



GENERAL SECRETARY
OF HEALTH AND CONSUMPTION

GENERAL DIRECTORATE OF
PUBLIC HEALTH, QUALITY
AND INNOVATION

**SITUATION AND EVALUATION REPORT
OF THE RISK OF VIRUS TRANSMISSION
CRIMEA-CONGO HEMORRHAGIC FEVER
(FHCC)
IN SPAIN**

July 2019



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STATUS REPORT. RISK OF FHCC IN SPAIN.

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DEFINITION OF THE PUBLIC HEALTH PROBLEM AND JUSTIFICATION:

Crimean-Congo hemorrhagic fever (CCHF) is one of the most widespread tick-borne diseases worldwide. It is considered an emerging disease in some European countries.

Spain is a country with risk of circulation of the Crimean-Congo hemorrhagic fever virus (VFHCC) due mainly to its geographical proximity to Africa, to the fact that it is an obligatory transit point for migratory birds from endemic areas, to the extensive presence of the vector responsible for the transmission and to the climatic conditions, similar to other areas where it has been shown the circulation of this virus.

In Spain, in 2010 the presence of CCHFV was detected for the first time in ticks captured in the province of Cáceres, and in 2016 the first cases in humans were identified. Since then, the presence of the virus has been confirmed in ticks of the *Hyalomma* genus, captured on wild animals and on vegetation, in the autonomous communities of Extremadura, Castilla-La Mancha, Castilla y León, Madrid and Andalusia. Also,

During 2018, studies have been carried out on animals that in these five autonomous communities have detected positive serologies both in wild animals and in households in all the regions studied.

These findings have highlighted the circulation of CCHFV in Spain and it has been considered pertinent to update the situation and the assessment of the risk of CCHF for Spain, the latest version of which was carried out in April 2017. The objective is that this information can be used as a tool for public health decision-making aimed at surveillance, prevention and control of the disease in Spain.



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This report has been prepared by:

M^a José Sierra, Lucía García San Miguel, Marta García, Beatriz Vila, Berta Suárez, Susana Monge, Sonia Fernández, Rocío Palmera, Jesús Pérez and Fernando Simón.

Coordination Center for Health Alerts and Emergencies (CCAES).

General Directorate of Public Health, Quality and Innovation.

Ministry of Health, Consumption and Social Welfare

Luis J. Romero and Elena García Villacieros.

Subdirector General for Animal Health and Hygiene and Traceability.

General Directorate of Health of Agricultural Production. Ministry of Agriculture, Food and Fisheries.

Agustin Estrada-Peña.

Department of Parasitology. Faculty of Veterinary Medicine.

Zaragoza's University

María Paz Sánchez-Seco, Ana Isabel Negro and Fernando de Ory.

Laboratory of arboviruses and imported viral diseases.

National Center for Microbiology. ISCIII. Ministry of Science, Innovation and Universities

Ricardo Molina, Maribel Jimenez.

Medical Entomology Laboratory.

National Center for Microbiology. ISCIII. Ministry of Science, Innovation and Universities

Beatrice Fernandez.

National Epidemiology Center. ISCIII. Ministry of Science, Innovation and Universities.

Consortium of Biomedical Research Network of Epidemiology and Public Health (CIBERESP)

Jose Antonio Oteo and Arantza Portillo.

Department of Infectious Diseases. Center for Rickettsiosis and Diseases Transmitted by Arthropod Vectors. San Pedro Hospital-Biomedical Research Center of La Rioja (CIBIR).

Montserrat Aguero.

Central Veterinary Laboratory of Algete. Subdirector General for Animal Health and Hygiene and Traceability.

General Directorate of Health of Agricultural Production.

Ministry of Agriculture and Fisheries, Food and Environment.

Sonia Olmeda

Department of Animal Health, Faculty of Veterinary Medicine. Complutense University of Madrid

Felix Valcarcel

Department of Animal Reproduction. National Institute of Agricultural and Food Research and Technology (INIA)



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Participants from the Autonomous Communities in the studies carried out:

Andalusia

Jesus Peinado Alvarez. SG for Health Protection. General Directorate of Public Health and Pharmaceutical Regulation.
Health counseling.

Castilla la Mancha

Pilar Fish Jimenez. Epidemiology Service. General Directorate of Public Health and Consumption.
Ministry of Health

Fatima Rodriguez Garcia. Food Hygiene Service. General Directorate of Public Health and Consumption. Ministry of Health.

Francisco Ruiz-Fons Regional Institute of Hunting Studies. CSIC. UCLM

Castile and Leon

Rufino Alamo Sanz. Public Health Information Service. General Directorate of Public Health.
Ministry of Health

Extremadura:

Julián Mauro Ramos Oil. SG of Epidemiology. General Directorate of Public Health.
Extremadura Health Service.

Julio Alvarez Cordoba. Public Health Coordinator. Health Directorate of the Badajoz Area.
Extremadura Health Service.

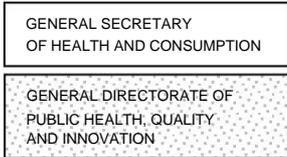
Madrid

Fernando Fúster Lorán, Eloy Marino and Ana Junco. SG of Environmental Health. General Directorate of Public Health.
Ministry of Health.

Maria Ordobas. SG of Epidemiology. General Directorate of Public Health. Ministry of Health.

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STATUS REPORT. RISK OF FHCC IN SPAIN.

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EXECUTIVE SUMMARY

Crimean-Congo hemorrhagic fever (CCHF) is one of the most widespread tick-borne diseases in the world, affecting populations in various parts of Africa, Asia, Eastern Europe and the Middle East. The disease-producing agent is the Crimean-Congo hemorrhagic fever virus (CCHFV), transmitted by the bite of hard ticks (Ixodidae), mainly of the *Hyalomma* genus. Seroepidemiological studies carried out in different endemic regions of Europe, Africa and Asia show that large herbivores (main hosts of the adult forms of *Hyalomma* spp.) have the highest prevalence of antibodies against the virus. Humans can be infected either by tick bites or by direct contact with secretions or fluids from an infected animal host during the acute phase. Person-to-person transmission may occur through direct contact with blood, secretions, body fluids, or aerosols from infected individuals or with contaminated inanimate objects, which occurs most frequently in healthcare personnel. Some cases of transmission have also been described.

vertical.

In recent years there have been outbreaks of this disease in Europe in Turkey and in Balkan countries. It is important to know which are the geographic areas in which there is a risk of transmission and how some factors such as climate change, land use or the availability of resources for prevention and control influence.

In September 2016, for the first time in Spain, the detection of an infected human case after exposure to ticks, possibly in the province of Ávila, and a second case in health personnel as a result of close contact with the first during admission. hospitable. In August 2018, the third confirmed case of CCHF was detected in a 74-year-old man who had participated in hunting activities in the province of Badajoz. In 2019, in the context of a research study at the University of Salamanca, another case was retrospectively identified that had been hospitalized in August 2018.

Since 2010, CCHFV had been repeatedly found in ticks captured in a region of Extremadura. Subsequently, in the studies carried out after the detection of the first human cases in 2016, CCHFV-positive ticks were also detected. in regions belonging to Extremadura, Castilla-La Mancha, Castilla y León, Madrid and Andalusia. All positive ticks were captured on wild animals, mainly deer, and on vegetation. No positive ticks were detected among those caught in domestic animals.

During 2018, a serological study was carried out on domestic and wild animals from the five autonomous communities in which ticks had been studied. The prevalence of infection in wild/ domestic animals detected was 69.5%/15.8% in those counties where the existence of infected *Hyalomma* ticks was known, 25.7%/3.7% in the counties that had the presence of virus-free ticks of this genus, and 2.7%/6.7% in the counties where ticks had not been identified.

These findings indicate that CCHFV circulates in Spain in more regions than initially suspected, so its extension is greater than expected. This highlights the need to carry out new studies that allow us to identify the existence of other areas of circulation of the virus in the rest of the country.

With the information available at this time, the appearance of new human cases on a sporadic basis cannot be ruled out. For this reason, it is important to inform about the measures to be adopted to avoid tick bites in areas with the presence of *Hyalomma*, especially in those where the presence or circulation of the virus has been detected. These recommendations must be addressed to the people who reside or visit these areas, especially to the groups at greatest risk due to their occupational exposure or their recreational activities.

Health professionals should also be informed about this disease, in a that a timely diagnosis be made in cases with compatible symptoms.

It is recommended that the surveillance and control of the circulation of VFHCC in Spain be addressed in a comprehensive and multidisciplinary manner, reinforcing coordination at the local, regional and national levels between the human, animal and environmental health sectors.

The risk of more sporadic cases of CCHFV transmission occurring in Spain is moderate in areas where ticks of the genus *Hyalomma* and especially in the population with a greater exposure to its bites that resides or frequent these areas. The impact of the disease is considered low given that although could be a serious disease the number of people affected would not be high and It has adequate means of isolation and control of cases.

1. EPIDEMIOLOGY OF CRIMEA-CONGO HEMORRHAGIC FEVER

The disease was first described in Crimea in 1944 among soldiers and farm workers. In 1969 it was verified that a virus isolated from a child in the Belgian Congo (now the Democratic Republic of the Congo) in 1956 was identical to the virus isolated in Crimea (1).

1.1 THE VIRUS

The CCHF virus belongs to the genus *Orthonairovirus*, of the *Nairoviridae* family. It is a single-stranded RNA virus whose genome is fragmented into 3 segments called the large (L), medium (M), and small (S) segments. As it is a virus with a segmented genome, new genetic variants can be generated by combining the segments of two different strains that have coinfecting the same individual. This phenomenon contributes to the great genetic variability presented by this virus and may have pathogenic and epidemiological consequences (2).

In the 1970s, it was thought that viruses isolated in different geographical areas had similar antigenic characteristics. However, sequencing studies have revealed a great genetic diversity, which would go against a recent origin of the virus. The diversity found in genetic studies shows variations of up to 20%, 31% and 23% in the nucleotides of the S, M and L segments respectively (2).

The L segment encodes RNA polymerase, the M encodes a glycoprotein precursor, and the S segment encodes the nucleocapsid protein. Considering the S segment of the genome, there are eight main genetic groups of the virus: 2 in Asia, 3 in Africa and 3 in Europe (3).

This form of grouping demonstrates that the different strains of CCHFV move over long geographical distances, since strains of the same lineage can appear in South Africa and West Africa or in China and Iraq. Conversely, different genetic lineages are detected in the same geographic area. This movement of the different types of genetic groups through various geographic territories may be related to the great geographic mobility of migratory birds carrying infected ticks and the trade between countries in cattle infected or carrying infected ticks (4,5).

1.2 BIOLOGICAL CYCLE

The agent cycle in nature is maintained by tick-vertebrate tick circulation. In order for the virus to establish itself in an area, vertebrates must coexist. susceptible to infection with levels of viremia sufficient to transmit it and ticks with vector competition.

Ticks of the *Hyalomma* genus are, at the same time, a reservoir and vector of the virus, being able to transmit it throughout their lives and to their offspring. The degree of association is such that the geographic distribution of the infection coincides with that of the population of this genus of ticks. The circulation of the virus is maintained between the immature forms of the vector and the small

vertebrates on which they feed (hares, hedgehogs, mice), which act as amplifying hosts. Once infected, the tick can transmit the agent throughout its life, mainly by feeding as adults on ungulates (goats, sheep, horses, pigs, camels or donkeys) (1). Antibodies against the virus have been detected in the serum of various domestic and wild animals such as cattle, donkeys, horses, goats, sheep, pigs, deer or bats in various regions of Europe, Asia and Africa. In these, unlike in humans, the infection does not cause apparent clinical disease, with seroprevalence rates of 13-42% having been detected in various studies (6-8).

The form of access to new territories is carried out through the passive transport of immature forms through migratory birds on their long-distance journeys or through the movement of cattle with adult forms. In birds, viremia is very rare, although experimental conditions have shown seroconversion and transmission of CCHFV from birds to ticks (9,10). As an exception, ostriches can have asymptomatic viremia of up to 4 days and have produced outbreaks in slaughterhouse workers (11,12).

In a study that assesses the factors that favor the circulation and possible expansion of CCHFV in the western part of the Palearctic region, it is concluded that the increase in temperature has little impact on the transmission routes of CCHFV in the population of ticks. The circulation of the virus is favored by the presence of adequate hosts for adult ticks. In the model proposed in this work, the variation in the rate of transovarian transmission of CCHFV in the tick was the main factor associated with variations in virus circulation in the tick population (13).

Various studies have revealed that the genetic diversity of viruses isolated in different geographical locations is greater than that of other viruses transmitted by arthropods, which reveals a wide dispersion of the virus (14). The entry of the agent into a new territory can be caused by the introduction of infected ticks to the area, either by migratory carrier birds or by the movement of infested livestock. The first hypothesis is supported by the fact of finding similar viruses in different locations and different viruses in nearby locations (5,14,15).

The emergence of this disease in southern and eastern Europe is attributed to changes climatic and ecological, amplified by anthropogenic factors. The modification of the use of soil, agricultural practices, hunting or livestock movements have an impact directly in the population of ticks and their hosts (16). Specifically, the changes have been related to the proliferation of hares and rabbits in fields used for agriculture abandoned and the consequent increase in the population of ticks that parasitize them (17,18). This increase in the population of perfectly adapted hosts and ticks to the climatology of the Mediterranean area, suggests that the VFHCC will continue its expansion and it is possible that new cases of disease will be diagnosed in the coming years.

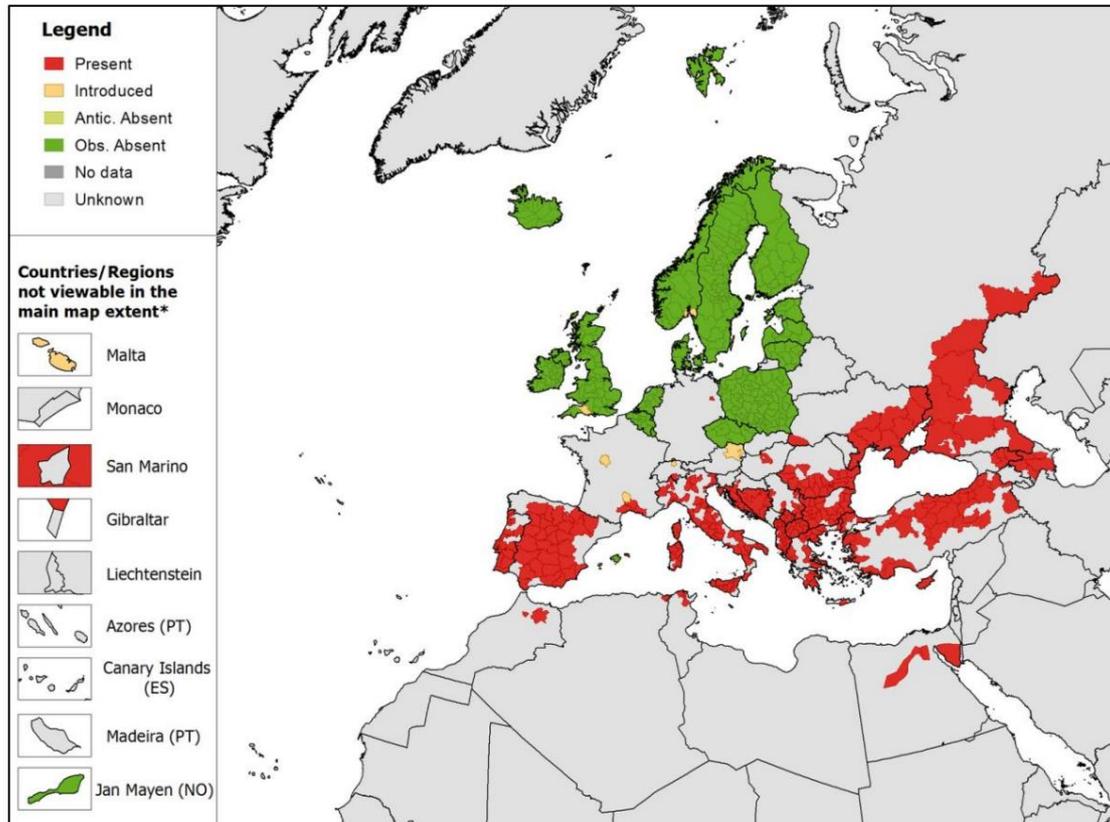
1.3 THE VECTOR

Epidemiological studies based on cases of CCHFV infection in humans and serological studies indicate that *Hyalomma* ticks are the most efficient vectors of this disease (19). The appearance of CCHF cases in Europe, Asia and Africa coincides, in general, with the distribution of the *Hyalomma tick*, mainly *H. marginatum* (Figure 1) (20). However, the virus has been isolated from at least 30 different tick species, including 28 ixodid and 2 argasid ticks, although the latter do not act as vectors of the disease due to their inability to replicate the virus in its interior.

Ticks of the *Hyalomma* genus belong to the ixodid family (hard ticks) that feed only once in each stage of their development (larva-nymph-adult). The vectorial role of this genus of ticks in the maintenance of CCHFV is highly varied. Thus, i) they can be infected by feeding on a viremic animal or born congenitally infected; ii) immature stages are capable of transmitting the virus by feeding on later stages (transstadial transmission); iii) an infected replete female can transfer the virus to her offspring (transovarian transmission) (21,22); iv) male ticks are capable of transmitting the infection to the female during copulation (sexual transmission) (23). The importance that co-feeding transmission may have in the maintenance of active foci of the virus. In this form of transmission, ticks without infect that feed in close proximity to infected ticks, over the same area from the same host, they would be infected without the need for viremia.

Although the main vectors/reservoir of CCHFV, ticks of the genus *Hyalomma*, have their origin in Mediterranean climates, they have been introduced in other areas. Currently *H. marginatum* is considered present in Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, France, Greece, Italy, Kosovo, Macedonia, Moldova, Montenegro, Portugal, Romania, Russia, San Marino, Serbia, Switzerland, Spain, Turkey and Ukraine (23, 25). *H. marginatum* has also been detected sporadically in animals, migratory birds and humans in Germany (26), Hungary (27) and the United Kingdom (28), with established populations of the vector existing in some of these places (Figure 1). *H. marginatum* is a common parasite of horses in southern Europe, so they could play a relevant role as carriers of ticks to new areas (17,29), in addition to the role of migratory birds or cattle movements.

The tick population in an area depends on the abundance of susceptible hosts on which to feed and climatic conditions suitable for the survival of non-parasitic stages (30). The change in climatic conditions seems to play an important role in the increase in the tick population. Changes in temperature or humidity affect the biology and ecology of these vectors, as well as that of their hosts or natural reservoirs (31).

Figure 1. Distribution of *H. marginatum* in Europe, January 2019.

Source: ECDC (25).

H. marginatum is capable of surviving, in a state of hypobiosis, within a very wide temperature range, from -7° to 30°C . To recover its activity and feed, it needs temperatures above $4\text{-}5^{\circ}\text{C}$ with optimal values for larvae of $14\text{-}16^{\circ}\text{C}$ and for adults between $22\text{-}27^{\circ}\text{C}$. In the northern hemisphere, it is considered a tick of warm months, whose activity depends on the environmental conditions of each area. In countries like Iran, the largest vectorial activity occurs in the months of August and September. In Pakistan, however, it follows a biannual distribution, between March and May and later, from August to October (20,32–34). Climate change, with rising temperatures, may shift this period between May and September to historically colder months (17,18).

The amount of water vapor in the atmosphere is the most important variable in the survival of the tick. In this case, the decrease in water vapor would considerably reduce the viability of the developing phases. A slight change in climate could change the seasonal period of transmission or shift the distribution to more northerly areas (35).

Finally, other factors such as the fragmentation of the plant habitat or the abandonment of farmland have been determining factors in the population of ticks and their hosts, which could be associated with an increase in the rates of contact between humans and ticks infected with CCHFV (18,36,37).

1.4 THE DISEASE IN HUMANS

Serological studies carried out in endemic countries indicate that infection in humans can be asymptomatic, although it is difficult to establish the percentage.

A study in Turkey with more than 3,000 samples studied indicated that 90% may have had a subclinical infection (38).

In those infected who present clinical manifestations, many may present with a mild nonspecific febrile illness. The natural history of the disease can be divided into four phases (39):

• Incubation period, lasting between 3 and 7 days (range 1 to 12), depending on the viral load and the route of transmission of the virus. After the tick bite infected, the incubation phase is generally 1 to 3 days, with a maximum of 9 days. The incubation period after contact with infected blood or tissue is somewhat longer, usually 5-6 days, with a documented maximum of 13 days (40).

• Pre-hemorrhagic period, in which the usual symptoms are fever, headache, myalgia and dizziness and lasts 4-5 days. Diarrhea, nausea or vomiting, hyperemia of the face, neck or chest, eye congestion or conjunctivitis may occur during this period.

• Hemorrhagic period, which usually lasts 2-3 days, in which they will appear from petechiae to ecchymoses on the skin or mucous membranes and hemorrhages. The main places of bleeding are the nose, the digestive system (hematemesis, melena or intra-abdominal), the uterus (menometrorrhagia), the urinary tract (hematuria) or the respiratory tract (hemoptysis). In this phase, hepatosplenomegaly is common. • Convalescence period that begins 10-20 days after the onset of the disease.

During this period, the presence of a weak pulse, polyneuritis, dyspnea, xerostomia, decreased visual acuity, hearing and memory loss has been described.

In cases of poor evolution, death generally occurs during the second week of illness (days 5-14) as a result of hemorrhage, multiple organ failure, and shock. The fatality rate is between 10% and 40%. However, in recent outbreaks in European countries (Bulgaria, Turkey and Russia) the lethality has been between 3% and 15% (14). Among people who recover, improvement usually begins on the 9th or 10th day after the onset of illness (40).

It is unknown whether the infection produces immunity against the virus, although no cases of CCHFV reinfection have been identified in the literature (41).

Transmission Mode

Transmission of the virus occurs through the bite of an infected tick of the *Hyalomma* genus (19). Infection can also occasionally be transmitted by exposure from non-intact skin or mucous membranes to infected cattle during slaughter or skinning of viremic animals, although the period of viremia in animals is very short (around a week) (19,22). Most cases occur in people related

with the livestock industry, wool carders, agricultural workers, slaughterhouses, hunters, veterinarians, and people who work in close contact with nature in endemic areas (42). Contagion from aerosols generated by rodent droppings in the field has also been described (32).

Human-to-human transmission may occur through close contact with blood, secretions, other body fluids, or organs of infected persons. The risk of transmission is greater in the later stages of the disease, as they are associated with higher viral loads along with diarrhoea, vomiting and bleeding. Outbreaks due to nosocomial transmission have been described in which health workers, without adequate protection conditions, became infected through direct contact with blood and/or by aerosolization of contaminated fluids from infected patients in advanced stages of the disease (32, 43–54).

The risk of transmission to close contacts and family members is low. In a study that included 57 close contacts of 12 confirmed cases, only one of the contacts was positive, and in another study that included 116 close contacts of 90 confirmed cases, none manifested symptoms or were positive for CCHFV (55,56). . After the first cases detected in Spain in 2016, more than 400 contacts were followed up and no new cases were detected (57).

The role of sexual transmission is uncertain, although specific cases have recently been described (23,58). Likewise, some cases of vertical transmission are described. The prognosis in these cases is uncertain, since both fatal cases and normal newborns have been observed (59–61).

There is no clear evidence of cases transmitted through transfusions or transplants, nor evidence of viremia during the incubation period or the period before the onset of symptoms (62). Infection among donors or recipients of donations has also not been described. Therefore, the available data is insufficient to make recommendations on donation safety. However, current plasma and platelet pathogen inactivation techniques have been shown to be effective in eliminating enveloped viruses such as CCHFV (63).

Diagnosis

Thrombocytopenia and leukopenia, increased transaminases, LDH, and CK, coagulation disorders, decreased fibrinogen, and increased fibrin degradation products are common in CCHF cases (64).

Diagnosis is made by virus isolation, PCR (specific, sensitive and rapid method) or serology (IgM and IgG antibodies are detected by ELISA and immunofluorescence assays from about 7 days after the onset of the disease) (65).

The virus is considered a level 4 biohazard agent that must be handled under adequate biosafety conditions (66).

Treatment

Support treatment is basic in case management. This includes transfusion of platelets, fresh frozen plasma, and red blood cells (67). Ribavirin has been proposed as a treatment for CCHF although there are no clinical trials that demonstrate its efficacy, which has only been assessed in observational studies. In recent years, favipiravir has been proposed as a treatment, although its efficacy is also under study (40,68).

In 1974, a vaccine was marketed in Bulgaria, which is administered to the military, health workers, farmers and the population living in endemic areas. In the rest of the Member States of the European Union its use is not approved (33).

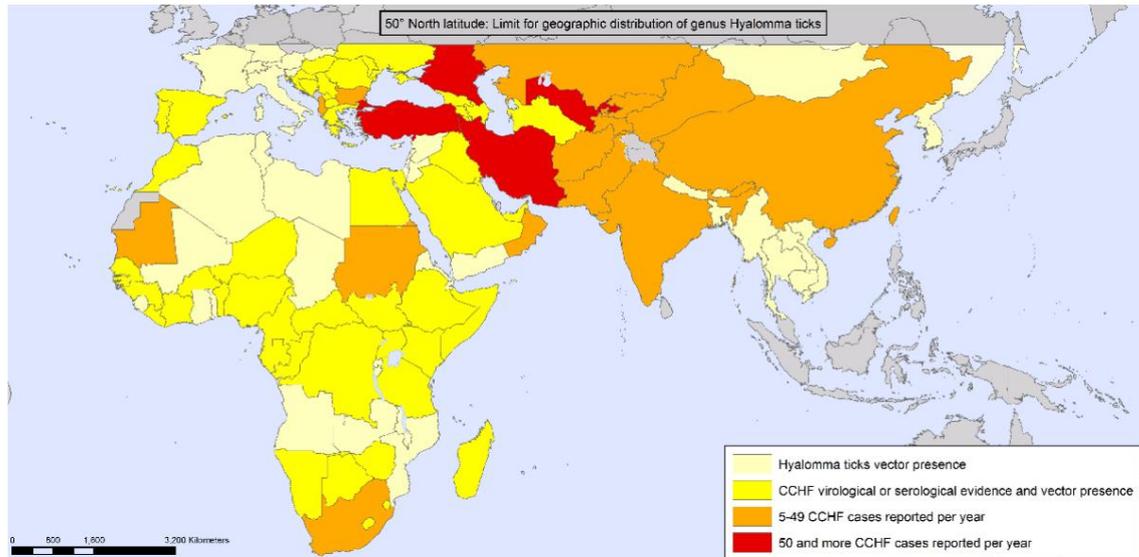
1.5 GEOGRAPHICAL DISTRIBUTION OF THE DISEASE

CCHF is one of the most widely distributed arboviruses in the world, with a extent from southern Russia and the Black Sea Region to southern Africa (37).

The geographic distribution of the CCHF coincides with that of ticks of the genus *Hyalomma*. CCHF is an endemic disease in the Balkan Region. In Europe, cases of human infection have been detected in Albania, Bulgaria, Greece, Kosovo, Serbia, Turkey, Armenia, Georgia, Ukraine, and the Russian Federation as well as in Kazakhstan, Tajikistan, Turkmenistan, and Uzbekistan (33,69). (Figure 2).

Between the period 1953-2008, more than 1,500 cases (70) were diagnosed in Bulgaria and in recent years 6 cases have been reported in 2010, 4 in 2011, 5 in 2012 (71), 8 in 2013, 8 in 2014, 4 in 2015 and 4 in 2016 (72). Infections in humans have occurred mainly in the eastern region of the country, in the spring and summer months, in people involved in agricultural activities and who are exposed to the tick bite (73). On the other hand, the United Kingdom in 2012 and 2014 reported two imported cases: the first was a person from Kabul (Afghanistan), who arrived in London via Dubai (74); the second was a case that had probably been infected in Bulgaria (75). Furthermore, in Germany in 2009, two cases of nosocomial infection occurred from a US soldier working in Afghanistan (51).

Figure 2. Geographic distribution of Crimean-Congo hemorrhagic fever, 2017 (76).



Source: WHO (76).

Turkey is the most affected country in the European region with more than 1,000 confirmed cases year. No cases had been detected in Turkey until 2002, when the first was identified in the Black Sea region (77). However, the reoccupation of land previously dedicated to agriculture that had been abandoned increased exposure to the tick bite and, therefore, the reemergence of the disease (37). Between 2002 and 2015, more than 9,500 cases of the disease were reported in Turkey, with a fatality rate of around 5% (45.78).

In Greece, the virus was identified for the first time in 1975, after the isolation of the AP92 strain in a veterinarian who became asymptotically infected in the laboratory. This strain had been isolated from *Rhipicephalus bursa* ticks found on goats in the Vergina region in 1975. Although antibodies against the virus were detected in the local population, no human cases were reported for the next 30 years. The first symptomatic human case diagnosed in Greece was confirmed in June 2008 in a person living on the border with Bulgaria (79,80). In 2018 there was a second case in a worker from Bulgaria (81).

In the territory of Kosovo, the first human case dates back to 1954 and since then cases have been reported every year (82). From 1995 to 2008, 487 cases were reported, of which 140 were confirmed (28).

In Albania, the first human case was described in 1986. From 2001 to 2006, an average of 10 cases per year were reported. The most affected areas were Kukës and Has, in the Northeast of the country (83).

After the identification of the virus in the Crimea region in 1944, almost 27 years passed without notification of new human cases, however, since 1999, the CCHF has re-emerged in the South and West regions of the Russian Federation (1). Outbreaks have been reported

in the provinces of Astrakhan, Rostov and Volgograd, in the Krasnodar and Stavropol Territories and in the Republics of Kalmykia, Dagestan and Ingushetia (28). The incidence of the disease has been increasing and between 1999 and 2014, 1,745 cases have been diagnosed in the Russian Federation with a case fatality rate of up to 4.3% (84).

The first reported cases in Africa date back to the 1950s in the Democratic Republic of the Congo (2 cases) and Uganda (12 cases, one of which died). Beginning in the 1980s, cases have been reported in South Africa, the Democratic Republic of the Congo, Mauritania, Burkina Faso, Kenya, Sudan, Tanzania, and Senegal. In general, the number of reported cases has been limited with the exception of Mauritania, where 38 cases were reported in 2004 with a case fatality rate of 31% (1).

In China, an outbreak of CCHF was retrospectively identified in 1965 in studies in humans, sheep, and ticks (85). The virus has been isolated from *Hyalomma* ticks in Pakistan in the 1960s and since then there have been outbreaks and sporadic cases, mostly in people who worked in contact with livestock (86). In early 2011, the first case of CCHF was detected in India in a nosocomial outbreak linked to Pakistan. (87).

In the Middle East region, Iran is one of the countries where the disease poses the greatest risk to public health. Since 2000, infections have been reported throughout the country and 23 of Iran's 30 provinces are endemic. Between 2000 and 2008, 1,297 probable cases of CCHF in humans from different provinces of the country were studied and 534 of them were positive (88). Furthermore, in recent decades, outbreaks of CCHF have been documented in other Middle Eastern countries such as Afghanistan, Iraq, Kuwait, Oman, Pakistan, Saudi Arabia, and the United Arab Emirates (16,20,64,88).

In addition to the known outbreaks around the world, seroprevalence studies have been carried out to find out the real circulation of the virus, both in ticks, as well as in animals and in humans, whether it is a healthy general population or risk groups. Table 1 shows the results of CCHFV seroprevalence studies carried out in different countries.

Table 1. Presence of Crimean-Congo fever virus in ticks and seroprevalence. (Ig G) in animals and humans, by country.

Ticks: capture; species; (positive %); technique; year; reference	Animals: species (seroprevalence %); technique; year; reference	Humans: population (seroprevalence %); technique; year; reference
Albanian		
About cattle; <i>H. marginatum</i> , <i>R. sanguineus</i> , and <i>R. bursa</i> ; (13.9% pools); 2007-2014; (89)	Goats (20%); ELISA;2007-14;(90)	
	Earned (75.7%); ELISA; 2010, 2013 and 2014; (91)	
	cattle (88.3%); ELISA; 2010, 2013 and 2014; (91)	
Bulgaria		
About cattle; <i>H. marginatum</i> (3.7%), <i>R. sanguineus</i> (1.6%) and <i>I. ricinus</i> (1.9%); RT-PCR; 2006-2010; (92)	Cattle (7.89%); IIF; 2006-2012; (92)	Healthy adults (2.8%); ELISA; 2011; (93)
	domestic ruminants (26%); anti VFHCC; (95)	General population (3.7%); ELISA and IIF; 2015; (96)
Greece		
	Sheep (25%); ELISA; 2014; (97)	Risk population (1%); Neutralization and IFI; 1981-1988; (98)
		General population (3.14%); ELISA; 2008-2009; (99)
		General population (4.2%); ELISA; 2009-2010; (100)
		General population (2.2%); ELISA; 2010-2011; (101)
India (Gujarat province)		
		General population (0.5%); ELISA; 2015-2017; (102)
Iran		
		ELISA general population (0.024%); population; 2002; (103).
Kosovo		
Livestock and vegetation; <i>H. marginatum</i> (29/297, 9.8%), <i>R. bursa</i> (10/108, 9.3%) and <i>I. ricinus</i> (1/7, 14.3%); RT-PCR; 2012; (104)	Cattle (18.4%), goats (20%), sheep (10%); IIF; 2012; (105)	General population (4%); ELISA; 2012; (105)
Mali		
	Cattle (66%); ELISA and IIF; (106)	
Mongolia		
Cattle and vegetation. <i>H. asiaticum</i> (1772 ticks; 1/893 pools +) and <i>D. nuttalli</i> (2811 ticks, 0 +); RT-PCR; 2013-2014; (107)		People areas <i>H. asiaticum</i> (1.4%); ELISA; 2013-2014; (107)
Poland		
	Cattle (0%); sandwich ELISA; (108)	
Democratic Republic of Congo		
	Goats and sheep (1.6%); ELISA; 2013; (109)	
Tunisia		
Livestock and vegetation; <i>H. scupense</i> and <i>H. dromedari</i> (310 ticks, 0+); RT-PCR; 2014 (110)		Risk population (5.2%); ELISA; 2014; (110)
Turkey		
	Goats (66%), sheep (31.8%), cattle (13%); ELISA; 2014; (111)	Healthy volunteers (19.6%); ELISA; (112)
		Rural population (10%); ELISA; 2009; (113)
	domestic ruminants (57%); ELISA; 2011;(95)	Case contacts (13.6%); ELISA; 2009-2010; (114)
		Ranchers and farmers (14.4%); ELISA; 2012; (115)
		Population at risk (12.8%); ELISA; 2006; (116)

2. SITUATION IN SPAIN

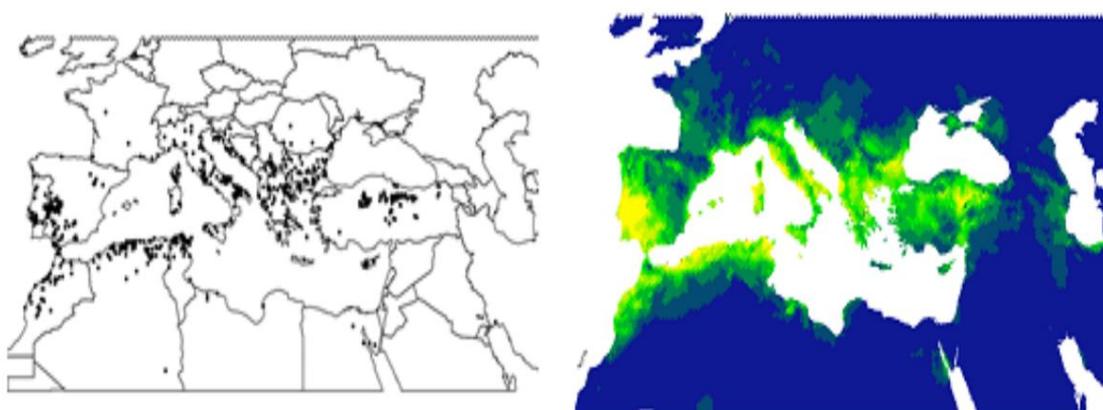
2.1 PRESENCE AND CHARACTERISTICS OF VECTORS

Ticks of the genus *Hyalomma* are extremely abundant in the central and southwestern peninsular, with two main species: *H. marginatum* and *H. lusitanicum* (117).

In Spain, the immature forms of *H. marginatum* have been found in small mammals and various bird species and the adult forms in cows, donkeys, foxes, wild boars, deer and hares. It is estimated that this species of tick would be distributed throughout the Mediterranean basin if the current climatic trend were to continue. In Spain it has been identified in Andalusia, Aragón, Castilla-La Mancha, Castilla y León, Ceuta, Extremadura, Madrid, La Rioja and the Valencian Community, being less abundant in the north of the peninsula (118–120).

The *H. marginatum* tick is more prevalent in the months of April-June in the peninsular area. Mild winters contribute to its survival, favoring the persistence of the virus (121).

Figure 3. Distribution of the tick *H. marginatum* in the Mediterranean basin (left image) and expected distribution with the current climate, obtained from historical climate data (right image).



Source: Estrada et al.

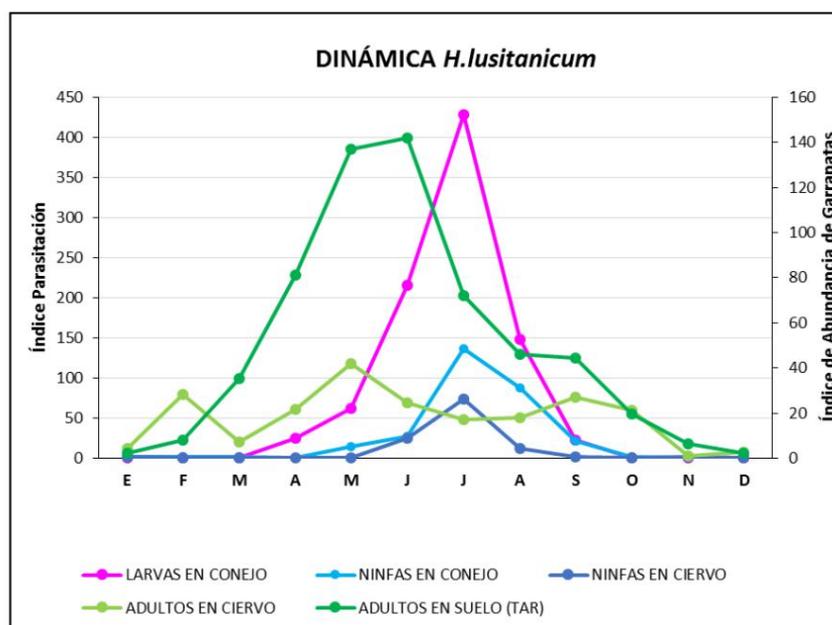
The blue color represents absence while the different shades of green through yellow indicate increasing suitability (or probability of higher or more abundant occurrence).

The other species of the genus *Hyalomma* present in Spain is *H. lusitanicum*, whose habitat is closely related to the abundance of rabbits, on which larvae and nymphs feed, and domestic and wild ungulates, on which adults feed (122,123). It is especially abundant in the central area of the peninsula (Community of Madrid and Castilla La Mancha) where it constitutes between 54 and 97% of the ticks collected from vegetation (117,118,123). It has also been described in other autonomous communities such as Extremadura, Andalusia (119), Castilla y León, the Canary Islands and Menorca, and in other countries such as Portugal, Italy (the south and Sicily), France and northern Morocco, Algeria, Tunisia and Libya (Figure 4).

Figure 4. Distribution of *H. lusitanicum* in the Western Palearctic.

Source: Williams et al. (124)

In the central peninsular area, *H. lusitanicum* is active practically all year round, although its period of maximum activity is centered in the months of April to October. Adults in vegetation increase gradually, reaching maximum activity in June, to progressively decrease, their activity being practically nil from November to February (123). Parasitization in animals follows similar patterns with three maximum parasitization peaks by adults, in February, June-July and October (123) and very intense parasitization by immatures in July and August (122).

Figure 5. Activity of *H. lusitanicum* in Castilla-La Mancha (La Garganta Farm, Ciudad Real). Parasitization index in deer and rabbits, and tick abundance index in vegetation. Period 2007-2010.

Source: Report of the *Comprehensive Control of the Population of Ticks project at the "La Garganta" Farm*. UCM-Villamagna SA contract.

2.2 PRESENCE AND CHARACTERISTICS OF THE VIRUS

2.2.1 Situation until 2016

2.2.1.1. Studies carried out on ticks

The first finding of VFHCC in Spain was made at the Biomedical Research Center of La Rioja (CIBIR) in ticks captured on deer in 2010 in Extremadura in an area bordering Portugal (125). The RNA of the 117 captured adult ticks was distributed in 12 batches, of which two were positive for CCHFV. The positive ticks belonged to the species *H. lusitanicum*, although it must be taken into account that in these studies the ticks sampled and analyzed were mostly *H. lusitanicum* and the number of *H. marginatum* was much lower.

These results were confirmed by the Arbovirus and Imported Viral Diseases Laboratory of the National Center for Microbiology (LAEVI-CNM). Phylogenetic analysis of positive strains showed high affinities with strains from Sudan, Mauritania, Senegal, and South Africa (125). Genetic research shows that the virus circulating in these countries is widely distributed throughout Africa and is known as Africa group 3 or genotype III (46,126). In genotype III are found the strains that circulate in the African continent, detected in Nigeria (1966), South Africa (1981, 1985, 1987, 1997), Burkina Faso (1983), Mauritania (1984, 2003), Senegal (1993), United Arab Emirates (1997) and in Sudan (2008, 2009). In Europe, however, the strains that circulate in endemic areas are mostly grouped into genotype V and genotype VI.

Subsequently, the LAEVI-CNM analyzed the presence of VFHCC in ticks collected in Extremadura during the years 2011, 2012 and 2013 and in others from Toledo, Huesca and Segovia in a timely manner in 2011 and 2012. The studies were carried out in collaboration with the Faculties Veterinary Medicine at the University of Zaragoza and the University of Extremadura in Cáceres. The detection method used for the amplification of the viral genome was developed in the Laboratory itself (127). Viral RNA was detected in 44 of the 1479 ticks captured, all of them from Cáceres, 43 were of the *H. lusitanicum* species and 1 of the *H. marginatum* species (127).

Between 2011 and 2013, 681 ticks of the species *Rhipicephalus* sp., *H. lusitanicum* and *H. marginatum* were analyzed. Positive results for CCHFV were obtained in 24 ticks, all of them from Extremadura and of the *H. lusitanicum* species. The genetic sequence could be determined in all 24 samples. The 24 sequences showed homology with genotype III, although in Spain 2 genetic variants within this genotype are distinguished. To the number of ticks analyzed above, we must add 272 ticks collected in Extremadura during 2014 in which 3 positive ticks were detected that could not be confirmed in subsequent analyses. Infected ticks were captured feeding on deer (128,129).

The Ministry of Health of the Junta de Castilla y León has a program for the prevention and control of anthroponoses transmitted by ticks. In 2014, in collaboration with the Biomedical Research Center of La Rioja (CIBIR), the presence of CCHFV in *H. marginatum* obtained from cattle at the slaughterhouse was studied. 231 specimens of *H. marginatum* were studied (188 specimens were obtained from animals from Castilla y León (4 from Ávila, 168 from Burgos, 1 from Salamanca, 10 from Soria and 5 from Valladolid) and 43 from other sources (1 from Badajoz, 12 from Cáceres, 5 from Ciudad Real and 25 from La Rioja) with negative results for CCHFV in all samples (120,130).

2.2.1.2. Studies carried out in humans

In a study carried out by the CIBIR during the years 2013 to 2015, in collaboration with the University of Extremadura, in 228 serum samples corresponding to hunters and ranchers from municipalities close to the focus in which the presence of CCHFV was detected for the first time in Cáceres and Antibodies against CCHFV were not detected in people bitten by ticks (including those bitten by *H. marginatum*) (120). However, in the 1980s, CCHF antibodies had been found in the sera of two individuals in southern Portugal (131).

2.2.2 Human cases detected

On September 1, 2016, the CNM confirmed VFHCC in samples from two patients in the Community of Madrid. The first case, a 62-year-old man with no history of travel outside of Spain, began with symptoms on August 16, 2016 and died nine days later; He reported having walked through the countryside on August 14 in a municipality in the province of Ávila¹ and having found a tick on his skin, although no bite wound was observed.

The second case occurred in a 50-year-old health worker who treated the previous case during her stay in the ICU between August 19 and 23. This secondary case developed symptoms on August 27. On August 30, she was referred to the High Level Isolation Unit of the La Paz Carlos III University Hospital. The patient was in isolation until September 18. More than 400 contacts of the two cases were identified and followed up for 14 days after the last possible exposure to infection (57). No new case was detected.

The sequence analyzed in these two cases corresponded to one of the variants detected among the positive ticks analyzed in previous years. The virus was classified within genotype III, South Africa and West Africa (132).

Two years later, in August 2018, the third confirmed case of CCHF was detected in a 74-year-old man with no travel history outside of Spain, who had participated in hunting activities in Helechosa de los Montes (Badajoz), and had reported bites from tick, although no bite wound was observed. In this case, the virus sequence obtained at the CNM showed genetic differences with the viruses from the 2016 patients in the S and L segments; although they continued to belong to genotype III, without

¹ Probable exposure in the municipality of Villarejo de Ávila.

However, the sequence of the S segment clustered with strains of genotype IV, the genotype containing mostly strains circulating in Asia.

In May 2019, in the context of a research project carried out by the University of Salamanca, whose objective was to find out the involvement of CCHFV in fevers of unknown origin, a case of CCHF was detected and confirmed by PCR at the LAEVI-CNM. in a person admitted in August 2018. During his admission, he received a diagnosis of unknown viral disease, with full recovery.

2.2.3 Studies carried out after the detection of human cases

After the detection of the first two human cases, a multi-phase study was launched to assess the situation and the risk of CCHFV infection in Spain. The first two phases of this study focused on the detection of the virus in ticks, the third on serological studies in domestic and wild animals, and the fourth, serological studies in humans, especially in risk groups, is in process.

development at this time.

First phase. Study of ticks captured on animals

The first phase was based on the sampling of ticks in the regions considered to be at greatest risk, according to the information available to date, belonging to the autonomous communities of Castilla-La Mancha, Castilla y León, Extremadura and Madrid. Eleven livestock districts were included in the study and sampling was carried out on domestic livestock and wildlife. The tick capture period began at the end of September 2016 and continued until the end of February 2017.

The sampling and analysis of these ticks was proposed as a marker of the presence or absence of virus in these areas, not as an estimate of the intensity of its circulation.

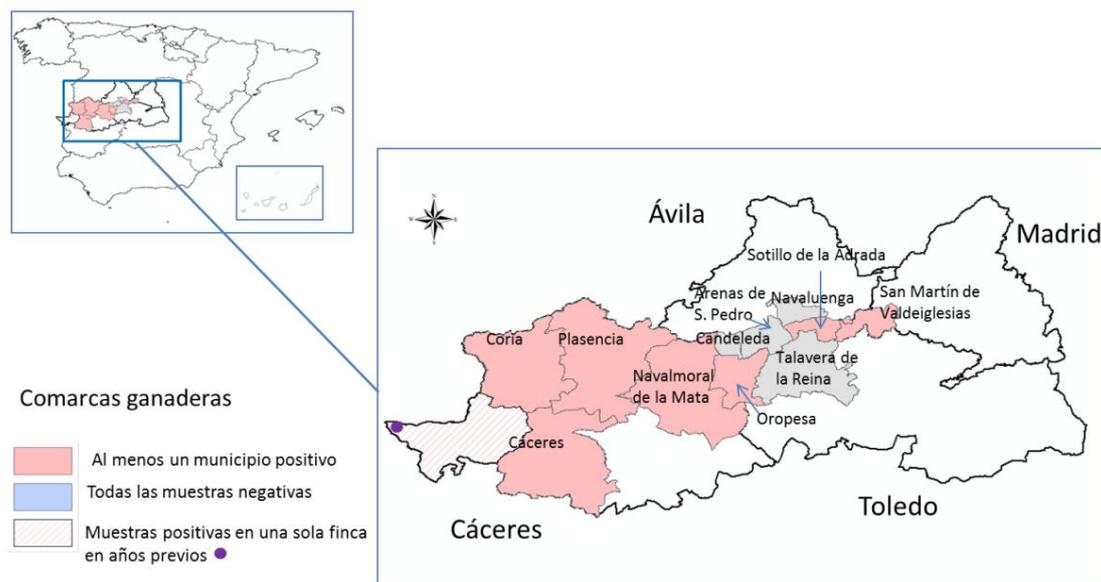
The analyzes of this first phase ended on March 31, 2017 and were carried out at the LAEVI CNM. The identification of the ticks was carried out by the Medical Entomology Laboratory of the CNM.

Within the framework of this phase, more than 9,500 ticks captured on domestic and wild animals were sent to the CNM. For the analysis these ticks were grouped, analyzing 3,959 groups of which all those from domestic animals were negative, and 128 of those from wild animals were positive. These results confirmed the presence of CCHFV in ticks captured on animals in municipalities of seven of the eleven livestock regions studied: 4 from the autonomous community of Extremadura, 1 from Madrid, 1 from Castilla y León and 1 from Castilla-La Mancha (Figure 6).).

The vast majority of ticks positive for the virus belonged to the *H. lusitanicum species*. The virus has also been identified from time to time in ticks of the species *Dermacentor marginatus* and *Rhipicephalus sp.*, although these ticks are not vectors .

authorities known to the FHCC. The vast majority of positive ticks were captured on deer.

Figure 6. Results of the Crimean-Congo hemorrhagic fever virus study in ticks collected from animals by livestock districts. April 4, 2017.



Source: self made. Coordination Center for Health Alerts and Emergencies.

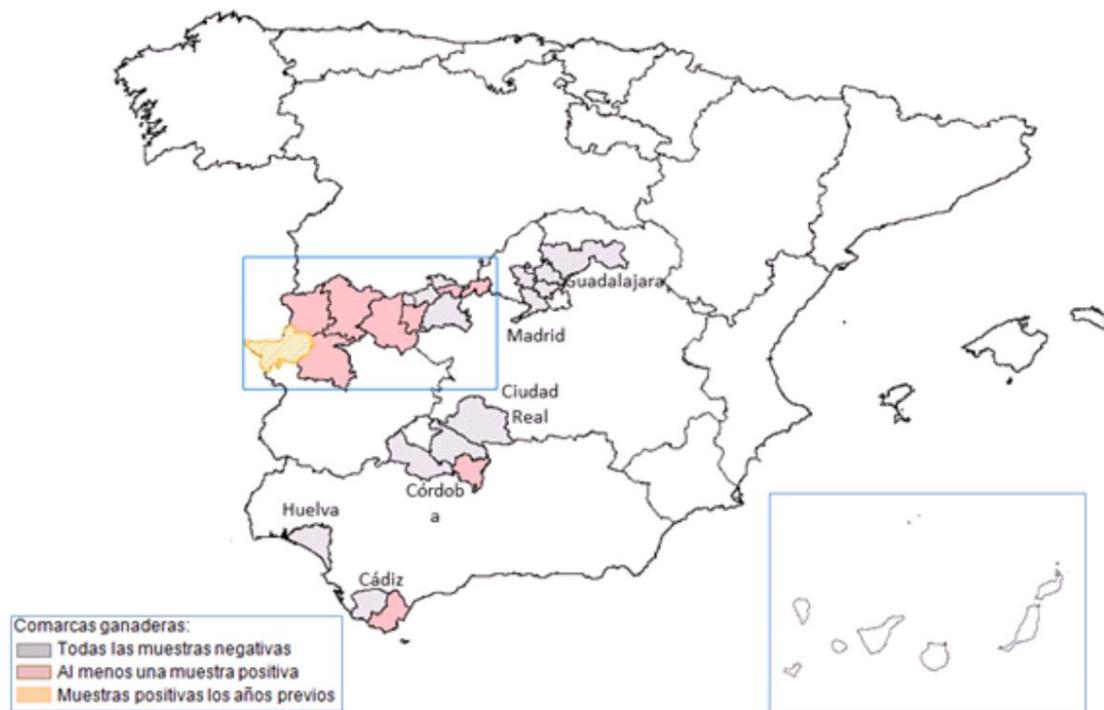
Second stage. Study on ticks captured in vegetation.

In the months of May to October 2017, the study was extended with the capture of ticks present in the vegetation. The collection of ticks in this study was entrusted to the National Institute of Agricultural and Food Research and Technology (INIA) and regions belonging to the following provinces were sampled: Cádiz, Córdoba, Huelva, Jaén, Ávila, Zamora, Ciudad Real, Cuenca, Guadalajara, Toledo and Madrid. 3,217 ticks were collected, mostly (80%) of the *H. lusitanicum* species. The scarce presence of *H. marginatum* can be explained by its low attraction for the capture techniques used and by its lower location on the vegetation. No ticks were obtained in Ávila and Zamora.

After identification of genus and species, the ticks were grouped into batches to be analyzed. 452 batches, a total of 1,356 ticks, were sent to the CNM for processing and molecular identification of CCHFV.

All lots were negative for CCHFV, except 5 of the 37 lots tested in one surveillance zone of Cádiz, and 2 of the 22 lots in a surveillance zone of Córdoba.

Figure 7. Combined results of the studies of the virus of the hemorrhagic fever of Crimea-Congo in ticks collected on animals and vegetation.



Source: self made. Coordination Center for Health Alerts and Emergencies.

Third phase. Serological study in animals

In the first months of 2018, coordinated by the Ministry of Agriculture, Fisheries and Food and carried out in collaboration with the autonomous communities, a serological study was carried out on domestic and wild animals from the five communities in which ticks had been found in the previous phases (Andalusia, Castilla-La Mancha, Castilla y León, Extremadura and Madrid).

In order to establish the risk of exposure to the virus, the counties were divided into 3 zones: zone 1 in the case of the presence of virus in ticks from wild or domestic animals (1A), or vegetation (1B); zone 2 if the vector was established but no virus had been detected in the previous phases; and zone 3 if there was a low probability of the presence of ticks of the *Hyalomma* genus.

Among the wild animals, samples of wild ruminants and wild boars were studied, and in their absence, hares and rabbits. As for domestic animals, samples were collected from extensive livestock (cattle, sheep and goats) older than 6 months, who had lived throughout their lives in a study area or with a similar risk of exposure.

The samples were analyzed at the Central Veterinary Laboratory of Algete using the ELISA ID Screen Double Ag multispecies technique. He did not perform a specific confirmation technique because it is not yet available.

In zone 1, 314 samples of wild animals and 467 of domestic animals were analyzed, in zone 2, 206 samples of wild animals and 309 of domestic animals were analyzed, and in zone 3 a total of 119 samples of wild animals and 326 of wild animals. domestic animals.

In zone 1, 16% of the samples from domestic animals were positive for CCHFV, and 70% of those from wild animals. In zone 2, despite the fact that no virus was found in ticks, 79% of samples from wild animals were positive. Among samples from domestic animals this percentage was 4%. In zone 3, with a low probability of the presence of ticks of the *Hyalomma genus*, 2% of positive samples were found in wild animals and 7% in samples from domestic animals. In this area, the vast majority of these positive samples were obtained from a single farm in which more specific studies are being carried out and confirming

this results.

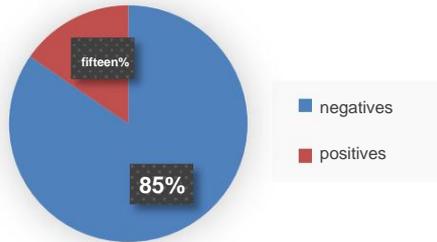
Figure 8 shows the results of these studies in the different areas.

Figure 8. Seroprevalence results of Crimean-Congo hemorrhagic fever virus infection in domestic and wild animals.

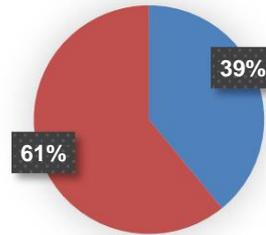
Zone 1. Objective: detect presence

Zone 1A.

**Domestic
% positive**

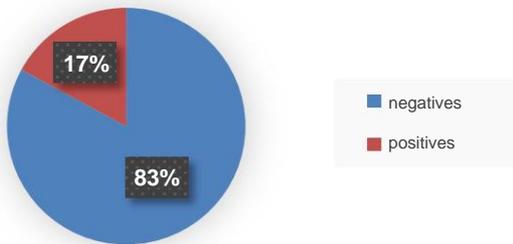


**wild
% positive**

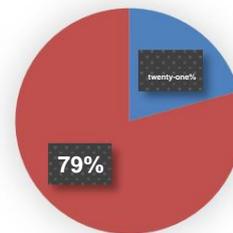


Zone 1B.

**Domestic
% positive**

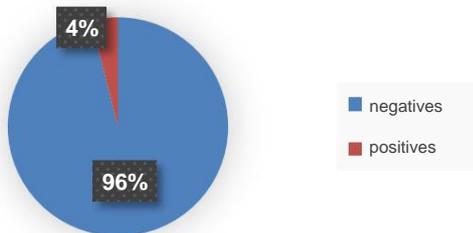


**Wild %
positive**

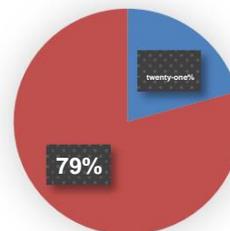


Zone 2. Objective: to demonstrate absence.

**Domestic
% positive**



**Wild %
positive**



Zone 3. Objective to demonstrate absence.



Prepared by: Ministry of Agriculture, Fisheries and Food.

Additionally, samples collected in 2016 from regions of the province of Ávila (Arena de San Pedro, Candeleda, Navaluenga and Sotillo de la Adrada) were available, where there was evidence of virus in a tick. 79 samples of domestic animals and 67 samples of wildlife (deer, mountain goats and wild boar) were analyzed. Of these, 33% were positive among domestic animals, and 58% among wild animals.

3. RISK ASSESSMENT FOR SPAIN

In Spain, the conditions for the appearance of autochthonous cases of CCHFV disease are present, since the elements necessary for the establishment of virus circulation are present: presence of the virus itself, competent vectors, hosts that can amplify the cycle, and climatic conditions and environmental conditions adequate to maintain the epidemiological cycle. There are also important transit areas for migratory birds from endemic areas of Africa that may arrive with infected vectors, as well as international movements of animals.

For CCHFV to pose a significant public health risk, a high population density of infected ticks in an area of high concentration of animal hosts and high contact with susceptible humans is required.

It is very likely that the introduction of the virus in Spain occurred through migratory movements of birds from Africa to Europe carrying infected ticks, since the west of the peninsula is part of the migratory route of these birds and the strain found both in infected ticks, as in human cases, are very similar to those that circulate in North Africa and are different from those that circulate in Eastern Europe.

This hypothesis was reinforced by the finding of *H. marginatum* ticks collected on migratory birds in Morocco that had similar genetic sequences of CCHFV to those found in 2010 in our country (5,125). The discovery in 2018 of viruses with sequences belonging to other genotypes must be analyzed in depth to determine their possible origin.

As described above, until 2016 the virus had only been detected in a specific area of the province of Cáceres, in ticks captured on farms near the border with Portugal. However, the detection of autochthonous cases and the findings of subsequent studies on ticks and animals confirm that in some areas of Spain there is a significant percentage of infected ticks and areas where the virus circulates, possibly having established a closed cycle between ticks and hosts.

These findings indicate that the extension of the CCHFV circulation in Spain is greater than expected and highlight the need to carry out larger studies, including serological studies in humans, to know the implications of this circulation on the disease. Human health.

The fact that the *H. lusitanicum* tick, the vector in which the virus has been detected so far, is not a common parasite of birds, would support the assumption that the virus circulates in different hosts in Spain and these ticks have been infected from these hosts.

On the other hand, the fact that the majority of CCHFV has been detected in ticks of the *H. lusitanicum* species can be explained by the fact that in the areas where the sampling has been carried out there is a greater abundance of this species, or by the months in which it is observed. They made the samplings (autumn/winter) in which this tick is more abundant than the *H. marginatum* species. Another hypothesis is that *H. lusitanicum* is spreading rapidly

through the movements of the wild boars it parasitizes, and that it is displacing *H. marginatum*.

The probability of infection for people is fundamentally determined by the intensity of exposure to ticks, since the period of viremia in infected animals is very short, and the mechanism of transmission from infected animals is much less important. The main risk group would therefore be workers exposed to tick bites, such as ranchers, forestry agents or farmers, and those who carry out slaughter, skinning of animals and wool carders. Likewise, hunters and people who carry out recreational activities outdoors in rural areas without proper protection would have a greater risk of bites. Although it is necessary to carry out new studies, with the available data it cannot be ruled out that, especially in these risk groups, more cases caused by this virus appear sporadically.

Person-to-person transmission by direct contact through skin or mucosal exposure to blood, body fluids, and tissues of symptomatic patients is possible, especially in later stages of the disease where viral load is higher. Hemorrhages can be an important source of exposure in relatives of the patient and health personnel. However, in the health field, with the use of standard infection prevention measures and the timely application of adequate containment measures (isolation of the patient, use of adequate personal protective equipment), the risk of transmission is controlled.

In terms of morbidity and mortality, the impact of CCHFV infection is determined, among other factors, by the clinical presentation of the infection. Although there seems to be a significant percentage of asymptomatic and subclinical cases, symptomatic cases have a high fatality rate, and can cause person-to-person transmission through close contact. A detailed study of the isolated virus would allow the evaluation of specific factors of pathogenicity. The Spanish population is susceptible to infection, but given the appearance of cases, our country has adequate means for its correct isolation and management.

For all that has been said, the risk of more sporadic cases of CCHF occurring in Spain is moderate in areas where ticks of the *Hyalomma* genus are present and especially in the population with greater exposure to their bites that resides or frequents said areas. The impact of the disease is considered low since, although it may be a serious disease, the number of people affected would not be high and adequate means of isolation and control of cases are available.

4. CONCLUSIONS

- Crimean-Congo hemorrhagic fever is an endemic disease in many countries in Europe, Africa, Asia, and the Middle East. The detection of a human case by nosocomial transmission highlights the importance of early detection and the need to always apply the measures. In Spain, ticks of the genus *Hyalomma*, which include the main species suitable for the prevention and control of infection in the health field and in those involved in the transmission of the CCHF virus, they are widely distributed in the particular territory in the event of any suspected case of hemorrhagic fever, national and the ecological and climatic conditions are favorable for its proliferation and for contact with its hosts.
- The probability of infection for people is determined by the intensity of exposure to infected ticks and to a much lesser extent to blood or tissues of infected animals. There is also a risk of person-to-person transmission by direct contact through exposure of non-intact skin or mucous membranes to blood, body fluids, and tissues of affected patients or by aerosols.
- In Spain, the virus was identified for the first time in 2010 in ticks of the *H. lusitanicum* species collected from a farm in Extremadura. In September 2016, the first autochthonous case of CCHF was diagnosed in Spain, which produced a secondary case, and two other autochthonous cases have subsequently been confirmed.
- The detection of a human case by nosocomial transmission highlights the importance of early detection and the need to always apply the appropriate infection prevention and control measures in the health field, and in particular in the event of any suspected case of hemorrhagic fever.
- Following the detection of the first human cases, several studies have been launched to assess the risk of infection in Spain both in ticks and in domestic and wild animals. The results of the studies carried out indicate that the Crimean-Congo haemorrhagic fever virus is circulating in a large area of Spain and therefore the sporadic appearance of new autochthonous human cases cannot be ruled out.
- The risk of more sporadic cases of transmission of the Crimean-Congo hemorrhagic fever virus in Spain is moderate in areas where ticks of the genus *Hyalomma* are present and especially in the population with greater exposure to their bites that resides or frequent these areas. The impact of the disease is considered low.

5. RECOMMENDATIONS

- ÿ Address the surveillance and control of the Crimean-Congo hemorrhagic fever virus in Spain in a comprehensive and multidisciplinary manner, including entomological surveillance of potentially vector tick species and reinforcing coordination at the local, regional and national levels between the sectors human, animal and environmental health.
- ÿ Strengthen tick bite prevention campaigns in risk areas and disseminate information on measures to prevent transmission of the disease aimed at risk groups, health workers and the general population, with special emphasis on areas where it has been detected. the presence or circulation of the virus and in the population groups that frequent them. People who work in contact with animals (domestic or wild) should observe the usual individual protection measures to minimize contact with the animal's blood and tissues as well as possible ticks.
- ÿ Inform health professionals about this disease so that an early diagnosis and timely management can be carried out if more cases of this infection occur. Carry out active surveillance of the disease in humans in those areas where the virus is identified and in the people who frequent them in order to detect possible cases early and limit their spread.
- ÿ Carry out studies in humans to help determine the extent, risk and impact of the circulation of the virus in different areas of Spain. Conducting seroprevalence studies in humans will help determine the level of exposure of the population to the virus and obtain data on asymptomatic infection.
- ÿ Evaluate the extension of the study areas to other autonomous communities.
- ÿ Investigate the viruses detected in Spain to know their characteristics and behaviour.

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