DISCONTOOLS

Crimean Congo Haemorrhagic Fever
Summary

Introduction

1. This note provides a brief summary of an analysis undertaken by a DISCONTOOLS group of experts on Crimean Congo Haemorrhagic Fever (CCHF). They reviewed the current knowledge on the disease, considered the existing disease control tools, identified current gaps in the availability and quality of the control tools and finally determined the research necessary to develop new or improved tools. Full details of the analysis can be downloaded from the web site at http://www.discontools.eu/

Disease profile

2. The virus which causes CCHF is a zoonotic arbovirus which is a member of the Orthonairovirus genus (*fam Nairoviridae, O. Bunyavirales*). There are 51 distinct viruses currently assigned to the genus Orthonairovirus and 29 related, unclassified, viruses according to the species demarcation criteria, i.e the orthonairovirids with less than 93% RdRP (viral polymerase) amino acid sequence identity represent different species. Based on sequence data seven main genotypes (I to VII) of CCHF virus (CCHFV) have been recognised, and nucleic acid sequence analysis has demonstrated extensive genetic diversity.

3. Most members of the Ortho*nairovirus* genus are transmitted by argasid or ixodid ticks. Once infected, the tick remains infected through its developmental stages. The mature tick may transmit the infection by bites to large vertebrates, such as livestock. The most relevant orthonairovirus, CCHFV, has been detected in around 31 species of ticks in seven genera of the family Ixodidae (hard ticks) acting both as vector and reservoir for the virus. Ticks of the genus *Hyalomma* are particularly important to the ecology, as they appear to be the most competent vector for the virus.

4. CCHFV has been isolated from a number of animal species including cattle, sheep, goats, hares, hedgehogs, dogs and mice. Antibodies have been reported in horses, donkeys, pigs, rhinoceroses, giraffes, buffaloes and other mammalian species. The virus infection has been commonly demonstrated among smaller vertebrate wildlife, such as hares and hedgehogs. They are believed to act as amplifying hosts and maintain the virus in nature and act as a source of the virus for the immature *Hyalomma* ticks which feed on them. In general adult ticks prefer large animals, like cattle, while immature ticks prefer smaller animals, like scrub hares and ground birds. Although CCHFV may infect a wide range of domestic and wild animals there is no evidence that the virus causes disease in animals. The viremia in animals lasts about 2 weeks. Many birds are resistant to infection, but ostriches are susceptible and may show a high prevalence of infection in endemic areas.

Risk

5. CCHF poses a serious threat to public health due to its high mortality rate, its modes of transmission, and its extensive geographical distribution. Ticks are a major source for the transmission of the virus to humans in open field settings (hikers, hunters…), either through bites or by crushing of an infected tick. Secondary cases are frequently seen due to human-to-human transmission via percutaneous or per mucosal exposure to blood and body fluids containing the virus. Others may acquire the virus from direct contact with blood or other infected tissues from viremic livestock. Cases have occurred in those involved with the livestock industry, such as agricultural workers, slaughterhouse workers and veterinarians. CCHF is listed in the WHO R&D blueprint priority diseases for research and product development.

6. Over the last years, CCHF outbreaks have become more frequent in several European countries and neighbouring areas, and an increase in the number of large outbreaks caused by CCHFV has been observed. Climate change, global trade, or long-range transport of infected ticks by birds can contribute to the spread of the disease. Vector distribution modelling suggests potential records of CCHFV further north and along mediterranean coastlines. CCHFV is widespread in nature due to the enzootic cycle of the virus between the small/ large mammals and the ticks. At present, there are very limited measures available to break the cycle. Studies on tick vector ecology, as well as the role of

animal reservoirs need to be part of plans for disease surveillance and risk assessment. It is therefore a disease to be approached under a One-Health framework.

Diagnostics

7. Commercial diagnostic kits are now available for detecting CCHF in animals. A number of assays exist for humans, including PCR, sandwich ELISA and IFA. Little information is available about how quickly antibody levels drop or whether the antibodies are protective. The diagnosis of suspected CCHF must be performed in high bio-safety level experienced laboratories. Lack of internationally recognized diagnostics standards for all-known clade CCHFVs makes reliable comparative data on the sensitivity and specificity of diagnostic tests not possible. Serum panels as well as virus highly needed to enable diagnostic capacity building in countries at risk. The development of rapid pen and bed site tests as wells as more sensitive and bio-safe diagnostic tools for CCHFV is also important.
8. CCHF can be diagnosed by isolating the virus from blood, plasma or tissues. Virus isolation is successful during the first days of illness when the viremia is high. Virus inoculation into newborn mice is more sensitive than cell based culture and can detect the virus for a longer period. CCHFV is identified by indirect immunofluorescence or reverse transcription-polymerase chain reaction (RT-PCR) assays.
9. The RT-PCR in clinical and tick samples has allowed the rapid laboratory diagnosis of the disease and molecular epidemiology studies. Whilst this technique is highly sensitive, attention has to be paid since a single set of primers is sometimes not capable to detect all CCHFV variants (due to the high genetic variability of the virus). Viral antigens can be detected by enzyme-linked immunoassay (ELISA) or immunofluorescence, but these tests are less sensitive than PCR.
10. Serology can identify animals that have been infected or exposed to CCHFV. An IgG ELISA can detect antibodies for the remainder of the animal's life. Other tests, including complement fixation and indirect fluorescent antibody, usually detect antibodies for shorter periods.

Vaccines

11. There are no CCHFV vaccines for animals since these are not clinically affected by the virus. However, an animal vaccine, preferable for minimizing tick biting virus transmission, would help to interrupt/diminish the CCHFV cycle, thus helping to reduce disease prevalence. For humans, an inactivated vaccine derived from mouse brain is commercialised and was used in the former Soviet Union and Bulgaria. The use of this vaccine lacks FDA or EMA approval so far. The major hindrance in developing vaccines against CCHFV is the wide genetic variation noted in different strains. This could be solved by vaccines promoting cell mediated immune responses against conserved antigens. Preclinical studies are evaluating several vaccine strategies (subunit, genetic and vector-based) with promising data on the identification of protective antigen targets. Nonetheless, the elicitation of both humoral and cell-mediated immune responses appears to be a key requirement for full efficacy.

Pharmaceuticals

12. None in animals as there is no evidence of clinical disease. General supportive care with treatment of symptoms is the main approach to managing CCHF in humans. According to the World Health Organization, if the patient meets the case definition for probable CCHF, oral ribavirin (RBV) treatment protocol needs to be initiated immediately with the consent of the patient/ relatives and strictly in consultation with the attending physician. Ribavirin is also recommended for prophylaxis of contacts but, currently, there is no consensus on the use of ribavirin due to very limited evidence of its efficacy. Preclinical data favours the use of Favipiravir, alone or in combination with RBV. New antivirals and repurposed drugs have been proposed (Baloxavir, 2′-Deoxy-2′fluorocytidine, Tygecicline). Monoclonal antibodies (against NP, GPc and GP38) have some preclinical evidence. However, the efficacy of novel antivirals or immunotherapeutic tools should be investigated further. Acaricides can be used on livestock and other domesticated animals to control ticks, particularly before slaughter or export.

Gaps in Knowledge

13. In spite of recent advances, there are still many significant areas of uncertainty in the understanding and knowledge about CCHF especially regarding pathogenesis, immunology, vaccinology, epidemiology and control. Studies on the interactions of CCHFV with hosts and vectors will be of great help to understand the pathogenesis of the disease. Several issues remain to be elucidated, such as length of the viraemic phase allowing ticks to become infected after biting. The development of effective methods to vector control will also be important. Studies on the evaluation of intervention and control strategies are necessary. Host factors associated with pathogenesis, disease severity and association of the immune response with the course and outcome of the disease in humans, are barely studied. Tools to monitor and predict virus migration along with potential movement of the associate ticks as a result of climate change and animal movements is an important requirement.

14. The knowledge about potential, re-assortment and recombination events between virus genomes is very limited and improving knowledge on the phylogeny and evolution of the virus would be beneficial. Unfortunately, research activities concerning CCHF disease have been restricted to very few institutes/laboratories. An important limitation is the occurrence of sporadic cases or outbreaks in areas with limited facilities, while the lack of specimens from patients, animals and ticks inhibits the basic and/or applied research programs.

15. Research is needed to fill these gaps in knowledge mainly to control CCHF in humans, as there is no evidence of clinical disease in animals. Apart from tick control, actions to break the virus transmission between animals and ticks might be possible. Full details of the gaps are shown in the Disease and Product Analysis for CCHF on the DISCONTOOLS web site.

Conclusions

16. CCHF is a human disease. Animals and ticks are involved in the virus cycle in nature. The seroprevalence in some animals is exceedingly high. Better diagnostic kits are needed to detect true anti-CCHFV antibodies in animals according to validated standards. A One-Health approach for developing animal vaccines could help to prevent the establishment of the enzootic cycle. However, human vaccines are also needed. The control of ticks and bio security to prevent contact between humans and potential sources of infection are the main ways of disease control at present. More studies should be performed on the human immune response to the virus, the virus-vector-host interactions, the CCHFV dynamics in reservoirs and vectors, the role of birds and wildlife and the role of climate change in the distribution of ticks and the establishment of new CCHF endemic areas.