A Population-Based Study of Neurologic Manifestations of Severe Influenza A(H1N1)pdm09 in California

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Background. Reported influenza-associated neurologic complications are generally limited to case series or case reports. We conducted a population-based study of neurologic manifestations associated with severe and fatal influenza A(H1N1)pdm09 (2009 H1N1) cases.

Methods. Medical records of patients with fatal or severe (hospitalized in intensive care unit) laboratory-confirmed 2009 H1N1 reported to the California Department of Public Health from 15 April 2009 through 31 December 2009 were reviewed to identify those with primary neurological manifestations. Cases with secondary neurologic manifestations (eg, hypoxia) were excluded. Primary influenza-associated neurologic complications (INCs) were classified into 4 groups: encephalopathy/encephalitis, seizures, meningitis, and other. Severe 2009 H1N1–associated neurologic incidence was calculated by using estimates of 2009 H1N1 illnesses in California.

Results. Of 2069 reported severe or fatal 2009 H1N1 cases, 419 (20%) had neurologic manifestations. Of these, 77 (18%) met our definition of INCs: encephalopathy/encephalitis (n = 29), seizures (n = 44), meningitis (n = 3), and other (Guillain–Barré Syndrome) (n = 1). The median age was 9 years (range, 4 months–92 years); the highest rate of disease was among pediatric Asian/Pacific Islanders (12.79 per 1 000 000) compared with pediatric white, non-Hispanics (3.09 per 1 000 000), Hispanics (4.58 per 1 000 000), and blacks (6.57 per 1 000 000). The median length of stay (LOS) was 4 days (range, 1–142), and there were 4 fatalities. The estimated incidence of INCs was 1.2 per 100 000 symptomatic 2009 H1N1 illnesses.

Conclusions. Influenza-associated neurologic complications were observed in 4% of patients with fatal or severe 2009 H1N1. They were observed most often in pediatric patients, and Asian/Pacific Islanders appear to be overrepresented compared with the California population. Most patients with INCs had a relatively short LOS, and there were few fatalities.

A spectrum of neurologic complications associated with seasonal influenza virus infection has been recognized and includes encephalopathy, seizures, and Guillain–Barré Syndrome (GBS) [1–5]. Similarly, influenza A(H1N1)pdm09 (2009 H1N1) virus infection has been associated with neurologic manifestations, but information about the spectrum of neurologic complications and burden of disease has been limited to case reports and small case series [6–12]. To better understand the frequency and characteristics of 2009 H1N1–associated neurologic events, we conducted a population-based study in California of severe and fatal 2009 H1N1 cases with neurologic manifestations.
METHODS

In April 2009, after the detection of 2009 H1N1 virus in California, the California Department of Public Health (CDPH), along with 61 local health jurisdictions, initiated surveillance for cases of severe 2009 H1N1. This surveillance has been previously described [13]. Briefly, cases were patients who were hospitalized or died and had laboratory evidence of 2009 H1N1 virus (all cases were polymerase chain reaction [PCR] positive; rapid tests alone were not sufficient). Cases were reported to the CDPH by local health departments using standardized case history forms (generally completed by the hospital infection preventionist). Data collected included demographic, clinical, and laboratory information; specific information about the presence or absence of altered mental status (AMS), encephalitis/encephalopathy, and seizures; and whether a lumbar puncture (LP) was performed.

Because only fatal or intensive care unit (ICU) cases were reported for the entire 2009 reporting period, only these cases were included. The CDPH clinical staff reviewed hospital medical records for cases with neurologic symptoms or documentation that an LP was performed. Cases with neurologic signs and symptoms determined by the CDPH clinical staff to be likely due to an indirect effect of 2009 H1N1 virus infection, such as pneumonia-related hypoxia, sepsis, multiorgan failure, or medication reactions, were considered to have secondary neurologic complications and were excluded (Figure 1). Cases with hepatic encephalopathy, stroke, or meningismus (symptoms consistent with meningitis but without evidence of meningeal inflammation) [14] were considered to have indeterminate neurologic complications and were also excluded. Patients whose neurological symptoms began >24 hours after admission were excluded. The remaining patients were considered to have primary influenza-associated neurologic complications (INC). The patient’s condition on discharge from the hospital was obtained from the hospital medical record. Based on the presentation and clinical course, INC cases were further classified in 1 of 4 ways:

1. Influenza-associated encephalopathy/encephalitis (IAE): defined as ≥24 hours of AMS or personality change without an identified secondary cause for AMS (eg, hypoxia) and includes patients with both encephalopathy and seizures;
2. Seizures: defined as clinical seizures without clinical or laboratory evidence of meningitis or encephalitis; febrile seizures according to the American Academy of Pediatrics (AAP) guidelines [15], or seizures not otherwise specified;
3. Meningitis: defined as signs or symptoms suggestive of meningitis (eg, nuchal rigidity) with cerebrospinal fluid (CSF) pleocytosis (includes patients with potential bacterial meningitis); or
4. Other: defined as neurologic manifestations not included in the above categories, (eg, GBS).

This study was reviewed by the State of California Committee for the Protection of Human Subjects and determined to be a public health response that did not require institutional review board approval.

Estimates of Severe 2009 H1N1–Associated Neurologic Incidence

An estimate of the incidence of INCs among H1N1 illnesses only was determined by using INC cases as the numerator. For the denominator, we extrapolated from the midlevel national estimates of 2009 H1N1 illnesses in the United States prepared by the Centers for Disease Control and Prevention (CDC) (www.cdc.gov/h1n1flu/estimates) and multiplied by 12% (California’s representative proportion of the US population). We also calculated the INC incidence within the general population by race and ethnicity among pediatric (aged <18 years) and adult cases using California population estimates from the California Department of Finance as the denominator.

RESULTS

Of 2069 ICU and/or fatal 2009 H1N1 cases occurring in California from 15 April 2009 through 31 December 2009, 419 (20%) were reported to have AMS, encephalopathy, and/or seizures and/or had an LP performed. Of these, 77 (18%) met the definition for having an INC (4% of all ICU and/or fatal cases in the study period). The median age was 9 years (range, 4 months–92 years). Twenty-nine (38%) had encephalopathy, 44 (57%) had seizures, 3 (4%) had suspected meningitis, and 1 (1%) had other neurologic manifestations (GBS).
The median time from onset of influenza symptoms to onset of neurologic symptoms was 1 day, and almost all (93%) had onset of neurologic symptoms within 5 days of illness onset. The remaining 336 cases with reported neurologic symptoms were excluded from further analysis: 223 (68%) were classified as secondary, 16 (4%) were classified as indeterminate (7 with strokes, 4 with hepatic encephalopathy, 4 with meningismus), 12 (4%) were infants aged <6 months who had an LP performed to exclude sepsis but had no clear neurologic signs or symptoms, and 90 (27%) had no acute neurologic manifestations (Figure 1).

Estimates of Severe 2009 H1N1 Neurologic Incidence
Extrapolating from national estimates prepared by the CDC, we estimated that approximately 6.6 million cases of symptomatic 2009 H1N1 illness occurred in California from 15 April through 31 December 2009. During this same period, 77 ICU and/or fatal 2009 H1N1 cases met our definition for having an INC for an incidence of 1.2 severe INCs per 100,000 persons ill with 2009 H1N1. The time period of all ICU and fatal 2009 H1N1 cases and influenza neurologic complications is shown in Figure 2.

Encephalopathy/Encephalitis Group
Twenty-nine patients were classified with influenza-associated encephalopathy/encephalitis (Table 1). The median age was 17 years (range, 1–92 years). Sixteen (55%) were pediatric cases, and 20 (69%) were male. Among all cases, 15 (52%) were white, non-Hispanic, 7 (24%) were Asian/Pacific Islander, 4 (14%) were black, non-Hispanic, and 3 (10%) were Hispanic (Table 1). The rate among pediatric Asian/Pacific Islander encephalopathy/encephalitis cases was almost 4 times that of white cases (Table 2). Underlying disorders/conditions of encephalopathy cases included reactive airway disease (6), obesity (2), diabetes mellitus (2), sickle-cell disease (1), renal disease (1), intraventricular hemorrhage/hydrocephalus in former premature infant (1), Down syndrome (1), and brain tumor (1).

Almost all experienced fever (26; 90%) and respiratory symptoms (25; 86%) prior to admission. Cerebrospinal fluid results were generally unremarkable; of the 27 patients with LPs performed, only 3 patients had a CSF white blood cell (WBC) count >10 cells/mL and only 1 had a CSF WBC count >100 cells/mL. Modest CSF protein elevations (>45 mg/dL but <100 mg/dL) were noted in 6 patients; none had hypoglycorrhachia.

Eight patients (28%) experienced seizures; 4 of these patients were intubated. In total, 8 (28%) patients with encephalitis required intubation, most for protection of airway status. Of the 25 patients with neuroimaging performed, 3 (12%) patients had scans demonstrating acute changes; 2 with significant cerebral edema and 1 with bilateral frontal, temporal, and thalamic signal abnormalities consistent with acute necrotizing encephalitis. Most (25; 86%) patients received influenza antiviral

Table 1. Demographics and Clinical Characteristics of All Influenza-Associated Neurologic Complications

<table>
<thead>
<tr>
<th></th>
<th>All Influenza-Associated Neurologic Complications (n = 77)a</th>
<th>Encephalopathy (n = 29)</th>
<th>Seizure (Only) (n = 44)</th>
<th>Meningitis (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45 (58)</td>
<td>20 (69)</td>
<td>24 (55)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>Median age in years (range)</td>
<td>9 (&lt;1–92)</td>
<td>17 (1–92)</td>
<td>3 (&lt;1–59)</td>
<td>1 (&lt;1–65)</td>
</tr>
<tr>
<td>Pediatric (aged &lt;18 years)</td>
<td>56 (73)</td>
<td>16 (55)</td>
<td>38 (86)</td>
<td>2 (67)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>24 (31)</td>
<td>15 (52)</td>
<td>8 (18)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>28 (36)</td>
<td>3 (10)</td>
<td>23 (52)</td>
<td>2 (67)</td>
</tr>
<tr>
<td>Black</td>
<td>5 (6)</td>
<td>4 (14)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>16 (21)</td>
<td>7 (24)</td>
<td>8 (18)</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>4 (5)</td>
<td></td>
<td>4 (9)</td>
<td></td>
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<tr>
<td>Clinical course (all ages)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Median length from onset to admission in days (range)</td>
<td>1 (0–20)</td>
<td>2 (0–15)</td>
<td>1 (0–20)</td>
<td>1 (0–6)</td>
</tr>
<tr>
<td>Median length of stay in days (range)</td>
<td>4 (1–142)</td>
<td>4 (1–34)</td>
<td>4 (1–142)</td>
<td>8 (5–15)</td>
</tr>
<tr>
<td>Median time from onset to antiviral treatment in days (range)</td>
<td>2 (0–21)</td>
<td>2 (0–15)</td>
<td>2.5 (0–21)</td>
<td>6.5 (0–16)</td>
</tr>
<tr>
<td>Intubated</td>
<td>27 (35)</td>
<td>9 (31)</td>
<td>16 (36)</td>
<td>2 (67)</td>
</tr>
<tr>
<td>Fatal</td>
<td>4 (5)</td>
<td>1 (3)</td>
<td>2 (5)</td>
<td>1 (33)</td>
</tr>
</tbody>
</table>

Data are No. (%) unless otherwise indicated.

* One additional influenza-associated neurologic complication classified as other neurologic manifestation.
treatment within 48 hours of hospitalization, but all received such treatment after neurologic symptoms had begun. Almost half of encephalopathy/encephalitis patients (14; 48%) were started on acyclovir because of initial suspicion of herpes simplex encephalitis (HSE); none had confirmed HSE.

In general, the clinical outcome for these patients was good. Most patients returned to their baseline status by discharge; the median length of stay (LOS) was four days (range, 1–34 days). One of the more severe cases involved a male patient aged 55 years who presented with AMS and seizures and had

Figure 2. Time period of all intensive care unit/fatal influenza A(H1N1)pdm09 (2009 H1N1) cases and severe 2009 H1N1 cases with neurologic complications. Abbreviation: ICU, intensive care unit.

Table 2. Race and Ethnicity of Severe Influenza A(H1N1)pdm09 Cases With Neurologic Complications, California, 15 April 2009 Through 31 December 2009

<table>
<thead>
<tr>
<th></th>
<th>All Influenza-Associated Neurologic Complications (n = 77)</th>
<th>Encephalopathy/Encephalitis (n = 29)</th>
<th>Seizure (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Rate per 1 000 000 Rate Ratio 95% CI</td>
<td>No. Rate per 1 000 000 Rate Ratio 95% CI</td>
<td>No. Rate per 1 000 000 Rate Ratio 95% CI</td>
</tr>
<tr>
<td><strong>Pediatric (aged ≤18 years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>10 3.09 … …</td>
<td>5 1.54 … …</td>
<td>4 1.23 … …</td>
</tr>
<tr>
<td>Hispanic</td>
<td>24 4.58 1.5 1.3–1.9</td>
<td>2 0.38 0.2 &lt;1–1.8</td>
<td>21 4.01 3.2 2.1–21.6</td>
</tr>
<tr>
<td>Black</td>
<td>4 6.57 2.1 2.0–2.2</td>
<td>3 4.93 3.2 1.5–5.3</td>
<td>1 1.64 1.3 &lt;1–1.8</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>14 12.79 4.1 3.5–5.5</td>
<td>6 5.48 3.6 0.9–7.9</td>
<td>8 7.31 5.9 4.0–37.3</td>
</tr>
<tr>
<td><strong>Adult (aged &gt;18 years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>14 1.06 … …</td>
<td>10 0.76 … …</td>
<td>4 0.30 … …</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4 0.43 0.4 &lt;1–1.7</td>
<td>1 0.11 0.1a …</td>
<td>2 0.22 0.7a …</td>
</tr>
<tr>
<td>Black</td>
<td>1 0.60 0.6 &lt;1–1.3</td>
<td>1 0.60 0.8a …</td>
<td>… … …</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>2 0.53 0.5 &lt;1–1.0</td>
<td>1 0.27 0.4a …</td>
<td>… … …</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

* Confidence intervals not calculated due to very small sample sizes.
an MR image consistent with acute necrotizing encephalopathy. He was discharged after 14 days and noted to be fully oriented but with speech and gait impairments. Follow-up several months later determined that he returned to his neurologic baseline. One fatality occurred in a woman aged 28 years with diabetes mellitus who presented with AMS and lethargy and was found to have hyperthermia (temperature of 107°F in the emergency room) and cerebral edema. She subsequently developed multiorgan failure and cardiopulmonary arrest.

**Seizure Group**
In 44 patients, the primary neurologic manifestation was seizure(s). Of these, 23 (52%) patients were Hispanic, 8 (18%) were white, non-Hispanic, 8 (18%) were Asian/Pacific Islander, 1 (2%) was black, and 4 (9%) were other or unknown race (Table 1). Most (38; 86%) were children aged ≤18 years; the rate of pediatric seizure cases was highest among Asian/Pacific Islander and Hispanic patients (Table 2). Twenty (44%) patients met the AAP definition for febrile seizures; 19 were complex febrile seizures, and 1 was a simple febrile seizure. One additional case did not fulfill case criteria for febrile seizures due to age (6 years) but otherwise had symptoms compatible with complex febrile seizures. All of the remaining 24 patients had underlying medical disorders: neurologic (22) or metabolic (2).

An LP was performed in 20 (45%); all were unremarkable. Seventeen (39%) had an MR image or computed tomographic scan performed, and none had significant findings. Sixteen (36%) were intubated, most often for airway protection, for a median duration of 2 days. The median LOS for this group of patients was 4 days (range, 1–142 days). Two fatalities occurred in this group, both in patients with preexisting neurologic conditions.

**Meningitis Group**
Three cases were classified as meningitis based on their clinical symptomatology (fever, stiff neck) and CSF pleocytosis. Two were in the pediatric age group, and 1 was an adult. Two patients had marked CSF pleocytosis (CSF WBC count >1000 cells/mL) and were suspected to have bacterial meningitis but had negative CSF cultures in the setting of prior antibiotic administration; 1 case was fatal.

**Other Group**
Only 1 case with another neurologic syndrome was identified. An adult Asian female in her early 30s developed lower extremity weakness and cranial nerve palsies 2 weeks after the onset of respiratory illness and was still positive for 2009 H1N1 by reverse-transcription PCR at the time of admission. She was ultimately diagnosed with GBS.

**DISCUSSION**
Neurologic manifestations associated with influenza are diverse [1–5]. The relative frequency of these INCs, however, has not been well characterized, particularly in the United States. Our review of >2000 ICU and/or fatal 2009 H1N1 cases provided us with a unique opportunity to study the relative frequency of neurologic manifestations associated with severe 2009 pandemic influenza. In our cohort of 2009 H1N1 ICU and/or fatal cases in California, INCs were found in 4% of ICU and/or fatal cases. A diverse group of neurologic complications including seizures, encephalitis/encephalopathy, meningismus, and GBS were identified.

The frequency of INCs identified in our study is similar to what has been reported in smaller series of 2009 H1N1 INC cases. In a study of 63 pediatric patients hospitalized with 2009 H1N1 at a single tertiary care hospital in Italy, 3 (5%) had neurologic complications [6]. Similarly, neurologic complications were described in 5 (6%) of 83 children with 2009 H1N1 from a single institution in the United Kingdom, with seizures and altered sensorium being the most common INCs [7]. In Israel, 14 (19%) of 74 hospitalized children with 2009 H1N1 experienced INCs [12]. In the United States, 18 of 303 (6%) children hospitalized with 2009 H1N1 had INCs reported [16].

Encephalopathy/encephalitis was one of the most severe and frequently reported INCs in our study. Influenza-associated encephalopathy is generally described as a rapidly progressive encephalopathy presenting early in the course of influenza illness, occurring most commonly in children aged <5 years, and associated with high morbidity and mortality [1–3]. Consistent with prior reports, most of our IAE cases occurred just after the onset of febrile respiratory symptoms and occurred most often in pediatric patients. Children in our study, however, had a higher median age, and there were no fatalities among children in our encephalitis/encephalopathy cohort [1–3]. The lack of fatalities also contrasts with findings from a recent Japanese study that identified encephalopathy as a leading cause of death associated with 2009 H1N1 in children but is similar to a US study of seasonal influenza in which no deaths were reported among IAE patients [17, 18]. Notably, the only fatality observed among our encephalopathy/encephalitis cases was in a young Asian woman. Her clinical course of AMS, hyperthermia, seizures, and fulminant cerebral edema is similar to the course described in pediatric IAE cases [2, 8].

Acute necrotizing encephalopathy is characterized by the acute onset of fever and encephalopathy and distinctive neuroimaging findings of bilateral thalamic inflammation and is a well-recognized and serious subcategory of IAE. Many case reports of acute necrotizing encephalopathy associated with
2009 H1N1 have described patients ranging in age from 3 to 20 years with variable outcomes [8, 9, 19]. Surprisingly, only 1 case of acute necrotizing encephalopathy was identified in our cohort and occurred in an adult male patient who, despite a complicated and prolonged hospital stay, survived and returned to baseline clinical status. Reye syndrome, another form of encephalopathy associated with influenza, is characterized by fatty metamorphosis of the liver and elevated levels of serum alanine aminotransferase, aspartate aminotransferase, or ammonia [20]. No cases of Reye syndrome were identified in our cohort. However, 4 cases had AMS secondary to hepatic failure thought to be a complication of their 2009 H1N1 illness (classified as indeterminate).

In addition to IAE, seizures were frequent INCs in our cohort. Seizures have consistently been one of the most common INCs for both seasonal influenza and 2009 H1N1 [4, 7, 12, 17, 21–23]. In our cohort, seizures in previously healthy children were characterized as febrile seizures, whereas among individuals with underlying neurologic disorders, seizures were often of prolonged duration and difficult to control. Notably, there were 2 fatalities in this subset of INCs, which further reinforces the importance of annual influenza vaccination for those with underlying neurologic disorders. Indeed, another study of critically ill children with 2009 H1N1 found that a preexisting neurologic condition was an independent risk factor for death [24].

In our cohort, the disproportionate frequency of INC cases among pediatric API patients was also notable. This disproportionate number of API patients was not seen when all ICU/fatal pediatric cases (including cases without neurological manifestations) were examined; incidence rates were slightly lower among whites (3.46 per 100,000) but similar across other racial/ethnic groups (5.3 per 100,000 Hispanics, 5.6 per 100,000 blacks, and 5.5 per 100,000 Asian/Pacific Islanders). Higher rates of influenza-associated encephalopathy have been observed in Japan for seasonal influenza, and a higher rate of INCs has been described in children hospitalized in China, compared with the United States [1, 2, 23]. To our knowledge, the increased proportion of API patients with INCs has not been previously reported in the United States. Although the reason is unclear, host factors are likely contributory.

A recent study in Japan found a higher frequency of thermolabile carnitine palmitoyltransferase II gene (CPT II) in IAE cases than in healthy controls [25]. The CPT II is a gene responsible for the regulation of mitochondrial fatty acid. One hypothesis is that during periods of high fevers specific thermolabile phenotype CPT variations cause mitochondrial failure that ultimately leads to the pathogenesis of brain edema seen in IAE [26]. Even more recently, another study found this same CPT variation in 2 unrelated Chinese boys with IAE, expanding the spectrum of genetic predisposition [27]. Whether these findings are applicable, the reason for the increased proportion of API patients with INCs in our study is unknown and warrants further study. Other disorders of mitochondrial fatty acid beta oxidation, such as glutaric aciduria type 2, may also play a role [28].

We attempted to describe only primary neurologic manifestations and excluded patients with what we considered secondary (eg, hypoxia) events related to 2009 H1N1. However, because many patients presented with multiple complications and comorbidities, it was often difficult to make a definitive differentiation between primary and secondary events. The lack of standard INC case definitions was particularly problematic and thus led to some cases being classified as indeterminate. For example, 6 patients initially thought to have encephalitis because of fever and AMS were ultimately diagnosed with stroke. In light of recent studies demonstrating an association between influenza and stroke [29–32], we chose to characterize stroke as an indeterminate event. Similarly, hepatic encephalopathy is included in some studies as a neurologic complication of influenza, but we also characterized these cases as indeterminate [33]. Yet another group of patients presented with symptoms suggestive of meningitis but without evidence of meningeal inflammation, and these cases were also considered to be indeterminate. These cases are notable because, although no evidence of meningeal inflammation was evident on CSF examination, the severity of symptoms was such that they prompted performance of LP and/or neuroimaging. Standardization of case definitions for INCs is needed for more accurate comparisons across studies.

The focus of our study population was ICU and/or fatal cases; therefore, hospitalized 2009 H1N1 patients with neurologic manifestations who were less severely ill were not characterized. In particular, febrile seizures were likely underestimated because these cases would not necessarily be admitted, particularly to the ICU [21]. Moreover, we only reviewed cases with neurologic symptoms on or near admission; postinfectious complications, such as GBS or acute disseminated encephalomyelitis, may have been missed. Additionally, the case history form was intended to capture many different clinical manifestations with only a minor emphasis on neurologic events. As a result, some neurologic events may not have been identified by the questions on our form. Similarly, our ability to assess individual neurologic events was limited to documentation in hospital medical records. Our findings might underestimate the number of patients with severe 2009 H1N1–associated INCs if some cases were not reported to the CDPH. Finally, patients who were not suspected to have 2009 H1N1 (eg, those without respiratory symptoms) may not have been tested for influenza and would not have been included in this study.

Despite its limitations, our study is one of the first population-based studies focusing on neurologic events associated with severe influenza illness. These neurologic events were
diverse and included encephalopathy/encephalitis, seizures, meningitis, and GBS. Although other reports have emphasized the severity of illness due to 2009 H1N1–associated encephalopathy/encephalitis, most patients in our study had a relatively benign course. Pediatric admissions were common, and Asian/Pacific Islander patients, especially those presenting with seizure or encephalopathy, appeared to be overrepresented. Further investigation into the association between race/ethnicity and INCs is warranted.

Notes

Acknowledgments. We gratefully acknowledge the contributions of the clinicians throughout California and the staff in the California local health departments who diligently worked to help acquire the epidemiologic and clinical information and ensured that these cases were reported to the CDPH.

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the opinion of the CDC.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. The editors consider relevant to the content of the manuscript have been disclosed.

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