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Evaluation of Diagnostic and Therapeutic Approaches for Suspected Influenza A(H1N1)pdm09 Infection, 2009–2010

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Analyze the use of diagnostic testing in cases of influenza-like illness
- Evaluate the use of antiviral medications for outpatient cases of influenza-like illness
- Evaluate the use of antiviral medications for inpatient cases of influenza-like illness
- Assess the care of patients with influenza-like illness and lower respiratory tract infections

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To assess adherence to real-time changes in guidelines for influenza diagnosis and use of oseltamivir during the 2009 influenza A(H1N1) pandemic, we reviewed medical records of patients with confirmed or suspected influenza-like illness (ILI) and those with no viral testing in a large Los Angeles (California, USA) hospital. Of 882 tested patients, 178 had results positive for influenza; 136 of the remaining patients received oseltamivir despite negative or no results. Oseltamivir use was consistent with national recommendations in >90%. Of inpatients, children were less likely than adults to have ILI at testing and to receive oseltamivir if ILI was found. Of outpatients, children were more likely to have positive test results; 20% tested did not have ILI or other influenza signs and symptoms. Twenty-five of 96 test-positive patients and 13 of 19 with lower respiratory tract disease were, inappropriately, not treated. Variations between practice and national recommendations could inform clinical education in future influenza seasons.

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In April 2009, the novel influenza A(H1N1) pandemic influenza virus (influenza A[H1N1]pdm09) was identified as the cause of influenza outbreaks. Influenza

disease caused by this strain rapidly spread, and in June 2009, the World Health Organization (WHO) declared a global pandemic. Disease activity peaked during May–June 2009, again in October 2009, and essentially disappeared by May 2010 (*1*–*3*). As with previous pandemics, the strain reemerged in the United States during the subsequent 2010–2011 influenza season and accounted for ≈25% of characterized strains (*4*).

During the pandemic, the Centers for Disease Control and Prevention (CDC) issued several guidances for healthcare providers for the identification and treatment of patients with suspected influenza A(H1N1)pdm09 disease (Figure 1). Several rapid influenza diagnostic tests for identification of the 2009 H1N1 strain were available, but their poor sensitivity soon became clear (*5*–*7*). CDC recommended that the neuraminidase inhibitor oseltamivir be used as a first-line treatment during the pandemic (*8*). Available data suggested that the drug was clinically effective, but only when given within <48 hours of symptom onset (*9*–*11*). These guidelines changed during the course of the pandemic as real-time epidemiologic, virologic, and clinical data emerged (*8*,*12*–*15*).

CDC initially recommended priority use of antiviral drugs for only hospitalized patients and those at increased risk for influenza-related complications. This recommendation reflected the knowledge that most persons infected with A(H1N1)pdm09 virus had self-limited, mild-to-moderate disease; that commercial and stockpiled supplies of oseltamivir were limited; and that the development of resistance was a concern, particularly since no other effective and easily administered antiviral drugs were available (*15*–*18*). Questions remained, however, with regard to the overall risks and benefits and appropriate dosage of the drug for very young and obese patients. In September 2009, CDC advised that rapid influenza diagnostic tests be prioritized for patients who were hospitalized or for whom a diagnosis of influenza could inform clinical decision making. Furthermore, CDC reinforced the idea that presumptive treatment should be administered to this group of patients and expanded the target group for treatment to include outpatients with risk factors for severe disease, even when test results were unknown (*5*). Clinical judgment was clearly a key factor in the clinical management of patients with possible A(H1N1) pdm09 disease.

Much has been published with regard to the epidemiology, virology, and clinical spectrum of A(H1N1) pdm09 illness (*19*,*20*), but no information is available with regard to diagnostic and therapeutic decision making of physicians or their adherence to national guidelines for ill patients. We conducted this study to evaluate the adherence of physicians to contemporaneous national guidelines for diagnosis and use of oseltamivir among patients with suspected or confirmed A(H1N1)pdm09 virus infection in the inpatient and outpatient settings.

Methods

The study population included all persons who accessed care from May 1 to December 31, 2009, at Harbor–UCLA Medical Center (HUMC) in Los Angeles, California. HUMC is a 538-bed, urban, academic, teaching hospital; it serves a diverse population, which is ≈55% Latino, 11% Caucasian, 24% black, 4% Asian, and 4% Pacific Islander.

We conducted a retrospective cohort study to evaluate 3 issues: 1) adherence of clinicians to national recommendations for use of osteltamivir among patients with suspected or confirmed influenza virus infection; 2) appropriateness of patient selection for diagnostic testing; and 3) the likelihood of clinicians to prescribe antiviral drug therapy for persons with known influenza-like illness (ILI) or lower respiratory tract infection (LRTI), 2 conditions for which CDC specifically recommended antiviral drug therapy. For the first 2 objectives, we identified child and adult inpatients and those seen in the emergency department with A(H1N1)pdm09 disease by using 4 overlapping data sources, including the following: 1) prospectively collected electronic A(H1N1)pdm09 virus laboratory-based surveillance data obtained by the HUMC clinical virology laboratory and the Infection Prevention and Control Department; 2) electronic, pharmacy-based oseltamivir utilization data; and 3) data on point-of-care testing performed in the emergency department. These data were combined, and we reviewed the medical records of all patients with a positive laboratory test for influenza in the outpatient setting and of inpatients who

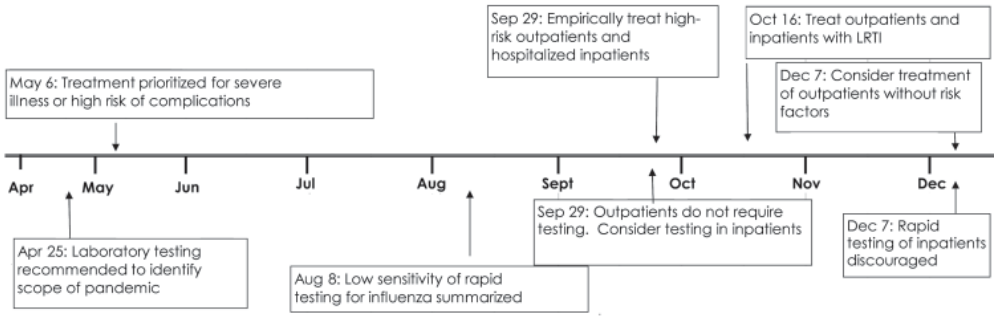

Figure 1. Centers for Disease Control and Prevention (CDC) guidance during the 2009 pandemic of influenza A(H1N1)pdm09 disease. LRTI, lower respiratory tract infection.

had a laboratory test that was positive for influenza virus or were prescribed oseltamivir. Approval for human subjects research was obtained from the Los Angeles Biomedical Research Institute.

We performed a comprehensive review of medical records by using a standardized data collection instrument to identify demographic information and clinical characteristics of patients with the illness, including symptoms and signs and results of viral diagnostic testing and chest radiographs. Use of and indications for oseltamivir, including dose and duration of use, were recorded and, if oseltamivir was not prescribed, reasons for not using the drug were noted. We also recorded whether the patient exhibited risk factors for complications and death (from a preselected list that included concomitant cardiopulmonary, renal, liver, endocrine, blood, or metabolic disorders; immunosuppressive conditions; aspirin therapy; and neurologic conditions), diagnoses at admission or discharge, and length of stay.

We defined suspected influenza as illness in any patient for whom oseltamivir was prescribed by the treating clinician. We defined confirmed influenza disease as illness in a patient with a positive laboratory test result for the virus. To evaluate adherence to guidelines, we used the contemporaneous CDC definition for ILI (fever and cough with or without sore throat) and defined severe illness as requiring intensive care, a documented oxygen saturation of <92%, or both.

To assess the likelihood of clinicians to prescribe antiviral drug therapy for persons with known ILI or LRTI, we identified all inpatients and outpatients with possible upper or lower respiratory tract influenza disease by using International Classification of Diseases, Ninth Revision (ICD-9) diagnostic codes as follows: 079.89 (viral infection), 079.99 (viral infection not otherwise specified [NOS]), 460 (nasopharyngitis, acute), 462 (pharyngitis, acute), 465.8 (infectious upper respiratory, multiple sites, acute), 465.9 (infectious upper respiratory, multiple sites, acute NOS), 466.0 (bronchitis, acute), 466.19 (bronchiolitis, acute, due to other infectious organism), 478.9 (disease, upper respiratory /NOS), 480.1 (pneumonia caused by respiratory syncytial virus), 480.8 (pneumonia caused by virus), 480.9 (viral pneumonia unspecified), 484.8 (pneumonia in other infectious disease), 485 (bronchopneumonia, organism NOS), 486 (pneumonia, organism NOS), 487.0 (influenza with pneumonia), 487.1 (influenza with respiratory manifestation), 487.8 (influenza with manifestation), 488.1 (influenza caused by identified novel H1N1 influenza virus), 490 (bronchitis NOS), 780.6 (fever), 784.1 (pain, throat), 786.2 (cough) (*21*). The validity of the ICD-9–based ascertainment was assessed by using prospective emergency department triage ILI surveillance data collected beginning October 21, 2009, through the end of the study period.

From this group, we randomly selected 100 persons, stratified by age (50 persons ≤18 and 50 >18 years of age) by using SAS 9.2, Proc Samplesurvey (SAS Institute, Cary, NC, USA). Using medical record review, we then identified persons with ILI (defined above) or LRTI, defined by the presence of at least 1 specific lower respiratory tract sign, including tachypnea, retractions, or hypoxia (oxygen saturation <92%), and/or abnormal auscultatory findings (crackles/crepitations or wheezing), and/or unequivocal and abnormal radiographic findings.

We performed descriptive analyses of the above variables by using SAS version 9.2. Testing of proportions was performed by using χ^2 or Fisher exact test as appropriate. All reported p values are 2-tailed and were considered significant if $p<0.05$.

Results

Entire Cohort

We identified 882 patients who were tested for influenza virus during the study period, among whom 178 (20%) tested positive. An additional 136 received oseltamivir but were not tested or had a negative laboratory test result for influenza virus. Overall, 232 (74%) of 314 patients had ILI, and 82 (26%) of 314 had a positive test result for influenza virus but did not meet the CDC-defined criteria for ILI. Of these 82, 36 (44%) had other signs or symptoms consistent with influenza, such as headache, myalgia, nausea, or diarrhea. We identified 218 (69%) inpatients among the 314 patients with confirmed or suspected influenza. Of those 314 patients, 55 (18%) were <2 years of age, 129 (41%) were 2–18 years of age, 89 (28%) were 19 to <50 years of age, 32 (10%) were 51 to <65 years of age, and 9 (3%) were >65 years of age. An underlying medical condition was recognized in 88 (48%) children (most commonly, asthma) and in 95 (52%) adults (most commonly, immunosuppression).

Oseltamivir was prescribed for 86 (66%) of 130 children and 89 (87%) of 102 adults with ILI. Oseltamivir was prescribed at the correct dosage and duration of therapy for 229 (95%) of 240 patients, and 216 (90%) of 240 patients received the drug <48 hours after symptom onset. Another 16 received the drug within 72 hours of disease onset. Severe illness was identified in 132 (42%) of 314 patients, 118 (89%) of whom received oseltamivir (Figure 2).

Inpatients

Of 218 inpatients who received a diagnosis of or treatment for influenza, 107 (49%) were children, and 111 (51%) were adults. Laboratory testing was performed

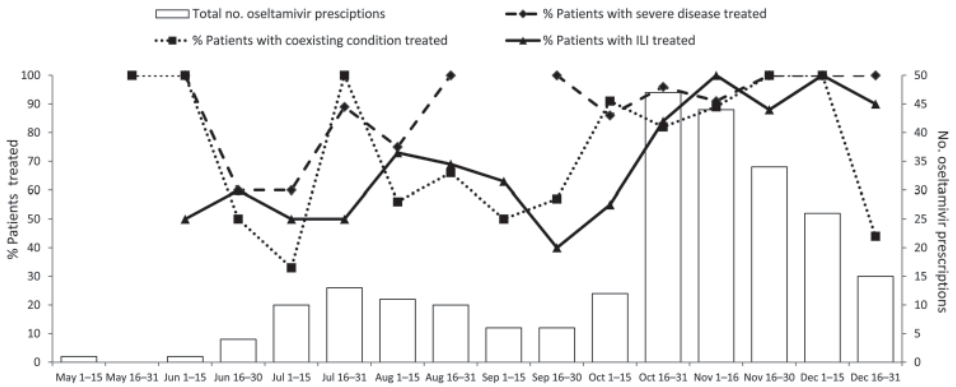

Figure 2. Total number of patients treated with oseltamivir by category, presence of influenza-like illness (ILI), and disease severity, Los Angeles, California, USA, 2009.

for 177 (81%) inpatients, and 74 (42%) were positive for influenza virus (Table). Oseltamivir was administered to 198 (91%) of 218 inpatients, among whom 110 (50%) had a negative test or no laboratory testing performed. Of the remaining 88 with a positive test result, 5 did not receive oseltamivir because the patient refused, the patient was "well appearing," or patient's onset of symptoms occurred >48 hours before they received a diagnosis.

Of the inpatients, we identified 68 (64%) of 107 children and 86 (77%) of 111 adults who had ILI at the time of laboratory testing ($p<0.04$). Oseltamivir was given to 58 (85%) of the 68 children with ILI and 84 (98%) of 86 adults with ILI ($p<0.02$). Oseltamivir was prescribed for 145 (94%) of 155 inpatients with an underlying medical condition and for 118 (91%) of 129 patients with severe illness.

The median interval from illness onset to initiation of antiviral treatment was 2 days (range 1–8). The dosage or duration of therapy, or both, was incorrect for 11 (5%) inpatients; for 6 inpatients, no adjustment was made for renal insufficiency. Of those 6 inpatients, 2 had chronic renal insufficiency after a transplant, 1 had diabetic nephropathy, and 3 had pneumonia and renal insufficiency. Three obese patients received a doubled dose of oseltamivir.

Receipt of the vaccine against influenza A(H1N1) pdm09 virus was documented in 61 (28%) of 218 patients, but 59 (97%) of them received the vaccine at hospital discharge. Only 1 patient had received the seasonal influenza vaccine before admission, and none received vaccine at discharge.

Outpatients

We identified 664 patients who underwent rapid influenza diagnostic testing, of whom 77 (19%) of 398 children and 19 (7%) of 266 adults tested positive ($p<0.001$). Twenty percent of tests were carried out on patients without CDC-defined ILI and for whom no other indication was present. As noted in Figure 3, only 11%

Table. Patients who underwent testing or treatment for influenza by category, Los Angeles, California, USA, 2009*

Test results and treatment	Inpatients†	Outpatients‡
Influenza diagnostic test		
Patients tested for influenza		
Total	177/218 (81)	664/664 (100)
Adults	79/111 (71)	398/398 (100)
Children	98/107 (92)	266/266 (100)
Positive influenza test result		
Total	74/177 (42)	96/664 (14)
Adults	18/79 (23)	19/398 (5)
Children	56/98 (57)	77/266 (29)
ILI among patients with a positive test result		
Total	44/74 (59)	77/96 (80)
Adults	14/18 (78)	16/19 (84)
Children	30/56 (54)	61/77 (79)
Oseltamivir prescribed		
Patients with positive influenza test result	53/74 (72)	22/96 (23)
Patients with coexisting condition	145/155(94)	15/28 (54)
Patients with severe influenza disease	118/129 (91)	0/3 (0)
Median time from illness onset to treatment, d	2 (1–8)	2 (1–5)

*Values are no./total no. (%) unless otherwise indicated. ILI, influenza-like illness.
†For inpatients who received a diagnostic test for influenza, N = 218; for outpatients who received a diagnostic test, N = 664. For inpatients who received oseltamivir, N = 218. In the outpatient setting, study cohort was identified through diagnostic testing only. Use of oseltamivir was evaluated only among those for whom a diagnostic test result was positive (N = 96).

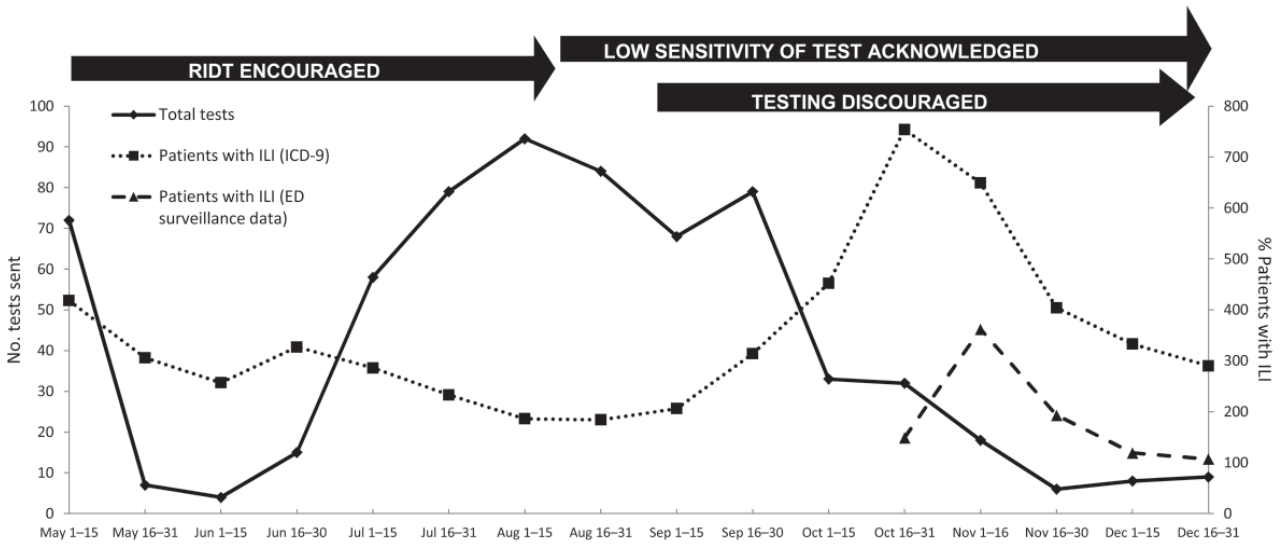

Figure 3. Rapid influenza diagnostic testing (RIDT) performed for outpatients with influenza-like illness (ILI), Los Angeles, California, USA, 2009.

(73/664) of these tests were performed >2 weeks after CDC actively discouraged their use.

Oseltamivir was prescribed for 37 (48%) of 77 outpatient children and 5 (26%) of 19 adults who tested positive for influenza (p>0.05), all at the appropriate dose and duration. As recommended, 35 (83%) of 42 received the drug <48 hours from symptom onset, and the remaining patients received the drug within 72 hours of symptom onset. Of 54 (56%) of 96 patients who tested positive and did not receive oseltamivir, 25 (46%) were not treated according to CDC guidelines, and 8 (15%) refused therapy. The reasons for not initiating oseltamivir therapy included onset of symptoms >48 hours previously and lack of an underlying medical condition. For 21 (39%) of the untreated patients, we found no documentation of the reason for withholding therapy.

We found 3 outpatients who had severe illness, none of whom received oseltamivir, and the reasons for withholding therapy could not be determined. Conversely, 16 (3%) of 522 patients with a negative test result received oseltamivir. The most common reasons documented for initiating therapy in this group included an underlying medical condition or concomitant diagnosis of pneumonia, ILI, or both, each consistent with CDC guidelines.

Therapy for Patients with ILI or LRTI Not Tested for Influenza Virus

We reviewed records of 50 randomly selected outpatients with ICD-9 codes for ILI who were not tested for influenza virus. Only 3 patients (6%) received oseltamivir (as recommended by CDC). Of the remainder who did not receive the drug, the duration of illness was >48 hours, the patient was "well appearing," or no underlying risk factors were found. The median time from illness onset to obtaining medical attention was 3.7 days (range 0–14 days); 22 (44%) sought treatment within 48 hours. Thirteen (26%) had an underlying medical condition (7 children and 6 adults). For each, however, there was an appropriate reason for withholding therapy, per CDC guidelines.

Among 50 outpatients with ILI and LRTI, 14 (28%) were admitted, 2 to the intensive care unit. The median time from illness onset to obtaining medical attention was 3 days (range 0–28 days); 31 (62%) of 50 sought treatment >48 hours after symptom onset. Eight of 25 (32%) children and 5 (20%) of 25 adults received oseltamivir, and 6 patients received the drug <48 hours from symptom onset. Oseltamivir was administered to 6 (38%) of 16 patients with severe illness and to 7 (25%) of 28 who had an underlying medical condition. The reason for not prescribing oseltamivir was documented in 5 charts, and the reasons included were that symptom onset was >48 hours from the visit to the hospital and that the patient was "well appearing." Overall, 13 (68%) of 19 patients with LRTI who sought treatment within 48 hours of illness onset did not receive oseltamivir as recommended by CDC.

Discussion

We believe that this study provides useful information with regard to the diagnostic and therapeutic behaviors of clinicians caring for patients with possible influenza virus infection. Although our data reflect physician behavior during the 2009–10 influenza A (H1N1) pandemic, the findings are likely applicable to any influenza year because diagnostic test performance, disease intensity, antiviral

agent resistance, and virus strain affect clinical decision making each year.

We were interested in 2 general concepts: practice performance when influenza was clinically suspected and the potential for missed therapeutic opportunities when it was not. For the former, we found that providers' practices were often consistent with CDC guidelines but notable deficiencies were also identified. In particular, a substantial proportion of potentially high-risk patients were not empirically treated, and a reason to withhold therapy could not be documented. This dynamic is similar to that for other medical conditions for which clinical practice guidelines are available: provider behavior at variance with the guideline may reflect available patient-level information or other immediate concerns (*22*,*23*). In any case, we have identified potential areas for targeted education of healthcare providers that should be supplemented by rapid dissemination and follow-up of national guidelines if and when they change over time.

We also found inconsistencies in the use of antiviral drug therapy, which was often at variance with contemporaneous guidelines. In our population, 25% of patients who received oseltamivir did not have ILI or another clear indication for treatment. During the pandemic, the drug was recommended for inpatients with ILI and outpatients with ILI and risk factors for severe illness if they had sought treatment within 48 hours of symptom onset (*5*). However, although too many outpatients without ILI received oseltamivir, too few (32%) received the drug despite having LRTI, a consistent indication for therapy. For most patients with LRTI, we could not identify a reasonable justification for withholding therapy. Not surprisingly, all of these patients received antibacterial agents, yet it remains unclear whether the clinicians actively considered influenza virus as a primary pathogen or risk factor for the presumed bacterial superinfection. Influenza virus infection and its association with secondary bacterial infection is well documented with influenza A(H1N1) pdm09 virus infection and with interepidemic disease (*24*–*27*). Treatment with antiviral drugs in this setting may lessen illness when superinfection exists (*26*,*28*). In this circumstance, greater recognition of the possibility of influenza virus infection and use of antiviral drug therapy may mitigate illness and lessen hospital costs (*29*,*30*).

We found that diagnostic practices were often inconsistent with contemporaneous guidelines. Nearly one third of patients were tested for influenza virus, despite the lack of ILI and ≈20% had no other indication for which testing might otherwise be justified (e.g., headache, myalgia). Previous work has shown that relatively few patients with influenza virus infection have systemic signs without fever, sore throat, or cough (*31*). Although changes in CDC recommendations were quickly disseminated to hospital clinicians by management memo, email, or face-to-face meetings, even more rapid communication and follow-up reminders may have enhanced adherence to guidelines.

We found that the dosage and duration of oseltamivir were generally consistent with CDC guidelines in ≈90% of all treated patients, and specifically for all outpatients. HUMC required the use of a preauthorization drug form that noted the appropriate age- and weight-based dose; an outpatient prescription for oseltamivir would not have been released without a completed form. Such tools have been shown to limit dosing errors (*32*,*33*). Also consistent with the CDC guidelines, >90% of hospitalized patients and patients with severe illness in our study received oseltamivir. Among outpatients, we noted that for ≈50%, an appropriate rationale for not providing oseltamivir was documented in the medical record.

Among the small number of dosing errors identified, >40% were related to inappropriate adjustment for renal insufficiency. More than 90% of oseltamivir is metabolized to oseltamivir carboxylate, 99% of which is eliminated by renal excretion, thus requiring dosage adjustment in this setting. Antimicrobial drug dosing errors are common (*34*,*35*), and a failure to adjust for renal impairment is a frequent underlying reason (*36*,*37*). Although controlled data are not available, oseltamivir has been associated with the development of thrombocytopenia, particularly when renal clearance is artificially lowered by concomitant administration of the drug probenicid (*38*). Attention should be given to patients' renal function, particularly in the elderly (diminished renal clearance) and in those for whom higher doses may be recommended, such as the severely ill or obese (*8*).

We identified clinical management differences between how clinicians prescribed treatment for adult patients and how they prescribed treatment for children. Children who were inpatients were significantly less likely to have ILI at the time of testing and to receive treatment for ILI. When testing was carried out, children were also more likely to test positive for influenza virus than were adults, possibly because of the higher virus load in this population. These data also may reflect more overall testing of children, particularly young children who are more likely than adults to have nonspecific signs and symptoms (lethargy, poor feeding, abdominal pain) (*39*,*40*). In addition, infants and young children may not articulate symptoms of ILI (e.g., sore throat), leading to increased nonspecific testing and treatment of this population.

The main strength of this study is the comprehensive nature of case ascertainment, which included laboratory-based information and review of all prospectively collected logs for emergency department point-of-care testing. However, some patients who underwent testing for

influenza virus may not have been noted in the outpatient log system. We appreciate that ICD-9 code data for ILI and LRTI may be nonspecific, but our prospectively collected ILI data (albeit for a limited portion of the surveillance period) validated the temporal trends for this diagnosis in the outpatient setting. We also did not include data from medical outpatient (nonemergency department) clinics where other patients with influenza may have been identified and treated, perhaps skewing our data to those who were more ill. As a retrospective study, our conclusions depend solely upon information documented in the medical record, which may be incomplete. Also, the use of an antiviral agent authorization form most likely improved the dosing practice, as has been shown in other settings (*32*,*33*). Last, our study population includes only a single academic medical center and therefore may not be representative of the region or the nation.

To our knowledge, similar studies of physician behavior with regard to influenza disease, and for A(H1N1) pdm09 disease in particular, have not been reported. We have identified variations in clinical practice in relation to national guidelines that suggest potential areas of education for future influenza seasons.

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Dr. Vijayan performed this work as a Fellow in Pediatric Infectious Diseases at Harbor–UCLA Medical Center. She is currently an assistant professor of pediatrics at the University of Florida, Gainesville. Her research interests include preventing infections, such as influenza and pertussis in mothers and their infants through maternal immunization, and diagnosis and management of travel- and migration-associated disease.

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