Workshop on a

Risk Assessment of Crimean Congo Haemorrhagic Fever in Western Europe

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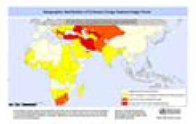

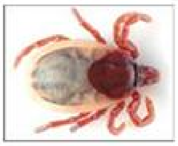

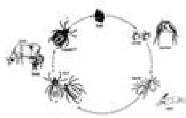

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Executive Summary

The recent incursions of exotic vector-borne livestock diseases into new areas have stressed the need for disease detection and control. Better knowledge of vector-borne diseases and more insight into the possible pathways for introduction and subsequent spread of these diseases is a prerequisite for efficient and cost effective risk management. On behalf of the Dutch Ministry of Economic Affairs, Agriculture and Innovation (EL&I) a framework for risk assessment of emerging vector-borne livestock diseases was developed by the Central Veterinary Institute (CVI) and the Agricultural Economics Research Institute (LEI), both part of Wageningen University and Research centre.

This framework was first tested in 2011 by applying it to the case of Rift Valley fever (RVF), a mosquito-borne viral zoonotic livestock disease. In 2012 the framework was further tested by applying it to the case of Crimean Congo Haemorrhagic fever (CCHF), a tick-borne viral haemorrhagic disease. In both cases the choice of disease was based on concern for future incursions of these diseases into Western Europe and a real interest in the results of these risk assessments, despite the expected uncertainties.

The CCHF virus (CCHFV) risk was assessed using the framework in a workshop with 22 participants, each an expert on a topic relevant for CCHFV risk assessment. It was found that the most likely introduction route of CCHFV into Western Europe is through infected ticks hitchhiking on migratory birds. Local wildlife, such as deer and wild boar will aid the further spread from point of entry. Large distance spread (within Europe) can subsequently be caused by the international trade in livestock. Due to the absence of clinical disease in animals and the slow life-cycle of *Hyalomma* (and other ticks), detection of the infection in livestock is unlikely until a human case is diagnosed. The likelihood of a human case greatly depends on the probability of establishment of *Hyalomma* tick in Western Europe. Warmer and dryer areas, such as the Mediterranean basin, are thought suitable for tick survival and establishment. The wetter and milder northern parts of Western Europe are thought to be unsuitable for survival of *Hyalomma* ticks. It is not known whether or not tick species native to Western Europe are efficient CCHFV vectors and able to function as a reservoir for CCHFV. Based on international experience, this was considered unlikely.

Overall, it is believed that introductions of CCHFV into Western Europe are likely to have occurred in the past and will continue to occur regularly. Global climate change may tip the balance between unsuccessful and successful establishment of the main vector and thus of the infection. At present, the detection of a CCHFV infected tick in Western Europe is not thought to cause much impact. However, detection of CCHFV in livestock or in a person, which has locally (*i.e.* in Western Europe) acquired the infection, could result in significant social and economic negative effects, due to high levels of public anxiety, and restrictions in international trade. Risk communication can play an important role in minimizing such consequences.

1. Background

Increases in international trade and globalisation contribute to rapid and wide geographical spread of infectious livestock and zoonotic diseases. Furthermore, changes in climate, ecology, land use, and social welfare are contributing to the expansion and establishment of the causative agents of such diseases beyond their original habitat. The recent incursions of exotic vector-borne livestock diseases (e.g. Bluetongue Virus, West Nile Virus, Rift Valley fever Virus) into areas hitherto free from such diseases have stressed the need for the development of surveillance and control measures. Better knowledge of vector-borne diseases and more insight into the possible pathways for introduction and subsequent spread of these diseases is a prerequisite for efficient and cost effective risk management.

Import risk analysis for livestock diseases is usually based on the guidelines given by the World Organisation for Animal Health (OIE). In contrast, the assessment of the risk of introduction, establishment, spread and impact of exotic vector-borne diseases requires a multidisciplinary approach, taking into account epidemiology, virology, entomology, ecology and climatology.

On behalf of the Dutch Ministry of Economic Affairs, Agriculture and Innovation (EL&I) a framework for risk assessment of emerging vector-borne livestock diseases was developed by the Central Veterinary Institute (CVI) and the Agricultural Economics Research Institute (LEI), both part of Wageningen University and Research centre. This framework was built using components of internationally accepted frameworks available for veterinary risk analysis, pest risk analysis and microbial risk assessment. The newly developed framework outlines the different steps in risk assessment of emerging vector-borne diseases in flowcharts, provides checklists on variables to consider in the assessment, and contains a structured questionnaire to assess the risk qualitatively and a toolkit with methods and databases available for risk assessment of vector-borne diseases. Furthermore, the framework will help to identify existing knowledge and data gaps that need to be solved to adequately address the risk. More information on the framework is given in annex III.

This framework was first tested in 2011 by applying it to the case of Rift Valley fever (RVF), a mosquito-borne viral zoonotic livestock disease. In short, it was concluded that the probability of entry and establishment of RVF in Western Europe is low, but that the impact of the disease, on society as a whole, will be major to massive. The full report can be obtained by the secretariat of the Central Veterinary Institute, Part of Wageningen UR. In 2012 the framework was further tested during a two day workshop by applying it to the case of Crimean Congo Haemorrhagic fever (CCHF), a tick-borne viral haemorrhagic disease.

2. CCHF workshop 2012

On 23rd and 24th May 2012, an international workshop was organized at the Central Veterinary Institute, part of Wageningen UR, Lelystad, the Netherlands, focusing on the risk of CCHF for Western Europe. Probabilities of introduction of CCHF virus, establishment, spread and persistence of the virus, and magnitude of potential consequences were assessed using the framework for risk assessment of exotic vector-borne livestock diseases.

The main objectives of the workshop were (1) a first assessment of the risk of CCHF for Western Europe using the framework, (2) a test of the framework for completeness, practicality, and applicability to tick borne diseases and (3) an exchange of opinions on the risk of CCHF. Both national and international experts on CCHF were invited to the workshop representing different disciplines, such as virology, epidemiology, entomology, economics, policy, and public health.

Two separate breakout groups organized to assess the risk of CCHF for Western Europe (see Figure 1) based on the framework. Objectives for the two groups were:

- To test the applicability of the framework for risk assessment of tick-borne diseases
- To identify (key) variables contributing to the risk of CCHF to Western Europe
- To assess the CCHF risk for Western Europe qualitatively

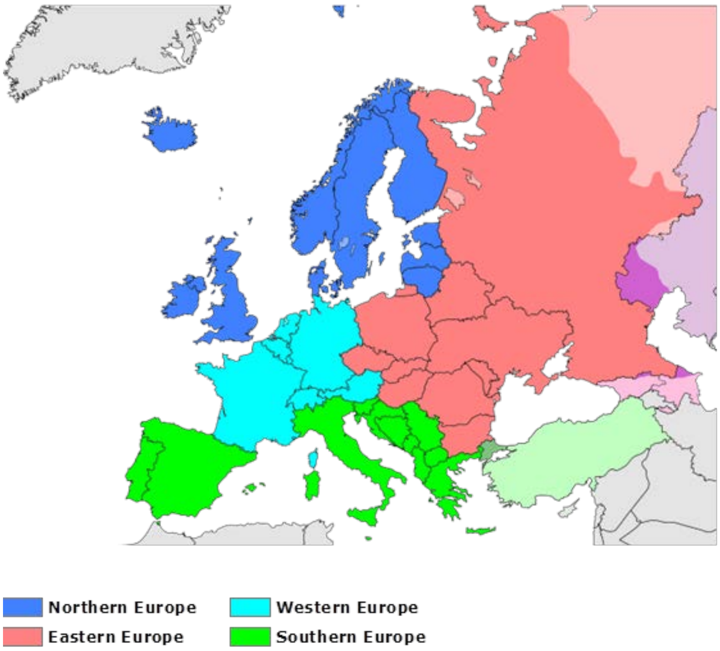


***Figure 1**. UN country grouping of Europe. Western Europe comprises Austria, Belgium, France, Germany, Liechtenstein, Luxembourg, Monaco, the Netherlands and Switzerland.*

All questions of the framework were answered qualitatively and results were summarized for each step of the framework to estimate the probability and/or impact of aspect of CCHFV introduction, establishment, spread and persistence. The risk assessment was performed over four breakout sessions: (1) probability of entry, (2) transmission dynamics, (3) likelihood of persistence, and (4) impact of disease. Each break out session was introduced by a brief presentation giving background information and/or examples on how to complete each section of the framework. At the end of each break out session, results were presented to and discussed amongst all delegates focusing on (a) identification of key parameters, (b) feedback on the framework, and (c) the risk of CCHF for Western Europe.

Results of the workshop will be used to advise the Dutch Ministry of EL&I on the development of risk proportionate preparedness plans in the Netherlands.

The workshop was attended by nine international and thirteen Dutch delegates. International delegates represented organizations working on CCHF in different regions of the world (France, Italy, Spain, Turkey, and the United Kingdom), as well as two representatives of the Food and Agriculture Organisation (FAO), Rome, Italy, and one of the World Health Organisation (WHO), Geneva, Switzerland. Dutch delegates represented organizations that work on CCHF from different perspectives (Animal Welfare, Public Health, Virology, Entomology, Economics, and Policy development). Most delegates were affiliated with research organisations. A list of participants is given in Annex II.

3. Results

3.1 Risk of CCHFV introduction into Western Europe

Areas of distribution of pathogen
The WHO has produced a map of the global distribution of CCHFV (Figure 2), based on reported human cases of CCHF. This seems a logical approach, particularly as there is no standard (ELISA) test for detection in livestock available, and testing of ticks is rarely done. As a result, it can be difficult to detect CCHFV circulation. When using maps purely based on reported human cases it is important to keep in mind that such maps represent merely the reported occurrence of human disease rather than the (complete) distribution of the virus. There are three factors which contribute to this discrepancy:

1. Subclinical disease: (e.g. Turkey) one report mentions 88% of cases in Turkey are subclinical but there is a large uncertainty and variation in this percentage; it is also thought that with longer virus circulation in an area, clinical disease diminishes [1].
2. Underreporting and non-detection (e.g. Senegal): the disease is not recognized or diseased individuals did not seek medical care; this is expected to be the case in countries with poor health care systems
3. CCHFV circulation has not yet resulted in human cases (e.g. Spain): an incursion of the virus into a new area will firstly result in infected wildlife and possibly livestock. Neither wildlife nor livestock show symptoms of disease. Thus, an incursion will likely go undetected until first detection of infection in a human.

An alternative would be to base the different areas of distribution on the different genotypes of the virus. These cover geographically compact areas, and can exhibit different transmission characteristics and virulence. Drawbacks are that these areas need to be extrapolated for countries with underreporting and that it would amount to many areas.

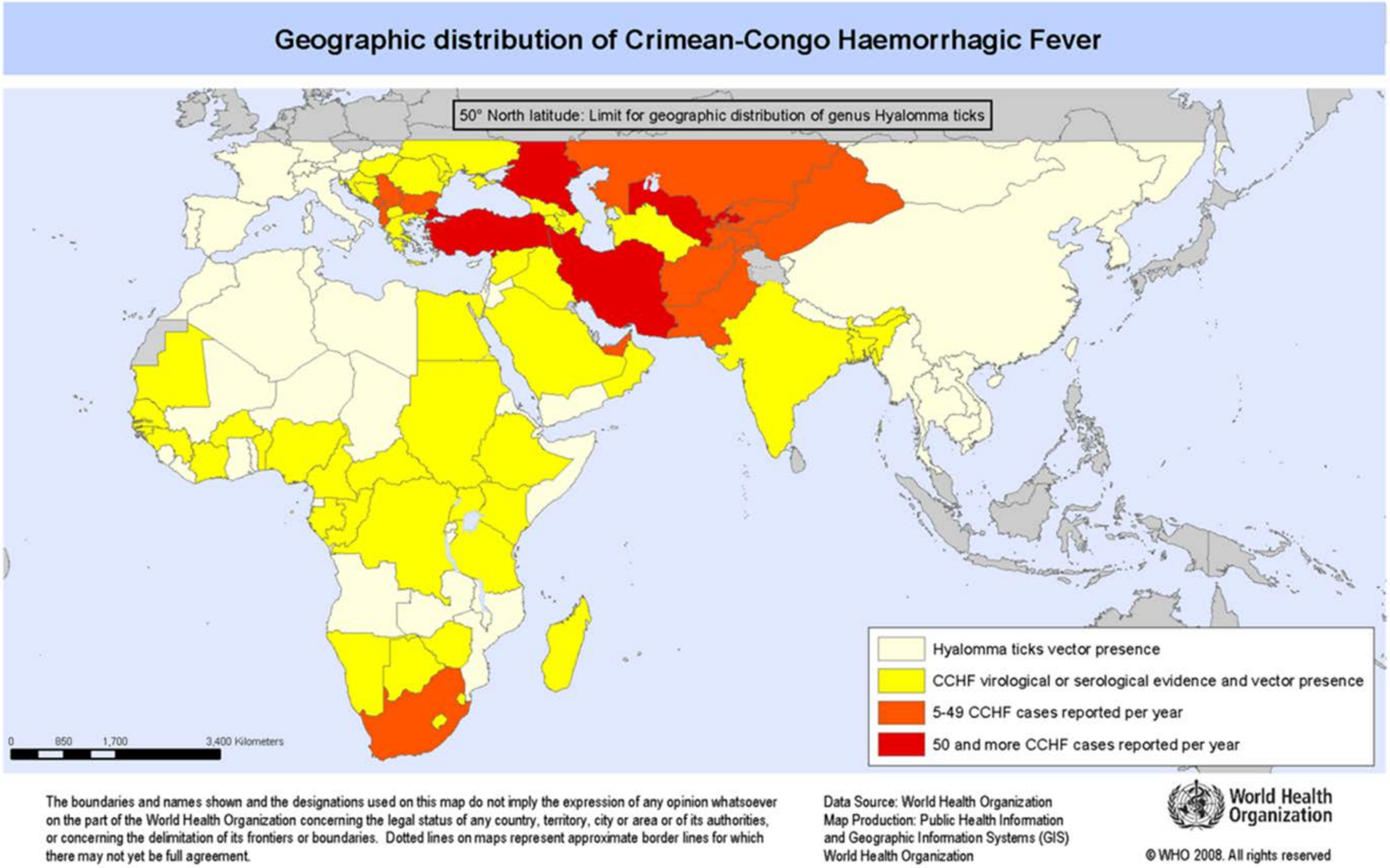
Areas currently thought to be free of CCHFV but which are thought suitable for CCHFV circulation and possibly endemicity include:

- Southern Balkans: In this area *Hyalomma*[1] is already present and some cases of CCHF have been documented. Likelihood of endemicity and further spread is high.
- Turkey: In parts of Turkey (especially the North) CCHFV is already endemic. Studies indicate that 10-15% of the human population and 80% of the livestock population in Northern Turkey is positive. Areas of endemicity are likely to expand within Turkey.
- Spain: large parts of the country are thought suitable for *Hyalomma* survival. These areas are frequented by migratory birds which are known to be capable of carrying ticks over large distances and thus introduce these to novel areas. Already one CCHFV infected *Hyalomma* was detected in Spain in 2010 [2]. But no infected animals/humans have been detected yet.
- Southern parts of France are thought to be particularly suitable for *Hyalomma* as it has similar climatological conditions as northern Turkey.
- Russia (southern): Suitable habitat for *Hyalomma* and large quantities of migratory birds.
- Asia (southern): Suitable habitat for *Hyalomma* and large quantities of migratory birds

Prevalence of CCHFV in current area of distribution
Little is known about the prevalence of CCHFV in tick populations; however, this is estimated to be around 5% in *Hyalomma* ticks.
Local variation due to absence/presence of suitable and different types of hosts, as well as host/vector ratio may influence the prevalence of CCHFV in tick populations. Further research is needed to determine the prevalence of CCHFV in ticks.

[1] Ticks of the genus *Hyalomma* are the major vector for CCHFV. For more details see Annex IV: CCHF essentials

Figure 2: Current area of distribution



Pathways for CCHFV introduction
Six possible pathways for CCHFV introduction of the vector into Western Europe were identified:

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

On-going globalisation has resulted in more efficient, faster and cheaper travel for people. Travellers may arrive viraemic in a CCHFV-free area following the bite of a tick or contact with virus contaminated fluids or animal products within the current area of distribution of CCHFV. In addition, military personnel who are stationed in basic accommodation or outdoors in endemic areas are at increased risk of contracting the disease. Ticks may be introduced on military equipment which is brought back to the Netherlands from training or peace keeping missions, although is not known whether such equipment offers suitable hiding places for ticks. However, while it cannot be completely excluded the risk of CCHFV introduction through these routes is thought to be very low.

Livestock is an important host of CCHFV. Most livestock species are viraemic for 7-14 days. Livestock may carry while on transport and introduce them in a new area. The route is limited by the duration of the transport, because the feeding time of *Hyalomma* is approximately 14 days after which the tick will detach from the host. Livestock may carry multiple ticks which are easily missed upon clinical inspection prior to transport. The international trade in livestock is a sizeable industry and every year a vast quantity of livestock is traded between EU member states. Trade with countries outside the EU is subject to stringent rules; particularly import from outside the EU is very difficult and rarely economically viable. Furthermore, trade with endemic areas is prohibited. Thus, the risk of introduction of a viraemic animal, or a CCHFV vector on livestock into the EU through trade is very small. However, once introduced, the international trade in livestock may play an important role in distributing the infection, or the vector, to other European countries.

The role of pets in CCHFV epidemiology has not been described, and is expected to be very limited. The international trade in pets (e.g. dogs, cats and horses) is not as sizeable as the international trade in livestock, but is less controllable and the introduction of pets from outside the EU, particularly from Morocco, occurs frequently. Other exotic diseases and ticks have been introduced into the EU along this route, such as *Hyalomma* ticks on race horses, and a case of rabies in a dog in 2012. Nevertheless, the risk of introduction along this route is thought to be low.

Birds are not a host for CCHFV, with the exception of ostriches. However, the detection of ticks on migratory birds has been documented [3]. Western Europe is along several migratory bird routes and each year millions of migratory birds frequent Western Europe. The birds are likely to carry *Hyalomma* ticks, which might establish a population. The risk of introduction of CCHFV by infected *Hyalomma* ticks is thought to be high. It is probable that previous introductions have occurred and more introductions are likely, possibly on an annual basis.

Western Europe has both a rich variety and an abundance of wildlife. Large mammals such as deer and wild boar have large territories, and particularly young males roam over large distances in search of new territories. Trade in wildlife is adherent to stringent regulations which are overseen by CITES[2]. The risk of CCHFV, or its vector, is high in Eastern Europe from which a slow spread to Western Europe is possible. The risks associated with the trade in wildlife are thought to be very low with one exception: prey animals for hunting, which are traded between Eastern and Western Europe in large quantities. This is an often forgotten high-risk practice.

Trade in raw meat could pose a problem (popular in Turkey) when it is illegally imported into Western-Europe. Also ostrich meat from South Africa could be a possible introduction route, where large outbreaks on ostrich farms have occurred. The risks associated with trade in animal products are negligible. The risk of infection through contact with, or consumption of, an animal product is negligible.

It was not thought that (the international trade in) reptiles play an important role in CCHFV introduction since CCHFV transmitting *Hyalomma* species does not feed on reptiles.

[2] The Convention on International Trade in Endangered Species of Wild Fauna and Flora. www.cites.org

Import and export control

The import of livestock from outside the EU, and in particular areas with CCHFV endemicity is illegal. This does not mean it doesn't occur, but quantities will be low and is not thought to pose a major risk of introduction. The trade in livestock within the EU is subject to inspection. CCHFV infection does not cause any, or at most only mild, symptoms in livestock. There is no reason to assume this is different in Western European breeds. Therefore, the detection of CCHFV viraemia in livestock is highly improbable, particularly as there is no specific test available to detect CCHFV infection in livestock. The detection of ticks on livestock is also thought to be improbable, and if found, is unlikely to result in the detection of *Hyalomma* ticks.

Movements of pets within Europe are well regulated, but difficult to monitor. Most borders are "open", meaning a border that enables free movement of people between different jurisdictions with limited or no restrictions to movement, which makes enforcement difficult. The exception is the border with the United Kingdom which has stringent controls. Importing pets from outside the EU is subject to stringent regulation and the import of large quantities of pets is likely to be difficult without proper paper work. In order for pets to introduce an infected tick into Western Europe, the pet will have to be transported by airplanes, which are subject to further control measures. The occasional tourist may however willingly and successfully smuggle a pet in a car. However, since the distance from CCHFV endemic areas to Western Europe is large, the time travelled will be more than the feeding time of the tick. Adult ticks feed for on average 14 days. Thus, any tick will likely have fallen off somewhere on-route.

Migratory birds and migratory or free-moving wildlife cannot be controlled. Trade in wildlife however is a practice which is possibly less regulated than trade in livestock and may be insufficient to prevent the spread of diseases.

The trade in animal products is subject to stringent regulations. Most CCHFV endemic areas overlap with Foot and Mouth Disease (FMD) areas from which import is prohibited. Finally, as CCHFV is sensitive to freezing, frozen raw meat should be considered a negligible introduction route

Conclusion on risk of introduction

The most important introduction route from outside the EU is thought to be migratory birds. Birds are capable of transporting large numbers of CHHFV infected ticks over both short (local) and long (migration) distances. The estimated prevalence (by experts present) of CCHFV in ticks was around 5%. Thus, the probability that a bird introduces an infected tick from an endemic area is thought to be considerable and is likely to have occurred in the past on more than one occasion.

Infected ticks can also be introduced by livestock movements. However, strict regulations apply to trade in livestock and there are import bans on livestock from CCHFV endemic areas. Should CCHFV become endemic (undetected) in some part of Europe, then the risk for further spread, and introduction into Western Europe, will likely be increased through the trade in livestock.

There have also been reports from the Netherlands, Germany, Great Britain, Sweden and Norway of finding *Hyalomma* and other ticks in the wild, on a race horse, cattle and a bird [3, 4, 5, 6, 7, 8].

Key parameters identified for further research were:

- CCHFV prevalence in tick populations, both adult ticks and nymphs
- Which bird species are most likely to introduce *Hyalomma* ticks, how frequent, and where are these most likely to detach.
- Hunting practices, and in particularly the trade in prey animals from one hunting area to another

3.2 Transmission dynamics

Probability of transmission

Whether or not CCHFV can become established in Western-Europe depends on:

- Presence of essential host species (such as rodents, sheep and other livestock)
- Whether *Hyalomma* ticks can survive once introduced
- Whether other vectors, particularly local ticks (*Ixodes* spp.), can act as competent vectors and reservoir for CCHFV

Most *Hyalomma* species (including *H. marginatum*) are 2-host ticks, meaning that both immature stages, larvae and nymphs, feed on the same individual host, while adults feed on a second host. Hosts for immatures include small mammal species such as rodents, rabbit, hare, mouse, hedgehog, etc., and also birds; those for adults include larger wildlife species or livestock. All these hosts are abundant in Western Europe and many are competent transmission hosts for CCHFV. The briefer the period of infectivity in the host, the more restrictive the conditions for ticks to acquire the virus from hosts fed on previously by infected ticks [9].

It is thought that there are several biotopes (particularly the dryer and warmer areas) in Western Europe which are suitable for *Hyalomma* survival and establishment. These areas are:

- Southern France
- Southern parts of the Alps
- Southern Germany

This is a rough regional identification, and micro-climates suitable for *Hyalomma* establishment may exist throughout (Western) Europe. Furthermore, climate change may prove to be an important factor in facilitating or inhabiting the distribution of *Hyalomma*. So far, *Hyalomma* has been limited to areas South of the 50^{o} parallel. This may change as a result of climate change and a slow spatial distribution northward may be observed. A worrying indication of this is that the "tick-season" in Western Europe is extending which is thought to be one of the reasons why we see an increase in detected Lyme disease cases in humans in the Netherlands. The main limiting factor for *Hyalomma* to move more north is thought to be its dependence on a stable dry and warm weather period for a minimum of 15 days which is needed for the nymphs to moult into the next stage (adults). If the circumstances are not good enough for the nymphs they are not able to moult into an adult tick and will die during the winter. Another limiting factor is that *Hyalomma* thrives in relatively low humidity; this is contrary to European tick species which prefer higher relative humidity. Relative humidity affects the nymphs during the moulting stage during which they are highly susceptible to fungal infection. The development of a more detailed habitat map would be of benefit for (passive) surveillance purposes.

The virus might adapt to, or might already be able to survive in, other species of ticks. As described by Hoogstraal [10], ticks are widely distributed in Western Europe, including the Netherlands. Should adaption to a native tick species occur, than the likelihood of persistence is thought to be high.

Probability of establishment

Once a tick contaminated with CCHFV is introduced, the probability of the tick finding and biting a suitable host is high irrespective of pathway of entry. The host density of both small and large wildlife in Western Europe is high and ticks can survive for long periods of time, waiting or searching, for a suitable host. The host preference of *Hyalomma* is varied and wide, thus the probability of finding a first local host is high. The probability of onward spread of CCHFV from a first infected host to other vectors is low due to absence of *Hyalomma* ticks for further spread. Ticks only feed once per life-stage and for CCHFV the transmission from one type of host to the same type of host requires a whole life-cycle including transovarial transmission. This makes the transmission cycle of CCHFV slow. However, since ticks remain infected throughout their lives and have (very) high rates of vertical transmission, the basic reproduction number (R_0) may still be higher than 1.

Very little is known about the precise conditions of viraemia in vertebrates required for transmission from tick to tick via vertebrate hosts. The mechanism of non-viraemic transmission between co-feeding ticks has been demonstrated for nymphs co-feeding with adults of *Hyalomma truncatum* and *H. impeltatum* in a laboratory setting with guinea pigs. Co-feeding between ticks of different stages is, however, irrelevant to this *Hyalomma*-based system because both immature tick stages feed on the same individual of one type of host (small animals) and adults feed on another type of host (large mammals). Persistent cycles, therefore, depend on vertical transmission from infected adults via their eggs to larvae (transovarial transmission, TOT). Infected females transmit the virus to 17% of their eggs [11, 12]. If a feeding larva or nymph acquires infection from a host, it cannot transmit it to a new susceptible host until it feeds again as an adult; this new host only feeds adults ticks, so any uninfected adults that acquire the virus from this host must pass it to their larvae for onward transmission. TOT does occur via *H. marginatum* ticks, but with rather low efficiency, but this nevertheless amplifies the number of infected ticks from a single female to many larvae.

Sexual transmission between adult ticks may also occur, but this can only act as an additional contribution to the transmission potential (R_0 value). The strong implication of this biology is that CCHFV may rely on contributions from other tick species to ensure sustained transmission cycles in Nature. If so, and other tick species are competent, this implies that ticks in Western Europe may possibly already be latently competent.

Ticks are the effective reservoir hosts because they survive much longer than the period of infectivity in livestock (in which there is no known carrier state) and longer than the lifespan of rodents.

Suitable habitat and climate for *Hyalomma* is more or less opposite to the most common native tick in Western Europe. Suitable hosts may wander through different ecological habitats picking up different tick species. Therefore, different tick species may found co-feeding on a single host, allowing for cross-infection of tick species. *Hyalomma* needs dry circumstances, while native ticks prefer more humid circumstances.

A number of tick species are known to be vector competent, either under natural circumstances or under laboratory conditions [10], but it is unknown to what extent these tick species contribute to sustained CCHFV transmission cycles.

Probability of spread

Wildlife and livestock infected with CCHFV show no or only mild specific symptoms. Therefore, CCHFV can circulate in wildlife and livestock for years without detection. Detection is most likely in those areas where wildlife, livestock and humans are active. Since farm animals do not show any clinical signs of infection, detection is most likely a result of a human case, frequently a farmer, hunter or those who recreate in the country side. The slow spread and mild symptoms in animals results in a long high risk period (period during which CCHFV can spread unchecked without being detected) which may last for years until first detection in a human.

The implication of this long high risk period is that both local and long distance spread among wildlife and livestock within Western Europe may have occurred prior to first detection. Birds may contribute to both local and long distance spread, depending on the species of bird and season of tick activity. Also, other wildlife may contribute to short and long distance spread of CCHFV or its vector. Particularly wildlife such as foxes, wild boar and deer are known to cover large distances while searching for food, a mate or new territory. The transport of and trade in livestock are likely to contribute to long distance spread of the virus or its vector either by carrying infected ticks, or by carrying the CCHF virus themselves. Infected animals remain infectious for around 14 days, although the exact length of infectious period varies by species and is not exactly known for western European breeds. The detection of *Hyalomma* ticks on domestic livestock and horses in both Great Britain and the Netherlands supports this theory. People can contribute as well to the spread of CCHFV, and particularly its vector, by carrying a tick attached to the skin, in clothes or in luggage. Ticks are very capable of surviving long periods under various circumstances.

Surveillance of the presence of ticks and frequency of introduction by migratory birds may help in identifying the risk of short and long distance spread. Each year many migratory birds are caught and ringed for other research activities. Thus, such surveillance activities are likely to be low cost and achievable. Surveillance of tick distribution and density of distribution, such as the tick-radar initiative initiated by the RIVM and Wageningen University [14], may increase our understanding in the key parameters of tick biology (particularly *Hyalomma*), such as speed of distribution, habitat preferences, length of active period, and likelihood of persistence of invasion. Furthermore, surveillance of CCHFV in native tick species would be vital in understanding the epidemiology of CCHFV in Western Europe. Following introduction and first detection of CCHFV, surveillance of CCHFV circulation in wildlife and livestock is difficult due to the absence of a CCHFV specific diagnostic test. Following the first detection of a locally acquired CCHFV infection in a person, it would be informative to commence a large-scale serosurveillance in livestock. However, in order to achieve this, a rapid cheap diagnostics test needs to be developed first. Surveillance of CCHF in humans following confirmed CCHFV circulation in wildlife is likely achieved through the mandatory reporting of cases. Active follow-up of patients could help in understanding risk factors for contracting disease in Western Europe. Furthermore, risk maps can be developed and used to inform where surveillance activities are most likely to be informative.

Lessons can be learned from Turkey’s response to CCHFV spread. The main control measures taken were to educate the local population on tick awareness and the prevention of bites. Furthermore, insecticides were used to try to control the tick population. This did not result in a decrease of the number of reported human cases. Furthermore the tick population appears to have increased despite the measures taken. A possible explanation for this is the on-going reforestation in large areas which results in the creation of suitable habitat for *Hyalomma* ticks and its hosts. In Bulgaria people at risk are vaccinated against CCHFV by an inactivated virus vaccine. In Turkey this vaccine is not used, because no reliable data is available about its effectiveness.

Conclusion

In conclusion, there is no shortage of suitable hosts for *Hyalomma* ticks in (Western) Europe and these are also susceptible to CCHFV. Any CCHFV infected *Hyalomma* tick introduced is therefore likely to find and feed on a suitable host. This tick can start the first transmission cycle.

However, the establishment of CCHFV requires the presence of a vector population. Therefore, either *Hyalomma* spp. must be capable of survival and reproduction in the environment in which it was introduced, or a local tick species proves to be a suitable vector. The experience where CCHFV was introduced into Madagascar which resulted in endemicity despite the absence of *Hyalomma* highlights the possibility of local ticks to act as efficient reservoir and vector. *Hyalomma* ticks, including those infected with CCHFV virus, are probably introduced into Western Europe by migratory birds every year. The *Hyalomma* tick has apparently not established a viable population in this region and also no outbreak of CCHF has been observed. If local tick species are competent vector, it is therefore not understood why establishment of CCHFV in Western Europe has not occurred yet.

Once CCHFV circulation has been established, local spread will be a result of bird movements and other wildlife movements, while long distance spread will be the result of migratory bird and livestock movements.

Establishment and spread of CCHFV are likely to go unnoticed for long periods, possibly even years, until a first detection in human. Detection in livestock or wildlife is thought to be unlikely, because infected animals show mild or no symptoms.

CCHFV transmission, establishment and spread in Western Europe is thought to be possible, albeit less likely in Northern parts than in the Southern parts.

3.3 Likelihood of persistence

Introductions of CCHFV into Western Europe are thought to occur occasionally or even annually, with migratory birds carrying CCHFV infected *Hyalomma* being the most likely entry route. However, survival of *Hyalomma* in Western Europe is not thought to be likely due to the generally cold and wet climate. Survival may be possible during prolonged periods of warm and dry weather during which an introduced tick may bite and transmit CCHFV to wildlife, livestock or a person. The life cycle of the *Hyalomma* tick is slow, and the duration is unknown in the cooler more humid conditions of Western Europe. These factors make it unlikely that introduction would result in any sizable outbreak. There are however two circumstances when an outbreak may occur. Firstly, one infected adult female tick can produce many thousands eggs of which on average 17% will be infected [11, 12]. Thus, should an introduction occur in a habitat favourable for *Hyalomma* survival, an outbreak of CCHF may occur, but not witnessed due to absence of symptoms, in small wildlife. The second year CCHFV may infect large wildlife, livestock and possibly humans. Secondly, if native tick species prove to be vector competent, an outbreak may occur, though still unlikely to be detected, in wildlife and livestock. Detection is only likely when a person contracts the disease.

In livestock and larger wildlife, herd immunity is not likely to play an important role since the replacement rate of livestock and wildlife is high relative to the epidemic growth rate of CCHFV. Therefore, herd immunity is slow to develop in livestock and larger wildlife species and will not be a mitigating factor of an outbreak. Furthermore, ticks can also infect each other by co-feeding (i.e. feeding simultaneously close to each other) on an immune host, and turn-over of early-stage hosts is large (e.g. one to four reproduction cycles per year for hares) leaving the early-stage host populations practically susceptible.
Thus, herd immunity of livestock, large and small wildlife is unlikely to play a mitigating role in slowing down the spread of CCHFV to other ticks.

As noted, an outbreak of CCHF will build slowly and may go unnoticed for many years until the first human case(s) occur. A first detection of CCHF in Western Europe is therefore likely to be the result of an earlier introduction and the virus may have spread over a larger area. This makes eradication following detection difficult, as the infection is likely to have spread over a large area. This is more likely to occur in Southern and Eastern Europe than Western Europe. Once a population of *Hyalomma* tick has become established, it is more likely that the virus may then adapt to other, indigenous, tick species due to higher levels of exposure of indigenous ticks to CCHFV. However, for such indigenous ticks to start play an important role in the epidemiology of CCHFV, the ticks will need to be able to transovarially transmit the virus. Transovarial transmission is a prerequisite (*sine qua non*) for transmission for two-host ticks (like *Hyalomma*). Immature ticks feed on one host species and adults on other host species and there is no overlap between host species of the immature and adult stages.

The different ecology of ticks in Western Europe and the completely naïve host population might both contribute to new transmission patterns and survival strategies, which makes it very difficult to predict the likelihood of persistence. In fact, little is known about the role of ungulates and small wildlife species. It would be interesting to conduct a series of experiments (under BSL4 conditions) on such mammal species, to study their amplifying capacity. Also the range of movement (either natural or by human activity) in Western-Europe might differ from endemic areas and thus influence the extent of spread.

Conclusion
In conclusion, it is expected that once *Hyalomma* is introduced in areas suitable for survival, CCHFV might be able to spread slowly but surely and may do so for years before detection. A large-scale outbreak of CCHFV is not expected. An outbreak of CCHFV in local human population is not expected to amount to more than an isolated case, or perhaps a small cluster of cases. Adaptation of the virus to indigenous tick species increases the likelihood of persistence, but such adaptation is highly speculative.

3.4 Impact of CCHF

Economic consequences

The impact of CCHF on economy depends heavily on the control measures that may be applied following detection. There is no specific EU directive that specifies obligatory measures; in the Netherlands there is currently no CCHF contingency plan. However, CCHF is on the OIE–listed diseases list (former A- and B – disease list). Imports into the EU of live animals are prohibited from endemic areas if the animal tests positive for CCHFV (EU-regulation 206/2010).

Consequences for agriculture

Although the consequences of CCHFV infection in Western European livestock and wildlife is not known, animals infected with CCHFV in endemic areas show no or little symptoms of infection. There is no reason to assume this is different for animals in Western Europe. Thus, infection of CCHFV in Western European livestock or wildlife will almost certainly go unnoticed and particularly as CCHFV is unlikely to be considered by veterinarians as a plausible explanation for cattle with mild and vague symptoms. Furhtermore, there is no diagnostic test available should a veterinarian want to test for CCHFV.
When only a positive tick or wild animal (non-livestock) is found, there are unlikely to be any consequences for the agricultural sector. However, when detected in livestock, (import) restrictions will be taken by other countries resulting in economic losses. Other costs include eradication and surveillance costs including extra precautions on slaughterhouses. Culling of animals is not indicated and does not contribute to CCHF control and eradication. Culling may still be executed since there is no protocol specific for CCHFV eradication and control, thus strategies adopted will most likely be based on infectious disease protocols, which often include culling. Especially if as in the case of CCHF human health is under threat, more control measures that potentially seriously affect animal welfare may be taken.

There are two main types of livestock farming that can be identified in Western Europe: (1) intensive held livestock, and (2) extensive, or biologically held livestock. Intensive farming results in more human contact and intervention but contact with ticks is less likely. Extensive, or biological farming, requires less contact between humans and animals, but animals are more likely to come into contact with ticks and hence to become infected by a tick borne disease like CCHF. Particularly biological farming may put livestock at risk as such farming practice is often required to keep natural barriers and more green spaces which are suitable for small wildlife which is essential for the nymph stages of ticks. Thus, persistence of infections and human cases are more likely to occur around extensive and biological farming sites.

Consequences for human health

Cases of CCHF in Western Europe are likely to be sporadic and isolated. Large outbreaks of CCHF in humans in Western Europe are not expected. Those most at risk of contracting CCHFV infection are those with frequent contact with livestock, wildlife or those who are active in areas where ticks are present such as hunters and hikers. This means that for Western Europe the risk group is similar to those who are at risk of contracting Lyme disease. The transmission cycles for *Borrelia burgdorferi* that causes Lyme disease, however, are far more robust than those for CCHFV, so the distribution and abundance of CCHFV-infected ticks are likely to be much more restricted. On the other hand, CCHFV can be transmitted to those who come into contact with infected animal products, such as slaughterhouse personnel, veterinarians and hunters. Symptoms in humans are very unspecific and range from a mild flu-like illness to severe haemorrhagic fever. Therefore, detection of CCHFV in a patient is likely to be delayed. WHO indicates a mortality rate of around 30%, while in Turkey, the observed mortality rate is around 5% and dropping further still. This is thought to be a result of better (more rapid) diagnosis and CCHF awareness of medical staff. Thus, consequences of CCHF for human health on population level are minimal.

Social-ethical consequences

The disease burden – defined as loss of QALY's (quality adjusted life years) – will be very high for infected people. But the effect on society as a whole (i.e. mainly non-infected people) will be largest due to the scare of contracting the disease. This will depend on whether or not the infection was imported (e.g. tourist), or if the infection was contracted locally and on the severity of disease; more severe disease expression will likely result in more consequences. In addition, media coverage and public education also play a role in risk perception. A case of severe haemorrhagic fever resulting in the death of a person may result in a media hype resulting in more consequences. People might fear meat products, going into tourist areas, etc. These effects of public fear feed back into the economic consequences. For example, people may start to avoid certain animal products resulting in a drop in prices. Foreign media coverage may result in loss of tourist revenue to minimize the risk of a scare. Public communication will be very important in a crisis situation.

Environmental consequences
Wildlife might be targeted in control measures, depending on the role they play in the transmission. In Russia the culling of birds, particularly crows, is a common measure to control the spread of CCHFV. Decreasing the number of wild boars can possibly be adopted to prevent further spreading of CCHFV. Such a strategy might be counterproductive since hunting activities will initiate more wild boar movement. Effectiveness of wildlife control or eradication programmes needs further investigation, as ticks have a slow life cycle and the removal of wildlife from CCHFV endemic areas will result in the natural migration of wildlife from neighbouring areas. The consequences for biodiversity can be quite large when wildlife is culled. The use of insecticides for the killing of ticks could have major consequences for other invertebrate wildlife and furthermore for species that depend on invertebrates for survival, such as certain birds and rodents.

Vector control would be possible for *Hyalomma* ticks because they actively seek out their host. This behaviour can be used for trapping them (similar to tsetse flies in Africa). Such targeted vector control would have a small environmental impact, but the traps first need to be developed. Non-targeted vector control, e.g. with acaricides, would have a large impact as it also affects other species, such as mites. Insecticides are used (in the Netherlands) against exotic mosquitoes, but mostly in industrial areas (where imported goods are stored) with limited environmental impact.

Conclusion
In conclusion, first detection of CCHF in Western Europe is likely to be in an isolated single human case. The consequences of this are thought to be small but will mainly depend on the severity of disease, media coverage and public education and information by government bodies. The detection of CCHF in a human may result in the (unnecessary) culling of wildlife and livestock resulting in further public unrest. Therefore, preparation of eradication, control, surveillance and communication protocols is very important as the public perception of the risk is key in the effective management (proportionate control measures) of an outbreak. The impact of CCHFV detection in a tick or wildlife is directly related to vector and wildlife control and is expected to be low, but this depends on the extent to which infection has spread. It is thought to be likely for CCHFV to circulate in the environment for many years before first detection. Culling of livestock is not indicated since the tick is the primary reservoir for CCHFV. In fact, there are many examples where culling of wildlife has an adverse effect on controlling a disease (e.g., the culling of foxes to control rabies has proved unsuccessful and even contributed to further spread of the disease). Culling only stimulates fast regenerates of established populations (leading to higher susceptibility level) and to more animal movements, changing the endemic equilibrium.
The impact of detection of CCHFV in livestock is thought to have potentially major economic consequences due to the closure of borders for livestock and their products. Communication protocols for different scenarios following the detection of CCHFV should be made as preparation of a possible outbreak of CCHF in order to minimize the impact.

Furthermore, detection of CCHFV in Western Europe is likely to spark renewed interest in the development of diagnostics, treatments and prevention tools such as cocktails of monoclonal antibodies and vaccines which are not currently available. The purpose of animal vaccines would be to control the infection, at the risk of economic losses because vaccinated animals might not be accepted (by consumers, processing industry, or trade partners). The purpose of a human vaccine would be to control human cases. Development of such a vaccine (needing first an animal model) is at this moment not economically opportune, because of the low incidence in Western-Europe. This might change when CCHF incidence rises, giving an economic as well as ethical incentive for vaccine development. This can be regarded as indirect costs following detection.

4. Conclusions, recommendations & further research

4.1 Risk assessment CCHF in Western Europe

Conclusions

Risk of CCHF introduction into Western Europe

- Entry of CCHFV into Western Europe is most likely through ticks hitch-hiking on (long-distance) migratory birds either from the African continent, Eastern Europe, Middle East or Asia. The large numbers of annual migratory birds make it likely that previous introductions already have occurred.

Transmission dynamics

- The reproduction number, R_0 of CCHFV in Western Europe is presently expected to be below one, with the exception of warmer and drier areas such as Southern France, South facing Alps, and local "hotspots". This assessment is based on the likelihood of survival of *Hyalomma* in Western Europe and its ecological needs. If tick species native to Western Europe prove efficient CCHFV vectors, then the R_0 value may reach critical value and exceed one.
- Long - distance spatial spread within (Western) Europe is most likely the result of bird movements and transport of livestock; local and regional spread is most likely the result of wildlife movements such as wild boar and deer.
- CCHFV may be present in livestock and wildlife for years prior to first detection
- There is an abundance of hosts in Western Europe for both the immature stages and the adult stage of *Hyalomma* ticks.
- Detection of CCHFV in Western Europe will most likely be the result of a more severe case of disease in a person. Mild cases and subclinical infections are unlikely to be diagnosed as or tested for CCHFV.
- When in place, CCHFV detection may also result from active tick surveillance. But only if most of the collected ticks are also tested for various infections (in pooled samples).

Likelihood of persistence

- *Hyalomma* ticks are not expected to be able to survive in most areas of Western Europe due to the generally wet and cold climate conditions. Local "hotspots" with a micro-climate may exist in Western Europe allowing for the survival of *Hyalomma*. Based in climatic conditions, *Hyalomma* is expected to be able to survive in the Mediterranean Basin. Climate change may allow *Hyalomma* ticks to move further west and north.
- Ticks are the CCHFV reservoir. For 2-host ticks, such as *Hyalomma marginatum* vertical transmission is essential for persistence of CCHFV. Sexual transmission, transmission during co-feeding (if possible) and especially infection of ticks during feeding on viraemic animals contribute to further increasing the R_0 value.
- Adaptation of CCHFV to other tick species is a high risk for persistence and endemicity in presently uninfected areas like most of Europe.

Impact of CCHF

- CCHF is a serious zoonotic infection that may occasionally result in haemorrhagic disease and death in humans. Diagnose is difficult and there is no specific therapy or prevention available. The overall human disease burden is, however, expected to be low.
- It is not known to what degree Western European livestock will suffer from CCHFV infection. Most likely infection with CCHFV will only result in mild, if any, clinical symptoms.
- *Hyalomma* ticks display a different behaviour to ticks (*Ixodes* spp. and *Dermacentor* spp.) native to Western Europe. *Hyalomma* ticks actively hunt for hosts and can cover relatively large distances while "hunting". Native tick species hide in undergrowth waiting for a suitable host to walk by. This may have consequences for public education
- Risk groups for contracting CCHFV are the same risk group as those who are at risk of contracting Lyme disease: outdoor tourists, farmers and veterinarians. The only marked difference is in the fact that CCHFV may also be contracted following contact with infected animals (veterinarians and hunters), with infected animal products (slaughterhouse personnel), infected humans (health care workers), and following the removal and squeezing of ticks (pet owners).

- Detection of CCHFV in Western Europe is likely to result in economic losses due to export bans of animal products and possibly reduced consumption of animal products by the local population. Tourism is not thought to be affected much. The severity of impact will greatly depend on whether detection was in a tick, wildlife, livestock or person. Quality of media coverage and timeliness of public education by government bodies will also play an important role in risk perception and mitigation and thus in the national impact of an epidemic.

Recommendations

- Early detection of *Hyalomma* ticks and CCHFV circulation in wildlife is of utmost importance in limiting epidemiological and economic consequences. Continuation of the active tick surveillance in the Netherlands is therefore recommended, not only for detection of CCHFV, but also for other tick-borne diseases. Active tick surveillance is also recommended for other (Western) European countries, if not yet in place.
- Plans should be made on actions to be taken upon detection of *Hyalomma* ticks in (Western) Europe.
- Development and evaluation of control and eradication schemes is recommended in order to:
    - minimize disease burden in the (human) population
    - minimize the impact on the trade in animals and animal products.
    - minimize public scare
    - avoid costly and inefficient measures
- Existing contingency plans for infectious diseases are not suitable to vector borne diseases. Culling of livestock will only result in huge economic losses, but is not expected to contribute much to a reduced transmission rate of the virus. Indeed, it might even result in more rapid spread of disease. Vector control, on the other hand, is considered of utmost importance, since the vector is the primary reservoir for CCHFV.
- A (European) contingency plan for CCHF is recommended.
- Appropriate public communication on the disease in case of an outbreak is of utmost importance. Public health authorities and veterinary authorities should closely work together, under the one-health strategy, and communicate a coordinated message. The media should be included for effective communication. The communication strategy should be part of the contingency plan.

Further research points

- Frequency of introduction by migratory birds
- Development of risk maps to target surveillance activities
- Vector competence of *Hyalomma* and Western European ticks
- Development of practical diagnostic tests
- Development of a vaccine should be considered

4.2 Framework

Conclusions

- The framework and questionnaire were considered helpful in structuring the risk assessment process
- Overall satisfaction and appreciation was higher than during the 2011 workshop on RVF. This was surely in part due to changes implemented following the recommendations of the 2011 RVF workshop

Recommendations

- The framework needs further adjustment to incorporate the specifics of tick-borne diseases which have more specific features than vector-borne diseases or infectious disease specifics
- A few minor errors in the framework were detected and these will be corrected
- Not all answering categories were logical or consistent. These will need to be fine-tuned
- Further testing on parasitic diseases was recommended such as *Echinococcosus* and *Cysticercosis*
- Extension of the framework to zoonotic vector-borne infections which do not cause disease in livestock

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Annex I: Programme

Programme CCHF workshop 23rd May 2012

10.00	Arrival, coffee
10.20	Welcome, introduction to the workshop & framework presentation
10.40	Guest presentations by:
	Aykut Özkul (10:40)
	Zati Vatansever (11:00)
	Ana de la Torre (11:20)
11:40	Discussion
12:00	5 minute coffee break
12:05	Instructions for break out groups
12.20	Break out groups "*probability of entry*"
13:20	Lunch
13:50	Reporting back from break out groups & discussion
14:20	Instructions for break out groups
14:35	Break out groups "*transmission dynamics*"
15:35	Coffee
16:00	Reporting back from break out groups & discussion
16:30	Departure to evening venue
17:00	Social activity (outdoors)
18:00	Drinks
18:30	Dinner
21:30	Back to hotel

Programme CCHF workshop 24th May 2012

8:15	Transport by CVI bus from hotel to CVI
8:30	Coffee
8:45	Summary previous day & discussion
9:00	Instructions for break out groups
9:15	Break out groups "*likelihood of persistence*"
10:00	Reporting back from break out groups & discussion
10:30	Coffee
11:00	Instructions for break out groups
11:15	Break out groups "*impact of disease*"
12:15	Reporting back from break out groups & discussion
12:45	Round table discussion
13:45	Conclusion & closure
14:00	Lunch

Annex II: List of participants

Group	Name	Institute	Country	Email
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1	Zati Vatansever	Kafkas University	TR	zativet@gmail.com

Annex III: Framework in depth

The framework for risk assessment of exotic vector-borne livestock diseases was presented by Aline de Koeijer (CVI). The framework identifies the main steps in risk assessment of exotic vector-borne livestock diseases and provides a toolbox for (quick) assessments. The framework evaluates both the likelihood of introduction of a disease into an area at risk and its subsequent spread and consequences. The main steps in the risk assessment framework are: (1) the probability of entry, i.e., the probability that the pathogen causing the disease enters the area at risk by any pathway, and (2) transmission dynamics including (a) the probability of transmission, i.e., the probability that the pathogen is able to spread to other susceptible hosts in the area at risk implying that at least a competent vector should be present somewhere and that at any time environmental conditions are suitable for virus replication and spread (b) the probability of establishment, i.e., the probability that the pathogen can spread from vector to host and vice versa given the conditions of introduction (pathway, time and place), and (c) the extent of spread, i.e., the extent to which the pathogen is able to spread in time and space, considering both local dispersal and long-distance spread, accounting for the number of animals/herds infected and the geographic area affected, (3) the likelihood of persistence, i.e., the likelihood that the pathogen will assert itself in the area at risk for a prolonged period resulting in endemicity, and (4) the impact of the disease being present in the area on the livestock sector and – if zoonotic – on human health, including economic, socio-ethical and environmental consequences. The framework provides (a) flowcharts identifying the key variables contributing to each step, (b) extensive checklists with all parameters that contribute to the risk of each step, (c) a structured questionnaire to assess the risk of each step, and (d) an overview of databases and methods available to qualify or quantify the risk of each step. Use of the questionnaire allows for consistency in risk assessment of vector-borne livestock diseases as the questionnaire systematically addresses all steps of the framework.

The key variables contributing to the probability of entry are the current area of distribution of the pathogen and the pathways along which the pathogen can be transported from the current area of distribution to the area at risk. In addition, the probability of entry can be mitigated by import and export regulations. The main parameter to consider for the current area of distribution is the prevalence of the pathogen in both hosts and vectors. Parameters to consider for the pathways for introduction are the numbers transported and the infection pressure along the pathway. Possible pathways for introduction are: import of infected live animals, import of contaminated biological material, import of contaminated animal products, entry of an infected vector, and entry of infected humans. Furthermore, it should be kept in mind that illegal imports might be as important as legal imports.

The transmission dynamics are determined by the interactions between the pathogen, the host and the vector resulting in transmission of disease. Transmission of disease is influenced by pathogen characteristics, vector-host interactions, and independent factors like temperature and the environment. Transmission is a dynamic non-linear process and can be summarized in the basic reproduction ratio (or number), usually referred to as R_0. R_0 is defined as the expected number of new infections per "typical" infected individual in a susceptible population. This number can usually be defined from a few basic features of the system, i.e., the vector-host ratio which is determined by vector abundance and host density, the transmission probabilities from host to vector and from vector to host when biting occurs, and the biting rate, the life span of the vector, and the extrinsic incubation period, all of which are temperature dependent. Only if $R_0 > 1$, transmission can result in epidemic spread of the disease.
If an infection can spread within a favourable area and season, the next question in the risk assessment is whether the infection will fade out due to depletion of susceptible hosts or due to lack of overwintering mechanisms. If so, the impact of the disease will be restricted to a single epidemic. If fade-out is not expected the infection can persist resulting in endemicity. Persistence is possible if replacement of hosts is fast in comparison to the timescale at which the infection spreads and if the pathogen is able to overwinter in the host or the vector, either directly or by vertical transmission. Another mechanism contributing to persistence of the pathogen is the phenomenon of non-zero vector activity during winter as was observed for bluetongue virus serotype 8 in North-western Europe.

The key variables contributing to the impact of the disease are the epidemic size, i.e. the number of animals and/or farms that are infected, the geographical area that is affected by the disease, the control measures applied and their effectiveness and the potential zoonotic character of the pathogen resulting in human disease. Three impact categories are distinguished. First, economic losses in the livestock sector and, if the disease is zoonotic, economic losses due to human health effects are evaluated. Both can be subdivided in direct and indirect impacts. Furthermore, economic losses due to side-effects, e.g. impact on tourism, should be considered. Second, socio-ethical consequences, including human disease burden, animal welfare, destruction of healthy animals and animal products, and side-effects such as restricted access to natural areas are evaluated. And third, environmental impact, including effects of disease and control measures, especially vector control, on biodiversity and nature values is evaluated.

To conclude, the framework is a tool for risk assessment of exotic vector-borne livestock diseases that can be used for risk management purposes. Its main assets are:

- Providing insight into the main elements contributing to the risk of vector-borne livestock diseases, information that is of utmost importance in setting prevention and control measures.
- Identifying essential missing knowledge and data contributing to targeted research in the field of exotic vector-borne livestock diseases.
- Contributing to consistency in risk assessments of vector-borne livestock diseases, which makes comparisons between diseases and geographical areas feasible.

Following the testing of the framework by applying it to a mosquito-borne disease, the framework is now at the stage that it should be tested on a tick-borne disease. The complexity and multi-year life cycle with different stages, and different feeding hosts as well as the zoonotic character of CCHF will allow for a second extensive test of the framework.

Annex IV: CCHF essentials

This annex contains background information on CCHF and the life cycle of the *Hyalomma* tick (Figure 4) which is the primary vector and reservoir for CCHF. This information was not generated during the workshop but is added to this report in order to provide essential background information on CCHF for readers of this report. The information below can also be found on the websites of WHO and CDC [15,16]. CCHF is a viral haemorrhagic fever. The virus which causes CCHF is a *Nairovirus*, a group of related viruses forming one of the five genera in the *Bunyaviridae* family of viruses. This is the same family of viruses to which Rift Valley Fever (RVF), a mosquito borne zoonoses, belongs to. Although primarily a zoonosis, sporadic cases and outbreaks of CCHF affecting humans do occur. The disease is endemic in many countries in Africa, Eastern Europe and Asia. The disease was first described in the Crimea in 1944 and given the name Crimean haemorrhagic fever. In 1969 it was recognized that the pathogen causing Crimean haemorrhagic fever was the same as that responsible for an illness identified in 1956 in the Congo and linkage of the 2 place names resulted in the current name for the disease and the virus. CCHF can cause severe disease in humans, with a high mortality rate (5%-30%).

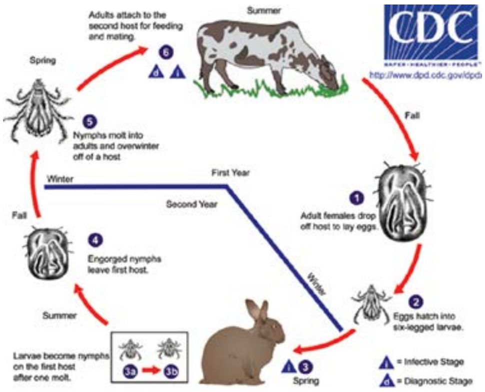

Figure 3: Hyalomma life cycle

CCHF reservoirs and vectors

A number of tick genera are capable of becoming infected with CCHF virus, but the most efficient and common vectors for CCHFV appear to be members of the *Hyalomma* genus (Figure 3). Trans-ovarian (transmission of the virus from infected female ticks to offspring via eggs) and venereal transmission have been demonstrated amongst some vector species. Once infected, the tick remains infected through its developmental stages, and the mature tick may transmit the infection to large vertebrates, such as livestock. The CCHF virus may infect a wide range of domestic and wild animals.

Many birds are resistant to infection, but ostriches are susceptible and may show a high prevalence of infection in endemic areas.

Figure 4: *Hyalomma marginatum*

Animals become infected with CCHFV from the bite of infected ticks. Domestic ruminant animals, such as cattle, sheep and goats, are viraemic (virus circulating in the bloodstream) for around one week after becoming infected. Humans who become infected with CCHFV acquire the virus from direct contact with blood or other infected tissues from livestock during this time, or they may become infected from a tick bite. The majority of cases have occurred in those involved with the livestock industry, such as agricultural workers, slaughterhouse workers and veterinarians. Also, nosocomial infections from infected patients to health works can occur.

Clinical features in humans

The length of the incubation period for the illness appears to depend on the mode of acquisition of the virus. Following infection via tick bite, the incubation period is usually one to three days, with a maximum of nine days. The incubation period following contact with infected blood or tissues is usually five to six days, with a documented maximum of 13 days. Onset of symptoms is sudden, with fever, myalgia (aching muscles), dizziness, neck pain and stiffness, backache, headache, sore eyes and photophobia (sensitivity to light). There may be nausea, vomiting and sore throat early on, which may be accompanied by diarrhoea and generalised abdominal pain. Over the next few days, the patient may experience sharp mood swings, and may become confused and aggressive. After two to four days, the agitation may be replaced by sleepiness, depression and lassitude, and the abdominal pain may localize to the right upper quadrant, with detectable hepatomegaly (liver enlargement). Other clinical signs which emerge include tachycardia (fast heart rate), lymphadenopathy (enlarged lymph nodes), and a petechial rash (a rash caused by bleeding into the skin), both on internal mucosal surfaces, such as in the mouth and throat, and on the skin. The petechiae may give way to ecchymosis (like a petechial rash, but covering larger areas) and other haemorrhagic phenomena such as melena (bleeding from the upper bowel, passed as altered blood in the faeces), haematuria (blood in the urine), epistaxis (nosebleeds) and bleeding from the gums. There is usually evidence of hepatitis. The severely ill may develop hepato-renal (i.e., liver and kidney) and pulmonary failure after the fifth day of illness. The mortality rate from CCHF is approximately 30%, with death occurring in the second week of illness. In those patients who recover, improvement generally begins on the ninth or tenth day after the onset of illness.

Diagnosis

Diagnosis of suspected CCHF is performed in specially-equipped, high biosafety level laboratories. IgG and IgM antibodies may be detected in serum by enzyme-linked immunoassay (the "ELISA" or "EIA" methods) from about day six of illness. IgM remains detectable for up to four months, and IgG levels decline but remain detectable for up to five years. Patients with fatal disease do not usually develop a measurable antibody response and in these individuals, as well as in patients in the first few days of illness, diagnosis is achieved by virus detection in blood or tissue samples. There are several methods for doing this. The virus may be isolated from blood or tissue specimens in the first five days of illness, and grown in cell culture. Viral antigens may sometimes be shown in tissue samples using immunofluorescence or EIA. More recently, the polymerase chain reaction (PCR), a molecular method for detecting the viral genome, has been successfully applied in diagnosis.

Treatment in humans

General supportive therapy is the mainstay of patient management in CCHF. Intensive monitoring to guide volume and blood component replacement is required. The antiviral drug ribavirin has been used in treatment of established CCHF infection with apparent benefit. Both oral and intravenous formulations seem to be effective. The value of immune plasma from recovered patients for therapeutic purposes has not been demonstrated, although it has been employed on several occasions.

Prevention and control

Although an inactivated, mouse brain-derived vaccine against CCHFV has been developed and used on a small scale in Eastern Europe, there is no safe and effective vaccine widely available for human use. The tick vectors are numerous and widespread and tick control with acaricides (chemicals intended to kill ticks) is only a realistic option for well-managed livestock production facilities. Persons living in endemic areas should use personal protective measures that include avoidance of areas where tick vectors are abundant and when they are active (spring to fall); regular examination of clothing and skin for ticks, and their removal; and use of repellents. Persons who work with livestock or other animals in the endemic areas can take practical measures to protect themselves. These include the use of repellents on the skin (e.g. DEET) and clothing (e.g. permethrin) and wearing gloves or other protective clothing to prevent skin contact with infected tissue or blood. When patients with CCHF are admitted to hospital, there is a risk of nosocomial spread of infection. In the past, serious outbreaks have occurred in this way and it is imperative that adequate infection control measures be observed to prevent this disastrous outcome. Patients with suspected or confirmed CCHF should be isolated and cared for using barrier nursing techniques. Specimens of blood or tissues taken for diagnostic purposes should be collected and handled using universal precautions. Sharps (needles and other penetrating surgical instruments) and body wastes should be safely disposed of using appropriate decontamination procedures. Healthcare workers are at risk of acquiring infection from sharps injuries during surgical procedures and, in the past, infection has been transmitted to surgeons operating on patients to determine the cause of the abdominal symptoms in the early stages of (at that moment undiagnosed) infection. Healthcare workers who have had contact with tissue or blood from patients with suspected or confirmed CCHF should be followed up with daily temperature and symptom monitoring for at least 14 days after the putative exposure.

Annex V: Presentations on CCHF

Three delegates were invited to share their experience with CCHF in the morning session of 23rd of May: Prof. Aykut Özkul, Prof. Zati Vatansever, and Dr Ana de la Torre. Presentations were given on the past and current situation in Turkey and on the risk assessment of CCHF in Turkey following the detection of *Hyalomma* ticks in Spain. All presentations were received with much enthusiasm.

Short summary of presentation by Prof. Aykut Özkul

The first case of CCHF in Turkey was detected in 2002. However, there is serologic evidence of circulation of CCHF virus in humans since the 1970's. The main virus circulating is the European 1 lineage virus. Until date, there have been over 6400 cases of CCHF recorded in humans resulting in 322 deaths. No clinical manifestations have been detected in animals. The yearly incidence has steadily increased and there may be many more, undetected, subclinical cases. Most cases occur in the months June and July. The main clinical symptoms are fever, headache and vomiting. The disease is endemic in the Northern part of Turkey with a mountainous area near the Black See. All cases of CCHF are within the known area of distribution of the *Hyalomma* tick which is believed to be the main, possibly the only, tick which carries and transmits the CCHF virus. Most cases live in villages or in rural areas and the main risk factor is working outdoors: farmers, builders and hunters, etc. In a bid to reduce the burden of disease, the government actively distributes brochures and posters to educate the public and health-care workers on CCHF, how to avoid being bitten by ticks, and how to remove them (not squashing!). The general public is also taught how to recognize different types of ticks.

Short summary of presentation by Prof. Zati Vatansever

Over 900 tick species are known to science, 28 of which are associated with spread of diseases to humans. Both climate and landscape determines which ticks can be found locally. There are two main types of ticks: (1) ambushing ticks which wait in overhanging vegetation and are dependent on humidity for survival, and (2) hunter ticks which do not climb but actively hunt for prey and can be found in more arid areas. Several tick species can transmit CCHFV, the main tick associated with the human CCHF cases in Turkey is the *Hyalomma marginatum* tick. This is an aggressive hunting tick with a two year life cycle. Immature (larvae and nymphs) feed on small wildlife and ground-feeding birds (peak of activity in July - august), while adult ticks feed on livestock, sheep and wild boar (peak of activity in May and June). *Hyalomma* becomes active when the temperature reaches temperatures over 10 degrees Celsius. The optimal temperature is between 22-27 ^{0}C and a 75-100% relative humidity. Habitat suitable for tick survival is increasing in Turkey as a result of national policy for reforestation. Thus the risk of infection is increasing.

Short summary of presentation by Dr Ana de la Torre

Spain is officially free of CCHF, despite the detection of a CCHFV positive *Hyalomma* tick in Western Spain in 2010. The CCHFV strain found was very similar to strains found in sub-Saharan Africa and the tick was probably introduced by a migratory bird. Climate change, resulting in warmer and dryer areas in Spain, is believed to increase the likelihood of tick survival (particularly *Hyalomma*) and thus contributes to an increased risk of CCHFV circulation in Spain. In Spain both small and large mammals are abundant, which is essential for the survival of *Hyalomma*. Therefore a qualitative risk assessment had been undertaken which included the mapping of deer and sheep and mapping of areas suitable for survival of *Hyalomma*. By combining these maps, an overall risk map was developed detailing the area's most at risk for CCHFV persistence/spread once introduced. Moreover, a quantitative and spatial risk assessment was performed to identify the risk of CCHFV introduction in Spain by migratory risk. The positive sample in 2010 was in an area indicated as a medium risk area according to the risk map. The risk assessment concluded that Spain is free of CCHF, but conditions are suitable for *Hyalomma* and CCHF virus circulation.

Annex VI: Evaluation report

A completed questionnaire was returned by 10 (75%) of the external participants (15). No active follow up was attempted to increase the response rate. One questionnaire was completed only half. Two participants answered question 47 (Overall, how satisfied were you with this workshop) as A (very dissatisfied). Since their answers did not match with their other scoring and comments, it was assumed that they meant to answer E (very satisfied). A similar error was made during the RVF workshop in 2011. Thus, the questions, or the answering categories, need to be adjusted. For question 25 (The reporting back of this session captured adequately what was discussed during the break out group) the answering category was missing resulting in a low response rate on this question. Furthermore, the numbering of the questions is erroneous and will need to be adjusted. Reduce answering categories from 5 to 3 for ease of completion and evaluation. Two people encircled mostly 4 and 5 together. In the evaluation the lowest score was entered for evaluation. This means that scoring presented here is slightly lower than the true scoring. Reducing answering categories from 5 to 3 will help to prevent this.

In conclusion, this workshop was again (very) well evaluated and (very) well appreciated by participants.
Specific points:

- Organisation was good.
  - Next time also send some background information on disease evaluated as not all participants can be expected to be experts on all aspects of the disease
- Time schedule is still tight.
  - No easy solution for this. As some participants would like the workshop to be shorter while other would like more time
- Presentations at the beginning of the workshop always score well.
  - Perhaps allocate more time for more presentations and discussion.
- One person was less satisfied with the workshop and scored lower scores. This person was also the only one indicating a one-day workshop to be sufficient.
  - Since all other participants wanted more time, perhaps better information prior to the workshop could help fine-tune expectations.
- Questionnaire contained some errors
  - These will be adjusted, number of questions further reduced and more space will be given for general feedback

Evaluation Day 1

Q1: The objectives of the workshop were clear when I received the invitation

1	2	3	4	5
		10%	50%	40%

Q2: I was satisfied with the information received prior to the workshop (objectives, travel arrangements, venue, hotel, etc.)

1	2	3	4	5
			30%	70%

Q3: Any comments relating to Q1 & Q2?

Welcome & Introduction to workshop

Q4: The objectives of the workshop were presented clearly?

1	2	3	4	5
			60%	40%

Q5: Any comments relating to Q4?

Overview of CCHF situation worldwide

Q6: Overall, the presentations were informative

1	2	3	4	5
		20%	20%	60%

Q7: There was sufficient time for the presentations

1	2	3	4	5
	10%	20%	30%	30%

Q8: Any comments relating to Q6 & Q7?

- *Schedule was a bit tight*

- *It was a lot of new information in a short time. Some basic info on disease, tick, ecology on paper before the workshop would have been useful.*

Introduction to framework

Q 9: The framework was clearly presented

1	2	3	4	5
			60%	40%

Q 10: The objectives of the break out groups were clear

1	2	3	4	5
			40%	60%

Q 11: The instructions for the break out groups were clear

1	2	3	4	5
		20%	20%	60%

Q 12: Any comments relating to Q9 - Q11?

- *Misschien had incompatibiliteit van het framework voor vectorgebonden zoonoses meer specifiek aangekaart kunnen worden. Dus opsplitsing in de vraagstelling: kennis hiaat of mismatch met het framework. Nu liep dat een beetje doorelkaar. (English: maybe incompatibility of the framework for vector-borne zoonoses should have been addressed more clearly. The discussion should have been divided into knowledge gaps or mismatch of the framework. These discussions were mixed.)*

Break out group session 1 "probability of entry"

Q 13: The introduction to this break out group was helpful

1	2	3	4	5
			50%	50%

Q 15: The objectives for this session were clear

1	2	3	4	5
			40%	60%

Q 16: The objectives for this session were achieved

1	2	3	4	5
		20%	40%	40%

Q 17: The chairing of this session was conducive to the discussion

1	2	3	4	5
		1	50%	50%

Q 18: The reporting back of this session captured adequately what was discussed during the break out group.

1	2	3	4	5
		10%	50%	50%

Q 19: Any comments relating Q13 - Q18?

- *Iets meer tijd om de uitkomsten te bespreken was helderder geweest. Ik had het idee dat er nog wat open eindjes achterbleven. Ook werd nog vrij inhoudelijk gewisseld tussen entry probability en transmission* *dynamics. Ik denk dat dat deels ook komt doordat de vragen niet 100% compatibel waren op de inhoud van CCHF (English: Little more time to discus the outcomes would have resulted in clearer results. I had the idea that there are still some loose ends. The discussions of probability of entry and transmission dynamics mixed up and I think that this partly because the questions were not 100% compatible to the subject of CCHF)*

- *(q 18) Presentation of discussion might be presented accordingly with structure of questionnaire. Need for end-point result for each session (overall conclusion of QRA) (Comment evaluator: same comment for other breakout sessions)*
- *Too short time*
- *We did not really answer (all) the questions*

Break out group session 2 “transmission dynamics”

Q 20: The introduction to this break out group was helpful

1	2	3	4	5
		13%	43%	53%

Q 22: The objectives for this session were clear

1	2	3	4	5
		13%	43%	53%

Q 23: The objectives for this session were achieved

1	2	3	4	5
		13%	63%	33%

Q 24: The chairing of this session was conducive to the discussion

1	2	3	4	5
		13%	43%	53%

Q 25: The reporting back of this session captured adequately what was discussed during the break out group.

1	2	3	4	5
		12%	56%	22%

Q 26: Any comments relating Q20 - Q25

Evaluation Day 2

Break out group session 3 "likelihood of persistence"

Q 27: The introduction to this break out group was helpful

1	2	3	4	5
		13%	33%	53%

Q 29: The objectives for this session were clear

1	2	3	4	5
		13%	33%	53%

Q 30: The objectives for this session were achieved

1	2	3	4	5
		23%	43%	33%

Q 31: The chairing of this session was conducive to the discussion

1	2	3	4	5
		13%	43%	43%

Q 32: The reporting back of this session captured adequately what was discussed during the break out group.

1	2	3	4	5
		13%	43%	43%

Q 33: Any comments relating Q27 - Q32
We were turning a bit in circles between probability of establishment / persistence and the non-presence of *Hyalomma* currently in Western Europe.

Break out group session 4 "impact of disease"

Q 34: The introduction to this break out group was helpful

1	2	3	4	5
		13%	33%	53%

Q 36: The objectives for this session were clear

1	2	3	4	5
		13%	33%	53%

Q 37: The objectives for this session were achieved

1	2	3	4	5
		13%	53%	33%

Q 38: The chairing of this session was conducive to the discussion

1	2	3	4	5
		13%	53%	33%

Q 39: The reporting back of this session captured adequately what was discussed during the break out group.

1	2	3	4	5
		13%	63%	23%

Q 40: Any comments relating Q34 - Q39

- *Partly absent, good impression, interesting point*

General questions about break out groups

Q 41: The group size was appropriate

1	2	3	4	5
			45%	65%

Q 42: There was enough time to work through the framework questions

1	2	3	4	5
	22%	22%	22%	32%

Q 43: There was enough time for discussion

1	2	3	4	5
	12	12%	42%	32%

Q 44: Any comments relating Q41 - Q43

- *Misschien “teveel” discussie door experts onderling. Ook erg belangrijk voor het wetenschappelijk proces en de uitwisseling, maar minder voor de doelstelling het framework toe te passen. Maar goed, deze workshop was dus ook erg waardevol voor het delen van kennis tussen experts, waarbij het gebruiken van het framework een constructieve ruggengraat biedt. Dat zie ik als meerwaarde t.o.v. bijvoorbeeld alleen presentaties.(English: Maybe "too much" discussion among the experts. Also very important to the scientific process and the exchange, but less when application of the framework is the target. Anyway, this workshop was also very valuable for sharing knowledge between experts,* *in which the framework provided a constructive backbone. I see that as an added value compared to e.g. only presentations.)*

- *Would be great to have as “conducting documents” the presentations that were presented regarding sessions.*

- *Different per session. First session not enough time, later sessions were ok. Group discussions after break out group work was nice*

In conclusion

Q 46: Overall, the objectives of the workshop were achieved

1	2	3	4	5
		13%	73%	13%

Q 46: If you disagree, please explain why.

- *Highlighted needs for further research. Next step: how to translate in risk management options?*

- *Agree, maar voor mijn gevoel waren er nog aardig wat open eindjes. Ik heb dag twee ook niet bijgewoond, dat zou dat kunnen verklaren. Maar ik ben wel benieuwd wat de vervolgstappen van CVI zijn. En natuurlijk naar de “samenvatting” van dag 2. (Englidh: Agree, but I felt there were quite a few loose ends. I have not attended day two, which might explain this feeling. But I am curious what the next steps of CVI will be. And of course of the summary of day 2.)*

Q 47: Overall, how satisfied were you with this workshop? (circle one option below)

1	2	3	4	5
			50%	50%

Q 48: Do you have any remarks concerning the overall time schedule of the workshop?

- *Could be done in one day*
- *If the meeting would begin one hour later, I think we would be able to arrive this day instead of the day before*
- *Lunch break earlier*
- *Was ok. 2nd day a bit too early to come by train. Lunch late in afternoon.*

Q 49: Do you have any other remarks about this workshop such as the venue, hotel, lunch or dinner?

- *Prima geregeld. Goed dat de juiste experts aanwezig waren. Jammer dat CMV ontbrak. (English:Good organisation. The rigth experts were present. A pity that Center Montoring Vectors was absent.)*
- *No, Thank you very much for this nice meeting*
- *Everything was very well organised.*
- *Lelystad is far away! ;)*

Q 50: Do you have any other feedback that would help us in organizing a future workshop?

- *Great team work!*

- *Misschien nog duidelijker de concrete aanbevelingen / output naar voren brengen tijdens de meeting. Dat geeft een belonend effect “kijk, dit hebben we toch even samen bereikt” idee. (English: Perhaps specific recommendations / output should be formulated during the meeting. This gives a rewarding effect, "This is what we would like to achieve together")*
- *A “state of the art” would help for the experts attending to the meetings.*
- *Only success when all the experts are present. (One group missed an entomologist during day 2)*

Q 51: Do you have any other feedback that would help us in organizing a future workshop?

- *Misschien nog duidelijker de concrete aanbevelingen / output naar voren brengen tijdens de meeting. Dat geeft een belonend effect “kijk, dit hebben we toch even samen bereikt” idee. (English: Perhaps specific recommendations / output should be formulated during the meeting. This gives a rewarding effect, "This is what we would like to achieve together")*
-