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# Épidémiologie des encéphalites aiguës infectieuses : similitudes et différences entre une étude prospective nationale et la base de données hospitalière en France en 2007

Sylvain Bernard

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**UNIVERSITÉ JOSEPH FOURIER**  
**FACULTÉ DE MÉDECINE DE GRENOBLE**

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**THÈSE**

**PRÉSENTÉE POUR L'OBTENTION DU DOCTORAT EN MÉDECINE  
DIPLOME D'ÉTAT**

**Sylvain Raymond BERNARD**

Née le 13 Décembre 1981 à Montbrison

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Monsieur le Professeur Jean Paul STAHL, Président du Jury

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*Ce travail est dédié à la mémoire de mon parrain, Monsieur François Thibert.*

# Épidémiologie des encéphalites aiguës infectieuses: similitudes et différences entre une étude prospective nationale et la base de données hospitalière en France en 2007

## RÉSUMÉ

### Introduction

Plusieurs études rétrospectives reposant sur les bases de données hospitalières ont décrit l'épidémiologie des encéphalites aiguës infectieuses mais peu de données prospectives sont disponibles. L'objectif principal de notre étude était de comparer les données prospectives multicentriques d'une étude nationale menée en France en 2007 avec les données rétrospectives de la base de données hospitalière nationale : le Programme de Médicalisation des Systèmes d'Information (PMSI), afin de déterminer l'utilité éventuelle du PMSI comme outil de surveillance des tendances épidémiologiques des encéphalites en France.

### Méthodes

Les cas d'encéphalite aiguë ont été extraits du PMSI par l'utilisation des codes correspondants de la Classification Internationale des Maladies (CIM) de l'Organisation Mondiale de la Santé (OMS) (version 2007). Les caractéristiques démographiques, la distribution des agents étiologiques ainsi que les taux de mortalité ont été analysés puis comparés aux données de l'étude prospective en utilisant le logiciel Stata11®.

### Résultats

253 cas étaient inclus dans l'étude et 1694 ont été identifiés dans le PMSI en 2007. L'étiologie était connue dans 52% des cas dans l'étude et dans 38% des cas dans le PMSI ( $p < 0.001$ ). Les virus Herpes-simplex et Varicelle-zona étaient les plus fréquemment retrouvés dans les deux bases, en proportions égales (~20% et 8% respectivement). La répartition des agents pathogènes moins fréquents tels que *Borrelia burgdorferi*, *Mycoplasma pneumonia* et Cytomegalovirus était elle aussi similaire. Les caractéristiques démographiques (âge, sexe) et la durée d'hospitalisation n'étaient pas significativement différents. Le taux de mortalité globale et par agent étiologique était identique dans les deux bases (~10%). La proportion d'encéphalites liées à *Listeria monocytogenes* (LM) et *Mycobacterium tuberculosis* (MT) était

significativement plus faible dans le PMSI par rapport à l'étude (LM: 2% vs 5%,  $p=0.001$ ; MT 2% vs 8%,  $p<0.001$ ). Les cas sans diagnostic étiologique étaient plus fréquents dans le PMSI, mais les caractéristiques démographiques et le taux de mortalité étaient similaires à ceux de l'étude.

### **Conclusion:**

À notre connaissance aucune étude publiée n'a comparé ces deux types de données pour les encéphalites aiguës. Le PMSI présente des limites en raison de l'absence de définition précise des cas, des possibles erreurs de classifications des méningites en encephalitis et du délai d'obtention des données de la base. Néanmoins nos résultats suggèrent que le PMSI peut être utile comme outil de surveillance des tendances et ce à de faibles coûts. La connaissance des principales limites de cet outil est indispensable à son utilisation à des fins de surveillance épidémiologique.

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## **ABBREVIATIONS**

CMV: Cytomegalovirus

EBV: Epstein Barr virus

HIV: Human Immunodeficiency virus

HSV: Herpes Simplex virus

ICD 10: International classification of diseases 10<sup>th</sup> revision

IDSA: Infectious diseases society of America

IIQ: Interval interquartile

LCM: Lymphocytic choriomeningitis

LT: *Listeria monocytogenes*

MT: *Mycobacterium tuberculosis*

PMSI: Programme de médicalisation des systèmes d'information

TBE: Central European Tick Borne encephalitis

TE: Toxoplasmic encephalitis

TV: Toscana virus

VZV: Varicella Zoster virus

WHO: World health organization

WNV: West Nile virus

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## ABSTRACT

The epidemiology of infectious encephalitis has been described through hospital discharge database and few prospective studies. The aim of our work was to compare the results from the French national hospital discharge database (PMSI) and from a French national multicentre prospective study in 2007 to evaluate if PMSI could be used for the surveillance of encephalitis. Encephalitis cases were identified in the PMSI using ICD10 codes. The demographic characteristics, the distribution of causative agents and the case-fatality ratio were compared. 253 cases were included in the study and 1694 cases were identified from the PMSI in 2007. Causative agents were identified in 52% of cases in the study and 38% in the PMSI ( $p<0.001$ ). Herpes simplex virus and Varicella zoster virus were the most frequent etiological agents in both databases with comparable frequencies. The distribution of less frequent germs was also similar (*Borrelia burgdorferi*, *Mycoplasma pneumoniae*, Cytomegalovirus). The demographical data, hospital length of stay were not significantly different. The case-fatality ratio was not different in both databases, overall and by germs. *Listeria monocytogenes* (LM) and *Mycobacterium tuberculosis* (MT) were significantly less frequent in PMSI than in the prospective study (LM: 2% vs 5%,  $p=0.001$ ; MT 2% vs 8%,  $p<0.001$ ). Cases with no aetiological diagnosis were more frequent in the PMSI but their general demographical characteristics and case-fatality rate did not differ. Data from the PMSI probably have some limitations due to the absence of case definition and to the possible misclassification. However our results suggest that PMSI may be used as a basic surveillance tool with limited costs.

**Keywords:** Encephalitis, epidemiology, hospital discharge database, France, herpes simplex virus.

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## INTRODUCTION

Few epidemiological studies on acute encephalitis were population-based [1-3] because the syndrome is rare and its infectious causes are miscellaneous. Published studies mainly used national hospital discharge to define the disease burden and give an overview of causes during several years [4-9]. However, the usefulness and limitations of national databases for encephalitis surveillance has not been evaluated. Acute encephalitis is a severe clinical syndrome, resulting from an inflammation of the brain associated with neurologic dysfunction [10,11]. Infectious diseases are the main known causes, but immune mediated encephalitis have also recently been described with increasing acknowledged contribution [2,12,13]. More than 100 different pathogens have been recognized as causative agents of encephalitis but demonstrating a causative relationship is sometimes complex [14,15]. Viruses are responsible for most diagnosed aetiologies, and herpes viruses are the most commonly identified pathogens in industrialized country. Herpes simplex virus (HSV) accounted for approximately 20% of total cases in recent population based studies, followed by Varicella Zoster virus (VZV) and *Mycobacterium tuberculosis* (MT) [1,2,10,16]. Nevertheless, epidemiology of encephalitis throughout the world is characterized by the predominance of cases of unknown origin despite extensive laboratory investigation [1,2,17]. In the last decades, emergent or re-emergent infectious diseases causing encephalitis raised a medical interest worldwide, especially West Nile virus [18], Nipah virus [19], Enterovirus 71 [20], *Mycoplasma pneumonia* [21], European Tick borne encephalitis virus [22], Lacrosse virus [23]. However, these causative agents are responsible for outbreaks, more easily identified and diagnosed than sporadic cases. According to previous studies, global impact includes high mortality rates (4 to 12 %) [2,8], long term hospitalisations (15 to 30 average days) [1,9] and severe sequelae as physical, cognitive, emotional, behavioral, and social difficulties [16,24,25]. Encephalitis is probably an underestimated public health issue. Even if incidence is low, it remains a serious clinical syndrom and effective preventive or therapeutic interventions exist against some pathogens as HSV, varicella or measles. In France, infectious encephalitis are not mandatorily notifiable, but a few infections possibly responsible for encephalitis are: listeriosis, measles, rabies. Epidemiological data about infectious encephalitis are available from the national hospital discharge database [7] and from a prospective population based study conducted in 2007 [1]. The aim of our work was to compare the data from the French national hospital discharge database (Programme de Médicalisation des Systèmes

d'Information, « PMSI ») and from the prospective study conducted in 2007 to evaluate if the reliability of the PMSI as a tool for longitudinal surveillance of encephalitis in France.

## METHODS

### Data sources

253 patients were enrolled in the prospective study [1]. According to the case definition, patients were aged 28 days or more, lived in mainland France, were hospitalized in public hospitals, were negative for HIV and had to stay in hospital 5 days or more for surviving patients. Data collected encompassed demographical and clinical data, and the identified causative agent when applicable. The data were computed using Stata11®. The PMSI is a national exhaustive and continuous database, which describes public and private hospital activity in France. For each hospitalization, the diagnosis and the medical acts are computed in the database according to the World Health Organization (WHO) International Classification of Diseases codes, 10th revision-2007 version (ICD-10-2007 version). Demographical data (age, sex), length of stay, hospital location and death occurring during hospitalization are also recorded.

We selected records in the PMSI using the following criteria to match as much as possible with the case definition used in the prospective study:

- Patients aged 28 days or more- hospitalized in mainland France from 1 January to 31 December 2007 in a public hospital.
- An encephalitis-associated hospitalization was defined as a hospitalization for which at least one of the ICD-10-2007 version (WHO) codes for encephalitis was listed as a discharge diagnosis (principal, related or secondary). The ICD-10-2007 version codes for encephalitis used to select the records are listed in Table 1.

The record linkage number, based on an encrypted number, was used to identify patients with multiple hospitalizations, and only data from the first hospitalization were taken into account in the analysis.

To maintain comparability between hospital discharge data and the prospective study, patients matching the following criteria were excluded:

- surviving patients with an hospital stay fewer than 5 days,
- record with any ICD-10-2007 code consistent with HIV infection (R75, Z21, B20-B24, F024),

- record included codes for intracranial abscess (G06, G07), prion diseases (A810) and cerebral malaria (B500).

Furthermore, if hospitalization with unexplained or unspecified encephalitis code (Table 1) was associated with any other code consistent with encephalitis mimicking pathologies, these cases were excluded. Toxic (G92, F10-F16, F18, F19, T40-T44) autoimmune (G35-G37, M30-36, D86), metabolic (G40.5, E05, E10.0), vascular (G43, G45, G46, I60, I63-I68), neoplastic (C79.3, C70-C72), psychiatric (F28, F29) and congenital (G80, G60, G10-13) diseases were considered as potential encephalitis mimickers. When encephalitis associated code appeared in secondary diagnosis, hospitalization was included if the principal discharge diagnosis was linked to the encephalitis (compatible symptom or complication). For example, principal diagnosis: R40 (somnolence, stupor and coma), and secondary diagnosis: B00.4 (herpesviral encephalitis).

### **Causes of encephalitis**

In the PMSI, aetiological agents were determined using the specific infectious encephalitis codes when they exist in the ICD-10-2007 (for example, B02.0: Zoster encephalitis). Some pathogens hadn't a specific encephalitis code in ICD-10-2007 version as *Mycoplasma pneumoniae* or Cytomegalovirus. For these cases, etiological agent was retained for diagnosis if one code listed in Table 2 (in principal, related or secondary diagnosis) was associated with a code of unspecified or unexplained encephalitis aetiology (Table 1).

We classified acute encephalitis hospitalisations in the PMSI by known cause or unknown cause and compared them with prospective study results.

### **Analysis**

Encephalitis associated cases were computed using Stata® statistical software, version 11 (Stata Corp) and described with regards to aetiology, age, gender, district of residence, duration of hospital stay and death during hospitalization. Comparison with the prospective study was made according to the same available data with use of 2-sided *t* tests or non parametric tests for continuous variable and chi square or fisher exact test for categorical variables. Comparisons were assessed for statistical significance at the 0.05 level.

**Table 1.** List of diagnosis code in ICD-10-2007 version used for extraction of encephalitis cases

ICD-10-CM Code	Diagnosis
<b>Known cause</b>	
B00.4	Herpesviral encephalitis
B01.1	Varicella encephalitis
B02.0	Zoster encephalitis
B05.0	Measles complicated by encephalitis
B26.2	Mumps encephalitis
A85.0	Enteroviral encephalitis
A85.1	Adenoviral encephalitis
A82	Rabies
A83.0	Japanese encephalitis
A83.1	Western equine encephalitis
A83.2	Eastern equine encephalitis
A83.3	Saint-Louis encephalitis
A83.4	Australian encephalitis
A83.5	California encephalitis
A83.6	Rocio virus disease
A84.0	Far Eastern tick-borne encephalitis [Russian spring-summer encephalitis]
A84.1	Central European tick-borne encephalitis
<b>Unknown cause</b>	
Unspecified cause	
A83	Mosquito-borne viral encephalitis
A83.8	Other mosquito-borne viral encephalitis
A83.9	Mosquito-borne viral encephalitis, unspecified
A84	Tick-borne viral encephalitis
A84.8	Other tick-borne viral encephalitis
A84.9	Tick-borne viral encephalitis, unspecified
A85	Other viral encephalitis, not elsewhere classified
A85.2	Arthropod-borne viral encephalitis, unspecified
A85.8	Other specified viral encephalitis
A86	Unspecified viral encephalitis
A88.8	Other specified viral infections of central nervous system
A89	Unspecified viral infection of central nervous system
G04.2	Bacterial meningoencephalitis and meningomyelitis, not elsewhere classified
G05.0	Encephalitis myelitis and encephalomyelitis in bacterial diseases classified elsewhere
G05.1	Encephalitis myelitis and encephalomyelitis in viral diseases classified elsewhere
G05.2	Encephalitis myelitis and encephalomyelitis in others infectious and parasitic diseases classified elsewhere
Unexplained cause	
G04.8	Other encephalitis, myelitis and encephalomyelitis
G04.9	Encephalitis, myelitis and encephalomyelitis, unspecified
G05	Encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere
G05.8	Encephalitis myelitis and encephalomyelitis in others diseases classified elsewhere



**Table 2.** List of diagnosis codes in ICD-10-2007 version used for etiological identification when unknown causes code of encephalitis was extracted.

ICD-10-CM Code	Diagnosis
<b>Bacterial</b>	
A17.8	Other tuberculosis of nervous system
A17.9	Tuberculosis of nervous system, unspecified
A32.1	Listerial meningitis and meningoencephalitis
A69.2	Lyme disease
B96.0	Mycoplasma pneumonia as the cause of diseases classified to other chapters
A49.3	Mycoplasma infection, unspecified
A28.1	Cat-scratch disease
A21.9	Generalized tularaemia
A52.1	Symptomatic neurosyphilis
A48.1	Legionnaire's disease
A77.1	Spotted fever due to Rickettsia conorii
A78	Q fever
A27.8	Other forms of leptospirosis
<b>Viral</b>	
B02.8	Zoster with other complications
B01.8	Varicella with other complications
B25.8	Other cytomegaloviral diseases
B25.9	Cytomegaloviral disease, unspecified
B27.0	Gammaherpesviral mononucleosis
J10.8	Influenza with other manifestations, other influenza virus identified
J11.8	Influenza with other manifestations, virus not identified
B06.0	Rubella with neurological complications
A92.3	West Nile virus infection
A90	Dengue fever
A91	Dengue haemorrhagic fever
<b>Parasitic</b>	
B45.1	Cerebral cryptococcosis
B58.2	Toxoplasma meningoencephalitis

## RESULTS

### Hospital discharge data (PMSI)

In 2007, a total of 1,694 non-HIV patients were recorded in the PMSI with acute encephalitis in mainland France. The most frequently identified aetiology of encephalitis was Herpes simplex virus infection, which accounted for 320 cases (19%). Varicella zona virus (146 cases or 8%), *Mycobacterium tuberculosis* (30 cases or 2 %) and *Listeria monocytogenes* (LM) (31 cases or 2%) were also common identified aetiologies. The aetiology of 1047 encephalitis patients (62%) was unknown. The number of encephalitis hospitalization was higher for men (913 admissions, 54%) than for women (781 admissions, 46%) and median age was 52 years (IIQ : 24-71). Age group 0-15 years represented 18% of all admissions for acute encephalitis, median age in this group was 6 years (IIQ : 3-10). The case fatality rate for encephalitis was 9.5% in 2007. All French districts recorded at least one case of encephalitis during this year, and the number of cases was linked to the population density (Figure 1). Overall during the year 2007, 35,557 hospital days were associated with all encephalitis (first hospital stay only), no seasonality was observed by month for the main aetiological groups, for the encephalitis of unknown origin and for the total population.

### Comparison with prospective data

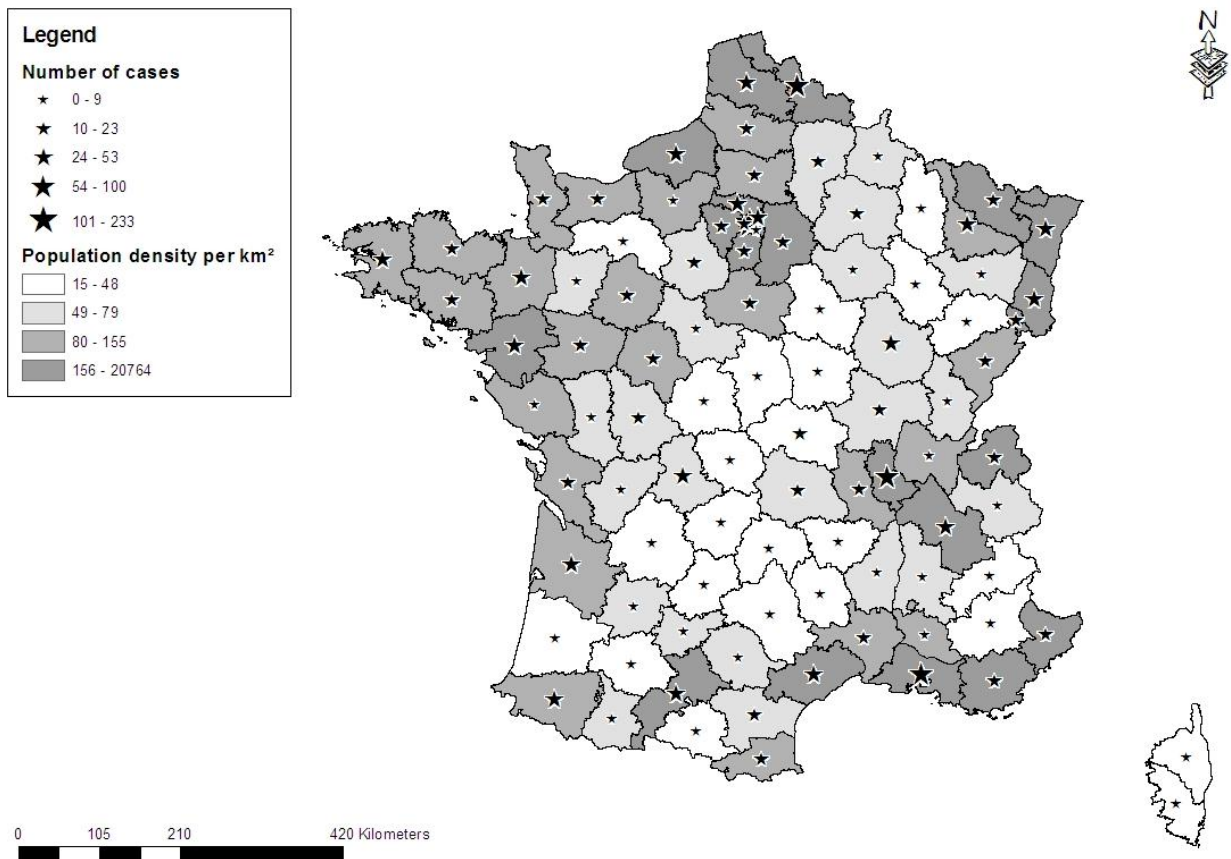
Table 3 displays the characteristics of both population (PMSI and prospective study) and their comparison (age, sex, age group, length of stay, proportion of known causes and lethality). No significant difference for global mean and median age was observed between the PMSI and the study. The number of cases in the age group 0-15 years was higher in prospective study than in PMSI (18% vs 10%,  $p=0.002$ ), the proportion of encephalitis with identified aetiology was higher in prospective study (52% vs 38%,  $p<0.001$ ) and the mean length of stay was longer in PMSI (30 days vs 20 days,  $p<10^{-4}$ ). There were no significant differences between the PMSI and the study in the overall case fatality rate.

The most frequent aetiological agents associated with encephalitis were the same in the two databases, nevertheless the number of encephalitis due to *Mycobacterium tuberculosis* and *Listeria monocytogenes* were significantly lower in PMSI than in prospective study (2% vs 8%,  $p<10^{-4}$  and 2% vs 5%,  $p=0.001$  respectively) (Table 4). Epidemiological data were compared within each aetiological group for the main causative agents (Table 5). No differences were observed for HSV and *Mycobacterium tuberculosis* encephalitis for mean

age, sex, age group, length of stay and lethality. Older mean age and higher lethality (70 vs 57 years,  $p=0.03$  and 46% vs 16%,  $p=0.03$ ) was found in *Listeria monocytogenes* encephalitis patients in the prospective study.

For encephalitis of unknown causes, we found a high number of patients in the age group 0-15 years and a shorter mean length of stay in PMSI (18 vs 28 mean days,  $p<0.001$ ) but no difference was observed on lethality. Other pathogens associated with encephalitis as CMV, *Mycoplasma pneumonia*, *Borrelia burgdorferi*, EBV, Central European Tick borne encephalitis virus, Enterovirus, *Legionella pneumophila*, Influenza virus, *Cryptococcus neoformans*, *Francisella tularensis* were found in both databases (Table 6). Toscana virus, West Nile virus and *Rickettsia conorii* associated encephalitis were only found in prospective study. Lymphocytic choriomeningitic virus, *Toxoplasma gondii*, Measles virus, Mumps virus, *Bartonella henselae* associated encephalitis were only found in hospital discharge database. No comparisons were made for these rare pathogens due to the short number of cases.

**Figure 1.** District of residence of patients with encephalitis extracted from PMSI, France in 2007.



**Table 3.** Global comparison between prospective and hospital discharge data, France in 2007.

Characteristic	Prospective study n=253	Hospital discharge data (PMSI) n=1,694	P-value
Age, median years ( $\pm$ IIQ)	54 ( $\pm$ 24)	52 ( $\pm$ 27)	0.29
Age <16 years, n (%)*	26 (10)	305 (18)	0.002
Age 17-74 years, n (%)*	181 (72)	1050 (61)	0.003
Age > 74 years, n (%)*	46 (18)	339 (20)	0.49
Women, n (%)	99 (39)	781 (46)	0.038
Causes identified, n (%)	131(52)	647 (38)	<0.001
Length of stay, median days ( $\pm$ IIQ)	30 ( $\pm$ 27)	20 ( $\pm$ 22)	<10 <sup>-4</sup>
Lethality, n (%)	27 (11)	160 (9)	0.54

\* the global distribution of age was significantly different between the prospective study and the PMSI, with p=0.004

**Table 4.** Distribution of mainly causes of encephalitis found in the prospective study and the PMSI in France in 2007.

Main causes	Prospective study, (n=253)	PMSI, (n=1694)	P-value
Herpes simplex virus	55 (22%)	320 (19%)	0.284
Varicella zona virus	20 (8%)	146 (8%)	0.705
<i>Mycobacterium tuberculosis</i>	20 (8%)	30 (2%)	<10 <sup>-4</sup>
<i>Listeria monocytogenes</i>	13 (5%)	31 (2%)	0.001
Others	23(9%)	120 (7%)	0.26
Non specified causes	122 (48%)	1049 (62%)	<10 <sup>-4</sup>

Data are number (% of all cases).

**Table 5.** Comparison of demographical characteristic and lethality by principal etiologic agent and unknown causes between prospective and PMSI in France in 2007.

Etiologic agent	HSV			VZV			<i>Mycobacterium tuberculosis</i>			<i>Listeria monocytogenes</i>			Non-specified causes		
	Prospective study (n=55)	PMSI (n=320)	P-value	Prospective study (n=20)	PMSI (n=146)	P-value	Prospective study (n=20)	PMSI (n=30)	P-value	Prospective study (n=13)	PMSI (n=31)	P-value	Prospective study (n=122)	PMSI (n=1049)	P-value
Age, mean years ( $\pm$ SD)	56 ( $\pm$ 17)	58 ( $\pm$ 20)	0.3	55 ( $\pm$ 31)	49 ( $\pm$ 34)	0.4	53 ( $\pm$ 21)	54 ( $\pm$ 21)	0.8	70 ( $\pm$ 12)	57 ( $\pm$ 20)	0.03	46 ( $\pm$ 24)	45 ( $\pm$ 26)	0.7
Age<16 years, n(%)	1 (2)	12 (4)	0.9	3 (15)	43(29)	0.71	0	1 (3)	0.77	0	1 (3)	0.77	14 (11)	212 (20)	0.11
Age 16-74 years, n (%)	48 (87)	223(70)	0.11	6 (30)	49 (34)	0.41	17 (85)	22 (74)	<0.001	8 (62)	23 (74)	0.08	90 (74)	664 (63)	0.001
Age > 74 years, n (%)	6 (11)	85 (26)	0.07	11 (55)	54 (37)	0.17	3 (15)	7 (23)	0.08	5 (38)	7 (23)	0.001	18 (15)	173 (17)	0.13
Women, n (%)	31 (56)	170(53)	0.77	15 (75)	88 (60)	0.23	12 (60)	16 (53)	0.77	9 (69)	17 (55)	0.51	71 (58)	546 (52)	0.212
Length of stay, mean days ( $\pm$ SD)	34 ( $\pm$ 23)	28 ( $\pm$ 26)	0.005	26 ( $\pm$ 17)	22 ( $\pm$ 32)	0.01	45 ( $\pm$ 31)	39 ( $\pm$ 28)	0.5	28 ( $\pm$ 24)	27 ( $\pm$ 22)	0.8	28 ( $\pm$ 29)	18 ( $\pm$ 19)	<0.001
Lethality, n (%)	3 (5)	36 (11)	0.1	3 (15)	13 (1)	0.4	6 (30)	4 (13)	0.1	6 (46)	5(16)	0.03	6 (5)	96 (9)	0.1

**Table 6.** Rare causes of encephalitis found in prospective study and PMSI in France in 2007.

Rare etiologic agent	Prospective study, (n=23)	PMSI, (n=120)	P-value
<b>Cytomegalovirus</b>	3 (2%)	10 (2%)	.2
<b>Epstein barr virus</b>	3 (2%)	8 (1%)	0.4
<b>Tick borne encephalitis virus</b>	3 (2%)	3 (0,5%)	0.03
<b>Lyme disease</b>	2 (2%)	24 (4%)	.4
<i>Mycoplasma pneumonia</i>	2 (2%)	20 (3%)	.5
<b>Enterovirus</b>	2 (2%)	5 (1%)	0.4
<i>Legionella pneumophila</i>	1 (1%)	5 (1%)	0.99
<b>Cryptococcus neoformans</b>	1 (1%)	5 (1%)	0.99
<b>Influenza disease</b>	1 (1%)	4 (1%)	0.8
<i>Francisella tularensis</i>	1 (1%)	1 (0.5%)	0.21
<b>Toscana virus</b>	2 (2%)	--	--
<i>Rickettsia conorii</i>	1 (1%)	--	--
<b>West Nile virus</b>	1 (1%)	--	--
<b>Lymphocytic choriomeningitis virus</b>	--	7 (1%)	--
<i>Toxoplasma gondii</i>	--	7 (1%)	--
<b>Mumps</b>	--	5 (1%)	--
<b>Measles</b>	--	4 (0.5%)	--
<i>Bartonella henselae</i>	--	3 (0.5%)	--
<b>Other causes</b>	--	6 (1%)	--

Data are number (% of known causes). Other causes included Leptospirosis, Pneumococcus, Japanese encephalitis, Rubella, Adenovirus.

## DISCUSSION

The main strengths of the prospective study are a single case definition and the investigation of a wide range of pathogens, but this type of study is too expensive to be conducted on a continuous basis for epidemiological surveillance. National hospital discharge database has the advantages to be continuous, exhaustive and available at low cost but its accuracy is doubtful. When compared with multicentre prospective study [1], encephalitis related cases in the national hospital discharge in France in 2007 revealed a good consistency for basic information. The most frequent causative agents identified were the same in both databases: HSV, VZV, *Mycobacterium tuberculosis* and *Listeria Monocytogenes*. These findings suggest that the PMSI might provide reliable data to study the trends in encephalitis aetiologies. We found less similarity for rare pathogens like arboviroses. Cautious interpretation of the PMSI is needed for these rare cases with important implications for health authorities. However in non endemic countries, these cases are usually imported, and their emergence presents as outbreak, more easily detectable [26]. No variables allow distinguishing imported and autochthonous cases in the PMSI. Moreover, not all arboviral infections have a specific code in the ICD-10-2007 version.

HSV (19%) and VZV (8%) remained the main causes of acute encephalitis in both databases, as previously described. In the literature, they account generally for 13 to 22 % and 5 to 6% of all encephalitis cases respectively [2,5,8]. Our results suggest that PMSI might be used for a rapid and cheap evaluation of these pathogens. The number of death occurring during hospitalization in PMSI (9%) and prospective study (11%) was similar for the total population and by aetiological group. We observed a difference for LM (16% vs 46% respectively) which could be explain by the enrolment of older cases in the prospective study (mean age, 57 vs 70 years). Global lethality rate was higher than that previously described in retrospective studies based on national hospital discharge database from England (6,5%) [5] and North America (7%) [4], but it was similar to the lethality in a recent prospective study from England (12%) [2].

Several limitations of the PMSI as an epidemiological tool were highlighted studying our work. The absence in ICD-10 -2007 version of specific code for rare pathogens with important public health issue is one of them. Smaller frequencies were observed in PMSI than in prospective study for *Mycobacterium tuberculosis* and *Listeria monocytogenes*. It probably reflected the lack of specific code in ICD-10-2007 version. For tuberculosis, no code for encephalitis is available; a specific code existed only for meningitis (A17.0 Tuberculous



meningitis) and was not included in our study. Misclassification of encephalitis in meningitis could explain the lower frequency of tuberculosis encephalitis cases found in PMSI. In the English prospective study, the proportion of tuberculosis was also higher (5%) than in PMSI [2] and was similar to the proportion of tuberculosis in the French prospective study that we compared with the PMSI, suggesting that the data from the prospective study are more reliable than those in the PMSI for tuberculosis-associated encephalitis. No specific code existed to distinguish encephalitis and meningitis due to *Listeria monocytogenes*. The code A32.1 (Listerial meningitis and meningo-encephalitis) was not extracted to avoid an overestimation of encephalitis due to *Listeria monocytogenes* (see methods). Cases were identified by using the association of listeriosis code with a code for unexplained or unspecified encephalitis (Table 1). It could explain lower number of cases found in PMSI. For lower mortality rate we showed that younger patients were coded in the PMSI. Such misclassification could be explained by the absence of case definition for the PMSI, and by the widespread use of the term “meningitis” for all central nervous system infection due to Listeriosis in everyday language.

French metropolitan area is concerned essentially by 3 possibly autochthonous arboviroses: West Nile virus (WNV), Toscana virus (TV) and Central European Tick Borne encephalitis (TBE). Arboviroses raised the medical interest in France in 2000 after equine WNV epidemic in Camargue, France [27]. Since then, a multispecies public surveillance system was implemented for the Mediterranean coastal areas of France, TV was added to the system in 2010. However the occurrence of WNV autochthonous infection in France is rare and TV is mainly responsible for meningitis rather than encephalitis. For TBE no active surveillance exist because the number of TBE is supposed to be low in France (between 5 and 10 per year) and is generally limited to eastern region (Alsace) which is the occidental limit of the European endemic zone [28]. Three TBE, 1 TV and 1 WNV encephalitis (imported) were found in the prospective study. In PMSI, Only 3 TBE and 1 Japanese encephalitis (imported) were registered. The absence of TV and WNV in PMSI is probably linked to the absence of specific code in ICD-10-2007 version which is an important limit of the use of PMSI for epidemiological study on arboviroses in France. In 2010, several European countries had experimented WNV epidemic (Greece, Romania, Italia) [29-32] and ten cases of neuroinvasive TV disease occurred in France [33]. These results suggest the importance of maintaining specific surveillance for these arboviroses in France and in Europe, and that the PMSI might not be of great value for such rare pathogens. Moreover, as the PMSI is not

available in real time, it has not the required reactivity to be used as an early detection and alert tool.

Cases of measles and mumps associated with encephalitis were found in PMSI only. Measles complicated by acute encephalitis was probably overestimated in the PMSI, the incidence of this complication in the PMSI (1/1000) suggested that 4000 cases could have occurred in 2007, while the outbreak of measles in France began in 2008 with 600 declared cases (cases were obligatory notifiable to public health authorities since 2005) [34]. Until now, 20000 cases and 10 related deaths have been declared to the French Institute for Public Health Surveillance. The cases found in PMSI in 2007 seemed to have been an indicator of epidemic resurgence, nevertheless the late availability (two years delay) of the basis was a limitation of his epidemiological potential to rapidly detect a re-emergence. We noted that a specific encephalitis code exist for these diseases which is interesting compared to the lack of accuracy for arboviroses. Adding specific codes for arboviroses might probably improve the database quality for the surveillance of their trends.

The absence of case definition in PMSI is another limitation to carry out epidemiological studies or surveillance. Mistakes during coding may happen particularly for rare pathogen not well known by all coders. Two entities rarely associated with encephalitis have been found in PMSI and appeared doubtful. The first one is toxoplasmic encephalitis (TE) which is a rare disease in non immunocompromised patients. Only few cases were published in immunocompetent patients [35,36] and seven cases of TE were found in PMSI without association with concordant codes for HIV or other immunodeficiency. Similarly Lymphocytic choriomeningitis (LCM) virus is rarely a cause of encephalitis; usually his clinical spectrum is broad and non-specific as flulike [37]. We found 7 cases in PMSI and we suspect that this entity was mistaken for lymphocytic meningitis. Another characteristic case is rabies, one was registered for a patient of 78 years who died the first day of hospitalization. Rabies is mandatorily notifiable in France and its specific diagnosis is available in the Institut Pasteur only. No case was declared and no specific research was positive in France in 2007. The current knowledge about rare diseases suggest some probable misclassifications for some cases and no conclusion could be done, it illustrates the need to continue quality control in coding which have been implemented since few years to sensitize physicians to make accurate coding.

The wide range of aetiological agents explored in the prospective study can explain the smaller number of unknown causes found than in PMSI. Furthermore, the diagnosis tools for rare aetiological agents may not be available in secondary or primary care hospital. Between

2000 and 2002 in France, a retrospective study was conducted using PMSI to define encephalitis epidemiology, unknown causes represented 80% of all cases which is higher than the 62% found in the 2007 database [7]. The observed differences could be explained by the recent change of the hospital funding in France. Indeed, since 2004 public hospital funding has been depending exclusively on codification of each hospitalization by principal, related and secondary diagnosis from ICD-10-2007 version [38]. This change probably improved the exhaustivity and accuracy of the database. The number of unknown causes (62%) is similar of other retrospective study based on national hospital discharge database conducted in North America (59, 5%) and Australia (69, 8%), but the management and exploration of causes of encephalitis might be different in other countries.

The main limitation of our work was the assumption that the prospective study was representative of the global situation in France. We showed that cases occurring in age group 0-15 years were underreported in prospective study. Hospital national discharge might to be more accurate for this group. Previous retrospective study generally found that infants account generally for 19% to 30% which is close to the 18% we found in PMSI. By contrast, we have no element suggesting that the adult population in the prospective study might not be representative of adult encephalitis in France, and the similarities between the French and English results suggest a good representativity of the patients enrolled in the prospective study.

## CONCLUSION

No previous study had compared these two types of data for several aetiologies simultaneously and tried to assess the reliability of the PMSI as an epidemiological tool. The PMSI could be a useful database for trends study. We showed that PMSI was reliable for the most frequent aetiological agents of encephalitis, nevertheless it lacks accuracy and sensitivity for rare pathogens. Moreover, because of the delay before the database is available, it lacks reactivity and can not be used to detect early public health threats. Quality control of coding and enhancing completeness of the list of codes could improve PMSI epidemiological possibilities, notably for encephalitis and infectious diseases.

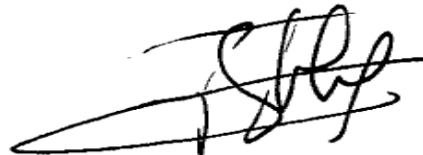
**VU ET PERMIS D'IMPRIMER**

Grenoble, le 21/8/2011

**LE DOYEN**

  
J.P. ROMANET  


**LE PRESIDENT DE LA THESE**

  
Professeur J.P. STAHL

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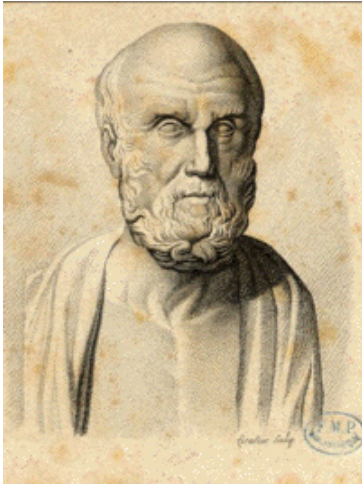
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# *Serment médical d'Hippocrate*

*En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.*

*Je donnerai mes soins gratuitement à l'indigent, et n'exigerai jamais un salaire au-dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.*

*Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe; ma langue taira les secrets qui me sont confiés et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime.*

*Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.*

*Je garderai le respect absolu de la vie humaine. Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.*

*Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leur père.*

*Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.*

*Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.*