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Characteristics and Outcomes of Influenza-Associated Encephalopathy Cases Among Children and Adults in Japan, 2010–2015

Hideo Okuno,[1,2] Yuichiro Yahata,[1] Keiko Tanaka-Taya,[1] Satoru Arai,[1] Hiroshi Satoh,[1] Saeko Morino,[1] Tomoe Shimada,[1] Tomimasa Sunagawa,[1] Timothy M. Uyeki,[3] and Kazunori Oishi[1]

[1]Infectious Disease Surveillance Center, National Institute of Infectious Diseases, Tokyo, and [2]Department of Epidemiology for Infectious Diseases, Osaka University, Graduate School of Medicine, Japan; and [3]Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Background. Influenza-associated encephalopathy (IAE) can result in severe neurologic disease with high mortality. Most IAE cases are reported among children worldwide. Understanding of IAE among adults is limited.

Methods. Data were collected on IAE cases reported through the National Epidemiological Surveillance of Infectious Diseases database in Japan from 2010 through 2015. IAE cases were stratified by age category and analyzed using descriptive statistics to assess differences in characteristics and outcomes.

Results. Among 385 IAE cases, median age at diagnosis was 7 years (range, 0–90), and 283 (74%) were aged <18 years. Mean seasonal incidence of IAE cases among children and adults (aged ≥18 years) was 2.83 and 0.19 cases per 1 000 000 population, respectively. IAE incidence did not vary by predominant influenza A virus subtype. IAE frequency was highest in school-aged (5–12 years) children (38%), followed by children aged 2–4 years (21%) and adults aged 18–49 years (11%). The proportion of cases with seizures was more common in children. There were more cases with cerebrospinal fluid pleocytosis among adults than in children ($P < .01$), especially among those aged 18–49 (17%) and 50–64 (19%) years. Case fatality proportion was highest in those aged 40–64 (17%) and ≥65 (20%) years.

Conclusions. We found differences in the clinical features of IAE between adults and children in Japan. Although IAE incidence was higher in children, mortality was higher in adults. Efforts are needed to prevent and improve survival of patients with IAE, especially in adults.

Keywords. influenza-associated encephalopathy; influenza; adults; children; severity.

Acute encephalitis or encephalopathy is associated with severe neurologic sequelae and high mortality [1]. Influenza virus infection of the respiratory tract may be associated with acute encephalitis or encephalopathy [1]. Cases of influenza-associated encephalopathy (IAE) have been reported since the late 1990s in Asian countries, including Japan, and other countries [2–4]. During the 2009 H1N1 pandemic, IAE cases were reported worldwide [5–9]. Most IAE cases reported to date have occurred among children. Few studies have been conducted among adults to characterize the clinical features associated with IAE cases, although some fatal adult cases have been reported [9–13].

In Japan, acute encephalitis or encephalopathy is classified as a category 5 notifiable disease by the Act on Prevention of Infectious Diseases and Medical Care for Patients Suffering Infectious Diseases (Infectious Diseases Control Law). All clinicians who diagnose a patient with acute encephalitis or encephalopathy of infectious etiology, including IAE, are required to report the case to the National Epidemiological Surveillance of Infectious Diseases (NESID). Japan is one of the few countries with national surveillance data on IAE cases. An analysis of IAE cases in Japan prior to and during the 2009 H1N1 pandemic did not assess differences in clinical characteristics or mortality by age group [5].

Our aim in this study was to compare the clinical characteristics and outcomes of IAE cases in adults and children reported through national surveillance in Japan since the 2009 H1N1 pandemic.

METHODS

Case Definitions of Influenza-Associated Encephalopathy

The case definition of acute encephalitis or encephalopathy in the NESID includes patients who had disturbed consciousness caused by the inflammatory change of brain parenchyma and

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Correspondence: K. Oishi, (oishik@niid.go.jp).

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were hospitalized for at least 24 hours or died and who had at least 1 of following signs and symptoms: a body temperature of 38°C or higher, a central nervous system manifestation, or a preceding infectious symptom [5]. Patients were excluded if they were determined to have noninfectious diseases such as metabolic disorders, trauma, cerebrovascular disorders, and/or brain tumors. Acute encephalitis or encephalopathy cases caused by notifiable arthropod-borne infections such as Japanese encephalitis virus and West Nile virus are reported separately in the NESID. Clinicians who diagnose patients with acute encephalitis or encephalopathy are required to report the following through the NESID: causative pathogen, sex, age, signs and symptoms, cerebrospinal fluid (CSF) pleocytosis, location of the reporting hospital or clinic, source of infection, date of onset, and date of death if patients had died by the time of notification. In addition, clinicians and local public health laboratories are required to use laboratory diagnostic methods, to the best extent possible, to detect the suspected pathogen(s) of acute encephalitis or encephalopathy. However, reporting of laboratory diagnostic methods for microbiologic agents, vaccine status, underlying diseases, neurologic sequelae, and medical treatment is not mandatory. In this study, IAE was defined as an acute encephalitis or encephalopathy case that was reported to NESID as influenza virus infection with type A or B. We excluded cases reported with a diagnosis that included other pathogens.

Data Collection and Analyses

We defined the influenza season as the period from week 36 of each year to week 35 of the next year and collected data on IAE cases reported to the NESID from the 2010 through 2015 influenza seasons. We collected data on the following variables from the NESID database in order to describe the characteristics of IAE cases: age, sex, signs and symptoms (fever, seizure, vomiting, and neck stiffness), CSF pleocytosis, influenza virus type (A or B), and outcome of death. We analyzed the data by age group (<2, 2–4, 5–12, 13–17, 18–49, 50–64, and ≥65 years) on the basis of risk for complications and hospitalizations associated with seasonal influenza. Fisher exact test and χ^2 test were used to evaluate differences between proportions. Wilcoxon-Mann-Whitney test was used to evaluate differences between medians. All comparisons were 2-sided, and a P value < .05 was considered to be significant. All analyses were conducted using JMP 11.0.0 statistical software (JMP Statistical Discovery, North Carolina).

In Japan, nationwide sentinel surveillance of influenza-like illness (ILI) is conducted yearly. Approximately 5000 sentinel hospitals and clinics (3000 pediatric and 2000 internal medicine clinics) report the number of ILI cases diagnosed with influenza weekly to local public health centers. Influenza is diagnosed using clinical criteria (sudden onset, high fever, upper respiratory tract inflammation, and general malaise or other systemic symptoms) or laboratory findings [14, 15]. ILI surveillance data were analyzed to assess trends in influenza activity and to estimate the number of influenza outpatients who visited medical institutions during the study period [15–19].

The National Institute of Infectious Diseases (NIID) is notified regarding the results of isolation/detection of infectious agents from prefectural and municipal public health institutes (PHIs). The NIID data are based on the laboratory identification done by PHIs for the respiratory specimens collected at sentinel clinics and hospitals under NESID and, occasionally, at nonsentinel sites and health centers. We collected these data on laboratory identification of influenza viruses in order to assess the predominant influenza type and influenza A virus subtypes in each season.

Ethics

According to the Guidelines for Epidemiological Studies established by the Ministry of Health, Labor, and Welfare and the Ministry of Education, Culture, Sports, Science, and Technology of Japan, this study did not require approval from an ethics committee [20]. Informed consent was not required from patients as NESID surveillance data analyses were performed in accordance with the Infectious Diseases Control Law.

RESULTS

Of the 385 IAE cases reported during the study period, 216 (56%) were male, and the median age at diagnosis was 7 years (range, 0–90; Supplementary Table 1). Influenza virus was the most frequently identified pathogen in acute encephalitis or encephalopathy cases reported among children and adults (Supplementary Figure 1). The majority (74%) of IAE cases were reported in children (Supplementary Table 1); the number of cases was highest among patients aged 5–12 years (n = 146, 38%), followed by those aged 2–4 years (n = 81, 21%) and 18–49 years (n = 41, 11%). Fever was the most commonly reported sign or symptom (n = 347, 90%), followed by seizure (n = 222, 58%), vomiting (n = 60, 16%), and CSF pleocytosis (n = 15, 4%). The overall case-fatality proportion (CFP) was 9% (36/385); for fatal cases (n = 36), the median duration from IAE onset to death was 1 day (range, 0–9).

The proportion of pediatric IAE cases associated with influenza B virus (n = 77, 81%) was higher than those associated with influenza A virus (n = 206, 71%), although this difference was not significant (P = .06; Supplementary Table 1). Among all IAE cases, the proportion with any signs and symptoms or CSF pleocytosis was not significantly different between those with influenza A virus compared to those with influenza B virus. The CFP was similar between IAE cases with influenza A (n = 26, 9%) and influenza B (n = 10, 11%, P = .69).

During the past 5 influenza seasons, the median number of IAE cases among all ages per season was 88 (range, 64–105). The reported numbers of IAE cases coincided with the epidemic

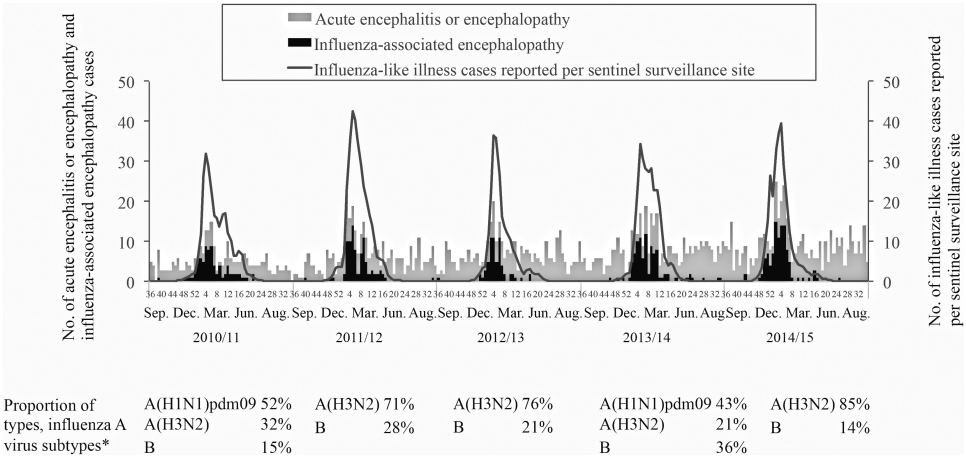

Figure 1. Epidemiologic curve of influenza-associated encephalopathy cases, influenza-like illness cases, and proportion of influenza A virus subtypes detected during each season in Japan, 2010–2015. Influenza-associated encephalopathy cases are shown by week of diagnosis in black; total cases of acute encephalitis or encephalopathy are shown in gray. A line graph indicates the number of influenza-like illness cases reported per sentinel surveillance site for the same period in Japan. *Proportion of influenza A virus subtypes and influenza B viruses identified by laboratory confirmation through prefectural and municipal public health institutes by season. The data are available on the website of the National Institute of Infectious Disease, Japan (http://www.nih.go.jp/niid/en/influenza-e.html).

curve of ILI cases reported per sentinel surveillance site (Figure 1). A(H3N2) virus predominated during the 2011–2012, 2012–2013, and 2014–2015 influenza seasons, while A(H1N1) pdm09 virus was most common during the 2010–2011 and 2013–2014 influenza seasons (Figure 1).

The incidence of IAE did not differ among regions throughout Japan (Supplementary Figure 2). The incidence of IAE was highest in children aged 2–4 years (3.8–6.0 cases per season per 1 000 000 population; Figure 2); after this age group peak, the incidence of IAE generally decreased with increasing age in children. Additionally, the incidence of IAE in adults was lower than that in children during each season. The incidence of IAE in children and adults did not differ by season, although the predominant influenza A virus subtype varied by season (Figures 1 and 2). The mean incidence of pediatric and adult IAE cases was 2.83 (standard deviation [SD], 0.52) and 0.19 (SD, 0.06) cases per season per 1 000 000 population, respectively.

Among the number of IAE cases per estimated patient visit for ILI by year (Supplementary Figure 3), patients aged <5 years (0.8–1.6 cases per estimated 100 000 ILI patient visits), 5–9 years (0.6–1.0 cases per estimated 100 000 ILI patient visits), and those aged ≥60 years (0.3–1.3 cases per estimated 100 000 ILI patient visits) had the highest rates.

The frequency of fever did not differ between pediatric and adult IAE cases (P = .42; Table 1). The frequency of seizures was significantly higher in children than in adults with IAE (66% vs 35%, P < .01). The proportion with seizures differed significantly among pediatric age groups (P < .01); seizures were most frequently reported in young children aged <2 years (n = 30, 91%), followed by those aged 2–4 years (n = 64, 79%). Neck stiffness was more

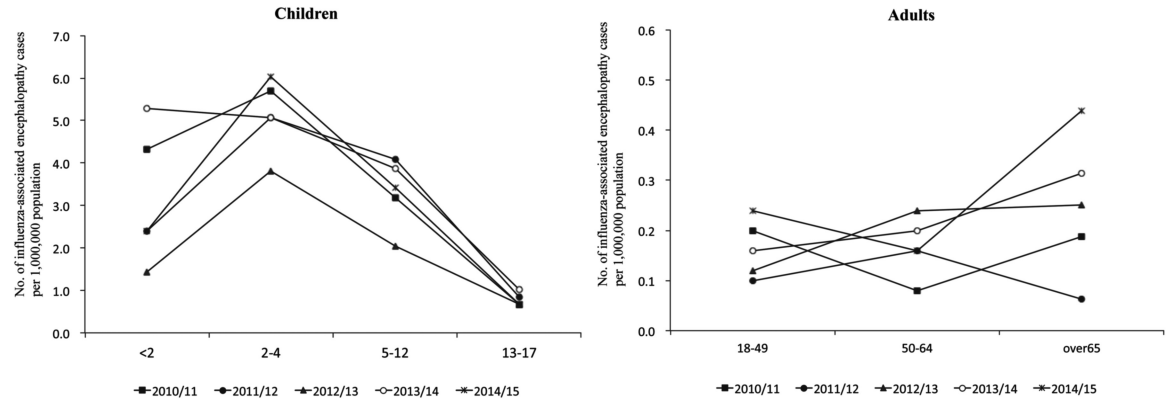

Figure 2. Age distribution of influenza-associated encephalopathy cases per 1 million population, 2010–2015. The population for each age group was based on national census data (http://www.stat.go.jp/data/jinsui/2.htm). A(H3N2) virus was predominant among influenza A virus subtypes in 2011–2012, 2012–2013, and 2014–2015. A(H1N1)pdm09 virus was predominant during 2010–2011 and 2013–2014.

Table 1. Signs and Symptoms of Influenza-Associated Encephalopathy Cases by Age Group and Outcome in Japan, 2010–2015

		Signs and Symptoms													
		Fever[a]			Seizures			Vomiting[b]			Neck Stiffness			Cerebrospinal Fluid Pleocytosis		
	N[c]	n	(%)	*P* Value	n	(%)	*P* Value	n	(%)	*P* Value	n	(%)	*P* Value	n	(%)	*P* Value
Age groups, y																
Children	283	253	89	–	186	66	–	43	15	–	2	1	–	4	1	–
<2	33	30	91		30	91[d]		2	6			0			0	
2–4	81	76	94		64	79[d]		8	10			0			0	
5–12	146	128	88		80	55[d]		30	21		2	1		4	3	
13–17	23	19	83		12	52[d]		3	13			0			0	
Adults	102	94	92	.42[e]	36	35	**< 0.01[e]**	17	17	.72[e]	8	8	**< 0.01[e,f]**	11	11	**< .01[e,f]**
18–49	41	37	90		15	37		9	22			0		7	17	
50–64	21	20	95		5	24		2	10		3	14		4	19	
≥65	40	37	93		16	40		6	15		5	13			0	
Outcome																
Fatal	36	34	94	–	17	47	–	10	28	–		0	–		0	–
Nonfatal	349	313	90	.36	205	59	0.18	50	14	**.03**	10	2	0.61[f]	15	4	.38[f]

[a]No significant differences in proportion with fever were identified among pediatric (*P* = .34) or adult (*P* = .78) age groups.
[b]No significant differences in proportion with vomiting were identified among pediatric (*P* = .06) or adult (*P* = .43) age groups.
[c]Number of influenza-associated encephalopathy cases.
[d]The proportion with seizures was significantly different among pediatric (*P* < .01), but not adult (*P* = .44), age groups.
[e]Comparison of the proportion of signs and symptoms and cerebrospinal fluid pleocytosis between pediatric and adult influenza-associated encephalopathy cases.
[f]Fisher exact test.

commonly reported in adults than in children with IAE (8% vs 1%, *P* < .01), especially those aged 50–64 (n = 3, 14%) and ≥65 (n = 5, 13%) years. CSF pleocytosis was more frequently reported among adults than children with IAE (11% vs 1%, *P* < .01; Table 1). The proportion of cases with vomiting did not differ between children and adults with IAE; however, vomiting was significantly higher among fatal (n = 10, 28%) than nonfatal IAE cases (n = 50, 14%, *P* = .03).

Of the 36 (9%) fatal IAE cases, more were reported among adults (n = 14, 14%) than among children (n = 22, 8%, *P* = .08), but was not significantly different (Table 2). Although the CFP did not differ significantly among adult IAE cases (*P* = .25), the CFP was highest among patients aged ≥65 years (n = 8, 20%), followed by those aged 50–64 years (n = 3, 14%). Since all 3 fatal cases in the 18–49 age group occurred among adults aged 40–49 years, the

Table 2. Number of Fatal Cases and Case-Fatality Proportion of Influenza A and Influenza B Virus-Associated Encephalopathy Cases, by Age Group in Japan, 2010–2015

	Influenza A and Influenza B			Influenza A		Influenza B		
	Fatal /Total	CFP[a]	*P* Value	Fatal /Total	CFP	Fatal /Total	CFP	*P* Value
Children (age in years)	**22/283**	**8**	–	**17/206**	**8**	**5/77**	**7**	**.62[b]**
<2	3/33	9[c]		2/26	8	1/7	14	
2–4	6/81	7[c]		5/63	8	1/18	6	
5–12	10/146	7[c]		8/103	8	2/43	5	
13–17	3/23	13[c]		2/14	14	1/9	11	
Adults	**14/102**	**14**	**.08[d]**	**9/84**	**11**	**5/18**	**28**	**.07[b,e]**
18–49	3/41[f]	7[c,g]		2/34	6	1/7	14	
50–64	3/21	14[c,g]		3/18	17	0/3	0	
≥65	8/40	20[c]		4/32	13	4/8	50	

Abbreviation: CFP, case-fatality proportion.
[a]CFP was defined as death at the time of report per number of reported influenza-associated encephalopathy (IAE) cases.
[b]Comparison of the proportion of influenza A and B virus infections among pediatric and adult IAE cases.
[c]CFP was not significantly different among age groups for pediatric (*P* = .76) or adult IAE cases (*P* = .25).
[d]Comparison of the proportion of fatal IAE cases between pediatric and adult age groups.
[e]Fisher exact test.
[f]All 3 patients who died among those aged 18–49 years were aged 40–49 years.
[g]CFP in patients aged 40–64 years was 17% (6/35).

CFP in those aged 40–64 years was 17% (6/35). The CFP was similar between pediatric IAE cases with influenza A compared with influenza B ($P = .62$). Although the CFP with influenza B (n = 5, 28%) was higher than for influenza A (n = 9, 11%) among adult IAE cases, this difference was not significant ($P = .07$).

DISCUSSION

In this study, we demonstrated differences in the clinical characteristics of IAE cases between children and adults. The frequency of seizures was significantly higher among young children aged <5 years than in adults, while CSF pleocytosis was more frequently reported among adults aged 18–49 and 50–64 years. Additionally, the highest case fatality proportion was in IAE cases aged ≥40 years. To our knowledge, this is the first study to compare the clinical characteristics and severity among adults and children with IAE reported through national surveillance.

Although CSF pleocytosis was rarely identified in children with IAE, CSF pleocytosis among adults with IAE has been described in case reports [21–23]. The numbers of CSF white blood cells (WBC) may increase following a seizure, intracranial hemorrhage, and/or some inflammatory conditions [24]. Previous studies have shown that influenza viral RNA from influenza has rarely been detected in the CSF of IAE patients by reverse-transcription polymerase chain reaction [25, 26]. Additionally, elevated cytokines (interleukin-6, -8, -10), caused by systemic inflammatory response syndrome triggered by influenza virus infection, have been hypothesized to play an important role in the pathogenesis of IAE [22, 27]. The pathogenesis of IAE in adults may be more likely to result in inflammation of the central nervous system than in children. Data on the total number of lumber punctures performed with CSF results, including other CSF abnormalities such as elevated protein, were not reported through the NESID. Therefore, additional studies are required to understand the higher frequency of CSF pleocytosis among adults than pediatric IAE cases.

While the CFP was not significantly different between pediatric and adult IAE cases, the highest CFP was observed in those aged ≥65 years. Previous case reports and case series have reported some fatal cases among adults aged <40 years with IAE [10, 22, 28–31]. Among children with IAE, the CFP was similar for influenza A and B virus infections. However, a higher CFP was observed in adult IAE cases with influenza B than influenza A. Although this difference was not statistically significant, it highlights the often-overlooked severity of influenza B virus complications in older adults.

From 1997 through 2002, the CFP for pediatric IAE cases was estimated to be approximately 30% in Japan [2, 32]. Hoshino et al conducted a nationwide survey of the pediatric departments at 520 hospitals from 2007 through 2010 and reported that the CFP for pediatric IAE cases had decreased to approximately 7% [1]. This was consistent with the CFP of 8% among pediatric IAE cases in our study. National guidelines for management of IAE in children, which were published in 2005 [33] and 2009, emphasized the importance of supportive care including control of seizures, intracranial hypertension, and high temperature and therapies such as high-dose pulse corticosteroids and antiviral treatment. These guidelines might have contributed to improved outcomes in children.

In our study, the incidence of IAE was much higher in children than in adults (Figure 2). Glaser et al reported that during the 2009 H1N1 pandemic, the incidence of IAE among the Asian/Pacific islander population in California was estimated to be 5.48 cases among children and 0.27 cases among adults per 1 000 000 persons, respectively [34]. This higher IAE incidence among children is consistent with our findings in Japan after the 2009 H1N1 pandemic. Based on data from 3 influenza seasons, Britton et al reported a mean annual incidence of IAE of 2.8 per 1 000 000 persons among Australian children aged ≤14 years [35]. Although the estimated incidence of IAE among adults was low overall in our study, the rate of IAE cases per estimated number of ILI patient visits (Supplementary Figure 3) was high in young children and adults aged ≥60 years.

In response to the higher incidence of pediatric IAE cases observed from 2009 through 2010, Gu et al hypothesized that the pathogenesis of IAE caused by A(H1N1)pdm09 might be different from that caused by seasonal influenza viruses [5]. Another study conducted during the 2009 H1N1 pandemic reported that patients with A(H1N1)pdm09 infection were more likely to have IAE compared to those with seasonal influenza [36]. However, no differences in the pathophysiology between patients with IAE due to A(H1N1)pdm09 virus and those with IAE due to seasonal influenza viruses were identified in previous studies [13, 29, 30]. Although it remains unclear whether A(H1N1)pdm09 virus infection is associated with a higher risk of IAE compared to other influenza viruses, we did not observe any differences in the incidence of IAE among patients with the predominant subtypes of influenza virus infection each season.

Various studies have classified IAE into different clinical syndromes that vary by severity and outcomes [1, 37, 38]. The differences in clinical characteristics we described suggest that clinical syndromes may vary between adults and children with IAE. Additional analyses are required to characterize clinical syndromes among IAE cases of all ages with the findings of neuroimaging studies that were not available from the NESID. This higher severity among adult IAE cases is clinically important for selecting therapeutic strategies. The Japanese guidelines for management of pediatric IAE cases and increased awareness of IAE by pediatricians and parents may have contributed to improved survival of children with IAE over the past 15 years. The high mortality of IAE in older adults suggests that studies are needed in order to reduce the high mortality of IAE in adults.

There are several limitations of our study. There was a possibility of reporting bias; severe cases may have been more likely to be reported than mild encephalopathy cases by clinicians. Additionally, the clinical data and outcomes were collected at the time of reporting, and a follow-up report was not required when patients died or developed new clinical features after the initial notification. This might have led to underreporting of some clinical features and fatal outcomes among IAE cases. We were not able to collect data on disposition after hospital discharge, such as to a rehabilitation facility, or whether neurologic sequelae were present in survivors. Therefore, we may have underestimated the severity of IAE cases in survivors in all age groups by only analyzing the outcome of death. It is possible that IAE cases are more likely to be identified and reported in children than in adults because of high awareness of IAE by Japanese pediatricians and parents. If a clinician who provides care for an adult patient with IAE does not suspect influenza or perform influenza testing, an alternative etiology for IAE might be given. Therefore, it is possible that the reported number of IAE cases in adults is an underestimate of IAE cases that have occurred. We were not able to analyze data on influenza vaccination and therefore could not assess influenza vaccination coverage by age group or by outcome.

In the NESID, systematic testing for pathogens associated with encephalitis or encephalopathy is not required for reporting patients with acute encephalitis or encephalopathy. While most patients with acute encephalitis or encephalopathy are tested for common etiologies such as Herpes simplex virus (HSV), reporting of laboratory testing methods that were performed is not mandatory. If HSV or another pathogen is detected in a patient with acute encephalitis or encephalopathy, it is reported through the NESID. For our analyses, we only included acute encephalitis or encephalopathy cases in which the only infectious pathogen reported was influenza virus. While coinfection with another cause of acute encephalitis or encephalopathy and misclassification remains possible, we believe that this was unlikely. Finally, the influenza virus subtypes, A(H3N2) and A(H1N1)pdm09, were not determined because the influenza A virus subtype identification was not required according to the notification criteria for IAE cases, and most Japanese healthcare providers use rapid influenza diagnostic tests that do not identify the influenza A virus subtype. Therefore, further investigation is needed to compare the relative clinical features and outcomes of IAE cases between influenza A(H3N2) and A(H1N1)pdm09 viruses.

In conclusion, our study of national surveillance data in Japan demonstrated differences in the clinical features and outcomes of IAE between adults and children. CSF pleocytosis was more frequently reported among adults with IAE. While the case fatality proportion was at least 7% in all age groups, mortality was higher in older adults, particularly those with influenza B virus infection. Education of physicians who provide care to adults with IAE is needed as are efforts to prevent and improve survival of patients with IAE, especially adults.

Supplementary Data

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

Notes

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Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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