FUTURE RESEARCH

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It is our hope that this book will stimulate research, and identify new areas of study, for Crimean-Congo hemorrhagic fever (CCHF). To gain a better overall picture of this disease, a multidisciplinary approach is needed. This should include not only virologists, entomologists, clinicians, epidemiologists, and veterinarians, but also climatologists, sociologists, anthropologists, and others. The dynamics of the enzootic environment and transmission cycle of the virus need to be better understood. For example, the role, if any, of ticks other than *Hyalomma marginatum marginatum* needs to be more carefully examined. At the time of potential global warming, the role of various climatic factors on CCHF transmission will become increasingly important. Global information systems and remote sensing using satellites will be important tools to produce better spatial and temporal maps for CCHF. In addition, mathematical modeling, which can simulate *in silico* CCHF epidemics under a variety of different conditions, holds great promise. However, it must be keep in mind that all these predictive models need to be critically validated using data from real disease outbreaks whenever possible.

Laboratory research with the virus has been hampered by the need to work with it under a high level of biocontainment; in most cases, this means a biosafety level 4 (BSL-4) laboratory. With the recent increased interest and funding for biodefense and emerging infectious disease-related work, more BSL-4 laboratories are being built, especially in the USA and Europe. This increased availability of appropriate biocontainment laboratories should lead to more research on the virus itself. New antiviral drugs and improved vaccines are sorely needed for this disease. Also critical is the need for an appropriate animal model of CCHF, not only to study the pathogenesis of disease, but also to test potential new antiviral drugs and vaccines. As alluded to elsewhere in this book, studies on the pathogenesis of CCHF could also shed light on the pathogenesis of other viral hemorrhagic fevers, such as Ebola. A particularly interesting area in this regard is the study of the host response to infection. It is possible that different individuals respond differently to infection or different strains of the virus produce slightly

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different disease in their hosts. This knowledge could identify specific groups of people who are at more risk of serious disease or could provide clues for the development of new therapies for CCHF and other important viral diseases.

Of course these thoughts only scratch the surface. No one can know for sure what the future holds for CCHF or any other disease, but hopefully these ideas will provide a starting point.

FREQUENTLY ASKED QUESTIONS (FAQ) ABOUT CRIMEAN-CONGO HEMORRHAGIC FEVER

This FAQ section was structured to provide a basic knowledge for health-care workers, the media, or anyone else who is responsible for providing the public with information about Crimean-Congo hemorrhagic fever (CCHF). These questions were compiled from numerous academic and public seminars, conferences, and radio and television programs.

Q: What is a viral hemorrhagic fever?
A: A viral hemorrhagic fever is a viral disease, which has a tendency to disrupt the clotting of the blood, so that patients may develop uncontrolled bleeding. Usually fever, body aches, and other flu-like symptoms also are seen. Many common diseases can resemble viral hemorrhagic fever, but the term is reserved for a particular group of diseases associated with a high death (fatality) rate. In addition to CCHF they include Lassa fever, Rift Valley fever, Alkhumra, Omsk hemorrhagic fever, Kyasanur forest disease, Argentine, Bolivian, Brazilian, and Venezuelan hemorrhagic fevers (caused by Junin, Machupo, Sabia, and Guanarito viruses, respectively), and Marburg and Ebola hemorrhagic fevers. Although the clinical pictures are similar, the viruses are not closely related to each other, and are transmitted in a variety of ways.

Q: What is CCHF?
A: CCHF is a tick-borne viral disease of humans, which occurs in Africa, south-eastern Europe, and Asia, below the 50° parallel.

Q: Why does it have the name "Crimean-Congo hemorrhagic fever"?
A: A disease given the name Crimean hemorrhagic fever was first recognized on the Crimean Peninsula in 1944, although the virus which causes the disease was only identified in 1967. Meanwhile, in 1956 a virus given the name Congo was isolated from a child with fever in the former Belgian Congo or (now Democratic Republic of the Congo). In 1969, it was discovered that the two viruses were the

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same. Consequently, the virus and the disease were called "Crimean-Congo hemorrhagic fever."

Q: Where does the virus come from?
A: The virus is transmitted mainly by *Hyalomma* ticks, adults of which have distinctive brown and white bands on their legs. The virus can remain in the ticks for long periods, and even pass through the eggs to infect the next generation of ticks.

Immature *Hyalomma* ticks (larvae and nymphs) feed on ground-frequenting (or ground-feeding) birds (guinea fowl, partridges, rooks) and small mammals up to the size of hares. Adult *Hyalomma* ticks feed on livestock such as cattle, sheep, and goats, as well as on wild animals such as antelope, wild boar, and ostriches.

Animals bitten by infected ticks do not develop the disease, but can circulate the virus in their blood for a few days, up to 1 week, and thereafter become immune to further infection. Noninfected ticks become infected if they feed on the animals during the short period when virus is in circulation, thus ensuring that the virus is perpetuated.

Q: Can CCHFV live in vectors other than ticks, such as mosquitoes?
A: No, mosquitoes or other arthropods (other than ticks) have not been implicated as vectors of CCHFV.

Q: How do humans become infected?
A: Humans can become infected from being bitten by infected ticks, or even from squashing ticks if fluid from the ticks gets into cuts and breaks in the skin, or onto mucous membranes. Humans can also become infected if blood from infected livestock or wild animals comes into contact with broken skin (cuts and abrasions) or mucous membranes during the short period that the animals have the virus in circulation. On farms, this usually happens when young animals become infected as a result of being exposed to ticks, and humans are then exposed to blood during procedures such as the castration of calves, slaughtering of lambs, vaccination of animals, the cutting of identity notches in the ears, or the attachment of ear tags. Occasionally, animals that have been reared under tick-free conditions come into contact with ticks and the virus late in life, and so slaughtering mature animals can also result in human infection. Although the proportion of mature animals that will have virus in circulation may be extremely low, many thousands of animals are slaughtered each day at abattoirs. Hunting and butchering of wild animals can also be a source of human infection.

Similarly, humans can become infected through the contact with the blood and the body fluids of the patients. The relatives of the patients, who are in close

contact with CCHF patients or the health-care workers can become infected while caring their patients. The major route is being exposed to the blood of the infected patients.

Q: What is the life cycle of the tick vector?
A: *Hyalomma marginatum* group of ticks are two-host ticks and have activity in the summer. Immature forms (larvae and nymphs) feed on small animals (hare, ground-frequenting birds) for about 2–3 weeks and drop off the ground as engorged nymphs. Here starts an inactive period of 3 weeks (can be as much as 4 months longer if interrupted by winter) when the engorged nymphs transform to adults. Adult *Hyalomma* ticks hide on the ground and actively "run" toward an animal host (large mammal) when they sense certain signals (CO_2, vibration, visual objects, body temperature). Adults feed on animals for 1–2 weeks and mate meanwhile. Engorged females drop off the host, produce up to 7,000 eggs, and die.

Q: Where do the ticks get virus from?
A: The main source of virus infection for the tick is hares. Larvae and nymph acquire the virus from infected hares and the adult stage remains infected after molting (transstadial transmission). Livestock and large wild animals, during their short viremic period, can also serve as a source of virus for ticks. Engorged infected females can transmit the virus to their eggs, and subsequently to their progeny (transovarial transmission). Transovarial transmission rate in *Hyalomma* ticks is quite low, and its role in CCHF epidemics is not known exactly. There is also the "nonviremic transmission" phenomenon, in which noninfected ticks can acquire the virus by co-feeding with infected ticks on a CCHFV refractile host (e.g. birds).

Q: Where do people get tick bites?
A: In case of CCHF, most of the human tick bites are from unfed adult *Hyalomma* ticks. With regard to the biology of *Hyalomma marginatum* group ticks, it can be supposed that the areas frequented by hares and ground-feeding birds are of potential risk.

Q: Does CCHFV transmit through eating of contaminated animals?
A: No. To our knowledge no such transmission has been reported. This would be highly due to the high acid content of our stomachs.

Q: Which people are at risk of becoming infected?
A: People who are at particular risk of becoming infected with CCHFV include those involved in agriculture and stockbreeding, such as farmers and farm

laborers, milkmaids, sheep shearers, veterinarians, abattoir workers, persons who slaughter animals, hunters, close contacts of the infected patients, and the health-care workers.

Within abattoirs those who come into contact with fresh blood are at greatest risk. Once the carcasses have been bled out and hung to mature there is a sudden increase in the acidity of the meat, and the virus cannot survive in the carcass. Ostriches appear to be the only birds in which there is similar circulation of detectable levels of virus in blood as occurs in mammals. There is no indication that meat processed and matured according to standard abattoir practices constitutes a danger to consumers. Partially fed ticks, which detach from the hides of recently slaughtered animals, may attach indiscriminately to hosts available in their environment, and thus infect slaughtermen.

Apart from people directly involved in the livestock industry, persons at risk of being bitten by ticks include those who live in the countryside and town dwellers who visit the countryside for occupational or recreational purposes, including hunting and hiking. People are not always aware of being bitten by ticks, and in patients with CCHF, ticks have been found attached in concealed areas, such as on the scalp, pubic regions, and between the toes.

Health-care workers, or close contacts of patients, can acquire the infection from contact of broken skin or mucous membranes with the blood or blood-tinged body fluids and wastes of the patient. The only time that the infection has been seen in clusters of people is when they have been exposed to a common source of the virus, for example, while slaughtering animals. In contrast, there have been several instances of secondary spread of the infection from patients to health-care personnel, and this has usually involved needlestick injuries in hospitals.

Q: How common is the disease and how often is it fatal?
A: The disease is common in Africa, southeastern countries of Europe, and Asia. The case fatality rate (the rate of dying after getting the disease) is around 5–30%.

Q: What are the signs and symptoms of the disease?
A: The disease has a short incubation period followed by a very sudden onset of illness. People usually become sick within 1–3 days of being bitten by a tick, or 5–6 days after exposure to the blood of infected livestock or humans.

People abruptly develop a severe headache with sore and reddened eyes, fever with cold chills, and intense body aches, particularly involving the muscles of the lower back and thighs, and feel extremely unwell. Body temperatures do not necessarily remain high and may fluctuate during the course of the day. There may be nausea and vomiting, and sometimes abdominal pain and diarrhea early in the course of the disease. At this stage, blood tests already show abnormal liver function, and a decrease in blood platelets, which are involved in the clotting of blood.

After about 5 days, the patients may develop a rash of pink blotches on the body, followed by various bleeding tendencies, depending on the severity of the

illness. They bruise easily, often have nose bleeds, and may pass blood in their stool and/or urine. Stools seldom contain fresh blood; they usually have a dark and tarry appearance. Small or large red spots of bleeding into the skin appear, and there may be large confluent areas of bleeding into the skin around injection sites and in skin folds such as in the armpits or groin. Patients may vomit blood and bleed from the gums, and women may develop heavy uterine bleeding. Blood continues to ooze from needle puncture sites. There can also be internal bleeding, including intracerebral bleeding. Patients can go into a coma as the liver, kidney, and lung functions fail, and death can occur 5–14 days after the onset of illness, usually from heart failure.

Patients who recover show sudden improvement by day 10 of their illness. Virus remains detectable in human blood for up to 2 weeks after the onset of illness, but once the results of blood tests indicate that patients' body functions have recovered, and they feel well and are no longer bleeding; they can be discharged from hospital.

Q: What is the treatment for CCHF?
A: Treatment essentially consists of supportive therapy, which comprises intravenous feeding of the patient and replacement of blood and clotting factors. Severely ill patients may be placed on ventilators and other life support systems. The antiviral drug ribavirin has been used to treat patients, but the drug is not 100% effective; however, this is currently the only drug available to treat the disease.

Q: Why does the case fatality rate differ from country to country?
A: This remains an unanswered question, but could result from several reasons: (1) the virulence of different virus strains may be different; (2) access to health systems in different countries differ; (3) there could be more underlining "background" infections in some countries compared to others.

Q: What action should be taken if a person is suspected of having CCHF?
A: The disease may be suspected when a person suddenly becomes sick with headache, fever and chills, muscle pains, and possibly nausea, vomiting, and diarrhea, less than 1 week after being bitten by a tick, squashing ticks, or coming directly into contact with fresh blood or blood-tinged body fluids and organs of livestock, wild animals, or human CCHF patients. A doctor should be consulted immediately if the disease is suspected, and if the doctor believes that the suspicion is justified, the patient should be hospitalized and isolated immediately.

Q: What measures can be taken to prevent exposure to infection?
A: Persons in CCHF-endemic rural areas can use certain pyrethroid acaricides (permethrin, 0.5%) to treat clothing such as socks and outerwear (acaricides are insecticides used against ticks). Formulations which are generally available from

shops that sell equipment for camping and outdoor activities, include aerosol sprays and sachets of concentrated acaricide used to prepare emulsions into which clothing is dipped.

Insect repellents such as DEET can be used on the skin to preventing tick bites. But it should be kept in mind that the effective concentration of DEET to repel ticks is much higher than that used for mosquitoes. The use of DEET on small children should be avoided.

Long trousers and long-sleeved shirts should be preferred. When being in an area of high risk, personal inspection of your clothes should be made every 2 h, and total body inspection is advised at the end of the day. Virus transmission from the attached tick increases over time, so prompt tick removal is important.

Abattoir workers, veterinary staff, farm workers, and hunters should use appropriate impervious protective clothing and gloves when engaged in activities which carry a risk of exposure to animal blood. Although it is incumbent upon employers to supply protective clothing and safety instructions, employees must take responsibility for adhering to the safety regulations.

Veterinary regulations promulgated for ostrich abattoirs require that birds should be treated with an appropriate acaricide and held in tick-free facilities for 14 days before slaughter. Similar regulations would be impossible to implement for other livestock. Vast numbers of cattle, sheep, and goats are slaughtered each day, and the costs of constructing tick-free holding pens of suitable capacity would be prohibitive, as would the costs and logistics of holding and feeding the animals and supervising the operation. A potential alternative would be the development of a veterinary anti-tick and anti-CCHFV vaccine that is applied to farm animals as a public health measure, but such research would require special funding.

Q: Can the virus transmit through inhalation?
A: No, there is no report on inhalational transmission of the virus. Therefore, the universal precautions are generally considered sufficient for the protection of close contacts and health-care workers.

Q: Can a cured patient get the infection a second time?
A: After recovery, the patients are immune to further infection. It is not uncommon for recovered patients to remember little or nothing about the events of their illness. To our knowledge, there is lifelong immunity after the disease.

Q: Is there a vaccine for the infection?
A: At present there is no human vaccine, and the lack of potential demand for such a vaccine inhibits its development. A vaccine against CCHF was used in Bulgaria, but the experience is limited to one country.

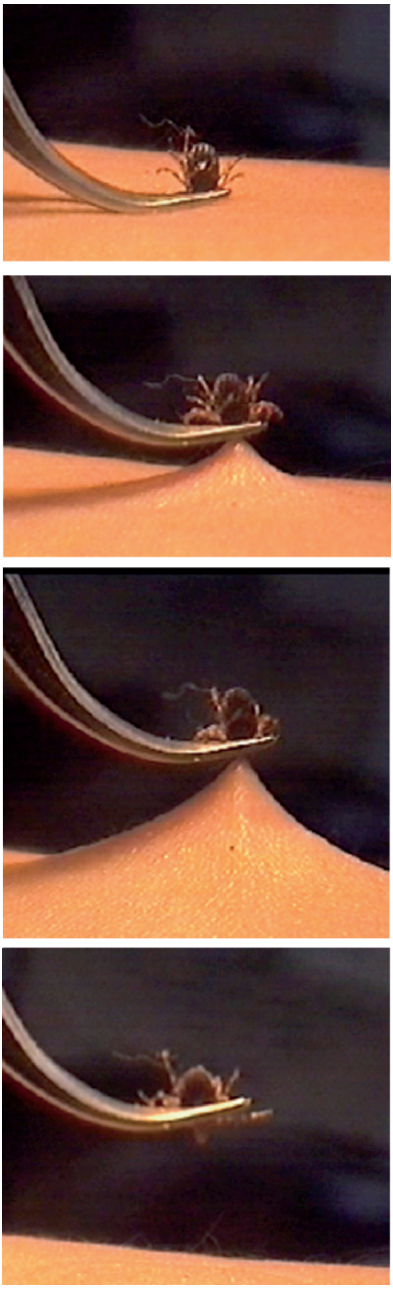

Fig. 1. Pictures showing the proper way to remove an attached tick. (Courstey of Dr. Zati Vatansever, Ankara University, Ankara, Turkey.)

Q: Is there a causal relation of global warming and the occurrence of the disease?
A: Possibly, but not demonstrated yet. Since the virus-infected ticks become more active in the warmer months, global warming will increase the number of warm days in the year, thus resulting in more active ticks and more opportunity for people to become infected.

Q: Is CCHFV a potential bioterrorism agent?
A: Yes, CCHFV is listed as a Category C bioterrorism agent by the US Centers for Disease Control and Prevention.

Q: How can I take a tick out if I see one attached to me?
A: Attached ticks should be taken out gently and cautiously (Fig. 1). Ticks' mouthparts have reverse harpoon-like barbs designed to penetrate and attach to the skin. Here is how we suggest removing an attached tick:

1. Use fine-point tweezers to grasp the tick at the place of attachment as close to the skin as possible.
2. Gently pull the tick straight out.
3. Place the tick in a small vial labeled with your name, address, and the date.
4. Wash your hands and disinfect the bite site with isopropyl alcohol.
5. Record the date, area on your body of the tick attachment, and your general health at the time.
6. Call your doctor to determine if treatment is warranted.
7. If possible, have the tick identified or tested by a laboratory, your local health department, or a veterinarian.
8. Do not attempt to prick, crush, or burn the attached tick as this may cause it to release infected fluids into your skin. Also, do not try to smother the tick (e.g. applying petroleum jelly or nail polish).

Acknowledgments

We thank Robert Swanepoel and Zati Vatansever for their contributions to this section.