The role of Veterinary Medicine in controlling of Crimean-Congo Hemorrhagic Fever (CCHF)

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Introduction

- Crimean Congo haemorrhagic fever virus (CCHFV) is an RNA virus belonging to the ***Nairovirus*** genus of the family ***Bunyaviridae*** (Daniel Oluwayelu *et al.* 2018) , A zoonotic disease in many countries of Asia, Africa, the Middle East and south eastern Europe .

- Crimean-Congo haemorrhagic fever virus (CCHFV) is a deadly human pathogen of the utmost seriousness being highly lethal causing devastating disease symptoms that result in intense and prolonged suffering to those infected.

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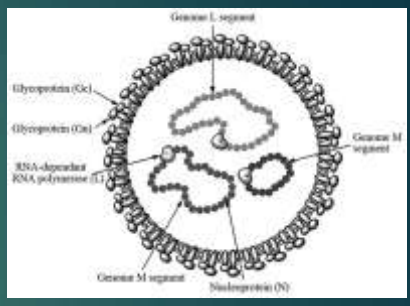


Introduction

- CCHFV is transmitted to humans by Hyalomma ticks and contact with the blood of viremic livestock. CCHFV is the most widespread tick-borne virus on earth.

- During the past 40 years, this virus has repeatedly caused sporadic outbreaks responsible for relatively low numbers of human casualties, but with an alarming fatality rate between 10% and 50% (Flusin *et al*., 2010) and of up to 80% in clinically infected patients (Ajab Khan, et al. 2018, Dowall SD, et al. 2017).
- The fatality rate differences may be due to phylogenetic variation of the virus, transmission route, and/or different treatment facilities (Gupta S, et al,. 2017).
- It is a concern that recent data shows the geographic distribution of Hyalomma ticks is expanding.

History

- CCHFV is thought to have originated in Africa 1000-5000 year ago, although strain Ap92 found in Greece is also considered an ancient lineage.

- The natural reservoir it is quite possible that the earliest account of infection with Crimean-Congo virus is that found in the 'Kitab al-Hawi' (a medical textbook) composed by the Persian clinician Abu Bakr al-Razia, also known as Rhazes (c. 854 – 932). He describes three cases in which the symptoms exhibit a remarkable similarity with those of CCHF.

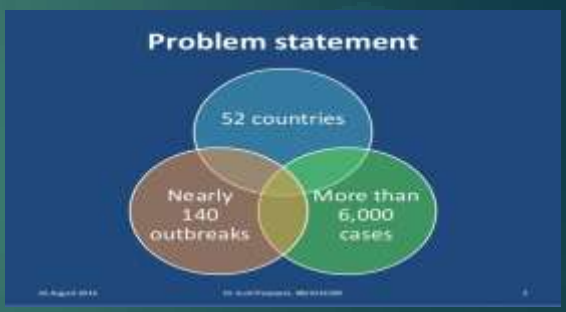
- Subsequently, a follower of Avicenna, the 12th century Persian royal physician , Husayn Gorgani, also described a case in Tajikistan.

History

- The disease was first described in the Crimea Soviet military personnel in 1944 and given the name Crimean hemorrhagic fever.
- Congo virus was first isolated in Africa from the blood of a febrile patient in Zaire in 1956.
- In 1967, (Simpson et al). described 12 cases of a feverish illness of which 5 were laboratory infections; the virus was isolated by the inoculation of blood into new-born mice.
- Simpson showed that these viruses were similar to the one isolated in 1956.

Geographic Distribution

- CCHF is one of the most important and the most widespread tick-borne viral disease of human beings in the world.
- Since its discovery, nearly 140 outbreaks involving more than 5,000 cases have been reported worldwide.
- A total of 52 countries have been recognized as endemic or potentially endemic regions, reporting a substantial number of cases every year (Ashfon L, 2018)



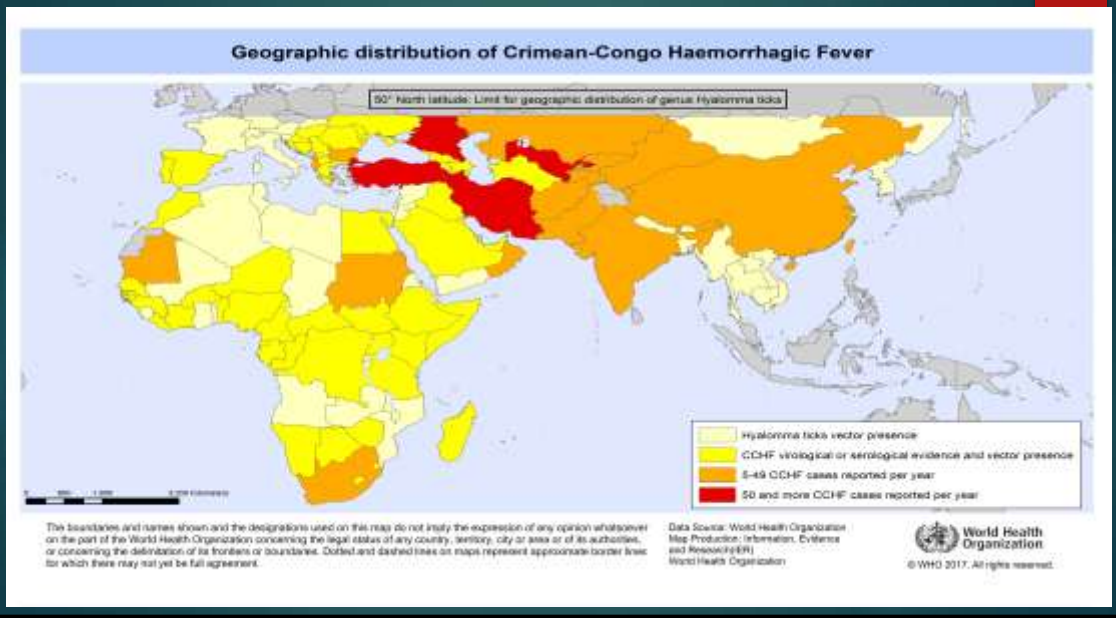
Geographic Distribution

Geographic Distribution

- **CCHF virus (CCHFV) has been observed in over 30 countries, including in Africa (Democratic Republic of Congo, South Africa, Nigeria, Senegal, Uganda, Tanzania, Mauritania, Kenya), Asia (Pakistan, Afghanistan, Tajikistan, Uzbekistan, Kazakhstan, China), the Middle East (Iran, Iraq, United Arab Emirates, Saudi Arabia, Oman), and southeastern Europe (the Russian Federation, Bulgaria, Albania, Kosovo, Turkey, Greece, and Spain) .**

- **Since 2000 the infection has caused epidemics in Turkey, Iran, Russia, Uganda and Pakistan (Johnson S, et al,. 2018)**

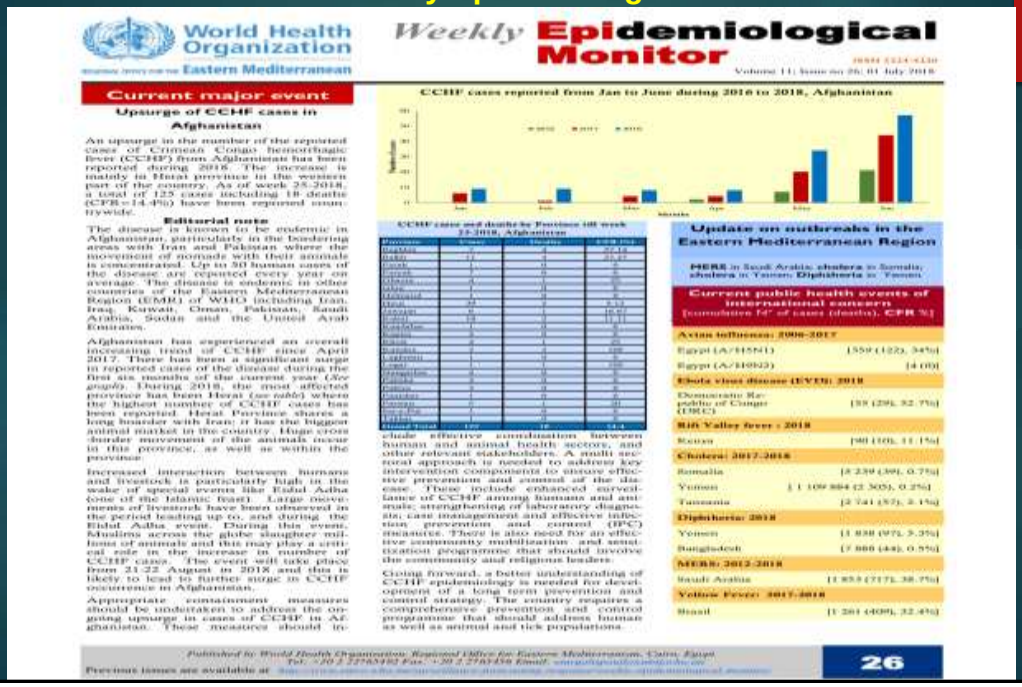
Geographic distribution of Crimean-Congo hemorrhagic fever virus. Countries in red report more than 50 human cases annually to the WHO, and those in orange report fewer than 50 cases



Geographic Distribution

- During 2018, the most affected province has been Herat where the highest number of CCHF cases has been reported.
- Herat Province shares a long boarder with Iran; it has the biggest animal market in the country. Huge cross -border movement of the animals occur in this province, as well as within the province (WHO, 2018).
- CCHF is endemic in the Baluchistan province, Pakistan. There is an ongoing trade of animals and animal skins with movement intra Pakistan and between neighboring countries i.e. Afghanistan and Iran (WHO report, 2013).

WHO EMRO Weekly Epidemiological Monitor:



World Health Organization
Eastern Mediterranean

Weekly Epidemiological Monitor

Volume 11, Issue no 26, 01 July 2018

Current major event

Upsurge of CCHF cases in Afghanistan

An upsurge in the number of the reported cases of Crimean Congo hemorrhagic fever (CCHF) from Afghanistan has been reported during 2018. The increase is mainly in Herat province in the western part of the country. As of week 25.2018, a total of 125 cases including 18 deaths (CFR=14.4%) have been reported countrywide.

Editorial note

The disease is known to be endemic in Afghanistan, particularly in the bordering areas with Iran and Pakistan where the movement of nomads with their animals is concentrated. Up to 30 human cases of the disease are reported every year on average. The disease is endemic in other countries of the Eastern Mediterranean Region (EMR) of WHO including Iran, Iraq, Kuwait, Oman, Pakistan, Saudi Arabia, Sudan and the United Arab Emirates.

Afghanistan has experienced an overall increasing trend of CCHF since April 2017. There has been a significant surge in reported cases of the disease during the first six months of the current year (*See graph*). During 2018, the most affected province has been Herat (*see table*) where the highest number of CCHF cases has been reported. Herat Province shares a long boarder with Iran; it has the biggest animal market in the country. Huge cross border movement of the animals occur in this province, as well as within the province.

Increased interaction between humans and livestock is particularly high in the wake of special events like Eidul Adha (one of the Islamic feast). Large movements of livestock have been observed in the period leading up to, and during the Eidul Adha event. During this event, Muslims across the globe slaughter millions of animals and this may play a critical role in the increase in number of CCHF cases. The event will take place from 21-22 August in 2018 and this is likely to lead to further surge in CCHF occurrence in Afghanistan.

Appropriate containment measures should be undertaken to address the ongoing upsurge in cases of CCHF in Afghanistan. These measures should include effective zoonotization between human and animal health sectors, and other relevant stakeholders. A multi sectoral approach is needed to address key intervention components to ensure effective prevention and control of the disease. These include enhanced surveillance of CCHF among humans and animals; strengthening of laboratory diagnosis; case management and effective infection prevention and control (IPC) measures. There is also need for an effective community mobilization and sensitization programme that should involve the community and religious leaders.

Going forward, a better understanding of CCHF epidemiology is needed for development of a long term prevention and control strategy. The country requires a comprehensive prevention and control programme that should address human as well as animal and tick populations.

CCHF cases reported from Jan to June during 2016 to 2018, Afghanistan

CCHF cases and deaths by Province till week 25-2018, Afghanistan

Province	Cases	Deaths	CFR (%)
Badghis	1	0	0.0
Balkh	11	1	9.1
Farah	1	0	0.0
Faryab	1	0	0.0
Ghazni	1	0	0.0
Ghor	1	0	0.0
Helmand	1	0	0.0
Herat	84	7	8.3
Jawzjan	8	1	12.5
Kabul	11	1	9.1
Kandahar	1	0	0.0
Kapisa	1	0	0.0
Khost	1	0	0.0
Kunar	1	0	0.0
Laghman	1	0	0.0
Logar	1	0	0.0
Nangarhar	1	0	0.0
Nimroz	1	0	0.0
Paktya	1	0	0.0
Paktika	1	0	0.0
Parwan	1	0	0.0
Samangan	1	0	0.0
Sar-e Pul	1	0	0.0
Takhar	1	0	0.0
Grand Total	125	18	14.4

Update on outbreaks in the Eastern Mediterranean Region

MERS in Saudi Arabia; **cholera** in Somalia; **cholera** in Yemen; **Diphtheria** in Yemen

Current public health events of international concern (cumulative N° of cases (deaths), CFR %)

Avian influenza: 2006-2017	
Egypt (A/H5N1)	359 (122), 34%)
Egypt (A/H9N2)	4 (0)
Ebola virus disease (EVD): 2018	
Democratic Republic of Congo (DRC)	59 (29), 32.7%)
Rift Valley fever : 2018	
Kenya	90 (10), 11.1%)
Cholera: 2017-2018	
Somalia	8 239 (30), 0.7%)
Yemen	1 109 884 (2 305), 0.2%)
Tanzania	2 741 (57), 2.1%)
Diphtheria: 2018	
Yemen	1 838 (97), 5.3%)
Bangladesh	7 868 (44), 0.5%)
MERS: 2012-2018	
Saudi Arabia	1 853 (717), 38.7%)
Yellow Fever: 2017-2018	
Brazil	1 281 (408), 32.4%)

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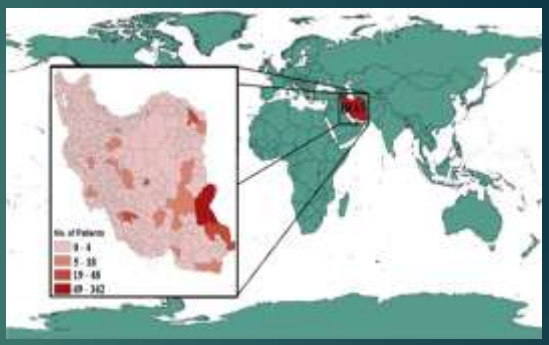
CCHF in Iran

- **In the year 1353, Dr. Asefi collected 60 cases in the cities of Ardebil, Sarab and Khalkhal, under the name of a hemorrhagic disease, with precision, clinical signs and describes the course of the disease, and the congenital hemorrhagic fever, but it was not possible to determine the etiology of the disease at that time.**



CCHF in Iran

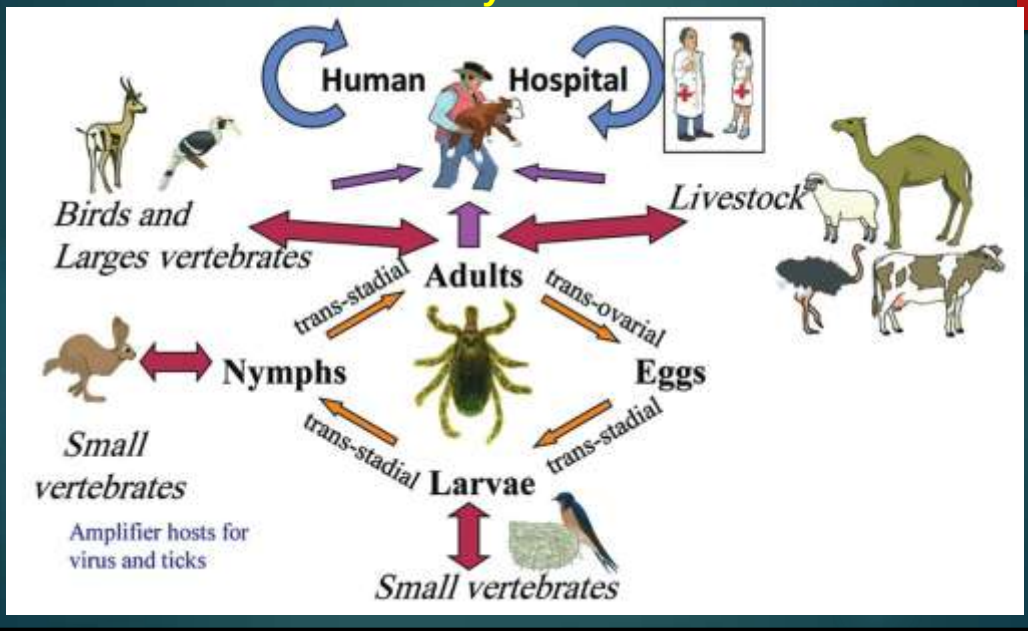
- The first report of the positive serology of CCHF in Iran was given to the livestock in the slaughterhouse of Tehran by the Russian Chumakov (1970).
- In 1974, Saidi published the serological evidence of the disease from the school-children's serum sample.
- In 1975 in a large study of serologic positive evidence in the study of human serum and livestock in the East Azarbaijan region.
- The first clinically proven case of CCHF, which was confirmed by viral culture and serological tests, was reported by Rokhsari in 1999 from Shahrekord and then from West Azarbaijan.

CCHF in Iran

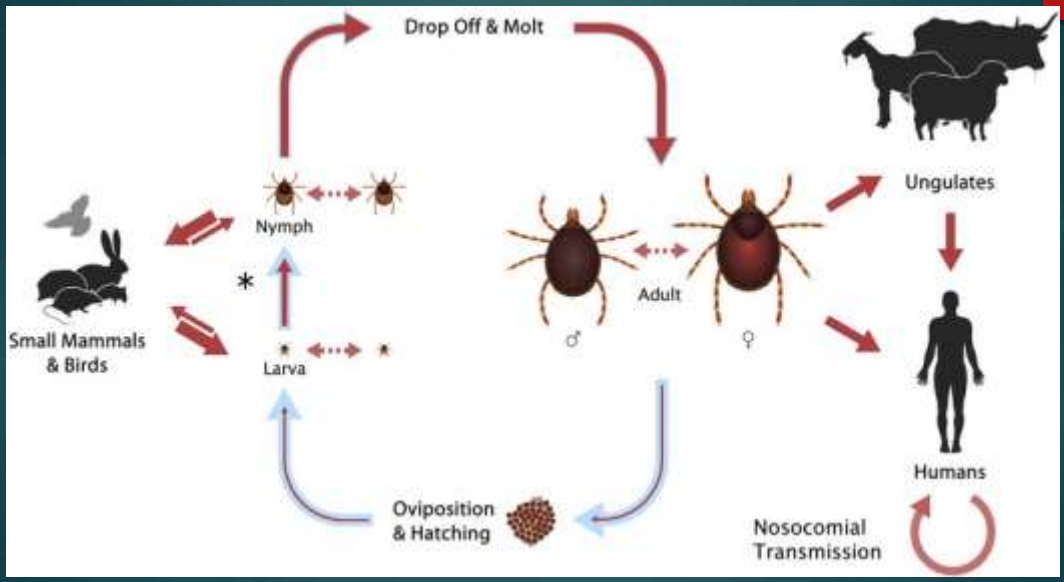
- Since 1999, CCHF has been reported in 26 of the 31 provinces of Iran, with the greatest numbers of cases in Sistan and Baluchestan, Isfahan, Fars, Tehran, Khorasan, and Khuzestan.
- Only five provinces (Mazandaran, Ardabil, Ilam, Kohgiluyeh and Boyer-Ahmad, and Alborz) have not reported human infections, but at least two of these are known to have cattle and ticks harbouring CCHFV (Chinikar S, et al. 2012).

Geographical Distribution of Confirmed CCHF Cases from June 2000 to February 2015, Iran

CCHF virus Cycle in nature



CCHF virus Cycle in nature



Factors for emergence of CCHF

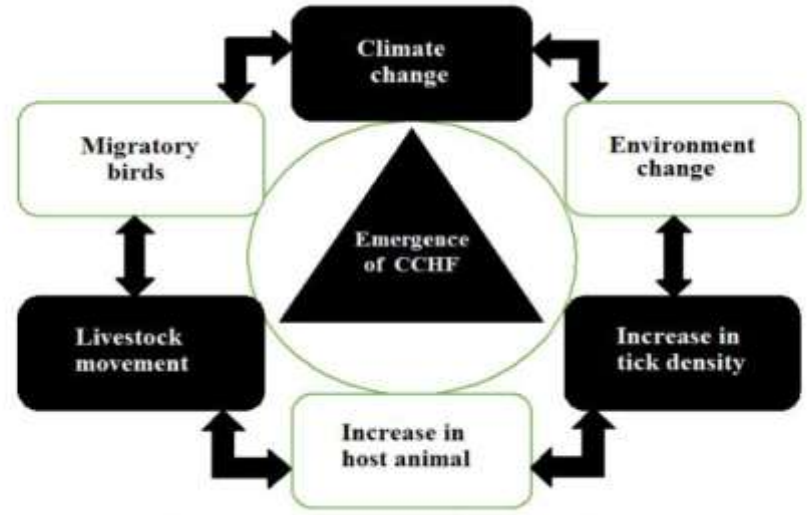


Figure 3. Factors for emergence of Crimean–Congo hemorrhagic fever (CCHF).

Transmission

- Transmitted by ticks
  - *Hyalomma* spp. are principal vectors
    - Transovarial
    - Transstadial
    - Venereal
  - Other ixodid ticks
  - Biting midges?
  - Soft ticks

Six possible pathways for CCHFV

1. Human mobility (including military movements)
2. Trade in livestock
3. Migratory bird movements
4. Trade in, and movements of mammal wildlife
5. Trade in animal products
6. Pet movements

Transmission

- Considering the main transmission roots, high-risk occupations for CCHF are those in close contact with the vector and/or infected hosts including:
- Farmers,
- Shepherds,
- Abattoir workers (slaughterhouse worker)
- Veterinarians and veterinary staff
- Laboratory experts,
- Hospital personnel
- Butchers
- The staff of restaurants and kabab,s shops
-

Transmission in Human

Sacrificing on Eid Al-Adha

- On **Eid-al-Adha religious occasion**, millions of livestock are sacrificed all over the country. Local people in suburbs and rural areas are rarely familiar with guidelines on proper slaughtering; therefore, infections like CCHF, if neglected, could have catastrophic consequences.

Disease In Animals

- According to the World Health Organization reports, out of 1709 pathogens, 832 agents (49%) of animals are transmitted to humans.
- Of the 156 newly diagnosed diseases in humans, 114 of them (73%) are transmitted from animals to humans.
- Animals play a crucial role in the life cycle of ticks, and in the transmission and amplification of the virus and are, therefore, in the focus of veterinary public health.

Disease In Animals

- Many species of wild and domesticated mammals
  - Hosts for immature ticks
    - Small mammals such as:
    - Hares

Hedgehogs

Rodents (Gargili A, et al. 2013)

Disease In Animals

- Hosts for mature ticks
- Large herbivores such as cattle, could provide virus for tick-borne transmission to highly susceptible humans and therefore play an important role in the epidemiology of the disease (Oluwayelu, et al. 2018)

sheep

Goats

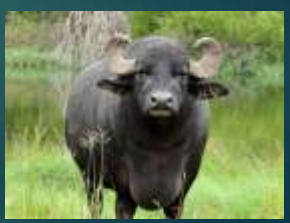
Disease In Animals

- Antibodies have been reported in horses,

- Donkeys,

Buffalo (CFSPH, 2007)

- Camels (Saidi S et al. 1975)



Disease In Animals

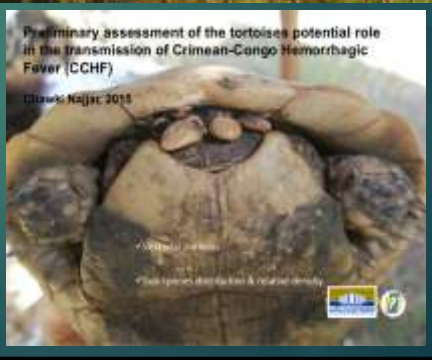
- Most species of **birds are seronegative** and are thought to be resistant to infection; however, antibodies can be found in **ostriches**, and these animals become viremic after experimental inoculation.

- Low CCHFV viremia was also reported from an experimentally infected blue-helmeted **guinea fowl** (Numidia meleagris).

- Antibodies have been reported in a **magpie**.

Disease In Animals

- **Other potential hosts**
  - Birds mostly seronegative Many birds are resistant to infection, but ostriches are susceptible)



  - **Reptiles rarely affected**

Although immature Hyalomma anatolicum ticks sometimes feed on reptiles, antibodies to CCHFV have only been reported from one reptile, a tortoise from Tadzhikistan.

Disease In Animals

- A wide spectrum of domestic animal species has been investigated internationally, including cattle, sheep, goats, horses, pigs, dogs, and chickens.

- Using the AGDP test with antigens prepared from CCHFV strains isolated in then-Soviet republics, antibodies were detected in blood sera from two bats in France, from an area bordering with Spain (Spengler JR, et al. 2016).

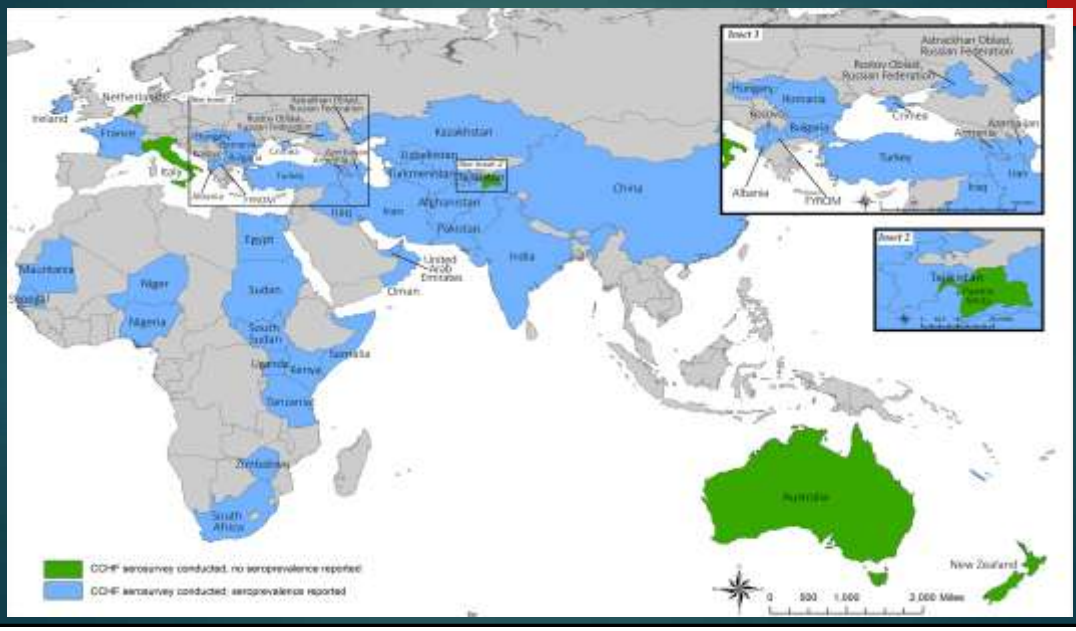
Symptoms in animals

- CCHF virus infections are asymptomatic in animals.
- Experimentally infected sheep and cattle show only transient and mild elevation in body temperature and become viremic for one week (CFSPH, 2007).
- Asymptomatic viremia lasting up to 7–15 days has been described in several vertebrate animal species, and CCHFV has been isolated from their blood and tissues livestock and small mammals.

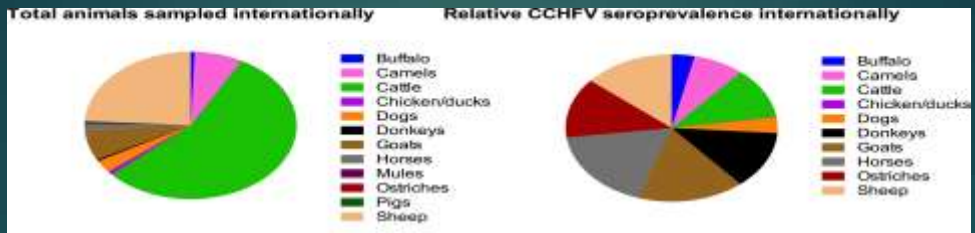
Symptoms in animals

- No post mortem lesions have been reported in animals except newborn rodents (Goswami TK, et al. 2013).
- **Sheep** have been recognized as very important CCHFV reservoirs in certain endemic regions, and have been epidemiologically linked to human cases on several occasions (Spengler JR, et al. 2016).

Geographic summary of countries represented in CCHFV seroepidemiological surveys (Spengler JR, et al. 2016)



Total international CCHFV seroprevalence reported in domestic animals by species (Spengler JR, et al. 2016)



	n	% CCHFV seropositive	Studies	No. countries represented
Buffalo	433	6.00	9	3
Camels	5272	13.41	15	11
Cattle	39684	19.33	75	34
Chicken/ducks	616	0.16	4	3
Dogs	1978	6.00	1	1
Donkeys	230	21.74	6	4
Goats	4617	28.07	33	15
Horses	1180	30.68	7	5
Mules	105	0.00	2	1
Ostriches	97	22.68	2	2
Pigs	222	0.00	3	3
Sheep	17244	23.85	49	25

Seroprevalence of CCHF in Animals in the World

- High seroprevalence in domestic animals include 79.1% seropositive cattle (Afghanistan) , 75.0% sheep (Afghanistan) (Mustafa ML, et al. 2011), 66.0% goats (Turkey) , 58.8% horses (Tantawi H, et al. 1981) , and 39.5% donkeys (Tajikistan).
- High seroprevalence has also been reported in camels; the highest percentage of seropositive camels was reported in Kenya at 26%.
- Considerable seroprevalence was consistently reported in hares 3%–22%, buffalo 10%–20%, and rhinoceroses 40%–68% (Spengler JR, et al. 2016).

Seroprevalence of CCHF in Animals in the World

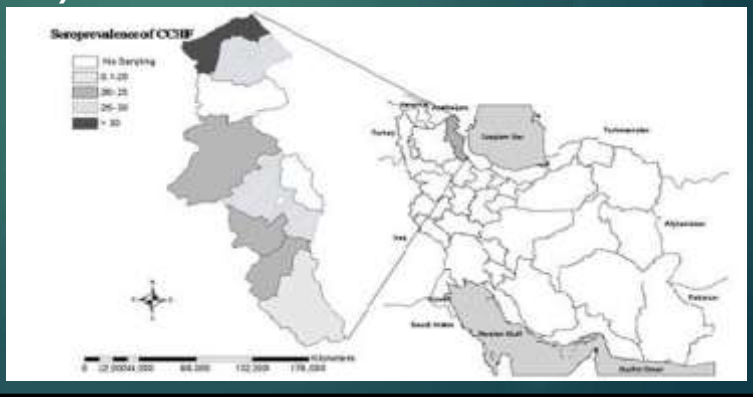
- Of the total of 121 samples examined, 97 (75.7%) were positive to anti-IgG with ELISA test. The highest positivity rate was among cows (88.3%) and in Albania.
- This finding suggested that cattle may play an important role in the epidemiology of the disease (Kadriaj P, et al. 2018).
- Anti-CCHFV antibodies were found in 22/92 (23.9%) ostriches (*Struthio camelus*). Of note, antibodies were detected in 6/9 (66.6%) ostriches in association with a human CCHF case in a worker who became ill after slaughtering ostriches on a farm in South Africa (Spengler JR, et al. 2016).

Seroprevalence of CCHF in Animals in Iran

- In Iran, antibodies to CCHFV in sheep and cattle were first detected in 1970. (Chumakov M, and Smirnova S, 1972).
- The first confirmed human case of CCHF was diagnosed in Iran in August 1999, when a patient died of severe gastrointestinal bleeding at a hospital in the southwest part of the country (Mardani M, et al. 2009)
- The detection of IgG in livestock revealed that 35.8% of 5842 sera were positive for CCHFV IgG.
- Sistan and Baluchistan Province, which borders Afghanistan and Pakistan, showed the highest infection rate in the country (Mostafavi E, et al. 2013)

Seroprevalence of CCHF in Animals in Iran

- The seroprevalence of anti-CCHF IgG antibodies in Ardabil in sheep was 27.34%.
- The highest seropositivity for CCHF was detected in Parsabad County (45.57%), and the lowest was in Khalkhal (17.78 %) (mostafavi E. et al. 2017).



Seroprevalence of CCHF in Animals in Iran

- Blood samples were collected from 876 animals in five different provinces of Iran. Serological evidence of infection was noted in 52 (5.9%) of 876 dairy cattle. Antibody prevalence increased with age; 78.8 seroprevalence in cattle older than 3 years versus 21.2% in animals less than 2 years old.
- There was a difference between provinces representing north-east (11.7%) and east (2%) of Iran (Lotfollahzadeh S, et al. 2011).

Seroprevalence of CCHF in Animals in Iran

- During the years 2003 to 2005, of 448 livestock sera collected form different townships of Khorasan, IgG antibodies were noted in 77.5% of 298 sheep samples and 46% of 150 goat samples (Bokaie S, et al. 2008).

- In Esfahan, 372 local and 372 imported sheep were randomly selected and the presence of CCHF-related IgG antibody and tick on their body were investigated.

- Totally, 286 (76.9%) of local and 223 (57.8%) of imported sheep were seropositive. Ticks were found on the body surface of 115 (31%) local sheep (Ataei B, et al. 2006).

Seroprevalence of CCHF in Animals in Iran

- Using ELISA method, IgG antibodies against CCHF virus were detected in 15(27.8%) out of 54 sheep examined whereas none of the high risk human samples were positive in Hamedan, a western region of Iran (Telmadarraiy Z, et al. 2008).

- 270 blood samples were collected from sheep in Mazandaran between 2010 and 2011, and ELISA test for CCHF virus was carried out on the blood samples.

- The CCHF infection rate according to this study was 3.7% (Mostafavi E, et al. 2012)

Seroprevalence of CCHF in Animals in Iran

- Fars province is the third most prevalence province. In Jahrom, between 2015 and 2016, 240 livestock serum samples investigated for the presence of anti-CCHF IgG using ELISA assay.
- The rate of seropositivity according to different livestock was as follows: 30 goats (69.8%), 8 sheep (18.6%) and 5 cows (11.6%).
- The results of this study indicate that the rate of CCHF in livestock from Jahrom city is lower than other parts suggesting that the risk of human transmission is low in this region (Shabani M, et al. 2018).

Demographic features of livestock in Jahrom (Shabani M, et al. 2018)

Variables		N (%)
	Gender	
Male		85 (35)
Female		155 (65)
	Age groups (Years)	
<3		29 (12.1)
3-5		59 (24.6)
>5		152 (63.3)
	Livestock	
Goat		148 (61.7)
Sheep		63 (26.2)
Cattle		29 (12.1)
	Imported livestock	

Seroprevalence of CCHF in Animals in Iran

- in Iran, 1/5 (20%) ostriches tested in association with four CCHF cases in workers from two ostrich farms were also found to be positive for CCHFV IgG (Mostafavi E, et al. 2013).
- Experimental infection has shown that viremia in ostriches is very short in duration (Swanepoel R, et al. 1998).

Diagnosis of CCHF

1. Serology including:
   - Virus neutralization assays
   - Reverse passive hemagglutination inhibition (RPHI) assays
   - Agar gel diffusion precipitation (AGDP)
   - Complement fixation (CF) assays
   - Indirect immunofluorescence assays (IFA)
   - Indirect or sandwich enzyme-linked immunoassays (ELISA) and competitive ELISA (CELISA)
2. Antigen detection
3. Reverse transcriptase polymerase chain reaction (RT-PCR) assay
4. Virus isolation by cell culture.

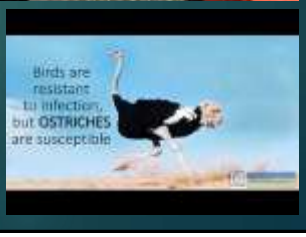
Prevention and Control

Prevention and Control

- **Cattle, sheep and goats, have been investigated in the largest number of seroepidemiological studies.**

- **Despite a high tick burden in many avian species, anti-CCHFV antibodies have not been detected in birds, with the exception of guinea fowl and ostriches.**

- **Epidemiological evidence and serological data show that handling livestock species (i.e., cattle, sheep, goats, ostriches) can serve as a source of disease transmission to humans.**
- **CCHFV seroepidemiological data in animals is an indicator of potential disease foci.**



Prevention and Control (WHO, 2018)

- Tick control with **acaricides** is only a realistic option for well-managed livestock production facilities.
- **Quarantine for animals** before they enter slaughterhouses or routinely **treat ruminants with acaricides 4 weeks prior to slaughter**. This activity will decrease the risk of the animal being viraemic during slaughter.
- **Wear mask, gloves and gowns** when slaughtering and butchering animals in slaughterhouses or at home to prevent skin contact with infected animal tissue or blood

Tick Control

- **Avoid tick bites**
  - Tick repellents
  - Environmental modification
  - Avoidance of tick habitat
  - Examination of skin and clothing for ticks
  - Clothing to prevent tick attachment
- **Acaricides (animals)**

A worker at a cattle market is spraying sacrificial animals against CCHFV (4 weeks prior to slaughter)

Can acaricide treatment of sheep control tick?

Prevention and Control

Control in Human

- Separate livestock from the place of residence
- Do not squash tick by hand or on the body of the livestock

- Avoid body contact with bloodstream and blood

Control in Human

- Do not kill animals in unauthorized places

Killing animals in the street for Eid

- Provide the meat from safe and slaughtered places
- Observe the safety principles when dealing with fresh meat, liver and other livestock breeding.

Control in Human

- Personal protection methods in contact with animal discharge and blood (wearing gloves, long dresses, drops, masks and glasses)

- Personal protection methods for ticks and insects.
- Avoid traveling at livestock sites
- Avoid eating pork roast, raw meat, raw liver, (keeping liver, heart, grains in the refrigerator for 48 hours).

Recommended practices for prevention of CCHF during care and slaughter of animals

Animal care personnel, abattoir staff

- Should be trained about animal care, animal welfare and slaughtering.

- Must take precautions against accidental exposure to blood and fluids of animals.
- Should take precautions to prevent serious injury to themselves and others.
- **Should wash their hands.**

Animal care personnel, abattoir staff

- Should wear gloves and other protective clothing during animal slaughter and handling of animals, their tissues or body fluids.

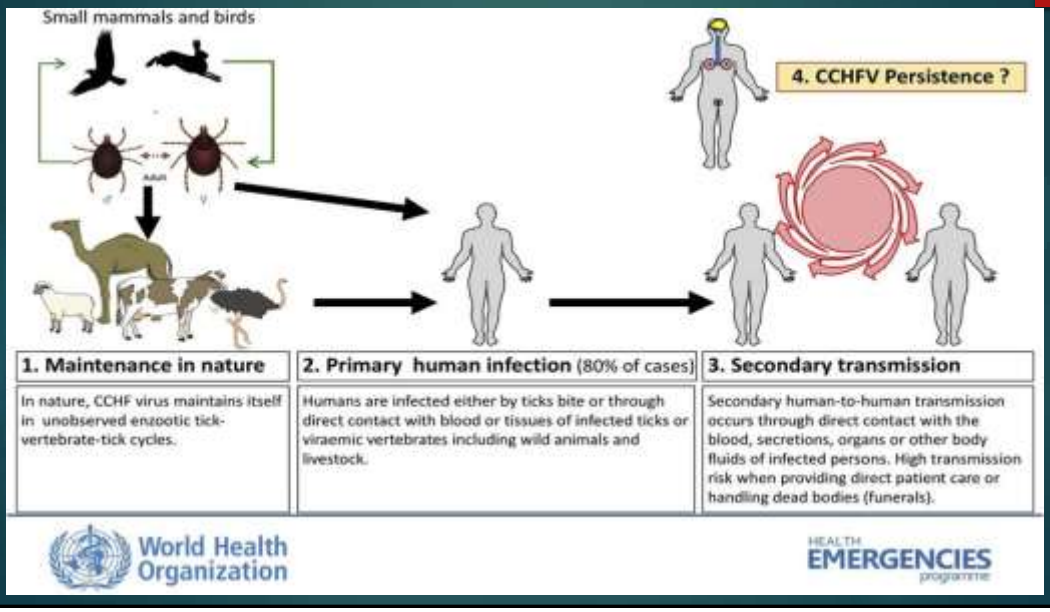
- Should not handle the hide without gloves.
- Prevent tick bites during skinning and tanning the hides.

- **Inspect their body each day to check for ticks and remove the attached ticks on skin with fine-tipped tweezers. Showering may help wash off unattached ticks.**
  - **Don't touch or crush the tick with your bare hands.**
  - **Don't try to remove the tick with your fingers.**

Training to Farmers and other people

Training to Farmers and other people

Maintenance of CCHF in nature and modes of transmission to and between humans



Prevention and Control

- The development of a vaccine to prevent infection in human populations at risk would provide protection against CCHFV.
- Whilst protection for humans should reduce the number of cases of CCHF, an animal vaccine might also reduce the risk of zoonotic transmission, and the pool of ticks carrying CCHFV.
- **Veterinary vaccines** may subsequently reduce the frequencies of naïve ticks acquiring CCHFV infection during blood feeding on viremic livestock.(Dowall SD, et al. 2017).

CCHF Vaccine

- A vaccine derived from inactivated mouse brain is used in Bulgaria, but is not widely available, and efficiency and safety have to be re-evaluated, as well as specific human immunoglobulin used for post-exposure prophylaxis.

CCHF Vaccine

- Modified Vaccinia virus Ankara, was used to develop a recombinant candidate vaccine expressing the CCHF virus nucleoprotein.
- Cellular and humoral immunogenicity was confirmed in 2 mouse strains, including type I interferon receptor knockout mice, which are susceptible to CCHF disease.
- Despite the immune responses generated post-immunization, the vaccine failed to protect animals from lethal disease in a challenge model (Dowall SD, et al. 2016)

Prevention and Control

- Overall, as our neighboring countries – including Afghanistan, Pakistan, and Turkey – are also endemic for CCHF, particularly high risk regions are in serious danger for further outbreaks if prevention planning and prompt control programs are not provided.