Epidemiol. Infect. (2012), **140**, 753–764. © Cambridge University Press 2011
doi:10.1017/S0950268811001002

Trend of hospital utilization for encephalitis

P. BARBADORO*, A. MARIGLIANO, A. RICCIARDI, M. M. D'ERRICO AND E. PROSPERO

Department of Biomedical Science, Section of Hygiene, Preventive Medicine and Public Health, Università Politecnica delle Marche, Ancona, Italy

(*Received 4 May 2011; first published online 21 June 2011*)

SUMMARY

Encephalitis generally results in a serious illness requiring hospitalization. The aim of this study was to describe the epidemiology of hospitalization for encephalitis in Italy, taking into account the geographical distribution, aetiology, seasonality and evolution of hospitalization rates over recent years. The mean hospitalization rate was 5·88/100 000. For most of these hospitalizations ($n=13\,119$, 55·6%), no specific cause of encephalitis was reported. The most common aetiological category was 'viral', which accounted for 40·1% ($n=4205$) of such hospitalizations (rate 1·05/100 000). Within this category, herpes virus was the leading causative agent ($n=1579$, 0·39/100 000). This report highlights a significant increase of 'viral encephalitis not otherwise specified' (ICD-9 code 049·9) *vs.* a reduction of all other causes. A seasonal pattern was noted in people aged $\geqslant 65$ years in this group. Specific surveillance of encephalitis without known origin should be reinforced in order to identify the potential role of emerging pathogens and to design preventive interventions.

Key words: Encephalitis.

INTRODUCTION

Encephalitis is a brain inflammatory process associated with neurological dysfunction [1], caused by different processes: immune disorders, cancer, vascular disorders, and infectious diseases [2, 3]. Infectious encephalitis is mainly caused by viruses, such as herpes simplex virus (HSV) [4–7]. However, recent studies have reported the role of bacteria [8], fungi [9], and parasites [10]. Moreover, concern has been raised regarding the emergence or re-emergence of rare or unknown pathogens causing encephalitis during outbreak events [11–14]. Despite the availability of diagnostic tools, the aetiological origin of encephalitis remains undetermined in most patients [6, 14–19]. Encephalitis generally results in a serious illness requiring hospitalization. Severe encephalitic illness can lead to death, and survivors frequently experience ongoing neurological sequelae with important public health implications [20]. In Italy, encephalitis is not a notifiable disease, apart from viral meningoencephalitis, and data about incidence or clusters of this disease are not routinely available; thus, the occurrence of encephalitis is not well documented.

The aim of this study was to describe the epidemiology of encephalitis in Italy, in particular taking into account the geographical distribution, aetiology,

* Author for correspondence: Dr P. Barbadoro, Department of Biomedical Sciences, Section of Hygiene, Public Health and Preventive Medicine, Università Politecnica delle Marche, Piazza Roma 2, 60100 – Ancona, Italy.
(Email: p.barbadoro@univpm.it)

Fig. 1. Distribution of Italian Regions by ISTAT geographical areas.

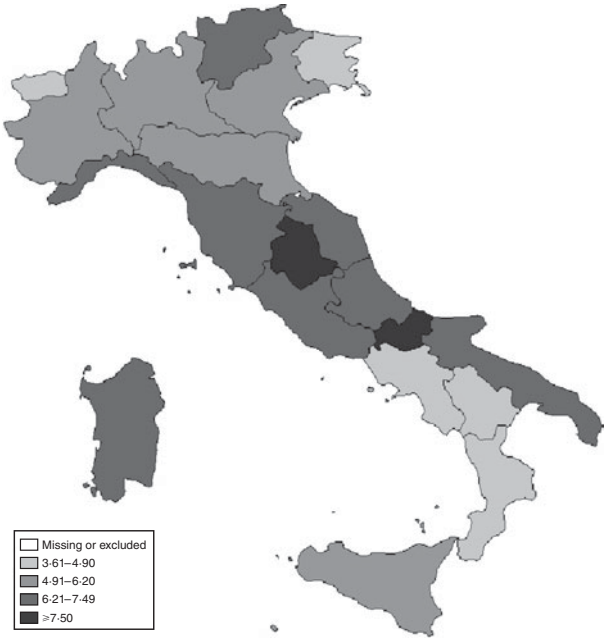

Fig. 2. Hospitalization rate (per 100 000) for all-cause encephalitis by region of residence, Italy, 1999–2005.

and evolution of hospitalization rates over recent years.

METHODS

Data source

Hospital discharge data from the National Hospital Discharge Database (http://www.salute.gov.it/ricoveriOspedalieri/ric_informazioni/sceltadia.jsp) were examined for the 7-year period 1999–2005. The National Hospital Discharge Database includes all the principal discharge diagnosis coded according to the International Classification of Diseases, 9th Revision – Clinical Modification (ICD-9-CM) for patients hospitalized in all the hospitals in Italy from 1999 to 2005. The data were grouped by region, sex and age group (<1, 1–14, 15–64, $\geqslant 65$ years); moreover, individual data about the date of admission and discharge were provided by the Ministry of Health.

Definition

An encephalitis-associated hospitalization was defined as a hospitalization for which one of the ICD-9-CM codes for encephalitis was listed as the principal discharge diagnosis. Encephalitis was classified into the following aetiological categories: 'viral', 'other infectious', 'post-immunization', 'post-infectious', 'toxic', 'other specified' and 'unknown' as previously done by Khetsuriani *et al*. [16].

Data analysis

Encephalitis-associated hospitalizations were analysed according to aetiological categories, year of discharge, patient's age and sex, geographical region (North-West, North-East, Center, South, Islands), and duration of hospital stay. The Italian regions were comprised as follows: North-West (Valle d'Aosta, Piemonte, Liguria, Lombardia); North-East (Trentino Alto Adige, Veneto, Friuli-Venezia-Giulia, Emilia-Romagna); Center (Toscana, Marche, Umbria, Lazio); South (Campania, Abruzzi, Molise, Basilicata, Puglia, Calabria), and the Islands (Sicilia, Sardegna). The distribution of Italian regions by geographical areas is shown in Figure 1. SaTScan™ software was then used for analysis of clusters on a regional basis [21, 22]. SaTScan™ employs Kulldorff's spatial scan statistic to identify and test clusters of encephalitis hospitalization. The scan statistic identifies the most likely (unusual) cluster. A Poisson model in SaTScan™ was used during the analysis. Hospitalization clustering was performed using purely spatial, temporal, and spatial–temporal scenarios separately. The maximum cluster size was set at the recommended value (50% of the total population at risk). For the analysis of clusters, regional distribution of cases was assessed. Moreover, the centroid of each of the 20 regions of Italy has been calculated

https://doi.org/10.1017/S0950268811001002 Published online by Cambridge University Press

Table 1. *Codes for encephalitis from the International Classification of Diseases, 9th Revision – Clinical Modification (ICD-9-CM); no. of total hospitalizations and rates × 100 000 population, in Italy from 1999 to 2005*

Category of encephalitis, aetiology, code	Diagnosis	Total no.	Rate per 100 000	95% CI
Known cause				
Viral				
045·0	Acute bulbar poliomyelitis	186	0·046	0·040–0·053
049·8	Other specified non-arthropod-borne encephalitides	553	0·138	0·127–0·150
052·0	Post-varicella encephalitis	743	0·185	0·172–0·199
054·3	Herpetic meningo-encephalitis	1579	0·393	0·374–0·413
056·01	Encephalomyelitis due to rubella	18	0·004	0·002–0·006
062·0	Japanese encephalitis	6	0·001	0·000–0·003
062·1	Western equine encephalitis	2	0·0005	0·0001–0·0018
062·2	Eastern equine encephalitis	2	0·0005	0·0001–0·0018
062·3	St Louis encephalitis	4	0·001	0·000–0·003
062·4	Australian encephalitis	0		
062·5	California virus encephalitis	1	0·0002	0·0000–0·0014
062·8	Other specified mosquito-borne viral encephalitis	41	0·010	0·007–0·014
063·0	Russian spring-summer encephalitides	26	0·006	0·004–0·009
063·1	Louping ill	3	0·001	0·000–0·003
063·2	Central European encephalitis	64	0·016	0·012–0·020
063·8	Other specified tickborne encephalitis	19	0·005	0·003–0·008
066·2	Venezuelan equine encephalitis	0		
071	Rabies	10	0·002	0·001–0·004
072·2	Mumps encephalitis	182	0·045	0·039–0·052
323·0	Encephalitis in viral diseases classified elsewhere	766	0·191	0·178–0·205
Other infectious				
013·6	Tuberculous encephalitis	110	0·027	0·022–0·032
036·1	Meningococcal encephalitis	44	0·011	0·008–0·015
090·41	Congenital syphilitic encephalitis	5	0·001	0·000–0·003
094·81	Syphilitic encephalitis	22	0·005	0·003–0·008
130·0	Toxoplasmic encephalitis	514	0·128	0·117–0·140
136·2	Meningoencephalitis due to *Naegleria* species	15	0·004	0·002–0·006
323·1	Encephalitis in rickettsial disease classified elsewhere	40	0·010	0·007–0·014
323·2	Encephalitis in protozoal disease classified elsewhere	26	0·006	0·004–0·009
323·4	Other encephalitides due to infection classified elsewhere	1313	0·327	0·310–0·345
Post-immunization				
323·5	Encephalitis following immunization procedures	290	0·072	0·064–0·081
Post-infectious				
055·0	Post-measles encephalitis	129	0·032	0·027–0·038
323·6	Post-infectious encephalitis	1544	0·385	0·366–0·405
Toxic				
323·7	Toxic encephalitis	181	0·045	0·039–0·052
Other specified				
323·8	Other causes of encephalitis	2037	0·507	0·485–0·529
Unknown causes				
323·9	Unspecified cause of encephalitis	8911	2·220	2·174–2·266
049·9	Viral encephalitis not otherwise specified	4019	1·001	0·970–1·033
062·9	Unspecified mosquito-borne encephalitis	16	0·004	0·002–0·006
063·9	Unspecified tickborne encephalitis	47	0·012	0·009–0·016
064	Viral encephalitis trasmitted by other and unspecified arthropods	126	0·031	0·026–0·037
Total		23 594	5·877	5·87–5·89

https://doi.org/10.1017/S0950268811001002 Published online by Cambridge University Press

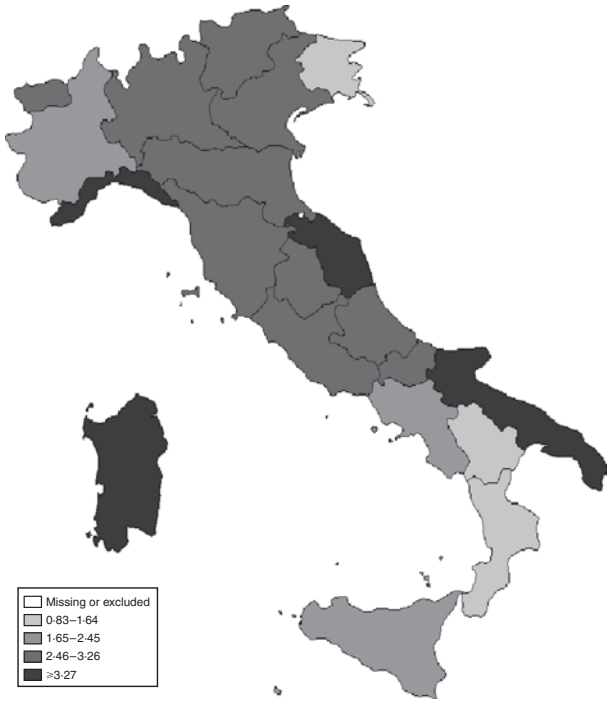

Fig. 3. Hospitalization rate (per 100 000) for known-cause encephalitis by region of residence, Italy, 1999–2005.

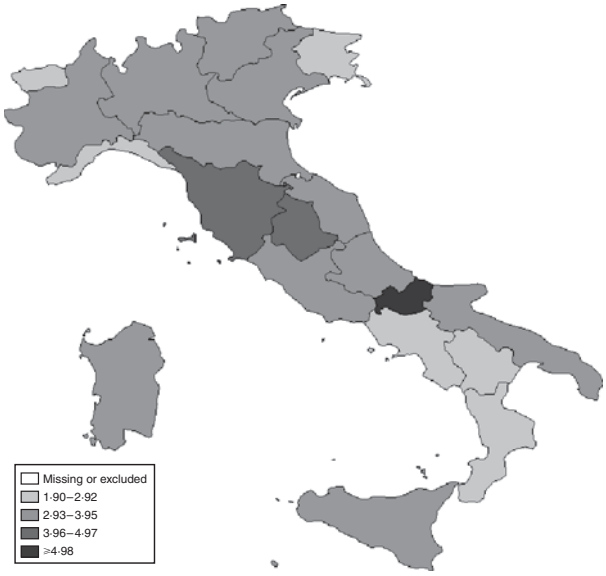

Fig. 4. Hospitalization rate (per 100 000) for unknown-cause encephalitis by region of residence, Italy, 1999–2005.

and its coordinates have been used as reference position for each geographical entity.

Hospitalization rates were calculated by use of denominators derived from the Italian National Institute of Statistics (http://demo.istat.it/). Rates were expressed as the estimated number of hospitalizations per 100 000 population. Confidence intervals were calculated by using Poisson approximation. The Cochrane–Armitage test for trend was used to assess the significance of variation of hospitalization rates over the years. In order to evaluate seasonality and trend of recorded rates, time-series analysis (TSA) was performed by calculating the weighted moving average and the estimated trend after exponential smoothing. The data were analysed using an additive model where the observed hospitalization rates were considered to be the sum of three independent components: seasonal, trend, and the remainder. Decomposition of seasonal trends was performed using R software. R is an open source project that is distributed under the GNU General Public License. For analysis, the 'ast' package was used [23–25]. The individual data (showing date of admission) were not available for the years before 2001, because of the lack of specific data from the Ministry of Health. Level of significance was set at 0·05.

RESULTS

From 1999 to 2005, encephalitis accounted for 23 594 hospitalizations in Italy. The average annual rate of encephalitis hospitalization was 5·88/100 000 population (95% CI 5·87–5·89). The total number and hospitalization rate for each ICD-9-CM code included in the analysis are listed in Table 1. The annual rate for total hospitalizations (per 100 000) was significantly higher for men than for women (Table 2) both for all-cause (average rate 6·43, 95% CI 6·32–6·54 in men *vs.* 5·35, 95% CI 5·25–5·45 in women), unknown cause (3·57, 95% CI 3·49–3·66 in men *vs.* 2·98, 95% CI 2·91–3·06 in women) and known cause (average rate 2·86, 95% CI 2·79–2·92 in men *vs.* 2·37, 95% CI 2·30–2·44 in women) encephalitis. The highest incidence was found in infants (10·09/100 000, 95% CI 9·04–11·06), this higher incidence was found both for known and unknown causes. Incidence rate in infants was followed by people aged ⩾65 years with a 7·97/100 000 (95% CI 7·77–8·17) hospitalization rate. People living in the Centre had the highest rate (6·85, 95% CI 6·67–7·04) especially for unknown cause (3·92, 95% CI 3·78–4·06). Regional distribution of hospitalization for encephalitis (all cause, known cause, unknown cause) is showed in Figures 2–4, respectively. Satscan software analysis has highlighted different clusters of hospitalization. For post-infective encephalitis, a high rate of clustering was detected during 2000–2002 in the Liguria region

https://doi.org/10.1017/S0950268811001002 Published online by Cambridge University Press

Table 2. *Encephalitis-associated hospitalizations by sex, age group and region, National Hospital Discharge Data, Italy, 1999–2005*

	No. of hospitalizations, by category of encephalitis					
	All cause		Unknown cause		Known cause	
Variable	No. per 100 000 population (95% CI)	Total no. ± S.E.	No. per 100 000 population (95% CI)	Total no. ± S.E.	No. per 100 000 population (95% CI)	Total no. ± S.E.
Sex						
Male	**6·43 (6·32–6·54)**	12 518 ± 718	**3·57 (3·49–3·66)**	6955 ± 290	**2·86 (2·79–2·92)**	5450 ± 207
Female	5·35 (5·25–5·45)	11 076 ± 560	2·98 (2·91–3·06)	6164 ± 235	2·37 (2·30–2·44)	4827 ± 161
Age group, years						
<1	**10·09 (9·04–11·06)**	379 ± 62	**4·66 (4·01–5·39)**	175 ± 61	**5·43 (4·72–5·22)**	204 ± 77
1–14	7·04 (6·82–7·)	3759 ± 430	2·97 (2·83–3·12)	1585 ± 117	4·01 (3·84–4·18)	2174 ± 188
15–64	5·00 (4·92–5·08)	13474 ± 580	2·88 (2·82–2·94)	7777 ± 250	2·11 (2·06–2·17)	5697 ± 159
⩾65	**7·97 (7·77–8·17)**	5982 ± 613	4·77 (4·62–4·93)	3582 ± 283	3·20 (3·07–3·33)	2400 ± 154
Region						
North-East	5·49 (5·32–5·66)	4115 ± 343	2·98 (2·86–3·11)	2235 ± 139	2·51 (2·40–2·63)	1880 ± 102
North-West	5·93 (5·78–6·08)	6249 ± 468	3·11 (3·00–3·22)	3280 ± 178	2·82 (2·72–2·92)	2969 ± 153
Centre	**6·85 (6·67–7·04)**	5267 ± 495	**3·92 (3·78–4·06)**	3017 ± 215	2·92 (2·80–3·04)	2250 ± 138
South	5·30 (5·16–5·45)	5188 ± 382	2·98 (2·97–3·09)	2915 ± 159	2·32 (2·23–2·42)	2273 ± 110
Islands	5·98 (5·76–6·21)	2775 ± 313	3·60 (3·45–3·78)	1672 ± 147	2·38 (2·24–2·52)	1103 ± 78

Bold values indicate significant at $P<0·05$.

[rate 1·3/100 000; relative risk (RR) 3·28, $P<0·001$]. In particular measles virus was responsible for a cluster of encephalitis hospitalizations in Basilicata, Puglia, Campania, Molise, Calabria, Abruzzi, and Lazio during 2002–2003 (rate 0·2/100 000, RR 15·57, $P<0·001$). Chickenpox was responsible for a cluster of encephalitis hospitalizations in Puglia in 2001–2002 (rate 0·6/100 000, RR 3·56, $P<0·001$). As for hospitalizations of unknown cause, high rate clustering was detected in 2003–2005 in Umbria, Marche, Abruzzi, Toscana and Lazio (rate 4·1/100 000, RR 1·28, $P<0·001$). In particular, regarding 'viral encephalitis not otherwise specified', high rate clustering was detected during 2003–2005 in Emilia-Romagna, Umbria, Marche, Toscana, and Liguria in people aged ⩾65 years with a rate of 0·5/100 000 (RR 2·08, $P<0·001$). For most of these hospitalizations ($n=13\,119$, 55·6%), no specific cause of encephalitis was reported (3·27 hospitalizations/100 000 population, 95% CI 3·26–3·28). Encephalitis with known cause accounted for 10 475 hospitalizations (44·4%), with an average of 1496 hospitalizations per year (rate 2·61/100 000 population, 95% CI 2·61–2·62). For hospitalizations associated with encephalitis of known cause, the most common aetiological category was 'Viral' (Table 3), which accounted for 40·1% ($n=4205$) of such hospitalizations. Within this category, herpes virus was the leading causative agent (1579 hospitalizations, 37·5%), followed by chickenpox virus (743 hospitalizations, 17·7%). Rates for encephalitis caused by the most frequent viral pathogens are detailed in Table 4. We observed a trend towards an increase in herpetic and post-varicella encephalitis; on the other hand there was a reduction in polio, mumps and post-measles encephalitis. Codes for other known infectious causes were noted for 19·9% of hospitalizations associated with encephalitis of known cause. The ICD-9 code 323·4 ('Other encephalitis due to infection classified elsewhere') accounted for most discharge diagnoses in this category ($n=1313$, 62·8%). Of the individual infectious causes, toxoplasmic encephalitis was the most frequent (514 hospitalizations, 24·6%) followed by tuberculosis (110 hospitalizations, 5·2%). Codes for 'Other specified encephalitis' and 'Post-infectious' were each noted in 19% ($n=2037$) and 16% ($n=1673$) of discharge diagnoses for hospitalizations associated with encephalitis of known cause, while post-immunization and toxic encephalitis accounted only for 2·8% and 1·7% of encephalitis-associated discharge diagnosis, respectively, in this category. The all-cause hospitalization rate (per 100 000) (Fig. 5)

https://doi.org/10.1017/S0950268811001002 Published online by Cambridge University Press

Table 3. *Encephalitis-associated hospitalizations (main diagnosis), by disease category, National Hospital Discharge Database, Italy, 1999–2005*

Category of encephalitis, aetiology	Hospitalizations (1999–2005)		
	Total no.	% of total	hospitalization rate per 100 000 population (95% CI)
Known cause	**10 475**	**44·4**	**2·61 (2·6–2·62)**
Viral	**4205**	**40·1**	**1·05 (1·05–1·05)**
North-East	868	20·6	1·16 (1·13–1·19)
North-West	1150	27·3	1·09 (1·07–1·11)
Centre	924	22	1·20 (1·17–1·23)
South	829	19·7	0·85 (0·83–0·87)
Islands	434	10·3	0·94 (0·90–0·98)
Other infectious	**2089**	**19·9**	**0·52 (0·52–0·52)**
North-East	281	13·4	0·38 (0·36–0·4)
North-West	518	24·8	0·49 (0·48–0·50)
Centre	374	17·9	0·49 (0·47–0·51)
South	671	32·1	0·69 (0·67–0·71)
Islands	245	11·7	0·53 (0·50–0·56)
Post-immunization	**290**	**2·8**	**0·07 (0·07–0·07)**
North-East	82	28·3	0·11 (0·10–0·12)
North-West	102	35·2	0·1 (0·09–0·11)
Centre	61	21	0·08 (0·07–0·09)
South	36	12·4	0·04 (0·04–0·04)
Islands	9	3·1	0·02 (0·01–0·03)
Post-infectious	**1673**	**16**	**0·42 (0·42–0·42)**
North-East	198	11·8	0·26 (0·25–0·27)
North-West	529	31·6	0·5 (0·49–0·51)
Centre	348	20·8	0·45 (0·43–0·47)
South	357	21·3	0·36 (0·35–0·37)
Islands	241	14·4	0·52 (0·49–0·55)
Toxic	**181**	**1·7**	**0·05 (0·05–0·05)**
North-East	16	8·8	0·02 (0·02–0·02)
North-West	46	25·4	0·04 (0·04–0·04)
Centre	47	26	0·06 (0·05–0·07)
South	36	19·9	0·04 (0·04–0·04)
Islands	36	19·9	0·08 (0·07–0·09)
Other specified	**2037**	**19·4**	**0·51 (0·51–0·51)**
North-East	430	21·1	0·57 (0·55–0·59)
North-West	620	30·4	0·59 (0·58–0·6)
Centre	491	24·1	0·64 (0·62–0·66)
South	341	16·7	0·35 (0·34–0·36)
Islands	155	7·6	0·33 (0·31–0·35)
Unknown cause	**13 119**	**55·6**	**3·27 (3·26–3·28)**
North-East	2235	17	2·98 (2·94–3·02)
North-West	3280	25	3·11 (3·08–3·14)
Centre	3017	23	3·92 (3·87–3·97)
South	2915	22·2	2·98 (2·95–3·01)
Islands	1672	12·8	3·6 (3·52–3·68)
Total	**23 594**	**100**	**5·88 (5·87–5·89)**

showed a trend towards reduction from 6·20 (95% CI 6·00–6·41) in 1999 to 5·88 (95% CI 5·68–6·08) in 2005 ($P<0·05$), a similar trend was observed for a reduction in encephalitis of known cause from 3·06 (95% CI 2·92–3·21) in 1999 to 2·50 (95% CI 2·37–2·63) in 2005 ($P<0·05$), while the hospitalization rate for unknown-cause encephalitis remained unchanged ($P>0·05$).

In Figure 6, the temporal trend of hospitalization rates for all-cause encephalitis by age is shown.

While hospitalization rates for all-cause encephalitis, and for known-cause encephalitis showed a declining trend in all age groups (except for people aged $\geqslant$65 years), hospitalization rates for unknown-cause encephalitis were quite stable in all age groups over time. TSA has indicated an aggregation of cases during the first 6 months of the year in the known-cause encephalitis group (Fig. 7), and a lack of a sound seasonality for hospitalizations of unknown cause (Fig. 8). The focus on hospitalizations of unknown cause highlighted a trend towards reduction ($P<0·001$) for 'unspecified cause of encephalitis' (ICD-9 code 323·9), conversely an increase ($P<0·001$) in 'viral encephalitis not otherwise specified' (ICD-9 code 049·9) was recorded. Therefore, the subsequent analysis of distribution of 'viral encephalitis not otherwise specified' (ICD-9 code 049·9) hospitalizations over time (Fig. 9), has shown a significant increase in people aged $\geqslant$65 years ($P<0·001$). Decomposition of hospitalization rates for ICD-9 code 049·9 has shown a seasonal pattern with peaks in January–March and July–August, that was particularly evident in people aged $\geqslant$65 years (Fig. 10). Overall, during the study period, 382 089 hospital days were associated with all-cause encephalitis, giving an average of 54 584 hospital days annually. The average hospital stay was $15\pm8·8$ days. Of these hospital days, 207 499 were associated with unexplained encephalitis (annual average 29 643 days), and 174 590 hospital days were associated with encephalitis of known cause (annual average 24 941 days). Hospitalizations associated with encephalitis of known cause had significantly longer average duration ($15·3\pm9·3$ days) than did hospitalizations associated with unknown cause ($13·3\pm3·5$ days, $P<0·001$).

DISCUSSION

The present study has analysed the epidemiology of hospitalizations caused by encephalitis in Italy during

https://doi.org/10.1017/S0950268811001002 Published online by Cambridge University Press

Table 4. *Rate of hospitalization per 100 000 inhabitants (95% CI) associated with most frequent viral encephalitis*

	1999		2000		2001		2002		2003		2004		2005		
Encephalitis (ICD-9 code)	No. (±S.E.)	Rate* (95% CI)	No. (±S.E.)	Rate (95% CI)	No. (±S.E.)	Rate (95% CI)	No. (±S.E.)	Rate (95% CI)	No. (±S.E.)	Rate (95% CI)	No. (±S.E.)	Rate (95% CI)	No. (±S.E.)	Rate (95% CI)	*P*†
Herpetic meningo-encephalitis (054·3)	1·35 (±2·7)	0·24 (0·20–0·28)	187 (±4·5)	0·33 (0·29–0·38)	268 (±7·70)	0·47 (0·42–0·53)	224 (±5·9)	0·39 (0·34–0·44)	254 (±7·1)	0·44 (0·39–0·50)	246 (±6·7)	0·42 (0·37–0·48)	265 (±7·4)	0·45 (0·40–0·51)	<0·01
Post-varicella encephalitis (052·0)	5 (±0·02)	0·01 (0·00–0·02)	75 (±1·14)	0·13 (0·10–0·16)	142 (±2·97)	0·25 (0·21–0·29)	148 (±3·16)	0·26 (0·22–0·30)	130 (±2·58)	0·23 (0·19–0·27)	141 (±2·89)	0·24 (0·20–0·28)	102 (±1·76)	0·17 (0·14–0·21)	<0·01
Acute bulbar poliomyelitis (045·0)	62 (±0·86)	0·11 (0·09–0·14)	53 (±0·68)	0·09 (0·07–0·12)	22 (±0·18)	0·04 (0·03–0·06)	15 (±0·10)	0·03 (0·02–0·05)	15 (±0·10)	0·03 (0·02–0·05)	9 (±0·05)	0·01 (0·00–0·02)	10 (±0·05)	0·02 (0·01–0·03)	<0·01
Mumps encephalitis (072·2)	72 (±1·07)	0·13 (0·10–0·16)	50 (±0·62)	0·09 (0·07–0·12)	29 (±0·27)	0·05 (0·03–0·07)	15 (±0·10)	0·03 (0·02–0·05)	7 (±0·03)	0·01 (0·00–0·02)	6 (±0·02)	0·01 (0·00–0·02)	3 (±0·01)	0·01 (0·00–0·01)	<0·01
Post-measles encephalitis (055·0)	8 (±0·04)	0·01 (0·00–0·02)	10 (±0·05)	0·02 (0·01–0·03)	3 (±0·01)	0·01 (0·00–0·01)	64 (±0·90)	0·11 (0·09–0·14)	38 (±0·41)	0·07 (0·05–0·09)	2 (±0·01)	0·01 (0·00–0·01)	4 (±0·01)	0·01 (0·00–0·02)	<0·01

* Rate per 100 000.

† Cochrane–Armitage test for linear trend.

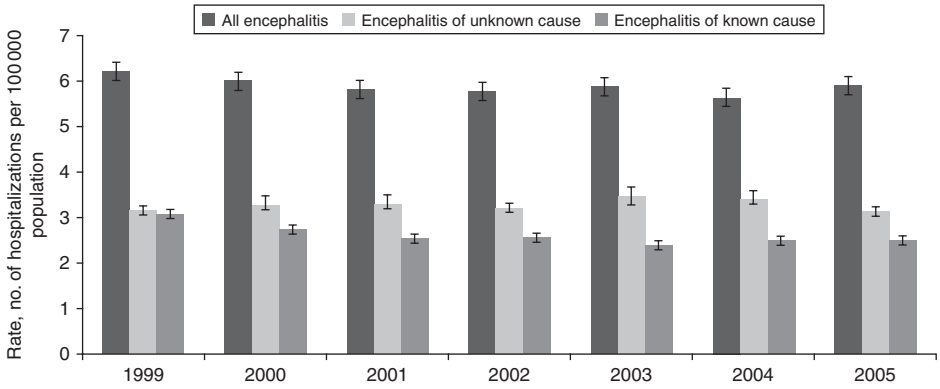

Fig. 5. Rates of hospitalization (per 100 000) associated with encephalitis, by year, according to data from the National Hospital Discharge Database, Italy, 1999–2005 (95% CI).

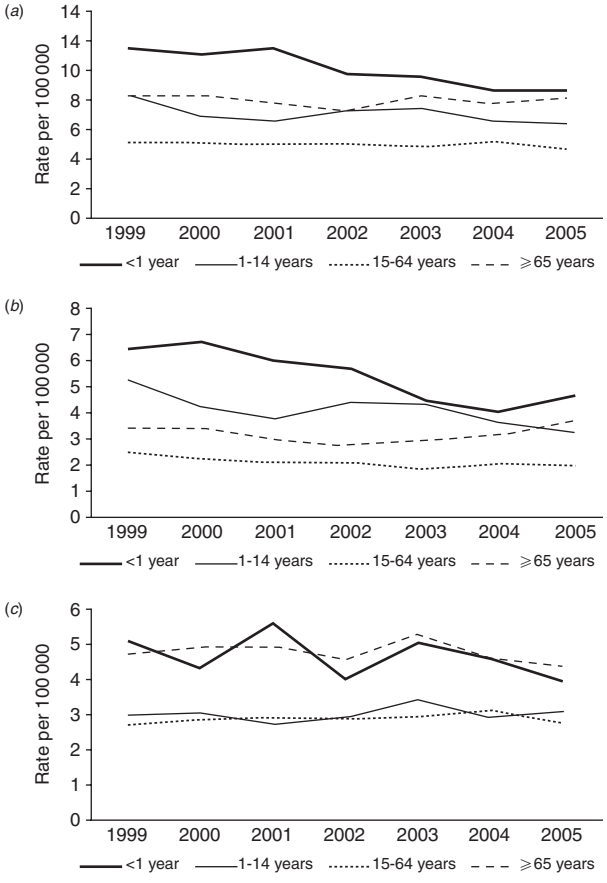

Fig. 6. Distribution of hospitalization rates (per 100 000) for encephalitis of (*a*) all-cause, (*b*) known cause and (*c*) unknown cause, by age group.

1999–2005. The overall hospitalization rate recorded in Italy is similar to that recorded in Australia [26], but lower to that recorded in the USA [16], possibly because the latter study also considered secondary discharge diagnoses. Men appeared to be at higher risk of encephalitis than women as previously reported [16, 26]. Regarding age group, infants had the highest frequency rate of hospitalization according to a report by Khetsuriani *et al.* [16]. Despite the importance of prompt diagnosis in order to implement the appropriate therapy [2] more than half of hospitalizations for encephalitis in Italy were of unknown cause. These data are in line with those of the Khetsuriani *et al.* study, who found no specific aetiology in 59·5% of cases [16]. Moreover, the California Encephalitis Study found that 63% of hospitalized patients with encephalitis had encephalitis of unknown aetiology, despite extensive laboratory testing [6]. Concerning viral encephalitis, our results are lower to those reported by Davison *et al.* from the UK with 1·5 cases/100 000 population [15]. In accord with other studies, our study shows the main role of herpetic virus as a cause of encephalitis [6, 15, 16, 26–28]. The average length of stay was longer in Italy compared to that reported by Khetsuriani *et al.* [16] Duration of hospitalization associated with encephalitis of known cause was significantly longer than that for unknown cause, similarly to that recorded in the USA [16].

Moreover, our report highlights the general decrease in all-cause encephalitis, and the reduction in encephalitis of known cause, and on the other hand, the increase in encephalitis of unknown cause, especially in the Centre of the peninsula. The recorded clusters indicate the outbreak caused by measles in the Campania region during 2002 [29]; the cluster recorded in Puglia might be linked to a particular form of chickenpox virus with strong tropism for the central nervous system isolated in the same year in Toscana [30].

https://doi.org/10.1017/S0950268811001002 Published online by Cambridge University Press

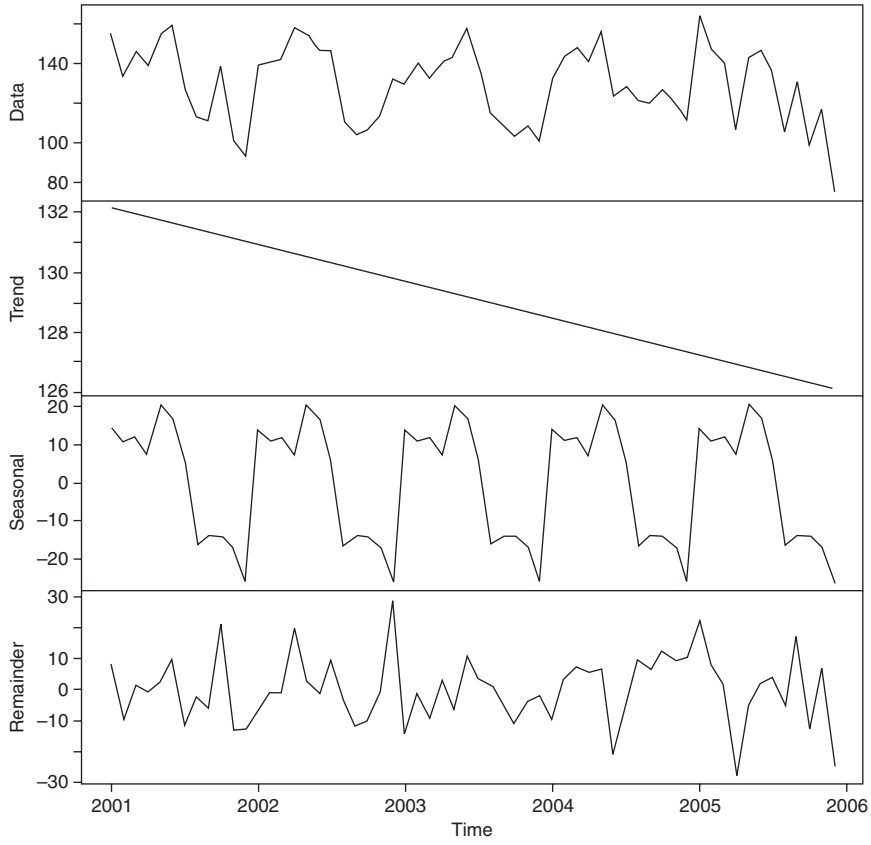

Fig. 7. Seasonal decomposition of the encephalitis hospitalizations (known cause) rate series for 2001–2005 by locally weighted scatterplot smoothing.

In accord with the findings of Khetsuriani *et al*., no clear seasonality for all-cause encephalitis hospitalizations was observed, while encephalitis of known cause occurred more often during the first 6 months of the year. The analysis of hospitalization with ICD-9 codes included in the unknown subgroup (i.e. codes 323·9 and 049·9) highlighted an important increase in hospitalization associated with 'viral encephalitis not otherwise specified' (ICD-9 code 049·9), *vs*. a reduction in 'unspecified causes of encephalitis' (ICD-9 code 323·9). Seasonal decomposition showed the possible role of an infectious aetiology, through clear spikes in January–March and July–August, especially in those aged $\geqslant$65 years. Therefore, this increasing trend of encephalitis of unknown cause suggests the hypotheses of the involvement of an unknown pathological agent, or the implication of usually identified causes that could be missed frequently. Moreover, in Italy, owing to its particular climate, geographical position, and political role in the Mediterranean area, exotic pathogens such as the Chikungunya virus in 2007 [31] and the West Nile virus in 2008 [32] have already been reported.

Some limitations of the study should be mentioned. First, the hospital discharge database may have some coding errors, even if a good quality of discharge data occurred in Italy over recent years; nevertheless, only principal discharge diagnoses have been included in the analysis, limiting the sensitivity of results. Second, the administrative hospital discharge database could not be relied upon to confirm that all coded encephalitis cases were acute. Third, ICD-9 codes do not cover all encephalitis cases; for instance they do not include coding for the novel forms of encephalitis such as autoantibody-associated cases. Despite the above limitations, the study of acute encephalitis has already underlined the emergence of multiple virulent pathogens [33]. There is growing evidence that an increasing number of viruses can cause encephalitis in humans. For this reason it might be important to make efforts to identify whether uncommon infectious agents are involved in unexplained causes of encephalitis. Our findings raise some questions: might

https://doi.org/10.1017/S0950268811001002 Published online by Cambridge University Press

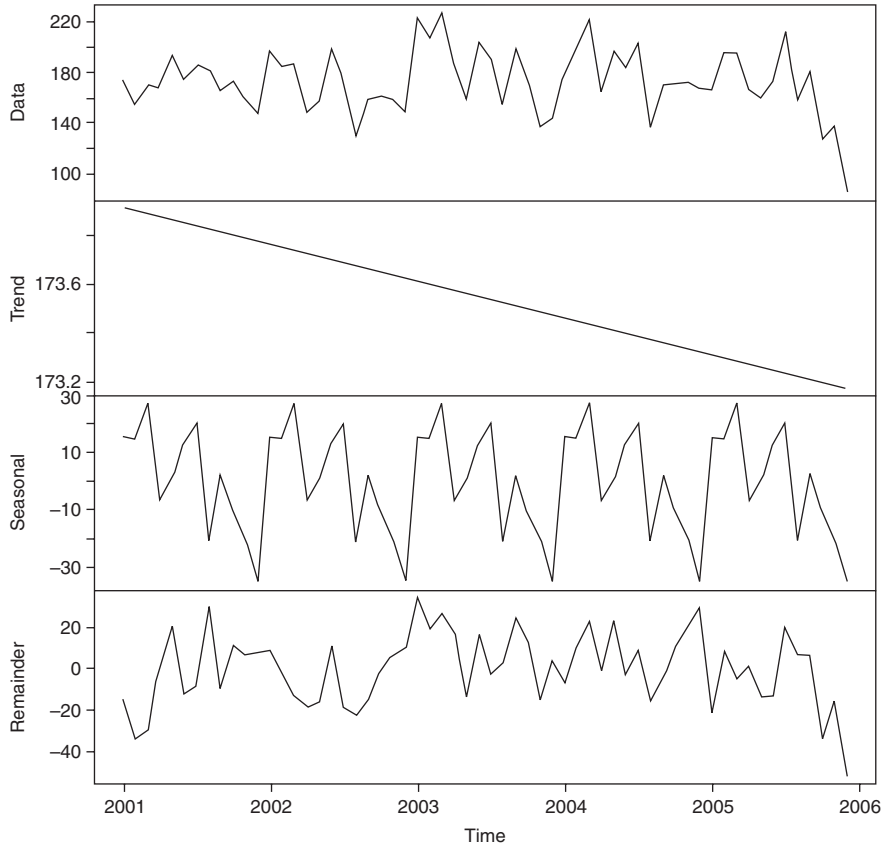

Fig. 8. Seasonal decomposition of the encephalitis hospitalizations (unknown cause) rate series 2001–2005 by locally weighted scatterplot smoothing.

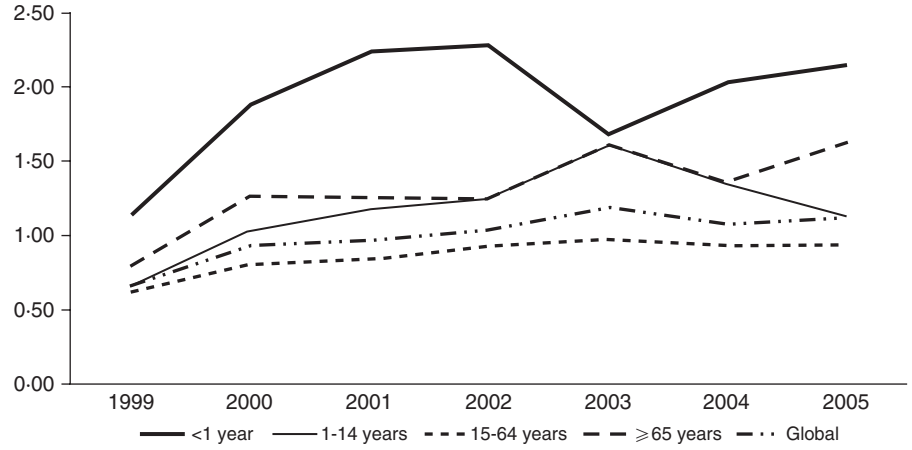

Fig. 9. Distribution of hospitalization rates for 'viral encephalitis not otherwise specified' (ICD-9 code 049·9) over time by age group. * Cochrane–Armitage test for trend $P < 0{\cdot}05$ for 1–14 years, 15–64 years, ⩾65 years, and globally.

this increase in viral encephalitis of unknown cause suggest the emergence of a novel agent because of climate change [34], or do other factors play an equal or even more important role in it? In conclusion, specific surveillance of encephalitis of unknown origin should be reinforced in order to assist in pathogen identification and allow timely public health action to evaluate the possibility of prevention strategies.

https://doi.org/10.1017/S0950268811001002 Published online by Cambridge University Press

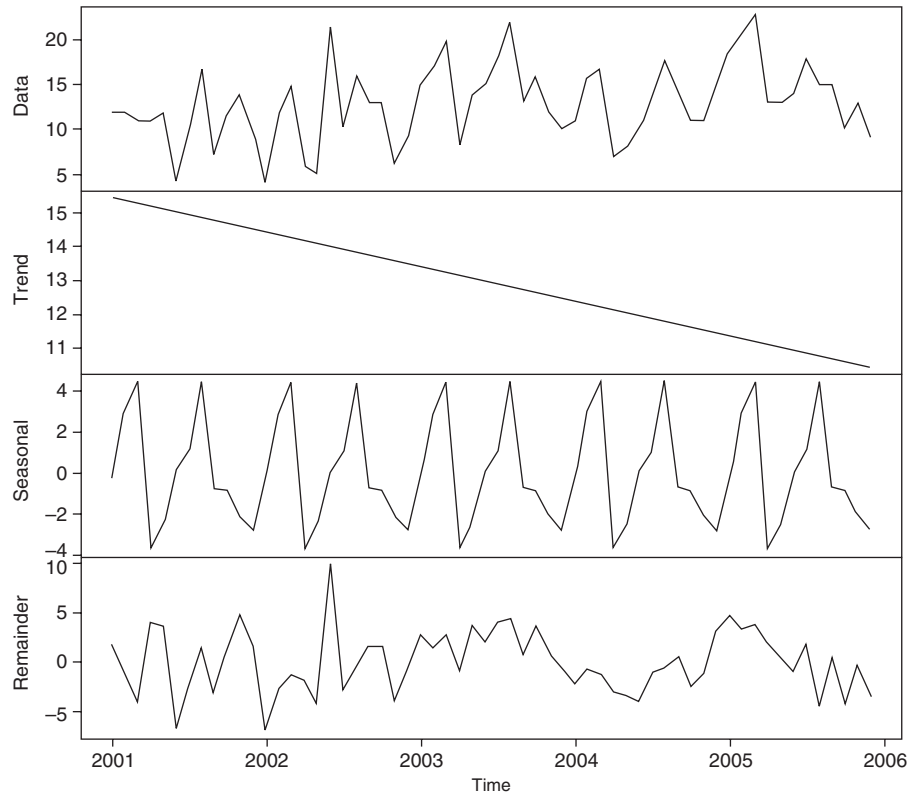

Fig. 10. Seasonal decomposition of the ICD-9 code 049·9 'viral encephalitis not otherwise specified' hospitalization series for 2001–2005, in people aged $\geqslant$65 years).

ACKNOWLEDGEMENTS

The authors thank Dr Francesco Bevere, Dr.ssa Lucia Lispi, and Dott.Ing. Pietro Granella from the Italian Ministry of Health, Health Planning Directorate at the Department of Quality.

DECLARATION OF INTEREST

None.

REFERENCES

1. **Tunkel AR, *et al.*** The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. *Clinical Infectious Diseases* 2008; **47**: 303–327.
2. **Stone MJ, Hawkins CP.** A medical overview of encephalitis. *Neuropsychological Rehabilitation* 2007; **17**: 429–449.
3. **Solomon T, Hart JJ, Beeching NJ.** Viral encephalitis: a clinician's guide. *Practice Neurology* 2007; **7**: 288–305.
4. **Shoji H, *et al.*** Acute viral encephalitis: the recent progress. *Internal Medicine* 2002; **41**: 420–428.
5. **Chaudhuri A, Kennedy PG.** Diagnosis and treatment of viral encephalitis. *Postgraduate Medical Journal* 2002; **78**: 575–583.
6. **Glaser CA, *et al.*** In search of encephalitis etiologies: diagnostic challenges in the California Encephalitis Project, 1998–2000. *Clinical Infectious Diseases* 2003; **36**: 731–742.
7. **Tattevin P.** Infectious meningoencephalitis in non-immunocompromised adult: state of the art [in French]. *Revue de Médecine Interne* 2009; **30**: 125–134.
8. **Domenech C, *et al.*** Role of *Mycoplasma pneumoniae* in pediatric encephalitis. *European Journal of Clinical Microbiology and Infectious Diseases* 2009; **28**: 91–94.
9. **Chakrabarti A.** Epidemiology of central nervous system mycoses. *Neurology India* 2007; **55**: 191–197.
10. **Murray WJ, Kazacos KR.** Raccoon roundworm encephalitis. *Clinical Infectious Diseases* 2004; **39**: 1484–1492.
11. **Campbell GL, *et al.*** West Nile virus. *Lancet Infectious Diseases* 2002; **2**: 519–529.
12. **Bellini WJ, *et al.*** Nipah virus: an emergent paramyxovirus causing severe encephalitis in humans. *Journal of Neurovirology* 2005; **11**: 481–487.
13. **Wang SM, *et al.*** Enterovirus 71, one virus and many stories. *Pediatrics Neonatology* 2008; **49**: 113–115.
14. **Granerod J, *et al.*** Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infectious Diseases* 2010; **10**: 835–844.

15. **Davison KL, *et al.*** Viral encephalitis in England 1989–1998: what did we miss? *Emerging Infectious Diseases* 2003; **9**: 234–240.
16. **Khetsuriani N, Holmann RC, Anderson LJ.** Burden of encephalitis–associated hospitalizations in the United States, 1988–1997. *Clinical Infectious Diseases* 2002; **35**: 175–182.
17. **Koskiniemi M, *et al.*** Infections of the central nervous system of suspected viral origin: a collaborative study from Finland. *Journal of Neurovirology* 2001; **7**: 400–408.
18. **Koskiniemi M, *et al.*** Epidemiology of encephalitis in children: a prospective multicentre study. *European Journal of Pediatrics* 1997; **156**: 541–545.
19. **Trevejo RT.** Acute encephalitis hospitalizations, California, 1990–1999: unrecognized arboviral encephalitis? *Emerging Infectious Diseases* 2004; **10**: 1442–1449.
20. **Granerod, J, Crowcroft NS.** The epidemiology of acute encephalitis *Neuropsychological Rehabilitation* 2007; **17**: 406–428.
21. **Kulldorff M, *et al.*** Evaluating cluster alarms: a space-time scan statistic and brain cancer in Los Alamos, New Mexico. *American Journal of Public Health* 1998; **88**: 1377–1380.
22. **Kulldorff M, *et al.*** A space-time permutation scan statistic for disease outbreak detection. *PLoS Medicine* 2005; **2**: e59.
23. **R Development Core Team.** R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria (http://www.r-project.org). Accessed 9 February 2011.
24. **Masarotto G.** ast. R package version 0.6. 2005 (http://sirio.stat.unipd.it). Accessed 9 February 2011.
25. **Ricci V.** Analisi delle serie storiche con R. 2005 (http://cran.r-project.org/doc/contrib/Ricci-ts-italian.pdf). Accessed 9 February 2011.
26. **Huppatz C, *et al.*** Etiology of encephalitis in Australia, 1990–2007. *Emerging Infectious Diseases* 2009; **15**: 1359–1365.
27. **Mailles A, Vaillant V, Stahl JP.** Infectious encephalitis in France from 2000 to 2002: the hospital database is a valuable but limited source of information for epidemiological studies [in French]. *Medicine et Maladies Infectieuses* 2007; **37**: 95–102.
28. **Lee TC, *et al.*** Encephalitis in Taiwan: a prospective hospital-based study. *Japanese Journal of Infectious Diseases* 2003; **56**: 193–199.
29. **Ciofi Degli Atti ML, *et al.*** Assessment of measles incidence, measles-related complications and hospitalisations during an outbreak in a southern Italian region. *Vaccine* 2006; **24**: 1332–1338.
30. **Frenos S, *et al.*** An increasing incidence of chickenpox central nervous system complications in children: What's happening in Tuscany? *Journal of Clinical Virology* 2007; **38**: 358–361.
31. **Moro ML, *et al.*** Chikungunya virus in North-Eastern Italy: a seroprevalence survey. *American Journal of Tropical Medicine and Hygiene* 2010; **82**: 508–511.
32. **Angelini P, *et al.*** West Nile virus circulation in Emilia-Romagna, Italy: the integrated surveillance system 2009. Eurosurveillance 2010; **15**(16).
33. **Sejvar JJ.** The evolving epidemiology of viral encephalitis. *Current Opinion in Neurology* 2006; **19**: 350–357.
34. **Gould EA, *et al.*** Impact of climate change and other factors on emerging arbovirus diseases. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2009; **103**: 109–21.