Epidemiological scenario of Q fever hospitalized patients in the Spanish Health System: What's new

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ABSTRACT

Objectives: The objective of this study was to assess the epidemiology and burden of Q fever (QF) in Spain.
Methods: We designed a retrospective descriptive study using the minimum basic data set in patients admitted to hospitals of the National Health System between 1998 and 2015 with a diagnosis of Q fever (ICD-9: 083.0.).
Results: We found 4214 hospitalized patients with a mean age (±SD) of 50.9 ± 19.3 years. The male/female ratio was 3:1. The incidence rate was between 0.41 and 0.65 cases per 100,000 person-years over the 18-year period. The highest incidence of cases was from March to August ($p = 0.024$). 21.1% patients had pneumonia, 17.5% had liver disease, and only 3.2% had endocarditis. The average hospital stay was 13.8 days (± 12.8). A total of 117 (2.8%) patients died. The total mean cost of QF is approximately €154,232,779 (€$36,600 \pm 139,422$ per patient).
Conclusions: QF is an important zoonosis in Spain with a stable incidence rate and high cost for hospitalization. Older patients have a more severe clinical picture and higher mortality, which can be decreased with early clinical suspicion.

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Introduction

Q fever (QF), whose causative agent is *Coxiella burnetii*, is a zoonosis and is a significant public health problem. QF has three types of reservoirs: i) domestic or peridomestic animals, mainly goats, sheep and cattle and to a lesser extent cats and dogs. ii) "wild" animals, mainly rodents and small mammals, and occasionally birds, reptiles, amphibians and fish; and iii) ticks (Pérez-Arellano et al., 2018; Musso and Raoult, 1995). QF can present as sporadic cases or through outbreaks in a specific region. Risk groups include exposed professionals, and pregnant women, immunocompromised patients, and patients with valvular disease at risk for chronic Q fever after acute infection (Million et al., 2013). Currently, the greatest risk factor is living in or traveling to an endemic area (Hartzell et al., 2008; Hackert et al., 2012; Stern et al., 2018; Handy Marshall et al., 2018).

QF is considered a benign disease (Damasceno and Guerra, 2018; Greiner et al., 2018), since only 2–5% of the patients diagnosed with QF require hospitalization (Greiner et al., 2018;

Fraile Fariñas and Muñoz Collado, 2010). Infection in humans occurs mainly by inhaling pseudospores, although other avenues of minor importance include transfusions, interhuman transmission and tick bites (Damasceno and Guerra, 2018; Honarmand, 2012; Milazzo et al., 2002; Kruszewska et al., 1996).

QF has a wide spectrum of disease manifestations, with two main clinical presentations: i) *acute Q fever* can present with intermediate duration fever associated with respiratory manifestations and/or liver disorders, and ii) *persistent localized infections* can be developed after an acute infection (symptomatic or not) with vascular (endocarditis, aneurysms or vascular grafts) or osteoarticular involvement Fournier et al., 1998. Both forms can present with nonspecific symptoms (Million et al., 2013; Stern et al., 2018; Dahlgren et al., 2015a; National Notifiable Diseases Surveillance System (NNDSS), 2009; Anderson et al., 2013; Kampschreur et al., 2015; Delsing et al., 2010), and these forms of presentation can vary widely according to the geographical location. Historically, it is more frequent as pneumonia in the north (Cilla et al., 2008) and as acute hepatitis in the central and southern regions (Fraile Fariñas and Muñoz Collado, 2010).

With respect to epidemiology, QF is distributed worldwide (Damasceno and Guerra, 2018), with a variable global incidence rate (Eldin et al., 2017). In Europe, the incidence rate varies widely between countries: 0.09 cases/100,000 in the United Kingdom (Halsby et al., 2017) to 2.5–4 cases/100,000 in France (Pérez-Arellano et al., 2018; Hackert et al., 2012). In Spain, it is an endemic and a notifiable disease (Ministerio de Sanidad Servicios Sociales e Igualdad, 2015). Since 2013, the number of human cases reported by Spain has continuously increased, which is mostly explained by the reporting system changing from voluntary to compulsory (Centre for Disease Prevention and Control E, 2019). We do not know the Spanish incidence rate, and it varies widely depending on the region of focus (Alende-Castro et al., 2018). The largest number of case notifications occurs in Pais Vasco (Fraile Fariñas and Muñoz Collado, 2010; Cilla et al., 2008) and Andalucia (Fraile Fariñas and Muñoz Collado, 2010), and there are still more cases in rural areas (Eldin et al., 2017).

The mortality rate of QF is less than 3% (Anderson et al., 2013; Eldin et al., 2017; Woldehiwet, 2004), though a recent study in California described a lethality rate of 10% (Akamine et al., 2019). We have not found studies about the economic impact of QF in Spain.

The aim of our study was to evaluate the epidemiological and economic impact of in-patients diagnosed with QF in Spain between 1998 and 2015.

Methods

This is a retrospective longitudinal descriptive study of hospitalized patients diagnosed with *Coxiella burnetii*, *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM), 083.0, in Spanish public hospitals between January 1, 1998 and December 31, 2015, an 18-year study period.

This study analyzes the data provided by hospital discharge records (HDR). HDR meets all hospital discharges produced in the network of general hospitals in the NHS (National Health System). The data contained in this record are those established in the hospitalization minimum data set (CMBD in Spanish) provided by the Health Information Institute of the Ministry of Health and Equality. CMBD provides the usual demographic data (age, sex, and place of residence), clinical variables (diagnoses and procedures) and variables related to the episode of hospitalization as a circumstance of admission (urgent or programmed), patient discharge (discharge to address, transfer to another hospital or death), average stay and cost estimates. Diagnoses and procedures collected were coded using the ICD-9-CM. **Primary diagnosis** is

the pathological process that is considered the main cause or reason for the patient's admission to the hospital, according to optional criteria. **Secondary diagnoses** coexist with it at the time of admission or develop throughout the hospital stay and influence the duration of treatment or treatment. Patients with missing data were excluded from the study.

Statistical analysis

The incidence rates were calculated by dividing the number of new cases of disease *(numerator)* per year/period by the population at risk *(denominator)* in a period of time (person-years) ($\times$100,000) and expressed as *"cases per 100,000 person-years"*. As it is not possible to accurately measure disease-free periods, the total number of person-time at risk can be estimated approximately and satisfactorily when the size of the population is stable, multiplying the average population size studied by the duration of the observation period. Thus, the population at risk was obtained from annual data published by the National Institute of Statistics (INE, http://www.ine.es/). Incidence rates were computed by autonomous community and year to assess temporal and geographical patterns. Results in terms of mean rates by autonomous community were plotted in maps for the whole study period.

The lethality rate was calculated by dividing the number of deaths (numerator) by the number of patients with a specific disease (denominator) ($\times$ 100).

The cost estimate was the weighted average of the average costs of the GRD of all cases of a given unit, group or process. It was calculated by multiplying the number of cases of each GRD and Level of Severity by their average cost and dividing by the total number of cases of said unit. These data were calculated for each case/patient by the CMBD. We estimated the average cost ($\pm$ SD, Standard deviation) for the total of cases/patient cohort.

The results were expressed as absolute value (n) and percentage (%) for categorical variables and as the mean, standard deviation (SD), median, and range (minimum value, maximum value) for continuous variables. The chi-square test was used to compare the association between categorical variables, such as clinical and demographic variables, and the measured outcome was expressed as the odds ratio (OR) together with the 95% CI for OR. Continuous variables were compared using Student's t-test or the Mann–Whitney test for two groups, depending on their normal or non-normal distribution. ANOVA allowed us to analyze the influence of independent nominal variables on a continuous dependent variable. A p-value <0.05 was considered statistically significant Data analysis was performed using SPSS 23 (*Statistical Package for the Social Sciences*).

Ethics statement

This study obtained data from CMBD provided by the Ministry of Social Services of Health and Equality (Ministerio de Servicios Sociales, Sanidad e Igualdad, MSSSI). Researchers working can request databases by completing a questionnaire available on the MSSSI website, where a signed confidentiality commitment is required. All patient data are anonymized and identified by the MSSSI before they are provided to the applicants. According to this confidentiality commitment signed with the MSSSI, researchers cannot provide the data to other researchers; they must request the data directly from the MSSSI. The study protocol was approved by the Clinical Research Ethics Committee of the Complejo Asistencial Universitario de Salamanca (CAUSA). Because it is an epidemiological study, written consent was not obtained. All data analyzed were anonymized.

Results

Incidence rates

Between January 1998 and December 2015 (18-year study period), a total of 4214 cases with ICD-9-CM: 083.0 (QF) were registered with HDR in Spain. Chronologically, we observed an irregular distribution of cases throughout the study period, a minimum value of 183 cases (4.3%) in 2001, and a maximum value of 304 cases (7.2%) in 2013. The period incidence rate was 0.53 cases per 100,000 person-years. The annual incidence rates ranged between a minimum and maximum value of 0.41–0.65 cases per 100,000 person-years in 2009 and 2013, respectively, as shown in Figure 1. Attending to primary diagnosis, we found an incidence rate of 0.38 cases per 100,000 person-years.

Geographic and temporal distribution

When analyzing incidence rates in Spain, we observed differences between Spanish autonomous communities. Islas Canarias and Islas Baleares had the highest incidence rates (1.48 and 1.43 cases per 100,000 person-years, respectively) (Figure 2). In total, 25% of patients come from municipalities of less than 5000 inhabitants, and 75% (3/4) of patients come from municipalities greater than 5000 inhabitants.

Figure 3 shows the distribution of QF cases according to the month in which it was diagnosed. Months with the highest incidence of cases were from March to August (p = 0.024).

Clinical features of QF-related hospitalizations

The main clinical and epidemiological data of the patient cohort are shown in Table 1. Most cases were men (3147, 74.7%). Thus, the male/female ratio was 3:1. The mean (±SD) age was 50.9 (±19.3) years. Only 1.9% (78) of cases occurred in the pediatric population. A total of 589 patients (13.98%) were between 0 and 29 years old. Most patients (2189, 51.95%) were between 30–59 years old. A total of 1385 of the patients (32.87%) were between 60 and 89 years old. Only 51 patients were ≥ 90 years old in our cohort. Three out of four cases (3071, 72.9%) were main diagnosis, and the mean hospital stay was 13.8 (±12.8)

days. Table 2 shows that the variables obtained statistically significant results when comparing patients with primary diagnosis vs. secondary diagnosis (p < 0.05). The mean age was lower among patients with primary diagnosis, 49.2 ± 18.5 vs. 55.4 ± 20.4, and the mean hospital stays increased by 5 days among patients with secondary diagnostics, 17.5 ± 16.1 vs. 12.4 ± 10.9.

The most frequent comorbidities in these patients were respiratory diseases, digestive diseases, circulatory diseases, other infectious and parasitic diseases, and neoplasms, in order of frequency. A total of 891 (21.1%) patients were diagnosed with pneumonia, 736 patients had liver disease (17.5%), and 136 (3.2%) had endocarditis. Others were 59 pericarditis, 10 meningitis, 14 encephalitis/myelitis. Attending to the main diagnosis, the highest pneumonia incidence rate was in Aragon and Islas Baleares (IR: 0.08, both of them), and the highest hepatitis incidence rate was in Islas Baleares, Islas Canarias and Castilla y León (IR: 0.02) (Figures 3 and 4).

There were no significant differences between age (<50 years vs. ≥50 years) and the primary diagnosis of hepatitis (45.3% vs. 54.7%, p = 0.550). However, we found significant differences when the primary diagnosis was pneumonia (40% vs. 60%, p = 0.025). The diagnosis of pneumonia was more frequent in > 50 years.

Mortality and economic analysis

A total of 117 (2.8%) patients died. Of these, 46 deaths were patients with the primary diagnosis code (43/3071, 1.5%). Table 3 shows the clinical and epidemiological characteristics of the patients who died.

The lethality rate was 1.50 per 100 (range, minimum value 0 per 100 in 2005 and maximum value 3.37 per 100 in 2013). Figure 1 shows the number of deaths (QF primary diagnosis) each year and annual lethality rates per 100. When analyzing lethality rates in Spain, we observed differences between Spanish autonomous communities. Asturias had the highest lethality rate (7.69 per 100), followed by Cantabria (5.71 per 100), both in Northern Spain (Figure 2). When we focused on the primary diagnosis, we observed the highest lethality rate in Cantabria (5.88) and the second highest rate in Aragón (3.09). Deaths due to pneumonia predominated in Asturias (50%) and Galicia (20%), while hepatitis
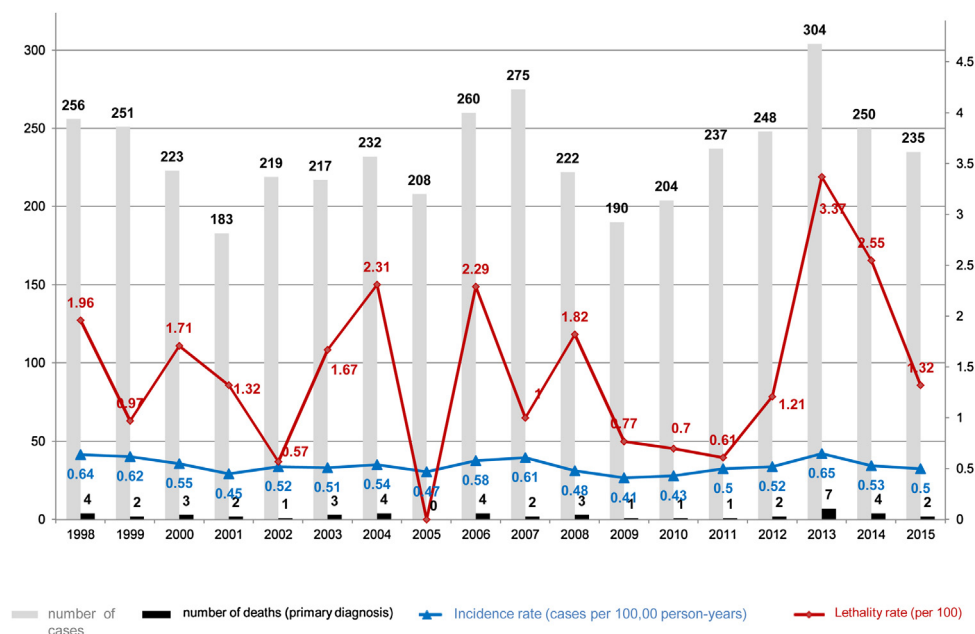

Figure 1. Temporal distribution of number of cases, number of deaths, incidence rate, and lethality rate.
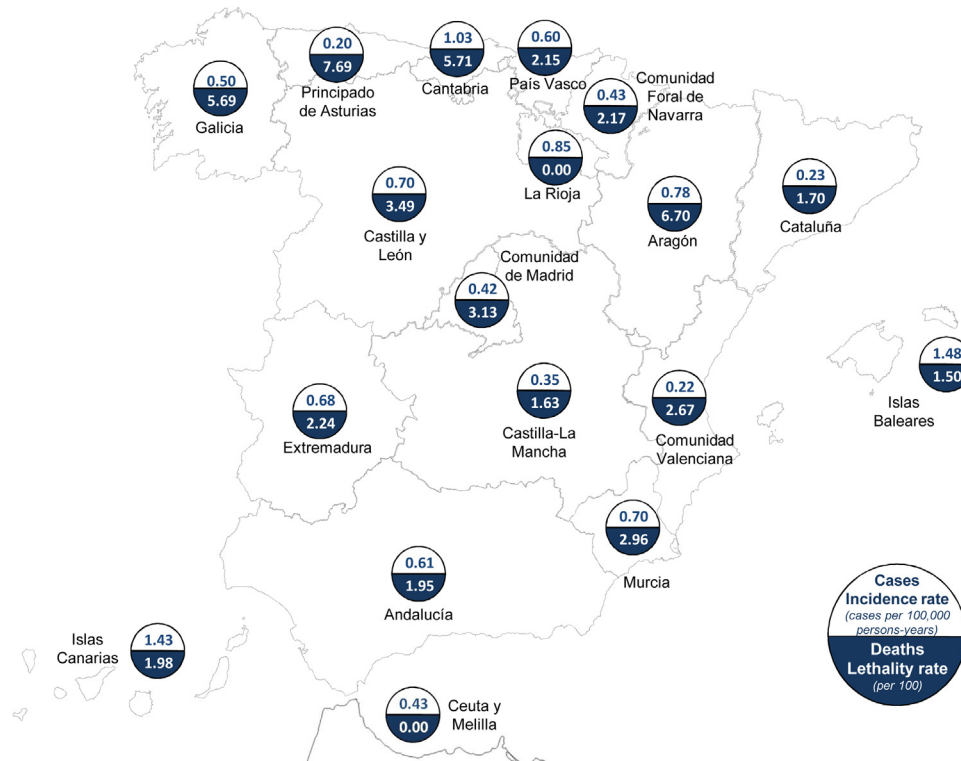
Figure 2. QF incidence and lethality rates by region, Spain (1997–2015).
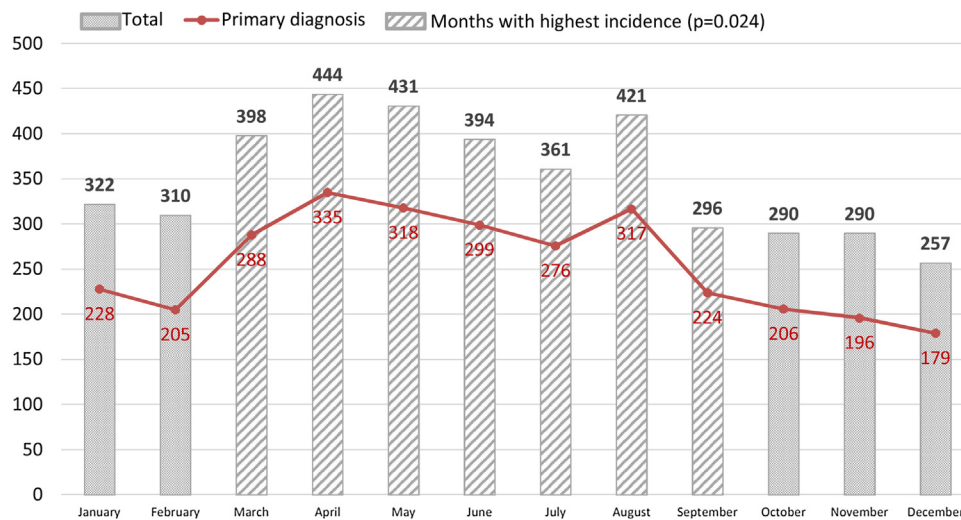

Figure 3. Distribution of cases of QF in-patients during the months of the year, total cases and primary diagnosis.

was the main cause of mortality in Murcia (66.67%) and Comunidad Valenciana (25%).

Finally, we estimated the global cost of this cohort of patients, and the main data are shown in Table 4. Hospital admitted patients with a diagnosis of QF in Spain (from 1998 to 2015) had a total cost of approximately €154,232,779. Mean (±SD) cost per patient, €36,600 ± 139,422.

Discussion

Incidence rates

A total of 4214 cases of QF (codes ICD-9-CM: 083.0) were registered with HDR in Spain between January 1998 and December 2015. The period incidence rate for our cohort of patients was 0.53 cases per 100,000 person-years, and it remained stable (or even slightly decreased between 1998 and 2015).

Our data provide a higher incidence rate in Spain compared to rates described in other European countries, such as the British Isles, with a stable incidence of approximately 0.15 to 0.35 cases per 100,000 inhabitants (Wallensten et al., 2010; Wilson et al., 2010; Hussain-Yusuf et al., 2012), while in France, the annual incidence of acute QF is 2.5/ 100,000 persons (Frankel et al., 2011). It is remarkable that the incidence in Spain remains stable compared to another French study where the incidence shows a continuous increase (Frankel et al., 2011). This phenomenon might have several explanations: i) use of new techniques that increase the diagnostic possibilities (Bolaños-Rivero et al., 2017a), ii) a better knowledge of the disease and, therefore, of its suspicion, iii) a

Table 1
Main epidemiological and clinical data of patients.

Variable	N = 4214 cases (100%) n (%)
Age	
Mean ± SD, years	50.9 ± 19.3
Gender	
Male	3147 (74.7)
Diagnosis causing the hospitalization	
Primary diagnosis	3071 (72.9)
Secondary diagnosis	1143 (27.1)
Pneumonia	891 (21.1)
Primary diagnosis	142/891 (15.9)
Secondary diagnosis	749/891 (84.1)
Liver disease	736 (17.5)
Primary diagnosis	53/736 (7.2)
Secondary diagnosis	683/736 (92.8)
Acute and sub-acute endocarditis	136 (3.2)
Primary diagnosis	21/136 (15.4)
Secondary diagnosis	115/136 (84.6)
Hospital readmission	
Hospital readmission[a]	3784 (89.8)
New episode	430 (10.2)
Overall mortality	117/4214 (2.8)
Q-fever (primary diagnosis) mortality	46/3071 (1.5)
Pneumonia (primary diagnosis) mortality	7/142 (4.9)
Liver disease (primary diagnosis) mortality	5/53 (9.4)
Hospital stay	
Mean ± SD, days	13.8 ± 12.8

[a] Hospital readmission: for the same year and center within 30 days after a previous discharge.

more adequate record of the number of cases, iv) different patterns of disease transmission (Bolaños-Rivero et al., 2017b), and v) the presence of outbreaks that increase the incidence of the disease. This French study shows a maximum incidence between March and August, which is identical to our data (Frankel et al., 2011). Although the real impact of QF in Spain may be greater, we only see the tip of the iceberg.

Geographic and temporal distribution

Although classic Q fever has been considered a predominantly rural disease (due to contact with animals, mainly cattle and goats), only 25% of our cases are of rural origin (<5,000 inhabitants) (Pérez-Arellano et al., 2018) and there are a significant number of cases (75%) from urban areas, which do not have contact with animals. Classically, Andalucía and Pais Vasco are the communities with the highest incidence rate described (Fraile Fariñas and Muñoz Collado, 2010; Cilla et al., 2008). Therefore, in our study, we obtained the highest incidence rates in Islas Canarias and Baleares with no clear explanation.

Clinical features of QF-related hospitalizations

In general, although cases in children and the elderly are described, QF is a disease that predominantly affects adults in middle age and with a male predominance (Pérez-Arellano et al., 2018). Therefore, most patients diagnosed with QF in Europe are in the age range of 15–45 years according to the literature (Eldin et al., 2017). Our cohort has a significantly higher mean age (50.9 ± 19.3 years) as expected, and our cases in elderly and pediatric ages are very few in possible relation to the mechanisms of acquisition of this pathology.

In our study, the male/female ratio was 3:1, and in previous studies, we found a similar ratio of 2.5:1 (Pérez-Arellano et al., 2018; Parker et al., 2006). Among the factors involved, hormonal modifications (protective role of 17-ß-estradiol) that take place after puberty have been described in addition to the risk and environmental exposure (Emmanouil and Raoult, 2012; Leone et al., 2004; Raoult et al., 2005). In our work, 15.9% patients had pneumonia, 7.2% had liver disease and 3.2% patients had endocarditis. It is difficult to compare these results with those provided in the literature for several reasons: i) In our work, exclusively admitted patients are evaluated, so the less severe forms are underrepresented. ii) The definitions of "pneumonia" and "hepatitis" are not unequivocal. For example, "hepatitis" could mean a hepatitis A-like syndrome, or a two-fold increase in serum liver enzymes (Bolaños-Rivero et al., 2017a). iii) As it happens when different countries are compared, there is also a different distribution of clinical forms within Spain: pulmonary in the north and "hepatic" in the south and in the Canary Islands (Bolaños et al., 2003; Jado et al., 2012). In addition to the different bacterial load, there are data to suggest that strain differences are important in

Table 2
Primary diagnosis *vs* secondary diagnosis of QF.

	Primary diagnosis N₁ = 3071, n (%)	Secondary diagnosis N₂ = 1143, n (%)	p-Value OR (95%CI)[a]
Age			
Mean ± SD, years	49.2 ± 18.5	55.4 ± 20.4	<0.001
≥50	1431 (46.6)	703 (61.5)	1.8 (1.5–2.1)
<50	1640 (53.4)	440 (38.5)	
Gender			
Male	2333 (76.0)	814 (71.2)	0.002
Female	738 (24.0)	329 (28.8)	1.3 (1.1–1.5)
Type of hospital admission			
Urgent	2758 (89.8)	982 (85.9)	<0.001
Programmed	300 (9.8)	160 (14.0)	1.5 (1.2–1.8)
Others/unknown	13 (0.4)	1 (0.1)	
Hospital readmission			
Hospital readmission	2819 (91.8)	965 (84.4)	<0.001
New episode	252 (8.2)	178 (15.6)	2.1 (1.6–2.5)
Type of discharge			
Home	2976 (96.9)	1029 (90.0)	<0.001
Transfer to another hospital	21 (0.7)	28 (2.4)	
Voluntary discharge	9 (0.3)	6 (0.5)	
Transfer to social-health center	7 (0.2)	5 (0.4)	
Others/unknown	12 (0.4)	4 (0.3)	
Hospital stay			
Mean ± SD, days	12.4 ± 10.9	17.5 ± 16.1	<0.001
Exitus letalis	46 (1.5)	71 (6.2)	>0.001, 4.3 (2.9–6.3)

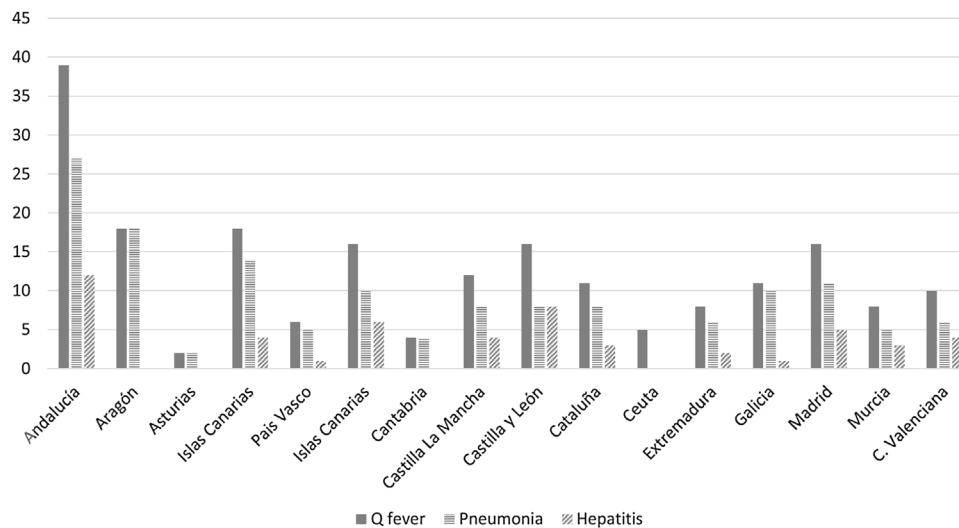[a] Only when it is a significant p-value.

Figure 4. Number of cases of QF of in-patients in Spain during 1997–2015 (primary diagnosis).

Table 3
Main variables association with mortality of QF in-patients.

	N₀ = 117 *Exitus letalis* n (%)	p-Value, OR (95%CI)[a]
Age		
Mean ± SD, years	69.9 ± 15.4	<0.001
≥50 years	106 (90.6)	9.8 (5.2–18.3)
<50 years	11 (9.4)	
Gender		
Male	82 (70.1)	0.246
Female	35 (29.9)	
Diagnosis causing the hospitalization		
Secondary diagnosis	71 (60.7)	<0.001
Primary diagnosis	46 (39.3)	4.3 (2.9–6.3)
Type of hospital admission		
Urgent	110 (94.0)	0.177
Programmed	7 (6.0)	
Hospital readmission		
New episode	26 (22.2)	<0.001
Hospital readmission	91 (77.8)	2.6 (1.6–4.1)
Hospital stay		
Mean ± SD, days	22.8 ± 21.4	<0.001

[a] Only when it is a significant p-value.

their association with clinical manifestations (Jado et al., 2012). These data suggest the need to include QF in our differential diagnosis when an in-patient has pneumonia, hepatitis or endocarditis (Leone et al., 2004). In addition, some studies describe a significantly lower average age in patients with hepatitis and greater age in patients with pulmonary involvement, and the results of our work corroborate lung involvement.

Mortality analysis

Our lethality rate was 2.8%, which is similar to the rate described in the USA from 2000 to 2012 (2%) (Dahlgren et al., 2015b). Nevertheless, a recent study in California described a lethality rate of 10% (Akamine et al., 2019), and the death attributed to QF was associated with an average diagnostic delay of 65.5 days (Akamine et al., 2019). Our data show that older patients have a more severe clinical picture and higher mortality. These findings seem to tip the balance towards the first hypothesis: the scarce clinical suspicion has delayed the diagnosis. Therefore, efforts to carry out a timely diagnosis and an earlier initiation of treatment are essential to improve the prognosis (Raoult and Marrie, 1995) and may result in fewer hospitalizations and fewer severe complications. This result is supported by our work, where the lethality rate is higher in Asturias and Cantabria (7.69 and 5.71, respectively), although the highest incidence rate is not in these communities. In addition, regions with higher incidences have lower mortality. An explanation would be a greater clinical suspicion, which would condition a diagnosis and earlier treatment, thus reducing the mortality rate. A very slight decrease in the mortality rate was observed during the period of our study (1.96 in 1998 and 1.32 in 2015). Although we cannot extrapolate our results to the general population (since we only include hospitalized patients), it is possible to appreciate that they are in the same line as available literature (Akamine et al., 2019).

It is remarkable that in our study, the small reduction in the incidence rate was greater than that in the mortality rate. We think that there could be two possible causes for this: i) the scarce clinical suspicion that we have about the presence of this pathology or ii) the lower tendency to hospitalize these patients for trivializing the clinical symptoms.

Economic analysis

The mean hospital stay for our cohort of patients was 13.8 ± 12.8 (p < 0.001), but it increased noticeably when we focused on the patients who died (22.8 ± 121.4). We have not found data on hospital stay in the available literature.

We also calculated the approximate cost of in-patients with a diagnosis of QF in Spain (from 1998 to 2015): €154,232,778.60. The mean (±SD) cost per patient was €36,600.09 (±139,421.85). Note that the highest mean (±SD) cost occurs in patients who died €51,814.29 (±215,505.52) (p < 0.001). We were also not able to find data about the economic cost of QF anywhere.

It should be noted that the difference in costs according to involvement is higher in patients with hepatitis. We must not forget that we have only taken into account the costs in terms of hospitalization, but according to the literature, up to 20% of these patients suffer a chronic fatigue syndrome (Hickie et al., 2006; Reukers et al., 2019) after the referral of the QF, which incurs additional costs due to sick leave and medical consultations. The cluster of cases collected from patients diagnosed with this syndrome is in Europe and Australia (Hickie et al., 2006).

Table 4
Main burden data of QF in-patients.

	N	Descriptive statistics Mean ± SD	p-Value
Cost by diagnosis			
Q-Fever primary diagnosis	3071	38,706.82 ± 136,553.41	0.108
Q-Fever secondary diagnosis	1143	30,939.75 ± 146,763.57	
Cots by type (primary diagnosis)			
Pneumonia	142	23,123.73 ± 88,066.07	0.001
Hepatitis	53	52,566.41 ± 176,565.36	
Cost by type of hospital admission			
Urgent	3740	33,351.86 ± 126,270.37	0.008
Programmed	460	51,259.83 ± 207,084.28	
Cost by type of hospital readmission			
Hospital readmission	3071	37,201.61 ± 141,040.00	0.406
New episode	430	31,306.68 ± 124,300.10	
Cost in mortality			
Overall mortality	117	51,814.29 ± 215,505.52	<0.001
Primary diagnosis mortality	46	70,396.45 ± 196,525.91	
Global cost			
Total, €	4214	154,232,778.60	
Mean ± SD, €	4214	36,600.09 ± 139,421.85	

Limitations and conclusions

Even if the CMBD provides information from a network of hospitals that covers more than 99% of the population living in Spain (http://www.msssi.gob.es/), this study provides fairly accurate estimates of the incidence. The main limitations of this study are determined by several factors: i) the use of sources such as the CMBD for purposes other than research and clinical care; ii) the use of the ICD-9 code, which has certain classification limitations with respect to the ICD-10, which is more modern and has fewer qualifying errors; iii) encoding error may exist and cannot be amended as the data included in the CMBD are irreversible; iv) not being able to access the medical history prevented us from confirming the diagnosis and identifying the possible associated factors involved, such as work activity and the difficulty of assessing the origin of patients (rural vs. urban), and does not provide information about tests used for QF diagnosis, which impairs the quality of the data; v) in considering only patients in public hospitals and not including nonhospital cases or private centers, for example, those who are ill who are not admitted or who did not receive medical care, in addition to those treated in private hospitals, would be excluded, thus, hospital records underestimate the real burden of QF in Spain. This study only reflects the patients who died while hospitalized, which could underestimate the mortality; and finally, vi) the estimated cost is approximate and less than the real cost, since in this work, only hospital costs have been included. In any case, our findings reported here have potential implications for public policy.

We aimed to relieve the lack of official epidemiological data, but we also contributed to generating hypotheses that will be worthy of exploration in further investigations.

We have demonstrated that QF is an important zoonosis in Spain with a period incidence rate that remained stable. The overall mortality rate is approximately 3%, and older patients have a more severe clinical picture and higher mortality. Additionally, having an early clinical suspicion can influence a decrease in mortality. Additionally, this study shows a high cost for hospitalization due to QF. Finally, there is a need for a common national strategy on data collection, monitoring, and reporting, which would facilitate a more accurate picture and strategic control measures design. Improving human and animal QF surveillance will be useful, both in gaining extended disease knowledge and reducing morbidity and related costs. Furthermore, industrial and regulatory measures

need to be implemented in parallel, as an integrated and multisectoral approach is the only way to successfully prevent and control QF. The CMBD could be a good complementary epidemiological analysis system for the study of hospital management of QF.

Conflict of interest statement and funding source

Ethical approval

The study protocol was approved by the Clinical Research Ethics Committee of the Complejo Asistencial Universitario de Salamanca (CAUSA). Because it is an epidemiological study, written consent was not obtained. All data analyzed were anonymized.

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