



RAPID RISK ASSESSMENT

Crimean–Congo haemorrhagic fever in Spain

8 September 2016

Main conclusions and options for response

On 31 August 2016 the autonomous Community of Madrid, Spain, reported two cases of infection with Crimean–Congo haemorrhagic fever (CCHF) virus. The primary case is a 62-year-old man with potential exposure to CCHF virus in the countryside in the province of Avila (Spain). The secondary case is a 50-year-old healthcare worker who attended the primary case during his ICU admission. These are the first autochthonous clinical cases of CCHF in Spain and in south-western Europe.

Recent detection of CCHF virus in ticks from the autonomous Community of Extremadura in western Spain, indicates the circulation of CCHF virus among wildlife. Therefore, the occurrence of CCHF virus infection is not an unexpected event in Spain. Nosocomial transmission of CCHF can occur even in a non-endemic region when appropriate infection prevention and control (IPC) measures have not been observed.

The probability of CCHF virus infection in Spain is low. However, other sporadic cases are possible. The risk of further human-to-human transmission in hospital settings can be significantly reduced by applying timely appropriate IPC measures.

The options for risk reduction are suggested as follows:

- Enhanced awareness of the importance of early diagnosis and laboratory confirmation among healthcare providers in areas with potential circulation of CCHF virus. Timely and appropriate case management is crucial for the reduction of case fatality.
- Standard precautions, preferably combined with contact and droplet precautionary measures, should be taken when caring for patients presenting with haemorrhagic fever syndrome, including when there is suspicion of CCHF.
- Laboratory tests on patient samples present a high risk of transmission and should only be conducted under appropriate biological containment conditions.
- As a precautionary measure, risk groups should be informed about the mode of transmission and urged to comply with advice on the prevention of tick bites. Risk groups in potentially affected areas are primarily:
 - people working in close proximity to animals, especially livestock (e.g. agricultural workers in animal husbandry or slaughterhouse workers, veterinarians);
 - people exposed to tick-to-human transmission through their outdoor activities (e.g. hunters, forest workers, hikers); and
 - healthcare providers at risk of human-to-human transmission.
- In order to better target preventive measures and raise clinical awareness, areas with CCHF virus circulation and areas suitable for CCHF circulation in the Iberian Peninsula should be defined by multidisciplinary investigations; in particular performing CCHF risk mapping, ecological and environmental studies, sero-surveys in host species and entomological investigations.

- Ribavirin for post-exposure prophylaxis should be considered after high-risk exposure, despite the low quality of evidence for its effectiveness.
- Genome sequencing of the CCHF viruses detected in Spain will provide additional information on the genetic diversity of viruses circulating in the Iberian Peninsula.
- Since sporadic cases of the disease in affected areas in Spain are possible, transfusion and transplant professionals should be aware of possible CCHF exposure in affected areas. However, no specific measures for the safety of substances of human origin (SoHO) are recommended at this stage.
- Further studies on the ecology of CCHF in the Iberian Peninsula are needed to delineate the areas at risk for tick-borne transmission.

Source and date of request

ECDC internal decision, 2 September 2016.

Public health issue

This document assesses the risk associated with the occurrence of two cases of Crimean–Congo haemorrhagic fever in Spain.

Consulted experts

ECDC internal response team in alphabetical order: Kaja Kaasik Aaslav, Denis Coulombier, Dragoslav Domanovic, Josep Jansa, Marc Struelens, Bertrand Sudre, Wim Van Bortel, Hervé Zeller.

Experts from the following institutions contributed to this risk assessment: Fernando Simon, M^a José Sierra, Berta Suárez, Laura Reques, Rocío Palmera, Lucía García San Miguel, Laura Montero of the Spanish Coordinating Centre for Health Alerts and Emergencies at the Ministry of Health Social Services and Equality; Agustín Estrada-Peña, University of Zaragoza, Zaragoza; and the WHO Regional Office for Europe and WHO Headquarters.

ECDC acknowledges the valuable contributions of all experts. All experts have submitted declarations of interest and a review of these declarations did not reveal any conflicts of interest. Although experts from the World Health Organization (WHO) reviewed the risk assessment, the views expressed in this document do not necessarily represent the views of WHO.

Disease background information

CCHF virus

Crimean–Congo haemorrhagic fever (CCHF) is a tick-borne viral disease caused by a virus belonging to the genus *Nairovirus* of the Bunyaviridae family [1]. The virus circulates in a silent enzootic tick-vertebrate-tick cycle. There is no evidence that the virus causes disease in animals. Ticks from the *Hyalomma* genus are considered the principal vectors of CCHF virus. *Hyalomma marginatum* is the main vector for CCHF virus in the Balkans. The virus has been identified in *Hyalomma lusitanicum* in western Spain close to the border with Portugal [2]. Seven genotypes have been recognised by genetic analysis: three in Africa, two in Europe, and two in Asia [1]. CCHF virus is a BSL4 pathogen and should be handled in containment level 4 but diagnostics can be conducted in lower BSL levels after inactivation of the biological samples [3].

Clinical presentation

The incubation period ranges from one to 13 days and varies according to the type of transmission and viral load [1,4,5]. The incubation period is usually one to three days for transmission by tick bite, but may range between three and seven days after exposure to blood or bodily fluids. The incubation period can be shorter with exposure to blood or bodily fluids from a patient with high viral loads at later stages of disease [6].

Symptoms of CCHF include high fever, muscle pain, dizziness, photophobia, abdominal pain, diarrhoea, vomiting and, in severe cases, haemorrhage [7]. CCHF may cause severe disease in humans, with a case-fatality ratio ranging from 5% to 30% [8,9].

CCHF epidemiology

Small mammals, such as hare and hedgehogs, and birds are hosts for the immature stages of the ticks and serve as amplifying hosts. Domestic animals, such as cattle, goats and sheep, and wild game are the usual hosts for the adult ticks.

The main mode of transmission is a bite from an infected Ixodid tick, mostly of the *Hyalomma* genus. The tick bite can be unnoticed and exposure to the virus can occur upon crushing the tick. The virus can also be transmitted by direct contact with blood or tissues from viraemic livestock or patients at risk of nosocomial infections [10,11].

People working in close proximity to animals, especially livestock (e.g. agricultural workers in animal husbandry or slaughterhouse workers, veterinarians) and people exposed to tick-to-human transmission through their outdoor activities (e.g. hunters, forest workers, hikers) can be at higher risk of exposure. Healthcare providers caring for patients infected with CCHF virus are at risk of human-to-human transmission. Sexual transmission has been recently suspected [12]. Close contacts and relatives of patients with CCHF are at low risk of community-based transmission [13].

CCHF virus has a widespread distribution throughout Africa, the Balkans, the Middle East, and western and south-central Asia. In the European Union, CCHF is endemic in the Balkan region and sporadic cases are reported every year from Bulgaria (14 cases in 2008, eight cases in 2009, six cases in 2010, four cases in 2011, four cases in 2012 and eight in 2013) [14]. One isolated case was detected in Greece in 2008, close to the border of Bulgaria [15]. In 2014, 25 EU/EEA countries provided information on CCHF through the European Surveillance System (TESSy): eight cases were reported from Bulgaria and one from the United Kingdom (the latter imported from Bulgaria) [14,16]. The other EU/EEA countries reported no cases in 2014. In 2012, an imported case was diagnosed in Scotland, UK. This fatal case had travelled by air from Kabul, Afghanistan, via Dubai to London [17].

In the WHO European Region, Turkey remains the most affected country. CCHF has been an emerging zoonosis in the country since 2002. Overall, 9 787 cases have been reported by the Ministry of Health of Turkey between 2002 and 2015 with a 4.8% case fatality ratio [8]. A multicentre retrospective cross-sectional study in nine Turkish regional CCHF reference centres covering the years 2002 to 2014 identified 25 nosocomial laboratory-confirmed infections, including four fatal cases, from 51 exposed healthcare workers [10].

Person-to-person and nosocomial transmission is occasional but not unusual for CCHF virus infection [11,18,19]. The risk is higher during the later stages of the disease because of the higher viral loads. Nosocomial transmission is usually related to direct contact with the blood and bodily fluids of infected patients or needle-stick injuries [9,20]. Airborne transmission of CCHF virus is possible during aerosol-generating medical procedures such as endotracheal intubation [21]. Standard IPC precautions during aerosol-generating medical procedures should be applied, including use of a single airborne precaution room, airway protective FFP2/N95 mask, or equivalent standard, and eye protection.

Very few nosocomial cases of CCHF have been reported in the EU. In Germany, two cases were reported among healthcare workers in 2009 [22]. The index case was a US soldier who worked in field operations in Afghanistan. The healthcare workers, who received the antiviral drug ribavirin as prophylaxis, did not present with symptoms.

There is no validated specific antiviral therapy for CCHF. Treatment relies on supportive care, including the administration of thrombocytes, fresh frozen plasma and erythrocyte preparations. Ribavirin has been used to treat CCHF infection with apparent benefit, although more studies are needed. Both oral and intravenous formulations seem to be effective. No safe nor effective vaccine is widely available for human use. The value of using human immunoglobulins from recovered patients for treatment requires further evaluation. Oral ribavirin has been used for post-exposure prophylaxis after very high risk exposures [1,8,19].

Background on ticks and CCHF in Iberian Peninsula

Hyalomma marginatum and *Hyalomma lusitanicum* ticks are both present in the south-eastern part of the Iberian Peninsula (Spain and Portugal) [23].

CCHF virus has been detected in *Hyalomma lusitanicum* ticks collected in 2010 in the province of Cáceres, Spain (two pools out of 12 were positive; in total 117 adult ticks were tested). Based on a 200-base-pair fragment of the CCHF virus genome, this virus was found more closely related to genotype III circulating in Africa than to genotype V from the Balkans [2].

Between 2010 and 2013, 681 ticks were collected in the autonomous Community of Extremadura of Spain. Twenty-four *Hyalomma lusitanicum* ticks were found positive by PCR for CCHF with a sequence homology to genotype III occurring in Africa [24]. Two sequence variants within genotype III were identified, one variant in one positive tick and the other one in the remaining 23 ticks. In 2014, from 272 collected ticks from the Extremadura region, three *Hyalomma lusitanicum* ticks collected from a deer, a fox and a bovine were found positive for CCHF.

Preliminary genetic analysis, based on a small fragment of the CCHF virus genome, showed that the sequences of CCHF virus from the two human cases (2016) are similar to the CCHF sequence variant observed in the 23 positive *Hyalomma lusitanicum* ticks from 2010–2013 [24].

In addition, CCHF virus was detected in *Hyalomma marginatum* ticks collected on migratory birds in Morocco in April 2011 [25]. Several of the inspected bird species migrate from Africa to Europe which supports the hypothesis of CCHF virus circulation between western Africa and the Iberian Peninsula. Migratory birds contribute to the dissemination of infected ticks but are not susceptible to CCHF virus infection.

In a study from 2014, 231 *Hyalomma marginatum* ticks were negative for CCHF virus by PCR. They included 188 ticks collected on cattle from Castile and Leon (4 in Avila, 168 in Burgos, 1 in Salamanca, 10 in Soria and 5 in Valladolid), 25 in La Rioja, 12 in Cáceres, 5 in Ciudad Real and 1 in Badajoz [26].

CCHF antibodies were not detected in individuals at risk or bitten by ticks in the area where CCHF virus has been previously detected in Cáceres [27]. In the 1980s, CCHF antibodies were detected in two humans in southern Portugal [28].

Event background information

On 31 August 2016, the autonomous Community of Madrid reported two cases of infection with CCHF virus.

- The primary case was a 62-year-old man. The onset of symptoms was on 16 August 2016. He was admitted to the hospital on 18 August and transferred to the intensive care unit (ICU) of the Infanta Leonor Hospital in Madrid on 19 August 2016. The case was transferred to a high-level isolation ICU at the Gregorio Marañón Hospital in Madrid on 23 August. He died on 25 August 2016. The patient was hiking in Ávila province on 14 August where he most likely got infected through contact with a tick (through a tick bite or by crushing a tick).
- The secondary case is a 50-year-old healthcare worker who took care of the patient while in the ICU between 19 and 23 August. The secondary case developed symptoms on 27 August 2016 and was hospitalised in an isolation unit. The case is presenting with severe disease but with favourable evolution according to the medical team.

None of the two cases had a recent travel history outside Spain before the onset of symptoms. Both cases were confirmed by PCR at the National Centre for Microbiology. At-risk contacts have been identified and their follow-up is ongoing. On 6 September, all risk contacts were asymptomatic.

Spanish national authorities are closely monitoring this event. They have issued communication material on prevention and control of CCHF for health professionals and the general public. They are coordinating surveillance, prevention and control activities at different levels and sectors including environmental, human and animal health sectors as well as entomological and animal surveillance in areas at risk of CCHF virus circulation.

ECDC threat assessment for the EU

This is the first detection of autochthonous human cases of CCHF in Spain.

Risk for tick-borne transmission

Autochthonous tick-borne transmission of CCHF virus in Spain is plausible and expected because:

1. CCHF virus was previously detected in *Hyalomma lusitanicum* ticks collected in the province of Cáceres in the northern part of the autonomous Community of Extremadura which borders Portugal [2];
2. the main vector of CCHF virus, *Hyalomma marginatum*, is present in the country [29];
3. the climatic conditions are suitable for the maintenance of the epidemiological cycle [30].

The probability of infection in Spain remains low. However, additional sporadic cases may occur in the future.

Risk for nosocomial transmission

A case of nosocomial CCHF infection was detected during this event in Spain, a country where CCHF human disease was previously unknown to occur. Nosocomial transmission is usually associated with the lack of, or improper use of, personal protective equipment when caring for a patient. It may occur during early contact with healthcare services, before CCHF is recognised in the source patient and appropriate protective measures implemented. This is particularly true in areas where CCHF has not been detected before. Once CCHF is known to occur in a region, nosocomial transmission tends to occur at later stages of the disease, most probably related to high viraemia when source patients present severe manifestations.

Risk for transmission via substances of human origin

Transmission of CCHF virus through tick bites or direct contact with blood and bodily fluids of infected patients suggests that virus transmission is possible through transfusion or transplantation. There is no evidence of

viraemia during the incubation period, prior to onset of symptoms [31]. The incidence of infection among donors is undocumented, and no cases of donor-derived CCHF have been reported. Therefore, the risk for transmission of CCHF through substances of human origin remains uncertain. Available data are insufficient to make evidence-based CCHF safety recommendations for deferral of donors. Pathogen inactivation of plasma and platelets and multiple pathogen reduction steps used in the fractionation process have been shown to be effective in the removal of enveloped viruses such as CCHF virus.

References

1. Bente DA, Forrester NL, Watts DM, McAuley AJ, Whitehouse CA, Bray M. Crimean-Congo hemorrhagic fever: history, epidemiology, pathogenesis, clinical syndrome and genetic diversity. *Antiviral Res.* 2013 Oct;100(1):159-89.
2. Estrada-Pena A, Palomar AM, Santibanez P, Sanchez N, Habela MA, Portillo A, et al. Crimean-Congo hemorrhagic fever virus in ticks, Southwestern Europe, 2010. *Emerg Infect Dis.* 2012 Jan;18(1):179-80.
3. Fernandez-Garcia MD, Negredo A, Papa A, Donoso-Mantke O, Niedrig M, Zeller H, et al. European survey on laboratory preparedness, response and diagnostic capacity for Crimean-Congo haemorrhagic fever, 2012. *Euro Surveill.* 2014;19(26).
4. Vorou R, Pierroutsakos IN, Maltezos HC. Crimean-Congo hemorrhagic fever. *Curr Opin Infect Dis.* 2007 Oct;20(5):495-500.
5. Nabeth P, Thior M, Faye O, Simon F. Human Crimean-Congo hemorrhagic fever, Senegal. *Emerg Infect Dis.* 2004 Oct;10(10):1881-2.
6. Naderi HR, Sheybani F, Bojdi A, Khosravi N, Mostafavi I. Fatal nosocomial spread of Crimean-Congo hemorrhagic fever with very short incubation period. *Am J Trop Med Hyg.* 2013 Mar;88(3):469-71.
7. European Centre for Disease Prevention and Control. Factsheet for health professionals: Crimean-Congo haemorrhagic fever (CCHF) 2016 [updated 2016 Mar 08]. Available from: http://ecdc.europa.eu/en/healthtopics/emerging_and_vector-borne_diseases/tick_borne_diseases/crimean_congo/factsheet-health-professionals/Pages/factsheet.aspx.
8. Leblebicioglu H, Ozaras R, Irmak H, Sencan I. Crimean-Congo hemorrhagic fever in Turkey: Current status and future challenges. *Antiviral Res.* 2016 Feb;126:21-34.
9. World Health Organization. Crimean-Congo haemorrhagic fever. Fact sheet. Geneva: World Health Organization; 2013. Available from: <http://www.who.int/mediacentre/factsheets/fs208/en/>.
10. Leblebicioglu H, Sunbul M, Guner R, Bodur H, Bulut C, Duygu F, et al. Healthcare-associated Crimean-Congo haemorrhagic fever in Turkey, 2002-2014: a multicentre retrospective cross-sectional study. *Clin Microbiol Infect.* 2016 Apr;22(4):387 e1-4.
11. Ftika L, Maltezos HC. Viral haemorrhagic fevers in healthcare settings. *J Hosp Infect.* 2013 Mar;83(3):185-92.
12. Pshenichnaya NY, Sydenko IS, Klinovaya EP, Romanova EB, Zhuravlev AS. Possible sexual transmission of Crimean-Congo hemorrhagic fever. *Int J Infect Dis.* 2016 Apr;45:109-11.
13. Izadi S, Salehi M, Holakouie-Naieni K, Chinikar S. The risk of transmission of Crimean-Congo hemorrhagic fever virus from human cases to first-degree relatives. *Jpn J Infect Dis.* 2008 Nov;61(6):494-6.
14. European Centre for Disease Prevention and Control. Annual Epidemiological Report – Emerging and vector-borne diseases – 2014 [Internet]. Stockholm: ECDC; 2014 [updated 2015 Nov 19]. Available from: http://ecdc.europa.eu/en/publications/Publications/emerging-vector-borne-diseases_annual-epidemiological-report-2014.pdf.
15. Papa A, Maltezos HC, Tsiodras S, Dalla VG, Papadimitriou T, Pierroutsakos I, et al. A case of Crimean-Congo haemorrhagic fever in Greece, June 2008. *Euro Surveill.* 2008 Aug 14;13(33).
16. Lumley S, Atkinson B, Dowall S, Pitman J, Staplehurst S, Busuttill J, et al. Non-fatal case of Crimean-Congo haemorrhagic fever imported into the United Kingdom (ex Bulgaria), June 2014. *Euro Surveill.* 2014;19(30).
17. Atkinson B, Latham J, Chamberlain J, Logue C, O'Donoghue L, Osborne J, et al. Sequencing and phylogenetic characterisation of a fatal Crimean-Congo haemorrhagic fever case imported into the United Kingdom, October 2012. *Euro Surveill.* 2012;17(48).
18. Parlak E, Koşan Z, Ertürk A, Parlak M, Özkut Z. A nosocomial outbreak of Crimean-Congo hemorrhagic fever. *Journal of Microbiology and Infectious Diseases.* 2015;5(1):5-9.
19. Celikbas AK, Dokuzoguz B, Baykam N, Gok SE, Eroglu MN, Midilli K, et al. Crimean-Congo hemorrhagic fever among health care workers, Turkey. *Emerg Infect Dis.* 2014 Mar;20(3):477-9.
20. Gozel MG, Dokmetas I, Oztop AY, Engin A, Elaldi N, Bakir M. Recommended precaution procedures protect healthcare workers from Crimean-Congo hemorrhagic fever virus. *Int J Infect Dis.* 2013 Nov;17(11):e1046-50.
21. Pshenichnaya NY, Nenadskaya SA. Probable Crimean-Congo hemorrhagic fever virus transmission occurred after aerosol-generating medical procedures in Russia: nosocomial cluster. *Int J Infect Dis.* 2015 Apr;33:120-2.

22. Conger NG, Paolino KM, Osborn EC, Rusnak JM, Gunther S, Pool J, et al. Health care response to CCHF in US soldier and nosocomial transmission to health care providers, Germany, 2009. *Emerg Infect Dis.* 2015 Jan;21(1):23-31.
23. Williams HW, Cross DE, Crump HL, Drost CJ, Thomas CJ. Climate suitability for European ticks: assessing species distribution models against null models and projection under AR5 climate. *Parasit Vectors.* 2015;8:440.
24. Ministerio de Sanidad, Servicios Sociales e Igualdad. Informe de situación y evaluación del riesgo de transmisión de Fiebre Hemorrágica de Crimea-Congo (FHCC) en España, septiembre 2016. [Internet]. Madrid2016 [cited 2016 Sep 9]. Available from: http://www.msssi.gob.es/profesionales/saludPublica/ccayes/alertasActual/Crimea_Congo/docs/Informe_situacion_evaluacion_CrimeaCongo_sep2016.pdf.
25. Palomar AM, Portillo A, Santibanez P, Mazuelas D, Arizaga J, Crespo A, et al. Crimean-Congo hemorrhagic fever virus in ticks from migratory birds, Morocco. *Emerg Infect Dis.* 2013 Feb;19(2):260-3.
26. Junta de Castilla y León, Progrmaa de prevención y control de enfermedades transmitidas por garrapatas. Garrapatas fijadas en las personas, patógenos y nivel de alimentación. en castilla y león en 2014. : Junta de Castilla y León.; 2014. Available from: <http://www.saludcastillayleon.es/ciudadanos/en/sanidadambiental/enfermedades-transmitidas-garrapatas.files/574057-Resultados%20garrapatas%202014%20final.pdf>.
27. Santibáñez S, Muñoz-Sanz A, Palomar AM, Portillo A, García-Álvarez L, Márquez FJ, et al. Estudio serológico del virus de la fiebre hemorrágica de Crimea-Congo en Cáceres. *Enfermedades Infecc Microbiol Clínica.* 2014;Especial congreso:33(Especial congreso 1):416.
28. Filipe AR, Calisher CH, Lazuick J. Antibodies to Congo-Crimean haemorrhagic fever, Dhori, Thogoto and Bhanja viruses in southern Portugal. *Acta Virol.* 1985 Jul;29(4):324-8.
29. European Centre for Disease Prevention and Control. Tick maps [Internet]. 2016 [cited 2016 Sep 5]. Available from: <http://ecdc.europa.eu/en/healthtopics/vectors/vector-maps/Pages/VBORNET-maps-tick-species.aspx>.
30. Estrada-Pena A, Ruiz-Fons F, Acevedo P, Gortazar C, de la Fuente J. Factors driving the circulation and possible expansion of Crimean-Congo haemorrhagic fever virus in the western Palearctic. *J Appl Microbiol.* 2013 Jan;114(1):278-86.
31. Tishkova FH, Belobrova EA, Valikhodzhaeva M, Atkinson B, Hewson R, Mullojonova M. Crimean-Congo hemorrhagic fever in Tajikistan. *Vector Borne Zoonotic Dis.* 2012 Sep;12(9):722-6.