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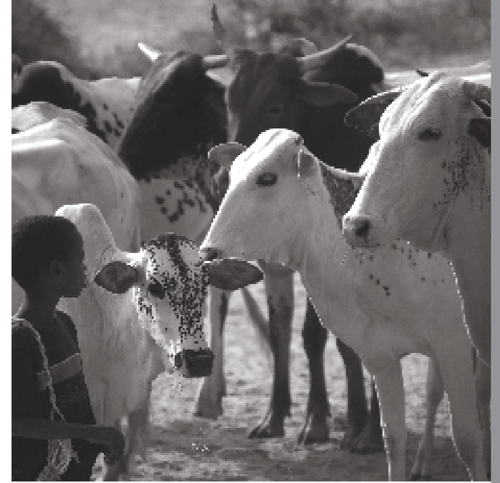

report

THE LAST HURDLES TOWARDS RIFT VALLEY FEVER CONTROL

5–7 March 2014
Ad hoc workshop on the current state of
Rift Valley fever vaccine and diagnostics development
Rome, Italy

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Acronyms

ABADRU	Arthropod-Borne Animal Diseases Research Unit
AHRI	Animal Health Research Institute
AU-IBAR	African Union Interafrican Bureau for Animal Resources
BDSL	Biological Diagnostic Supplies Limited
BSL-2	biosafety level-2
CBPP	contagious bovine pleuropneumonia
CCPP	contagious caprine pleuropneumonia
CDC	United States Centers for Disease Control and Prevention
CISA-INIA	Centro de Investigación en Sanidad Animal, Instituto Nacional de Investigación y Tecnología Agraria y Alimentaria
CVB	Center for Veterinary Biologics
CVI-WUR	Central Veterinary Institute Wageningen University and Research Centre
CVL	Central Veterinary Laboratories
DAFF	South African Department of Agriculture, Forestry and Fisheries
DHS	United States Department of Homeland Security
DIVA	differentiating between infected and vaccinated animals
ELISA	enzyme-linked immunosorbent assay
FAO	Food and Agriculture Organization of the United Nations
FAZD	National Center for Foreign Animal and Zoonotic Disease Defense
FDA	Food and Drug Administration
GALVmed	Global Alliance for Livestock Veterinary Medicines
GF-TADS	Global Framework for Transboundary Diseases
GOVS	General Organization for Veterinary Services
GTPV	goat pox virus
IAEA	International Atomic Energy Agency
IBD	infectious bursal disease
IFAH	International Federation for Animal Health
IM	intramuscular
IV	intravenous
KEVEVAPI	Kenya Veterinary Vaccines Production Institute
L	large
LNERV	Laboratoire National D'Elevage et de Recherches Vétérinaires
LSD	lumpy skin disease
LSDV	lumpy skin disease virus
M	medium
MSD-AH	Merck Sharp & Dohme Animal Health
MVA	Modified Vaccinia Ankara
NAHLN	National Animal Health Laboratory Network
ND	Newcastle disease
NDV	Newcastle disease virus
NICD	National Institute for Communicable Diseases

nm	nanometer
NSR	non-spreading RVFV
OBP	Onderstepoort Biological Products
OIE	World Organisation for Animal Health
PACE	Pan African programme for the Control of Epizootics
PANVAC	Pan African Veterinary Vaccine Centre
PARC	Pan African Rinderpest Campaign
PCR	polymerase chain reaction
pfu	plaque-forming units
PPR	peste des petits ruminants
RT-PCR	reverse transcription polymerase chain reaction
RVF	Rift Valley fever
RVFV	Rift Valley fever virus
S	small
SADC	South African Development Community
SC	subcutaneous
SPS	sanitary and phytosanitary
USDA	United States Department of Agriculture
VLP	virus-like particles
VN	virus neutralization
VRI	Veterinary Research Institute
VRP	virus replicon particles
VSVRI	Veterinary Serum and Vaccine Research Institute
WAHIS	World Animal Health Information System
WHO	World Health Organization

Abstract

In the past decade, significant progress has been made in the development of Rift Valley fever (RVF) vaccines, and several next-generation vaccines are currently being evaluated for registration. To assess the status of vaccination and diagnostic options available for animal and public health, the Food and Agriculture Organization of the United Nations (FAO) held an Ad hoc Workshop on the Current State of Rift Valley fever Vaccine and Diagnostics Development at FAO headquarters in Rome on 5–7 March 2014. Global experts in RVF vaccine development, world leading veterinary vaccine manufacturers, the chief veterinary officers from Egypt, Kenya, Mauritania, Senegal and Sudan, and representatives of key regional and global animal and human health agencies attended the meeting.

Issues related to the application of classical vaccines in RVF-endemic areas were discussed, as well as safe and effective new combination and novel vaccines that may soon become available. The challenge now is to have these vaccines available at the right time and place.

Participating subject matter experts made nine recommendations based on new research findings and recent disease control experience in RVF-endemic countries and regions. These recommendations are meant to guide vaccine research and development, quality assessment and production, and to strengthen laboratory diagnostic capacity. The Technical Workshop presentations and recommendations represent another step forward in strengthening RVF control strategies worldwide.

Background

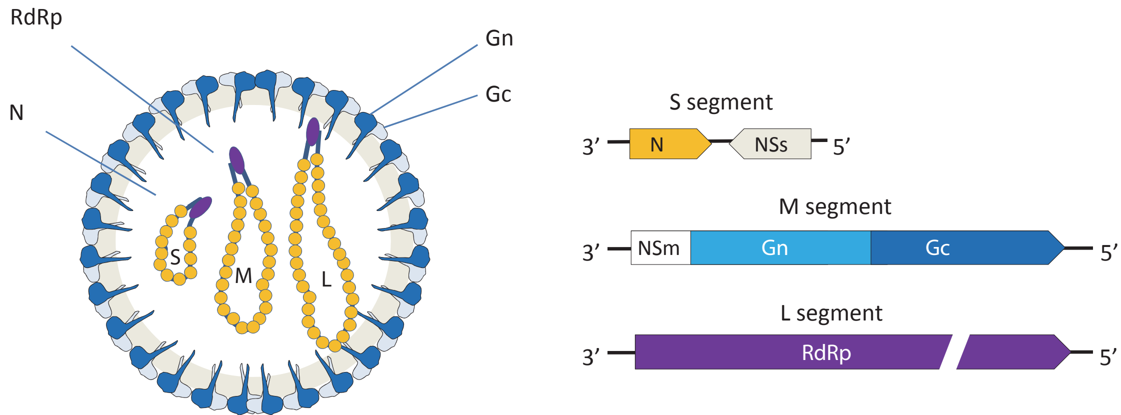
Rift Valley fever virus (RVFV) is a member of the *Phlebovirus* genus, one of the five genera of the *Bunyaviridae* family (Elliott,1996). RVFV virions are spherical particles of approximately 100 nanometre (nm) in size. The outer surface of the virion comprises capsomers of the structural glycoproteins Gn and Gc, which are embedded in a lipid bilayer (Figure 1). The virion contains an RNA genome that is divided into three segments, each named after their respective size. The large (L) segment encodes the viral RNA-dependent RNA polymerase. The medium (M) segment encodes a glycoprotein precursor that is co-translationally cleaved into Gn and Gc, and two accessory proteins. The first of these proteins is a 14-kDa nonstructural protein named NSm, which was shown to have an anti-apoptotic function (Won *et al.,* 2007). The function of the second protein, a 78-kDa protein, is presently unclear. The small (S) segment encodes a nucleocapsid (N) protein and a nonstructural protein, named NSs, which counteracts host innate immune responses and is, therefore, considered the major virulence factor of the virus (Billecocq *et al.* 2004; Bouloy *et al.* 2001; Le May *et al.*, 2004; Kalveram *et al.*, 2011; Ikegami *et al.*, 2009; Habjan *et al.*, 2009).

Culicine and *Aedine* mosquito vectors transmit RVFV among susceptible animals. The isolation of the virus from adult male and female *A. lineatopennis* mosquitoes reared from field-collected larvae has demonstrated that the virus can be transmitted to the eggs of this mosquito species (Linthicum *et al.*, 1985). Apart from the possible long-term persistence of RVFV in *Aedes* mosquito eggs, it is generally accepted that the virus can circulate at low level in both domestic and sylvatic cycles. After the mass hatching of mosquito eggs during periods of heavy rainfall, the virus can "spillover" from wild ruminants to herds of domesticated ruminants, resulting in large epizootics (Figure 2). RVFV has been isolated from more than 30 mosquito species belonging to 10 different genera (Meegan and Bailey, 1989).

Ruminants are the major target species of RVFV, of which sheep are the most susceptible. Lambs under the age of two weeks generally do not survive the infection and even in adult sheep, mortality can approach 30 percent. A characteristic feature of RVF outbreaks are the so-called "abortion storms" where nearly all gestating animals in sheep herds abort. Goats and cattle are somewhat less susceptible to disease, but high mortality ratios and abortions also occur in these species. Humans can be infected via the bite of infected mosquitoes, although most cases are attributed to contact with bodily fluids released during the slaughtering of viremic animals (Figure 2). The infection in humans is generally benign and manifests as a flu-like illness. However, an estimated 1 percent of infected humans develop severe complications, which can result in fatal encephalitis or hemorrhagic fever (Bird and Nichol, 2012).

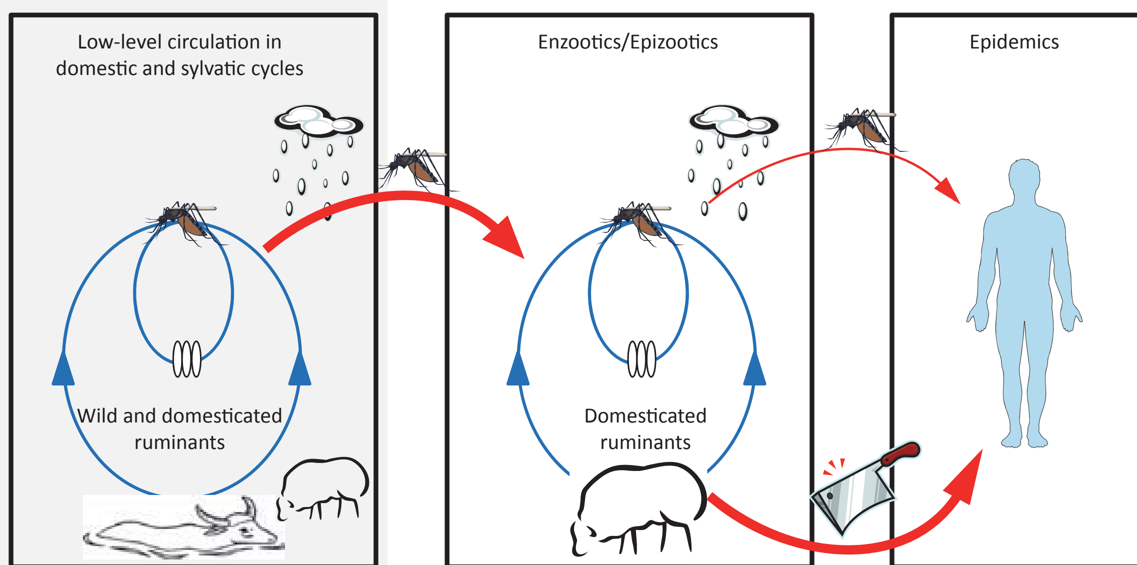
Two types of veterinary vaccines were originally developed for the control of RVFV in livestock. The first is based on adjuvanted, formalin-inactivated virus. When properly inactivated, this vaccine can be safely applied during all physiological stages of life in livestock. Optimal efficacy, however, depends on booster vaccinations and yearly re-vaccinations. K. C. Smithburn attenuated the virus by repetitive intracerebral passage in mice to develop a live-attenuated vaccine (Smithburn, 1949).

Figure 1
The RVFV virion and genome composition



The glycoprotein shell of the RVFV virion is composed of heterodimers of the glycoproteins Gn and Gc, which are embedded in a lipid bilayer. The genome of the virus is divided into an S, M and L segment. Each RNA segment is encapsidated by nucleocapsid (N) protein, resulting in the formation of ribonucleoproteins. The complementarity of the terminal ends results in the formation of panhandle structures and circularization of the RNA segments. The RNA-dependent RNA polymerase (RdRp) protein is associated with the viral ribonucleoproteins.

Figure 2
Cartoon representing the transmission cycles of RVFV



In endemic areas, the virus is maintained in a sylvatic cycle involving wild ruminants, possibly other mammalian hosts and mosquitoes. An explosion of the mosquito population can result in spillover to domesticated ruminants, resulting in epizootics and, potentially, an enzootic situation. Human epidemics result from contact with animal fluids released during slaughtering of viremic animals or, less frequently, via mosquito bites.

Vaccines based on the Smithburn virus are produced and applied in several African countries and are known to provide long-lasting, perhaps lifelong, immunity after a single vaccination. A drawback of these vaccines, however, is that they are not safe for gestating ruminants. Although the Smithburn vaccine produced by Onderstepoort Biological Products (OBP) in Onderstepoort, South Africa is considered safe for adult animals outside the gestation period, a Smithburn vaccine produced in Egypt was reported to cause serious side-effects even in non-pregnant ruminants (Botros *et al.*, 2006; Kamal, 2009). Of note, the Smithburn vaccine virus causes viremia in vaccinated animals, which explains the fear of spread of the virus via mosquito vectors, as well as the concerns about possible reassortant events with wild-type viruses. The drawbacks of classical RVF vaccines have stimulated the development of safer alternatives.

In the first section of this report, issues related to the past and present control of RVFV in endemic areas are described. In the second part, next-generation vaccines are described that have gone beyond the proof of concept phase and are either already used in the field, or are being evaluated in registration trials. Brief attention will be paid to vaccines of optimal theoretical safety that are not yet in registration trials. The report ends with conclusions and recommendations to assist chief veterinary officers and other decision-makers in countries at risk for RVF outbreaks to make optimal use of recent developments in RVF control strategies. These recommendations can also help to inform vaccine researchers and manufacturers.

Introduction

Rift Valley fever (RVF) is a zoonotic viral disease that threatens animal and human health, as well as food security and livelihoods. Because the virus is transmitted by a large and diverse number of arthropod species, it has the potential to spread widely and rapidly when environmental conditions are conducive to an outbreak. RVF was first diagnosed in 1931 and has since been reported in most countries in East, West and Southern Africa. In 2000, it was detected in the Arabian Peninsula, having spread outside of Africa for the first time.

In January 2011, a technical meeting was held at the Food and Agriculture Organization of the United Nations (FAO) headquarters in Rome, Italy to discuss RVF vaccine development, progress and constraints. The meeting resulted in a series of recommendations to policy-makers, vaccine manufacturers and the scientific community. In November 2012, the OIE Inter-Regional Conference on RVF was held in Kenya. Over 70 participants from the Middle East and Africa met to develop surveillance and control strategies for RVF. That meeting produced recommendations on disease surveillance strategies, trade issues, vaccine selection and quality control.

Building on this series of RVF meetings, and in recognition of the recent progress made in the development of more effective RVF virus vaccines, FAO organized a meeting at headquarters to promote the development of RVF virus vaccines and diagnostics. The meeting brought together 53 leaders in vaccine and diagnostic research, development and manufacturing, as well as policy-makers and representatives of global animal health agencies. The chief veterinary officers of Egypt, Kenya, Mauritania, Senegal and Sudan discussed national and regional concerns and priorities for vaccines and diagnostics. Participating in three days of open and productive exchange, this unique group of experts discussed the latest research and experience in the use of classical vaccines in endemic areas, and shared information on new vaccines that are currently used in the field or are being evaluated in registration trials.

Past and present control of RVFV in endemic areas

KENYA

This report includes data provided by Dr Murithi Mbabu, Deputy Director of Veterinary Services, Head of Central Veterinary Laboratories, Nairobi, Kenya.

The first confirmed outbreak of RVF occurred in 1930 on a farm located near the shores of Lake Naivasha in Kenya. It was characterized by hyperacute mortality among newborn lambs and abortions (Daubney *et al.*, 1931; Findlay and Anon, 1931; Findlay, 1932). The scientists involved in the investigation of this outbreak quickly recognized that a virus was the causative agent and that mosquitoes were involved in the viral pathogen transmission. Although sheep were most affected, goats and cattle, as well as humans, were found to be susceptible to the virus. Between 1936 and 1950, no further cases of RVF were reported in Kenya. The virus re-emerged in 1951, causing an outbreak that affected an estimated 100 000 sheep (Murithi *et al.*, 2011). Between 1951 and 2007, 11 outbreaks were reported with an average interepidemic period of 3.6 years (Murithi *et al.*, 2011). The outbreak in 1997–1998 was the largest ever recorded in sub-Saharan Africa. This outbreak not only affected livestock, but also resulted in thousands of human clinical cases and hundreds of fatalities (Woods *et al.*, 2002).

Based on accumulated data from previous outbreaks, areas of high and medium risk were defined. In high-risk areas, the strategy is to vaccinate livestock continuously, whereas in medium-risk areas, vaccination is conducted during the alert phase. Currently, due to limited funding, only sheep and goats are vaccinated. Because vaccination not only prevents livestock morbidity and mortality, but also prevents human disease, vaccination programmes are considered a public good and are, therefore, financed and coordinated by the Kenyan Government.

At present, only the Smithburn live-attenuated vaccine is used in Kenya, which is produced by the Kenya Veterinary Vaccines Production Institute (KEVEVAPI) and quality controlled by the African Union Pan African Veterinary Vaccine Centre (AU-PANVAC). In the Kenyan field experience, vaccination with this Smithburn vaccine has caused no untoward effects in non-pregnant animals and provides solid protection. Farmers are aware that vaccination with the Smithburn vaccine can result in abortion, but have decided that this is an acceptable risk. This drawback of the Smithburn vaccine, however, explains the desire to register the Clone 13 vaccine in Kenya. To date, this vaccine appears to be safe for gestating animals. With support from the Global Alliance for Livestock Veterinary Medicines (GALVmed), the Clone 13 vaccine was purchased from OBP and used in a field trial in Kenya. The results of this trial have not been finalized, but preliminary reports indicate that the Clone 13 vaccine was efficacious in all three species evaluated (i.e. sheep, cattle and goats).

The Central Veterinary Laboratories (CVL) diagnose RVFV infections in Kenya, and aim to detect outbreaks and facilitate trade. Diagnostic efforts are most intense

in endemic areas during periods of heavy rainfall. Diagnostic tools include real-time reverse transcription polymerase chain reaction (RT-PCR) tests provided by CDC and enzyme-linked immunosorbent assay (ELISA) tests supplied by CDC or Biological Diagnostic Supplies Limited (BDSL) Ayrshire, Scotland, United Kingdom. Sera of humans, cattle, sheep, goats, camels and wildlife are analysed by inhibition ELISA tests that detect both IgG and IgM antibodies. An ELISA that specifically detects IgM antibodies is used when samples are found positive in the inhibition ELISA, to allow the detection of recently infected animals. Although camel sera are tested using these assays, it would be valuable if appropriate serum panels would become available to validate these ELISA tests.

Despite existing support systems, additional efforts are required to further improve diagnostic capability in Kenya. Training programmes are needed to improve sampling procedures and there needs to be a reliable supply chain of vaccines and diagnostics. Sufficiently trained personnel are also needed to respond adequately to outbreaks.

SOUTH AFRICA

This report includes data provided by Drs Bethuel Nthangeni, Ian Louw, Jacob Modumo and Theresa Smit from OBP, Pretoria, South Africa and Dr Michael Modisane, Department of Agriculture, Forestry and Fisheries, Pretoria, South Africa.

In 1951, the same year that RVFV re-emerged in Kenya, the virus caused a severe and widespread outbreak in South Africa, affecting both sheep and cattle (Joubert *et al.*, 1951). Mortality in adult sheep was estimated at 60 percent and among cattle at 20 percent. Nearly all gestating sheep and cows aborted and abortions were also reported among wild springbok and blesbok (Joubert *et al.*, 1951). During this epidemic, significant numbers of human cases were reported. The first reported cases were three veterinarians and two assistants who became ill after performing a necropsy on a deceased bull. Cases of similar illness among veterinary surgeons, farmers and native labourers were subsequently described (Joubert *et al.*, 1951; Gear *et al.*, 1951). A retrospective serosurvey suggested that approximately 20 000 human RVF cases occurred without fatalities (Schulz, 1951). South Africa experienced another serious epizootic in 1975. In this outbreak, thousands of lambs and hundreds of sheep and cattle died, and the first human fatalities were reported (van Velden, *et al.*, 1977; McIntosh *et al.*, 1980). The virus re-emerged in South Africa in 2008 (Archer *et al.*, 2011; WHO, 2010), where it remained active until 2011 (Metras *et al.*, 2012).

During the outbreak of 2009 in the Northern Cape, farmers preferred to use the inactivated vaccine produced by OBP for safety reasons. Farmers started to use the live-attenuated Smithburn vaccine only after the inactivated vaccine was no longer available. After the registration of Clone 13, this vaccine was used during the outbreak of 2010–2011. During this outbreak, rumours appeared about the poor efficacy of the vaccine, which are now attributed to improper use of the vaccine or to interruption of the cold chain. This notion is supported by independent studies performed in Kenya with properly handled Clone 13 vaccine, where participating farmers were generally satisfied with the performance of the vaccine. Should a new outbreak occur in South Africa, it is expected that farmers will use the Clone 13

vaccine alongside the inactivated vaccine to vaccinate pregnant ewes. Non-pregnant animals are preferably vaccinated with Clone 13, although some farmers still prefer the Smithburn vaccine. Both vaccines are produced at OBP under biosafety level-2 (BSL-2) containment.

The fact that RVF is notifiable, but not a "controlled disease" according to the Animal Diseases Act No. 35 of 1984, complicates its effective control in South Africa. According to this act, livestock owners have the responsibility to vaccinate their livestock at their own expense.

EGYPT

This report includes data provided by Dr Sayed M. Zeidan, Director of Veterinary Serum and Vaccine Research Institute (VSVRI), Agricultural Research Center, Ministry of Agriculture and Land Reclamation, Cairo, Egypt.

The largest RVF outbreak in history occurred in Egypt in 1977–1978. This outbreak is believed to have affected over 200 000 humans, suggesting that the outbreak affected millions of ruminants. The virus is thought to be endemic in this country and new introductions are believed to occur via importation of infected livestock from the Horn of Africa and Sudan, where the virus is also endemic. Since 1978, a vaccine based on formalin-inactivated virus formulated with aluminium hydroxide gel is used to vaccinate all susceptible animals twice per year, totalling an average of 14 million doses. Despite this biannual vaccination with inactivated vaccine, a second outbreak occurred in 1993–1994. In response to this outbreak, Smithburn vaccine was purchased by the Veterinary Research Institute (VRI) from Onderstepoort, South Africa, and imported by the Egyptian General Organization for Veterinary Services (GOVS). This vaccination campaign, as well as those performed during the outbreaks of 1993–1994, 1996–1997 and 2003, with either imported or locally produced Smithburn vaccine, were all considered failures. The reasons for these failed vaccination programmes remain undetermined and are undoubtedly complex in nature. It is important to consider the possibility that the failure of these vaccination programmes could have contributed to the unusually short interepidemic periods observed in Egypt.

At present, the Egyptian Government aims to vaccinate all cattle, sheep and camels intended for breeding purposes, with inactivated vaccine. Vaccine efficacy is evaluated by virus neutralization (VN) tests, where a titre of 1.5 log10 is considered protective. Considering the promising results obtained with the Clone 13 vaccine in Kenya, Namibia and South Africa, it would be valuable if the Clone 13 vaccine became available in Egypt.

In Egypt, the Animal Health Research Institute (AHRI) is responsible for the diagnosis of RVFV infections and GOVS is responsible for logistics and selection of animal species to be sampled. Serum samples obtained from sheep, goats, cattle and camels are regularly tested for RVFV-specific IgG and IgM antibodies. Animals in governorates bordering neighbouring countries are tested for RVFV antibodies every month, and sera from animals to be imported are tested for the presence of IgG and IgM antibodies. When there is a suspicion that animals to be slaughtered are infected with the virus, organ samples are collected and submitted for further diagnostic testing, which includes histopathology and immunohistochemistry. Additional

diagnostic assays for the detection of RVFV that are applied in Egypt include immunofluorescence, agar-gel immunodiffusion and RT-PCR followed by sequencing. Virus isolation is performed using cell lines as well as mice.

A high committee comprised of members from AHRI, GOVS, VSVRI and the Central Laboratory for Evaluation of Veterinary Biologics evaluates the results from diagnostic monitoring. Based on the periodic report of this high committee, GOVS defines the epidemiological status in the country and designs an appropriate vaccination programme.

SUDAN

This report includes data provided by Dr Tamador M.A. Elhassan of the Veterinary Research Institute Virology department, Rift Valley fever unit, Khartoum-Soba, Sudan.

The first evidence of RVFV presence in Sudan was described in 1936 by Findlay and co-workers, who reported seroprevalence of RVFV antibodies in four human sera from Sudan (Findlay *et al.*, 1936). The first recorded epizootic in this country occurred 37 years later, in 1973. Apparent mortality rates in this outbreak were remarkable: 90 percent in lambs, 70 percent in older sheep, 50 percent in goats and 20 percent in calves (Davies, 1990). A subsequent seroprevalence study using cattle sera collected between 1979 and 1981 in Sudan, demonstrated a positive percentage of 14 percent, suggesting that RVFV was enzootic in these areas in this time period.

The next outbreak took place 34 years later, in 2007, soon after the virus caused outbreaks in Kenya, Somalia and the United Republic of Tanzania (Hassan *et al.*, 2011; Aradaib *et al.*, 2013). During this outbreak, an estimated 75 000 humans were infected, with 747 reported cases and 230 fatalities. The number of affected animals during this outbreak was never reported, but the number of human cases suggests that millions of ruminants were infected.

In 2007, RVF vaccination was done for the first time in Sudan. Two vaccines were imported from South Africa: the live-attenuated Smithburn vaccine and the formalin-inactivated, aluminium hydroxide-adjuvanted inactivated vaccine. Of each vaccine type, 500 000 doses were imported. The Smithburn vaccine was used for non-pregnant animals and for animals kept for export, whereas the inactivated vaccine was used for young and pregnant animals that received a booster vaccination after six months. From 2007–2009, Smithburn vaccine imported from South Africa was used, and during 2010, a different Smithburn vaccine, RiftVax, was used. Since 2011, animals are no longer vaccinated, apart from mandatory vaccination of male sheep designated for exportation to Saudi Arabia. These animals are placed in quarantine for two weeks post-vaccination to ensure that protective immunity is established before being transported.

The regional VRI RVF unit is responsible for the diagnosis of RVF and the seromonitoring after vaccination. Diagnostic assays presently used in Sudan are the IgG and IgM ELISAs from ID-VET (Montpellier, France) and conventional PCR. In outbreak situations, the Department of Animal Health and Epizootic Disease Control, and the Ministry of Animal Resources, Fisheries and Range Land work together in epidemiological surveys.

SENEGAL AND MAURITANIA

This report includes data provided by Dr Mbargou Lo, Director of Veterinary Services of Senegal and Dr Mohamed Guéya, Deputy Chief of Veterinary Services of Mauritania.

Senegal and Mauritania are grouped here, since most outbreaks in these areas have occurred proximal to the Senegal River basin, which forms a natural border between these countries. The first outbreak in these areas occurred after the completion of the Diama dam in 1986. The establishment of this dam resulted in the permanent presence of fresh stagnant water, which created novel mosquito breeding sites. One year later, a serious RVF outbreak occurred in southern Mauritania with an estimated 224 human fatalities (Jouan *et al.*, 1988). Re-emergence of the virus in this area caused additional fatalities among humans in 1998 (Nabeth *et al.*, 2001), 2010 (El Mamy *et al.*, 2011) and 2012 (WHO, 2012). In 2013, small outbreaks in Dorcas gazelle, goats and cattle were reported to OIE, demonstrating continued circulation of the virus in Senegal. In 2014, a vaccination trial using imported inactivated vaccine is planned in high-risk areas and the ultimate objective is to perform routine vaccination of sheep, goats and cattle along the Senegal River basin. Extensive safety trials, both under controlled conditions and in the field, were performed with the Clone 13 vaccine in Senegal. These trials did not reveal any adverse events attributable to the vaccine. Clone 13 vaccine could soon be registered for use in Senegal and bordering countries.

The Laboratoire National d'Elevage et de Recherches Vétérinaires (LNERV) assists veterinary services of Senegal and neighbouring countries in RVFV diagnostics. RVF diagnostic assays (RT-PCR, ELISA, virus isolation) are used for active surveillance in endemic areas along the Senegal River and passive surveillance in other herds when an outbreak is suspected. Species that are under surveillance are sheep, goats, cattle and camels.

Role of international organizations in RVF control

THE ROLE OF THE WORLD ORGANISATION FOR ANIMAL HEALTH (OIE)

Drs Joseph Domenech and Susanne Munstermann, from OIE, Paris, France, presented a review of the RFV situation worldwide and the evolution of the articles of the relevant *Terrestrial Code* chapter and of the relevant *Manual* chapter, both prepared in 2013, which will be discussed and considered for adoption during the OIE General Assembly in May 2014. (Note: The newly revised RVF chapters of the *Code* and *Manual* referred to here were, indeed, adopted by the OIE General Assembly in May 2014). A summary of key recent RVF meetings is included as Annex 1.

The OIE is an intergovernmental organization that aims to "improve animal health, veterinary public health, animal welfare, and consolidate the animal's role worldwide". RVF is included on the list of multiple species diseases, infections and infestations that OIE member countries are obliged to report. The OIE manages the World Animal Health Information System (WAHIS) and through several information tools it provides public access to the information held in WAHIS.

OIE standards, guidelines and recommendations related to RVF are described in two publications: chapter 8.11 of the *Terrestrial Animal Health Code*, also referred as the *Terrestrial Code* (http://www.oie.int/en/international-standard-setting/terrestrial-code/access-online/), and chapter 2.1.14 of the *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals,* also referred to as the *Terrestrial Manual* (http://www.oie.int/en/international-standard-setting/terrestrial-manual/access-online/). In response to excessively long trade bans after East African RVF outbreaks, which led to the establishment of illegal, parallel trade routes, the *Terrestrial Code* chapter on RVF was reviewed in 2013. The goal was to be less prescriptive and to provide trade partners with a range of tools.

Major changes in the new Code chapter, adopted in May 2014 are:

- The exact period after which trade can resume after an outbreak of RVF is no longer prescribed (formerly six months).
- A distinction is made between *interepizootic* and *epizootic* periods, rather than *free* or *non-free* of disease, in acknowledgement that once a country is infected it is almost impossible to eliminate RVFV. The definition of a free country/zone is, therefore, now based on historical freedom or continuous surveillance with no evidence of virus circulation for at least ten years.
- Dromedary camels are included in the definition of ruminants.
- The infective period is 14 days (formerly 30 days).
- Provided animals have undergone ante- and post-mortem inspection, meat is considered safe for trade.
- The chapter makes provisions for safe importation from countries that are in the interepizootic period as well as for those that encounter an epizootic in the country. For both situations, surveillance is of utmost importance and is, therefore, further specified in a new article.
- An article for the safe importation of ruminant semen has been added.

Major changes to the *Manual* chapter as adopted in May 2014 are:

- The introductory article describing the disease, its distribution, epidemiology, susceptible animals, differential diagnosis, clinical signs and pathology as well as virus characteristics, was further developed and the role of the camel was highlighted.
- More specific test protocols have been included.
- A table of test methods and their purpose of use has been developed.
- Specific protocols for conventional and RT-PCR as well as ELISA (Double AB sandwich capture assay) have been added.
- Protocols have been added to the ELISA section.
- A table of current RVF vaccine strains has been added, which reflects the outcomes of the 2011 Rome workshop, including characteristics of vaccine strains suitable for vaccine production.
- Methods of vaccine manufacture and requirements for licensing have been detailed and should serve as a reference point for vaccine producers.

OIE also makes information related to RVF outbreaks available. In the second semester of 2012 through the first semester of 2013, nine countries reported cases of RVF or suspected RVF to the OIE: Democratic Republic of the Congo, Malawi, Mauritania, Mozambique, Namibia, Niger, Rwanda, Saudi Arabia and Senegal. In this period, routine vaccination was applied in Egypt, Kenya, Mozambique, Namibia and the United Republic of Tanzania. In the same period, vaccination was prohibited in Angola, Ethiopia, Sudan and Uganda.

THE ROLE OF THE AFRICAN UNION PAN AFRICAN VETERINARY VACCINE CENTRE (AU-PANVAC)

Communicated by Dr Karim Tounkara, Director, Dr Nick Nwankpa, Senior Veterinary Vaccine Officer and Dr Sanne-Charles Bodjo, Senior Animal Disease Diagnosis Reagent Officer.

AU-PANVAC (Debre Zeit, Ethiopia) was established in 1993 to support the Pan African Rinderpest Campaign (PARC) and the Pan African Programme for the Control of Epizootics (PACE). PANVAC has been mandated by the AU Member States to provide international independent quality control of veterinary vaccines that are either produced in Africa or are imported into the continent. The quality control of veterinary vaccines by AU-PANVAC prior to use in the field is mandatory for all veterinary vaccines that are to be used in Africa, and is provided to AU Member States for free. A minimal fee is applied for countries that are not members of the AU.

The role of PANVAC was considered pivotal in the eradication of rinderpest in Africa and is extended to all veterinary vaccines including RVF vaccines. AU-PANVAC is directly linked to the Department of Rural Economy and Agriculture of the African Union Commission and is currently involved in certifying the quality of vaccines for the control of peste des petits ruminants (PPR), contagious bovine pleuropneumonia (CBPP), contagious caprine pleuropneumonia (CCPP), sheep and goat pox, lumpy skin disease (LSD), Newcastle disease (ND), infectious bursal disease (IBD), blackleg and hemorrhagic septicaemia.

The main RVF vaccine manufacturers in Africa are OBP in South Africa, KEVEVAPI in Kenya and VSVRI in Egypt. The vaccines produced by these manufacturers are quality

controlled by PANVAC in accordance with the procedures described in the OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals.*

Quality control of live RVFV vaccine batches includes:
- freedom from bacterial, fungal and viral contamination;
- safety for target animals;
- identity, established by reverse-transcription PCR;
- potency, established after incubation of the RVF vaccine at 37° for one week;
- residual moisture content using a gravimetric method.

Quality control of inactivated RVFV vaccine batches includes:
- freedom from bacterial, fungal and viral contamination;
- safety for target animals;
- identity test using RT-PCR;
- potency assessment (immune response elicited by vaccination of sheep);
- completion of inactivation using inoculation of vaccine with susceptible cell culture;
- determination of residual inactivant content using a colorimetric method.

AU-PANVAC owns a repository of veterinary vaccine seeds including those for the production of RVF vaccines and has production cell lines available that can be provided upon request. AU-PANVAC is committed to the continued provision of quality service thereby ensuring the independent quality control of RVF vaccines in Africa.

THE ROLE OF THE AFRICAN UNION INTERAFRICAN BUREAU FOR ANIMAL RESOURCES (AU-IBAR)

Communicated by Prof. Dr Ahmed El Sawalhy, Director and Head of Mission AU-IBAR, Nairobi, Kenya.

The African Union Interafrican Bureau for Animal Resources (AU-IBAR) was established in 1951 to help control rinderpest in Africa. Today, AU-IBAR provides leadership in the development of animal resources for Africa. AU-IBAR acknowledges that RVF is one of the most significant zoonotic diseases of Africa. Between 2003 and 2013, 14 countries have reported RVF outbreaks to AU-IBAR: Angola, Botswana, Comoros, Democratic Republic of the Congo, Gambia, Kenya, Madagascar, Mauritania, Namibia, Senegal, South Africa, Swaziland, United Republic of Tanzania, Zimbabwe. Circulation of RVFV in 18 additional countries is suspected due to isolation of the virus or serological evidence: Burkina-Faso, Cameroon, Central African Republic, Chad, Congo, Egypt, Ethiopia, Gabon, Guinea, Niger, Nigeria, Malawi, Mali, Mozambique, Somalia, Sudan, Uganda and Zambia.

The challenges that are acknowledged by AU-IBAR include concerns about the differences in legal frameworks governing the control of RVF, the lack of control strategies in some countries where RVF is endemic, the insufficient capacities for inspection of veterinary biological products at entry points, the different requirements for the importation of existing vaccines and diagnostics, the differences in requirements for registration of new vaccines and diagnostics, and the insufficient number of facilities where laboratory and field trials can be performed to evaluate novel vaccines.

AU-IBAR calls for national and regional public education as well as for sensitization of decision-makers regarding the novel opportunities for RVF prevention and control. To prevent situations where countries find themselves without vaccines after a long interepidemic period, AU-IBAR calls for a pooling of resources in the form of regional vaccine banks. Finally, AU-IBAR supports the role of AU-PANVAC to facilitate capacity building of African laboratories in diagnostic testing, vaccine production and communication with regulatory authorities.

THE ROLE OF THE GLOBAL ALLIANCE FOR LIVESTOCK VETERINARY MEDICINES (GALVMED)

Communicated by Dr Baptiste Dungu, former Senior Director, Research and Development, GALVmed; Dr Mehdi Elharrak, Senior Director, Research and Development MCI-Santé Animale, Morocco; Dr Kariuki Njenga, Virologist and Head Integrated Human-Animal Health Programme, Global Disease Detection Centre, Kenya and Dr Danny Goovaerts, Interim Director Research and Development GALVmed.

GALVmed is a not-for-profit partnership developing veterinary vaccines, veterinary drugs and associated market processes to make these products widely available and affordable to the 750 million people in the developing world dependent on livestock for their livelihoods. GALVmed contributes to improving human health and livelihoods in developing countries by supporting the development of livestock vaccines and diagnostics. GALVmed aims to contribute to improved RVF control in endemic areas through increased availability of field diagnostic tests and emergency vaccines.

GALVmed has supported and continues to support safety and efficacy studies in East, West and South Africa to facilitate registration of the Clone 13 vaccine in these areas, with the ultimate objective to establish regional vaccine banks.

Another initiative that is supported by GALVmed is the development of a multivalent vaccine for the control of lumpy skin disease virus (LSDV), sheep pox virus, goat pox virus (GTPV) and RVFV. The first of these approaches is based on a genetically modified LSDV that contains the genes encoding the RVFV glycoproteins Gn and Gc (Wallace *et al*., 2007; Wallace and Viljoen, 2005; Wallace *et al.*, 2006). Unfortunately, due to disappointing results related to efficacy, further development of this vaccine was not pursued by GALVmed. As an alternative, a combination vaccine is currently being developed that is based on freeze-drying a mixture of Clone 13 and LSD vaccine virus. This vaccine is under development at OBP.

Finally, GALVmed is collaborating with the company BBI (Cardiff, United Kingdom) to develop a RVF penside diagnostic test. This penside test can be used for the screening of sentinel animals and to facilitate trade.

DEVELOPMENT OF RVF COUNTERMEASURES IN THE UNITED STATES OF AMERICA

Communicated by Dr Michele Colby, Branch Chief of the Homeland Security Advanced Research Projects Agency, Science and Technology Directorate and Dr Frederic Descamps, Associate Director Regulatory Affairs Biologicals of Zoetis.

Dr Colby presented the perspectives of the United States Department of Homeland Security (DHS) on specific issues discussed during the workshop and Dr Descamps, Associate Director Regulatory Affairs Biologicals of Zoetis, provided views from the International Federation for Animal Health (IFAH).

The DHS supports the development of RVF countermeasures for the control of future potential epizootics in the United States of America, and to restore the trade status after such events. Hence, the vaccines to be developed are meant for emergency vaccination, rather than for routine or annual vaccination. It was noted that the greatest economic impact of a potential future epizootic in the United States of America would result from damage to the cattle industry.

The major requirements for vaccines to be used in the United States of America are in accord with the recommendations for vaccine safety and efficacy as described in the previous FAO report (Kortekaas, Zingeser, *et al.*, 2011). Apart from specific requirements related to onset and duration of immunity that are beyond the scope of the present report, additional requirements include the following: The vaccine should be produced at BSL-2 or lower biosafety level and should meet United States Department of Agriculture (USDA) Center for Veterinary Biologics (CVB) requirements for cattle, sheep and, preferably, goats. Vaccines should be licensable in the United States of America and be compatible with serological assays than enable differentiating infected from vaccinated animals (DIVA) testing. The vaccines should preferably be manufactured in the United States of America and be stockpile-compatible with a minimum shelf life of two years. Ideally, the vaccines should have demonstrated efficacy in an appropriate non-human primate model to substantiate safety for humans and facilitate potential future licensing for human use under the Food and Drug Administration (FDA) Animal Rule (Kortekaas, 2014).

Diagnostic assays to be applied in the United States of America should be suitable for use in laboratories of BSL-2 or lower biosafety level. Diagnostic assays should meet USDA CVB 9CFR validation requirements. The assay reagents should be available in the United States of America for purchase and use by the National Animal Health Laboratory Network (NAHLN). Preferably, the assays are produced and licensed for use in the United States of America. Furthermore, the serological assays should be capable of simultaneous detection of antibodies against different RVFV proteins (Gn, Gc, N, NSs, NSm), or simultaneous detection of viral RNA derived from all three RVFV genome segments.

DHS has supported the evaluation of several vaccines that are discussed below, and several IFAH companies are working on the development and registration of selected vaccines. The MP-12 vaccine was evaluated through USDA Agricultural Research Service and was removed from the select agent list. The USDA and the Canadian Centre for Veterinary Biologics granted a conditional license for this vaccine. Considering that the MP-12 vaccine is not suitable as a DIVA vaccine, DHS also supported the development of the MP-12ΔNSm vaccine through FAZD, and the rZH501ΔNSs-ΔNSm vaccine (DDvax, see below), through the United States Army Research Institute for Infectious Diseases. These vaccine viruses are now also excluded from the select agent list. Finally, DHS is supporting the development of a DIVA-compatible subunit vaccine.

Recent developments in RVF vaccinology

CLONE 13

In 1995, a natural isolate of RVFV, named Clone 13, was described that contains a large (69 percent) deletion in the NSs gene and was found to be highly attenuated in mice (Muller *et al.*, 1995; Vialat *et al.*, 2000). More recent studies have addressed the safety and efficacy of the Clone 13 vaccine in sheep (Dungu *et al.*, 2010) and cattle (von Teichman, 2011). In these trials, the vaccine was found to be safe and highly efficacious. The Clone 13 virus does not cause detectable viremia in ruminants, which minimizes the risk of vaccine virus transmission to the foetus or to mosquito vectors. Importantly, Clone 13 vaccination was shown to be safe for gestating ewes in both early and late pregnancy, and a single vaccination of gestating ewes was shown to prevent RVFV-induced abortions (Dungu *et al.*, 2010).

The commercialization of the Clone 13 vaccine in South Africa by OBP in 2010 has been a major step towards RVF control; more than 19 million doses have already been used in the field. Since that time, GALVmed has played an important role in stimulating the widespread use of the vaccine in several additional African countries. In collaboration with the CDC, the veterinary services and OBP, large field trials with Clone 13 were performed in Kenya to facilitate registration. The results of these studies await publication.

The Clone 13 vaccine is also registered in Botswana and Namibia, which both recognize South African registration. It is used in several Southern African Development Community (SADC) countries, such as Mozambique and Zambia, without registration. A safety trial with Clone 13 was performed in Senegal, which included pregnant animals, goats and ewes, where no adverse reactions to vaccination were noted and no evidence of transmission to contact animals was found. In 2011, a field trial was performed, where 110 sheep and 24 goats were vaccinated. During a period of one year, no adverse reactions attributable to vaccination were noted. The results of this study will be used to facilitate registration of Clone 13 in Senegal and other countries (communicated by Dr Dungu [GALVmed] and Dr Elharrak [MCI-Santé Animale, Morocco]). One of the objectives of GALVmed is to develop a regional control strategy, building from Mauritania and Senegal, and to establish a Clone 13 vaccine bank with the possible involvement of Morocco.

Although results of controlled animal trials suggest a high level of efficacy and safety of the Clone 13 vaccine, its efficacy, as well as that of the Smithburn vaccine, was questioned by some farmers during the South African RVF outbreak of 2010–2011. These farmers perceived that the vaccines were ineffective, and suggested that their animals were infected with a "new strain" of RVFV. Considering that RVFV comprises only a single serotype, other explanations have to be sought to explain these observations. Possible explanations include improper use of the vaccine and failure to maintain the cold-chain. A recent study by Daouam and co-workers demonstrated that the Clone 13 virus is stable in lyophilized form when stored at 4°C

for more than 12 months, but that the virus is unstable at temperatures above 22ºC (Daouam *et al.*, 2014). Further investigation of Clone 13 vaccination failures should be rigorously investigated.

MP-12 AND DERIVATIVES

The first RVF vaccine for which a provisional licence was recently granted by the USDA and the Canadian Centre for Veterinary Biologics, is the MP-12 vaccine. This mutagen-attenuated virus was created in the 1980s and was shown to induce a protective immune response in sheep and cattle after a single vaccination (Morrill *et al.*, 1987; Morrill *et al.*, 1991, Morrill *et al.*, 1997). Although the virus causes a low-level viremia, it was shown to be safe for gestating ewes when administered during the second or third trimester of gestation (Morrill *et al.*, 1987; Morrill *et al.*, 1991). In a recent study, vaccination of ewes during the first trimester of gestation with either MP-12 or authentic recombinant arMP-12 did not cause untoward effects in the ewes, although one of four ewes of each group was found to carry a dead foetus at the end of the experiment (Morrill, Laughlin *et al.*, 2013). Safety studies in rhesus monkeys have demonstrated that inoculation with MP-12 causes a low-level viremia and is not completely innocuous (Morrill, 2003). Nevertheless, the CDC and the National Institutes of Health have deemed the virus sufficiently safe to be handled in BSL-2 containment facilities. The license for marketing of the MP-12 vaccine was recently transferred to Zoetis (Florham Park, New Jersey, United States of America).

To develop a MP-12-based vaccine that allows for DIVA testing, arMP-12 viruses were created that lack either the NSs or NSm-coding regions. A study on the immunogenicity of the resulting arMP-12ΔNSs and arMP-12ΔNSm vaccine viruses demonstrated that the immunogenicity of the former was relatively poor, whereas the arMP-12ΔNSm induced neutralizing antibody responses that were at least as high as those elicited by vaccination with the parental virus (Morrill *et al.*, 2013). In a subsequent efficacy study, 3 to 4-month-old Rideau/Arcott cross sheep were vaccinated with 10^6 plaque-forming units (pfu) of arMP-12ΔNSm via subcutaneous (SC) route. Challenge of mock-vaccinated sheep with 10^7 pfu of isolate ZH501, administered via SC route, resulted in high fever and viremia, from which vaccinated sheep were protected (Weingartl *et al.*, 2014).

The immunogenicity of the arMP-12ΔNSm vaccine was subsequently determined in pregnant ewes at 30–50 days of gestation (communicated by Dr Watts, University of Texas, El Paso, Texas). Within a range of 10^2-10^5 pfu, high neutralizing antibody titres were induced by SC inoculation within 14 days. Sheep that received doses of 10^2 or 10^3 pfu did not reveal any untoward effects and all foetuses remained healthy. At higher vaccine doses, vaccine virus was isolated from the blood of one of ten and of one of six ewes vaccinated with 10^4 pfu and 10^5 pfu of arMP-12ΔNSm, respectively. One ewe that was vaccinated with a dose of 10^4 pfu displayed haematuria and carried a dead, autolyzed foetus. However, it remains unclear whether the foetal mortalities in the study of Morrill and co-workers with arMP-12, as well as those in the studies with arMP-12ΔNSm, were caused by the vaccine viruses.

The immunogenicity of the arMP-12ΔNSm vaccine after SC or intramuscular (IM) administration of 4 to 6-month-old heifer and steer calves was also determined. Vaccination with doses of 10^3, 10^4 and 10^5 pfu did not result in detectable

viremia or any adverse effects and induced neutralizing antibodies within 10 days after vaccination, which continued to incline until day 35. The requirements to register the arMP-12ΔNSm vaccine are currently being evaluated.

R566

With the aim to develop a live-attenuated vaccine of optimal safety, scientists of Institut Pasteur made use of laboratory reassortment to create a virus that carries the L and M segments of MP-12 and the S segment of Clone 13. The resulting virus, named R566, contains attenuating mutations on all three genome segments and is, therefore, theoretically safer than the parental viruses (Bouloy and Flick, 2009). The efficacy of R566 was recently studied within the framework of the "Castellum project", a public-private partnership supported by the Dutch Ministry of Economic Affairs with involvement of Merck Sharp & Dohme Animal Health (MSD-AH), (communicated by Dr Kortekaas, CVI-WUR, Lelystad, the Netherlands). In this trial, groups of eight lambs were vaccinated via the SC route with a dose of 10^6 pfu of R566 or with a dose of 10^6 50 percent tissue culture infective dose ($TCID_{50}$) of NSR-Gn replicon particles, delivered via the IM route (see below for more details about this vaccine). As a control of optimal efficacy, the Clone 13 vaccine was used at a dose of 10^5 pfu (SC route). None of the lambs displayed any adverse effects until the moment of challenge infection. Three weeks after vaccination, all lambs were challenged with 10^5 $TCID_{50}$ of virulent RVFV (strain 35/74), delivered via the intravenous (IV) route. All unvaccinated lambs developed high viremia and fever and three lambs did not survive the infection. Vaccination with the NSR-Gn and Clone 13 vaccines provided complete protection from viremia, fever and clinical signs, whereas three R566-vaccinated lambs displayed low levels of viral RNA for one day shortly after challenge infection, two of which also displayed pyrexia around these time points. Moreover, the same two lambs were found to contain low levels of viral RNA in their spleens upon necropsy. The results of this study suggest that the NSR-Gn and Clone 13 vaccines are more efficacious than R566.

DDVAX

A highly promising live-attenuated vaccine virus that combines a deletion of the NSs and NSm proteins was created by Dr Bird and co-workers of the CDC (Bird *et al.*, 2008). This vaccine, rZH501ΔNSs-ΔNSm, which is now named "DDvax", was shown to be safe and highly effective in a rat model. Furthermore, vaccinated animals that survived an otherwise lethal challenge dose could be serologically differentiated from naïve, experimentally-infected animals by detection of NSs antibodies (Bird *et al.*, 2008). In a collaborative study of CDC and Deltamune (Pty) Ltd (Pretoria, South Africa) that followed, the vaccine was shown to be completely safe for gestating ewes (communicated by Dr Bird). A total of 20 ewes were vaccinated with a dose of 10^4 pfu DDvax at 42 days of gestation and all delivered healthy lambs. Vaccinated ewes (n=9) that were challenged at 122 days post-vaccination with 10^6 pfu (IV route) of the highly virulent recombinant ZH501 strain were protected from viremia and clinical signs, and delivered healthy lambs, whereas all six unvaccinated control ewes aborted (Bird *et al.*, 2011). Based on the results obtained from the sheep trials, the South African Department of Agriculture, Forestry and Fisheries (DAFF) granted Deltamune permission to vaccinate animals with the DDvax vaccine on pasture.

During the workshop, several ongoing studies were briefly reported, involving animals held in pasture at Deltamune farms until challenge infection. The first study aims to demonstrate efficacy and safety of the DDvax vaccine in calves. Five animals per group were vaccinated with doses of 10^3, 10^4 10^5 or 10^6 pfu. No adverse effects associated with vaccination were observed. Serology results are awaited. In a second study, a 10-fold and 100-fold increased dose of DDvax were tested for safety and efficacy in gestating ewes. Ewes and foetuses and/or lambs were monitored for adverse events. The results of this trial have yet to be reported. Finally, it is important to note that the DDvax vaccine was shown to be safe in marmosets (n=6), which prompted the removal of the DDvax virus from the select agent list and its downscaling to BSL-2.

It is relevant to mention that the study described above demonstrated proof of the concept of a 3-way DIVA ELISA, based on detection of antibodies against the N protein, NSs and NSm proteins (Bird *et al.*, 2011) (communicated by Dr Nichol, CDC). The performance of the NSs and NSm ELISAs were subsequently evaluated by analyses of sera obtained from naturally infected livestock. These experiments demonstrated that the majority of naturally infected animals develop antibodies against both nonstructural proteins, but that the antibody levels have waned when the analysis is performed 420 days after infection. With the aim to improve NSs- and NSm-based DIVA diagnostics, the Luminex technology is currently being evaluated.

To summarize research reported, DDvax vaccine was evaluated in a total of 42 adult sheep (including 29 pregnant ewes), 20 cattle and 6 marmosets without any adverse effects noted. The vaccine is being further evaluated in a partnership of CDC, Deltamune and Merial.

VECTOR-BASED RVF VACCINES

Apart from the evaluation of live-attenuated RVFV viruses as vaccines, the use of vector vaccines was also discussed. A Modified Vaccinia Ankara (MVA) virus that expresses the RVFV structural glycoproteins Gn and Gc was previously created and evaluated in mice, with promising results (Lopez-Gil *et al.*, 2013). These results prompted further studies in target animals, which were reported by Dr Brun (CISA-INIA, Madrid, Spain). Groups of six sheep were vaccinated via the SC route with 10^8 pfu of MVA-GnGc or, as controls, inoculated with the MVA parental virus or saline. Sheep were challenged 14 days post-vaccination with a high dose of RVFV, delivered via the SC route. The results of this experiment showed that a single or double vaccination with MVA-GnGc does not provide full protection against viremia and clinical signs. Full protection from challenge infection was also not achieved when the MVA-GnGc vaccine was administered twice, with a two-week interval, followed by a challenge infection three months later.

A more recent vector approach that was also described by Dr Brun, is based on a non-replicating chimpanzee adenovirus ChAdOx1. The work recently published by Dr Warimwe and co-workers (The Jenner Institute, University of Oxford, Oxford, United Kingdom) demonstrated high efficacy of this vaccine in mice (Warimwe *et al.*, 2013). A direct comparison of the ChAdOx1-GnGc vaccine with the MVA-GnGc vaccine demonstrated that the former induces higher neutralizing antibody levels in mice, suggesting that this vaccine may be more efficacious than MVA-GnGc. The immunogenicity of the ChAdOx1-GnGc vaccine is currently being evaluated in RVFV target species.

A vector vaccine that was already extensively evaluated in livestock is the Newcastle disease virus (NDV) that expresses the RVFV Gn and Gc proteins (Kortekaas, de Boer *et al.*, 2010; Kortekaas, Dekker *et al.*, 2010; Kortekaas *et al.*, 2012.). The resulting NDV-GnGc vaccine was developed at the CVI and is now being evaluated for efficacy and safety by Deltamune. Environmental safety studies have recently demonstrated that the NDV-GnGc virus is completely safe for sheep as well as for poultry, which is the most susceptible natural target species of NDV. Moreover, the vaccine virus was found not to spread from vaccinated sheep to co-housed poultry. After these extensive safety trials, DAFF recently granted permission to perform vaccination experiments in the field at Deltamune facilities. These developments are expected to facilitate the licensing of this vaccine.

REPLICON PARTICLES

Replicon particles are virus particles that are phenotypically indistinguishable from the authentic virus, are capable of infecting cells in which they can replicate their genome segments, but are incapable of autonomous spreading. By virtue of these features, replicon particles optimally combine the efficacy of live-attenuated vaccines with the safety of inactivated vaccines.

RVFV replicon particles are incapable of autonomous spreading because they lack the M genome segment that encodes the structural glycoproteins. Combining L and S viral RNA segments, which are either provided by a stable cell line or by "transcription" plasmids, with the glycoproteins Gn and Gc, provided by an "expression" plasmid, produces the particles. Two similar methods to produce RVFV replicon particles were developed by Kortekaas *et al.*, 2011 and Dodd *et al.*, 2012.

The initial studies by Kortekaas *et al.* demonstrated that a single vaccination via the IM route is fully protective in mice (Kortekaas *et al.*, 2011). More elaborate studies in mice were performed by Dodd and co-workers, who demonstrated that virus replicon particles (VRPs) are innocuous in two-day old suckling mice and that a single dose of as little as 10^4 pfu protects mice from a challenge dose of 100 000 times the LD50 (50 percent lethal dose). Finally, the mice were protected 24 hours after vaccination, further underscoring the remarkable efficacy of this vaccination strategy.

The method developed by Kortekaas and co-workers resulted in particles that were named non-spreading RVFV (NSR). The first generation of these particles was shown to protect lambs from viremia and clinical signs, although low levels of challenge virus RNA could not be prevented by a single vaccination with a dose of 10^7 $TCID_{50}$ (Kortekaas *et al.*, 2012). To this end, the vaccine was further improved by creating NSR particles that express the Gn gene, which is normally encoded by the M genome segment, from the S genome segment. The resulting NSR-Gn particles were shown to induce superior neutralizing antibody responses and cellular immune responses in mice, when compared with the NSR progenitor. A vaccination challenge in lambs subsequently demonstrated that a single vaccination with only $10^{6.3}$ $TCID_{50}$ of NSR-Gn provides sterile immunity (Oreshkova *et al.*, 2013).

As briefly noted above, the efficacy of the NSR-Gn vaccine was recently compared with the R566 vaccine virus in a trial where Clone 13 was used as a positive control (communicated by Dr Kortekaas). This experiment, again, demonstrated that a single vaccination of lambs with NSR-Gn provides solid protection against fever, viremia and clinical signs.

The remarkable efficacy and undisputed safety of replicon particles renders them one of the most exciting vaccination strategies, particularly for currently unaffected countries where vaccines based on live-attenuated RVFV may not be readily accepted.

DNA AND SUBUNIT VACCINES

The promising results obtained with DNA vaccines in mouse trials, and the demonstrated ability of a DNA vaccine to accelerate immune responses elicited by an attenuated vaccine in sheep (Lorenzo *et al.*, 2008), prompted the further evaluation of this approach. A DNA vaccine based on the Gn and Gc glycoproteins was evaluated in sheep, either alone or combined in prime-boost vaccinations with MVA-GnGc (communicated by Dr Brun, CISA-INIA). Sheep were vaccinated with two-week intervals, either three times with the DNA vaccine or two times with the DNA vaccine, followed by a vaccination with MVA-GnGc. In the same trial, sheep were vaccinated twice with the MVA-GnGc vaccine (see previous section on vector-based RVF vaccines), which proved to be more efficacious than the DNA vaccine regiments. These results suggest that DNA vaccines for RVF control require further optimization.

Several groups (de Boer *et al.*, 2010; Mandell, Koukuntla, Mogler, Carzoli, Freiberg *et al.*, 2010; Mandell, Koukuntla, Mogler, Carzoli, Holbrook *et al.*, 2010; Koukuntla *et al.*, 2012) developed subunit vaccines based on either the Gn ectodomain or virus-like particles (VLPs), and a single vaccination with an adjuvanted Gn-based subunit vaccine was demonstrated to protect lambs from viremia, pyrexia and mortality (Kortekaas *et al.*, 2012). More recently, Kansas State University has developed a baculovirus-based subunit vaccine comprising both Gn and Gc, and has evaluated the immunogenicity of this vaccine in sheep. Six vaccinated sheep had developed neutralizing antibodies at 14 days post-vaccination and received a second vaccination 7 days later, which strongly boosted the neutralizing antibody response. The results of further evaluations of this vaccine are awaited.

Recent developments in RVFV diagnostics

COMMERCIALLY AVAILABLE ELISAS

In addition to new vaccines, new diagnostic tools have become available in the past decade. A variety of RVF diagnostic kits are produced under a joint venture agreement by the company BDSL and the National Institute for Communicable Diseases (NICD, Johannesburg, South Africa). Types include a kit with an inhibition (competitive) ELISA for detection of antibodies in all species, kits that specifically detect IgG or IgM antibodies and a kit that can be used for antigen detection. The performances of most of these ELISAs are reported in the literature (Paweska, Burt *et al.*, 2003; Paweska, Smith *et al.*, 2003; Paweska, Burt *et al.*, 2005, Paweska, Mortimer *et al.*, 2005; Paweska *et al.*, 2007; Paweska *et al.*, 2008; Jansen van Vuren and Paweska, 2009, 2010; Fafetine *et al.*, 2012).

More recently, two RVFV ELISAs were commercialized by ID-VET (Montpellier, France). The first is a competitive ELISA that can be used for the detection of antibodies in ruminants. The second is an ELISA that can be used to specifically detect IgM antibodies.

NOVEL DEVELOPMENTS IN RVFV DIAGNOSTICS

Despite the commercial availability of RVFV ELISAs in Europe and South Africa, DHS and USDA are supporting the development of novel ELISAs and other diagnostic tools that meet USDA validation requirements for licensing in the United States of America. Novel competition ELISAs capable of detecting antibodies against the N, Gn and NSs proteins were developed at the University of Wyoming (Miller *et al*., in preparation, communicated by Dr Wilson, USDA). FAZD (Texas, United States of America) has recently developed a multi-species competitive ELISA that is being validated and the centre also has plans to develop an IgM ELISA (communicated by Dr Clavijo).

A quadruplex real-time PCR was recently developed that can be used for the simultaneous detection of all three genome segments, and can distinguish between wild-type and NSs-deleted viruses (Wilson *et al.*, 2013). Field-deployable and high-throughput formats are currently being evaluated (Dr Wilson, USDA Arthropod-Borne Animal Diseases Research Unit [ABADRU]).

Finally, a novel VN test was developed at the CVI. This VN test makes use of a novel attenuated RVFV that expresses the enhanced green-fluorescent protein. Experiments with sheep sera obtained from controlled animal trials demonstrated that this novel VN test is at least 10-fold more sensitive than the conventional VN test. Analysis of 92 negative field sera from the Netherlands revealed no false-positive results. Analysis of 88 African field sera, including sheep, goat, cattle and buffalo sera were evaluated with the classical and novel VN tests in collaboration with the laboratory of Prof Paweska of the NICD. These experiments confirmed the higher sensitivity of the novel VN test. Whereas the classical VN test needs to be performed under BSL-3

conditions, the novel VN test can be safely performed outside biosafety containment facilities. Finally, whereas the classical VN test takes five to seven days to read out results, the novel VN test produced results after only 24–48 hours (Kortekaas *et al.*, manuscript in preparation).

Conclusions

The Ad hoc Technical Workshop on RVF vaccines and diagnostics was a forum for the presentation and discussion of the current state of key tools for achieving RVF control – vaccines and diagnostic tests. In discussing currently available vaccines, the participating experts noted that despite the drawbacks of classical vaccines, both inactivated vaccines as well as those based on the Smithburn virus have been valuable for the control of RVF.

Clone 13 vaccine, already available in several African countries, has been demonstrated to have a high level of efficacy and safety under field conditions, making it an excellent choice for RVF control in the interim before next-generation vaccines and/or combination vaccines become available on the market. The experts attending the workshop agreed that Clone 13 is presently the preferred live-attenuated vaccine for use in RVF-endemic areas. However, new, novel and combination vaccines currently being developed and tested show tremendous potential for the control of RVF. FAO and the partner agencies in this meeting should continue to inform and advise CVOs and decision-makers in animal health on new vaccination options as they become available. Table 1 and Figure 3 summarize information on several of the vaccines currently being evaluated by pharmaceutical companies.

Table 1: RVFV livestock vaccines[a]

Type	Commercially available	Industry involved:	Safe in pregnant animals	Single dose	Reference
Inactivated	√	N.A.	No	√	Barnard, 1979; Randall *et al.,* 1964.
Smithburn	√	N.A.	No	No	Smithburn, 1949
MP-12	No	Zoetis	?[b]	√	Morrill *et al.,* 1987, 1991, 1997.
arMP-12-ΔNSm	No	Under development	?[b]		Morrill *et al.,* 2013; Weingartl *et al.,* 2014; Morrill *et al.,* 2013.
Clone 13	√	N.A.	√	√	Muller *et al.,* 1995; Dungu *et al.,* 2010; von Teichman *et al.,* 2011.
R566	No	MSD-AH	?	√	Kortekaas *et al.,* 2014.
DDvax[c]	No	Merial, Deltamune	√	√	Bird *et al.,* 2008, 2011.
NDV-GnGc[d]	No	Deltamune	?	√	Kortekaas, de Boer *et al.,* 2010; Kortekaas, Dekker *et al.,* 2010.
NSR-Gn	No	MSD-AH	?	√	Oreshkova *et al.,* 2013.

[a] Only vaccines that are commercialized or considered for further development by industry are listed.

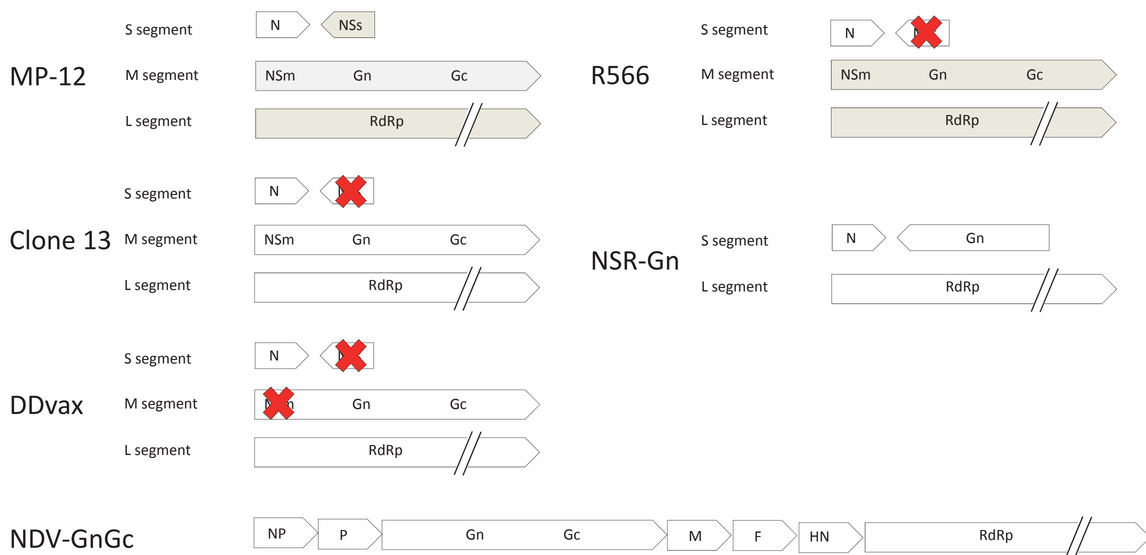
[b] Foetal mortalities occurred in vaccinated ewes although these could not be attributed to the use of the vaccines.

[c] DDvax was previously named ΔNSs-ΔNSm rRVFV.

[d] NDV-GnGc was previously named NDFL-GnGc.

N.A.: not applicable, ?: Unknown

Figure 3
Genome composition of live-attenuated
and replicon-based RVF vaccines that are currently being evaluated by industry.



The MP-12 vaccine virus was created by mutagenesis of the viral genome. Mutagenized genes derived from MP-12 are shaded. The R566 vaccine virus combines the M and L segment of the MP-12 vaccine virus with the S segment of Clone 13. Red crosses indicate large or complete deletions of the NSs gene or NSm-coding regions in Clone 13, DDvax and R566. The NDV-GnGc vaccine virus was created by introducing an GnGc-expression cassette in the NDV genome [85]. NSR-Gn particles comprise only an L segment and an S segment of which the NSs gene is replaced by the Gn gene [62].

The availability of live-attenuated vaccines that are safe, even for pregnant animals, eliminates the need for inactivated vaccines. However, should the demand for inactivated vaccines remain, RVF vaccine viruses that do not require BSL-3 containment should be used to produce these vaccines. This would not only reduce production costs considerably, but would also reduce safety concerns about infection of personnel involved in vaccine production.

Now that highly effective RVF vaccines can be used for the widespread vaccination of livestock, the challenge remains to have these vaccines available at the right time and place. Two strategies were discussed that could result in the effective control of RVF. In the first strategy, RVF vaccines are used to maintain herd immunity in high-risk areas, preferably by vaccination with live-attenuated vaccines to minimize vaccination costs. Regional stockpiles should become available for emergency vaccination programmes, which should be carefully coordinated by national or regional animal health agencies.

In the second strategy, multivalent vaccines are used that not only protect livestock from RVFV, but also from at least one other, preferably endemic, high-impact pathogen. This strategy could provide farmers with an incentive to vaccinate their livestock and ensure year-round herd immunity against RVFV. However, it must be

appreciated that the development of such vaccines is challenging. The vaccine needs to be inexpensive and effective against both pathogens, preferably after a single-dose vaccination. GALVmed is currently supporting the development of such a multivalent vaccine comprising Clone 13 and a LSD vaccine virus, which could provide protection against LSDV, sheep pox virus GTPV and RVFV.

The meeting experts also discussed reports of vaccine failure during RVF outbreaks to prevent future vaccination failure. Data suggest that the cold-chain dependence of vaccines based on live-attenuated RVFV strongly depends on the selected vaccine stabilizers. Vaccine manufacturers should, therefore, pay appropriate attention to stabilizers and demonstrate stability of the final product after incubation at different temperatures. The participants stressed the importance of establishing the stability of vaccines under environmental conditions typical of RVF-endemic countries. Equally important is the timing of vaccine application; although protection elicited by live vaccines is relatively swift, in some cases vaccination campaigns commence after animals are already infected with RVFV. There have also been reports of campaigns where needles are not changed between animals, which could result in needle transmission of the virus. To prevent the failure of future vaccination programmes, responsible authorities at the national and/or regional levels should support ongoing education of farmers and veterinarians in correct vaccine use, and should help fund and coordinate vaccination programmes.

The presentations and discussion in this meeting have demonstrated that the development of new RVFV control tools has continued apace since the previous FAO meeting on RVF in 2011, and that the previous recommendations were acknowledged in these developments. The novel vaccines that are in registration trials appear to fulfil the recommendations on vaccine safety and efficacy. However, several of the previous recommendations continue to require our attention. Taking these into consideration, the workshop participants formulated new recommendations intended to facilitate the final steps towards widespread RVFV control.

Recommendations

The Ad hoc Workshop on the Current State of Rift Valley fever Vaccine and Diagnostics Development is the most recent in an important series of regional and global expert workshops and meetings focusing on developing the most efficient and effective means for early detection, prevention or control of RVF.

The meeting recommendations below are divided into two distinct sets. The first set of recommendations builds on and reinforces important research activities and other actions recommended in preceding RVF meetings, particularly those held in Rome (2011) and Mombasa (2012).

In this context, pertinent recommendations reinforced by this meeting are:

1. Surveillance systems should be strengthened, applying a One Health approach, with an active partnership of the national ministries responsible for public health, agriculture and livestock.
2. Recognizing that Clone 13 vaccine is safe and efficacious against RVF, countries at risk for RVF are strongly encouraged to register Clone 13 vaccine.
3. Research scientists and vaccine manufacturers are encouraged to explore the development and testing of new, safe and efficacious multivalent or combination vaccines selected for maximal utility and marketability, by region.
4. Although DIVA is an important property of any future vaccine, absence of this feature should not hinder or block the development or licensing of an effective RVF vaccine. The provisions in the OIE *Terrestrial Animal Health Code* for importation from countries/zones infected with RVFV support this recommendation.
5. FAO is encouraged to develop implementation strategies and protocols for the application of RVF vaccines under prevention or emergency use, in close collaboration with PANVAC and other regional organizations.
6. Given that the use of needles to inject vaccines is time-consuming and costly, and may actually exacerbate the spread of wild virus if applied in epidemic settings, rigorous testing and registration of safe, effective and economically feasible needle-free vaccination delivery systems and compatible vaccines are strongly encouraged.
7. The ongoing initiative to move towards centralized drug and vaccine registration in different African regions is strongly supported.
8. Post-registration vaccine quality assurance in the African Union through standardized periodic vaccine testing and monitoring in accordance with OIE standards is vigorously encouraged.
9. Regions and/or subregions are encouraged to establish strategically located RVF vaccine banks, preferably with a rolling stock of vaccines that can be used for both prevention and outbreak response.

The following set of recommendations are based on new research findings and experience of RVF-endemic countries and regions as presented in the Ad hoc Workshop on the Current State of Rift Valley fever Vaccine and Diagnostics Development:

1. Recognizing significant progress made that facilitates RVF vaccine research and development, including the fact that:
   a. MP-12 is now registered under a conditional license in both the United States of America and Canada;
   b. MP-12 and DDvax vaccine strains have been downgraded to BSL-2 handling;
   at least three vaccine candidates (DDvax, NDV-GnGc, and MP-12) are now being evaluated in registration trials that may offer new options in prevention and outbreak response;
   c. continued research and development of these vaccines for use in countries at risk for RVF is strongly encouraged in collaboration with national and regional authorities.
2. Research scientists and vaccine manufacturers are strongly encouraged to expedite the development of safe and effective RVF vaccines by facilitating field assessments of candidate vaccines in accordance with national standards.
3. Production and quality assessment processes for RVF vaccines under development should be encouraged in line with standards that meet or exceed those described in the OIE *Manual.*
4. The process of developing RVF vaccines must include the determination of the stability of each vaccine. Shelf life claims should be supported by independent review. Stability studies should be in accordance with the OIE *Manual* chapter 2.1.14, section C, where applicable.
5. RVF in dromedary camels is a concern to animal and public health authorities in several regions. Practical and accurate serological diagnostic tests for RVFV infection in camels should be developed and validated for both IgM and IgG. Simultaneously, the development and approval of RVF vaccine for use in camels is strongly encouraged, and should be done in conjunction with the national Livestock Services of those countries concerned with RVF in camels.
6. In order to increase the availability of RVF diagnostic tests, the FAO-IAEA joint division should support the validation of new tests and publish the results in a timely manner.
7. Efforts to strengthen laboratory diagnostic capacity, including proficiency testing and quality control for national and regional laboratories, should be standardized and promoted with support from FAO, IAEA and OIE, in partnership with national and regional authorities.
8. Routine vaccination of animal populations at elevated risk for RVF using effective and safe vaccines is strongly encouraged. It should be done in strict accordance with FAO protocols and recommendations, and in keeping with manufacturers' instructions.
9. Given their unique experience in preventing and responding to RVF outbreaks, South Africa should be encouraged to document and share communication strategies and educational tools developed for the public and animal health sectors, as well as communications targeting farmers both prior to, and during, outbreaks.

Annex 1

Recommendations from select RVF conferences and meetings

RVF has been the subject of several previous conferences and meetings, which underlines its importance as one of the priority diseases with enormous economic impact for Africa and the Middle East. The disease has been identified by the Global Framework for Transboundary Diseases (GF-TADs) as a priority disease and has, therefore, been inserted into the five-year action plans for the two regions concerned.

CAIRO, EGYPT, 2007

http://www.oie.int/doc/ged/D4246.PDF

Participants in the Conference came from North and East Africa and the Middle East. The meeting was organized jointly by OIE, FAO and AU-IBAR.

Recommendations included:

- develop surveillance guidelines for vector-borne diseases;
- provide training and technical assistance to affected countries;
- promote good veterinary governance;
- develop diagnostic tests and vaccines;
- develop regional control strategies under GF-TADs;
- develop prediction models at subregional level;
- improve communication between OIE, FAO, WHO and national ministries of health and ministries of agriculture (One Health concept);
- import/export to be governed by standards in the OIE *Terrestrial Code*;
- promote the use of the intraregional trade health certificate as developed in Cairo in 2004.

BLOEMFONTEIN, SOUTH AFRICA, 2009

http://www.rr-africa.oie.int/en/en_index_annex19.html

Participants in this conference came from East and southern Africa and focused on the apparent reoccurrence of the disease in southern Africa.

Recommendations included:

- good veterinary governance to be promoted;
- harmonized preventive measures in ecological subregions with similar risk characteristics to be defined;
- research and development of diagnostics and vaccines to be supported by OIE and FAO;
- research needed on epidemiology and the role of wildlife in Southern Africa;
- socio-economic impact of disease outbreaks to be studied and communication strategy to be developed;
- intersectoral collaboration to be strengthened (One Health concept);

- southern African countries to have emergency preparedness plans;
- countries to comply with reporting obligations to WAHIS;
- OIE to update *Manual* and *Code* chapters;
- laboratory capacity in national laboratories to be strengthened;
- OIE to support twinning on RVF to have a second Reference Laboratory in the region;
- SADC countries to develop forecast capacity;
- SADC to develop a regional RVF control strategy;
- OIE to consult with WHO to promote research for human vaccine development.

ROME, FAO-WHO EXPERT CONSULTATION ON RVF OUTBREAK FORECASTING MODELS, 2008

http://www.who.int/csr/resources/publications/WHO_HSE_GAR_BDP_2009_2c.pdf

A group of experts came together to share experiences, identify gaps and explore potential improvements in RVF outbreak models. The objectives of the workshop were to review the natural history of RVF, review the forecasting models and risk distribution maps available and being developed, and propose how these tools might be improved.

Recommendations include:

- The accuracy of RVF potential major outbreak area maps should be increased in order to improve forecasting models.
- The specificity of RVF forecasting models should be increased.
- Models should be improved in space and time; an alert signal should be sent six months before the start of an animal outbreak.
- RVF forecasting models should be used in combination with livestock trade/movement data.
- The participation of ministries of meteorology and ministries of health should be encouraged.

GF-TADS MEETING ON RVF VACCINE DEVELOPMENT, ROME, 2011

http://www.fao.org/3/a-i2310e/index.html

The aim of this meeting was to discuss how the most promising RVFV vaccines can be selected and commercialized. Desired characteristics with respect to safety and efficacy were established, and the advantage of using DIVA vaccines was discussed. The conclusions that emanated from the discussions were used to formulate recommendations to the scientific community, policy-makers and industry, which aim to facilitate global preparedness for future RVFV incursions.

Recommendations included:

- The relative risks and benefits of RVF vaccination in the face of an outbreak should be evaluated to inform FAO and OIE, and allow them to make the most appropriate recommendations for the integrated control of RVF.
- The development of a strategy for a global vaccine stockpile for use in RVF-endemic areas and emergency vaccination campaigns should be encouraged.
- The benefits of multivalent vaccines to increase uptake of RVF vaccines in specific at-risk populations should be evaluated.

- Second generations of live-attenuated vaccines hold great promise, e.g. Clone 13 in South Africa.
- The use of viral vectors for the control of RVF is a promising approach.
- DNA vaccines in combination with MVA vectors should be considered.
- The potential of next generation vaccines to be used as DIVA vaccines should be explored.

MOMBASA, NOVEMBER 2012

http://www.rr-africa.oie.int/en/news/20121127.html

Over 70 veterinary professionals and scientists from the Middle East and Africa met in Mombasa, Kenya to assess the situation of RVF in the area around the Red Sea and the Indian Ocean, including its challenges and options for prevention and control. Participants discussed the current state of RVF in the Middle East and the Horn of Africa, its impact on trade between the two regions and reviewed recommendations from previous seminars and conferences. The focus of the conference was to debate the use of new prevention and control tools, including new vaccines, diagnostic tools, and early warning and rapid response models.

Recommendations from the previous meetings were still valued. New ideas included:

- re-establish the FAO/OIE GF-TADS study group on RVF;
- develop targeted surveillance and control strategies, which also take into account lessons learned from successful experiences in affected countries;
- apply appropriately the existing sanitary and phytosanitary (SPS) measures and OIE standards for trade of live animals, animal products, promoting transparent sanitary information exchange;
- develop regionally harmonized approaches and projects aimed at the facilitation of safe trade between Africa and the Middle East;
- enhance intersectoral collaboration between national animal and public health ministries;
- ensure safety and efficacy of vaccines: RVF vaccine produced in Africa to comply with OIE standards and quality certified by PANVAC; and promote the registration of Clone 13 vaccine;
- support accelerated development and registration of diagnostic tests and vaccines and strengthen collaboration with private/NGO and industry partners in view of this;
- national authorities to integrate the “Risk-based decision-making framework” into their national context;
- FAO/OIE and partners to develop early warning system models to fit the different ecosystems in Africa and the Middle East; assist transfer and capacity building of appropriate early warning systems to regional institutions.

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Participant contact information

ALPHABETICAL ORDER

Tammy Beckham (Organizing Committee)
Director
National Center for Foreign Animal and Zoonotic Disease Defense
2501 Earl Rudder Freeway South, Suite 701
College Station, Texas 77843-2129
United States of America
Tel: +1 979 845 2855
TBeckham@tvmdl.tamu.edu

Daniel Beltran-Alcrudo
Animal Health Officer
Animal Production and Health Division
FAO
Viale delle Terme di Caracalla
00153 Rome, Italy
Tel: +39 06 570 53823
Daniel.BeltranAlcrudo@fao.org

Brian H. Bird
Veterinary Medical Officer, Viral Special Pathogens Branch
U.S. Centers for Disease Control and Prevention
Mailstop G14
Atlanta, Georgia 30329-4018
United States of America
Tel: +1 404 639 1438
Bbird1@cdc.gov
Che3@cdc.gov

Josephine Birungi
Technology Manager
Biosciences Eastern and Central Africa (BecA) Hub
International Livestock Research Institute (ILRI)
PO Box 30709
00100 Nairobi, Kenya
Tel: +254 20 422 3384 (or +1 650-833-6660 United States of America direct)
Fax: +254 20 422 3001
J.Birungi@cigar.org
Skype: jobirungi
Hub.africabiosciences.org
Ilri.org

Alejandro Brun
Centro de Investigación en Sanidad Animal.
Instituto Nacional de Investigación y
Tecnología Agraria y Alimentaria (INIA)
Ctra de Valdeolmos-El Casar s/n
Valdeolmos
28130 Madrid, Spain
Tel: (switchboard): +34 91 620 23 00
Fax: +34 91 620 22 47
Mobile: 630913031
brun@inia.es

Filip Claes
Laboratory Unit
Animal Production and Health Division
FAO
Viale delle Terme di Caracalla
00153 Rome, Italy
Tel: +39 06 570 53525
Filip.Claes@fao.org

Alfonso Clavijo
The FAZD Center
2501 Earl Rudder Fwy S, Ste. 701
College Station, Texas 77845
United States of America
Tel: +55 21 3661 9080
AClavijo@tvmdl.tamu.edu
clavijo@paho.org

Michelle Colby
Agriculture Defense Branch Chief
Chemical and Biological Division
Department of Homeland Security, Science and Technology Directorate
Washington, DC
United States of America
Tel:+1 202 254 6883
Fax: +1 202 254 6170
Michelle.colby@hq.dhs.gov

Frederic Descamps
Associate Director Regulatory Affairs
Biologicals Veterniary Medicine Research and Development
Zoetis
Mercuriusstraat 20
B-1930 Zaventem, Belgium
Tel: +32 (0)2 74 68074
Fax: +32 (0)2 40 12406
Mobile: +32 (0) 498 113925
Frederic.Descamps@zoetis.com

Joseph (Jemi) Domenech
Chargé de Mission
OIE
12 Rue de Prony
75017 Paris, France
Tel: +33 (0) 1 44 15 18 88
j.domenech@oie.int
http://www.oie.int

Mehdi El Harrak
Senior Director of Research and Development
MCI-Sante Animale
PO Box 278, Mohammedia
28810, Morocco
Tel: +212 523 30 31 32
m.elharrak@mci-santeanimale.com

Tamador M.A. Elhassan
Rift Valley fever Head Unit
Veterinary Research Institute, Virology Department
Khartoum-Soba, Sudan
Tel: +24 991 295 0987
tamadormohamed@yahoo.com

Ahmed El Idrissi
Animal Health Officer
Animal Production and Health Division
FAO
Viale delle Terme di Caracalla
00153 Rome, Italy
Tel: +39 06 57053650
Ahmed.ElIdrissi@fao.org

Ahmed El Sawalhy
Director and Head of Mission
AU-IBAR
Westlands Road, Museum Hill, Kenindia Business Park
PO Box 30786-00100
Nairobi, Kenya
Tel : +254 20 3674000
Fax : +254 20 3674341
Ahmed.elsawalhy@au-ibar.org
www.au-ibar.org

Danny Goovaerts
Interim Director, Research and Development
GALVmed
Doherty Building, Pentlands Science Park
Bush Loan, Penicuik Edinburgh
EH26 OPZ
Scotland, United Kingdom
Tel: +32 (0) 487 657986
dannygoovaerts@skynet.be
Danny.Goovaerts@GALVMED.ORG

Mohamed Gueya
Deputy Chief Veterinary Officer
Dar Naim, 178
Nouakchott, Mauritania
Tel: 00 222 36100164
ouldnet@yahoo.fr

Akiko Kamata
Animal Health Officer
Animal Production and Health Division
FAO
Viale delle Terme di Caracalla
00153 Rome, Italy
Tel: +39 06 570 54552
Akiko.Kamata@fao.org

Alasdair King
Associate Director Institutional Sales
MSD-AH
Wim de Körverstraat 35
PO Box 31
5830 AA Boxmeer, the Netherlands
Tel: +31 485 587635
Fax: +31 485 587491
alasdair.king@merck.com
www.msd-animal-health.com

J. A. (Jeroen) Kortekaas
Project Leader
Central Veterinary Institute - Wageningen University and Research Centre
PO Box 65
NL-8200 AB Lelystad, the Netherlands
Visiting address:
Edelhertweg 15
8219 PH Lelystad, the Netherlands
Tel: +31 320 238 198
Fax: +31 320 238 225
Mobile: +31 6 20919110
jeroen.kortekaas@wur.nl
www.cvi.wur.nl

Nicolas Krieger
Legislative Veterinary Officer
European Commission
Directorate-General for Health and Consumers
Animal Health (G2)
FR101 03/88
B-1049 Brussels, Belgium
Tel: +32 229 85845
Nicolas.KRIEGER@ec.europa.eu
http://ec.europa.eu/food/animal/index_en.htm

Thomas (Tom) Ksiazek (Chair, Organizing Committee)
Professor
Galveston National Laboratory
Pathology Department
University of Texas Medical Branch
301 University Blvd
Galveston, Texas 77555-0610
United States of America
Tel: +1 409 266 6902
Fax: +1 409 266 6810
tgksiaze@UTMB.EDU

Mbargou Lo
Director Veterinary Services
Ministère de l'Elevage
37 Avenue Pasteur
Dakar, Senegal
Tel: 221 77 636 8110
mbargoulo@voila.fr

Juan Lubroth (Organizing Committee)
Chief Veterinary Officer
Animal Production and Health Service
FAO
Viale delle Terme di Caracalla
00153 Rome, Italy
Tel +39 06 570 54184
Fax +39 06 570 53023
Juan.Lubroth@fao.org
http://www.fao.org/ag

Louis Maartens
Deltamune (Pty) Ltd
PO Box 14167, Lyttelton, 0140, South Africa
248 Jean Ave, Lyttelton
Centurion, South Africa
Tel : +27 12 664 5730
Fax : +27 86 623 6371
louism@Deltamune.co.za

Rees Murithi Mbaabu
Officer In-charge
Central Veterinary Laboratories (CVL) Kabete, Kenya
Private Bag 00625 Kangemi
Nairobi, Kenya
Tel: +254 722 360620
murithimbabu@yahoo.com

Samia Metwally
Animal Health Officer (Virologist)
Animal Production and Health Division
FAO
Viale delle Terme di Caracalla
00153 Rome, Italy
Tel: +39 06 570 55838
Fax:+39 06 570 53152
Samia.Metwally@fao.org

Jules Minke
Head of Research and Projects Biologics
Merial
245 rue Marcel Merieux
69007 Lyon, France
Tel: +33 4 72 72 2997
Fax : +33 4 72 72 2963
Mobile : +33 6 7399 5688
jules.minke@merial.com

Federica Monaco
Istituto Zooprofilattico Sperimentale
dell'Abruzzo e del Molise "G. Caporale"
Campo Boario
64100 Teramo, Italy
Tel: +39 0861 332446
Fax: +39 0861 332251
f.monaco@izs.it
www.izs.it

Rob Moormann (Organizing Committee)
Virologist/Professor in Vaccinology
Division of Virology, Central Veterinary Institute, Animal Sciences Group,
Wageningen UR
PO Box 65,
8200AB Lelystad, Netherlands
Division of Virology, Faculty of Veterinary Medicine, Utrecht University
Yalelaan 1
3584 CL Utrecht, Netherlands
Tel: +31 320 238242
Mobile : +31 6 51677347
rob.moormann@wur.nl and r.j.m.moormann@uu.nl
Visiting address: Edelhertweg 15, Lelystad, Netherlands

Véronique Moulin
Geo Head Ruminants Research and Development
Project Leader Ruminants Research and Development
Intervet International BV
Wim de Körverstraat 35
PO Box 31
5830 AA Boxmeer, Netherlands
veronique.moulin@merck.com
Tel: +31 (0)485 587732
Fax: +31 (0)485 585317
Mobile: +31 (0)6 11591057
www.msd-animal-health.com

Susanne Munstermann
OIE
12 Rue de Prony
75017 Paris, France
Tel: +33 (0) 1 44 15 18 88
s.munstermann@oie.int
http://www.oie.int

Craig Nessler
Director
Texas A&M AgriLife Research
Agriculture and Life Sciences Building
600 John Kimbrough Boulevard, Suite 512
2142 TAMU College Station, Texas 77843
United States of America
Tel: +1 979 845 8486
Fax: +1 979 458 4765
Email: CNessler@tamu.edu

Stuart Nichol (Organizing Committee)
Team Leader, Viral Special Pathogens Branch
U.S. Centers for Disease Control and Prevention
Mailstop G14
Atlanta, Georgia 30329-4018
United States of America
Tel: +1 404 639 1122
stn1@cdc.gov

M. Kariuki Njenga
Virologist and Head
Integrated Human-Animal Health Program, GDD-Kenya
CTS Global, Inc
Assigned to: Centers for Disease Control and Prevention
Tel: +254 20 2723008
Fax +254 20 271 4745
Mobile: +254 722 208925
byi6@cdc.gov

Felix Njeumi
Animal Health Officer
Animal Production and Health Division
FAO
Viale delle Terme di Caracalla
00153 Rome, Italy
Tel: +39 06 570 53941
Felix.Njeumi@fao.org

Bethuel Nthangeni
Chief Scientific Officer
Onderstepoort Biological Products SOC Ltd
Private Bag X07
Onderstepoort, South Africa
Tel: +27 (0)12 522 1549
Fax: +27 (0)12 522 1591
bethuel@obpvaccines.co.za

Elizabeth Parker
Animal Health Officer (Programming Unit)
Animal Production and Health Division
FAO
Viale delle Terme di Caracalla
00153 Rome, Italy
Tel: +39 06 570 55428
Fax: +39 06 570 55 740
Elizabeth.Parker@fao.org

Claudia Pittiglio
Remote Sensing, Spatial Modeling, GIS
Animal Health and Production Division
FAO
Viale delle Terme di Caracalla
00153 Rome, Italy
Tel: +39 06 570 56371
Claudia.Pittiglio@fao.org

Ludovic Plee
Epidemiologist - Response Veterinary Officer
Crisis Management Center - Animal Health (CMC-AH)
FAO
Viale delle Terme di Caracalla
00153 Rome, Italy
Tel: +39 06 570 55206
Ludovic.Plee@fao.org

Eran Raizman
Senior Animal Health Officer
Animal Production and Health Division
FAO
Viale delle Terme di Caracalla
00153 Rome, Italy
Tel: +39 06 570 52360
Eran.Raizman@fao.org

Pierre Rollin
Medical Officer, Viral Special Pathogens Branch
U.S. Centers for Disease Control and Prevention
Mailstop G14
Atlanta, GA 30329-4018
United States of America
Tel: +1 404 639 1124
pierre.rollin@cdc.hhs.gov
pyr3@cdc.gov

Jeremy Salt
Director EU Biologicals
Veterinary Medicine Research and Development
Zoetis, Belgium SA
Mercuriusstraat 20
B-1930 Zaventem
Brussels, Belgium
Tel: +32 (0) 2 746 81 66
Mobile: +32 (0) 499 547 431
Jeremy.salt@zoetis.com

Massimo Scacchia
Istituto Zooprofilattico Sperimentale
dell'Abruzzo e del Molise "G. Caporale"
Campo Boario
64100 Teramo, Italy
Tel: +39 0861 3321
Fax: +39 0861 332251
m.scacchia@izs.it
www.izs.it

Robert (Bob) Swanepoel
51 Albert Road
Irene, South Africa
Tel: +27 (0) 73 818 1815
Bob.swanepoel@up.ac.za

Hannes Swart
Deltamune (Pty) Ltd
PO Box 14167, Lyttelton, 0140, South Africa
248 Jean Ave, Lyttelton, Centurion, South Africa
Tel: +27 (0)86 572 3089
Mobile: +27 (0)83 251 8479
hannes@deltamune.co.za

Markos Tibbo
Livestock Officer
FAO, Regional Office for the Near East and North Africa
11 A1 Eslah El-Zerai Sheet, Dokki
PO Box 2223
Cairo, Egypt
Tel: +20 23331 6143
Mobile: +20 10666 87159
Markos.Tibbo@fao.org

Karim Tounkara
Director
Pan African Veterinary Vaccine Centre
African Union (AU)/PANVAC
PO Box 1746
Debre Zeit, Ethiopia
Tel: + 251 11 437 12 86; + 251 11 433 80 01
Fax: + 251 11 433 88 44
Mobile: + 251 911 93 49 38
karim.tounkara@hotmail.com

Hermann Unger
Animal Production and Health
IAEA
Vienna International Centre, PO Box 100
A-1400 Vienna, Austria
Tel: +431 2600 21644
H.Unger@iaea.org

David B. Wallace
Senior Research Scientist in Molecular Virology
Project Leader in NGV Programme
ARC-Onderstepoort Veterinary Institute (ARC-OVI)
P/Bag X5
Onderstepoort, 0110 South Africa
Tel: + 27 (0)12 529 9442
Fax: + 27 (0)12 529 9249
WallaceD@arc.agric.za

Doug Watts
Office of Research and Sponsored Projects
Executive Director of Veterinary Services and Institutional Biosafety
Co-Director of Infectious Disease and Immunology
Border Biomedical Research Center
University of Texas at El Paso
500 W. University
El Paso, Texas 79968
United States of America
Tel: +1 915 7478715
Fax: +1 915 7475808
dwatts2@utep.edu

William (Bill) C. Wilson
Research Microbiologist
Arthropod-Borne Animal Diseases Research Unit
Center for Grain and Animal Health Research
USDA, Agricultural Research Service
1515 College Ave.
Manhattan, Kansas 66502
United States of America
Tel: 785 537 5570
Fax: 785 537 5560
Mobile: 785 410 3003
Email: william.wilson@ars.usda.gov

Sayed Mohamed Zeidan
VSVRI
PO Box 131
Abbasia, Cairo, Egypt
Tel: +202 23421009
Fax: +202 23428321
Mobile: +2 01002679195
Office email: svri@idsc.gov.eg
Personal email: sayed.zeidan@yahoo.com

James (Jim) Zingeser
Epidemiologist
Animal Production and Health Division
FAO
Viale delle Terme di Caracalla
00153 Rome, Italy
Tel: +39 06 570 55918
Fax: +39 06 570 53023
Mobile: +39 348 118 8489
Email: James.Zingeser@fao.org
Skype: j.zingeser

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In the past decade, tremendous progress has been made in the development of Rift Valley fever (RVF) vaccines, and several next-generation vaccines are currently being evaluated in registration trials. However, due to the sporadic, yet explosive nature of RVF outbreaks, the challenge remains to have these vaccines available at the right time and place. Innovative, appropriate diagnostics will aid in the selection of vaccines and will help to determine when to vaccinate animals. To address these issues, the Food and Agriculture Organization of the United Nations (FAO) organized a technical workshop in March 2014. The workshop was supported by the National Center for Foreign Animal and Zoonotic Disease Defense (FAZD) and the United States Centers for Disease Control and Prevention (CDC), in collaboration with representatives of the Central Veterinary Institute, Wageningen University and Research Centre (CVI-WUR), the World Organisation for Animal Health (OIE) and the International Atomic Energy Agency (IAEA). Global experts in RVF vaccine development, leading veterinary vaccine manufacturers and the chief veterinary officers from Egypt, Kenya, Mauritania, Senegal and Sudan attended the meeting. Issues related to the application of classical vaccines in endemic areas were discussed, as well as novel vaccines that are already used in the field or are currently being evaluated in registration trials. These vaccines are expected to fulfil the features related to safety and efficacy recommended in the previous FAO meeting, held in Rome in January 2011. Due to these developments, we have entered a new era in which effective vaccines for the widespread vaccination of livestock will be available. Logistical and political issues are the last major hurdles to RVF control.

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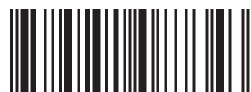

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