

Listeriosis in Spain based on hospitalisation records, 1997 to 2015: need for greater awareness

Zaida Herrador^{1,2}, Alin Gherasim^{3,4}, Rogelio López-Vélez^{2,5}, Agustín Benito^{1,2}

1. National Centre for Tropical Medicine, Health Institute Carlos III (ISCIII in Spanish), Madrid, Spain

2. Network Biomedical Research on Tropical Diseases (RICET in Spanish), Madrid, Spain

3. National Centre of Epidemiology, Health Institute Carlos III (ISCIII in Spanish), Madrid, Spain

4. Network Biomedical Research Centre in Epidemiology and Public Health (CIBERESP in Spanish), Madrid, Spain

5. National Referral Unit for Tropical Diseases, Infectious Diseases Department, Ramón y Cajal Hospital, Instituto Ramón y Cajal de Investigación Sanitaria, Madrid, Spain

Correspondence: Zaida Herrador (zherrador@isciii.es)

Citation style for this article:

Herrador Zaida, Gherasim Alin, López-Vélez Rogelio, Benito Agustín. Listeriosis in Spain based on hospitalisation records, 1997 to 2015: need for greater awareness. *Euro Surveill.* 2019;24(21):pii=1800271. <https://doi.org/10.2807/1560-7917.ES.2019.24.21.1800271>

Article submitted on 21 May 2018 / accepted on 18 Sep 2018 / published on 23 May 2019

Introduction: Listeriosis is a food-borne disease of public health importance that has recently been involved in prolonged outbreaks. Despite its relevance, listeriosis is under-reported in many European countries. **Aim:** We aimed to describe listeriosis epidemiology in Spain from 1997–2015. **Methods:** We performed a retrospective study using the Spanish hospitalisation database. We calculated the mean number of hospitalisations per year and region. Pregnancy and neonatal-related listeriosis rates were computed. Relation between death and the presence of underlying health conditions was explored. **Results:** Between 1997–2015, 5,696 listeriosis hospitalisations occurred, showing a constantly increasing trend. Higher hospitalisation rates were located in the north of the country compared to southern regions. The age group ≥ 65 years old was the most represented (50%). Pregnant women and newborns accounted for 7% and 4% of hospitalisations, respectively. An underlying immunocompromising condition was present in 56.4% of patients: cancer (22.8%), diabetes mellitus (16.6%) and chronic liver disease (13.1%). Death occurred in 17% of patients, more frequently among those ≥ 65 years old (67.5%), with sepsis (39.9%) or with meningoencephalitis (19.2%). **Conclusion:** Listeriosis is an emergent public health problem in Spain that calls for targeted action. Further prevention strategies are urgently needed, including food safety education and messaging for all at-risk groups.

Introduction

Listeriosis is an infectious disease caused by bacteria of the genus *Listeria* spp. *L. monocytogenes* is the major pathogenic species in both animals and humans. *L. monocytogenes* is a Gram-positive, rod-shaped organism that can grow in aerobic and anaerobic conditions [1], is widely distributed in the environment and is able to contaminate a wide variety of foods or beverages

(soft cheese, deli meats, unpasteurised milk, refrigerated smoked seafood, etc.) [2]. The bacteria can multiply at refrigerator temperatures [3]; therefore, contaminated products are often kept for several days or even weeks, e.g. in the household/restaurants, and may be eaten on multiple occasions, which can complicate the identification of the incriminated food source [4].

The clinical syndromes of listeriosis include: febrile gastroenteritis, sepsis, central nervous system (CNS) involvement in the form of encephalitis, meningoen- cephalitis and focal infections such as pneumonia myo-endocarditis and septic arthritis, etc [5]. Invasive listeriosis most commonly affects pregnant women, neonates, elderly people and people with chronic conditions or weakened immune response [6]. Listeriosis has one of the highest case fatality rates among all food-borne infections; when it affects the CNS, the mortality rate is above 50% and neurological sequelae are present in more than 60% of survivors [2]. Listeriosis is also associated with fetal and neonatal death.

Worldwide, listeriosis is an emerging infection of public health concern [7]. In Europe, human listeriosis peaked in incidence during the 1980s, showed a general decline during the 1990s and stabilised in the 2000s [8]. More recent data show an increasing trend since 2008 [9]. This increase seems to be related to the ageing of the population and the increase in life expectancy of immunocompromised patients, but also to changes in the ways food is produced, stored, distributed and consumed around the world [10]. Although listeriosis is often a sporadic disease [11], large food-borne outbreaks have occurred during the last decade in Europe and the United States (US) [12]. In South Africa, an outbreak with more than 1,024 laboratory-confirmed listeriosis cases, as at 2 May 2018, has been

ongoing since the start of 2017, with a 28.6% case fatality rate [13].

In Spain, food safety criteria (FSC) for *L. monocytogenes* follow European Commission (EC) regulations [14,15]. Before 2015, when it was added to the list of mandatory notifiable diseases, regions could voluntarily report listeriosis to the Microbiological Information System (Sistema de Información Microbiológica, SIM) [16]. Using the centralised hospital discharge database (Conjunto Mínimo Básico de Datos, CMBD), we aimed to describe the epidemiology of listeriosis in Spain from 1997–2015.

Methods

Data analysis

Using the CMBD database, we performed a retrospective descriptive study of listeriosis epidemiology between 1 January 1997–31 December 2015. The CMBD database receives notifications from around 98% of the public hospitals in Spain [17]. The National Health System (NHS) provides free medical care to 99.5% of the Spanish population; however, those who are not covered by the NHS can also be treated at public hospitals [18]. For this study, the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) was used [19]. The case definition was a patient with ICD-9-CM diagnostic listeriosis (ICD-9 code: 027.0), placed in any diagnostic position. Relevant underlying conditions were also explored by searching for all related conditions in any diagnostic position. According to the literature, some of these conditions are malignant neoplasm (ICD-9 code: 140–209), diabetes mellitus (ICD-9 code: 250), chronic liver disease (ICD-9 code: 571), HIV infection (ICD-9 code: 042) and other immunosuppressive condition (ICD-9 code: 279).

In order to assess temporal and geographical patterns, the average number of hospitalisations per year and region (Comunidad Autónoma, CC.AA) were calculated. The population figures from the National Statistics Institute (Instituto Nacional de Estadística, INE) website were used to determine the population at risk [20]. Mortality data and live birth statistics, available since 1998, were also obtained from the INE website. To estimate the number of pregnant women, the following previously published method was applied: the fertility rate was multiplied by nine-twelfths of the population of women of reproductive age, since pregnancy lasts an average of 9 months. Similarly, the abortion/miscarriage rate was multiplied by a sixth of the population of women of reproductive age, since abortion usually occurs after 2 months of pregnancy. These two numbers were added to estimate the number of women who were pregnant per year during the study period [21].

Hospitalisation trends were assessed by age group and region. Results in terms of mean rates by CC.AA were plotted on maps using the Geographical Information

System QGIS free software version 2.18.13 (QGIS Development Team).

Socio-demographic and clinical data were extracted from the CMBD. Age was categorised in four groups: ≤ 15 , 16–44, 45–64 and ≥ 65 years old, to provide an overview of children, young adults, older adults and elderly people. Hospitalisation costs were calculated using diagnostic cost groups based on diagnosis-related groups (DRGs) for hospitalised patients and their age, sex and resource consumption. DRGs represent a medical-economic entity, i.e. a set of diseases requiring analogous management resources [22].

Frequencies and percentages were used to summarise data. The association between related health conditions and death was assessed using a chi-squared test. Logistic regression models were obtained using a manual backward stepwise procedure and risk ratios (RRs) were computed with 95% confidence intervals (CI). Age was included as an adjustment variable and p values < 0.05 were considered statistically significant. Data analysis was performed using STATA software version 14 (StataCorp LLC, College Station, US).

Ethical statement

This study involves the use of patient medical data from the CMBD. These data are hosted by the Ministry of Health, Consumer Affairs and Social Welfare (MSCBS). Researchers working in public and private institutions can request access to the database by filling in and signing a questionnaire available on the MSCBS website. In this questionnaire, a signed confidentiality commitment is required. All data are anonymised and de-identified by the MSCBS before it is made available to applicants [17].

Results

Spatial and temporal trends in Spain

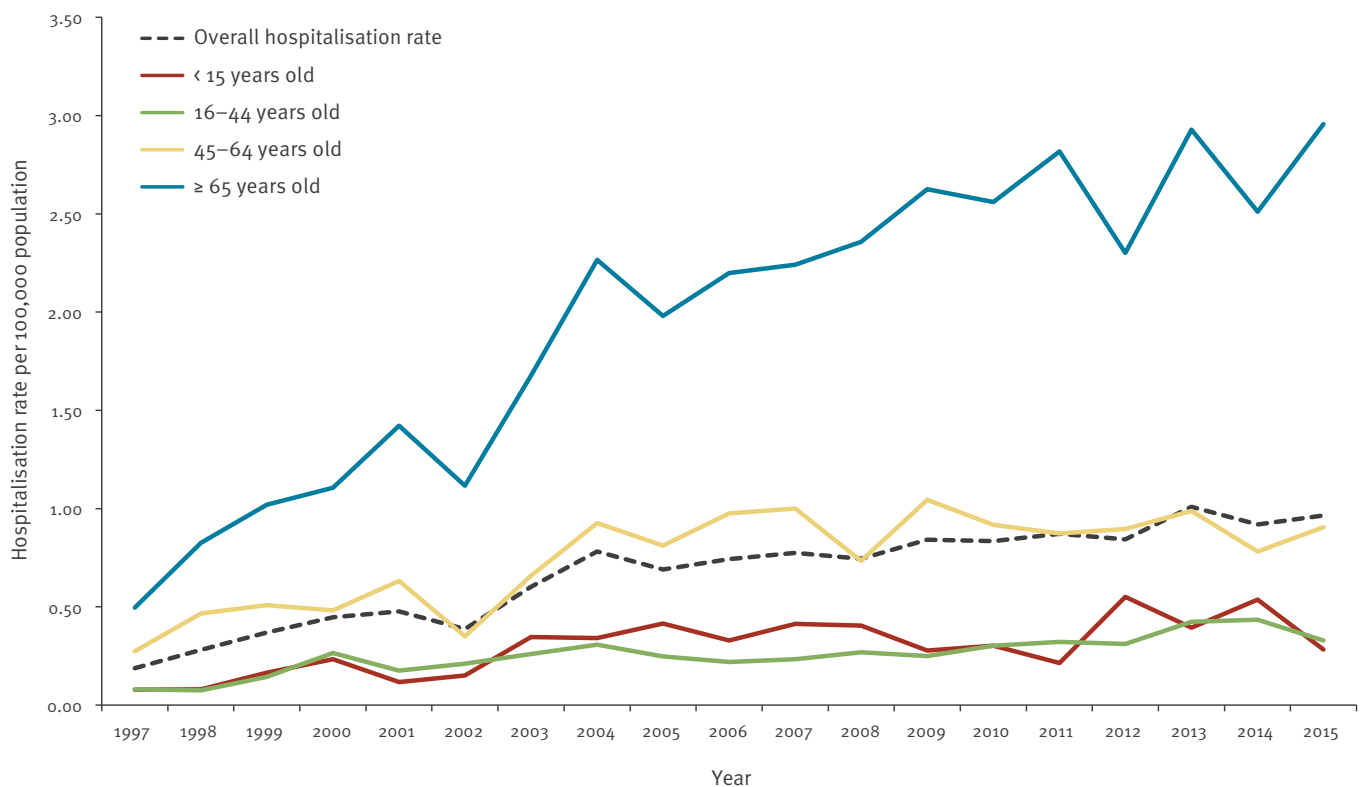
Between 1997–2015, there were 5,696 hospitalisations with diagnosis of listeriosis in any diagnostic position recorded in the CMBD database. The ICD-9 code for listeriosis was positioned as first diagnosis in 3,110 (54.6%) of all such hospitalisations and as second diagnosis in 1,802 (31.6%). The mean listeriosis hospitalisation rate for the study period was 0.67 per 100,000 population (range: 0.19 in 1997 to 1.01 in 2013), with an increasing trend over the study period ($p = 0.017$).

When comparing listeriosis hospitalisation rates by age group, relevant and significant differences emerged ($p < 0.05$). The age group ≥ 65 years old showed the highest rate, followed by 45–64 year olds. For those ≥ 65 years old, the mean hospitalisation rate in 2004–15 was more than twice that of the previous period: 2.48 vs 1.09 per 100,000 population, respectively (Figure 1).

Regarding the regional distribution, most CC.AA with higher hospitalisation rates were located in the north

FIGURE 1

Listeriosis hospitalisation rate by age group, Spain, 1997–2015 (n = 5,696)



of the country. Catalonia had the highest incidence rates of listeriosis hospitalisations (23.19 hospitalisations/100,000 population), followed by Cantabria (18.87/100,000 population), Rioja (17.09/100,000 population), Basque country (17.03/100,000 population) and Galicia (14.82/100,000 population) (Figure 2).

Socio-demographic characteristics and clinical features of listeriosis-related hospitalisations

The mean age of the 5,696 listeriosis-hospitalised patients was 58.6 years, with a median value of 64.5 years (Interquartile range (IQR): 47–75). Of those hospitalised, 59% were male (Table 1). The median age was 66 years (IQR: 53–75) in men and 61 years (IQR: 35–76) in women. As shown in Figure 1, the age group ≥ 65 years old was the most represented (50%). Males predominated in the age groups 45–64 years old (68.1%) and ≥ 65 years old (63%), while females represented 64.6% of those 15–44 years old (Figure 3; $p < 0.01$).

Certain parallels were observed between the increase in the number of people ≥ 65 years old who were hospitalised for listeriosis and the increase in life expectancy in Spain during the same period (Supplementary Figure 1).

The average length of hospital stay for listeriosis was 21.4 days. We found a wide range for the hospitalisation costs, with a median value of EUR 6,327 per case (IQR: 4,680–6,858), with no significant changes over time (Table 1).

Meningoencephalitis and/or septicaemia was seen in 43.3% and 8% of listeriosis hospitalisations, respectively. Males developed meningoencephalitis more often than women (47.4% vs 37.3%; $p < 0.01$). No differences were observed between males and females for septicaemia. Meningoencephalitis was more frequent among the age group 45–64 years old (50.1%), while those ≥ 65 years old were more likely to have developed septicaemia (9.2%; $p < 0.01$).

Fatal outcome occurred in 17% of all listeriosis hospitalisations. The mean mortality rate was 0.06 per 100,000 population. Patients aged ≥ 65 years old accounted for 67.5% of deaths ($p < 0.001$). Fatal outcome happened in 19.2% of meningoencephalitis (RR: 1.26; 95% CI: 1.12–1.41; $p < 0.01$) and 39.9% of patients with septicaemia (RR: 2.66; 95% CI: 2.34–3.03; $p < 0.01$).

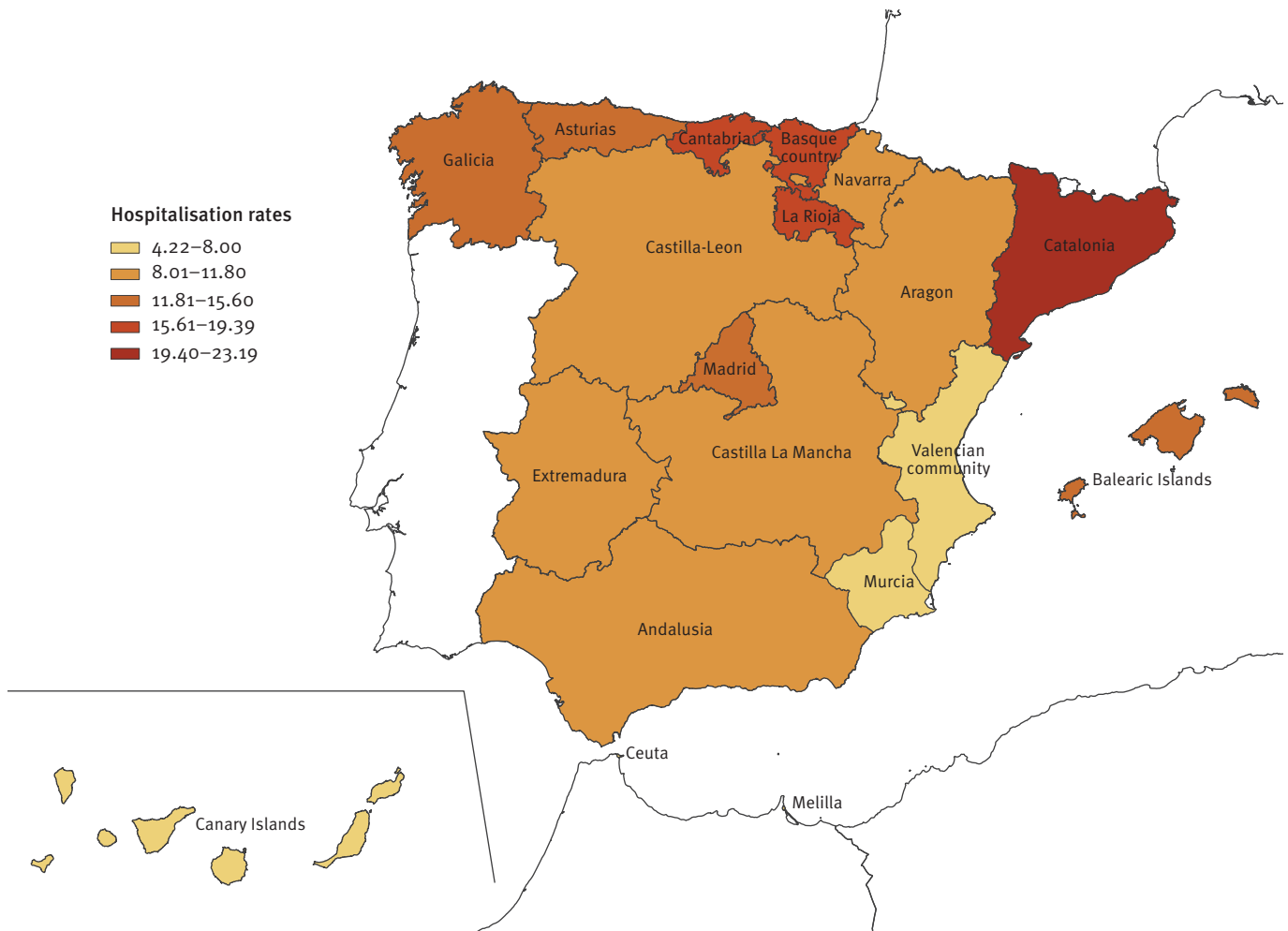
Pregnancy-related listeriosis and neonatal listeriosis

Pregnant women accounted for 7% ($n = 396$) of listeriosis hospitalisations. The mean infection rate during pregnancy was 7.19 per 100,000 pregnant women, showing several peaks (Figure 4) and a significant increase during the study period. No fatal outcomes were registered among pregnant women ($p < 0.001$).

Neonatal infections represented 4% ($n = 225$) of the overall listeriosis hospitalisations. The mean neonatal infection rate for the study period was 2.75 per 100,000

FIGURE 2

Listeriosis hospitalisation incidence rates per 100,000 population, by region, Spain, 1997–2015 (n = 5,696)



live births, indicating an increase from 1998–2007 (no cases were registered in 1997). This was followed by a steady decline in 2008–09, an increase from 2010–14 and finally a steady decline from 2015. Fatal outcome was less frequent in infected neonates than in the overall population (8.9% vs 17.3%; $p < 0.01$).

Immunodeficiency-related listeriosis

Underlying immunocompromising conditions were observed in 56.4% (3,213/5,696) of the hospitalised patients: malignant neoplasm (n = 1,298; 22.8%), diabetes (n = 943; 16.6%), chronic liver disease (n = 747; 13.1%), HIV infection (n = 151; 2.7%) and other immunocompromising conditions (n = 69; 1.2%). Within the malignant neoplasm group, particularly frequent diagnoses were secondary malignant neoplasm (n = 480; 8.4%; ICD-9: 196–198), malignant neoplasm of trachea bronchus and lung (n = 164; 2.9%; ICD-9: 162), lymphoid leukaemia (n = 146; 2.6%; ICD-9: 204), other malignant neoplasms of lymphoid and histiocytic tissue (n = 132; 2.3%; ICD-9: 202), malignant neoplasm of colon (n = 94; 1.7%; ICD-9: 153) and malignant neoplasm of liver and intrahepatic bile ducts (n = 67; 1.3%; ICD-9: 155).

Hospitalised patients aged ≥ 65 years old were more likely to have malignant neoplasm and/or diabetes mellitus ($p < 0.01$), while chronic liver disease was more frequent in patients 45–64 years old (45.9%; $p < 0.01$). HIV-related listeriosis in 15–44 year old patients accounted for 55% of the listeriosis-hospitalised patients with HIV ($p < 0.01$).

Relation between fatal outcome and the presence of an underlying health condition was explored and adjusted by age. Fatal outcome occurred more frequently in hospitalised patients with listeriosis and co-diagnosis of diabetes mellitus (adjusted RR: 1.33; 95% CI: 1.10–1.60) and/or malignant neoplasm (aRR: 1.90; 95% CI: 1.63–2.22). Among the most prevalent malignant neoplasms, only secondary malignant neoplasm and malignant neoplasm of trachea, bronchus and lung increased the risk of death (Table 2).

Discussion

This study provides a 19-year review of listeriosis hospitalisations in Spain. To date, the few articles that have been published on listeriosis epidemiology in Spain were focused on outbreak investigations or based on incomplete information sources [23–25]. To

TABLE 1

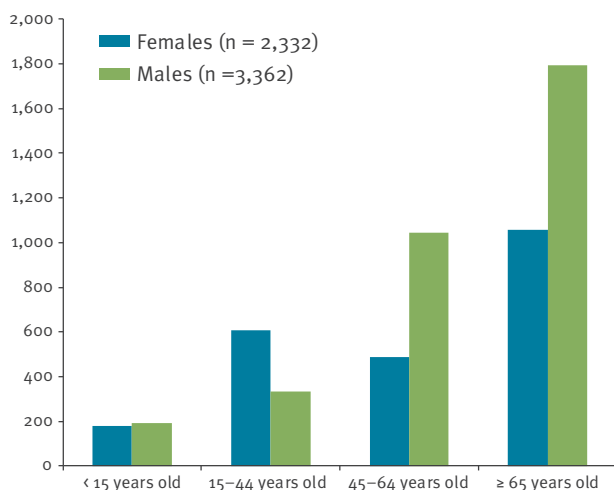
Socio-demographic characteristics of listeriosis hospitalisations, Spain, 1997–2015 (n = 5,696)

Variables		N	%
Sex	Male	3,362	59.0
	Female	2,332	41.0
Age group (years)	≤15	373	6.5
	15–44	943	16.6
	45–64	1,532	26.9
	≥65	2,848	50.0
Type of admission	Urgent	5,212	91.7
	Programmed	469	8.3
Type of discharge	Home	4,245	75.4
	Transfer	420	7.4
	Death	968	17.2
Variables	Mean	Median	IQR
Age (years)	58.6	64.5	47–75
Hospitalisation length of stay (days)	21.4	17	9–26
Hospitalisation cost (Euros)	38,157	6,327	4,680–6,858

IQR: interquartile range.

FIGURE 3

Number of listeriosis hospitalisations by sex and age group, Spain, 1997–2015 (n = 5,694)



our knowledge, this is the first study to address listeriosis epidemiology nationwide.

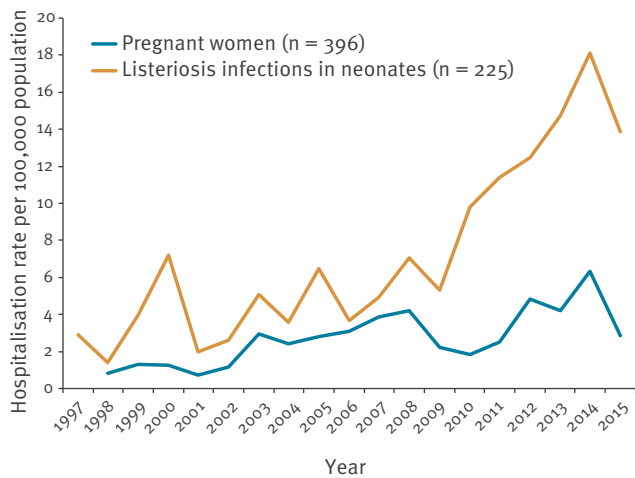
Between 1997–2015, a total of 5,696 listeriosis-related hospitalisations occurred in Spain. From 2009–13, there were 588 listeriosis cases reported to SIM, the

European Surveillance System (TESSy) and the corresponding yearly European Food Safety Authority (EFSA) reports [26]; however, 2,051 listeriosis-related hospitalisations were recorded in the CMBD, indicating considerable under-reporting. Even if this indicates that the epidemiological scenario is quite uncertain, in 2012 the Spanish listeriosis rate reported to EFSA was the second highest of any country in the European Union (EU) (0.93, vs an EU-wide incidence rate of 0.41/100,000 population) [27]; this indicates that more attention needs to be given to preventing and controlling this disease in Spain.

Our results suggest an increasing trend of listeriosis infection in Spain during the study period (1997–2015). In the last decade, listeriosis incidence rates have increased or remained stable at relatively high levels across Europe. Despite the application of the FSC for *L. monocytogenes* in ready-to-eat (RTE) foods from 2006 onwards, a statistically significant increasing trend of human invasive listeriosis has been reported in the EU/European Economic Area (EEA) from 2009–13 [28]. From 2012–16, between 1,754 and 2,555 *L. monocytogenes* cases were reported annually to TESSy by 30 EU/EEA countries [3]. In the absence of systematic and national surveillance in several European countries, under-reporting may be masking an even worse scenario. In Spain, listeriosis became a mandatory

FIGURE 4

Listeriosis hospitalisation rates in pregnant women and neonates, per 100,000 live births, Spain, 1998–2015 (n = 621)



notifiable disease in 2015 [29]. As demonstrated in the Netherlands, public health investment in surveillance can yield an increase in reported cases of listeriosis [30]; therefore, an increase in listeriosis detection may be expected in the future.

The increasing proportion of susceptible persons in the general population is a feasible contributing factor to this increased incidence [31]. In our study, listeriosis rates increased mostly in those ≥ 65 years old; according to the 2015 EFSA report, the proportion of cases in this age group steadily increased from 56% in 2008 to 64% in 2015 [9], which is similar to our results.

Another potential contributing factor to the overall increase in listeriosis is the rise in consumption of RTE foods. European surveys have revealed associations between listeriosis and several parameters, including food packaging types, preparation practices and storage temperatures; the stage of sampling with respect to shelf life; and a lack of education and training of food handlers [11].

The emergence of particularly virulent strains of *Listeria* spp. is also of concern for public health. It has been demonstrated that *L. monocytogenes* can exhibit tolerance to quaternary ammonium disinfectants, as well as temperature-dependent resistance to phages, which can be gained through acquisition of new genes as well as mutations in existing genes [32]. Moreover, it seems that differences among strains have an impact on virulence of specific immunocompromised subpopulations [8]. Another possible explanation is the increased consumption of drugs that reduce gastric acidity. In humans, the low pH of the stomach provides a significant barrier to *Listeria* spp. infection and it has been demonstrated that patients taking medications that reduce gastric acid (like proton pump inhibitors

(PPI)) are at increased risk of infection [33]. In 2010, PPI became the most commonly consumed active compound in Spain, in terms of number of packages sold. In fact, in comparison to other European countries, Spain leads gastric anti-secretory drug consumption with the number of prescriptions soaring 70% over the European average [34].

During the study period, only a few listeriosis outbreaks in Spain were reported in the literature, mostly in the Basque country. These outbreaks were related to the consumption of Latin-style fresh cheese made from pasteurised milk in Portugal [35] and cooked ham [36]. In both situations, health professionals were informed and were recommended to strongly consider the diagnosis of listeriosis in high-risk individuals. Genetic studies also revealed the occurrence of an outbreak in Castilla-Leon, which was unreported and thus the source of the outbreak was not traced [37]. Several outbreaks due to the consumption of 'vegetables and juices and other products thereof' were also reported to EFSA during 2010–16 [3]. Furthermore, the prevalence of *L. monocytogenes* in RTE products in markets in northern Spain was recently studied, finding that smoked fish was the most frequently contaminated food category [38]. These findings and the outbreaks mentioned above influenced Spain's change to mandatory national reporting of listeriosis cases in 2015 [16]. The Spanish Agency for Consumer Affairs, Food Safety and Nutrition (Agencia Española de Seguridad Alimentaria y Nutrición) receives several notifications every year and informs the regional authorities via the national Food Alert Network and the European Commission Services via the Rapid Alert System for Food and Feed; at the national level, contaminated products are recalled from markets [39]. It is nevertheless possible that additional outbreaks and/or clusters may have gone unnoticed due to the lack of surveillance.

Improvements in listeriosis surveillance (including accurate microbiological investigations) with active collaboration between public health officials and food regulatory officials should improve the situation. Data sharing at the European level is also essential, given that many food-borne disease outbreaks happen in a multi-country setting [3]. Without further action, yearly numbers are likely to continue to grow, for the aforementioned reasons.

We found relevant disparities between regions, with higher hospitalisation rates mostly in the north of the country. This might be due to differences in dietary habits, food consumption or regulations; the population's average age; differences in educational preventive measures and/or that health professionals are more prone to seek listeriosis diagnosis. However, further investigation is needed to confirm these hypotheses.

In this study, we found that from 1997–2015 *Listeria* spp. infection in Spain was more common among males. The

TABLE 2

Related health conditions and fatal outcome in listeriosis hospitalisations, Spain, 1997–2015 (n = 5,696)

Related health conditions			Death				RR	95% CI	aRR	95% CI
			No		Yes					
			n	%	n	%				
Malignant neoplasm	All	Yes	950	73.19	348	26.81	1.90	1.69–2.13*	1.90	1.63–2.22*
		No	3,778	85.90	620	14.10				
	Secondary malignant neoplasm	Yes	317	66.04	163	33.96	2.20	1.91–2.53*	2.61	2.12–3.21*
		No	4,411	84.57	805	15.43				
	Malignant neoplasm of trachea bronchus and lung	Yes	104	63.41	60	36.59	2.22	1.81–2.75*	2.59	1.86–3.60*
		No	4,624	83.59	908	16.41				
	Lymphoid leukaemia	Yes	121	82.88	25	17.12	1.00	0.70–1.45	0.85	0.55–1.32
		No	4,607	83.01	943	16.99				
	other malignant neoplasms of lymphoid and histiocytic tissue	Yes	100	75.76	32	24.24	1.44	1.06–1.96*	1.36	0.90–2.05
		No	4,628	83.18	936	16.82				
	Malignant neoplasm of colon	Yes	73	77.66	21	22.34	1.32	0.90–1.94	1.12	0.69–1.84
		No	4,655	83.10	947	16.90				
Malignant neoplasm of liver and intrahepatic bile ducts	Yes	49	73.13	18	26.87	1.59	1.07–2.37*	1.43	0.83–2.48	
	No	4,679	83.12	950	16.88					
HIV infection		Yes	129	85.43	22	14.57	0.85	0.58–1.26	1.49	0.93–2.41**
		No	4,599	82.94	946	17.06				
Diabetes mellitus		Yes	781	82.82	162	17.18	1.01	0.87–1.18	1.33	1.10–1.60*
		No	3,947	83.04	806	16.96				
Chronic liver diseases		Yes	603	80.72	144	19.28	1.16	0.99–1.36**	1.13	0.92–1.38
		No	4,125	83.35	824	16.65				

aRR: adjusted risk ratio; CI: confidence interval; RR: relative risk.

* p < 0.05; ** p < 0.10.

origin of the sex preference of *L. monocytogenes* infection has not yet been clarified, but it seems to be related to susceptibility to infection, as demonstrated for other infectious diseases [40]. The highest hospitalisation rate for both sexes was seen in the ≥ 65 age group, with a higher rate for males than for females. However, females accounted for more hospitalisations in the age group 15–44, which is believed to largely reflect pregnancy-related listeriosis. The mean length of hospital stay and associated costs, including for those individuals who ultimately died as a result of their infections, were quite high, close to those in an outbreak in Canada [41]. In a study carried out in the

Netherlands, perinatal listeriosis accounted for the highest cost-of-illness per infected case among the 14 most frequent food-related pathogens [42].

Death occurred in 17% of the listeriosis hospitalisations observed in this study. In the literature, the overall listeriosis mortality rate ranged from 20–30% [43], a bit higher than the rate we encountered. Considering that we only analysed hospitalised patients, the opposite should have been expected. Nevertheless, non-invasive listeriosis cases were also identified. In fact, fatal outcome in listeriosis hospitalisations was significantly associated with being ≥ 65 years old, the

presence of meningoencephalitis or septicaemia, and some underlying conditions.

An increasing trend in listeriosis hospitalisation rate was observed in pregnant women. According to a recent EFSA report, listeriosis cases in Europe have increased among women aged 25–44. It is believed that these cases are mainly pregnancy related [28]. In the US and France, the incidence of listeriosis in pregnant women declined in the 1990s after the implementation of industrial, regulatory and educational measures. Moreover, the incidence of pregnancy-related listeriosis was lower in French regions with a low prevalence of toxoplasmosis [44], which may be related to differences in educational measures to prevent both diseases. In Spain, there is currently no screening for listeriosis during pregnancy, nor specific dietary recommendations for pregnant women [45]; therefore, dietary recommendations and screening activities during pregnancy should be introduced.

Malignant neoplasm, mostly hematologic disease, was observed in 22.8% of listeriosis-related hospitalisations. Cancer and immunosuppressive therapy were among the most frequently recorded comorbid conditions in non-pregnancy-associated cases of listeriosis, mainly due to impaired cell-mediated immunity and other underlying conditions [5]. Moreover, the mortality rate of *L. monocytogenes* infection is elevated in cancer patients, as infections can be more difficult and time consuming to treat [46]. Secondary malignant neoplasm and malignant neoplasm of trachea, bronchus and lung were the malignant neoplasms with the highest probability of fatal outcome. In a review of listeriosis cases reported in France from 2001–08, patients with lung and pancreatic cancer had the highest case fatality rate of listeriosis [47].

Fatal outcome also occurred more frequently in hospitalised patients with chronic liver diseases and/or diabetes mellitus, although statistical difference only remained significant for diabetes mellitus after adjustment by age. According to a review of listeriosis cases worldwide, patients with cancer and type 2 diabetes mellitus have five times the risk of contracting listeriosis [48]. Diabetes mellitus may lead to an immunocompromised state by decreased efficacy of cell-mediated immunity; for example, diabetic patients are twice as susceptible to bacterial meningitis as patients who are not diabetic [49]. Moreover, patients with diabetes may have additional immunocompromising conditions. Health professionals should be aware of this and specific food recommendations should be given to these patients, together with other public health general interventions.

Limitations and conclusions

Our study has several limitations. Even if the CMBD provide information from a network of hospitals that covers more than 99% of the population in Spain [13], hospital discharge records do not include cases managed in an

outpatient setting or asymptomatic cases; thus, hospital records underestimate the real burden of listeriosis in Spain. Moreover, the CMBD does not provide information about the laboratory tests used for listeriosis diagnosis, which impairs the quality of the data. Also, we could not identify mother-baby pairs, as the personal information necessary to do this is missing from this database due to data protection.

In conclusion, our report highlights that listeriosis is an important public health problem in Spain that needs to be prioritised, especially due to its increasing trend and severity. Listeriosis surveillance needs to be improved and further targeted prevention is urgently needed, including food safety education and messaging in all at-risk groups. Implementing, for example, the US Centre for Disease Control's recommendations for the prevention of listeriosis for the general public—especially high-risk populations—may be a starting point [25]. Furthermore, industrial and regulatory measures needs to be implemented in parallel, as an integrated and multi-sectoral approach is the only way to successfully prevent and control listeriosis.

Acknowledgments

We would like to thank the General Sub-direction of the Institute for Health Information, Spanish Ministry of Health, Consumer Affairs and Social Welfare, for providing the information on which this study is based. The corresponding author's affiliation centre belongs to the ISCIII-Sub. Gral. Redes- Network Biomedical Research on Tropical Diseases (RICET in Spanish) grant RD16CIII/0003/0001, RD16/0027/0020, RD16CIII/0003/0001 and the European Regional Development Fund. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest

None declared.

Authors' contributions

ZH: Conceptualisation, data curation, formal analysis, methodology, project administration, writing – original draft, writing – review and editing.
AG: Formal analysis, methodology, writing – original draft, writing – review and editing.
RLV: Conceptualisation, formal analysis, writing – review and editing.
AB: Conceptualisation, project administration, writing – review and editing.

References

1. Goulet V, King LA, Vaillant V, de Valk H. What is the incubation period for listeriosis? *BMC Infect Dis.* 2013;13(1):11. <https://doi.org/10.1186/1471-2334-13-11> PMID: 23305174
2. de Valk H, Jacquet C, Goulet V, Vaillant V, Perra A, Simon F, et al. Surveillance of listeria infections in Europe. *Euro Surveill.* 2005;10(10):9-10. <https://doi.org/10.2807/esm.10.10.00572-en> PMID: 29208120
3. European Food Safety Authority (EFSA), European Centre for Disease Prevention and Control (ECDC). Multi-country outbreak of *Listeria monocytogenes* serogroup IVb, multi-locus

- sequence type 6, infections probably linked to frozen corn. Stockholm: ECDC; 2018. Available from: <http://ecdc.europa.eu/en/publications-data/multi-country-outbreak-listeria-monocytogenes-serogroup-ivb-multi-locus-sequence>
4. Hoelzer K, Pouillot R, Dennis S. Animal models of listeriosis: a comparative review of the current state of the art and lessons learned. *Vet Res (Faisalabad)*. 2012;43(1):18. <https://doi.org/10.1186/1297-9716-43-18> PMID: 22417207
 5. Silk BJ, Date KA, Jackson KA, Pouillot R, Holt KG, Graves LM, et al. Invasive listeriosis in the Foodborne Diseases Active Surveillance Network (FoodNet), 2004-2009: further targeted prevention needed for higher-risk groups. *Clin Infect Dis*. 2012;54(Suppl 5):S396-404. <https://doi.org/10.1093/cid/cis268> PMID: 22572660
 6. Schlech WF 3rd. Listeria gastroenteritis--old syndrome, new pathogen. *N Engl J Med*. 1997;336(2):130-2. <https://doi.org/10.1056/NEJM199701093360211> PMID: 8988894
 7. Pal M, Ayele Y, Kundu P, Jadhav VJ. Growing Importance of Listeriosis as Food borne Disease. *J Excip Food Chem*. 2017;3(04):1-4. <https://doi.org/10.4172/2472-0542.1000133>
 8. European Food Safety Authority (EFSA). Scientific Opinion of the Panel on Biological Hazards on a request from the European Commission on Request for updating the former SCVPH opinion on Listeria monocytogenes risk related to ready-to-eat foods and scientific advice on different levels of Listeria monocytogenes in ready-to-eat foods and the related risk for human illness. *EFSA J*. 2007;599:1-42.
 9. European Food Safety Authority, European Centre for Disease Prevention and Control. The European Union summary report on trends and sources of zoonoses, zoonotic agents and food borne outbreaks in 2015. *EFSA J*. 2016;14. <https://doi.org/10.2903/j.efsa.2016.4634>
 10. Centers for Disease Control and Prevention (CDC). Preliminary FoodNet Data on the incidence of infection with pathogens transmitted commonly through food--10 States, 2008. *MMWR Morb Mortal Wkly Rep*. 2009;58(13):333-7. PMID: 19357633
 11. Varma JK, Samuel MC, Marcus R, Hoekstra RM, Medus C, Segler S, et al. Listeria monocytogenes infection from foods prepared in a commercial establishment: a case-control study of potential sources of sporadic illness in the United States. *Clin Infect Dis*. 2007;44(4):521-8. <https://doi.org/10.1086/509920> PMID: 17243054
 12. European Food Safety Authority (EFSA). The Community Summary Report on Trends and Sources of Zoonoses, Zoonotic Agents, Antimicrobial resistance and Foodborne outbreaks in the European Union in 2006. *EFSA J*. 2007; 5(12):130r.
 13. World Health Organization (WHO). Listeriosis – South Africa. Geneva: WHO; 2018. Available from: <http://www.who.int/csr/don/02-may-2018-listeriosis-south-africa/en/>
 14. European Commission. Commission regulation (EC) No 1441/2007 of 5 December 2007 amending Regulation (EC) No 2073/2005 on microbiological criteria for foodstuffs. Luxembourg: Publication Office of the European Union. Available from: <https://eur-lex.europa.eu/eli/reg/2007/1441/oj>
 15. European Commission. Commission regulation (EC) No 365/2010 of 28 April 2010 amending Regulation (EC) No 2073/2005 on microbiological criteria for foodstuffs as regards Enterobacteriaceae in pasteurised milk and other pasteurised liquid dairy products and Listeria monocytogenes in food grade salt. Luxembourg: Publication Office of the European Union. Available from: <https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=L:2010:107:0009:0011:EN:PDF>
 16. de Sanidad M, Sociales e Igualdad S. [Ministry of Health, Social Services and Equality]. Orden I. SSI/445/2015, de 9 de marzo, por la que se modifican los anexos I, II y III del Real Decreto 2210/1995, de 28 de diciembre, por el que se crea la Red Nacional de Vigilancia Epidemiológica, relativos a la lista de enfermedades de declaración obligatoria, modalidades de declaración y enfermedades endémicas de ámbito regional. [Order I. SSI / 445/2015, of March 9, which modifies the annexes I, II and III of Royal Decree 2210/1995, of December 28, by which the National Network of Epidemiological Surveillance is created, relating to the list of diseases of compulsory declaration, declaration modalities and endemic diseases of regional scope]. Spanish. [Accessed: 06 Sep 2018]. Available from: http://www.boe.es/diario_boe/txt.php?id=BOE-A-2015-2837
 17. Ministerio de Sanidad, Servicios Sociales e Igualdad. [Ministry of Health, Social Services and Equality]. Hospital Discharge Records in the National Health System. Centralised Hospital Discharge Database [Accessed: 22 Mar 2018]. Available from: <https://www.msbs.gob.es/estadEstudios/estadisticas/cmbdhome.htm>
 18. de Sanidad M, Sociales e Igualdad S. [Ministry of Health, Social Services and Equality]. Norma estatal 2012. Notas Metodológicas. [State standard 2012. Methodological Notes]. [Accessed: 22 Mar 2018]. Spanish. Available from: https://www.msbsi.gob.es/estadEstudios/estadisticas/docs/NormaGRD2012/2012_norma_estatal_not_metod.pdf
 19. Centers for Disease Control and Prevention (CDC). International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Atlanta: CDC; 2004.
 20. Instituto Nacional de Estadística (INE). [National Institute of Statistics]. Population figures and Demographic Censuses, Spain. Madrid: INE; 2016. Available from: http://www.ine.es/en/inebaseDYN/cp30321/cp_resultados_en.htm
 21. Jamieson DJ, Honein MA, Rasmussen SA, Williams JL, Swerdlow DL, Biggerstaff MS, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet*. 2009;374(9688):451-8. [https://doi.org/10.1016/S0140-6736\(09\)61304-0](https://doi.org/10.1016/S0140-6736(09)61304-0) PMID: 19643469
 22. de Sanidad M, Consumo y Bienestar S. (MSCBS) [Ministry of Health, Consumer Affairs and Social Welfare]. Norma estatal 2017. Notas Metodológicas. [State standard 2017. Methodological Notes]. Madrid: MSCBS. [Accessed: 21 May 2019]. Spanish. Available from: https://www.msbs.gob.es/estadEstudios/estadisticas/docs/CMBD/Nota_difus_Norma_Estatal_2017.pdf
 23. Garrido V, Torroba L, García-Jalón I, Vitas AI. Surveillance of listeriosis in Navarre, Spain, 1995-2005--epidemiological patterns and characterisation of clinical and food isolates. *Euro Surveill*. 2008;13(49):19058. <https://doi.org/10.2807/ese.13.49.19058-en> PMID: 19081001
 24. Valero FP, Rafart JV. Estudio de la incidencia de listeriosis en España. *Gac Sanit*. 2014;28(1):74-6. <https://doi.org/10.1016/j.gaceta.2013.03.004>
 25. Lamont RF, Sobel J, Mazaki-Tovi S, Kusanovic JP, Vaisbuch E, Kim SK, et al. Listeriosis in human pregnancy: a systematic review. *J Perinat Med*. 2011;39(3):227-36. <https://doi.org/10.1515/jpm.2011.035>
 26. García Béjar-Bermejo B, Martín López A, Rivas Soler A. [Risk profile for Listeria monocytogenes ready-to-eat meat-based food products in Spain] Perfil de riesgo de Listeria monocytogenes en alimentos derivados cárnicos listos para su consumo en España. Valencia: Universidad Politécnica de Valencia; 2014. Spanish. Available from: <https://riunet.upv.es/bitstream/handle/10251/54508/GARC%20C3%8DA-B%20C3%89JAR%20-%20Perfil%20de%20riesgo%20de%20Listeria%20monocytogenes%20en%20alimentos%20derivados%20c3%A1rnicos%20%28Evalu...pdf?sequence=2&isAllowed=y>
 27. European Food Safety Authority (EFSA). The European Union summary report on trends and sources of zoonoses, zoonotic agents and food-borne outbreaks in 2012. *EFSA J*. 2014;12(2):3547.
 28. Ricci A, Allende A, Bolton D, Chemaly M, Davies R, Escámez PSF, et al. Listeria monocytogenes contamination of ready to eat foods and the risk for human health in the EU. *EFSA J*. 2018; 16(1):e05134.
 29. Boletín Oficial del Estado (BOE) [Official State Gazette]. Ministerio de Sanidad, Servicios Sociales e Igualdad (MSSSI) [Ministry of Health, Social Services and Equality]. Orden SSI/445/2015, de 9 de marzo, por la que se modifican los anexos I, II y III del Real Decreto 2210/1995, de 28 de diciembre, por el que se crea la Red Nacional de Vigilancia Epidemiológica, relativos a la lista de enfermedades de declaración obligatoria, modalidades de declaración y enfermedades endémicas de ámbito regional [Orden SSI/445/2015 of 9 Mars modifying Annexes I,II and III of the Royal Decree 2210/1995, published in 28th December, establishing the National Epidemiological Surveillance Network, related to the list of diseases of compulsory declaration, declaration modalities and endemic diseases of regional scope]. Available from: <http://www.boe.es/boe/dias/2015/03/17/pdfs/BOE-A-2015-2837.pdf>
 30. Hedberg C. Listeria in Europe: the need for a European surveillance network is growing. *Euro Surveill*. 2006;11(6):75-6. <https://doi.org/10.2807/esm.11.06.00628-en> PMID: 16801698
 31. Koch J, Stark K. Significant increase of listeriosis in Germany--epidemiological patterns 2001-2005. *Euro Surveill*. 2006;11(6):85-8. <https://doi.org/10.2807/esm.11.06.00631-en> PMID: 16801695
 32. Buchanan RL, Gorris LG, Hayman MM, Jackson TC, Whiting RC. A review of Listeria monocytogenes: An update on outbreaks, virulence, dose-response, ecology, and risk assessments. *Food Control*. 2017;75:1-13. <https://doi.org/10.1016/j.foodcont.2016.12.016>
 33. Gahan CG, Hill C. Listeria monocytogenes: survival and adaptation in the gastrointestinal tract. *Front Cell Infect Microbiol*. 2014;4:9. <https://doi.org/10.3389/fcimb.2014.00009> PMID: 24551601
 34. Simó Miñana J. Use of prescription drugs in Spain and Europe. *Aten Primaria*. 2012;44(6):335-47. PMID: 22018798

35. de Castro V, Escudero J, Rodriguez J, Muniozgueren N, Uribarri J, Saez D, et al. Listeriosis outbreak caused by Latin-style fresh cheese, Bizkaia, Spain, August 2012. *Euro Surveill.* 2012;17(42):17.
36. Pérez-Trallero E, Zigorraga C, Artieda J, Alkorta M, Marimón JM. Two outbreaks of *Listeria monocytogenes* infection, Northern Spain. *Emerg Infect Dis.* 2014;20(12):2155-7. <https://doi.org/10.3201/eid2012.140993> PMID: 25418800
37. Ariza-Miguel J, Fernández-Natal MI, Soriano F, Hernández M, Stessl B, Rodríguez-Lázaro D. Molecular Epidemiology of Invasive Listeriosis due to *Listeria monocytogenes* in a Spanish Hospital over a Nine-Year Study Period, 2006-2014. *BioMed Res Int.* 2015;2015:191409. <https://doi.org/10.1155/2015/191409> PMID: 26539467
38. Garrido V, Vitas A, García-Jalón I. Survey of *Listeria monocytogenes* in ready-to-eat products: prevalence by brands and retail establishments for exposure assessment of listeriosis in Northern Spain. *Food Control.* 2009;20(11):986-91. <https://doi.org/10.1016/j.foodcont.2008.11.013>
39. Spanish Agency for Consumer Affairs (AECOSAN). Food Safety and Nutrition. Enfermedades de transmisión alimentaria [Food-borne diseases]. AECOSAN. [Accessed: 31 Mar 2018]. Spanish. Available from: http://www.aecosan.msssi.gob.es/AECOSAN/web/seguridad_alimentaria/detalle/enfermedades_transmision_alimentaria.htm
40. Pasche B, Kalaydjiev S, Franz TJ, Kremmer E, Gailus-Durner V, Fuchs H, et al. Sex-dependent susceptibility to *Listeria monocytogenes* infection is mediated by differential interleukin-10 production. *Infect Immun.* 2005;73(9):5952-60. <https://doi.org/10.1128/IAI.73.9.5952-5960.2005> PMID: 16113316
41. Thomas MK, Vriezen R, Farber JM, Currie A, Schlech W, Fazil A. Economic Cost of a *Listeria monocytogenes* Outbreak in Canada, 2008. *Foodborne Pathog Dis.* 2015;12(12):966-71. <https://doi.org/10.1089/fpd.2015.1965> PMID: 26583272
42. Mangen M-JJ, Bouwknegt M, Friesema IHM, Haagsma JA, Kortbeek LM, Tariq L, et al. Cost-of-illness and disease burden of food-related pathogens in the Netherlands, 2011. *Int J Food Microbiol.* 2015;196:84-93. <https://doi.org/10.1016/j.ijfoodmicro.2014.11.022> PMID: 25528537
43. Hernandez-Milian A, Payeras-Cifre A. What is new in listeriosis? *BioMed Res Int.* 2014;2014:358051. <https://doi.org/10.1155/2014/358051> PMID: 24822197
44. Girard D, Leclercq A, Laurent E, Lecuit M, de Valk H, Goulet V. Pregnancy-related listeriosis in France, 1984 to 2011, with a focus on 606 cases from 1999 to 2011. *Euro Surveill.* 2014;19(38):20909. <https://doi.org/10.2807/1560-7917.ES2014.19.38.20909> PMID: 25306879
45. de Sanidad M, Sociales e Igualdad S. (MSSSI) [Ministry of Health, Social Services and Equality]. Control Serológico de Infecciones de Transmisión Vertical en La Mujer Embarazada [Serological Control of Vertical Transmission Infections in Pregnant Women]. Madrid: MSSSI; 1993. Spanish. Available from: <http://www.msps.es/ciudadanos/proteccionSalud/mujeres/docs/serologiacompleto.pdf>
46. Evans EW, Redmond EC. An assessment of food safety information provision for UK chemotherapy patients to reduce the risk of foodborne infection. *Public Health.* 2017;153:25-35. <https://doi.org/10.1016/j.puhe.2017.06.017> PMID: 28822850
47. Goulet V, Hebert M, Hedberg C, Laurent E, Vaillant V, De Valk H, et al. Incidence of listeriosis and related mortality among groups at risk of acquiring listeriosis. *Clin Infect Dis.* 2012;54(5):652-60. <https://doi.org/10.1093/cid/cir902> PMID: 22157172
48. Siegman-Igra Y, Levin R, Weinberger M, Golan Y, Schwartz D, Samra Z, et al. *Listeria monocytogenes* infection in Israel and review of cases worldwide. *Emerg Infect Dis.* 2002;8(3):305-10. <https://doi.org/10.3201/eid0803.010195> PMID: 11927029
49. van Veen KEB, Brouwer MC, van der Ende A, van de Beek D. Bacterial meningitis in diabetes patients: a population-based prospective study. *Sci Rep.* 2016;6(1):36996. <https://doi.org/10.1038/srep36996> PMID: 27845429

This article is copyright of the authors or their affiliated institutions, 2019.

[License, supplementary material and copyright](#)

This is an open-access article distributed under the terms of the Creative Commons Attribution (CC BY 4.0) Licence. You may share and adapt the material, but must give appropriate credit to the source, provide a link to the licence and indicate if changes were made.

Any supplementary material referenced in the article can be found in the online version.