

Pregnancy-related listeriosis in France, 1984 to 2011, with a focus on 606 cases from 1999 to 2011

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This study describes trends in the incidence of pregnancy-related listeriosis in France between 1984 and 2011, and presents the major characteristics of 606 cases reported between 1999 and 2011 to the French Institute for Public Health Surveillance through the mandatory notification system. The incidence of pregnancy-related listeriosis decreased by a factor of 12 from 1984 to 2011. This reduction was a result of progressive implementation of specific *Listeria monocytogenes* control measures in food production. A lower incidence of pregnancy-related listeriosis was observed in regions with a lower prevalence of toxoplasmosis. Given that dietary recommendations in pregnancy target both toxoplasmosis and listeriosis prevention, we suppose that recommendations may have been delivered and followed more frequently in these regions. Cases reported between 1999 and 2011 (n=606) were classified as maternal infections with ongoing pregnancy (n=89, 15%), fetal loss (n=166, 27%), or live-born neonatal listeriosis (n=351, 58%). The majority of live-born neonatal listeriosis cases (n=216, 64%) were preterm births (22–36 weeks of gestation), of whom 14% (n=30) were extremely preterm births (22–27 weeks of gestation). Eighty per cent of mothers reported having eaten high risk food during pregnancy. A better awareness of dietary recommendations in pregnant women is therefore necessary.

Introduction

Invasive listeriosis is a rare but severe infection caused by *Listeria monocytogenes*, a bacterium capable of growing at low temperatures but destroyed by heat. Human listeriosis is mainly transmitted by food [1,2] and generally affects immunocompromised individuals, pregnant women and newborns [3]. The symptoms of listeriosis in pregnant women are non-specific and often include an influenza-like syndrome. The main risk associated with listeriosis during pregnancy is haematogenous transmission to the fetus through the placenta. Listeriosis can develop at any time during pregnancy [4] and can result in fetal loss, preterm

birth and/or neonatal infection [5]. Transmission to the fetus can also occur through ingestion of amniotic fluid [6]. Nosocomial transmission is occasionally reported in maternity units [7,8]. The proportion of pregnancy-related listeriosis decreased strongly between the 1980s and 1997, from nearly 50% to less than 25% of all invasive listeriosis cases [9]. The objectives of this study were to describe trends in the incidence of pregnancy-related listeriosis in France between 1984 and 2011, and the major characteristics of the 606 cases recorded between 1999 and 2011.

Methods

Data sources

The main indicator used to describe the annual incidence of pregnancy-related listeriosis is the rate of number of cases per number of live births in the French population. The number of live births is recorded every year by the French Statistical Office (Institut National de la Statistique et des Etudes Economiques; INSEE) [10]. The number of cases was retrieved from different sources for the following periods:

- 1984–1991: studies by the French National Health Laboratory [9,11].
- 1992–1998: National Listeria Reference Centre (NLRC) database. NLRC started ascertaining cases nationwide in 1992 because of a listeriosis outbreak [12]. The number of cases related to that outbreak has not been considered for the calculation of the annual incidence rate. In 1997, the sensitivity estimation of case ascertainment was 76% [9].
- 1999–2011: mandatory notifications. Listeriosis has been listed for mandatory notification in France since 1999. Accordingly, each diagnosed case must be declared by clinicians and laboratories to the regional health agency. Sensitivity was estimated at 87% in 2001 [13] and at 92% in 2006 (data not shown), using the capture–recapture method. The mandatory notification includes demographic, clinical, and laboratory

information [14]. Moreover, upon diagnosis, mothers are asked to complete a standard food questionnaire on their eating habits in the past two months. After validation of the content, the mandatory notifications and the food questionnaires are sent by the regional health agencies to the French Institute for Public Health Surveillance (InVS).

The annual incidence rate was estimated from 1984 to 2011, considering the sensitivity of each data source.

Case definition

In France, the diagnosis of listeriosis is made when *L. monocytogenes* is isolated from a normally sterile site in a patient presenting symptoms clinically compatible with listeriosis. A case is considered pregnancy-related when it involves a pregnant woman, a miscarriage, a stillbirth, or a newborn less than 28 days-old. When *L. monocytogenes* is isolated from both the pregnant woman and her newborn child, this is counted as a single case. Gestational age is given by the number of weeks of amenorrhoea. According to the information on the mandatory notification form, we categorised each case as ongoing pregnancy (diagnosis of invasive listeriosis in a pregnant woman with no concomitant delivery), fetal loss (miscarriage if gestational age is less than 22 weeks of gestation (WG), stillbirth if

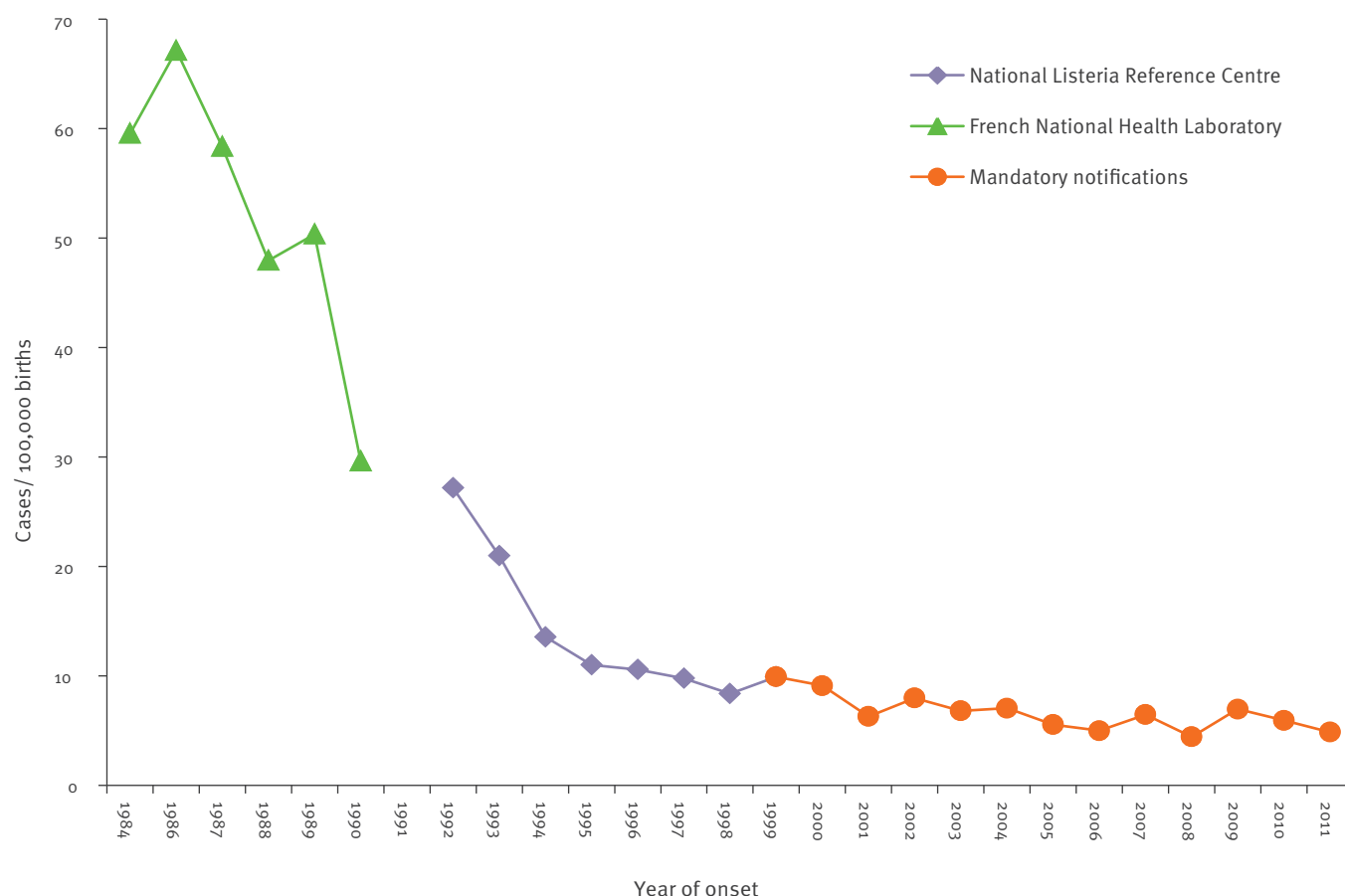
it is at least 22 WG), or live-born neonatal listeriosis (*L. monocytogenes* infection diagnosed in a newborn before 28 days of age). Live-born neonatal listeriosis was subclassified as ‘early neonatal cases’ (diagnosed between birth and day 6) or ‘late neonatal cases’ (diagnosed between day 7 and day 28). Early neonatal cases were classified as confirmed cases (*L. monocytogenes* isolated in the neonate’s cerebrospinal fluid (CSF) or the neonate’s blood), probable cases (*L. monocytogenes* isolated from placenta, the mother’s blood, or the neonate’s gastric aspirate), or possible cases (positive swab(s) from the neonate’s surface sites). Finally, neonatal listeriosis was defined as an infection of the newborn [≥ 22 WG independent of its vital status, i.e. stillbirths and live-born neonatal listeriosis].

Confirmation and characterisation of *L. monocytogenes* isolates by NLRC

Listeria isolates from pregnancy-related listeriosis referred to NLRC were confirmed with API Listeria (API, Appareil et Procédé d’Identification, bioMérieux, Marcy l’Etoile, France) [15] and serotyped by the slide agglutination method until January 2005 [16] and by multiplex PCR [17] starting February 2005. According to our experience, the PCR groups correspond fully to the four major serovars that cause human disease. Ongoing subtyping was conducted by

FIGURE 1

Incidence of pregnancy-related listeriosis, France, 1984–2011



DNA macrorestriction profiles analysis (pulsed-field gel electrophoresis; PFGE) according to standard protocols [18]. Isolates with indistinguishable *Apal* and *Ascl* DNA macrorestriction profiles, first based on visual comparison of banding patterns (since 2006 using BioNumerics 6.6 software; Applied Maths Saint-Martens-Latem, Belgium), were considered to be the same pulsovar. Susceptibility to a panel of 23 antibiotics was determined for each strain by disk diffusion according to guidelines from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and Clinical and Laboratory Standards Institute (CLSI) [19–21].

Statistical analyses

Results are expressed as numbers and percentages for categorical variables and as mean±standard deviation (SD) or median (range) for continuous variables as appropriate. Associations between categorical variables were assessed using the chi-squared test or Fischer's exact test as appropriate. Associations between continuous and categorical variables were assessed using Student's t-test or Kruskal–Wallis test as appropriate. Correlation between continuous variables was assessed using Pearson's or Spearman's correlation coefficients as appropriate. Statistical analysis was performed using Stata11.

Results

Incidence of pregnancy-related listeriosis

The annual incidence rate of pregnancy-related listeriosis per 100,000 live births fell from 60 (n=453) to 5 (n=35) cases per 100,000 live births between 1984 and 2011, a decline by a factor of 12. It decreased markedly between 1986 and 1996, gradually from 1996 to 2006 and was then stable until 2011 (Figure 1). From 1999 to 2011, the overall incidence rate of pregnancy-related listeriosis was 6.1 per 100,000 live births and varied according to the region from 2.2 to 13.6. It was highest in the Paris region and in the south-west of France (Figure 2). The incidence rate of pregnancy-related listeriosis was independent of the incidence rate of non-pregnancy-related listeriosis in all the regions of France ($r=0.16$, $p=0.07$). Pregnancy-related listeriosis was more frequent from July to September than during the rest of the year (mean: 5.0 ± 2.6 vs 3.5 ± 2.0 cases per month, $p<0.001$). Seasonal incidence of pregnancy-related listeriosis was not parallel to the incidence observed for non-pregnancy-related listeriosis which was higher from May to July than during the rest of the year (mean: 21.7 ± 1.2 vs 16.3 ± 2.7 cases, $p=0.008$) (Figure 3).

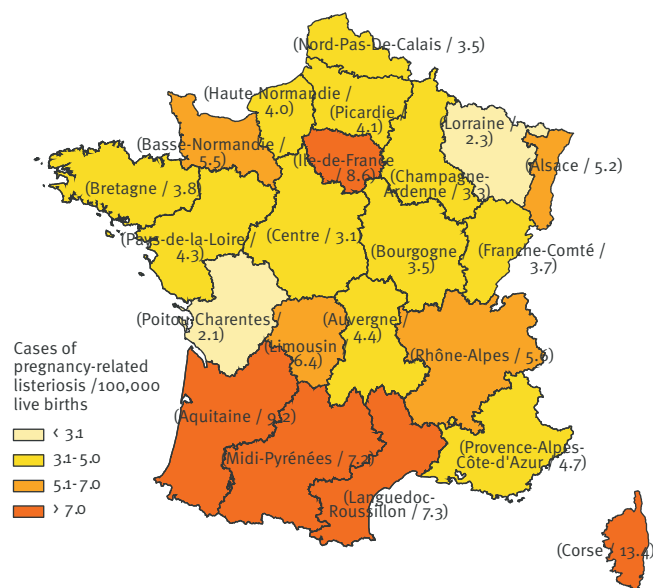
Cases from 1999 to 2011

We focused our study on the period 1999 to 2011, after the introduction of mandatory notification of listeriosis in France. A total of 3,413 cases of listeriosis were recorded from 1999 to 2011, of which 606 (18%) were considered pregnancy-related (Table 1). The mean age of the mothers was 29.5 ± 6.1 years. There was

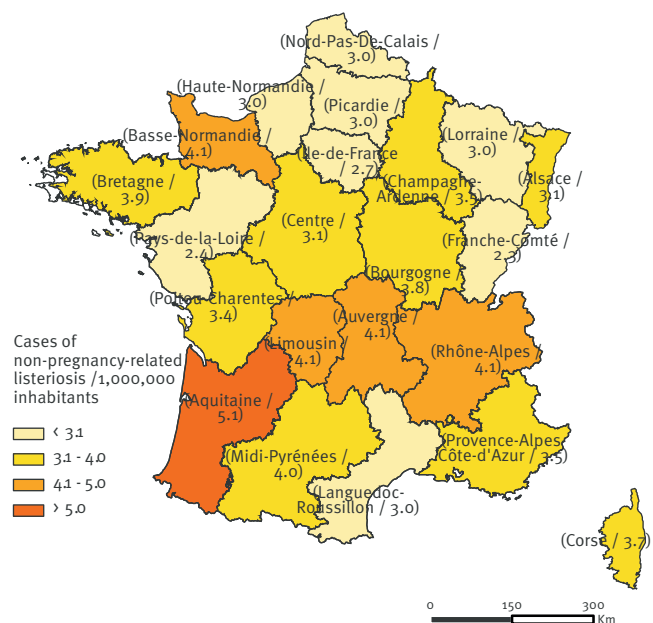
FIGURE 2

Average annual incidence rates of listeriosis, by Région, France, 1999–2011 (n=606)

A. Pregnancy-related listeriosis



B. Non-pregnancy-related listeriosis



Software used to draw the map: IGN-GéoFLA, using administrative boundaries from 1999.

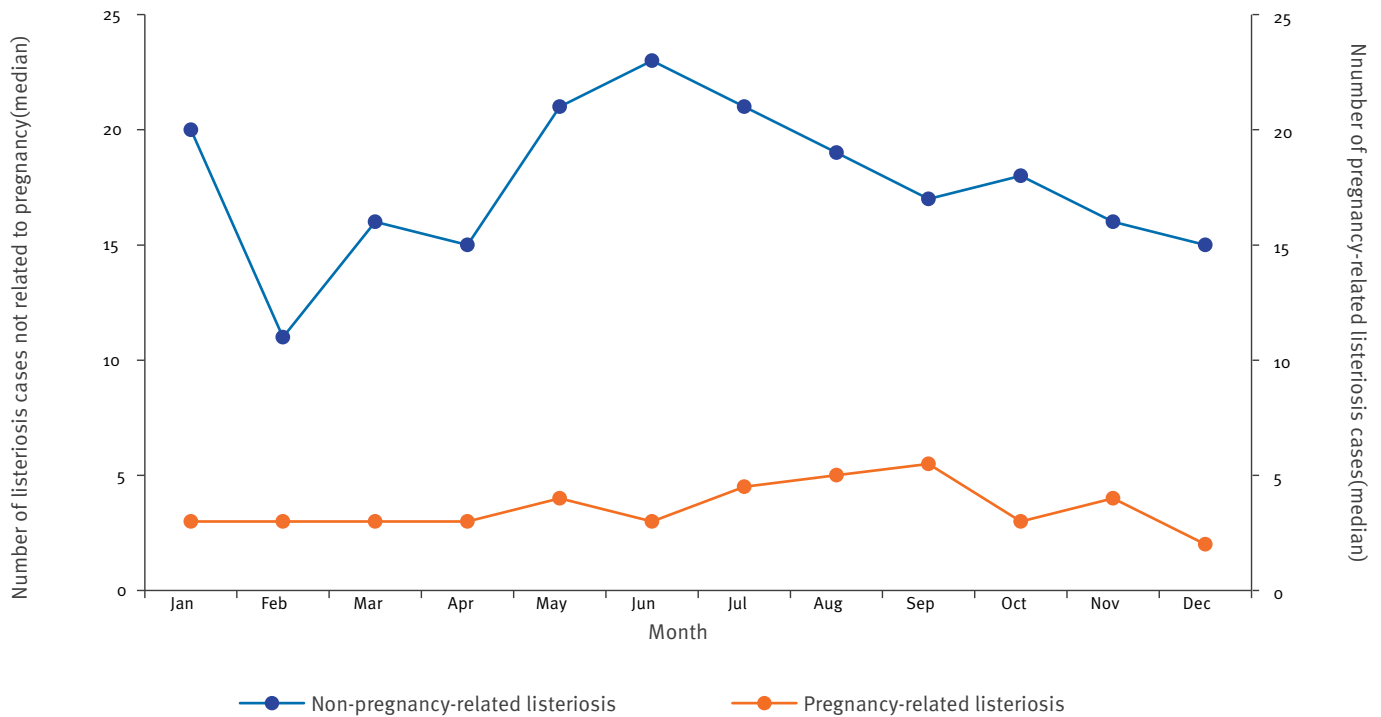
Data source: InVS, October 1013.

no significant difference to the mean age of mothers in the general population who gave birth in France in 2010 (mean: 29.7 ± 5.3) [22]. There were three twin pregnancies which resulted in six live-born neonatal listeriosis cases.

Among the 603 mothers with pregnancy-related listeriosis notified from 1999 to 2011, 15 (3%) were immunocompromised (eight human immunodeficiency virus (HIV)-positive including one with acquired

FIGURE 3

Median number of listeriosis cases per month, France, 1999–2011 (n=606)



immunodeficiency syndrome (AIDS), two with rheumatoid polyarthritis, two with haemorrhagic rectocolitis, two under immunosuppressive therapy but with unknown comorbidity, and one with chronic lymphocytic leukaemia). All mothers survived. Gestational age at diagnosis was recorded for 585 cases (Table 2). The median gestation period at diagnosis was 32 weeks (range: 5–41 weeks). Maternal infection was confirmed by *L. monocytogenes* isolates in blood (n=272, 45%) and/or placenta (n=215, 35%) and/or CSF (n=3, 0.01%). Of the women with meningitis, one lost the fetus at 12 WG, the two other women gave birth to a live neonate.

Among the 603 mothers, 509 (84%) completed the food questionnaire (Table 1). During the two months before diagnosis, 405 (80%) mothers had eaten at least one high risk product not recommended during pregnancy, mainly pâté (51%), and smoked salmon (33%). In south-western France, where listeriosis incidence is highest, mothers more often reported the consumption of high-risk products than in other regions, in particular of a type of pâté called rillettes (26% vs 16%, $p<0.05$), and Pyrénées' cheeses (20% vs 5%, $p<0.001$). They also reported eating uncooked meat more frequently (40% vs 17%, $p<0.001$).

Ongoing pregnancy

Ongoing pregnancies were infrequent (n=89/603, 15%) and were diagnosed at (median) 30 WG (range: 7–39 WG). All cases were confirmed by *L. monocytogenes*-positive blood culture. All mothers were treated with antibiotics (information on the type of antibiotic were not available to the authors) and only one of the

newborns was infected with *L. monocytogenes*. Review of this case revealed that the mother had had fever at 28 WG. She was treated with cephalosporins that are ineffective against *L. monocytogenes* [23]. When the result of the blood culture was available, she had no more fever and treatment was not changed. Three weeks later, she delivered a newborn with invasive listeriosis (positive blood culture).

Fetal loss

Pregnancies resulted in 166 fetal losses (27%). There was a median of 13 (range: 9–21) fetal losses per year. Fetal losses occurred at a median of 21 WG (range: 5–37 WG) and 90% occurred before 28 WG (Table 2). There were 95 (57%) miscarriages and 71 (43%) stillbirths which occurred at a median of 18 WG (range: 5–21 WG) and 25 WG (range: 22–37 WG) respectively. Fetal loss decreased significantly with gestational age at diagnosis ($p<0.001$) (Table 2).

Live-born neonatal listeriosis

Live-born neonatal listeriosis accounted for 58% (n=351) of pregnancy-related listeriosis and occurred at a median gestation period of 35 weeks (range to 22–41 weeks) in the 337 cases for whom gestational age was known. A majority of live-born neonates (n=216, 64%) were preterm births (i.e. 22–36 WG), of whom 14% (n=30) were extremely preterm births (i.e. 22–27 WG) (Table 2).

Among the neonatal cases, 329 (94%) were early neonatal cases. Among them, the median gestation period at birth was 35 WG (range: 22–41 WG) with

TABLE 1

Characteristics of pregnancy-related listeriosis cases, France, 1999–2011 (mothers n=603, births n=606)

Characteristics	Population	Missing data
Age of mothers, in years: mean (\pm SD)	29.5 (\pm 6.1)	10
Type of pregnancy-related listeriosis: n (%)		
Foetal loss (miscarriage or stillbirth)	166 (27%)	0
Live-born neonatal listeriosis	351 (58%)	0
Maternal infection with ongoing pregnancy	89 (15%)	0
Gestational age: median (range)	32 (5–41)	21
Completed food questionnaire: n (%)	509 (84%)	0
At least one not recommended product consumed: n (%)	405 (80%)	0
Number of different types of not recommended food products consumed: median (range)	3 (1–14)	0
Type of not recommended products consumed: n (%)		
Pâté	256 (51%)	0
Dried sausage	208 (41%)	0
Smoked salmon	165 (33%)	0
Unpasteurised cheeses	101 (20%)	0

95% (n=314) diagnosed less than 48 hours after birth. There were 109 (33%) confirmed invasive cases and among them 14 (13%) cases had *L. monocytogenes* culture-positive CSF. Among the 195 probable cases, there were 132 (68%) cases with maternal infection (placenta or maternal blood culture-positive) and 63 (32%) cases with no evidence of maternal infection but *L. monocytogenes* isolated from the neonate's gastric aspirate. There were only 25 (8%) possible cases with *L. monocytogenes* isolated exclusively from the neonate's surface swabs. Twenty-six (8%) early neonatal cases died. The median duration of life before death was 1 day (range: 0–24 days). Neonatal case fatality fell with gestational age, from 33% in highly preterm births (<28 WG) to 2% in infants born at term (p=0.05).

Among the 18 cases of late neonatal listeriosis, the median gestation period was 39 WG (range: 35–41 WG). It was significantly longer than the gestation period of the early neonatal listeriosis cases (p<0.001). All of them had *L. monocytogenes* culture-positive CSF. Three clusters of nosocomial infection by possible cross-infection between pairs of neonates born at the same time in the same hospital were identified. In all three clusters, the first baby had an early onset listeriosis and the second baby presented, several days later, a late neonatal listeriosis. In each pair the *L. monocytogenes* strains belonged to the same PCR serogroup and exhibited indistinguishable PFGE patterns. None of the late neonatal cases died. Information on treatment was not available to the authors.

Microbiological analyses

L. monocytogenes strains were sent to NLRC for 589 cases of pregnancy-related listeriosis: PCR serogroup IVB was predominant (n=362; 61%), followed by IIB

(n=111; 19%), IIA (n=109; 19%), and IIC (n=7; 1%). In the population with non-pregnancy-related listeriosis, the distribution of PCR serogroups was IVB (n=1,487; 46%), followed by IIA (n=810; 25%), IIC (n=521; 16%) and IIB (n=443; 14%) which differed significantly from the distribution in the population with pregnancy-related listeriosis (p<0.001). There was no association between PCR serogroup and fetal loss (p=0.17) or between PCR serogroup and neonatal death (p=0.08). For neonates, the PCR serogroup distribution was similar in cases with *L. monocytogenes* culture-positive CSF and for cases that were not neuro-invasive (p=0.43). No resistance was observed to any clinically relevant antibiotics recommended for the treatment of listeriosis.

Discussion

In France, the incidence of pregnancy-related listeriosis decreased markedly from 1986 to 1996. A similar reduction in the incidence of listeriosis was observed in the United States (US) between 1989 and 1993 and coincided with the implementation of industrial, regulatory, and educational measures [24]. Previous analyses have suggested that a substantial part of the decrease in illness due to *L. monocytogenes* from 1986 to 1996 in France was related to control measures implemented at the food production level [9]. The first *Listeria* control measures, implemented in France in 1986, targeted manufacturers producing cheese for exportation to the US, since American authorities had imposed a 'zero *Listeria*' rule on imported cheeses. These control measures were subsequently extended to all cheese producers in France in 1988. In 1992, a large outbreak involving 279 cases throughout France, including 92 pregnancy-related cases, prompted the French Ministry of Health to issue recommendations to pregnant women to avoid certain foods. After this

TABLE 2

Pregnancy-related listeriosis cases by gestational age at diagnosis, France, 1999–2011 (n=585)

Gestational age at diagnosis	All cases		Maternal infection with ongoing pregnancy		Foetal loss (miscarriage + stillbirth)		Live-born neonatal listeriosis		
	n=585	%	n=87	%	n=161	%	n=337	%	Deaths n=26
<14 WG	23	4%	8	9%	15	9%	0	0	0
14–21 WG	92	16%	17	20%	75	47%	0	0	0
22–27 WG	98	17%	13	15%	55	34%	30	9%	10
28–31 WG	79	14%	9	10%	10	6%	60	18%	10
32–36 WG	163	28%	32	37%	5	3%	126	37%	4
≥37 WG	130	22%	8	9%	1	1%	121	36%	2

WG: weeks of gestation.

outbreak, control measures were extended to include all foods potentially contaminated with *L. monocytogenes*, and hygiene measures were strengthened throughout the food distribution chain. Between 1992 and 1996, the proportion of highly contaminated food-stuffs (≥ 100 colony-forming units/g) fell substantially. Between 1994 and 2000, additional measures were implemented, such as systematic withdrawal of contaminated foods from the market and distribution of information leaflets to pregnant women by their physicians. The incidence of pregnancy-related listeriosis in France continued to fall gradually from 1996 to 2006 and has been stable since 2006. The incidence of pregnancy-related listeriosis in England, which was, in 1985, 10 times lower than in France, also decreased substantially over the same period, from 45 cases in 1985 to 15 to 20 cases per year in the early 2000s [25].

Over the last two decades, the sensitivity of the surveillance system has increased. Capture–recapture studies estimate that 76% of laboratory-confirmed cases were ascertained in 1997 [9], before introduction of the mandatory notification in 1998. This proportion was estimated at 87% in 2001 [13] and at 92% in 2006 (data not shown). Consequently, the decrease in incidence observed since 1997 is slightly underestimated.

The geographical distribution was not the same for pregnancy-related and other cases. The higher incidence seen in the south-west of France, both for pregnancy-related and other cases, is puzzling. As listeriosis is transmitted by food, this higher incidence could be a consequence of specific eating habits in this region. The food questionnaire highlighted a higher consumption only for a few high-risk products in this region. However, the questionnaire focused on food products that are mostly available throughout the country like pasteurised milk cheeses. Thus, it is possible that certain high-risk products available only in the south-west and not listed in the questionnaire, contributed to this higher incidence. Another hypothesis could be that mothers in the south-west were less aware of dietary preventive measures than in the

rest of the country. Indeed, the proportion of women in this region consuming rillettes, a high-risk product specifically targeted by the dietary recommendations, was higher than elsewhere. In France, dietary recommendations in pregnancy target both listeriosis and toxoplasmosis prevention. Interestingly, toxoplasmosis seroprevalence in pregnant women is higher in south-western France than in other regions of the country [26], supporting the hypothesis that mothers in the south-west may be less aware of dietary preventive measures. Furthermore, as women not immunised against toxoplasmosis are screened each month during their pregnancy in order to detect a seroconversion, they have a regular opportunity to receive these recommendations. We hypothesise that toxoplasmosis-positive pregnant women are less likely to be informed about dietary prevention measures than toxoplasmosis-negative pregnant women. This hypothesis is supported by the correlation between the regional incidence of pregnancy-related listeriosis and the regional seroprevalence of toxoplasmosis in pregnant women ($r=0.53$, $p=0.01$) [26].

Overall, most mothers had consumed several types of foods not recommended during pregnancy. This highlights the need to improve health education of mothers during pregnancy, in particular in certain regions. Regarding the seasonality, there is a time lag between the seasonal peak in pregnancy-related listeriosis cases and the other forms of listeriosis. As has been recently established, the incubation period for pregnancy-related listeriosis (median of 28 days, ranging from 17 days to 67 days), is much longer than the incubation period for other clinical forms of listeriosis [27]. This may explain that, even if the peak in exposure occurs in the same season, the peak in diagnosis of pregnancy-related cases is some weeks later than other cases.

Pregnancy-related listeriosis mostly affects healthy women without additional predisposing conditions [28,29]. Indeed, in our study, only 3% of the mothers had additional predisposing conditions.

From 1999 to 2010, 18% of reported listeriosis cases occurred in pregnant women or neonates. This proportion was similar in other countries such as the US (16%, from 2004 to 2007) [30], Germany (15%, from 2001 to 2005) [31], and England (12%, from 2001 to 2008) [25]. In our study, 27% (n=166) of pregnancy-related cases resulted in fetal loss, compared to 20% in the US (from 2004 to 2007) [30] and 33% in Denmark (from 1994 to 2005) [5]. The proportion of cases with ongoing pregnancy in our study (15%) was similar to the proportion reported in Denmark (13%) [5].

The proportion of preterm births among listeriosis cases is extremely high: 70% of 408 neonatal listeriosis cases were preterm births, compared with 7% of the total 14,832 births in a survey carried out in France in 2010 (relative risk (RR): 9.5; 95% confidence interval (CI): 8.5–10.8) [22]. The discrepancy is even higher for severely premature births (<32 WG): 38% of neonatal listeriosis cases vs 2% of all births in France (RR: 25.7; 95% CI: 20.9–31.6), and extremely premature births (22–27 WG): 21% versus 0.7% of all births in France (RR: 31.2; 95% CI: 23.8–42.6) [22]. The prognosis for fetal survival among pregnancy-related listeriosis improves with an increasing gestation period at diagnosis, in particular after 28 WG. Indeed, 87% of fetal losses were diagnosed before 28 WG. Compared with the study by Humbert et al on 601 pregnancy-related listeriosis cases in France between 1970 and 1975, our study shows that the proportion of preterm birth among live-born neonatal cases has not changed (64% vs 63%) [32]. However, the case fatality ratio has fallen dramatically: 33% in the period from 1970 to 1975 versus 4% in the period 1999 to 2011 ($p < 0.001$) [32], probably due to the progress in neonatal care. The proportion of stillbirths in preterm infants (22–31 WG) with neonatal listeriosis is higher than in preterm infants of a general population cohort (Epipage study) (39% vs 25%, $p < 0.001$) [33]. In contrast, the case fatality ratio of live-born preterm neonates with listeriosis is similar to the case fatality ratio of the live-born preterm neonates of Epipage (22% vs 20%, $p = 0.22$).

The PCR serogroup distribution differed significantly among pregnancy-related listeriosis and non-pregnancy-related listeriosis. Serogroup IVB, which is the most common PCR serogroup in human listeriosis [5,14,34,35], was more frequent than in non-pregnancy-related listeriosis and serogroup IIB was less frequent.

This study was based on mandatory notifications made by physicians and microbiologists in the context of the French national surveillance programme on listeriosis and therefore has some limitations. As no information on clinical symptoms was available, we considered neonates with *L. monocytogenes* isolated exclusively from surface swabs as possible listeriosis cases although they may not actually have been infected. Moreover, we have no information on the long-term sequelae in the newborn. The MONALISA

study (Multicentric Observational National Analysis of LIsteriosis and ListeriA; <http://clinicaltrials.gov/show/NCT01520597>), a prospective study on listeriosis, will present detailed clinical, biological and microbiological data of all incident cases of listeriosis in France from the end of November 2009 until 2013, including pregnancy-related cases, and provide extensive information on the prognosis of newborns.

Conclusion

Pregnancy-related *L. monocytogenes* infection is a rare but severe infection in pregnancy. The proportion of fetal loss (27%) and, for neonatal listeriosis, the proportion of preterm birth (64%) is extremely high. Fortunately, there has been a marked decrease in incidence from 1984 to 2006 related to the implementation of specific *L. monocytogenes* control measures at the food production level. It is important to maintain these measures, which have proven their efficacy. The incidence of pregnancy-related listeriosis was lower in regions where the prevalence of toxoplasmosis was lower, and this may be related to differences in the distributed information about preventing toxoplasmosis and listeriosis. This suggests that promotion of dietary recommendations could contribute to the prevention of listeriosis in pregnancy. As 80% of mothers reported having eaten high-risk food during pregnancy, fetal loss (13 cases/year) could be reduced by improving awareness of pregnant women, in particular about dietary recommendations.

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Conflict of interest

None declared.

Authors' contributions

Delphine Girard analysed and interpreted data, drafted and revised the manuscript. Alexandre Leclercq performed typing of the *Lm* strains, and participated in writing the manuscript. Edith Laurent collected and analysed data. Marc Lecuit and Henriette De Valk interpreted data and revised the article for intellectual content. Véronique Goulet conceptualised and designed the study, designed the data collection instruments, interpreted data, participated in writing the article. All authors approved the final manuscript as submitted.

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