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SHORT COMMUNICATION

The spatial pattern of human exposure to Crimean–Congo haemorrhagic fever virus is not consistent with red deer-based risk predictions

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Abstract

The objective of this study was to evaluate the spatial risk of exposure to Crimean–Congo haemorrhagic fever virus (CCHFV) infection of healthy blood donors in an enzootic region with a predicted risk gradient based on a virus–animal interaction risk model. We designed a cross-sectional study to test if the exposure pattern of the human population to CCHFV spatially matches the predicted risk. We randomly selected 1384 donors from different risk gradients and analyzed their sera searching for CCHFV antibodies. None of the selected blood donors showed exposure to CCHFV. This study shows that exposure risk spatial patterns, as predicted from animal-tick-virus models, does not necessarily match the pattern of human-infected tick interactions leading to CCHFV infection and CCHF cases, at least in a region of predicted moderate infection risk. The findings suggest that future studies should bear the potential drivers of tick-human encounter rates into account to more accurately predict risks.

KEYWORDS
blood donors, CCHFV, enzootic area, risk gradients, serosurvey

1 | INTRODUCTION

Crimean–Congo haemorrhagic fever virus (CCHFV) is a tick-borne pathogen whose main reservoirs are ticks of the genus *Hyalomma* (Bente et al., 2013). The infection can also be contracted through contact with viraemic animals or humans (Papa et al., 2017). In recent years, CCHF has appeared in the World Health Organization (WHO) list of the most important emerging infectious diseases, and it is considered a priority disease with pandemic potential (WHO, 2021).

The clinical picture in humans ranges from asymptomatic or mild cases with non-specific symptoms to severe fever with fatal haemorrhagic disease (Bodur et al., 2012). Most infections are subclinical (Bodur et al., 2012; WHO, 2021), so the true incidence of CCHFV infections could be underestimated. Exposure to CCHFV triggers the development of high and persistent levels of detectable specific antibodies (Negredo et al., 2021a), so detecting them could aid in estimating the rate of exposure of the population at risk. For this reason, serosurvey studies conducted in humans may help corroborate CCHFV exposure risk in regions where the circulation of the virus (in the principal vector or vector/virus hosts) was previously evidenced. Those studies would also allow estimating the rate at which the overall population is exposed in the region and assessing the risk of emergence of severe human CCHF cases. CCHFV infection cannot be controlled by immunization with a vaccine, so the only way to prevent cases is by the identification of risk hotspots. Thus, Public Health authorities could implement preventative measures on those hotspots.

Since 2013, confirmed CCHF human cases have emerged in Spain: one in 2013; two in 2016; two in 2018; three in 2020 and two in 2021 (Negredo et al., 2017, 2021a, 2021b), pointing out the need to assess the rate of exposure to the virus of humans in risk areas (Monsalve-Arteaga et al., 2020, 2021). A recent study performed by our group (Cuadrado-Matías et al., 2022) mapped the risk of exposure to CCHFV in peninsular Spain using the red deer (*Cervus elaphus*) as a model, a widespread and abundant wild ungulate in Spain that hosts high burdens of *Hyalomma* ticks. This study identified the southwestern quarter of Spain as the highest risk region in the country. Eight of nine primary human cases reported for the last years in Spain were, indeed, registered in or bordering this region. Further, a recent study reported that 21% of the (fed) ticks collected in southwestern Spain were infected with CCHFV (Moraga-Fernández et al., 2021). That study reported for the first time the presence of the virus in ticks in the province of Ciudad Real, in south-central Spain. This province displays a contrasting spatial risk scenario of CCHFV exposure according to the predictions of the red deer model. No human cases have been reported to date in the province. That makes this region a potentially ideal scenario to test if predicted CCHFV exposure risk patterns from an animal-virus model spatially match the risk pattern of exposure to the virus of the human population. Therefore, the purpose of our study was, through a One Health approach, to estimate the risk of exposure to CCHFV infection of the human population in Ciudad Real under a variable gradient of predicted exposure risk from the virus–animal model.

2 | MATERIALS AND METHODS

A retrospective cross-sectional study was designed to analyze the prevalence of exposure to CCHFV in serum samples from blood donors collected at the Transfusion Center of 'Hospital General Universitario de Ciudad Real' (south-central Spain; Figure 1) between October 2017 and October 2018. The collection of blood donor samples was composed of 11,313 serum samples widely covering the Ciudad Real province (44 municipalities). These samples were also used in a previous study carried out at the 'Instituto Maimonides de Investigación Biomédica de Córdoba (IMIBIC)' to estimate the prevalence of Hepatitis E virus infection (Rivero-Juarez et al., 2019).

The present study was designed based on the map of CCHFV predicted exposure risk from a virus-red deer model at the UTM 10 × 10 km spatial resolution (Cuadrado-Matías et al., 2022; Figure 1) and on the availability of samples from the four different risk gradients identified in the region. The province of Ciudad Real is environmentally very heterogeneous, including densely forested areas on the west and large areas of cereal crop plains on the north-east. It also presents high climatic contrasts (Durán-Martínez et al., 2013). That heterogeneity drastically influences the population density and distribution of *Hyalomma lusitanicum* ticks (the most abundant *Hyalomma* tick – Ruiz-Fons et al., 2013 – and the principal candidate vector of CCHFV in the region) and its principal hosts (wild ungulates; Acevedo et al., 2007, 2008).

In a cross-sectional epidemiological approach, and to assess the overall exposure rate of the human population in the study area using a representative sub-sample, we calculated the minimum sample size required to estimate CCHFV exposure prevalence at the highest spatial resolution unit at which blood donor information was available, the municipality (Figure 1). That was estimated for an expected exposure prevalence of 2% according to previous findings in neighbour regions (upper limit of the 95% confidence interval of the estimated 0.58% seroprevalence; Monsalve Arteaga et al., 2020), a 5% precision and a 95% confidence. In parallel, the sample size required per risk gradient class (low, moderate, high, or very high) was estimated as the minimum required sample size to detect a statistically significant difference between populations with variable expected prevalence. We assume that if spatial risk patterns for the human population follow the same patterns as those predicted for deer populations in the study region, the highest prevalence of exposure would occur in people living in municipalities classified as very high-risk, followed by inhabitants of municipalities with high, moderate, and low risk. We ignored what the low, moderate, high, and very high exposure levels may be in the human population in the study area, so we took these values from the scientific literature, specifically from studies carried out in Mediterranean regions. The highest values documented in humans at the local scale are those documented in Greece (Sidira et al., 2012) and Romania (Ceianu et al., 2012), which are around 28%. In endemic areas of Anatolia, the prevalence ranges from 9.2% (Vatansever et al., 2007) to 13.6% (Koksal et al., 2014). In most serological surveys in Greece, Bulgaria, Kosovo, Tunisia and in non-endemic areas of Turkey, prevalence values are around 3%–4% (Christova et al., 2013; Fajs et al., 2014; Sargianou et al., 2013; Wasfi et al., 2016; Yagci-Caglayik et al., 2014). In contrast, studies in non-endemic Spanish areas show a limited exposure of 0.58% (Monsalve-Arteaga et al., 2020). Assuming that prevalence would be around 28% in predicted very high-risk areas, 11% in high-risk areas, 4% in moderate risk areas and 0.6% in low-risk areas, we estimated the minimum sample size required to compare between risk regions and obtain a statistically significant difference with a 95% confidence, a similar sample size among regions and a 0.95 statistical power.

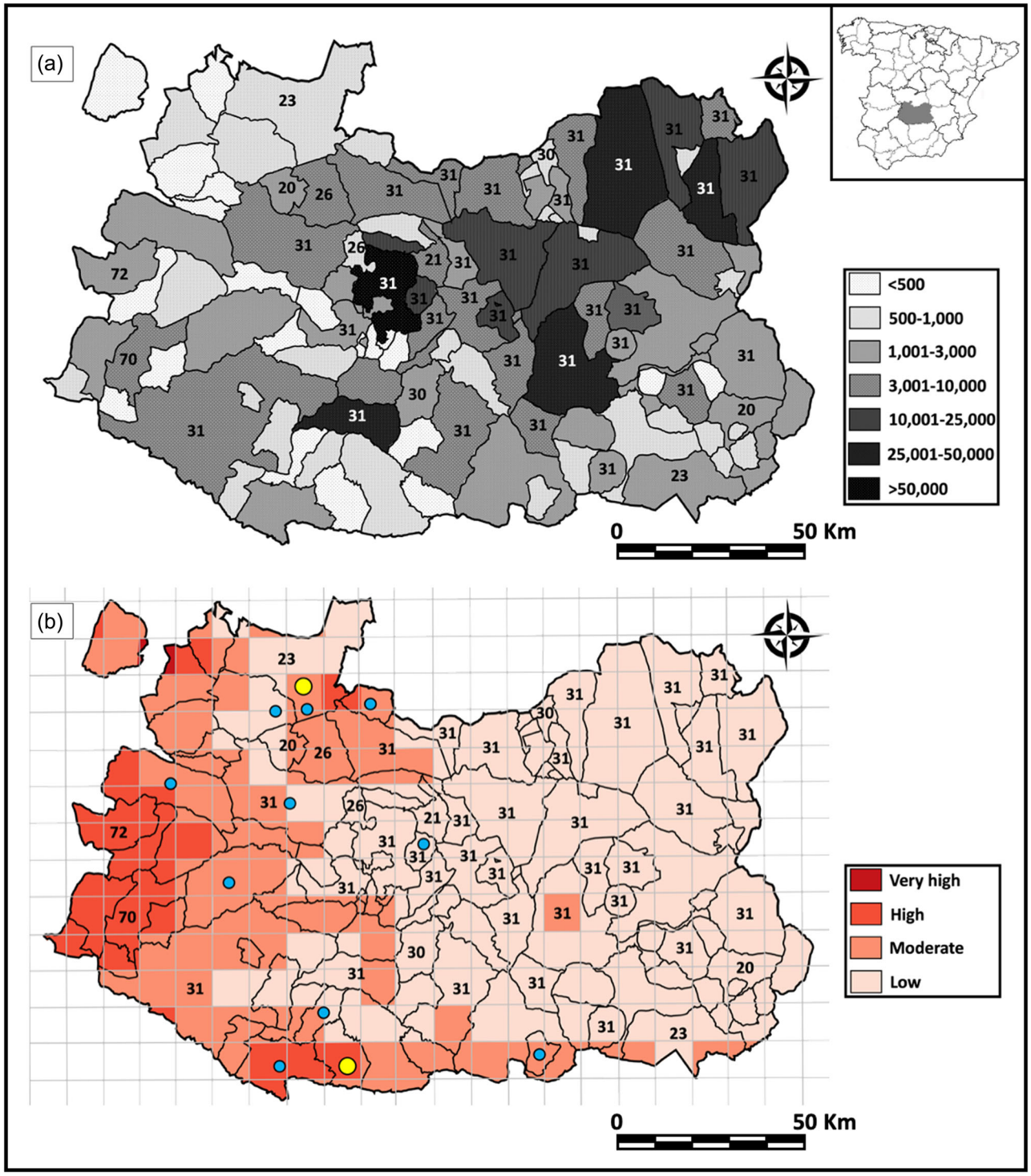

FIGURE 1 Spatial representation of the serosurvey performed in Ciudad Real province according to a gradient of increasing risk of Crimean–Congo haemorrhagic fever virus (CCHFV) infection based on a predictive model built with data from red deer (*Cervus elaphus*) surveyed across the Iberian Peninsula (Cuadrado-Matías et al., 2022). (a) The 2020 human census (www.ine.es/) against sample size per municipality. (b) Predictions of CCHFV exposure risk at UTM 10 × 10 km spatial resolution in relation to municipality boundaries and sample size per municipality. Dots represent *Hyalomma lusitanicum* ticks analyzed by RT-PCR, with blue dots for negative findings and yellow dots for positive confirmed CCHFV-infected ticks (Moraga-Fernández et al., 2021)

TABLE 1 Proportion of samples selected according to this risk gradient and expected Crimean–Congo haemorrhagic fever virus (CCHFV) exposure prevalence according to published literature

Risk gradient	Expected CCHFV exposure prevalence	Samples analyzed (N = 1384)
Very high	28% (Ceianu et al., 2012; Sidira et al., 2012)	0% (0)
High	11% (Koksal et al., 2014; Vatansever et al., 2007)	10.3% (142)
Moderate	4% (Christova et al., 2013; Fajs et al., 2014; Sargianou et al., 2013; Wasfi et al., 2016; Yagci-Caglayik et al., 2014)	14.5% (201)
Low	0.6% (Monsalve-Arteaga et al., 2020)	75.2% (1041)

Samples were selected in a balanced way according to the age (three classes: <30 years old, 30–50 years old, and >50 years old) and sex of donors per municipality.

To detect IgG antibodies against CCHFV, we used a commercial CCHF double antigen multi-species ELISA kit (IDScreen® CCHF Double Antigen Multispecies, IDVet, Grabels, France). A study carried out to validate the double-antigen ELISA showed a specificity of 100% and a sensitivity of 99% (Sas et al., 2018), and it has recently proven to be a useful tool for the diagnosis of a retrospective CCHF human case (Negredo et al., 2021a).

Continuous and categorical variables were expressed as the median and quartiles (Q1–Q3) and as the number of cases (percentage), respectively. All analyses were carried out using the SPSS statistical software package version 18.0 (IBM Corporation, Somers, NY, USA) and Epitools (Sergeant, 2018).

This study was designed and performed according to the Helsinki Declaration. All samples are integrated in 'Biobanco del Sistema Sanitario Pública de Andalucía (Nodo Hospital Universitario Reina Sofía-IMIBIC)'. All donors were provided with and signed an informed consent form. The CEIC (Clinical Research Ethics Committee) of the 'Hospital de Ciudad Real' approved the collection of the samples.

3 | RESULTS AND DISCUSSION

This study was carried out as a representative survey of the risk for the overall human population in an area where CCHFV circulates enzootically in an animal-tick silent cycle (Cuadrado-Matías et al., 2022; Moraga-Fernández et al., 2021). The 0.4% of the surface of Ciudad Real province was identified as under very high risk of CCHFV infection based on the red deer exposure risk model. In addition, 10.5% of the land was at high risk, 30.6% at moderate risk and 58.5% at low risk. Of the selected donors, 24.8% were in an area where the risk was high or moderate. The proportion of samples that were selected according to the risk gradient is shown in Table 1. The election of blood donor samples with unknown risk constituted a blind assessment of the risk for the overall population. However, this choice may involve biases for more in-deep risk assessment studies derived from the socio-economic context that leads people to donate blood, the ease of access to donation services, and the donor recruitment campaigns launched, which are most likely to be carried out with higher effort in more populated areas. Thus, we could not control any previous risk, for example, history of tick bites or professional risks.

The sample size needed to estimate the prevalence of exposure at the municipal level based on the expected prevalence of 2% was 31 samples. The minimum required sample size to find a statistically significant difference in exposure between high-risk and low-risk areas with a 0.95 power and a 95% confidence at the expected prevalence was 147 samples. We considered that, in practice, the small surface of the study area under very high risk was negligible and it was not considered for the estimation of the required sample size to compare between regions with different predicted risks. A total of 1384, apparently healthy, blood donors were selected and analyzed in this cross-sectional serosurvey. Of these, 637 (46%) were men. The age of donors was categorized into three classes: (i) <30 years (21.5% of the samples); (ii) 30–50 years (35.1%) and over 50 years (31.3%). There were 130 donors for whom sex and age data were not available. None of the samples reacted positively to the CCHFV double-antigen ELISA, which meant a seroprevalence of 0% (Clopper-Pearson exact 95% confidence interval [CI]: 0.00–0.27). This finding shows negative results regardless of whether the exposure risk of the area of residence was low (95% CI: 0.00–0.35), moderate (95% CI: 0.00–1.82) or high (95% CI: 0.00–2.56). In this line, a very low or null CCHFV seroprevalence was also shown in recent studies carried out in Spain (Monsalve-Arteaga et al., 2020; Palomar et al., 2017). The survey carried out by Palomar et al. (2017) did not find CCHFV specific IgG antibodies in 228 serum samples of humans that had reported to have regular contact with ticks. The study that Monsalve-Arteaga et al. (2020) performed in the Northern Spanish Plateau used blood donor samples, and it showed a seroprevalence between 0.58% and 1.16% in 516 donors. In that study, 21% of donors reported high-risk activity, and even 15% recalled having been bitten by ticks. The design of our study is based on the predictions of a CCHFV exposure risk model based on red deer and the evidence of positive ticks in the study region, but no CCHF cases have been notified to date in humans in the province of Ciudad Real. However, the studies by Palomar et al. (2017) and Monsalve-Arteaga et al. (2020) selected samples from some subjects who have had close contact with ticks, and some of them were from areas where human cases of CCHF were confirmed.

The overall negative findings in the province of Ciudad Real were unexpected, mainly because the model on which we based the study design did, indeed, accurately identify the areas of Spain where most primary human cases had occurred. The 75.2% of the selected donors were from the low-risk area because this area concentrates a major

part of the human population in the province. The negative findings in this area were within expectations. However, we expected to find evidence of virus exposure in 24.8% of the donors that were from moderate and high-risk areas (41.5% of the land surface). These negative findings show that the overall exposure risk of the human population in the province is very low. Our approach would have indeed been 95% certain to detect at least a positive sample if the overall exposure in the study area was 0.25%. That is undoubtedly reflecting that even though the model captures major spatial risk hotspots, the actual risk for the human population relies on a more complex array of events that modulate the exposure of humans to CCHFV infected ticks. Since the emergence of human CCHF almost always needs the interaction of CCHFV infected vectors and humans, a holistic approach is required to estimate real exposure risks (Gilbride et al., 2021). Future studies should be undertaken also under a One Health approach, but taking into account the factors that drive virus-tick-human interactions. In this sense, some studies advise this fact, both in Crimean–Congo (Gilbride et al., 2021; Sorvillo et al., 2020) and globally in zoonotic pathogens (Rees et al., 2021; Scoones et al., 2017).

The results obtained in this serosurvey, taken together with previous findings in Spain, indirectly suggest that the risk of exposure to CCHFV should be more linked to high-risk activities in risk hotspots rather than only to living close to or in high-risk areas (Gunes et al., 2009; Shahid et al., 2020). Delivering thus the appropriate information on tick bite prevention recommendations to the adequate stakeholders may also reduce the risk for those whose activities are of high risk and carried out in high-risk regions. Furthermore, a major part of the CCHFV infections in humans will be subclinical (Bodur et al., 2012) and this justifies both the need of carrying out a higher survey effort in the human population to better estimate real risks, especially in risk hotspots and in areas with reported local cases and of specifically targeting those patients with compatible signs for retrospective and prospective CCHF surveys. A prospective study carried out in 133 patients with fever of undiagnosed cause did indeed identify a case of acute CCHFV infection and two antibody-positive cases (Monsalve-Arteaga, 2021). That study showed that CCHFV infection is an identifiable cause of fever of unknown origin in Spain. Future studies based on the One Health approach should specifically target people at high risk of exposure to ticks to be more precise in understanding what, indeed, occurs in the south-western quarter of Spain.

In conclusion, this study shows that exposure risk, as predicted from animal-tick-virus models, does not necessarily spatially match the probability pattern of human-infected tick interactions leading to CCHFV infection and CCHF cases in the overall human population, at least in a region of predicted moderate infection risk. Our findings suggest that future studies and data-driven risk modelling approaches should bear the potential drivers of tick-human encounter rates into account to predict risks and inform Public Health authorities better for CCHF prevention.

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ETHICS STATEMENT

This study was designed and performed according to the Helsinki Declaration. All samples are integrated in 'Biobanco del Sistema Sanitario Pública de Andalucía (Nodo Hospital Universitario Reina Sofía-IMIBIC)'. All donors were provided with and signed an informed consent form. The CEIC (Clinical Research Ethics Committee) of the 'Hospital de Ciudad Real' approved the collection of the samples.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

The study was designed by MF, Antonio Rivero-Juárez and Francisco Ruiz-Fons. MF and Raúl Cuadrado-Matías performed the serological analyses. MF, Raúl Cuadrado-Matías and Francisco Ruiz-Fons drafted the manuscript. All the authors revised and agreed with the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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