



Mediterranean spotted fever rickettsiosis in Italy, 2001–2015: Spatio-temporal distribution based on hospitalization records

Diana Gomez-Barroso^{a,*,1}, Maria Fenicia Vescio^{b,1}, Antonino Bella^b, Alessandra Ciervo^b, Luca Busani^b, Caterina Rizzo^b, Giovanni Rezza^b, Patrizio Pezzotti^b

^a Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP), National Center for Epidemiology, Carlos III Institute of Health, Madrid, Spain

^b Department of Infectious Diseases, Istituto Superiore di Sanità, Rome, Italy

ARTICLE INFO

Keywords:

Mediterranean spotted fever
Spatial models
Italy
Ticks
Epidemiology
Geography

ABSTRACT

The Mediterranean spotted fever (MSF) rickettsiosis is the predominant rickettsial disease among the spotted fever group (SFG) rickettsiae in the Mediterranean countries and North Africa. Its causative agent is *Rickettsia conorii*, although, SFG rickettsiosis - cases due to *Rickettsia monacensis*, *Rickettsia massiliae* and *Rickettsia aeschlimannii* were also described. A retrospective study based on hospital discharge records with a diagnosis of SFG rickettsiosis was carried out to describe the spatial pattern, the trend of the disease, and the epidemiological characteristics of persons hospitalized in the period 2001–2015. Standardized hospitalization ratios were calculated at municipal level using the European population. Smoothed maps were produced using a localised smoothing Poisson model. The mean annual standardized hospitalization rate was 1.36/100,000 person years (95%CI: 1.34; 1.39). Rates showed strong summer seasonality and tended to decrease over time. During the study period, 28.89% of municipalities had smoothed standardized hospitalization ratios greater than 1 and 14.01% above 20. Higher standardized hospitalization ratios were found in areas along the Tyrrhenian coast, especially in the south of Calabria and in the islands of Sardinia and Sicily, where the disease is of public health relevance.

1. Introduction

Spotted fever group rickettsiosis (SFG rickettsiosis) rickettsiae are emerging/re-emerging agents of tick-borne diseases in humans. The Mediterranean spotted fever (MSF) is the predominant SFG rickettsiosis disease in the Mediterranean countries (Ciceroni et al., 2006) and it is caused by *R. conorii*. SFG rickettsiosis is endemic in North Africa and Southern European countries bordering the Mediterranean sea (Sousa et al., 2003) including Italy, especially in the Southern (Sardinia, Sicily, Calabria) and Central regions (Brouqui et al., 2007), where most cases occur from June to September (Bernabeu-Wittel and Segura-Porta, 2005; Vescio et al., 2008). The disease in humans is characterized by generic flu-like symptoms or lymphadenopathies with or without a consistent rash and sometimes an eschar (“tache noire”), at the site of the tick bite. Symptoms are usually mild, but sometimes can be severe or even lethal, in subjects with predisposing conditions associated with diabetes, alcoholism, cirrhosis, glucose-6-phosphate dehydrogenase deficiency, male gender, inappropriate antibiotic treatment, delay in treatment and advanced age (Raoult and Roux, 1997).

Until recently, SFG rickettsiosis was thought to be the only tick-borne rickettsiosis endemic in Italy. In the last decade, different SFG rickettsiosis pathogens, have been associated with human diseases such as *R. monacensis*, *R. massiliae* and *R. aeschlimannii* which cause a SFG rickettsiosis disease (Madeddu et al., 2012, 2016; Torina et al., 2010; Tosoni et al., 2016; Vitale et al., 2006). These have been identified in various arthropod hosts such as *Rhipicephalus sanguineus* sensu lato, *Hyalomma* spp., *Amblyomma* spp., *Ixodes* and *Dermacentor* (Parola et al., 2013) which can parasitize a great variety of vertebrates in different habitats, including the dog in a domestic environment (Parola, 2004).

A human case of SFG rickettsiosis is not always recognizable from its clinical picture and some infections may remain undiagnosed (e.g. cases with atypical clinical manifestations) (Colomba et al., 2006; ECDC, 2013; Rovey et al., 2008). A seroprevalence study carried out in Spain showed that 4–8% of the general population had antibodies to SFG rickettsiosis despite the absence of a previous clinical history of MSF (Bernabeu-Wittel et al., 2006; Cardeñosa et al., 2006). A study carried out in 2006 among forest rangers in the North East of Italy found a seroprevalence of 4% (Cinco et al., 2006), while another study carried

* Corresponding author at: Calle Monforte de Lemos 5., 28029, Madrid, Spain.

E-mail address: dgomez@externos.isciii.es (D. Gomez-Barroso).

¹ Dr Gomez-Barroso and Dr. Vescio equally contributed to this work.

out in Sicily found a seroprevalence of rickettsiosis in humans of 37% (Livio et al., 2007).

In Italy, SFG rickettsiosis is a mandatory notifiable disease since 1990, nevertheless, due to under-notification and under-ascertainment of cases, true incidence of the disease remains unknown. Alternative sources of data are the hospital discharge records, available for a long period of time in the whole country. We used both data from the surveillance system and the hospital discharge records to carry out a retrospective study with the following objectives: to compare data of both systems, to estimate SFG rickettsiosis impact on hospitalizations, to provide the characteristics of people hospitalized, to describe the geographical distribution of the hospitalizations and the calendar and seasonal trends in the Italian resident population from January 1st, 2001 to December 31st, 2015.

2. Material and methods

2.1. Data sources

The following sources of routinely collected data were analysed for the years 2001–2015: statutory notification data from the National Database Infectious Disease (NDID) and hospitalization data from the National Hospital Discharge Database (NHDD) both held by the Italian Ministry of Health.

2.1.1. Statutory notification data

National SFG rickettsiosis surveillance relies on the reporting by physicians of all suspected cases of non-typhus rickettsiae group of fevers, to Local Health Authorities (LHAs). LHAs notify the regional health authorities who verify surveillance reports (checking if the clinical diagnosis is supported by laboratory tests and the results obtained) and transmit individual data to the Ministry of Health.

Collected data include information on name, age, gender, nationality, province of residence (no information on place of exposure is available).

2.1.2. National hospital discharge data

The NHDD contains demographic and health data regarding discharged patients, which all public and privately-owned hospitals are legally required to report. Personal data are encrypted in a way that for a person with more than one discharge this will be always identified with the same anonymous identifier. For each patient, the main discharge diagnosis and up to five additional secondary diagnoses may be listed. Diagnoses are coded by using the nomenclature of the International Classification of Diseases (ICD)-Clinical Modification (CM), 9th edition.

Codes 082.0 (spotted fevers), 082.1 (Boutonneuse fever) and 082.9 (tick-borne rickettsiosis, unspecified) as either primary or any of the five secondary diagnoses were used for the purposes of this analysis.

Information on age, gender and date of hospital admission, place of residence and birth (municipality, province and region) of the cases as well as information about the hospitals, which provided the service (province and region), were retrieved from the dataset.

For subjects with more than one discharge associated to SFG rickettsiosis during the study period, only the first discharge in time order was considered.

3. Statistical analysis

3.1. Descriptive analysis

Resident population figures stratified by age-group, sex and municipality for the years 2001–2015 were provided by the Italian National Institute of Statistics (ISTAT, 2014). Crude, age and gender-specific hospitalization rates, and age and sex standardized hospitalization rates (SHR) with 95% confidence intervals (CI) were calculated using the

2013 European population as a standard (Eurostat, 2013). Annual and monthly trends of SFG rickettsiosis were calculated. Monthly statutory notifications rate for rickettsiosis were calculated.

3.2. Spatial analysis

Municipalities (NUTS 4) were the spatial unit of the analysis. A map with the municipality boundaries for the year 2014 was downloaded from the ISTAT website (ISTAT, 2014). For the spatial analysis, only data from the NHDD were used, as data from the national statutory notification system were available only by province. Because information about the true site of infection was not available, the regions of residence were compared to those of hospitalization. For all patients, it was assumed that the infection took place at the municipality of residence. For the foreigners it was used the municipality in which they were hospitalized (N = 32; 0.26%).

If the municipality of residence was missing, it was used the municipality of birth (N = 1002; 8.33%). If both places of birth and of residence were missing it was used the hospital province (N = 89; 0.74%). Missing municipalities were randomly imputed based on distribution of the cases in the municipalities within the province (N = 102; 0.85%).

Map reference system was ED-1950-UTM, zone 32 N. Standardized hospitalization (SH) ratios and 95% CI were calculated at municipality level and displayed in a map. The expected number of cases of hospitalization was estimated for each geographical unit (i.e. municipality in our study). Indirect standardization method using the 2013 European population as a reference (Eurostat, 2013) was used. The 76.38% of SH ratios had a value between 0 and 1. Choropleth cut points in the maps were chosen *ad hoc* to appreciate differences among municipalities with SH ratios above 1.

Smoothing was carried out to generate smoothed SH ratios using a localised Poisson log linear random effect model with a piecewise constant intercept component (Lee and Sarran, 2015). The spatially smooth variation was done using Condicional Autoregressive model (CAR) (Leroux et al., 1999). The neighbourhood matrix was calculated using the 5 nearest municipalities. Bayesian estimation of the model was computed using the simulation algorithm Markov chain Monte Carlo (MCMC). This model allows large jumps in the mean surface between adjacent areal units and capture localised autocorrelation (i.e. autocorrelation between some pairs of adjacent areal units while other adjacent pairs exhibit different values) which traditional CAR models are insufficiently flexible to capture. The model was implemented in the R software environment (R Development Core Team, 2013), via the freely available CARBayes package (Lee, 2017). The same analysis was carried out, separately for the periods 2001–2007 and 2008–2015, to evaluate if there were a change in the spatial distribution. Further models were carried out varying the definition of proximity in the adjacency matrix, yielding quite similar results.

4. Results

4.1. Study area

According to the ISTAT, Italy had a population of 60,782,668 in 2014, distributed in 20 regions and 8057 municipalities (see Fig. 1). The population largely varies from municipalities with 36 inhabitants to municipalities with 2,863,322 inhabitants.

4.2. Statutory notification data

A total of 5989 cases of non-typhus rickettsiosis were notified in the study period, giving an average annual incidence of 0.88 (95%CI:0.80; 0.96) per 100,000 population. The annual incidence declined from 1.30 (95%CI: 1.21; 1.39) per 100,000 in 2001 to 0.34 (95%CI: 0.29; 0.39) per 100,000 in 2015 (Fig. 2). Reported cases showed a strong



Fig. 1. Spatial distribution of administrative (i.e., regions, provinces and municipalities) areas in Italy.

seasonality with cases peaking during the summer period. Cases were strongly concentrated in the provinces of the two main islands (Sicily and Sardinia), of the southern part of Calabria region and in the southern coastal provinces of Lazio region (data not shown in figure).

4.3. Hospital discharge data

4.3.1. Distribution pattern of regions of hospitalization and of regions of residence

Region of residence and hospitalization coincided for the majority of cases (96.3%). 3.7% of cases from northern regions have been hospitalized in the South of Italy (see Fig. 3, Table 1).

4.3.2. Socio-demographic characteristics and temporal trends

Between 2001 and 2015, 13,147 discharges of SFG rickettiosis were identified. Of them, 961 records pertaining to day hospitals and 154 referring to repeated accesses were excluded from analyses leaving a total of 12,032 hospitalized cases (Table 2). The median age was 53 years (range 1–87 years).

The crude annual hospitalization rate was 1.36/100,000 persons year (95%CI: 1.33; 1.38) during the study period. Also the age and sex SHR was 1.36/100,000 (95%CI: 1.34; 1.39). Both rates tended to decrease until the age of 24 and then to increase with increasing age (Table 2). The crude hospitalization rate was 1.04 (95%CI: 1.01; 1.07) in females and 1.69 (95%CI: 1.66; 1.73) in males, with a statistically significant higher risk in males compared to female [incidence rate ratio (IRR) = 1.64; 95%CI: 1.56; 1.69]. The 83.36% of cases had an

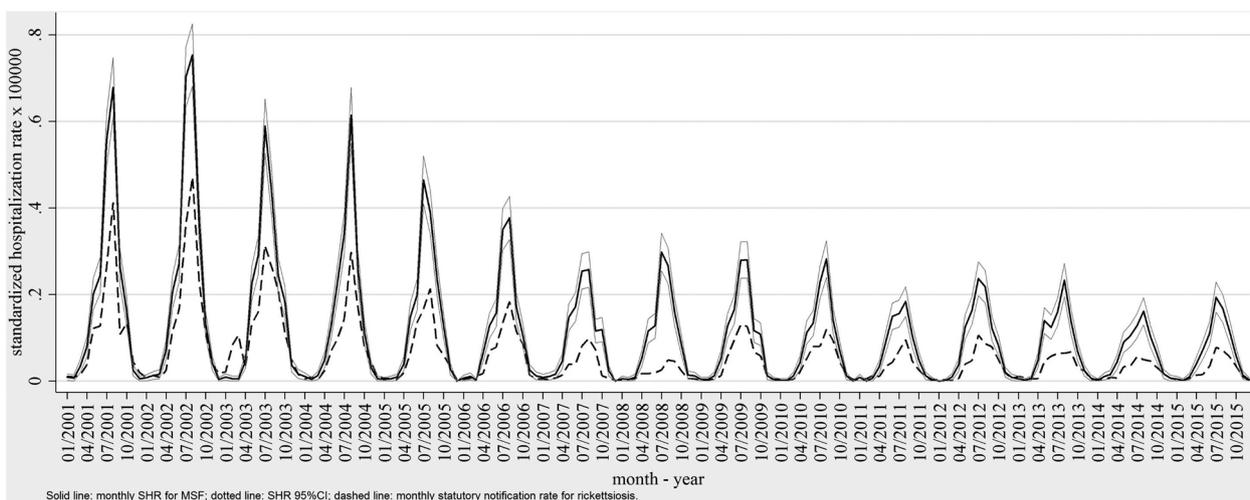


Fig. 2. Age and sex SHR of SFG rickettsiosis by month and year of occurrence in Italy for the period 2001–2015 and respective 95%CI. Statutory notification rate for rickettsiosis by month and year.

urgent admission, 61.55% a length of stay of less than 7 days and 95.09% a home discharge. The 0.35% of cases underwent surgery (mainly diagnostic interventions such as lumbar puncture and paracentesis) and the 0.36% died.

The monthly SHR shows a clear seasonal pattern with most cases being hospitalized from April to September. The hospitalization rates tended to decrease throughout the whole period, although the decrease was of smaller magnitude after 2007 (see Fig. 2).

4.3.3. Spatial analysis

Figs. 4 and 5 show the patterns of SH ratios and smoothed SH ratios. These were similar, with higher values along the Tyrrhenian coast, in particular in the south of Calabria and in the islands of Sardinia and Sicily, although SH ratios range decreased after smoothing from 0 to 1414.67 to 0.01-765.02. In the whole country, 28.89% of municipalities

had smoothed SH ratios greater than 1 and 14.01% above 20. Out of the municipalities with smoothed SH ratios greater than 1, the 78.84% was observed in Latium, 72.86% in Calabria, 95.13% in Sicily and 87.27% in Sardinia. While among those with smoothed SH ratios greater than 20, the 27.46% was observed in Sicily, 25.60% in Sardinia, 17.63% in Calabria and 10.36% in Latium.

A secondary analysis was carried out separately for the periods 2001–2007 and 2008–2015. Both results showed similar patterns of smoothed SH ratios, which similar to those obtained for the whole period.

5. Discussion

We analysed the data of 12,032 hospitalized cases of SFG rickettsiosis occurring in Italy between 2001–2015. The median yearly SHR

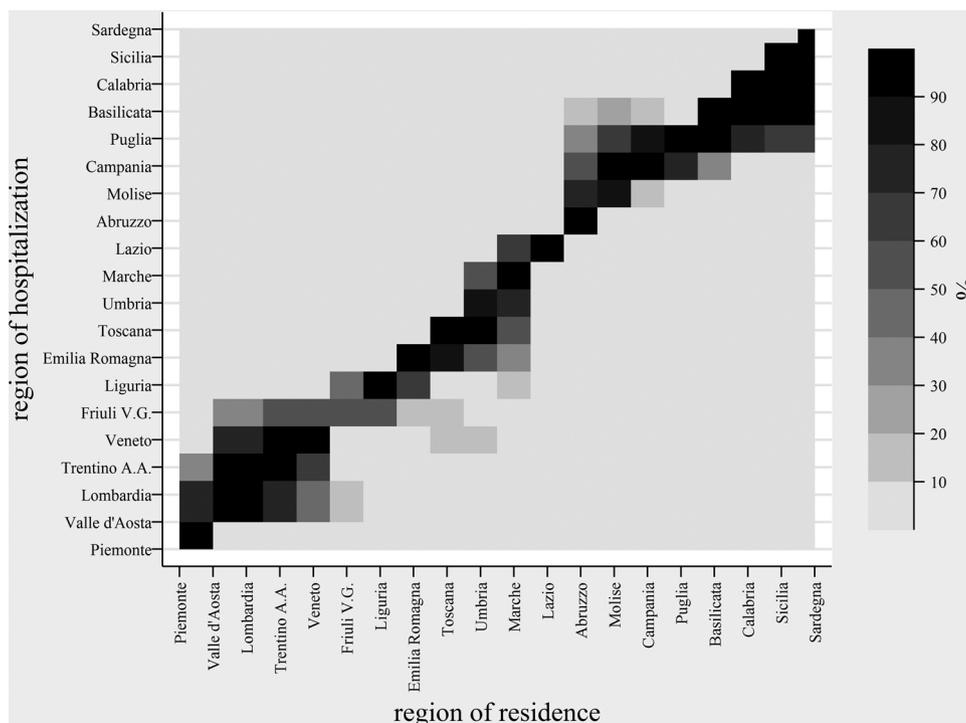


Fig. 3. Heatmap of region of hospitalization and of residence of SFG rickettsiosis cases hospitalized in Italy from 2001 to 2015. Shades of gray represent the percentage of cases by region of residence hospitalized in the same region or in the other regions.

Table 1 Comparison between regions of hospitalization and the regions of residence of SFG rickettsiosis cases hospitalized in Italy from 2001 to 2015.

Region of hospitalization	Region of residence																		
	Piemonte	Lombardia	Trentino A.A.	Veneto	Friuli V.G.	Liguria	Emilia Rom.	Toscana	Umbria	Marche	Lazio	Abruzzo	Molise	Campania	Puglia	Basilicata	Calabria	Sicilia	Sardegna
Piemonte	68	3	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	1	0
Lombardia	0	101	0	0	0	0	0	0	0	0	1	0	0	1	0	0	1	1	0
Trentino A.A.	0	0	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Veneto	1	0	0	41	2	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Friuli V.G.	0	0	0	0	3	0	1	1	0	0	0	0	0	0	0	0	0	0	0
Liguria	6	7	0	1	0	184	0	1	0	0	0	1	0	0	1	0	0	1	1
Emilia Romagna	1	0	0	0	0	85	0	0	0	0	0	0	0	0	0	0	0	1	0
Toscana	0	0	0	0	0	1	119	1	0	2	0	0	0	0	0	0	0	2	1
Umbria	0	0	0	1	0	1	43	1	43	0	4	0	0	0	1	0	0	0	0
Marche	0	0	0	0	0	0	0	0	72	0	0	0	0	0	0	0	0	0	0
Lazio	0	2	0	1	1	0	5	973	5	1	1	2	1	11	0	1	1	2	1
Abruzzo	0	0	0	0	0	0	0	0	0	1	1	114	2	0	0	0	0	0	0
Molise	0	0	0	0	0	0	0	0	0	0	1	0	57	10	1	0	0	0	0
Campania	1	1	0	0	0	0	0	0	0	1	1	0	0	365	0	0	1	0	1
Puglia	0	0	0	0	0	0	1	0	0	0	0	0	0	0	27	0	0	0	0
Basilicata	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	32	0	0	0
Calabria	11	23	0	0	0	2	1	0	0	0	7	1	0	0	1	0	1,066	0	0
Sicilia	14	47	2	8	4	8	10	11	0	0	11	1	0	0	1	0	6	6,263	0
Sardegna	8	12	1	5	0	6	4	8	0	1	8	1	0	1	1	0	0	3	2,081

Table 2 Main characteristics of hospitalized cases of SFG rickettsiosis occurred in Italy, between 2001 and 2015.

	N	(%)
sex		
males	7281	(60.51)
females	4751	(39.49)
age group		
0-4	655	(5.45)
5-14	1135	(9.44)
15-24	681	(5.66)
25-49	3020	(25.11)
50-64	3147	(26.17)
65+	3387	(28.17)
type of admission		
programmed	1971	(16.38)
emergency room	10030	(83.36)
others/unknown	31	(0.26)
surgical intervention		
no	11990	(99.65)
yes	42	(0.35)
length of stay		
≤ 7	7406	(61.55)
> 7	4626	(38.45)
type of discharge		
home	11441	(95.09)
transfer	100	(0.83)
others/unknown	448	(3.72)
exitus	43	(0.36)

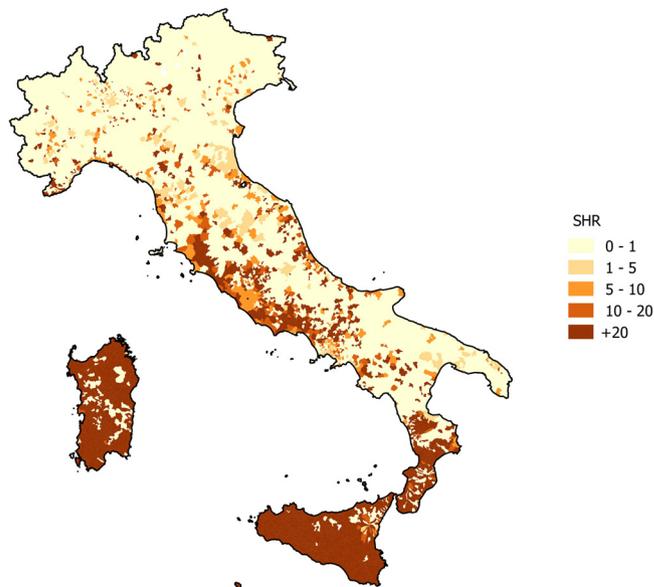


Fig. 4. Standardized Hazard Ratios (n. of hospitalized cases/100,000) for SFG rickettsiosis from 2001 to 2015, Italy.

was 1.36/100,000, which is consistent with a previous study based on data from the Italian Ministry of Health yielding an incidence of 1.6 per 100,000 population between 1998–2002 (Ciceroni et al., 2006). It is of note that hospitalized cases were around three times of the non-typhus rickettsiosis cases reported to the NSS, suggesting an important under reporting rate. Our hospitalized cases were about 2.4 times higher than that found in a study carried out on hospitalizations in Spain (0.56 per 100,000 population) between 1997 and 2014 (Herrador et al., 2017) and about 1.5 (0.89 per 100,000) times higher than those found in Portugal in a study based on official mandatory notification cases

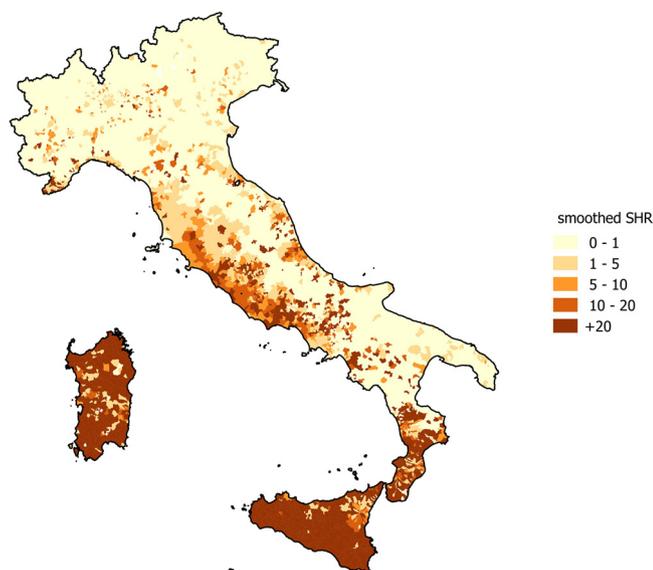


Fig. 5. Smoothed SHR (n. of hospitalized cases/100,000) for SFG rickettsiosis from 2001 to 2015, Italy.

between 1989 and 2003 (Sousa et al., 2003). As observed in Italy and elsewhere, the highest risk was found in men aged 25 and over (Herrador et al., 2017; Vescio et al., 2008). Furthermore, we found a mortality rate of 0.36%, while in Spain SFG rickettsiosis hospitalized cases had a mortality rate of 0.80% (Herrador et al., 2017).

The SHR tended to decrease throughout the whole period, although the decrease was of smaller magnitude after the year 2007. A similar decline was found in almost all Mediterranean countries (ECDC, 2013; Rovey et al., 2008). The actual reasons behind such decline are unknown; however, a general reorganization of the different regional and National Health Systems (Graziani et al., 2016), changes in farm activities involving contact with animals, a greater care of domestic animals, and an increased awareness of the population about vector borne diseases, might have reduced exposure probability, as also modifications in the health management of the cases after some national directives of the public health system, that promoted treatments at community level through general practitioners reducing the chance to have a hospital admission.

The monthly SHRs showed a clear seasonal pattern, with most cases being hospitalized from April to September, similarly to what found in other Mediterranean countries (Herrador et al., 2017; Sousa et al., 2003). The higher amount of cases in spring and summer is likely to depend on environmental factors, such as temperature and humidity (Parola et al., 2013). Previous studies have also found that high temperatures (Estrada-Peña, 2008; Vescio et al., 2012), especially in the spring and summer, the lack of rainfall (for example, in Spain), and the reduced number of days of frost (for example in France), may influence tick activity and abundance. In accordance with this hypothesis it is of note that Sicily, Sardinia and most municipalities in Calabria have a Mediterranean sub-tropical climate with long warm winters and dry summers.

Smoothed SH ratios were higher along the Tyrrhenian coast, in particular in the south of Calabria and in the islands of Sardinia and Sicily. To the best of our knowledge, no other published work shows the geographical distribution of SFG rickettsiosis in Italy, and the three studies displaying geographical patterns (Ciceroni et al., 2006; ECDC, 2013; Graziani et al., 2016), take into account rickettsiosis altogether without making any distinction between diseases. Two of them were based on data derived from compulsory notifications and studied, at the regional level, two different periods of time. The first one, for the period

1998–2001, presented a spatial distribution of the incidences (Ciceroni et al., 2006); the second one, for the period 2001–2009, found the highest amount of cases in Sicily, Sardinia, Calabria and Lazio (ECDC, 2013). The other study used data from the hospital discharge records for the period 2009–2013 at the province level, showing higher incidences in the south Italy and in the islands (Graziani et al., 2016). The main difference with our study was that we observed in some municipalities of the Lazio Region smoothed SH ratios as high as those found in the south of the country.

Cases occurrence may be also influenced by host availability and the prevalence of rickettsiosis (Parola et al., 2013). Studies of rickettsial prevalence carried out in south-eastern Sardinia (Satta et al., 2011) and in Sicily (Torina et al., 2010) found that 0.9%–2% of feeding *R. sanguineus sensu lato* ticks collected from mammalian hosts were positive for *Rickettsia* species. A study carried out on 650 dogs, from all over Italy, in the period 2003–2006, found that 0.4%, 1.4%, and 3.3% of the dogs were positive to *Rickettsia* spp., in north, central, and southern Italy, respectively (Solano-Gallego et al., 2008). To this regard, it has been estimated that about one million stray cats and dogs live in Italy (Slater et al., 2008). These may be at high risk of acquiring vector-borne pathogens, for their general conditions and because, when infected are neither monitored or treated (Otranto and Dantas-Torres, 2010).

According to current vector net maps, *R. sanguineus sensu lato* was found in all areas with high smoothed SH ratios for SFG rickettsiosis, although in some areas where *R. sanguineus sensu lato* was present, such as Apulia, just a few cases were reported (ECDC, 2017). These maps, however, tell us only if the ticks are present or not, without providing any indication about their population density prevalence of rickettsiae in ticks among them. This is similar to what has been reported also for other vector-borne diseases (e.g. Crimean-Congo haemorrhagic fever), for which cases do not occur in all the areas where vectors are present, but only in a small subset of them (Estrada-Peña et al., 2010).

Generally, *R. conorii* is considered the main etiologic agent of the SFG rickettsiosis but in recent years, other *Rickettsia* species involved in human infections, were identified through molecular methods (Parola et al., 2013) also in our country.

The extraordinary increase of information focused by molecular techniques has favoured the identification of new rickettsiae in ticks and humans. Moreover, different SFG rickettsiosis pathogens, formerly limited to specific tick species or to a restricted ecological area, have been identified in various arthropod hosts and /or in unusual geographic regions (Parola et al., 2013).

Emerging pathogens include different species such as *R. monacensis*, *R. massiliae*, *R. aeschlimannii*, *R. Helvetica* and *R. sibirica*. As mentioned above, not only *R. sanguineus sensu lato*, but also several other arthropod vectors can transmit the disease, including *Hyalomma* spp, *Amblyomma* spp, *Ixodes* and *Dermacentor* species (Otranto and Dantas-Torres, 2010). Generally, clinical diagnosis of SFG rickettsiosis is supported and confirmed by serological methods, and antibodies are detectable from 7 to 14 days of illness. The wide range of the antigenic cross-reactivity among rickettsial SFG indicates the exposition to different species, but does not allow the identification of the etiological agent (Portillo et al., 2017). Unfortunately, in this study no microbiological data was available to better discriminate the etiologic agent of SFG rickettsiosis.

In Italy, several human cases were described with SFG rickettsiosis disease due to *R. monacensis*, *R. massiliae*, *R. aeschlimannii* (Madeddu et al., 2016, 2012; Tosoni et al., 2016; Vitale et al., 2006), and different agents were recognized in ticks (Blanda et al., 2017; Chisu et al., 2017; Mancini et al., 2015). This scenario suggests that also other rickettsia species, not only *R. conorii* are present in our country and are relevant for the SFG rickettsiosis evolution and epidemiology.

We can highlight some limitations. Having no data on the site of the infection we assumed that this took place at the municipalities of residence, but this may not be true for all subjects. We observed that some cases living in the regions of northern Italy have been hospitalized in

southern Italian regions, where they probably acquired the infection. Having had more precise information on the site of infection, the North-South gradient in the geographical distribution of the disease would be even more enhanced.

Some records were not complete. When missing, information about the municipality of residence, was imputed on the basis of the distribution of cases in other municipalities of the province of residence, however this problem was only found in a small percentage of cases.

The case definition used in this work is based on hospital discharge codes provided by the various hospitals where SFG rickettsiosis cases were hospitalized. Such diagnosis of discharge can be influenced by various factors and vary between hospitals. To address this problem, we have considered all disease-related codes at any position in diagnostic records (primary and secondary diagnosis). In addition, it is possible that some less serious cases, did not go to the hospital, leading to selection bias, although SFG rickettsiosis hospitalized cases were higher than those notified for the whole rickettsiosis in the same years. This could result in an underestimation of the SH ratios, yet the decision to go to the hospital or not depends mainly on the severity of symptoms, and we have no reason to believe that differed across Italian hospitals. However, the database of hospital discharge records, has some limits due to the lack of homogeneity, completeness and accuracy of the data, and the variation of the classification system over time (Graziani et al., 2016).

SH ratios were subject to high variability due to the small number of cases occurring in areas with small population-at-risk. To show more clearly the geographical pattern of SFG rickettsiosis cases in Italy we used a smoothing techniques (Elliott et al., 2001). A localised approach was used because a lot of municipalities had little/ no risk (Lee and Sarran, 2015).

Since also rickettsia species other than *R. conorii* are present in our country (Madeddu et al., 2016, 2012; Tosoni et al., 2016; Vitale et al., 2006) we cannot rule out that patients who have been included in series of MSF cases may have had other types of rickettsiosis. Therefore we preferred the term SFG rickettsiosis disease to MSF.

Some issues regarding the vector and reservoir of this disease remain undefined: for example, the effects of climate change and host populations, in particular stray dogs and other mammals, that share urban or periurban environment with people, could have effects on vector distribution and spread of the disease. Therefore, further studies are needed to investigate the association between meteorological and environmental variables with SFG rickettsiosis cases and the effect of climate change in Mediterranean countries.

6. Conclusions

In Italy, hospitalization rates tended to decrease over the study period as experienced in other EU countries, though the disease is still present and additional efforts are required to further reduce the risk.

Overall, at the national level, the SHR was higher than in other Mediterranean countries. However, there was a great variability in the spread of SFG rickettsiosis across the territory. There were areas with zero cases in the north and the Adriatic coast of the country, while almost all cases had been reported in the Tyrrhenian coast and the Islands, where incidences are high and SFG rickettsiosis remains a public health problem.

Declarations of interest

None.

Funding

This study has been partially funded by Istituto de Salud Carlos III through the project “PI15/01398” (Co-funded by European Regional Development Fund/European Social Fund “Investing in your future”).

Acknowledgements

We would like to thank CIBERESP for the mobility grant awarded to Diana Gómez-Barroso that has given her the opportunity to carry out her research for 2 months at Istituto Superiore di Sanità, Roma, Italy.

References

- Bernabeu-Wittel, M., Segura-Porta, F., 2005. Enfermedades producidas por *Rickettsia*. *Enferm. Infecc. Microbiol. Clin.* 23, 163–172.
- Bernabeu-Wittel, M., del Toro, M.D., Noguera, M.M., Muniain, M.A., Cardena, N., Márquez, F.J., Segura, F., Pachón, J., 2006. Seroepidemiological study of *Rickettsia felis*, *Rickettsia typhi*, and *Rickettsia conorii* infection among the population of southern Spain. *Eur. J. Clin. Microbiol. Infect. Dis.* 25, 375–381. <https://doi.org/10.1007/s10096-006-0147-6>.
- Blanda, V., Torina, A., La Russa, F., D'Agostino, R., Randazzo, K., Scimeca, S., Giudice, E., Caracappa, S., Cascio, A., de la Fuente, J., 2017. A retrospective study of the characterization of *Rickettsia* species in ticks collected from humans. *Ticks Tick Dis.* 8, 610–614. <https://doi.org/10.1016/j.tiddis.2017.04.005>.
- Brouqui, P., Parola, P., Fournier, P.E., Raoult, D., 2007. Spotted fever rickettsioses in southern and Eastern Europe. *FEMS Immunol. Med. Microbiol.* 49, 2–12. <https://doi.org/10.1111/j.1574-695X.2006.00138.x>.
- Cardena, N., Noguera, M.M., Font, B., Segura, F., Muñoz, T., Sanfeliu, I., 2006. Serological evidence of human infection with rickettsial strain Bar29 in Catalonia, northeastern Spain. *Eur. J. Clin. Microbiol. Infect. Dis.* 25, 541–543. <https://doi.org/10.1007/s10096-006-0176-1>.
- Chisu, V., Leulmi, H., Masala, G., Piredda, M., Foxi, C., Parola, P., 2017. Detection of *Rickettsia hoogstraalii*, *Rickettsia helvetica*, *Rickettsia massiliae*, *Rickettsia slovacica* and *Rickettsia aeschlimannii* in ticks from Sardinia, Italy. *Ticks Tick Borne Dis.* 8, 347–352. <https://doi.org/10.1016/j.tiddis.2016.12.007>.
- Ciceroni, L., Pinto, A., Ciarrocchi, S., Ciervo, A., 2006. Current knowledge of rickettsial diseases in Italy. *Ann. N. Y. Acad. Sci.* 1078, 143–149. <https://doi.org/10.1196/annals.1374.024>.
- Cinco, M., Luzzati, R., Mascioli, M., Floris, R., Brouqui, P., 2006. Serological evidence of *Rickettsia* infections in forestry rangers in north-eastern Italy. *Clin. Microbiol. Infect.* 12, 493–495. <https://doi.org/10.1111/j.1469-0691.2006.01385.x>.
- Colomba, C., Saporito, L., Polara, V.F., Rubino, R., Titone, L., 2006. Mediterranean spotted fever: clinical and laboratory characteristics of 415 Sicilian children. *BMC Infect. Dis.* 6, 60. <https://doi.org/10.1186/1471-2334-6-60>.
- ECDC, 2013. Epidemiological Situation of Rickettsioses in EU/EFTA Countries. *Epidemiological Situation of Rickettsioses in EU/EFTA Countries*.
- ECDC, 2017. *Ixodes Ricinus* - Current Known Distribution. October 2017. .
- Elliott, P., Wakefield, J.C., Best, N.G., Briggs, D.J., 2001. *Spatial Epidemiology: Methods and Applications*. Oxford University Press.
- Estrada-Peña, A., 2008. Climate, niche, ticks, and models: what they are and how we should interpret them. *Parasitol. Res.* 103 (Suppl. 1), S87–S95. <https://doi.org/10.1007/s00436-008-1056-7>.
- Estrada-Peña, A., Vatansever, Z., Gargili, A., Ergönül, O., 2010. The trend towards habitat fragmentation is the key factor driving the spread of Crimean-Congo haemorrhagic fever. *Epidemiol. Infect.* 138, 1194–1203. <https://doi.org/10.1017/S0950268809991026>.
- Eurostat, 2013. Revision of the European Standard Population - Report of Eurostat's Task Force - 2013 Edition. [WWW Document]. URL (Accessed 7.18.18). <http://ec.europa.eu/eurostat/web/products-manuals-and-guidelines/-/KS-RA-13-028>.
- Graziani, C., Duranti, A., Morelli, A., Busani, L., Pezzotti, P., 2016. Zoonosi in Italia Nel Periodo 2009-2013. ISTITUTO SUPERIORE DI SANITÀ.
- Herrador, Z., Fernandez-Martinez, A., Gomez-Barroso, D., León, I., Vieira, C., Muro, A., Benito, A., 2017. Mediterranean spotted fever in Spain, 1997-2014: epidemiological situation based on hospitalization records. *PLoS One* 12. <https://doi.org/10.1371/journal.pone.0174745>.
- ISTAT, 2014. Demo-Geodemo. - Mappa, Popolazione, Statistiche Demografiche Dell'ISTAT [WWW Document]. URL (Accessed 7.18.18). <http://demo.istat.it/>.
- Lee, D., 2017. CARBayes: Spatial Generalised Linear Mixed Models for Areal Unit Data. CARBayes: Spatial Generalised Linear Mixed Models for Areal Unit Data.
- Lee, D., Sarran, C., 2015. Controlling for unmeasured confounding and spatial misalignment in long-term air pollution and health studies. *Environmetrics* 26, 477–487. <https://doi.org/10.1002/env.2348>.
- Leroux, B., Lei, X., Brelow, N., 1999. Estimation of disease rates in small areas: a new mixed model for spatial dependence. *Models in Epidemiology, the Environment and Clinical Trials*. M. Halloran, & D. Berry, New York, pp. 135–178.
- Livio, M., Mobilia, A., Abbate, S., Saffioti, G., Nicolosi, L., Isaia, S., Calabrese, C., Graceffa, C., 2007. [Ticks bite in foresters]. *G. Ital. Med. Lav. Ergon.* 29, 811–812.
- Madeddu, G., Mancini, F., Caddeo, A., Ciervo, A., Babudieri, S., Maida, I., Fiori, M.L., Rezza, G., Mura, M.S., 2012. *Rickettsia monacensis* as cause of Mediterranean spotted fever-like illness, Italy. *Emerg. Infect. Dis.* 18, 702–704. <https://doi.org/10.3201/eid1804.111583>.
- Madeddu, G., Fiore, V., Mancini, F., Caddeo, A., Ciervo, A., Babudieri, S., Masala, G., Bagella, P., Nunnari, G., Rezza, G., Mura, M.S., 2016. Mediterranean spotted fever-like illness in Sardinia, Italy: a clinical and microbiological study. *Infection* 44, 733–738. <https://doi.org/10.1007/s15010-016-0921-z>.
- Mancini, F., Ciccozzi, M., Lo Presti, A., Cella, E., Giovanetti, M., Di Luca, M., Toma, L., Bianchi, R., Khoury, C., Rezza, G., Ciervo, A., 2015. Characterization of spotted fever group *Rickettsiae* in ticks from a city park of Rome, Italy. *Ann. Inst. Super. Sanita* 51,

- 284–290. https://doi.org/10.4415/ANN_15_04_07.
- Otranto, D., Dantas-Torres, F., 2010. Canine and feline vector-borne diseases in Italy: current situation and perspectives. *Parasite Vectors* 3 (2). <https://doi.org/10.1186/1756-3305-3-2>.
- Parola, P., 2004. Tick-borne rickettsial diseases: emerging risks in Europe. *Comp. Immunol. Microbiol. Infect. Dis.* 27, 297–304. <https://doi.org/10.1016/j.cimid.2004.03.006>.
- Parola, P., Paddock, C.D., Socolovschi, C., Labruna, M.B., Mediannikov, O., Kernif, T., Abdad, M.Y., Stenos, J., Bitam, I., Fournier, P.-E., Raoult, D., 2013. Update on tick-borne rickettsioses around the world: a geographic approach. *Clin. Microbiol. Rev.* 26, 657–702. <https://doi.org/10.1128/CMR.00032-13>.
- Portillo, A., de Sousa, R., Santibáñez, S., Duarte, A., Edouard, S., Fonseca, I.P., Marques, C., Novakova, M., Palomar, A.M., Santos, M., Silaghi, C., Tomassone, L., Zúquete, S., Oteo, J.A., 2017. Guidelines for the detection of *Rickettsia* spp. *Vector Borne Zoonotic Dis.* 17, 23–32. <https://doi.org/10.1089/vbz.2016.1966>.
- R Development Core Team, 2013. R: The R Project for Statistical Computing [WWW Document]. URL (Accessed 7.18.18). <https://www.r-project.org/>.
- Raoult, D., Roux, V., 1997. Rickettsioses as paradigms of new or emerging infectious diseases. *Clin. Microbiol. Rev.* 10, 694–719.
- Rovero, C., Brouqui, P., Raoult, D., 2008. Questions on Mediterranean spotted fever a century after its discovery. *Emerg. Infect. Dis.* 14, 1360–1367. <https://doi.org/10.3201/eid1409.071133>.
- Satta, G., Chisu, V., Cabras, P., Fois, F., Masala, G., 2011. Pathogens and symbionts in ticks: a survey on tick species distribution and presence of tick-transmitted microorganisms in Sardinia, Italy. *J. Med. Microbiol.* 60, 63–68. <https://doi.org/10.1099/jmm.0.021543-0>.
- Slater, M.R., Di Nardo, A., Pediconi, O., Villa, P.D., Candeloro, L., Alessandrini, B., Del Papa, S., 2008. Free-roaming dogs and cats in central Italy: public perceptions of the problem. *Prev. Vet. Med.* 84, 27–47. <https://doi.org/10.1016/j.prevetmed.2007.10.002>.
- Solano-Gallego, L., Trotta, M., Caldin, M., Furlanello, T., 2008. Molecular survey of *Rickettsia* spp. in sick dogs in Italy. *Zoonoses Public Health* 55, 521–525. <https://doi.org/10.1111/j.1863-2378.2008.01149.x>.
- Sousa, R., de, Nóbrega, S.D., Bacellar, F., Torgal, J., 2003. [Epi demologic features of Mediterranean spotted fever in Portugal]. *Acta Med. Port.* 16, 429–436.
- Torina, A., Alongi, A., Scimeca, S., Vicente, J., Caracappa, S., de la Fuente, J., 2010. Prevalence of tick-borne pathogens in ticks in Sicily. *Transbound. Emerg. Dis.* 57, 46–48. <https://doi.org/10.1111/j.1865-1682.2010.01101.x>.
- Tosoni, A., Mirijello, A., Ciervo, A., Mancini, F., Rezza, G., Damiano, F., Cauda, R., Gasbarrini, A., Addolorato, G., Internal Medicine Sepsis Study Group, 2016. Human *Rickettsia aeschlimannii* infection: first case with acute hepatitis and review of the literature. *Eur. Rev. Med. Pharmacol. Sci.* 20, 2630–2633.
- Vescio, M.F., Piras, M.A., Ciccozzi, M., Carai, A., Farchi, F., Maroli, M., Mura, M.S., Rezza, G., Study Group, M.S.F., 2008. Socio-demographic and climatic factors as correlates of Mediterranean spotted fever (MSF) in northern Sardinia. *Am. J. Trop. Med. Hyg.* 78, 318–320.
- Vescio, F.M., Busani, L., Mughini-Gras, L., Khoury, C., Avellis, L., Taseva, E., Rezza, G., Christova, I., 2012. Environmental correlates of Crimean-Congo haemorrhagic fever incidence in Bulgaria. *BMC Public Health* 12, 1116. <https://doi.org/10.1186/1471-2458-12-1116>.
- Vitale, G., Mansuelo, S., Rolain, J.-M., Raoult, D., 2006. *Rickettsia massiliae* human isolation. *Emerg. Infect. Dis.* 12, 174–175. <https://doi.org/10.3201/eid1201.050850>.