



## Short Communication

Increased incidence and mortality from *Listeria monocytogenes* infection in SpainElena Vázquez<sup>1</sup>, Oscar de Gregorio-Vicente<sup>1</sup>, Vicente Soriano<sup>1</sup>, Carmen Álvarez-Domínguez<sup>1</sup>, Octavio Corral<sup>1</sup>, Víctor Moreno-Torres<sup>1,2,\*</sup><sup>1</sup> UNIR Health Sciences School and Medical Center, Madrid, Spain<sup>2</sup> Internal Medicine Department, Health Research Institute Puerta de Hierro-Segovia de Arana (IDIPHIM), Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain

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## ABSTRACT

**Objectives:** *Listeria monocytogenes* (LM) is a health threat worldwide given its high mortality and the growing of high-risk susceptible populations.

**Methods:** All hospitalizations with a diagnosis of LM in the National Registry of Hospital Discharges were examined in Spain from 2000 to 2021.

**Results:** A total of 8152 hospital admissions with LM were identified. The mean age was 59.5 years and 48% were immunosuppressed (IS).

The rate of LM hospitalizations increased from 5 per 1 million population in 2000 to 8.9 in 2021 ( $p < 0.001$ ). A foodborne outbreak in Andalusia determined a sharp increase in admissions with LM during 2019. The COVID-19 pandemic and lockdowns were associated with a decrease in LM admissions.

The overall in-hospital mortality was 16.7%. The number of deaths in patients hospitalized with LM rose from 7.8 per 100,000 deceased in 2000 to 18 in 2021 ( $p < 0.001$ ). After adjustment, age  $>65$  years (odds ratio [OR] = 2.16), sepsis (OR = 2.60), meningoenophalitis (OR = 1.72), endocarditis (OR = 2.0), neonatal listeriosis (OR = 2.10) and IS (OR = 2.09) were associated with mortality.

**Conclusions:** The number of patients hospitalized with LM in Spain has increased significantly from 2000 to 2021. The increase in the rate of admissions and deaths was largely driven by the growing proportion of elderly and IS patients.

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## Introduction

Although most cases of listeriosis are sporadic, *Listeria monocytogenes* (LM) is an important cause of major epidemic outbreaks from contaminated food worldwide [1]. Despite its relatively low prevalence, LM is an important health threat given the high mortality rate and the growing risk populations, such as the elderly, immunosuppressed (IS) individuals, pregnant women, unborn babies, and newborn infants [1,2].

In Spain, along with the rest of Europe, the incidence of listeriosis has increased since the 2000s, including a relatively high number of suspected cases [3–5]. Moreover, increased mortality rates have been noted in the most vulnerable populations. Consequently,

the Spanish Government, following the European Union 2015 summary report, declared listeriosis as a mandatory notifiable disease in 2015 [6]. Despite the previous, updated reports from the European Food Safety Authority and European Centre for Disease Prevention and Control highlighted listeriosis as the fifth most common zoonosis and one of the most serious foodborne diseases in the European Union [7]. Herein, we report time trends, outcomes, and the main clinical and epidemiological features of patients hospitalized with LM in Spain during the last 2 decades. We also aimed to examine the factors associated with increased listeriosis mortality.

## Methods

We performed an analysis on data extracted from the Spanish National Hospital Discharge Database (SNHDD), a public access registry belonging to the Spanish Government. The SNHDD in-

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cludes nationwide demographic and epidemiological data and up to 20 hospital discharge diagnoses. From 1997 to 2015, the ninth version of the International Classification of Diseases, ninth revision (ICD-9) coding list was used. From 2016 to date, the tenth revision (ICD-10) has been applied. The ICD codes included are displayed in the Supplementary Table 1. Epidemiological information about the Spanish general population was retrieved from the National Statistics Institute ([www.ines.es](http://www.ines.es)).

### Study population

We identified all hospital admissions of patients with listeriosis from 2000 to 2021, using ICD-9 code 027.0 and ICD-10 code A32. Listeriosis clinical forms, relevant comorbidities, and other conditions (immunosuppression, pregnancy status) were also recorded from the hospital discharge reports, using the enhanced ICD-Clinical Modification tools (Supplementary Table 1).

### Statistical analysis

Epidemiological trends in hospital admissions and mortality were analyzed during the study period, considering as reference the whole Spanish population, by Poisson regression and the linear-by-linear trend test.

In addition to descriptive statistics, a binary logistic regression analysis was performed to determine factors associated with increased listeriosis mortality. We chose older age (>65 years), clinical forms of listeriosis (sepsis, meningoenzephalitis, endocardi-

tis, and neonatal listeriosis), immunosuppression, pregnancy, and alcoholism as study variables, and mortality as outcomes. Data are expressed as odds ratio (OR) and 95% confidence interval (CI).

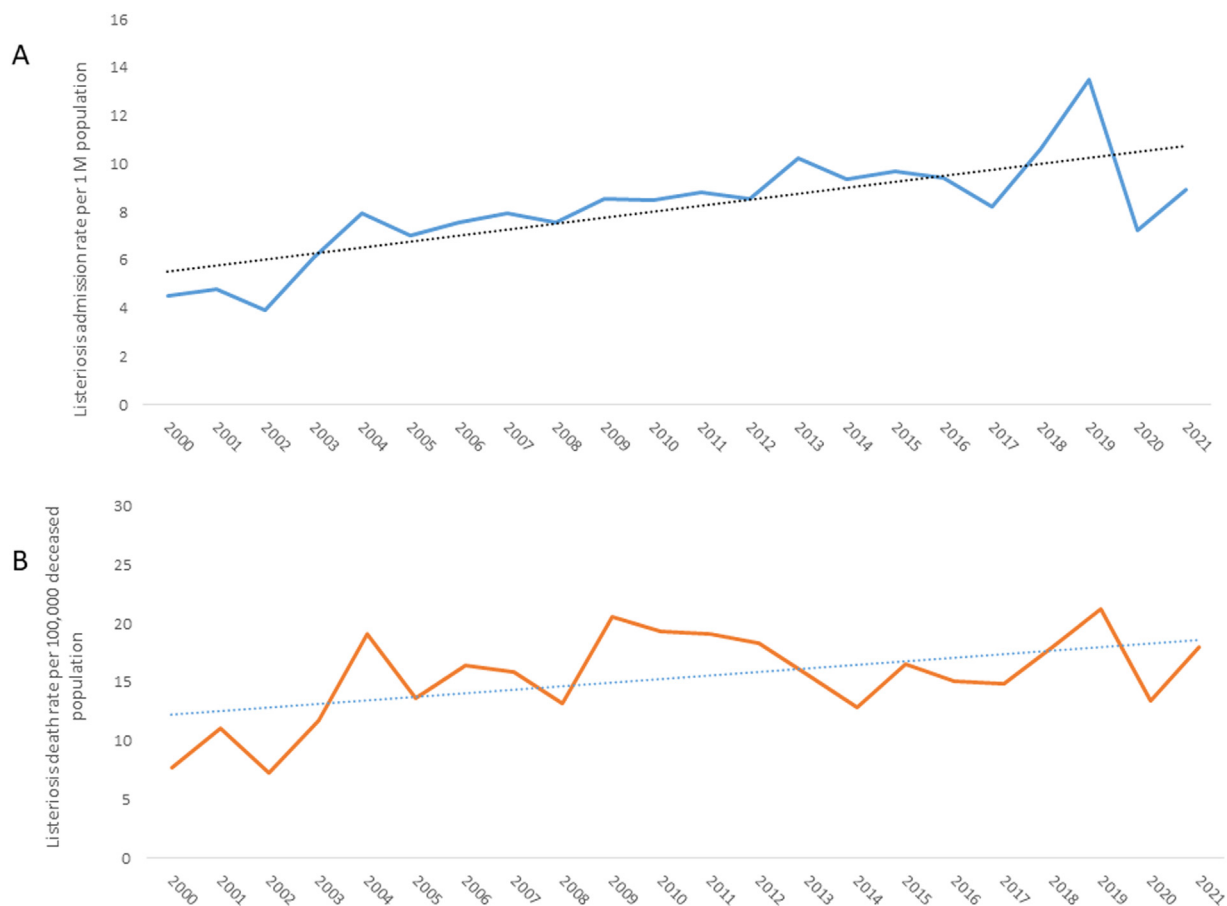
For all analyses, a significance for values below 0.05 was used. All statistical analyses were performed using SPSS version 26.0 (IBM, Madrid, Spain).

### Ethics

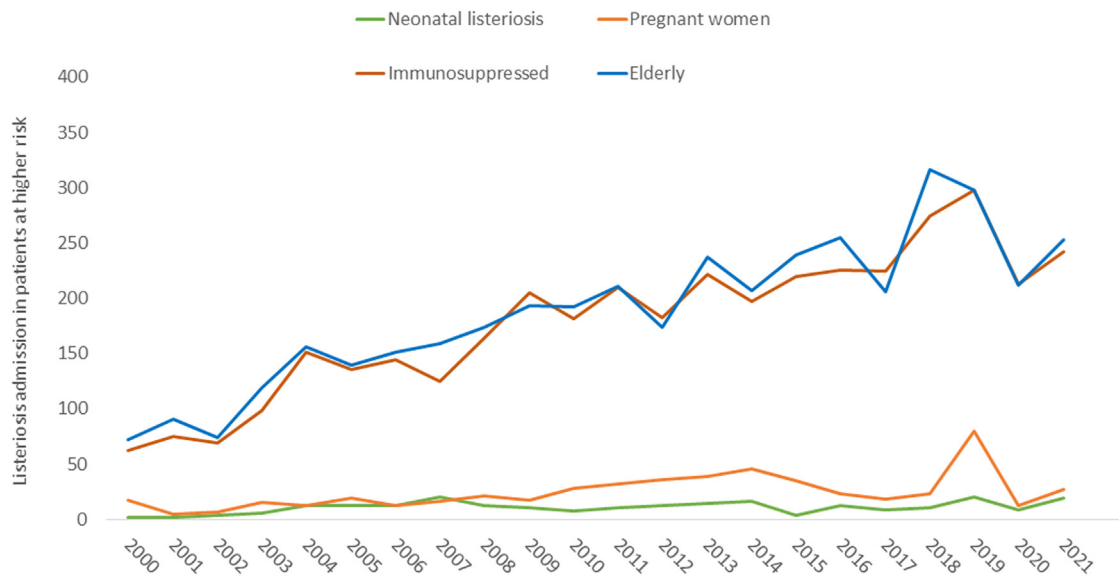
The study was approved by the Universidad Internacional de La Rioja (UNIR) Ethics Committee (ref. PI: 035/2024) and complies with the Declaration of Helsinki. The data were provided after all potential patient identifiers had been deleted, and all data were given anonymously. According to the Spanish law, informed consent was not required for the study.

### Results

Between 2000 and 2021, a total of 8152 hospital admissions with a diagnosis of LM were identified nationwide. The mean length of admission was 20.5 days, and the mean age was 59.5 years. Overall, 4747 (58.6%) were male, 540 (6.6%) were pregnant women, 684 (8.4%) were alcoholics, and 3196 (48%) were IS patients. The latter group was represented by patients with diabetes mellitus (19.4%), solid organ tumors (14.8%), hematologic neoplasms (9.3%), chronic kidney disease (9.7%), autoimmune disease (7.3%) and liver disease (5.9%). The major clinical presenta-



**Figure 1.** Listeriosis admission rate, per 1 million population (1.a), and rate of deaths per 100,000 deceased population (1.b), in Spain, between 2000 and 2021. The figure shows the admission rate because of listeriosis, in Spain, between 2000-2021, per 1 million population (1.a), and the rate of death during hospital admission because of listeriosis per 100,000 deceased population in Spain, between 2000 and 2021 (1.b).



**Figure 2.** Trends of hospital admissions because of listeriosis in patients at higher risk, in Spain between 2000 and 2021. The figure shows the number of admissions of patients at higher risk of fatal listeriosis, including elderly patients, pregnant women, immunosuppressed, and those with neonatal listeriosis.

tion of patients hospitalized with LM was as follows: sepsis (962; 11.8%), meningoen­cephalitis (3,112; 38.2%), endocarditis (77; 0.9%), and neonatal listeriosis (450; 5.5%). The overall in-hospital mortality during the study period for patients with listeriosis was 16.7%.

### Epidemiology

The overall rate of LM admissions during the study period was 8.2 per 1 million population. It increased significantly over the study period from 5 admissions per 1 million population in 2000 to 8.9 in 2021 ( $p < 0.001$ ) (Figure 1a). Of note, after a significant increase in admissions during 2019 (13.5 admissions per 1 million population), there was a drastic decrease in 2020 (7.2 admissions per 1 million population), driven by the COVID-19 pandemic. The absolute number of deaths because of LM in Spain rose from 7.8 per 100,000 deceased in 2000 to 18 per 100,000 deceased population in 2021 ( $p < 0.001$ ) (Figure 1b).

The increase in both the rate of hospital admissions and mortality over time in patients with LM was mostly driven by the increased proportion of elderly and IS patients (Figure 2). Changes in their respective figures were from 34% to 57% in 2000 and from 39.5% to 60% in 2021 ( $p < 0.001$ ).

### Mortality

After adjustment, age over 65 years old (OR = 2.16, 95% CI: 1.89-2.47), sepsis (OR = 2.60, 95% CI: 2.21-3.04), meningoen­cephalitis (OR = 1.72, 95% CI: 1.52-1.95), endocarditis (OR = 2.0, 95% CI: 1.15-3.46), neonatal listeriosis (OR = 2.10, 95% CI: 1.39-3.18) and immunosuppression (OR = 2.09, 95% IC 1.84-2.38) were all independently associated with death (Supplementary Table 2). Mortality in the latter group was mostly driven by liver disease (OR = 2.43, 95% CI: 2.78-4.43) and advanced or metastatic solid tumors (OR = 2.62, 95% CI: 3.26-4.47).

### Discussion

Previous information about listeriosis in Spain comes from monocentric or concrete regions, short-term, and/or outdated reports [3,5]. Given its significant health burden/costs, and high mor-

tal­ity, we considered warranted to update the current status of this neglected medical condition.

During the last 2 decades, hospital admissions because of LM have significantly increased in Spain. This trend matches with other recent reports worldwide [1,3,8]. In Spain, a survey already noted this trend until 2015 [3]. A dramatic increase in both incidence and mortality because of listeriosis occurred in Spain in 2019, associated with the largest listeriosis outbreaks in Europe to date [7]. It occurred in the south of Spain and was related to the consumption of stuffed pork from a single producer [4]. However, hospitalizations with LM during 2020 decreased drastically, largely driven by all health care measures taken to control the COVID-19 pandemic [9].

The growing impact of LM on the most vulnerable patients is an important finding of our study. The multivariate analysis confirmed that older age, immunosuppression, and severe or invasive disease were the major determinants of death in patients hospitalized with listeriosis. This agrees with previous reports [1,2]. We also noted a temporal increase in listeriosis incidence driven by the rising number of patients older than 65 years and with immunosuppression for any reason. In turn, the mortality in these vulnerable populations was higher. Similar trends have been noticed in other European countries and overseas [8,10].

We should acknowledge several limitations of our study. First, this was a retrospective study, so medical histories could not be reviewed to verify data accuracy, particularly concerning the causes of death. Moreover, important information regarding disease course, treatment, microbiology, origin, and setting was not available and could have provided more solid conclusions. Similarly, only microbiologically positive cases from discharge reports were included in the SNHDD, and therefore retrieved and analyzed. Whereas this fact could lead to more confident results, it would provide an underestimation of total cases, because a significant proportion of suspected cases were not taken into consideration. Our analysis was restricted to hospital admissions, and therefore clinically mild forms of listeriosis might have been disregarded and managed without hospitalization.

In summary, our findings increase concern about the health burden of listeriosis in Spain. Despite being declared a mandatory notifiable disease by the Spanish Ministry of Health in 2015, our analysis of hospitalizations shows that, far from improving,

numbers are getting worse. Furthermore, incidence and mortality are increasingly growing as a result of affecting more vulnerable groups, such as the elderly and the IS, in turn at increasing mortality risk.

Specific programs addressing surveillance and prevention of human listeriosis are warranted. Additional measures to prevent foodborne contagion and outbreaks from animal reservoirs should be undertaken.

#### Declaration of competing interests

None declared.

#### CRediT authorship contribution statement

**Elena Vázquez:** Conceptualization, Investigation, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Oscar de Gregorio-Vicente:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Vicente Soriano:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing. **Carmen Álvarez-Domínguez:** Conceptualization, Investigation, Supervision, Validation, Visualization, Writing – review & editing. **Octavio Corral:** Conceptualization, Investigation, Supervision, Validation, Visualization, Writing – review & editing. **Víctor Moreno-Torres:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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#### Ethical approval

The study was approved by the UNIR Ethics Committee (ref. PI: 035/2024) and complies with the Declaration of Helsinki. The data were provided after all potential patient identifiers had been deleted, and all data were given anonymously. According to the Spanish law, informed consent was not required for the study.

#### Acknowledgments

None declared.

#### Data sharing statement

The data proceeds from a public registry from the Spanish National Hospital Discharge Database. All data are freely available. The database from the Spanish Ministry of Health can be accessed upon request. Data are anonymously given.

#### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.ijid.2024.107089](https://doi.org/10.1016/j.ijid.2024.107089).

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