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**A Population Based Observational Study of Childhood Encephalitis in Children Admitted to Pediatric Intensive Care Units in England and Wales**

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## ABSTRACT

**Background:** Encephalitis is a serious neurologic condition which can result in admission to intensive care. Yet, there are no studies on pediatric intensive care unit (PICU) admission rates and usage of intensive care resources by children with encephalitis in England and Wales. The objectives of this study were to (i) define the PICU incidence and mortality rates for childhood encephalitis, (ii) describe usage of intensive care resources by children with encephalitis admitted to PICU, and (iii) explore the associated cost from PICU encephalitis admissions.

**Methods:** Retrospective analysis of anonymized data for 1031 children (0-17 years) with encephalitis admitted (January 2003 to December 2013) to PICU in England and Wales.

**Results:** The PICU encephalitis incidence was 0.79/100,000 population/year (95%CI 0.74-0.84), which gives an annual total of 214 bed days of intensive care occupancy for children admitted with encephalitis and an estimated annual PICU bed cost of £414,230 (IQR 198,111-882,495) for this cohort. PICU encephalitis admissions increased during the study period (annual percentage change = 4.5%, 95%CI 2.43%-6.50%,  $p < 0.0001$ ). In total, 808/1024 (78.9%) received invasive ventilation while 216/983 (22.0%) and 50/890 (5.6%) cases received vasoactive treatment and renal support, respectively. There were 87 deaths (8.4%), giving a PICU encephalitis mortality rate of 0.07 /100,000 population (0-17 years)/year (95%CI 0.05-0.08).

**Conclusions:** These data suggest that encephalitis places a significant burden to the healthcare service. More work is needed to improve outcomes for children with encephalitis.

**Keywords:** incidence, severe encephalitis, ADEM, intensive care, mortality, cost

## **Background**

Encephalitis is a syndrome of neurologic dysfunction due to inflammation of the brain parenchyma. The clinical course is variable and severe disease can occur, necessitating admission to intensive care. However, there are no studies reporting data for children with all-cause encephalitis admitted to intensive care in England and Wales.

A previous study of adults and children in England estimated the cost of encephalitis to the National Health Service (NHS) to be £40 million per year.<sup>1</sup> This estimate did not include associated costs from admission to intensive care. Data on usage of intensive care resources by children with encephalitis are necessary to complement existing data to fully understand the disease burden.

We describe a cohort of children with encephalitis admitted to pediatric intensive care in England and Wales during a 10-year period. We aimed to describe PICU encephalitis admission rate trends, incidence and mortality rates, and to explore usage of intensive care resources by children with encephalitis in England and Wales. In addition, we explored the associated bed cost from PICU encephalitis admissions.

## **Methods**

### ***Patient identification and datasets***

Data for patients (0-17 years) that had a documented diagnosis of encephalitis admitted to any of the 29 PICUs of the National Health Service (NHS) hospitals in England and Wales (January 1, 2003 to December 31, 2013) were obtained from the Paediatric Intensive Care Audit national network (PICANet) database. PICANet<sup>2</sup> includes demographic and clinical information on all children admitted to any PICUs in England and Wales. In PICANet, diagnoses are entered as primary (main reason for the admission) or secondary (additional diagnoses that may or may not

have required intensive care). Encephalitis cases were identified using the Clinical Terms 3 (Read) codes. A Read code is a five-character length code used to categorize each PICU admission and is mapped to the World Health Organization International Classification of Diseases (ICD-10) codes. A list of Read codes used in the database search is shown in (Table, Supplemental Digital Content 1, <http://links.lww.com/INF/D411>). Of the cases identified, only those that had the terms ‘encephalitis’, ‘encephalomyelitis’ or ‘meningoencephalitis’ in the diagnosis entered in PICANet were included in this study. Data available from PICANet included age on admission, sex, the need for and duration of invasive ventilation, renal support and vasoactive treatment, PICU length of stay, Pediatric Index of Mortality 2 (PIM2) scores on admission, and mortality (any patient death that occurred while in PICU or within one calendar month following discharge). The PIM2 score (0-100%) is used to predict the risk of mortality for patients admitted to PICU.<sup>3</sup>

#### ***Classification of cases and definitions***

Identified cases were assigned to five age groups: <1 year, 1-4years, 5-9years, 10-14years and ≥15years, and three main etiologic groups: ‘Infective’ if a causal pathogen featured in the diagnosis recorded in PICANet, ‘Immune-mediated’ if a known causal autoantibody target (e.g. N-methyl-D-Aspartate receptor (NMDAR) featured in the diagnosis or they had a diagnosis of a demyelinating form of encephalitis including acute disseminated encephalomyelitis (ADEM), and ‘Unspecified’ encephalitis if they did not meet either of these criteria.

Patients in the infective encephalitis group were further assigned to two main subgroups: viral and bacterial encephalitis. Only cases where a specific virus featured in the diagnosis were assigned to the viral encephalitis subgroup which comprised the three main etiologies:

Herpes Simplex Virus (HSV), enterovirus (EV) and Varicella Zoster Virus (VZV) encephalitis.

As described elsewhere,<sup>4</sup> length of stay on PICU was categorized into <1, 1 to <3, 3 to <7, 7 to <14, 14 to <28 and  $\geq 28$  days. PIM2 was categorized into five categories of risk: <1%, 1 to <5%, 5% to <15%, 15% to <30% and  $\geq 30\%$ .

### **Statistical analysis**

The population estimates of people (0-17 years) in England and Wales remained stable during the study period therefore the PICU encephalitis incidence and mortality rates were calculated using the mid-year (2008) population estimates (11.8 million) obtained from the Office of National Statistics database.<sup>5</sup> The annual percentage change (APC) in admissions during the study period was calculated by Poisson regression, where the  $APC = (\exp(\beta) - 1) \times 100$  and  $\beta$  represents the model coefficient for year. Descriptive statistics were used to report demographic data and clinical characteristics. Data on duration of invasive ventilation, vasoactive treatment, and renal support were not available for all patients. Where presented, the denominators for these outcomes represent the number of cases with available data that received each treatment. Skewed data were expressed as median and interquartile range (IQR). Pearson's chi-squared and Fisher's tests were used to compare categorical outcomes across the three main etiologic groups and between survivors and non-survivors. The Kruskal Wallis test was used to compare continuous variables across the main etiologic groups. The Wilcoxon-Mann-Whitney test was used to compare continuous variables between the viral and bacterial subgroups. The Wilcoxon-Mann-Whitney test was also used to compare average ADEM PICU incidence rates before (2003-2006) and after (2008-2013) publication of the consensus definition for ADEM in 2007.<sup>6</sup> The PICU encephalitis bed cost was calculated using an

estimated PICU bed day cost of £1932.<sup>7</sup> A significance level of 0.05 was chosen for testing statistical hypotheses. Data were analyzed using SPSS 22 and Graph pad prism 7.0.

### **Ethical approval**

Collection of personally identifiable data was approved by the Patient Information Advisory Group (now the NHS Health Research Authority Confidentiality Advisory Group).<sup>8</sup> Ethical approval was granted by the Trent Medical Research Ethics Committee, ref. 05/MRE04/17.

### **Results**

There were 1031 encephalitis cases (PICU incidence rate: 0.79/100,000/year (95% CI 0.74-0.84)). Encephalitis accounted for 0.58% of all PICU admissions in the study period (total number of admissions=178686). Trends in encephalitis PICU admissions and incidence are shown in (Fig., Supplemental Digital Content 2, <http://links.lww.com/INF/D412>) and Figure 1. Encephalitis PICU admissions varied by time period and increased (APC=4.5%, 95% CI 2.43% to 6.50%,  $p < 0.0001$ ) during the study period. Characteristics and outcomes for all cases are shown in (Table, Supplemental Digital Content 3, <http://links.lww.com/INF/D413>). The majority (567/1031; 55.0%) of cases were male. In total, 808/1024 (78.9%) encephalitis cases received invasive ventilation. The median duration of invasive ventilation (days) for the encephalitis cases that were ventilated (n=806) was 3.0 (IQR 2.0-5.0). Vasoactive treatment and renal support were required in 216/983 (22.0%) and 50/890 (5.6%) cases, respectively. The median PIM2 score (%) on admission was 3.3 (IQR 1.9-4.8), most cases (n=699, 67.8%) had a PIM2 score of 1-5% on admission.

We categorized cases into three main etiologic diagnostic groups: infective (n=202, 19.6%), immune mediated (n=83, 8.1%) and unspecified (n=746, 72.4%) encephalitis. A breakdown of the number of children by specific etiologic diagnosis is shown in Table 1. The proportion of



children with UNS encephalitis was highest across all age groups while the proportion of children with IMM encephalitis was lowest in the <1 year age group). The number of admissions assigned to the infective and immune mediated but not the unspecified encephalitis group increased during the study period: APC (infective) =9.97%, 95% CI 5.13%-15.03%,  $p<0.0001$  and APC (immune mediated) =18.77%, 10.30-27.89,  $p<0.0001$ . Summary statistics for each main etiologic diagnostic groups and comparison between these groups are shown in (Table, Supplemental Digital Content 3, <http://links.lww.com/INF/D413>). Children assigned to the infective encephalitis group were younger than those assigned to the immune and unspecified encephalitis groups. The median duration of invasive ventilation was longer for the immune mediated than the unspecified encephalitis group. The proportion of children that received renal support was higher in the immune encephalitis group than in the unspecified and infective encephalitis groups. PICU length of stay was longer for children in the immune mediated group than the infective and unspecified encephalitis groups. The median PIM2 score on admission was lower for children in the immune mediated encephalitis group than the unspecified and infective groups. There were no significant differences in the sex distribution, proportion of children that received invasive ventilation, and vasoactive treatment, and mortality across the main etiologic groups.

The documented specific diagnoses for the infective encephalitis group (n=202) include herpes simplex virus encephalitis (n=72, 35.6%), 'meningococcal encephalitis' (n=65, 32.2%), varicella zoster virus encephalitis (n=28, 13.9%), enteroviral encephalitis (n=12, 5.9%), malaria encephalitis (n=9, 4.5%), tuberculous encephalitis/meningoencephalitis (n=6, 3.0%), listeria encephalitis (n=4, 2.0%), influenza encephalitis (n=3, 1.5%), mumps encephalitis (n=2, 1.0%), and measles encephalitis (n=1, 0.5%). Cases in the infective encephalitis group were further

categorized into two main subgroups: viral (n=118/202; 58.4%) and bacterial (n=75/202; 37.1%). Children assigned to the viral encephalitis subgroup were younger than those assigned to the bacterial encephalitis subgroup (Table, Supplemental Digital Content 4, <http://links.lww.com/INF/D414>). There were no significant differences between children in the viral and bacterial encephalitis subgroups for the other outcomes of interest that were assessed (Table, Supplemental Digital Content 4, <http://links.lww.com/INF/D414>). There were no significant differences between the three main viral etiologies - HSV, VZV, EV (data not shown). The calculated average PICU incidence and mortality rates for the main viral etiologies are summarized in Table 2.

83 cases (8.1%) were assigned to the immune mediated group of which 74 (89.2%) had a diagnosis of ADEM, most of these (n=40, 54.1%) were male. This puts the PICU ADEM incidence in England and Wales at 0.06/100,000 population/year (95% CI 0.03-0.080.5-0.7). An increasing trend in the number of ADEM admissions was observed during the study period (APC=14.22%, 95% CI 5.23% to 23.86%, p=0.0014). Between 2003 and 2006, there were 13 ADEM admissions, giving an ADEM PICU incidence of 0.03/100,000/year (95% CI 0.01-0.05) in this period. Between 2008 and 2011, there were 56 ADEM admissions to PICU, giving an ADEM PICU incidence of 0.08/100,000/year (95% CI 0.04-0.12) during this period. The ADEM PICU incidence between 2008 and 2011 was significantly higher than between 2003 and 2006 (p=0.0190). There were 4 deaths (5.4%) in the ADEM group giving a mortality rate of 0.003/100,000 population/ year (95% CI 0.0009-0.008). The documented diagnoses for other cases in the immune mediated group included NMDAR encephalitis (n=4, 4.8%), Rasmussen's encephalitis (n=2, 2.4%), limbic encephalitis (n=1, 1.2%), Hashimoto's encephalitis (n=1, 1.2%), and 'autoimmune encephalitis' (n=1, 1.2%).

The median PICU length of stay (days) for all cases was 2.3 (IQR 1.1-4.9) with a mean of 4.66 (95% CI 4.1-5.1). Using a median length of stay of 2.3 days (IQR 1.1-4.9), and a population size of 11.8 million in England and Wales, a calculated PICU encephalitis incidence rate of 0.79/100,000/year equates to 214 bed days of intensive care occupancy per year for children admitted to PICU with encephalitis. Based on a PICU bed-day cost of £1932, we estimate a PICU encephalitis bed cost of £414,230 (IQR 198,111-882,495) per year for this cohort. Overall, there were 87 deaths (8.4%) in the studied cohort, which puts the PICU encephalitis mortality rate in England and Wales (0-17 years) at 0.07 /100,000/year (95% CI 0.05-0.08). Deaths in the encephalitis group accounted for 1.1% of all PICU deaths in the study period. A comparison between encephalitis patients that survived and those that did not is shown in Table 3 (for full Table, Supplemental Digital Content 5, <http://links.lww.com/INF/D415>). The proportion of children that received invasive ventilation, renal support, and vasoactive treatment was higher in the non-survivors compared with survivors. The duration of invasive ventilation and the PIM2 score on admission were longer in the non-surviving than the surviving group. There were no significant differences in age, sex distribution, main etiologic group split, and length of PICU stay between survivors and non-survivors.

## **Discussion**

To our knowledge, this is the first study to describe a cohort of children in an intensive care setting with all-cause encephalitis in England and Wales and to define incidence and mortality rates for this cohort. It is also the first study to show use of intensive care resources for the support of children with encephalitis in England and Wales. From our data, we estimate that the incidence and mortality rates for all-cause severe encephalitis in children 0 to 17 years of age in England and Wales are 0.79/100,000/year (95% CI 0.74-0.84) and 0.07/100,000/year (95% CI

0.05-0.08) respectively. Our data suggest a high use of intensive care resources by children with severe encephalitis and gives an insight to the disease burden.

In this study, an encephalitis diagnosis was made in 0.58% of all PICU admissions and mortality in children with a diagnosis of encephalitis accounted for 1.1% of all PICU deaths in the study period. The proportion of deaths in this study was 8.4%. These figures are relatively lower than was reported in a previous Hong Kong study of PICU encephalitis admissions in children<sup>9</sup> in which encephalitis admissions accounted for 2.7% and 11.8% of all PICU admissions and deaths respectively, and the proportion of deaths was 28%. The previous study was a single center study of children less than 12 years with a diagnosis of infective encephalitis. Furthermore, the catchment population in that study was 1.1 million of which approximately 25% were children less than 12 years. Thus, differences in methodology, and the size and structure of the sampling population may account for the relative differences in the proportion of deaths reported in the Hong Kong study and this study. Requirement for invasive ventilation and vasoactive treatment was higher in non-survivors than survivors, in keeping with a previous Hong Kong study.<sup>9</sup> This finding possibly reflects a more severe clinical course in non-survivors compared with survivors. However contrary to data from the same study,<sup>9</sup> we found no difference in the sex distribution of survivors and non-survivors.

The reason for increasing trend in all encephalitis admissions in this study is unknown.

The increasing number of ADEM admissions in this study reflects data from a previous study of encephalitis admissions in England.<sup>10</sup> Particularly, ADEM incidence for the period after publication of the consensus definition for ADEM (2008-2013) was significantly higher than for the period preceding this among children admitted to PICU. While this observation is likely to

reflect an increase in case recognition, the possibility that this increase was due to a true rise in the number of cases cannot be ruled out.

The findings in the ADEM cohort in this study are similar to previously reported data on ADEM PICU admissions in England and Wales<sup>11</sup> in terms of PICU ADEM incidence rate, age distribution, proportion of cases requiring invasive ventilation (including the duration of ventilation) and vasoactive treatment. The proportion of ADEM cases that were ventilated in our cohort is similar to the findings in an earlier ADEM PICU study in France.<sup>12</sup> The PICU ADEM mortality rate and proportion of deaths in this study are both two times lower than previously reported in England and Wales.<sup>11</sup> The proportion of deaths in the ADEM group in our cohort was 4.5 times lower than reported was reported in a previous French adult intensive care study.<sup>12</sup> The lower proportion of deaths in this study could reflect an improvement in outcomes for patients with ADEM due to timelier institution of immunomodulatory treatments as a result of earlier and improved case ascertainment with the more widespread use of MRI in the management of patients with suspected encephalitis. The higher mortality rate in the French ADEM study<sup>11</sup> could reflect the more severe disease course and poorer outcomes in adults than children with ADEM.<sup>13</sup>

Our study gives useful insight into the burden of severe encephalitis. Eighty percent of patients with a diagnosis of encephalitis admitted to PICU received invasive ventilation while 20% and 6% respectively received vasoactive treatment and renal support during the PICU admission. The overall cost implications of encephalitis is not known. In a study of PICU admissions in Spain,<sup>14</sup> the estimated mean fixed cost of an admission was \$608 per patient per day with a mean variable cost of approximately \$218 per patient per day. In another study of PICU admissions,<sup>15</sup> the mean incremental cost of mechanical ventilation was estimated at \$1,522 per day. Our estimated

annual PICU encephalitis bed cost does not take into consideration treatment costs and additional costs for procedures such as invasive ventilation and is therefore an underestimate of the PICU cost burden of encephalitis.

### **Limitations**

The strength of this paper is that it provides across-the-board data on encephalitis admissions to all PICUs in England and Wales during the study period. However, there are some limitations. Mapping of Read codes to WHO ICD 10 codes is not entirely straightforward and some encephalitis cases may have been missed. The data analyzed in this study were anonymized so it was not possible to account for multiple PICU admissions during the same hospitalization period which might contribute to an overestimation of the true PICU encephalitis incidence. Reported readmission rates to PICU are low, between 2 and 4%,<sup>18,19</sup> therefore a significant overestimation of PICU encephalitis incidence in this study is less likely.

We did not have access to clinical records or microbiologic results for our study cohort. This made it not possible to ascertain the specific etiologic diagnoses especially in the bacterial encephalitis/meningoencephalitis group that may well represent cases of meningitis and not encephalitis. However, we included them in the study since they met the inclusion criteria which was defined a priori. Classification of cases into the different etiologic groups was based on the diagnosis at the time of discharge. Since it is possible that a specific etiologic diagnosis could be reached after discharge from PICU as testing results become available, there is the possibility of misclassification, particularly for those in the unspecified encephalitis group.

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**Legend:**

**Figure 1:** Trends in the annual incidence of all-cause encephalitis admissions to pediatric intensive care (0-17years) in England and Wales

**Supplementary Digital Content 1:** Read codes used to search the PICANet database and their matching ICD 10 codes. (table)

**Supplementary Digital Content 2:** All-cause encephalitis admissions to pediatric intensive care (0 -17 years) in England and Wales (figure)

**Supplementary Digital Content 3:** Summary of baseline characteristics (table)

**Supplementary Digital Content 4.** Table showing comparison between viral and bacterial encephalitis groups (table)

**Supplementary Digital Content 5:** Comparison between PICU encephalitis survivors and non-survivors (table)

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Table 1: Number of children admitted to PICU with encephalitis by specific etiologic diagnosis and gender

	Male	Female	Total
Acute disseminated encephalomyelitis	40	34	74
Herps simplex virus encephalitis	43	29	72
Meningococcal encephalitis	40	25	65
Varicella encephalitis	15	13	28
Enteroviral encephalitis	6	6	12
Malaria encephalitis	5	4	9
Tuberculous encephalitis	4	2	6
Listeria encephalitis	2	2	4
N-methyl-D-aspartate receptor antibody encephalitis	3	1	4
Influenza encephalitis	1	2	3
Mumps encephalitis	1	1	2
Rasmussen's encephalitis	0	2	2
Measles encephalitis	1	0	1
Hashimoto's encephalitis	0	1	1
Limbic encephalitis	1	0	1
Autoimmune encephalitis	0	1	1
Unspecified encephalitis	404	342	746
Total	566	465	1031

Key: PICU=Paediatric intensive care unit

Table 2: PICU encephalitis incidence and mortality for the three main viral etiologies

	Herpes simplex virus encephalitis	Varicella zoster virus encephalitis	Enterovirus encephalitis
No. of admissions	72	28	10
PICU incidence rate (95% CI)	0.06/100,000/year (0.03 - 0.08)	0.02/100,000/year (0.01 - 0.03)	0.01/100,000/year (0.002 - 0.013)
No. of deaths	7	3	0
PICU mortality rate (95% CI)	0.005/100,000/year (0.003 - 0.008).	0.002/100,000/year (0.000 - 0.005)	0

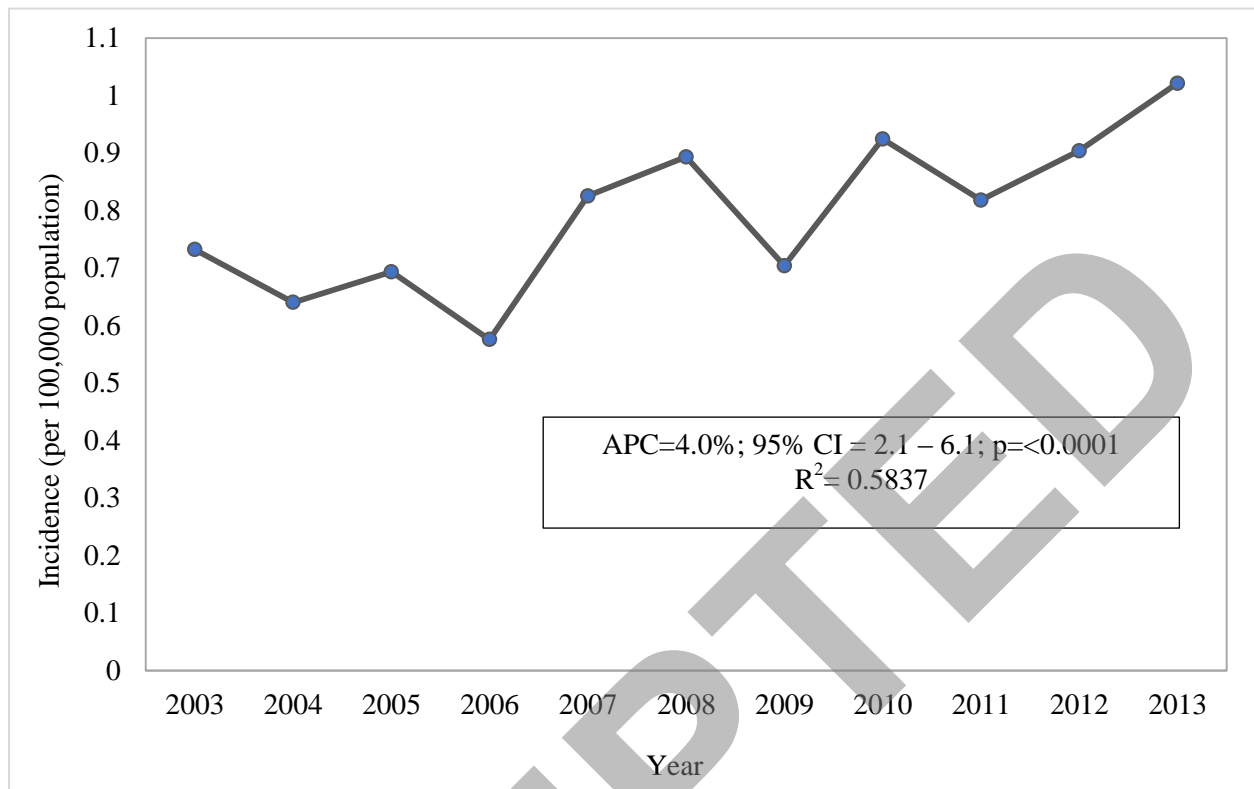
Key: Incidence and mortality rates are per 100,000 population aged 0-17 years in England and Wales. PICU=Paediatric intensive care unit

Table 4: Comparison between PICU encephalitis survivors and non-survivors

	Total	Survived (n=944, 91.6%)	Died (n=87; 8.4%)	P value (Pearson's chi squared)
Sex				0.4309
Male	567	523 (92.2)	44 (7.8)	
Female	464	421 (90.7)	43 (9.3)	
Age				0.3090
<1y	195	173 (88.7)	22 (11.3)	
1-4y	330	304 (92.1)	26 (7.9)	
5-9y	239	216 (90.4)	23 (9.6)	
10-14y	206	193 (93.7)	13 (6.3)	
15y+	61	58 (95.1)	3 (4.9)	
Main etiological group				0.2181
Infective	202	180 (89.1)	22 (10.9)	
Immune mediated	83	79 (95.2)	4 (4.8)	
Unspecified	746	685 (91.6)	61 (8.2)	
Invasive ventilation				<0.0001
Yes	808	726 (89.9)	82 (10.1)	
No	216	213 (98.6)	3 (1.4)	
Missing	7			
Renal support				0.0040
Yes	50	40 (80.0)	10 (20.0)	
No	840	779 (92.7)	61 (7.3)	
Missing	141			
Vasoactive treatment				<0.0001
Yes	216	161 (74.5)	55 (25.5)	
No	767	740 (96.5)	27 (3.5)	
Missing	48			
PIM2 category				<0.0001
<1%	96	94 (97.9)	2 (2.1)	
1 to <5%	699	670 (95.9)	29 (4.1)	
5 to <15%	180	160 (88.9)	20 (11.1)	
15 to <30%	19	13 (68.4)	6 (31.6)	
30%+	37	7 (18.9)	30 (81.1)	

Key: Data shown are total number (%). PICU= Pediatric intensive care unit; PIM2= Pediatric Index of Mortality score, second edition.

Figure 1: Trends in the annual incidence of all-cause encephalitis admissions to pediatric intensive care (0-17years) in England and Wales



Key: APC = annual percentage change in admissions during the study period, calculated using Poisson regression analysis; CI = confidence interval;  $R^2$  = goodness of fit measure for linear regression models.