# SCIENTIFIC REPORT submitted to EFSA

# Scientific Review on Crimean-Congo Hemorrhagic Fever[1]


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## OBJECTIVES

The main objectives of the present work are:

- to prepare a comprehensive review of the latest available knowledge on Crimean Congo Hemorrhagic Fever (CCHF) including a complete and updated description of disease characteristics and major factors implicated in disease transmission and persistence in domestic, in zoo, exotic or wild species;
- to collect data on worldwide CCHF occurrence;
- to prepare an exhaustive scientific review of the latest available knowledge on the biology and ecology of Hyalomma spp. and the main other tick species considered as vectors;
- to collect data and information on worldwide distribution of Hyalomma and of the main other tick species considered as vectors;
- to analyse the data collected to verify, where possible, significant clusters and possible factors responsible of the clustering.

## DEFINITION

Crimean-Congo hemorrhagic fever (CCHF) is a viral zoonosis transmitted by ticks widely distributed in Africa, Asia, and Eastern Europe that cause severe outbreaks in humans. (WHO 2009).

## THE VIRUS

The CCHF virus (CCHFV) is a member of the Nairovirus genus of the family *Bunyaviridae*. The family *Bunyaviridae* includes 5 genera:

Orthobunyavirus;
Hantavirus;
Phlebovirus;
Tospovirus.;
Nairovirus
CCHFserogroup
CCHFV
Hazara virus
Nairobi sheep disease serogroup
Nairobi Sheep Disease virus (NSDV)
Dugbe virus

The genus Nairovirus includes 7 serogroups, the most important of these are the CCHF group, which includes the CCHFV and Hazara viruses and the Nairobi Sheep Disease group which includes the Nairobi sheep disease virus and the Dugbe virus.
The CCHFV, the NSDV and the Dugbe virus are the only members of the genus that can cause disease in humans.
The viruses belonging to the genus Nairovirus are transmitted by ticks (argasids or ixodids); amongst them CCHV is the most significant for public health.

Nairobi sheep disease virus of East Africa is believed to be identical to Ganjam virus of India and is a tick-borne pathogen of sheep and goats which sporadically causes benign illness in humans (Davies et al. 1978). Dugbe virus is a tick-borne virus commonly associated with mild infection of cattle and sheep in West Africa and infrequently causes benign human disease. The classification of the Nairovirus was originally based on their antigenic relatedness; however, the groupings have subsequently been substantiated through demonstration of morphological and molecular affinities between the viruses (Calisher and Karabatsos 1989) (Burt and Swanepoel 2005b).

Studies have been conducted on the morphological structure of the CCHFV which, like most of the Nairovirus, has the same structural, morphological, physical and chemical characteristics as those of other members of the *Bunyaviridae* family:

- double lipid layer envelope about 5-7 nm thick;
- spherical shape with diameter of 90-120 nm;
- glycoprotein spikes, 8-10 nm long.

The virions contain three main structural proteins: two envelope glycoproteins (GN and GC) and a nucleocapsid protein (N) plus minor quantities of viral transcriptase or L (large) protein (Burt and Swanepoel 2005b).

The RNA is a single-stranded with negative polarity (*ss*-) and is divided into three segments (L=Large, M=Medium and S=Small) with an overall molecular weight of 6.2-7.5 x $10^6$.

The segments are surrounded by a nucleocapsid inside the virion.

The large segment (L) code for the RNA-dependent RNA polymerase (protein L); the medium segment (M) code for the glycoproteins GN and GC and the small segment (S) encode the nucleocapsid protein (N) which is the most conserved viral protein.

As with the other genera of the *Bunyaviridae* family, the viral glycoproteins have the following functions:

- binding with the receptors on susceptible cells;
- induction of the immune response;
- selecting the tick host.

When the virus binds to the cell, it penetrates by endocytosis. Replication occurs in the cytoplasm and once the virions are mature they are liberated via budding from the cytoplasmic vesicles present in the Golgi apparatus or the plasma membrane.

Little information is available on the stability of the CCHFV, but once enveloped, it is sensitive to lipid solvents, and it is known that its infectivity is destroyed by low concentrations of formalin and 3-propriolactone. The virus is labile in infected human tissues after host death, but the examination of specimens from human patients appears to show that infectivity is preserved for at least a few days at room temperature in separated serum. Infectivity is destroyed by boiling or autoclaving, but the virus is stable at temperatures below -60°C.

Due to its ability for human-to-human transmission, to cause infections in laboratory workers, and the severity of the disease in humans, CCHFV is placed in biohazard class IV. This dictates that culture of the virus is permitted only in maximum-security biosafety level 4 (BSL-4) laboratories.

### *PHYLOGENETICS*

The genetic reassortment may occur in ticks co-infected with different types of CCHF viruses, since the virus persists for long periods in ticks. The reason why M-RNA segment

reassortment is more frequently observed is not clear, however, strong interrelation between N protein encoded in the S-RNA segment and RNA polymerase encoded in the L-RNA segment may be required to produce viable virus.

In addition, the virus is thought to be highly adapted to a particular species of host ticks in endemic region, and the S- and L-RNA segments may have evolved together in a particular tick. In contrast, the M-RNA segment sequence may not be restricted in a particular tick species, thus the reassortment event is frequently observed in the M-RNA segment.

The genetic diversity in S-RNA segment sequence was demonstrated for many CCHFV isolates from different regions of the world (Deyde et al. 2006). A partial sequence of S-RNA segment has been used for phylogenetic analyses. However, recent studies indicated the possibility of recombination of the S-RNA segments, although relatively rare (Deyde et al. 2006).

Thus, it would be better to use the full sequence data of the S-RNA segment in a comprehensive phylogenetic analysis. The analysis showed that CCHF viruses grouped in seven different clades:

1. African clade 1 comprising isolates in Senegal,
2. African clade 2 comprising those in Uganda and some in South Africa,
3. African clade 3 comprising those in South and West Africa,
4. European clade 1 comprising those in Russia, Turkey, and Balkan region (Bulgaria, Kosovo),
5. European clade 2 composed of a single Greek isolate AP92,
6. Asian clade 1 comprising those in Middle East, Pakistan, Iran,
7. Asian clade 2 comprising those in China, Uzbekistan, Kazakhstan.

Among these clades, European clade 2 is most distantly related to other clades including European clade 1. S-RNA segment segregate isolate according to their geographical origin. It is to mention that AP92 strain was only isolated from *Rhipicephalus bursa* ticks and there were no clinical cases even though seroepidemiological survey demonstrated asymptomatic infection in human (Morikawa et al. 2007) (Antoniadis and Casals 1982). On the contrary, in 2008 two different fatal cases have been recorded in Greece caused by strains similar to those found in the Balkan Peninsula, Russia, and Turkey, but differed greatly from the previous Greek strain AP92 (Papa et al. 2008).

The genetic difference between European clades 1 and 2 may be due to genetic isolation of Greek isolate by adjacent mountain ranges but not to the different tick species since an extensive survey of ticks in Turkey demonstrated that the CCHF viruses of European clade 1 were detected by RT-PCR in both *Hyalomma marginatum marginatum* and *R. bursa* (Tonbak et al. 2006).

In rural condition CCHF viruses are thought to be introduced through import of infected and/or tick-infested livestock such as sheep and cattle. It has been shown that two genetic lineages of CCHF viruses, Asian clade 1 and African clade 1, exist in Iran (Chinikar et al. 2004) and the latter is thought to be introduced by livestock trade (Burt and Swanepoel 2005a).

Within the Asian clade 2, the viruses are clustered in two subclades, the first subclade including the viruses in China and Uzbekistan where *Hyalomma asiaticum* tick is a major vector, and the second in Tajikistan and Kazakhstan where *Dermacentor niveus* is a major vector, indicating that a long-term association with a particular tick species plays a crucial role in genetic diversity among the clade (Yashina et al. 2003).

Recent phylogenetic analyses based on L segment showed that the L tree topology was similar to the S tree topology (Deyde et al. 2006) and L-segment reassortment has been suggested for some isolates in Senegal (Deyde et al. 2006).
On the other hand, the phylogenetic topology based on M-RNA segment sequences of CCHF viruses is different from that based on S-RNA segments (Deyde et al. 2006) (Morikawa et al. 2007).
These analyses show that CCHF viruses are likely to be grouped in six different phylogenetic clades :

- clade M1 comprising isolates in China, Pakistan (Matin isolate), Oman, and South Africa (SPU97/85 and SPU415/85 isolates);
- clade M2 comprising those in Uzbekistan, Tajikistan, China, Pakistan, Iran, Iraq, South Africa and Nigeria;
- clade M3 comprising those in Congo (UG3010 isolate), Senegal, China (7001 and 79 121 isolates) and maybe Uzbekistan (Uzbek/TI10145 isolate which sequence is only partially determined (GenBank Acc. AY093627);
- clade M4 comprising those in Russia, Kosovo and Turkey; and
- other two clades are composed of Greek isolate AP92 and Mauritanian isolate ArD39554, respectively.

Essentially identical M tree can be obtained in phylogenetic analyses using partial sequence data of the M-RNA segment even when the extremely variable mucin-like domain is used (Hewson et al. 2004; Morikawa et al. 2007) indicating that recombination within the M-RNA segments did not occur during evolution of the CCHF viruses.
The possible M-RNA segment reassortment events between geographically distant regions are frequently observed (Chamberlain et al. 2005). Such an M-RNA segment reassortment between most geographically distant regions is observed in Chinese isolates, 7001 and 79 121, which were isolated from a patient in 1970 and from a jerboa in 1979, respectively, in Bachu region of the Xinjiang Autonomous Region in Western China. The M-RNA segments of these isolates are closely related to those of Senegal isolates within the clade M4.
Birds are refractory to CCHFV viremia except ostriches, but many migrating birds are known to be infested by immature ticks, such as those belonging to the *H. marginatum* group, thus the virus was likely to be introduced to China by intercontinental migration of birds carrying infected ticks and then the genetic reassortment of M-RNA segment occurred between the African clade 1 and the Asian clade 2 type viruses (Morikawa et al. 2007).

## GEOGRAPHIC DISTRIBUTION OF CCHF

Of the viral zoonoses transmitted by ticks, CCHF has the widest geographic distribution, its involved Asia, Africa and Europe. It's mainly affected by the presence of the ticks of the genus *Hyalomma*.
The main part of data on epidemics is present in the literature and on reports of surveillance network that consider also the little amount of official data.
Since the complexity of the epidemiology of CCHF where transmission of infection occurs when there is an overlap of activities between reservoir, vector, and humans, and different relationship occurs according to the location, it's necessary to study each single situation.
Anyway, many data and consideration present in the literature on the natural outbreaks condition are reported in chapters on vector competence and virus-host interaction (pag 33 and 35).

The table N°1 in appendix B and three maps in appendix A (fig. 1, 2, 3) summarize reports of main epidemics in the last 50 years.

## TICK VECTORS SPECIES OF CCHF IN EURASIA

Ticks were suspected of transmitting CCHFV shortly after the disease was formally described in the mid-1940s and inoculation of tick suspensions into human volunteers confirmed that ticks contained a filterable agent that caused CCHF. CCHFV was detected in *Hyalomma marginatum* ticks shortly after the disease was described. Since the initial studies in the1940s, CCHFV has been isolated from ticks in several occasions (Hoogstraal 1979); to date CCHFV has been isolated from at least 30 species of ticks both argasids and ixodids.

Only members of three ixodid genera, namely *Dermacentor*, *Hyalomma* and *Rhipicephalus* have been shown to be capable of transmitting infection trans-stadially and trans-ovarially and to another animals. In turn, these animals can themselves acquire infection from infected tick (Hoogstraal 1956), (Swanepoel et al. 1998; Swanepoel 1998); in contrast, several studies indicate that argasid (soft) ticks are not competent CCHFV vectors.

Consequently, the mere isolation of virus from an arthropod does not incriminate it as an actual vector. Although relatively few studies have examined the ability of ticks to actually transmit CCHFV, those that have examined vector competence have consistently shown that ixodid (hard) ticks, particularly members of the genus *Hyalomma* are highly susceptible to infection with CCHFV and that infected ticks can transmit this virus by bite.

The most part of the epidemiological evidence and the field observation suggest that *Hyalomma* spp. are the principal vectors, and the known distribution of the virus broadly coincides with the global distribution of these ticks that are present in central and southern Eurasia and in Africa. *Hyalomma* ticks are mainly abundant in warm, arid, and semiarid, generally harsh lowland and middle altitude biotopes, and those with long dry seasons (Horak et al. 2001).

Many of the Eurasian competent vectors of CCHF belong to the Mediterranean tick fauna. The Mediterranean region is a zone of complex biogeography, because the diversity of habitats and the sudden landscape changes observed as a consequence of the altitudinal variation.

However, the landscape in the region is very variable, and therefore vegetation and climate characteristics may change suddenly in some countries. The relief is also a contributing factor to this variability. Drastic changes in elevation may contribute to severe variations in climate. The variability of climate features provides a tick fauna rich in species, some of them specific to the Mediterranean region (Estrada-Peña et al. 2004).

Arid or semiarid steppes of the central Asia are also good environment for some of *Hyalomma* tick vectors of CCHF.

### *HYALOMMA MARGINATUM*

#### Identification

*Hyalomma marginatum* is a hard tick species complex occurring in southern Europe, southern Asia and most of Africa. It is characteristic of steppe, savanna and lightly wooded hill and valley biotopes with fairly low humidity. *H. marginatum* is a two-host species moulting from

larva to nymph on its first host (especially hares, hedgehogs and ground-dwelling birds) and infesting the second host (mainly sheep, goats, swine, cattle and horses) as an adult. As an ixodid tick, it is a slow feeder spending several days on its host while firmly attached by its hypostome. The extraordinarily long duration of host attachment during the preimaginal development (12–26 days) enables the passive transport of the immature *Hyalomma marginatum* stages by migrating birds over hundreds or even thousands of kilometers (Manilla 1998c; Rechav et al. 1987).

*Hyalomma marginatum* subspecies are the most important vectors of CCHFV. There are four *H. marginatum* subspecies which differ in their geographical distribution: *H. m. turanicum*, *H. m. isaaci*, *H. m. rufipes*, and *H. m. marginatum*. The only European subspecies is *Hyalomma m. marginatum.* (Merck & Co. 2008)

#### *HYALOMMA MARGINATUM MARGINATUM*

### Ecobiology

*Hyalomma m. marginatum* is a two-host tick well adapted to different climatic zones: arid, sub-arid, sub-humid and humid. From area to area, different types of vegetation represent its biotope. This species has a great capacity to support a wide range of temperature and humidity conditions.

### Geographic range

*Hyalomma m. marginatum* inhabits the Mediterranean climatic zone as well as steppe and foothill landscapes (southwestern Palaearctic Region) from the Caspian Sea to southern Ukrainia and Bulgaria, and spreads westward to Spain, Portugal, and Marocco and Algeria (Manilla 1998c). *Hyalomma m. marginatum* in Turkey, where it is one of the most important vectors of CCHF, seems to be geographically restricted to parts of the middle Black Sea region of Turkey (Tonbak et al. 2006).

### Ethology

Immature stages of *Hyalomma m. marginatum* are common parasites of wild and domestic birds, mainly passeriformes but also falconiformes, galliformes, gruiformes, charadriformes, strigifromes, coraciformes, as well as European brown hares *(Lepus europeus*), hedgehogs, wild ungulates. Adults are mainly found on domestic and wild ungulates (Manilla 1998c) (Ruiz-Fons et al. 2006). The association to wild birds of the immature stages enhance the opportunity of dispersion into new areas (Manilla 1998d) (Kampen et al. 2007) (Manilla 1982) (Pietzsch et al. 2008).

### Seasonal dynamic

Adults are characterized by a peak of activity during hot season. However, they remain on animals during the whole season.

## Control

An effective control could be reached only for adults by localized acaricide treatment. *Hyalomma m. marginatum* is difficult to control on livestock even by regular acaricide application as engorged nymphs are continuously being brought in from other areas by birds (Manilla 1998d).

### *HYALOMMA MARGINATUM RUFIPES*

## Identification

Adults *Hyalomma marginatum rufipes* are large ticks with dark-brown bodies, long mouthparts, a heavily punctated scutum, small, round and bright eyes, and long, red and white banded legs. They differ from *Hyalomma truncatum*, which is present in the same geographic area, in that the whole scutum is punctated and in the males it is more circular than the rather elongate shape of the latter tick. Furthermore, *H. m. rufipes* differ from *H. m. marginatum* for its more hairy spiracular plate. However, it is virtually impossible to distinguish between the species by means of the naked eye (Manilla 1998c; Norval and Horak 2004).

## Ecobiology

*H. m. rufipes* has a two-host life cycle, which under field conditions in South Africa takes a year to complete (Horak 1982).

## Geographic range

This tick is widely distributed in sub-saharian Africa (ethiopian biogeografic region), and appears to be absent only from the winter rainfall areas of the Western Cape Province, the mountainous areas of Lesotho and KwaZulu-Natal where snow falls in winter, and some humid, subtropical habitats along the east coast and in the north-east. It is also present in the drier regions of the southern and north-western provinces of Mozambique, south-eastern and north-western Botswana, central and northern Namibia, southern Angola, most of Zimbabwe, southern and western Zambia, central and north-eastern Tanzania, central and southern Kenya, western Burundi, eastern Uganda, and in Somalia, Sudan, Ethiopia and in West Africa (Norval and Horak 2004), (Horak 1998) (Mattioli et al. 1997). Isolate populations have been establised also along Nile river valley and in southern part of the Volga river valley. It is sporadically reported also in Mediterranean area probably introduced by migratory birds. Parasitism of birds by the immature stages undoubtedly contributes to the extensive distribution of this species (Pegram et al. 1981) (Manilla 1998d; Norval and Horak 2004).

## Ethology

Adults parasitize domestic and wild ungulates, showing a preference for the larger species. They attach mainly in the hairless peri-anal region and on the lower perineum and genitalia. The immature stages are parasitic on hares, particularly scrub hares (*Lepus saxatilis*), as well as on ground-frequenting birds (Norval and Horak 2004) (Walker 1974).

### Seasonal dynamic

The adults are most numerous in the early part of the wet season and the immature stages in the dry season.

### Control

Control can be accomplished by localized acaricide treatment, but as other birds associated ticks, *H. m. rufipes* is difficult to control on cattle herds even by regular acaricide application as engorged nymphs are continuously being brought in from other areas by birds (Norval and Horak 2004)

#### *HYALOMMA TRUNCATUM*

### Identification

Adults of *Hyalomma truncatum* are medium-sized ticks with long mouthparts and dark-brown bodies, beady eyes, and long, red and white banded legs. The posterior surface of the scutum in males is characterized by a depression containing numerous large punctations; otherwise it is comparatively smooth (Norval and Horak 2004).

### Ecobiology

*H. truncatum* has a two-host life cycle, which normally takes a year to complete under field conditions in South Africa.

### Geographic range

This tick is adapted to dry climates of sub-Saharian Africa. It is absent in Lesotho and, with the exception of the Eastern Cape, the eastern half of the Free State, south-eastern Gauteng and Mpumalanga, and southern KwaZulu-Natal, it is present throughout South Africa, Zimbabwe and much of Mozambique. It is also present in south-eastern and north-western Botswana; central and northern Namibia; southern Angola; western, southern, central and eastern Zambia; central and southern Malawi; south-western and north-eastern Tanzania; southern, central and western Kenya; and eastern Uganda (Howell et al. 1978), (Norval and Horak 2004) (Santos Dias 1993). It also occurs in many countries in north-eastern, central and West Africa (Mattioli et al. 1997), (Pegram et al. 1981). At a local level, the abundance of *H. truncatum* is influenced by the abundance of hares, which are the preferred hosts of the immature stages (Horak et al. 2001).

### Ethology

The preferred hosts of the adults are large ungulates, both domestic and wild. They attach in the tail switch, around the anus, on the lower perineum, and on the legs, including around the feet. The immature stages feed on hares, mainly scrub hare *(Lepus saxatilis)* and on certain rodents, particularly gerbils (Norval 1982).

### Seasonal dynamic

Adults occur in the greatest numbers in the late wet summer months and the immature stages in the dry autumn to spring months (Horak 1982).

### Control

Hand-dressing of the preferred attachment sites with an acaricide will assist in controlling the adults. It is impractical to control the immature stages because of their preference for hares and rodents. Genetic resistance has been described in West African indigenous cattle; studies conducted in N'Dama and Gobra zebu cattle in The Gambia showed the former to possess a higher degree of resistance than Gobras against adult ticks belonging to two genera characterized by long hypostome, such as *Amblyomma variegatum*, *H. truncatum* and *H. m. rufipes*. N'Dama appears to be a unique breed in that it exhibits resistance to several parasitic diseases, including helminths, tse tse transmitted trypanosomosis and tick borne pathogens infections when compared to other cattle breeds in West Africa, suggesting that the use of this cattle will be of benefit to limit the use of chemicals in traditional farming (Mattioli et al. 2000).

#### *HYALOMMA DETRITUM*

### Identification

Adult *Hyalomma detritum* are medium-sized ticks with long mouthparts, a very dark-brown, smooth, shiny scutum, and long reddish or yellowish-brown legs which may have paler bands. This tick species is the most abundant cattle ixodid found in the sub-humid and the semi-arid zones with a prevalence of 84% and 82.02% of tick population collected on cattle during one year, respectively. In the humid area, *H. detritum* population represents only 4% of tick sampling. *H. detritum*, a stable dwelling tick, is strongly associated with cattle. However, it can be found in areas surrounding the cowshed. Nymphs of *H. detritum* are usually found in wall crevices and cracks, under the rocks and even under the dried manure where they hibernate in the farm.

### Ecobiology

*H.detritum* has a two-host life cycle with the adults feeding in summer and the larvae and nymphs in autumn. The detached engorged nymphs undergo a winter diapause and moult to adults the following summer. The life cycle is often associated with barns, stables and sheds, and livestock become infested when they are housed in these structures. This tick species is the most abundant cattle ixodid found in the sub-humid and the semi-arid (Bouattour et al. 1999).

### Geographic range

This *Hyalomma* is spread in central Asia from northern India to Middle East, in southern Balkans, southern Europe and along the Mediterranean coast of Africa as far as Algeria and

Morocco in the west. It is also present in Sub-Saharan Africa in North-Central Sudan, which it may have invaded from the Red Sea coast or via the Nile river valley (Manilla 1998c)

### Ethology

Domestic cattle and horses are the most common hosts, but sheep, goats and camels may also be infested. All stages of development feed on the same host species. Adults attach on the inner thighs, udder, scrotum and perineum of cattle.

#### *HYALOMMA ANATOLICUM AND HYALOMMA EXCAVATUM*

### Identification

The study of the ecology, development and epizootic role of these two similar species, *Hyalomma anatolicum* and *Hyalomma excavatum,* is very difficult. The taxonomic status of these ticks is not even uniformly agreed on today. Their occurrence within the same geographical area, the presence of hybrid forms, morphological variations and impossibility of distinguishing the larvae and nymphs of both subspecies complicate this work. Ecological conditions apparently determine which form will develop in a given location (Apanaskevich 2003), (Liebish et al. 1989).

A recent study which had compared the morphology of each stage of the two species of several specimens belonging to different collection, allows to definitely separate two specific identities *H. anatolicum* and *H. excavatum* (Apanaskevic and Horak 2005).

### Ecobiology and Ethology

*H. excavatum* was always to undergo a three-host type of development while *H. anatolicum* usually developed as a two-host type.

The numerous *H anatolicum* immatures and adults that often parasitize livestock and also wild ungulates cause unthriftiness (Ruiz-Fons et al. 2006). Immatures of the subspecies *H. excavatum* (a 3-host parasite) infest chiefly burrowing rodents in somewhat different biotopes in the same environments as *H. anatolicum*. Adults of both subspecies may infest the same animal. In addition to livestock, deer and rabbits serve as hosts.

#### *HYALOMMA ANATOLICUM*

### Ecobiology

*H. anatolicum* no longer can be considered a field tick form. With the adaptation to cattle as their host animal, these ticks have become adapted to the biotope “stall” and have adopted a type of nest parasitism as a life style.

### Geographic range

*H. anatolicum* is common in the southern Mediterranean area and also in eastern Africa (Sudan, Somalia and Ethiopia) and central Asia (Rasulov 2007), (Ahmed et al. 2007).

### Ethology

Cattle, buffaloes, and dromedaries usually function as hosts for *H. anatolicum.* Ecological conditions apparently determine which form will develop in a given location. Preliminary observations in the field in Egypt and in Syria indicate that the adults of the larger subspecies (*H. excavatum*) parasitize mainly on dromedaries and prefer an extremely arid environment. Populations of the smaller *H. anatolicum*, however, are found more often in irrigated areas. Morphologically distinct specimens of *H. anatolicum* (from cattle) and of *H. a. excavatum* (from dromedaries) parasitized in various sequences mice, rabbits, cattle and dromedaries. Larvae were found to parasitize on the head (eyelids, ears), nymphs on the eyelids, between the bases of the horns and on the dorsal neckline back to the withers. Adults were usually located on the medial sides of the legs, on the scrotum or udder and the inguinal region. A large number of males were found on the feet of the cattle, crown ridge, pastern and between the cleats (Liebisch et al. 1989).

### Seasonal dynamic

The highest rate of the infestation of cattle by *H. anatolicum* occurred in February to March and in September. Larvae were especially active in March / April and in October. Nymphs were most common in May/June and October / November**.**

### Control

The control of ticks with acaricides must include the treatment of the animals as well as the stalls**.** The activity of *H. anatolicum* adults is of a bimodal nature. In order to prevent the development of egg laying females, the control measures must be carried out in April and October, when the larvae and nymphs are active. For both species there is some use of spray treatments of the walls of dairy houses, but it is more effective in the long term to render the walls smooth with mortar (Latif and Walker 2004).

#### *HYALOMMA EXCAVATUM*

### Ethology

Adults are esophilous mainly found on horses, camels, buffalo, antelope but also on dogs, fox and jackals. Endophilous immature stages feed mainly on rodents and lagomorphs**.**

### Geographic range

Distribution of H. excavatum is somewhat more limited than that of H anatolicum, but its winter season population densities are often greater

### Seasonal dynamic

Depending on climatic conditions the life-cycle last 1or 2 years. Usually adults are active during between December and August, while immature stages are mainly found during spring.

#### *HYALOMMA DROMEDARII*

### Identification

Adult *Hyalomma dromedarii* are large ticks with long mouthparts. The scutum of the male is characterized by posterior grooves and ridges. The colour of these ticks varies from yellow-brown to nearly black. The legs are paler than the scutum and may be ringed by paler bands.

### Ecobiology, geographic range and ethology

*H. dromedarii* has a two or a three-host life cycle. The preferred hosts are camels, but cattle, sheep, goats and horses may also be infested. Adults attach on the inner thighs, udder and scrotum of camels. The larvae and the nymphs feed on small burrowing animals and hares, but the nymphs may also infest camels, cattle and horses. The larvae may feed and moult to nymphs on small mammal or on hare and the adults feed on large herbivores (Hoogstraal and Kaiser 1958). Larvae may feed on small mammal hosts, drop off and moult to nymphs, which can then either attach to other small mammal hosts or feed on the same large animals as the adults. The life cycle appears to be continuous throughout the year. This tick is common wherever camels occur in the far, middle and near East. It is also present in Mauritania in West Africa and in Morocco, Algeria, Tunisia and Libya in North Africa and is well-adapted to an arid and even desert environment. In north-eastern and East Africa, it occurs in Sudan; Eritrea; northern, eastern and southern Ethiopia; northern Kenya; and north-eastern Uganda (Norval and Horak 2004).

#### *HYALOMMA IMPELTATUM*

### Identification

*Hyalomma impeltatum* needs to be distinguished from *H.dromedarii*, with which it shares similar morphological features, hosts, and geographical areas.
The scutum of female *H. impeltatum* has a distinctly sinuous posterior margin compared to slightly sinuous in *H. dromedarii*. The genital aperture is bordered on each side by a slight bulge that gives the genital area a trilobed appearance distinctive to this species (Estrada-Peña et al. 2004).

### Ecobiology

*H. impeltatum* is xerophilic tick that occurs mainly in Mediterranean steppe and desert climates (Estrada-Peñaet al. 2004).

### Geographic range

*H. impeltatum* is more widely distributed though the Sahara in comparison with other species of ticks, except *H. dromedarii.* This is due to its association with draught camel trains on

trade routes in this desert. The range of *H. impeltatum* include the North African countries and Sudan, Eritrea, Somalia, Northern Kenya, northern Tanzania, Chad and those West African countries with steppe climates. It's also present in the middle East countries (Estrada-Peña et al. 2004).

### Ethology

*H. impeltatum* is a three hosts tick. All large domestic animals can serve as hosts of the adult ticks, particularly cattle on which high infestations are recorded. Camels are also commonly infested. The immature stages feed on small animals like rodents, hares and ground birds.

### Seasonal dynamic

Adults are present on animals throughout the year. Immature stages infest their hosts in summer and autumn (Estrada-Peña et al. 2004).

#### *RHIPICEPHALUS ROSSICUS*

### Identification

*Rhipicephalus rossicu*s is a moderated sized, light to medium-brown tick belonging to the *Rhipicephalus sanguineus* group. The broadly elongate spiracle and relatively impunctate scuta in both male and female and a small circular deep set porose areas in the female are distinctive features that allow to separate it from *R. sanguineus.*

### Ecobiology

*R. rossicus* is an esophilic ticks well adapted to the lowland areas and mountain steppe of Eastern Europe and central Asia (Walker et al. 2000).

### Geographic range

It's known to be present from Europe (Poland, Romania, Bulgaria) to western Kazakhstan and Sinai Peninsula of Egypt (Walker et al. 2000).

### Ethology

*R. rossicus* is a three host tick with life cycle that takes 2 to 3 years to complete. Adults feed on domestic animals, hedgehogs and occasionally on humans. Immatures are mainly parasite of hedgehogs, hares, and rodents (Walker et al. 2000).

### Seasonal dynamic

Adults are active during in late spring and early summer; larvae appear to at the same time in April and also peak in May to June with a further possible peak in August, while the nymphal peak take place from June to July (Walker et al. 2000).

## LIST OF POTENTIAL SPECIES AS VECTORS FOR CCHF

Even if *Hyalomma* species are considered the main vectors of CCHF, the virus has been isolated from several species of ticks. Table N°2 summarizes data on vectorial competence of different tick species, some of them very spread in Europe such as *Ixodes ricinus, Dermacentor marginatus* and *Rhipicephalus sanguineus*. These potential vectors has been selected considering the risk linked to their spread in Europe and considering that they are frequently recorded as parasite of human beings.

### *IXODES RICINUS*

### Identification

*Ixodes ricinus* is a tick mainly of the Paleaerctic region and typically is found in cool humid environments of Europe such as woodlands, with deer as its main host. This tick was one of the earliest to be formally described and has been intensively studied in Europe because of its role there in the transmission of a wide range of pathogens to domestic animals and humans (Estrada-Peña et al. 2004). It was supposed to be involved in the transmission of CCHFV in the forests of Moldavia and Bulgaria (Hoogstraal 1979). Males *Ixodes ricinus,* as all males of the *Ixodes* genus, are smaller than the females. Femaes of *Ixodes ricinus* have long mouthparts and need to be distinguished from other genera such as *Hyalomma*, *Amblyomma* and *Aponomma*, the latter two not present in Europe. In contrast to these genera, *Ixodes* have dark brown to black body and legs, without enamel. *Ixodes* are also without eyes.
The genus *Ixodes* belongs to the sub-family Ixodinae that is a large group of ixodid ticks also called Prostriata which differs from the Metastriata. The distinctive feature is the position of the anal groove which passes to the anterior of the anus in prostriate compared to passing posterior to the anus in the metastriate ticks. This characteristic is most obvious in female *Ixodes*, in males the anal groove passes between large flat ventral plates (Manilla 1998d) (Estrada-Peña et al. 2004).

### Ecobiology

It is common in wetter areas of all European countries. The species occurs in deciduous and coniferous woodlands that have populations of deer; in grazings of cattle and sheep that are unimproved; rough grasslands; usually at higher altitude and in high rainfall areas.

### Geographic range

*I. ricinus is* found on Ireland in the west through Great Britain, all of Europe southward to the Caspian Sea, northern Iran, and western Russia.
*I. ricinus* is also present in northern Africa restricted mainly to the cooler and more humid areas (rainfall of more than 800 mm per year) of the Mediterranean climatic region that are associated with the Atlas mountains (Keirans and Durden 2005) (Estrada-Peña et al. 2004).

## Ethology

*I. ricinus* is a three host ticks that behaves as endophilous during larval stage and as esophilous during nymphal and adult stages.
*I. ricinus* has a very wide host range, including many species of mammals, birds and even lizards. It has been recorded on about 237 hosts (Gern 1994). *I. ricinus* is the most frequent in Europe among the about 30 tick species that feed on humans (Keirans and Durden 2005). In spite of such a variety of hosts, the majority of *I. ricinus* tìcks feed on only a few mammalian species and tick infestation is frequently limited to only a part of the host population. Typically, the over dispersed distribution of ticks on their hosts results in a significant proportion of the hosts carrying large numbers of ticks that feed together.
Over dispersion arises from the non-random distribution of questing ticks and host genetic, behavioral and immunological heterogeneities. These factors determine the differential probabilities of an individual host picking up ticks. In central-southern Europe, the most abundant rodent hosts of immature *I. ricinus* are frequently yellow-necked mice (*Apodemus flavicollis*) and bank voles (*Myodes* former *Clethrionomys glareolus*) and the most frequent host of adults and nymphs is roe deer (*Caprelous caprelolus*) to which is linked the possibility of dispersion of ticks (Manilla 1998a) (Labuda and Nuttall 2008).

## Seasonal dynamic

*I. ricinus,* is spread has a northern distribution and is active in colder climates, generally has two peaks of activity, in the spring and autumn but the period and the length are variable according the season and the latitutide. However, generally in each year *I. ricinus* only feeds once and only passes through one developmental stage, thus taking at least 3 years to complete its life cycle.
Ticks that do not find a host in the autumnal activity period will overwinter to become active again the following spring, hence the life cycle can take up to 6 years to complete. This may be a survival strategy to different climate (Manilla 1998a) (Labuda and Nuttall 2008).

### *DERMACENTOR MARGINATUS*

## Identification

The characteristics of the genus *Dermacentor* are mainly: short mouthparts with a basis capituli of straight lateral margins, both sexes usually have white enamel ornamentation and the males have very large fourth coxae. This tick has white enamel on the scutum or conscutum (Estrada-Peña et al. 2004) (Manilla 1998b). Two species can be found in Europe and in the Mediterranean region *Dermacentor marginatus* and *Dermacentor reticulatus* the latter is mainly a parasite of dog, sometimes both species can be found on the same host. Therefore, separation of both species is important. In both sexes, the most important feature is the presence of a palpal spur in *D. reticulatus,* which is absent in *D. marginatus*. In the females, most prominent details are the shape of porose areas, the size of the gap between internal and external spurs on coxa I and the size of the lips in the genital aperture. In the males, cornua are long in *D. reticulatus* (short in *D. marginatus*) and the lateral groove is in the form of punctations only in *D. reticulatus* (there is no groove visible) (Estrada-Peña et al. 2004).

### Ecobiology

*D. marginatus* is a very common tick in the Mediterranean region. In the European part, this tick is restricted to with dense bush and tree cover. It is common under oak and pine vegetation (Manilla 1998b).

### Geographic range

*D. marginatus* is a Palearctic species widely distributed in northern Europe and northwestern Asia. It's found in Germany, Switzerland, southern and central France, Italy, and Spain; and eastwards into Central Asia. It also occurs in Morocco (Keirans and Durden 2005).

### Ethology

This is a three-host tick and the entire life cycle can be completed in one year. Adult activity is during end of autumn through into winter. Adults of *D. marginatus* infest domestic ruminants and wild ungulates, in central Italy it's strictly associated to wild boar (*Sus scrofa*) (Manilla 1998b). Dogs may be infested with adults and humans are liable to infestation with immature stages. Immature stages feed mostly on small mammals, like rodents, some medium-sized carnivores and also birds (Estrada-Peña et al. 2004).

### Seasonal dynamic

Adults are active throughout the spring, summer, and early fall and feed readily on available hosts. However, because the wide variety of climate conditions this pattern is susceptible to variation. In colder areas, seasonal activity of adults may begin sooner in the year, and have a pronounced period without activity in the middle of the winter. Under Mesomediterranean conditions, this period of inactivity may not exist (Manilla 1998b) (Estrada-Peña et al. 2004). However, the day length and ambient temperatures that the ticks experience before feeding determine the ovipositional response. Females that seek hosts and feed during periods of increasing day length, i.e. in spring or early summer, will lay their eggs almost immediately. In contrast, females exposed to declining day length prior to feeding delay oviposition until the following spring (Sonenshine 2005).

#### *RHIPICEPHALUS SANGUINEUS*

### Identification

*Rhipicephalus sanguineus* is universally known as "the kennel tick" (Manilla 1998b) (Estrada-Peña et al. 2004) (Walker et al. 2000). It is a medium sized, pale yellowish-brown or reddish-brown tick. The *R. sanguineus* group comprises several tick species. The biosystematic status of the majority of them has been confused (Estrada-Peña et al. 2004; Walker et al. 2000). Two species of this group closely resemble *R. sanguineus, R. camicasi*, and *R. turanicus*. Females of *R. sanguineus* are differentiated from those of *R. camicasi* and *R. turanicus* by the genital aperture which is usually a broadly V shape in *R. sanguineus* compared to a narrow U in *R. camicasi* and *R. turanicus*. Both sexes of *R. sanguineus* have spiracle plates with tails, which are narrow, less than the width of the adjacent festoon. In *R. turanicus*, these tails are broad. Males of *R. sanguineus* do not have a depression of the

cervical fields compared the small depression there in *R. camicasi* (Estrada-Peña et al. 2004; Walker et al. 2000).

### Ecobiology

It's a three-host tick strictly associated with dog, this strict relationship affects its biology. Most of ixodid ticks particularly three-host ticks, spend 94–97% of their life off-host, within their habitat where they are at influence of many factors, such as habitat structure and climate (Randolph 2004) for this reason ixodid ticks exhibit exophilic behavior, they tend to rest outdoors (Dantas-Torres 2008). Conversely, *R. sanguineus* ticks are often endophilic, although this tick can survive in open environments (mainly in tropics and subtropics) it is highly adapted to living in dog kennels and in homes of humans, so they are often found indoors. They have a strong tendency to crawl upward and they can be seen climbing the walls of infested houses. The off-host tick stages may hide in any kind of cracks, usually close to the host sleeping or resting place (Dantas-Torres 2008). This endophilic behavior is untypical of *Rhipicephalus* ticks, which are usually entirely exophilic (Estrada-Peña et al. 2004). It has recently been demonstrated that *R. sanguineus* ticks are less dependent upon a moisture-rich habitat for survival, which facilitates their establishment within regions that are unfavorable for maintaining water balance. The ubiquity and worldwide distribution of *R. sanguineus* are distinguishing features, which imply that it is capable of surviving in a wide range of potential habitats (Yoder et al. 2006).

### Geographic range

*R. sanguineus* is probably the most widely distributed tick in the world. Circumglobally it is found approximately between the latitudes of 50°N and 30°S, and its preference for dogs has facilitated its worldwide distribution (Walker et al. 2000).

### Ethology

*R. sanguineus* is a three host monotrophic tick; dogs are hosts for all stages of development. Adults attach on the ears, neck and shoulders, nymphs are also found on the ears and shoulders, and larvae attach particularly to the stomach and flanks. Humans are likely to have immature stages of this tick attempt to attach to them. Hosts other than dogs such as cattle goats and some wild carnivorous are occasional hosts and are usually only infested when dogs are present to maintain a population of the tick. Dogs are the maintenance hosts while hosts other than dogs can be considered only occasional host (Walker et al. 2000) (Estrada-Peña et al. 2004).

### Seasonal dynamic

Since it's mainly endophylic there is not a strict seasonality: the duration of the life cycle of *R. sanguineus* may vary from country to country and from region to region. Field studies indicate that *R. sanguineus* ticks can complete two or several generations per year. Under field conditions, moulting and engorgement periods may vary widely among populations and they are directly influenced by factors such as temperature and host availability (Dantas-Torres 2008)

## TICK BIOLOGY

### *IDENTIFICATION*

Ticks are highly specialized obligate, bloodsucking, non permanent ectoparasitic arthropods that feed on mammals, birds, reptiles, and amphibians (Anderson and Magnarelli, 2008). They belong to the class Arachnida, which as a group are distinguished from the class Insecta by having four pair of legs as nymphs and adults, lacking both antennae and wings (Keirans and Durden 2005) and having different structure in the mouthpart: palps, chelicerae and hypostome with a recurved teeth that allows the tick to anchor to his hosts. Ticks can be diveded into three families, the Argasidae (soft ticks), Ixodidae (hard ticks) and Nutalliellidae of which only one species is known, which is not of medical importance. Ticks are found on all continents of the world including Antarctica. They are relative few species (about 865), but their small numbers belie their importance as vectors of pathogens. They are second only to mosquitoes in their importance as vectors of diseases to humans and are undoubtedly the prime vectors of pathogens to both wild and domestic animals. While several species of ticks may occasionally attach to humans, relatively few species commonly bite humans and only some of these are able to transmit diseases to human beings (Keirans and Durden 2005). The reasons are mainly linked to the eco-biology and ethology of each tick species (Manilla 1998c).

The structure of a tick is fused into two parts, consisting of the capitulum (gnathosoma) and the body (idiosoma), to which the legs are attached. As distinctive features larvae have six legs while nymphs and adults have eight legs. Nymphs lack the ventral genital apertures of adults. Male of hard ticks can be distinguished from the female by the presence of a complete chitinous scutum covering all the surface of the body. The scutum covers only partially the female's body allowing the extension of the skin during the engorgement. Unfed adult ticks range in length from 2 mm to 20 mm. Blood-engorged females may be 25 to 30 mm in length and weigh up to 100 times their pre-engorgement weights.

All the mouthparts are found on the capitulum each of them has a different function during the feeding: the two four-segmented palps, each of which in ixodid ticks has numerous chemosensory sensillae located in the small distal fourth segment. The palps do not enter the wound; they are pressed laterally and horizontally against the skin during feeding. The pair of sclerotized, two-segmented tubular chelicerae extends from the basis capituli and is located medially to the palps. Two highly moveable and sharp cutting digits are located at the extremities of the cheliceral shafts. The digits are situated laterally and are used to cut the skin during feeding. The relatively large medially positioned hypostome with ventral, backward pointing denticles (teeth) on its external surface has its internal surface covered dorsally by the chelicerae and is used as a holdfast organ and food canal. The size and shape of the hypostome and arrangement of denticles vary among species and are important features used in identifying species. Blood passes from the host through this food canal, formed by the hypostome ventrally, and by the chelicerae dorsally. Saliva, containing proteolytic enzymes that digest and liquefy tissues, moves from the tick to the host through this channel. The basis capituli, the basal portion of the capitulum, is attached to the tick body by a flexible membrane (Anderson and Magnarelli 2008) (Manilla 1998b) (Estrada-Peña et al. 2004).

***LIFE CYCLE***

All feedings of ticks at each stage of the life cycle are parasitic. Ticks feed only on the blood of their hosts. Stages of development of ixodid ticks include egg, a six-legged larva, one eight-legged nymphal instars, and eight-legged male and female adults. Blood meals, with a few exceptions, are needed for development of the larvae and nymphs to the next stage of development and for reproduction in the adult stage.
In many instances, pathogens acquired by larval feedings are passed to the subsequent life stages, a phenomenon known as trans-stadial transmission (Anderson and Magnarelli 2008). Life cycles of hard-bodied ticks are classified according to the number of times the three feeding stages change hosts and whether juvenile ticks moult on or off their hosts. Accordingly, species are classified as one-host, two host, or three-host ticks (Anderson and Magnarelli 2008) this also affects the control strategies and the transmission of pathogens between different developmental stages.

### Three hosts ticks

This is the commonest type of life cycle of hard ticks. Larvae develop in the eggs until ready to hatch, usually in several weeks (Estrada-Peña et al. 2004). In general, ticks remain on their host animals only while feeding, although some spend time crawling. These ticks feed to completion as larvae, drop off their host to the ground, and moult into nymphs. Nymphs attach to another host animal, feed to completion, and drop to the ground. After moulting into adults, each female attaches to a host, mates, completes engorgement, and drops to the ground, where in time she lays a batch of eggs up to 3000 or more eggs (Anderson and Magnarelli 2008). Ticks that have recently hatched from eggs or from moulting have soft bodies and are inactive for one to two weeks until the external body wall hardens. The life cycle of three host ticks is slow, from six months to several years.

### One host and two hosts ticks

This is a less common type of life cycle but it occurs in all the *Boophilus* sub-genus of the *Rhipicephalus* genus and in other genera. Eggs are laid on soil. Larvae hatch after several weeks of development and crawl onto vegetation to search for a host. When they have completed feeding they remain attached to the host and moulting occurs there. The nymphs then feed on the same host and also remain attached. After another moult, the adults hatch and then feed on the same host. The adults will change position on the same host for mating. Thus all three feedings of any individual tick occur on the same individual host. The life cycle of one-host ticks is usually rapid (about one month and three weeks), it is typical of high specialised tick *Rhipicephalus* (*Boophilus*). The two-host life cycle is similar but only the larvae and nymphs feed on the same individual host, and the adults will feed on another host this type of life cycle is quite common for *Hyalomma* genus.

***HOST PREFERENCE***

### Hunting strategies

Ticks have different ways of finding hosts: most esophylic ticks such as *I. ricinus* or *H. marginatum* employ the ambush strategy climb onto weeds, grasses, bushes, or other leafy

vegetation to wait for passing hosts. The height to which the ticks climb depends upon many factors. The later stages, especially the adults, climb higher in the vegetation where they are more likely to encounter larger animals such as deer, carnivores, and humans. Since the water balance is the limitative factor for the activities of these ticks, the ticks remain on the undersides of leaves or other protective cover with their legs folded. Here they can remain for many hours until increasing desiccation initiates a descent to the cooler, humid ground layer where they can replenish lost body water (Sonenshine 2005). In many species, larvae, that are most sensitive to the desiccation (Manilla 1998d), remain closest to the ground layer where they are most likely to encounter small mammals, ground-feeding birds, and other small vertebrate hosts (Sonenshine 2005). Host-seeking ticks of many species respond to a big variety of stimuli such as: shadows, vibrations, odors, tactile signals, and other stimuli indicating the presence of a host, whereupon they extend their forelegs anterolaterally and cling to the hair or clothing of the passing host (Sonenshine 2005). The dragging method for collecting ticks from vegetation take advantage of questing behavior, they cling to the cloth and do not immediately distinguish it from a living host. Even sound can attract ticks. The sounds produced by barking dogs have been reported to attract the brown dog tick (*Rhipicephalus sanguineus*), while sounds in the range emitted by cattle are known to attract larvae of the cattle tick (*Boophilus microplus*) (Sonenshine 2005).
Most of endophilic ticks usually wait for their host in nests, caves, or other environmental settings and when ticks are close to their hosts, they crawl to the host (Manilla 1998d).
The hunter strategy is the method used by several species that parasitize large mammals such as the desert inhabiting, xerophilic camel tick (*H. dromedarii*) or the southern African *Amblyomma* ticks. These hunter ticks remain buried in soil, sand, or duff where they are protected from extreme heat and desiccation. However, when excited by host odors, the ticks emerge and run rapidly across the ground to attack these hosts, often up to 2 or 3 m away. Hunter ticks can discriminate dark shapes against the bright background of the sky. They are easily excited by carbon dioxide, such as that emitted from a block of dry ice. Carbon dioxide in high concentrations is believed to act as a general excitant but may not facilitate identification of the source. In addition, tick pheromones and possibly host odors can provide the directional information that leads the ticks to cattle or other ungulate hosts (Barré et al. 1997). Odorants are detected by olfactory sensilla, especially the prominent multiporose sensillum in the Haller's organ on the first tarsus (Sonenshine 2005).

**Host specifity**

Ticks do not feed equally on all vertebrate animals. Many, perhaps most, ticks show some degree of host specificity, accepting only a limited variety of animals as a candidate blood source. Such ticks are host specific, i.e., they are restricted to a particular class, order, or even genus of vertebrates as hosts (Sonenshine 1994). True, or physiological host specificity, represents the result of:

1. the tick's ability to recognize and respond to specific host-originated compounds, especially odorants such as $CO_2$, $NH_3$, lactic acid, and other volatiles, reinforced by thermal and contact stimuli characteristic of the host body;

2. pharmacologically active compounds in tick saliva that enable the ticks to suppress (or evade) host homeostatic mechanisms, thereby enhancing blood flow into the feeding

pool but minimizing inflammatory responses that reveal presence of the tick (Sonenshine 1994).

Host preference is also affected by ecological determinants that have in influence on the resistance to the desiccation:

1. the habitat or habitats in which the ticks quest or hunt for hosts;
2. questing height, i .e., the elevation above the ground at which ticks rest while waiting for passing hosts;
3. the time of day when ticks actively seek hosts.

Therefore ticks which can tolerate substantial water loss can quest in relatively dry, meadow environments during daylight hours can climb relatively high on to grassy or weedy vegetation (e.g .,1 m). Resistance to the water loss is not only dependent to the species but in many cases also to the developmental stages; generally larvae are the most susceptible to the desiccation they usually remain closest to the ground layer where they are most likely to encounter small mammals, ground-feeding birds, and other small vertebrate hosts. The later stages, especially the adults, climb higher in the vegetation where they are more likely to parasitize larger animals such as deer, carnivores, and humans (Sonenshine 2005) (Manilla 1998d) (Sonenshine 1994).

Host specificity extends across a broad range of extremes from those that are **highly host specific** at one end to those that exhibit little, if any, specificity at the other. The latter are termed **low or non-specific or opportunistic** ticks. Examples of highly host-specific species include: the squirrel tick, *Ixodes marxi*, which lives in the nests of its arboreal hosts and feeds solely on sciurid rodents; and the cattle tick, *Boophilus microplus*, which feeds exclusively on cattle. Less rigorous patterns of host specificity are common, such as *Amblyomma tholloni* the African elephant bont tick which is mainly present only through the geographic range of this animals (Walker and Olwage 1987) or for many species of the genus *Aponomma* which feed mainly on reptiles (Manilla 1998d).

Often, such ticks will feed on a particular class of vertebrates, e.g. birds, but no other vertebrate animals. Many species exhibit restricted host ranges in one or two stages of the life cycle, but a much broader range of hosts in another period of the life cycle. An example is the so-called rabbit tick, *Haemaphysalis leporispalustris*. Actually, this species is best described as a "bird-rabbit tick" since the larvae and nymphs readily attack an immense variety of ground-feeding birds (as well as rabbits), while the adults feed exclusively on lagomorphs.

Finally, the generalists constitute the opposite end of the host specificity spectrum. Such non-specific ticks feed readily on virtually all terrestrial vertebrates, although amphibians are rarely used. Examples include: (1) deer tick, *Ixodes scapularis*, which feeds on a wide variety of small mammals (including both insectivores and small rodents), medium-sized carnivores, deer, birds, reptiles and even man; (2) the European sheep tick (or castor bean tick), *Ixodes ricinus*, with a similar expansive host range; and (3) the argasid tick, *Ornithodoros hermsii*, which feeds on a wide range of small and medium-sized mammals (Sonenshine 1994).

# POPULATION DYNAMICS OF TICK VECTORS WITH POTENTIAL INVOLVEMENT WITH CCHF

***FIELD MONITORING METHODOLOGIES***

## Collection ticks from hosts

Tick specimens are frequently obtained from their hosts. It is seldom feasible to examine the whole of a livestock animal for ticks, but in some studies the animal is cast to the ground or held in a crush then one half of the body is searched fully. It is often more efficient to examine a sample of fixed areas of the host. This is very useful for ticks which are known to have sites where they prefer to feed (= predilection sites). For example, on a herd of cattle in the western Mediterranean parts, one can expect to find: *R. turanicus* adults on the ears; *H. marginatum* and *H. lusitanicum* adults on the dewlap, axillae, udder and groin; *R. (Boophilus) annulatus* generally on the shoulders, dewlap, and belly (Estrada-Peña et al. 2004). In Africa on a herd of cattle *R. appendiculatus* adults will be mostly found on the cattle's ears, *A. variegatum* will be on the dewlap, axillae, udder and groin, *B. decoloratus (Rhipicephalus (Boophilus) decoloratus)* or *B. microplus* will be more generally on the shoulders, dewlap, and belly, *H. truncatum* and *R. evertsi evertsi* will be mostly around the anus. An effective way to detect adult ticks, especially when they are engorging, is to feel the hair coat of the host with the palm of your hand. Smaller domestic animals in a clinic can be examined in the same way. To find immature ticks or unfed adults the hair can be parted systematically using forceps as a comb (Latif and Walker 2004).

To remove ticks from host skin whilst retaining their good condition for identification is necessary to use good quality steel forceps. The forceps is used to grip the tick firmly over its scutum and mouthparts as closely to the host skin as possible, then pull strongly and directly out from the skin. Usually the mouthparts will be removed with the rest of the tick and often with a plug of cement. Teeth may be damaged during removal of the mouthparts the tick from the host, for the identification of some genera observation of the arrangement of the teeth is necessary. Generally, for more easy identification is useful to have males in addition to females. If the ticks are required live for further studies they should be placed in strong tubes containing a piece of damp paper.

The ticks should be kept cool over ice but take care not to freeze them fatally. To preserve the ticks at the collection site place them directly into 70% alcohol. To label collection tubes in the field the best method is to use a lead pencil to write a small label on white card. This label is placed inside the tube with the ticks.

Labels on the outside of the tubes should only be written on tape wrapped completely around the tube. Field collection data should include date, site, collector, host species and other information relevant to the study (Latif and Walker 2004).

## Collection of ticks from vegetation and from other environment

Some species of ticks can be collected whilst they are unfed and questing on vegetation. If they are sufficiently dense in numbers adult can be picked from grass stems (Latif and Walker 2004; Estrada-Peña et al. 2004).

More often, it is efficient to use a trap, which mimics a host. This consists of a cloth 1m square which is dragged slowly across the vegetation for 5 m to 10 m (for approximately 30

seconds of walking; or a longer distance depending on local knowledge). Larvae, nymphs and adults will grip onto the dragging cloth temporarily and can be collected with a forceps. A white cloth of cotton toweling is effective. It is fitted with a bar at the front and a cord for pulling it. This method works well for larvae and nymphs of questing species but is less efficient for adults and hunting species (Latif and Walker 2004; Estrada-Peña et al. 2004). A sweep net can be used to collect adults which quest on long vegetation; these are made of a very strong frame with a thick cloth bag. Traps using carbon dioxide as an attractant can be used to collect ticks (Gray 1985).
Endophilic and domestic ticks can be collected direct from the nests or shelters of their hosts using forceps to probe in cracks and under pieces of dry dung, spiders webs etc. This is very effective for moulting nymphs and adults of *Hyalomma* ticks in cattle housing (Estrada-Peña et al. 2004; Latif and Walker 2004). During collection is necessary to protect whole body from tick bite by wearing long trousers over long boots and long sleeves with closures at the wrists.

***ABUNDANCE***

## Factors influencing the abundance of CCHF vectors in Eurasia

Because of the ubiquity of the putative vertebrate hosts of CCHFV, and their common infestation by ticks of many genera including *Hyalomma*, host availability is unlikely to be a limiting ecologica1 factor in the distribution, or even the prevalence, of this virus. Moreover, a non viremic route has been indicated by reports of transmission among co-feeding ticks via hosts that do not develop viremia above threshold level. This may add both qualitatively (more species than conventionally recognized acting as hosts) and quantitatively to the transmission potential (Randolph and Rogers 2007).
The principal environmental factors responsible for the enzootic distribution of CCHFV within the steppe, savanna, semi-desert, and foothill ecotypes of the Paleartic, Oriental, and Ethiopian faunal regions are those that enhance the prevalence of *Hyalomma* ticks. The only exceptions are in the deciduous forests of Moldavia and on the island of Madagascar. In Moldavia, *I. ricinus, Dermacentor* and *Rhipicephalus* species have replaced *Hyalomma* species, probably because of changes in the practices of handling cattle herds (Hoogstraal 1979). In Madagascar, where *Hyalomma* ticks do not occur, the virus has been isolated only from *B. microplus,* and there are no human infections (Linthicum and Bailey 1994).
In a given region, CCHFV transmission is greatest in limited foci where climatic factors and/or environmental changes are conducive to the survival of *Hyalomma* ticks and their hosts These areas are different according geographic areas and different species requirements. They may be along river floodplains with rich grasslands (Astrakhan Oblast), shrub and tree vegetation (Uzbekistan), desert or semi-desert, sparse forests scattered in desert (Kazakhstan), and forests and thickets of rough steppe lands (Rostov Oblast) (Linthicum and Bailey 1994) (Watts et al. 1988).

### *Abiotic factors*

Abiotic factors are more likely to determine patterns of epidemiological risk, because they affect the rates of many of the tick population processes critica1 to the dynamics of tick-borne disease systems (Randolph and Rogers 2007).

## Environmental conditions

In general, CCHF outbreaks have developed against a background of favourable climatic factors and environmental changes beneficial for the survival of large numbers of *Hyalomma* ticks and of the hosts of both their immature and adult stages. In the former Soviet Union, environmental changes include wartime neglect of agricultural lands, introduction of susceptible military personnel or new settlers into an infected area, wide scale collectivisation of agriculture, changing pasture patterns, converting floodplains to farmland, and flood control.

During World War 2, after the occupation of Crimea (1941–44), normal agricultural activities were disrupted and the common sport of hunting European hares was abandoned. When Soviet troops reoccupied the hilly Crimean steppes in 1944, hares had become excessively abundant and neglected pastures were overgrown with weeds, and the first outbreak of the modern era was documented (Ergonul 2006). A similar explanation was suggested for the outbreak in Turkey the fields in the affected region had been abandoned from hunting and pasturing between 1995 and 2001 because of terrorist activities (Ergonul 2006) in this period, the numbers of small mammals (e.g., hares) and wild animals (e.g., wild boars) increased. After 2001, the fields became available again or hunting and pasturing, and cattle and sheep were exposed to virus-carrying ticks (Ergonul 2006).

More gradual environmental changes such as wide-scale changes in agricultural practices, changing pasture patterns, conversion of flood plains and marshy deltas to farmland and pastures, and flood control measures can create new habitats for vectors and hosts, and lead to increased disease transmission.

## Climatic influences

In temperate regions the foci of enzootic CCHF are typically in areas characterized by warm summers and relatively mild winters (Hoogstraal 1979). The number of days with a temperature of over 5°C in April; and the daily mean temperature in April in the region of Turkey affected by the recent outbreak, were reported to be increased in the years before the outbreak (Ergonul et al. 2005).

However, climate change is not necessarily the cause of the marked increased incidence of a variety of tick-borne diseases in many parts of Europe over the past two decades (Randolph and Rogers 2007).

### Eurasia

In Eurasia, CCHF foci are found in the transitional atmospheric humidity zone between the forest-steppe and desert in which the sum of the effective annual temperature above 10°C is between 2,800 and 5,000°C (Watts et al. 1988). In the lowland desert and semi-desert area of southern Tadzhikistan, enzootic foci are where the sum of annual temperatures ranges from 3,000°C to as high as 6,000°C in warm years. In southern Tadzhikistan, the annual rains range from 150 to 300 mm (Linthicum and Bailey 1994).

*H. marginatum*, the primary tick vector in Eurasia, cannot survive when winter temperatures fall below a monthly mean temperature of - 20°C (Hoogstraal 1979). A decline in vector populations leads to a decline in CCHF viral activity. In the winter of 1968-1969,

temperatures dropped to - 30°C and remained at -20°C or lower for more than 2 months, and the ground froze to a depth of 1 m in the enzootic area of the Republic of Kirzig. Consequently, the adult tick abundance index per cow fell from approximately 20 in 1968 to less than 0.1 in May 1969, and no CCHF cases were reported during the summer of 1969. CCHFV did remain enzootic in two species (*R. rossicus* and *D. marginatus*) that are better adapted at surviving at cold temperatures than *H. marginatum* (Watts et al. 1988) (Linthicum and Bailey 1994).

Africa and Middle East

In Eurasia and northern Africa CCHF foci are found in arid deserts and semi-deserts, and in South Africa in semi-arid high-altitude regions. In tropical areas in Africa, CCHF enzootic areas can range from wet central African forests to the very sparsely vegetated, arid Sahelian areas of West Africa, and the semi-arid high-altitude scrub vegetation areas of East Africa (Linthicum and Bailey 1994).

In Mauritania, Saluzzo (Saluzzo et al. 1985) reported that the geographic distribution of CCHFV closely fits the distribution of *H. m. rufipes*. *H. m. rufipes* (and sometimes *H. impeltatum*) is the most frequent vector in southern Mauritania; however, it is replaced in the very arid semi-desertic regions of northern Mauritania by *H. dromedarii*, which is not usually infected with the virus in the area. *H. dromedarii* is thought to be very well adapted to the desert environment (Hoogstraal, 1956), and able to withstand low humidity and extremes in temperatures.

Swanepoel and collaborators (Swanepoel et al. 1987) in a serosurvey performed in South Africa described that antibody prevalence to CCHFV was higher in areas with higher densities of *Hyalomma* species.

Antibodies to CCHF virus were absent from most herds along the southern coast, and there was a tendency for the proportion of positive herds and positive cattle within herds to increase northwards to Zimbabwe, where there were abundant tick populations. Similar findings have been reported for wild mammals in South Africa by Shepherd et al. (Shepherd et al. 1987). The climate along the coast where *Hyalomma* ticks are less abundant is defined as dry sub-tropical with hot, dry summers and cool, moderately rainy winters (Linthicum and Bailey 1994). In more northern South Africa and Zimbabwe, where *Hyalomma* tick populations are high, the climate is defined as semi-arid tropical characterized by light precipitation, rapid evaporation, and always warm or hot.

In Kenya, *Hyalomma* species are usually found in dry woodland, bushland, and wooded and/or bushed grassland. These areas range from semi-arid to very arid with annual rainfall ranging from 250 to 750 inches. Only *H. truncatum* is found (rarely) in the wetter areas (Walker 1974).

In Uganda, *H. m. rufipes* is usually collected from locations with an annual rainfall of 500-1,000 mm with a 4-7-month continuous dry season. In Tanzania *H. m. rufipes* is usually found in areas with an annual rainfall of 380-900 mm. (Matthysse and Colbo 1987) In West Africa, it is found in areas with a mean annual rainfall of 150-750 mm and it usually disappears in regions with rainfall above 1,250 mm, with the exception of southern Senegal and western Guinea, which have a very intense rainy reason (up to 2,000 mm) followed by a long and severe dry season (Morel 1969).

*H. truncatum* is normally found in the dry savanna and steppe regions of Africa, characterized by Combretum and Acacia species of vegetation. It is more restricted to drier regions than *H.*

*m. rufipes*. In Uganda, it is restricted to regions of long continuous dry seasons over 3- 7 months long, and with a mean annual rainfall of 650-1,300 mm (Matthysse and Colbo 1987). In Tanzania, it is present in areas with an annual rainfall of 650-1,500 mm, while in Kenya, it can be found in areas of less than 250 mm of rainfall (Walker 1974).
*H. impeltatum* also occurs in very dry regions. In Kenya, it is reported to occur in areas receiving less than 250 mm of rainfall per year (Walker 1974).

Microclimate may also have a direct impact on tick behavior in particular the height on the vegetation at which they quest for hosts, affecting tick-host contact rates and therefore pathogen transmission potential (Randolph and Storey 1999). Adult ticks, which typically quest at higher levels in the vegetation than do immature stages, will be unavailable to smaller hosts species moving about at ground level. At the same time, host dynamics and behavior vary independently, also determining contact rates. Any seasonal variation in the differential availability of each host species results in different tick-host ratios in different places.
Smaller hosts show stronger seasonal cycles of abundance wherever the climate dictates seasonal breeding, but even among larger hosts exposure to ticks may vary with, for example livestock husbandry practices or changes in behavior (e.g. squirrels shifting from ground- to tree-based foraging in the summer) (Craine et al. 1995) (Randolph and Rogers 2007).

## Climate changing implication and modelling

In general, it is possible to affirm that despite some evidence it is difficult to implicate climate change as the main cause increasing prevalence of tick borne disease. Climate change models are required that take account of the dynamic biological processes involved in vector abundance and pathogen transmission affecting the complex ecology and epidemiology of tick borne disease such CCHF, Tick Borne Encephalithis and Lyme borreliosis in order to predict future tick borne scenarios
Recently, studies on possible effects on climate changing on *Hyalomma marginatum* distribution and on influence of climate changing on tick borne disease have been reviewed by Gray and collaborators (Gray et al. 2008):
*Hyalomma marginatum*'s possible northern spread and establishment of permanent populations is thus of much significance, especially since immature stages are frequently found on migratory birds flying to temperate Europe.
The life cycle of this tick is faster in southern parts of its distribution range (northern Africa) with larvae active as early as February, but clearly slower in northern, colder regions, with immature active as late as June. Analysis of the recorded distribution of the tick show that, according to climate requirements, there are two clear clusters of populations. One cluster extends from the northern geographical limit of the species in the Balkans (approx., latitude 44◦N) and into Turkey and the Middle East. The second one is restricted to Africa north of the Sahara and western parts of Spain. Analysis of the climate niche of the first cluster clearly points to a temperature-related limiting factor for these northern populations. Temperatures between September and December are critical for the establishment of permanent populations. Cumulative temperatures between September and December have an average of 800◦C in places where the tick has permanent populations, and below 400◦C in sites not colonized by *H. marginatum*. This finding seems to be related to the factors that affect molting of immature stages and are not connected to the extremely cold winter temperatures

that prevent overwintering adults surviving into the next year, as suggested by Hoogstraal (Hoogstraal 1979). If temperatures are high enough to allow molting before the cold winters, unfed adults can survive the next active season. Field observations recorded the feeding of nymphs in late summer in Turkey, with the resulting unfed flat adults commonly overwintering in the first few centimeters below the soil surface. Regulatory variables for these northern populations appear to act on thermo dependent phases of the tick life cycle. On the other hand, climate niche analysis of the southern cluster of tick communities points to a strict dependence on rainfall and potential evaporation, but this may not be relevant if specimens from the southern range can adapt to the colder conditions of the northern cluster.
Although migratory birds are carriers of immature *Hyalomma* ticks and could potentially introduce them into currently *Hyalomma*-free areas in the spring, their climate requirements and current climate data do not suggest that they can become established. Mid-March and early April are the main periods of mass arrival of birds in Spain on their way to northern Europe.
In the current climatic conditions, it is highly improbable that engorged nymphs can survive in sufficient numbers to be founders of new permanent populations in northern Europe. Immature *H. marginatum* are found on local (no migratory) birds in central Spain around late May and early June, which is too late for northern African and southern European populations of *H. marginatum* to mix because of the current climate barriers imposed by their respective climate requirements at the moment of bird migration. If climate change includes the predicted temperature increases, *H. marginatum* ticks may become established in northern latitudes but it is debatable whether initial introduction will occur as a result of bird migration alone because very small numbers of ticks, all immature stages, would be involved. It is more likely that, as autumn and winter temperatures rise, establishment of *H. marginatum* will mainly result from the introduction of adult females feeding on wild and domestic ruminants via the middle East and the Balkans, where there is much uncontrolled movement of livestock.

Models

Climatic models have been built to predict possible dispersion and establishment of tick in free area but the real effectiveness of them is still under study since many other factors such as vegetation patterns or host abundance operating at different levels restrict the effective dispersal and establishment of potential invaders.
The basic concept underlying species occurrence modeling is the definition of the ecological niche: each species is found within specific ranges for environmental variables that support individual survival and reproduction. Species occurrence can be predicted by inclusion of appropriate climate variables in what are commonly referred to as climate suitability models (CSMs): the relationships are generalized from a sample of correlations of species presence with specific values of environmental variables. However, these CSM are unsuitable if an adequate understanding of the factors operating over the transmission of a disease is necessary. The many variables involved in such processes, like hosts, densities of questing infected ticks, and a perception of the small scale of foci, are only adequately addressed with models designed to describe seasonal dynamics.
While some models with biological content have been produced for tick species such as *Boophilus microplus*, *Amblyomma americanum*, and *Ixodes scapularis*, none are currently available for European ticks. Such models are a priority to adequately understand the impact

of climate change on tick populations, provided that adequate data are used for important components such as host densities and microhabitat suitability (Gray et al. 2008). However, despite the absence of such data in climate suitability models, these models have proved useful in the elucidation of tick-borne disease foci for the recent outbreak of CCHF in Turkey. It identified habitat fragmentation has as a critical factor in the spatial and temporal distribution of human cases. In highly fragmented habitats, the risk of contact between humans and infected ticks appears highest. The spatial distribution map for *Hyalomma* ticks in Turkey is currently used to focus surveillance studies on areas with higher than expected number of CCHF cases. These areas are currently intensively surveyed for CCHF virus in *Hyalomma* ticks on wild and domestic livestock to improve risk maps for this important disease which is expected to continue to cause outbreaks in Turkey in the years to come. (Estrada Pena et al. 2007).

Other climatic model based considering temperatures and rainfall predicts that large areas of Europe would potentially be affected by an increase in the climate suitability for *Rhipicephalus spp.* and *H. marginatum* after an increase in temperature and decrease in rainfall. Decreasing temperatures in Europe are predicted to result in habitat loss for *B. annulatus*, *R. bursa*, and *H. marginatum*. Gray and collaborators stress that this is an evaluation of the climate suitability for these tick species, since changes in vegetation, host availability, and animal movements were not included in the models (Gray et al. 2008).

## Conclusion

Transmission of infection occurs when there is an overlap of activities between reservoir, vector, and humans, and differs according to the pathogens and the location. Climate change may impact all of these stages and their interactions. Although changes in climate will directly affect tick survival, activity, and development, there is no good evidence that rising temperatures will result in a greater abundance of ticks by simply increasing rates of development; rather changes in development rates will make tick cohorts available to different diapause windows (largely determined by day length), thus changing patterns of seasonal activity. Indirect effects of climate change will impact the number of infected ticks by affecting vegetation. For example, a warming climate in central Europe is likely to result in a decrease of Norway spruce (*Picea abies*) and the areas involved will probably be colonized by beech (*Fagus sylvatica*), the fallen leaves of which provide a favorable microclimate for survival of the free-living tick stages. Additionally, climate change will also have indirect effects on tick-borne pathogen transmission by affecting the survival and abundance of tick maintenance hosts, such as deer, and pathogen-reservoir hosts such as rodents and birds. Climate change may also influence disease risk by affecting the long-term use of land (e.g., farming, tourism, etc.), and weather patterns have an effect by influencing short-term human behavior such as picnics and mushroom picking.

Climate effects are more easily noticeable close to the geographical distribution limits of both vector and disease. The magnitude of the effects of climate change in an endemic area depends on local conditions and vulnerability, and is determined not only by ecological conditions but may be influenced by socioeconomic factors, human migration and settlement, ecosystems and biodiversity, migrating patterns of birds, land-use and land cover changes, human cultural and behavioral patterns, and immunity in the population.

Since some of these conditions are in turn influenced by climate change, a complex chain of processes exists that makes the precise factors responsible for changes in disease incidence

often difficult to assess. Much current research effort attempts to match datasets collected for different purposes and in order to reduce confounding variables, it is evident that data from long-term studies on disease incidence, tick biology, tick distribution and tick abundance, host abundance and distribution, and relevant vegetation biology, specifically in relation to climate change, are required. Such data will permit the development of models to predict future tick borne disease scenarios, which take account of dynamic biological processes instead of simply the likelihood of occurrence of climate suitability for particular tick species (Gray et al. 2008).

### *Biotic factors*

#### Vector competence

To maintain the CCHV in the natural cycle ticks have become infected from an infected host during feeding by previous tick stages as long as they maintain sufficient vira1 load during interstadial development and moulting. They must then be able to develop mature infections in the salivary glands for onward transmission to the next host. Each of these steps depends on the ability of a microbe to overcorne the many intrinsic biological (molecular, cellular, physiological, and physical) barriers during its passage from host to host via the vector. Even then, although biologically possible, this cycle may not proceed with sufficient force to support persistent transmission cycles. That depends on the quantitative balance of the rates of all the processes involved in each complete transmission cycle (Randolph and Rogers 2007).
In comparison to other tick borne virus such as Tick Borne Enchephalitis virus not enough is known quantitatively about the necessary biotic conditions for the maintenance of CCHFV cycles in nature to allow a firm conclusion on the relative roles, potential, or realized of the various biologically competent tick species (Randolph and Rogers 2007).

#### Tick Biology

There are several aspects of the biology of CCHF vectors that could affect the abundance of the vectors. Most of what is known has been determined from studies in the laboratory with very little field research completed. These factors are:

1. **Oviposition and fecundity:** Ixodid ticks oviposit once in a life time. Eggs are laid without regard to location at on time approximately 1-3 weeks after detaching from the host. For the main vectors these period has been assessed by laboratory trials. The period of oviposition in *H. impeltatum* can range from 16 to 50 days (Logan et al. 1989b). Usually, numerous eggs are laid, although the number can vary tremendously. *H. marginatum* female can lay from 4,300 to 15,500 eggs, while Knight (Knight et al. 1978) found that *H. m .rufipes* females can lay from 3,184 to 13,180 eggs. *H. impeltatum* female can lay from 713 to 15,904 eggs with a mean hatch rate of 84% (Logan et al. 1989b). *H. truncatum* females lay from 4,434 to 8,210 eggs with a mean hatch rate of 48% (Linthicum et al. 1991).
2. **Fecundity:** The overall fecundity of a tick population in a given year can be expressed as a product of the total number of eggs oviposited by individual females of a generation that successfully hatch and the number of generations completed during that year. In nature, the shortest time required to complete a tick generation may be 4 or 5

months; however, climatic conditions and host availability may increase generation time and decrease the overall fecundity of a given population. Hoogstraal (Hoogstraal 1979) reported that *H. m. marginatum, H. truncatum*, and other *Hyalomma* species in Eurasia complete only one generation per year because of the severe winter climate.

3. **Density and biting activity:** Epidemics of CCHF coincide with an elevated population density and increased feeding of *Hyalomma* ticks. During the outbreaks in Bulgaria, adult *H. marginatum*, the principal vector, appeared, reached maximum population densities, and declined in close association with the occurrence of human cases, peak numbers of cases, and decreasing number of cases, respectively (Hoogstraal 1979). In the Central Asian republics of the former USSR, the seasonal distribution of CCHF cases were closely associated with the seasonal dynamics of *H. anatolicum*, the suspected vector (Linthicum and Bailey 1994).
4. **Longevity:** Adult ticks can survive for very long periods of time, months, or years, without blood feeding, if climatic conditions and availability of hosts are not favourable. *H. marginatum* can survive for more than 800 days without a blood-meal under optimal laboratory conditions. Adult *H. truncatum, H . impeltatum, H. rufipes, A . variegatum, R. appendiculatus, R . e. evertsi, R . pulchellus,* and *R. sanguineus* have been held in the laboratory without blood-feeding for up to 1 year (Linthicum and Bailey 1994).
5. **Life cycle and host preference:** Different type life cycles have great influence in the maintenance of CCHFV. They are before described for each species considered. CCHF disease epidemiology appears to be controlled by ticks with a long life cycle (Linthicum and Bailey 1994). The host preferences of potential tick vectors of CCHF virus are important in understanding the natural ecology of the disease. It is important to understand biological parameters such as number of hosts parasitized by an individual tick during its lifetime, the potential variety of hosts parasitized, and the degree of host specificity. All stages of *Boophilus* species ticks are completed on the same vertebrate host and they rarely attack man. The role of one-host ticks in the ecology of CCHF virus is still unclear. However, the recently demonstrated laboratory importance of non-viremic hosts (such as cattle in some cases) in the transmission of the virus suggests that *Boophilus* species may well be involved in virus amplification.

   Two-host ticks can be regarded as two subgroups based on whether or not they utilize the same or different species of hosts to develop into the immature and adult stages. Species that attach as larvae and adults to the same species of host include *R. bursa, R. e. evertsi, H. detritum, H. anatolicum*, and sometimes *H. truncatum*. All stages of *R. e evertsi* normally infest domestic or wild herbivores, but larvae may sometimes infest small mammals such as rodents and hares (Hoogstraal 1956). *H. detritum* commonly feed on cattle and horses. The adults feed in the summer and the nymphs undergo a winter diapause (Hoogstraal 1956). Tick species in which the immatures and adults feed on two dissimilar host species include *H. m. marginatum, H. turanicum,* and *H. m. rufipes*. Larvae and nymphs of *H. m. marginatum* feed primarily on small wild mammals and birds, while adults are commonly found on cattle, horses, sheep, goats, and camels (Hoogstraal 1956). *H. m. rufipes* adults are most commonly found on domestic cattle but also on horses, sheep, goats, and large wild animals like buffalo and giraffe. Immatures feed on a variety of birds and also on hares (Linthicum and Bailey 1994).

In Eurasia, the following three-host ticks have been associated with CCHF: *I. ricinus, H. punctata, D. marginatus, D. daghestanicus, H. asiaticum, R. pumilio, R. rossicus, R. sanguineus*, and *R. turanicus.* In Africa, *H. impeltatum, H. nitidum, H. truncatum, A. variegatum, R. pulchellus*, and *R. appendiculatus* have been associated with CCHF virus. These three-host species are considered to be primarily involved in the ecology of CCHF virus as enzootic vectors of the disease and not in transmission to humans.

Although very few tick species have been incriminated in the transmission of CCHF virus to humans, almost all the species associated with the virus are known to feed on humans under some circumstances.

6. **Host immunity and host resistance:** The subject of acquired resistance is known for the Ixodidae. The effects of resistance range from simple rejection, lowered engorged weight, prolongation of feeding time, and interference with feeding to death of the tick on the host. Many ixodid ticks can induce a host reaction to repeated tick feedings, which results in resistance; however, observations in Hyalomma species conflict. Domestic rabbits did not develop resistance to H. excavatum and H. dromedarii, but they did develop resistance to D. pictus and R. sanguineus, while guinea pigs developed a limited resistance to H. truncatum larvae (Linthicum and Bailey 1994). Genetic resistance has been described in West African indigenous cattle; studies conducted in N'Dama and Gobra zebu cattle in The Gambia showed the former to possess a higher degree of resistance than Gobras against adult ticks species belonging to two genera characterized by long hypostome, such as A. variegatum, H. truncatum and H. marginatum rufipes (Mattioli et al. 2000).

## VECTOR COMPETENCE OF TICK SPECIES

### *VIRUS-HOST INTERACTION (TRANSMISSION CYCLES)*

Infection or even transmission competence per se are not necessarily sufficient for persistent cycles if the pattern of attachment by different tick stages does not allow sufficient amplification (Randolph and Rogers 2007). For CCHFV, for which transovarial transmission does occur but is not very efficient (Wilson et al. 1991) at least two tick stages must feed on any one host. Immature stages of *Hyalomma* species, or indeed most other tick species from which CCHFV has been isolated, are much more commonly recorded on small mammals and birds than on ruminants. In a national park in Cape Province, South Africa, there was a complete separation between immature stages of *H. m. turanicum* and *H. truncatum* on hares (the most highly infested host species), ground-feeding birds or small rodents, and adult ticks on zebra and eland (*Taurotragus orix*). This pattern of tick biology raises the distinct possibility that, while ruminants may be vital in feeding adult ticks and therefore supporting tick populations and domestic livestock infected by these adult ticks may be instrumental in bringing CCHFV to humans, smaller vertebrates may be the principle maintenance hosts (Randolph and Rogers 2007). An additional complication for CCHF is the variability shown by *H. truncatum* and *H. m. rufipes* between a two-host feeding pattern (i.e. both larvae and nymphs feeding from the same host and adults from a second) and three-host feeding pattern (each stage feeding on a different host), apparently depending on the species of larva1 hosts (Randolph and Rogers 2007).

For two-hosts ticks showing distinct host relations as immature stages and adults (above), the sustainability of natural virus transmission cycles depends on the efficiency of complete vertical transmission, including transovarial transmission, and the degree of amplification amongst immature stages feeding together on the same host individual. This latter factor is augmented by the commonly observed aggregated distribution of ticks amongst their hosts, with the few hosts that carry many ticks making an essential, disproportionately large, contribution (Randolph et al. 1999) (Randolph and Rogers 2007).

The biology of vertebrates implicated in the ecology of CCHFV is important in understanding the transmission cycles of this zoonosis. Humans become infected when they interrupt the natural CCHFV enzootic cycles. Because of the diversity of ecological and zoogeographic habitats of CCHF foci, the qualitative and quantitative aspects of the biology of each vertebrate involved in maintaining the enzootic cycle of the virus must be determined (Hoogstraal 1979; Linthicum and Bailey 1994).

The horizontal transmission of the virus from viremic vertebrates to tick vectors is important in the ecology of the virus. The density of susceptible vertebrate species is a critical factor in determining the prevalence of ticks infected and capable of transmitting the virus.

Transovarial transmission can occur with different effectiveness according the strain and the speciese ov vectors playing an important role in maintaining the virus in specific ecological conditions.

The virus through transovarial and transstadial transmission can remain in ticks for extended periods in the absence of susceptible vertebrate populations.

Other modes of transmission of infection that probably play a role in the maintenance of virus in nature include sexual transmission of infection in ticks and the phenomenon of nonviremic

transfer of infection between ticks cofeeding on a host. Nonviremic transmission of infection between ticks is believed to be facilitated by factors present in tick saliva and has been demonstrated for CCHF virus with infected adult and non infected immature *H. truncatum* ticks and *H. impeltatum* ticks fed together on non viremic mammals (Burt and Swanepoel 2005b).

Okorie (Okorie 1980) demonstrated that six hours after inoculation of 3.5 $LD_{50}$ CCHFV into *H.m.rufipes* nymphs and adults, there was complete adsorption of virus into the cells of the adults, while there was still residual virus present in nymphs. The eclipse period in adults lasted for over 24 h after inoculation. In both nymphs and adults, the peak content of virus was obtained by day 4 post-inoculation. The peak virus content (7.4 $\log^{10}$) in nymphs was much higher than that (4.6 $\log^{10}$) in adults inoculated directly.

This suggests that CCHFV replicates faster in the immature nymphal stage of *H.m.rufipes* than in the adult stage. During metamorphosis of nymphs to adults, a drop in virus content, followed by an increase in the new stage was revealed. This drop in virus concentration could be explained by the fact that tissues of ectodermal origin are destroyed by lysis and replaced during metamorphosis. The increase in the titre could therefore be due to re-establishment of infection in the new tissues. CCHFV content in *H.m.rufipes* increased after a blood meal. This may be due to the increased cell activity after feeding, when old epithelial cells slough into the lumen and new cells replace them. This cell activity might have favored replication of CCHFV, as previously suggested. It is also significant that unfed male and female adults had about the same virus content until after engorgement, when the level of virus in the females became higher than in the males. The detection of CCHFV in the unfed adults, 185 days post-inoculation, shows that the virus persists for a long time in *H.m.rufipes*.

Human infections with CCHFV are infrequent and irregular, but may be related to human association with increased densities of vertebrates and their associated tick species, as has been observed in the Crimean and in the Turkish epidemics (Hoogstraal 1979) (Linthicum and Bailey 1994 ) (Ergonul 2006).

Table N°3 from Linthicum and Bailey (Linthicum and Bailey 1994) modified reasumes data on experimental infection in ticks while comprehensive data on vectorial competence are shown in table N°2.

Data present in the two table show that there are still limited studies on the role of ticks to serve as vectors and reservoirs of CCHF virus. However it's evident that the most important vectors to man are species of *Hyalomma,* although species of certain other ixodid genera are susceptible to infection and probably contribute in a subsidiary manner.

CCHF viral infection has been demonstrated for many species feeding upon viremic vertebrates, Engorged nymphs of *H. m.rufipes*, *H. truncatum,* and *R. e. evertsi* became infected after intracoelomic inoculation. Transmission of CCHFV to a vertebrate host has been demonstrated for many species.

Larvae of *H. truncatum* and *H. impeltatum* were infected while co-feeding with corresponding CCHFV-infected adults on non-viremic guinea pigs (non-viremic transmission).

It has been shown the transmission of CCHF virus was transstadially to nymphs and adults, and horizontally to guinea pigs serving as host of nymphs and adults. It also has been observed venereal transmission of CCHF virus from male to female *H. truncatum.*

Even if experimental studies on the role of transovarial transmission in infected ticks are not conclusive and may depend upon the strain of CCHFV used in the studies, it has been described in different species.
On the contrary, experimental studies demonstrated transstadial transmission of CCHFV consistently in all ticks infected by feeding on a viremic vertebrate (Linthicum and Bailey 1994).

**CCHF virus in "non human vertebrates" and its association with ticks**

Introduction

Like most arthropod-borne agents causing human disease, CCHF virus is generally a zoonosis circulating unnoticed in nature in an enzootic tick-nonhuman vertebrate-tick cycle.
Zoonotic agents generally cause little or no damage to their usual hosts, but exceptions to this generalization do occur. Before 1968, ignorance of the role of non human vertebrates in the CCHF epidemiological process was total (Hoogstraal 1979). Much progress on the knowledge of the role of non human vertebrates in the epidemiology of CCHF has been made in the recent past. Ticks can become infected with CCHF virus while feeding on infected vertebrates before the host develops antibodies to the virus. If there are no vertebrates susceptible to CCHFV infection, horizontal transmission cannot occur. For horizontal transmission of CCHFV to occur, vertebrates must be susceptible to both the virus and to the tick vectors (Linthicum and Bailey 1994).

Reptiles

In 1973 in Tadzhikistan, a Horsfield Tortoise, *Testudo horsfieldi*, 1 of 209 examined in the agar gel diffusion and precipitation (AGDP) test, was positive for CCHF antibodies (Pak 1973) it probably could be explained as false positive reaction. Considering that information available are scare on the role of reptiles should be better investigated since reptiles such as lizards, tortoises or snake can act as a host of immature of some tick species vector of CCHFV.

Birds

Until the 1984 birds were though to be refractory to the infection to CCHF viremia even though some species support large numbers of CCHF-infected ticks. In November 1984 a case of Crimean-Congo haemorrhagic fever (CCHF) occurred in a worker who became ill after slaughtering ostriches (*Struthio camelus*) on a farm near Oudtshoorn in the Cape province of South Africa. Antibodies to CCHFV were detected in the sera of 22/92 ostriches from farms in Oudtshoorn district, including 6/9 from the farm where the patient worked, but not in the sera of 460 birds of 37 other species. In pathogenicity studies domestic chickens proved refractory to CCHF infection, but viraemia of low intensity (maximum titre 2.5 $\log^{10}$ mouse ic $LD_{50}$/ml) followed by a transient antibody response occurred in blue-helmeted guinea fowl (*Numidia meleagris*) (Shepherd et al. 1987).
Following the occurrence of a further outbreak of CCHF among workers at ostrich abattoir in South Africa in 1996, the role of these birds in maintaining CCHFV was experimentally investigated in 9 susceptible young ostriches. Infected ostriches developed viraemia which was demonstrable on days 1-4 following infection, with a maximum intensity on day 2 in 1 of

the birds. Virus was detectable in visceral organs such as spleen, liver and kidney up to day 5 post-inoculation, while 1 day after it could no longer be found in blood. No infective virus was detected in samples of muscle, but viral nucleic acid was detected by reverse transcription-polymerase chain reaction in muscle from a bird sacrificed on day 3 following infection. After this experiment was concluded that keeping the birds free of ticks for 14 days before slaughter could reduce the risk of infection at abattoirs (Swanepoel et al. 1998).
The role of ground-feeding birds in CCHFV' ecology has been investigated also in West Africa. During a field studies performed in Senegal in two areas where numerous CCHFV isolations were obtained from *H. m. rufipes* adult ticks collected on ungulates, 175 wild ground-feeding birds main host of *H. m. rufipes*, immature ticks were captured and sera collected. CCHF antibodies were detected by ELISA in 6/22 red-beaked hornbills (*Tockus erythrorhynchus*), 2/11 glossy starlings (*Lamprotornis* sp.) and 1/3 guinea fowls. The virus was isolated also from *H. m. rufipes* nymphs collected on a hornbill (Zeller et al. 1994b). Afterwards an experimental model for investigating the role of birds in the CCHFV transmission cycle was developed. Following CCHFV isolate inoculation, antibodies were detected by ELISA in one red-beaked hornbill and one glossy starling, but not in two laughing doves (*Streptopelia senegalensis*) and six domestic chickens *(Gallus gallus)*. Virus transmission to larvae and nymphs was obtainedwith the red-beaked hornbill and glossy starling, even though these birds had undetectable viremias.
This experiment demonstrated the possibility that birds can infect ticks through the so called phenomenon of nonviremic transmission of infection and that cycle of transmission of virus between ticks and aviremic ground-feeding birds represent a potential reservoir and amplification mechanism of CCHFV in West Africa (Zeller et al. 1994b).
In the Stavropol and in the Oblast region rook (*Corvus frugileus*) has also been recognized as one of the main maintenance host of *H. m. marginatum* immature ticks (Grigor'ev et al. 2001) (Berezin et al. 1965).

Large wild mammals

The results of antibody surveys indicate that high rates of infection occur in livestock, the role of large vertebrates in the perpetuation of CCHF virus is theoretically limited by the fact that they are host of adult *Hyalomma* ticks in which transovarial transmission occurs with low frequency (Burt and Swanepoel 2005b). The prevalence of antibody to CCHF in the sera of wild vertebrates in South Africa and Zimbabwe is generally low but is highest in large herbivores with a mass similar to or greater than the kudu antelope which are the preferred hosts of adult *Hyalomma* ticks. Shepherd and collaborators (Shepherd et al. 1987 ) found the following prevalence rates of antibody to CCHFV: 100% (n = 3) of giraffe (*Giraffa cameleopardalis*) 54% (n = 13) of rhinoceros (*Ceratotherium simum* and *Diceros bicornis*); 43% (n = 137) of eland (*Taurotragus oryx*); 20% (n = 287) of buffaloes (*Syncerus caffer*); 22% (n = 87) of kudu (*Tragelaphus strepsiceros*) (Burt et al. 1993) (Shepherd et al. 1987 ). Previously also baboons and gazelles resulted positive to AGDP test in a survey performed in Kenya (Hoogstraal, 1979).

Small wild mammals

Medium-sized and small mammals are important hosts of many tick species; thus the success of these mammals, their ticks, and CCHFV survival are interrelated (Hoogstraal, 1979). The

occurrence of viremia has been demonstrated in various small mammals of Eurasia and Africa, such as susliks, hedgehogs, hares, and certain myomorph rodents (mice and rats); in some instances, it has been shown that these hosts are capable of infecting ticks (Burt and Swanepoel 2005b).

**Insectivorous**

The first CCHFV isolates from hedgehogs were in Nigeria from the four-toed hedgehog, *Erinaceus (Atelerix) albiventris*, taken in the savanna and on the Jos Plateau (Kemp et al. 1974).

In Eurasia, there may be a significant difference in the epidemiological role of the hedgehog species present in certain CCHF foci. The European hedgehog, *Erinaceus europaeus*, common in all Europe, serves as host of of several species of ixodid ticks (*Ixodes acuminatus, I. ricinus, Poleoixodes hexagonus, Haemaphysalis inermis, Haemaphysalis erinacei*, ecc) (Manilla 1998d).

The European hedgehog and the longeared hedgehog (*Hemiechinus auritus*) are common in the Caucasus both serve as hosts of immature *H. m. marginatum* and of immature and adult *R. rossicus* and *D. marginatus*.

Investigations on longeared hedgehog conducted in natural foci of CCHF in Caucasus demonstrated the role of this small mammal in maintaining the CCHFV. Several species of ticks (*H. m. marginatum*, *H. asiaticum*, *R. turanicus, R.rossicus* and *H. erinacei)* were collected from longeared hedgehog, in the same investigation blood collected from *E. europeus* resulted negative, while CCHFV was isolated from *R. rossicus* collected from it (Hoogstraal, 1979).

**Lagomorphs**

The European brown hare, *Lepus europaeus*, and the cape or Tolai hare, *L. capensis*, occur simultaneously in former-Soviet Union CCHF foci. Investigation conducted in Stavropol region has shown that European brown hare *(Lepus europaeus*) is one the main host of immature *H. m. marginatum* (Grigor'ev et al. 2001). Scrub hare (*Lepus saxatilis*), only present in Sub-saharian Africa, is recognized with rodents as the main host of *H. truncatum* immature (Horak et al. 2001).

In general, hares are important hosts of ticks in many CCHF foci and serve as amplifying hosts of the virus.

CCHFV was isolated from the blood and livers of 3 tick-infested *L. europaeus* taken in the Crimea (Hoogstraal 1979). In experimentally infected *L. europaeus* the virus was isolated from *H. m. marginatum* which they fed on viremic hares. During the experiment, the virus was detected in hare blood for 15 days, with the highest titer (3.6 log $LD_{50}$ 0.02 ml) on day 4 (Hoogstraal, 1979). Recently European brown hares were not positive in a serosurvey conducted in Albania (Papa et al. 2009). Experimental infection of scrub hares *L.saxatilis* demonstrated that a proportion scrub hares develop CCHF viremia of an intensity to be sufficient for infection of feeding immature ixodid ticks (Shepherd et al. 1989b) (Shepherd et al. 1991).

**Rodents**

Investigations into the role of rodents in CCHF foci where *Hyalomma m. marginatum* was the predominant tick revealed that immatures seldom if ever parasitize burrowing rodents

(Hoogstraal, 1979). Several rodents serve as host of immature CCHF tick vectors many data are coming from former Soviet Union and central Asia and were reviewed by Hoogstraal (Hoogstraal, 1979); the common field mouse (*Apodemus sylvaticus*) was infested by *R. rossicus* and *D. marginatus* in Rostov Oblast region, it was also positive for CCHF antibodies.
In the Murgab River Valley of Turkmenia, all long-clawed ground squirrels, *Spermophilopsis leptodactylus*, were infested by immature *H. asiaticum*, and antibodies to the virus were detected in the *S. leptodactylus* sera as well as in sera of this ground squirrel from the sandy Ashkhabad area.
The large-toothed suslik (or fulvous ground squirrel), *Citellus fulvus*, a common host of immature *H.asiaticum*, was numerous where the first human mortality from CCHF was recognized in the Kara-Tai foothills of Kzyl-Orda Oblast, Kazakhstan but was replaced by the great gerbil, *Rhombomys o. opimus,* in the Dzhalagash focus. This gerbil is also a favorite host of immature *H. asiaticum*. As recorded for Tadzhikistan and elsewhere, immatures of the important CCHFV vectors *H. anatolicum* and *H. m. marginatum* rarely feed on rodents as recently confirmed for the Stavropol region (Kotti et al. 2001) (Grigor'ev et al. 2001).
Saidi et al. (1975) detected antibodies to CCHFV in northern Iran in sera of the Williams' Jerboa, (*Allactaga euphrata williamsi)*, house mouse, (*Mus musculus bactrianus)* and Swinhoe's jird, (*Meriones crassus swinhoei)* (Saidi et al. 1975). Other data described several *Haemaphysalis*, *Hyalomma*, and *Rhipicephalus* and other ticks parasitizing Iranian rodents (Hoogstraal, 1979).
Synanthropic rodents were also investigated recently (2004) in southern Russia (L'vov et al. 2004)
African rodents were also investigated: antibodies to the virus were detected in the serum of a multimammate rat, *Praomys (Mastomys) natalensis*, from Senegal. The immature stages of several African tick species from which CCHFV has been isolated (from adult ticks infesting domestic animals) commonly feed on rodents (Hoogstraal, 1979).
Following an experimental infection with CCHFV of five African wild rodents, cape ground squirrels (*Xerus inauris*), red veld rats (*Aethomys chrysophilus*), white tailed rats (*Mystromys albicaudatus*), bushveld gerbils (*Tatera leucogaster*), and striped mice (*Rhabdomys pumilio*). Shepherd and collaborators hypothesized that wild rodents are unlikely to be of importance as maintenance hosts of the virus in southern Africa even if they are host of immature of some African CCHF tick vectors (Shepherd et al. 1989b).
In general the role of rodents in ecology of CCHF virus in still equivocal it differs significantly in foci of different ecological and zoogeographic zones depending on the intimacy, numbers, and species of ticks parasitizing immature rodents in their nests (Hoogstraal, 1979).

Domestic animals

Domestic ruminants can develop demonstrable viremia usually lasts 1 week and are capable of infecting ticks (Shepherd et al. 1989a) but it is not known how significant a role they play in the ecology of disease. The role of wild and domestic animals as reservoirs of CCHFV depends on the level of viremia during infection, as only viremia above a certain threshold level will be sufficient to infect feeding ticks. Generally slaughtering of viremic animals or squashig ticks feeding on viremic animal is frequent source of infection for human as

described in Africa and Asia to Saudi Arabia in 1990, the United Arab Emirates in 1994-1995, and Oman in 1995 (Williams et al. 2000) (Swanepoel et al. 1998).
Gonzalez (Gonzalez et al. 1998) experimentally demonstrated that in sheep viraemia appeared for a period of zero to nine days and also that pre-immunized sheep develop in experimental condition limited but effective viraemia. Antibody response persist at least for 3 years, so it was concluded that despite the relatively short period of viraemia and a short turnover in local herds (1 to 3 years), sheep in a endemic condition such in their lifetime can be infected and reinfected. During the same experiment the observation on vertical transmission were inconclusive: that virus was not detectable in offspring born from a mother that experienced viraemia.
Lambs raised and fed by infected mothers did not become infected. However, they acquire passive immunity by feeding on colostrum and milk that contain mostly IgA and IgGl antibody types. They excluded a hypothetical chronic carrier state; sheep would represent a periodically efficient amplifier regarding the seasonality of the enzootic manifestations (Gonzalez et al. 1998).
Horses are not virus reservoirs in nature but they are useful in the laboratory to obtain serum for diagnostic and possibly for therapeutic purposes while experimentally infected donkeys develop a low-level CCHFV viremia (Hoogstraal, 1979) they also develop antibodies response.
Antibodies against CCHF have been found also in pigs.
Large animals (ruminants, equids or camels) are generally important as a main host of several *Hyalomma* ticks such as *H. anatolicum, H. m. marginatum* involved in the natural CCHF outbreaks.
Surveys of domestic animal sera can be useful to reveal the presence of otherwise unrecognized CCHFV circulation, as well as the prevalence of infection and thus the risk of human exposure to infected tick bites. For example, the results of such surveys did alert Armenian public health authorities to this risk, and almost immediately afterward, laboratory-confirmed human cases were diagnosed in this Republic (Hoogstraal, 1979).
The table N° 4 shows some data on serological surveys on CCHF in domestic animals.
In general, results of seroepidemiological surveys in areas where CCHF is endemic (enzootic) reveal a high level of sero- prevalence in domestic animals particularly among cattle and sheep showing that testing of domestic animals can be useful to reveal the virus circulation.

#### *EXPERIMENTAL STUDIES*

The experimental studies on CCHF are not numerous; it's probably due to the necessity to have high security (BSL4) facilities to manipulate the virus. The most part of them are performed by South African researcher and French researcher who worked in West Africa. The table N°5 lists some references and information on experimental studies on CCHF, some references on vector competence experimental studies are also listed in table N°3.

#### *FIELD STUDIES (INCLUDING EPIDEMIOLOGICAL EVIDENCE)*

There are several field studies present in literature; they are performed around all the geographic area where CCHF is present mainly in conseguence of natural outbreaks.
In general, results of seroepidemiological surveys of humans, expecially in remote areas, showed the incidence of unreported or misdiagnosed CCHF infections in various populations.

Results of seroepidemiological surveys and of attempts to isolate the virus from wild and domestic vertebrates suggested the role of different vertebrates as active virus reservoirs, as non-reservoirs but significant contributors to the tick vector population density, or as epidemiologically important members of the biocenose. Virus isolation rates from various tick species showed the role of individual species as a virus vector and/or reservoir and revealed the degree of risk to human health presented by these. Demonstration of transstadial survival and transovarial transmission of the virus in ticks provided evidence of the biological properties permitting CCHFV survival from season to season in dramatically different ecological and zoogeographical zones and in 1-host, 2-host, and 3-host ticks (Hoogstraal 1979).The table N°6 lists some references and features on field studies on CCHF.

## RISK FACTORS FOR CCHF IN HUMANS AND FOR SPREAD OF INFECTION ASSOCIATED WITH TICKS

People (in endemic foci) susceptible to tick bite and persons who are exposed to CCHF patients are at the highest risk of infection. People working outdoors, particularly those who work with domestic animals are at increased risk of tick bites or of crushing infected ticks. Those people butchering animals, caring for CCHF patients and laboratory workers handling virus material are at risk of contacting CCHFV.

In an enzootic area in rural northern Senegal, Chapman et al. (Chapman et al. 1991) found that risk factors included herding, sleeping outside during seasonal animal migrations, bite by *H. truncatum*, tick bite during the cool dry season, and contact with sick animals are mainly associated with males.

Excluding nosocomial infections, in which age and sex do not appear to be factors in CCHFV susceptibility, there is an unequal distribution between males and females based upon their differential exposure to CCHFV. More males than females, 10-49 years old, became infected in South Africa (Swanepoel et al. 1983). The risk of nosocomial infection in health-care workers is great, especially during the hemorrhagic period of disease. In Pakistan in 1976, 83% (n = 6) of exposed health-care and 46% (n = 26) of all potentially exposed persons, including family members, contracted CCHF (Burney et al. 1980). Furthermore risk associated with contact with infected animals has been well documented throughout the geographic range of CCHF. Possible aerosol transmission is also suspected but not confirmed.

Although CCHFV has been isolated from numerous species of ticks, *Hyalomma* spp. are considered the primary vectors in all CCHF enzootic areas except an environmentally altered focus in Moldavia. Risk areas are those where one or more species of *Hyalomma* occurs. In Rostov Oblast, Russia, the risk of human infection is directly proportional to the rate of attachment of *H. marginatum* on humans (Goldfarb et al. 1980). The distribution of CCHFV in Eurasia and Africa overlaps with the distribution of *Hyalomma* ticks (Hoogstraal 1956). Within the limits of the zoogeography of *Hyalomma* ticks, specimens are found clustered within specific ecologica zones. It is within these ecological zones that risk of CCHF infection is high (see paragraph on environmental conditions page 45).

The risk of diffusion of CCHV in free areas is linked to the possibility of *Hyalomma* infected ticks to reach and to establish in new areas. The probability is higher for tick associated with migrating birds (Manilla 1998c). Because all stages of ticks associated with CCHFV are parasitic, and because all ixodid and some argasid ticks feed for extended periods of time, they can be dispersed over long distances while attached to their hosts (Manilla 1998c). Hoogstraal (Hoogstraal 1979) reported that many bird species are responsible for the intra- and intercontinental dissemination of ticks associated with CCHF. The dispersal of ticks by birds may be restricted to a short distance during local post-breeding flights or extremely long distance during migration flights. In studies conducted on birds migrating through Egypt between 1955 and 1973, it was discovered that the birds migrating from Eurasia to Africa carried tick species that were characteristic of the fauna of Europe and Asia. More than 90% of the immature ticks found on birds migrating to the south between 1959 and 1981 were species associated with CCHFV. *H. m. rufipes* was the most common tick found on birds migrating north from sub-Saharan Africa to Eurasia in the spring (Linthicum and Bailey 1994). Furthermore in 2002 birds migrating from the Balkans were suggested to be the cause

of the outbreak in Turkey (Karti et al. 2004). The sporadic reports of *Amblyomma variegatum* in the Mediterranean was reported in 1977 in Italy and 10 years later in Greece also should be read under this light (Pascucci et al. 2007).
The Mediterranean Basin falls under the main trans-Saharan migratory routes, directly connecting free areas (Europe) and endemic zones (sub-Saharan Africa, Ethiopia). 500 native bird species are currently registered in Italy; of these, about two thirds are migratory birds; only a part of them flies across the Sahara very quickly (in about a week). Millions of birds leave every year their wintering African sites to fly to the nesting sites in North Europe; once they arrive on the Northern African coast, the birds divide themselves in three groups travelling along three different flight routes crossing the Mediterranean: one of these routes passes above Gibraltar, another one above Italy and the third one above south-east Europe. These bird species are called 'quick migrators', because during spring (April-May) they can fly no stop for over 4 000 km; the journey to the reproduction sites takes more or less a week. The nesting sites of some of these birds are in Italy, which falls under the Western migratory route at the limit of the 4 000 km; also many other birds however make a temporary stop (some days according to weather conditions) in the Italian peninsula, in order to rest and feed (refuelling).
Similarly, Italy hosts also the nesting sites of the 'slow migrators', so-called because they do not usually cross the Sahara desert, fly slowly and stop frequently according to climate conditions.
Figure 14 shows the main migratory flyways that link Africa to Europe and Central Asia, table 7 lists species of quick migratory birds that fly above Italy.

In rural areas where the extensive breeding of domestic animals is prevalent the movements of domestic animals to new feeding areas, markets, and abattoirs, and the migrations of wild mammals also contribute to the dissemination of CCHFV from enzootic areas. It was demonstrated by Morrill et al. (Morrill et al. 1990) that camels imported from Sudan and Kenya into Egypt were previously infected with CCHFV. In Mauritania, Saluzzo et al. (Saluzzo et al. 1985) described the need for studies directed towards the role of camels in the spread of CCHFV to northern Mauritania during migrations.
In Senegal, Wilson et al. (Wilson et al. 1991) reported that, although the spatial distribution pattern of IgG antibody to CCHFV could be affected by host migrations resulting from nomadic migrations, the distribution of the tick vectors may be an overriding factor. In Tadzhikistan, apparently infected ticks were introduced into the cooler central region, and into the Pamir Mountains with cattle and sheep herded from the south to summer pastures (Linthicum and Bailey 1994). In Africa, Causey (Causey et al. 1970) found in Nigeria that many CCHFV-infected ticks were found on domestic animals that had been driven to an abattoir.
The post-1967 findings in Asia, Europe, and Africa and the progress recently made in understanding the factors that led to the CCHF occurrence and re-occurrence have greatly expanded the knowledge of CCHF natural history. Within historic times, CCHF epidemics have been associated with environmental changes caused by war or by new agricultural practices such as collectivization, flood control, irrigation, virgin land exploitation, or increasing size and numbers of dairy herds. Recent studies are showing the presence of the virus and of sporadic human cases in an ever-increasing number of more or less "silent foci" in numerous biotopes of Eurasia and Africa. It's known that a surprising number and variety

of tick species maintain CCHF virus in nature. However, we have only a few rudimentary facts to answer the multifaceted question of how, when, and where new CCHF epidemics may appear. Use of new technologies in diagnostics and epidemiology will help to better assess and analyze the risk of occurrence or re-occurrence of CCHF epidemics (See chapter on climate changing implication and modelling pag 30).

Anyway, since understanding climate linkages to ecosystems and infectious diseases such as CCHF is not solid yet, development and application of surveillance systems - networks and early warning systems are the only feasible way to protect human and animal health and more in general ecosystem health.

## TICK SURVEILLANCE

Following outbreaks, several ad hoc survey and fields investigations have been performed (some listed in table N° 6), on the contrary structured surveillance system on tick are not present.

Vatansever and collaborators described (Vatansever et al. 2008) passive surveillance for tick bites in humans undertaken in the city of Istanbul (Turkey) in the summer and autumn of 2006. In the monitoring from 1,054 reported tick bites, most were females of *I. ricinus* (27%) and nymphs of *H. aegyptium* (50%). A few adults of *Hyalomma m. marginatum, R. sanguineus* and *D. marginatus* were also recorded. Climate features at 1-km resolution (monthly minimum temperatures in late summer and autumn and rainfall) and vegetation features at high resolution (density and heterogeneity of forest-type vegetation as well as distance of reporting site to these vegetation features) have been used to explain high reporting clusters for both *Ixodes* and *Hyalomma*. In fact while *Ixodes* is highly reported in dense highly heterogeneous vegetation patches, *Hyalomma* is commonly found in areas far from forest-type features and in the small, relatively dry vegetation patches within the urban fabric (Vatansever et al. 2008).

Again, an investigation on Ixodid ticks has been performed to investigate the distrbution of ticks in Turkey in 2007. *Ixodes* spp. were mostly seen in high rainfall and the intensive forest area of northern Turkey. Ticks of the genera *Haemaphysalis, Hyalomma, Boophilus, Dermacentor, and Rhipicephalus* are widespread throughout Anatolia. During the survey some species have been found to be sporadic: *A. varigeatum* in Hatay province (border to Syria), *B. kohlsi* in Southeastern Turkey (border of Syria), *Ornithodoros* in Central and East Anatolia, and *Otobius megnini* found in East Anatolia (Malatya Province) (Aydin and Bakirci 2007).

Following the first outbreak, investigation of vector and virus circulation (performing serology in cattle) in Anatolia in 2007 a survey on tick collected from cattle has been performed recording 80% of *H. m. marginatum* (Ertuk 2007).

Pascucci and collaborators (Pascucci and Cammà 2007) in a survey on tick bites on humans performed in a local hospital in central Italy recorded 166 tick bites registering high prevalence of *Ixodes ricinus* (85%), but also with 4% of tick bites referred to *H.m.marginatum*.

At intenational level it's very relevant the International Consortitum on Tick and Tick borne Disease (ICTTD-3) that is a Coordinated Action (CA) financially supported by INCO, the International Cooperation program of the European Union. The aim of the CA is to support a research program on tick-borne diseases jointly executed by a consortium of 43 institutions in 29 different countries. The CA will focus on tick-host-pathogen interactions to identify concrete means of control that reduce the prevalence of tick-borne diseases in (sub)tropical countries. The current ICTTD-3 program is a continuation of ICTTD-1 (1996-2000) and ICTTD-2 (2000-2004) and has developed into a large consortium of researchers working on ticks and tick-borne diseases, with over 1000 registered scientists worldwide. It has provided several publications and also a tick data-base and a tick virtual museum.

## TICK PREVENTION AND CONTROL

### *ACARICIDES*

Chemical acaricides, if correctly applied, are efficient and cost effective; they are however, often incorrectly used, chemical resistance is a serious global problem and the presence of chemical residues in food is increasingly an issue for consumers.

The control of CCHF through the application of acaricides to livestock is impractical, particularly under the extensive farming conditions which prevail in the arid areas where *Hyalomma* ticks are most prevalent.

Pyrethroid preparations are available that can be used to kill ticks which come into contact with human clothing. Following the outbreak of CCHF in an ostrich abattoir in South Africa in 1996, it was decided that ostriches should be treated for ticks with pyrethroids and kept in a tick-free environment for 2 weeks prior to slaughter to reduce the risk of exposing abattoir workers to CCHFV (Swanepoel et al. 1998).

Acaricides are usually applied to cattle in dipping tanks or baths (Stachurski and Lancelot 2006). For some types of problem, such as *Hyalomma* ticks on feet of sheep, a foot dipping bath is used.

Spray races are often used because they have the advantage of using smaller amounts of spraying fluid and this is easier to keep fresh. The cattle run through a heavy low pressure spray to become soaked, but areas like the ears and groin may not be treated fully (Latif and Walker 2004).

Small numbers of livestock can be treated with hand held sprayers. The usual type is a pressurised container as a back-pack with a spray lance. These deliver a heavy wetting spray to soak the whole animal. They are cheap to buy, but wasteful of acaricide. Selective treatment of preferred attachment sites may be delivered with small domestic sprayers. However, there is a danger of encouraging resistance to acaricides with partial treatments like this (Latif and Walker 2004).

Pour-on formulations of acaricides consist of high quality oil which spreads through the greasy hair coat of livestock. Pour-on formulations are expensive to buy but there is no wastage and they can be cheaper per animal in the long term. Oily formulations can be applied as selective spot-on treatments. Similarly, if an acaricide is formulated in grease, then ears and other sites can be treated. The pour-on formulations also can be used in applicators to treat wild antelope on game reserves. The animals are attracted to a feed bait and contact a porous surface soaked with the pour-on oil (Latif and Walker 2004).

When ticks are exposed to acaricides for a long time it is likely that some mutant strains of ticks will arise, by natural selection, that are able to survive the normal dose of acaricide. These are acaricide resistant strains and they may come to be the predominant type of tick in an area, reducing greatly the effectiveness of the acaricide. This can be overcome by using a different type of acaracide but with the risk of producing strains of ticks resistant to many of the available acaricides.

To avoid the onset of this problem or to slow down it there are several rules to follow:

- when acaricides are used they should be fresh and full strength as specified by the manufacturer;
- all the ticks on livestock being treated should be killed;

- the older types of acaricide should continue to be used until official veterinary advice is to change to another type; and
- newer types of acaricide should be kept in reserve for when all the older types become ineffective (Latif and Walker 2004).

The most common types of acaricides are:

- **The organophosphates:** includes coumaphos and chlorfenvinphos; these acaricides have been in use for many years and tend to have problems of toxicity and acaricide resistance. They are soluble in oils and need to be diluted for use as an emulsion in water.
- **The carbamates:** includes propoxur which has sometimes been used as an acaricide.
- **The formamidine group:** is represented by amitraz. This is an unusual acaricide because it is soluble in water and degrades rapidly, so it is made up fresh for each use. It is convenient for application in small hand sprayers.
- **The synthetic pyrethroids**: includes deltamethrin, fenvalerate and flumethrin. These are useful when older types of acaricide have resistance developed against them. However, there may be restrictions on their sale in some countries in order to reduce the rate at which new acaricides become poorly effective due to resistance. These synthetic pyrethroids can be formulated dilution in water or in oils as pour-on;
- **The phenylpyrazole group:** includes fipronil which is formulated for control of ticks on dogs;
- **Botanical materials:** include extract of neem tree, azadiractin.

***VACCINES***

It is available on the market from ten years a recombinat vaccine for *Boophilus microplus* based on a recombinant antigen, Bm86. It has god results in the field control of *B. microplus* in Australia, Recombinant Bm86, optimally, reduces tick reproductive capacity by 90% though its direct effect on tick mortality is less (Willadsen 2006). The knowledge of tick biochemistry remains fragmentary. Many more potential antigens have been proposed than have been tested. Tick antigen targets studied to date are from a restricted range of functional classes. They include structural proteins, particularly from salivary glands, hydrolytic enzymes and their inhibitors, particularly those involved in haemostatic processes and a range of membrane-associated proteins of unknown function (Willadsen 2006). Because vaccines are expensive and involve considerable risk, a high level of efficacy is required to offset these negatives. Hence, there has been little industry enthusiasm for further commercialization of anti-tick vaccines. However, exciting new developments, such as the ability to disrupt the male engorgement factor or the administration of combined anti-tick and antipathogen agent vaccines, might change this picture (Sonenshine et al. 2006). Our lack of understanding of what makes a particular tick species susceptible to vaccination is shown by limited experience with the existing vaccine.

Although it uses an antigen from *B. microplus*, it is even more efficacious against *B. annulatus* than against the homologous species (Fragoso et al. 1998). Significant protection against *B. decoloratus* (de la Fuente et al. 1999) and strong protection against *H. dromedarii* (de Vos 2001) have been reported while it is ineffective against *R. appendiculatus*. Such effects appear not to correlate with the degree of sequence conservation of the antigen across tick species (Willadsen 2006).

### *PHEROMONE-ASSISTED CONTROL*

Novel strategies for pheromone-assisted tick control have been recently developed.
In these strategies pheromone–acaricide-impregnated devices are used to lure and kill host-seeking ticks. Such strategies have proven effective in protecting livestock in southern Africa threatened by the "bont ticks" *A. hebraeum* and *A. variegatum*, and by the risk of heartwater *(Ehrlichia ruminantium)* infections, which often have a relatively high mortality rate. In one study, cattle treated with pheromone–acaricide-impregnated tail tags showed up to 94.9% control of bont ticks in one three-month trial and up to 99.3% tick control during a second three-month trial period (Norval et al. 1996). Also of interest is a recent research leading to the development of a novel tick-control device for use against *I. scapularis*. In this case, paste-like droplets (Last CallTM) impregnated with both acaricide and the components of the tick-assembly pheromone (guanine, xanthine and hematin) were used to create a device that could be applied to vegetation to attract and kill *I. scapularis* before they could infest humans or animals (Sonenshine et al. 2006).

### *GENETIC RESISTANCE*

Generally breed tick resistance might vary with the species of infesting tick; heterospecific resistance appears to be low or even absent among different genera of ticks, while a certain degree of cross-resistance is expressed to tick species belonging to the same genus (de Castro and Newson 1993). Genetic resistance has been described in West Africa for N'Dama indigenous cattle that have shown a higher degree of natural resistance against ticks with long hypostome such as some *Amblyomma* and *Hyalomma*. Generally evidence for a genetic trait for resistance to multihost ticks, such as *R. appendiculatus*, in *B. indicus* breeds is not as strong as for one-host ticks as *Boophlilus* that is hypotesized to be proportionally related to the amount of zebu (*B. indicus*) genes in the breed (Mattioli et al. 2000 ).

### *BIOLOGICAL CONTROL*

The idea of using biological agents to control ticks is appealing, though the practical difficulties of doing so have yet to be resolved. Biological control agents are in principle highly desirable but their efficacy, manufacture, application and stability present serious challenges.
Of particular focus have been fungi of the genera *Beauveria* and *Metarhizium*. For example in Kenya aqueous formulations of the spores of the fungi *Beauveria bassiana* and *Metarhizinnm rurisopliae* induced a high mortality and reduced fecundity and egg hatchability in *R. appendiculatus* feeding on cattle. These formulations also caused mortalities in all life stages of *A. variegatum* and *R. appendiculatus* in the vegetation. The comparative ease with which the spores of these fungi can be produced and artificially disseminated makes them promising potential agents for the control of ticks (Norval and Horak 2004).
Domestic chickens are opportunistic predators of ticks. They also could be used in rural condition. The indigenous varieties in particular, if allowed to scavenge amongst cattle, can consume considerable numbers of ticks, especially if the cattle are penned to dwellings in the late afternoon and during the early morning (Latif and Walker 2004).
Moreover the coexistence on the same pasture of wild birds as red and yellow-billed oxpeckers (*Buphagus erythrorhynchus* and *Buphagus africanus*) also should be considered as

control method. These birds, in fact, are virtually obligatory predators of ixodid ticks and they take large numbers of these parasites from both domestic cattle and from several wildlife species. The red-billed birds (*Buphagus erythrorhynchus*) favour *B. decoloratus* and *R. appendiculatus* as food items, whereas yellow-billed oxpeckers (*Buphagus africanus*) prefer the latter tick and *Amblyomma* spp (Bezuidenhout and Stutterheim 1980). This preference is probably due by the bigger beak of yellow-billed oxpeckers. As an aid to tick control on both wildlife and domestic cattle, red-billed oxpeckers have been reintroduced to several regions in which they originally occurred in South Africa, but from which they had in recent times disappeared (Van Someren 1951).

Other arthropods can also to be used in the biological control of ticks: chlacid wasps of the genus *Ixodiphagus* are obligatory parasitoids of ixodid ticks and most species will oviposit and develop only in the nymphal stage of the ticks. Several wasp larvae can successfully develop in a single engorged nymph, which is killed during this process. Two of the seven described species of these wasps occur in Africa, namely *Ixodiphagus hookeri* and *Ixodiphagus theilerae* (Hu et al. 1998; Mwangi et al. 1997; Norval and Horak 2004).

Ticks do not survive for long on pasture that is either heavily grazed and thus short and dry, or in areas where pasture land is rotated with crops. When intensively farmed land is fenced it is possible for cattle pastures to be cleared of ticks, by a combination of management and acaricide use, and then maintained tick free. This may be appropriate for control of *Boophilus* species and *R. appendiculatus.* Burning of pasture grasses kills many ticks but should only be used when the main reason is to improve grazing availability. An extreme case of pasture management is zero-grazing of dairy cattle, but there is a risk of unexpected reintroduction of ticks on cut fodder or newly introduced animals. However, in the case of *Hyalomma* infestations of dairy cattle, the ticks are adapted to living within the cattle housing, so these methods do not apply. Even if there is some use of spray treatments of the walls of dairy houses to for the control of some *Hyalomma* ticks adapted to live indoor, it is more effective in the long term to render the walls smooth with mortar (Latif and Walker 2004).

There is no single, ideal solution to the control of ticks. Integrated control scenarios representing increased scientific and practical complexity can be developed and recommended, the integrated control approach is probably the most effective way to control tick (Willadsen 2006; Jongejan and Uilenberg 1994; Young et al. 1988).

## DIAGNOSIS AND PATHOGENESIS

### *CLINICAL DIAGNOSIS*

An early diagnosis is essential both for the individual patient's prognosis and to enable the prompt implementation of protective measures.
With the exception of laboratory animals (newborn mice, rats and guinea pigs), humans seem to be the only host to manifest the disease. The typical course of CCHF in humans has four distinct phases:

- the incubation, lasting from 3-13 days;
- the pre-haemorrhagic phase, that can last from 1 day to a maximum of 7 days; it is characterized by a sudden and brutal onset with high fever;
- the haemorrhagic phase, that on average lasts 2-3 days and starts with petechiae on the mouth and skin. In this phase bleeding from the nose, gastrointestinal system, uterus, urinary and respiratory system is common this is the most dangerous phase for the risk of contagion between humans; and
- the convalescence; for those that survive begins 15-20 days after the onset of the disease.

Crimean-Congo haemorrhagic fever should be suspected in the event of appropriate clinical signs and the patient's history of:

- travel in endemic areas;
- tick bite;
- exposure to and contact with farm animals' blood and tissues in endemic areas; and
- exposure to and contact with hospitalized patients' blood and tissues with haemorrhagic syndrome.

The CCHFV is a BSL-4-classified pathogen (Biosafety Level 4, the highest level), therefore all hazardous procedures concerning patient management and the handling and disposal of infected material must be carried out as required for pathogens with this classification (maximum protection).
Only humans and newborn mice can become seriously ill and die from the disease.
Other animals, including primates, can be infected but show no clinical signs, presenting only a transient viraemia. The viraemic animal (ruminats are viraemic for a maximum of 1 week) do not shows any clinical sign being a risk for humans who come into contact with infected blood.
Humans are at highly risk of contagion while performing some professional duties such as:

- dehorning;
- castration;
- applying ear tags;
- slaughtering; and
- taking blood samples.

In humans the most important lesion is observed in the liver, histological examination of liver tissue may reveal: necrotic foci distributed only in some areas of the parenchyma, massive necrotic phenomena involving more that 75% of the hepatocytes and a variable degree of

haemorrhages. There is little or no cellular infiltrate in the necrotic areas, and it is not correlated to the degree of hepatocellular damage.
No histopathological finding is pathognomonic for CCHF while there are anatomopathological similarities to:

- other viral infections;
- bacterial infections;
- rickettsiosis;
- exposure to toxins.

***PATHOGENESIS***

CCHF pathogenesis is not yet completely known.
As with other viral diseases transmitted by arthropods, the CCHF virus undergoes a first replication in the inoculation site and then diffuses through the blood and lymphatic systems to the organs, particularly the liver (the preferred replication site).

The cellular elements most strongly affected during the infectious process are the mononuclear phagocytes and the endothelial cells.
The infection of mononuclear phagocytes and depletion of lymphoid cells boost the likelihood of the virus' spread within the body and protect it against the immune system's defence mechanisms. The occurrence of disseminated intravascular coagulation (DIC) appears to be an early and central event in the pathogenesis of the disease. The hepatocytes are a major target of the virus, and the occurrence of minimal inflammatory infiltration suggests that hepatocellular necrosis may be mediated by a direct viral cytopathic effect. Hepatocellular necrosis leads to further release of tumor necrosis factor and other procoagulants into the circulation, and ultimately to impairment of the synthesis of coagulation factors to replace those which are consumed in DIC. Widespread infection of endothelium with degenerative change rather than necrosis is associated with capillary dysfunction, which contributes to the occurrence of a hemorrhagic diathesis and the generation of a petechial rash (Burt and Swanepoel, 2005b).

***LABORATORY DIAGNOSIS***

The methods currently used in the diagnosis of CCHF are:

- virus isolation through intracranial or intraperitoneal inoculation of newborn mice;
- virus isolation on cell lines;
- electron microscopy;
- immunological tests to detect antigens;
- immunological tests to detect antibodies;
- molecular biology techniques.

## Direct diagnosis

### Virus isolation

The viraemia usually lasts for 7-8 days and sometimes up to 12 days from the onset of the disease. Infected blood kept at 4°C remains infectious for 10 days; after this threshold the test result is negative.
Isolation may be achieved in 2-5 days but due to the cells' poor sensitivity, the virus is found only if the sample is taken during high viraemia, which occurs during the first 5 days of the disease.
Depending on the type of cell line, the cytopathic effect (CPE) may be low or even absent. In anyway, CPE and plaques are generally seen only after several serial passages.
The virus can be isolated from blood, plasma and organs harvested during autopsy or intra vitam examination (liver, lungs, spleen, bone marrow, brain, kidney). In the event of death, tissues should be collected within 11 hours.
The traditional method of isolating the CCHFV includes intracranial (i.c.) or intraperitoneal (i.p.) inoculation of blood from acute phase patients or ticks homogenized into newborn mice.
CCHF virus replicates in a wide variety of primary-cell and line cell cultures, including Vero, chicken embryo-related cells (CER), and $BHK_{21}$ cells, but not usually to high titer. Since the virus is poorly cytopathic its presence in cell cultures is revealed by immunofluorescence in infected cells. The virus has been isolated and titers have been determined most frequently by intracerebral inoculation of suckling mice. Isolation of the virus in cell cultures can be achieved in 1 to 5 days compared to 5 to 8 days in mice, but mouse inoculation is more sensitive for isolating virus that is present at low concentrations (Burt and Swanepoel 2005b).

### Molecular tecniques

Use of molecular biology in diagnosis, particularly the Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) and Real-Time PCR, has provided a useful alternative to serological tests for the rapid diagnosis of CCHF.
The strengths of molecular methods are:

- high specificity;
- high sensitivity;
- diagnosis possible without culture the virus, which require the use of BSL-4 laboratories;
- the analysis of serum samples over time;
- fast answer (8 hours from receipt of the sample are sufficient for RT-PCR);
- the possibility of carrying out molecular epidemiological studies through investigation of viral RNA sequences; and
- detection of the virus during the first phase of infection or in subjects who died before the humoral response.

For diagnostic purpose the assay are tipically based on consensus nucleotide sequences primarily on the S segment.
The comparative analysis of the segment allows to detemine the origin and possible source of infection (Hoogstraal 1979; Morikawa et al. 2007; Zeller 2007).
Real-Time PCR offers further benefits over RT-PCR for the diagnosis of Crimean-Congo haemorrhagic fever, such as:

- fewer contaminations, as Real-Time PCR requires fewer passages and operator interventions than RT-PCR;
- reduced execution times, as this technique gives results in a few minutes whereas hours are required in the case of RT-PCR;
- higher sensitivity;
- higher specificity.

Antigen detection

The detction of CCHFV antigen is a useful rapide tecnique for the diagnosis of acute infection. The viral antigen can be detected by immunocapture enzyme-linked immunosorbent assay (ELISA) or reverse passive hemagglutination assay, but ELISA test is more sensitive (Zeller 2007). It has been demonstrated that antigenemia is more frequent in fatal cases than in non fatal cases.
Immunochemistry and in situ hybridization are also used to detect of CCHFV in paraffin embedded tissues (Zeller 2007).

**Indirect diagnosis**

Nairoviruses in general, including CCHF, induce a weak neutralizing antibody response, and serum samples frequently contain nonspecific inhibitors of virus infectivity. Hence, neutralization tests have found limited application for demonstrating antibody response.
Serologic tests used to study and diagnose CCHFV infection before 1980, such as complement fixation, immunodiffusion, and hemagglutination inhibition, suffered from a lack of sensitivity and reproducibility (Hoogstraal 1979). These problems were largely overcome with the introduction of the indirect IFA (Whitehouse 2004) and the development of enzyme-linked immunoassays (ELISA) for detecting IgG and IgM antibodies (Donets et al. 1982).
Both IgG and IgM antibodies are detectable by IFA by about 7 days after onset of illness and are present in the sera of survivors by day 9 (Shepherd et al. 1989a). The IgM antibody declines to undetectable levels by the fourth month after infection, and IgG titers may also begin to decline gradually at this time, but remain demonstrable for at least 5 years. Recent or current infection is confirmed by demonstrating seroconversion, or a fourfold or greater increase in antibody titer in paired serum samples, or IgM antibody in a single sample (Swanepoel 1995). An antibody response is rarely detectable in fatal cases and diagnosis is usually confirmed by isolation of the virus from the serum or liver biopsy specimens.
In ovines and bovines, IgM antibodies remain detectable only between the third and seventh week after infection, showing the low susceptibility of this species to the virus.
The ELISA test is less specific but more sensitive than immunofluorescence and serum neutralization tests.
An obvious limit of both tests is the need to use BSL-4 laboratories for antigen and reagent production; however, this has been recently overcome by the use of immunological assays incorporating recombinant CCHFV nucleoprotein used in an IFA or in an ELISA test (Tang et al. 2003) (Whitehouse 2004).
No laboratory diagnostic standards for animals are described in the Manual of Diagnostic Tests and Vaccines for Terrestrial Animals, while these are described, are described as well as Rift Valley Fever virus, for some Buniavirus causing disease in animals, such as Cache Valley virus (CVV), Akabane virus, Nairobi sheep disease (NSD) virus.

***DIFFERENTIAL DIAGNOSIS***

The vast majority of suspected cases of CCHF prove to be severe infections with more common agents, including bacterial septicemias, malaria, viral hepatitis, rickettsioses, and complications of human immunodeficiency virus-AIDS. In arriving at a diagnosis, it is important to take into account an accurate history of possible exposure to infection, signs and symptoms of illness, and clinical pathology findings (Burt and Swanepoel, 2005 b).
Differential diagnosis must consider the following diseases:

- Rickettsiosis
- Ehrlichiosis
- Leptospirosis
- Borreliosis (Lyme Disease)
- Q Fever
- Tick Borne Encephalithis (TBE)
- The infections that cause haemorrhagic diseases include:
    - Meningococcal infections;
    - Hantavirus haemorrhagic fever;
    - Malaria;
    - Yellow fever;
    - Dengue;
    - Omsk Haemorrhagic fever;
    - Monkey disease (Kyasanur Forest Disease); and
    - Rift Valley fever.

Other diseases to be considered include the so-called haemorrhagic fevers, such as Lassa fever, Ebola and Marbug disease, although this group of diseases should be considered as mainly confined to some areas of tropical Africa. Marburg and Ebola viruses cause sporadic outbreaks of highly lethal disease in tropical Africa, often in association with similar disease in non-human primates, but the source of these viruses in nature remains unknown.
Lassa fever virus causes chronic renal infection of *Mastomys spp.* rodents in West Africa, and transmission to humans occurs through contamination of food and house dust with rodent urine (Burt and Swanepoel, 2005b).

## CONTROL AND PREVENTION

In endemic areas, people most at risk of contracting CCHF are those who work and/or perform recreational activities in tick-infested locations or come into contact with infected animals or human blood or organs:

- farmers;
- hunters;
- travellers;
- campers;
- researchers;
- hospital medical personnel;
- butchers; and
- veterinarians.

The people most affected by CCHF are normally farmers; in fact almost 90% of the cases reported during the recent epidemic in Turkey were diagnosed in people in these categories (Bakir et al. 2005).

The most important risk factors are contact with blood and organs of viraemic cattle (open wounds, presence of tick vectors on hide) and infection through broken skin, accidental pricks with needle contaminated and bites from ticks. Veterinarians and butchers can contract the disease while slaughtering animals, particularly during the skinning process (involuntary squashing of ticks present on the hide of the animal) and bleeding.

Outbreaks in South Africa arose in slaughterhouse operators during the slaughter of ostriches, which were heavily infested with ticks but had no antibody reactions to CCHFV. The infection occurred when the infected ticks present on the carcasses were squashed during skinning (Swanepoel et al. 1998). Nevertheless meat from butchered animals do not pose a risk as in this substrate the CCHFV is quickly inactivated by a drop in pH, as occurs during the hanging process that the meat undergoes after slaughter.

Travelers, campers and rural dwellers can contract the virus after being bitten by infected ticks present in the area.

Hospital personnel caring for patients with bleeding from the nose, mouth and vagina are at particular risk. Thirty-three percent of medical workers who had contact with patients through accidental needle pricks developed CCHF and 8.7% contracted disease by other contacts with the patients' blood (van de Wal et al. 1985).

In view of the serological evidence that infection of livestock occurs on a wide scale in areas infested by *Hyalomma* ticks, it is surprising that so few human infections are diagnosed. This raises the possibility that many human infections are asymptomatic or mild and pass unnoticed, but the low prevalence of antibody generally detected in surveys and the sparse evidence of infection encountered among cohorts of cases of the disease suggest that a high proportion of CCHF infections does, in fact, come to medical attention. Possible explanations for the low incidence of infection which occurs in humans include the fact that viremia in livestock is short lived and of low intensity compared to that in other zoonotic diseases such as Rift Valley fever, which is more readily acquired from contact with infected tissues. Furthermore, despite the fact that a high proportion of patients acquire infection from ticks, humans are not the preferred hosts of *Hyalomma* ticks and are infrequently bitten in comparison to livestock (Burt and Swanepoel, 2005b).

The best method of preventing disease is to avoid or minimize exposure to the virus. This can be accomplished in a number of ways. Persons in high-risk occupations (i.e., slaughterhouse workers, veterinarians, sheep herders, etc.) should take every precaution to avoid exposure to virus infected ticks or virus-contaminated animal blood or other tissues. For example, wearing gloves and limiting exposure of naked skin to fresh blood and other tissues of animals are effective practical control measures. Likewise, medical personnel who care for suspected CCHF patients should practice standard barrier-nursing techniques.

In endemic areas, tick control by acaricides may not always be practical in many regions of the world where *Hyalomma* ticks are most prevalent, especially given the extensive farm ranges that predominate in the semi-arid areas preferred by ticks of the *Hyalomma* genus.

Furthermore, the *Hyalomma* species which act as vectors are two-host ticks or three-host ticks that spend at least one phase of their cycle far from the host, with the immature forms often feeding on different animals than the adults, such as hares, rodents and wild birds, which are difficult to reach with antiparasitic treatments (Whitehouse 2004).

However, treatment of livestock reduces the number of potentially infected ticks on farmed animals and thus diminishes the risk of both their contagion and indirect human contagion, and thus indirectly prevents transmission to humans.

Applying commercially available insect repellents (i.e., diethyl toluamide [DEET]) to exposed skin and the use of clothing impregnated with permethrin can give some protection against tick bites. As with other tick-borne diseases, inspection of one's body and clothes for ticks, and their prompt removal can minimize the risk of infection (Whitehouse 2004).

A suckling mouse brain, formalin-inactivated vaccine has been used in Bulgaria and other parts of Eastern Europe and the former Soviet Union. In the Rostov region of the former Soviet Union, 1500 persons received the vaccine and showed a high frequency of detectable antibody by the N test. Likewise, vaccine was given to several hundred human volunteers in Bulgaria, with resulting high antibody response. However, there is little experimental and field data on its efficacy, as the vaccine was only used for a short period of time and in small areas. With the relatively small target population of persons at-risk for contracting CCHFV, the large-scale development and production of a CCHF vaccine by modern standards seems unlikely (Whitehouse 2004).

No specific measures in response to outbreaks or provisions for animal movements are reported in the OIE Terrestrian Animal Health Code.

CCHF is considered in different international projects that provide surveillance network and sharing of knowledge on infectious disease such as the Arbo-Zoonet project financed by the Food, Agriculture and Fisheries, and Biotechnology programme of the European Union that consider emerging vector borne disease present in Europe or at risk of introduction in the European area such as CCHF, West Nile Disease and Rift Valley Fever and the network Episouth on communicable diseases in southern Europe financed by European Commission.

CCHF is also considered in the ECDC-funded European Network for Diagnostics of Imported Viral Diseases — Collaborative Laboratory Response Network (ENIVD-CLRN) that provide assistance in sharing protocols and materials and in performing external quality assurance.

In September 2008 an Expert Consultation on Crimean-Congo haemorragic fever prevention and control took place in European Centre for Disease Control (ECDC) HQ in Stockholm.

it was concluded that it is imperative to develop integrated control measures that include vector control, vaccination programmes, improved therapy strategies, diagnostic tools and

surveillance, public awareness, capacity building and improvement of infrastructure in endemic regions.

To achieve this it, it will be important for Member States and ECDC to link up to existing research networks and to foster collaboration with international partners like the World Health Organization (WHO) or the World Organisation for Animal Health (OIE).

The experts agreed that the surveillance of human CCHF cases should be strengthened. The development and the use of a standardised case definition between Member States would allow comparison of case reports. Rapid detection and confirmation of cases are essential to limit the spread of human disease. In this regard, the implementation of alert systems in endemic areas in slaughterhouses and hospitals, for example, has been shown to be useful. In addition, a strong laboratory capacity is important in endemic areas and areas where the virus could be expected to circulate.

Information drawn from vector and animal surveillance is crucial for predicting human risk for CCHF infection but also for other tick-borne diseases. Therefore, the standardisation of protocols for tick collection from animals, theiridentification and screening for possible human pathogens would be helpful; diagnostic capacity would need to be developed accordingly. Areas of risk for the establishment of the vector, considering climatic and ecologicalconditions in Europe, need to be identified and vector surveillance need to be strengthened respectively. Multidisciplinary research will allow better understanding of the epidemiology of CCHF in ticks, domestic livestockand wild animal populations, and will support the identification of human risk factors for infection and thedevelopment of better diagnostics, antiviral drugs and vaccines. Also, the identification of an animal model for testing would facilitate any further research, and allow studying host response to infection and evaluatingintervention and control strategies. Finally, the role of environmental change, including climate change, needs further assessment.

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# APPENDICES

## *APPENDIX A MAPS*

**Figure 1** Worldwide distribution of CCHF from 1944 to 1989

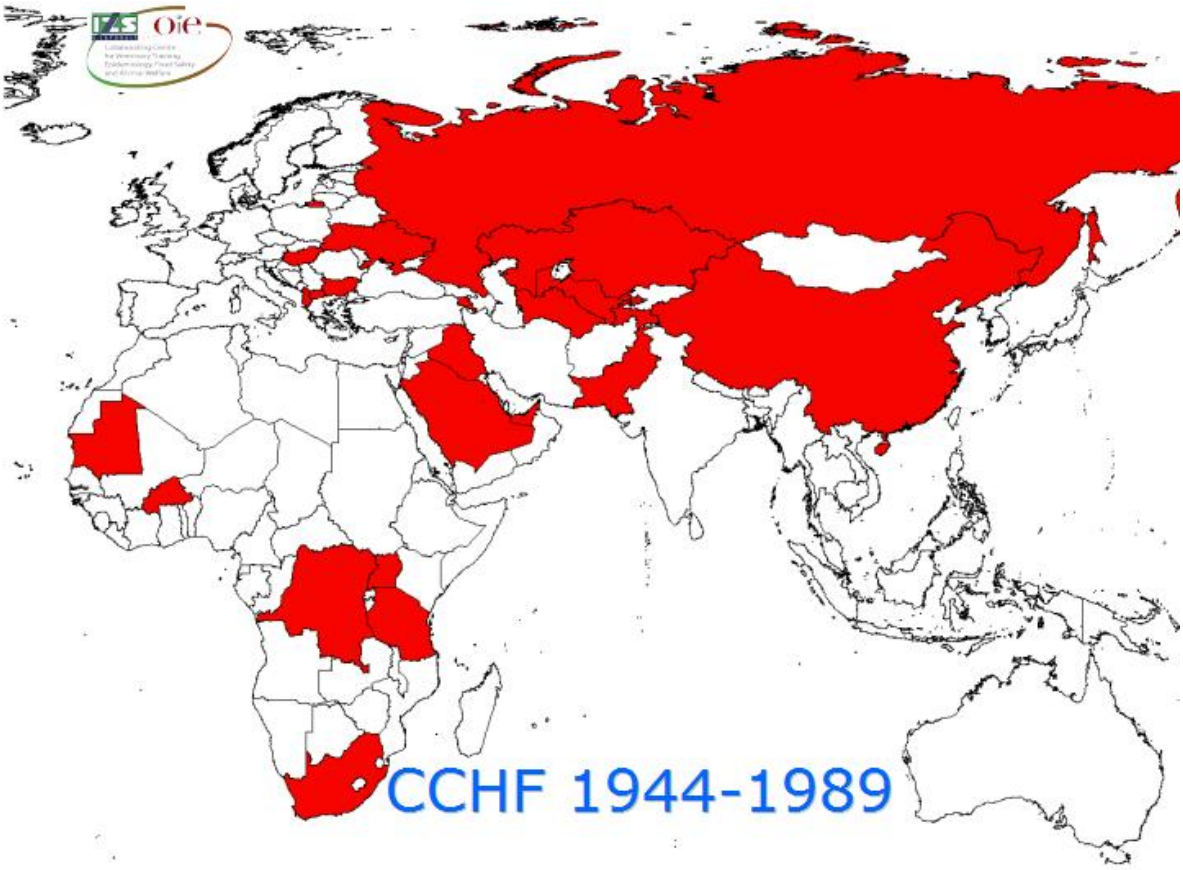


**Figure 2** Worldwide distribution of CCHF from 1944 to 1999

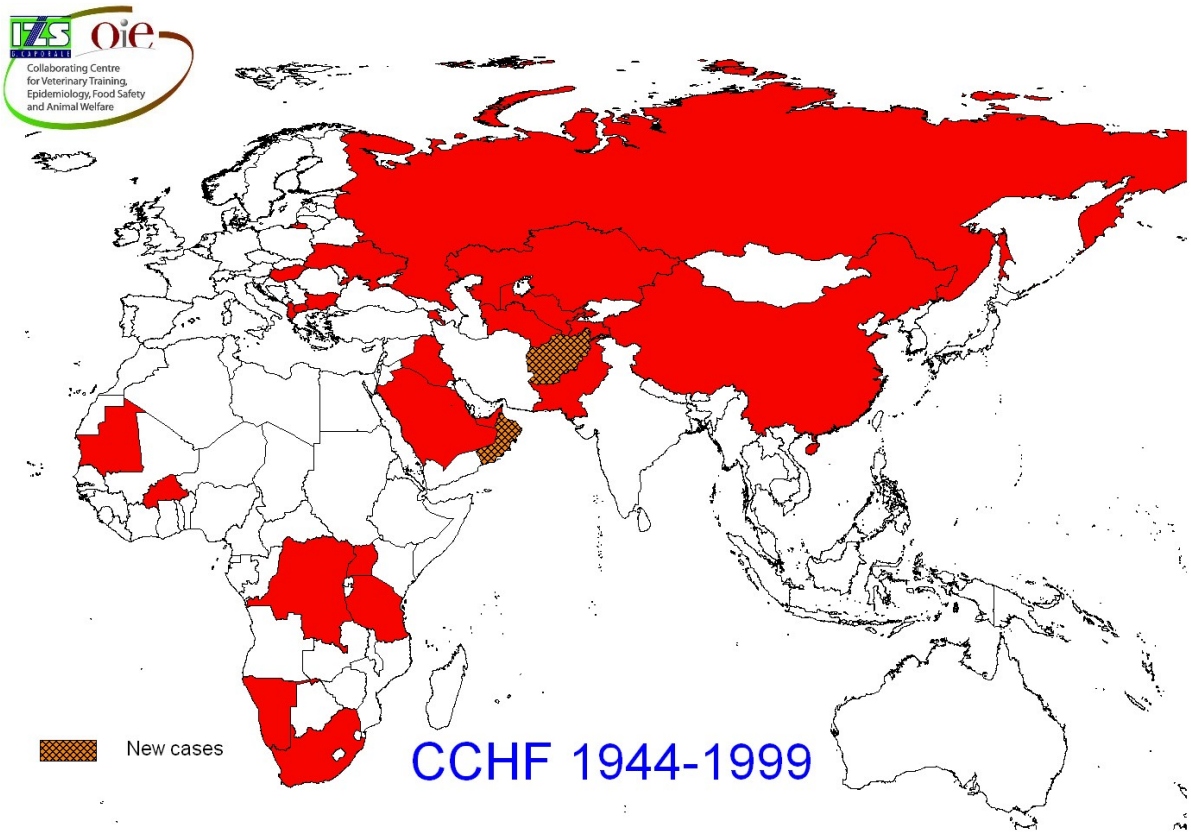


**Figure 3** Worldwide distribution of CCHF from 1944 to 2008

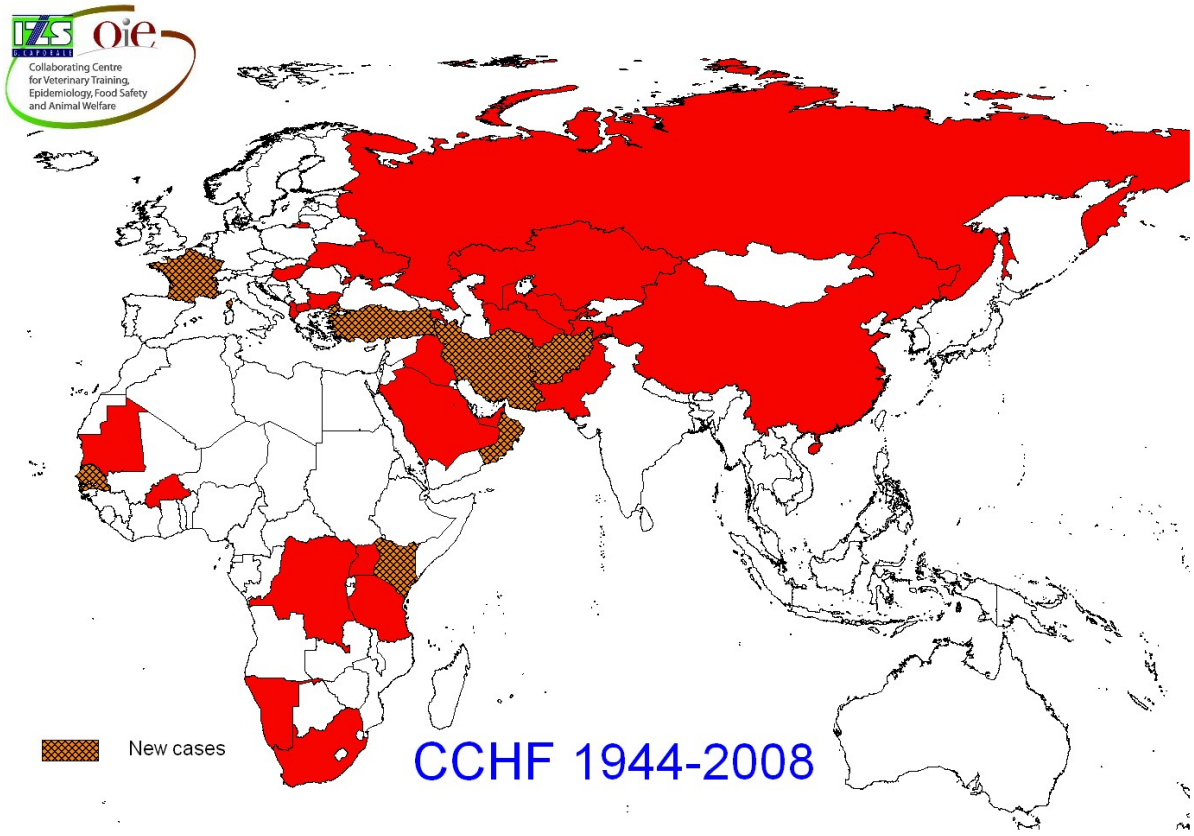


**Fig 4** Known and predicted distributions of *Hyalomma marginatum rufipes* in Africa from www.wec.ufl.edu/faculty/cummingg/Ticks/Appendix3_files/frame.htm accessed on 4 Sept.08

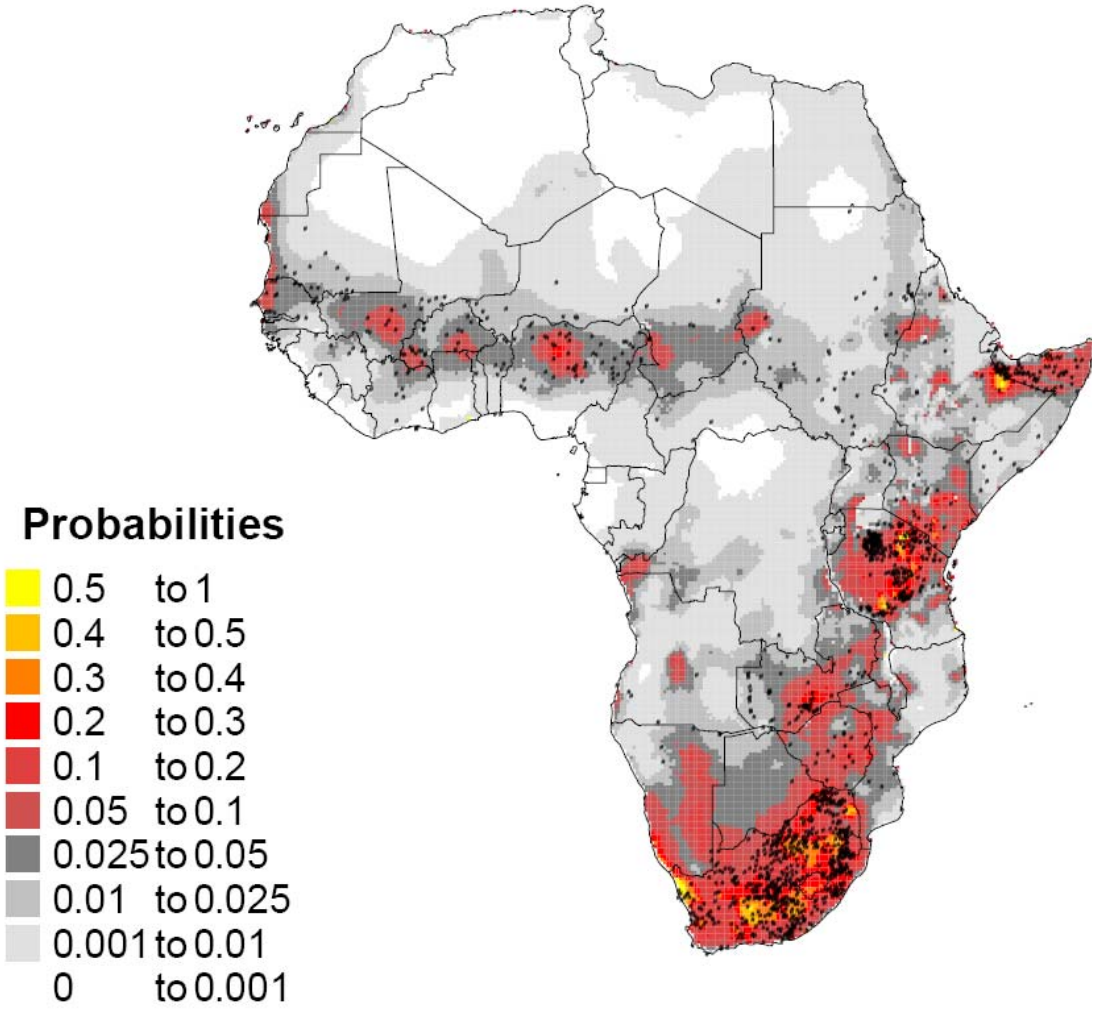


**Fig 5** Known and predicted distributions of *Hyalomma truncatum* in Africa from www.wec.ufl.edu/faculty/cummingg/Ticks/Appendix3_files/frame.htm 4 Sept.08

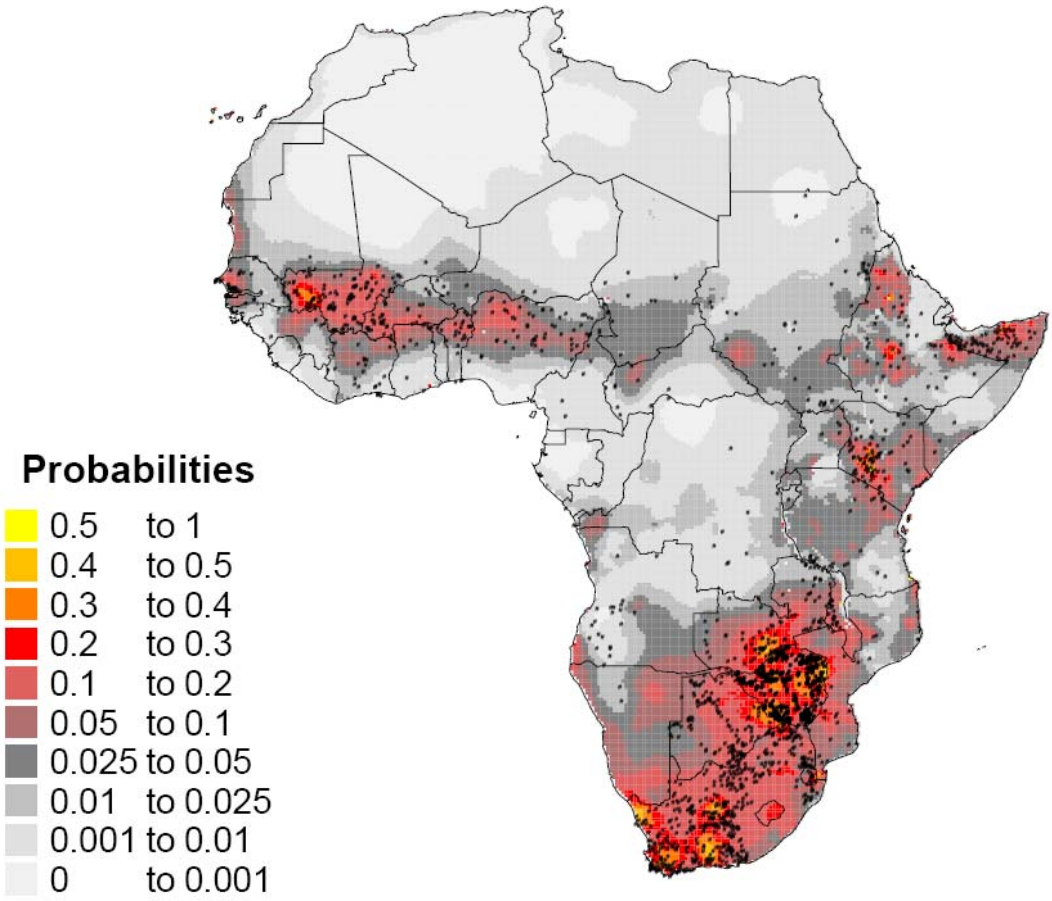


**Fig 6** Known and predicted distributions of *Hyalomma dromedari* in Africa from www.wec.ufl.edu/faculty/cummingg/Ticks/Appendix3_files/frame.htm 4 Sept.08

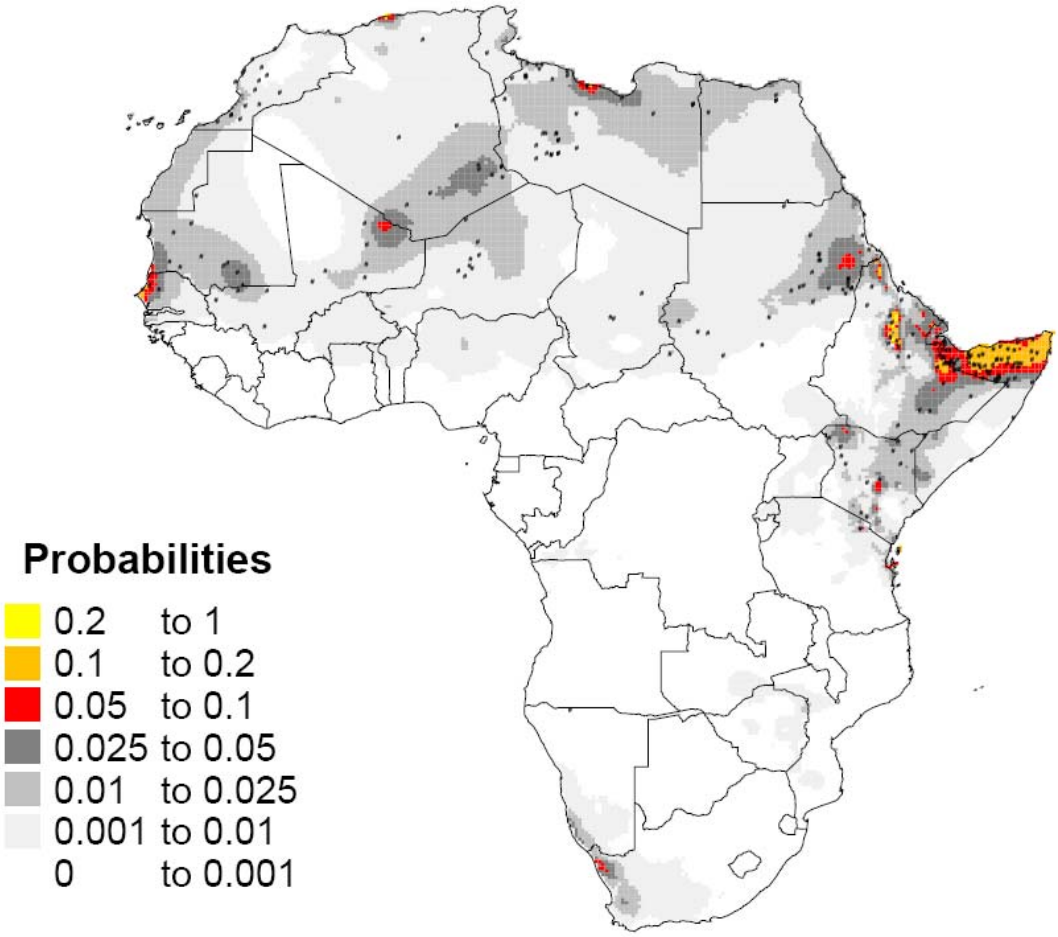


**Fig 7** Distribution of *Hyalomma marginatum marginatum* from Kolonin GV 2009 Fauna of Ixodid tick of the world Moscow www.kolonin.org acessed on 23 Sep. 09

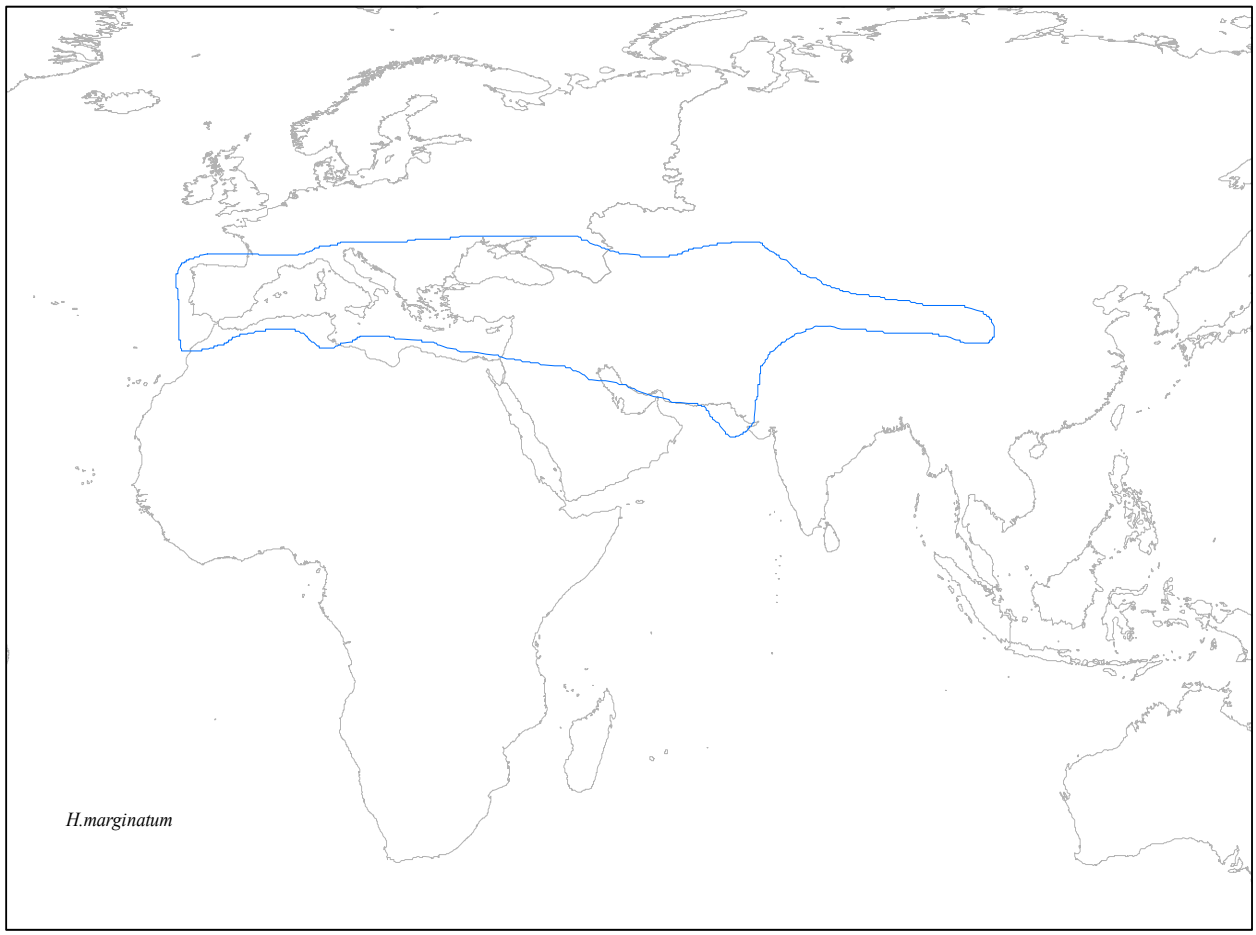


**Fig 8** Distribution of *Hyalomma anatolicum* from Kolonin GV 2009 Fauna of Ixodid tick of the world Moscow www.kolonin.org acessed on 23 Sep. 09

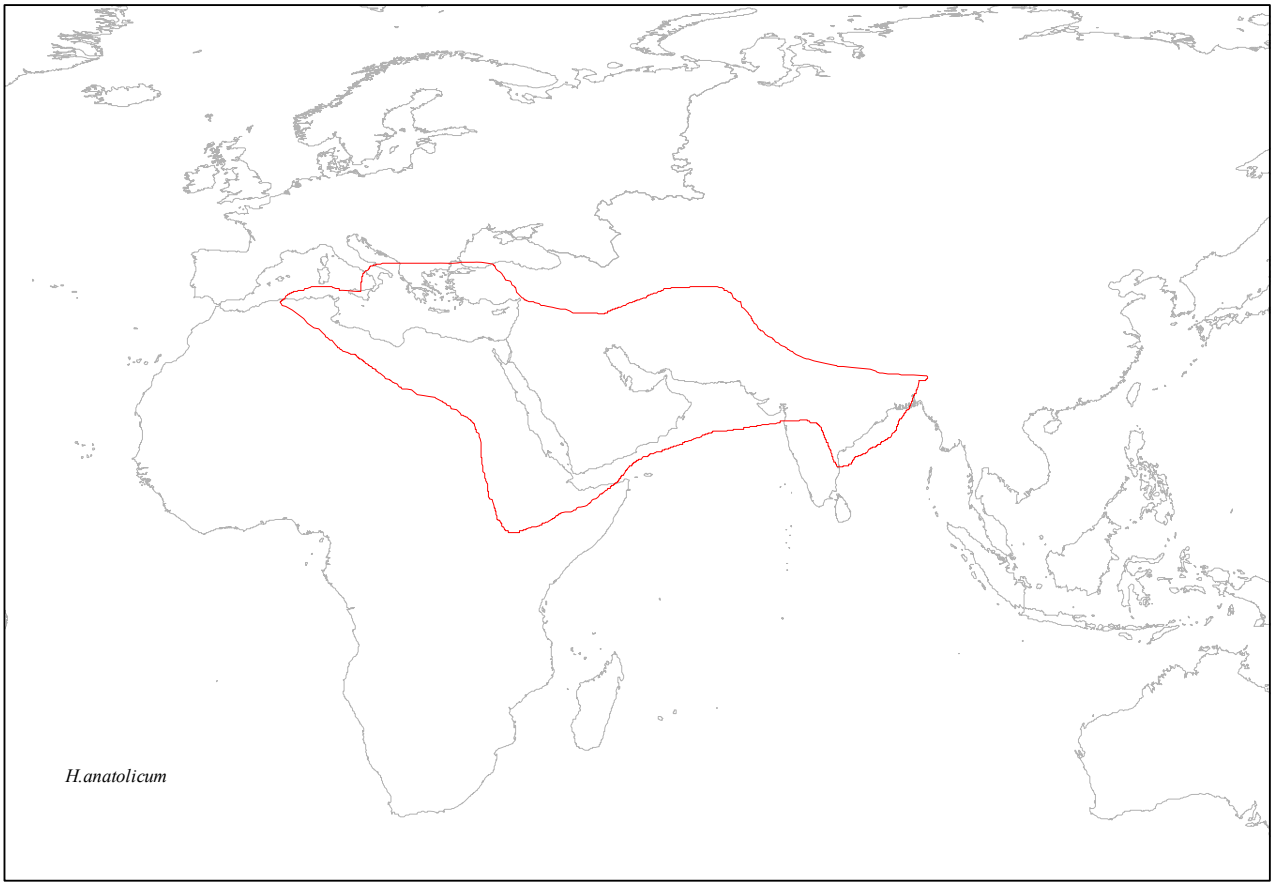


**Fig 9** Distribution of *Hyalomma impeltatum* from Kolonin GV 2009 Fauna of Ixodid tick of the world Moscow www.kolonin.org acessed on 23 Sep. 09

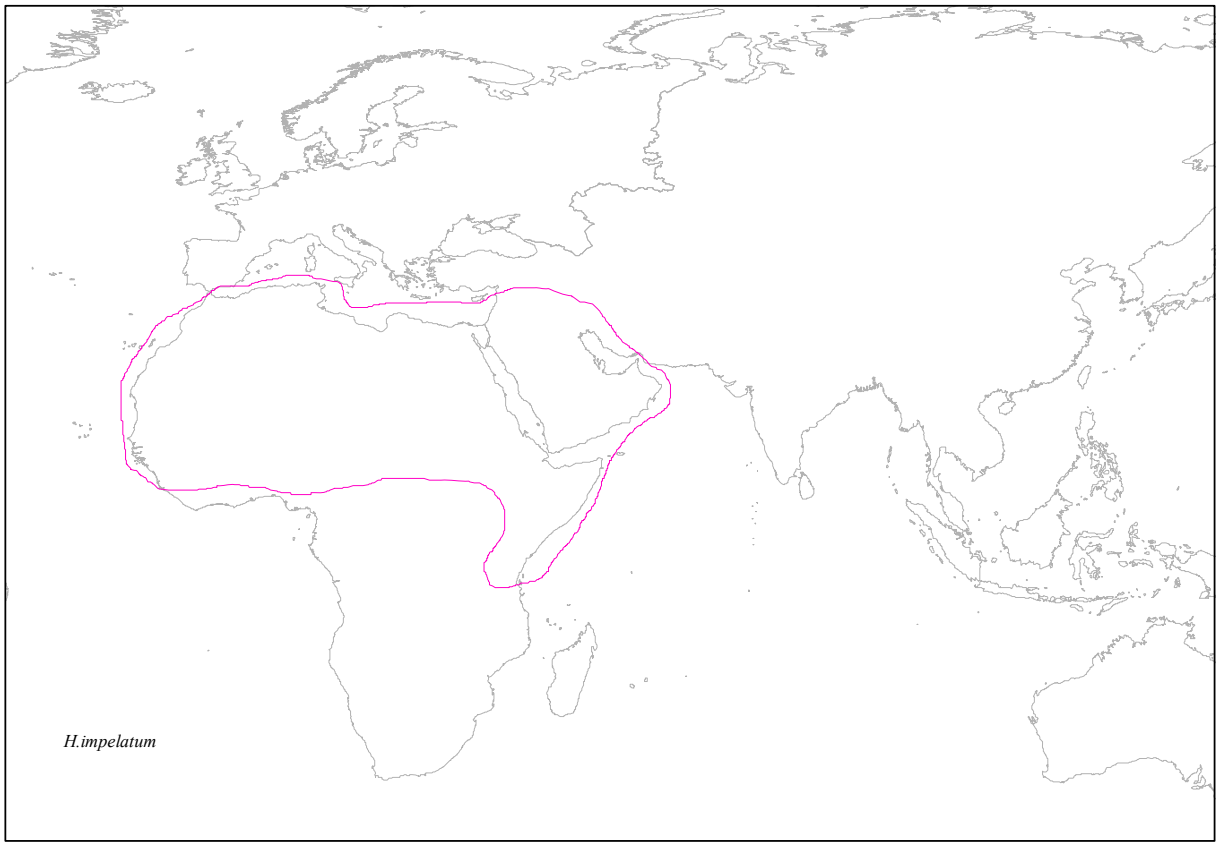


**Fig 10** Distribution of *Hyalomma excavatum* from Kolonin GV 2009 Fauna of Ixodid tick of the world Moscow www.kolonin.org acessed on 23 Sep. 09

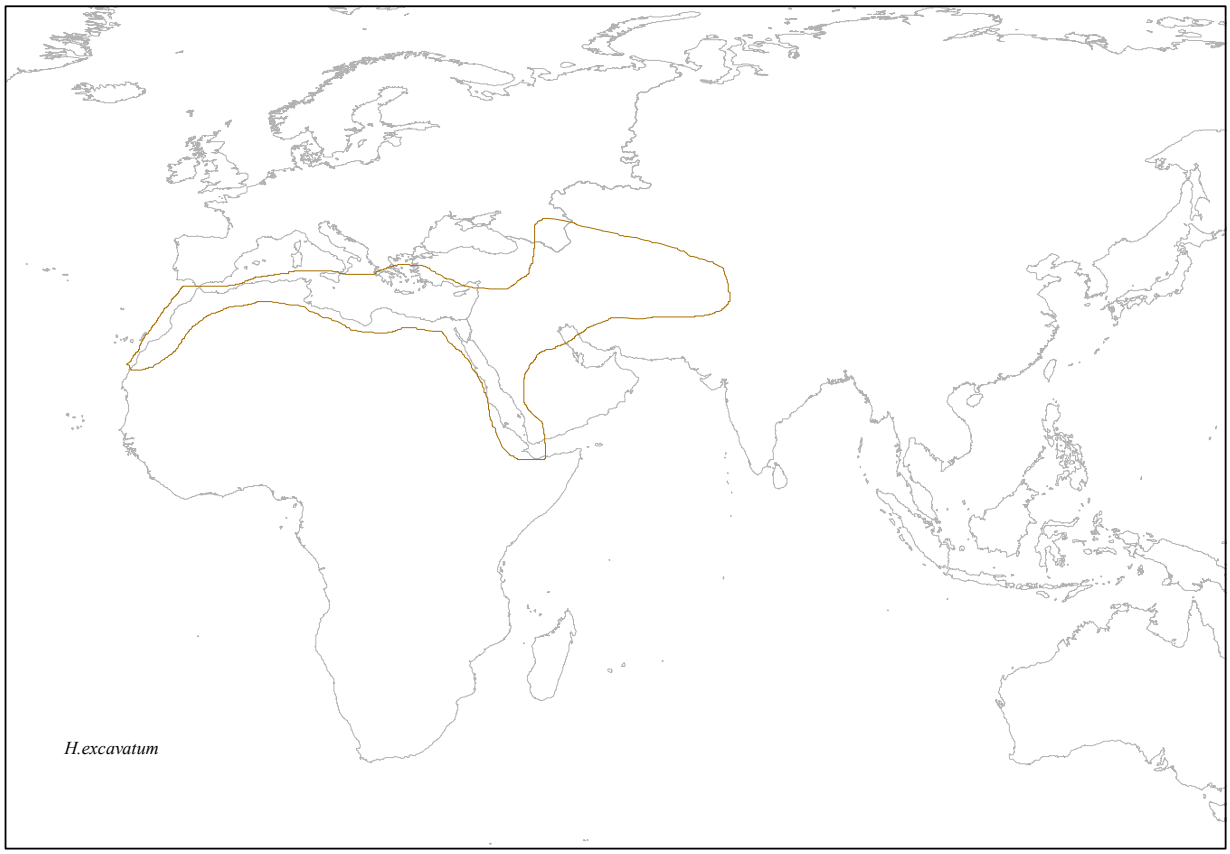


**Fig 11** Distribution of *Hyalomma truncatum* from Kolonin GV 2009 Fauna of Ixodid tick of the world Moscow www.kolonin.org acessed on 23 Sep. 09

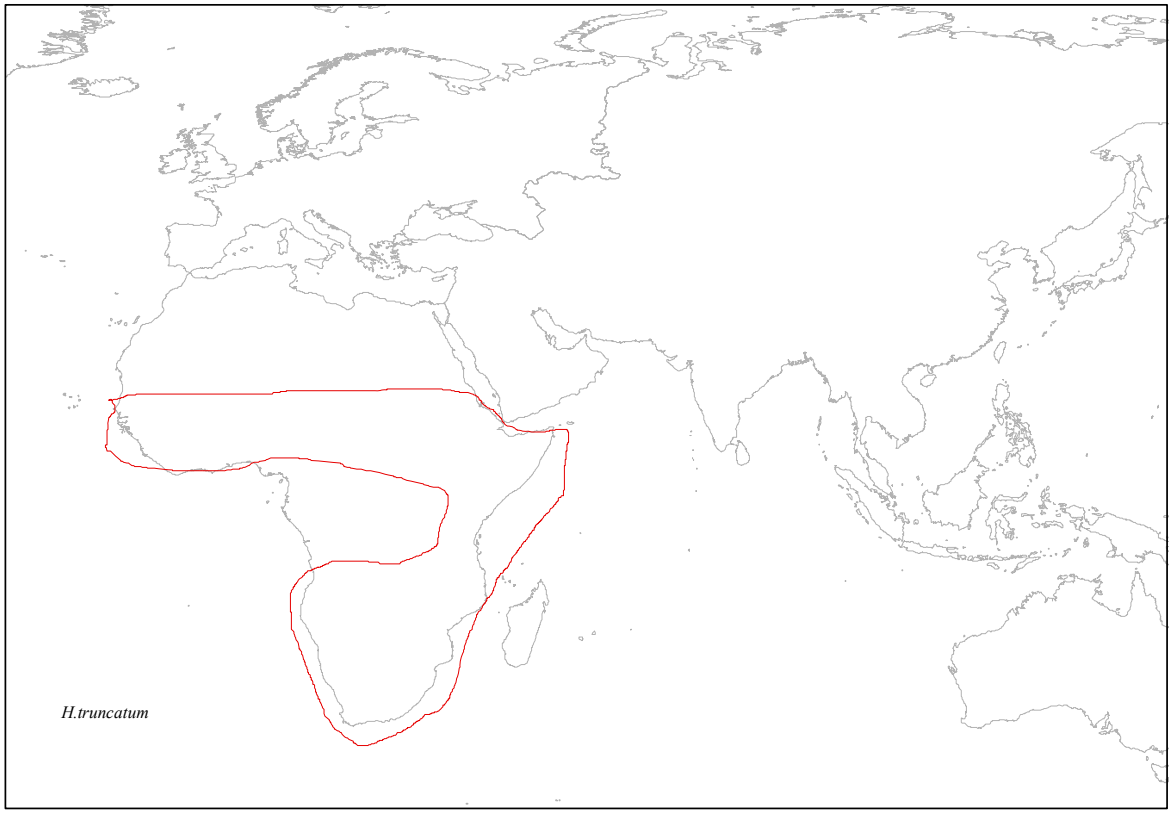


**Fig 12** Distribution of *Rhipicephalus rossicus* from Kolonin GV 2009 Fauna of Ixodid tick of the world Moscow www.kolonin.org acessed on 23 Sep. 09

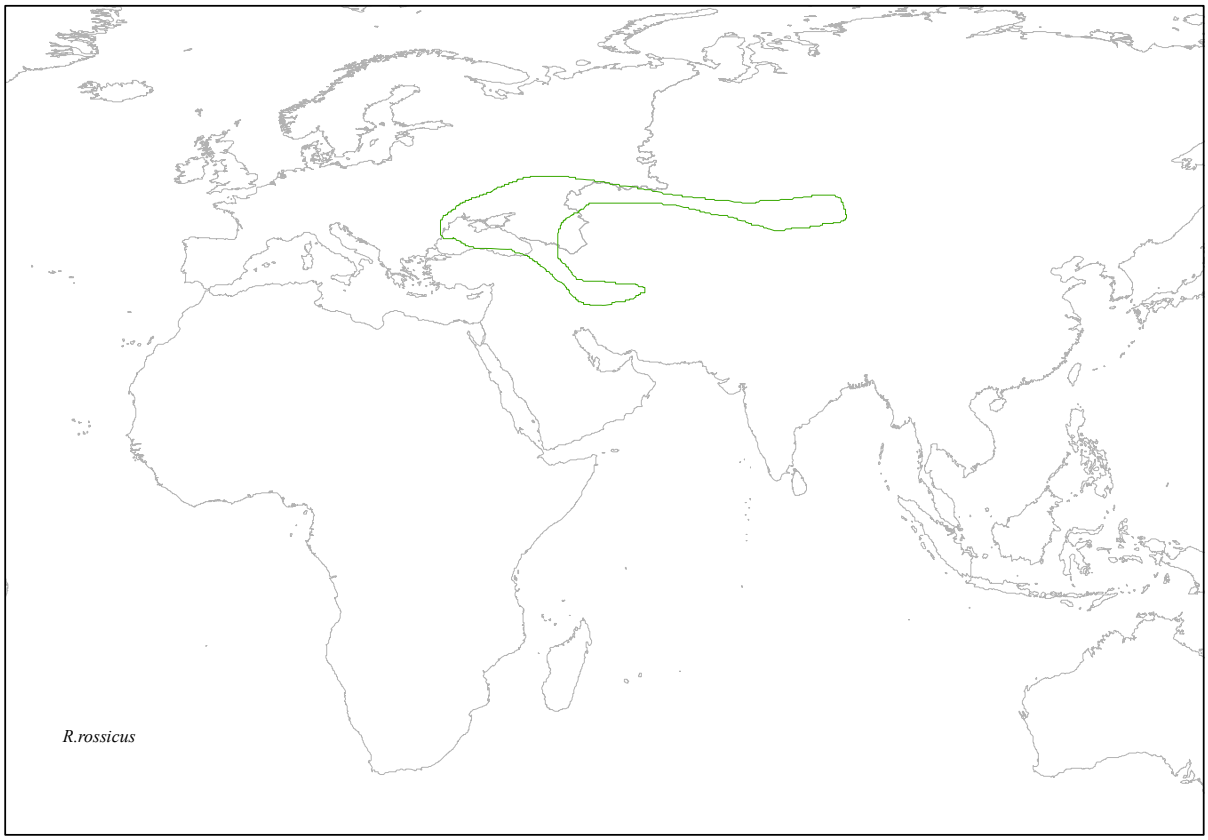


**Fig 13** Distribution of *Rhipicephalus sanguineus* from Kolonin GV 2009 Fauna of Ixodid tick of the world Moscow www.kolonin.org acessed on 23 Sep. 09

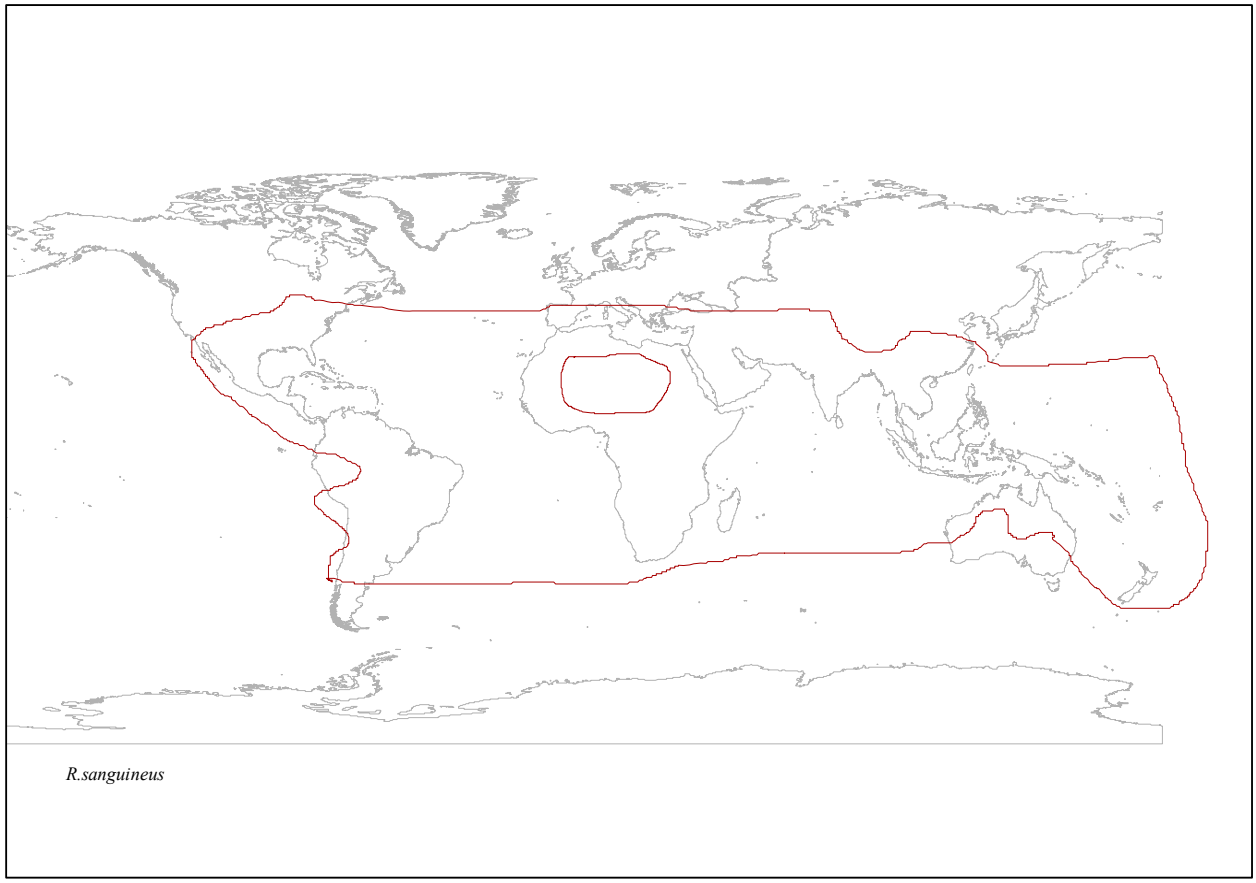
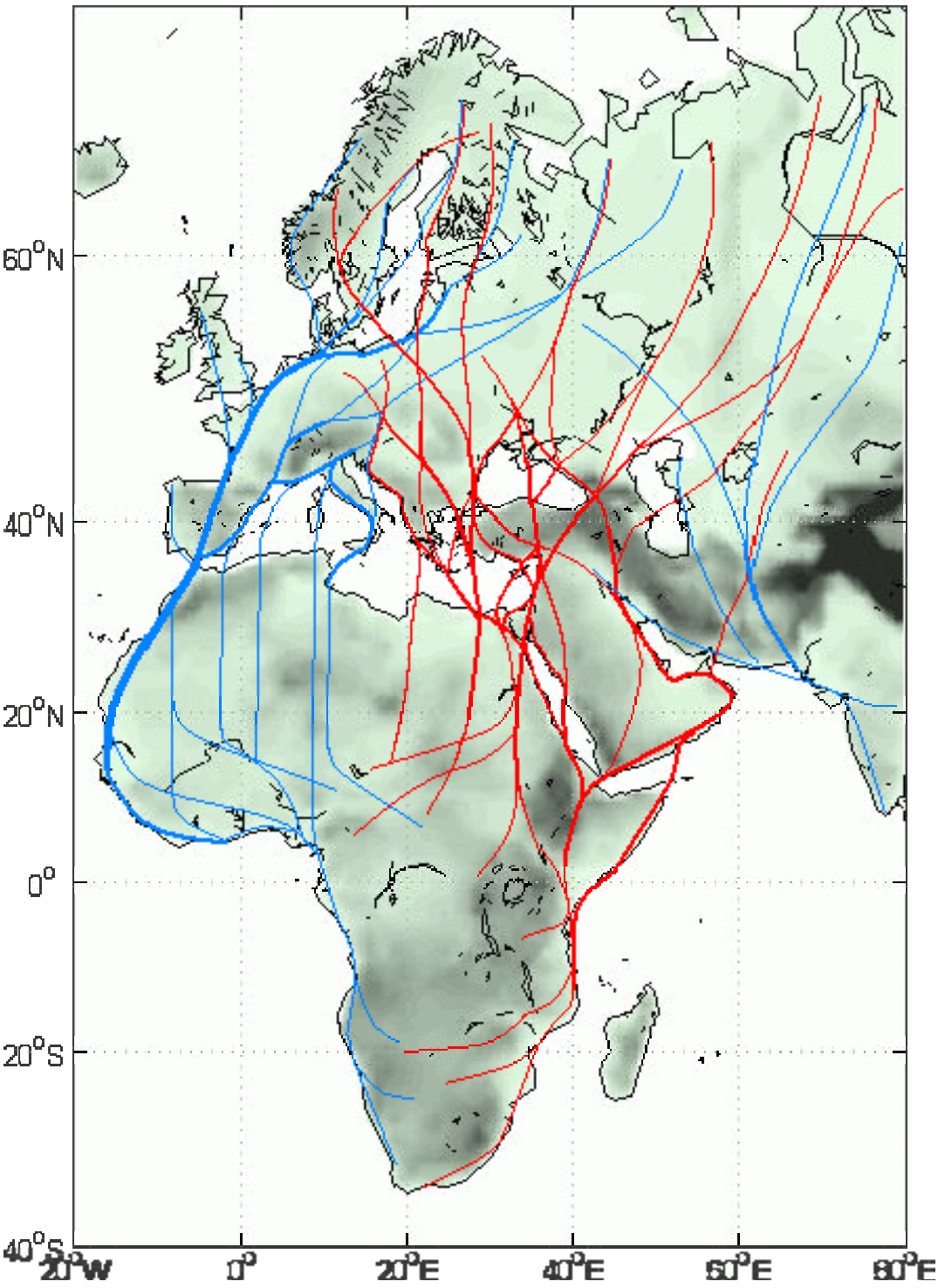


**Fig 14** African-Europe and Central Asia migratory flyways- SE EUROPEAN BIRD MIGRATION NETWORK (SEEN) www.seen-net.eu acessed on 6 Nov. 09



## *APPENDIX B TABLES*

**Table 1.** Reports of CCHF in the last 50 years

| *LOCATION* | *SPECIES* | *YEAR* | *REFERENCE* |
|---|---|---|---|
| ***Afghanistan*** | *Human* | *2002*<br>*2000*<br>*1998* | *Avsic-Zupanc T. 2008. Epidemiology and Current Geographical Distribution of Crimean-Congo Haemorrhagic Fever. Arbozoonet news 2, 8-15 (Avsic-Zupanc 2008)* |
| ***Albania*** | *Human* | *2002-06* | *Episouth. 2008. Epidemiology of Crimean–Congo haemorrhagic fever virus: Turkey, Russian Federation, Bulgaria, Greece, Albania, Kosovo. (Episouth 2008)* |
| ***Albania*** | *Ticks* | *2003-05* | *Papa A, Velo E, Papadimitriou E, Cahani G, Kota M, Bino S. Ecology of the Crimean-Congo Hemorrhagic Fever. 2009.Endemic Area in Albania. Vector Borne Zoonotic Dis. Apr 29. (Papa et al. 2009)* |
| ***Albania*** | *Human* | *2001* | *Papa, A., et al., Crimean-Congo hemorrhagic fever in Albania, 2001. 2002.Eur J Clin microbiol. Infect Dis, 21(8): p. 603-6.(Papa et al. 2002a)* |
| ***Albania*** | *Human* | *1985-87* | *Avšič-Županc T. 2007. Epidemiology of Crimean-Congo Hemorrhagic Fever in the Balkans, in Crimean-Congo Hemorrhagic fever. A Global Perspective, E.O.e.W. Ca, editor. Springer: p 75-88. (Avsic-Zupanc 2007)* |
| ***Armenia*** | *Human* | *1974* | *Episouth. 2008. Epidemiology of Crimean–Congo haemorrhagic fever virus: Turkey, Russian Federation, Bulgaria, Greece, Albania, Kosovo. (Episouth 2008)* |
| ***Bulgaria*** | *Human* | *2008* | *Episouth. 2008. Epidemiology of Crimean–Congo haemorrhagic fever virus: Turkey, Russian Federation, Bulgaria, Greece, Albania, Kosovo. (Episouth 2008)* |
| ***Bulgaria*** | *Human* | *1997-2005* | *Avsic-Zupanc T. 2008. Epidemiology and Current Geographical Distribution of Crimean-Congo Haemorrhagic Fever. Arbozoonet news 2, 8-15(Avsic-Zupanc 2008)* |
| ***Bulgaria*** | *Human* | *1975-96* | *Episouth. 2008. Epidemiology of Crimean–Congo haemorrhagic fever virus: Turkey, Russian Federation, Bulgaria, Greece, Albania, Kosovo. (Episouth 2008)* |
| ***Bulgaria*** | *Human* | *1953-74* | *Hoogstraal, H. 1979. the epidemiology of tickborne Crimean-Congo hemorrhagic fever in Asia, Europe, and Africa. J med entomol, 15, p. 307-417.(Hoogstraal 1979)* |

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|---|---|---|---|
| ***Burkina Faso*** | *Human* | *1983* | *Watts DM, Ksiazek TG, Linthicum KJ, Hoogstraal H 1988. Crimean-Congo hemorrhagic fever in: Monath TP, ed. The arboviruses: epidemiology an ecology, volume 2. Boca Ration, FL, USA: CRC Press, 1988: 177-260. (Watts et al. 1988)* |
| ***China*** | *Ticks*<br><br>*Human* | *2004-05* | *Sun S, Dai X, Muhetaer, et al. 2009.Epidemiology and Phylogenetic Analysis of the Crimean-Congo Hemorrhagic Fever Viruses in Xinjiang, China. J Clin Microbiol Jun 24. (Sun et al. 2009)* |
| ***China*** | *Human* | *1965-94*<br><br>*1997*<br><br>*2001-02* | *Papa, A., et al. 2002. Genetic characterization of the M RNA segment of Crimean Congo hemorrhagic fever virus strains, China. Emerg Infect Dis, 8(1): p. 50- 3. (Papa et al. 2002b)* |
| ***Democratic Republic of the Congo*** | *Human* | *1956* | *Hoogstraal, H., 1979. the epidemiology of tickborne Crimean-Congo hemorrhagic fever in Asia, Europe, and Africa. J med entomol, 1979. 15(4): p. 307-41.7 (Hoogstraal 1979)* |
| ***France-imported from Senegal*** | *Human* | *2004* | *Jaureguiberry, S., et al., 2005. Imported Crimean-Congo hemorrhagic Fever. J Clin Microbiol, 43(9): p. 4905-7.(Jaureguiberry et al. 2005)* |
| ***FYROM*** | *Human* | *1976* | *Vesenjak-Hirjan, J., V. Punda-Polic, and M. Dobe.1991. geographical distribution of arboviruses in Yugoslavia. J Hyg Epidemiol Microbiol Immunol, 35(2): p. 129-40. (Vesenjak-Hirjan et al. 1991)* |
| ***Greece*** | *Human* | *2008* | *Episouth. 2008. Epidemiology of Crimean–Congo haemorrhagic fever virus: Turkey, Russian Federation, Bulgaria, Greece, Albania, Kosovo. (Episouth 2008)*<br><br>*Papa A, Maltezou HC, Tsiodras S, Dalla VG, Papadimitriou T, Pierroutsakos I, Kartalis GN, and Antoniadis A. 2008. A case of Crimean-Congo haemorrhagic fever in Greece, June 2008. Eurosurveillance 13, 14 August 2008 (Papa et al. 2008)* |
| ***Greece*** | *Human* | *1980-81* | *Antoniadis A, Casals J. 1982. Serological evidence of human infection with Congo–Crimean hemorrhagic fever virus in Greece. Am J Trop Med Hyg 1982;31(5):1066–7(Antoniadis and Casals 1982).* |
| ***Hungary*** | *Human* | *1970* | *Horvath, L.B. 1976.Precipitating antibodies to Crimean haemorrhagic fever virus in human sera collected in Hungary. Acta Microbiol Acad Sci Hung. 23(4): p. 331-5. (Horvath 1976)* |

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|---|---|---|---|
| ***Iran*** | *Human* | *2003-06* | *Avsic-Zupanc T. 2008. Epidemiology and Current Geographical Distribution of Crimean-Congo Haemorrhagic Fever. Arbozoonet news 2, 8-15(Avsic-Zupanc 2008).* |
| ***Iran*** | *Human* | *2002* | *Izadi, S., et al. 2004. Crimean-Congo hemorrhagic fever in Sistan and Baluchestan Province of Iran, a case-control study on epidemiological characteristics. Int J Infect Dis, 8,. 299-306. (Izadi et al. 2004)* |
| ***Iran*** | *Human* | *2001* | *Avsic-Zupanc T. 2008. Epidemiology and Current Geographical Distribution ofCrimean-Congo Haemorrhagic Fever. Arbozoonet news 2, 8-15.(Avsic-Zupanc 2008).* |
| ***Iran*** | *Human* | *2000* | *Alavi-Naini, R., et al. 2006. Crimean-Congo hemorrhagic fever in Southeast of Iran. J Infect, 52(5): p. 378-82. (Alavi-Naini et al. 2006)* |
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| ***Russia- Astrakhan*** | *Human* | *1953-67* | *Hoogstraal H, 1979. The epidemiology of tickborne Crimean-Congo hemorrhagic fever in Asia, Europe, And Africa. J med entomol 15, 307-417 (Hoogstraal 1979).* |
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| ***Russia-Krasnodar*** | *Human* | *1948* | *Butenko, et al., 2007.Crimean-Congo Hemorrhagic Fever In Russia And Other Countries Of The Former Soviet Union, In Crimean-Congo Hemorrhagic Fever. A Global Perspective, E.O.A.W. Ca, Editor. 2007, Springer: Dordrecht. p. 99-114(Butenko et al. 2007).* |
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| ***Ukraine*** | *Human* | *1944-45* | *Hoogstraal, H. 1979. The epidemiology of tick borne Crimean-Congo hemorrhagic fever in Asia, Europe, And Africa. J Med Entomol 15(4): p. 307-417.(Hoogstraal 1979).* |
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| ***United Arab Emirates*** | *Human* | *1976* | *Suleiman, M.N., et al. 1980. Congo/Crimean haemorrhagic fever in Dubai. An outbreak at the Rashid Hospital. Lancet 2(8201): p. 939-41.(Suleiman et al. 1980)* |
| ***United Arab Emirates-Sharajah*** | *Human* | *1980* | *Watts DM, Ksiazek TG, Linthicum KJ, Hoogstraal H. Crimean-Congo hemorrhagic fever.1988. In: Monath TP, ed. The arboviruses: epidemiology an ecology, volume 2. Boca Ration, FL, USA: CRC Press, 1988: 177-260. (Watts et al. 1988)* |
| ***Uzbekistan*** | *Human* | *1973-83* | *Butenko, et al. 2007. Crimean-Congo Hemorrhagic Fever In Russia And Other Countries Of The Former Soviet Union, In Crimean-Congo Hemorrhagic Fever. A Global Perspective, E.O.A.W. Ca, Editor. 2007, Springer: Dordrecht. . p. 99-114.(Butenko et al. 2007)* |
| ***Uzbekistan*** | *Human* | *1948-63* | *Butenko, et al. 2007. Crimean-Congo Hemorrhagic Fever In Russia And Other Countries Of The Former Soviet Union, In Crimean-Congo Hemorrhagic Fever. A Global Perspective, E.O.A.W. Ca, Editor. 2007, Springer: Dordrecht. . p. 99-114.(Butenko et al. 2007)* |

Table 2. **Ticks as vectors of CCHFV (Turrel 2007 Modified)**

| | *Detection of CCHFV from ticks collected in nature* | *Replication and transmission of CCHFV by ticks that were inoculated intracoelomically in the laboratory* | *Replication and transmission of CCHFV by ticks that were orally exposed to CCHFV in the laboratory* | *Vertical transmission* | *References* |
|---|---|---|---|---|---|
| **Eurasian species** | | | | | |
| ***Dermacentor daghestanicus*** | *Reported* | *Not reported* | *Not reported* | *Not reported* | *(Hoogstraal 1979) (Watts et al. 1988)* |
| ***Dermacentor marginatus (Sulzer)*** | *Reported* | *Not reported* | *Reported* | *Not reported* | *(Hoogstraal 1979) (Watts et al. 1988) (Kondratenko 1976)* |
| ***Dermacentor niveus*** | *Reported* | *Not reported* | *Not reported* | *Not reported* | *(Onishchenko et al. 2005)* |
| ***Haemaphysalis parva (Neumann)*** | *Reported* | *Not reported* | *Not reported* | *Not reported* | *(Shchelkanov et al. 2005)* |
| ***Haemaphysalis punctata (Canestrini and Fanzago)*** | *Reported* | *Not reported* | *Not reported* | *Not reported* | *(Hoogstraal 1979) (Watts et al. 1988)* |
| ***Hyalomma anatolicum anatolicum (Koch )*** | *Reported* | *Not reported* | *Not reported* | *Not reported* | *(Onishchenko et al. 2005; Williams et al. 2000)* |
| ***Hyalomma anatolicum excavatum (Koch )*** | *Reported* | *Not reported* | *Not reported* | *Not reported* | *(Williams et al. 2000) (Causey et al. 1970)* |
| ***Hyalomma asiaticum asiaticum (Schulze and Schlottke)*** | *Reported* | *Not reported* | *Not reported* | *Not reported* | *(Onishchenko et al. 2005)* |
| ***Hyalomma detritum detritum (Schulze)*** | *Reported* | *Not reported* | *Not reported* | *Not reported* | *(Hoogstraal 1979) (Watts et al. 1988)* |
| ***Hyalomma dromedarii (Koch)*** | *Reported* | *Reported* | *Not reported* | *Not reported* | *(Watts et al. 1988) (Logan et al. 1990 )* |
| ***Hyalomma impeltatum (Schulze and Schlottke)*** | *Reported* | *Reported* | *Reported* | *Not reported* | *(Causey et al. 1970) (Dohm DJ 1996) (Logan et al. 1990 )* |

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|---|---|---|---|---|---|
| ***Hyalomma marginatum marginatum (Koch)*** | *Reported* | *Not reported* | *Reported* | *Reported* | *(Chumakov 1947)*<br>*(Tsilinsky et al. 1972)*<br>*(L' vov et al. 2002)*<br>*(Kondratenko 1976)*<br>*(Zgurskaya et al. 1971)* |
| ***Hyalomra marginatum rufipes (Koch)*** | *Reported* | *Reported* | *Reported* | *Reported* | *(Causey et al. 1970)*<br>*(Saluzzo et al. 1985)*<br>*(Zeller et al. 1994b)*<br>*(Faye et al. 1999a)*<br>*(Zeller et al. 1997)*<br>*(Okorie 1991)*<br>*(Shepherd et al. 1991)*<br>*(Faye et al. 1999a)*<br>*(Zeller et al. 1994a)*<br>*(Zeller et al. 1994b)*<br>*(Lee and Kemp 1970b)* |
| ***Hyalomma marginatum turanicum (Pomerantsev)*** | *Reported* | *Not reported* | *Not reported* | *Not reported* | *(Hoogstraal 1979)*<br>*(Watts et al. 1988)* |
| ***Ixodes ricinus (Linnaeus)*** | *Reported* | *Not reported* | *Not reported* | *Not reported* | *(Hoogstraal 1979)*<br>*(Watts et al. 1988)* |
| ***Rhipicephalus (Boophilus )annulatus (Say)*** | *Reported* | *Not reported* | *Not reported* | *Not reported* | *(Shchelkanov et al. 2005)* |
| ***Rhipicephalus bursa (Canestrini and Fanzago)*** | *Reported* | *Not reported* | *Not reported* | *Not reported* | *(Hoogstraal 1979)*<br>*(Watts et al. 1988)* |
| ***Rhipicephalus (Boophilus) decoloratus (Koch)*** | *Reported* | *Not reported* | *Not reported* | *Not reported* | *(Causey et al. 1970)* |
| ***Rhipicephalus sanguineus (Latreille)*** | *Reported* | *Not reported* | *Not reported* | *Not reported* | *(Hoogstraal 1979)*<br>*(Watts et al. 1988)* |
| ***Rhipicephalus rossicus (Yakimov and Kol-Yakimova)*** | *Reported* | *Reported* | *Reported* | *Reported* | *(Kondratenko 1976)*<br>*(Kondratenko et al. 1970)* |
| ***Rhipicephalus turanicus (Pomerantsev)*** | *Reported* | *Not reported* | *Not reported* | *Not reported* | *(Hoogstraal 1979)*<br>*(Watts et al. 1988)* |
| ***Argas lahorensis*** | *Reported* | *Not reported* | *Not reported* | *Not reported* | *(Hoogstraal 1979)*<br>*(Watts et al. 1988)* |
| ***Argas persicus (Oken)*** | *Reported* | *Not reported* | *Not reported* | *Not reported* | *(Watts et al. 1988)* |

**Other species**

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| ***Amblyomma variegatum*** | *Reported* | *Reported* | *Not reported* | *Not reported* | *(Causey et al. 1970)*<br>*(Zeller et al. 1997)*<br>*(Okorie 1991)*<br>*(Faye et al. 1999a)* |
| ***Hyalomma truncatum*** | *Reported* | *Reported* | *Reported* | *Reported* | *(Causey et al. 1970)*<br>*(Logan et al. 1989a)*<br>*(Faye et al. 1999a)*<br>*(Shepherd et al. 1991)*<br>*(Wilson et al. 1991)*<br>*(Gonzalez et al. 1992)* |
| ***Rhipicephalus appendiculatus (Neummann)*** | *Reported* | *Reported* | *Not reported* | *Not reported* | *(Watts et al. 1988)*<br>*(Logan et al. 1990 )* |
| ***Rhipicephalus evertsi (Neummann)*** | *Reported* | *Reported* | *Reported* | *Reported* | *(Swanepoel et al. 1983)*<br>*(Williams et al. 2000)*<br>*(Zeller et al. 1997)*<br>*(Faye et al. 1999b)* |
| ***Rhipicephalus guilhoni (Morel and Vassiliades)*** | *Reported* | *Not reported* | *Not reported* | *Not reported* | *(Zeller et al. 1997)* |
| ***Rhipicephalus (Boophilus) microplus (Canesterini)*** | *Reported* | *Not reported* | *Not reported* | *Not reported* | *(Hoogstraal 1979)*<br>*(Watts et al. 1988)* |
| ***Rhipicephalus pulchellus (Gerstacker)*** | *Reported* | *Not reported* | *Not reported* | *Not reported* | *(Hoogstraal 1979)*<br>*(Watts et al. 1988)* |

Table 3. **Data on experimental infection in ticks from Linthicum 1994 modified (Linthicum and Bailey 1994)**

| Species | Stage | Method of exposure | Infection | Transmission to | Reference |
|---|---|---|---|---|---|
| *H. dromedarii* Koch | Adult | Intracoelomic inoculation | + | Guinea pigs | Logan T, Linthicum K, Bailey C, Watts D, Dohm D, and Moulton J. 1990 Replication of Crimean-Congo hemorrhagic fever virus in four species of ixodid ticks (Acari) infected experimentally. J Med Entomol Jul;, 537-542. (Logan et al. 1990 ) |
| *H. impeltatum* Schulze and Schlottke | Larva | Co-fed with infected adults on a non-viremic guinea pig | + | Nymphs, adults, guinea pigs | Gordon S, Linthicum K, and Moulton J. 1993. Transmission of Crimean-Congo hemorrhagic fever virus in two species of *Hyalomma* ticks from infected adults to cofeeding immature forms. Am J Trop Med Hyg 48, 576-580. (Gordon et al. 1993) |
| *H. impeltatum* Schulze and Schlottke | Nymph | Co-fed with infected adults on a non-viremic guinea pig | + | Adults, guinea pig | Gordon S, Linthicum K, and Moulton J. 1993. Transmission of Crimean-Congo hemorrhagic fever virus in two species of *Hyalomma* ticks from infected adults to cofeeding immature forms. Am J Trop Med Hyg 48, 576-580. (Gordon et al. 1993) |
| *H. impeltatum* Schulze and Schlottke | Adult | Intracoelomic inoculation | + | Guinea pigs | Logan T, Linthicum K, Bailey C, Watts D, Dohm D, and Moulton J. 1990 Replication of Crimean-Congo hemorrhagic fever virus in four species of ixodid ticks (Acari) infected experimentally. J Med Entomol Jul; 537-542. (Logan et al. 1990) |
| *H. impeltatum* Schulze and Schlottke | Larvae<br>Nymphs | Feeding on viremic mouse | + | Nymph, adult Guinea pigs | Dohm DJ LT, Linthicum KJ, Rossi CA, Turell MJ. 1996. Transmission of Crimean-Congo hemorrhagic fever virus by *Hyalomma impeltatum* (Acari:Ixodidae) after experimental infection. J Med Entomol Sep 33, 848- |

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| | | | | | 851. (Dohm DJ 1996) |
| *H. m. marginatum* Koch | Larva | Viremic European hare, long-eared hedgehog | + | Nymphs, adults, rabbits, guinea pigs, F1 larvae and nymphs | Zgurskaya G, Berezin V, Smirnova S, and Chumakov M. 1971. Investigation of the question of Crimean hemorrhagic fever virus tansmission and interepidemic survival in the tick *Hyalomma plumbeum plumbeum*. In: Viral hemorrhagic fevers, Crimean hemorrhagic fever, Omsk hemorrhagic fever, and hemorrhagic fever with renal syndrome, Chumakov MP Ed. Trudy Inst Polio Virusn Entsefaltov Akad Med Nauk SSSR, 217-220 (Zgurskaya et al. 1971). |
| *H. m. marginatum* Koch | Larva | Viremic little suslik | + | Nymphs, adults | Kondratenko V. 1976. Importance of ixodid ticks in transmitting and preserving the Crimean hemorrhagic fever agent in infection foci. Parazitolgia, 297-302. (Kondratenko 1976). |
| *H. m. marginatum* Koch | Larva | Viremic Belgian hare | + | F1 larvae | Levi V, and Vasilenko S. 1972. Study on the Crimean hemorrhagic rever (CHF) virus transmission mechanism in *Hyalomma pl. plumbeum* ticks Epidemiol Mikrobiol Infekts Boles 9, 182-185 (Levi and Vasilenko 1972).<br><br>Zarubinsky VY, Kondratenko VF, Blagoveschchenskaya NM, Zarvbina LV, and Kuchin VV. 1976. Susceptibility of calves and lambs to Crimean hemorrhagic fever virus. Tezisy Dokl 9 Vses Konf Prirod Ochag Bolez Chelov Zhivot (Omsk), 130-131. (Zarubinsky et al. 1976). |
| *H. m. marginatum* Koch | Adult | Viremic little suslik, rabbit | + | F1 , F2 larvae, nymphs, and<br><br>adults, little<br><br>suslik, rabbit s | Kondratenko V. 1976. Importance of ixodid ticks in transmitting and preserving the Crimean hemorrhagic fever agent in infection foci. Parazitolgia, 297 302 (Kondratenko 1976). |

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| *H. m. marginatum* Koch | Larvae and Nymph | Intracoelomic inoculation | + | New born mice<br><br>Adults and nymph | Faye O, Cornet J, Camicas J, Fontenille D, and Gonzalez J. 1999. Experimental transmission of Crimean-Congo hemorrhagic fever virus role of 3 vector species in the maintenance and transmission cycles in Senegal. Parasite 6, 27-23 22 (Faye et al. 1999a). |
| *H. m. rufipes* Koch | Larva | Viremic scrub hare | + | Nymphs, adults, sheep | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks Epidemiol Infect 106, 373-382 (Shepherd et al. 1991). |
| *H. m. rufipes* Koch | Nymph | Intracoelomic inoculation | + | Adults, sheep | Shepherd A, Swanepoel R, Cornel A, and Mathee O. 1989. Experimental studies on the replication and transmission of Crimean-Congo hemorrhagic fever virus in some African tick species. Am J Trop Med Hyg 40, 326-333. (Shepherd et al. 1989a). |
| *H. m. rufipes* Koch | Nymph | Intracoelomic inoculation | + | Calf, adults, F1 larvae | Lee EH, and Kemp GE. 1970. Congo virus : experimental infection of *Hyalomma rufipes* and transmission to a calf. Bull Entomol Soc Niger 2, 133-135. (Lee and Kemp 1970a). |
| *H. m. rufipes* Koch | Nymph | Viremic scrub hare | + | Adults, sheep | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks Epidemiol Infect 106, 373-382. (Shepherd et al. 1991). |
| *H. m. rufipes* Koch | Nymph | Intracoelomic inoculation | + | Rabbits | Okorie T. 1991. Comparative studies on the vector capacity of the different stages of *Amblyomma variegatum* Fabricius md *Hyalomna rufipes* Koch for Congo virus, after intracoelomic inoculation Vet Parasitol 38, 215-223. (Okorie 1991). |
| *H. m. rufipes* Koch | Adult | Intracoelomic | + | Rabbits | Okorie TG. Congo virus-the development in the ixodid ticks-*Hyalomma* |

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| | | inoculation | | | *rufipes* and *Amblyomma variegatum* Fabricius Proc. International Congress on Entomology, Kyoto, 1980. p 331 (Okorie 1980).<br><br>Okorie TG, and Fabiyi A. 1980. The replication of Congo virus in *Hyalomma rufipes* Koch following intracoelomic inoculation. Vet Parasitol 7, 369-374. (Okorie and Fabiyi 1980). |
| *H. m. rufipes* Koch | Adult | Viremic cow | + | Hedgehogs | Causey O, Kemp G, Madbouly M, and David-West T. 1970. Congo virus from domestic livestock, African hedgehog, and arthropods in Nigeria. Am J Trop Med Hyg Sep; 19, 846-850 (Causey et al. 1970). |
| *H. m. rufipes* Koch | Adult | Viremic sheep | + | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks Epidemiol Infect 106, 373-382. (Shepherd et al. 1991). |
| *H. m. rufipes* Koch | Adult | Viremic cattle | + | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks Epidemiol Infect 106, 373-382. (Shepherd et al. 1991). |
| *H. truncatum* Koch | Larva | Viremic suckling mouse | + | Nymphs, adults | Logan T, Linthicum K, Bailey C, Watts D, and Moulton J. 1989. Experimental transmission of Crimean-Congo hemorrhagic fever virus by *Hyalomma truncatum* Koch. Am I Trop Med Hyg 40 207-212. (Logan et al. 1989a). |
| *H. truncatum* Koch | Larva | Viremic scrub hare | + | Adults | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks Epidemiol Infect 106, 373-382. (Shepherd et al. 1991). |

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| *H. truncatum* Koch | Larva | Viremic guinea pigs | + | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks Epidemiol Infect 106, 373-382. (Shepherd et al. 1991). |
| *H. truncatum* Koch | Larva | Viremic white-tailed rat | + | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks Epidemiol Infect 106, 373-382. (Shepherd et al. 1991). |
| *H. truncatum* Koch | Larva | Viremic Co-fed with infected adults on<br><br>a non-viremic guinea pig | + | Nymphs, adults, guinea pig | Gordon S, Linthicum K, and Moulton J. 1993. Transmission of Crimean-Congo hemorrhagic fever virus in two species of *Hyalomma* ticks from infected adults to cofeeding immature forms. Am J Trop Med Hyg 48, 576-580. (Gordon et al. 1993). |
| *H. truncatum* Koch | Nymph | Intracoelomic inoculation | + | Adults, sheep | Shepherd A, Swanepoel R, Cornel A, and Mathee O. 1989. Experimental studies on the replication and transmission of Crimean-Congo hemorrhagic fever virus in some African tick species. Am J Trop Med Hyg 40, 326-333. (Shepherd et al. 1989a).<br><br>Shepherd AJ, Leman PA, and Swanepoel R. 1989. Viremia and Antibody Response of Small African and Laboratory Animals to Crimean-Congo Hemorrhagic Fever Virus Infection Am J Trop Med Hyg 40, 541-547. (Shepherd et al. 1989b). |
| *H. truncatum* Koch | Nymph | Viremic scrub hare | + | Adults | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks Epidemiol Infect 106, 373-382. (Shepherd et al. 1991). |

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| *H. truncatum* Koch | Nymph | Viremic guinea pigs | - | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks Epidemiol Infect 106, 373-382. (Shepherd et al. 1991). |
| *H. truncatum* Koch | Adult | Intracoelomic inoculation | + | Guinea pigs | Logan T, Linthicum K, Bailey C, Watts D, Dohm D, and Moulton J. 1990 Replication of Crimean-Congo hemorrhagic fever virus in four species of ixodid ticks (Acari) infected experimentally J Med Entomol 27, 537-542. (Logan et al. 1990 ). |
| *H. truncatum* Koch | Adult | Viremic cattle | + | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks Epidemiol Infect 106, 373-382. (Shepherd et al. 1991). |
| *H. truncatum* Koch | Adult | Viremic sheep | - | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks Epidemiol Infect 106, 373-382. (Shepherd et al. 1991). |
| *H. truncatum* Koch | Adult | Intracoelomic inoculation | + | - | Gonzalez JP, Cornet JP, Wilson ML, and Camicas JL. 1991. Crimean-Congo haemorrhagic fever virus replication in adult *Hyalomma truncatum* and *Amblyomma variegatum* ticks. Res Virol 142,483-488. (Gonzalez et al. 1991). |
| *H. truncatum* Koch | Adult | Viremic sheep | + | F1 eggs | Wilson M, Gonzalez J, Cornet J, and Camicas J. 1991. Transmission of Crimean-Congo haemorrhagic fever virus from experimentally infected sheep to *Hyalomma truncatum* ticks. Res Virol 142, 395-404. (Wilson et al. 1991). |

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| *H. truncatum* Koch | Adult | Venereal from infected male tick | + | F1 eggs, larvae | Gonzalez J, Camicas J, Cornet J, Fay O, and Wilson ML. 1992. Sexual and transovarian transmission of Crimean-Congo haemorrhagic fever virus in *Hyalomma truncatum* ticks. Res Virol 143, 23-28 (Gonzalez et al. 1992). |
| *H. truncatum* Koch | Adult | Co-fed with infected tick on a rabbit | + | Rabbit | Gonzalez J, Camicas J, Cornet J, Fay O, and Wilson ML. 1992. Sexual and transovarian transmission of Crimean-Congo haemorrhagic fever virus in *Hyalomma truncatum* ticks Res Virol 143, 23-28. (Gonzalez et al. 1992). |
| *H. truncatum* Koch | Larvae and Nymph | Intracoelomic inoculation | + | New born mice<br>Adults and nymph | Faye O, Cornet J, Camicas J, Fontenille D, and Gonzalez J. 1999. Experimental transmission of Crimean-Congo hemorrhagic fever virus role of 3 vector species in the maintenance and transmission cycles in Senegal. Parasite 6, 27-23. 22 (Faye et al. 1999a). |
| *R. appendiculatus* Neumann | Adult | Intracoelomic inoculation | + | Guinea pigs | Logan T, Linthicum K, Bailey C, Watts D, Dohm D, and Moulton J. 1990 Replication of Crimean-Congo hemorrhagic fever virus in four species of ixodid ticks (Acari) infected experimentally. J Med Entomol 27, 537-542. (Logan et al. 1990 ). |
| *R. appendiculatus* Neumann | Adult | Viremic sheep | - | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks Epidemiol Infect 106, 373-382. (Shepherd et al. 1991). |
| *R. appendiculatus* Neumann | Adult | Viremic cattle | + | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks Epidemiol Infect 106, 373-382. (Shepherd et al. 1991). |
| *R. appendiculatus* Neumann | Larva | Viremic sheep | - | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean- |

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| | | | | | Congo haemorrhagic fever virus to ticks Epidemiol Infect 106, 373-382. (Shepherd et al. 1991). |
| R. *e. evertsi* Neumann | Larva | Viremic sheep | - | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks. Epidemiol Infect 106, 373-382. (Shepherd et al. 1991). |
| R. *e. evertsi* Neumann | Larva | Viremic scrub hare | - | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks. Epidemiol Infect 106, 373-382. (Shepherd et al. 1991). |
| R. *e. evertsi* Neumann | Nymph | Viremic scrub hare | - | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks. Epidemiol Infect 106, 373-382. (Shepherd et al. 1991). |
| R. *e. evertsi* Neumann | Nymph | Viremic sheep | - | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks. Epidemiol Infect 106, 373-382. (Shepherd et al. 1991). |
| R. *e. evertsi* Neumann | Adult | Viremic sheep | - | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks. Epidemiol Infect 106, 373-382. (Shepherd et al. 1991). |
| R. *e. evertsi* Neumann | Adult | Viremic cattle | + | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks. Epidemiol Infect 106, 373-382 (Shepherd et al. 1991). |
| *R. e. mimeticus* Donitz | Larva | Viremic guinea pig | - | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks. Epidemiol Infect 106, 373-382 |

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| | | | | | (Shepherd et al. 1991). |
| *R. e. mimeticus* Donitz | Larva | Viremic white-tailed rat | - | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks. Epidemiol Infect 106, 373-382. (Shepherd et al. 1991). |
| *R. e. mimeticus* Donitz | Nymph | Intracoelomic inoculation | + | Adults, sheep | Shepherd A, Swanepoel R, Cornel A, and Mathee O. 1989. Experimental studies on the replication and transmission of Crimean-Congo hemorrhagic fever virus in some African tick species. Am J Trop Med Hyg 40, 326-333. (Shepherd et al. 1989a).<br><br>Shepherd AJ, Leman PA, and Swanepoel R. 1989. Viremia and Antibody Response of Small African and Laboratory Animals to Crimean-Congo Hemorrhagic Fever Virus Infection. Am J Trop Med Hyg 40 541-547. (Shepherd et al. 1989b). |
| *R. pulchellus* Gerstacker | Adult | Intracoelomic inoculation | + | Guinea pigs | Linthicum 1994 (unpublished observations) (Linthicum 1994) |
| *R. rossicus* Yakimov and Koh1-Yakimova | Nymph | Viremic little suslik | + | Adults | Kondratenko V. 1976. Importance of ixodid ticks in transmitting and preserving the Crimean hemorrhagic fever agent in infection foci. Parazitolgia, 297-302. (Kondratenko 1976). |
| *R. rossicus* Yakimov and Koh1-Yakimova | Adult | Viremic little suslik, rabbit | + | F1 , F2 larvae, nymphs, and adults, little suslik, rabbits | Kondratenko V. 1976. Importance of ixodid ticks in transmitting and preserving the Crimean hemorrhagic fever agent in infection foci. Parazitolgiya, 297-302 (Kondratenko 1976). |
| *R . rossicus* Yakimov and Koh1-Yakimova | Adult | Viremic calf | - | - | Zarubinsky VY, Kondratenko VF, Blagoveschchenskaya NM, Zarvbina LV, and Kuchin VV. 1976. Susceptibility of calves and lambs to Crimean hemorrhagic fever virus. Tezisy Dokl 9 Vses Konf Prirod Ochag Bolez Chelov Zhivot (Omsk), |

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| | | | | | 130-131 (Zarubinsky et al. 1976). |
| *R. simus* Koch | Larva | Viremic sheep | - | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks Epidemiol Infect 106, 373-382 (Shepherd et al. 1991) . |
| *R. simus* Koch | Nymph | Viremic sheep | - | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks Epidemiol Infect 106, 373-382 (Shepherd et al. 1991). |
| *R. simus* Koch | Adult | Viremic sheep | - | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks Epidemiol Infect 106, 373-382. (Shepherd et al. 1991). |
| *A. hebraeum* Koch | Larva | Viremic sheep | - | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks Epidemiol Infect 106, 373-382. (Shepherd et al. 1991) . |
| *A. hebraeum* Koch | Larva | Viremic guinea pig | - | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks Epidemiol Infect 106, 373-382. (Shepherd et al. 1991) . |
| *A. hebraeum* Koch | Larva | Viremic white-tailed rat | - | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks Epidemiol Infect 106, 373-382. (Shepherd et al. 1991). |
| *A. hebraeum* Koch | Nymph | Intracoelomic inoculation | + | Adults, sheep | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks Epidemiol Infect 106, 373-382. (Shepherd et al. 1991). |

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| *A. hebraeum* Koch | Nymph | Viremic sheep | - | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks Epidemiol Infect 106, 373-382. (Shepherd et al. 1991). |
| *A. hebraeum* Koch | Nymph | Viremic guinea pig | - | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks Epidemiol Infect 106, 373-382. (Shepherd et al. 1991) . |
| *A. hebraeum* Koch | Adult | Viremic sheep | - | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks Epidemiol Infect 106, 373-382. (Shepherd et al. 1991). |
| *A. hebraeum* Koch | Adult | Viremic cattle | + | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks Epidemiol Infect 106, 373-382. (Shepherd et al. 1991). |
| *D. marginatus* (Sulzer) | Nymph | Viremic little suslik | + | Adults | Kondratenko V 1976. Importance of ixodid ticks in transmitting and preserving the Crimean hemorrhagic fever agent in infection foci. Parazitolgia, 297-302.(Kondratenko 1976). |
| *D. marginatus* (Sulzer) | Adult | Viremic little suslik, rabbit | + | F1 , F2 larvae nymphs, an d adults, little suslik, rabbits | Kondratenko V. 1976. Importance of ixodid ticks in transmitting and preserving the Crimean hemorrhagic fever agent in infection foci. Parazitolgiya, 297-302. (Kondratenko 1976). |
| *D. marginatus* (Sulzer) | Adult | Viremic calf | - | - | Zarubinsky VY, Kondratenko VF, Blagoveschchenskaya NM, Zarvbina LV, and Kuchin VV. 1976. Susceptibility of calves and lambs to Crimean hemorrhagic fever virus. Tezisy Dokl 9 Vses Konf Prirod Ochag Bolez Chelov Zhivot (Omsk), 130-131 (Zarubinsky et al. 1976). |

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| *A. variegatum* (Fabricius) | Adult | Intracoelomic inoculation | + | - | Gonzalez JP, Cornet JP, Wilson ML, and Camicas JL. 1991. Crimean-Congo haemorrhagic fever virus replication in adult *Hyalomma truncatum* and *Amblyomma variegatum* ticks. Res Virol 142, 483-488 (Gonzalez et al. 1991). |
| *A. variegatum* (Fabricius) | Larvae and Nymph | Intracoelomic inoculation | + | New born mice<br><br>Adults and nymph | Faye O, Cornet J, Camicas J, Fontenille D, and Gonzalez J. Experimental transmission of Crimean-Congo hemorrhagic fever virus role of 3 vector species in the maintenance and transmission cycles in Senegal. Parasite 6, 27-32. (Faye et al. 1999a). |
| *B. decoloratus* (Koch) | Adult | Viremic cattle | + | - | Shepherd A, Swanepoel R, Shepherd S, Leman P, and Mathee O. 1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks Epidemiol Infect 106, 373-382. (Shepherd et al. 1991). |
| *A. walkerae* Clifford, Kohls and Hoogstraal | Nymph | Intracoelomic inoculation | - | - | Shepherd A, Swanepoel R, Cornel A, and Mathee O. 1989. Experimental studies on the replication and transmission of Crimean-Congo hemorrhagic fever virus in some African tick species. Am J Trop Med Hyg 40, 326-333. (Shepherd et al. 1989a).<br><br>Shepherd AJ, Leman PA, and Swanepoel R. 1989. Viremia and Antibody Response of Small African and Laboratory Animals to Crimean-Congo Hemorrhagic Fever Virus InfectionAm J Trop Med Hyg 40, 541-547. (Shepherd et al. 1989b). |
| *A. walkerae* Clifford, Kohls and Hoogstraal | Adult | Intracoelomic inoculation | - | - | Shepherd A, Swanepoel R, Cornel A, and Mathee O. 1989. Experimental studies on the replication and transmission of Crimean-Congo hemorrhagic fever virus in some African tick species. Am J Trop Med Hyg 40, 326-333. (Shepherd et al. 1989a).<br><br>Shepherd AJ, Leman PA, and Swanepoel R. 1989. Viremia and Antibody Response of Small African |

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| *O. porcinus* Walton | Nymph | Intracoelomic inoculation | - | - | Shepherd A, Swanepoel R, Cornel A, and Mathee O. 1989. Experimental studies on the replication and transmission of Crimean-Congo hemorrhagic fever virus in some African tick species. Am J Trop Med Hyg 40, 326-333. (Shepherd et al. 1989a).<br><br>Shepherd AJ, Leman PA, and Swanepoel R. 1989. Viremia and Antibody Response of Small African and Laboratory Animals to Crimean-Congo Hemorrhagic Fever Virus Infection Am J Trop Med Hyg 40, 541-547. (Shepherd et al. 1989b). |
| *O. porcinus* Walton | Adult | Intracoelomic inoculation | - | - | Shepherd A, Swanepoel R, Cornel A, and Mathee O. 1989. Experimental studies on the replication and transmission of Crimean-Congo hemorrhagic fever virus in some African tick species. Am J Trop Med Hyg 40, 326-333. (Shepherd et al. 1989a).<br><br>Shepherd AJ, Leman PA, and Swanepoel R. 1989. Viremia and Antibody Response of Small African and Laboratory Animals to Crimean-Congo Hemorrhagic Fever Virus Infection Am J Trop Med Hyg 40, 541-547. (Shepherd et al. 1989b). |
| *O. savignyi* (Auduoin) | Nymph | Intracoelomic inoculation | - | - | Shepherd A, Swanepoel R, Cornel A, and Mathee O. 1989. Experimental studies on the replication and transmission of Crimean-Congo hemorrhagic fever virus in some African tick species. Am J Trop Med Hyg 40, 326-333. (Shepherd et al. 1989a).<br><br>Shepherd AJ, Leman PA, and Swanepoel R. 1989. Viremia and Antibody Response of Small African and Laboratory Animals to |

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| | | | | | Crimean-Congo Hemorrhagic Fever Virus Infection Am J Trop Med Hyg 40, 541-547. (Shepherd et al. 1989b). |
| *O. savignyi* (Auduoin) | Adult | Intracoelomic inoculation | - | - | Shepherd A, Swanepoel R, Cornel A, and Mathee O. 1989. Experimental studies on the replication and transmission of Crimean-Congo Hemorrhagic fever virus in some African tick species. Am J Trop Med Hyg 40, 326-333. (Shepherd et al. 1989a).<br><br>Shepherd AJ, Leman PA, and Swanepoel R. 1989. Viremia and Antibody Response of Small African and Laboratory Animals to Crimean-Congo Hemorrhagic Fever Virus Infection Am J Trop Med Hyg 40 541-547. (Shepherd et al. 1989b). |
| *O. sonrai* Sautet and Witkowski | Nymph | Viremic suckling mouse | - | - | Durden L, Logan TM, Wilson ML, and Linthicum KJ. 1993. Experimental vector incompetence of the soft tick *Ornithodorus sonrai* (Acari, Argasidae), for Crimean-Congo-hemorrhagic fever virus. J Med Entomol 30, 493-496 (Durden et al. 1993). |
| *O. sonrai* Sautet and Witkowski | Adult | Viremic suckling mouse | - | - | Durden L, Logan TM, Wilson ML, and Linthicum KJ. 1993. Experimental vector incompetence of the soft tick *Ornithodorus sonrai* (Acari, Argasidae), for Crimean-Congo-hemorrhagic fever virus. J Med Entomol 30, 493-496 (Durden et al. 1993). |

**Table 4.** Data on serological surveillance on CCHF in domestic animals

| ***LOCATION*** | ***SPECIES*** | ***SEROLOGY*** | ***YEAR*** | ***REFERENCE*** |
|---|---|---|---|---|
| *Albania* | *Goats* | *Serological* | *2003-05* | *Papa A, Velo E, Papadimitriou E, Cahani G, Kota M, Bino S. 2009. Ecology of the Crimean-Congo Hemorrhagic Fever Endemic Area in Albania. Vector Borne Zoonotic Dis. Apr 29. [Epub ahead of print] (Papa* |

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| | | surveillance | | et al. 2009) |
| Central African Republic | Zebu cattle | Serological surveillance | 1992-93 | Guilherme JM, Gonella-Legall C, Legall F, Nakoume E, Vincent J. Seroprevalence of five arboviruses in Zebu cattle in the Central African Republic. 1996. Trans R Soc Trop Med Hyg. Jan-Feb;90(1):31-3. (Guilherme et al. 1996 ) |
| China | Sheep, camels | Serological surveillance | 2004-05 | Sun S, Dai X, Muhetaer , et al. Epidemiology and Phylogenetic Analysis of the Crimean-Congo Hemorrhagic Fever Viruses in Xinjiang, China. 2009. J Clin Microbiol 47, 2536-2543.(Sun et al. 2009) |
| China | Sheep | Serological surveillance | 2001 | Qing T., Saijo M., Lei H., Niikura M., Maeda A., Ikegami T., Xinjung W., Kurane I., Morikawa S. 2003. Detection of immunoglobulin G to Crimean-Congo hemorrhagic fever virus in sheep sera by recombinant nucleoprotein-based enzyme linked immunosorbent and immunofluorescence assays. J Virol Methods 108 111-116 (Qing et al. 2003) |
| Greece | Sheep | Serological surveillance | 1971-76 | Avsic-Zupanc. 2007. Epidemiology of CCHF in the Balkans. In: "Crimean Congo Haemorrhagic Fever-A global prespective" (Ergonul O, and Whitehouse CA, eds.) Springer 75-88.(Avsic-Zupanc 2007 ) |
| Kosovo | Sheep, cattle | Serological surveillance | 1977 | Avsic-Zupanc. 2007. Epidemiology of CCHF in the Balkans. In: "Crimean Congo Haemorrhagic Fever-A global prespective" (Ergonul O, and Whitehouse CA, eds.) Springer 75-88.(Avsic-Zupanc 2007 ) |
| Niger | Cattle, sheep, goats, camels | Serological surveillance | 1984-88 | Mariner JC, Morrill J, Ksiazek TG. 1995.Antibodies to hemorrhagic fever viruses in domestic livestock in Niger: Rift Valley fever and Crimean-Congo hemorrhagic fever. Am J Trop Med Hyg. Sep;53(3):217-21. (Mariner et al. 1995 ) |
| Senegal | Birds | Serological surveillance | 1991-92 | Zeller HG, Cornet J.P and Camicas JL.1994. Crimean-Congo haemorrhagic fever virus infection in birds: field investigations in Senegal. Res. Virol. 145, 105-109. (Zeller et al. 1994b) |
| Senegal | Sheep | Serological surveillance | 1986-87 | Wilson ML, LeGuenno B, Guillaud M, Desoutter D, Gonzalez JP, Camicas JL. 1990. Distribution of Crimean-Congo hemorrhagic fever viral antibody in Senegal: environmental and vectorial correlates. Am J Trop Med Hyg. Nov;43(5):557-66. (Wilson et al. 1990 ) |
| South Africa | Ostriches | Serological surveillance | 1984 | Shepherd AJ, Swanepoel R, Leman P.A, Shepherd SP. 1987. Field and laboratory investigation of Crimean-Congo haemorrhagic fever virus (Nairovirus, family Bunyaviridae) infection in birds. Trans R Soc Trop Med Hyg. 81(6):1004-7. (Shepherd et al. 1987) |
| Sudan | Ruminats | Serological surveillance | 1997 | Hassanein KM, El-Azazy OM, Yousef HM. 1997. Detection of Crimean-Congo haemorrhagic fever virus antibodies in humans and imported livestock in Saudia Arabia. Trans R SOC Trop Med Hyg 91:356-537. (Hassanein et al. 1997) |
| Egypt | Domestic buffaloes, cattle, sheep and goat, donkeys, horses, mules, pigs and dogs. | Serological surveillance | 1977 | Darwish M A, Imam I Z E, Omar F M & Hoogstraal H. 1977. A seroepidemiological survey for Crimean-Congo hemorrhagic fever virus in humans and domestic animals in Egypt. J. Egypt. Public Health Assoc. 52: 156-63. (Darwish et al. 1977) |
| Iran | Cattle sheep and goats | Serological surveillance | 1975 | Saidi S, Casals J, Faghih MA. 1975. Crimean hemorrhagic fever-Congo (CHE'-C) virus antibodies in man, and in domestic and small mammals, in Iran. Am J Trop Med Hyg 24:353-357 (Saidi et al. 1975) |
| Iraq | Cattle sheep and goats | Serological surveillance | 1975 | Tantawi HH, Shony MO, Al-Tikriti SK. 1981. Antibodies to Crimean-Congo haemorrhagic rever virus in domestic animals in Iraq: a seroepidemiological survey. Int J Zoonoses 8:115-120. (Tantawi et al. 1981) |

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| *United Arab Emirates* | *Cattle sheep and goats* | *Serological surveillance* | *1994-1995* | *Khan AS, Maupin GO, Rollin PE, Noor AM, Shurie HH, Shalabi AG, Wasef S, Haddad YM,nSadek R, Ijaz K, Peters CJ, Ksiazek TG.1997. An outbreak of Crimean-Congo hemorrhagic fever in the United Arab Emirates, 1994-1995. Am J Trop Med Hyg 57:519-525. (Khan et al. 1997)* |
| *Zimbabwe* | *Cattle* | *Serological surveillance* | *1981-84* | *Swanepoel R, Shepherd AJ, Leman PA, Shepherd SP, McGillivray GM, Erasmus MJ, Searle LA, Gill DE. 1987.Epidemiologic and clinical features of Crimean-Congo hemorrhagic fever in southern Africa. Am J Trop Med Hyg. Jan;36(1):120-32. (Swanepoel et al. 1987)* |
| *South Africa* | *Cattle* | *Serological surveillance* | *1981-84* | *Swanepoel R, Shepherd AJ, Leman PA, Shepherd SP, McGillivray GM, Erasmus MJ, Searle LA, Gill DE. 1987.Epidemiologic and clinical features of Crimean-Congo hemorrhagic fever in southern Africa. Am J Trop Med Hyg. Jan;36(1):120-32. (Swanepoel et al. 1987)* |

Table 5**. Experimental studies on CCHF**

| ***REFERENCES*** | ***INVESTIGATION ON VECTORS*** | ***INVESTIGATION ON ANIMALS*** |
|---|---|---|
| *Burt FJ, Swanepoel R, Braack LE. 1993. Enzyme-linked immunosorbent assays for the detection of antibody to Crimean-Congo haemorrhagic fever virus in the sera of livestock and wild vertebrates. Epidemiol Infect Dec;111, 547-* | *No* | *Cattle, sheep* |

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| *57. (Burt et al. 1993 )* | | |
| *Dohm DJ, Logan TM, Linthicum KJ, Rossi CA, Turell MJ.1996. Transmission of Crimean-Congo hemorrhagic fever virus by Hyalomma impeltatum (Acari:Ixodidae) after experimental infection. J Med Entomol Sep;33, 848-51. (Dohm DJ 1996)* | *H. impeltatum* | *Guinea pigs* |
| *Faye 0, Cornet JP, Camicas TL, Fontenille D, & Gonzalez T.1999. Transmission experimentale du virus de la fievre hemorragique de Crimee-Congo : place de trois especes vectrices dans les cycles de maintenance et de transmission au Senegal. Parasite. 6, 27-32 (Faye et al. 1999a)* | *A.variegatum,*<br>*H.m. marginatum*<br>*H.m. rufipes*<br>*H. truncatum* | *No* |
| *Faye 0, Fontenille D, Thonnon J, Gonzalez J P, Cornet J P & Camicas JL. 1999. Transmission experimentale du virus de la fievre hemorragique de Crimee-Congo par la tique Rhipicephalus evertsi evertsi (Acarina Ixodidae).Bull Soc Pathol Exot 92, 143-147 (Faye et al. 1999b)* | *R. e. evertsi* | *No* |
| *Gordon SW, Linthicum KJ, Moulton JR. Transmission of Crimean-Congo hemorrhagic fever virus in two species of Hyalomma ticks from infected adults to cofeeding immature forms.1993. Am J Trop Med Hyg 48,576-80. (Gordon et al. 1993)* | *H. truncatum*<br>*H. impeltatum* | *Guinea pigs* |
| *Logan TM, Linthicum KJ, Bailey CL, Watts DM, Dohm DJ, Moulton JR. 1990. Replication of Crimean-Congo hemorrhagic fever virus in four species of ixodid ticks (Acari) infected experimentally. J Med Entomol 27,537-42 (Logan et al. 1990).* | *H. dromedarii,*<br>*H. impeltatum,*<br>*H. truncatum*<br>*R. appendiculatus* | *No* |
| *Okorie TG. Comparative studies on the vector capacity of the different stages of Amblyomma variegatum Fabricius and Hyalomma rufipes Koch for Congo virus, after intracoelomic inoculation. 1991. Vet Parasitol 38,215-23 (Okorie 1991)* | *H. m. rufipes*<br>*A. variegatum* | *No* |
| *Shepherd AJ, Swanepoel R, Leman PA, Shepherd SP. 1987.Field and laboratory investigation of Crimean-Congo haemorrhagic fever virus (Nairovirus, family Bunyaviridae) infection in birds. Trans R Soc Trop Med Hyg 81,1004-7.(Shepherd et al. 1987)* | *No* | *Domestic chickens, Guinea fowl* |
| *Shepherd AJ, Leman PA, Swanepoel R. 1989.Viremia and antibody response of small African and laboratory animals to Crimean-Congo hemorrhagic fever virus infection.1989. American Journal of Tropical Medicine & Hygiene. 40(5):541-7. (Shepherd et al. 1989a)* | *No* | *Small African wild mammals, laboratory animals* |
| *Shepherd AJ, Swanepoel R, Shepherd SP, Leman PA, Mathee O.1991. Viraemic transmission of Crimean-Congo haemorrhagic fever virus to ticks. Epidemiol Infect 106, 373-82 (Shepherd et al. 1991)* | *H. m. rufipes,*<br>*H. truncatum,* | *Cattle, sheep, scrub hares, white tailed rats, guinea-pigs* |

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| | *R. e. evertsi,*<br>*R. e. mimeticus,*<br>*R. appendiculatus,*<br>*R. simus,*<br>*A. hebraeum,*<br>*B. decoloratus* | |
| *Shepherd AJ, Swanepoel R, Cornel AJ, Mathee O. Experimental studies on the replication and transmission of Crimean-Congo hemorrhagic fever virus in some African tick species.1989. Am J Trop Med Hyg 40, 326-31 (Shepherd et al. 1989a)* | *H. m. rufipes,*<br>*H. truncatum,*<br>*R. e.mimeticus,*<br>*A. hebraeum* | *Sheep* |
| *Swanepoel R, Leman PA, Burt FJ, Jardine J, Verwoerd DJ, Capua I, Brückner GK, Burger WP. 1998. Experimental infection of ostriches with Crimean-Congo haemorrhagic fever virus. Epidemiol Infect 121, 427-32 (Swanepoel et al. 1998)* | *No* | *Ostriches* |
| *Zeller HG, Cornet JP, Camicas JL. 1994. Experimental transmission of Crimean-Congo hemorrhagic fever virus by west African wild ground-feeding birds to Hyalomma marginatum rufipes ticks. Am J Trop Med Hyg 50,676-81(Zeller et al. 1994a)* | *H. m. rufipes* | *Wild birds, domestic chickens* |

Table 6. **Field studies on CCHF**

| ***REFERENCES*** | ***INVESTIGATION ON VECTORS*** | ***INVESTIGATION ON ANIMALS*** | ***INVESTIGATION ON HUMANS*** |
|---|---|---|---|

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|---|---|---|---|
| *Altaf A, Luby S, Ahmed AJ, Zaidi N, Khan AJ, Mirza S, McCormick J, Fisher-Hoch S. 1998. Outbreak of Crimean-Congo haemorrhagic fever in Quetta, Pakistan: contact tracing and risk assessment. Trop Med Int Health 3, 878-82.(Altaf et al. 1998)* | *No* | *No* | *Yes* |
| *Athar M, Baqai H, Ahmad M, Khalid MA, Bashir N, Ahmad A, Balouch A, and Bashir K. 2003. Short report: Crimean-Congo hemorrhagic fever outbreak in Rawalpindi, Pakistan, February 2002 Am J Trop Med Hyg 69, 284-287.(Athar et al. 2003)* | *No* | *No* | *Yes* |
| *Bakir M, Ugurlu M, Basak D, Bodur H, Mehmet A, Tasyaran M, Vahaboglu H, and Group TCS. 2005. Crimean-Congo haemorrhagic fever outbreak in Middle Anatolia: a multicentre study of clinical features and outcome measures. J Med Microbiol 385-389.(Bakir et al. 2005)* | *No* | *No* | *Yes* |
| *Baskerville A, Satti A, Murphy F, and Dih S. 1981. Congo-Crimean haemorrhagic fever in Dubai: histopathological studies. J Clin Pathol 34, 871-874* | *No* | *No* | *Yes* |
| *Ertugrul B, Yavuz U, Kamil Y, Cetin T, Serkan O, Ozlem S, Ahmet C, Barcin O, Nermin E, and Serhan. S. 2009. An outbreak of Crimean-Congo hemorrhagic fever in western Anatolia, Turkey. Int J Infect Dis May 2009 acessed on 30 july 2009.(Ertugrul et al. 2009)* | *No* | *No* | *Yes* |
| *Burt FJ, Swanepoel R, and Braack LE. 1993. Enzyme - linked immunosorbent assays for the detection of antibody to Crimean-Congo haemorrhagic fever virus in the sera of livestock and wild vertebrates. Epidemiol Infect 111, 547-557.(Burt et al. 1993 )* | *No* | *Wild vertebrates* | *No* |
| *Butenko AM, Donets MA, Durov VI, Tkachenko V, A.., Perelatov VD, and Chumakov MP. 1971. Isolation of CHF virus from Rhipicephalus rossicus and Dermacentor marginatus ticks in Rostov Oblast and Krasnodar region. Trudy Inst Polio Virus Entsef Akad Med Nauk SSSR 19, 45-47. (Butenko et al. 1971)* | *R. rossicus*<br>*D. marginatus* | *No* | *No* |
| *Darwish MA, Hoogstraal H, Roberts TJ, Ghazi R, Amer T. 1983.A sero-epidemiological survey for Bunyaviridae and certain other arboviruses in Pakistan. Trans R Soc Trop Med Hyg 77,446-50 (Darwish et al. 1983).* | *No* | *Rodents, domestic animals* | *Yes* |
| *Drosten C, Minnak D, Emmerich P, Schmitz H, and Reinicke T. 2002. Crimean-Congo hemorrhagic fever in Kosovo. J Clin Microbiol 40, 1122-1123 (Drosten et al. 2002)* | *No* | *No* | *Yes* |
| *Filipe A, Calisher C, and Lazuick J. 1985. Antibodies to Congo-Crimean haemorrhagic fever, Dhori, Thogoto and Bhanja viruses in southern Portugal. Acta Virol 29, 324-328. (Filipe et al.* | *No* | *No* | *Yes* |

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| *1985)* | | | |
| *Fisher-Hoch S, McCormick J, Swanepoel R, Van Middlekoop A, Harvey S, and Kustner H. 1992. Risk of human infections with Crimean-Congo hemorrhagic fever virus in a South African rural community. Am J Trop Med Hyg 47, 337-345.(Fisher-Hoch et al. 1992).* | *No* | *Cattle, sheep, goats* | *Yes* |
| *Gonzalez JP, LeGuenno B, Guillaud M, Wilson ML. A fatal case of Crimean-Congo haemorrhagic fever in Mauritania: virological and serological evidence suggesting epidemic transmission. Trans R Soc Trop Med Hyg. 1990. 84,573-6. (Gonzalez et al. 1990 )* | *No* | *Sheep* | *Yes* |
| *Grigor'ev M, Evchenko I, and Shaposhnikova L. 2001. Role of some wild birds and mammals in the natural foci of Crimean haemorrhagic fever in Stavropol' region. Zh Mikrobiol Epidemiol Immunobiol 6 Suppl, 92-95.(Grigor'ev et al. 2001)* | *H.m.marginatum* | *Wild mammals, birds* | *No* |
| *Gunes T, Engin A, Poyraz O, Elaldi N, Kaya S, Dokmetas I, Bakir M, and Cinar Z. 2009. Crimean-Congo hemorrhagic fever virus in high-risk population, Turkey. Emerg Infect Dis 15, 461-464.(Gunes et al. 2009).* | *No* | *No* | *Yes* |
| *Hassanein K, El-Azazy O, and Yousef H. 1997. Detection of Crimean-Congo haemorrhagic fever virus antibodies in humans and imported livestock in Saudia Arabia Trans R Soc Trop Med Hyg 91, 356-537 (Hassanein et al. 1997)* | *No* | *Cattle, sheep, goats, camels, horses* | *Yes* |
| *Izadi S, Naieni K, Madjdzadeh S, and Nadim A. 2004. Crimean-Congo hemorrhagic fever in Sistan and Baluchestan Province of Iran, a case-control study on epidemiological characteristics. Int J Infect Dis 8, 299-306.(Izadi et al. 2004).* | *No* | *No* | *Yes* |
| *Jamil B, Hasan R, Sarwari A, Burton J, Hewson R, and Clegg C. 2005. Crimean-Congo hemorrhagic fever: experience at a tertiary care hospital in Karachi, Pakistan. Trans R Soc Trop Med Hyg 99, 577-584 (Jamil et al. 2005 ).* | *No* | *No* | *Yes* |
| *Kaul H, Shetty P, Ghalsasi G, and Dhanda V. 1990. Survey of ticks (Acarina: Ixodidae) for Crimean haemorrhagic fever virus activity in Jammu & Kashmir state, India. Indian J Med Res 91, 5-8. (Kaul et al. 1990)* | *B. microplus,*<br>*D.raskamensis,*<br>*H. bispinosa,*<br>*H. cornupunctata,*<br>*H. intermedia,*<br>*H. montgomeryi,*<br>*H. a. anatolicum,* | *Cattle, buffaloes, sheep, goats,camels, horses, dogs, mules, small mammals, rodents* | *No* |

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| | *H. detritum,*<br>*H. dromedarii,*<br>*H. m. isaaci,*<br>*I. himalayensis,*<br>*I. kashmiricus,*<br>*I. ovatus,*<br>*N. monstrosum,*<br>*R. sanguineus* | | |
| *Kemp GE, Causey OR, Setzer H. W., and Moore DL. 1974. Isolation of viruses from wild mammals in West Africa, 1966-1970. J Wildl Dis 10, 279-293.(Kemp et al. 1974).* | *No* | *Wild mammals* | *No* |
| *Maltezou HC, Papa A, Tsiodras S, Dalla V, Maltezos E, and Antoniadis A. 2009. Crimean-Congo hemorrhagic fever in Greece: a public health perspective. Int J Infect Dis Jan 18 [Epub ahead of print](Maltezou et al. 2009)* | *No* | *No* | *Yes* |
| *Mariner J, Morrill J, and 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.(Mariner et al. 1995 )* | *No* | *Cattle, sheep, goats, camels* | *No* |
| *Markeshin S, Smirnova S, and Evstaf'ev I. 1991. An evaluation of the status of natural foci of Crimean-Congo hemorrhagic fever in the Crimea. Zh Mikrobiol Epidemiol Immunobiol 9, 47-50. (Markeshin et al. 1991)* | *Ixodes spp., D.marginatus* | *No* | *No* |
| *Midilli K, Midilli M, Gargılı1 A, Ergonul O, Şengöz;G, Ozturk R, Bakar M, and Jongejan F. 2007. Imported Crimean-Congo hemorrhagic fever cases in Istanbul BMC Infect Dis 7, 54.(Midilli et al. 2007).* | *No* | *No* | *Yes* |
| *Rai MA, Khanani MR, Warraich HJ, Hayat A, and Ali SH. 2008. Crimean-Congo Hemorrhagic Fever in Pakistan. J Med Virol 80, 1004-1006.(Rai et al. 2008)* | *No* | *No* | *Yes* |
| *Onishchenko G, Tumanova I, Vyshemirskiĭ O, Kuhn J, Seregin S, Tiunnikov G, Petrova I, Tishkova F, Ospanov K, Kazakov S et al. 2005. Study of virus contamination of Ixodes ticks in the foci of Crimean-Congo hemorrhagic fever in Kazakhstan and Tajikistan. Zh Mikrobiol Epidemiol Immunobiol 1, 27-31.(Onishchenko et al. 2005)* | *H. asiaticum*<br>*D. niveus*<br>*H. anatolicum* | *No* | *No* |

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| *Ozkurt Z, Kik iI, Erol S, Erdem F, Yilmaz N, Parlak M, Gundogdu M, and Tasyaran M. 2006. Crimean-Congo hemorrhagic fever in Eastern Turkey: clinical features, risk factors and efficacy of ribavirin therapy. J Infect 52, 207-215.(Ozkurt et al. 2006) .* | *No* | *No* | *Yes* |
| *Papa A, Velo E, Papadimitriou E, Cahani G, Kota M, and Bino S. 2009. Ecology of the Crimean-Congo Hemorrhagic Fever Endemic Area in Albania. Vector Borne Zoonotic Dis April 29 [Epub ahead of print] (Papa et al. 2009)* | *Hyalomma spp.* | *Cattle, goats, birds* | *No* |
| *Rechav Y, Zeederberg ME, and Zeller DA. 1987. Dynamics of African tick (Acari : Ixodoidea) populations in a natural Crimean-Congo hemorrhagic fever focus J Med Entomol 24, 575-583(Rechav et al. 1987)* | *H. truncatum*<br>*H. rufipes.*<br>*R. e.evertsi*<br>*A. marmoreum*<br>*M. winthemi*<br>*Argas spp.* | *Large and small mammals* | *No* |
| *Rechav Y. 1986. Seasonal activity and hosts of the vectors of Crimean-Congo haemorrhagic fever in South Africa S Afr Med J 69, 364-368.(Rechav 1986)* | *H. truncatum*<br>*H. m. rufipes* | *Mammals, birds* | *No* |
| *Saidi S, Casals J, and Faghih MA. 1975. Crimean hemorrhagic fever-Congo (CHF-C) virus antibodies in man, and in domestic and small mammals, in Iran. Am J Trop Med Hyg 24, 353-357.(Saidi et al. 1975)* | *No* | *Domestic, small mammals* | *Yes* |
| *Karti S, Odabasi Z, and Korten V, et al. 2004. Crimean-Congo hemorrhagic fever in Turkey Emerg Infect Dis 19, 1379-1384.(Karti et al. 2004)* | *No* | *No* | *Yes* |
| *Sheikh AS, Sheikh AA, Sheikh N, Shan R, Asif M, Afridi M, and Tarik Malik M. 2005. Bi-annual surge of Crimean-Congo haemorrhagic fever (CCHF): a five-year experience. Int J Infect Dis, 9, 37-42. (Sheikh et al. 2005).* | *No* | *No* | *Yes* |
| *Shepherd AJ, Swanepoel R, Shepherd SP, McGillivray GM, and Searle LA. 1987 Antibody to Crimean-Congo hemorrhagic fever virus in wild mammals from southern Africa. Am J Trop Med Hyg 36, 133-142.(Shepherd et al. 1987 )* | *No* | *Wild mammals* | *No* |
| *Shepherd AJ, Swanepoel R, Leman PA, Shepherd SP. Field and laboratory investigation of Crimean-Congo haemorrhagic fever virus (Nairovirus, family Bunyaviridae) infection in birds. Trans R Soc Trop Med Hyg 81, 1004-1007. (Shepherd et al. 1987)* | *No* | *Ostriches, birds* | *Yes* |

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| *Swanepoel R, Shepherd A, Leman P, Shepherd S, and Miller G. 1985b. A common-source outbreak of Crimean-Congo haemorrhagic fever on a dairy farm. S Afr Med J 68, 635-637(Swanepoel et al. 1985b)* | *No* | *No* | *Yes* |
| *Swanepoel R, Shepherd A, Leman P, and Shepherd S. 1985a. Investigations following initial recognition of Crimean-Congo haemorrhagic fever in South Africa and the diagnosis of 2 further cases. S Afr Med J 68, 638-641.(Swanepoel et al. 1985a)* | *No* | *Cattle* | *Yes* |
| *Swanepoel R, Shepherd AJ, Leman PA, Shepherd SP, McGillivray GM, Erasmus MJ, Searle LA, and Gill DE. 1987. Epidemiologic and clinical features of Crimean-Congo hemorrhagic fever in Southern Africa. Am J Trop Med Hyg 36, 120-132(Swanepoel et al. 1987).* | *No* | *Cattle* | *Yes* |
| *Tonbak S, Aktas M, Altay K, Azkur A, Kalkan A, Bolat Y, Dumanli N, and Ozdarendeli A. 2006. Crimean-Congo hemorrhagic fever virus: genetic analysis and tick survey in Turkey. J Clin Microbiol 44, 4120-4124. (Tonbak et al. 2006)* | *H. m. marginatum*<br>*R. bursa*<br>*B. annulatus*<br>*H. sulcata* | *Cattle, sheep, goats* | *No* |
| *Zeller H, Cornet J, and Camicas J. 1994b. Crimean-Congo haemorrhagic fever virus infection in birds: field investigations in Senegal. Res Virol 145, 105-109(Zeller et al. 1994b).* | *H.m.rufipes* | *Birds* | *No* |
| *Wilson M, Gonzalez J, Cornet J, and Camicas J. 1991. Transmission of Crimean-Congo haemorrhagic fever virus from experimertally infected sheep to Hyalomma truncatum ticks. Res Virol 142, 395-404.(Wilson et al. 1990 )* | *No* | *Sheep* | *Yes* |

Table 7. **Species of quick migratory birds that fly above Italy (from Guberti 2005, personal comm.)**

| TAXONOMY NAME | SCIENTIFIC COMMON NAME |
|---|---|

| | | | |
|---|---|---|---|
| Order Ciconiformi | | | |
| | Family Ardeidae | *Ixobrychus minutus* | Little bittern (Fig.18) |
| | | *Nycticorax nycticorax* | Night heron |
| | | *Ardeola ralloides* | Squacco heron |
| | | *Ardea purpurea* | Purple heron (Fig.17) |
| Order Anseriformi | | | |
| | Family Anatidae | *Anas acuta* | Pintail |
| | | *Anas querquedula* | Garganey |
| Order Caradriformi | | | |
| | Family Recurvirostridae | *Himantopus himantopus* | Black-winged stilt |
| | Family Burinidae | *Burhinus oedicnemus* | Stone curlew |
| | Family Glareolidae | *Glareola pratincola* | Collared pratincole |
| | Family Charadriidae | *Charadrius dubius* | Little ringed plover |
| | | *Charadrius hiaticula* | Ringed plover |
| | | *Pluvialis squatarola* | Grey plover |
| | Family Scolopacidae | *Calidris canutus* | Knot |
| | | *Calidris alba* | Sanderling |
| | | *Calidris ferruginea* | Curlew sandpiper |
| | | *Calidris minuta* | Little stint |
| | | *Calidris temminckii* | Temminck's stint |
| | | *Philomachus pugnax* | Ruff |
| | | *Scolopax rusticola* | Woodcock |
| | Family Tringidae | *Limosa limosa* | Black-tailed godwit |
| | | *Limosa lapponica* | Bar-tailed godwit |
| | | *Numenius phaeopus* | Whimbrel |
| | | *Tringa nebularia* | Greenshank |
| | | *Tringa glareola* | Wood sandpiper |
| | | *Tringa ochropus* | Green sandpiper |

| | | | |
|---|---|---|---|
| | | *Actitis hypoleucos* | Common sandpiper |
| | | *Tringa erythropus* | Spotted redshank |
| | | *Tringa stagnatilis* | Marsh sandpiper |
| | Family Arenarinae | *Arenaria interpres* | Turnstone |
| | Family Laridae | *Larus fuscus* | Lesser black-backed gull |
| | Family Sternidae | *Chlidonias niger* | Black tern |
| | | *Chlidonias hybridus* | Whiskered tern |
| | | *Sterna hirundo* | Common tern |
| | | *Sterna albifrons* | Little tern |
| | | *Sterna sandvicensis* | Sandwich tern |
| Order Passeriformi | | | |
| | Family Irudinidae | *Hirundo rustica* | Swallow |
| | | *Delichon urbic*a | House martin |
| | | *Riparia riparia* | Sand martin |
| | Family Motacillidae | *Anthus trivial*is | Tree pipit |
| | | *Motacilla flava* | Yellow wagtail |
| | | *Anthus campestris* | Tawny pipit |
| | Family Turdidae | *Saxicola rubetra* | Whinchat |
| | | *Luscinia megarhynchos* | Nightingale |
| | Family Silvidae | S*ylvia borin* | Garden warbler |
| | | *Sylvia communis* | Common whitethroat |
| | | *Sylvia atricapilla* | Blackcap |
| | | *Sylvia cantillans* | Subalpine warbler |
| | | *Sylvia nisoria* | Barred warbler |
| | | *Sylvia curruca* | Lesser whitethroat |
| | | *Acrocephalus scirpaceus* | Reed warbler |
| | | *Acrocephalus arudinaceus* | Great reed warbler |
| | | *Acrocephalus palustris* | Marsh warbler |

| | | |
|---|---|---|
| | *Locustella luscinioides* | Savi's warbler |
| | *Acrocephalus schoenobaenus* | Sedge warbler |
| | *Locustella naevia* | Grasshopper warbler |
| | *Hippolais polyglotta* | Melodious warbler |
| | *Hippolais icterina* | Icterine warbler |
| | *Sylvia atricapilla* | Blackcap |
| | *Phylloscopus sibilatrix* | Wood warbler |
| | *Phylloscopus trochilus* | Willow warbler |
| | *Phylloscopus bonelli* ssp | Bonelli's warbler sp. |
| Family Muscicapidae | *Muscicapa striata* | Spotted flycatcher |
| | *Phoenicurus phoenicurus* | Common redstart |
| | *Saxicola rubetra* | Whinchat |
| | *Oenanthe hispanica* | Black-eared wheatear |
| | *Monticola saxatilis* | Rock thrush |
| Family Oriolidae | *Oriolus oriolus* | Golden oriole |
| Family Lanniida | *Lanius collurio* | Red-backed shrike |
| | *Lanius minor* | Lesser grey shrike |
| | *Lanius senator* | Woodchat shrike |
| Family Alaudidae | *Calandrella brachydactyla* | Short-toed lark |
| Order Accipitriformi | | |
| Family Accipitridae | *Pernis apivorus* | Honey buzzard |
| | *Milvus migrans* | Black kite |
| | *Circaetus gallicus* | Short-toed eagle |
| | *Circus pygargus* | Montagu's harrier |
| Family Falconidae | *Falco naumanni* | Lesser kestrel |
| | *Falco subbuteo* | Hobby |
| | *Falco eleonorae* | Eleonora's falcon |
| Order Strigiformi | | |

| | | |
|---|---|---|
| Family Strigidae | *Otus scops* | Scops owl |
| Order Galliformi | | |
| Family Phasianidae | *Coturnix coturnix* | Quail |
| Order Cuculiformi | | |
| Family Cuculidae | *Cuculus canorus* | Cuckoo |
| Order Caprimugiliformi | | |
| Family Caprimugilidae | *Caprimulgus europaeus* | Nightjar |
| Order Apodiformi | | |
| Family Apodidae | *Apus apus* | Common swift |
| | *Apus melba* | Alpine swift |
| Order Coraciphormi | | |
| Family Meropidae | *Merops apiaster* | European bee-eater |
| Family Upupidae | *Upupa epops* | Hoopoe |

***APPENDIX C DATA EXTRACTION***

## Search methods for identification of proper references

We searched the medical **electronic databases** (EDB) PubMed, OVID, Elsevier. The research also included the use of **MeSH Thesaurus** –with the Subject heading combination.
We also searched on the literature electronic free access data base of the US Armed Forces Pest Management Board (AFPMB).

We also checked the references database on Tick borne zoonoses of the Integrated Consortium on Ticks and Tick-borne Diseases ICTTD updated to 8 aprile 2009
Many references have been collected from the **bibliographies of references reviewed.**

We also searched for book contents in the web site Google books
The terms included in the search for the part of vectors and on the role played by tick vectors in the spread and maintenance of CCHF (in Eurasia in the EU, the Caucasus and Russia and also in Africa) were: tick vectors, Crimean Congo Haemorrhagic fever or CCHF crossed with the word population dynamics, abundance, competence, hosts, risk factors, prevention and control.

A specific research has been performed for the role of each class or order of animals involved in the maintenance of CCHFV.
Research has also been performed for the aspects relating to history, aethiology, pathogenesis and clinical diangosis.
The details of the search are shown below.

All the titles and, where available, abstracts collected in the EDBs were reviewed. The criteria for exclusion were: a) wrong subject material; b) insufficient information (only title available or not comprehensive abstract); c) language (if the paper is in a language different from English, French or Italian and the translation is not available, only the abstract was considered). If possible, complete papers were collected.

**Grey literature** sources were searched by using the Scirus and Google scholar searching engines. To ensure the quality of the results different criteria of selection were applied: firstly the results were screened according to the specificity of the contents, the second level of control was based on the source of data: academic web sites (url-extension ".edu") and official institution (url-extension ".org") were considered as additional value to guarantee the quality of the contents. The following step for the screening of the results is the Pdf format of the document searched to prevent changes of contents. The quality of the sources was further assessed according to classical criteria as the presence of the author name, the year of publication, the source and the references.
All the duplication from the results of the searches were considered only once.

**Results**

The number and tipology of items retrieved for each research are reported in the following tables:

| Queries | Pub med | | | | Sciencedirect | | | Ovid |
|---|---|---|---|---|---|---|---|---|
| Key words | Free | | Mesh | | Free | | | Free |
| | **Article** | **Rev** | **Article** | **Rev** | **Article** | **Review** | **Ref work** | **Article** |
| **Tick vectors CCHF** | **81** | **13** | **55** | **10** | **136** | **1** | **1** | **119** |
| **Tick vectors CCHF population dynamics** | **1** | **1** | **1** | **0** | **24** | **0** | **0** | **88** |
| **Tick vectors CCHF abundance** | **1** | **0** | **0** | **0** | **12** | **0** | **0** | **16** |
| **Tick vectors CCHF Competence** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **6** |
| **Tick vectors CCHF hosts** | **4** | **0** | **1** | **1** | **102** | **0** | **1** | **75** |
| **Tick vectors CCHF risk factors** | **4** | **0** | **4** | **1** | **72** | **0** | **20** | **40** |
| **Tick CCHF prevention and control** | **9** | **4** | **0** | **0** | **60** | **0** | **0** | **109** |

**Research on Scirus with key words: CCHF Tick vectors**

1. Journal sources (71)
2. ScienceDirect (48)
3. MEDLINE / PubMed (17)
4. Pubmed Central (3)

| Queries | Pub med | | | | Sciencedirect | | |
|---|---|---|---|---|---|---|---|
| Key words | Free | | Mesh | | Free | | |
| | **Article** | **Rev** | **Article** | **Rev** | **Article** | **Review/book** | **Ref work** |
| **Tick vectors CCHF Reptiles** | **2** | **1** | **0** | **0** | **5** | **1** | **0** |
| **Tick vectors CCHF birds** | **24** | **4** | **10** | **1** | **45** | **13** | **1** |
| **Tick vectors CCHF wild mammals** | **24** | **1** | **0** | **0** | **37** | **13** | **0** |
| **Tick vectors CCHF Insectivorous or insectivora** | **7** | **0** | **6** | **0** | **3** | **0** | **0** |
| **Tick vectors CCHF lagomorphs or lagomorpha** | **12** | **0** | **11** | **0** | **2** | **2** | **0** |
| **Tick vectors CCHF small mammals** | **33** | **3** | **0** | **0** | **47** | **15** | **0** |
| **Tick CCHF rodents or rodentia** | **25** | **0** | **0** | **0** | **65** | **21** | **1** |

**Research on Scirus with key words:**

**tick vectors CCHF Reptiles**

1. Pubmed Central (1)
2. Hindawi Publishing Corporation (1)

**tick vectors CCHF Birds**

1. ScienceDirect (13)
2. MEDLINE / PubMed (2)
3. Royal Society Publishing (1)

**tick vectors CCHF Wild mammals**

1. ScienceDirect (14)
2. MEDLINE / PubMed (2)

**tick vectors CCHF small mammals**

1. ScienceDirect (14)
2. Pubmed Central (2)
3. MEDLINE / PubMed (2)

**tick vectors CCHF Insectivorous or insectivora**

ScienceDirect (1)

**tick vectors CCHF Hares or lagomorphs or lagomorpha**

1. ScienceDirect (5)
2. MEDLINE / PubMed (2)

**tick vectors CCHF rodents or rodentia**

ScienceDirect (17)

MEDLINE / PubMed (2)

Pubmed Central (1)

| Queries | Pub med | | | | Sciencedirect | | |
|---|---|---|---|---|---|---|---|
| Key words | Free | | Mesh | | Free | | |
| | **Article** | **Rev** | **Article** | **Rev** | **Article** | **Review/Book** | **Ref work** |
| **History CCHF** | **23** | **5** | **0** | **0** | **136** | **23** | 1 |
| **CCHF Aetiology** | **406** | **46** | **298** | **17** | **333** | **37** | 2 |
| **CCHF Geographic Distribution** | **7** | **1** | **171** | **10** | **70** | **17** | 0 |
| **CCHF virus** | **422** | **47** | **0** | **0** | **110** | **28** | 1 |
| **CCHF clinical diagnosis, laboratory diagnosis** | **39** | **3** | **102** | **4** | **148** | **24** | 1 |
| **CCHF prevention and control** | **79** | **16** | **3** | **1** | **118** | **24** | 0 |

**Research on Scirus with key words:**
**CCHF History**

1. ScienceDirect (77)
2. Pubmed Central (7)

3. MEDLINE / PubMed (7)

**CCHF Virus , CCHF**

ScienceDirect (205)

MEDLINE / PubMed (128)

Pubmed Central (18)

**CCHF, CCHF Virus, geographic distribution**

1. ScienceDirect (31)
2. Pubmed Central (7)
3. BioMed Central (5)

**CCHF, CCHF virus, pathogenesis**

1. ScienceDirect (45)
2. Pubmed Central (5)
3. BioMed Central (3)

**CCHF, Clinical Diagnosis, Laboratory Diagnosis**

ScienceDirect (77)

MEDLINE / PubMed (6)

Pubmed Central (4)

**CCHF, prevention, control**

1. ScienceDirect (59)
2. Pubmed Central (7)
3. MEDLINE / PubMed (3)

**The search on Google books produced 15 items**

1. Biology of Ticks Daniel E. Sonenshine
2. Crimean Congo Haemorrhagic Fever-A global prespective Ergonul O. and Whitehouse C.A.
3. Disease ecology, Sharon K. Collinge, Chris Ray
4. Ecological dynamics of tick-borne zoonoses, Daniel E. Sonenshine, Thomas N. Mather
5. Emerging viruses in human populations, Edward Tabor
6. Encyclopedia of arthropod-transmitted infections of man and domesticated animals, M. W. Service, R. W. Ashford
7. Handbook of Zoonoses: section B. Viral, George W. Beran, James H. Steele
8. Hunter's tropical medicine and emerging infectious diseases, George William Hunter, G. Thomas Strickland, Alan J. Magill
9. Infectious Disease of Livestock COETZER J. A. W. & R. C .TUSTIN
10. Ixodida -Fauna d'Italia. Manilla G.

11. The Genus Rhipicephalus (Acari, Ixodidae): a Guide to the Brown Ticks of the World. Walker JB, Keirans JE, and Horak IG
12. Tick-borne diseases of humans, Jesse L. Goodman, David Tappen Dennis, Daniel E. Sonenshine
13. Ticks of Veterinary and Medical Importance: the Mediterranean Basin Estrada Peña A.
14. Viral haemorrhagic fevers, Colin R. Howard
15. Zoonoses, H. Krauss

Among grey literature 6 citations were found but they were not relevant or were written in language such as Russian or Turkish.

When it was possible, all the PDF files were collected.

PDF that are not cited in the reviews are also collected because considered useful for general aspects (on Arthropod Borne Disease or Haemorrhagic fevers for example).

Only all the references used and cited in the Bibliography of the review are inserted in the End-Note file.

Since many studies have been performed from 50's to 70's and for many geographic areas involved the old data are the only available, for the aspects linked to the epidemiology of the disease and risk of occurrence such as:

- vector competence,
- role of wild animals in maintaining the virus in the environment;
- field observation in outbreaks;

for drafting the review it has been considered not only the last 20 years of published available literature, peer-reviewed scientific papers, published documents and official reports, but also the older ones. For the chapter on ethiology, clinical and laboratory diagnosis it has been considered only the latest publications.

**Critical points:**

- great part of literature on CCHF ecology and epidemiology is old (from 50's to the end 70's);
- many papers are in languages such as Russian, Serbian and Turkish;
- many old papers are referred to countries of central Asia.

**Solution:**

- when present and in English or French it has been considered the Abstract of the paper;
- for some paper it has been possible to retrieve the whole translation in English on the web site of the US Armed Forced Pest Management Board;

- it has been considered the information present in those papers when cited in other paper written in English, anyway citing the source reference (derived literature).