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Burden of encephalitis-associated hospitalizations in the United States, 1998–2010

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ABSTRACT

Objective: To estimate the burden of encephalitis-associated hospitalizations in the United States for 1998–2010.

Methods: Using the Nationwide Inpatient Sample, a nationally representative database of hospitalizations, estimated numbers and rates of encephalitis-associated hospitalizations for 1998–2010 were calculated. Etiology and outcome of encephalitis-associated hospitalizations were examined, as well as accompanying diagnoses listed along with encephalitis on the discharge records. Total hospital charges (in 2010 US dollars) were assessed.

Results: An estimated 263,352 (standard error: 3,017) encephalitis-associated hospitalizations occurred in the United States during 1998–2010, which corresponds to an average of 20,258 (standard error: 232) encephalitis-associated hospitalizations per year. A fatal outcome occurred in 5.8% (95% confidence interval [CI]: 5.6%–6.0%) of all encephalitis-associated hospitalizations and in 10.1% (95% CI: 9.2%–11.2%) and 17.1% (95% CI: 14.6%–20.0%) of encephalitis-associated hospitalizations in which a code for HIV or a tissue or organ transplant was listed, respectively. The proportion of encephalitis-associated hospitalizations in which an etiology for encephalitis was specified was 50.3% (95% CI: 49.6%–51.0%) and that for which the etiology was unspecified was 49.7% (95% CI: 49.0%–50.4%). Total charges for encephalitis-associated hospitalizations in 2010 were an estimated \$2.0 billion.

Conclusions: Encephalitis remains a major public health concern in the United States. Among the large number of encephalitis-associated hospitalizations for which an etiology is not reported may be novel infectious and noninfectious forms of encephalitis. Associated conditions such as HIV or transplantation increase the risk of a fatal outcome from an encephalitis-associated hospitalization and should be monitored. *Neurology*® 2014;82:1–9

GLOSSARY

CI = confidence interval; **ICD-9-CM** = *International Classification of Diseases*, ninth revision, Clinical Modification; **IQR** = interquartile range; **NIS** = Nationwide Inpatient Sample; **RR** = rate ratio; **SE** = standard error; **WNV** = West Nile virus.

Encephalitis is an inflammatory process of the brain associated with neurologic dysfunction.^{1–4} Illness is generally severe and often requires hospitalization, with a case fatality rate of 5% to 30%.^{4–7}

Rapidly diagnosing the etiology of encephalitis and providing early treatment can improve outcomes.^{6,8–10} Infectious etiologies are identified more often than noninfectious etiologies.^{6,10–12} However, the clinical presentations of infectious and noninfectious encephalitides are often indistinguishable, and an etiology is not found in 40% to 80% of encephalitis cases.^{1,2,5,9,13–16} An improved understanding of encephalitis epidemiology could improve clinical management and public health.

During 1988–1997, an estimated 7.3 encephalitis-associated hospitalizations occurred annually per 100,000 persons in the United States, with approximately 1,400 deaths per year.¹⁷ Since then, several developments have likely affected encephalitis epidemiology in the United States. West Nile virus (WNV) emerged in the United States in 1999 and is the most important cause of epidemic

Supplemental data at
www.neurology.org

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encephalitis in North America.¹⁸ Immune-mediated encephalitides such as NMDA receptor antibody encephalitis are now recognized as being responsible for a greater burden of encephalitis than was previously thought.¹⁹ Management of HIV infection, which increases susceptibility to certain etiologies of encephalitis, is improving.^{17,20} Meanwhile, tissue and organ transplantation are increasingly utilized therapies that can increase encephalitis risk through medication-induced immunosuppression and, although rare, through transmission of pathogens.^{21–24}

To evaluate the burden of encephalitis in the United States, we analyzed hospital discharge data listing encephalitis during 1998–2010.

METHODS **Data source.** Hospital discharge data with an encephalitis diagnosis were analyzed retrospectively for the US general population using the Nationwide Inpatient Sample (NIS) for 1998–2010.^{25,26} The NIS is a nationally representative database of hospitalizations created by the Healthcare Cost and Utilization Project. It is the largest all-payer inpatient database in the United States, and it includes a 20% sample of US community hospitals from up to 45 states and approximates 20% of all US community hospitals. Hospitals are short-term, nonfederal general and specialty hospitals selected based on 5 sampling strata and once selected include 100% of their hospitalizations. The full NIS includes approximately 8 million unweighted hospitalizations per year.

Standard protocol approvals, registrations, and patient consents. Because use of this dataset specifically prohibits re-identification of patients, data are not individually identifiable per Health and Human Services Office for Human Research Protections guidance; therefore, this analysis was not considered to involve human subjects and was not subject to Institutional Review Board review requirements.

Definitions. An encephalitis-associated hospitalization was defined as a hospital discharge record with an *ICD-9-CM* code for encephalitis listed among the 15 diagnoses on that record.²⁷ The encephalitis *ICD-9-CM* codes included in the study are listed in table e-1 on the *Neurology*[®] Web site at www.neurology.org.^{27,28}

Encephalitis-associated hospitalizations were considered as having a specified etiology if the diagnosis belonged to one of the following cause-specific disease categories: “viral,” “other infectious,” “postimmunization,” “postinfectious,” “toxic,” or “other specified.” Encephalitis-associated hospitalizations of unspecified etiology lacked a cause-specific encephalitis diagnosis. While some discharge records listed more than one encephalitis *ICD-9-CM* code, the specified and unspecified etiologic categorizations were considered mutually exclusive.

Encephalitis-associated hospitalizations of persons infected with HIV were identified using the following *ICD-9-CM* codes: 042 (“HIV disease”), V08 (“asymptomatic HIV infection status”), or 079.53 (“HIV, type 2”). Encephalitis-associated hospitalizations of persons with a history of tissue or organ transplantation were identified using the following *ICD-9-CM* codes: 996.8 (“complications of transplanted organ”) or V42 (“organ or tissue replaced by transplant”).

Data analysis. Robust national estimates of the number of encephalitis-associated hospitalizations were calculated from the NIS using the Healthcare Cost and Utilization Project weighting methodology.^{25,26,29} Standard errors (SEs) of hospitalization estimates were calculated using SUDAAN software to account for the sampling design of the NIS and were used to calculate 95% confidence intervals (CIs) for hospitalization rates.³⁰ If the relative SE of national estimates exceeded 0.30 or if the number of unweighted hospitalizations in a strata was <30, the estimates were considered unreliable and not presented. The unit of analysis was a hospitalization.

Encephalitis-associated hospital discharge records were examined by age group, sex, region of hospital location, and admission month.²⁶ Discharge records were also examined for accompanying diagnoses and fatal outcomes. Hospital length of stay and hospital charges (in 2010 US dollars) were assessed.³¹ Hospital charges include only facility fees; physician charges are not included.²⁶ Some discharge records had missing information on patient sex (0.18% [SE: 0.03%]), length of stay (0.45% [SE: 0.20%]), and hospital charges (2.52% [SE: 0.44%]); adjustments were not made for missing data.

Annual and average annual hospitalization rates with 95% CIs were expressed as the weighted number of hospitalizations per 100,000 persons of the corresponding population. Denominators were taken from the National Center for Health Statistics’ annual bridged race population estimates for the study period.^{32,33} Rate ratios (RRs) and 95% CIs were calculated for the comparison of rates between groups.³⁴ Age-adjusted rates with 95% CIs were calculated using the direct method, with the 2000 projected US population as the standard.³⁵ SUDAAN software was used to perform *t* tests to compare length of stay, to calculate the median with interquartile range (IQR) for length of stay and for hospital charges, and to calculate the proportion with 95% CI of hospitalizations by group.²⁶ A *p* value <0.05 was considered statistically significant. A weighted least-squares technique that accounted for the NIS sample design was used to test for linear trends in annual encephalitis-associated hospitalization rates for 1998–2010.³⁶

RESULTS During 1998–2010, an estimated 263,352 encephalitis-associated hospitalizations occurred in the United States (SE: 3,017) (table 1). This corresponds to an average of 20,258 (SE: 232) encephalitis-associated hospitalizations per year, or an average annual encephalitis-associated hospitalization rate of 6.9 per 100,000 persons (95% CI: 6.8–7.1). The average annual age-adjusted encephalitis-associated hospitalization rate was 6.9 (95% CI: 6.7–7.0) per 100,000 persons. A fatal outcome occurred in an estimated 15,182 hospitalizations (SE: 345), or 5.8% (95% CI: 5.6%–6.0%) of all encephalitis-associated hospitalizations during the study period.

The proportions of encephalitis-associated hospitalizations for which the etiology was specified and for which the etiology was unspecified were similar: 50.3% (95% CI: 49.6%–51.0%) and 49.7% (95% CI: 49.0%–50.4%), respectively. The average annual encephalitis-associated hospitalization rates of specified and unspecified etiology were 3.5 (95% CI: 3.4–3.6) and 3.4 (95% CI: 3.4–3.5) per 100,000 persons, respectively. The average annual age-adjusted encephalitis-associated hospitalization rates of specified

Table 1 Encephalitis-associated hospitalizations by disease category, United States

Encephalitis disease category ^a	No. of hospitalizations, 1998–2010 (SE)	Percent of overall encephalitis-associated hospitalizations, 1998–2010 (95% CI)	Percent of overall encephalitis-associated hospitalizations, 1988–1997 ^b
Specified etiology	132,396 (1,943)	50.3 (49.6–51.0)	40.5
Viral	53,588 (778)	20.3 (19.9–20.8)	15.5
Other specified	48,474 (901)	18.4 (17.9–18.9)	5.5
Other infectious	14,835 (903)	5.6 (5.0–6.3)	13.8
Postinfectious	14,542 (466)	5.5 (5.2–5.8)	5.3
Toxic	1,128 (82)	0.4 (0.4–0.5)	0.9
Postimmunization	555 (56)	0.2 (0.2–0.3)	<0.1
Unspecified etiology	130,957 (1,565)	49.7 (49.0–50.4)	59.5
Total	263,352 (3,017)	100	100

Abbreviations: CI = confidence interval; SE = standard error.

^aMore than one encephalitis diagnosis may be listed on each discharge record for an encephalitis-associated hospitalization.

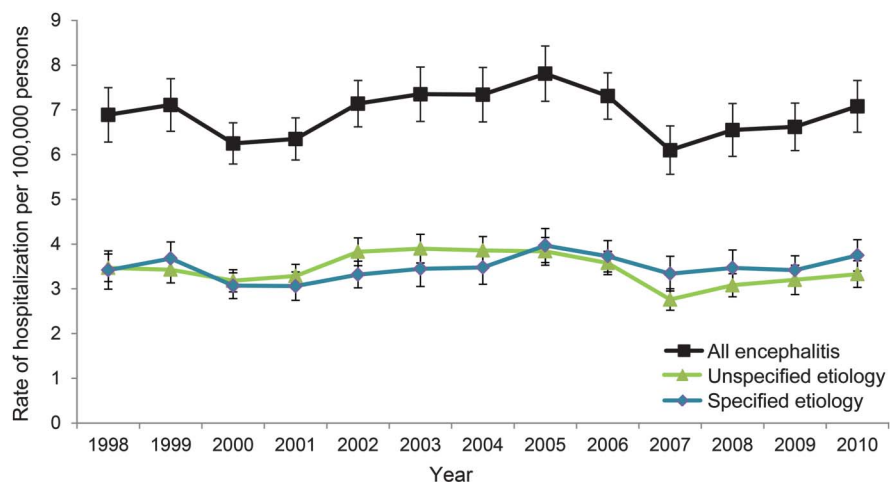
^bData source: Khetsuriani et al.¹⁷

and unspecified etiology were 3.5 (95% CI: 3.4–3.5) and 3.4 (95% CI: 3.3–3.5) per 100,000 persons, respectively. A fatal outcome occurred in 6.6% (95% CI: 6.3%–7.0%) of encephalitis-associated hospitalizations of specified etiology, compared with 4.9% (95% CI: 4.6%–5.2%) of those of unspecified etiology (RR: 1.4 [95% CI: 1.3–1.5], $p < 0.0001$).

Hospitalizations by year, sex, age group, geographic region, and season. The annual rates of encephalitis-associated hospitalizations varied with no apparent trend (figure 1); however, the rates of encephalitis-associated hospitalizations of unspecified etiology decreased during the study period ($p = 0.01$), while the rates for those of specified etiology increased

($p = 0.01$). The average annual rate of encephalitis-associated hospitalizations was higher for females compared with males (RR: 1.1 [95% CI: 1.1–1.1], $p < 0.0001$) (table 2). Persons aged 65 years or older had a higher encephalitis-associated hospitalization rate compared with persons younger than 65 years (RR: 2.2 [95% CI: 2.1–2.3], $p < 0.0001$). The West region of the country had the lowest rate of encephalitis-associated hospitalization of all regions ($p < 0.05$). No distinct seasonal trend could be identified for encephalitis-associated hospitalizations.

Viral causes of encephalitis. Among overall encephalitis-associated hospitalizations, 20.3% (95% CI: 19.9%–20.8%) were attributed to viral pathogens, making

Figure 1 Annual rates of encephalitis-associated hospitalizations, United States, 1998–2010

Annual rates of overall encephalitis-associated hospitalizations varied with no apparent trend. Annual rates of encephalitis-associated hospitalizations of unspecified etiology decreased ($p = 0.01$), whereas annual rates of encephalitis-associated hospitalizations of specified etiology increased ($p = 0.01$). Error bars represent 95% confidence intervals.

Table 2 Annual rates and numbers of encephalitis-associated hospitalizations by sex, age group, and region, United States, 1998–2010

Characteristic	Overall		Unspecified etiology		Specified etiology	
	Rate ^a (95% CI)	No. ± SE	Rate ^a (95% CI)	No. ± SE	Rate ^a (95% CI)	No. ± SE
Overall	6.9 (6.8–7.1)	263,352 ± 3,017	3.4 (3.4–3.5)	130,957 ± 1,565	3.5 (3.4–3.6)	132,396 ± 1,943
Sex						
Male	6.6 (6.4–6.7)	123,055 ± 1,613	3.4 (3.3–3.4)	62,773 ± 885	3.2 (3.1–3.3)	60,282 ± 1,046
Female	7.2 (7.1–7.4)	139,807 ± 1,698	3.5 (3.4–3.6)	67,865 ± 921	3.7 (3.6–3.8)	71,941 ± 1,118
Age, y						
<1	11.1 (10.1–12.1)	5,859 ± 269	3.7 (3.2–4.1)	1,946 ± 121	7.4 (6.6–8.2)	3,914 ± 206
1–4	4.7 (4.3–5.1)	9,759 ± 432	2.2 (2.0–2.4)	4,584 ± 230	2.5 (2.2–2.7)	5,175 ± 272
5–19	4.0 (3.7–4.2)	31,814 ± 1,089	2.0 (1.8–2.1)	15,656 ± 513	2.0 (1.9–2.2)	16,158 ± 687
20–44	5.7 (5.5–5.8)	76,650 ± 1,240	2.7 (2.6–2.8)	36,466 ± 610	3.0 (2.8–3.1)	40,184 ± 913
45–64	8.4 (8.1–8.6)	76,050 ± 1,061	4.3 (4.1–4.4)	38,869 ± 614	4.1 (3.9–4.2)	37,181 ± 702
≥65	13.2 (12.8–13.6)	63,063 ± 906	7.0 (6.7–7.2)	33,348 ± 641	6.2 (6.0–6.4)	29,715 ± 514
Region						
Northeast	7.1 (6.7–7.5)	49,901 ± 1,408	3.2 (3.0–3.4)	22,741 ± 678	3.8 (3.6–4.1)	27,159 ± 979
Midwest	6.9 (6.6–7.2)	58,829 ± 1,382	3.8 (3.6–3.9)	31,901 ± 788	3.2 (3.0–3.3)	26,928 ± 769
South	7.3 (7.0–7.6)	100,842 ± 1,932	3.6 (3.5–3.8)	50,257 ± 959	3.7 (3.5–3.9)	50,585 ± 1,296
West	6.2 (5.9–6.5)	53,781 ± 1,216	3.0 (2.8–3.1)	26,057 ± 670	3.2 (3.0–3.4)	27,724 ± 739

Abbreviations: CI = confidence interval; SE = standard error.

^aRate expressed per 100,000 persons of the corresponding population per year.

this the largest cause-specific disease category. Persons younger than 1 year followed by those aged 65 years or older had the highest rates of viral encephalitis-associated hospitalization. Herpetic meningoencephalitis accounted for 74.1% (95% CI: 73.0%–75.2%) of all viral encephalitis-associated hospitalizations (39,713 [SE: 613] hospitalizations during the study period) (figure 2). Infants younger than 1 year experienced the highest herpetic meningoencephalitis-associated hospitalization rate (5.6 [95% CI: 5.0–6.3] per 100,000 persons younger than 1 year). The next most common viral diagnosis was “other specified non-arthropod-borne viral encephalitis,” which was listed in 11.6% (95% CI: 11.0%–12.4%) of viral encephalitis-associated hospitalizations.

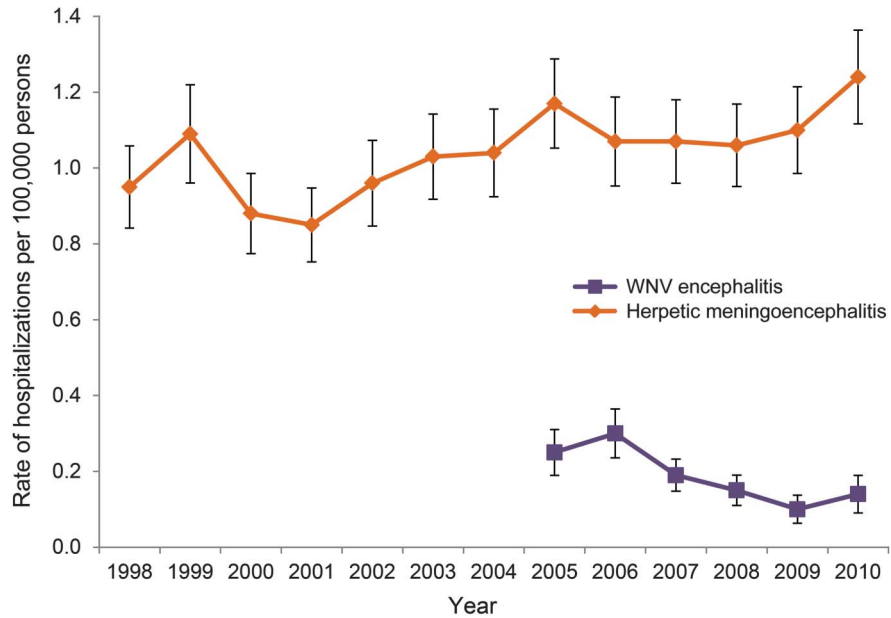
WNV encephalitis was the third most common viral encephalitis diagnosis, with 3,522 (SE: 192) hospitalizations during the study period (6.6% [95% CI: 5.9%–7.3%] of viral encephalitis-associated hospitalizations) (figure 2). Females had a lower average annual rate of hospitalization with WNV encephalitis compared with males (RR: 0.5 [95% CI: 0.4–0.6], $p < 0.0001$). The hospitalization rate for WNV encephalitis was higher among persons aged 65 years or older compared with those younger than 65 years (RR: 7.5 [95% CI: 6.1–8.9], $p < 0.0001$). The Northeast region had a lower rate of WNV

encephalitis-associated hospitalization than the Midwest, South, and West regions combined (RR: 0.3 [95% CI: 0.2–0.5], $p = 0.001$). The burden of WNV encephalitis was highest in August and September; 68.1% (95% CI: 64.0%–71.9%) of WNV encephalitis-associated hospitalizations occurred during these 2 months. A fatal outcome occurred in 8.0% (95% CI: 6.2%–10.2%) of WNV encephalitis-associated hospitalizations.

Other specified causes of encephalitis. The “other specified” disease category accounted for 18.4% (95% CI: 17.9%–18.9%) of overall encephalitis-associated hospitalizations, making this the second most abundant cause-specific disease category. This was the only cause-specific disease category for which females had a greater average annual rate of hospitalization compared with males (RR: 2.1 [95% CI: 1.9–2.2], $p < 0.0001$). The most common associated diagnosis within this category was systemic lupus erythematosus, listed in 42.3% (95% CI: 40.9%–43.7%) of these hospitalizations.

Other infectious causes of encephalitis. “Other infectious” causes of encephalitis accounted for 5.6% (95% CI: 5.0%–6.3%) of overall encephalitis-associated hospitalizations. *Toxoplasma* encephalitis was the most frequently listed diagnosis in this disease category (63.8% [95% CI: 59.3%–68.1%]),

Figure 2 Annual rates of herpetic meningoencephalitis-associated and West Nile virus encephalitis-associated hospitalizations, United States, 1998–2010



Data for West Nile virus (WNV) encephalitis-associated hospitalizations were not available prior to 2005. Annual rates of herpetic meningoencephalitis-associated hospitalizations increased ($p < 0.0001$), whereas annual rates of WNV encephalitis-associated hospitalizations decreased ($p < 0.0001$). Error bars represent 95% confidence intervals.

followed by “other encephalitis due to infection classified elsewhere” (18.4% [95% CI: 16.0%–21.1%]) and meningococcal encephalitis (12.0% [95% CI: 10.3%–14.0%]).

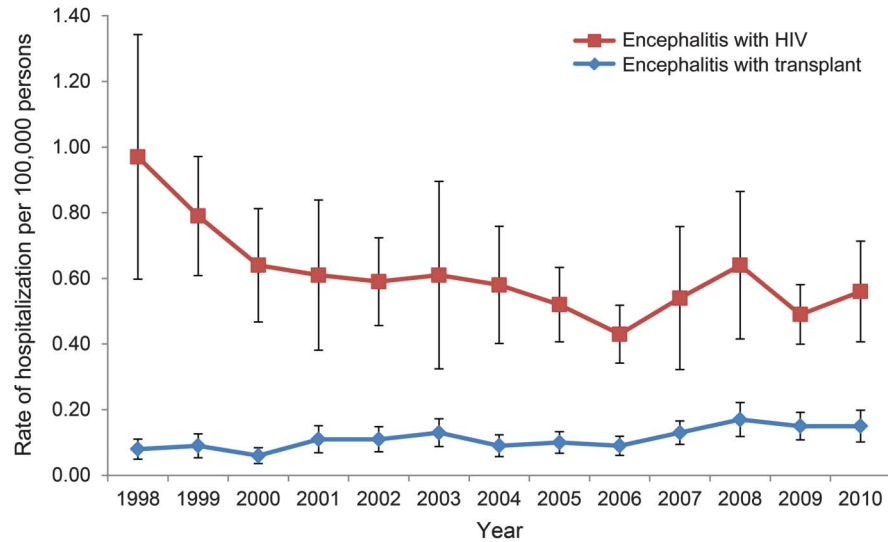
Postinfectious causes of encephalitis. The postinfectious disease category accounted for 5.5% (95% CI: 5.2%–5.8%) of overall encephalitis-associated hospitalizations. The “postinfectious encephalitis” diagnosis (*ICD-9-CM* codes 323.6, 323.61, and 323.62) accounted for the majority of hospitalizations in this disease category (90.3% [95% CI: 89.0%–91.4%]), followed by postvaricella (9.1% [95% CI: 8.0%–10.4%]).

HIV and transplantation. HIV was listed in 8.8% (95% CI: 8.1%–9.6%) of encephalitis-associated hospitalizations during the study period. The annual rates of encephalitis-associated hospitalizations in which HIV was and was not listed are shown in figures 3 and 4, respectively. The proportion of overall encephalitis-associated hospitalizations in which HIV was listed was similar for 1998–2001 (11.3% [95% CI: 9.7%–13.1%]) and 2007–2010 (8.5% [95% CI: 7.3%–9.8%]). The majority of encephalitis-associated hospitalizations with HIV were of specified etiology (66.6% [95% CI: 63.9%–69.3%]). The most common specified encephalitis diagnosis was toxoplasmosis (39.0% [95% CI: 34.8%–43.4%]) of encephalitis-associated hospitalizations with HIV, followed by herpetic meningoencephalitis (9.1% [95% CI: 8.1%–10.3%]) and “other specified causes of

encephalitis” (8.8% [95% CI: 7.8%–9.9%]). The majority of encephalitis-associated hospitalizations with HIV were for males (68.1% [95% CI: 66.3%–69.9%]) and for those aged 20 to 44 years (65.1% [95% CI: 63.4%–66.7%]). A fatal outcome occurred in 10.1% (95% CI: 9.2%–11.2%) of encephalitis-associated hospitalizations with HIV, compared with 5.3% (95% CI: 5.1%–5.6%) of those in which HIV was not listed (RR: 1.9 [95% CI: 1.7–2.1], $p < 0.0001$).

A transplant was listed in 1.6% (95% CI: 1.5%–1.8%) of encephalitis-associated hospitalizations during the study period. The annual rates of encephalitis-associated hospitalizations in which a transplant was and was not listed are shown in figures 3 and 4, respectively. The proportion of overall encephalitis-associated hospitalizations in which a transplant was listed increased from 1.3% (95% CI: 1.0%–1.5%) for 1998–2001 to 2.3% (95% CI: 2.0%–2.6%) for 2007–2010. The majority of encephalitis-associated hospitalizations with a transplant were of specified etiology (55.2% [95% CI: 51.6%–58.8%]). The most common specified encephalitis diagnosis was “other specified causes of encephalitis” (18.9% [95% CI: 16.3%–21.8%]) of encephalitis-associated hospitalizations with a transplant, followed by herpetic meningoencephalitis (17.6% [95% CI: 15.0%–20.6%]) and “other specified non-arthropod-borne viral encephalitis” (5.2% [95% CI: 3.7%–7.3%]). A fatal outcome occurred in 17.1% (95% CI: 14.6%–20.0%) of encephalitis-associated hospitalizations with a transplant,

Figure 3 Annual rates of encephalitis-associated hospitalizations in which HIV or a transplant was listed, United States, 1998-2010



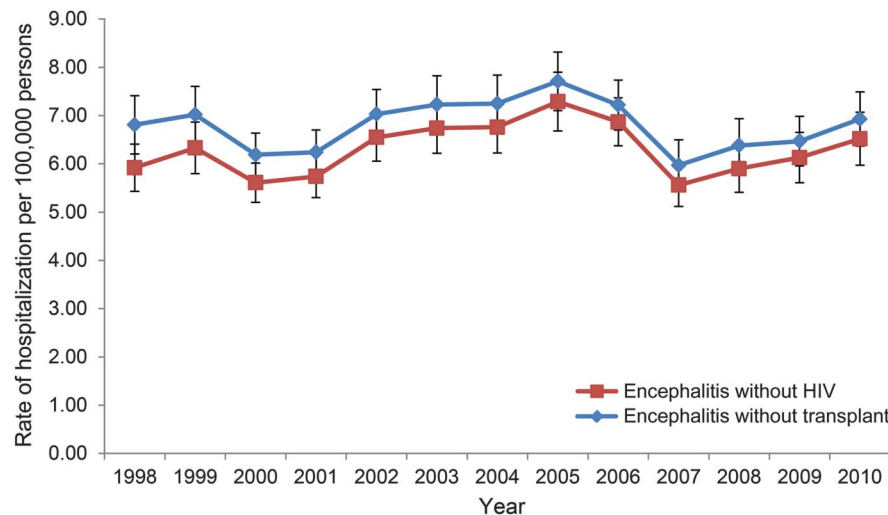
Annual rates of encephalitis-associated hospitalizations in which HIV was listed decreased ($p = 0.002$), whereas annual rates of encephalitis-associated hospitalizations in which a transplant was listed increased ($p < 0.0001$). Error bars represent 95% confidence intervals.

compared with 5.6% (95% CI: 5.4%–5.8%) of those in which a transplant was not listed (RR: 3.1 [95% CI: 2.6–3.6], $p < 0.0001$).

Hospital length of stay and charges. The mean encephalitis-associated hospitalization length of stay was 11.2 days (SE: 0.1; median: 6.4 days [IQR: 3.1–13.0 days]). The mean length of stay was shorter in 1998 (10.7 days [SE: 0.4]) compared with 2010 (12.6 days [SE: 0.4]) ($p = 0.0002$).

The median charge of an encephalitis-associated hospitalization was \$23,518 (IQR: \$11,733–\$52,427) in 1998 and \$48,852 (IQR: \$23,831–\$104,835) in 2010 (the median charge of a hospitalization from any cause was \$10,276 in 1998 and \$17,549 in 2010). The median charge of an encephalitis-associated hospitalization in 2010 of specified and of unspecified etiology was \$53,839 (IQR: \$25,594–\$118,828) and \$44,101 (IQR: \$22,119–\$94,352), respectively. The median charge

Figure 4 Annual rates of encephalitis-associated hospitalization in which HIV or a transplant was not listed, United States, 1998-2010



Rates of encephalitis-associated hospitalizations in which HIV or a transplant was not listed varied with no apparent trend ($p = 0.15$ and $p = 0.93$, respectively). Error bars represent 95% confidence intervals.

of an encephalitis-associated hospitalization in 2010 for WNV encephalitis and for herpetic meningoencephalitis was \$89,645 (IQR: \$58,094–\$225,496) and \$58,082 (IQR: \$29,650–\$114,644), respectively. The median charge of an encephalitis-associated hospitalization with a transplant in 2010 was \$96,455 (IQR: \$48,582–\$306,204). Total charges for encephalitis-associated hospitalizations in 2010 were an estimated \$2.0 billion.

DISCUSSION This study underscores the large burden of encephalitis in the United States. Annually, an estimated 20,258 encephalitis-associated hospitalizations occurred during 1998–2010. Nearly 6% of encephalitis-associated hospitalizations ended in a fatal outcome, compared with 1.9% for all hospitalizations within the NIS for 2010, attesting to the severity of encephalitis as a clinical entity.³⁷ Charges for encephalitis-associated hospitalizations, not including physician charges, were estimated at \$2.0 billion for 2010, with the median charge of an encephalitis-associated hospitalization in 2010 US dollars that more than doubled from 1998 to 2010.

The average annual rate of encephalitis-associated hospitalization during 1998–2010 appears similar to that reported for 1988–1997.¹⁷ The proportion of encephalitis-associated hospitalizations ending in a fatal outcome during 1998–2010 was lower than that for 1988–1997 (7.4%).¹⁷

Viral etiologies of encephalitis formed the largest cause-specific disease category in this study, as was the case for 1988–1997.¹⁷ As in other studies, herpesviruses were the most common group of viruses identified.^{3–5,16} This is consistent with the fact that they are one of the few etiologies of encephalitis for which there is an effective therapy, and thus they are among the most common pathogens tested for in patients with encephalitis. While WNV was listed in the NIS less frequently, it is notable because it emerged in the United States in 1999. The number of WNV encephalitis-associated hospitalizations might be underestimated by this study because a unique WNV encephalitis code was not created until 2004. Nevertheless, the trend in overall rate and patterns observed by sex, geography, age, and seasonality for WNV that we observed after 2004 were consistent with previously reported data.³⁸

Improvements in the management of HIV likely account for the decline in the proportion of overall encephalitis-associated hospitalizations that were listed with HIV from 1988–1997 to 1998–2010.^{17,20} The burden of *Toxoplasma* encephalitis-associated hospitalizations also decreased between these 2 time periods, similar to previous reports.²⁰ This may partially explain the decline in the percentage of overall encephalitis-associated hospitalizations attributed to the “other

infectious” disease category from 13.8% during 1988–1997 to 5.6% during 1998–2010.¹⁷ Despite these improvements, hospitalizations for encephalitis with HIV, as well as those with a tissue or organ transplant, were more likely to have a fatal outcome compared with hospitalizations without these conditions. This may reflect a decreased ability to overcome infection as a result of immunosuppression associated with HIV and transplantation. We also observed an increase in the rate of encephalitis-associated hospitalizations listing a transplant during the study period. While encephalitis can be challenging to diagnose in the transplant setting, this trend should be monitored given the growing use of tissue and organ transplantation.^{23,39}

Up to one-third of acute encephalitides with an identified etiology may be immune-mediated.² This study has limited ability to describe the burden of certain immune-mediated encephalitides because unique *ICD-9-CM* codes for many of these diseases do not exist. For instance, NMDA receptor antibody encephalitis does not have its own *ICD-9-CM* code, despite recent recognition that it may be a major cause of immune-mediated encephalitis.^{6,12} We suspect that immune-mediated encephalitis-associated hospitalizations are likely captured under the “other specified,” “postimmunization,” and “postinfectious” disease categories.^{1,17} Of note, more than 40% of encephalitis-associated hospitalizations of the “other specified” disease category also listed systemic lupus erythematosus, an important autoimmune disease. Furthermore, the percentage of overall encephalitis-associated hospitalizations listing an “other specified” disease category diagnosis increased from 5.5% during 1988–1997 to 18.4% during 1998–2010, which possibly reflects greater recognition and testing for immune-mediated encephalitides.¹⁷

Hospital discharge data for encephalitis, as used in this study, are a useful, inexpensive, and convenient tool for encephalitis surveillance.³ However, there are limitations. The data presented are for hospitalizations and not cases of encephalitis. In some instances, disease burden may have been overestimated because of nonspecific *ICD-9-CM* codes that included illnesses in addition to encephalitis (such as myelitis). Other diseases did not have a specific code and were therefore captured under a general code or were not included in the study at all. Furthermore, coding practices are not standardized.

Encephalitis remains a major health concern in the United States. Perhaps as a result of improvements in diagnostic technologies, there appeared to be fewer cases of encephalitis-associated hospitalizations that were of unspecified etiology in this study compared with 1988–1997 when the majority went unspecified (60%).^{1,2,8,17} Driven by forces such as globalization

and environmental alterations, it is highly likely that emerging infectious encephalitis such as WNV will continue to appear in the United States. Furthermore, segments of the population that are immunosuppressed will continue to be at risk for opportunistic encephalitis pathogens.^{10,40} Trends in encephalitis must therefore be monitored. In doing so, clinical management and public health interventions related to encephalitis will be enhanced.

AUTHOR CONTRIBUTIONS

Neil M. Vora drafted the manuscript, and all coauthors revised the manuscript. Statistical analysis was completed by Robert C. Holman and Jason M. Mehal. Data interpretation was performed by all authors. All authors gave final approval of the version to be published.

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