Revision of the RVF chapter in the OIE
Terrestrial Manuel

D.Goovaerts, IFAH

Mombasa, November 14th 2012

Meeting of OIE *ad hoc* group on RVF

- Paris meeting October 9-11th
- Chapter 2.1.14 of the Manual on Diagnostics Tests and Vaccines for Terrestrial Animals
- Taking into account updated version instructions for authors of Biological Standards Commission in 2012

General method

- Review based on existing 2.1.14 chapter on RVF
- Chapter on Introduction
- Chapter on Diagnostic Techniques
- Chapter on Requirement of Vaccines for Terrestrial Animals

Diagnostic methods

Detailed protocols on antigen detection

- **Cell-culture isolation**
- **Agarose gel-based RT PCR**
- **Real-time RT-PCR**
- **Antigen capture Elisa**

Detailed protocols on antibody detection

- **IgM capture Elisa**
- **Indirect IgG Elisa**
- **Virus Neutralization test**

Test methods[1] available and their purpose

Method	Purpose			
	Surveillance	Laboratory confirmation of clinical cases[2]	Humoral immune status in individual animals or populations post-vaccination	Population free from infection
Isolation in cell cultures	+	+++[5]	na	–
Isolation in suckling mice[4]	+	+	na	–
Polymerase chain reaction	+[3]	+++	na	–
Antigen detection	+[3]	++[5]	na	–
Histopathology	–[3]	++	na	–
Enzyme-linked immunosorbent assay	+++	++[5]	+++	+++ (in non vaccinated animals)
Virus neutralisation	++	++[5]	+++	+++ (in non vaccinated animals)

Test methods available and their purpose (footnotes)

1.This table provides general guidance on the use of the diagnostic tests methods. For a definitive interpretation, combined epidemiological, clinical, laboratory information should be evaluated carefully.

2. Laboratory confirmation of clinical cases should require a combination of at least two positive results from two different diagnostic tests methods: either positive for virus/viral RNA and antibodies or positive for IgM and IgG.

3. These test methods can be used for specific purposes, for example: surveillance of abortion.

4. Not preferred for animal welfare and safety reasons.

5. Depending of the stage of the disease, virus and/or antibodies will be detected.

6. Histopathology is particularly useful if immunohistochemistry can be done

Requirements for vaccines

Vaccines currently considered:

- **Live attenuated Smithburn RVF**
- **Live attenuated Clone-13 RVF vaccine**
- **Inactivated RVF vaccines**
- **Experimental human vaccine TSI-GSD-200**

Specifics on Manufacturing and batch testing

- **No virulent strains to be used as inactivated vaccine seeds**
- **Details on seed characteristics**
- **Details on Methods of Manufacturing (in process controls and inactivation controls added)**

Requirements for vaccines (continued)

Requirements for authorization

- Safety of live vaccines (reverse to virulence, shed and spread, overdose, young and pregnant animals)
- Safety of inactivated vaccines (overdose)
- Efficacy (young and pregnant animals)

Detailed guidelines and protocols provided

- As much as possible in line with international guidelines (e.g. Pharmacopeia)
- Scientifically designed protocols
- Primarily based on sheep


»THANK YOU

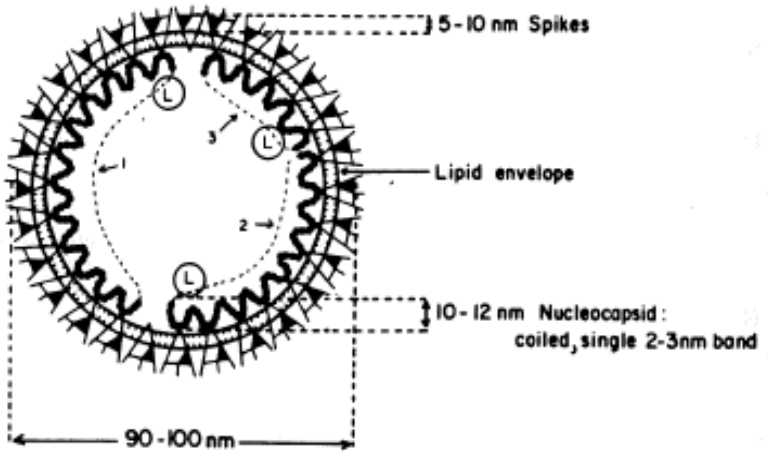
Vaccine Research on RVF

D.Goovaerts, IFAH

Mombasa, November 14th 2012

RVF Vaccine Development, Progress and Constraints

Proceedings of GF-TAD meeting January 2011 Rome FAO



Vaccine Developments and Research What is needed?

a. Safety

- no reversion to virulence;
- lack of abortion in vaccinated animals; and
- non-teratogenic.

b. Efficacy

- prevention of viremia;
- rapid onset of immunity;
- long-lasting immunity;
- prevention of abortion on challenge;
- prevention of clinical disease;
- produce immunity in young animals;
- target key susceptible ruminant species; and
- single-dose regimen.

Potential vacci

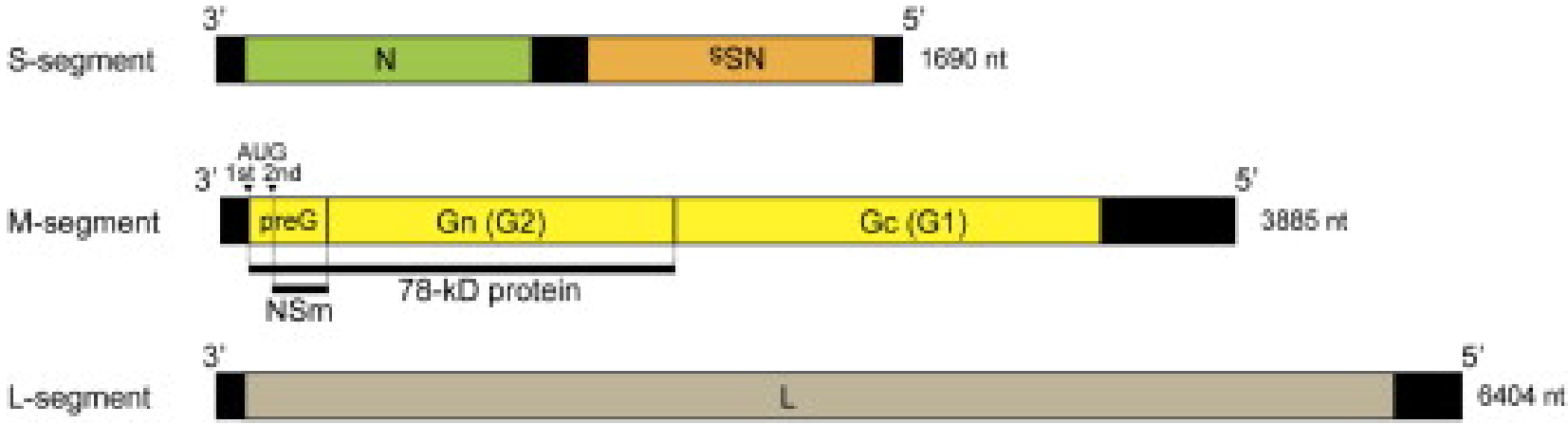
RVF vaccines

Live attenuated
- Smithburn
- Clone-13

Inactivated
- Smithburn
- based on virulent strains

Human inactivated vaccine TSI-GSD 200

Rift valley fever RNA genome



Tetsuro Ikegami

Molecular biology and genetic diversity of Rift Valley fever virus

Antiviral Research Volume 95, Issue 3 2012 293 - 310

http://dx.doi.org/10.1016/j.antiviral.2012.06.001

Vaccine Research candidates

Live attenuated
- MP-12
- R566
- Δ NSs/Δ NSm
- MP-12 Δ NSm, MP-12 Δ NSm

Vector vaccine strains
- rLSD RV (Gn, Gc)
- rKS-1/RVFV (Gn, Gc)
- rKS-1/RVF (NSm, Gn)
- NDV RVF (Gn) and NDV RVF (Gn, GC)

Subunit vaccine
- Based on GN ectodomain

Vaccine Research candidates (continued)

DNA vaccine

- plasmid DNA (Gn and Gc) or (N)
- plasmid DNA (Gn and C3D complement)
- plasmid DNA combination with MVA vector
- combination with alpha virus replicon vector

Virus like particles (VLP)

- Based on Gn and GC, with or without N
- Chimeric VLP with gag of Moloney Murine leukemia virus
- Mammalian and insect cell production systems
- Transcriptionally active VLP's

MP-12

- 12 passages with 5-fluorouracil from wildtype strain ZH548
- Encodes virulent S segment and attenuated M and L
- Safe in ruminants and humans
- Abortion and teratogenic in early pregnancy sheep

- Advantages;
  Live vaccine, efficacy
- Disadvantages
  Safety in early pregnancy, risk of reversion, point mutations
  No DIVA potential

R566

- Reassortant of Clone 13 (NSs deletion) with MP-12 (attenuated M and L segments), efficacy mice and sheep demonstrated

- Advantages;
  - Live vaccine, efficacy
  - At least attenuated as Clone 13 with less reassortant risk
  - DIVA potential

- Potential disadvantages?
  - Yields?, effective dose?

ZH501 Δ NSs/Δ NSm
MP-12 Δ NSm

- Efficacy in mice and sheep demonstrated

- Advantages;
  Live vaccine, efficacy,
  DIVA potential (NSs and NSm)
  Less likely reversion to wildtype

- Disadvantages
  Mutant based on ZH 501 classified as select agent in US

Vector vaccines

- Poxvectors, NDV vector, efficacy mice and sheep demonstrated

- Advantages;
  - Live vaccines, potential dual immunity
  - DIVA potential
  - Safety (no RVF)

- Potential disadvantages
  - Vector immunity, multiple vaccinations needed? DOI?

Subunit vaccines

- Baculo expressed, insect cell Sf9 expression system, efficacy in mice and lambs demonstrated

- Advantages;
  Safe, no RVF virus needed for production, DIVA potential

- Potential disadvantages
  Immunity comparable to inactivated vaccines? multiple vaccinations needed? DOI?

DNA vaccines

- Plasmid DNA encoding Gn, GC or combination with C3 or MVA. Efficacy in mice demonstrated

- Potential advantages;
  Safe, thermostable

- Disadvantages
  Multiple vaccinations needed, complicated immunisation protocols, price

Replicon vaccines

- Non-spreading RVFV replicons in BHK, BSR cells, Alphavirus or adenovirus replicons. Efficacy in mice and sheep (non-spreading) demonstrated

- Potential advantages;
  Safe, no RVF virus for production

- Potential disadvantages
  Multiple vaccinations needed? Commercial production systems

Conclusions

- A large number of different RVF vaccine candidates exist. Some candidates are currently further developed for animal or possibly human vaccines.
- Depending on the approach each candidate has its individual advantages or disadvantages in the light of use in the field.
- Aspects to be considered for further vaccine development are animal safety and efficacy, but equally commercial production aspects, environmental and human safety aspects and costs


»THANK YOU