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A REVIEW ON CRIMEAN-CONGO HEMORRHAGIC FEVER WITH SPECIAL FOCUS ON IRAQI OUTBREAKS

Al Salihi K A [1*], Mahmoud Z Z [2], Younise M H [3], Tanveer Hussain [4]

[1] Department of Internal and preventive veterinary medicine/ College of Veterinary Medicine/ Al Muthanna University / Iraq. E-mail: kama-akool18@mu.edu.iq
https://orcid.org/0000-0002-5698-2678
[2] General surgery / Al-Hussain teaching hospital
[3] CAB F.M polyclinic of public health. Al- Hussain teaching hospital
[4] Head, Department of Molecular Biology & Biotechnology, Virtual University of Pakistan, Islamabad. E-mail: tanveer.hussain@vu.edu.pk
https://orcid.org/0000-0002-0300-0503

OPEN ACCESS
Corresponding Author :
Email. kama-akool18@mu.edu.iq
https://orcid.org/0000-0002-5698-2678

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*Corresponding author:
karima Akool Al Salihi: Email address:
kama-akool8@mu.edu.iq

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ABSTRACT

Crimean-Congo hemorrhagic fever (CCHF) is a serious viral disease caused by the CCHF Virus. It is primarily transmitted through tick bites or contact with secretions of infected animals or humans. CCHF has a wide geographic distribution, with cases reported in various parts of Africa, Asia, Europe, and the Middle East. CCHF is characterized by a range of clinical signs and symptoms, including high fever, headache, muscle and joint pain, gastrointestinal symptoms, and in severe cases, hemorrhagic manifestations. Diagnosis of CCHF involves a combination of clinical evaluation, laboratory testing (serological and molecular), and epidemiological information. Early detection and prompt medical attention are crucial for appropriate management and improving patient outcomes. CCHF has been reported in several regions of Iraq since 1979, and outbreaks were reported between 1989, 2009, 2010, 2018, 2021, and recently 2022 and 2023 outbreaks with exceptional recorded cases. Infection control measures, public health education, and surveillance are critical components of CCHF control efforts, targeting animals and humans. Given a high mortality rate associated with severe cases and the potential for CCHF outbreaks, continued research, international collaboration, and the development of effective vaccines and antiviral treatments are needed to alleviate the impact of CCHF on public health. Overall, CCHF is a significant public health concern that requires a comprehensive One Health approach to control and prevent its spread, safeguarding both human and animal populations. This review article intends to discuss the CCHF in light of the recent multiple reemergence of the disease in Iraq.

Keywords: CCHF, Iraq, tick bites, hemorrhagic manifestations, RT-PCR.

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Introduction

Crimean-Congo hemorrhagic fever (CCHF) is a severe deadly zoonotic, tick-borne viral disease. It is caused by the Crimean-Congo hemorrhagic fever virus (CCHFV). CCHFV belongs to the *Nairovirus* genus within the family Bunyaviridae (Belobo *et al.,* 2021). Primarily, the virus is transmitted to humans through tick bites, specifically ticks of the genus *Hyalomma*, which act as reservoirs and vectors. Direct contact with infected animals or humans' blood or other bodily fluids is also vital for spreading the virus (Kuehnert *et al.,* 2021; Hawman & Feldmann, 2018; Emmerich *et al.,* 2018; AlSalihi *et al.,* 2018). CCHF outbreaks have occurred sporadically in different parts of the world (Mirembe *et al.,* 2021; WHO, 1917; WHO, 2018; Al-Abri *et al.,* 2017; Appannanavar *et al.,* 2011; Messina *et al.,* 2015). CCHF disease poses a significant public health

concern due to its potential for nosocomial transmission, high case fatality rates (up to 40%), and its ability to cause outbreaks. The World Health Organization (WHO) classifies CCHF as a priority pathogen and recommends surveillance, prompt diagnosis, and implementation of preventive measures to control the disease (Ahmed *et al.,* 2021). CCHF cases often exhibit seasonal patterns, with increased incidence occurring during certain times of the year. In many endemic areas, CCHF cases are more commonly reported during the spring and summer months when tick activity is higher. However, cases can occur throughout the year, depending on the region and climate (Sahak *et al.,* 2019). The incubation period of CCHFV ranges from 1 to 13 days. Symptoms of the disease include fever, headache, dizziness, muscle aches, nausea, vomiting, and severe bleeding tendencies. In severe cases, CCHF can lead to hemorrhagic manifestations, multi-organ failure, and a high fatality rate (WHO, 2022). Laboratory diagnosis of CCHF involves detecting the presence of the virus or antibodies in the patient's blood. Enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) are commonly used diagnostic methods (Raabe *et al.,* 2020). Supportive care and early treatment are crucial in managing CCHF cases. Ribavirin, an antiviral drug, has shown some effectiveness in treating CCHF (de la Calle-Prieto *et al.,* 2018). Preventing CCHF involves implementing measures to reduce human exposure to infected ticks, such as wearing protective clothing, using insect repellents, and implementing tick control measures. Additionally, promoting awareness about the disease, proper handling and processing of animal products, and implementing infection control measures in healthcare settings are essential for prevention and control efforts (Aslam *et al.,* 2016). A literature review revealed scarce publications on CCHF disease and its previous and recent outbreaks worldwide, especially in Iraq. Consequently, this review article intends to emphasize various aspects of CCHF disease, focusing on the recent multiple reemergence of the disease in Iraq.

Methods

A search was done for relevant published papers associated with CCHF/ CCHFV in humans, animals, ticks, and countries based on preferred reporting articles for review protocol in 5 MEDLINE platforms, these are PubMed, ProQuest, EBSCOhost, Web of Science, and Ovid (Page *et al.,* 2021). The Crimean-Congo hemorrhagic fever, CCHF, CCHFV, humans, animals, ticks, tick vectors, RT-PCR, ELISA, and Iraq were used as search words. The search was continuous till 2023. All data and published articles regarding CCHF / CCHFV investigation, prevalence, reemergence, geographical distribution, tick factors, human cases outbreaks, clinical signs, fatality rate, and treatment and control were retrieved, reviewed, and verified based on inclusion criteria to avoid the errors and duplication to improve the quality of the extracted data. Relevant studies specific to all aspects of CCHF disease were recognized and used in writing this review article.

The Causative Organism

The cause of Crimean-Congo hemorrhagic fever (CCHF) is the Crimean-Congo hemorrhagic fever virus (CCHFV). It is overlooked as a hazard-group 4 pathogen, from which the term and majority of strain records originated. Furthermore, the genus comprises hazard-group 2 viruses classified as members by antigenic cross-reactivity. CCHFV belongs to the genus *Nairovirus* genus, the family Bunyaviridae, comprises more than 350 identified species classified into five

genera: *Nairovirus*, *Phlebovirus*, *Orthobunyavirus*, *Tospovirus,* and *Hantavirus* (Bente *et al.,* 2013; Bergeron *et al.,* 2010). All these genera are recognized to involve human pathogens except *Tospovirus*, which infects plants (Olaya *et al.,* 2019). Nairoviruses are tick-borne- viruses (Elliott *et al.,* 2000; Appannanavar *et al.,* 2011), which differentiated from other Bunyaviridae by their large genome L segments (Bente *et al.,* 2013; Marriott *et al.,* 1996). Under a transmission electron microscope, CCHFV reveals a sphere-shaped around 100 nm in diameter with a dense core (capsid) enclosed by protruding spikes and a lipid envelope (Whitehouse, 2004). CCHFV is an RNA-enveloped virus with a ~ 80-100 nm diameter and a tripartite RNA genome (John Chamberlain *et al.,* 2005; Marriott *et al.,* 1996). The lipid of the virus envelope is specked with spikes containing the glycoproteins (Gn and Gc) responsible for binding the virus to cellular receptors. The genome contains single-stranded RNA alongside negative polarity. It encloses three segments, small (s), medium (M), and large (L) segments, which are encapsidated by the nucleoprotein (NP), and the RNA-dependent RNA polymerase (RdRp), which is needed for transcription and genome replication in the host cell (Bente *et al.,* 2013; Schmaljohn & Hooper, 2001; Marriott *et al.,* 1996) (Figure. 1).

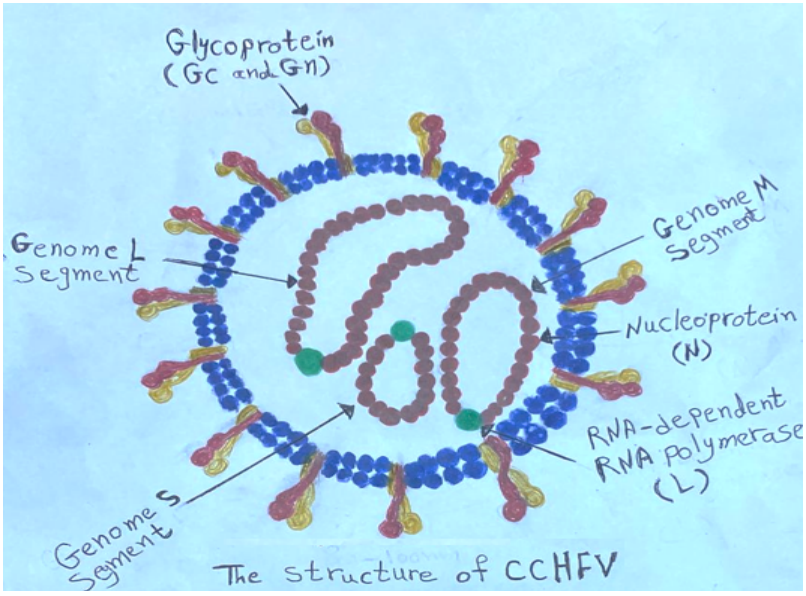

Figure. 1: Shows the structure of CCHFV (Bente *et al.,* 2013). (Hand drawn by the corresponding author)

The complete and partial analysis of the CCHFV S segment showed the seven genetic lineages of CCHFV related to the geographical area of virus detection (Shah Hosseini *et al.,* 2021; John Chamberlain *et al.,* 2005), including Asia 1, 2, Africa1, 2, 3 and Europe 1, 2 (Hewson, 2007; Deyde *et al.,* 2006; Volynkina *et al.,* 2022) (Table.1). Re-assortment and recombination of segments that occur with concurrent infections of vectors with viral strains of different lineages may lead to the emergence of new genetic variants of CCHFV (Zhou *et al.,* 2013; Lukashev, 2005; Hewson *et al.,* 2004). Vero, CER, SW13, and BHK21 are used to replicate CCHFV but do not produce high titers (Dai *et al.,* 2021) and poorly cytopathic effect in cell culture. CCHFV has been isolated since earlier, and the virus titers determined the intracerebral inoculation of suckling mice (Hoogstraal, 1979).

Table. 1 : Shows the phylogenetic classification of the virus based on S segments of the CCHF virus according to Shah Hosseini *et al.,* (2021)

No	Viral clades	Region
1	clade I (Africa 2)	KC344857/Hazara MF511221/South Africa HQ849545/DRC MH178082/Uganda DQ076413/Uganda KX013485/Uganda U88416/Uganda DQ144418/DRC DQ211650/Republic of Congo
2	clade II (Africa 1	JF706233/Egypt DQ211640/Senegal U88411/Senegal
3	clade III (Europe 2)	KT588640/Iran KY979164/Turkey LT673890/Greece MG516211/Greece DQ211638/Greece U04958/Greece KT599098/Algeria
4	clade IV (Africa 3)	U88410/Nigeria U15092/Central African Republic U15093/Burkina Faso KJ682820/Namibia KJ682821/South Africa KF793333/Mali DQ211641/Mauritania MF287636/Spain GQ862371/Sudan KR814836/Russia KX238958/Nigeria KJ682815/South Africa U88415/South Africa KY484040/South Africa DQ076415/Uganda DQ076416/South Africa
5	clade V (Europe 1)	DQ133507/Kosovo KM201260/Bulgaria KR011837/Bulgaria MF511207/Turkey KC846094/Albania KT931950/Iran KT588642/Iran KX013476/Russia KX056055/Russia DQ211644/Russia KR814852/Russia
6	clade VI (Asia 1)	FJ435407/Namibia KY362516/Oman MF289419/United Arab Emirates KX129738/Kazakhstan U15024/Madagascar AJ538196/Iraq KT931955/Iran U88414/Pakistan AF527810/Pakistan KJ196326/Iran AJ538198/Pakistan HM452305/Afghanistan MH037279/Oman DQ446212/Iran KC867274/Iran KY213714/India
7	clade VII (Asia 2)	FJ562093/China KY354080/China KJ676542/Iran AY299083/Mauretania KU242341/Iran KX013458/Turkmenistan KX013446/Tajikistan JF922674/India AY297692/Tajikistan AF481799/Uzbekistan KX013455/Kazakhstan AJ010648/China U88413/China DQ211642/China AY029157/China AF362080/China M86625/China

Route of virus transmission to humans

The virus is mainly transferred to people via tick bites, precisely ticks of the genus *Hyalomma*, which act as reservoirs and vectors (Hoogstraal, 1979). The ticks become infected with CCHFV through their blood meal on an infected animal. Later on, the virus replicates in the tick's midgut and circulates to the hemocoel, then spreads to the salivary glands and reproductive organs to be transferred to the next host through saliva. Consequently, CCHFV does not need to attach to the tick's midgut receptor because the blood meal is digested by the acidic intracellular parts of the gut epithelium (Sojka *et al.,* 2013; Dickson & Turell, 1992). The virus goes across numerous barriers within ticks during its replication and transmission. The vector of CCHFV gets a persistent infection due to the trans-ovarian and trans-dial transmission, which means the next generation to the next life stage, respectively (Gargili *et al.,* 2017). Therefore, ticks

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vectors were considered transmitters and survivors of the virus and responsible for the re-emergence of the disease in endemic geographical areas. Ticks can example, persist for long periods without feeding; accordingly, tick vectors serve as reservoirs of CCHFV infection even in the lack of vertebrate hosts. Researchers detected CCHFV in *H. marginatum* up to 700 days after an infectious blood meal. Moreover, the ticks have been approved to spread the virus by biting the vertebrate even after storage at 4 C for up to 10 months (Turell, 2007).

The mode of transmission of CCHFV to public

CCHF is considered an enzootic disease that is continuously existing symptomatic in animal populations within a specified area (Spengler *et al.,* 2016). It is important to note that CCHFV is not known to spread through casual contact, respiratory droplets, or contaminated food or water. Understanding the transmission routes is crucial for implementing preventive measures and minimizing the risk of CCHFV infection. There are various modes of transmission of CCHF to the public (Spengler *et al.,* 2016) (Figure. 2), including the following:

Tick-Borne Transmission

As mentioned above, the primary transmission mode to humans is through the bite of infected ticks, primarily from the genus *Hyalomma*. Ticks become infected with CCHFV by feeding on infected animals, typically livestock such as cattle, sheep, and goats. Humans can acquire the virus when infected ticks bite them. Ticks can remain infected with the virus throughout their life cycle, allowing them to pass it to their offspring. (Sojka *et al.,* 2013; Turell, 2007; Dickson & Turell, 1992). In Iraq, the virus circulates in many ticks genera, and some indications proposed 28 species across seven genera that could transmit CCHFV; these are *Hyalomma*, *Rhipicephalus*, *Boophilus*, *Ambylomma*, *Haemaphysalis* and *Ixodes* (Al Salihi *et al.,* 2018; Akuffo *et al.,* 2016). Nevertheless, *Hyalomma marginatum* is the only hard tick and the chief source of human infection (Alhilfi *et al.,* 2023). The infection occurs probably due to immature adult ticks feeding on host blood that they need at each stage of their maturation (Olaya *et al.,* 2019) (Figure. 2).

Contact with Infected Animals

Direct contact with infected animals' blood, tissues, or other bodily fluids can lead to CCHFV transmission to humans. This can occur during activities such as slaughtering, butchering, or handling infected animals or their tissues. Occupational exposure to infected animals, particularly in healthcare settings or veterinary care, poses a significant risk (Figure. 2) (Papa *et al.,* 2017).

Nosocomial Transmission

Nosocomial transmission (transmission within healthcare settings) (Figure. 2) has been reported in cases where healthcare workers have come into contact with infected patients' blood or body fluids and can result in severe hemorrhagic fever with case fatalities of ca.30% (Swanepoel, 1994; Swanepoel *et al.,* 1987). Likewise, limited human-to-human transmission of CCHFV can occur in healthcare settings, mainly through close contact with infected individuals' blood or bodily fluids. This transmission

type is relatively rare but can occur due to improper infection control practices, accidental needlestick injuries, or contact with contaminated medical equipment. It is important to implement strict infection control measures in healthcare facilities to prevent nosocomial transmission (Aradaib *et al.,* 2010). The nosocomial outbreaks have been reported in cities such as Al- Fulah, Kordufan, Sudan in 2008, where a 60 years old butcher was admitted to a hospital. The virus transmitted to the nurses provided care to this patient because of the shortage of personal protective equipment (PPE) and the application of rigorous infection control measures (Aradaib *et al.,* 2010, 2011). Slaughterhouses/abattoirs, the livestock industry, and veterinary practice are the high-risk groups for the disease (Nasirian, 2019; Sharifi-Mood *et al.,* 2014). In Iraq in 1979, CCHFV nosocomial transmission was also reported by a physician, and one health worker, who treated a hospitalized 24 years old lady, showed a deadly CCHFV disease in Al- Yarmouk Hospital/ Baghdad. The patient showed severe clinical signs and bleeding. Both health workers developed fever, headache, and bleeding from the gastrointestinal tract four days after close contact with this lady and died (Tantawi *et al.,* 1980). Moreover, nosocomial transmission was also reported in Iraq two times later, in 1992 (2 cases) and 1996 (1 case) (Abul-Eis *et al.,* 2012). Nosocomial infections were also reported in Turkey (Ergonul, 2006), South Africa (van Eeden *et al.,* 1985) United Arab Emirates (Suleiman *et al.,* 1980), Pakistan (Burney *et al.,* 1976), and Iran (Mardani, 2002).

Laboratory-Acquired Infections

Laboratory personnel and researchers can be at higher risk of acquiring CCHFV if they handle infected samples or work with the virus in a laboratory setting (Figure. 2). Strict biosafety measures and adherence to proper laboratory protocols are essential to prevent accidental laboratory-acquired infections (Whitehouse, 2007).

History of Crimean Congo Haemorrhagic fever and its occurrence in Iraq

Crimean-Congo hemorrhagic fever (CCHF) is a fatal zoonotic disease seen exclusively in humans. The CCHFV is circulating in many countries in Asia, Africa, and southern Europe (Figure. 3). The first identified CCHFV outbreak occurred in the mid-1944s in the Crimean peninsula, when Soviet troops re-occupied the areas under German occupation. The troops developed an acute febrile illness with a high incidence of bleeding and shock (Grashchenkov, 1945). The disease was later isolated in the Belgian Congo (Currently Democratic Republic of the Congo, DRC) in 1956. In 1969 the researcher recognized that both isolated viruses in 1944 and 1956 were identical (Casals,1969). Mixing the two places' names resulted in the current name for the disease and the virus, Crimean-Congo hemorrhagic fever. https://www.who.int/health-topics/crimean-congo-haemorrhagic-fever#tab=tab_1.

Geographic Distribution

CCHF is endemic in various regions across Africa, Asia, and Europe. Primarily, the virus is transmitted to humans through ticks of the genus *Hyalomma*, which act as both reservoirs and vectors of the virus. Domestic and wild animals, such as livestock and small mammals, can also become infected with CCHFV.

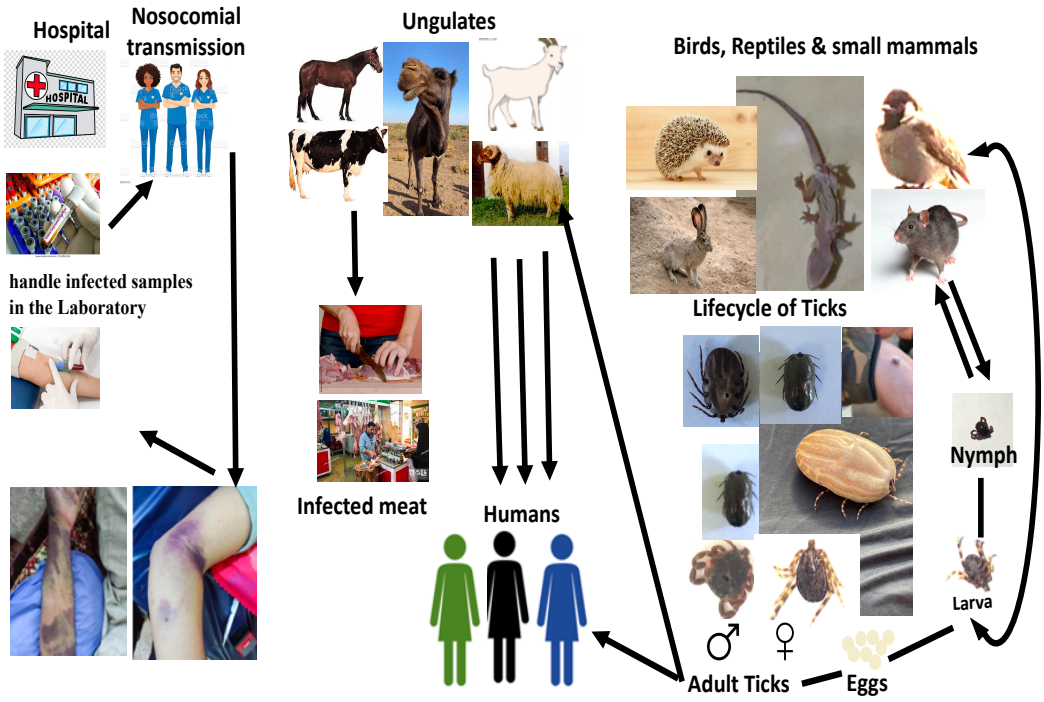

Figure. 2: Shows the mode of transmission of CCHFV to public including the nosocomial in hospital

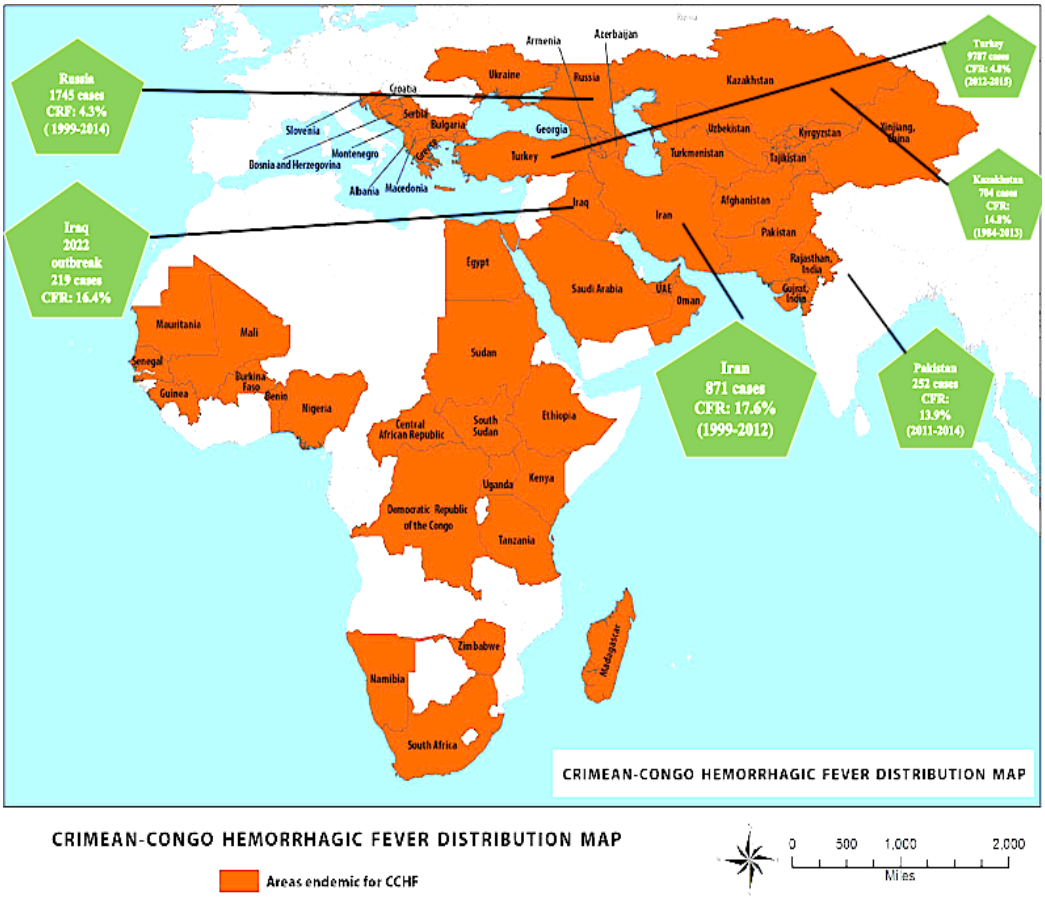

Figure. 3: Map of distribution of Crimean-Congo hemorrhagic fever in the world

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A. Asia

The disease was reported in different countries such as Iran, Afghanistan, Pakistan, Iraq, United Arab Emirates, Kuwait, Oman, Saudi Arabia, China, Tajikistan, India, Turkey, Georgia, and Russia (Table. 2).

B. Africa

The disease also is reported in some countries in Africa like South Africa, Egypt, Senegal, Mauritania, Kenya, Sudan, Madagascar, Niger, Nigeria, Ghana, and Uganda, as follows (Table. 3).

C. Europe

The disease also is endemic and reported in numerous European countries such as Albania, Bulgaria, Greece, Kosovo, Spain, as follow (Table.4)

D. Iraq

CCHF was unknown in Iraq before September 1979, when one lady was admitted to Al Yarmouk Hospital/ Baghdad on 07/09/1979 with hemorrhage symptoms and died after 2 days (Tantawi *et al.,* 1980). After 2 days, the same hemorrhagic symptoms, including fever, intestinal and general hemorrhage, appeared in two health workers (General practice and assistance nurse) who were in direct contact with the patient. Both health workers died, and this event gave attention to health authorities to investigate the cause and facts of this disease to take the precaution to quarantine some departments of Al Yarmouk Hospital to control the spreading of the disease. The Iraq Ministry of Health also informed the world health organization and the neighboring countries about taking precautions. The description of the first reported cases in Iraq in 1979 is listed in down according to Tantawi *et al.,* (1980).

- **First cases**

A 24-year-old female from Anbar province is located 110 kilometers northwest of Baghdad. The lady got sick on 30 September 1979 and was admitted to Anbar Hospital for her suspected abortion. She suffered from fever, headache, vomiting, diarrhea, stomach and intestinal pain, jaundice, and subcutaneous bleeding at the needle injection site. Later, she suffered from low blood pressure and acute shock, loss of consciousness, and died on 9 September 1979 (Tantawi *et al.,* 1980)..

- **Second case**

A 26-year-old male was working as a senior resident physician (SRP) in Al Yarmouk Hospital/ Baghdad. He treated the first patient, did the blood transfusion, and was in direct contact with her for the 3 days of her stay in the hospital before her death. The SRP suffered from flu-like syndrome on 14 September 1979, followed by severe abdominal pain, fever, increased heart rate, headache, congestion, and shock, and died on 19 September 1979 (Tantawi *et al.,* 1980)..

Table. 2: shows the CCHF endemic countries in Asia

No.	Country	description	year	Reference
1	**Iran**	•Sheep (45%Serology) (Chumakov) •Ornithodorus lahorensissoft ticks (Argasidae) in Northeastern Iran •nosocomial infection cases were detected in the northeast of Iran •clinical signs •risk professions •Serological and molecular evaluation •molecular epidemiology & genotypes circulating in Iran, includingAsia-1, Asia-2, Europe-1 and Europe-2	1970 1978 2009, 2011, 2012	Hoogstraal , 1979 Chinikar et al., 2009 Chinikar et al., 2013 A; Chinikar et al., 2012 A Chinikar et al., 2012 B Chinikar et al., 2012 C Chinikar et al., 2012 D Chinikar et al., 2013 A Kayedi et al., 2015 Chinikar et al., 2016 Chinikar & Shahhosseini, 2016 Shahhosseini et al., 2017 A Shahhosseini et al., 2017 B
2	**Afghanistan**	First record in Takhar province (Northeast Afghanistan) , 19 cases (2 died) The first multifocal outbreak from Afghanistan Engil district (Herat city) a seroprevalence in 11.2% of humans and 75% of livestock Serosurvey study found that the average age of CCHFV positive cases was 30 years. Case fatality 21.6%, seasonal prevalence Eid-al-Adha. Butchers (13.7%) and shepherds (11.8%) , the average period from beginning of symptoms and admission to the hospital was 4.9 days, whereas in fatal cases it was 4.7 days	1998 2008 2017-2018	Mofleh & Ahmad, 2012 Mustafa et al., 2011 Mustafa et al., 2009 Qaderi et al., 2021
3	**Pakistan**	•The virus was first isolated from Hyalomma ticks. •First human case / Rawalpindi/ when a laparotomy was performed on a patient with abdominal pain, haematemesis and melaena •the first CCHF case/ Baluchistan province (endemic area). •14 sporadic outbreaks reported from Pakistan & nine outbreaks occurred in Baluchistan province •CCHF cases with 44% and 33% fatality were reported in the Punjab province. •CCHFV strain /clade Asia-1	1960s 1976 1978 Since the year 2000 2002 and 2003	Jamil et al., 2005 Athar et al., 200 Kasi et al., 2019 Pirkani et al., 2006 Saleem et al., 2009 Rai et al., 2008 Zohaib et al., 2020
4	**Iraq**	First reported in human nosocomial reports / two confirmed fatal cases (one physician, one nurse). A positive seroprevalence / previous exposure of animal to CCHFV: 57.6% of sheep, 49.64% of goats, 29.28% of cattle, 58.73% of horses, and 23.23% of camels The annual number of confirmed CCHF cases varied from zero to six nosocomial two confirmed cases (physicians) nosocomial one confirmed case (physician) 11 confirmed and 28 suspected cases were reported. A case fatality ratio of 36% among confirmed cases has been reported in Iraq.	1979 1979 1980 1998 and 2009 1992 1996 2010	Al-Tikriti et al., 1981 Tantawi et al., 1981 Majeed et al., 2012. Ibrahim et al., 2014
5	**United Arab Emirates**	Before November 1993, no autochthonous cases of CCHFV infection had been identified First cases reported in Dubai/ an index case and five secondary nosocomial cases occurred. / The source of infection Cattle imported from Iraq, Kenya, and Pakistan 35 primary cases of CCHF were reported, with a case fatality ratio of 62%. The majority of the cases involved workers of livestock markets, butchers, and animal skin processors. a novel lineage of CCHFV/ detected in dromedary camels (Camelus dromedarius) and camel ticks (Hyalomma dromedarii) with potential reassortment of the M segment of the genome	1979 1994 and 1995	Schwarz et al., 1996 Rodriguez et al., 1997 Khan et al., 1997 Khalafalla et al., 2021Camp et al., 2019. Camp et al., 2021
6	**Kuwait**	4% of human sera / positive serological investigation in two hospitals no other published data available on CCHFV circulation.	1979 and 1982	Al-Nakib et al., 1984
7	**Oman**	Four patients by clinical presentation. Samples of imported and domestic animals exposure to CCHFV, and 22% of samples reacted CCHFV IgG positive. 19 tick pools out of 235 tick pools were positive CCHFV antigen / 16 identified as Hyalomma anatolicum A serological evidence (IgG) of animal exposure with CCHFV Seroprevalence study categorized butchers as a job with high potential for exposure to CCHFV	1995 2016	Williams et al., 2000 Body et al., 2016 Al-Abri et al.,. 2019
8	**Saudi Arabia**	•Not reported in Saudi Arabia until 1990. •An outbreak of viral hemorrhagic fever affected 7 abattoir workers / western Saudi Arabia / Mecca. •Serosurveys of abattoir workers detected 40 confirmed or suspected cases (12 deaths) of CCHF. •CCHFV had been introduced to Saudi Arabia by infected ticks on imported sheep arriving through Jeddah seaport	 1989 and 1990	El-Azazy & Scrimgeour, 1997 Memish et al., 2002
9	**China**	The first case was from the northwestern Xinjiang region in The virus firstly isolated from patients and ticks (Hyalomma asiaticum) The disease known "Xinjiang hemorrhagic fever", as the CCHF cases have only been reported from Xinjiang, Disease in outdoors working males during March to June, the active periods of the adult ticks Antibodies detected in the serum of livestock and humans in other areas, implying transmission may occur elsewhere in mainland China. 260 CCHF cases were reported in China with a 21% case fatality ratio. occasional epidemics , with 26 cases and five deaths, 51 cases and three deaths.	1965 1966 From 1965 to 1994 1997 2001	Papa et al., 2002, 8, 50. Morikawa et al., 2002. Han et al., 2002 Qing et al., 1999 Gao et al., 2010,
10	**Tajikistan**	•First confirmed cases •Per year, the average number of CCHF human cases 1-6. •In epidemic years over 20 cases •On occasion: ○21 cases ○26 cases ○29 cases ○37 cases ○29 cases •Tick bites have a lower case fatality ratio (22%) than those associated with direct contact with contaminated blood (50%) due to differences in viral load. •Men are twice as likely as women to develop CCHF due to occupational exposure to ticks or infected tissue/blood. •Farmers, field workers, butchers, and medical personnel are among the most vulnerable groups. •24% is the average case fatality ratio •nosocomial infections of hospital staff caring for an index patient who was infected via a tick bite, handling infected animal products, or unknown exposure routes.	1968 1967 2001 2007 2008 2009	Tishkova et al.,2012
11	**India**	•The first time reported from Gujarat . •Four deaths / three patient from nosocomial transmission. •Nosocomial transmissions outbreaks. •Phylogenetic analysis / clade Asia 2 with the highest similarity to strains from Tajikistan .	2011 2012 & 2013	Prajapati et al.,2012 Yadav et al., 2013 Yadav et al., 2014.
12	**Turkey**	The first case from Tokat. Similar clinical and laboratory findings between Tokat Cases and cases from neighboring cities of Yozgat in the spring and summer. More than 10,000 confirmed cases were reported with an overall case fatality ratio of 5%. Widespread in many provinces of southern areas of the Black-sea region, central and eastern Anatolia, with rural areas accounting for 69.4% of cases. 1.13:1is the male-to-female infection ratio A history of a tick bites during the months of May, June, and July related to the majority of CCHF patients. clades Europe-1 and Europe-2 are two different circulating strains.	2002 2003 Since 2002	Vatansever et al., 2007 Yilmaz et al., 2009. Estrada-Pena et al., 2007 Karti et al., 2004 Midilli et al., 2009
13	**Georgia**	•The first autochthonous case reported from a suburb of the capital city, Tbilisi, and the virus was transmitted by tick bite. •22 cases reported from January to September. •The highest annual case count since 2009. •A higher incidence of hemorrhagic symptoms than CCHF patients in neighboring Turkey (65% versus 23%, respectively). •No detailed genetic or phylogenetic information on the viral strains in this area are available.	2009 2014 2002–2007	Zakhashvili et al., 2009. Greiner et al., 2014 Yilmaz et al., 2009
14	**Russia**	•The first case reported by Chumakov. •First identification of agent from human outbreak in Crimea from 200 infected military personnel. •Occasional epidemics occurred in: ○Astrakhan (339 cases) ○ Rostov (377 cases) ○Stavropol between (263 cases), ○Krasnodar in (18 cases) sporadic cases occurred in several territories in the Southern Federal District in 2002. Europe-1 clade are circulating strains.	1944 1953 and 2005 1963 and 2005 1953 and 2005 1948	Butenko et al., 2007 Onishchenko et al., 2004 Lukashev et al., 2018

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Table. 3: shows the CCHF endemic countries in Africa

No	Country	Description	Year	Reference
1	South Africa	• Reported the first case during introducing the virus by infected tick vectors on migratory birds. • Antibodies were widely present in sera of livestock and wild vertebrates in South Africa, Zimbabwe, and Namibia, including sera that had been preserved for years. • Hy. truncatum is the only Hyalomma species known in the region with lower prevalence of antibodies along the southern coast and in the extreme northeast • Antibodies are most prevalent among large mammals including cattle, el and antelope, African buffaloes, giraffes, zebras, rhinoceroses, and ostriches / the preferred hosts of adult ticks • CCHFV antibodies are most often found in hares among small mammals. • 44% of CCHF cases in southern Africa reported a tick bite. • 40% reported contact with livestock blood or tissue. • 12% of cases did not report any direct contact with livestock or tick bite but lived in or visited rural areas, • 4% of cases were infected nosocomially. • The majority of CCHF cases were men (83%).	1981 1981 and 2006	Swanepoel et al., 1987 Burt et al., 2007.
2.	Egypt	• 3.13% of 1022 animal sera tested positive for CCHFV-reactive IgG. • Although CCHFV is endemic in Egypt, the exact dissemination of the virus in human populations is uncertain. • A total of 4 infected cases and one death were recorded in Egypt in 1981 and 2012.	September 2004 and August 2005	Mohamed et al., 2008Vorou et al., 2007 Temur et al., 2021
3	Senegal	• A preliminary study found CCHF infection in Senegalese livestock. • Isolation of the virus from ticks obtained in a Senegalese abattoir. • CCHFV infection is more common in men than in women in Senegal, because men are mainly involved in herding activities and a high risk of tick bite (Hyalomma truncatum) or contact with infected animals.	1970	Chapman et al., 1991
4	Mauritania	• CCHFV is endemic in southern Mauritania. • The first human case was identified and serologically confirmed. • In May, a fatal human case of CCHF was recorded in south-western Mauritania. • The first urban outbreak in Mauritania reported in six persons who admitted to the hospital with fever and hemorrhage; half of them died, and infection was confirmed by serology.	 1983 1988 2003	Gonzalez et al., 1990 Nabeth et al., 2004
5	Kenya	• Evidence of CCHF in Kenya is limited. • First discovered in Rhipicephalus pulchellus ticks obtained from a dying sheep in a veterinary laboratory in Kabete, Kenya. • First Human CCHF case recorded in Kenya, when a man with an acute hemorrhagic illness was admitted to a hospital in western Kenya.	 1970 2000	Sang et al., 2011
6	Sudan	• In Kordufan region, numerous outbreaks, of both nosocomial and household transmission, and sporadic cases. • A serosurvey suggested that CCHFV is present in other areas of the country as well, but disease incidence is apparently lower. • A nosocomial chain of transmission outbreak was recorded in a Sudanese rural hospital. • According to genetic analysis, CCHFV S segment sequences were most similar to those from South Africa, Mauritania, and Nigeria in clade 3.	 2008	Rahden et al., 2019 Aradaib et al., 2010 Aradaib et al., 2011
7	Madagascar	• The first CCHFV discovered in Rhipicephalus microplus ticks collected on cattle in a slaughterhouse in Antananarivo. • Madagascar CCHFV strains were more similar to strains from the Middle East and Asia than to African strains according to Phylogenetic studies. • In Mandoto, evidence of CCHFV infection was detected in human sera. • The prevalence of CCHFV infection among high-risk groups (e.g., slaughterhouse workers) in different geographical areas was determined by a national cross-sectional serologic survey. • The incidence of CCHFV infection among high-risk professionals was found to be low.	1985 1988 2008–2009	Mathiot et al., 1988 Andriamandimby et al., 2011
8	Niger	• A sero-survey study found that an archive of domestic animal sera collected in Niger between 1984 and 1988 were serologically positive for CCHFV, indicating the virus circulating in the country. • No human cases were reported.	1995	Mariner et al., 1995
9	Nigeria	• 24% of cattle and 2% of goats were serologically (IgG) positive for CCHFV. • Human population in northeastern Nigeria provided evidence of active and prior exposure to CCHFV. • Africa 3 clade is the strain circulated in Nigeria according to phylogenetic analysis of a human-derived CCHFV sequence.	2015	Oluwayelu, et al., 2015 Bukbuk et al., 2016
10	Ghana	• Hyalomma excavatum and Amblyomma variegatum were positive for CCHFV in a CCHF surveillance study. • Human serum samples obtained from the abattoir workers revealed the exposure to CCHFV by the presence of CCHFV-reactive IgG.		Akuffo et al., 2016
11	Uganda	• A surveillance system for viral hemorrhagic fevers has established Uganda. • The early detection of occasional CCHF outbreaks in humans was done by the surveillance system • The majority occurred in the central regions of Uganda. • Anti-CCHFV antibodies are present and prevalent in cattle. • Eight confirmed CCHF outbreaks. • There was a CCHF outbreak in the Agago District, involving three patients. Less than ten cases were documented in the following years. • In July 2018, the infection of two patients was confirmed by PCR in Isingiro District. • In the next seven months, 13 CCHF cases were confirmed in different regions. • However, it is unclear if the increase was attributable to improved surveillance or an actual increase in cases during this time period.	2010 between 2013 and 2017 2013	Balinandi et al., 2021 Mirembe et al., 2021

Table. 4: shows the CCHF endemic countries in Europe

No	Country	Description	Year	Reference
1	Albania	•An outbreak of eight cases of CCHF occurred in Albania during the spring and summer, with the infection of seven cases confirmed by laboratory tests. •A nosocomial infection was discovered, as well as a familial cluster of cases. •Genetic analysis revealed that the causative virus clustered together with other European CCHFV cases.	2001	Papa et al., 2002
2	Bulgaria	•Numerous CCHF cases were detected in Bulgaria, •The death ratio was around 17%. During this time. •20 nosocomial infections were reported. •The number of reported CCHF cases decreased, with a death ratio also decreasing to 11.4%. •The CCHFV strains from Bulgaria were found to cluster with other Balkan strains from Kosovo and Albania.	Between 1953 and 1974 Between 1975 and 1996	Papa et al., 2004
3	Greece	•The first fatal case of CCHF was discovered , in Northern Greece. •A CCHFV strain (AP92) was isolated from Rhipichephalus bursa ticks collected from goats in Northern Greece. •6.25% of residents showed antibodies to strain AP92 CCHFV, however, positive cases did not have any symptoms of CCHF. •A seroprevalence of CCHFV was 1% among the population surveyed, according to conducted survey •Approximately 3% were positive for CCHFV-reactive IgG. •No CCHF cases had been reported in Greece, it was suggested that the human antibodies were against strain AP92, which appears to be moderately pathogenic to humans and thus a good candidate for vaccine research. •The first serious case was recorded in a woman died in Komotini, a town in northeastern Greece. •Molecular analysis revealed that the causative strain (Rodopi) was genetically distinct from strain AP92.	2008 1975 1981 and 1988 2008–2009 2008	Maltezou et al., 2009 Antoniadis et al., 1990 Papa et al., 2011,
4	Kosovo	•The first cases of CCHF were reported. •Reported of three major outbreaks with a total of 186 serologically confirmed cases. •The hyper-endemic areas for CCHF were the central and southwestern parts of Kosovo. •CCHFV strain sharing a common ancestor with strains from Turkey according to a phylogenetic study.	1989 1995, 2001, and 2004,	Ahmeti et al., 2006 Humolli et al., 2010 Emmerich et al., 2018
5	Spain	•CCHFV discovered in Hyalomma ticks in Cáceres. •For the first time identified two autochthonous CCHF cases. •Reported of one autochthonous case dating back to 2013. •Seven human cases with molecular confirmation were recorded, three of which were fatal. •The CCHFV strain in Spain is similar to Africa-3 that identified in Mauritania. •Viral sequences found identical strain to those found in eastern Europe (genotype V, Europe-1) in a patient and ticks from deer and wild boar raise the likelihood of CCHFV being introduced into Spain through the animal trade. •The seropositive rates of animals found in southern Spain reflect an established tick-host-tick cycle in some regions, and segment re-assortment found in a sequenced virus from one case suggests the virus has a great ability to adapt.	2010 2016 2016 to 2020	Estrada Peña et al., 2012 De Arellano et al., 2017 Negredo et al., 2021 Portillo et al., 2021 Negredo et al., 2021
6	Imported Cases to Europe	• Travelers returning from CCHFV-endemic areas to non-endemic European countries have been recorded in the UK such as from oAfghanistan, Bulgaria, Zimbabwe) oFrance (returning traveler from Senegal) oGermany (returning travelers from Afghanistan and Bulgaria		Atkinson, et al., 2012 Lumley et al., 2014 Chamberlain, et al., 2013 Tarantola et al., 2006 Tall et al., 2009 Ölschläger et al., 2011 Conger et al., 2015

- **Third case**

A 45 years old female working in Al Yarmouk Hospital/ Baghdad as an assistant nurse serviced the first patient. On 10 September 1979, she suffered from fever, severe abdominal pain, and diarrhea. She was admitted to Al Yarmouk Hospital/ Baghdad on 13 September 1979, she left the hospital after recovery on 15 September 1979, but her health condition deteriorated at home. She was readmitted to the hospital on 18 September 1979, suffering from general bleeding and jaundice. Blood samples were collected, and the patient died on 19 September 1979. The postmortem examination was done (Tantawi *et al.,* 1980).

- **Forth case**

A 60-year-old female living in the Al Khadimyia district had no contact with the previous cases. The lady was visiting a crowded Karbala holy religion city and stayed for two nights before her sickness with symptoms of CCHF. She was admitted to Al Khadimyia Hospital on 18 September 1979 and suffered from fever, headache, loss of appetite, vomiting, jaundice, severe abdominal pain, and diarrhea. Clinical examination revealed hepatomegaly and bleeding symptoms. She recovered slowly after treatment and became healthy and in good condition on 11 October 1979 (Tantawi *et al.,* 1980)..

- **Fifth case**

A 26 years old pregnant female lived in the Abogarib district. This lady suffered from diarrhea and vaginal bleeding. She was admitted to Al Yarmouk Hospital/ Baghdad on 17 September 1979. Moreover, the patient was treated with uterine curettage. She left the hospital on 22 September 1979 after recovery. Five days later, she was readmitted to the hospital because her condition deteriorated, and suffering from vaginal bleeding, cutaneous petechial hemorrhagic, large subcutaneous bleeding, pneumonia, and toxemia. She died on 3 October 1979 (Tantawi *et al.,* 1980).

- **Sixth case**

A 55 years old man lived in Hayy al Qadisiyah / Baghdad; he worked as a sheep shepherd. He was admitted to Al Yarmouk Hospital on 7 October 1979, suffering from severe pain, fever, general bleeding, and obvious gastric, intestinal bleeding, and subcutaneous petechial bleeding (Figure. 4, 5). They suffered from kidney failure and died on 10 October, 1979 (Tantawi *et al.,* 1980).

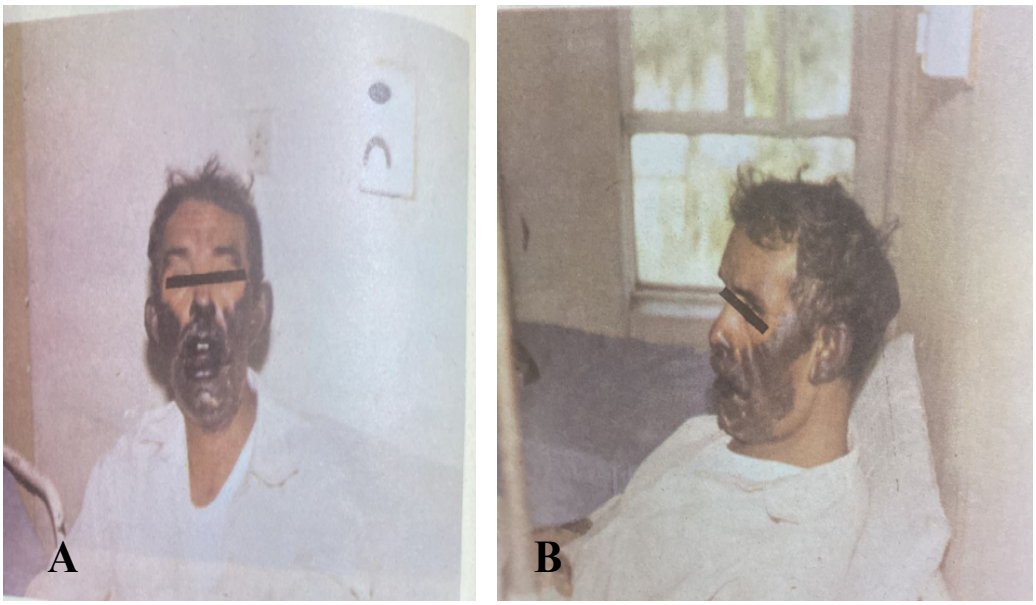

Figure. 4: Shows subcutaneous bleeding on the face (A) and ear (B) (Tantawi *et al.,* 1980)

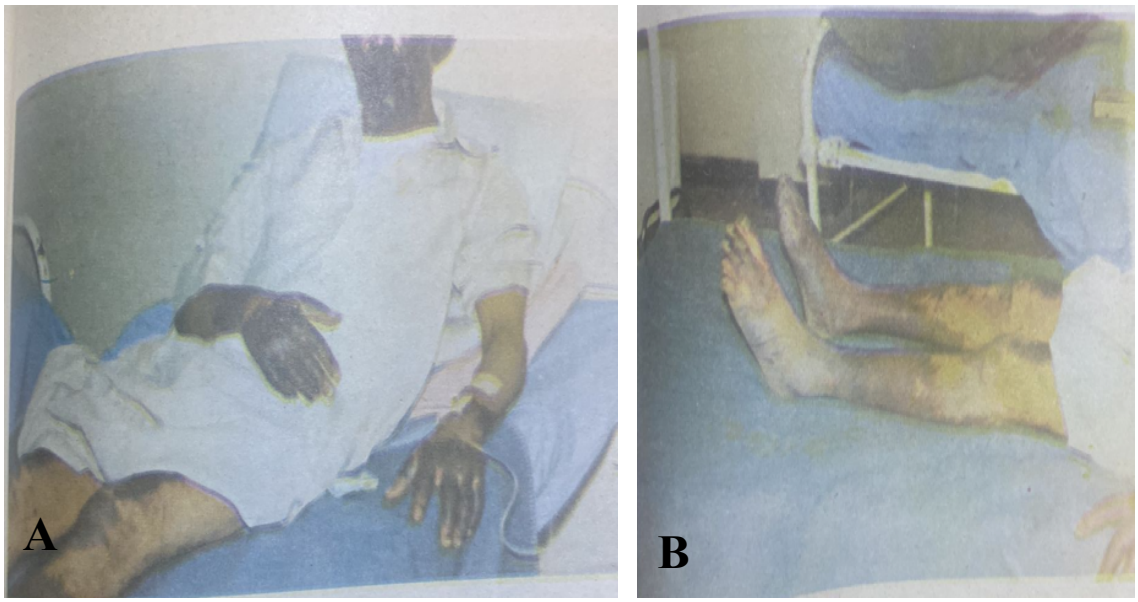

Figure. 5: Shows generalized subcutaneous bleeding hands, neck, face (A) and, legs (B) (Tantawi *et al.,* 1980)

- **Seventh case**

An 18 years old female lived in Al Tajy district/ Baghdad. She suffered from flu-like symptoms earlier but was admitted to Al Nuamin Hospital on 7 October 1979 because she did not recover. She was suspected of meningitis but later suffered from gastric and intestinal bleeding, jaundice, loss of consciousness, and coma and died on 13 October 1979 (Tantawi *et al.,* 1980).

- **Eighth case**

A 30 years old female who lived in Al-Thawra, formerly known as (currently Al Sadar city) / Baghdad, was admitted to Al Karama Hospital on 28 September 1979, suffering from flu-like symptoms like headache, fever, and severe pain; later, she developed gastric and intestinal bleeding. The patient was in worse condition and died on 12 October 1979 (Tantawi *et al.,* 1980).

- **Ninth case**

A 42 years female living in the Mahmoudiyah district quickly developed fever, headache, and epistaxis. She was admitted to Al Yarmouk Hospital/ Baghdad on 14 October 1979, suffering from jaundice and general bleeding. She recovered after intensive treatment and was discharged on 20 November 1979. The history of this case showed that this lady was in direct contact with sheep. (Figures. 6 A, B, C & 7) (Tantawi *et al.,* 1980).

- **Tenth case**

A 30 years old pregnant female living in Diyala Governorate was admitted to Al Elwya Hospital on 24 November 1979, suffering from vaginal bleeding, fever, and subcutaneous bleeding. She aborted on the same day and recovered after intensive care. She was discharged on 16 November 1979 (Figure. 8) (Tantawi *et al.,* 1980).

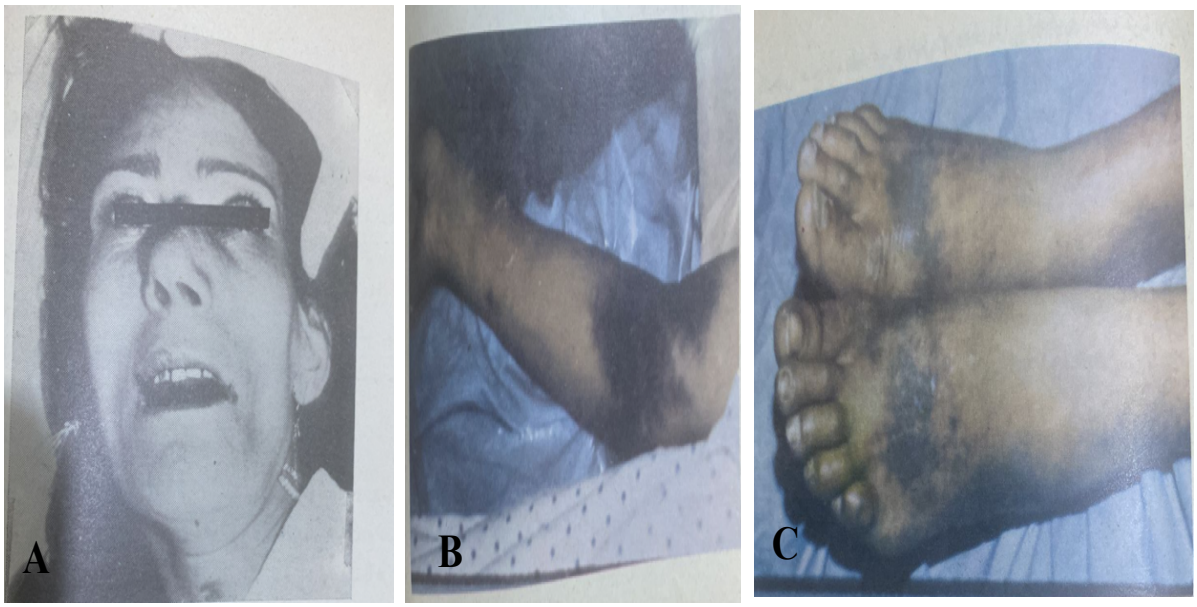

Figure. 6: Shows mouth bleeding (A); subcutaneous bleeding on the arm and foots of the patient (B &C) (Tantawi *et al.,* 1980)

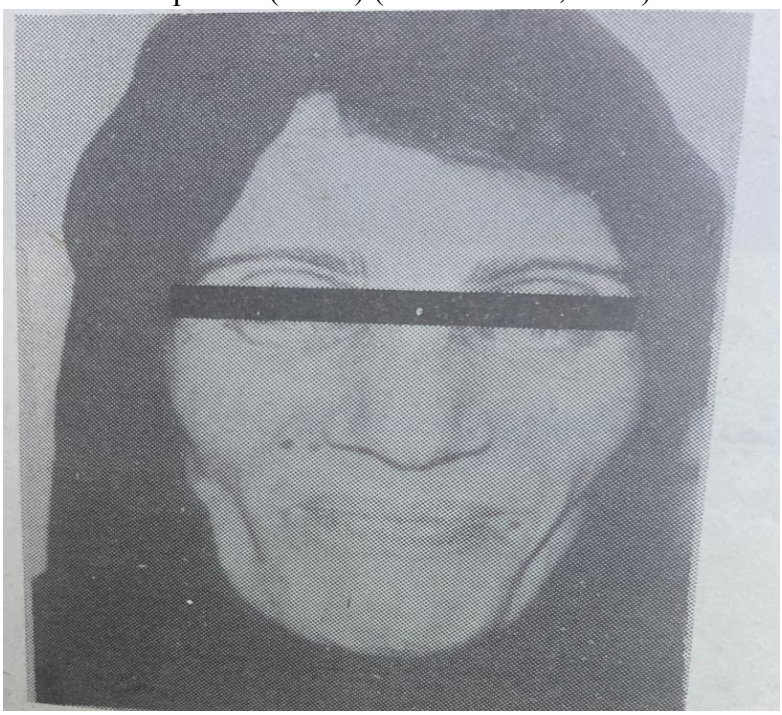

Figure. 7: Shows patient 2 months after recovery (Tantawi *et al.,* 1980)

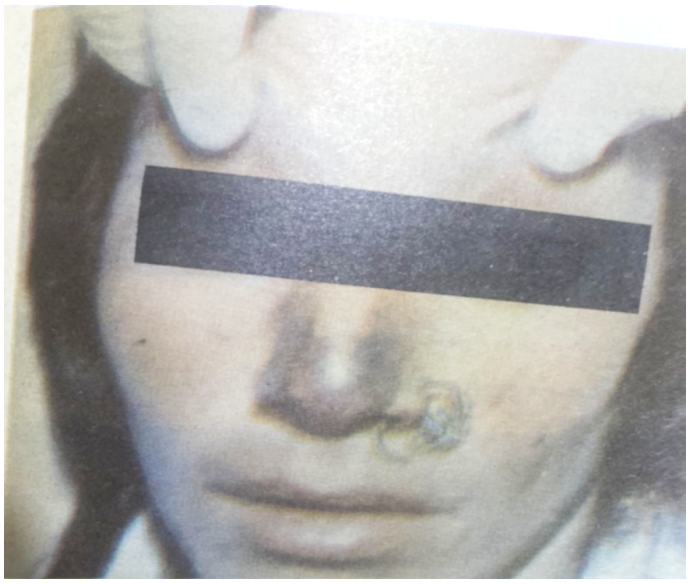

Figure. 8 : Shows subcutaneous nose bleeding (Tantawi *et al.,* 1980)

The first CCHF outbreak in Iraq revealed variations in the clinical symptoms, the briefing of patients clinical signs are presented in table. 5. (Tantawi *et al.,* 1980).

Table.5**:** Represents the clinical symptoms appeared on the first ten CCHF patients during the 1979 outbreak (Tantawi *et al.,* 1980)

No.	Symptoms	Number of cases
1	Fever	10
2	Headache	9
3	Abdominal pain	9
4	Vomiting	9
5	Loss of appetite	9
6	Pain of joints and pain	7
7	Diarrhea	4
8	Coughing	4
9	pharyngitis	3
10	Conjunctivitis	2
11	Chest pain	2
12	Bleeding ability	10
13	Bleeding of digestive system	7
14	Epistaxis	2
15	Lips bleeding	4
16	Back pain	9
17	Vaginal bleeding	5
18	Abortion	3
19	Subcutaneous bleeding	10
20	Hematuria	2
21	A pink rash on the palm of the hand	1
22	Blood Hypotension	9
23	General jaundice	10
24	Hepatomegaly	8
25	Nervous disturbances	4
26	Nervous shock	8
27	pneumonia	3
28	Toxemia	1
29	Renal failure	1
30.	Disturbance of adrenal glands	4
31	Oliguria	8

- Total number expressed these clinical were ten.
- Percentages of Male: Female was 2: 8
- Fatality rate was 70 %
- Number of pregnant women was three.
- Percentage of abortion was 100%.

The disease reemerged in April 1980 in Al Fudialia district / Baghdad when a 16 years old male was working as a horse carriage driver. Upon admission to the hospital, he claimed a tick had bitten him before developing CCHF symptoms. The patient also developed cutaneous and intestinal bleeding. The infection was confirmed via an elevation in antibodies. This patient recovered after intensive care. The disease was also confirmed by a butcher in deteriorated condition and died upon hospital admission. CCHF Virus aggregations were investigated in his liver by Electron microscope, which confirmed the infection. Later, CCHF became endemic in Iraq since the first report in 1979 with the re-emergence of outbreaks. The occurrence and publications of CCHF in Iraq since 1978 are presented in Table.6 (Tantawi *et al.,* 1980)

Pathogenesis of the CCHF

The exact mechanism by which viruses produce pathogenic effects is not fully known. Entirely the hemorrhagic fever viruses can hinder the host's immune functions and lead to susceptibility to disease (Geisbert and Lahrling, 2004). After a tick bite, the virus enters the host and replicates quickly (Figure. 9), and the normal function of the vascular system and lymphatic organs is changed (Feldmann *et al.,* 2003). CCHF pathogenesis is mainly related to the infection correlated with the epithelium (Schnittler & Feldmann, 2003). The continuous replication of the viral particles leads to damage to the epithelium. Later, the virus releases tissue-toxic factors that indirectly damage the host tissue. Virus particles also produce host-derived soluble factors that lead to endothelial activation and loss of proper cellular functions. Then, the damaged endothelium attracts the platelets to aggregate, leading to the activation of the intrinsic pathway of coagulation. It is an early obvious symptom that ends as a hemostatic failure. Hemo-phagocytosis related to cytopenia was a common finding reported in about half of the patients in Turkey (Karti *et al.,* 2004).

Previous studies showed that haemophagocytic lymphohistiocytosis occurred due to hyperactivation of monocytes resulting from elevated levels of Type 1T helper cytokine, such as Tumor Necrosis Factor α, Interferon γ, Interleukin 6, and Interleukin 1. (Fisman, 2000). Researchers found the roles of cytokines in the pathogenesis of CCHF, and the level of Type 1T helper cell cytokines was detected in patients who died and those who survived (Karti *et al.,* 2004). Moreover, the researchers found high levels of cytokines in patients who died from CCHF compared to survival patients who showed low levels. In serious cases, the levels of Interleukin 6 and Tumor Necrosis Factor α were higher, along with disseminated intravascular coagulation. The Interleukin10 level was contrariwise linked to them (Ergonul *et al.,* 2006). Although the receptor that allows the virus to move into the cell was not identified, researchers noted the cellular pathology associated with viral division among the cell. They found that the protein domains outside the cell, i.e., GC and GN glycoproteins, play an important function in the virus binding to the host cell. Moreover, the host cell nucleolin allowed the virus to cause cellular injury (Xiao *et al.,* 2011). While the entry of the virus to the host cell occurred via Clathrin-dependent endocytosis (Simon *et al.,* 2009).

Table.6: Represents the occurrence and publications of CCHF in Iraq since 1979

Year	CCHFV	Laboratory test		Percentage of infection	Reference
1980	Humans	Virus isolation			Tantawi et al., 1980
1981	Humans	Virus isolation			Al-Tikriti et al., 1981
1981	Sheep goat Cattle Horse camel small mammals	Serology		57.6% 49.64% 29.28% 58.73% 23.23% 14.28%	Tantawi et al., 1981
2010		The total numbers of positive patients to CCHF virus was 11 out of 44 suspected samples were examined from eight provinces during the period from January to December 2010 . The way of transmission is due to contact with blood and tissues of infected animals, and one patient slaughtered sheep in his house. ELISA was used to detect Crimean-Congo hemorrhagic fever (CCHF) virus-specific immunoglobulin M (IgM) in human serum samples.			Abul-Eis et al., 2010
Proceeding of the Eleventh Veterinary Scientific Conference, 2012; 99-103 Crimean-Congo Hemorrhagic Fever in Iraq During 2010 Emad S. Abul-Eis , Nabeel A.Mohammad and Suhad M.Wasein Ministry of Health / Public Health Directorate / CPHL /CCHF.REF.LAB		The total numbers of positive patients to CCHF virus was 11 out of 44 suspected samples were examined from eight provinces during the period from January to December 2010 . The way of transmission is due to contact with blood and tissues of infected animals, and one patient slaughtered sheep in his house. ELISA was used to detect Crimean-Congo hemorrhagic fever (CCHF) virus-specific immunoglobulin M (IgM) in human serum samples.			Proceeding of the Eleventh Veterinary Scientific Conference, 2012
2012	Humans	Serology: ELISA (IgM)			Majeed et al., 2012
2014	Humans	Serology: ELISA (IgM)		Low percentage	Ibrahim et al., 2014
Total cases reported in Iraq from 1979 – 2015 were 377 cases	Humans (377 cases)	Total death 39	Case per year 0-55	1979, 1980, 1990, 2010, 2013, 2015	Majeed et al., 2014 Al-Tikriti SK et al., 1981
2016	Human	Serology			Aziz et al., 2016.
Iraq, 2018		The total number of suspected cases was 143 cas- es. Most of the cases were males (59.4%), 15-45 years old (62.2%), and live in urban areas (58.7%). About three quarters of the cases (68.5%) did not fit the standard case definition adopted by Iraq CDC. Most of the suspected cases were reported in Diwaniya province (20.3%). Nearly half of the suspected cases (64, 44.7%) occurred in June. Only 7.0% of the total suspected cases were positive when tested by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR). The majority of confirmed cases (3, 30.0%) occurred in Diwaniya province.			Ali Hazim Mustafa, 2018
Crimean-Congo hemorrhagic fever in Iraq (2018-2022) and an educational review		During the year 2018, there were ten cases (including 3 from Diwaniyia province) confirmed by Reverse Transcriptase Polymerase Chain Reaction registered by the Iraqi Ministry of Health, and death occurred in eight of the cases. During the year 2021, the Iraqi Ministry of Health reported the registration of fifteen laboratory confirmed cases of Crimean-Congo hemorrhagic fever during the period from April to November 2021, and 5 deaths occurred. On the 27th of April 2022, the Iraqi Ministry of Health registered 17 cases of laboratory confirmed hemorrhagic fever occurred during the year 2022, and many cases were from ThiQar, and five deaths occurred. Conclusion: 42 cases of laboratory confirmed cases of Crimean-Congo hemorrhagic fever occurred in Iraq during the period from January, 2018 to May, 2022. The disease is still endemic in Iraq and was associated with a high mortality as 18 of the 42 confirmed cases died. Therefore, we are recommending using the available research evidence suggesting the early use of ribavirin in the treatment of patients, and also using ribavirin post-exposure prophylaxis and early ribavirin treatment for workers at medium- to-high risk.			Aamir Jalal Al-Mosawi, 2022
CCHF 2022 outbreak	Humans	In total, there were 219 confirmed cases of CCHF from 1st January 2022 to 26th June 2022. The first confirmed case was reported in March 2022, and cases continued to occur through June 2022. The median age of the cases was 34.5 years. The majority of cases were male (n=130, 59.4%), had an unspecified job (n=126, 57.5%) and lived in southern Iraq (n=142, 64.8%). The first case was reported in week 10 of 2022. Case numbers peaked in week 24 (30 cases were reported), and subsequently declined in week 25 (24 cases were reported). The case fatality rate was 16.4%.		2022	Riyadh Abdulameer Alhilfi et al., 2023
Outbreak 2022	Humans				https://www.who.int/emergencies /disease-outbreak-news/item/2022-DON386. (Accessed 15 June 2022).
CCHF outbreak 2022.	Humans				Shkaib et al., 2022
Iraq 2023 CCHF otubreak	Human				Al-kuraishy et al., 2023
Iraq reports more than 250 Crimean Congo Hemorrhagic Fever cases year to date		The Iraqi Ministry of Health reported that more than 250 cases of Crimean Congo hemorrhagic fever (CCHF) and more than 35 deaths have been recorded in all governorates of the country, since the beginning of 2023.			https://outbreaknewstoday.com/iraq-reports-more-than-250-crimean-congo-hemorrhagic-fever-cases-year-to-date-90216/#:~:text=The%20Iraqi%20Ministry%20of%20Health,since%20the%20beginning%20of%202023

Clinical signs of CCHF Disease

A human being is the only identified host with clinical signs related to CCHF Disease (Ergonul, 2007). The CCHF development has 4 phases, including the incubation phase, characterized by the replication of the virus in the host body; the pre-hemorrhagic phase; the hemorrhagic phase; and the convalescent phase (Tanir et al., 2009). The incubation period starts directly after the infected tick bites the host and usually lasts 3 to 7 days (Naderi et al., 2013). Additionally, the amount of viral load injected during the tick bite and the route of exposure are affected by the virus's incubation period (Kaya et al., 2011). However, a shorter incubation period occurs when the tick feeds on blood rather than other transmission routes. In infected animals, blood and tissue take ~5 days to develop CCHF. While on average, human-to-human transmission also takes 5-7 days (Swanepoel et al., 1987). Researchers also showed variations in the incubation period before admitting the patients to the hospital, such as 5 days in UAE and 5-6 days in Turkey (Ergönül et al., 2006). The pre-hemorrhagic phase is the second phase of the infection, in which the infected patient reveals signs of a fever that ranges from 39 to 41◦C (Yousaf et al., 2018). The CCHF patient shows severe headache, dizziness, and muscular pain (Ahmeti et al., 2014). The fever continues for 4-5 days and subsides subsequently (Hoogstraal, 1979). Diarrhea, vomiting, and nausea were also observed in some cases (Whitehouse, 2004). This phase persists for almost 3 days, and the different parts of the body, like the face and neck, become hyperemic (Saleem et al., 2016). Moreover, congested sclera and conjunctivitis are usually observed (Papa et al., 2015). The hemorrhagic phase is the third phase of CCHF, which is shorter and tends to be more noticeable in terms of clinical symptoms because of hemorrhages. It usually starts on the disease's 3rd to 5th day (Pshenichnaya et al., 2017). However, no connection is normally perceived between fever and hemorrhages in patients (Ergonul, 2007). Variations in the shape and size of hemorrhages ranged from ecchymotic to petechial lesions. Large hematomas were also reported in the skin and mucous membranes (Garrison et al., 2019). All CCHF patients suffer from increasing clotting time when the blood becomes thin enough to ooze out of the natural body orifices like gingival tissue, nose, and vagina (Mostafavi et al., 2014). Melena, hematuria, and menometorrhagia (bloody discharges from the uterus) are also seen in CCHF patients (Yilmaz et al., 2010). Some patients also showed hemoptysis in the hemorrhagic phase (Dogan et al., 2011). The hemorrhage phase is frequently confusing with appendicitis if there are no signs of external bleeding and patients only suffer from internal bleeding (Çelikba et al., 2005). However, inflammation of the appendix produces persistent pain. Nonetheless, additional investigations confirmed internal hemorrhages and bleeding of the cecum and internal and external oblique muscle with no pathology related to the appendix (Coetzee et al., 2017). CCHF patients also suffered from splenomegaly and hepatomegaly, which were inconsistent findings (Mendoza et al., 2018) because these clinical features occurred in recovered patients or in dead patients that suffered from grave bleeding (van Eeden et al., 1985). The convalescent is the last phase of CCHF disease in patients who survived the infection. It is started about 10-20 days after the infection.

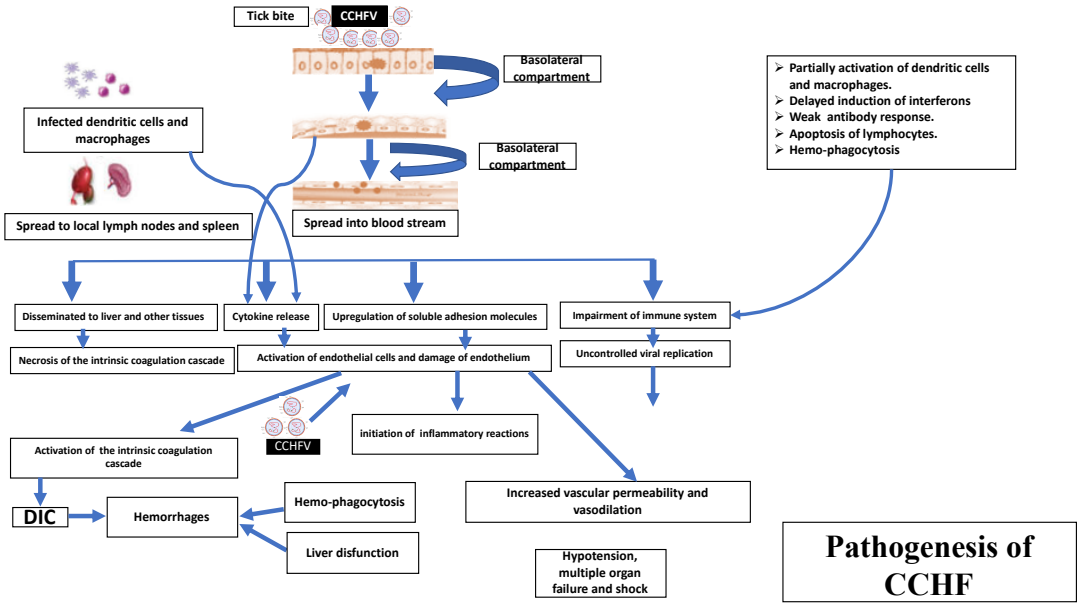

Figure. 9: Shows the pathogenesis of CCHF disease

Most survived patients revealed a weak pulse, tachycardia, and partial or complete alopecia, dyspnea, polyneuritis, xerostomia, deafness, memory loss, blindness, or weak eyesight (Nasirian *et al.,* 2020). Moreover, some surviving patients suffered from bradycardia and a drop in blood pressure (Erol *et al.,* 2012).

Diagnosis of CCHF disease

All febrile diseases are similar to others initially, and accurate and quick diagnosis is critical for patient management and prevention of transmission. Crimean-Congo hemorrhagic fever (CCHF) diagnosis comprises a combination of clinical evaluation and laboratory testing.
The key components of diagnosing CCHF are:

- **Case history**

The patient's history of tick bite or contact with a known, living in or visiting an endemic area, occupation, and out-of-doors activities can offer important perception. Nevertheless, a definitive diagnosis needs laboratory testing.

- **Clinical Evaluation**

A healthcare professional assess all suspected who revealed a specific symptoms of CCHF, medical history, and recent exposure to ticks or infected animals. CCHF should be suspected if the individual presents with fever, muscle aches, headache, and bleeding tendencies (e.g., nosebleeds, bleeding gums, or bruising).

- **laboratory diagnostics tests**

The laboratory diagnostics tests are accomplished directly by detecting the virus or indirectly via immunological tests that determine the host's immune response to

infection. The whole blood or serum/plasma is the preferred clinical specimen with precautions while handling the diagnostic specimens before inactivation because of virus biosafety concerns. Repeated samples should be collected from the patients to address some sensitivity issues. Quantitative reverse transcription PCR (qRT–PCR) is the rapid test of choice for detecting CCHFV. A few commercially existing assays are designed to detect the broader range of CCHFV lineages. The fabulous genetic variability of CCHFV through virus mutations and genomic segment reassortment or recombination may need CCHF lineage-specific assays to address geographical alterations (Gruber *et al.,* 2019). Countryside situations may benefit from simpler equipment approaches like loop-mediated isothermal amplification assays. Another approach to genome detection is antigen detection, mainly targeting CCHFV nucleoprotein (NP). Antigen detection assays can accurately diagnose CCHF infections but have lower sensitivity than qRT–PCR assays (Shrivastava *et al.,* 2021).

- **Viral isolation**

Virus isolation is another alternative method for the diagnosis of CCHFV disease. Viral Culture needs specialized laboratories, attempts may be made to isolate the CCHFV from blood or other body fluids. However, this method is time-consuming and carries a higher risk of laboratory-acquired infections, so it is not routinely performed.

- **Serology**

Serology is the method of choice used to detect the humoral immune response of the patient to CCHFV infection. Blood samples are collected to test for the presence of CCHFV-specific antibodies. Enzyme-linked immunosorbent assay (ELISA) and immunofluorescence assay (IFA) are commonly used serological tests. Commercial serological assay kits are available to detect human IgM and IgG antibodies to CCHFV. In severe cases, there was a delay or absence of antibody production that led to false negatives in severe CCHF cases in serological tests (Shepherd *et al.,* 1989). The diagnosis of CCHFV is often made in national or international reference laboratories. However, the capability for on-site testing helps to reduce delays in case management and public health interference. The functioning of the diagnostic laboratory should be commonly controlled and evaluated through participation in external quality assessment panels. Past experiences have identified performance weaknesses related to the sensitivity and specificity of qRT–PCR assays (Gruber *et al.,* 2019), showing persistent requirements for improved performance and standardized protocols. A previous study on CCHF-infected non-human primates revealed the development of clinical diseases such as fever, viremia, increased liver enzymes, thrombocytopenia, and occasional rash and vaginal bleeding associated with persistent CCHFV infection in the testes, whereas this animal showed granuloma of latent tuberculosis (Smith *et al.,* 2019). These results suggested that CCHFV may persist in immune-privileged sites. It is presently uncertain what are the reasons for the disease variability. However, the outbred genetics of cynomolgus macaques, differences in virus strains used, and official variation in euthanasia criteria may account for variable disease and crucial outcomes. Nonetheless, the cynomolgus macaque model accurately recapitulates many aspects of human disease and represents an essential model for the preclinical evaluation of anti-CCHFV therapeutics and vaccines.

- **Tick models**

To date, animal models have tremendously used needle-delivered CCHFV and ignored the influence of the tick and tick-derived factors on CCHFV pathogenesis. CCHFV must

circulate and be maintained in tick and vertebrate hosts, Like many other arthropod-borne viruses. This life cycle limits viral development and may affect virulence (Hua *et al.,* 2020). Although models of tick feeding in high inhibition have been established (Xia et al. 2016), much remains mysterious concerning the role and impact of the tick on CCHF and CCHFV pathogenesis.

Early diagnosis of CCHF is crucial for appropriate patient management, infection control, and public health measures. If CCHF is suspected, healthcare professionals should immediately notify the appropriate authorities and follow local guidelines and protocols for reporting and managing the disease.

Treatment of CCHFV Disease

The treatment of Crimean-Congo hemorrhagic fever virus (CCHFV) infection primarily involves supportive care, as there is currently no specific antiviral therapy approved for CCHFV. Most therapeutic options for CCHFV have focused on interfering with viral replication or modifying the host response to the infection (Table 6). Though many nominees have revealed hopeful preclinical data, clinical efficacy data for most remain inadequate. The key aspects of managing CCHFV infection include the following:

- Hospitalization: The suspected or confirmed CCHFV infection patients should be hospitalized in specialized isolation units with strict infection control measures to prevent the spread of the virus.
- Supportive Care: To manage symptoms, maintain vital organ function, and prevent complications the following supportive measures are applied:

I. Fluid and electrolyte management: Intravenous fluids are administered to maintain hydration and correct imbalances.

II. Blood component support: In severe cases with bleeding or low platelet count (thrombocytopenia), blood transfusions or platelet transfusions may be necessary.

III. Management of complications: Specific interventions are provided to address complications such as organ failure, hemorrhage, or shock. This may involve respiratory support, blood pressure stabilization, and treatment of coagulation abnormalities.

Table 6: Crimean–Congo haemorrhagic fever Treatments

Compound	Class	Target	Preclinical efficacy	Clinical efficacy	Comments
Corticosteroids	Anti-inflammatory	Host response	Not done	Limited data or benefit	More preclinical and/or clinical studies are needed
Monoclonal antibodies	Neutralizing or non-neutralizing	Viral proteins	Limited data in rodent models	No clinical data	More preclinical and/or clinical studies are needed
Ribavirin	Nucleoside analogue	RdRP	Controversial efficacy in rodent models	Controversial efficacy in patients	Poor efficacy; early treatment start needed; should be discontinued or used in combination therapy
Plasma or antibodies from survivors	Neutralizing or non-neutralizing	Viral proteins	Not done	Limited data or benefit	More preclinical and/or clinical studies are needed
Favipiravir	Nucleoside analogue	RdRP	Efficacy in rodent and NHP models	Limited data or benefit	Late treatment start effective in rodent models; clinical trials are needed
Molnupiravir	Nucleoside analogue	RdRP	No efficacy in rodent models	No clinical data	Unlikely to proceed
2′-Deoxy-2′-fluorocytidine	Nucleoside analogue	RdRP	Not done	No clinical data	More preclinical studies are needed

NHP, non-human primate; RdRP, RNA-dependent RNA polymerase.

Several treatment modules have used various medications, such as:

A. Antivirals

The nucleoside analog ribavirin is the only direct-acting antiviral widely used clinically in patients with CCHF. Nevertheless, controversial arguments are raised about treatment outcomes, and scarce publications support ribavirin's efficacy in treating CCHF infection (Ascioglu *et al.,* 2011; Johnson *et al.,* 2018). Additionally, early treatment may benefit the patient's recovery (Arab-Bafrani *et al.,* 2019). Animal studies approved the contradictory efficacy of ribavirin against CCHFV infection. They revealed significant protecting effects in fatally infected mice compared to ribavirin, favipiravir, or a derivative (H44). They significantly decrease viral loads in key target tissues of CCHFV death. Favipiravir or H44 treatment could even be initiated days after infection, including when mice exhibited advanced signs of disease, and still provide significant protective effects. These data suggest that favipiravir and related compounds may be effective in patients presenting to healthcare systems with advanced CCHF. Likewise, lethal recrudescent CCHFV infection was observed weeks after cessation of favipiravir treatment in infected mice, suggesting that early favipiravir treatment may not completely control the virus. Favipiravir was also effective in CCHFV-infected cynomolgus macaques, reducing viremia and viral load in several tissues. Although favipiravir has shown potential in preclinical animal models, effectiveness data in humans infected with CCHFV is limited, and clinical trials are needed to determine whether favipiravir can improve CCHF patient outcomes. 2′-Deoxy-2′-fluorocytidine has also shown promising results in vitro, suggesting this may be another effective antiviral against CCHFV. Molnupiravir, recently used to treat SARS-CoV-2 infection in humans, exhibits efficacy against CCHFV in vitro with similar inhibitory concentrations as favipiravir. Nevertheless, molnupiravir failed to protect against CCHFV infection in lethally infected mice even when treatment was started before infection.

Although ribavirin, favipiravir, and 2′-deoxy-2′-fluorocytidine are all thought to exert antiviral activity through catastrophic mutagenesis or inhibition of the viral replicase, additional small molecules acting through distinct mechanisms have been reported effective against CCHFV in vitro. TH3289, a compound with broad antiviral activity in vitro, has been shown to suppress CCHFV replication by modulating interactions between viral proteins and cellular chaperone proteins. Blockade of the catalytic activity of the CCHFV OTU domain with a synthetic ubiquitin variant was able to block CCHFV replication in vitro through interference with viral RNA synthesis. However, further validation of these potential antivirals against CCHFV in vivo is needed.

B. Antibody-based therapies

No specific antibody-based therapies are currently approved for treating Crimean-Congo hemorrhagic fever virus (CCHFV) infection (Hawman & Feldmann, 2021). However, antibody-based therapies are an active area of research and development, and new treatments may have emerged since then. The antibody-based therapies are involved monoclonal antibodies (mAbs) or polyclonal antibodies targeting the CCHFV (Kaplon *et al.,* 2023). These antibodies can potentially neutralize the virus, enhance the immune response, or modulate the course of the disease (Keshtkar-Jahromi *et al.,* 2011). They may be administered as single treatments or in combination with other therapeutic approaches (Zivcec *et al.,* 2017). Some experimental studies have shown promising results in animal models using monoclonal antibodies against CCHFV. These

antibodies have demonstrated the ability to neutralize the virus and reduce viral load, thereby improving survival rates (Bertolotti-Ciarlet *et al.,* 2005). However, it is important to note that further research is needed to evaluate the safety, efficacy, and optimal dosing of antibody-based therapies in humans (Golden *et al.,* 2019). The development and approval of antibody-based therapies for CCHFV infection would require rigorous clinical trials to assess their effectiveness and safety. These trials would involve testing the therapies in humans and comparing them to standard supportive care to determine their benefits and potential side effects. It's worth mentioning that the field of infectious disease therapeutics is constantly developing, and there may have been progressions in antibody-based therapies for CCHFV infection (Hawman *et al.,* 2012).

C. Prevention and vaccines

Although antivirals and antibody-based therapies for CCHFV have shown potential in preclinical models, the utility of these treatments is limited to well-developed healthcare systems with the ability to recognize and diagnose CCHFV infections rapidly, access to the drugs and the ability to begin treatment promptly. Therapies for patients in countries with limited healthcare resources or presenting to healthcare systems when showing advanced disease are likely to remain limited. Therefore, public health education to prevent exposure to CCHFV and vaccines is critically needed to address the public health threat of CCHFV infections in areas with limited access to health care.

D. Prevention

Preventing CCHFV infection involves addressing the many risk factors for CCHFV exposure. For farmers, wearing appropriate clothing such as long sleeves and pants, reducing activities in tick-infested areas, and using integrated pest management strategies (Figure. 10) to reduce tick populations in the farm environment can minimize the risk of CCHFV infection via tick bites. Furthermore, using protective equipment when slaughtering tick-invested livestock in backyard slaughter processes or slaughterhouses may reduce exposure to contaminated animal products. In the healthcare setting, personal protective equipment is essential to prevent transmission during care of CCHF patients. Educational promotions to notify people in endemic areas of the risk factors for CCHF, like tick bites and workplace dangers, may prompt at-risk populations to reduce their risk of exposure and to recognize and report early symptoms of CCHF. Quarantine of livestock potentially carrying CCHFV or CCHFV-infected ticks before transport or slaughter may also prevent exposure and limit the introduction of CCHFV into new areas.

Figure.10: Shows tick control by acaricide in CCHF disease endemic areas in Iraq

- **Anti-inflammatory drugs**

A dysregulated inflammatory response and cytokine storms in severe CCHF, like various hemorrhagic fevers, cause substantial immunopathology. Consequently, narrow tries have been made to use anti-inflammatory drugs in patients with CCHF to defeat the hyper-inflammatory host response. A previous study approved improved outcomes for patients with confirmed CCHF treated with high-dose methylprednisolone with ribavirin in ribavirin alone (Sharifi-Mood *et al.,* 2013). Corticosteroids also showed advantageous in severely ill patients (Dokuzoguz *et al.,* 2013). Conversely, some previous studies could be more extensive. A recent animal study in severely infected type I interferon-blockaded mice revealed that lacking the TNF receptor or treatment with an antibody to block TNF signal- ling could protect against lethal disease infection of mice (Golden *et al.,* 2022). The accessibility of clinically approved TNF therapeutics (Li *et al.,* 2017) and therapeutics against other host cytokines (Kopf *et al.,* 2010). may permit evaluation of this approach to treat CCHF.

Prevention of Crimean-Congo hemorrhagic fever disease

Prevention of Crimean-Congo hemorrhagic fever virus (CCHFV) infection involves decreasing the risk of exposure to infected ticks and animals (Kumar *et al.,* 2020). There are prevention strategies to control the spreading of CCHFV infection; these include:

- **Tick Avoidance**

o Wear protective clothing: When in tick-infested areas, wear long sleeves, long pants, and closed-toe shoes to minimize skin exposure.

o Use tick repellents: Apply insect repellents containing DEET (N,N-diethyl-meta-toluamide) to exposed skin or clothing.

o Perform tick checks: Conduct thorough body checks for ticks after spending time in tick-prone areas. A particular attention to hidden areas like the scalp, behind the ears, and armpits are required.

- **Animal Contact**

- Avoid direct contact: Limit contact with blood, body fluids, or tissues of animals, especially those that are sick or have died from unknown causes.
- Use protective measures: If contact with animals or their tissues is unavoidable (e.g., during veterinary work or slaughtering animals), wear gloves, masks, and other appropriate personal protective equipment (PPE).

- **Hygiene Practices**

- Hand hygiene: Wash hands thoroughly with soap and water after handling animals, animal products, or potentially contaminated materials.
- Safe food handling: Ensure that meat and animal products are properly cooked before consumption.

- **Environmental hygiene:**

Maintain cleanliness and hygiene in living areas, including removing ticks from the environment.

- **Occupational Safety**

Healthcare workers and other professionals who may come into contact with CCHFV-infected individuals or their samples should follow appropriate infection control precautions, including the use of PPE and safe handling of samples.

- **Public Health Surveillance**

Active surveillance and reporting of CCHFV cases to public health authorities can help identify and manage outbreaks promptly. The prevention strategies may vary depending on the geographical location and local risk factors. Hence, it is logical to refer local health authorities, such as the national health department or the Centers for Disease Control and Prevention, for precise recommendations and regulation suitable to specific region.

No commercially available vaccine is specifically permitted for protecting against Crimean-Congo hemorrhagic fever virus (CCHFV) infection in humans. However, vaccine improvement efforts for CCHFV are ongoing, and several vaccine candidates have shown promise in preclinical and early clinical trials.

CCHFV vaccines

The goals of vaccine candidates for CCHFV are to induce an immune response against the virus, thereby avoiding or decreasing the gravity of the disease. Multiple vaccine programs have been assessed in animal models for CCHFV, such as inactivated virus preparations and subunit vaccines (Kortekaas *et al.,* 2015; Scholte *et al.,* 2019).

Some vaccine like VLPs recombinant live-attenuated viruses, replication-deficient viral-vectored vaccines, and nucleic acid-based vaccines are revealed promising efficacy. These vaccine approaches to CCHFV have been broadly studied elsewhere (Tipih & Burt, 2020; Dowall *et al.,* 2017). Some vaccine platforms are as follows:

a) Inactivated Vaccines: These vaccines contain inactivated forms of the CCHFV, which are no longer infectious but can still stimulate an immune response. Inactivated vaccines have shown promising results in preclinical studies and have progressed to early clinical trials.

b) Viral Vector Vaccines: Viral vector-based vaccines use harmless viruses as carriers (vectors) to deliver specific genetic material of CCHFV into cells, triggering an immune response. This approach has shown potential in preclinical studies.

c) DNA Vaccines: DNA vaccines involve introducing specific genetic material of CCHFV into cells, producing viral proteins that stimulate an immune response. DNA vaccines have shown promise in preclinical studies but are still in the early stages of development. However, It is important to note that vaccine development is a complex and time-consuming process. Multiple testing phases, including preclinical studies in animals and subsequent clinical trials in humans, are required to evaluate the safety and efficacy of candidates' vaccines.

Conclusion

This review article is emphasized on the CCHF disease, its geographical distribution worldwide, and the recent outbreaks in different countries. It also focused on epidemiology, causative agents, pathogenesis, clinical signs, diagnostic methods,

treatment and prevention, and vaccination of CCHF disease. Special focus was done on the occurrence and outbreaks of CCHFV in Iraq. Moreover, an extensive geographical range and large populations at risk for infection with CCHFV, many leftovers are to be determined concerning the host and viral elements of CCHFV pathogenesis. Improving molecular virology tools and promoting small-animal models will aid further mechanistic vision into how CCHFV causes disease. For threatened populations, protective methods such as training, reduced tick interaction, treatment of livestock to control tick invasions, livestock quarantine, and protection for high-risk exposure activities need to be employed in endemic areas. Essentially, quick and consistent diagnostics, effective vaccines, and antivirals are needed to limit the burden of CCHF on patients and public healthcare systems. Constant aid from molecular virology, immunology, vaccinology, entomology, veterinary health, and public health will be required to address the further risk of CCHFV infection and disease in endemic areas.

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Author contribution

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References

Aamir Jalal Al-Mosawi (2022). Crimean-Congo hemorrhagic fever in Iraq (2018-2022) and an educational review. Biomedical and Biotechnological Sciences. 1(1); DOI: 19.0810/BBS.2022/0003

Abul-Eis S. Emad , Nabeel A.Mohammad and Suhad M.Wasein. (2012). Crimean-Congo Hemorrhagic Fever in Iraq During 2010 . Proceeding of the Eleventh Veterinary Scientific Conference,; 99-103. https://www.iasj.net/iasj/download/8688d47eb9035e30

Ahmed A, Saqlain M, Tanveer M, Tahir AH, Ud-Din F, Shinwari MI, Khan GM, Anwer N. (2021). Knowledge, attitude and perceptions about Crimean Congo Haemorrhagic Fever (CCHF) among occupationally high-risk healthcare professionals of Pakistan. BMC Infect Dis. 2021 Jan 7;21(1):35. doi: 10.1186/s12879-020-05714-z.

Ahmeti S, Raka L. (2006). Crimean-Congo haemorrhagic fever in Kosova: A fatal case report. Virol .J. 3: 2002–2007.

Ahmeti S, Ajazaj-Berisha L, Halili B, Shala A. (2014). Acute arthritis in Crimean-Congo hemorrhagic fever. *J Glob Infect Dis.* 6:79–81. doi: 10.4103/0974-777X.132052 .

Akuffo R, Brandful J, Zayed A, Adjei A, Watany N, Fahmy N, Hughes R, Doman B, Voegborlo S, Aziati D. (2016). Crimean- Congo hemorrhagic fever virus in livestock ticks and animal handler seroprevalence at an abattoir in Ghana. BMC Infect. Dis. 2016, 16, 324.

Al-Abri SS, Hewson R, Al-Kindi H, Al-Abaidani I, Al-Jardani A, Al-Maani A, Almahrouqi S, Atkinson B, Al-Wahaibi A, Al-Rawahi B. (2019). Clinical and molecular epidemiology of Crimean-Congo hemorrhagic fever in Oman. PLoS Negl. Trop. Dis. 13:e0007100. doi: 10.1371/journal.pntd.0007100.

Al-Abri SS, Abaidani IA, Fazlalipour M, Mostafavi E, Leblebicioglu H, Pshenichnaya N, Memish ZA, Hewson R, Petersen E, Mala P, Nhu Nguyen TM, Rahman Malik M, Formenty P, Jeffries R. (2017). Current status of Crimean-Congo haemorrhagic fever in the World Health Organization Eastern Mediterranean Region: issues, challenges, and future directions. Int J Infect Dis. 58:82-89. doi: 10.1016/j.ijid.2017.02.018.

Alhilfi RA, Khaleel HA, Raheem BM, Mahdi SG, Tabche C, Rawaf S. (2023). Large outbreak of Crimean-Congo haemorrhagic fever in Iraq, 2022. IJID Reg. 18;6:76-79. doi: 10.1016/j.ijregi.2023.01.007.

Ali Hazim Mustafa (2020). Epidemiological Profile of Crimean-Congo Hemorrhagic Fever, Iraq, 2018; Epidemiology Conference 2020; August 10-11, 2020 | London, UK. J Health Med Res. Volume and Issue: S(2). https://www.iomcworld.org/articles/epidemiological-profile-of-crimeancongo-hemorrhagic-fever-iraq-2018.pdf

Al-kuraishy HM, Al-Gareeb AI, El-Bouseary MM. *et al.* (2023). Crimean-Congo hemorrhagic fever in Iraq: Humanity before heroism. Wien Klin Wochenschr https://doi.org/10.1007/s00508-023-02230-3

Al-Nakib W, Lloyd G, El-Mekki A, Platt G, Beeson A, Southee T. (1984). Preliminary report on arbovirus-antibody prevalence among patients in Kuwait: Evidence of Congo/Crimean virus infection. Trans. R. Soc. Trop. Med. Hyg.;78:474–476. doi: 10.1016/0035-9203(84)90065-8.

Al-Salihi KA, Karim AJ, Jasim HJ, Kareem FA (2018). Epidemiology of ticks fauna of camels in samawah desert. Adv. Anim. Vet. Sci. 6(8): 311-316. **doI:** http://dx.doi.org/10.17582/journal.aavs/2018/6.8.311.316

Al-Tikriti S K, Al-Ani F, Jurji FJ, Tantawi H, Al-Moslih M, Al-Janabi N, Mahmud M I, Al-Bana A, Habib H, Al-Munthri H, Al-Janabi S, AL-Jawahry K, Yonan M, Hassan F., & Simpson DI. (1981). Congo/Crimean haemorrhagic fever in Iraq. Bulletin of the World Health Organization, 59(1), 85–90.

Andriamandimby SF, Marianneau P, Rafisandratantsoa JT, Rollin PE, Heraud JM, Tordo N, Reynes JM. (2008). Crimean-Congo hemorrhagic fever serosurvey in at-risk professionals, Madagascar, 2008 and 2009. J. Clin. Virol. 2011, 52, 370–372.

Antoniadis A, Alexiou-Daniel S, Malissiovas N, Doutsos J, Polyzoni T, LeDuc J, Peters C, Saviolakis G, Calisher C. (1990). Seroepidemiological survey for antibodies to arboviruses in Greece. In Hemorrhagic Fever with Renal Syndrome, Tick-and Mosquito-Borne Viruses; Springer: Vienna, Austria. 277–285.

Appannanavar SB, Mishra B. (2011). An update on crimean congo hemorrhagic Fever. J Glob Infect Dis. 3(3):285-92. doi: 10.4103/0974-777X.83537.

Arab-Bafrani Z, Jabbari A, Mostakhdem Hashemi M, Arabzadeh AM, Gilanipour A, Mousavi E. (2019). Identification of the crucial parameters regarding the efficacy of ribavirin therapy in Crimean-Congo haemorrhagic fever (CCHF) patients: a systematic review and meta-analysis. J Antimicrob Chemother. 1;74(12):3432-3439. doi: 10.1093/jac/dkz328.

Aradaib IE, Erickson BR, Karsany MS, Khristova ML, Elageb RM, Mohamed ME, Nichol ST. (2011). Multiple Crimean-Congo hemorrhagic fever virus strains are associated with disease outbreaks in Sudan, 2008–2009. PLoS Negl. Trop. Dis. 5:e1159. doi: 10.1371/journal.pntd.0001159.

Aradaib IE, Erickson BR, Mustafa ME, Khristova ML, Saeed NS, Elageb RM, Nichol ST. (2010). Nosocomial outbreak of Crimean-Congo hemorrhagic fever, Sudan. Emerg. Infect. Dis. 16:837. doi: 10.3201/eid1605.091815.

Ascioglu, S., Leblebicioglu, H., Vahaboglu, H. & Chan, K. A. (2011). Ribavirin for patients with Crimean–Congo hemorrhagic fever: a systematic review and meta-analysis. *J. Antimicrob. Chemother.* **66**, 1215–1222

Aslam S, Latif MS, Daud M, Rahman ZU, Tabassum B, Riaz MS, Khan A, Tariq M, Husnain T. (2016). Crimean-Congo hemorrhagic fever: Risk factors and control measures for the infection abatement. Biomed Rep. 2016 Jan;4(1):15-20. doi: 10.3892/br.2015.545.

Athar MN, Baqai HZ, Ahmad M, Khalid MA, Bashir N, Ahmad AM, Balouch AH, Bashir K. (2003). Short report: Crimean-Congo hemorrhagic fever outbreak in Rawalpindi, Pakistan. Am. J. Trop. Med. Hyg. 2003;69:284–287. doi: 10.4269/ajtmh.2003.69.284.

Atkinson B, Latham J, Chamberlain J, Logue C, O'Donoghue L, Osborne J, Carson G, Brooks T, Carroll M, Jacobs M. (2012). Sequencing and phylogenetic characterisation of a fatal Crimean–Congo haemorrhagic fever case imported into the United Kingdom. Euro surveillance. 17:20327.

Aziz TAG, Ali DJ, Jaff DO. (2016). Molecular and Serological Detection of Crimean-Congo hemorrhagic fever virus in Sulaimani Province, Iraq. J Bioscie Med. 2016; 4(4): 36-42. doi: http://dx.doi.org/10.4236/jbm.2016.44006.

BalinandiS, vonBrömssen C, Tumusiime A, Kyondo J, Kwon H, Monteil VM, Mirazimi A, Lutwama J, Mugisha L, Malmberg M. (2021). Serological and molecular study of Crimean-Congo hemorrhagic fever virus in cattle from selected districts in Uganda. J. Virol. Methods. 290: 114075.

Belobo JTE, Kenmoe S, Kengne-Nde C, Emoh CPD, Bowo-Ngandji A, Tchatchouang S, Sowe Wobessi JN, Mbongue Mikangue CA, Tazokong HR, Kingue Bebey SR, Atembeh Noura E, Ka'e AC, Guiamdjo Simo RE, Modiyinji AF, Ngongang DT, Che E, Kenfack S, Nzukui ND, Amvongo Adjia N, Babassagana IT, Mahamat G, Mbaga DS, Mbacham WF, Sadeuh-Mbah SA, Njouom R. (2021). Worldwide epidemiology of Crimean-Congo Hemorrhagic Fever Virus in humans, ticks and other animal species, a systematic review and meta-analysis. PLoS Negl Trop Dis. 22;15(4):e0009299. doi: 10.1371/journal.pntd.0009299.

Bente DA, Forrester NL, Watts DM, McAuley AJ, Whitehouse CA, Bray M. (2013). Crimean-Congo hemorrhagic fever: History, epidemiology, pathogenesis, clinical syndrome and genetic diversity. Antiviral Res100:159–89. doi: 10.1016/j.antiviral.2013.07.006

Bergeron E, Albariño CG, Khristova ML, Nichol ST. (2010). Crimean-Congo hemorrhagic fever virus-encoded ovarian tumor protease activity is dispensable for virus RNA polymerase function. J Virol. 84(1):216-26. doi: 10.1128/JVI.01859-09. PMID: 19864393; PMCID: PMC2798392.

Bernard C, Holzmuller P, Bah MT, Bastien M, Combes B, Jori F, Grosbois V and Vial L. (2022). Systematic Review on Crimean–Congo Hemorrhagic Fever Enzootic Cycle and Factors Favoring Virus Transmission: Special Focus on France, an Apparently Free-Disease Area in Europe. Front. Vet. Sci. 9:932304. doi: 10.3389/fvets.2022.932304

Bertolotti-Ciarlet A, Smith J, Strecker K, Paragas J, Altamura LA, McFalls JM, Frias-Stäheli N, García-Sastre A, Schmaljohn CS, Doms RW. (2005). Cellular localization and antigenic characterization of crimean-congo hemorrhagic fever virus glycoproteins. J Virol. 79(10):6152-61. doi: 10.1128/JVI.79.10.6152-6161.2005.

Body MHH, Abdulmajeed HA, Hammad MH, Mohamed SA, Saif SA, Salim A-M, Al-Maewaly M, Rajamony S. (2016). Cross-sectional survey of Crimean-Congo hemorrhagic fever virus in the sultanate of Oman. J. Vet. Med. Anim. Health. 2016;8:44–49

Bukbuk DN, Dowall SD, Lewandowski K, Bosworth A, Baba SS, Varghese A, Watson R J, Bell A, Atkinson B, Hewson R. (2016). Serological and virological evidence of Crimean-Congo haemorrhagic fever virus circulation in the human population of Borno State, northeastern Nigeria. PLoS Negl. Trop. Dis. 10: e0005126.

Burney MI, Ghafoor A, Saleen M, Webb PA, Casals J.(1976). Nosocomial outbreak of viral hemorrhagic fever caused by Crimean hemorrhagic fever-Congo virus in Pakistan, January. Am. J. Trop. Med. Hyg., 29: 941 – 7.

Burt FJ, Janusz TP, Swanepoel R. (2007). Crimean-Congo Hemorrhagic Fever. Springer; Berlin/Heidelberg, Germany:. Crimean-congo hemorrhagic fever in South africa; 131–141.

Butenko A, Karganova G. (2007). Crimean-Congo Hemorrhagic Fever. Springer; Berlin/Heidelberg, Germany: Crimean-Congo hemorrhagic fever in Russia and other countries of the former Soviet Union. 99–114.

Camp JV, Kannan DO, Osman BM, Shah MS, Howarth B, Khafaga T, Weidinger P, Karuvantevida N, Kolodziejek J, Mazrooei H. (2020). Crimean-Congo hemorrhagic fever virus endemicity in United Arab Emirates, 2019. Emerg. Infect. Dis. 26:1019–1021. doi: 10.3201/eid2605.191414.

Camp JV, Weidinger P, Ramaswamy S, Kannan DO, Osman BM, Kolodziejek J, Karuvantevida N, Abou Tayoun A, Loney T, Nowotny N. (2021). Association of dromedary camels and camel ticks with reassortant Crimean-Congo hemorrhagic fever virus, United Arab Emirates. Emerg. Infect. Dis. 27:2471–2474. doi: 10.3201/eid2709.210299.

Çelikba ̧s A, Ergönül Ö, Dokuzoguz B, Eren S, Baykam N, Polat-Düzgün (2005). A. Crimean–Congo Hemorrhagic Fever infection simulating acute appendicitis. J Infe*ct.* 50:363–5. doi: 10.1016/j.jinf.2004.05.020 .

Chamberlain J, Cook N, Lloyd G, Mioulet V, Tolley H, Hewson R. (2005). Co-evolutionary patterns of variation in small and large RNA segments of Crimean-Congo hemorrhagic fever virus. J Gen Virol. 86 (Pt 12):3337-3341. doi: 10.1099/vir.0.81213-0.

Chamberlain J, Atkinson B, Logue C H, Latham J, Newman E N, Hewson R. (2013). Genome sequenceofex-AfghanistanCrimean- Congo hemorrhagic fever virus

SCT strain, from an imported United Kingdom case in October 2012. Genome Announc. 2013, 1, e00161-13.

Chapman LE, Wilson ML, Hall DB, LeGuenno B, Dykstra EA, Ba K, Fisher-Hoch SP. (1991). Risk factors for Crimean-Congo hemorrhagic fever in rural northern Senegal. J. Infect. Dis. 164:686–692. doi: 10.1093/infdis/164.4.686.

Chinikar S, Bouzari S, Shokrgozar MA, Mostafavi E, Jalali T, Khakifirouz S, Nowotny N, Fooks AR, Shahhosseini N. (2016). Genetic diversity of Crimean Congo hemorrhagic fever virus strains from Iran. J. Arthropod-Borne Dis. 2016;10:127.

Chinikar S, Shahhosseini N. (2016). Phylogenetic analysis on emerging Arboviruses in Iran. Int. J. Infect. Dis. 2016;53:160. doi: 10.1016/j.ijid.2016.11.391.

Chinikar S, Shayesteh M, Khakifirouz S, Jalali T, Varaie FSR, Rafigh M, Mostafavi E, Shahhosseini N. (2013 A). Nosocomial infection of Crimean–Congo haemorrhagic fever in eastern Iran: Case report. Travel Med. Infect. Dis. 11:252–255. doi: 10.1016/j.tmaid.2012.11.009.

Chinikar S, Shahhosseini N, Bouzari S, Jalali T, Shokrgozar MA, Mostafavi E. (2013 B). New circulating genomic variant of Crimean-Congo hemorrhagic fever virus in Iran. Arch. Virol. 2013;158:1085–1088. doi: 10.1007/s00705-012-1588-0.

Chinikar S., Ghiasi S.M., Naddaf S., Piazak N., Moradi M., Razavi M.R., Afzali N., Haeri A., Mostafavizadeh K., Ataei B. **(2012 A).** Serological evaluation of Crimean-Congo hemorrhagic fever in humans with high-risk professions living in enzootic regions of Isfahan Province of Iran and genetic analysis of circulating strains. Vector Borne Zoonotic Dis. 12:733–738. doi: 10.1089/vbz.2011.0634.

Chinikar S, Shahhosseini N, Khakifirouz S, Varaie F, Rafigh M, Jalali T, Hasanzehi A. (2012 B). Crimean Congo haemorrhagic fever as an infectious virus in Iran, an epidemiology approach. Int. J. Med. Microbiol. 302:85.

Chinikar S, Moghadam AH, Parizadeh SJ, Moradi M, Bayat N, Zeinali M, Mostafavi E. (2012 C). Seroepidemiology of Crimean Congo hemorrhagic fever in slaughterhouse workers in north eastern Iran. Iran. J. Public Health.;41:72.

Chinikar S, Shahhosseini N, Khakifirouz S, Rafigh M, Hasanzehi A. (2012 D). Serological and molecular evaluation of Crimean-Congo haemorrhagic fever in Iranian probable patients. Int. J. Infect. Dis. 16:e250. doi: 10.1016/j.ijid.2012.05.883.

Chinikar S, Ghiasi S, Hewson R, Moradi M, Haeri A. (2010). Crimean-Congo hemorrhagic fever in Iran and neighboring countries. J. Clin. Virol. 47:110–114. doi: 10.1016/j.jcv.2009.10.014.

Conger NG, Paolino KM, Osborn EC, Rusnak J M, Günther S, Pool J, Rollin PE, Allan PF, Schmidt-Chanasit J, Rieger T. (2015). Health care response to CCHF in US soldier and nosocomial transmission to health care providers, Germany, 2009. Emerg. Infect. Dis. 21, 23.

Coetzee MJ, Blumberg LH, Paweska JT, Leman P, Swanepoel R, De Kock A. (2017). Crimean-Congo hemorrhagicc fever presenting with undiagnosed chronic myeloid leukemia. S Afr *J Infect Dis.* 32:142–4. doi: 10.4102/sajid.v32i4.41.

Deyde VM, Khristova ML, Rollin PE, Ksiazek TG, Nichol ST. (2006). Crimean-congo hemorrhagic fever virus genomics and global diversity. J Virol. 80:8834–42. doi: 10.1128/JVI.00752-06

Dai S., Wu Q., Wu X., Peng C., Liu J., Tang S., Zhang T., Deng F., Shen S. (2021). Differential Cell Line Susceptibility to Crimean-Congo hemorrhagic fever virus. Front. Cell. Infect. Microbiol. ;11:236. doi: 10.3389/fcimb.2021.648077.

de la Calle-Prieto F, Martín-Quirós A, Trigo E, Mora-Rillo M, Arsuaga M, Díaz-Menéndez M, Arribas JR. (2018). Therapeutic management of Crimean-Congo haemorrhagic fever. Enfermedades infecciosas y microbiologia clinica (English ed.). 36(8):517–22. doi: 10.1016/j.eimce.2017.04.016.

De Arellano ER, Hernández L, Goyanes MJ, Arsuaga M, Cruz AF, Negredo A, Sánchez-Seco MP (2017). Phylogenetic characterization of Crimean-Congo hemorrhagic fever virus, Spain. Emerg. Infect. Dis. 2017, 23, 2078.

Dickson DL, Turell MJ. (1992). Replication and tissue tropisms of Crimean-Congo hemorrhagic fever virus in experimentally infected adult Hyalomma truncatum (Acari: Ixodidae). J Med Entomol. 29:767–73. doi: 10.1093/jmedent/29.5.767

Dogan OT, Engin A, Salk I, Epozturk K, Eren SH, Elaldi N, et al. (2011). Evaluation of respiratory findings in Crimean-Congo hemorrhagic fever. Southeast Asian J Trop Med Public Health. 42:1100.

Dokuzoguz B, Celikbas AK, Gök ŞE, Baykam N, Eroglu MN, Ergönül Ö. (2013). Severity scoring index for Crimean-Congo hemorrhagic fever and the impact of ribavirin and corticosteroids on fatality. Clin Infect Dis. 2013 Nov;57(9):1270-4. doi: 10.1093/cid/cit527.

Emmerich P, Jakupi X, von Possel R, Berisha L, Halili B, Günther S, Cadar D, Ahmeti S, Schmidt-Chanasit J. (2018). Viral metagenomics, genetic and evolutionary characteristics of Crimean-Congo hemorrhagic fever orthonairovirus in humans, Kosovo. Infect Genet Evol. 65:6-11. doi: 10.1016/j.meegid.2018.07.010

Elliott RM, Bouloy M, Calisher CH, Goldbach R, Moyer JT, Nichol S. (2000) "Family Bunyaviridae," in *Virus Taxonomy: Classification and Nomenclature of Viruses. Seventh Report of the International Committee on Taxonomy of Viruses*., ed. I. van R. MHV (San Diego: Academic Press). p. 599–621.

El-Azazy O, Scrimgeour E. (1997). Crimean-Congo haemorrhagic fever virus infection in the western province of Saudi Arabia. Trans. R. Soc. Trop. Med. Hyg. 91:275–278. doi: 10.1016/S0035-9203(97)90072-9.

Ergonul O, Tuncbilek S, Baykam N, Celikbas A, Dokuzoguz B. (2006). Evaluation of serum levels of interleukin (IL)−6, IL-10, and tumor necrosis factor–α in patients with Crimean-Congo hemorrhagic fever. J Infect Dis. 193:941–4. doi: 10.1086/500836

Ergonul O. (2007). Clinical and pathologic features of hemorrhagic fever. Crimean-Congo hemorrhagic fever. 3:207–20. doi: 10.1007/978-1-4020-6106-6_16

Ergönül Ö. (2006). Crimean-Congohemorrhagicc fever. Lanc*et Infect Dis.* 6:203– 14. doi: 10.1016/S1473-3099(06)70435-2

Erol S, Özkurt Z, Özden K, Parlak M, Erol MK. (2012). Transient bradycardia in patients with Crimean-Congo hemorrhagic fever. T*urk J of Med Sci*. 42:753– 6. doi: 10.3906/sag-1106-38.

Estrada-Pena A, Zatansever Z, Gargili A, Aktas M, Uzun R, Ergonul O, Jongejan F. (2007). Modeling the spatial distribution of Crimean-Congo hemorrhagic fever outbreaks in Turkey. Vector-Borne Zoonotic Dis. 7:667–678.

Estrada Peña A, Palomar AM, Santibáñez P,Sánchez N, Habela M A, Portillo A, Romero L, Oteo JA. (2012). Crimean-Congo hemorrhagic fever virus in ticks, Southwestern Europe, 2010. Emerg. Infect. Dis. 2012, 18, 179.

Feldmann H, Jones S, Klenk HD, Schnittler HJ. (2003). Ebola virus: from discovery to vaccine. Nat Rev Immunol. 3:677–85. doi: 10.1038/nri1154 .
126.

Fisman DN. (2000). Hemophagocytic syndromes and infection. Emerg Infect Dis. 6:601. doi: 10.3201/eid0606.000608.

Gao X, Nasci R, Liang G. (2010). The neglected arboviral infections in mainland China. PLoS Negl. Trop. Dis. 4:e624.

Gargili A, Estrada-Peña A, Spengler JR, Lukashev A, Nuttall PA, Bente DA. (2017). The role of ticks in the maintenance and transmission of Crimean-Congo hemorrhagic fever virus: a review of published field and laboratory studies HHS Public Access. Antiviral Res. 144:93–119. doi: 10.1016/j.antiviral.2017.05.010

Garrison AR, Smith DR, Golden JW. (2019). Animal models for Crimean-Congo hemorrhagic fever human disease. Viruses. 11:590. doi: 10.3390/v11070590 .
Geisbert TW, Jahrling PB. (2004). Exotic emerging viral diseases: progress and challenges. Nat Med. 10:S110–S21. doi: 10.1038/nm1142 .

Golden JW, Shoemaker CJ, Lindquist ME, Zeng X, Daye SP, Williams JA, Liu J, Coffin KM, Olschner S, Flusin O, Altamura LA, Kuehl KA, Fitzpatrick CJ, Schmaljohn CS, Garrison AR. (2019) GP38-targeting monoclonal antibodies protect adult mice against lethal Crimean-Congo hemorrhagic fever virus infection. Sci Adv. 10;5(7):eaaw9535. doi: 10.1126/sciadv.aaw9535.

Gonzalez JP, LeGuenno B, Guillaud M, Wilson ML. (1990). A fatal case of Crimean-Congo haemorrhagic fever in Mauritania: Virological and serological evidence

suggesting epidemic transmission. Trans. R. Soc. Trop. Med. Hyg. 84:573–576. doi: 10.1016/0035-9203(90)90045-

Gruber CEM, Bartolini B, Castilletti C, Mirazimi A, Hewson R, Christova I, Avšič T, Grunow R, Papa A, Sánchez-Seco MP, Kopmans M, Ippolito G, Capobianchi MR, Reusken CBEM, Di Caro A. (2019). Geographical Variability Affects CCHFV Detection by RT-PCR: A Tool for In-Silico Evaluation of Molecular Assays. Viruses. Oct 16;11(10):953. doi: 10.3390/v11100953.

Han L, Tang Q, Zhao X, Saijo M, Tao X. (2001). Serologic studies of Xinjiang hemorrhagic fever in Bachu county,. Zhonghua Liu Xing Bing Xue Za Zhi = Zhonghua Liuxingbingxue Zazhi. 23, 179–181.

Hawman DW, Feldmann H. (2018). Recent advances in understanding Crimean-Congo hemorrhagic fever virus. *F1000Research*, *7*, F1000 Faculty Rev-1715. https://doi.org/10.12688/f1000research.16189.1

Hawman DW, Feldmann H. (2023). Crimean-Congo hemorrhagic fever virus. Nat Rev Microbiol. Jul;21(7):463-477. doi: 10.1038/s41579-023-00871-9.

Hawman DW, Meade-White K, Leventhal S, Feldmann F, Okumura A, Smith B, Scott D, Feldmann H. (2021). Immunocompetent mouse model for Crimean-Congo hemorrhagic fever virus. Elife. 8;10:e63906. doi: 10.7554/eLife.63906.

Hewson R. (2007). Molecular epidemiology, genomics, and phylogeny of crimean-congo hemorrhagic fever virus. In: Ergonul O, Whitehouse CA, editors. Crimean-Congo Hemorrhagic Fever. Dordrecht: Springer. 45–55. doi: 10.1007/978-1-4020-6106-6_5

Hewson R, Gmyl A, Gmyl L, Smirnova SE, Karganova G, Jamil B, et al. (2004). Evidence of segment reassortment in Crimean-Congo haemorrhagic fever virus. *J Gen Virol.* 85:3059–70. doi: 10.1099/vir.0.80121-0

Hoogstraal H. (1979). The epidemiology of tick-borne Crimean-Congo hemorrhagic fever in Asia, Europe, and Africa. J. Med. Entomol. 1979;15:307–417. doi: 10.1093/jmedent/15.4.307.

Hua BL, Scholte FE, Ohlendorf V, Kopp A, Marklewitz M, Drosten C, Nichol ST, Spiropoulou C, Junglen S, Bergeron É. (2020). A single mutation in Crimean-Congo hemorrhagic fever virus discovered in ticks impairs infectivity in human cells. Elife. 21;9:e50999. doi: 10.7554/eLife.50999.

https://www.who.int/emergencies /disease-outbreak-news/item/2022-DON386. (2022). Crimean-Congo hemorrhagic fever in Iraq n.d. (Accessed 15 June 2022).

https://outbreaknewstoday.com/iraq-reports-more-than-250-crimean-congo-hemorrhagic-fever-cases-year-to-date-90216/#:~:text=The%20Iraqi%20Ministry%20of%20Health,since%20the%20beginning%20of%202023

Ibrahim AS, Ibrahim KS, Mohammed MO, Al-Shaikhani MA, Barzanji AA., Saeed SJ, Muhiaden S, Bhnam MN. (2014). Crimean Congo hemorrhagic fever management in Erbil during 2010–2011. Eur. Sci. J. 10;14: 219–229. doi: 10.19044/esj.2014.v10n24p%25p

Jamil B, Hasan RS, Sarwari AR, Burton J, Hewson R, Clegg C. (2005). Crimean-Congo hemorrhagic fever: Experience at a tertiary care hospital in Karachi, Pakistan. Trans. R. Soc. Trop. Med. Hyg. 2005;99:577–584. doi: 10.1016/j.trstmh.2005.03.002.

Johnson S, Henschke N, Maayan N, Mills I, Buckley BS, Kakourou A, Marshall R. (2018). Ribavirin for treating Crimean Congo haemorrhagic fever. Cochrane Database Syst Rev. 5;6(6):CD012713. doi: 10.1002/14651858.CD012713.pub2.

Kaplon H, Crescioli S, Chenoweth A, Visweswaraiah J, Reichert JM. (2023). Antibodies to watch in 2023. MAbs. Jan-Dec;15(1):2153410. doi: 10.1080/19420862.2022.2153410.

Karti SS, Odabasi Z, Korten V, Yilmaz M, Sonmez M, Caylan R, AkdoganE, Eren N, Koksal I, Ovali E. (2004). Crimean-Congo hemorrhagic fever in Turkey. Emerg. Infect. Dis. 10:1379. doi 10.3201/eid1008.030928 .

Kasi KK, Sas MA, Sauter-Louis C, von Arnim F, Gethmann JM, Schulz A, Wernike K, Groschup MH, Conraths FJ. (2020). Epidemiological investigations of Crimean-Congo haemorrhagic fever virus infection in sheep and goats in Balochistan, Pakistan. Ticks Tick-Borne Dis. 2020;11:101324. doi: 10.1016/j.ttbdis.2019.101324.

Kayedi MH, Chinikar S, Mostafavi E, Khakifirouz S, Jalali T, Hosseini-Chegeni A, Naghizadeh A, Niedrig M, Fooks AR, Shahhosseini N. (2015). Crimean–Congo hemorrhagic fever virus clade iv (Asia 1) in ticks of western Iran. J. Med. Entomol.;52:1144–1149. doi: 10.1093/jme/tjv081.

Kaya A, Engin A, Güven AS, Içagasioglu FD, Cevit Ö, Elaldi N, et al. (2011). Crimean- Congo hemorrhagic fever disease due to tick bite with very long incubation periods.
Int J Infect Dis. 15:e449–e52. doi: 10.1016/j.ijid.2011.03.007

Keshtkar-Jahromi M, Kuhn JH, Christova I, Bradfute SB, Jahrling PB, Bavari S. (2011). Crimean-Congo hemorrhagic fever: current and future prospects of vaccines and therapies. Antiviral Res. 2011 May;90(2):85-92. doi: 10.1016/j.antiviral..02.010.

Khan AS, Maupin GO, Rollin PE, Noor AM, Shurie HHM, Shalabi AGA, Wasef S, Haddad YMA, Sadek R, Ijaz K. (1997). An outbreak of Crimean-Congo hemorrhagic fever in the United Arab Emirates, 1994–1995. Am. J. Trop. Med. Hyg. 57:519–525. doi: 10.4269/ajtmh.1997.57.519.

Khalafalla AI, Li Y, Uehara A, Hussein NA, Zhang J, Tao Y, Bergeron E, Ibrahim IH, Al Hosani MA, Yusof MF. (2021). Identification of a novel lineage of Crimean–Congo haemorrhagic fever virus in dromedary camels, United Arab Emirates. J. Gen. Virol.;102:001473. doi: 10.1099/jgv.0.001473.

Kortekaas J, Vloet RP, McAuley AJ, Shen X, Bosch BJ, de Vries L, Moormann RJ, Bente DA. (2015). Crimean-Congo Hemorrhagic Fever Virus Subunit Vaccines Induce High Levels of Neutralizing Antibodies But No Protection in STAT1 Knockout Mice. Vector Borne Zoonotic Dis. 15(12):759-64. doi: 10.1089/vbz.2015.1855.

Kopf M, Bachmann MF, Marsland BJ. (2010). Averting inflammation by targeting the cytokine environment. Nat. Rev. Drug Discov. 9:703–718

Kuehnert PA, Stefan CP, Badger CV, Ricks KM. (2021). Crimean-Congo Hemorrhagic Fever Virus (CCHFV): A Silent but Widespread Threat. *Current tropical medicine reports*. *8*(2), 141–147. https://doi.org/10.1007/s40475-021-00235-4

Kumar B , Manjunathachar HV, Ghosh S. (2020). A review on Hyalomma species infestations on humans and animals and progress on management strategies. Heliyon 6, e05675

Li P, Zheng Y, Chen X. (2017). Drugs for autoimmune inflammatory diseases: from small molecule compounds to anti-TNF biologics. Front. Pharmacol. https://doi.org/10.3389/ fphar.2017.00460

Lukashev AN. (2005). Evidence for recombination in crimean-congo hemorrhagic fever virus. J Gen Virol. 86:2333–8. doi: 10.1099/vir.0.80974-0

Lukashev A, Deviatkin A. (2018). Phylodynamics of Crimean Congo hemorrhagic fever virus in South Russia. *Infect. Genet. Evol.* 59:23–27. doi: 10.1016/j.meegid.2018.01.016.

Lumley S, Atkinson B, Dowall S, Pitman J, Staplehurst S, Busuttil J, Simpson A, Aarons E, Petridou C, Nijjar M. (2014). Non-fatal case of Crimean-Congo haemorrhagic fever imported into the United Kingdom (ex Bulgaria), June 2014. Euro surveillance . 19: 20864.

Majeed B, Dicker R, Nawar A, Badri S, Noah A, Muslem H. (2012). Morbidity and mortality of Crimean-Congo hemorrhagic fever in Iraq: Cases reported to the National Surveillance System, 1990–2010. Trans. R. Soc. Trop. Med. Hyg. 106:480–483. doi: 10.1016/j.trstmh.2012.04.006

Maltezou H C, Papa A, Tsiodras S, Dalla V, Maltezos E, (2009). Antoniadis,A.Crimean-Congo hemorrhagic fever in Greece: A public health perspective. Int. J. Infect. Dis., 13: 713–716.

Mardani M. (2002). Nesocomial Crimean-Congo hemorrhagic fever in Iran (1999 – 2000). Clin. Microbial. Infect. 7(1): 2201 – 2213.

Marriott AC, Nuttall PA. (1996). Molecular biology of nairoviruses. In: Elliott RM, editors. *The Bunyaviridae. The Viruses*. Boston, MA: Springer. doi: 10.1007/978-1-4899-1364-7_4

Mariner JC, Morrill J, Ksiazek T. (1995). Antibodies to hemorrhagic fever viruses in domestic livestock in Niger: Rift Valley fever and Crimean-Congo hemorrhagic fever. Am. J. Trop. Med. Hyg. 53: 217–221.

Mathiot C, Fontenille D, Digoutte J, Coulanges P. (1988). *Annales de l'Institut Pasteur/Virologie*. Elsevier; Masson, Paris: 1988. First isolation of Congo-Crimean haemorrhagic fever virus in Madagascar. 239–241.

Memish ZA. (2002). Infection control in Saudi Arabia: Meeting the challenge. Am. J. Infect. Control. 30:57–65. doi: 10.1067/mic.2002.120905.

Mendoza E, Warner B, Safronetz D, Ranadheera C. (2018). Crimean–Congo hemorrhagicc fever virus: Past, present and future insights for animal modeling and medical countermeasures. *Zoonoses Public Health.* 65:465–80. doi: 10.1111/zph.12469

Mirembe BB, Musewa A, Kadobera D, Kisaakye E, Birungi D, Eurien D, Nyakarahuka L, Balinandi S, Tumusiime A, Kyondo J, Mulei SM, Baluku J, Kwesiga B, Kabwama SN, Zhu BP, Harris JR, Lutwama JJ, Ario AR. (2019). Sporadic outbreaks of crimean-congo haemorrhagic fever in Uganda, July 2018-January 2019. PLoS Negl Trop Dis. 8;15(3):e0009213. doi: 10.1371/journal.pntd.0009213.

Messina JP, Pigott DM, Golding N, Duda KA, Brownstein JS, Weiss DJ, Gibson H, Robinson TP, Gilbert M, William Wint GR, Nuttall PA, Gething PW, Myers MF, George DB, Hay SI. (2015). The global distribution of Crimean-Congo hemorrhagic fever. Trans R Soc Trop Med Hyg. 109(8):503-13. doi: 10.1093/trstmh/trv050.

Midilli K, Gargılı A, Ergonul O, Elevli M, Ergin S, Turan, N, S ̧engöz G, Bakar M. (2009). The first clinical case due to AP92 like strain of Crimean-Congo hemorrhagic fever virus and a field survey. BMC Infect. Dis. 9:90.

Mofleh J, Ahmad A. (2012). Crimean-Congo haemorrhagic fever outbreak investigation in the western region of Afghanistan in 2008. EMHJ-East. Mediterr. Health J. 18:522–526. doi: 10.26719/2012.18.5.522.

Mohamed M, Said AR, Murad A, Graham R. (2008). A serological survey of Crimean-Congo haemorrhagic fever in animals in the Sharkia Governorate of Egypt. Vet. Ital. 44:513–517.

Morikawa S, Qing T, Xinqin Z, Saijo M, Kurane I. (2002). Genetic diversity of the M RNA segment among Crimean-Congo hemorrhagic fever virus isolates in China. Virology. 296, 159–164.

Mostafavi E, Pourhossein B, Chinikar S. (2014). Clinical symptoms and laboratory findings supporting early diagnosis of Crimean-Congo hemorrhagic fever in Iran. J Med Virol. 86:1188–92. doi: 10.1002/jmv.23922 .

Mustafa M, Leslie T, Mohareb E, Pinzon J, Zayed A, Ayazid E, Barthel R, Tucker C, Witt C. (2011). A Monitoring System for Crimean Congo Hemorrhagic Fever Epidemiology Studies in Afghanistan. 2011. Available online: https://core.ac.uk/reader/195381660

Mustafa ML, Ayazi E, Mohareb E, Yingst S, Zayed A, Rossi CA, Schoepp RJ, Mofleh J, Fiekert K, Akhbarian Z. (2009). Crimean-Congo hemorrhagic fever, Afghanistan. Emerg. Infecioust Dis. 17:1940–1941. doi: 10.3201/eid1710.110061.

Nabeth P, Cheikh DO, Lo B, Faye O, Vall I, Niang M, Wague B, Diop D, Diallo M, Diallo B. (2004). Crimean-Congo hemorrhagic fever, Mauritania. Emerg. Infect. Dis. 2004;10:2143–2149. doi: 10.3201/eid1012.040535

Naderi H, Sheybani F, Bojdi A, Khosravi N, Mostafavi I. (2013). Fatal nosocomial spread of Crimean-Congo hemorrhagic fever with very short incubation period. Am J Trop Med. 88:469. doi: 10.4269/ajtmh.2012.12-0337 .

Nasirian H. (2019). Crimean-Congo hemorrhagic fever (CCHF) seroprevalence: a systematic review and meta-analysis. Acta Trop. 196:102–20. doi: 10.1016/j.actatropica.2019.05.019

Nasirian H. (2020). New aspects about Crimean-Congo hemorrhagic fever (CCHF) cases and associated fatality trends: a global systematic review and meta-analysis. Comp Immunol Microbiol Infect Dis. 69:101429. doi: 10.1016/j.cimid.2020.101429.

Negredo A, Sánchez-Ledesma M, Llorente F, Pérez-Olmeda M, Belhassen-García M, González-Calle D, Sánchez-Seco M P, Jiménez-Clavero M Á. (2021). Retrospective Identification of Early Autochthonous Case of Crimean-Congo Hemorrhagic Fever, Spain, 2013. Emerg. Infect. Dis. 27:1754.

Negredo A, Sánchez-Arroyo R, Díez Fuertes F, deOry F, Budiño MA, Vázquez A, Garcinuño Á, Hernández L, Dela Hoz González C, Gutiérrez-Arroyo A. (2021). Fatal Case of Crimean-Congo Hemorrhagic Fever Caused by Reassortant Virus, Spain, 2018. Emerg. Infect. Dis. 27:1211.

Olaya C, Adhikari B, Raikhy G, Cheng J, Pappu HR. (2019). Identification and localization of Tospovirus genus-wide conserved residues in 3D models of the nucleocapsid and the silencing suppressor proteins. *Virol J.* 16:1– 15. doi: 10.1186/s12985-018-1106-4

Oluwayelu D, Afrough B, Adebiyi A, Varghese A, Eun-Sil P, Fukushi S, Yoshikawa T, Saijo M, Neumann E, Morikawa S. (2020). Prevalence of Antibodies to Crimean-Congo hemorrhagic fever virus in ruminants, Nigeria, 2015. Emerg. Infect. Dis. 26:744.

Onishchenko G, Efremenko V. (2004). Crimean-Congo haemorrhagic fever in southern Russia. Zhurnal Mikrobiol. Epidemiol. I Immunobiol. 4:86.

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D.(2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71. doi: 10.1136/bmj.n71.

Papa A, Tsergouli K, Tsioka K, Mirazimi A. (2017). Crimean-Congo hemorrhagic fever: tick-host-virus interactions. Front Cell Infect Microbiol. 7:1– 7. doi: 10.3389/fcimb.2017.00213

Papa A, Weber F, Hewson R, Weidmann M, Koksal I, Korukluoglu G, et al. (2015). Meeting report: first international conference on Crimean-Congo hemorrhagic fever. Antivir Res. 120:57–65. doi: 10.1016/j.antiviral.2015.05.005.

Papa A, Tzala E, Maltezou HC. (2011). Crimean Congo hemorrhagic fever virus, northeastern Greece. Emerg. Infect. Dis . 17:141.

Papa A, Ma B, Kouidou S, Tang Q, Hang C, Antoniadis A. (2002). Genetic characterization of the M RNA segment of Crimean Congo hemorrhagic fever virus strains, China. Emerg. Infect. Dis. 8, 50.

Papa A, Bino S, Llagami A, Brahimaj B, Papadimitriou E, Pavlidou V , Velo E, Cahani G, Hajdini M, Pilaca A. (2002). Crimean-Congo hemorrhagic fever in Albania, 2001. Eur. J. Clin. Microbiol. Infect. Dis. 21: 603–606.

Papa A, Christova I, Papadimitriou E, Antoniadis A. (2004). Crimean Congo hemorrhagic fever in Bulgaria. Emerg. Infect .Dis. 10:1465–1467.

Pirkani G.S., Jogezai E.K., Ilyas M. (2006). Crimean-Congo haemorrhagic fever (CCHF) in Balochistan. Prof. Med. J. 13:464–467.

Portillo A, Palomar AM, Santibáñez P, Oteo JA. (2021). Epidemiological Aspects of Crimean-Congo Hemorrhagic Fever in Western Europe: What about the Future? Microorganisms. 2021, 9, 649.

Prajapati DS, Patel KM, Patel RK, Sen DJ, Patel JS, Garg CS.(2011). Crimean-Congo hemorrhagic fever from tick-borne viral disease. *Int. J. Compr. Pharm. 2*, 0976–8157.

Proceeding of the Eleventh Veterinary Scientific Conference.(2012). 99-103

Pshenichnaya NY, Leblebicioglu H, Bozkurt I, Sannikova IV, Abuova GN, Zhuravlev AS, et al. (2017). Crimean-Congo hemorrhagic fever in pregnancy: a systematic review and case series from Russia, Kazakhstan, and Turkey. *Int J Infect Dis.* 58:58–64. doi: 10.1016/j.ijid.2017.02.019 .

Qaderi S, Mardani M, Shah A, Shah J, Bazgir N, Sayad J, Ghandchi E, Samsami M, Bagherpour JZ. (2021). Crimean-Congo hemorrhagic fever (CCHF) in Afghanistan: A retrospective single center study. Int. J. Infect. Dis. 2021;103:323–328. doi: 10.1016/j.ijid.2020.11.208.

Qing T, Prehaud C, Bouloy M. (1999). Sequencing and analysis of S gene segment of XHFV. Chin. J. Microbiol. Immunol.-Bejing. *19*, 461–465.

Raabe VN (2020). Diagnostic Testing for Crimean-Congo Hemorrhagic Fever. J Clin Microbiol. 2020 Mar 25;58(4):e01580-19. doi: 10.1128/JCM.01580-19.

Rai MA, Khanani MR, Warraich HJ, Hayat A, Ali SH. (2008). Crimean-Congo hemorrhagic fever in Pakistan. J. Med. Virol. 2008;80:1004–1006. doi: 10.1002/jmv.21159.

Rahden P, Adam A, Mika A, Jassoy C. (2019). Elevated Human Crimean–Congo hemorrhagic fever virus seroprevalence in Khashm el Girba, Eastern Sudan. Am. J. Trop. Med. Hyg. 100:1549–1551. doi: 10.4269/ajtmh.18-0977.

Riyadh Abdulameer Alhilfi, Hanan Abdulghafoor Khaleel, Baghdad Muayad Raheem, Sinan Ghazi Mahdi, Celine Tabche, Salman Rawaf (2023). Large outbreak of Crimean-Congo haemorrhagic fever in Iraq, 2022. IJID Regions 6 (2023) 76–79. https://doi.org/10.1016/j.ijregi.2023.01.007

Saleem M, Shah SZ, Haidari A, Idrees F. (2016). Prevalence of Crimean-Congo hemorrhagic fever in Pakistan and its new research progress. J Coast Life Med. 4:259–62. doi: 10.12980/jclm.4.2016J5-23

Sang R, Lutomiah J, Koka H, Makio A, Chepkorir E, Ochieng C, Yalwala S, Mutisya J, Musila L, Richardson JH. (2011). Crimean-Congo hemorrhagic fever virus in Hyalommid ticks, northeastern Kenya. Emerg. Infect. Dis. 2011;17:1502. doi: 10.3201/eid1708.102064.

Sahak MN, Arifi F, Saeedzai SA.(2019). Descriptive epidemiology of Crimean-Congo Hemorrhagic Fever (CCHF) in Afghanistan: Reported cases to National Surveillance System, 2016-2018. Int J Infect Dis. 88:135-140. doi: 10.1016/j.ijid.2019.08.016.

Saleem J, Usman M, Nadeem A, Sethi SA, Salman M. (2009). Crimean-Congo hemorrhagic fever: A first case from Abbottabad, Pakistan. *Int. J. Infect. Dis.* 13:e121–e123. doi: 10.1016/j.ijid.2008.07.023.

Scholte FEM, Spengler JR, Welch SR, Harmon JR, Coleman-McCray JD, Freitas BT, Kainulainen MH, Pegan SD, Nichol ST, Bergeron É, Spiropoulou CF. (2019). Single-dose replicon particle vaccine provides complete protection against Crimean-Congo hemorrhagic fever virus in mice. Emerg Microbes Infect. 8(1):575-578. doi: 10.1080/22221751.2019.1601030.

Schmaljohn C S, and Hooper JW. (2001). Bunyaviridae: the viruses and their replication, p. 1581-1602. In D. M. Knipe and P. M. Howley (ed.), Fields virology, 4th ed. Lippincott-Raven Publishers, Philadelphia, Pa.

Schnittler HJ, Feldmann H. (2003). Viral hemorrhagic fever—A vascular disease? Thromb Haemost. 89:967–72. doi: 10.1055/s-0037-1613397.

Shah Hosseini N, Wong G, Babuadze G, Camp JV, Ergonul O, Kobinger GP, Chinikar S, Nowotny N. (2021). Crimean-Congo Hemorrhagic Fever Virus in Asia, Africa and Europe. Microorganisms. 2021 Sep 9;9(9):1907. doi: 10.3390/microorganisms9091907.

Shahhosseini N, Chinikar S, Shams E, Nowotny N, Fooks AR. (2017 A). Crimean-Congo hemorrhagic fever cases in the North of Iran have three distinct origins. Virusdisease.;28:50–53. doi: 10.1007/s13337-016-0359-z.

Shahhosseini N, Jafarbekloo A, Telmadarraiy Z, Chinikar S, Haeri A, Nowotny N, Groschup MH, Fooks AR, Faghihi F. (2017 B). Co-circulation of Crimean-Congo hemorrhagic fever virus strains Asia 1 and 2 between the border of Iran and Pakistan. Heliyon. 2017;3:e00439. doi: 10.1016/j.heliyon.2017.e00439.

Sharifi-Mood B, Metanat M, Alavi-Naini R. (2014). Prevalence of crimean-congo hemorrhagic fever among high risk human groups. Int J High Risk Behav Addict. 3:5–8. doi: 10.5812/ijhrba.11520

Sharifi-Mood B, Alavi-Naini R, Metanat M, Mohammadi M, Shakeri A, Amjadi A. (2013). Efficacy of high-dose methylprednisolone in patients with Crimean-Congo haemorrhagic fever and severe thrombocytopenia. Trop Doct. 43(2):49-53. doi: 10.1177/0049475513486642.

Shepherd A J, Swanepoel R. & Leman PA. (1989). Antibody response in Crimean-Congo hemorrhagic fever. Rev. Infect. Dis. 11:S801–S806.

Shkaib Ahmad, Narmeen Hashmi, Javeria Arif Siddiqui, Amna Siddiqui, Shoaib Ahmad, Hashim Talib Hashim, Mohammad Yasir Essar (2022) . The nosebleed fever outbreak in Iraq: Challenges, efforts and recommendations. Annals of Medicine and Surgery 79 (2022) 104077.

Shrivastava N, Kumar JS, Yadav P, Shete AM, Jain R, Shrivastava A, Dash PK (2021) Development of double antibody sandwich ELISA as potential diagnostic tool for rapid detection of Crimean-Congo hemorrhagic fever virus. Sci Rep 11(1):14699. https://doi.org/10.1038/s41598-021-93319-0

Simon M, Johansson C, Lundkvist Å, Mirazimi A. (2009). Microtubule-dependent and microtubule-independent steps in Crimean-Congo hemorrhagic fever virus replication cycle. Virol. 385:313–22. doi: 10.1016/j.virol.2008.11.020

Smith DR, Shoemaker CJ, Zeng X, Garrison AR, Golden JW, Schellhase CW, Pratt W, Rossi F, Fitzpatrick CJ, Shamblin J, Kimmel A, Zelko J, Flusin O, Koehler JW, Liu J, Coffin KM, Ricks KM, Voorhees MA, Schoepp RJ, Schmaljohn CS. (2019). Persistent Crimean-Congo hemorrhagic fever virus infection in the testes and within granulomas of non-human primates with latent tuberculosis. PLoS Pathog. 26;15(9):e1008050. doi: 10.1371/journal.ppat.1008050.

Sojka D, Franta Z, Horn M, Caffrey CR, Mareš M, Kopác̆ek P. (2013). New insights into the machinery of blood digestion by ticks. Trends Parasitol. 29:276– 85. doi: 10.1016/j.pt.2013.04.002

Suleiman MN, Muscat-Baron JM, Harries JR, Satti AG, Platt GS, Bowen ET, Simpson DI., (1980). Crimean-Congo hemorrhagic fever in Dubai: an outbreak at the Rashid Hospital. Lancet.,2: 939 . 41.

Swanepoel R. (1994). Crimean-Congo hemorrhagic fever, p. 723-729. In G. R. Thomson, R. C. Tustin, and J. A. W. Coetzer (ed.), Infectious diseases of livestock, with reference to Southern Africa. Oxford University Press, Cape Town, South Africa.

Swanepoel R., Shepherd A., Leman P., Shepherd S., McGillivray G., Erasmus M., Searle L., Gill D.(1987). Epidemiologic and clinical features of Crimean-Congo hemorrhagic fever in southern Africa. Am. J. Trop. Med. Hyg. 1987;36:120. doi: 10.4269/ajtmh.1987.36.120.

Swanepoel R, Shepherd A, Leman P, Shepherd S, McGillivray G, Erasmus M, Searle L, Gill D. (1987). Epidemiologic and clinical features of Crimean-Congo hemorrhagic fever in southern Africa. Am. J. Trop. Med. Hyg. 36:120. doi: 10.4269/ajtmh.1987.36.120.

Tall A, Sall A, Faye O, Diatta B, Sylla R, Faye J, Faye P, Ly A, Sarr F, Diab H. (2009). Two cases of Crimean-Congo haemorrhagic fever (CCHF) in two tourists in Senegal in 2004. Bull. Soc. Pathol. Exot. 102:159–161.

Tanir G, Tuygun N, Balaban I, Doksöz O. (2009). A case of Crimean-Congo hemorrhagic fever with pleural effusion. Jpn J Infect Dis. 62:70–2.

Tantawi H, Shony M, Al-Tikriti S. (1981). Antibodies to Crimean-Congo haemorrhagic fever virus in domestic animals in Iraq: A seroepidemiological survey. Int. J. Zoonoses. 8:115–120.

Tantawi HH, Al-Moslih MI, Al-Janabi NY, Al-Bana AS, Mahmud MI, Jurji F, et al. (1980). Crimean-Congo haemorrhagic fever virus in Iraq: isolation, identification and electron microscopy. Acta Virol. 24:464–7.

Tantawi HH, Al-Moslih MI, Hassan FK, Al-Ani FS.(1980). Crimean-Congo Haemorrhagic Fever. First Edition/ Baghdad -1980. Iraqi Ministry of Health Publication. AL-Muthanna House For Printing& Publishing. Baghdad-Iraq

Tarantola A, Nabeth P, Tattevin P, Michelet C, Zeller H. (2006). Look back exercise with imported Crimean-Congohemorrhagic fever, Senegal and France. Emerg. Infect. Dis. 12:1424.

Temur AI, Kuhn JH, Pecor DB, Apanaskevich DA, Keshtkar-Jahromi M. (2021). Epidemiology of Crimean-Congo hemorrhagic fever (CCHF) in Africa-Underestimated for decades. Am. J. Trop. Med. Hyg. 2021 doi: 10.4269/ajtmh.20-1413.

Tipih T & Burt FJ. (2017). Crimean-Congo hemorrhagic fever virus: Advances in vaccine development. Biores. Open Access 9, 137–150 (2020); Dowall, S. D., Carroll, M. W. & Hewson, R. Development of vaccines against Crimean-Congo haemorrhagic fever virus. Vaccine 35, 6015–6023

Turell MJ. (2007). Role of ticks in the transmission of Crimean-Congo hemorrhagic fever virus. In: Ergonul O, Whitehouse CA, editors. Crimean-Congo Hemorrhagic Fever. Dordrecht: Springer. 143–54. doi: 10.1007/978-1-4020-6106-6_12 1

van Eeden P, Joubert JR, van de Wal, BW, King JB, de Kock A, Groenewald J. (1985) A nosocomial outbreak of Crimean-Congohemorrhagicc fever at Tygerberg Hospital-Part I. Clinical features. *S Afr Med J.* 68:711–7.

Van Eeden PJ, van Eeden SF, Joubert JR, King JB, van de Wal BW, Michell WL. (1985). A nosocomial outbreak of Crimean-Congo hemorrhagic fever at Tygerberg Hospital. Part II. Management of patients. S Afr Med J., 68: 718-721.

Vatansever Z, Uzun R, Estrada-Pena A, Ergonul O. (2007). Crimean-Congo hemorrhagic fever in Turkey. In *Crimean-Congo Hemorrhagic Fever*; Springer: Berlin/Heidelberg, Germany, pp. 59–74.

Volynkina A, Lisitskaya Y, Kolosov A, Shaposhnikova L, Pisarenko S, Dedkov V, et al. (2022). Molecular epidemiology of Crimean-Congo hemorrhagic fever virus in Russia. PLoS One. 17:e0266177. doi: 10.1371/journal.pone.0266177

Vorou R], Pierroutsakos I]N], Maltezou HC.(2007). Crimean-Congo hemorrhagic fever. Curr. Opin. Infect. Dis. 2007;20:495. doi: 10.1097/QCO.0b013e3282a56a0a.

Whitehouse, C.A. (2007). Risk Groups and Control Measures for Crimean-Congo Hemorrhagic Fever. In: Ergonul, O., Whitehouse, C.A. (eds) Crimean-Congo Hemorrhagic Fever. Springer, Dordrecht. https://doi.org/10.1007/978-1-4020-6106-6_20

Whitehouse C A. (2004). Crimean-Congo hemorrhagic fever. Antiviral Res. 64:145-160. doi: 10.1016/j.antiviral.2004.08.001.

Williams R, Al-Busaidy S, Mehta F, Maupin G, Wagoner K, Al-Awaidy S, Suleiman A, Khan A, Peters C, Ksiazek T. (2000). Crimean-Congo haemorrhagic fever: A seroepidemiological and tick survey in the Sultanate of Oman. Trop. Med. Int. Health. 5:99–106. doi: 10.1046/j.1365-3156.2000.00524.x.

WHO, (2022). Crimean-Congo haemorrhagic fever. https://www.who.int/news-room/fact-sheets/detail/crimean-congo-haemorrhagic-fever.

WHO, (2017). Crimean Congo Haemorrhagic Fever: Key facts 2017. Available from: https://www.afro.who.int/health-topics/crimean-congo-haemorrhagic-fever.

WHO, (2018). Crimean-Congo haemorrhagic fever World Health Organisation: World Health Oragnistaion; 2018. [updated 31 January 2013. Available from: http://www.who.int/news-room/fact-sheets/detail/crimean-congo-haemorrhag.

Xiao X, Feng Y, Zhu Z, Dimitrov DS. (2011). Identification of a putative Crimean-Congo hemorrhagic fever virus entry factor. Biochem Biophys Res Commun. 411:253–8. doi: 10.1016/j.bbrc.2011.06.109 .

Xia H, Beck AS, Gargili A, Forrester N, Barrett AD, Bente DA. (2016). Transstadial Transmission and Long-term Association of Crimean-Congo Hemorrhagic Fever Virus in Ticks Shapes Genome Plasticity. Sci Rep. 24;6:35819. doi: 10.1038/srep35819.

Yadav PD, Cherian SS, Zawar D, Kokate P, Gunjikar R, Jadhav S, Mishra AC, Mourya DT.(2013 A). Genetic characterization and molecular clock analyses of the Crimean-Congo hemorrhagic fever virus from human and ticks in India, 2010–2011. Infect. **Genet. Evol. 14, 223–231.**

Yadav PD, Gurav YK, Mistry M, Shete AM, Sarkale P, Deoshatwar AR, Unadkat VB, Kokate P, Patil DY, Raval DK.(2014). Emergence of Crimean-Congo hemorrhagic fever in Amreli district of Gujarat state, India, June to July 2013. Int. J. Infect. Dis. 18, 97–100.

Yilmaz R, Ozcetin M, Erkorkmaz U, Ozer S, Ekici F. (2009). Public knowledge and attitude toward Crimean Congo hemorrhagic fever in Tokat Turkey. Iran. J. Arthropod-Borne Dis. 3, 12.

Yilmaz G, Koksal I, Topbas M, Yilmaz H, Aksoy F. (2010). The effectiveness of routine laboratory findings in determining disease severity in patients with Crimean-Congo hemorrhagic fever: severity prediction criteria. *J Clin Virol.* 47:361– 5. doi: 10.1016/j.jcv.2010.01.010 .

Yousaf MZ, Ashfaq UA, Anjum KM, Fatima S. (2018). Crimean-Congo hemorrhagic fever (CCHF) in Pakistan: the "Bell" is ringing silently. *Crit Rev Eukaryot.* 28:93–100. doi: 10.1615/CritRevEukaryotGeneExpr.2018020593 .

Zivcec M, Guerrero LIW, Albariño CG, Bergeron É, Nichol ST, Spiropoulou CF. (2017). Identification of broadly neutralizing monoclonal antibodies against Crimean-Congo hemorrhagic fever virus. Antiviral Res. 2017 Oct;146:112-120. doi: 10.1016/j.antiviral.2017.08.014.

Zohaib A, Saqib M, Athar MA, Hussain MH, Sial A.-u.-R, Tayyab MH, Batool M, Sadia H, Taj Z, Tahir U. (2020). Crimean-Congo hemorrhagic fever virus in humans and livestock, Pakistan, 2015–2017. Emerg. Infect. Dis. 2020;26:773. doi: 10.3201/eid2604.191154.

Zhou Z, Deng F, Han N, Wang H, Sun S, Zhang Y, et al. (2013). Reassortment and migration analysis of crimean-congo haemorrhagic fever virus. J Gen Virol. 94:2536–48. doi: 10.1099/vir.0.056374-0

Ölschläger S, Gabriel M, Schmidt-Chanasit J, Meyer M, Osborn E, Conger NG, Allan PF, Günther S. (2011). Complete sequence and phylogenetic characterisation of Crimean–Congo hemorrhagic fever virus from Afghanistan. J. Clin. Virol. 50:90–92.