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Review

The impact of Crimean-Congo hemorrhagic fever virus on public health

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ABSTRACT

Climatic, environmental and economic changes, as well as the steadily increasing global trade and personal mobility provide ample opportunities for emerging pathogens with zoonotic potential to spread to previously unaffected countries. Crimean-Congo hemorrhagic fever virus (CCHFV) is considered to be one of the major emerging disease threats spreading to and within the European Union following an expanding distribution of its main vector, ticks of the genus *Hyalomma*. Every year more than 1000 human CCHF cases are reported from countries of southeastern Europe and Turkey. CCHFV can cause high case fatality rates and can be transmitted from human to human. There are no vaccine prophylaxis and therapeutic interventions available at present. Several EU-funded research projects focus currently on CCHFV which highlights the awareness for this problem at the European level. As public health deals with questions of prevention on a population level rather than healing and health on an individual level, the analysis of existing data plays a fundamental role to minimize its epidemic potential, by reducing infection risks, and to manage disease outbreaks. This review gives a summary of the current knowledge and data with focus at the interface between public health and CCHFV. Based on this knowledge, guidelines for the risk classification of a region and for outbreak prevention are given. This review will assist decision makers and public health authorities in understanding risk scenarios and in deciding on effective countermeasures, as well as human and veterinary scientists by highlighting existing gaps in knowledge.

Contents

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1. Introduction

Crimean-Congo hemorrhagic fever virus (CCHFV) is a member of the genus *Nairovirus* within the family *Bunyaviridae*. Since arthropods serve as transmission vectors, CCHFV is assigned to the group of Arboviruses (Arthropod-borne virus). Ticks of the genus *Hyalomma* are considered to be the main vector and also constitute the natural reservoir, as reviewed by Whitehouse (2004). *Hyalomma* spp. are present on the ground and infest small and large mammals (e.g. hedgehogs, hares, foxes, sheep, and cattle). Ticks therefore play a pivotal role in the CCHFV transmission cycle (tick-vertebrate-tick cycle) (Zeller et al., 1994). Although viremia in animals can last for up to two weeks, animals do not show clinical signs (Gunes et al., 2011).

CCHFV is an emerging virus with zoonotic potential. Tick bites constitute the main infection route for humans (Gunes et al., 2009). However, contact with body fluids, tissue or blood of viremic animals also represents infection risks for humans.

Fig. 1. Distribution of *Hyalomma marginatum* ticks in Europe. The dotted line shows the northern limit of distribution of *H. marginatum*. The black dots indicate isolation of CCHFV, the white dots detection of CCHFV-specific antibodies. This figure was originally published in Parasitology Research and is re-used with kind permission from Springer Science and Business Media (Hubalek and Rudolf, 2012).

Additionally, there are several reports about person-to-person transmission by unprotected handling of infected blood or material from CCHF patients, by accidental needle stick injuries, and by accident or inadequate protection measures during surgeries, which are the main reasons for nosocomial infections (Chinikar et al., 2010; Ergonul et al., 2007; Mourya et al., 2012).

CCHFV infections of humans can cause a severe hemorrhagic fever (CCHF) with lethality rates ranging from 5% to 80% (Yen et al., 1985; Yilmaz et al., 2008). Scientific data on the virulence of CCHFV and the morbidity rates following infections in humans are scarce. According to the literature 10–20% of infected humans develop clinical signs (Bodur et al., 2012; Goldfarb et al., 1980). There is no safe vaccine available and therapeutic interventions are restricted to supportive measures. Because of the classification of CCHFV as a Biosafety Level 4 pathogen by the World Health Organization (WHO) and the Centre for Disease Control and Prevention (CDC), high biocontainment facilities are required for work with infectious material or with the virus itself (Bronze et al., 2002; Keshtkar-Jahromi et al., 2011).

2. Epidemiology

2.1. Vector distribution

Although CCHFV was isolated from 31 tick species, until now only a few species were shown to be competent as a vector. The spread of CCHFV primarily coincides with the distribution of *Hyalomma* ticks as its main vector. To date, these ticks have been found in regions of many countries in southeastern Europe (Fig. 1). Ticks are not only relevant as vectors but also play a role as natural reservoir, since the virus can be transmitted transstadially, transovarially or by venereal route within the tick population. Another possible route of transmission from one tick to another is by co-feeding (Gonzalez et al., 1992; Gunes et al., 2011; Wilson et al., 1991; Zeller et al., 1994).

Regions with warm climate and high fragmentation of the landscape vegetation (grasslands, bush lands, forests and agricultural land) are suitable habitats for *Hyalomma* ticks and correlate with high risk areas for CCHFV infections in Turkey (Estrada-Pena et al., 2007). *Hyalomma* ticks can be found in diverse geographical regions like steppe, savannah, semi-desert, farmland and foothills, but also along river floodplains with rich grasslands and shrub and woodland vegetation. Populations of these ticks currently establish up to 46°N (latitude north) as the northern limit of distribution. The Alps and Balkan mountains seem to act as natural barriers for their distribution (EFSA, 2010; Hornok and Horvath, 2012).

The role of *Ixodes ricinus* ticks, the most common tick species in central Europe, in the transmission and spread of CCHFV remains unknown, but can presumably be neglected, as has been reviewed previously (Estrada-Pena et al., 2012b; Hubalek and Rudolf, 2012). Furthermore, it is unlikely that these ticks have a large impact on the transmission of this virus, since this species is geographically widespread and abundant in many parts of Europe where no CCHF cases have been reported (EFSA, 2010).

Table 1
Number of human CCHF cases/number of deaths (lethality rate in %) reported from southeastern Europe and Turkey. Information on case numbers was extracted from the published literature (Avšič-Županc, 2008; Humolli et al., 2010; Kunchev and Kojouharova, 2008; Maltezou et al., 2010; Yilmaz et al., 2008). x = no data available.

Year	Albania	Bulgaria	Greece	Kosovo	Turkey
1953–1974		1105/190 (17)		x	
1975–1996		279/32 (11)		x	
1985–1987	32/5 (17)	x		x	
1995	x	x		46/7 (15)	
1996	x	x		9/5 (56)	
1997	x	20/4 (20)		0/0 (0)	
1998	x	15/3 (20)		1/0 (0)	
1999	x	5/2 (40)		3/2 (67)	
2000	x	10/1 (10)		1/0 (0)	
2001	7/0 (0)	18/5 (28)		31/7 (22)	
2002	x	56/12 (21)		14/3 (21)	17/0 (0)
2003	x	14/2 (14)		6/3 (50)	133/6 (5)
2004	x	18/6 (33)		16/2 (13)	249/13 (5)
2005	x	14/2 (14)		11/5 (46)	266/13 (5)
2006	x	7/2 (29)		4/2 (50)	438/27 (6)
2007	x	x		2/0 (0)	713/33 (5)
2008	x	6/1 (17)	1/1 (100)	5/1 (20)	1315/63 (5)
2009	x	x	0/0 (0)	12/2 (17)	1300/62 (5)

2.2. Distribution of the virus

Human infections with CCHFV have been notified in more than 30 countries of Asia, the Middle East, southeastern Europe and Africa, as reviewed by Whitehouse (2004). From 1953 till 2010, altogether around 6000 human cases were reported from southeastern Europe, namely from Albania, Bulgaria, Greece, Kosovo and Turkey. Annual case numbers in humans increased over the last years in Turkey, either caused by an increase in numbers of CCHFV infections or by a better awareness and improved surveillance (Table 1). In animals data on CCHFV infection are rarely existent. In Turkey, seroprevalence rates in domestic animals of up to 79% were reported in the endemic areas (Gunes et al., 2009). Apart from countries with notified CCHF cases, CCHFV was recently found for the first time in Spain (Estrada-Pena et al., 2012d).

2.2.1. Albania

In Albania, CCHF was for the first time diagnosed in 1986. Lethality rates in the years 1985–1987 were nearby 17% (Avšič-Županc, 2008). Between 2001 and 2006 an average of five human cases per year was reported. Endemic areas are the provinces Has and Kukes at the border to the Republic of Kosovo. A seroprevalence rate of 20% (2/10) was found in goats by immunofluorescence assay (IFA) in the province of Has in 2003. Investigations of ticks in Kukes in 2005 resulted in a prevalence of 3% (1/31 positive tick pools in nested reverse transcription polymerase chain reaction (RT-PCR)) (Papa et al., 2009).

2.2.2. Bulgaria

In Bulgaria, CCHF was first recognized in 1950 and is a notifiable disease since 1953. In 1974, a vaccination program was initiated for risk groups and people living in endemic areas. The numbers of CCHF cases in the following years decreased from 1105 clinical cases between 1953 and 1974 to 279 cases between 1975 and 1996 (Avšič-Županc, 2008; Papa et al., 2004, 2011a). The lethality rate, calculated on the basis of 1568 reported human cases notified between 1953 and 2008, was approximately 17%. The endemic areas of Bulgaria are in the central and in the eastern parts of the country where the seroprevalence in animals reaches up to 50% (Maltezou et al., 2010; Papa et al., 2004).

2.2.3. Greece

In Greece CCHFV was isolated for the first time from a *Rhipicephalus bursa* tick in 1975. The seroprevalence investigated by immunodiffusion assay in goat and sheep sera, which were collected between 1969 and 1978 in the northern part of the country, was 32.9% (139/422) and 11.6% (34/294), respectively. In the time period between 1981 and 1988, the average antibody prevalence in humans was 1.1% for the whole of Greece, but no human CCHF cases were reported. It was assumed that the antibody response had been induced by the CCHFV strain AP92, which seemed to be non-pathogenic for humans (Papa et al., 2010, 2011b; Papadopoulos and Koptopoulos, 1980). Surprisingly, in the western part of Turkey a closely related strain, KMAG-Hu-07-01, was responsible

for a small outbreak in 2007. During this outbreak only two of 40 individuals with CCHFV-specific IgM antibodies, tested by enzyme-linked immunosorbent assay (ELISA) (Vector-Best, Novosibirsk, Russia), showed mild clinical symptoms, which indicates a low pathogenicity of this strain for humans (Midilli et al., 2009).

In 2008, the first clinical human case was reported from Greece close to the Bulgarian border. A subsequently conducted epidemiological study (2008–2009) revealed an antibody prevalence rate of 3.1% in humans (ELISA, Vector-Best, Novosibirsk, Russia) living in and around this region (Papa et al., 2010, 2011b). A following study (2009–2010) showed an antibody prevalence of 4.2% (ranging from 0% to 27.5% in ELISA, Vector-Best, Novosibirsk, Russia) in humans for the whole country (Sidira et al., 2012). This study also supported the theory of an apathogenic character of CCHFV strain AP92.

2.2.4. Kosovo

In the Republic of Kosovo, former Yugoslavia, the first CCHF case was reported in 1954 followed by the first outbreak in 1957. A second outbreak among shepherds at the border to FYROM (Former Yugoslavian Republic of Macedonia) occurred in 1970. More outbreaks were notified in 1991/1992, 1995/1996 and in 2001. Since this time, an average of 10 sporadic cases has been recorded each year. The endemic regions are in the central and the South-western part of the country. The seroprevalence rate in humans was 5.2% in 1991/1992 but increased to 24.3% in 1995 (ELISA). The seroprevalence in sheep was 32.6% (Avšič-Županc, 2008; Humolli et al., 2010; Jameson et al., 2012; Papa et al., 2002b), and the virus prevalence in ticks collected in 2001 was 15% (41/273 positives in quantitative RT-PCR) (Duh et al., 2006).

2.2.5. Turkey

The first CCHF case was discovered in the province Tokat, in the northern part of Turkey, in 2002. In 2003, CCHF became a notifiable disease. Since then, the annual number of clinical cases was far higher than the case number in all other European countries combined (Table 1). The majority of human CCHF cases occurred in middle and eastern Anatolia (Karti et al., 2004; Maltezou et al., 2010; Yilmaz et al., 2008). A sero-epidemiological study was performed in the endemic districts Tokat and Sivas in 2006, which revealed seroprevalence rates of 12.8% in the rural and 2% in the urban population (ELISA, Vector-Best, Novosibirsk, Russia). CCHFV-specific antibodies were found in 79% of the domestic animals tested originating from these areas (Gunes et al., 2009), and 20% of the *Hyalomma* ticks were tested positive in an antigen capture ELISA (Vector-Best, Novosibirsk, Russia) for CCHFV (Gunes et al., 2011). Moreover, during a small outbreak in the European part of Turkey (Thrace) in 2007, where no outbreaks had been reported before, a seroprevalence rate of 5.26% CCHFV-specific antibodies was found in humans by ELISA (Vector-Best, Novosibirsk, Russia) (Midilli et al., 2009).

2.3. Impact of climate and other factors on the distribution of vector and virus

Climatic factors like mild winters, warm autumns, a decrease in rainfall, changes in land cultivation and usage, as well as changes in the populations of reservoir species contribute to an increase of suitable habitat areas for ticks. *Hyalomma* ticks prefer warm summers and relatively mild winters. An increase of the average annual temperature, especially in late autumn, allows the ticks to molt faster, which in turn enables the engorged nymphs to molt into adults before winter at which stage they have a higher chance of overwintering (EFSA, 2010; Gray et al., 2009). Mild winters also increase the survival rate of the ticks resulting in large populations and high tick prevalences within the respective region, which may lead to a spread into neighboring territories (Ergonul, 2006; Papa et al., 2002a). These factors potentially enhance the survival and circulation of the virus within the tick population.

In addition to increasing temperatures in winter, a decrease of rainfall and an increase of the evapo-transpiration in summer, as well as the population density of suitable animal hosts may have an impact on the availability of new habitats for ticks, and may also facilitate spread towards northern latitudes (EFSA, 2010; Estrada-Pena et al., 2012e; Gray et al., 2009).

In case of *Hyalomma marginatum*, environmental changes, such as changing pasture patterns, conversion of flood plains and marshy deltas to farmland, as well as flood control measures enhance the suitability of habitats. For Turkey, a high habitat fragmentation with small agricultural fields correlates with high infection rates (EFSA, 2010; Estrada-Pena et al., 2007; Vorou, 2009).

Changes in ecological conditions, such as an increase in bush land, as a consequence of a neglected use of agricultural land or of deforestation measures to gain farmland, contribute to an increase in adequate habitats for *Hyalomma* ticks and their reservoir animals. Likewise, decreased hunting activities have an additive effect. Before the first outbreak in Turkey in 2002, no hunting and agricultural activities had been carried out in the respective area for more than seven years, due to political unrest. This led to a higher density of wildlife (e.g. hares) and, in consequence, to an increased density in the tick population. When agricultural activities were resumed in 2001, humans and domestic animals were exposed to increased tick numbers. A similar observation was made in the former Soviet Union, Bulgaria, Albania and in Kosovo (Estrada-Pena et al., 2007; Jameson et al., 2012; Papa et al., 2009; Vorou, 2009).

Changes in climate can directly affect survival, activity, and development of ticks. The spread of CCHFV to new tick habitats can occur by migratory birds carrying infected ticks, and via tick-infested livestock or wildlife movements. Although the probability of an introduction of CCHFV to non-affected European countries by migrating birds is considered to be low (Gale et al., 2012), CCHFV infected ticks were found in Spain in 2010. Since the isolated strain genetically clustered together with strains recorded in Mauritania and Senegal, this indicates that there is indeed a risk of introduction of CCHFV from endemic areas to unaffected regions (Estrada-Pena et al., 2012d). Unfortunately, the lack in understanding of tick-host-virus interactions on a molecular level and of all factors which influence tick and virus epidemiology hampers the development of risk assessment models, as has been reviewed by Estrada-Pena et al. (2012a,b); Vorou (2009).

Whenever an infected vector is transferred into a suitable habitat and a stable population develops, there is a reasonably high risk for the establishment of a new CCHFV endemic area. Vice-versa, recent experiences from outbreaks in Turkey, Kosovo, Bulgaria and Albania have shown how unlikely it is that a stable *Hyalomma* population will disappear and that an endemic area will be cleared of CCHFV (Gunes et al., 2011; Humolli et al., 2010; Papa et al., 2004). In general, the potential virus spread and the formation of new risk areas can be discussed for several different viruses e.g. tick-borne encephalitis virus (TBEV). In any case, if a virus is detected in a region for the first time, it is most often hard to decide whether the virus spread to the respective region a short time ago or if it has been circulating undetected for a long time (Suss, 2011). For example, the fact that the virus was not detected in Turkey before 2002 does not necessarily mean that it was not circulating earlier in the area of the first outbreak, but can perhaps be explained by noting that, because no hunting or agricultural activities were performed, few people were at risk of a tick bite. This may also be the case for some other countries where, until now, CCHFV has not been notified.

3. Infection risk

3.1. Zoonotic potential of CCHFV and paths of transmission

3.1.1. Tick-related infections

To date, only few reports of the prevalence of CCHFV in ticks have been published. A prevalence of 15% CCHFV-positive ticks was found in Kosovo in 2001 by quantitative RT-PCR (Duh et al., 2006), 3% in Albania in 2005 by nested RT-PCR (Papa et al., 2009) and up to 20% in Turkey in 2007 by antigen-capture ELISA (Vector-Best, Novosibirsk, Russia) (Gunes et al., 2011). Tick bites represent the most important route of infection for humans, although the frequency of tick bites in human cases seems to differ between the countries. In Albania, 17.3% of patients had a history of a tick bite (Papa et al., 2009), whereas in Turkey the number was much higher; according to one study, 68.9% of CCHF patients reported a tick bite as a possible route of infection (Yilmaz et al., 2009). Investigations of healthy persons with a history of a tick bite resulted in an antibody prevalence of only 10% in ELISA (BDSL, Scotland, UK) (Tekin et al., 2010). The reasons for this may be both a low prevalence of CCHFV in these ticks and poor virus transmission efficiency. However, in Turkey, infection by tick bite seems to be the main source for human CCHF cases. Further investigations on factors modulating the transmission efficiency of CCHFV are necessary. Titers of 6.8×10^7 copies per milliliter homogenate have been found in ticks by quantitative RT-PCR (Papa et al., 2009).

In Turkey, the adult ticks are active from April to November, whereas the active period of the larvae is from June to late autumn. Due to this, the risk of a CCHFV infection is much higher in late spring till late summer when the activity of ticks is highest and when different stages of *Hyalomma* ticks are present (Estrada-Pena et al., 2011; Gunes et al., 2011). Nearly 70% of the human cases in Turkey were reported in June and July (Yilmaz et al., 2009). Either way, it is important that clinicians are aware that CCHFV infections can also occur during the winter period (Koksal et al., 2011).

Tick bites are not the only cause of infections for humans. Infections with CCHFV can also result from crushing infected ticks, leading to a massive virus release that may be inhaled or transmitted via skin contact (Gunes et al., 2011; Swanepoel et al., 1998). In general, not only the density of *Hyalomma* ticks, the virus prevalence in these ticks, the geographical landscape and the climate in the respective area pose a risk of infection to humans. A change in human behavior during warm days, e.g. increased outdoor activities or an increase in work in agriculture, may also lead to an increased overlap with the ticks' activity, which may consequently result in an increased number of tick bites and human infections (EFSA, 2010; Gunes et al., 2011; Yilmaz et al., 2009).

3.1.2. Animal-related infections

Animals play a crucial role in the life cycle of ticks and, therefore, in the transmission and amplification of the virus. Viremia or antibodies have been detected in a broad range of wild and domestic mammals (Causey et al., 1970; Shepherd et al., 1989; Wilson et al., 1991). Only birds, with the exception of ostriches, rarely seem to become infected with CCHFV (Shepherd et al., 1987; Swanepoel et al., 1998; Zeller et al., 1994).

Although viremia in mammals can last for up to two weeks, they do not show any clinical signs (Gunes et al., 2011). Albeit only few data are available and more research is necessary, it can be assumed that contact with body fluids, tissue or blood of viremic animals may pose a risk of infection for humans, in particular abattoir workers, veterinarians, shepherds and farmers. Out of the 1670 human CCHF cases in Turkey between 2004 and 2007, a total of 61.7% ($n = 1031$) were reported to have had close contact with animals; 34.1% ($n = 569$) were farmers, whereas only 9.9% ($n = 165$) had direct contact with animal blood, other body fluids or animal tissue. Because the percentages of patients who had contact with animals and those who reported a tick bite (68.9% and 61.7%, respectively) were comparable, it seems likely that tick-infested animals transmit ticks to humans, and that the cause of infections is rather due to tick bites. Larger numbers of livestock animals, and there with a higher prevalence of ticks, may be the reason for the increased numbers of human CCHF cases in small villages (69.4%; $n = 1159$) compared to that in towns (20.9%; $n = 349$) or city centers (9.7%; $n = 162$) (Gunes et al., 2009; Mourya et al., 2012; Yilmaz et al., 2009).

3.1.3. Human-to-human transmission

CCHFV can be transmitted from human to human during the viremic phase of illness. Viral loads of up to 10^{10} genome copies per milliliter detected by quantitative RT-PCR were found in the blood of patients with a fatal outcome (Duh et al., 2007). Due to these high titers, contact with the blood of CCHF patients poses a particular risk of infection. Especially patients with bleeding in the lungs, nose, mouth, gums, vagina and at injection sites spread virus into the environment and need to be handled carefully (Athar et al., 2005). Unprotected contact with other body fluids like saliva or urine may also cause a risk to humans (Bodur et al., 2010). A transmission of the virus from one patient to another by sharing the same room was also reported (Gurbuz et al., 2009).

The infection risk can be reduced by using adequate personal protection measures, so that the rate of CCHFV infections in health care workers (HCWs) is equal to that in the general population (Ergonul et al., 2007). Among the large number of CCHF patients in Turkey between 2004 and 2007, only 0.4% (6/1670) were HCWs. The prevalence of CCHFV-specific antibodies in HCWs working in endemic areas of Turkey is also low with 2% (3/150) investigated by ELISA (BDSL, Scotland, UK) (Tekin et al., 2010; Yilmaz et al., 2009). In addition, contact transmission in general seems not to be particularly efficient in causing disease. During an outbreak in Turkey 22.8% of the CCHF patients' relatives or friends were found to be positive for CCHFV-specific IgG antibodies by ELISA (BDSL, Scotland, UK). Though it was assumed that these antibodies were elicited by contact exposure to the patients, it cannot be excluded that CCHFV-specific antibodies were already pre-existing. Nobody in this group developed clinical symptoms (Tekin et al., 2010). This is supported by another publication from Pakistan, where all family members of a patient came into contact with the blood of a patient, but none of them developed clinical symptoms, and by the low number of secondary cases and the absence of tertiary cases during this outbreak (Altaf et al., 1998; Papa et al., 2007).

Overall, most nosocomial infections have been the result of dealing with CCHF patients without adequate protection measures, through subcutaneous infection by needle injuries, accidents during surgery, or from handling blood and other body fluids without gloves, while having unrecognized skin damage (Altaf et al., 1998; Aradaib et al., 2010; Ergonul et al., 2007). However, detailed case-control studies are needed to verify this assumption. Comparing the relatively low numbers of infections by direct human-to-human transmission, infections following tick bites are much more common in endemic areas. In a study in South Africa, the mean incubation time after blood or tissue contact was 5.6 days, whereas the mean incubation time after a tick bite was 3.2 days (Swanepoel et al., 1987). Further investigations of the transmission doses and routes and their implication for developing CCHF are necessary in order to make a statement regarding the risk of infection.

3.2. Groups at risk and human behavior

Only a relatively small group of persons within a population have an increased occupational risk of acquiring CCHF: shepherds,

farmers, veterinarians, slaughterhouse workers, soldiers and HCWs. Another group at risk are relatives and friends of patients before their hospitalization and isolation. In endemic areas all persons living in a rural environment or travelling from cities to the countryside (especially campers and soldiers) are at risk of infection. In respect to the large number of patients (68.9%) reporting a tick bite as a possible cause of infection in Turkey, human behavior significantly influences the risk of infection. This includes crushing of ticks, the handling of highly infested animals as well as working, hiking or camping in suitable tick habitats. Contact with viremic animals or human patients poses another risk factor. In general, skin contact with blood or other body fluids of humans or animals should be avoided. The meat of animals is considered to be non-infectious because of the postmortal acidification process. In any case, cooking meat will effectively destroy the virus (Ergonul, 2006; Sidira et al., 2012; Tekin et al., 2010; Whitehouse, 2004; Yilmaz et al., 2009).

4. Protection

4.1. Protection of the population at large

To protect the public, monitoring programs in ticks and animals should be implemented to define endemic or high-risk areas and to detect virus spread at an early stage (Vorou, 2009). The infection rate in ticks can be used as an indicator for defining the endemic status of a region (Gunes et al., 2011). If a human CCHF case is diagnosed, national authorities should be informed which will notify the case to the European Centre for Disease Prevention and Control (ECDC) and the WHO. After notification, the information can be circulated via Early Warning and Response System (EWRS) and ProMed. Surveillance studies should be initiated in the outbreak areas or countries within the human population to reduce the risk of new infections. Information on tick bites and associated complications in residents should be collected (Papa et al., 2008; Vorou, 2009; Yilmaz et al., 2008).

The number of people involved in an outbreak is usually low. The reaction time in terms of inducing public health measures, the management of contact persons and the prompt isolation of infected individuals (identified by first clinical symptoms and risk definitions described in Section 5.2) before the onset of hemorrhagic manifestations probably has a considerable impact on the total number of infections (Dunster et al., 2002; Gurbuz et al., 2009; Papa et al., 2010; van de Wal et al., 1985).

The application of tick-control products on a broad scale to protect the public and domestic animals from tick-borne diseases has to be performed carefully, because through natural selection the percentage of ticks which are resistant to the majority of chemical groups of acaricides and insecticides can increase. Therefore, acaricides should be used as specified by the manufacturer: they should kill all ticks on treated animals, and they should be used according to the rotating principle to avoid resistance. Environmental side-effects in consequence of their use are possible, and must be taken into account. Alternative strategies such as anti-tick vaccines, genetically tick-resistant breeds of livestock, semiochemicals and the use of biocontrol agents are currently being developed (EFSA, 2010). The risk of the introduction of infected ticks by animal transport from endemic to non-endemic regions can be reduced by the use of repellents on transported animals (Vorou, 2009). Additionally, the spread of *Hyalomma* ticks and the introduction of CCHFV into new habitats by wild animals may be reduced by strict control of the population size, through well-coordinated hunting activities (Estrada-Pena et al., 2007; Papa et al., 2009; Vorou, 2009).

4.2. Protection of individuals

The first and best means of protection for humans is to avoid situations with an increased infection risk. Humans should avoid visiting tick habitats during the active tick season. If this is not possible, the body and clothing should be inspected for ticks after any stay outside. In addition, long trousers, sleeves and repellents on clothes and skin should be used. In case ticks are found they should be removed as fast as possible (WHO, 2001). Attached ticks should be grasped with fine-tipped tweezers as close to the skin surface as possible and pulled upward without twisting. No nail polish or petroleum jelly, nor heat should be used. After removing the tick, the bite area and hands should be thoroughly cleaned with alcohol or soap and water (CDC, 2011). The tick should not be crushed after its removal.

People with an increased risk of infection due to contact with blood or other body fluids of potentially infected animals should wear gloves to avoided a percutaneous exposure (Ergonul et al., 2007). In general, the use of gloves while handling livestock is recommended in endemic areas. In order to protect abattoir workers, tick repellents should be applied to animals originating from endemic areas two weeks before slaughtering to keep them free of ticks (Swanepoel et al., 1998).

4.3. Case management

Potentially CCHFV-infected patients should be isolated and treated in separate rooms (Fig. 2) (Bannister, 2010; Wirtz et al., 2002). After isolation, the hospital and laboratory staff should immediately be informed and educated with respect to barrier nursing techniques and precautions (e.g. use of gloves, masks, gowns and face-shields or goggles with side shields) (Ergonul

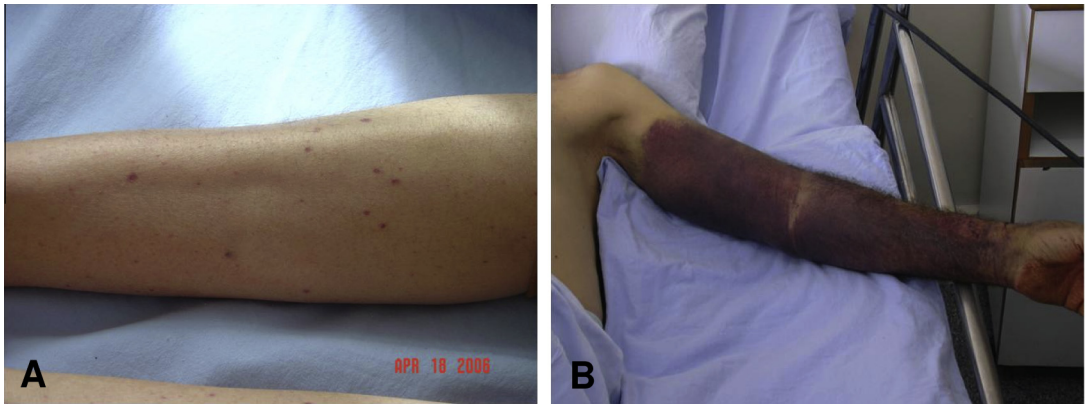

Fig. 2. Hemorrhagic manifestations in CCHF patients. A high variability can be observed, ranging from petechia hemorrhages (A), to large hematomas (B). The pictures have been kindly provided by Prof. Hurrem Bodur, Ankara Numune Education and Research Hospital, Turkey.

Table 2
Classification of risks by the contact with CCHF patients and the corresponding measures. Data and table modified from (Bannister, 2010; Wirtz et al., 2002).

Kind of contact	Risk category	Measures for people with contact
• Casual contact, such as staying in the same room or public transport, receptionists • Caring medical staff, if full-protective overalls and breathing masks were used	Low	• Measurement of body temperature until day 14 after the last contact
• Close contact such as nursing of the patient before hospitalization • Protected people (gloves, mask) taking blood and other samples • Person with longer close contact to the ill patient e.g. during flights	Moderate	• Measurement of body temperature until day 14 after the last contact • Prohibition of work such as teaching, patient treatment, homes for the elderly
• Unprotected contact with blood or other body fluids of a patient • Unprotected contact with a patient with bleeding and/or coughing	Increased	• Measurement of body temperature until day 14 after the last contact • Prohibition of work • Separation at home • Observation of blood parameters • Daily diagnostic
• Percutaneous contact to blood or other body fluids, including needle injuries, or contact with not-intact skin of HCWs • Mucosal exposure to blood or other body fluids	High	• Measurement of body temperature until day 14 after the last contact • Prohibition of work • Isolation in hospital • Observation of blood parameters • Daily diagnostic • (Postexposure treatment with ribavirin)

et al., 2007; van de Wal et al., 1985). In the next step, the reference laboratory should be contacted to confirm a possible CCHFV infection by specific diagnostic assays. Infection specialists and epidemiologists should be contacted to obtain detailed epidemiological information. A risk assessment should be accomplished, and the respective officials should be informed to forward a report to the WHO. If necessary, the transfer of the patient to a specialist unit should be organized. Last but not least, the hospital management should be aware that the HCWs might be extremely concerned about the risk to their own health. Therefore, a well-organized information and education management is indispensible, and supportive assistance by psychologists is recommended (Bannister, 2010; Papa et al., 2010; Yilmaz et al., 2009).

Only patient specimens that are essential for diagnosis and monitoring should be collected and handled by experienced staff with care to avoid self-inoculation and to reduce the high amount of accidents in hospitals. Similarly, glass containers should be avoided; disposable sharp objects should be disposed of in appropriate containers for sharp materials immediately after use, and used needles should not be broken, recapped or removed from disposable syringes (ENIVD, 2001). The rooms of patients should be disinfected, and all potentially infectious materials should be autoclaved.

HCWs caring for CCHF patients should be regularly monitored, and those with possible exposure to the virus should be followed up for at least 14 days by complete blood counts and diagnostic tests (Ergonul, 2006; van de Wal et al., 1985; van Eeden et al., 1985). For effective treatment, and for deciding upon adequate measures, a categorization of people with contact with patients into different risk groups has been proven practicable (Bannister, 2010; Wirtz et al., 2002). The differentiation of the contacts varies from low-risk contacts, such as staying in the same room, to high-risk contacts, caused for example by needle injuries. A classification of risk categories and a list of corresponding suitable measures are given in Table 2. In case clinical signs are seen, the above-mentioned procedure should start from the beginning with the isolation of the patient.

5. Diagnosis of CCHF

5.1. Availability of diagnostic tools

There are a few IgG and IgM ELISAs, as well as IFA slides commercially available for the detection of CCHFV-specific human antibodies (Table 3). Additionally, there is one antigen-capture ELISA on the market. Unfortunately, some of these assays are difficult to order or not offered to international customers. In addition to these commercial assays, several in-house ELISAs, as well as IFA tests have been published for testing human sera. Unfortunately, most of these assays are only sparsely documented in the literature and comprehensible data on the diagnostic sensitivity and specificity are rarely available. An exception are five ELISAs and three IFAs which have been validated (Emmerich et al., 2010; Mourya et al., 2012; Qing et al., 2003; Saijo et al., 2002a,b). So far, only one study has compared the available tests with each other (Vanhomwegen et al., 2012). The lack of human CCHF sera in acceptable numbers and the absence of a generally agreed 'gold standard' test pose the greatest difficulty for test development and validation.

For virus detection, several quantitative RT-PCRs (Drosten et al., 2002; Duh et al., 2006; Midilli et al., 2009; Papa et al., 2007; Wolfel et al., 2007) have been published. In 2008, twenty European laboratories were capable of performing CCHFV diagnostics, and some of them had the BSL4 infrastructure that allowed virus isolation (Maltezou et al., 2010).

There are only few assays available for the detection of CCHFV-specific antibodies in animals (Table 3). This is unfortunate, because the presence of such antibodies in animals could be used as an indicator for the circulation of the virus in an area.

5.2. Diagnosis of human cases

The first indications to assume the occurrence of a CCHFV infection are common clinical findings such as fatigue, high fever, myalgia, headache and loss of appetite, in combination with a history of a tick bite, contact with blood or body fluids of ruminants in a risk area, or direct contact with a CCHF patient. Typical laboratory findings in CCHF patients are thrombocytopenia, leukopenia and increased levels of transaminases. Patients are defined as CCHF cases when virus RNA is confirmed in the blood or body fluids by quantitative RT-PCR, or when CCHFV-specific IgM or IgG antibodies are detected by immunological assays like IFA or ELISA. Since the elicitation of neutralizing antibodies by a CCHFV infection is weak, diagnosis by neutralization assay is less sensitive than ELISA (Burt et al., 1994; Yilmaz et al., 2009).

In general, virus can be detected for up to two weeks after the first clinical symptoms occur. An IgM antibody response is detectable from the fourth day after the onset of disease for up to four months. IgG antibodies can be found from day six after the incuba-

Table 3
Assays for the detection of CCHFV-specific IgM or IgG, or for the detection of viral antigen. IFA: immunofluorescence assay. ELISA: enzyme-linked immunosorbent assay.

Assay		Target species	Developer of the assay	Studies that have used the assay (examples)
Commercial assays	IgM ELISA	Human	BDSL, Dreghorn, Scotland	
			Vector-Best, Novosibirsk, Russia	(Mourya et al., 2012)
	IgG ELISA		Vector-Best, Novosibirsk, Russia	(Bodur et al., 2012; Gunes et al., 2009; Mustafa et al., 2011; Sidira et al., 2012)
	IgM IFA		Euroimmun, Luebeck, Germany	
	IgG IFA		Euroimmun, Luebeck, Germany	
	Antigen capture ELISA	Virus	Vector-Best, Novosibirsk, Russia	(Gunes et al., 2011)
In-house assays	IgM ELISA	Human	(Mourya et al., 2012)	(Mourya et al., 2012)
			(Garcia et al., 2006)	(Garcia et al., 2006)
			(Dowall et al., 2012)	(Dowall et al., 2012)
			(Emmerich et al., 2010)	
			(Tang et al., 2003)	
			(Burt et al., 1994)	(Burt et al., 1994)
	IgG ELISA	Human	(Dowall et al., 2012)	(Dowall et al., 2012)
			(Garcia et al., 2006)	(Garcia et al., 2006)
			(Burt et al., 1994)	(Burt et al., 1994)
			(Emmerich et al., 2010)	
			(Samudzi et al., 2012)	
			(Saijo et al., 2002a)	(Tang et al., 2003)
			USAMRIID, Fort Detrick, USA	(Mustafa et al., 2011)
	IgM IFA	Human	(Burt et al., 1994)	(Burt et al., 1994)
	IgG IFA		(Saijo et al., 2002b)	
			(Burt et al., 1994)	(Burt et al., 1994)
			(Xia et al., 2011)	(Xia et al., 2011)
	IgG Western-Blot assay	Human	(Xia et al., 2011)	(Xia et al., 2011)
	IgM ELISA	Sheep, cattle	(Burt et al., 1993)	(Burt et al., 1993)
	IgG ELISA	Sheep	(Burt et al., 1993)	(Burt et al., 1993)
			(Qing et al., 2003)	
			(Garcia et al., 2006)	(Garcia et al., 2006)
		Cattle	(Garcia et al., 2006)	(Garcia et al., 2006)
		Animals	CDC, Atlanta, USA	(Mourya et al., 2012)
			USAMRIID, Fort Detrick, USA	(Mustafa et al., 2011)
	Competitive ELISA	Species independent	(Burt et al., 1993)	(Burt et al., 1993)
	Antigen capture ELISA	Virus	(Burt et al., 1993)	(Burt et al., 1993)
			(Saijo et al., 2005)	

tion period up to five years. It is, however, necessary to consider that there is a considerable variation in the immune response and viral load among CCHF patients. Several predictors for lethality are being discussed. A viral load of over 10^8 RNA copy numbers per milliliter can often be found in patients with fatal outcome, but there is no clear correlation between antibody response and clinical signs (Cevik et al., 2007; Duh et al., 2007; Kubar et al., 2011).

The capacity of immunological assays is limited so that the diagnosis of cases with a weak or absent antibody response is hampered. In this case the detection of virus by molecular methods, such as RT-PCR, is recommended. Nevertheless, RT-PCR also has its limitations as a diagnostic tool due to a reduced sensitivity because of strain variations and because the virus can only be detected during the viremic phase. The patient needs to be transferred to a hospital within the first days after the onset of disease to obtain RT-PCR positive results (Duh et al., 2006). It is therefore recommended to perform RT-PCR in combination with immunological assays for the diagnosis of CCHFV infection (Drosten et al., 2003). Virus isolation can be achieved using LLC-MK2, Vero, BHK-21 and SW-13 cells. As the cytopathic effect of CCHFV in cells can be slight or absent, application of specific monoclonal antibodies for IFA testing may be indicated, as reviewed by Whitehouse (2004).

6. Treatment and vaccination

Patients should be monitored closely, in terms of clinical parameters, and the blood indices should be analyzed regularly to allow adjusting the treatment. In general, treatment of CCHF is limited to supportive measures. In case of extensive blood loss transfusions and injections of blood substitutes and aminocaproic acid are indicated. To support the hematological treatment fresh frozen plasma, thrombocyte solutions and erythrocyte preparations can be given. In addition, respiratory support may be required (Keshtkar-Jahromi et al., 2011; Leblebicioglu et al., 2012; Vorou, 2009).

The efficacy of ribavirin in antiviral treatment remains controversial. Ribavirin has been shown to inhibit the replication of CCHFV in cell culture, in newborn mice and in IFN-KO mice, providing a rationale for its use in humans (Tignor and Hanham, 1993; Watts et al., 1989; WHO, 2008, 2011). However, in affected humans its antiviral potency has only been shown in observational studies, as extensively reviewed by Keshtkar-Jahromi et al. (2011). Some studies suggest that its use in the early phase of the infection, during the replication of the virus, supports the convalescence of patients (Tasdelen Fisgin et al., 2009, 2010; Tignor and Hanham, 1993). However, amelioration or a positive effect on the course of the acute clinical disease and viremia seem to be low (Bodur et al., 2011), and the treatment of persons with ribavirin has to be performed in consideration of possible side-effects (Duygu et al., 2012).

In a recent study, the application of hyperimmune globulin appeared to reduce the time of viremia and to increase the survival rate in patients, but it unfortunately did not include a negative control group (Kubar et al., 2011). However, the results could be compared with those of a previous study in the same hospital. After application of immunoglobulin, CCHFV-specific RNA could be detected only in one case (1/26) lasting for more than one week after the onset of clinical symptoms, and only 14% (1/7) of the patients with a viral load of over 10^9 RNA copy numbers per milliliter died. This was an improvement, since virus RNA can generally be

detected for up to two weeks, and in comparison to the previous study where 80% (8/10) of the patients with a similar viral load died (Cevik et al., 2007; Kubar et al., 2011). In general, the benefits of an anti-CCHFV immunoglobulin therapy or the application of CCHFV-specific monoclonal antibodies has to be evaluated further by clinical trials (Keshtkar-Jahromi et al., 2011).

Since 1974, a vaccine has been used to protect military personnel, medical and agricultural workers against CCHFV infections in endemic areas of Bulgaria (Papa et al., 2004). The initiation of the vaccination program resulted in a decrease of CCHF cases in the following years. Because of the lack of epidemiological data of the neighboring countries, it cannot be excluded that other factors may also have had an impact on the decreased numbers of human cases. A change in the behavior of people, for example, could have led to a reduced exposure to ticks, or the reporting of cases may have changed. Before its use in Bulgaria, the vaccine was developed and used in the Soviet Union. It is based on brain tissue of CCHFV-infected mice inactivated by chloroform and heat (Papa et al., 2011a). It is the only vaccine available, and is currently produced by Bul Bio – National Center of Infectious and Parasitic Diseases Ltd.

CCHFV vaccines based on inactivated viruses must be produced in maximum bio-containment facilities, which are not easily available. The development of modern vaccines, e.g. virus-like particle-based vaccines or DNA vaccines, is hampered by the lack of adequate animal models for efficiency testing, as reviewed by Keshtkar-Jahromi et al. (2011). Until now, only two mouse models have been tested, and further investigations are needed (Bente et al., 2010; Bereczky et al., 2010). Despite rising annual numbers of diagnosed cases, the development of a vaccine for humans does not promise enough profit for the industry at present. As an alternative approach the use of vaccines for domestic animals could be considered, as animal vaccines can be developed more easily, and may therewith minimize human case numbers.

7. Public health risk perception

Risk perception has to be regarded and evaluated separately for different groups, e.g. the European Commission, countries with and without endemic areas, the national ministries, the public health institutions, the health care systems, and the public. It becomes clear that health education and information on prevention and behavioral measures have a high priority to enhance the public risk perception. Risk perception of the public in turn has a high potential to decrease the probability of infections and to influence the effectiveness of public health interventions positively. In this respect, integration and mutual exchange of information between all actors concerned, i.e. public health institutions, HCWs and the public, is crucial to ensure a fast and efficient risk communication. In Turkey for example, where CCHF cases are regularly reported the public awareness is high, and public health activities and risk mitigation measures are closely intertwined. However, CCHF has not yet been acknowledged as a serious threat for the public in all countries affected.

CCHFV is an important topic for the European community. The EU commission is therefore funding several EU projects within the seventh framework program, i.e. ARBO-ZOONET, CCH Fever, EDENext and ENIVD. The frequency of human-tick contacts is particularly high in areas where the tick population can grow. If CCHFV prevalence increases in ticks, then human cases can be expected (Kunchev and Kojouharova, 2008). The possibility that the virus can be spread by tick-infested birds and livestock animals has to be taken into account. However, the awareness of the disease in countries not affected so far, but that share a common border with countries where CCHFV is endemic, tends to be low (Vorou, 2009). This was seen in Greece in 2008 when the first case of CCHF was diagnosed only after the death of a patient, although, in the same year, human CCHF cases were reported from Turkey and Bulgaria, near the border to Greece (Kunchev and Kojouharova, 2008; Papa et al., 2010). Farmers in non-endemic regions should be aware of the risk of infection when working with animals from endemic or outbreak areas, especially when these animals are highly infested by ticks (Vorou, 2009).

In general, there is a lack of data of the risk awareness of the public. The results of a risk perception study performed with visitors to health centers in Ankara, Turkey, in 2006 showed that 87% of the participants had heard of the disease (Çilingiroglu et al., 2010). Around 90% of them remembered that ticks transmit the disease, 60% were aware that direct contact with blood of a patient could lead to an infection, and 72% knew that contact with blood of infected animals represented a risk factor. More than half of them (65%) knew that protection measures exist, and nearly 83% could list the most common symptoms. It can therefore be concluded that the awareness of the disease in countries with a good education program seems to be relatively high. Nevertheless, further studies about risk perception in endemic areas and surrounding countries should be performed.

8. Public health management

8.1. Management and communication

The distribution of CCHFV in southeastern Europe and the risk of virus spread is a challenge for the European community. In general, for evaluation of the situation regarding any vector-transmitted pathogen and for the decision if additional measures should be implemented, a systematic approach for the analysis, assessment and governance of emerging health risks should be followed (Schmidt et al., 2013). It is the task for decision makers, public health authorities and also for scientists to protect the population, to prevent virus spread and the establishment of new endemic areas. For this purpose, protocols and strategies should be harmonized and standardized on a regional, as well as national and international (e.g. European) level (Ahmed et al., 2009; Vorou, 2009). In this context, the authors suggest the following strategies for the management and control of CCHFV: The first step is the classification of countries and/or regions into risk zones. The classification ranges from areas with no risk of introduction of CCHFV and no infection risk for the population, e.g. Germany (zone 0; Fig. 3) to endemic areas with a permanent risk for humans, e.g. regions Tokat and Sivas in Turkey (zone 4; Fig. 3). A region is defined as an endemic area, if human cases have been reported, or if the virus has been detected in animals or ticks for at least two consecutive years.

The second step is the implementation of strategies and measures to characterize and to handle the risk. These steps become more salient when the risk zone classification is higher, and are of particular importance for risk zone 4 (endemic areas). The suggested strategy can be used as a guideline by countries for implementing the measures according to the respective level. The implementation of measures starts from level 0. On this level, two kinds of countries can be found: those in which no measures are necessary, because they belong to risk zone 0, or countries where no management measures are organized, although there is a risk of CCHFV infections (Fig. 4). When the measures from all previous levels have been implemented, the highest level (level 5) includes the last measures in trying to control CCHFV.

To detect the spread of CCHFV into new countries, and to recognize outbreaks from their beginning, international standardized surveillance programs for infections in humans, domestic animals

Zone	Country Definition	Measures
4	→ countries with endemic areas	→ level 1,2,3,4,5 (level 2 annual)
3	→ border to an endemic area	→ level 1,2,3,4 (level 2 annual)
2	→ Hyalomma population exist → animal transports from endemic areas	→ level 1,2,3 (level 2 regular)
1	→ suitable habitat for Hyalomma ticks → no animal transport from endemic areas	→ level 1,2 (level 2 sporadic)
0	→ no suitable habitat for Hyalomma ticks → no animal transports from endemic areas	→ level 0-1

Fig. 3. Guidelines for the classification of risk zones (0–4). The table indicates characteristics that affect the risk of CCHFV circulation in a particular country, based on which countries can be classified into different risk zones. The management measures (level 0–5) listed in Fig. 4 refer to these risk zones. Sporadic, regular and annual signifies how often the measures should be implemented.

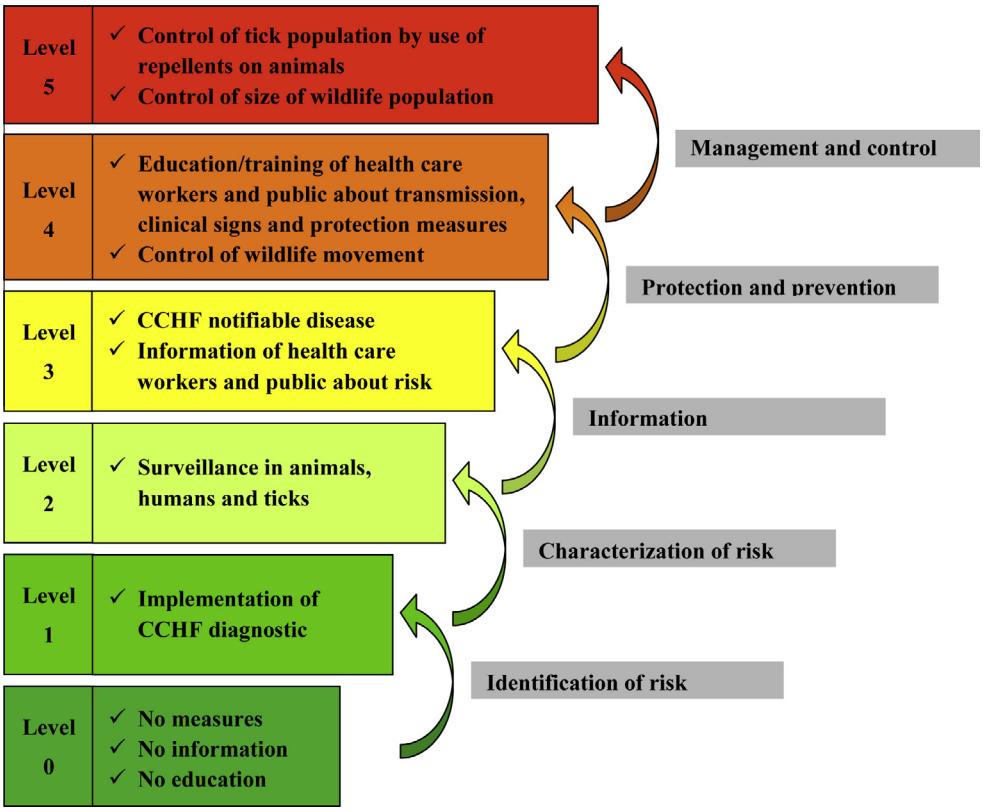

Fig. 4. Levels of measures for the management of CCHFV. The figure provides guidance to select appropriate management measures according to risk zone (Fig. 3) and to indicate the implementation of additional measures. The measures are built on one another, beginning with risk identification and proceeding to the control of the risk posed by CCHFV.

and ticks should be implemented in endemic and in non-affected countries bordering with endemic areas (zone 3, 4; Fig. 3). The application of repellents on livestock animals in endemic areas reduces the population of ticks and therewith decreases the risk of introducing ticks into non-endemic areas by animal transport (level 5; Fig. 4). In addition, use of repellents on animals two weeks before slaughtering can considerably reduce the risk for abattoir workers to become infected through exposure to ticks or contact with blood of viremic animals (Swanepoel et al., 1998).

The guidelines for the classification (Fig. 3) and the management levels (Fig. 4) can generally be adapted to other tick-borne diseases, such as tick-borne encephalitis or Lyme borreliosis. Here, the main vectors are *Ixodes* ticks, and the main characteristic for the classification into risk levels focuses on the habitat, rather than on animal transport. For the management of these diseases it is more important to educate HCWs in the diagnosis than to implement personal protection and barrier nursing (level 4). In the case of TBEV, vaccination programs can be implemented. Since mainly small wild mammals are involved in the infection cycle, the use of repellents on livestock has a negligible effect (Charrel et al., 2004; Heyman et al., 2010; Hubalek and Rudolf, 2012; Kallio-Kokko et al., 2005).

In order to develop accurate risk maps and forecasting models a joint database for tick-borne diseases and their occurrence, including surveillance data and studies on ticks, should be built up. Training courses and information brochures that aim at outbreak

response, surveillance strategies and the notification system should be organized on an European level for public health authorities. Information about best practice to avoid tick bites, and protection measures to reduce the risk of infection should be distributed to the public and among HCWs, not only in countries with endemic areas but also in neighboring countries and those importing animals from risk areas (Vorou, 2009). A good education program is exceptionally important in preventing an outbreak. In case of CCHF, human-to-human transmissions can be prevented by immediate hospitalization and isolation of patients before the onset of hemorrhagic manifestations (Papa et al., 2010). Moreover, regular training courses for HCWs will keep the delay of healthcare referrals and initial misdiagnoses to a minimum, and therewith reduce the lethality rate (Tasdelen Fisgin et al., 2010). Therefore, it is essential to inform HCWs and the public about the first indications of CCHFV infections.

Well-coordinated communication of first or new cases is of imminent importance for preventing further infections. In order to achieve this, some rules in regard to risk communication should be considered (WHO, 2005). An efficient outbreak management is based on trust between the technical staff, policy makers and communicators, but also on trust between the public and the outbreak management, and the trust of managers in the ability of the public to tolerate worrying news. A convenient starting point for establishing trust is transparency and the integration of the different groups in the information and management process. Transparency has the largest impact on trust to demonstrate that competent decisions are being made. An early announcement is the best way to prevent rumors or misinformation. Before initial or new cases are announced to the public, all partners involved in the risk management should be informed by well-established communication channels. Because the first announcement is usually based on incomplete information, it is essential to communicate new knowledge and findings to the public. The way of communication, in particular the announcements, should take the knowledge and the opinion of the public about the specific risk into account. Rumors or incorrect information should not be ignored, but corrected by well-prepared announcements. The communication should include information about protection measures to give the public a sense of control over their own safety (Bannister, 2010).

8.2. Information material and communication channels

In some countries, the public, practitioners and veterinarians become informed about CCHF, protection measures and adequate behavior in case of an emergency only (Kunchev and Kojouharova, 2008). After the first human case in Greece, the Hellenic Centre for Disease Control and Prevention (HCDCP) sent guidelines for the management of suspected CCHF cases and infection control measures to all hospitals in northern Greece (Papa et al., 2008). Residents of the area where the infections occurred were informed about tick bite prevention measures, and HCWs received guidelines for the proper removal of ticks.

In Turkey in 2004, following the advice of a scientific advisory commission, the Ministries of Health and the ministry of Agriculture and Rural Affairs initiated a nationwide surveillance and control program, including educational measures, on the risk of CCHF transmission, tick removal, general protection measures and on the early detection of cases. In addition, brochures, posters and TV spots for public and health care workers were produced (Yilmaz et al., 2008). In endemic areas, door-to-door educational programs were implemented concerning safe tick removal, the exposure risk through body fluids and blood of livestock animals, and the use of tick repellents. In general, media such as television play a key role in educating the public, as most people acquire their knowledge about CCHF from TV (Çilingiroglu et al., 2010).

9. Conclusion

Addressing its potential impact on public health, this review summarizes the current understanding of CCHFV to provide a broad basis for the risk assessment and the development of prevention strategies. In respect to the wide distribution of CCHFV, the broad host range of its vectors, the good adaptation of the virus to the vector population together with its potential to be transmitted from human to human (e.g. by nosocomial infections), the high lethality rate, and the limited therapeutic interventions make CCHFV a significant public health threat in southeastern Europe.

It should be mentioned that, due to the lack of knowledge concerning the epidemiology of CCHF, it cannot be excluded that the virus had been circulating in many countries of southeastern Europe, Africa and Asia a long time before it was detected for the first time. This leads to speculations that the detection of virus in new areas may rather be a result of the increased attention than virus introduction. Nevertheless, considering the distribution of ticks and the ecologic and climatic changes in Europe, there is some probability that CCHFV can spread over a much larger area than its current geographical range (Estrada-Pena et al., 2012d; Maltezou et al., 2010).

By summarizing aspects of CCHFV relevant to public health, this review highlights the need for further studies and points out gaps in current knowledge. It underlines the importance to strengthen public health preparedness in general, and to establish or refine adequate diagnostic tools for systematic human, veterinary, vector and pathogen surveillance, especially in areas where CCHF is expected to occur in the future. In order to prevent the introduction of CCHFV into new areas and to protect the public, this paper provides guidelines for classifying the risk of each country and/or region as a basis for managing the risk posed by CCHFV. These guidelines for the classification and management levels can also be adapted and applied for other tick-borne diseases. As the awareness of CCHFV as a serious threat to public health has grown, the first transnational approaches in regard to risk evaluation, diagnostics and surveillance studies have been initiated. More international exchanges about this important public health issue are certainly needed in future.

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References

Ahmed, J., Bouloy, M., Ergonul, O., Fooks, A., Paweska, J., Chevalier, V., Drosten, C., Moormann, R., Tordo, N., Vatansever, Z., Calistri, P., Estrada-Pena, A., Mirazimi, A., Unger, H., Yin, H., Seitzer, U., 2009. International network for capacity building for the control of emerging viral vector-borne zoonotic diseases: ARBO-ZOONET. Euro Surveill., 14.

Altaf, A., Luby, S., Ahmed, A.J., Zaidi, N., Khan, A.J., 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, 878–882.

Aradaib, I.E., Erickson, B.R., Mustafa, M.E., Khristova, M.L., Saeed, N.S., Elageb, R.M., Nichol, S.T., 2010. Nosocomial outbreak of Crimean-Congo hemorrhagic fever, Sudan. Emerg. Infect. Dis. 16, 837–839.

Athar, M.N., Khalid, M.A., Ahmad, A.M., Bashir, N., Baqai, H.Z., Ahmad, M., Balouch, A.H., Bashir, K., 2005. Crimean-Congo hemorrhagic fever outbreak in Rawalpindi, Pakistan, February 2002: contact tracing and risk assessment. Am. J. Trop. Med. Hyg. 72, 471–473.

Avšič-Županc, T., 2008. Epidemiology and current geographical distribution of Crimean-Congo haemorrhagic fever. <http://www.arbo-zoo.net/_data/arbozoonet-news_No2.pdf>, pp. 8–15.

Bannister, B., 2010. Viral haemorrhagic fevers imported into non-endemic countries: risk assessment and management. Br. Med. Bull. 95, 193–225.
Bente, D.A., Alimonti, J.B., Shieh, W.J., Camus, G., Stroher, U., Zaki, S., Jones, S.M., 2010. Pathogenesis and immune response of Crimean-Congo hemorrhagic fever virus in a STAT-1 knockout mouse model. J. Virol. 84, 11089–11100.
Bereczky, S., Lindegren, G., Karlberg, H., Akerstrom, S., Klingstrom, J., Mirazimi, A., 2010. Crimean-Congo hemorrhagic fever virus infection is lethal for adult type I interferon receptor-knockout mice. J. Gen. Virol. 91, 1473–1477.
Bodur, H., Akinci, E., Ascioglu, S., Onguru, P., Uyar, Y., 2012. Subclinical infections with Crimean-Congo hemorrhagic fever virus, Turkey. Emerg. Infect. Dis. 18, 640–642.
Bodur, H., Akinci, E., Onguru, P., Carhan, A., Uyar, Y., Tanrici, A., Cataloluk, O., Kubar, A., 2010. Detection of Crimean-Congo hemorrhagic fever virus genome in saliva and urine. Int. J. Infect. Dis. 14, e247–e249.
Bodur, H., Erbay, A., Akinci, E., Onguru, P., Bayazit, N., Eren, S.S., Kubar, A., 2011. Effect of oral ribavirin treatment on the viral load and disease progression in Crimean-Congo hemorrhagic fever. Int. J. Infect. Dis. 15, e44–e47.
Bronze, M.S., Huycke, M.M., Machado, L.J., Voskuhl, G.W., Greenfield, R.A., 2002. Viral agents as biological weapons and agents of bioterrorism. Am. J. Med. Sci. 323, 316–325.
Burt, F.J., Leman, P.A., Abbott, J.C., Swanepoel, R., 1994. Serodiagnosis of Crimean-Congo haemorrhagic fever. Epidemiol. Infect. 113, 551–562.
Burt, F.J., Swanepoel, R., Braack, L.E., 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.
Causey, O.R., Kemp, G.E., Madbouly, M.H., David-West, T.S., 1970. Congo virus from domestic livestock, African hedgehog, and arthropods in Nigeria. Am. J. Trop. Med. Hyg. 19, 846–850.
CDC, 2011. Tick Removal. Centers for disease control and prevention. <http://www.cdc.gov/ticks/removing_a_tick.html> (accessed 2.11.12.).
Cevik, M.A., Erbay, A., Bodur, H., Eren, S.S., Akinci, E., Sener, K., Onguru, P., Kubar, A., 2007. Viral load as a predictor of outcome in Crimean-Congo hemorrhagic fever. Clin. Infect. Dis. 45, e96–e100.
Charrel, R.N., Attoui, H., Butenko, A.M., Clegg, J.C., Deubel, V., Frolova, T.V., Gould, E.A., Gritsun, T.S., Heinz, F.X., Labuda, M., Lashkevich, V.A., Loktev, V., Lundkvist, A., Lvov, D.V., Mandl, C.W., Niedrig, M., Papa, A., Petrov, V.S., Plyusnin, A., Randolph, S., Suss, J., Zlobin, V.I., de Lamballerie, X., 2004. Tick-borne virus diseases of human interest in Europe. Clin. Microbiol. Infect. 10, 1040–1055.
Chinikar, S., Ghiasi, S.M., Moradi, M., Goya, M.M., Shirzadi, M.R., Zeinali, M., Meshkat, M., Bouloy, M., 2010. Geographical distribution and surveillance of Crimean-Congo hemorrhagic fever in Iran. Vector Borne Zoonotic Dis. 10, 705–708.
Çilingiroglu, N., Temel, F., Altintas, H., 2010. Public's knowledge, opinions and behaviors about Crimean-Congo hemorrhagic fever: an example from Turkey. Kafkas Univ. Vet. Fak. Derg. 16, 17–22.
Dowall, S.D., Richards, K.S., Graham, V.A., Chamberlain, J., Hewson, R., 2012. Development of an indirect ELISA method for the parallel measurement of IgG and IgM antibodies against Crimean-Congo haemorrhagic fever (CCHF) virus using recombinant nucleoprotein as antigen. J. Virol. Methods 179, 335–341.
Drosten, C., Gottig, S., Schilling, S., Asper, M., Panning, M., Schmitz, H., Gunther, S., 2002. Rapid detection and quantification of RNA of Ebola and Marburg viruses, Lassa virus, Crimean-Congo hemorrhagic fever virus, Rift Valley fever virus, dengue virus, and yellow fever virus by real-time reverse transcription-PCR. J. Clin. Microbiol. 40, 2323–2330.
Drosten, C., Kummerer, B.M., Schmitz, H., Gunther, S., 2003. Molecular diagnostics of viral hemorrhagic fevers. Antiviral Res. 57, 61–87.
Duh, D., Saksida, A., Petrovec, M., Ahmeti, S., Dedushaj, I., Panning, M., Drosten, C., Avsic-Zupanc, T., 2007. Viral load as predictor of Crimean-Congo hemorrhagic fever outcome. Emerg. Infect. Dis. 13, 1769–1772.
Duh, D., Saksida, A., Petrovec, M., Dedushaj, I., Avsic-Zupanc, T., 2006. Novel one-step real-time RT-PCR assay for rapid and specific diagnosis of Crimean-Congo hemorrhagic fever encountered in the Balkans. J. Virol. Methods 133, 175–179.
Dunster, L., Dunster, M., Ofula, V., Beti, D., Kazooba-Voskamp, F., Burt, F., Swanepoel, R., DeCock, K.M., 2002. First documentation of human Crimean-Congo hemorrhagic fever, Kenya. Emerg. Infect. Dis. 8, 1005–1006.
Duygu, F., Kaya, T., Baysan, P., 2012. Re-evaluation of 400 crimean-congo hemorrhagic Fever cases in an endemic area: is ribavirin treatment suitable? Vector Borne Zoonotic Dis. 12, 812–816.
EFSA, 2010. Scientific Opinion on the Role of Tick Vectors in the Epidemiology of Crimean-Congo Hemorrhagic Fever and African Swine Fever in Eurasia, pp. 1–156.
Emmerich, P., Avsic-Zupanc, T., Chinikar, S., Saksida, A., Thome-Bolduan, C., Parczany-Hartmann, A., Langroudi, A.G., Moradi, M., Ahmeti, S., Gunther, S., Schmidt-Chanasit, J., 2010. Early serodiagnosis of acute human Crimean-Congo hemorrhagic fever virus infections by novel capture assays. J. Clin. Virol. 48, 294–295.
ENIVD, 2001. Management and Control of Viral Haemorrhagic Fevers and other highly contagious viral pathogens. <http://www.enivd.de/netz.pdf> (accessed 05.01.).
Ergonul, O., 2006. Crimean-Congo haemorrhagic fever. Lancet Infect. Dis. 6, 203–214.
Ergonul, O., Zeller, H., Celikbas, A., Dokuzoguz, B., 2007. The lack of Crimean-Congo hemorrhagic fever virus antibodies in healthcare workers in an endemic region. Int. J. Infect. Dis. 11, 48–51.
Estrada-Pena, A., Ayllon, N., de la Fuente, J., 2012a. Impact of climate trends on tick-borne pathogen transmission. Front. Physiol. 3, 64.
Estrada-Pena, A., Jameson, L., Medlock, J., Vatansever, Z., Tishkova, F., 2012b. Unraveling the ecological complexities of tick-associated Crimean-Congo hemorrhagic fever virus transmission: a gap analysis for the western Palearctic. Vector Borne Zoonotic Dis. 12, 743–752.
Estrada-Pena, A., Martinez Aviles, M., Munoz Reoyo, M.J., 2011. A population model to describe the distribution and seasonal dynamics of the tick *Hyalomma marginatum* in the Mediterranean Basin. Transbound. Emerg. Dis. 58, 213–223.
Estrada-Pena, A., Palomar, A.M., Santibanez, P., Sanchez, N., Habela, M.A., Portillo, A., Romero, L., Oteo, J.A., 2012d. Crimean-Congo hemorrhagic fever virus in ticks, Southwestern Europe, 2010. Emerg. Infect. Dis. 18, 179–180.
Estrada-Pena, A., Sanchez, N., Estrada-Sanchez, A., 2012e. An assessment of the distribution and spread of the tick *Hyalomma marginatum* in the western palearctic under different climate scenarios. Vector Borne Zoonotic Dis. 12, 758–768.
Estrada-Pena, A., Zatansever, Z., Gargili, A., Aktas, M., Uzun, R., Ergonul, O., Jongejan, F., 2007. Modeling the spatial distribution of crimean-congo hemorrhagic fever outbreaks in Turkey. Vector Borne Zoonotic Dis. 7, 667–678.
Gale, P., Stephenson, B., Brouwer, A., Martinez, M., de la Torre, A., Bosch, J., Foley-Fisher, M., Bonilauri, P., Lindstrom, A., Ulrich, R.G., de Vos, C.J., Scremin, M., Liu, Z., Kelly, L., Munoz, M.J., 2012. Impact of climate change on risk of incursion of Crimean-Congo haemorrhagic fever virus in livestock in Europe through migratory birds. J. Appl. Microbiol. 112, 246–257.
Garcia, S., Chinikar, S., Coudrier, D., Billecocq, A., Hooshmand, B., Crance, J.M., Garin, D., Bouloy, M., 2006. Evaluation of a Crimean-Congo hemorrhagic fever virus recombinant antigen expressed by Semliki Forest suicide virus for IgM and IgG antibody detection in human and animal sera collected in Iran. J. Clin. Virol. 35, 154–159.
Goldfarb, L.G., Chumakov, M.P., Myskin, A.A., Kondratenko, V.F., Reznikova, O.Y., 1980. An epidemiological model of Crimean hemorrhagic fever. Am. J. Trop. Med. Hyg. 29, 260–264.
Gonzalez, J.P., Camicas, J.L., Cornet, J.P., Faye, O., Wilson, M.L., 1992. Sexual and transovarian transmission of Crimean-Congo haemorrhagic fever virus in *Hyalomma truncatum* ticks. Res. Virol. 143, 23–28.
Gray, J.S., Dautel, H., Estrada-Pena, A., Kahl, O., Lindgren, E., 2009. Effects of climate change on ticks and tick-borne diseases in Europe. Interdiscip. Perspect. Infect. Dis. 2009, 593232.
Gunes, T., Engin, A., Poyraz, O., Elaldi, N., Kaya, S., Dokmetas, I., Bakir, M., Cinar, Z., 2009. Crimean-Congo hemorrhagic fever virus in high-risk population, Turkey. Emerg. Infect. Dis. 15, 461–464.
Gunes, T., Poyraz, O., Vatansever, Z., 2011. Crimean-Congo hemorrhagic fever virus in ticks collected from humans, livestock, and picnic sites in the hyperendemic region of Turkey. Vector Borne Zoonotic Dis. 11, 1411–1416.
Gurbuz, Y., Sencan, I., Ozturk, B., Tutuncu, E., 2009. A case of nosocomial transmission of Crimean-Congo hemorrhagic fever from patient to patient. Int. J. Infect. Dis. 13, e105–e107.
Heyman, P., Cochez, C., Hofhuis, A., van der Giessen, J., Sprong, H., Porter, S.R., Losson, B., Saegerman, C., Donoso-Mantke, O., Niedrig, M., Papa, A., 2010. A clear and present danger: tick-borne diseases in Europe. Expert Rev. Anti Infect. Ther. 8, 33–50.
Hornok, S., Horvath, G., 2012. First report of adult *Hyalomma marginatum* rufipes (vector of Crimean-Congo haemorrhagic fever virus) on cattle under a continental climate in Hungary. Parasit. Vectors 5, 170.
Hubalek, Z., Rudolf, I., 2012. Tick-borne viruses in Europe. Parasitol. Res. 111, 9–36.
Humolli, I., Dedushaj, I., Zupanac, T.A., Mucaj, S., 2010. Epidemiological, serological and herd immunity of Crimean-Congo haemorrhagic fever in Kosovo. Med. Arch. 64, 91–93.
Jameson, L.J., Ramadani, N., Medlock, J.M., 2012. Possible drivers of crimean-congo hemorrhagic fever virus transmission in Kosova. Vector Borne Zoonotic Dis. 12, 753–757.
Kallio-Kokko, H., Uzcategui, N., Vapalahti, O., Vaheri, A., 2005. Viral zoonoses in Europe. FEMS Microbiol. Rev. 29, 1051–1077.
Karti, S.S., Odabasi, Z., Korten, V., Yilmaz, M., Sonmez, M., Caylan, R., Akdogan, E., Eren, N., Koksal, I., Ovali, E., Erickson, B.R., Vincent, M.J., Nichol, S.T., Comer, J.A., Rollin, P.E., Ksiazek, T.G., 2004. Crimean-Congo hemorrhagic fever in Turkey. Emerg. Infect. Dis. 10, 1379–1384.
Keshtkar-Jahromi, M., Kuhn, J.H., Christova, I., Bradfute, S.B., Jahrling, P.B., Bavari, S., 2011. Crimean-Congo hemorrhagic fever: current and future prospects of vaccines and therapies. Antiviral Res. 90, 85–92.
Koksal, I., Yilmaz, G., Iskender, S., Arslan, M., Yavuz, I., Aksoy, F., Vatansever, Z., 2011. The first Crimean-Congo hemorrhagic fever case in the winter season from Turkey. Intervirology 54, 144–145.
Kubar, A., Haciomeroglu, M., Ozkul, A., Bagriacik, U., Akinci, E., Sener, K., Bodur, H., 2011. Prompt administration of Crimean-Congo hemorrhagic fever (CCHF) virus hyperimmunoglobulin in patients diagnosed with CCHF and viral load monitorization by reverse transcriptase-PCR. Jpn. J. Infect. Dis. 64, 439–443.
Kunchev, A., Kojouharova, M., 2008. Probable cases of Crimean-Congo-haemorrhagic fever in Bulgaria: a preliminary report. Euro Surveill., 13.
Leblebicioglu, H., Bodur, H., Dokuzoguz, B., Elaldi, N., Guner, R., Koksal, I., Kurt, H., Senturk, G.C., 2012. Case management and supportive treatment for patients with Crimean-Congo hemorrhagic fever. Vector Borne Zoonotic Dis. 12, 805–811.
Maltezou, H.C., Andonova, L., Andraghetti, R., Bouloy, M., Ergonul, O., Jongejan, F., Kalvatchev, N., Nichol, S., Niedrig, M., Platonov, A., Thomson, G., Leitmeyer, K., Zeller, H., 2010. Crimean-Congo hemorrhagic fever in Europe: current situation calls for preparedness. Euro Surveill. 15, 19504.

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

Mourya, D.T., Yadav, P.D., Shete, A.M., Gurav, Y.K., Raut, C.G., Jadi, R.S., Pawar, S.D., Nichol, S.T., Mishra, A.C., 2012. Detection, isolation and confirmation of Crimean-Congo hemorrhagic fever virus in human, ticks and animals in Ahmadabad, India, 2010–2011. PLoS Negl. Trop. Dis. 6, e1653.

Mustafa, M.L., Ayazi, E., Mohareb, E., Yingst, S., Zayed, A., Rossi, C.A., Schoepp, R.J., Mofleh, J., Fiekert, K., Akhbarian, Z., Sadat, H., Leslie, T., 2011. Crimean-Congo hemorrhagic fever, Afghanistan, 2009. Emerg. Infect. Dis. 17, 1940–1941.

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

Papa, A., Bozovi, B., Pavlidou, V., Papadimitriou, E., Pelemis, M., Antoniadis, A., 2002b. Genetic detection and isolation of crimean-congo hemorrhagic fever virus, Kosovo, Yugoslavia. Emerg. Infect. Dis. 8, 852–854.

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

Papa, A., Dalla, V., Papadimitriou, E., Kartalis, G.N., Antoniadis, A., 2010. Emergence of Crimean-Congo haemorrhagic fever in Greece. Clin. Microbiol. Infect. 16, 843–847.

Papa, A., Drosten, C., Bino, S., Papadimitriou, E., Panning, M., Velo, E., Kota, M., Harxhi, A., Antoniadis, A., 2007. Viral load and Crimean-Congo hemorrhagic fever. Emerg. Infect. Dis. 13, 805–806.

Papa, A., Maltezou, H.C., Tsiodras, S., Dalla, V.G., Papadimitriou, T., Pierroutsakos, I., Kartalis, G.N., Antoniadis, A., 2008. A case of Crimean-Congo haemorrhagic fever in Greece, June 2008. Euro Surveill., 13.

Papa, A., Papadimitriou, E., Christova, I., 2011a. The Bulgarian vaccine Crimean-Congo haemorrhagic fever virus strain. Scand. J. Infect. Dis. 43, 225–229.

Papa, A., Tzala, E., Maltezou, H.C., 2011b. Crimean-Congo hemorrhagic fever virus, northeastern Greece. Emerg. Infect. Dis. 17, 141–143.

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. 9, 713–716.

Papadopoulos, O., Koptopoulos, G., 1980. Crimean-Congo Hemorrhagic Fever (CCHF) in Greece: Isolation of the Virus from Rhicicephalus Bursa Ticks and a Preliminary Serological Survey. In: J.V.-H.e. (Ed.), Arboviruses in the Mediterranean Countries, Gustav Fischer Verlag, Stuttgart, New York.

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.

Saijo, M., Qing, T., Niikura, M., Maeda, A., Ikegami, T., Prehaud, C., Kurane, I., Morikawa, S., 2002a. Recombinant nucleoprotein-based enzyme-linked immunosorbent assay for detection of immunoglobulin G antibodies to Crimean-Congo hemorrhagic fever virus. J. Clin. Microbiol. 40, 1587–1591.

Saijo, M., Qing, T., Niikura, M., Maeda, A., Ikegami, T., Sakai, K., Prehaud, C., Kurane, I., Morikawa, S., 2002b. Immunofluorescence technique using HeLa cells expressing recombinant nucleoprotein for detection of immunoglobulin G antibodies to Crimean-Congo hemorrhagic fever virus. J. Clin. Microbiol. 40, 372–375.

Saijo, M., Tang, Q., Shimayi, B., Han, L., Zhang, Y., Asiguma, M., Tianshu, D., Maeda, A., Kurane, I., Morikawa, S., 2005. Antigen-capture enzyme-linked immunosorbent assay for the diagnosis of crimean-congo hemorrhagic fever using a novel monoclonal antibody. J. Med. Virol. 77, 83–88.

Samudzi, R.R., Leman, P.A., Paweska, J.T., Swanepoel, R., Burt, F.J., 2012. Bacterial expression of Crimean-Congo hemorrhagic fever virus nucleoprotein and its evaluation as a diagnostic reagent in an indirect ELISA. J. Virol. Methods 179, 70–76.

Schmidt, K., Dressel, K.M., Niedrig, M., Mertens, M., Schüle, S.A., Groschup, M.H., 2013. Public health and vector-borne diseases – a new concept for risk governance, zoonoses and public health, in press.

Shepherd, A.J., Leman, P.A., 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, A.J., Swanepoel, R., Leman, P.A., Shepherd, S.P., 1987. Field and laboratory investigation of Crimean-Congo haemorrhagic fever virus (Nairovirus, family Bunyaviridae) infection in birds. Trans. R. Soc. Trop. Med. Hyg. 81, 1004–1007.

Sidira, P., Maltezou, H.C., Haidich, A.B., Papa, A., 2012. Seroepidemiological study of Crimean-Congo haemorrhagic fever in Greece, 2009–2010. Clin. Microbiol. Infect. 18, E16–E19.

Suss, J., 2011. Tick-borne encephalitis 2010: epidemiology, risk areas, and virus strains in Europe and Asia – an overview. Ticks Tick Borne Dis. 2, 2–15.

Swanepoel, R., Leman, P.A., Burt, F.J., Jardine, J., Verwoerd, D.J., Capua, I., Bruckner, G.K., Burger, W.P., 1998. Experimental infection of ostriches with Crimean-Congo haemorrhagic fever virus. Epidemiol. Infect. 121, 427–432.

Swanepoel, R., Shepherd, A.J., Leman, P.A., Shepherd, S.P., McGillivray, G.M., Erasmus, M.J., Searle, L.A., Gill, D.E., 1987. Epidemiologic and clinical features of Crimean-Congo hemorrhagic fever in southern Africa. Am. J. Trop. Med. Hyg. 36, 120–132.

Tang, Q., Saijo, M., Zhang, Y., Asiguma, M., Tianshu, D., Han, L., Shimayi, B., Maeda, A., Kurane, I., Morikawa, S., 2003. A patient with Crimean-Congo hemorrhagic fever serologically diagnosed by recombinant nucleoprotein-based antibody detection systems. Clin. Diagn. Lab. Immunol. 10, 489–491.

Tasdelen Fisgin, N., Doganci, L., Tanyel, E., Tulek, N., 2010. Initial high rate of misdiagnosis in Crimean Congo haemorrhagic fever patients in an endemic region of Turkey. Epidemiol. Infect. 138, 139–144.

Tasdelen Fisgin, N., Ergonul, O., Doganci, L., Tulek, N., 2009. The role of ribavirin in the therapy of Crimean-Congo hemorrhagic fever: early use is promising. Eur. J. Clin. Microbiol. Infect. Dis. 28, 929–933.

Tekin, S., Barut, S., Bursali, A., Aydogan, G., Yuce, O., Demir, F., Yildirin, B., 2010. Seroprevalence of Crimean-Congo haemorrhagic fever (CCHF) in risk groups in Tokat Province of Turkey. Afr. J. Microbiol. Res. 4, 214–217.

Tignor, G.H., Hanham, C.A., 1993. Ribavirin efficacy in an in vivo model of Crimean-Congo hemorrhagic fever virus (CCHF) infection. Antiviral Res. 22, 309–325.

van de Wal, B.W., Joubert, J.R., van Eeden, P.J., King, J.B., 1985. A nosocomial outbreak of Crimean-Congo haemorrhagic fever at Tygerberg Hospital. Part IV. Preventive and prophylactic measures. S. Afr. Med. J. 68, 729–732.

van Eeden, P.J., van Eeden, S.F., Joubert, J.R., King, J.B., van de Wal, B.W., Michell, W.L., 1985. A nosocomial outbreak of Crimean-Congo haemorrhagic fever at Tygerberg hospital. Part II. Management of patients. S. Afr. Med. J. 68, 718–721.

Vanhomwegen, J., Alves, M.J., Zupanc, T.A., Bino, S., Chinikar, S., Karlberg, H., Korukluoglu, G., Korva, M., Mardani, M., Mirazimi, A., Mousavi, M., Papa, A., Saksida, A., Sharifi-Mood, B., Sidira, P., Tsergouli, K., Wolfel, R., Zeller, H., Dubois, P., 2012. Diagnostic assays for crimean-congo hemorrhagic fever. Emerg. Infect. Dis. 18, 1958–1965.

Vorou, R.M., 2009. Crimean-Congo hemorrhagic fever in southeastern Europe. Int. J. Infect. Dis. 13, 659–662.

Watts, D.M., Ussery, M.A., Nash, D., Peters, C.J., 1989. Inhibition of Crimean-Congo hemorrhagic fever viral infectivity yields in vitro by ribavirin. Am. J. Trop. Med. Hyg. 41, 581–585.

Whitehouse, C.A., 2004. Crimean-Congo hemorrhagic fever. Antiviral Res. 64, 145–160.

WHO, 2001. Crimean-Congo haemorrhagic fever. <http://www.who.int/mediacentre/factsheets/fs208/en/> WHO (accessed 13.).

WHO, 2005. WHO Outbreak communication guidelines. <http://www.who.int/infectious-disease-news/IDdocs/whocds200528/whocds200528en.pdf> WHO (accessed 13.).

WHO, 2008. WHO model formulary. <http://apps.who.int/medicinedocs/documents/s16879e/s16879e.pdf> WHO (accessed 13.).

WHO, 2011. WHO Model Lists of Essential Medicines. In: Organization, W.H. (Ed.), <http://www.who.int/medicines/publications/essentialmedicines/en/>.

Wilson, M.L., Gonzalez, J.P., Cornet, J.P., Camicas, J.L., 1991. Transmission of Crimean-Congo haemorrhagic fever virus from experimentally infected sheep to Hyalomma truncatum ticks. Res. Virol. 142, 395–404.

Wirtz, A., Niedrig, M., Fock, R., 2002. Management of patients in Germany with suspected viral haemorrhagic fever and other potentially lethal contagious infections. Euro Surveill. 7, 36–42.

Wolfel, R., Paweska, J.T., Petersen, N., Grobbelaar, A.A., Leman, P.A., Hewson, R., Georges-Courbot, M.C., Papa, A., Gunther, S., Drosten, C., 2007. Virus detection and monitoring of viral load in Crimean-Congo hemorrhagic fever virus patients. Emerg. Infect. Dis. 13, 1097–1100.

Xia, H., Li, P., Yang, J., Pan, L., Zhao, J., Wang, Z., Li, Y., Zhou, H., Dong, Y., Guo, S., Tang, S., Zhang, Z., Fan, Z., Hu, Z., Kou, Z., Li, T., 2011. Epidemiological survey of Crimean-Congo hemorrhagic fever virus in Yunnan, China, 2008. Int. J. Infect. Dis. 15, e459–e463.

Yen, Y.C., Kong, L.X., Lee, L., Zhang, Y.Q., Li, F., Cai, B.J., Gao, S.Y., 1985. Characteristics of Crimean-Congo hemorrhagic fever virus (Xinjiang strain) in China. Am. J. Trop. Med. Hyg. 34, 1179–1182.

Yilmaz, G.R., Buzgan, T., Irmak, H., Safran, A., Uzun, R., Cevik, M.A., Torunoglu, M.A., 2009. The epidemiology of Crimean-Congo hemorrhagic fever in Turkey, 2002–2007. Int. J. Infect. Dis. 13, 380–386.

Yilmaz, G.R., Buzgan, T., Torunoglu, M.A., Safran, A., Irmak, H., Com, S., Uyar, Y., Carhan, A., Ozkaya, E., Ertek, M., 2008. A preliminary report on Crimean-Congo haemorrhagic fever in Turkey, March – June 2008. Euro Surveill., 13.

Zeller, H.G., Cornet, J.P., Camicas, J.L., 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, 676–681.