International Journal of Infectious Diseases 96 (2020) 165–171

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Murine typhus. How does it affect us in the 21st century? The epidemiology of inpatients in Spain (1997–2015)

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A R T I C L E I N F O

Article history:
Received 25 March 2020
Received in revised form 11 April 2020
Accepted 18 April 2020

Keywords:
Murine typhus
Endemic typhus
Fever of intermediate duration
Rickettsia typhi
Epidemiology
Spain

A B S T R A C T

Objective: The aim of this study was to analyze the epidemiological impact of murine typhus in patients who required hospitalization in the National Health System (SNS) in Spain between 1997 and 2015.
Background: Murine typhus (MT) is a zoonosis caused by *Rickettsia typhi*. MT is transmitted from rats, cats, dogs, and opossums to humans by their fleas. The clinical picture is characterized by headache, fever, rash, and liver function alteration. The prevalence of MT is considered underestimated since most cases are mild and self-limited. However, up to 10% of patients develop serious complications such as pneumonia or acute kidney injury and may even need admission to intensive care units.
Methods: This was a retrospective longitudinal descriptive study of inpatients diagnosed with *Rickettsia typhi* infection (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM], 081.0) in Spanish public hospitals between January 1, 1997, and December 31, 2015. Data were obtained from the Minimum Basic Data Set (MBDS, CMBD in Spanish), which includes information about inpatients admitted to the National Health System (NHS) hospitals provided by the Health Information Institute of the Ministry of Health and Equality.
Results: Ninety-nine inpatients were included. The incidence rate of MT was 0.12 (95% CI, 0.09-0.14) cases per one million person-years. Cases were irregularly distributed throughout the period of study, with a slight upward trend between 2013 and 2015. The Canary Islands had the highest incidence rate: 2.17 (95% CI, 1.69–2.64) cases per one million person-years (80 cases). Most patients were men (63.6%). The mean age (±SD) was 46.4 years (±19). Five patients were under 15 years old. Approximately 85.9% of cases required urgent hospital admissions. The average hospital stay was 11 days (±9.9). Only 1 patient died.
Conclusions: Although considered uncommon, the incidence of MT seems to be increasing slowly. Most cases occurred in middle-aged men between late summer and early autumn in Spain. The Canary Islands and Andalusia registered the highest number of cases. The MBDS is an appropriate approach to study MT hospital management.

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https://doi.org/10.1016/j.ijid.2020.04.054

Introduction

Endemic (murine) typhus is a febrile syndrome caused by different species of the genus *Rickettsia*. Although *Rickettsia typhi* is considered the primary causative agent of endemic typhus, this syndrome can be caused by other flea-borne *Rickettsia* species, such as *Rickettsia felis,* and the recently identified *R. felis*-like organisms *Rickettsia asembonensis* and *Candidatus Rickettsia senegalensis* (Civen and Ngo, 2008; Azad and Beard, 1998; Bernabeu-Wittel and Segura-Porta, 2005; Howard and Fergie, 2018; Bolaños et al., 2004; Robaina -Bordón et al., 2020). The classic *Rickettsia typhi* life cycle involves commensal rats of the subgenus *Rattus* (such as *R. rattus* and *R. norvegicus*) and their fleas (especially *Xenopsylla cheopis*). Adaptation to new reservoirs (cats, dogs, opossums) and vectors, in particular the cat flea (*Ctenocephalides felis*), has led to the reappearance of cases of infection caused by *Rickettsia typhi* in developed countries.

In most cases, the clinical picture is mild and self-limited, characterized by a fever of intermediate duration, headache, arthromyalgia, and rash (Robaina -Bordón et al., 2020; Taylor et al., 1986; Dumler et al., 1991; Silpapojakul et al., 1996; Bernabeu-Wittel et al., 1999; Miguélez et al., 2003; Psaroulaki et al., 2012; Anyfantakis et al., 2013; Grouteau et al., 2020). The most frequent laboratory test abnormalities are thrombocytopenia, hyponatremia, hypertransaminasemia, dissociated cholestasis, and haematuria (Robaina -Bordón et al., 2020; Taylor et al., 1986; Dumler et al., 1991; Silpapojakul et al., 1996; Bernabeu-Wittel et al., 1999; Miguélez et al., 2003; Psaroulaki et al., 2012; Anyfantakis et al., 2013; Grouteau et al., 2020). The diagnostic suspicion of MT is based on clinical manifestations and epidemiological data, while diagnostic confirmation is usually made by serology (Robaina -Bordón et al., 2020; Taylor et al., 1986; Dumler et al., 1991; Silpapojakul et al., 1996; Bernabeu-Wittel et al., 1999; Miguélez et al., 2003; Psaroulaki et al., 2012; Anyfantakis et al., 2013; Grouteau et al., 2020). Molecular diagnosis can be useful in the first two weeks of the disease (Bolaños-Rivero et al., 2017). *R. typhi* infection is a zoonosis of universal distribution. Although MT has occasionally been described in travelers (Angel-Moreno et al., 2006; Delord et al., 2014), it is usually an autochthonous disease found in Southeast Asia, North America, South Africa, Australia, and some European countries (mainly Greece) (Dumler et al., 1991; Taylor et al., 1986; Silpapojakul et al., 1996; Bernabeu-Wittel et al., 1999; Miguélez et al., 2003; Psaroulaki et al., 2012; Anyfantakis et al., 2013; Grouteau et al., 2020). However, the overall importance of this infection is not well known.

The seroprevalence of endemic typhus ranges from 1 to 20% according to several studies (Bolaños-Rivero et al., 2011; Niang et al., 1998), which implies a high frequency of infection, at least in some areas. On the other hand, a clinical series of MT cases are scarce, with the maximum number of patients being 250 in unicentric series (Robaina -Bordón et al., 2020), which suggests that the usual form of MT is mild and/or that there is little diagnostic suspicion of this disease. However, several series of severe complications of MT have been reported, with the main ones described being renal (Hernández-Cabrera et al., 2004), pulmonary (van der Vaart et al., 2014), hepatic (Silpapojakul et al., 1996), neurological (Stephens et al., 2018), and multi-systemic complications (Bernabeu-Wittel et al., 1998). Elevated age, associated comorbidities, late onset of treatment, and antimicrobial coverage with trimethoprim-sulfamethoxazole are considered the main risk factors for complications. The overall epidemiology in Spain is unknown, probably because it is not a notifiable disease. The objective of this study is to evaluate the impact of murine typhus in the Spanish National Health System during the period from 1997-2015.

Material and methods

This was a retrospective longitudinal descriptive study of inpatients diagnosed with *Rickettsia typhi* infection (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM], 081.0) in Spanish public hospitals between January 1, 1997, and December 31, 2015. Data were obtained from the Minimum Basic Data Set (MBDS, CMBD in Spanish), which includes information about inpatients admitted to the National Health System (NHS) hospitals provided by the Health Information Institute of the Ministry of Health and Equality.

This study analysed data provided by Hospital Discharge Records (HDRs). HDRs bring together all data on hospital discharges produced in the network of general hospitals of the NHS. The data contained in these records are those established in the MBDS, which is the primary information source about morbidity and healthcare processes of inpatients. HDRs provide primary demographic (age, sex, and place of residence) and clinical (diagnoses and procedures) data as well as variables related to the hospitalization process itself, such as the type of admission (urgent or programmed), destination of the patient (home medical discharge, transfer to another hospital or death), and average hospital stay. Diagnoses and procedures collected were coded according to the International Classification of Diseases, Clinical Modification (ICD-9-CM). *Principal diagnosis* was defined as the condition that caused hospital admission. *Secondary diagnoses* (up to 13) are “other diagnoses” or conditions that coexist at the time of admission or develop subsequently that affect patient care during hospitalization.

Diagnostic criteria for murine typhus were a patient with a compatible clinical picture (undifferentiated febrile illness, a rash, thrombocytopenia, or mildly elevated liver function tests) and confirmed serological test. Patients with missing data were excluded from the study.

Statistical analysis

The incidence rates were calculated by dividing the number of new cases of murine typhus (numerator) by the population at risk in a period of time (denominator) multiplied by 1,000,000. It was expressed as "cases per one million person-years." As it is not possible to accurately measure disease-free periods, person-time at risk was estimated by multiplying the average population size by the duration of the period of observation. Information on the population at risk was obtained from annual data published by the National Institute of Statistics (INE in Spanish). The 95% confidence interval (95% CI) for incidence rates were calculated. Incidence rates were calculated for each autonomous region and year to assess temporal and geographical patterns. The results in terms of mean rates by autonomous regions were plotted in maps for the whole study period. The results were expressed as absolute values and percentages for categorical data and as the mean $\pm$ the standard deviation (SD) or median followed by its interquartile range (IQR[Q3-Q1]) or simple range (minimum value, maximum value) for continuous variables. The chi-squared test was used to compare the association between categorical variables in different patient groups. Measured outcomes were expressed as the odds ratio (OR) followed by its 95% CI. Continuous variables were compared with Student’s t-test if data followed a normal distribution or the Mann-Whitney test if not. An ANOVA was used to analyze continuous variables among three or more groups.

Additionally, the corresponding regression models were applied for multivariate analysis. A p-value of less than 0.05 was considered to indicate statistical significance. Data analysis was performed using IBM SPSS Statistics version 23.0 (Statistical Package for the Social Sciences, Inc. Chicago, IL, USA).

Ethics statement

This study is based on the medical data of patients collected in the MBDS. These data are the responsibility of the Ministry of Social Services of Health and Equality (MSSHE) that retains and organizes them. All patient data furnished by the MBDS are anonymized and identified by the MSSHE before being given to applicants. According to this confidentiality commitment signed with the MSSHE, researchers cannot provide these data to other researchers. The protocol and ethics statement of this study were approved by the Clinical Research Ethics Committee of the Complejo Asistencial Universitario de Salamanca (CAUSA). Since the data were collected from an epidemiological database, written consent was not obtained.

Results

Incidence

There were 99 registered cases of murine typhus infection in Spain between January 1997 and December 2015. The incidence rate was 0.12 (95% CI, 0.09-0.14) cases per one million person-years. The incidence rate in men was double that of women, 0.15 (95% CI, 0.11-0.19) *vs.* 0.08 (95% CI, 0.05-0.11) cases per one million person-years. Cases were irregularly distributed throughout the period of study, with a slight upward trend between 2013 and 2015. The minimum annual incidence rate was 0.05 (95% CI, 0.02-0.12) cases per one million person-years (two cases) in 1997 and 2000. The maximum yearly incidence rate was 0.25 (95% CI, 0.10-0.39) cases per one million person-years (11 cases) in 2006 (Figure 1).

Geographic distribution and seasonality

The Canary Islands had the highest incidence rate: 2.17 (95% CI, 1.69-2.64) cases per one million person-years (80 cases). No cases were registered in some autonomous regions (Figure 2).

The temporal distribution of MT cases is shown in Figure 3, being more frequent between August and October.

Clinical data

Most of the patients (63,6%) were men. The mean age (±SD) was 46.4 years (±19). Five patients were under 15 years old. The clinical and epidemiological characteristics of the participants are shown in Table 1. Eighty-five (85.9%) cases involved urgent hospital admissions. Most patients (96, 97%) returned home after hospital discharge. Murine typhus was recorded as the principal diagnosis in 86 (86.9%) cases. Differences between patients with a principal diagnosis of murine typhus and patients in whom their secondary diagnosis included murine typhus are listed in Table 2. It should be noted that the average hospital stay increased by eight days among patients with a secondary diagnosis of MT, 17.8 ± 18.3 *vs.* 10.0 ± 7.5 ($p = 0.004$). Seventy-two (72.7%) patients were residents in urban areas, and 22.2% came from rural areas (urban/rural ratio, 3:1; $p < 0.001$). The characteristics of rural and urban cases are described in Table 3.

Figure 4 shows the main clinical manifestations associated with this infection. Thirty-three (33.3%) patients were cared for by the Internal Medicine Service, and 15 (15.2%) were treated at the Infectious Diseases Service. In one-third of the cases, it was impossible to know which hospital service treated the patients. We have no data about patients who required admission in an intensive care unit. Only one (1%) patient (an 85-year-old female living in Andalusia) died.

Discussion

Between January 1997 and December 2015, a total of 99 cases with murine typhus had registered HDRs in Spain, with an incidence rate of 0.12 cases per million person-years. This incidence is lower than that reported in other countries, such as Korea (0.8 cases per million person-years) (Chang et al., 2018) or Croatia (5.7 cases per million person-years) (Punda-Polić et al., 2008). Although several factors can explain these differences (i.e., economic level or particular characteristics of the biological cycle), an essential feature is that our study probably underestimates the real impact of MT in the general population since only hospitalized patients have been included. In fact, taking into account that the estimated percentage of patients with *Rickettsia typhi* infection requiring hospital admission is approximately 22% (Robaina -Bordón et al., 2020), the incidence of MT could be five times higher than that calculated between 1997 and 2015. With these data in mind, we suggest that MT ought to be a notifiable disease in Spain. Despite the significant variations during the studied period, endemic typhus should be considered a re-emerging disease since its incidence seems to be increasing slowly in recent years (Raoult and Roux, 1997).

In Spain, most MT cases of inpatients were reported in the Canary Islands and Andalusia, which is consistent with the global series communicated by other authors (Bernabeu-Wittel and Segura-Porta, 2005; Robaina -Bordón et al., 2020; Miguélez et al.,

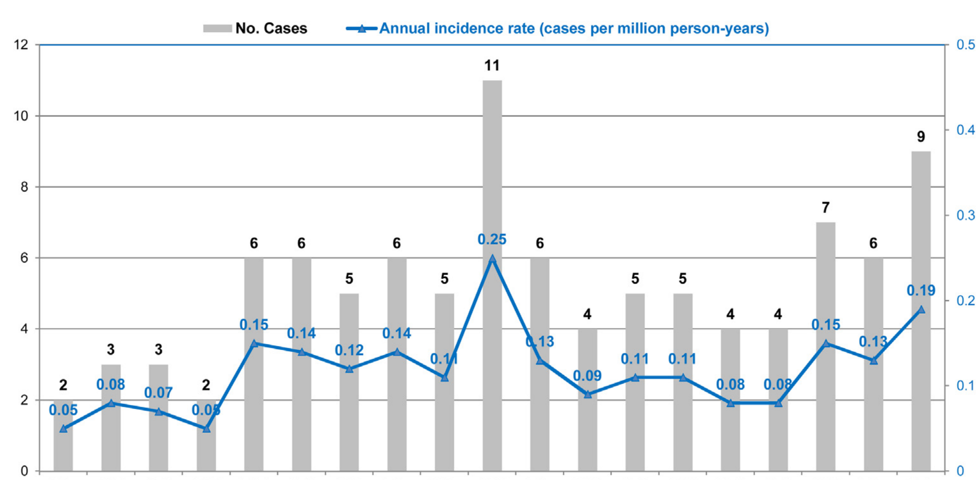

Figure 1. Temporal distribution of cohort (1997-2015) total population of Spain: cases and annual incidence rate *(cases per million person-years)*.

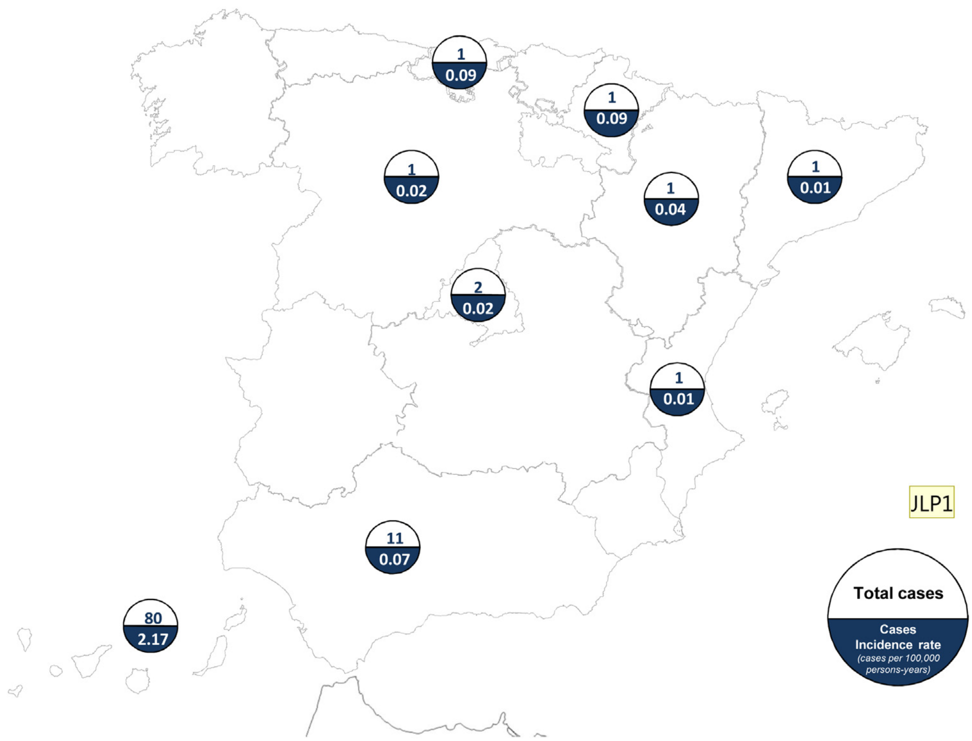

Figure 2. Distribution of the cases and incidence rates (cases per million persons-years) according to the Autonomous Community to which the hospital belongs.

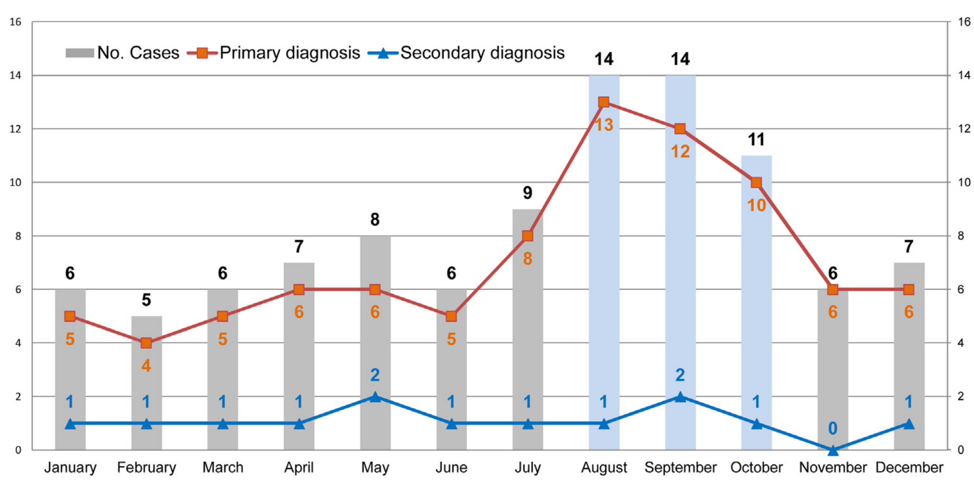

Figure 3. Temporary distribution (months of the year) of cases of murine typhus.

2003). Differences in incidence between autonomous regions could be explained by the existence of different forms of biological cycles. Additionally, it should be noted that these communities maintained a high risk of poverty during the period studied, which may increase the possibility of exposure to the "classic cycle" (Instituto Nacional de Estadística, 2015). In any event, we endorse Didier Raoult's phrase about Q fever, in this case, applied to murine typhus: "differences in prevalence are mainly related to differences in interest" (Raoult, 1994). Regarding the origin areas, 72.7% of patients were residents in urban areas, and 22.2% came from rural areas. The data associated with the place of residence reported in other publications vary considerably. In some series, patients are mostly concentrated in rural areas (Miguélez et al., 2003; Psaroulaki et al., 2012; Chaliotis et al., 2012; Tsioutis et al., 2014), while in others, they mainly live in cities, especially those with major international seaports (Bernabeu-Wittel and Segura-Porta, 2005; Howard and Fergie, 2018; Adjemian et al., 2010; Kuo et al., 2017). This discrepancy may reflect the existence of different forms of the biological cycle, which confirms that the ecology of endemic typhus is complex. The seasonal prevalence of murine typhus during late summer and autumn observed in our series has been described previously (Tsioutis et al., 2017). This temporal pattern seems to be related to the increased propagation activity of the vector linked to higher temperatures; however, it should be noted that the same seasonal predominance does not occur in certain areas, suggesting different transmission profiles (Civen and Ngo, 2008; Murray et al., 2017).

Endemic typhus is diagnosed predominantly in middle-aged men in Spain, with a similar male-to-female ratio (2:1) to other clinical series (Miguélez et al., 2003) but higher than that in others

Table 1
Main data of patients included in the study.

Variable	N = 99 cases (100%) n (%)
Age (years)	
Mean ± SD	46.4 ± 19.0
Median (IQR)	44 (63–33)
0-14 years	5 (5.1)
15-44 years	45 (45.5)
45-74 years	41 (41.4)
≥75 years	8 (8.1)
Gender	
Male	63 (63.6)
Female	36 (36.4)
Diagnosis causing the hospitalization (ICD-9-CM: 083.0)	
Principal/main diagnosis	86 (86.9)
Second diagnosis	13 (13.1)
Rural vs. urban cases	
Rural	22 (22.2%)
Urban	72 (72.2%)
Unknown	5 (5.1%)
Comorbidity	
Kidney involvement	6 (6.1)
Lung involvement	9 (9.1)
Neurological involvement	13 (13.1)
Mental and behavioral disorders	32 (32.3)
Cardiovascular involvement	43 (43.4)
Type of hospital admission	
Urgent	85 (85.9)
Programmed	14 (14.1)
Hospital readmission	
Hospital readmission (30 days after a previous discharge)	95 (96.0)
New episode	4 (4.0)
Type of discharge	
Home	96 (97.0)
Transfer to another Hospital	1 (1.0)
Transfer to social-health center	1 (1.0)
Exitus letalis	1 (1.0)
Hospital stay (days)	
Mean ± SD	11.0 ± 9.9
Median (IQR)	8 (13–5)
Range (Minimum value, Maximum value)	(2, 70)

Table 3
Rural *vs.* urban cases in study.

Variable	Rural	Urban	Unknown	Total
Age (years)				**p = 0.566**
< 45	9 (40.9)	38 (50.2)	3 (60.0)	50 (50.5)
≥ 45	13 (59.1)	34 (47.2)	2 (40.0)	49 (49.5)
Gender				**p = 0.615**
Men	15 (68.2)	44 (61.1)	4 (80.0)	63 (63.6)
Women	7 (31.8)	28 (38.9)	1 (20.0)	36 (36.4)
Total	**22 (100)**	**72 (100)**	**5 (100)**	**99 (100)**

(Chang et al., 2018). However, when the incidence of clinical cases (Robaina -Bordón et al., 2020) is compared with the infection rate in the same geographical region (Bolaños-Rivero et al., 2011), the latter indicates a similar distribution, which suggests that the clinical manifestation of the disease varies according to sex. The mean age of our patients is similar to that reported by other authors in the MT global series, although in our study, admitted patients presented a more serious clinical picture. These data disagree with the description of a more serious clinical picture of this disease in people over 65 years of age (Tsioutis et al., 2014).

Most, 86.9%, of the cases of MT were registered as a principal diagnosis; only 13.1% of the cases were registered as a secondary diagnosis. The visceral manifestations of MT are quite variable depending on the published series. In this series, cardiovascular events predominate, although the study design cannot exclude that they correspond to pre-existing diseases. However, in other studies, pulmonary (Tsioutis et al., 2017) or renal (Hernández-Cabrera et al., 2004) manifestations predominate. The explanation of these differences may be due to any of three different factors: *i)* the methodology of the study, *ii)* the complementary examinations performed in each patient (i.e., performing lumbar puncture increases the number of patients diagnosed with meningitis) (Hernández-Cabrera et al., 2004) and *iii)* the potential existence of *R. typhi* strains with different tissue tropisms. The average hospital stay is ten days in cases with a primary diagnosis, although it is

Table 2
Main diagnosis *vs* secondary diagnosis.

Variables	Main diagnosis N_1 = 86 n (%)	Second diagnosis N_2 = 13 n (%)	p-value*
Age (years)			
Mean ± SD	45.8 ± 18.9	50.0 ± 19.7	0.351
<45 years	45 (52.3)	5 (38.5)	
≥45 years	41 (47.7)	8 (61.5)	
Gender			
Male	52 (60.5)	11 (84.6)	0.092
Female	34 (39.5)	2 (15.4)	
Rural vs. urban cases total			0.757
Rural	20 (90.9)	2 (9.1)	
Urban	62 (86.1)	10 (13.9)	
Unknown	4 (80.0)	1 (20.0)	
Clinical/Comorbidity			
Acute renal failure, unspecified	4 (4.7)	2 (15.4)	0.131
Type of hospital admission			
Urgent	73 (84.9)	12 (92.3)	0.474
Programmed	13 (15.1)	1 (7.7)	
Hospital readmission			
Hospital readmission	84 (97.7)	11 (84.6)	0.126
New episode	2 (2.3)	2 (15.4)	
Type of discharge			
Home	84 (97.7)	12 (92.3)	0.073
Transfer to another Hospital	0	1 (7.7)	
Transfer to social-health center	1 (1.2)	0	
Exitus letalis	1 (1.2)	0	0.696
Hospital stay (days)			
Mean ± SD	10.0 ± 7.5	17.8 ± 18.3	0.007*

* Statistical significance level of 5% ($p < 0.05$).

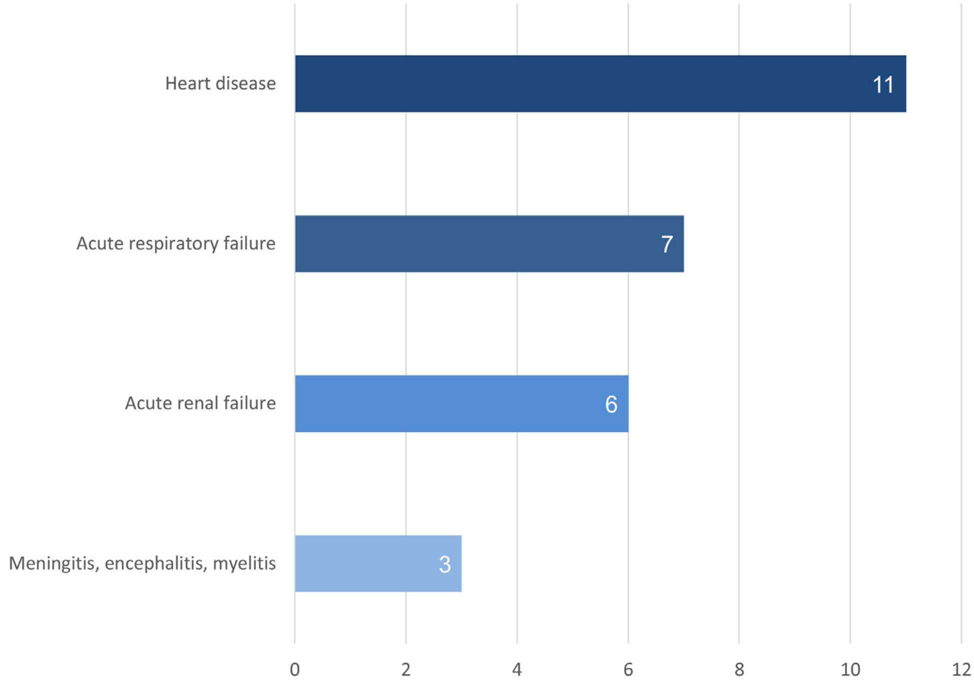

Figure 4. Clinical manifestations associated with murine typhus.

significantly longer in cases with a secondary diagnosis. We have not found a series of patients admitted with MT similar to that provided in this study, with which to make a comparison. The mortality of MT in this series is low (1%), which is consistent with the available data (Robaina -Bordón et al., 2020). However, this study may also underestimate mortality since it includes only patients who died while hospitalized. Additionally, having an early clinical suspicion and treatment can influence a decrease in mortality.

The MBDS provides data from public hospitals in Spain that cover more than 99% of the population; thus, this study provides relatively accurate estimates of the incidence of MT. The main *limitations* of this study are due to several factors:

[1] The use of sources such as the MBDS for purposes other than health care and research,
[2] The use of the ICD-9 for codification, which has some limitations in comparison with the ICD-10 in that ICD-10 is more recent and has fewer qualifying errors,
[3] The potential existence of encoding errors,
[4] The impossibility of accessing patient data to verify data, and
[5] The MBDS includes only public hospital inpatients, not patients in ambulatory hospitals or those with private health insurance.

Therefore, as discussed above, these data underestimate the real incidence of MT in Spain during the period of this study.

In summary, our data suggest that MT is a re-emerging zoonosis in Spain. Most cases occurred in middle-aged men between late summer and early autumn in Spain. The Canary Islands and Andalusia registered the highest number of cases. Also, MT is not as mild as traditionally believed. Finally, we insist on the need for a common national strategy for data collection to monitor and report new cases, aiming to facilitate a more accurate picture of TM infection and to make strategic control measures. The MBDS could be an excellent approach to study MT hospital management.

Conflict of interest statement and funding source

All authors declare no potential conflicts of interest and no sources of support.

Ethical approval

The procedures described here were carried out following the ethical standards outlined in the 2013 revised version of the Declaration of Helsinki. Additionally, this study was approved by the Bioethics Committee of CAUSA. At all times, we maintained the confidentiality of the patients' personal data.

Informed consent

Not applicable.

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