 (85.2%) |
| Clinical testing for influenza | 127/1183 (10.7%) | 1183/1183 (100%) |

| Type of test | Type of test |
| Rapid | 19/279 (6.8%) | 279/279 (100%) |
| Molecular | 100/834 (12%) | 834/834 (100%) |
| Both | 8/70 (11.4%) | 70/70 (100%) |

Clinical outcome

| Required oxygen support | 87 (6.4%) | 758 (55.6%) |
| ICU admission | 38/378 (10.1%) | 286 (75.7%) |
| Intubated | 13/72 (18.1%) | 59/72 (81.9%) |
| Length of hospitalization (days), mean | 4 ± 5.7 | 3.9 ± 6.5 |
| Length of hospitalization (days), median | 2 [2–4] | 2 [1–4] |
### TABLE 2  Generalized linear mixed-effects model evaluating predictors of testing

| Variable                                | Odds ratio | 95% CI     | p value |
|-----------------------------------------|------------|------------|---------|
| Age (years)                             | 0.93       | [0.91, 0.96] | <0.001  |
| Sex, male                               | 0.90       | [0.75, 1.09] | 0.28    |
| Race/ethnicity: non-Hispanic White      | REF        | REF        | REF     |
| Race/ethnicity: non-Hispanic Black      | 0.86       | [0.65, 1.14] | 0.30    |
| Race/ethnicity: Hispanic                | 1.08       | [0.82, 1.41] | 0.59    |
| Race/ethnicity: other                   | 1.08       | [0.78, 1.48] | 0.66    |
| Fever                                   | 1.94       | [0.97, 3.88] | 0.062   |
| Cough                                   | 1.06       | [0.58, 1.94] | 0.85    |
| Fever and cough                         | 0.81       | [0.40, 1.68] | 0.58    |
| Duration of illness (days)              | 0.97       | [0.93, 1.01] | 0.18    |
| Chronic lung disease                    | 0.64       | [0.51, 0.81] | <0.001  |
| Neuromuscular disease                   | 5.35       | [3.58, 8.01] | <0.001  |
| Immunocompromised                       | 2.88       | [1.66, 5.01] | <0.001  |
| Congenital heart disease                | 2.52       | [1.59, 3.99] | <0.001  |
| Influenza vaccination ≥6 months          | 1.09       | [0.86, 1.38] | 0.48    |
| Insurance: public                       | REF        | REF        | REF     |
| Insurance: private                      | 0.78       | [0.63, 0.98] | 0.030   |
| Insurance: public and private           | 0.96       | [0.62, 1.49] | 0.86    |
| Insurance: self-pay                     | 1.01       | [0.58, 1.76] | 0.98    |
| Peak months                             | 0.84       | [0.69, 1.02] | 0.073   |

Note: Bold values denote statistical significance.

### TABLE 3  Generalized linear mixed-effects model evaluating predictors of treatment

| Variable                                | Odds ratio | 95% CI     | p value |
|-----------------------------------------|------------|------------|---------|
| Age (years)                             | 1.04       | [0.99, 1.09] | 0.17    |
| Sex, male                               | 1.19       | [0.83, 1.70] | 0.34    |
| Race/ethnicity: non-Hispanic White      | REF        | REF        | REF     |
| Race/ethnicity: non-Hispanic Black      | 1.41       | [0.81, 2.45] | 0.22    |
| Race/ethnicity: Hispanic                | 1.38       | [0.83, 2.29] | 0.22    |
| Race/ethnicity: other                   | 0.73       | [0.31, 1.70] | 0.46    |
| Fever                                   | 5.01       | [0.64, 39.4] | 0.13    |
| Cough                                   | 2.19       | [0.29, 16.8] | 0.45    |
| Fever and cough                         | 0.68       | [0.08, 5.64] | 0.72    |
| Duration of illness                     | 0.92       | [0.84, 0.99] | 0.035   |
| Chronic lung disease                    | 0.60       | [0.38, 0.95] | 0.028   |
| Neuromuscular disease                   | 1.86       | [1.04, 3.31] | 0.035   |
| Immunocompromised                       | 2.63       | [1.38, 4.99] | 0.003   |
| Congenital heart disease                | 1.31       | [0.65, 2.61] | 0.45    |
| Influenza vaccination ≥6 months          | 0.82       | [0.51, 1.31] | 0.41    |
| Insurance: public                       | REF        | REF        | REF     |
| Insurance: private                      | 0.74       | [0.47, 1.16] | 0.20    |
| Insurance: public and private           | 0.53       | [0.18, 1.52] | 0.24    |
| Insurance: self-pay                     | 0.51       | [0.12, 2.20] | 0.37    |
| Peak months                             | 0.76       | [0.51, 1.13] | 0.17    |

Note: Bold values denote statistical significance.
appropriate antiviral treatment decisions in children. More studies are needed to evaluate the effect of test methodology on treatment decisions and to confirm potential improved adherence to treatment recommendations since introduction of the NAAT to hospitals.

Strengths of this study include the large pediatric sample size, multi-center involvement over a large geographic area, and prospective enrollment and collection of data. Our study also has some important limitations. These data are from 2015 to 2016 and only a single influenza season, so additional years are needed to determine the frequency of antiviral treatment and testing for influenza over multiple seasons. New NAAT assays are now more readily available and their faster turnaround times may affect antiviral treatment and testing decisions. We used parental reporting for influenza vaccine history because this information would be readily available to clinicians. Although parental reports of immunization were found to be a reliable predictor of immunization documented in the medical record in some studies, the frequencies may be optimistic given that they were found to be lower if parental report is subsequently subjected to hard-copy verification. Lastly, our sites were major university-affiliated hospitals and may not represent the practice in all hospitals that care for children.

In summary, antiviral treatment continued to be suboptimal in 2015–2016 in hospitalized children with ARI or febrile illnesses, including those with clinically proven influenza, despite recommendations to treat hospitalized children with confirmed or suspected influenza regardless of symptom duration. Identification of high-risk groups in addition to testing seemed to positively affect treatment frequencies. Further studies may provide a better understanding of barriers to antiviral treatment among hospitalized children and promote increased use of antivirals for hospitalized children with suspected or confirmed influenza infection.

ACKNOWLEDGMENTS
We would like to thank the New Vaccine Surveillance Network, our clinical trial associates, and the families who participated in this study. This work was supported by the Centers for Disease Control and Prevention Cooperative New Vaccine Surveillance Network. REDCap was used for data collection (UL1 TR000445 from NCATS/NIH).

AUTHOR CONTRIBUTIONS
Lubna Hamdan: Conceptualization; data curation; formal analysis; methodology; visualization. Varvara Probst: Data curation; formal analysis; investigation; methodology. Zaid Haddadin: Formal analysis; investigation; methodology. Herdi Rahman: Data curation; formal analysis; software; validation; visualization. Andrew Speiker: Conceptualization; data curation; formal analysis; software; supervision; validation. Simon Vandekar: Conceptualization; data curation; formal analysis; software; supervision; validation. Laura Stewart: Conceptualization; methodology; project administration; resources; validation. John Williams: Conceptualization; investigation; methodology; resources. Julie Boom: Conceptualization; investigation; methodology; resources. Flor Munoz: Conceptualization; investigation; methodology; resources. Janet Englund: Conceptualization; investigation; methodology; resources. Rangaraj Selvarangan: Conceptualization; investigation; methodology; validation. Mary Allen Staat: Conceptualization; investigation; methodology; resources. Geoffrey Weinberg: Conceptualization; investigation; methodology; resources. Parvin Azimi: Conceptualization; investigation; methodology; resources. Eileen Klein: Conceptualization; investigation; methodology; resources. Monica Mcneal: Conceptualization; investigation; methodology; resources. Laila Sahnı: Conceptualization; investigation; project administration; resources. Monica Singer: Conceptualization; investigation; methodology; resources. Peter Szilágyi: Conceptualization; investigation; methodology; resources. Christopher Harrison: Conceptualization; investigation; methodology; resources. Manish Patel: Conceptualization; data curation; investigation; methodology; project administration; resources; supervision; validation. Angela Campbell: Conceptualization; investigation; methodology; project administration; resources; supervision; validation. Natasha B. Halasa: Conceptualization; funding acquisition; investigation; methodology; resources; supervision; validation; visualization.

PEER REVIEW
The peer review history for this article is available at https://publons.com/publon/10.1111/irv.12927.

DATA AVAILABILITY STATEMENT
Unidentified Datasets analyzed during this study are available through the New Vaccine Surveillance Network, CDC

ORCID
Andrew J. Speiker ◦ https://orcid.org/0000-0002-0548-8311
Natasha B. Halasa ◦ https://orcid.org/0000-0002-6381-1826

REFERENCES
1. Doyle JD, Campbell AP. Pediatric influenza and illness severity: what is known and what questions remain? Curr Opin Pediatr. 2019;31(1):119-126. https://doi.org/10.1097/MOP.0000000000000721
2. Poehling KA, Edwards KM, Griffin MR, et al. The burden of influenza in young children, 2004–2009. Pediatrics. 2013;131(2):207-216. https://doi.org/10.1542/peds.2012-1255
3. Rolfs MA, Foppa IM, Garg S, et al. Annual estimates of the burden of seasonal influenza in the United States: a tool for strengthening influenza surveillance and preparedness. Influenza Other Respi Viruses. 2018;12(1):132-137. https://doi.org/10.1111/irv.12486
4. Burden of Influenza: CDC; 2020 [updated October 5, 2020]. https://www.cdc.gov flu/about/burden/index.html
5. Nayak J, Hoy G, Gordon A. Influenza in children. Cold Spring Harb Perspect Med. 2021;11(1):a038430. https://doi.org/10.1101/cshperspect.a038430
6. Uyeki TM, Bernstein HH, Bradley JS. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 update on diagnos- is, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza (vol 68, pg E1, 2019). Clin Infect Dis. 2019;68(10):1790. https://doi.org/10.1093/cid/ciz044
7. Launay E, Ovetchkine P, Saint-Jean M, et al. Novel influenza A (H1N1): clinical features of pediatric hospitalizations in two successive waves. Int J Infect Dis. 2011;15(2):E122-E130. https://doi.org/10.1016/j.ijid.2010.08.006
8. Ferdinands JM, Olsho LE, Agan AA, et al. Effectiveness of influenza vaccine against life-threatening RT-PCR-confirmed influenza illness in US children, 2010–2012. J Infect Dis. 2014;210(5):674-683. https://doi.org/10.1093/infdis/jiu185

9. Coffin SE, Leckerman K, Keren R, Hall M, Localio R, Zaoutis TE. Oseltamivir shortens hospital stays of critically ill children hospitalized with seasonal influenza: a retrospective cohort study. Pediatric Infectious Disease Journal. 2011;30(11):962-966. https://doi.org/10.1097/INF.0b013e318232ded9

10. Katzen J, Kohn R, Houk JL, Ison MG. Early oseltamivir after hospital admission is associated with shortened hospitalization: a 5-year analysis of oseltamivir timing and clinical outcomes. Clin Infect Dis. 2019; 69(1):52-58. https://doi.org/10.1093/cid/ciy600

11. Muthuri SG, Venkatesan S, Myles PR, et al. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Resp Med. 2014;2(5): 395-404. https://doi.org/10.1016/S2213-2600(14)70041-4

12. Williams JT, Cunningham MA, Wilson KM, Rao S. Rising oseltamivir use among hospitalized children in a postpandemic era. Hosp Pediatr. 2016;6(3):172-178. https://doi.org/10.1542/hpeds.2015-0126

13. Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. Cochrane Database Syst Rev. 2014;4(4):CD008965. https://doi.org/10.1002/14651858.CD008965.pub4

14. Harper SA, Bradford JS, Englund JA, et al. Seasonal influenza in adults and children—diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis. 2009;48(8): 1003-1032. https://doi.org/10.1086/598513

15. Committee On Infectious Diseases. Recommendations for prevention and control of influenza in children, 2018–2019. Pediatrics. 2018;142(4):e20182367. https://doi.org/10.1542/peds.2018-2367

16. Appiah GD, Chaves SS, Kirley PD, et al. Increased antiviral treatment among hospitalized children and adults with laboratory-confirmed influenza, 2010–2015. Clin Infect Dis. 2017;64(3):364-367. https://doi.org/10.1093/cid/ciw745

17. Garg S, Chaves SS, Perez A, et al. Reduced influenza antiviral treatment among children and adults hospitalized with laboratory-confirmed influenza infection in the year after the 2009 pandemic. Clin Infect Dis. 2012;55(3):E18-E21. https://doi.org/10.1093/cid/cis442

18. Rha B, Curns AT, Lively JY, et al. Respiratory syncytial virus-associated hospitalizations among young children: 2015–2016. Pediatrics. 2020;146(1):e20193611. https://doi.org/10.1542/peds.2019-3611

19. Feldstein LR, Ogokeh C, Rha B, et al. Vaccine effectiveness against influenza hospitalization among children in the United States, 2015–2016. J Pediatric Infect Dis Soc. 2020;10(2):75-82. https://doi.org/10.1093/jids/piaa017

20. Diggle PJ, Heagerty P, Liang K-Y, Zeger SL. Analysis of Longitudinal Data. Oxford University Press Second [paperback] edition. 2014. 1 online resource (xv, 379 pages).

21. Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York: Wiley; 1987.

22. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res. 2007;16(3): 219-242. https://doi.org/10.1177/0962280206074463

23. Schrag SJ, Shay DK, Gershman K, et al. Multistate surveillance for laboratory-confirmed, influenza-associated hospitalizations in children: 2003–2004. Pediatr Infect Dis J. 2006;25(5):395-400. https://doi.org/10.1097/01.inf.0000214988.81379.71

24. Dawood FS, Fiore A, Kamimoto L, et al. Burden of seasonal influenza hospitalization in children, United States, 2003 to 2008. J Pediatr. 2010;157(5):808-814. https://doi.org/10.1016/j.jpeds.2010.05.012

25. Whitley RJ, Hayden FG, Reisinger KS, et al. Oral oseltamivir treatment of influenza in children. Pediatr Infect Dis J. 2001;20(2): 127-133. https://doi.org/10.1097/00006454-200102000-00002

26. Venkatesan S, Myles PR, Leonardi-Bee J, et al. Impact of outpatient neuraminidase inhibitor treatment in patients infected with influenza A(H1N1)pdm09 at high risk of hospitalization: an individual participant data metaanalysis. Clin Infect Dis. 2017;64(10):1328-1334. https://doi.org/10.1093/cid/cix127

27. Lindegren ML, Griffin MR, Williams JV, et al. Antiviral treatment among older adults hospitalized with influenza, 2006–2012. PLoS One. 2015;10(3):e0121952. https://doi.org/10.1371/journal.pone.0121952

28. Information on Rapid Molecular Assays, RT-PCR, and other Molecular Assays for Diagnosis of Influenza Virus Infection: CDC; 2019 [updated October 21, 2019]. https://www.cdc.gov/flu/professionals/diagnosis/molecular-assays.htm?web=1&wdLOR=c89DDA4A7-B204-4789-80DB-BCB4F4C0BE24

29. Su S, Fry AM, Kirley PD, et al. Survey of influenza and other respiratory viruses diagnostic testing in US hospitals, 2012–2013. Influenza Other Respi Viruses. 2016;10(2):86-90. https://doi.org/10.1111/irv.12355

30. Merckx J, Wali R, Schiller I, et al. Diagnostic accuracy of novel and traditional rapid tests for influenza infection compared with reverse transcriptase polymerase chain reaction: a systematic review and meta-analysis. Ann Intern Med. 2017;167(6):394-409. https://doi.org/10.7326/M17-0848

31. Kumar S, Henrickson KJ. Update on influenza diagnostics: lessons from the novel H1N1 influenza A pandemic. Clin Microbiol Rev. 2012; 25(2):344-361. https://doi.org/10.1128/CMR.05016-11

32. Noyola DE, Demmler GJ. Effect of rapid diagnosis on management of influenza A infections. Pediatr Infect Dis J. 2000;19(4):303-307. https://doi.org/10.1097/00006454-200004000-00008

33. El Feghaly RE, Nolen JD, Lee BR, et al. Impact of rapid influenza molecular testing on management in pediatric acute care settings. J Pediatr. 2021;228:271-277. https://doi.org/10.1016/j.jpeds.2020.08.007

34. Brown C, Clayton-Boswell H, Chaves SS, et al. Validity of parental report of influenza vaccination in young children seeking medical care. Vaccine. 2011;29(51):9488-9492. https://doi.org/10.1016/j.vaccine.2011.10.023

35. Ogokeh CE, Campbell AP, Feldstein LR, et al. Comparison of parental report of influenza vaccination to documented records in children hospitalized with acute respiratory illness, 2015–2016. J Pediatric Infect Dis Soc. 2020;10(4):389-397. https://doi.org/10.1093/jids/piaa110

How to cite this article: Hamdan L, Probst V, Haddadin Z, et al. Influenza clinical testing and oseltamivir treatment in hospitalized children with acute respiratory illness, 2015–2016. Influenza Other Respi Viruses. 2022;16(2):289-297. doi:10.1111/irv.12927