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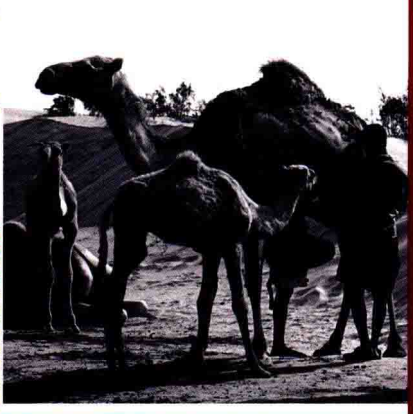

RIFT VALLEY FEVER VACCINE DEVELOPMENT, PROGRESS AND CONSTRAINTS

GF-TADs meeting
January 2011

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FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS
Rome, 2011

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List of acronyms

ABADRU	Arthropod-Borne Animal Diseases Research Unit
AHRI	Animal Health Research Institute
AHVLA	Animal Health and Veterinary Laboratories Agency
ANSES	Agence nationale de sécurité sanitaire de l'alimentation, de l'environement et du travail
ARBO-ZOONET	International Network for Capacity Building for the Control of Emerging Viral Vector Borne Zoonotic Diseases
ARS	Agricultural Research Service
CDC	United States Centers for Disease Control and Prevention
CFIA	Canadian Food Inspection Agency
chimVLP	chimeric virus-like particles
CIRAD	Centre International de Recherche Agronomique pour le Développement
CISA-INIA	Centro de Investigacíon en Sanidad Animal-Instituto Nacional de Investigacíon y Tecnología Agraria y Alimentaria
CPV	capripox virus
CReSA	Centre de Recerca en Sanitat Animal
CVI-WUR	Central Veterinary Institute of Wageningen University and Research Centre
DIVA	Differentiating Infected from Vaccinated Animals
EC	European Commission
EDEN	Emerging Diseases in a Changing European Environment
EDENext	Biology and Control of Vector-Borne Infections in Europe
EFSA	European Food Safety Authority
ELISA	Enzyme-Linked Immunosorbent Assay
ENCRAD	European Network for the Coordination of Rift Valley Fever Animal Experimentation and Diagnostics
EPIZONE	Network of Excellence for Epizootic Disease Diagnosis and Control
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FLI	Friedrich Löeffler Institut
GALVmed	Global Alliance for Livestock Veterinary Medicines

GF-TADs	Global Framework for the Progressive Control of Transboundary Animal Diseases
GTPV	goat pox virus
IAEA	International Atomic Energy Agency
IFAH	International Federation for Animal Health
IM	intramuscular
IN	internasal
IV	intravenous
KARI	Kenya Agricultural Research Institute
LSD	lumpy skin disease
LSDV	lumpy skin disease virus
MoMLV	Moloney murine leukemia virus
MVA	Modified Vaccinia Ankara
NDV	Newcastle disease virus
NHP	non-human primate
NICD	National Institute for Communicable Diseases
OIE	World Organisation for Animal Health
OP	Onderstepoort
PKR	RNA-dependent protein kinase
RVF	Rift Valley fever
RVFV	Rift Valley fever virus
SC	subcutaneous
SPPV	sheep pox virus
USAMRIID	United States Army Medical Research Institute of Infectious Diseases
USDA	United States Department of Agriculture
UTMB	University of Texas Medical Branch
VLP	virus-like particles
VNT	virus-neutralization tests
VPH	Veterinary Public Health

Abstract

In November 2010, the Food and Agriculture Organization of the United Nations (FAO) issued a request to policy-makers, representatives of international organizations and foremost scientists involved in vaccine development for the control of Rift Valley fever (RVF), to attend a workshop entitled "Rift Valley fever vaccine development, progress and constraints". The workshop was organized under the umbrella of the Global Framework for the Progressive Control of Transboundary Animal Diseases (GF-TADs), a joint initiative of FAO and the World Organisation for Animal Health (OIE). It was supported by the Dutch Ministry of Economic Affairs, Agriculture and Innovation, and the United States Centers for Disease Control and Prevention (CDC), with the participation of the World Health Organization (WHO), the International Atomic Energy Agency (IAEA) and the Central Veterinary Institute of Wageningen University and Research Centre (CVI-WUR). The meeting was held at FAO headquarters in Rome, Italy from 19 to 21 January 2011. Views on the current and future control of RVF were presented, and the stages of development of candidate vaccines were reported by key stakeholders in vaccine development from international organizations and related industry. The desired characteristics of vaccines for application in different areas of the world were debated, as were the advantages of applying Differentiating Infected from Vaccinated Animals (DIVA) vaccines. The necessity of establishing emergency vaccine banks for livestock was discussed, as was the need for a human vaccine to protect farmers, veterinarians and others at elevated risk for RVF. It was concluded that robust challenge models must become available to facilitate rational selection of novel veterinary vaccines, and that incentives for vaccine manufacturers should be established to ensure that these vaccines come to market in a timely manner. A total of 11 recommendations to policy-makers, industry and the scientific community were formulated to facilitate this process.

Contents

Past and present control of RVFV: What is needed

Compilation of presentations provided by Hermann Unger, Pierre Rollin, Stephane de La Rocque, Truuske Gerdes and Samia Ahmed Kamal

Rift Valley fever virus (RVFV) is a phlebovirus of the *Bunyaviridae* family. The virus contains a three-segmented genome, comprising a large (L), medium (M) and small (S) genome segment (Elliott, 1996). The L segment encodes the viral RNA-dependent RNA polymerase, and the M segment encodes at least two non-structural proteins of unknown function, collectively referred to as NSm and the structural glycoproteins Gn and Gc (Gerrard and Nichol, 2007). The L and M genome segments are of negative-sense polarity, whereas the S genome segment is of ambisense polarity. This genome segment contains the non-structural NSs gene in the antigenomic orientation and the gene encoding the nucleocapsid (N) protein in genomic orientation. The NSs protein is responsible for repressing innate host immune responses and is considered the main virulence factor of the virus (Ikegami *et al.*, 2009; Bouloy *et al.*, 2001; Billecocq *et al.*, 2004; Muller *et al.*, 1995; Habjan *et al.*, 2009a).

RVFV was first identified as the causative agent of an epizootic among sheep on a farm near Lake Naivasha in the Great Rift Valley of Kenya in 1930 (Daubney, Hudson and Garnham, 1931). The investigators of this outbreak were able to show that the disease was caused by a virus that infected sheep, goats and cattle, as well as humans, and that the virus was transmitted by mosquitoes (Daubney, Hudson and Garnham, 1931). In the 80 subsequent years, the geographic distribution of the virus expanded to include most countries of the African continent, the Arabian Peninsula (Bakhy and Memish, 2003). and islands in the Indian Ocean, including Madagascar (Gerdes, 2004), Comores and Mayotte (Sissoko *et al.*, 2009). Recent history makes clear that RVFV has a strong capacity to emerge and establish in previously unaffected areas. This capacity is at least partially attributed to the broad host range of the virus, and the ability to be transmitted by at least 30 different species of mosquito belonging to six different genera (for a recent review see [Pepin *et al.*, 2010]). RVFV outbreaks are generally preceded by the mass hatching of RVFV-infected eggs of floodwater *Aedes* mosquitoes, triggered by periods of unusually heavy rainfall. *Aedes* mosquitoes transmit the virus to susceptible mammalian species, and several other mosquito species are subsequently involved in further dissemination of the virus. Mosquitoes potentially capable of transmitting RVFV are not confined to the current habitat of RVFV, which explains the growing concern for future RVFV incursions into Europe, Australasia and the Americas.

Newborn lambs and gestating ewes are the animals most vulnerable to RVFV infection. The disease in newborn lambs generally results in over 90 percent mortality (Coetzer, 1977). The mortality rate in adults is estimated at 20 percent (Coetzer, 1977; Coetzer, 1982), but differs between breeds. Infection of gestating sheep and goats results in a high number

of abortions, which often signals the start of RVF epidemics. The human case-fatality rate is historically estimated to be below 1-2 percent, although several outbreaks have resulted in considerably higher mortality rates (Al-Hamzi *et al.*, 2003; Davies, 2010; Adam, Karsany and Adam, 2010; Rakotoarivelo, 2011; Madani *et al.*, 2003).

Outbreaks following first incursions of RVFV in a given area can result in explosive epidemics, involving both humans and livestock. This tendency is exemplified by the epidemic that followed the first introduction of RVFV in Egypt in 1977. The epidemic resulted in an estimated 300 000 human clinical cases and 600 deaths. Neonatal mortality and abortions occurred among cattle, sheep, goats and water buffalo. Camels were also affected. Since the first introduction of RVFV in Egypt, the virus has been maintained in an enzootic cycle, and continues to cause occasional outbreaks (Arthur *et al.*, 1993).

Between 2000 and 2001, a serious RVFV epidemic occurred in Saudi Arabia and Yemen (Madani *et al.*, 2003), and was the first report of RVF outside the African continent. This "virgin-soil" outbreak was very serious, particularly among humans, yielding a mortality rate of 14 percent. Since that time, no major epidemics have occurred in the Arabian Peninsula, although the virus may have persisted in these areas (Elfadil *et al.*, 2006).

RVFV is able to persist silently in endemic areas with low levels of circulation, as observed in western and central Africa. The ecology of RVF is still not completely understood, as exemplified by recent outbreaks in South Africa. In 2008, RVF outbreaks occurred in four South African provinces (Limpopo, North West, Gauteng and Mpumalanga). In 2009, small RVF outbreaks were reported in the KwaZulu-Natal Province (KZN). A major epizootic followed in 2010, which was 36 years after the last South African epizootic. Interestingly, no clinical cases of RVFV were reported in the KZN Province in 2010. The National Institute for Communicable Diseases (NICD) identified a new genotype, which was unrelated to isolates collected in 2008 and 2009. This finding suggests either that different strains were recently introduced into the country, or that these viruses silently persisted in this area.

The control of RVF outbreaks requires various actions, from limiting circulation of animals to reducing human risk through health and hygiene awareness campaigns and targeted interventions for populations at risk. FAO and WHO have a common strategy to implement contingency plans during RVF outbreaks, and vaccination is an important tool. Currently, there are two classical RVFV vaccines that are available in South Africa, which have been used to control recent outbreaks. The first, is based on the inactivated whole RVFV. For optimal efficacy, this vaccine requires a booster vaccination and annual re-vaccination. The second vaccine is the so-called live-attenuated Smithburn vaccine (Smithburn, 1949). This vaccine can provide lifelong immunity and is, therefore, a less expensive and more effective alternative to the inactivated vaccine. However, due to residual virulence, the Smithburn virus can cause abortion and foetal malformations when administered to gestating adults. There is need for a vaccine of equal, or greater, efficacy than the live-attenuated Smithburn vaccine, that is as safe as the inactivated vaccine. The recent release of a novel live-attenuated vaccine with improved safety (i.e. the Clone-13 vaccine) is considered a major advance in the battle against RVFV. This vaccine, as well as alternative candidate vaccines, will be discussed below.

The aim of this meeting was to discuss how the most promising RVFV vaccines can be selected and brought to market. Desired characteristics with respect to safety and efficacy

were established, and the advantage of using DIVA vaccines was discussed. This report describes the views from international organizations, policy-makers and industry on the future control of RVFV, and provides an overview of the *status quo* of RVFV vaccine development. The solid conclusions that emanated from the discussions were used to formulate 11 recommendations to the scientific community, policy-makers and industry, which aim to facilitate global preparedness for future RVFV incursions.

View from international organizations and industry

OIE ACTIVITIES AND STANDARDS RELATED TO RVF

François Diaz

OIE is an intergovernmental organization with a mandate from its 178 member countries and territories to improve animal health, veterinary public health (VPH) and animal welfare worldwide.

RVF is a disease listed by the OIE within the current category of multiple species diseases. Arising from its mandate, the OIE has developed different standards, guidelines and recommendations related to RVF. They are laid down in two publications: the *Terrestrial Animal Health Code* (hereafter referred to as the *Terrestrial Code*, and downloadable from http://www.oie.int/en/international-standard-setting/terrestrial-code/access-online/), and the *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (hereafter referred to as the *Terrestrial Manual* and downloadable from http://www.oie.int/en/international-standard-setting/terrestrial-manual/access-online/).

The aim of the *Terrestrial Code* is, among other things, to assure the sanitary safety of international trade in terrestrial animals and their products. It is also an essential tool for supporting the mandate of the OIE in the area of improving animal health and welfare worldwide through the application of the standards on animal disease surveillance and recommended control methods. Chapter 8.11 on RVF is based on general provisions for minimum requirements for veterinary services and RVF. Recommendations include provisions for ruminants such as camels and their products. The horizontal chapters, 1.4 on animal health surveillance, 1.5 on surveillance for arthropod vectors of animal diseases and 4.3 on zoning and compartmentalization, also provide useful guidelines for the surveillance and control of RVF.

As a companion volume to the *Terrestrial Code*, the *Terrestrial Manual* provides internationally agreed diagnostic laboratory methods and requirements for the production and control of vaccines and other biological products for all OIE-listed diseases including RVF (Chapter 2.1.14). In particular, it specifies prescribed tests for health screening for international trade or movement of animals. The chapter on RVF provides information on requirements for the production and control of vaccines, based on classical live-attenuated virus, as well as information on vaccines based on inactivated whole virus. The second-generation vaccines, MP-12 and Clone-13 (see below), are mentioned, but requirements of these vaccines are not yet described in the chapter. The *Terrestrial Manual* also contains eleven introductory chapters that deal with a variety of general subjects of interest to veterinary laboratory diagnosticians. Chapter 1.1.8 on principles of veterinary vaccine production is particularly relevant for this workshop. With the objective of ensuring the production and availability of uniform and consistent vaccines of high quality, the chapter describes require-

ments and procedures intended to be general in nature and consistent with published standards that are available for guidance in the production of veterinary vaccines.

In its network of reference laboratories and collaborating centres, the OIE and its members can rely on two OIE Reference Laboratories, located in France and South Africa, for support and expertise.

Finally, different communications on RVF have been done by the OIE and/or in partnership with OIE through publications (e.g. *OIE Scientific and Technical Review*), and regional meetings and workshops (e.g. Workshop on RVF Control and Preventive Strategies in the Middle East and the Great Horn of Africa, Cairo, Egypt, 2007; Laboratory training course on RVF diagnosis, Dar es Salaam, Tanzania, 2008; and Regional Seminar on Re-emergence of Rift Valley fever in Southern Africa: how to better predict and respond, Bloemfontein, South Africa, 2009).

VIEW FROM THE EUROPEAN COMMISSION

Ramunas Freigofas

On 11 October 2005, the European Food Safety Authority (EFSA) published a scientific opinion paper called "*The Risks of Rift Valley Fever Incursion and its Persistence in the Community*" (http://www.efsa.europa.eu/fr/efsajournal/doc/238.pdf). This report assessed three major issues: the risk of introduction of RVFV into the European Union (EU), the risk of exposure to RVFV and the risk of RVFV persistence in the EU. It was concluded that early warning systems should be established. Countries where RVF is endemic should be monitored, and sentinel herds should be established in countries most at risk, predominantly by wind-borne mosquito vectors. The ecology of mosquito vectors must be studied so that the risk of persistence can be better estimated, and effective vector control strategies can be implemented. Veterinarians should be trained to recognize the disease in the field, and contingency plans should be established to be able to respond adequately to a future RVFV incursion. Sufficient laboratory capacity and staff must be available to handle RVF diagnostics, and effective vaccines for both livestock and humans should be developed and made available.

The European Commission (EC) recognizes the threat of a future RVFV incursion into the EU and its potential consequences for the community. This recognition is exemplified by the establishment of the EC-funded Sixth Framework projects: Emerging Diseases in a Changing European Environment (EDEN) [http://www.eden-fp6project.net] and Network of Excellence for Epizootic Disease Diagnosis and Control (EPIZONE) [http://www.epizone-eu.net/default.aspx]; and the Seventh Framework projects: International Network for Capacity Building for the Control of Emerging Viral Vector Borne Zoonotic Diseases (ARBO-ZOONET) [http://www.arbo-zoo.net/about_2/index.html] and Biology and Control of Vector-Borne Infections in Europe (EDENext) [http://www.edenext.eu/]. In all of these programmes, RVF is an important research focus.

In conclusion, the EC recognizes RVF as a real threat to the EU, and acknowledges the need for standardized diagnostics and vaccines that should be established by coordinated international activities. Nevertheless, the European Commission's Directorate General for Health and Consumer Policy document, *Expert opinion on vaccine and/or diagnostic banks for major animal diseases* (SANCO/7070/2010) does not list RVFV as a pathogen for which it is recommended to stockpile vaccines. It is important to note, in this respect, that the

experts who attended the current meeting recommend the establishment of a global RVF vaccine stockpile for emergency vaccination campaigns in all countries at risk.

VIEW FROM THE USDA

William C. Wilson and Cyril G. Gay

The United States Department of Agriculture (USDA) acknowledges the threat of a possible future RVFV incursion into the United States. Currently available commercial vaccines from South Africa and Egypt are considered inadequate for application as emergency vaccines in the United States, and, therefore, the USDA supports the development of alternative vaccines. Supported by the USDA, the Arthropod-Borne Animal Diseases Research Unit (ABADRU, Manhattan, KS, United States of America) has developed enzyme-linked immunosorbent assay (ELISA) tests based on the N, Gn and NSs proteins that, in conjunction with virus-neutralization tests (VNT), can be used to measure immune responses elicited by vaccine candidates. ABADRU has also developed real-time RT-PCR tools to detect and quantify viral RNA. One of the vaccine candidates that is being evaluated with USDA and the United States Department of Homeland Security supported by ABADRU, is the MP-12 vaccine (See section entitled The MP-12 virus). Animal models that are available for studies through the USDA and its partners are a hamster cytokine model at the Colorado State University, young animal models at the Canadian Food Inspection Agency (CFIA) and ABADRU and a larger-scale young animal model at the Kenya Agricultural Research Institute (KARI). The USDA has the objective of evaluating the potential of next-generation RVF vaccines to prevent transmission of the virus in the target animal species, with the ultimate aim of preventing the spread of RVF virus to human populations. The USDA acknowledges the need for a United States emergency stockpile of a selected RVF vaccine for veterinary application, and the added value of a DIVA vaccine for this purpose. Of note, is the need to stockpile vaccines that have been designed for the purpose of controlling disease epizootics. It is important that the development and selection of vaccines suitable for stockpiling be based on a gap analysis of the available scientific information and countermeasures.

VIEW FROM GALVmed

Baptiste Dungu

The objective of the Global Alliance for Livestock Veterinary Medicines (GALVmed) is to make a sustainable difference in access to animal health medicines by impoverished livestock keepers in developing countries. Specifically, the minimum targets are to develop, register and launch four to six vaccines, diagnostic products and pharmaceuticals by 2015. These objectives are to be achieved by collaborating with partner agencies in developing countries to ensure sustainable research, production, delivery and access of these products to poor livestock keepers. The GALVmed activities include the prioritization of diseases that have the highest impact on poor livestock keepers to understand the key barriers to developing new products that will reduce disease impact in developing countries. GALVmed also seeks to identify assets, to fill key expertise gaps and, finally, to plan and manage animal health development projects.

Important points of concern that are recognized by GALVmed are the limited continuous vaccination in African countries due to the cost of vaccination, the safety concerns applicable to the classical live-attenuated Smithburn vaccine, the irregularity of outbreaks

and the lack of a vaccination policy issued by governments. Overcoming these concerns not only requires the availability of improved vaccines, but improved vaccination strategies as well.

The ideal RVF vaccine should be safe to produce, safe to all animals regardless of the physiological stage, should have no residual virulence, should not provide a risk of introduction into the environment (shedding, persistence in animals, etc.) and should not be capable of transmission to humans or other species. The vaccine should provide protection in all susceptible species and provide a quick onset of immunity, in young animals, also. Immunity should be long-lived and the vaccine should stop transmission by preventing virus amplification in the vaccinated animal. The vaccine should be easy to administer, provide protection after a single vaccination, be suitable for stockpiling and cost effective for both producers and users.

Vaccination strategies that are considered by GALVmed can be divided into strategies for endemic regions and strategies for areas with first introductions. For application in endemic areas with irregular occurrence of RVF, the use of multivalent vaccines is considered to be advantageous, encouraging uptake of vaccination and reduction of costs. Development of multivalent vaccines that are supported by GALVmed include the vector vaccines based on capripox viruses (CPV) (See section entitled Capripox viruses as vaccine vectors) and the combination vaccine consisting of the Clone-13 and the lumpy skin Neethling vaccine strain, freeze-dried together. Potentially, these vaccines can be used to control CPV infections (lumpy skin disease [LSD] in cattle, and sheep and goat pox in these two livestock species) and concomitantly to provide immunity to RVF.

To control epidemics in previously free zones, a non-replicating vaccine is preferred that provides rapid onset of immunity, even in young animals. Furthermore, it would be advantageous if such a vaccine would enable DIVA to monitor spread of the virus both within and outside the vaccinated population.

GALVmed supported the launch of the Clone-13 vaccine (See section entitled The Clone-13 virus), which is now used in the field in South Africa, and encourages the establishment of a bank of this vaccine, initially aimed at covering southern and eastern Africa. Field trials with Clone-13 in Kenya and Senegal are planned. In addition, GALVmed is supporting further development of the CPV-vectored vaccines that can be used as multivalent vaccines, together with the registration trials for the combination RVF-LSD vaccine. Finally, GALVmed is aiding the development and establishment of a pen-side diagnostic test from the Agricultural Research Council-Onderstepoort Veterinary Institute (ARC-OVI), by funding the effort and bringing technical expertise from contract research organizations. It is clear that GALVmed not only actively supports the development of novel vaccines and diagnostics, but is also involved in bringing these control tools to poor livestock keepers in the field.

VIEW OF THE ANIMAL HEALTH INDUSTRY

Barbara Freischem

International Federation of Animal Health (IFAH) acknowledges the disadvantages of the classical RVFV vaccines and is following the experiences with the novel Clone-13 vaccine with great interest. IFAH underscores that the safety of any potential RVF vaccine is critical. In view of the known effects of current vaccines, there should be focus on reversion

to virulence, safety in pregnant animals, reassortment potential as well as environmental safety, including the potential uptake by vectors.

There is no shortage of promising experimental vaccines, but there is limited follow-through from research and development to production. A relevant consideration for this lack of follow-through is the limited marketability of a commercial RVFV vaccine. To stimulate the marketing of specific vaccines, it is important to ensure a "level playing field". Characteristics should be defined for new vaccines with respect to safety, efficacy, stability in storage for bulk and manufacturability of the final product, including capacity for "surge production" and DIVA capability. Furthermore, it is important to provide incentives for vaccine manufacturers either through direct public funding for vaccine development, or, more effectively, by creating dependable markets through the establishment of vaccine banks. These vaccine banks could also be created in concerned countries or regions, and be deployed ad hoc to help fight outbreaks elsewhere.

In conclusion, it is important to agree on standards for new vaccines, provide incentives for manufacturers (e.g. research funding, creation of markets) and find new ways of working together. These goals could be achieved by a consortium approach based on a public-private partnership established for the good of all.