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Oseltamivir Use Among Children and Adults Hospitalized With Community-Acquired Pneumonia

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Background. Data on oseltamivir treatment among hospitalized community-acquired pneumonia (CAP) patients are limited.

Methods. Patients hospitalized with CAP at 6 hospitals during the 2010–2012 influenza seasons were included. We assessed factors associated with oseltamivir treatment using logistic regression.

Results. Oseltamivir treatment was provided to 89 of 1627 (5%) children (<18 years) and 143 of 1051 (14%) adults. Among those with positive clinician-ordered influenza tests, 39 of 61 (64%) children and 37 of 48 (77%) adults received oseltamivir. Among children, oseltamivir treatment was associated with hospital A (adjusted odds ratio [aOR], 2.76; 95% confidence interval [CI], 1.36–4.88), clinician-ordered testing performed (aOR, 2.44; 95% CI, 1.47–5.19), intensive care unit (ICU) admission (aOR, 2.09; 95% CI, 1.27–3.45), and age ≥2 years (aOR, 1.43; 95% CI, 1.16–1.76). Among adults, oseltamivir treatment was associated with clinician-ordered testing performed (aOR, 8.38; 95% CI, 4.64–15.12), hospitals D and E (aOR, 3.46–5.11; 95% CI, 1.75–11.01), Hispanic ethnicity (aOR, 2.06; 95% CI, 1.18–3.59), and ICU admission (aOR, 2.05; 95% CI, 1.34–3.13).

Conclusions. Among patients hospitalized with CAP during influenza season, oseltamivir treatment was moderate overall and associated with clinician-ordered testing, severe illness, and specific hospitals. Increased clinician education is needed to include influenza in the differential diagnosis for hospitalized CAP patients and to test and treat patients empirically if influenza is suspected.

Keywords. community-acquired pneumonia; influenza; oseltamivir.

Community-acquired pneumonia (CAP) is a common cause of hospitalization in the United States [1–3]. Influenza viruses are a known cause of CAP [4, 5]. Pneumonia is the most common severe complication of influenza virus infection in all age groups [6–9]. The Advisory Committee on Immunization Practices (ACIP), Infectious Disease Society of America (IDSA), and Pediatric Infectious Disease Society (PIDS) guidelines currently recommend use of influenza antiviral treatment in all hospitalized patients with suspected or confirmed influenza [10–12], particularly during the influenza season [10, 12]. Furthermore, the IDSA guidelines recommend influenza testing for hospitalized patients with CAP during the influenza season [10, 12, 13]. Although studies have reported on influenza testing and antiviral treatment and factors associated with antiviral treatment among hospitalized patients with influenza, the factors associated with antiviral treatment specifically among hospitalized patients with CAP are not well described.

The Centers for Disease Control and Prevention (CDC) Etiology of Pneumonia in the Community (EPIC) study was a prospective, multicenter, population-based, active surveillance study of the incidence and etiology of CAP among children and adults requiring hospitalization in the United States [4, 5]. We describe the epidemiologic and clinical factors associated with oseltamivir treatment among patients enrolled in the EPIC study.

METHODS

Study Setting and Population
Children (<18 years) and adults hospitalized with clinical and radiographic CAP were prospectively enrolled between January 2010 and June 2012 at 8 hospitals in Chicago, Memphis, Nashville, and Salt Lake City; full details of the EPIC study have previously been described [4, 5]. Demographic and clinical data were collected by patient interview and medical chart abstraction using a standardized form and entered into a centralized database. Outpatient influenza antiviral data were derived from patient interview, and inpatient antiviral data were derived from medical chart abstraction. This study was approved by the institutional review boards at each institution and the CDC. For this analysis, the 6 hospitals (3 pediatric, 3 adult) with available data were included.
Influenza Laboratory Testing
Naso/oropharyngeal swabs were systematically obtained from all enrolled patients for influenza virus testing using real-time reverse-transcription polymerase chain reaction (PCR) in the research laboratory at each site (hereafter referred to as research-associated influenza tests). These results were not available to clinicians at any time during clinical care. Clinician-ordered influenza tests and oseltamivir use was based on the clinician’s judgment, independent of the study protocol. Influenza diagnostic tests types and availability differed among hospitals as reported in the results.

Statistical Analysis and Definitions
All patients who received an antiviral agent received oseltamivir; 4 patients received oseltamivir plus an additional influenza antiviral agent. Because oseltamivir was most common, we limited the analysis to oseltamivir specifically. We compared the demographic and clinical characteristics, including clinical testing practices, between patients treated and not treated with oseltamivir. Treatment was defined as receiving oseltamivir during hospitalization for any period of time, including if treatment was started as an outpatient before hospitalization. Patients who received oseltamivir before but not during hospitalization were excluded.

For each study year, influenza season was defined as October 1–April 30 except for the first year, which was defined as January 1, 2010–April 30, 2010 because enrollment began on January 1, 2010. Influenza season reflected periods when any influenza viruses were circulating based on laboratory-confirmed influenza surveillance in the study hospital regions [14] and laboratory-confirmed influenza positive tests in the EPIC study [4, 5]. We also performed a sensitivity analysis limiting the influenza season to peak periods of influenza circulation (January–March).

Documentation of clinician-ordered influenza testing was not a mandatory variable in the EPIC study. However, all 3 pediatric hospitals (hospitals A, B, C) recorded this consistently and are included. Data on clinician-ordered testing were incomplete for 2 adult hospitals (n = 436 patients) that were excluded, and thus 3 of 5 adult hospitals (D, E, F) are included.

We conducted bivariate analysis to assess associations between covariates and oseltamivir treatment using \( \chi^2 \) or Fisher’s exact test for categorical variables and the \( t \) test or one-way analysis of variance test for continuous variables; Wilcoxon rank-sum test was used to assess differences in distribution for nonnormally distributed variables (\( P < .05 \)). Covariates of interest were based on published literature and epidemiological plausibility, and included age, sex, race and ethnicity, study hospital, household college education status, health insurance status, chronic conditions, obesity (in children), morbid obesity (in adults), current smoker (in adults), antibiotics before admission, self-reported influenza vaccination (reported for the study, not necessarily to clinicians), admission ≤48 hours from illness onset, clinician-ordered testing, intensive care unit (ICU) admission, invasive mechanical ventilation, and hypoxia on presentation. For those treated with oseltamivir, ICU admission and invasive mechanical ventilation were defined as ICU admission or invasive mechanical ventilation within 2 calendar days before or after oseltamivir initiation.

We used multivariable logistic regression to identify factors independently associated with oseltamivir treatment for children and adults separately. The multivariable models were developed using manual selection based on bivariate analyses (\( P < .20 \)) and other epidemiologically or biologically plausible variables based on literature [11, 15–17]. Due to overfitting concerns in the pediatric model, we report a parsimonious model for children only that excluded nonsignificant covariates; when comparing the parsimonious model to a fuller model, the likelihood ratio test was \( P > .05 \), indicating that the dropped covariates did not significantly impact the outcome. Data were analyzed using SAS version 9.3 statistical software (SAS Institute, Cary, NC).

RESULTS
Study Population and Influenza Testing
The final study population included 1627 children and 1051 adults (Figures 1–2). Clinician-ordered influenza tests were performed on 1134 of 1627 (70%) children, and 61 (5%) had positive results; the most common test types performed included both PCR and rapid influenza diagnostic tests (RIDTs) (31%), PCR alone (22%), direct fluorescent antibody (DFA) alone (21%), both PCR and DFA (16%), and RIDTs alone (6%). Clinician-ordered influenza tests were performed on 581 of 1051 (55%) adults, and 48 (8%) had positive results; the most common test types performed included PCR alone (95%), both RIDTs and DFA (2%), and RIDTs alone (1%) (Table 1). Test types differed by hospital (Table 2).

Research-associated influenza tests identified 150 patients (83 of 1627 [5%] children, 67 of 1051 [6%] adults) with influenza-associated CAP during influenza season. Because clinician-ordered influenza testing was not routinely performed, influenza-associated CAP was missed in 13 of 83 (16%) children and 11 of 67 (16%) adults who were positive by research-associated influenza tests (Table 3); another 26 of 83 (31%) children and 18 of 67 (27%) adults had negative clinician-ordered tests but positive research-associated tests. Among the 26 children with negative clinician-ordered tests but positive research-associated tests, 9 (35%) were negative by both PCR and RIDTs, 8 (31%) by DFA alone, 5 (19%) by PCR alone, and 4 (15%) by both PCR and DFA. Among the 18 adults with negative clinician-ordered tests but positive research-associated tests, all clinician-ordered tests were PCR.

Of 61 children who tested positive by clinician-ordered testing, 17 (28%) were negative by research-associated influenza tests
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(Table 3), among whom 8 (47%) were only positive by RIDTs, 5 (29%) by PCR alone, 3 (18%) by DFA alone, and 1 (<1%) by both PCR and DFA. Of 48 adults who tested positive by clinician-ordered testing (Table 3), 10 (21%) were negative by research-associated tests but positive by clinician-ordered PCR alone.

**Oseltamivir Treatment**

During an influenza season (October–April), 89 of 1627 (5%) children received oseltamivir during their CAP hospitalization, ranging from 3% to 8% between the 3 hospitals; 143 of 1051 (14%) adults received oseltamivir during their CAP hospitalization, ranging from 4% to 19% between the 3 hospitals. When the influenza season was restricted to January–March for each study year, 63 of 899 (7%) children and 106 of 530 (20%) adults received oseltamivir.

Among patients with clinician-ordered tests performed, 75 of 1134 (7%) children and 129 of 581 (22%) adults received oseltamivir. Whereas, among patients without a clinician-ordered test performed, 14 of 493 (3%) children and 14 of 470 (3%) adults received oseltamivir. Among patients positive by clinician-ordered testing, 39 of 61 (64%) children and 37 of 48 (77%) adults received oseltamivir. In comparison, among patients positive by research-associated testing, 41 of 83 (49%) children and 34 of 67 (51%) adults received oseltamivir. Among the 39 children and 29 adults with influenza identified by research-associated but not clinician-ordered testing, 11 (28%) children and 6 (21%) adults received oseltamivir.

**Characteristics Associated With Oseltamivir Treatment in Children**

On bivariate analysis, compared with children not treated (n = 1538), children treated with oseltamivir (n = 89) were older (median age, 3 years; interquartile range [IQR], 1–8 years vs median age, 2 years; IQR, 0–2 years); and significantly more likely to be enrolled at hospital A (vs B or C), require ICU admission (29% vs 19%) or invasive mechanical ventilation (19% vs 6%), and less likely to be Hispanic (11% vs 21%) or have received influenza vaccination (14% vs 25%) (Table 4). Children treated with oseltamivir were significantly more likely than those not treated to have a clinician-ordered influenza test (84% vs 69%) and a positive result (44% vs 1%) (Table 4); 39 of 61 with a positive result (64%) were treated. Among children with negative results from a clinician-ordered influenza test...
test, 36 of 1073 (3%) were treated, and among children with no clinician-ordered influenza test performed, 14 of 493 (3%) were treated. There was no significant difference in the median days from illness onset to admission (3 days in both groups) (Table 4). In particular, children who were clinically tested for influenza but not given oseltamivir (n = 1059) were as likely as those who did receive oseltamivir (n = 75) to have been admitted >48 hours from illness onset (62% vs 57%, P = .45).

In multivariable analysis, enrollment at hospital A (adjusted odds ratio [aOR], 2.76; 95% confidence interval [CI], 1.36–4.88), clinician-ordered influenza testing (aOR, 2.46; 95% CI, 1.47–5.19), ICU admission (aOR, 2.09; 95% CI, 1.27–3.45), and age ≥2 years old (aOR, 1.43; 95% CI, 1.16–1.76) were associated with oseltamivir treatment (Table 4). Patients who were Hispanic were less likely to receive oseltamivir (aOR, 0.49; 95% CI, 0.24–0.99).

**Characteristics Associated With Oseltamivir Treatment in Adults**

On bivariate analysis, compared with adults not treated (n = 908), adults treated with oseltamivir (n = 143) were of similar age (median age, 55 years; IQR, 46–67 vs median age, 58 years; IQR, 47–71) but were significantly more likely to be Hispanic (18% vs 9%), enrolled at hospitals D or E, require ICU admission (39% vs 21%) or invasive mechanical ventilation (17% vs 5%), and have hypoxia on presentation (34% vs 24%) but less likely to have received influenza vaccination (11% vs 29%) (Table 5). Adults treated with oseltamivir were significantly more likely than those not treated to have a clinician-ordered influenza test (90% vs 50%) and shorter median days from illness onset to admission (3 days vs 4 days) (Table 5). Adults treated with oseltamivir were also more likely to have a positive clinician-ordered influenza test; among 48 adults with a positive influenza test, 37 (77%) were treated. Among adults without a clinician-ordered influenza test performed, 14 of 533 (17%) were treated. Among adults with a negative clinician-ordered influenza test, 92 of 533 (17%) were treated. Among adults without a clinician-ordered influenza test performed, 14 of 470 (3%) were treated. In particular, adults who were clinically tested for influenza but not given oseltamivir (n = 452) were as likely as those who did receive oseltamivir (n = 129) to have been admitted >48 hours from illness onset (66% vs 64%, P = .52).

**Table 2. Oseltamivir Treatment and Type of Influenza Testing Method by Study Hospital Among Patients Who Had a Clinician-Ordered Test Performed**

<table>
<thead>
<tr>
<th>Hospital (No. of Patients Enrolled at Hospital)</th>
<th>Oseltamivir Treatment Treatment No. (%)</th>
<th>Total No. of Tests Performed</th>
<th>PCR No. (%)</th>
<th>RIDT No. (%)</th>
<th>DFA No. (%)</th>
<th>Viral Culture No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pediatric hospital</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital A (n = 585)</td>
<td>46 (7.9)</td>
<td>744</td>
<td>367 (49.3)</td>
<td>364 (48.9)</td>
<td>0 (0)</td>
<td>13 (1.7)</td>
</tr>
<tr>
<td>Hospital B (n = 564)</td>
<td>29 (5.2)</td>
<td>645</td>
<td>223 (34.5)</td>
<td>0 (0)</td>
<td>421 (65.3)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Hospital C (n = 488)</td>
<td>14 (2.9)</td>
<td>333</td>
<td>217 (65.2)</td>
<td>85 (25.6)</td>
<td>24 (72)</td>
<td>7 (2.1)</td>
</tr>
<tr>
<td>Hospitals A, B, C (n = 1627)</td>
<td>89 (5.5)</td>
<td>1722</td>
<td>807 (46.9)</td>
<td>449 (26.1)</td>
<td>445 (25.8)</td>
<td>21 (1.2)</td>
</tr>
<tr>
<td><strong>Adult hospital</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital D (n = 603)</td>
<td>98 (16.3)</td>
<td>398</td>
<td>398 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hospital E (n = 181)</td>
<td>34 (18.8)</td>
<td>79</td>
<td>79 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hospital F (n = 267)</td>
<td>11 (4.1)</td>
<td>128</td>
<td>83 (64.8)</td>
<td>28 (21.9)</td>
<td>16 (12.5)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Hospitals D, E, F (n = 1051)</td>
<td>143 (13.6)</td>
<td>605</td>
<td>560 (92.6)</td>
<td>28 (4.6)</td>
<td>16 (2.6)</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

Abbreviations: DFA, direct fluorescent antibody; PCR, real-time polymerase chain reaction; RIDT, rapid influenza diagnostic test.

A total of 1134 children had clinician-ordered tests performed.

A total of 581 adults had clinician-ordered tests performed.
In multivariable analysis, having a clinician-ordered influenza test (aOR, 8.38; 95% CI, 4.64–15.12), enrollment at hospitals D or E (aOR, 3.46−5.11; 95% CI, 1.75–11.01), Hispanic ethnicity (aOR, 2.06; 95% CI, 1.18–3.59), and ICU admission (aOR, 2.05; 95% CI, 1.34–3.13) were associated with oseltamivir treatment (Table 5).

### Table 3. Comparison Between Clinician-Ordered Influenza Tests and Research-Associated PCR Tests Results Among Children and Adults

<table>
<thead>
<tr>
<th>Study PCR Test Positive n (%)</th>
<th>Study PCR Test Negative n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric hospital n = 83</td>
<td>n = 1544</td>
<td>n = 1627</td>
</tr>
<tr>
<td>Clinician test positive 44 (53.0)</td>
<td>17 (1.1)</td>
<td>61 (3.8)</td>
</tr>
<tr>
<td>Clinician test negative 26 (31.3)</td>
<td>1047 (67.8)</td>
<td>1073 (66.0)</td>
</tr>
<tr>
<td>Clinician test not performed 13 (15.7)</td>
<td>480 (31.1)</td>
<td>493 (30.3)</td>
</tr>
<tr>
<td>Adult hospital n = 67</td>
<td>n = 984</td>
<td>n = 1051</td>
</tr>
<tr>
<td>Clinic test positive 18 (26.9)</td>
<td>515 (62.3)</td>
<td>533 (60.7)</td>
</tr>
<tr>
<td>Clinic test not performed 11 (16.4)</td>
<td>459 (46.6)</td>
<td>470 (44.7)</td>
</tr>
</tbody>
</table>

Abbreviations: PCR, real-time polymerase chain reaction.

### Table 4. Bivariate and Multivariate Analysis of Select Factors Associated With Oseltamivir Treatment Among Children Hospitalized With All-Cause CAP During Influenza Season

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Oseltamivir Treatment (n = 89)</th>
<th>No Oseltamivir Treatment (n = 1627)</th>
<th>P Value α</th>
<th>Unadjusted Odds Ratio (95% CI)</th>
<th>Adjusted Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥2 years</td>
<td>61 (68.5)</td>
<td>814 (52.9)</td>
<td>&lt;.01</td>
<td>1.94 (1.23–3.07)</td>
<td>1.43 (1.16–1.76)</td>
</tr>
<tr>
<td>Female sex</td>
<td>41 (46.1)</td>
<td>720 (46.8)</td>
<td>.89</td>
<td>0.97 (0.63–1.49)</td>
<td>—</td>
</tr>
<tr>
<td>Hispanic race/ethnicity</td>
<td>10 (11.2)</td>
<td>320 (20.8)</td>
<td>.03</td>
<td>0.48 (0.25–0.94)</td>
<td>0.49 (0.24–0.99)</td>
</tr>
<tr>
<td>Study hospitals</td>
<td>&lt;.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital A</td>
<td>46 (51.7)</td>
<td>539 (35.1)</td>
<td>2.89</td>
<td>1.57–5.32</td>
<td>2.76 (1.47–5.19)</td>
</tr>
<tr>
<td>Hospital B</td>
<td>29 (32.6)</td>
<td>525 (34.1)</td>
<td>1.87</td>
<td>0.98–3.58</td>
<td>1.72 (0.88–3.37)</td>
</tr>
<tr>
<td>Hospital C</td>
<td>14 (15.7)</td>
<td>474 (30.8)</td>
<td>.54</td>
<td>0.96 (0.63–1.47)</td>
<td>—</td>
</tr>
<tr>
<td>At least college education in household</td>
<td>46 (51.7)</td>
<td>811 (52.7)</td>
<td>.33</td>
<td>0.81 (0.53–1.24)</td>
<td>0.68 (0.43–1.06)</td>
</tr>
<tr>
<td>Had health insurance</td>
<td>89 (100)</td>
<td>1509 (98.4)</td>
<td>.40</td>
<td>N/A1</td>
<td>—</td>
</tr>
<tr>
<td>Any chronic condition in household</td>
<td>40 (44.9)</td>
<td>772 (50.2)</td>
<td>.03</td>
<td>0.81 (0.53–1.24)</td>
<td>0.68 (0.43–1.06)</td>
</tr>
<tr>
<td>Asthma/reactive airway disease</td>
<td>29 (32.6)</td>
<td>505 (32.8)</td>
<td>1.0</td>
<td>0.99 (0.63–1.56)</td>
<td>—</td>
</tr>
<tr>
<td>Any preterm birth</td>
<td>6/28 (21.4)</td>
<td>143/724 (19.8)</td>
<td>.83</td>
<td>1.11 (0.44–2.78)</td>
<td>—</td>
</tr>
<tr>
<td>Neurological conditions</td>
<td>10 (11.2)</td>
<td>117 (76)</td>
<td>.22</td>
<td>1.54 (0.78–3.05)</td>
<td>—</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>3 (3.4)</td>
<td>108 (70)</td>
<td>.28</td>
<td>0.46 (0.14–1.49)</td>
<td>—</td>
</tr>
<tr>
<td>Obesity (BMI percentile &gt;95)</td>
<td>4 (4.5)</td>
<td>114 (74)</td>
<td>.4</td>
<td>0.59 (0.21–1.63)</td>
<td>—</td>
</tr>
<tr>
<td>Antibiotics before admission</td>
<td>20 (22.5)</td>
<td>378 (24.8)</td>
<td>.65</td>
<td>0.89 (0.53–1.48)</td>
<td>—</td>
</tr>
<tr>
<td>Received influenza vaccine (self-report)</td>
<td>12/86 (14.0)</td>
<td>331/1335 (25.0)</td>
<td>.02</td>
<td>0.49 (0.26–0.92)</td>
<td>—</td>
</tr>
<tr>
<td>Admission ≤48 hours from illness onset</td>
<td>3/9 (3.3)</td>
<td>583 (37.9)</td>
<td>.26</td>
<td>1.28 (0.83–1.97)</td>
<td>—</td>
</tr>
<tr>
<td>Median days from illness onset to admission (IQR)</td>
<td>3 (2−5)</td>
<td>3 (2−6)</td>
<td>.30</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Clinician-ordered influenza test</td>
<td>75 (84.3)</td>
<td>1059 (68.9)</td>
<td>.01</td>
<td>2.42 (1.36–4.33)</td>
<td>2.46 (1.35–4.49)</td>
</tr>
<tr>
<td>Positive test among those performed</td>
<td>39/75 (45.3)</td>
<td>22/1059 (1.4)</td>
<td>.01</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Research study PCR test positive</td>
<td>41 (46.1)</td>
<td>42 (2.7)</td>
<td>.01</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ICU admission</td>
<td>26 (29.2)</td>
<td>299 (19.4)</td>
<td>.03</td>
<td>1.71 (1.07–2.75)</td>
<td>2.09 (1.27–3.45)</td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>17 (19.1)</td>
<td>88 (5.7)</td>
<td>&lt;.01</td>
<td>4.06 (1.84–9.64)</td>
<td>—</td>
</tr>
<tr>
<td>Hypoxia*</td>
<td>42 (47.2)</td>
<td>590 (38.4)</td>
<td>.10</td>
<td>1.44 (0.94–2.19)</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CAP, community-acquired pneumonia; CI, confidence interval; EPIC, Etiology of Pneumonia in the Community; ICU, intensive care unit; IQR, interquartile range; N/A, not applicable; PCR, real-time polymerase chain reaction; Ref, reference.

*P value is comparing characteristics associated with oseltamivir treatment vs no oseltamivir treatment.

Any underlying medical conditions included asthma/reactive airway disease, chromosomal disorders including Down syndrome, chronic kidney disease, chronic liver disease, congenital heart disease, diabetes mellitus, immunosuppression (either due to chronic condition or medication, malignancy [but not skin cancer], human immunodeficiency virus infection with CD4 count >200 cells/mm³), neurological disorders (including seizure disorder, cerebral palsy, scoliosis), preterm birth (defined as gestational age <37 weeks at birth for those children who were <2 years of age at time of hospitalization, n = 752), and splenectomy.

Preterm birth (defined as gestational age <37 weeks at birth for those children who were <2 years old at time of hospitalization), n = 762.

Received influenza vaccine excludes children <6 months of age (n = 206) so overall denominator = 1421; patients were considered vaccinated if they received vaccine at least 2 weeks before admission by self-report to EPIC study. Influenza vaccine not added to multivariable model because vaccination status not necessarily reported to clinician.

Hypoxia: at presentation defined as oxygen saturation <92 or FiO₂ liters >0 or percentage of supplemental oxygen use >21.

All children who received influenza antiviral agents had health insurance.
**Table 5. Bivariate and Multivariate Analysis of Select Factors Associated With Oseltamivir Treatment Among Adults Hospitalized With All-Cause CAP During Influenza Season**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Oseltamivir Treatment (n = 143) No. (%)</th>
<th>No Oseltamivir Treatment (n = 908) No. (%)</th>
<th>P Value*</th>
<th>Unadjusted Odds Ratio (95% CI) (n = 1051)</th>
<th>Adjusted Odds Ratio (95% CI) (n = 1051)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 years</td>
<td>42 (29.4)</td>
<td>355 (39.1)</td>
<td>0.03</td>
<td>0.65 (0.44–0.95)</td>
<td>0.70 (0.45–1.08)</td>
</tr>
<tr>
<td>Female sex</td>
<td>72 (50.4)</td>
<td>476 (52.4)</td>
<td>0.65</td>
<td>0.92 (0.65–1.31)</td>
<td>—</td>
</tr>
<tr>
<td>Hispanic ethnicity</td>
<td>26 (18.2)</td>
<td>84 (9.3)</td>
<td>&lt;0.01</td>
<td>2.18 (1.35–3.53)</td>
<td>2.06 (1.18–3.59)</td>
</tr>
<tr>
<td>Study hospital &lt;.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital D</td>
<td>98 (68.5)</td>
<td>505 (55.6)</td>
<td></td>
<td>4.52 (2.38–8.58)</td>
<td>3.46 (1.75–6.83)</td>
</tr>
<tr>
<td>Hospital E</td>
<td>34 (23.8)</td>
<td>147 (16.2)</td>
<td></td>
<td>5.38 (2.65–10.9)</td>
<td>5.11 (2.37–11.01)</td>
</tr>
<tr>
<td>Hospital F</td>
<td>11 (7.7)</td>
<td>256 (28.2)</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>College education or more</td>
<td>90 (62.9)</td>
<td>552 (60.8)</td>
<td>0.27</td>
<td>1.10 (0.76–1.58)</td>
<td>1.07 (0.71–1.61)</td>
</tr>
<tr>
<td>Had insurance</td>
<td>130 (90.9)</td>
<td>836 (92.5)</td>
<td></td>
<td>0.81 (0.45–1.51)</td>
<td>—</td>
</tr>
<tr>
<td>Any chronic condition**</td>
<td>109 (76.2)</td>
<td>731 (80.5)</td>
<td>0.73</td>
<td>0.78 (0.51–1.18)</td>
<td>0.74 (0.46–1.18)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>52 (36.4)</td>
<td>375 (41.3)</td>
<td>0.26</td>
<td>0.81 (0.56–1.17)</td>
<td>—</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>46 (32.2)</td>
<td>290 (31.9)</td>
<td>0.96</td>
<td>1.01 (0.69–1.47)</td>
<td>—</td>
</tr>
<tr>
<td>Diabetes</td>
<td>43 (30.1)</td>
<td>227 (25.0)</td>
<td>0.21</td>
<td>1.29 (0.88–1.90)</td>
<td>—</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>23 (16.1)</td>
<td>143 (15.8)</td>
<td>0.92</td>
<td>1.03 (0.63–1.66)</td>
<td>—</td>
</tr>
<tr>
<td>Chronic heart disease</td>
<td>50 (35.0)</td>
<td>361 (40.0)</td>
<td>0.28</td>
<td>0.82 (0.56–1.18)</td>
<td>—</td>
</tr>
<tr>
<td>Morbid obesity (BMI ≥40 kg/m²)</td>
<td>18 (12.6)</td>
<td>76 (8.4)</td>
<td>1.0</td>
<td>1.58 (0.91–2.72)</td>
<td>1.63 (0.87–3.04)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>34 (23.8)</td>
<td>214 (23.8)</td>
<td>0.96</td>
<td>1.01 (0.67–1.53)</td>
<td>—</td>
</tr>
<tr>
<td>Antibiotics before admission</td>
<td>24 (16.8)</td>
<td>201 (22.1)</td>
<td>0.15</td>
<td>0.71 (0.45–1.13)</td>
<td>0.91 (0.55–1.51)</td>
</tr>
<tr>
<td>Received influenza vaccine (self-report)</td>
<td>15 (10.5)</td>
<td>262 (28.9)</td>
<td>&lt;0.01</td>
<td>0.29 (0.17–0.50)</td>
<td>—</td>
</tr>
<tr>
<td>Admission ≤48 hours from illness onset</td>
<td>54 (37.8)</td>
<td>326 (35.9)</td>
<td>0.69</td>
<td>1.08 (0.75–1.56)</td>
<td>1.03 (0.69–1.54)</td>
</tr>
<tr>
<td>Median days from illness onset to admission (IQR)</td>
<td>3 (2–6)</td>
<td>4 (2–8)</td>
<td>0.05</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Clinician-ordered influenza test</td>
<td>129 (90.2)</td>
<td>452 (49.8)</td>
<td>&lt;0.01</td>
<td>9.30 (5.27–16.38)</td>
<td>8.38 (4.64–15.12)</td>
</tr>
<tr>
<td>Positive test/test done</td>
<td>37/129 (28.7)</td>
<td>11/452 (2.4)</td>
<td>&lt;0.01</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Research study PCR test positive</td>
<td>34 (23.8)</td>
<td>33 (3.6)</td>
<td>&lt;0.01</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ICU admission</td>
<td>55 (38.5)</td>
<td>187 (20.6)</td>
<td>&lt;0.01</td>
<td>2.41 (1.66–3.50)</td>
<td>2.05 (1.34–3.13)</td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>24 (16.8)</td>
<td>47 (5.2)</td>
<td>&lt;0.01</td>
<td>3.70 (2.18–6.26)</td>
<td>—</td>
</tr>
<tr>
<td>Hypoxia†</td>
<td>48 (33.6)</td>
<td>218 (24.0)</td>
<td>0.02</td>
<td>1.60 (1.10–2.34)</td>
<td>1.47 (0.94–2.29)</td>
</tr>
<tr>
<td>Median PSI score† (IQR)</td>
<td>79 (49–102)</td>
<td>78.5 (52–106)</td>
<td>0.54</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CAP, community-acquired pneumonia; CI, confidence interval; EPIC, Etiology of Pneumonia in the Community; ICU, intensive care unit; IQR, interquartile range; PCR, real-time polymerase-chain-reaction; PSI, pneumonia severity index; Ref, reference.

*P Value is comparing characteristics associated with oseltamivir treatment vs no oseltamivir treatment.

**Underlying medical conditions included chronic lung disease (asthma, chronic obstructive pulmonary disease, obstructive sleep apnea), chronic heart disease (ie, coronary artery disease, congestive heart failure, but not hypertension), immunosuppression (either due to chronic condition or medication, malignancy [but not skin cancer], human immunodeficiency virus infection with CD4 count >200 cells/mm³), diabetes mellitus, chronic kidney disease (with or without dialysis), neurological disorders (epilepsy, cerebral palsy, dementia, history of stroke), chronic liver disease (hepatitis, cirrhosis, hepatic failure), and splenectomy.

*Patients were considered vaccinated if they received vaccine at least 2 weeks before admission by self-report to EPIC study. Influenza vaccine not added to multivariable model because vaccination status not necessarily reported to clinician.

†Hypoxia: at presentation defined as oxygen saturation <92 or FiO₂ liters >0 or percentage supplemental oxygen use >21.

‡Pneumonia severity index is a clinical prediction rule for CAP-related mortality based on gender, age, nursing home status, mental status, heart rate, respiratory rate, blood pressure, temperature, select underlying medical conditions, select laboratory values, and presence of pleural effusion [40].

**DISCUSSION**

During the 2010–12 influenza seasons, oseltamivir treatment was provided to 5% children and 14% adults hospitalized with CAP and enrolled in the EPIC study. Treatment was significantly associated with clinician-ordered influenza testing, and more strongly when there was a positive result with two thirds of these patients treated. However, only half of patients with influenza-associated CAP identified by research-associated testing were treated, likely due to missing or negative clinician-ordered tests. Severe illness and enrollment at specific hospitals were also significantly associated with oseltamivir treatment.

The proportion of patients with a CAP hospitalization during an influenza season who received oseltamivir treatment was low in our study, and it was only slightly higher but still suboptimal when the influenza season was restricted to 3 months during peak influenza circulation. In the United States, influenza antiviral use increased sharply during the 2009 H1N1 pandemic [16, 18, 19] and declined subsequently, particularly in children [20, 21]. Previous reports of the use of influenza antiviral treatment have included patients with all-cause acute respiratory illness and/or laboratory-confirmed influenza but not CAP. Data from the New Vaccine Surveillance Network from 2004 to 2009 demonstrated that only 1.5% of children hospitalized with acute respiratory illness who were positive for influenza by research-associated testing (not disclosed to clinicians) received influenza antiviral treatment [22]. In contrast, in studies that
specifically focused on hospitalized patients with labora-
tory-confirmed influenza based on tests performed at a clinician’s
discretion, the proportion of patients who received antiviral
treatment was higher, ranging from 21% to 84% in children
and 54% to 82% in adults [7, 16, 18–21]. Direct comparisons
between studies are difficult because our study focused on CAP
hospitalization rather than all-cause acute respiratory illness or
only laboratory-confirmed influenza.

During the influenza season, the IDSA influenza and
IDSA/PIDS CAP guidelines encourage influenza testing in all
patients hospitalized with suspected influenza, and IDSA also
recommends testing for hospitalized patients with CAP. Thus,
the modest levels of influenza testing and oseltamivir use we
observed among hospitalized CAP patients during influenza
season suggest it is worth exploring potential reasons why
physicians did not prescribe oseltamivir. This may be because
physicians did not consider influenza in the differential diag-
nosis for CAP, were reluctant to treat patients without a posi-
tive influenza test (who may be positive for other pathogens),
lacked awareness of local influenza circulation, or perceived
a lack of antiviral efficacy, particularly when patients pres-
ent >48 hours from illness onset [23–26]. In addition, not all
influenza tests are equal and PCR tests are expensive, leading
to barriers to accessing sensitive, specific, and timely influenza
tests, which can hinder treatment [27]. Due to low sensitivity
and negative predictive value of RIDTs, negative RIDT results
alone do not exclude influenza virus infection; antiviral treat-
ment should not be withheld from these patients if influenza
is suspected, and further testing with molecular assays is rec-
ommended when available, because they have higher sensitiv-
ity and specificity [12, 13]. Continued efforts for the improved
development of influenza diagnostics including affordable
molecular-based diagnostic tests are needed to help inform
testing and treatment practice [28]. In addition, improve-
ments in hospital-based algorithms for influenza testing and
for empiric treatment, similar to conventional CAP standing
orders for antibiotics, may improve adherence with IDSA/
PIDS guidelines.

Observational studies of hospitalized adults with labora-
tory-confirmed influenza have demonstrated that patients with
positive RIDTs were more likely to receive influenza antiviral
treatment [16, 29]. Likewise, in a study of hospitalized adults
with influenza virus infection from 2006 to 2012 across 4 hos-
pitals, clinician-ordered laboratory-confirmed influenza by
RIDTs, PCR, or viral culture was independently associated with
antiviral treatment [17]. Although a positive influenza test was
strongly associated with oseltamivir treatment in our study, just
having a clinician-ordered influenza test performed regardless
of the result was also significantly associated with treatment.
The diagnosis of influenza based purely on clinical signs and
symptoms has modest sensitivity and specificity [30–32], and
thus it is challenging to rely on clinical diagnosis alone for

testing and treatment decisions, including in patients hospital-
ized with CAP. Our findings that clinician-ordered influenza
testing strongly correlated with oseltamivir treatment under-
scores the importance of increasing adherence to current PIDS,
IDSA, and ACIP guidelines, which recommend influenza test-
ing in hospitalized persons with CAP during the influenza sea-
son and empiric antiviral use while awaiting results.

We found enrollment at specific hospitals influenced cli-
nician-ordered testing, type of influenza test ordered, and influ-
enza antiviral treatment in children and adults, even between
hospitals in the same city. Other observational studies have also
noted variability in antiviral prescribing across ambulatory and
hospital sites [15, 23, 33]. This variation in influenza antiviral
prescribing patterns between clinicians, and between hospitals,
highlights the need for understanding the factors associated
with this heterogeneity.

In our study, being of Hispanic race/ethnicity was associated
with an increased probability of oseltamivir treatment among
adults but a decreased probability among children; the reasons
for which are unclear but may have been related to study hos-
ital. A recent study found that being of Hispanic ethnicity or
other or unknown race/ethnicity increased the odds of a person
with laboratory-confirmed influenza receiving a clinical influ-
enza diagnosis [34]. In addition, (1) racial-ethnic differences
in vaccination coverage and (2) access to care were reported
during the 2009 H1N1 pandemic among Spanish-speaking
Hispanics and warrants further study [35, 36].

In our study, children ≥2 years old hospitalized with CAP were
more likely to receive influenza antiviral treatment than younger
children. Similar findings were reported from a previous popu-
lation-based study of children hospitalized with laboratory-con-
firmed influenza during the 2010–2011 influenza season [20].
This may be due to lack of recognition of influenza in children
<2 years old with CAP or in children who test positive for res-
piratory syncytial virus, which is a more frequent cause of CAP
in this age group [5, 26]. Providers may also be less comfortable
using influenza antiviral agents in children <2 years. Oseltamivir
was not approved by the US Food and Drug Administration to
 treat influenza infection in children <1 year old until December
2012 [37]. In our analysis, after excluding children <1 years of
age, the association between age ≥2 years and oseltamivir treat-
ment remained significant (Supplemental Table 1).

Intensive care unit admission was also associated with
oseltamivir treatment in both children and adults hospitalized
with CAP. This may indicate that influenza may be more likely
to be considered in the differential diagnosis of ICU patients hospi-
talized with CAP, or patients with more severe disease or who do
not improve, which then prompts influenza testing and subse-
quent treatment. The benefits of oseltamivir in critically ill chil-
dren and adults with influenza have been demonstrated [38, 39].

This study has limitations. First, although oseltamivir treat-
ment was associated with clinician-ordered testing, the factors
that led to testing cannot be determined directly. Second, we were unable to evaluate the timing of the availability of clinician-ordered testing results compared with oseltamivir initiation and other factors because we lacked complete information on dates and times of the clinician testing, particularly among children, because this was independent of the study protocol. Third, the study hospitals were mostly urban medical centers in 3 geographic regions, and thus our findings may not be generalizable to other settings. Furthermore, we lacked clinician-ordered testing information from 2 of 5 adult hospitals, which may further limit the generalizability. Finally, the true influenza status of the patient was unknown in situations when the research-study PCR and clinician-ordered PCR results were discordant.

CONCLUSIONS

In conclusion, 5% of children and 14% of adults hospitalized with CAP during an influenza season received oseltamivir, and approximately half of patients hospitalized with influenza-associated CAP were treated with oseltamivir despite ACIP and IDSA recommendations for treatment of all patients hospitalized with suspected influenza. Oseltamivir treatment was associated with clinician-ordered testing, severe disease, and study hospital. Studies are needed to better understand the reasons why oseltamivir prescribing among patients hospitalized with CAP is not higher. In addition, increased clinician education is needed to include influenza in the differential diagnosis for hospitalized patients with CAP and to test and treat patients empirically if influenza is suspected.

Supplementary Data

Supplementary materials are available at Open Forum 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.

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References


