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ORIGINAL ARTICLE

# Non-Typhi, non-Paratyphi *Salmonella*-related hospitalisations in Spain: trends, clinical aspects, risk factors for worse prognosis and hospital costs

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## Abstract

This study reviews non-typhoid *Salmonella* (NTS)-related hospitalisations at National level in Spain between 2010 and 2015. NTS hospitalisations were obtained from the National Registry of Hospitalisations. A descriptive analysis of the hospitalisations was performed, including hospitalisation rates (HR) and case-fatality rates (CFR%) calculation. For those with NTS as Main Diagnosis logistic regression were used to estimate the relationship between the different factors and death outcome. 21,660 registered NTS-related hospitalisations were described (88.8% with *Salmonella* coded as Main Diagnosis). Average $HR_{2010–2015}$ was 7.7 (range, 7.3 to 8.1) hospitalisations/100,000 population. Those with NTS infections as Secondary Diagnosis were on average ($p < 0.001$) older (47.9 vs. 36.5 years), presented worse Charlson Comorbidity Index (2.1 vs. 1.2), higher CFR% (4.8% vs. 0.7%), spent more days hospitalised (15.1 vs. 5.8 days), and generated more costs (6173 vs. 4272 euros/per hospitalisation) than those with NTS as Main Diagnosis. For those with NTS as Main Diagnosis increased risk of death was related to being > 64 years old (OR = 20.99; $p < 0.001$); presenting septicaemia (OR = 15.82; $p < 0.001$) or localised infections (OR = 3.98; $p = 0.061$); Charlson Comorbidity Index > 3 (OR = 4.57; $p < 0.001$); a non-HIV co-infection (OR = 1.80; $p = 0.013$); other risk factors (OR = 5.70; $p < 0.001$); bowel perforation (OR = 70.30; $p < 0.001$); or acute renal failure (OR = 1.95; $p = 0.001$). In those with *Salmonella* as Main Diagnosis, among all complications, bowel perforation presented the strongest association with death outcome. Clinical practice guidelines can help to identify patients at risk of bowel perforation to reduce the fatality of the disease.

**Keywords** Salmonella · Salmonellosis · Outcomes · Costs · Rates · Comorbidities · Hospitalisations · Epidemiology

## Introduction

Non-typhoid *Salmonella* (NTS) is widely spread throughout the nature. It can survive in a wide range of hosts which complicates the control of the disease and increase the risk of acquiring the infection through food products. Main serotypes associated with human cases of salmonellosis are *Salmonella enterica* subsp. enterica serovar Typhimurium (*S.* Typhimurium) and *Salmonella enterica* subsp. enterica serovar Enteritidis (*S.* Enteritidis) [1]. Similarly to the rest of Europe, in Spain, we observed a decreasing trend for confirmed human salmonellosis for both serotypes since 2008 till 2012 [2]. However, that decreasing EU trend ended during 2012–2016, and the proportion of human *S.* Enteritidis cases increased by 2016 [3].

The reporting of food-borne outbreaks (FBO) of human salmonellosis is mandatory in the European Union according to the Zoonoses Directive 2003/99/EC. However, case-based surveillance did not start till the year 2015 in Spain, in which salmonellosis was officially included as a mandatory notifiable disease nationwide [4]. In the year 2015, 15 of the 19 Spanish regions notified cases to the National Centre for Epidemiology, although some regions started to notify in 2014 (13 of the 19 regions) [2].

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Prior to 2014 and 2015, the only dataset providing information about *Salmonella* human cases at the national level in Spain was the National Registry of Hospitalisations. This Registry collects hospital discharges information since 1987. It covers more than 95% of the public/private hospitals and 99% of the discharges in Spain, and in some regions covers 100% in the last 10 years [5]. However, in spite of the availability of the National Registry of Hospitalisations, there are no recent studies about *Salmonella*-related cases or hospitalisations at the National level. Up to our knowledge, the latest study developed by Gil Prieto et al. evaluated the epidemiology of hospital-treated *Salmonella* infections in Spain between 1997 and 2006 [6].

The aim of this study is to review the clinical data, evaluate the hospital burden (including costs), and assess the risk factors related to a higher risk of death of hospitalised patients suffering NTS infections between 2010 and 2015. This study can help to establish a comparison point to evaluate future changes in the burden of the disease. Hospitalisation registries also can be a source of data, not only to evaluate the epidemiology and the clinical outcomes of the most severe cases of *Salmonella* infections, but to support the evaluation of the quality and performance of the surveillance systems [7], and data provided in this manuscript can be useful to support this evaluation in the case-based surveillance start-up phase.

## Methods

We carried out an observational retrospective study. The study population consisted of patients discharged from the hospital with non-Typhi non-Paratyphi *Salmonella*-related hospitalisations in Spain from January 1 of 2010 to December 31 of 2015.

### Data source and collection

Hospitalisations associated with NTS infections were obtained from the National Registry of Hospitalisations of the Ministry of Health, Consumption and Social Welfare. This registry compiles a minimum basic data set (MBDS) using the International Classification of Diseases, ninth revision (ICD-9) till 2016. The MBDS includes information on sex, age, date of birth, date of admission and date of discharge, geographical location of cases/hospitals (autonomous community, province and municipal code), outcomes and hospital-related costs. This registry collects up to 14 diagnoses related to the hospitalisation (Main Diagnosis and 13 Secondary Diagnoses). We selected all hospitalisation discharges with ICD-9 code 003.XX (Other *Salmonella* infections) in any diagnosis position (Main Diagnosis or Secondary Diagnoses). That code includes any confirmed infection or food-borne disease by *Salmonella* spp., except *Salmonella enterica* serovar Typhi (*S.* Typhi) or *Salmonella enterica* serovar Paratyphi (*S.* Paratyphi).

Hospitalisations cost calculation was done by the Ministry of Health, Consumption and Social Welfare using a country-based methodology. Parameters used to calculate costs include clinical information and previous year's costs obtained from the National Network of Hospital Costs Database. The diagnostic cost group was based on the Diagnosis Related Groups-All Patient Refined (GRD-APR) for the hospitalised patient depending on discharge ICD classification, age, sex, and resources consumption. The cost of each *Salmonella* hospitalisation included in this study was provided by the Ministry of Health, Consumption and Social Welfare with the rest of variables included in the MBDS [5].

### Statistical analysis

We calculated the absolute annual number of hospitalisations and the hospitalisation rates (per 100,000 population) due to NTS infections for all cases and by age-group. As a denominator for rates calculation, we used population estimates obtained from the National Institute of Statistics. Changes in the hospitalisation rates were evaluated using a Poisson regression model and considering year as a continuous variable to evaluate a possible continuous positive trend in the rates during the period.

Intra-hospital deaths and hospitalisation related case-fatality rates (CFR%) were calculated for the whole cohort and by diagnostic relevance (*Salmonella* diagnosis as Main Diagnosis or Secondary Diagnoses), sex, age group and clinical presentation.

To evaluate symptoms, comorbidities and risk factors related to worse prognosis, we reviewed those reported in previous literature [1, 8–13]. Diagnoses and their correspondent ICD-9 codes identified in other manuscripts are described in Table 1. Additionally, Charlson Comorbidity Index (CCI) was calculated using the 14 diagnoses provided in the dataset to consider the health status of the patient in terms of comorbidities [14]. For comparison of means, we used the *t*-test or the Wilcoxon rank-sum text when non-normal distribution of the data was observed. Proportions were compared using the chi-square test with Fisher's correction, when necessary.

Univariable and multivariable logistic regression were used to estimate the relationship between the different factors and death outcome, adjusted by age, sex, CCI, and clinical form of the disease. The model included only those hospitalisations with NTS infection as Main Diagnosis and those with a unique clinical form to avoid bias in the estimation of the association measures due to cumulative or multiplier effect by the coexistence of more than one clinical form.

Statistical significance was set at $p < 0.05$. All analyses were performed using Stata version 12.

**Table 1** Symptoms, comorbidities/risk factors and complications related to worse prognosis and outcomes ICD-9 codes

| | Diagnosis | ICD-9 codes |
|---|---|---|
| Symptoms | Diarrhoea | 787.91 |
| | Fever | 780.60 |
| | Hypotension | 458.8 and 458.9 |
| | Seizures | 780.3X |
| | Dehydration and hypovolaemia | 276.51 and 276.52 |
| Risk factors for infection or worse prognosis (comorbidities and co-infections) | Inflammatory bowel diseases | 555.X |
| | Co-infections | 001 to 139 (excluding 003 code) and 466.XX codes reporting bronchiolitis |
| | HIV | 042 and 079.53 |
| | Immune disorders | 279.XX |
| | Prematurity | 765.XX |
| | Congenital heart diseases | 745, 746 and 747 |
| | Congenital genitourinary diseases | 754 and 753 |
| | Malignancies (except metastatic solid tumours) | 140 to 239 (excluding 196.x to 199.1 codes) |
| | Metastatic solid tumour | 196.x to 199.1 |
| | Down syndrome | 758.0 |
| | Kawasaki disease | 446.1 |
| | Prader-Will syndrome | 759.81 |
| Complications derived from *Salmonella* infection | Ulcerative colitis | 556.X |
| | Thrombosis | 453.XX |
| | Bowel perforation | 569.83 |
| | Septic arthritis | 711.XX |
| | Gastrointestinal bleeding | 578.1, 578.9 |
| | Acute renal failure | 584.X, especially 584.9 |
| | Appendicitis | 540.X |

## Results

### Demographics and clinical features

Between 2010 and 2015, 21,660 NTS-related hospitalisations were registered at the National Registry of Hospitalisations. Among them, 18,157 (83.8%) hospitalisations reported NTS infection ICD-9 codes as Main Diagnosis and in 3503 (16.2%) hospitalisations NTS ICD-9 codes appeared as Secondary Diagnoses. Hospitalisations were more frequent in males vs. females (55.4% vs. 44.6%; $p < 0.001$). For all hospitalisations, the hospital CFR% was 1.4%. Gastroenteritis was the most frequent presentation (89.7%; 19,438 hospitalisations), followed by septicaemia (4.8%; 1032 hospitalisations). Most of the infections cursed with only one clinical form (97.5%; 21,128 hospitalisations). Two or more clinical forms were described in 532 (2.5%) hospitalised patients (Table 2). More than one clinical forms were more frequent in those patients > 64 years old compared to those ≤ 9 years (3.8% vs. 0.9%; $p < 0.001$). Most of the patients with more than one clinical form presented a combination of gastroenteritis with septicaemia (70.3%; 374/532). Gastroenteritis was more frequent among those ≤9 years old compared to those > 64 years old (95.5% vs. 85.5%; $p < 0.001$) in contrast to the other clinical forms (5.4% vs. 18.2%; $p < 0.001$), especially septicaemia (1.1% vs. 8.1%; $p < 0.001$). Overall, 1056 (4.9%) patients required a re-admission.

For those with NTS infections as Secondary Diagnoses, Main Diagnosis was very heterogeneous (799 different ICD-9 codes reported). The most frequent were related to unspecific diagnosis or symptoms/complications associated with *Salmonella* infection itself. As some examples of Main Diagnoses when NTS infection was a Secondary Diagnosis for the patient: "Acute Renal Failure, non-specified (ICD-9: 584.9)" appeared in 10.79% hospitalisation registries; "Unspecified Bacteraemia (ICD-9: 790.7)" in 3.8%; "Dehydratation (ICD-9: 276.51)" in 3.4%; "Unspecified Septicaemia (ICD-9: 038.9)" in 3.1%; and "Other and unspecified non-infectious gastroenteritis and colitis (ICD-9: 558.9)" in 2.6% hospitalisation registries.

An intra-hospital microbiological confirmation was registered in 8759 (40.4%) hospitalisations. Microbiological tests were more frequently requested during the hospital stay for patients with *Salmonella* as Main Diagnosis than in those with *Salmonella* infection coded as Secondary Diagnosis (41.4% vs. 35.4%, $p < 0.001$).

**Table 2** Hospitalised patients and case-fatality rates related to non-Typhi, non-Paratyphi *Salmonella* infection by demographics and clinical features

| Variable | Hospitalisations | | Intra-hospital deaths | |
|---|---|---|---|---|
| | *N* | % | *N* | CFR% |
| *Salmonella* spp. diagnosis relevance | | | | |
| All hospitalisations | 21,660 | 100.0 | 302 | 1.4 |
| *Salmonella* spp. infection as main diagnosis | 18,157 | 83.8 | 134 | 0.7 |
| *Salmonella* spp. infection as secondary diagnoses | 3503 | 16.2 | 168 | 4.8 |
| Sex | | | | |
| Male | 12,008 | 55.4 | 195 | 1.6 |
| Female | 9651 | 44.6 | 107 | 1.1 |
| Unknown | 1 | 0.0 | 0 | 0.0 |
| Age distribution | | | | |
| 0–4 | 4789 | 22.1 | 5 | 0.1 |
| 5–9 | 2516 | 11.6 | 0 | 0.0 |
| 10–14 | 1146 | 5.3 | 2 | 0.2 |
| 15–64 | 6743 | 31.1 | 84 | 1.2 |
| 65–84 | 5413 | 25.0 | 165 | 3.0 |
| > 84 | 1053 | 4.9 | 46 | 4.4 |
| CCI | | | | |
| ≤ 3 | 20,920 | 96.6 | 232 | 1.1 |
| > 3 | 740 | 3.4 | 70 | 9.5 |
| Year | | | | |
| 2010 | 3420 | 15.8 | 46 | 1.3 |
| 2011 | 3496 | 16.1 | 53 | 1.5 |
| 2012 | 3771 | 17.4 | 48 | 1.3 |
| 2013 | 3671 | 16.9 | 52 | 1.4 |
| 2014 | 3526 | 16.3 | 48 | 1.4 |
| 2015 | 3776 | 17.4 | 55 | 1.5 |
| Hospital readmissions | | | | |
| Yes | 1056 | 4.9 | 52 | 4.9 |
| Discharge type | | | | |
| Discharge to home | 20,956 | 96.7 | | |
| Discharge to other hospital | 196 | 0.9 | | |
| Volunteer discharge | 43 | 0.2 | | |
| Intra-hospital death | 302 | 1.4 | 302 | 100.0 |
| Discharge to social-sanitary centre | 121 | 0.6 | | |
| Other or unknown | 42 | 0.2 | | |
| Clinical form* | | | | |
| Gastroenteritis | 19,438 | 89.7 | 141 | 0.73 |
| Septicaemia | 1032 | 4.8 | 108 | 10.47 |
| Localised infections | 429 | 2.0 | 21 | 4.90 |
| -Meningitis | 13 | 0.06 | 1 | 7.69 |
| -Pneumonia | 25 | 0.12 | 4 | 16.00 |
| -Arthritis | 46 | 0.21 | 0 | 0.00 |
| -Osteomyelitis | 33 | 0.15 | 0 | 0.00 |
| -Other, localised | 317 | 1.5 | 16 | 5.05 |
| Other specific *Salmonella* infections | 348 | 1.6 | 19 | 5.46 |
| Non-specific *Salmonella* infections | 950 | 4.4 | 35 | 3.68 |
| Co-existing clinical forms number | | | | |
| 1 | 21,128 | 97.5 | 280 | 1.3 |
| 2 | 527 | 2.4 | 22 | 4.2 |
| 3 | 5 | 0.02 | 0 | 0.0 |

*Patients can present more than 1 clinical form during the same hospitalisation

Source: National Registry of Hospitalisations. Ministry of Health, Consumption, and Social Welfare

By diagnosis relevance (Table 3), we observed differences in age, CCI, hospital stay and costs in those with NTS infections as Main Diagnosis and those with NTS infections as Secondary Diagnoses. Those with NTS infections as Secondary Diagnosis were older, presented worse CCI, spent more days hospitalised and generated more costs to the hospital ($p < 0.001$).

On average, NTS-related cost per hospitalisation was 4579.5 euros per patient, 4272.0 euros for those with NTS infections as Main Diagnosis of and 6172.9 euros for those with NTS infections as Secondary Diagnoses. On average, overall cost per year due to hospitalisations related to NTS was 16,531,865 euros (range 15,640,580 to 17,633,025 euros) and amounted 99,191,190 euros for the whole period (2010–2015).

**Table 3** Age, CCI, hospital stay and costs for all the *Salmonella* associated hospitalisations by diagnosis relevance

| Variable | Diagnosis relevance | *N* | Mean | SD | Range | Median | IQ Range | *p* value* |
|---|---|---|---|---|---|---|---|---|
| Age | All | 21,660 | 38.4 | 31.3 | 0 to 101 | 38 | 5 to 68 | |
| | Main diagnosis | 18,157 | 36.5 | 31.3 | 0 to 101 | 32 | 5 to 67 | < 0.001 |
| | Secondary diagnoses | 3503 | 47.9 | 29.8 | 0 to 99 | 57 | 16 to 74 | |
| CCI | All | 21,660 | 0.6 | 1.4 | 0 to 14 | **0** | 0 to 0 | |
| | Main diagnosis | 18,157 | 0.4 | 1.2 | 0 to 12 | 0 | 0 to 0 | < 0.001 |
| | Secondary diagnoses | 3503 | 1.2 | 2.1 | 0 to 14 | 0 | 0 to 2 | |
| Hospital stay (days) | All | 21,660 | 7.1 | 8.4 | 0 to 279 | **5** | 4 to 8 | |
| | Main diagnosis | 18,157 | 6.0 | 5.8 | 0 to 279 | 5 | 3 to 7 | < 0.001 |
| | Secondary diagnoses | 3503 | 12.8 | 15.1 | 0 to 237 | 8 | 5 to 14 | |
| Costs | All | 21,660 | 4579.5 | 4105.8 | 0 to 113,331.6 | 4009.7 | 3813.84 to 4347.02 | |
| | Main diagnosis | 18,157 | 4272.0 | 2733.9 | 2244.2 to 113,331.6 | 4009.7 | 3905.37 to 4122.27 | < 0.001 |
| | Secondary diagnoses | 3503 | 6172.9 | 7904.5 | 0 to 113,331.6 | 4401.7 | 3467.86 to 6274.48 | |

*Statistical note: *p* values retrieved using Wilcoxon rank-sum test (for median) or *t* test (for means assuming a normal distribution) were identical
Source: National Registry of Hospitalisations. Ministry of Health, Consumption, and Social Welfare

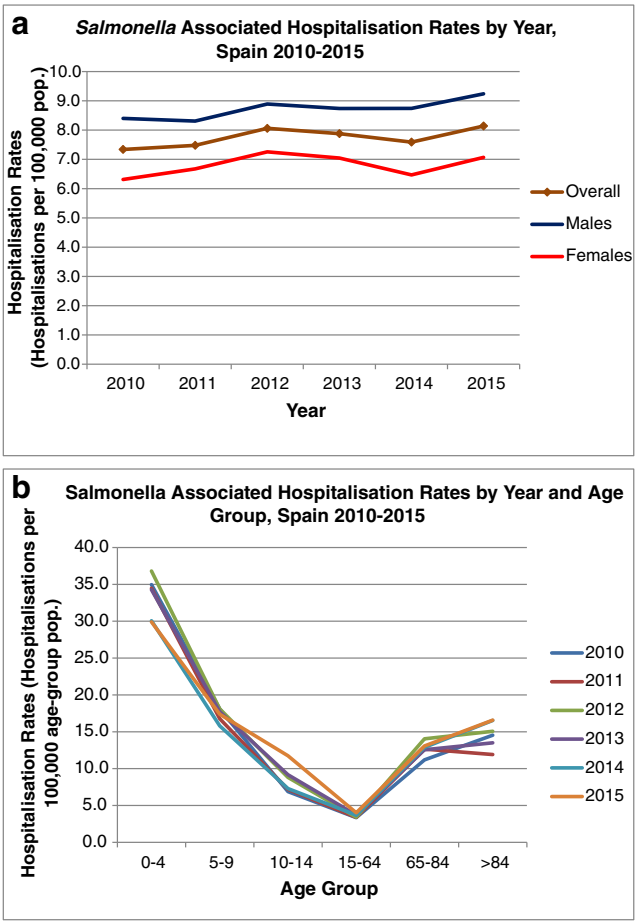
Costs and hospital length of stay increased with age. In those with NTS as Main Diagnosis costs increased from 3969.6 euros in 0–4 age group to 4387.5 euros in > 84 age group and length of stay increased from 4.7 to 8.3 days in the same age-groups. In those with NTS as Secondary Diagnoses costs increased from 5282.1 in 0–4 age group to 5645.2 euros in > 84 age group and length of stay increased from 9.8 to 17.2 days in the same age-groups.

### Hospitalisation rates, 2010–2015

For the whole period 2010–2015, overall hospitalisation rate was 7.7 (range 7.3 to 8.1) hospitalisations per 100,000 population (Fig. 1a). Considering age groups (Fig. 1b), those between 0 and 4 years were the most affected by salmonellosis with an average hospitalisation rate (AHR) for the period of 33.5 (range 29.9 to 36.8). NTS infection impact was still high in those between 5 and 9 years (AHR 17.3; range 15.8 to 18.1); those between 65 and 84 years (AHR 12.7; range 11.2 to 14.1) and those with more than 84 years (AHR 14.8; range 11.9 to 16.6). Those between 10 and 14 years (AHR 8.5; range 6.9 to 11.7) and those between 15 and 64 years (AHR 3.6; range: 3.4 to 4) presented lower hospitalisation rates. Except for those between 5 and 9 years old ($p = 0.335$), the rest of the age groups presented an increasing trend ($p < 0.05$) during the period.

### Intra-hospital CFR% and factors for worse prognosis

In contrast with the high rates of the disease in those between 0 and 4 years, CFR% was low (0.1%) with only five reported deaths: three of them presented co-infections (one methicillin-resistant *Staphylococcus aureus* infection; one bronchiolitis by respiratory syncytial virus and one rotavirus infection), one of them presented "non-specified Septicaemia" (code 038.9) and the other one Down syndrome.




***Source:*** *National Registry of Hospitalisations. Ministry of Health, Consumption, and Social Welfare.*

**Fig. 1** *Salmonella* spp. associated hospitalisations rates by year (**a**) and age group (**b**). Spain. 2010–2015

CFR% increased with age reaching 3.0% in those between 65 and 84 years of age (2.35% for the 65 to 74 years age group and 3.69% in the 75 to 84 years age group) and 4.4% in those > 84 years old. CRF% also increased when CCI was > 3 compared to those with CCI ≤ 3 (9.5% vs. 1.1%; $p < 0.001$) and in those with NTS codes as a Secondary Diagnoses compared to those in which NTS infection was the Main Diagnosis (4.8% vs. 0.7%; $p < 0.001$).

Table 4 shows the frequency in the hospitalised patients of symptoms, comorbidities/risk factors related to worse prognosis and complications. We observed a low proportion of patients with symptoms information about diarrhoea, fever and hypotension: 0.53 to 1.19 of the hospitalised patients with those symptoms in their MBDS clinical records. Seizures were reported in 193 (0.89%) of hospitalised patients and dehydration and hypovolaemia in 3401 (15.70%) hospitalised patients.

The most frequent risk factor for worse prognosis was the presence of co-infections during the hospitalisations. CFR% for those with co-infections (without HIV) was 4.07% and in the case of HIV co-infection, it increased to 6.28% ($p = 0.178$). Most HIV co-infections were related to hospitalisations with NTS as Secondary Diagnoses (3.2% in those with NTS as Secondary Diagnoses vs. 0.43% in those with NTS as Main Diagnosis; $p < 0.001$). The presence of other risk factors with higher CFR% was Down syndrome (CFR% = 6.90%); immune disorders (CFR% = 5.00%), prematurity (CFR% = 5.56%) and metastatic solid tumours (CFR% = 10.88%). Patients with salmonellosis and inflammatory bowel diseases (IBD) presented a CFR% of 0.52% (Table 4).

Regarding the complications (Table 4), acute renal failure was the most frequent complication (present in 4144 hospitalised patients; 19.13%). This complication was more

**Table 4** Frequency and intra-hospital deaths by symptoms, comorbidities/risk factors related to worse prognosis and complications

| Diagnostic group | Diagnosis | Hospitalisations | | Intra-hospital deaths | |
|---|---|---|---|---|---|
| | | *N* | % | *N* | CFR% |
| Symptoms | | | | | |
| | Diarrhoea | 219 | 1.01 | 3 | 1.37 |
| | Fever | 258 | 1.19 | 3 | 1.16 |
| | Hypotension | 115 | 0.53 | 6 | 5.22 |
| | Seizures | 193 | 0.89 | 3 | 1.55 |
| | Dehydration and hypovolaemia | 3401 | 15.70 | 27 | 0.79 |
| Risk factors for infection or worse prognosis (comorbidities and co-infections) | | | | | |
| | Inflammatory bowel diseases | 194 | 0.9 | 1 | 0.52 |
| | Co-infections | 2868 | 13.24 | 121 | 4.22 |
| | -Non-HIV patients with co-infections | 2677 | 12.36 | 109 | 4.07 |
| | -HIV | 191 | 0.88 | 12 | 6.28 |
| | Immune disorders | 140 | 0.65 | 7 | 5.00 |
| | Prematurity | 18 | 0.08 | 1 | 5.56 |
| | Congenital heart diseases | 0 | 0.00 | – | – |
| | Congenital genitourinary diseases | 0 | 0.00 | – | – |
| | Malignancies (except metastatic solid tumours) | 1280 | 5.91 | 50 | 3.91 |
| | Metastatic solid tumour | 331 | 1.53 | 36 | 10.88 |
| | Down syndrome | 29 | 0.13 | 2 | 6.90 |
| | Kawasaki disease | 1 | 0.00 | 0 | 0.00 |
| | Prader-Will syndrome | 0 | 0.00 | – | – |
| Complications derived from *Salmonella* infection | | | | | |
| | Ulcerative colitis | 181 | 0.84 | 1 | 0.55 |
| | Thrombosis | 76 | 0.35 | 3 | 3.95 |
| | Bowel perforation | 18 | 0.08 | 6 | 33.33 |
| | Septic arthritis | 41 | 0.19 | 3 | 7.32 |
| | Acute renal failure | 4144 | 19.13 | 149 | 3.60 |
| | Appendicitis | 72 | 0.33 | 0 | 0.00 |
| | Gastrointestinal bleeding | 85 | 0.39 | 7 | 8.24 |

Source: National Registry of Hospitalisations. Ministry of Health, Consumption, and Social Welfare

frequent in those over 64 years old than in those < 10 years old (38.9% vs. 0.57%; $p < 0.001$). Patients with bowel perforation, gastrointestinal bleeding and septic arthritis presented higher CFRs% (CFRs% 33.33%, 8.24% and 7.32%, respectively) than those with acute renal failure (CFR% 3.60%) as a complication.

Table 5 shows the univariable and multivariable analysis of the association (OR) between the death outcome in hospitalised patients with NTS infection and the different factors evaluated in this study. The association measure presenting only the results for those with NTS infection as Main Diagnosis shows that, once adjusted by age and clinical form, sex is not a risk factor for death. Increased death risk was related to being older, especially > 64 years old (OR = 20.98; $p < 0.001$), presenting septicaemia (OR = 15.82; $p < 0.001$) or localised infections (OR = 3.98; $p = 0.061$), CCI > 3 (OR = 4.57; $p < 0.001$), a non-HIV co-infection (OR = 1.80; $p = 0.013$), other risk factors for infection or worse prognosis (OR = 5.70; $p < 0.001$), bowel perforation (OR = 70.30; $p < 0.001$) or acute renal failure (OR = 1.95; $p = 0.001$).

HIV (including AIDS) infections were excluded from the model because HIV presence implies CCI > 3 (HIV sums 6 points to CCI calculation). Malignancies sum 6 points to CCI when they are metastatic solid tumours and 2 points for the

**Table 5** Univariable and multivariable logistic regression model for death outcome in hospitalised patients with *Salmonella* infections

| Variable | Univariable | | Multivariable | |
|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI |
| Sex (ref. male) | .57 | .40 to .82 | .76 | .50 to 1.14 |
| Age group | | | | |
| 0–9 | Ref. | – | Ref. | – |
| 10–64 | 16.69 | 4.00 to 69.56 | 6.42 | 1.50 to 27.54 |
| More than 64 | 65.00 | 16.02 to 263.68 | 20.99 | 5.03 to 87.58 |
| Clinical form* | | | | |
| Gastroenteritis | Ref. | – | Ref. | – |
| Septicaemia | 33.84 | 22.98 to 49.83 | 15.82 | 10.46 to 23.93 |
| Localised infections | 5.05 | 1.22 to 20.90 | 3.98 | .94 to 16.92 |
| Other specific *Salmonella* infections | 2.72 | .37 to 19.81 | 2.06 | .28 to 15.28 |
| Non-specific *Salmonella* infections | 2.73 | .99 to 7.56 | 2.06 | .72 to 5.86 |
| CCI > 3 (Ref. CCI ≤ 3) | 10.74 | 6.87 to 16.78 | 4.57 | 2.70 to 7.56 |
| Diarrhoea | ** | | – | |
| Fever | .73 | .10 to 5.27 | – | |
| Hypotension | 5.20 | 1.62 to 16.69 | $ | |
| Convulsions | ** | | – | |
| Dehydration and hypovolaemia | .58 | .34 to 1.02 | $ | |
| Non-HIV co-infections | 3.47 | 2.32 to 5.18 | 1.80 | 1.13 to 2.87 |
| HIV co-infections | 5.48 | 1.71 to 17.60 | $ | |
| Malignancies (except metastatic solid tumours) | 3.25 | 2.38 to 4.42 | $ | |
| Metastatic solid tumour | 9.66 | 6.70 to 13.94 | $ | |
| Other risk factors for infection or worse prognosis (excluding co-infections and malignancies) | 4.71 | 3.68 to 6.05 | 5.70 | 2.19 to 14.83 |
| Ulcerative colitis | 1.09 | .15 to 7.82 | – | |
| Bowel perforation | 82.53 | 19.52 to 348.89 | 70.30 | 12.04 to 410.53 |
| Thrombosis | 7.17 | 1.71 to 30.03 | $ | |
| Septic arthritis | ** | | – | |
| Gastrointestinal bleeding | 2.55 | .35 to 18.57 | – | |
| Acute renal failure | 5.89 | 4.18 to 8.30 | 1.95 | 1.31 to 2.90 |
| Appendicitis | ** | | – | |

*OR by clinical form was only calculated for those patients with a unique clinical form to avoid bias in the estimations

**No deaths

$ Excluded from the model. No statistical significant association measures with death outcomes when adjusted by other risk factors

Source: National Registry of Hospitalisations. Ministry of Health, Consumption, and Social Welfare

rest of malignancies. This factor also lost their association when adjusted by CCI as it is explained by it. Patients with malignancies and CCI ≤ 3 had a CFR% of 3.14% and those with malignancies and CCI > 3 had a CFR% of 10.78% ($p < 0.001$).

## Discussion

In Spain, there are no recent detailed population studies about *Salmonella* cases or hospitalisations at the national level. *Salmonella* National Surveillance System results have been published in two reports with the only 2 years data available (2014 and 2015) [2, 15], but no patients clinical information was provided in those reports. Last national study using the National Hospitalisation Registry covered the period from 1997 to 2006 and evaluated mainly salmonellosis hospitalisation trends, costs and hospital stays not focusing also in other clinical aspects of the disease [6].

At the regional level, there is a study from Cores-Calvo et al. that evaluated *Salmonella* infection trends between 2005 and 2014 in the Spanish area of Salamanca [16]. Results from all cases in the area (primary care and hospitalised cases) showed that 23.6% of all cases required hospitalisation. Similarly to Cores-Calvo et al. [16] and the National Surveillance System reports [2, 15], it was observed an increasing trend in the hospitalisations rates (from 7.3 to 8.1) during the same period that affected to most of the age groups (except 5–9 years old age-group).

However, comparing results presented in this study with the previous study using the National Hospitalisation Registry [6], the AHR decreased from 16.18 between 1997 and 2006 to 7.7 hospitalisations per 100,000 population between 2010 and 2015 (more than 50% of reduction). Though, case-fatality rates did not experience similar reduction (1.4% in both studies). High efforts have been implemented since 2008 through the Spanish National Control Programme for reduction of the prevalence of *Salmonella* infection in poultry. It could be considered a relevant determinant for the AHR decrease between the two periods (1997–2006 and 2010–2015). However, a positive trend was observed in our data and that indicates that further efforts are needed to control the disease.

Regarding the symptoms, it was observed that the National Hospitalisation Registry does not seem to collect properly mild symptoms for this disease. It would have been expected a higher proportion than the observed in this study, for example, of diarrhoea, fever or hypotension when almost 90% of patients develop gastroenteritis clinical form in our population sample.

A low percentage of patients (2.5%) presented more than one clinical form during the hospitalisation and 12.61% of the patients developed non-gastrointestinal forms (4.8% of them septicaemia and 2% localised infections). Other studies reported similar percentages [1, 17, 18].

Regarding risk factors for worse prognosis and complications, co-infections and acute renal failure were the most frequent. We found similar percentages of co-infections reported by Huang et al. [8], but we observed a lower presence of HIV co-infection in our population than in the prior study using the same dataset. Gil Prieto et al. reported 11.6% of HIV cases in those with *Salmonella* as Secondary Diagnoses between 1997 and 2006 [6] while between 2010 and 2015 only 3.2% of HIV cases were observed in the same sub-group.

Similar to other studies, acute renal failure was especially frequent in our sample, especially in those over 64 years old, while children presented it as a rare event [11–13].

A previous study using the same dataset and evaluating the hospitalisations related to meningococcal disease developed by Ordóñez-León GY et al. [19] reported unspecific disease codes when the infectious disease should be the main cause of hospitalisation. For example, that study reported 7.4% of the hospitalisations in which meningococcal disease was coded as a Secondary Diagnosis. However, in some cases, Main Diagnosis was bacteraemia, hypovolemic shock, unspecified bacterial agent and unspecific septicaemia, among others.

In addition to this misclassification, in the case of *Salmonella* hospitalisations, it was expected a higher proportion of cases of NTS coded as Secondary Diagnoses. The reason was that in contrast to meningococcal disease, *Salmonella* can present asymptomatic infections and patients can be carriers of the disease [20]. Therefore, patients with *Salmonella* as Secondary Diagnosis were expected to be a heterogeneous population. This was reflected indeed in the results; there were more hospitalisations with *Salmonella* as Secondary Diagnoses (16.2%) than for meningococcal disease (7.4%) [19]. Also, the patients in this group were older and with worse CCI than those with NTS as Main Diagnosis. This suggests that Secondary Diagnoses can be related to other diseases hospitalisations with *Salmonella* as a complication detected during the hospitalisation. Obviously, this means that both groups (Main Diagnosis vs. Secondary Diagnoses) have to be evaluated separately. When *Salmonella* is the Main Diagnosis, the disease is 6 days limited on average and presents low fatality rates (0.7%). On the other hand, when *Salmonella* is a Secondary Diagnosis, the disease presents worse outcomes (12.8 days of stay on average; CRF% = 4.8%) most probably derived from the diseases causing hospitalisation and/or asymptomatic/late progression forms.

Regarding death outcomes, we evaluated risk factors for death outcome in those with NTS as Main Diagnosis to avoid other diseases influence in the outcomes. Death events have been related previously to bacteraemia, bowel perforation of toxic megacolon and other comorbidities [10, 21]. However, the risk of death estimation was not provided in those studies. Risk of death was 70.3 times higher in those that presented a

bowel perforation event compared to those who not, adjusted by the other covariables. Chao et al. evaluated which factors can lead to a bowel perforation in children [22], being possible to identify which patients were at risk of perforation. It was proposed that early effective fluid resuscitation and rectal tube insertion may be helpful to prevent the occurrence of intestinal perforation. Further research to identify patients at risk of perforation can help to reduce bowel perforation events. Clinical practice guidelines can implement clinical management recommendations for those patients with salmonellosis at risk of perforation. This may help to reduce the death event in patients with NTS infections.

Risk of death was also high for those > 64 years compared to those < 10 years; for those without gastroenteritis and especially with septicaemia; and those with CCI > 3, thrombosis or acute renal failure or co-infections other than HIV.

The relationship between IBD and *Salmonella* infection is still unknown. Some authors suggest that IBD is a risk factor for salmonellosis. Other authors, in contrast, suggest that *Salmonella* infections are a risk factor for IBD or its progression [23–26]. In any case, we observed that hospitalised patients with IBD and co-existent salmonellosis presented low CFR% and the combination of both diseases seem not to be associated with a high risk of intra-hospital progression to death.

Our study has some limitations. The main limitation of the National Registry for Hospitalisation is that it does not collect information about microbiological determinations results in its minimum basic data set (MBDS) and we could not evaluate differences in the clinical pattern by the pathogen. As a more positive note, National Hospitalisation Registry coverage is almost 100% and *Salmonella* coding is provided only when the pathogen is identified. So we were able to describe almost all confirmed hospitalisations in Spain. Using this registry, we are limited to those cases requiring hospitalisation, that differs with primary care cases population, especially because hospitalisations are more frequent in older patients with more comorbidities. However, to avoid bias in estimation of the risk of death, we adjusted by CCI which is intimately related to progression. Other limitation is that this Registry is not adequate to evaluate mild symptoms associated with *Salmonella* infection like fever or diarrhoea. Additionally, we observed the need to review the use of Main Diagnosis to avoid unspecific codes on it. This would help to stratify correctly between Main and Secondary Diagnoses of *Salmonella* infections. We did not evaluate the effect of the different risk factors in those hospitalisations with NTS as Secondary Diagnoses in this work. We consider that this group is a very heterogeneous group and requires an especial attention, as it is also the group which presents higher mortality, costs and hospital stays. Grouping by co-existing diseases in a future study would provide further relevant information to understand which factors are related to worse prognosis in patients with Salmonella as Secondary Diagnoses and how to reduce the impact of the disease for patients and health services. Finally, we did not evaluate in our logistic regression each of the comorbidities separately, but further studies can be developed in any of the relevant sub-groups.

## Conclusions

NTS hospitalisations showed a slight increase in the rates during the period 2010 to 2015. However, hospitalisation rates were reduced in more than 50% compared to previous studies using the same source with data on 1997–2006 period. NTS infection is, in general, a self-limiting infectious disease with an average of 6 days of hospitalisation in those cases requiring hospitalisation. Though, the infection can be complicated by several factors as age, worse CCI, extra-intestinal clinical forms, co-infections and other comorbidities. Intra-hospital case-fatality rates increased notably when salmonellosis was a secondary disease for patients. In those with *Salmonella* as Main Diagnosis, among all complications, bowel perforation presented the strongest association with death outcome, followed by other factors as age > 64 years old and septicaemia clinical presentation. Clinical practice guidelines can help to identify patients at risk of bowel perforation to reduce the fatality of the disease. On average, the cost per hospitalisation related to NTS was higher for those with NTS infections as Secondary Diagnosis than for those with NTS infections as Primary Diagnosis and also increased with age. On average, the overall cost per year due to hospitalisations related to NTS was 16,531,865 euros.

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### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no competing interests.

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