

# CRIMEAN-CONGO HEMORRHAGIC FEVER VIRUS, TICKS AND BASE MEASURES

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## ABSTRACT

Crimean-Congo haemorrhagic fever (CCHF) is a viral haemorrhagic fever of the Nairovirus, of the Bunyaviridae family of viruses. CCHF virus possesses a negative-sense RNA genome consisting of three RNA segments: the large (L), medium (M), and small (S) segments. For an arthropod-borne virus, the genomic plasticity of CCHF virus is surprisingly high. It seems likely that genetic reassortment may primarily occur during coinfection of ticks due to the transient nature of vertebrate infections relative to the long-term persistent virus infections seen in ticks and their obligation to obtain blood meals at metamorphic junctures. Substantially, movement of genetic lineages of CCHF virus,

particularly over greater distances and between regions not linked by livestock trade, likely also involves migratory animals or birds that are either infected or are carrying virus-infected ticks. Consequently, however migratory birds those mediate genetic lineages of CCHF exist critical point for CCHF struggle such as avian influenza, ticks should be targeted at first. Especially, fields with high risk should be out of order for pasturing and disinfected with repellent medicines. Acaricide treatment of livestock in CCHFV endemic areas is effective in reducing the population of infected ticks.

• **Key Words:** Crimean-Congo haemorrhagic fever virus, tick, measures. *Nobel Med 2009; 5(2): 10-14*

## ÖZET

### KIRIM-KONGO KANAMALI ATEŞİ VIRÜSÜ, KENELER VE TEMEL ÖNLEMLER

Kırım-Kongo Kanamalı Ateşi (KKKA), Bunyaviridae ailesi virüslerinden Nairovirüs'ün yapmış olduğu viral kanamalı ateşi hastalıktır.

KKKA virüsü büyük (L), orta (M) ve küçük (S) olmak üzere üç adet RNA segmentinden oluşmuş negatif RNA sarmalından oluşmaktadır. Artropod aracılı bir virüs olmasına rağmen KKKA virüsünün genetik değişkenliği dikkat çekici bir şekilde yüksektir. Görünen o ki, kenelerin yaşamsal döngüsünü devam ettirmek için kanla sürekli beslenmesi gerektiğinden ve infeksiyon

sürecinin vertebralılardaki kadar kısa süreli olmaması nedeniyle, virüsün genetik yapıdaki değişikliklerini kenelerde gerçekleştirdiği ko-infeksiyonlarla sağlamaktadır. KKKA virüsünün genetik değişkenliğinde büyükbaş hayvan ticaretinden çok kuşlar ya da bunların taşıdığı keneler aracılık etmektedir. Sonuç olarak, her ne kadar göçmen kuşlar genetik değişkenlikte önemli rol alsalar da; KKKA hastalığı ile mücadelede keneler birincil hedef olmalıdırlar. Özellikle hayvanların otladığı yüksek riskli alanlar repellentlerle dezenfekte edilmelidir. Zira, akarasid adı verilen maddelerle yapılan dezenfeksiyon, KKKA' nin endemik olduğu yerlerde infekte kene sayısını azaltmakta önemli derecede etkin olmuştur.

• **Anahtar Kelimeler:** Kırım-Kongo kanamalı ateşi virüsü, kene, önlemler. *Nobel Med 2009; 5(2): 10-14*

## INTRODUCTION

Crimean-Congo hemorrhagic fever (CCHF) is a viral haemorrhagic fever of the Nairovirus, a group of related viruses forming one of the five genera in the Bunyaviridae family of viruses. All of the 32 members of the Nairovirus genus are transmitted by argasid or ixodid ticks, but only three have been implicated as causes of human disease: the Dugbe and Nairobi sheep viruses and CCHF, which is the most important human pathogen amongst them. Tree topology supports previous evidence for the existence of three groups of genetically related isolates, A, B and C (Figure 1).<sup>1</sup> Within group A there are two clades: an African clade and a predominantly Asian clade comprising isolates from Pakistan, China, Iran, Russia and Madagascar. Group B includes isolates from southern and West Africa and Iran, and group C includes a single isolate from Greece (Figure 2). Despite the potential which exists for dispersal of the virus between Africa and Eurasia, it appears that circulation of the virus is largely compartmentalized within the two land masses and the inference is that the geographic distribution of phylogenetic groups is related to the distribution and dispersal of tick vectors of the virus.<sup>1, 2</sup>

CCHF virus possesses a negative-sense RNA genome consisting of three RNA segments: the large (L), medium (M), and small (S) segments. The S segment encodes a nucleoprotein (NP), the M segment encodes a glycoprotein precursor, which is cleaved into mature glycoproteins, G1 and G2, and the L segment encodes RNA polymerase (Figure 3). Discrepancies among the virus S, M, and L phylogenetic tree topologies document multiple RNA segment reassortment events. An analysis of individual segment datasets suggests

genetic recombination also occurs. For an arthropod-borne virus, the genomic plasticity of CCHF virus is surprisingly high.<sup>1-4</sup> As expected, the greatest accumulation of mutations was seen in the surface glycoprotein encoding M RNA segment (31% nucleotide and 27% amino acid divergence). This may reflect varying positive selection operating in the form of immune selection or selection for efficient attachment to different combinations of arthropod and vertebrate host cells in different natural cycles throughout the virus geographic range. The virus exists across numerous ecologic zones, with different *Hyalomma* species tick vectors important in different regions.<sup>3-6</sup> CCHF virus M segment reassortment events are more frequent than for S and L segments or more frequently result in high fitness viable virus. Reassortment between viruses from different geographic groups and its dependence on coinfection reinforces the point, that movement and mixing of viruses over large geographic distances is occurring with some frequency. It seems likely that genetic reassortment may primarily occur during coinfection of ticks due to the transient nature of vertebrate infections relative to the long-term persistent virus infections seen in ticks and their obligate need to obtain blood meals at metamorphic junctures.<sup>7</sup>

Virus was isolated from 30 kinds of tick which include 28 Ixodidae, 2 Argasidae. *Hyalomma marginatum marginatum*, *H.m.rufipes* ve *H.anatolicum* *anatolicum* are the most common porter-ticks but *Ixodes ricinus*, *Dermacentor* spp., *Rhipicephalus* spp. and *Boophilus annulatus* could have be porters in some countries.<sup>8</sup> Once infected, the tick remains infected through its developmental stages and the mature tick may transmit the infection to large vertebrates, such as livestock. →

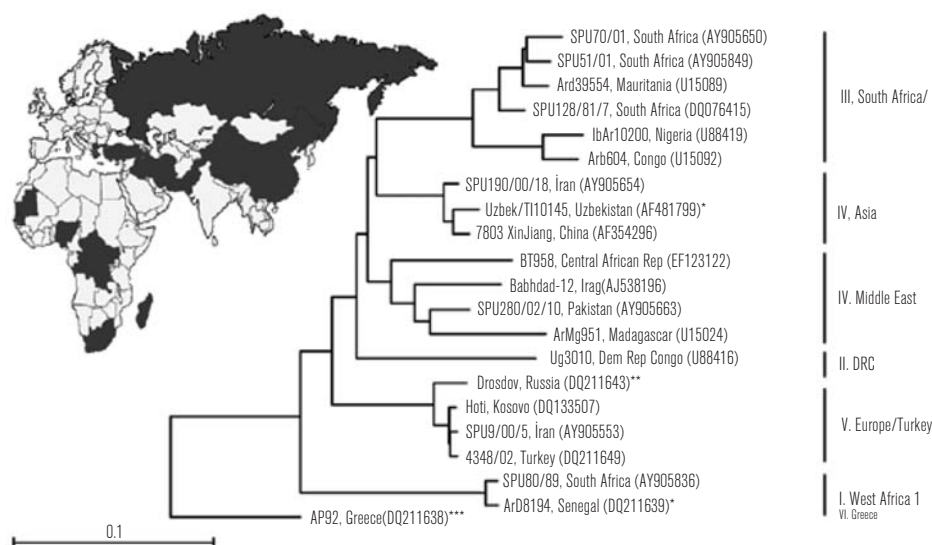


Figure 1. Phylogenetic analysis of Crimean-Congo hemorrhagic fever virus (CCHFV)<sup>1</sup>

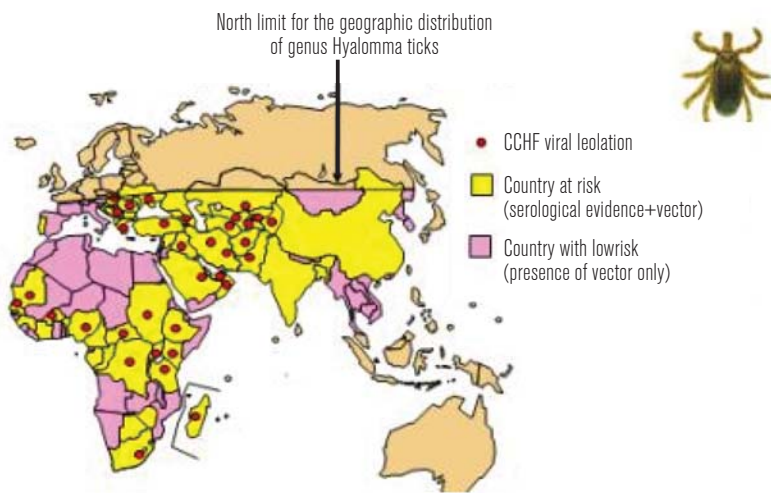


Figure 2. Geographic distribution of CCHF virus. Context: World Health Organization (WHO)

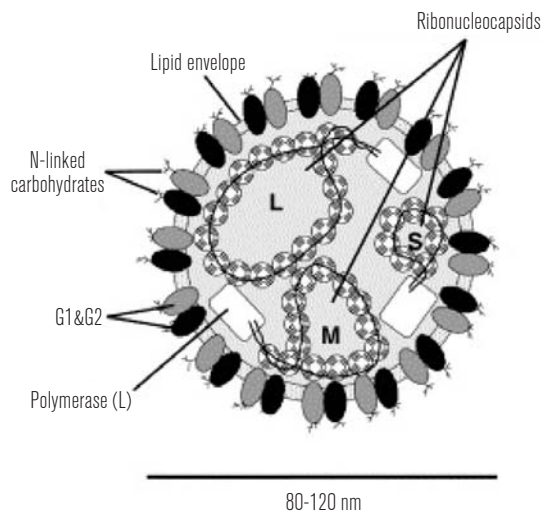


Figure 3. Viral structure of CCHF virus<sup>33</sup>

Domestic ruminant animals, such as cattle, sheep and goats are viraemic (virus circulating in the bloodstream) for around one week after becoming infected (Figure 4).<sup>8</sup>

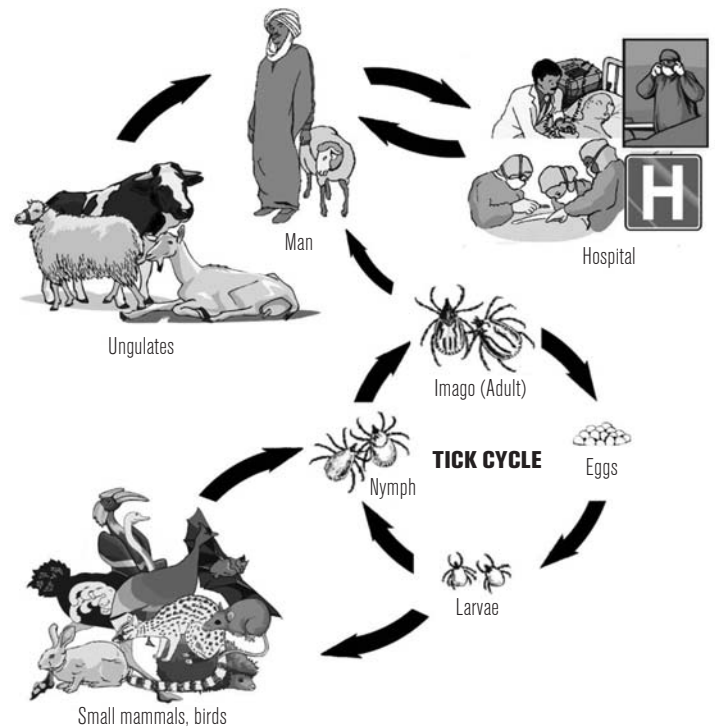
However, CCHFV or antibodies to it have been found in numerous smaller wild mammalian species, including hedgehogs, bats, hares, mice, rats, squirrels, eland antelopes, gerbils, genets.<sup>9-15</sup> These animals rarely have large numbers of ticks, but the large populations of these animals may indirectly create a strong density of ticks. Infection in these animals generally results in inapparent or subclinical disease but generates viremia levels capable of supporting virus transmission to uninfected ticks. Antibodies against CCHF virus have been detected in the sera of horses, donkeys,

goats, cattle, sheep, and pigs in various regions of Europe, Asia, and Africa.<sup>16</sup> Although CCHFV has never been definitively isolated from large mammals in the wild, antibodies to CCHFV have been found in foxes in Central Europe and in baboons and gazelles in Africa.<sup>11, 17</sup> Natural infection of large domestic mammals does occur, such as in camels, horses, and donkeys; in fact, cattle in Central Europe and goats and sheep in western Africa are the primary reservoirs for CCHFV infection in those areas.<sup>18, 19</sup> High prevalences of antibody occur in domestic ruminants in areas infested by *Hyalomma* ticks and the virus causes inapparent infection or mild fever in cattle, sheep and goats, with viraemia of sufficient intensity to infect ticks.<sup>9, 20</sup> Movement of CCHF virus-infected livestock (or uninfected livestock carrying infected ticks) via trade may explain some of the movement of virus genetic lineages within regions. For instance, there is considerable movement of sheep and goats into the Arabian Peninsula from countries in the horn of Africa or Iran and Pakistan, particularly in association with major religious festivals. The genetic links seen between virus strains and detailed epidemiologic and genetic analysis of past CCHF virus outbreaks in United Arab Emirates and Oman are consistent with this view.<sup>21</sup> Furthermore these researchers also showed that even sheep that were infected previously and had anti-CCHF virus IgG can be reinfected and transmit the virus.<sup>22</sup>

CCHFV is transmitted to humans through one of the following modes: 1-the bite of a tick, 2-contact with the tissues or blood of a recently slaughtered infected animal in the viremic phase of infection (butchers are particularly at risk), 3-contact with the blood of viremic-phase patients, most frequently in a hospital setting.<sup>23-27</sup> Human epidemics of CCHF rarely affect more than a few individuals. Human-to-human transmission of CCHFV is rare, except in the presence of hemorrhage, unsafe injections, unprotected venipuncture, or other types of hospital exposures. It is believed that infected blood plays an important role; in Pakistan in 1976, 10 hospital staff members who had contact with a patient with CCHF became ill and all those infected had been heavily exposed to blood from the infected patient.<sup>28</sup>

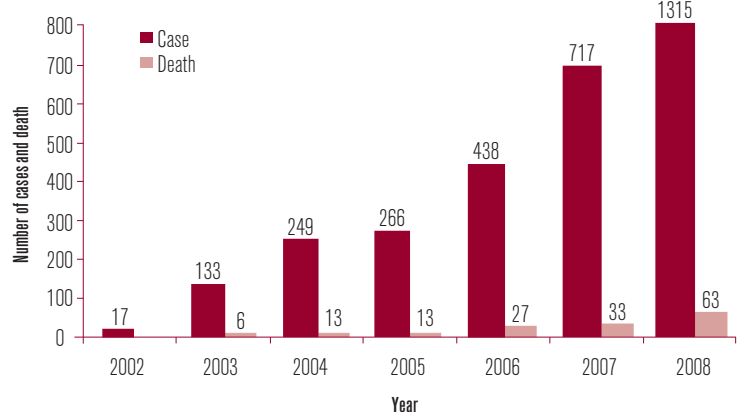
The role of birds in the ecology and epidemiology remains unclear. Antibodies to CCHFV have been detected in many species of wild birds (hornbills, guinea fowl, and blackbirds) and in one domestic bird (ostriches).<sup>15, 29</sup> Their role in virus transmission has been demonstrated experimentally.<sup>30</sup> For example, birds experimentally infected with CCHFV remained healthy, with no evidence of viremia or antibody response. This also seems to mimic the natural →

situation because work by the same group showed that even though CCHFV could be isolated from nymphal ticks collected from over 600 birds, the birds remained ser-negative and no virus could be isolated from their blood or organs. Thus, it appears that birds are refractory to CCHF infection, even though they can support large numbers of CCHF-infected ticks.<sup>31</sup> One interesting exception is ostriches, which become infected with CCHFV and have been the source of several cases of CCHF associated with the slaughtering ostriches in South Africa. Although some studies have suggested birds are not readily infected with CCHF virus, ostriches and several West African ground-feeding birds have been shown to be susceptible to infection, and even refractory species could move attached infected ticks without themselves becoming infected.<sup>30, 31</sup> Examination of major migratory bird flyways suggests this type of movement could provide a plausible explanation for virus lineage linkages between such areas as West and South Africa, for instance. Substantially, movement of genetic lineages of CCHF virus, particularly over greater distances and between regions not linked by livestock trade, likely also involves migratory animals or birds that are either infected or are carrying virus-infected ticks.<sup>7</sup>



**Figure 4.** Example of CCHF virus circulation: transmission by the *Hyalomma marginatum rufipes* ticks. Context: Pierre Nabeth. Crimean-Congo Haemorrhagic Fever Virus In Emerging Viruses in Human Populations (Edward Tabor, editor) Elsevier Science, 2007, England). Figure-3, p 307.

CCHF has been emerged in Turkey since 2002, in which suspicious deaths became an outbreak in middle region of Anatolia and were confirmed by ELISA and PCR methods. Between 2000 and 2003 years six exitus in 150 cases, in 2004 13 exitus in 249, in 2005 13 exitus in 266, in 2006 27 exitus in 438, in 2007 33 exitus in 717 and in 2008 63 exitus in 1315 cases reveal that CCHF is a infectious disease problem for Turkey at that and should be examined not only about treatment which had been issued but also about ticks, rural areas, preventive measures which had not been taken up comprehensively yet (Figure 5).<sup>32</sup> Moreover, Turkey should collaborate with endemic countries such as Iran, Russian, Greece, Bulgaria etc. which have neighborhood, since CCHF is not a local infectious disease problem.



**Figure 5.** Number of Crimean-Congo hemorrhagic fever cases and deaths in Turkey between 2002-2008.<sup>32</sup>

Consequently, however migratory birds those mediate genetic lineages of CCHF exist critical point for CCHF struggle such as avian influenza, ticks should be targeted at first. Since increasing infected ticks rates lead to reassortment of virus due to virus has not proofreading mechanism and tends to mutation.<sup>2</sup> So livestock and their pasturing rural areas should be researched about carrying infected ticks and virus mutation by tick and virologic sampling. Fields with high risk should be out of order for pasturing and disinfected with repellent medicines. Acaricide treatment of livestock in CCHFV endemic areas is effective in

reducing the population of infected ticks.<sup>27</sup> The migratory birds should be pursued all season and their residence should be researched for infected ticks and virologic sampling.

This problem could not be resolved just local measures so endemic countries should collaborate about measures, instructions about bird, livestock and their carrying infected tick existence and virologic studies.<sup>21</sup> CCHF cases are related with person that encounter tick-born and work about breeding, so that people that live in rural areas and breeds, should be educated →

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about ticks and CCHA. Control and disinfection programs should be put into practice for domestic ruminant animals which contact the rustic unsure areas and probable infected ticks carrying by veterinarians.<sup>21</sup> Suppression of rodent populations

apparently reduced the numbers of *D. marginatus* in Europe and *H. a. asiaticum* in the Asian deserts and semideserts. Hyalomma ticks were reduced in Europe by controlling hares and hedgehogs. Control of birds could also limit the dispersion of tick vectors.<sup>33</sup>



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