

# Epidemiology of Q fever in humans in four selected regions, Spain, 2016 to 2022

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**Background:** Q fever is a bacterial zoonosis caused by *Coxiella burnetii*. Spain has the highest number of notified human cases in Europe. Small ruminants are a key reservoir for the pathogen, transmission from animals to humans is usually airborne. **Aim:** We aimed at exploring temporal and spatial epidemiological patterns of sporadic and outbreak cases of Q fever in four Spanish regions with the highest number of notified cases. **Methods:** We extracted data on Q fever cases in the Canary Islands, Basque Country, La Rioja and Navarre between 2016 and 2022 from the Spanish National Epidemiological Surveillance Network. We calculated standardised incidence ratios (SIR), spatial relative risks (sRR) and posterior probabilities (PP) utilising Besag-York-Mollié models. **Results:** There were 1,059 notifications, with a predominance of males aged 30–60 years. In Basque Country, La Rioja and Navarre area, 11 outbreaks were reported, while no in the Canary Islands. A seasonal increase in incidence rates was observed between March and June. In the Canary Islands, elevated sRR was seen in La Palma, Gran Canaria, Lanzarote and Fuerteventura. In Basque Country, La Rioja and Navarre area, the highest sRR was identified in the south of Biscay province. **Conclusion:** Goats were the main source for humans in outbreaks reported in the literature. Seasonal increase may be related to the parturition season of small ruminants and specific environmental conditions. Local variations in sRR within these regions likely result from diverse environmental factors. **Future One Health-oriented studies are essential to deepen our understanding of Q fever epidemiology.**

## Introduction

Q fever is a bacterial zoonosis caused by *Coxiella burnetii* affecting humans and many animal species worldwide. The disease is considered underreported [1]. In livestock, the infection is often unnoticed, except

during abortion waves [2]. In humans, the acute form of Q fever commonly manifests either as atypical pneumonia or febrile acute hepatitis [1]. Approximately 1-5% of the patients may develop a chronic form of the illness, endocarditis or vascular infection, with a mortality rate of approximately 15% [3]. Diagnosis of Q fever is mainly based on serological testing or PCR [1].

*Coxiella burnetii* is an obligate intracellular pathogen with two antigenic forms, phase I and phase II, relevant for diagnosis of the acute and chronic forms. The bacterium has two morphological forms: the large cell variant (LCV) and the small cell variant (SCV) [1]. The LCV is a metabolically active form replicating within host cells, while the SCV is a dormant form found in the environment, also named spore-like due to its capacity of resisting harsh conditions and persisting in soils or food [1,4].

The bacterium has been isolated from over 100 animal species [5], including at least seven tick species [6]. The main reservoirs are sheep, goats and cattle. Infected females (domestic and wild animals) excrete large amounts of bacteria during parturition or abortion via faeces, vaginal mucus, aborted fetuses, placenta, urine and milk [7]. The main route is through inhalation of contaminated particles. This can occur both close to and far from the source, as the bacterium can move up to 30 km with the wind [8]. Foodborne transmission is considered less common [4]. Human-to-human transmission has been observed in certain instances but is considered rare. Other modes of transmission, such as vertical or tick-borne have not been documented in humans so far [1].

A large Q fever outbreak occurred in the Netherlands between 2007 and 2010, with 4,000 notified cases and more than 40,000 estimated cases,

## KEY PUBLIC HEALTH MESSAGE

### What did you want to address in this study and why?

Q fever is a bacterial disease caused by *Coxiella burnetii* affecting humans and animals. Since 2016, Spain has notified the highest number of Q fever cases in Europe. However, our understanding of how the disease occurs and spreads is still limited. To learn more, we conducted a study in the four regions of Spain where Q fever cases are most common: the Canary Islands, Basque Country, La Rioja and Navarre.

### What have we learnt from this study?

Q fever was more frequent among males aged 30–60 years. Cases tended to increase each year between March and June, which aligns with the time when sheep and goats give birth and environmental conditions may be more favourable. Goats seem to be the main source of the disease in these areas.

### What are the implications of your findings for public health?

Our study suggests that local climate conditions and livestock activities may affect transmission of the bacterium. Therefore, our findings further support the necessity of adopting a One Health-approach for effective preventive and control measures, including surveillance.

demonstrating that Q fever can pose a substantial public health threat [9]. In Europe, Spain has had the highest number of annually notified human cases since 2016 (0.7 cases per 100,000 population) [10]. Case series have been described in most of the Spanish territory [11]. Since 2015, Q fever has been a notifiable disease in humans in Spain. Notifications are sent to the Spanish National Network of Epidemiological Surveillance (RENAVE). According to the latest reports, the autonomous communities with the highest notification rates between 2016 and 2018 were the Canary Islands, Basque Country, La Rioja and Navarre [12].

Our main objective was to explore the epidemiology of Q fever and to determine possible risk factors in four regions of Spain where the disease is endemic. We also evaluated the spatial distribution in these regions at a municipal level.

## Methods

We extracted data from the RENAVE database on notified Q fever cases in humans in the Canary Islands, Basque Country, Navarre and La Rioja, between 1 January 2016 and 31 December 2022. The data were extracted on 28 April 2023 by the Spanish System for Epidemiological Surveillance (SIVIES), a software that provides access to the nationwide surveillance databases of the RENAVE. A large outbreak with 108 notified cases in Basque Country occurring between 2020 and 2021 [13] was not included in our study due to incomplete data at the time of extraction. Data from the entire country are presented in Supplementary Table S1, S2 and S3.

## Geographical scope

The Canary Islands, situated in the Atlantic Ocean and part of Macaronesia, are located 100 km west of the

coast of Morocco. The regions of Basque Country, La Rioja and Navarre are situated in the north of the Iberian Peninsula, near the Pyrenees Mountains and the Bay of Biscay (Figure 1). These three regions were treated as a single area, called the north area in this paper.

## Case definition and study variables

The case definition was based on the European Union decision [14], covering clinical, epidemiological and laboratory criteria (Box). Probable cases fulfilled the clinical criteria with an epidemiological link. Confirmed cases had both the clinical and the laboratory criteria. Outbreaks were defined as two or more Q fever cases with an epidemiological association.

## Epidemiological description

We studied sociodemographic data (age and sex) in each area. We calculated frequencies, percentages and incidence rates (IR) stratified by sex and age groups of 5 years measured as cases per 100,000 person-years. To calculate the IR, we used resident population estimates per region from the Spanish National Institute for Statistics (INE) as of 1 January each year of the study. We included probable and confirmed cases in the analyses.

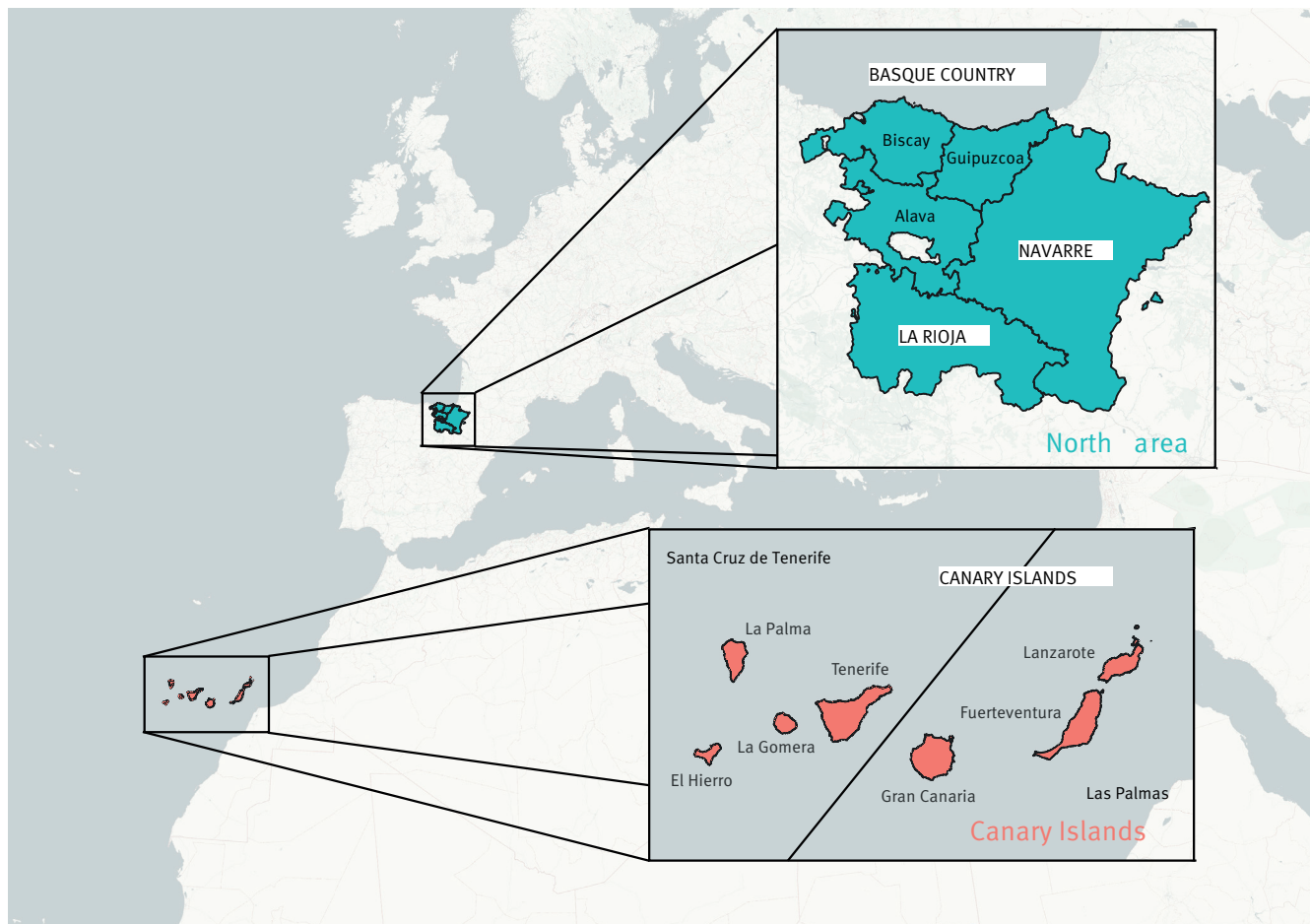
For outbreaks, we collected data on region, date and exposures. The location of the case was determined by the municipality where the infection was contracted and if unknown, the municipality of the residency.

## Temporal evolution

We studied changes in the monthly IR by sex and plotted the monthly IR to provide an exploratory evaluation of possible temporal trends or seasonality. The date of symptom onset was considered as the case date. If

**FIGURE 1**

Map presenting regions included in a study of epidemiology of Q fever in humans, Spain, 2016–2022



unavailable, the closest registered date (case notification date or hospitalisation date) was used.

### Spatial analysis

We used indirect standardisation methods to calculate the age-standardised incidence ratios (SIR) per municipality. The population of the Canary Islands and the north area was split into age groups of 5 years in the years between 2016 and 2022.

Using a Bayesian Poisson regression model proposed by Besag-York-Mollié [15], we smoothed the SIR values to obtain spatial relative risks (sRR) for each municipality, as a measure of a relative risk adjusted by a spatial component accounting for the cases observed in adjacent municipalities. We calculated posterior probabilities (PP) for each municipality to assess the credibility of the sRR. We considered  $PP > 0.8$  in the municipalities as significant. These three measures were visualised through choropleth maps.

We used the statistical software R version 4.3.0 (<https://www.r-project.org/>) and Microsoft Excel 16.0 to calculate basic epidemiological measures and R-INLA package for estimations of sRR and PP. To create

the maps, we used open-source QGIS in the version 3.24.3 (<https://www.qgis.org/en/site/>).

### Results

#### Epidemiological description and outbreaks

Between 2016 and 2022, 15,017,716 person-years were observed in the Canary Islands and 590 cases were notified. The IR was estimated to 3.93 per 100,000 person-years. One fatality was notified in a female (case-fatality ratio (CFR): 0.17%). Of these 590 cases, 508 (86.1%) were confirmed, 434 (73.6%) in males. The IR was 5.84 per 100,000 person-years for males and 2.07 for females.

In the north area with 22,228,977 person-years observed, 469 cases were notified, resulting in an IR of 3.12 per 100,000 person-years. Two fatalities were notified in males (CFR: 0.42%). Of the 469 cases, 285 (60.8%) were confirmed and 329 (70.1%) were males. The IR was 3.03 per 100,000 person-years for males and 1.30 for females (Table).

Data about notified cases, crude IR and age-standardised IR for the entire country by region and study year are presented in Supplementary Table S1, S2 and S3.

## Box

### Criteria for categorisation of Q fever cases

#### Clinical criteria:

A person who has at least one of the following:

- Fever
- Pneumonia
- Hepatitis

#### Laboratory criteria:

At least one of the following:

- Isolation of *Coxiella burnetii* from a clinical specimen
- Detection of *Coxiella burnetii* nucleic acid in a clinical specimen
- *Coxiella burnetii* specific antibody response (IgG or IgM phase II)

#### Epidemiological criteria:

At least one of the following two epidemiological links:

- Exposure to a common source
- Animal to human transmission

In the Canary Islands, no Q fever outbreaks were reported. In the north area, 104 cases (22.2%) were linked to at least 11 outbreaks.

Of the outbreaks included in the dataset, the largest one with 15 notified cases occurred in Basque Country July–August 2017, with no exposure factors identified. Another outbreak with 12 notified cases occurred in La Rioja November–December 2019 in a tourist apartment near a goat farm in the municipality of Jalón de Cameros. Two additional outbreaks, each with 11 cases, were notified in 2016, both in Basque Country and associated with exposure to ruminant farms. Figure 2 shows the location of the cases in these outbreaks.

Between 2016 and 2019 in the Canary Islands, 94 cases were notified in 2016, 97 in 2017, 92 in 2018 and 111 in 2019. However, during the coronavirus disease 2019 (COVID-19) pandemic years, the number of notified cases declined: 76 cases were notified in 2020, 51 in 2021 and 70 in 2022.

In contrast, more variation was seen in the north area in the pre-pandemic years, with 93 cases in 2016, 116 cases in 2017, 69 cases in 2018 and 92 cases in 2019. During the pandemic, the decline in notified case numbers was more pronounced in the north area than in the Canary Islands, with only 17 and 15 cases notified in 2020 and 2021. In 2022, 76 cases were recorded.

The monthly IR analysis (Figure 3) revealed a potential seasonal distribution of Q fever in both areas. Most notifications were between March and June. In the north area, the IR peak appeared earlier than in the Canary Islands, also during the COVID-19 pandemic.

### Spatial analysis

Figure 4A depicts the municipal distribution of SIR in the Canary Islands. Among the seven islands, four were notably affected: the eastern islands of Fuerteventura, Lanzarote and Gran Canaria and the western island of La Palma. The sRR shows a similar distribution pattern highlighting differences in risk between the islands (Figure 4B). In many municipalities of these islands, the PP were  $> 0.8$ , indicating a high level of credibility (Figure 4C).

In the north area, the distribution of SIR was heterogeneous, as shown in Figure 4D. Most municipalities with high incidence were concentrated to Basque Country, with a few hotspots in La Rioja and Navarre. We identified a region covering an area of approximately 2,250 km<sup>2</sup> that extends from the northern part of the Alava province to the southern part of the Biscay province displaying a high risk (Figure 4E). Additionally, we identified some other areas with elevated risk, mainly around Logroño, the capital city of La Rioja and the westernmost part of the Pyrenees Mountains in Navarre. Figure 4F illustrates the PP in these identified high-risk areas, which are primarily  $> 0.8$ .

### Discussion

Spain has the highest number of notified Q fever cases in Europe, but the epidemiological knowledge of the disease is still limited [10,12]. The endemicity has been confirmed in seroprevalence studies in the Basque and the Canarian populations [16,17].

The highest Q fever IR was in males aged 30–60 years, as in previously published studies from Spain [11]. This could be related to an occupational exposure, which is well documented in the literature. In a meta-analysis, the seroprevalence of Q fever in slaughterhouse workers was estimated to be higher than 25% [18]. Furthermore, agriculture workers in the United States were more likely to be seropositive than occupants of other domains [19]. Similar associations have been observed in Europe [20]. Nevertheless, it is important to note that further analysis will be necessary to completely assess occupation as a risk factor.

TABLE

Annual incidence rate (per 100,000 population) of Q fever, by age group and sex, in selected regions of Spain 2016–2022<sup>a</sup>

Age group (years)	Canary Islands		North area <sup>b</sup>	
	Male n = 434	Female n = 156	Male n = 329	Female n = 140
< 15	0.39	0.21	0.25	0.59
15–19	2.77	0.54	2.60	0.79
20–24	4.39	0.74	2.71	0.41
25–29	8.42	1.08	3.94	1.34
30–34	7.32	1.56	5.21	2.46
35–39	8.45	2.20	5.38	2.75
40–44	8.30	3.07	<b>5.40</b>	2.24
45–49	8.39	3.30	3.71	1.92
50–54	<b>9.22</b>	3.96	3.71	1.16
55–59	8.29	4.56	2.88	1.93
60–64	5.82	3.37	2.85	1.89
65–69	4.27	2.14	1.66	0.46
70–74	2.47	1.27	1.15	0.83
75–79	1.99	1.63	1.31	0.00
≥ 80	2.12	0.26	2.51	0.50
Total	4.98	1.76	2.46	1.07

<sup>a</sup> Data from an outbreak in Basque Country 2020–2021 are not included.

<sup>b</sup> North area covers Basque Country, La Rioja and Navarre.

Maximum value is presented in bold.

However, particularly due to the capability of *C. burnetii* SCV variant to persist in the environment and be transported over long distances, a proportion of the infected individuals may not have been exposed to known risk factors such as direct contact with livestock. This was seen in the Netherlands in the 2007–2010 outbreak, where some cases lived in the vicinity of goat farms without direct contact with animals [9]. Furthermore, most cases included in a Spanish systematic review were from urban environments [11]. This may represent a limitation in comprehending risk factors for Q fever.

In our study, 11 outbreaks were notified, all in the north area. Although we had limited information on exposures associated with the outbreaks, a prevailing factor was the connection, occupational or not, with ruminant farms. At least three outbreak reports within the same time frame and geographical area have been previously documented.

One of the outbreaks included in our study (July–August 2017) occurred among workers of a courier pet company with 10 confirmed and six probable cases, with an attack rate of 25% [21]. The possible source of the infection was contaminated dust within pet holding facilities, likely after a transport of miniature goats. The probability of the involvement of other animal species was considered low based on the *C. burnetii* genotype determination.

Another outbreak occurring between December 2016 and February 2017 was associated with a dairy goat farm in Biscay following a large abortion wave in does.

The first cases were a group of seven farm workers. Weeks later, an additional four cases were notified in a group of visitors to the farm. The attack rate was 78% among workers and 31% among visitors [22].

The most recently notified outbreak spanned between December 2020 and October 2021 involving 108 notified cases among visitors to a natural cave in the southern Biscay province. *Coxiella burnetii* DNA was detected in faecal, dust and aerosol samples inside the cave and in dust samples from 44 farms located within a buffer of 7 km [13]. Unfortunately, data about this outbreak were not available in the database at the time of extraction.

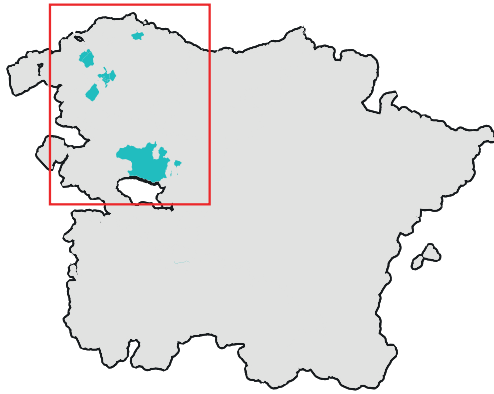
Previously, sheep were considered the main reservoir in the provinces of the north area, based on seroprevalence studies [23]. However, the outbreaks notified in the last 10 years have been linked to goats. This is a relevant observation given that data from the National Livestock Survey indicates that sheep population in these regions is up to seven times greater than the goat population [24]. No outbreaks were reported in the Canary Islands during the study period. The reasons for this, including under reporting and difficulties in detecting a common exposure to extensive farms, need to be elucidated.

The numbers of Q fever notifications showed a consistent trend over the years, except for 2020 and 2021. The decline in notifications during these years could be attributed to the COVID-19 pandemic effects on the surveillance system, which may have also impaired the declaration and registration of outbreaks, regionally

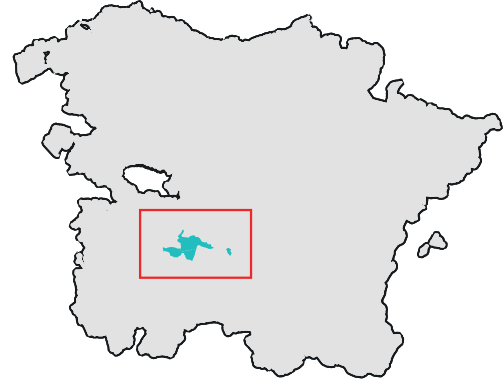
## FIGURE 2

Geographical location, date and number of cases of four largest reported Q fever outbreaks in the north area, Spain, 2016–2017 (n = 49)<sup>a</sup>

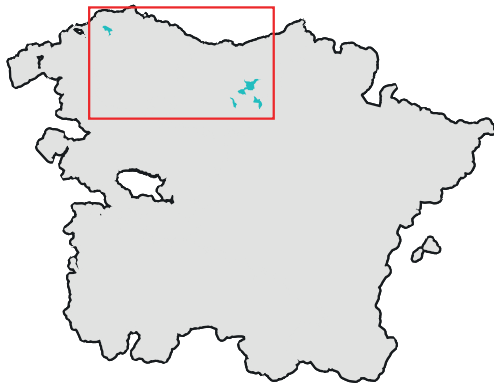
Outbreak 1: Jul–Aug 2017, 15 cases



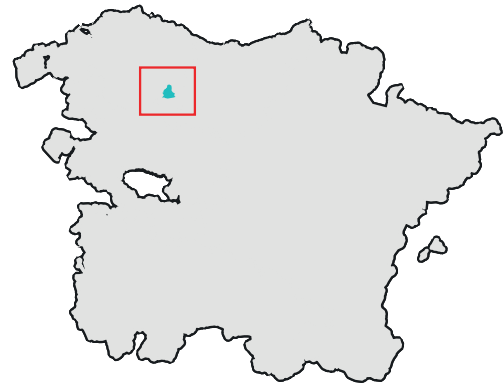
Outbreak 2: Nov–Dec 2019, 12 cases



Outbreak 3: Mar–Apr 2016, 11 cases



Outbreak 4: May–Jun 2016, 11 cases



<sup>a</sup> North area covers Basque Country, La Rioja and Navarre.

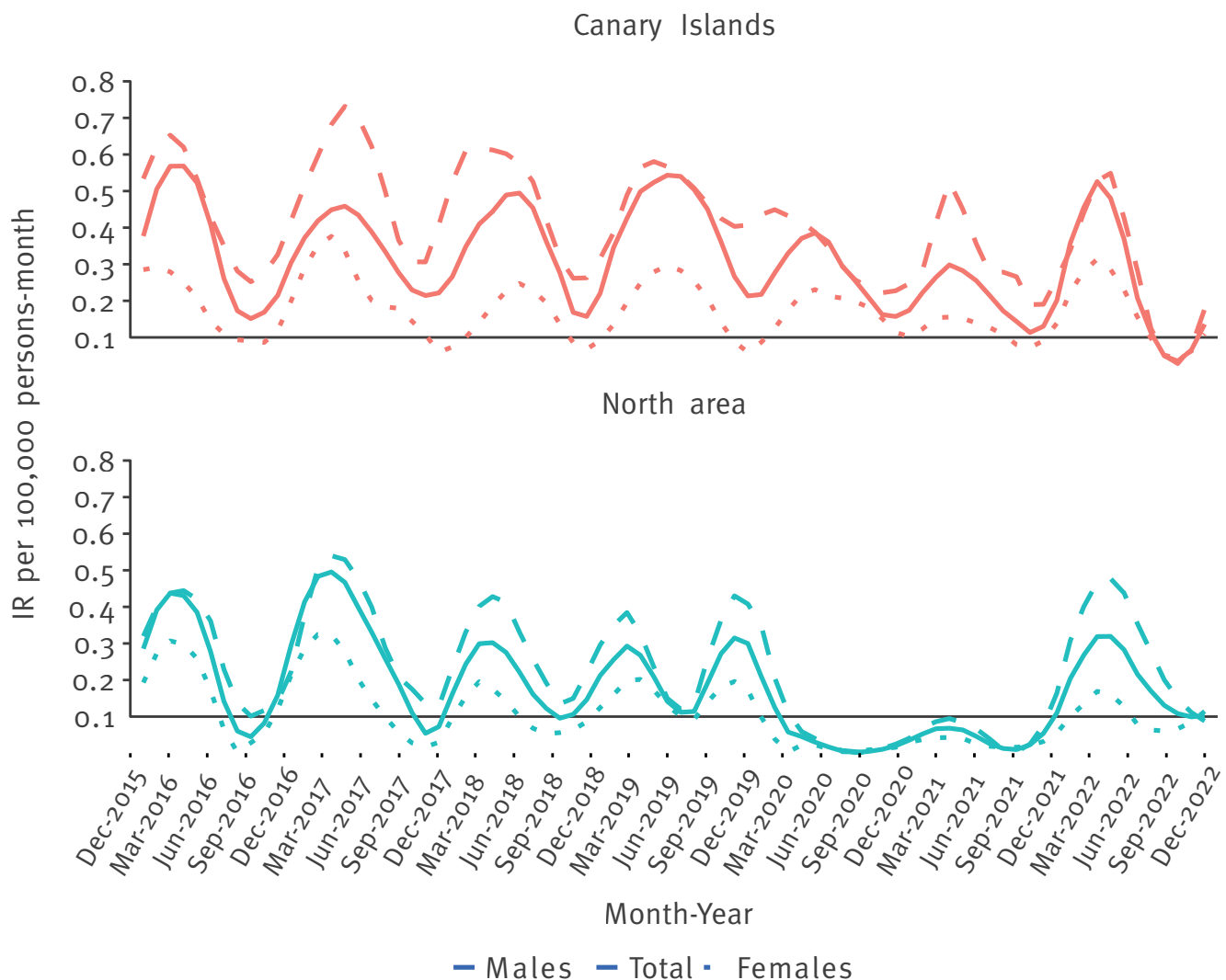
and nationally. However, this decline was not uniform as in the Canary Islands the notifications were sustained compared with the north area. In 2022, notifications were at pre-pandemic levels.

An interesting feature is a possible seasonal pattern, which may require further analysis. Except for the pandemic years, monthly IR consistently peaked between March and June. In some Spanish studies from cases [11], including the north area [25] and the Canary Islands [26], most notifications were in spring. The parturition period of small ruminants coincides with these months, which could facilitate the spread of these bacteria [27]. In addition, the increase of airborne particles, microbial and non-microbial, in the air, mainly due to favourable environmental conditions, could further increase the risk.

In the municipal-level spatial model of the Canary Islands, variations in sRR between different islands was apparent. On three of the westernmost islands El Hierro, La Gomera and Tenerife, lower sRR were estimated in contrast to the easternmost islands

Fuerteventura, Lanzarote and Gran Canaria. These differences may stem from climatological and weather-related factors. Wind or vegetation may have an impact on bacterial dispersion [8]. The Canary Islands are characterised by a diverse landscape, the western islands are subtropical and humid, and the eastern islands are arid and influenced by dust storms from the Sahara Desert. Although the precise influence of these factors on the epidemiology of Q fever on the islands is unclear, divergent winds of the archipelago have different airborne bacterial composition [28].

Similarly, in the north area, we identified differing sRR values across the territory. The highest sRR and PP values are found between the Basque provinces of Biscay and Alava. In this rural, mountainous area, which includes the Gorbeia Natural Park, several of the aforementioned outbreaks have occurred [13,21]. Livestock farming in Basque Country is prominent with small-scale sheep and goat farms managed in a traditional manner, sometimes lacking resources, which may hinder implementation of preventive measures such as hygiene practices or testing. A significant association

**FIGURE 3**Monthly incidence rate (per 100,000 population) of Q fever, by sex, in selected regions of Spain, 2016–2022<sup>a,b</sup>

<sup>a</sup> Data from an outbreak in Basque Country 2020–2021 are not included.

<sup>b</sup> North area covers Basque Country, La Rioja and Navarre.

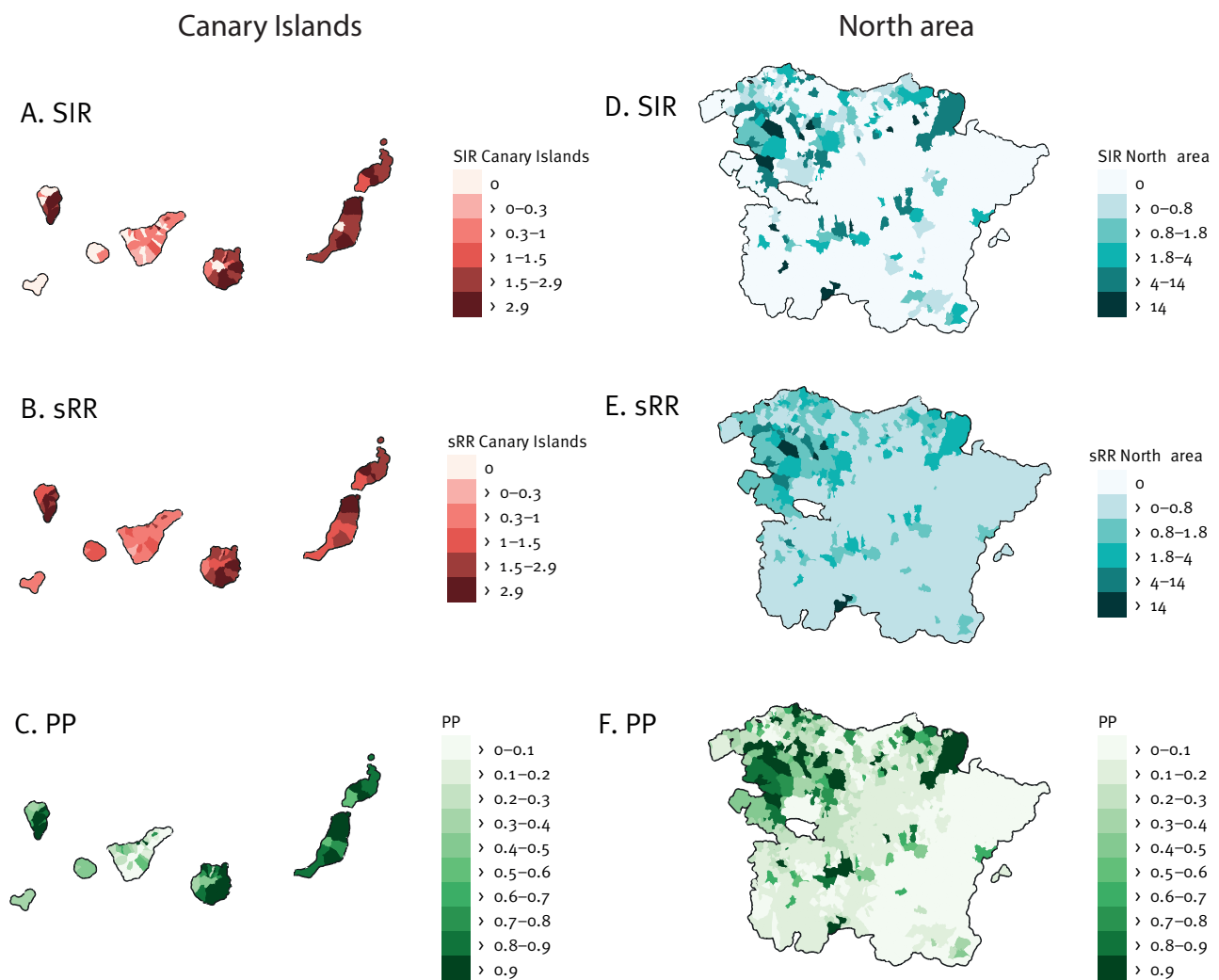
was found in the Biscay province between a positive PCR result for *C. burnetii* from farm dust samples and reported outbreaks in humans [25]. These same areas were flagged as high risk in our study. *Coxiella burnetii* DNA has also been detected in deer and wild boar spleens in Biscay [29].

An interesting fact about these two endemic regions is their shared characteristic of high human population density [30], which can lead to a concentration of farms, due to limited available space. The provinces of Basque Country are the smallest in Spain and have abundant valleys and mountains. Likewise, the Canary Islands are a group of relatively small islands with a mountainous terrain. Differences of sRR at the municipal level could also respond to factors related with the livestock industry like the concentration of deliveries in specific months or the urbanisation of grazing areas.

We recognised some limitations. The quality of information provided by regional surveillance systems depends on the level of alertness and the resources and priorities set by each region. The frequent localisation of notification centres in urban areas may lead to an overrepresentation of cases occurring within urban settings. Moreover, inaccuracies in the location of the acquisition of the infection may arise. The impact of the COVID-19 pandemic on surveillance networks may have introduced additional difficulties, including problems in outbreak registration. Focusing on a limited number of regions restricted the geographical scope of the study. Considering plausible factors influencing Q fever transmission, the lack of environmental and climatological data, information on leisure activities, along with related to reservoirs represent additional limitations in risk assessment studies.

**FIGURE 4**

Standardised incidence ratio, spatial relative risk and posterior probability of Q fever, by region, in selected regions of Spain, 2016–2022<sup>a,b</sup>



PP: posterior probabilities for each municipality to assess the credibility of the sRR; SIR: age-standardised incidence ratio per municipality; sRR: spatial relative risk.

<sup>a</sup> Data from an outbreak in Basque Country 2020–2021 are not included.

<sup>b</sup> North area covers Basque Country, La Rioja and Navarre. Spain.

## Conclusion

Control measures aimed at reducing Q fever incidence in humans should prioritise a coordinated One Health approach involving surveillance and outbreak management complemented by animal public health measures. In Spain, preventive activities predominantly focus on biosecurity protocols. The Ministry of Agriculture, Fisheries and Food has recently issued a programme that emphasises these measures [31]. Vaccination of livestock is not mandatory but strongly recommended. Additionally, further One Health-orientated epidemiological studies considering the complex interplay between human health, animal health and the environment to develop a comprehensive understanding of Q fever transmission dynamics and risk factors are needed.

## Ethical statement

Ethical approval was not needed for this study because human samples were collected as part of surveillance activities.

## Funding statement

This research received no specific funding.

## Use of artificial intelligence tools

None declared.

## Data availability

All the data are publicly available at the sources referenced in the text.

## Acknowledgements

A partial set of the data of this manuscript has already been published in Spanish Surveillance Bulletins.

## Conflict of interest

None declared.

## Authors' contributions

DC contributed to the collection of data, design, analysis and drafted the first version. RMER and DiGB provided technical and methodological support. RMER, DaGB, IJ and DiGB critically contributed to the discussion and the elaboration of the final manuscript.

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