Rift Valley Fever
Summary

Introduction

1. This note provides a brief summary of analysis undertaken by DISCONTOOLS groups of experts on Rift Valley fever (RVF). They reviewed and updated regularly 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 website at http://www.discontools.eu/ by selecting Disease Database, then the specific disease and highlighting the variables of interest. This is completed by selecting "create a report" which can then be downloaded as either a PDF or Excel spread sheet. The full gap analysis matrices for Rift Valley Fever can be found on the website and downloaded here.

Disease profile

2. RVFV is able to infect many species of animals causing severe disease in domesticated animals including cattle, sheep, camels and goats. RVF outbreaks are characterized by high rates of abortion and neonatal mortality, with sheep being the most susceptible to the disease. Humans are very susceptible with flu-like symptoms prevailing, although serious complications including retinal lesions, encephalitis and haemorrhagic fever may develop in 1-2% of patients. RVF virus is usually transmitted among ruminants through bites from infected mosquitoes which are the biological vectors. After first incursions, the virus is generally maintained by low-level circulation among ruminants and mosquitoes and possibly by transovarial transmission of the virus to mosquito eggs. Transmission of RVF virus by mechanical means via biting flies is also possible. Human infections are generally attributed to contact with raw meat, blood and other body fluids during the slaughtering of viremic animals.

3. RVF has been recognised mainly in African countries with some incursions into the Middle East and Indian Ocean islands. RVF usually occurs in epizootics in Africa, which may involve several countries in a region. The first reported occurrence of disease outside Africa occurred in 2000 when cases were confirmed in Saudi Arabia and Yemen. Imported human cases have been documented in China and in Europe between 2017 and 2019.

4. Epizootics follow the periodic cycles of exceptionally heavy rain, which may occur very rarely in semi-arid zones (25–35-year cycles), or more frequently (5–15-year cycles) in higher rainfall savannah grasslands. During the inter-epizootic period low level RVFV activity may occur. Rainfall and mosquito population density are the critical factors.

Risk

5. A number of reviews have concluded that the risk of the introduction and spread of RVF virus in Europe is low. Recent evidence following the reappearance of RVFV in East Africa, including Sudan, the Nile Valley, the Indian Ocean islands and, more recently, in West Africa (Mauritania, Mali) suggests that the virus remains active and that spread of the virus is sensitive to climate changes. Other changes due to socio-economic effects, increasing human populations, demand for meat and uncontrolled movements of livestock all indicate that the risk of an introduction into the Mediterranean basin and central Europe will continue to increase.

6. There remains a concern that RVF virus could spread in Europe and Asia after a first introduction. The movement of viremic animals into previously unaffected areas where vectors are present has the potential to result in epidemics and epizootics. This is particularly noticeable in Northern African countries where seropositive animals are frequently detected.

Diagnostics

7. A range of diagnostic tests exist including the virus neutralisation test (VNT) and ELISA. The VNT remains the gold standard but whilst it is very specific it is also costly, time consuming, and requires a high biosecurity laboratory. Using indirect detection with ELISA is quick, sensitive and specific. These ELISAs are progressively replacing VNT. A competition ELISA which allows diagnosis of ruminant sera is commercially available, although additional (confirmation) ELISAs should be developed and commercialized. Other potential developments could include i) a pen-side diagnostic test, ii) tests in order to Differentiate Infected from Vaccinated Animals (DIVA).

Vaccines

8. Both live-attenuated and inactivated vaccines are available for veterinary use and have been applied in the field for many years. Each type has disadvantages and there is an urgent need for a vaccine with equal, or greater, efficacy to the live-attenuated Smithburn vaccine but which is as safe as the inactivated vaccine.

In endemic countries the correct application of vaccines would be important to reduce the spread of the virus from viraemic to naive animals during a RVF outbreak. The release onto the market of the Clone-13 vaccine, with improved safety was considered a major advance in the battle against RVF. The Clone-13 virus was isolated from a benign human case and contains a ~70% deletion in the gene encoding the NSs protein, which is the major virulence factor of the virus. In the US, the mutagenised MP12 vaccine strain has a conditional license (to Zoetis Inc.) for veterinary emergency use but not for a general commercial use.

9. Natural infection and vaccination with an effective vaccine induces high neutralizing antibody titres which correlate with protection. Only one dose of the live vaccine (Smithburn strain) is required to provide long-term immunity but the vaccine may induce foetal abnormalities and/or abortion in ruminants. It is also pathogenic for humans (febrile syndrome).

10. The inactivated vaccine does not have these side effects, but provides a lower level of protection and duration of immunity and its production is more expensive. At least two inoculations with frequent boosters are required to ensure the desired level of protection, rendering it not very practical for use in countries where large numbers of ruminant herds are nomadic. As the inactivated vaccines are used in areas where RVF is not endemic the knowledge of their efficacy is limited as natural field challenge does not occur. The requirement for multiple doses in order to provide protection may be problematic in endemic areas.

11. The MP12 and the Clone 13 vaccine were shown to be safe for sheep and cattle, also at young age. These vaccines do not spread into the environment and cause no, or very low viremia, which ensures that the vaccine viruses will not be transmitted by mosquitoes feeding on vaccinated animals. However, safety trials have demonstrated that administration of an overdose during the first trimester of gestation may result in virus transmission to the ovine fetus leading to associated stillbirths and malformations. Other live-attenuated vaccines developed using more rational reverse genetics approaches have demonstrated a higher safety profile in preclinical animal models and are expected to progress to the clinical development phase.

12. Development of a DIVA diagnostic assay intended for these types of attenuated vaccines has shown to be problematic although it is being investigated further. Nonetheless, other vaccines compatible with current diagnostics for DIVA determination (subunit, DNA, mRNA or viral vector-based) have been also developed. These have also proven efficacy and could be a safer alternative to attenuated vaccines.

13. Emergency vaccination seems to be the only effective way to control the disease. There are no vaccines licensed for use in Europe.

Pharmaceuticals

14. There may be some potential for the use of antivirals for post-exposure treatment of infected humans but there is presently little or no incentive for pharmaceutical companies to develop such products.

Knowledge

15. There are still significant areas of uncertainty in the understanding and knowledge about RVF especially in relation to pathogenesis, immunology, vaccinology, vector ecology, epidemiology and control. Human physiopathology is also largely unknown. A substantial effort is needed to better understand the ecology of RVFV vectors and epidemiological processes in Africa, to develop predictive and quantitative risk models and maps, identify key environmental drivers, and to implement risk-based surveillance and control methods. Full details of the gaps are shown in the Disease and Product analysis for RVF on the DISCONTOOLS website.

Conclusions

16. Currently, RVF is a disease that is confined to the African continent, the Arabian Peninsula and some islands off the coast of Southern Africa. Northern African countries usually report positive serology in animals. Countries outside the current habitat of RVFV, including the US and Europe are at risk of an introduction, analogous to Zika virus in South America, West Nile fever in the US or Bluetongue in Europe. The number of imported human cases out of the endemic zones is also increasing.

17. Experts indicate that the initial control strategy of a RVF outbreak in Europe would be vaccination. Although no vaccine is registered yet in Europe, several research initiatives are underway to advance the development of vaccines that can be applied in Europe as emergency vaccines. Anticipation of an incursion of RVF into Europe by developing contingency plans, registering vaccines and development of novel diagnostic tools is recommended.