

ORIGINAL ARTICLES

Surveillance report

SURVEILLANCE OF HUMAN LISTERIOSIS IN FRANCE, 2001-2003

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Mandatory notification of listeriosis began in France in 1999. Enhanced public health surveillance, including routine molecular characterisation of *Listeria monocytogenes* strains, epidemiologic follow up of cases, and collection of food samples, has improved the sensitivity of outbreak detection and response. The incidence of listeriosis declined from 4.5 cases/million in 1999-2000 to approximately 3.5 cases/million during the period 2001-2003. Clinical, demographic and microbiological characteristics of listeriosis in France remained stable during this time period. Maternal-fetal infections accounted for 24% of all cases. Serovar 4b accounted for 49% of cases and 60% of case clusters. The incidence of listeriosis in France has declined and is now lower than in several other European countries.

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Key words: Listeriosis, surveillance, molecular epidemiology**Introduction**

Since 1999, surveillance of human listeriosis in France has been based on two complementary approaches: mandatory notification of cases, monitored by the national public health institute (Institut de Veille Sanitaire, InVS), and the voluntary submission of *Listeria monocytogenes* strains to the national reference centre (CNR, Centre national de Référence des Listeria, Institut Pasteur, Paris). The CNR centralises and characterises *L. monocytogenes* strains from all sources and notifies the InVS of all *L. monocytogenes* strains of human origin. The aim of the mandatory notification system is to obtain clinical, demographic, and food consumption information on each patient to allow tracking of the temporal trends in disease occurrence and to identify possible common sources of exposure among cases in clusters detected by the CNR [1].

Methods**Definitions**

A case is defined by isolation of *L. monocytogenes* from a patient with a clinically compatible illness. A case is considered maternal/neonatal (MN) when it involves a pregnant woman, a miscarriage, a stillbirth, or a newborn under one month old. When *L. monocytogenes* is isolated from both the pregnant woman and her newborn child, it is counted as a single case. If a case fits none of these groups, it is considered non-maternal/neonatal (non-MN). Patients are considered to be at risk if they have an underlying pathology weakening their immune system, including cancer, blood malignancy, organ transplant,

chronic haemodialysis, liver failure, diabetes, HIV, treatment with cytolytic or corticosteroid immunosuppressants.

Collection of data

Information collected on the notification sheet includes the department of residence of the patient, his/her age, the clinical form of disease, the possible existence of an underlying pathology at the time of listeriosis diagnosis and whether the patient was still living at the time of the follow-up. The food questionnaire was administered face to face or by telephone, and includes a list of food items, thought to be likely sources of *Listeria*, that may have been consumed in the two months before onset of illness. This includes food items previously identified as vehicles in outbreaks, and foods which have been previously found to be contaminated by *L. monocytogenes*, and are consumed uncooked. Given the wide variety of such products existing in France, this list is not exhaustive and does not take into account certain products rarely consumed in France. The questionnaire consists of a list of 76 items in four categories: seafood products (seven items): fish-based products, smoked fish, shrimp and shellfish; vegetable products (three items): packaged lettuce, packaged prepared raw vegetables and soy sprouts; dairy products (34 items): 33 cheeses and unpasteurised milk; cold cuts, cooked meats and meat-based products (32 items): pâté, ham, sausages, meat products with gelatine, poultry-based products.

Food samples

Since August 2001 officers of the departmental veterinary services (DDSV, Directions Départementales des Services Vétérinaires) and officers of the departmental consumer protection services (DDCCRF, Direction départementale de la consommation, de la Concurrence et de la Répression des Fraudes) have collected food samples from patients households to look for *L. monocytogenes* [2]. These investigations are restricted to patients whose central nervous system has been affected, because these forms of listeriosis have shorter incubation periods and are more likely to occur in outbreaks than other forms. Strains isolated from these samples are analysed at the CNR and compared with the patient's strain to identify foods responsible for case clusters and allow the timely implementation of control measures to stop the spread of the disease and prevent outbreaks.

Analysis of strains by the CNR

Strains are confirmed to be *L. monocytogenes*; in parallel they are characterised by serotyping and analysis of DNA macrorestriction profiles according to standard protocols [1,3,4]. Isolates with indistinguishable ApaI and AscI macrorestriction profiles, based on visual comparison of banding patterns, were considered to be the same pulsovar. Sensitivity to antibiotics is studied using diffusion techniques. Resistance is confirmed using MIC determination (E-test method) by the antibiotic resistance national reference centre

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(CNR de la résistance aux antibiotiques, Institut Pasteur, Paris). Eleven antibiotics (ampicillin, chloramphenicol, ciprofloxacin, erythromycin, gentamicin, kanamycin, rifampicin, streptomycin, tetracycline, trimethoprim and vancomycin) are tested.

Management of listeriosis clusters

A cluster is defined as the occurrence of at least three listeriosis cases over a period of 14 weeks and involving strains of the same pulsovar. After a cluster is detected by the CNR, the 'listeria group' is informed. It is composed of representatives of InVS, the CNR for Listeria, and the Ministries of Agriculture, Health and Economy (consumers protection directorate). The InVS analyses patient data (notification forms and food questionnaires) and, if cases appear to be linked, the 'listeria group' develops and coordinates the investigations needed to identify a possible common source and implement appropriate measures to prevent the spread of disease.

Quality of the monitoring system

The sensitivity of the system for reporting diagnosed cases of listeriosis has been estimated at 87% by the capture-recapture method comparing data collected in 2001 by mandatory notification with the data reported by the EPIBAC network [5].

Results

Epidemiological characteristics

The annual incidence of listeriosis in France decreased in 2001 [TABLE 1] and stabilised at the lower rate with 3.4 cases/1 000 000 inhabitants notified in 2003. From 2001 to 2003, the mean number of cases per year was 206, with 49 maternal/neonatal cases and 157 non-maternal/neonatal cases. Between 2001 and 2003, the mean regional incidence was 3.0 cases/1 000 000 inhabitants (range 0-5.1) [FIGURE 1]. Regional distribution of cases did not differ significantly from one region to another during the study period. A seasonal effect, with

TABLE 1

Principal characteristics of listeriosis cases identified by disease notification and isolate submission to the National Listeria Reference Laboratory, France, 1999-2003

		1999	2000	2001	2002	2003
France (all regions)	Case notified	269	263	188	220	209
	Case with strain submitted to CNR	254	250	186	218	199
Incidence per 1 000 000 inhabitants		4.5	4.4	3.1	3.6	3.4
Clinical form	Non-maternal-neonatal	202	199	144	165	162
	Maternal-neonatal	67	64	44	55	47
Deaths	Adult	47	34	46	35	26
	Neonatal and fetal	19	23	13	22	13
	Total	66	57	59	57	39
Clinical form, non-maternal-neonatal						
Risk factor	No detectable pathology	32	32	16	27	26
	Known risk	140	130	107	113	117
	Other pathology	20	32	18	22	16
	Unknown	10	5	3	3	3
Sex	Female	78	74	55	70	73
	Male	124	125	89	95	89
Serovar (all forms)	% serovar 4b	51	54	42	56	47
	% serovar 1/2a	24	30	33	22	27
	% serovar 1/2b	29	13	22	17	22
	% serovar 1/2c	5	3	3	3	5

an increase of cases during summer, was observed [FIGURE 2]. The mean number of cases for the period from May to August was 262, compared with 118 cases for the other four month periods.

Maternal/neonatal forms

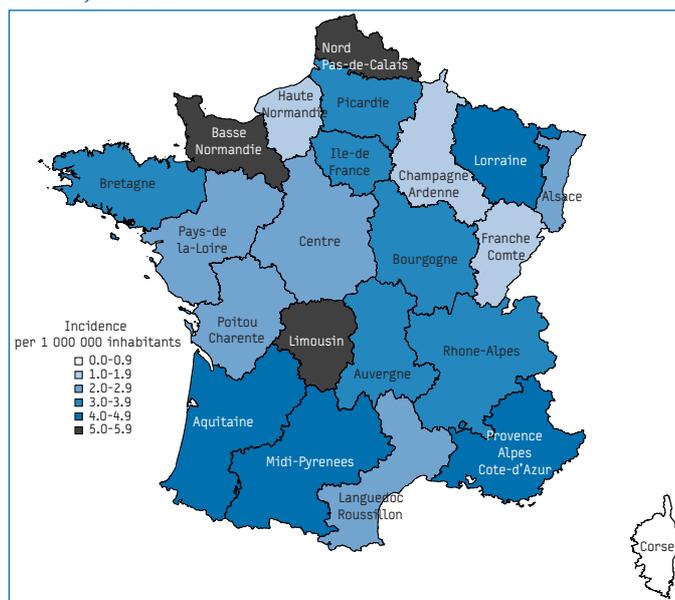
Maternal/neonatal forms represented 24% of cases. From 2001 to 2003, 48 cases of neonatal or fetal mortality were notified: 21 miscarriages, 19 stillbirths and 8 newborns who died within the first 48 hours after birth.

Non-maternal/neonatal (non-MN) forms

The non-MN forms were more common in males (57% of cases from 2001 to 2003). This was observed both for subjects with no risk factors, and for subjects with underlying listeriosis risk factors. The presence or absence of underlying pathology was known for 462 of the 471 non-MN cases notified between 2001 and 2003. Of these 462 patients, 337 (73%) had an underlying risk factor, 56 were affected by pathology not considered to be a risk factor for listeriosis, and 69 had no known pathology at the time of admission to hospital. One hundred and seven patients died within 10 days after diagnosis (20% lethality).

FIGURE 1

Listeriosis incidence per million inhabitants, by region, France, 2001-2003

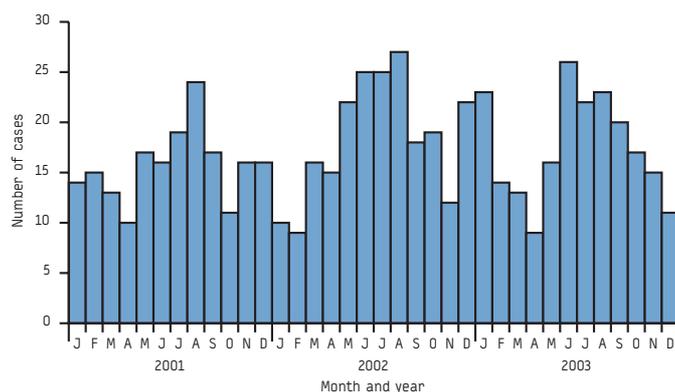


Source: InVS Notifiable Disease Reports

FIGURE 2

Number of listeriosis cases by month, France, 2001-2003

Source: InVS Notifiable Disease Reports



Strain analysis

From 2001 to 2003, the CNR received 603 *L. monocytogenes* strains which accounted for 98% of cases notified to the INVS [TABLE 1]. Approximately half of all strains were serovar 4b (4b: 49% of the strains, 1/2a: 27%, 1/2b: 20%, 1/2c: 4%, 3a and 3b <1%). Distribution of serovars by clinical form [TABLE 2] showed that:

- i) a higher proportion of strains of serovar 1/2b were isolated from MN infections (27%) than from non-MN forms (18%) ($p=0.02$),
- ii) a higher proportion of strains of serovar 1/2c were isolated from non-MN forms (5%) than from MN forms (1%) ($p=0.03$),
- iii) among non-MN forms, serovar 4b was frequently isolated from CNS infections. Within the strains of serovar 4b, 42% were isolated from CNS infections. Values for the other serovars were 32.8% (1/2a), 28.1% (1/2b), and 23.8% (1/2c), respectively ($p = 0.0006$).

In 2003, 92 pulsovars were identified with between one and 15 strains per pulsovar, resulting in a total discrimination index (that is, the probability that two randomly chosen strains would have different pulsovars) of 0.980. Three resistance profiles were observed. Three strains were resistant to ciprofloxacin (serovar 1/2a), two were resistant to tetracycline and trimethoprim (serovar 1/2a) and one was resistant to tetracycline alone (serovar 1/2b).

TABLE 2

Distribution of 603 strains of *Listeria monocytogenes* from human cases, by serovar and clinical form, France, 2001-2003

	1/2a n (%)	1/2b n (%)	1/2c n (%)	4b n (%)	Other n (%)
Non-maternal-neonatal (n=462)	134 (29)	82 (18)	21 (5)	221 (48)	4 (1)
Central nervous system infection(n=165)	44	23	5	93	0
Bacteraemia (n=270)	83	56	15	112	4
Focal infection (n=27)	7	3	1	16	0
Maternal-neonatal (n=141)	29 (21)	38 (27)	1 (1)	73 (52)	0 (0)
Total (n=603)	163 (27)	120 (20)	22 (4)	294 (49)	4 (<1)

Source: National Listeria Reference Laboratory

Investigation of clusters

Between 2001 and 2003, the CNR reported 25 clusters. The median size of clusters was five cases, with a range of 3-14 cases per cluster. Fifteen clusters (60%) were due to serovar 4b strains. Cases involved in clusters represented 26% of notified cases during this period. Analysis of the cases' food consumption histories identified suspected food vehicles for several clusters and triggered further investigations and control measures at production site. In three outbreaks, a *L. monocytogenes* strain of the case-associated pulsovar was identified in a food product consumed by several cases, confirming the food item as the source of the outbreak.

Discussion

The incidence of listeriosis in France decreased substantially from 1987 through 1997 after control measures were implemented

by the food industry in response to several large outbreaks [5]. Following implementation of mandatory notification, incidence has further declined from 4.5 cases/1 000 000 in 1999-2000 to approximately 3.5 cases/1 000 000 during the period 2001-2003. As this reduction concerns all forms of listeriosis (targeted or not by food recommendations) this further decline is likely due to a reduction of exposure to contaminated product [5]. This reduction could be the consequence of more effective recall of contaminated products from the marketplace following a directive issued by the Ministry of Agriculture in 1998 that standardised recall procedures. In addition, mandatory notification with routine, standardised collection of food consumption histories has allowed prompt cluster investigations and identification of the source of outbreaks, thus reducing the number of cases exposed to implicated products.

The proportion of maternal-neonatal cases which had declined significantly from 1987 (51% of all cases) to 1997 (24% of all cases) has not changed since 1997. Other clinical and demographic characteristics of listeriosis in France (male to female sex ratio, case fatality rate) have also remained stable. Serovar 4b remains the most common serovar and accounts for a disproportionate share of case clusters and central nervous system infections, as previously noted [6].

Conclusion

Thanks to the joint efforts of food producers, government and health authorities, the incidence of listeriosis in France, which in the 1980s exceeded that of other industrialised countries, is now lower than in several other European countries and is at the same level as the United States, which applies a 'zero-tolerance policy' for Listeria in foods [7,8]. Although there have been fewer episodes than in preceding years, there remains a risk for case clusters and outbreaks due to contaminated food [9].

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