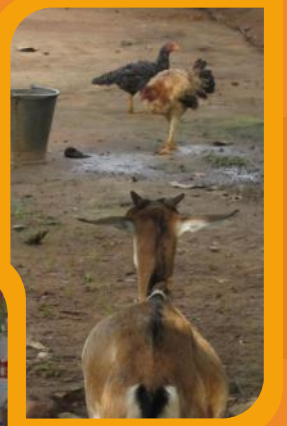
GALVmed

Protecting livestock, saving human life

Rift Valley Fever

Strategy for RVF vaccination





Dr Victor Mbao

Mombasa, Kenya
November 2012

Layout

- Impact of RVF
- RVF control & importance of vaccination
- RVF vaccines quick overview: current & those in the pipeline
- Vaccination strategies & options
- GALVmed contribution to improved vaccination strategies

Rift Valley Fever and its impact

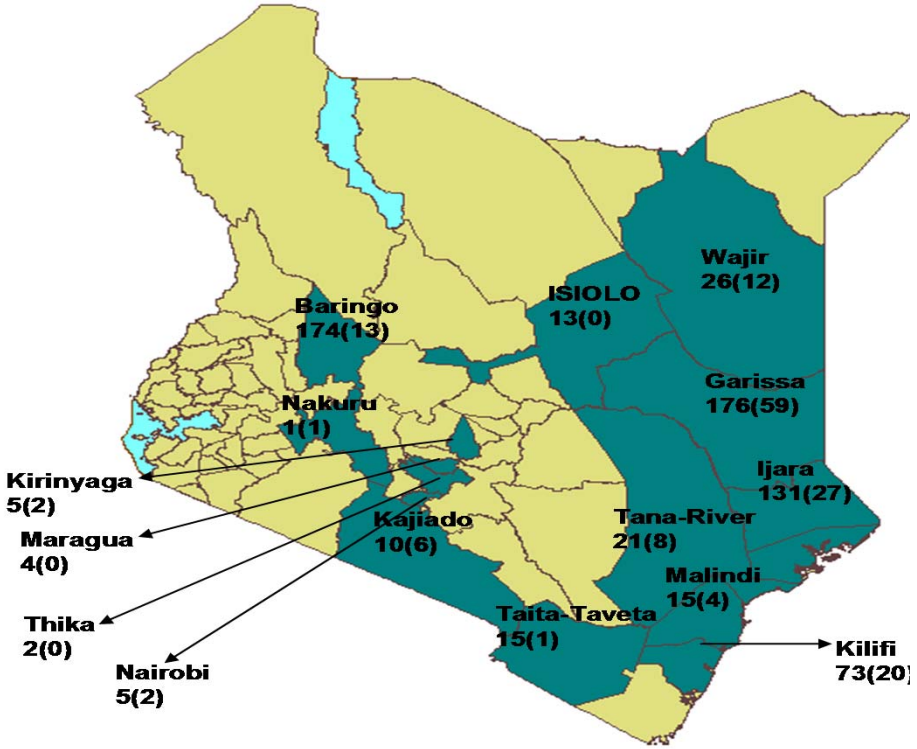
• Localised in Africa, spread to the Middle East in 2000. Considered a big threat to other regions including Europe. Included in the list of potential biological warfare agents.

• 2007 outbreak in Kenya & Tanzania: more than 300 human fatalities, thousands of mortality in livestock. Destroyed meat industry.

• Kenya: cost of livestock outbreak (animal productivity, government spending): US$ 54m. In Garissa region, 89% of the households reported that RVF had affected their herds, 18.5% reported a case of human RVF in their own household, 20-60% loss of work productivity reported in surviving cases

PUBLIC HEALTH IMPACT

• Egypt 1997: 200000 human cases, 600 reported fatalities
• Mauritania 1987: over 300 fatalities
• Sudan 2007-7008: 738 human cases, 230 deaths
• South Africa 2010: 242 lab-confirmed human cases with 26 deaths
• Mauritania 2010: 63 human cases, 13 deaths



RVF control

- Epidemics result from the synergy of at least three factors which can vary considerably:
  - (i) the presence and circulation of the phlebovirus by **mosquito vectors**;
  - (ii) the number of mosquito breeding sites and hatching frequency, two parameters which are both highly dependent on **environmental conditions**, particularly rainfall events; and
  - (iii) the **distribution of domestic animal hosts**, essentially ruminants (goats, sheep and cattle), vulnerable to increased vector/host contacts at night.

- Vector control difficult to implement
- Complicating factors: Cyclical nature of the disease; variable inter epizootic periods;
- Use of sentinel animals highly dependent on good diagnostic methods (not always available)

- **Essentially reliant on surveillance & vaccination**

GALVmed
Protecting Livestock – Saving Human Life

GALVmed

Protecting livestock,
saving human life

RVF vaccines & vaccination

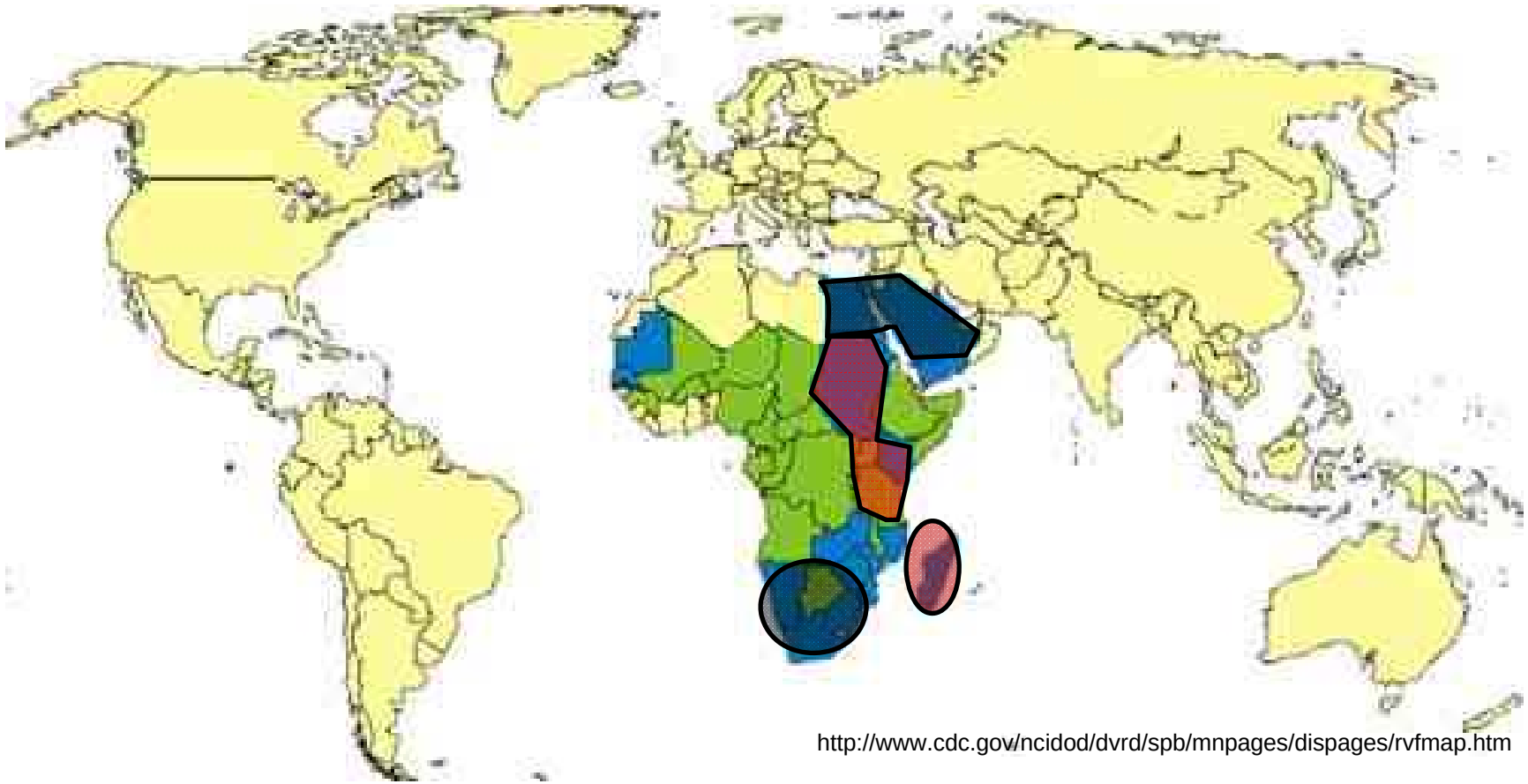




RVF vaccines

- 2 types of vaccines currently used
  - Live attenuated based on Smithburn strain: South Africa & Kenya
  - Live attenuated based of Clone 13: South Africa
  - Inactivated: South Africa & Egypt
- Several initiatives for new vaccines
- Vaccination not practiced in some enzootic regions

RVF distribution and Vaccination



http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/rvfmap.htm

Yearly or regular **Outbreak-associated**

GALVmed
Protecting Livestock – Saving Human Life

RVF situations and control approaches

RVF Situation	Examples of countries	Current Control strategy
Endemic with regular outbreaks	Kenya, Tanzania, Egypt, Senegal, Mali	Vaccination at sign of outbreak Egypt: continuous vaccination No vaccination
Endemic with sporadic/re-occurring outbreaks	South Africa, Saudi Arabia	Continuous/yearly vaccination
Free high risk	Middle East, North Africa	(Active) surveillance
Free low risk	Europe, Americas	Surveillance, talks of vaccine banks

Currently no vaccination in West Africa

- Senegal & Mali (continuous serological evidence); Mauritania (recent outbreaks)
- No vaccination due to concerns about vaccine safety

Limited continuous vaccination of livestock in Africa:

- Cost of yearly vaccination
- Safety concerns: difficulties to determine physiological stages of pregnant animals
- Irregularity of outbreaks (years without signs of outbreak)
- Policy aspects: vaccination not always covered by government

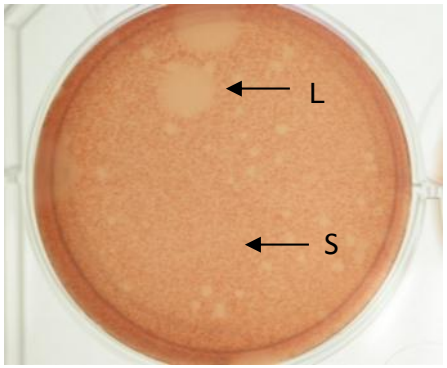
Ideal RVF vaccine (Product profile)…

- *Generic characteristics*
  - **Safety**
    - Safe to produce
    - Safe to all physiological stages of animals
    - No residual virulence
    - No risk of introduction into the environment (shedding, persistence in animals etc.)
    - No risk of spread to human or other species
  - **Efficacy**
    - Protection of all susceptible species
    - Quick onset of protective immunity, including in young animals
    - Long lasting immunity
    - STOP TRANSMISSION: prevent amplification of RVFV in ruminants
  - **Vaccination**
    - Cost effective for producers and users
    - Single vaccination
    - Ease of application
    - Suitable for stockpiling (vaccine or antigen bank) and quick availability

- *Endemic regions*
  - **Continuous vaccination: yearly vaccination of susceptible livestock**
    - Need to know how many vaccinations may be required to build a life long immunity
  - **Efficacy**
    - Solid protective immunity after 1 vaccination

- *Free regions*
  - Quick onset of protective immunity
  - Protective in young animals and possibly newborn naïve animals
  - Sterilizing immunity
  - DIVA

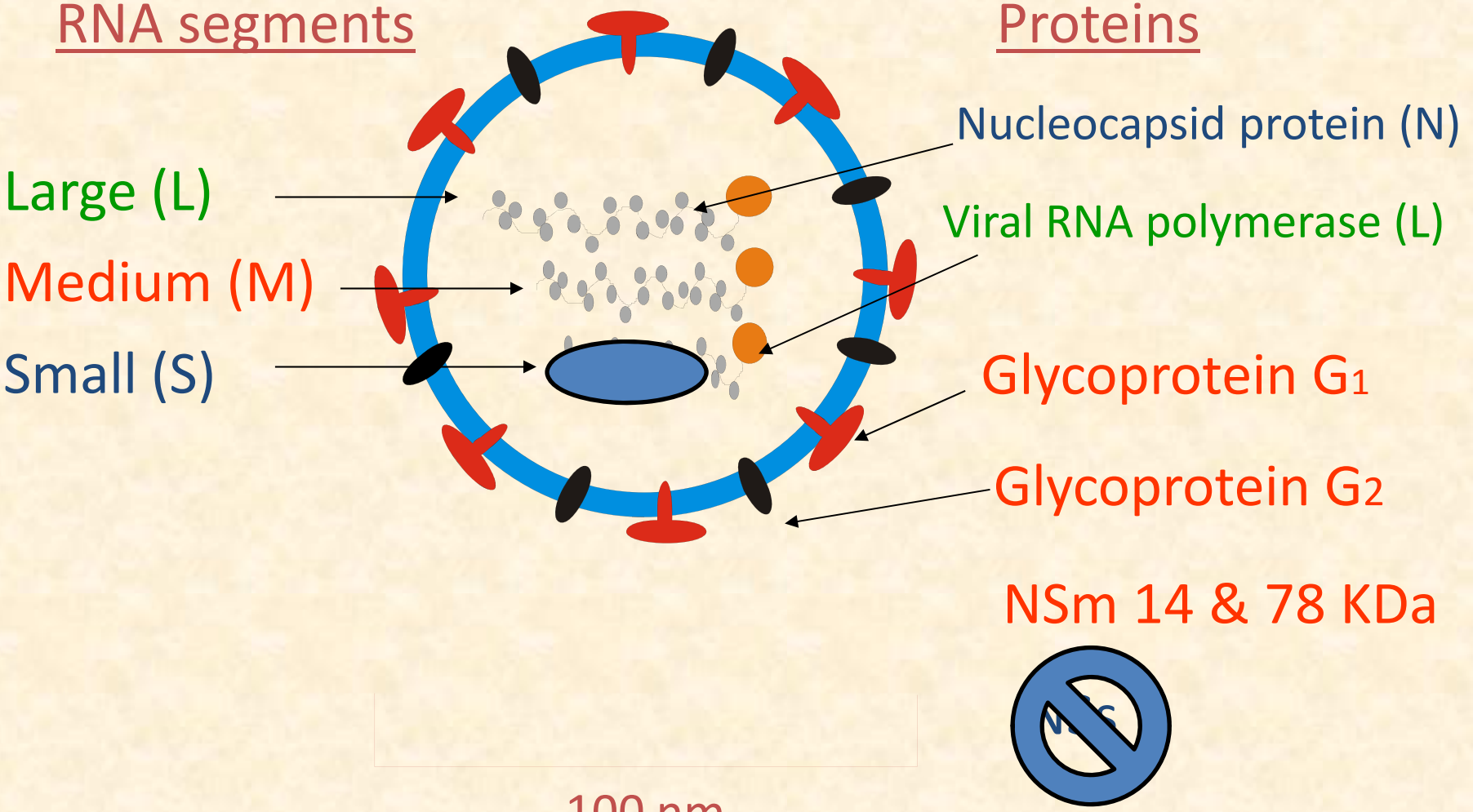
RVF traditional Vaccines

VACCINE	STRAIN	ADVANTAGES	DISADVANTAGES
Inactivated (OBP, VSVRI) 	Pathogenic field strain	● Safe in pregnant animals ● Can be used in outbreak	● Short term immunity ● Multiple vaccinations required ● Risk of handling virulent strain during production ● Colostral immunity present but poor ● Sheep better protected than cattle ● 100 x more antigen required than for live attenuated ● Longer production lead time
Live Attenuated (OBP, KEVEVAPI) 	Smithburn	● Highly immunogenic ● Single dose ● Good immunity (within 21days) ● Effective and easy production ● Safer production ● Large batches: >4m doses	● Potential residual virulence ● Teratogenic for foetus ● Potential risk of reversion to virulence ● Not advisable for use in outbreaks ● Theoretical possibility of transmission by mosquitoes (?)

New vaccines & Candidates evaluated in Target animals

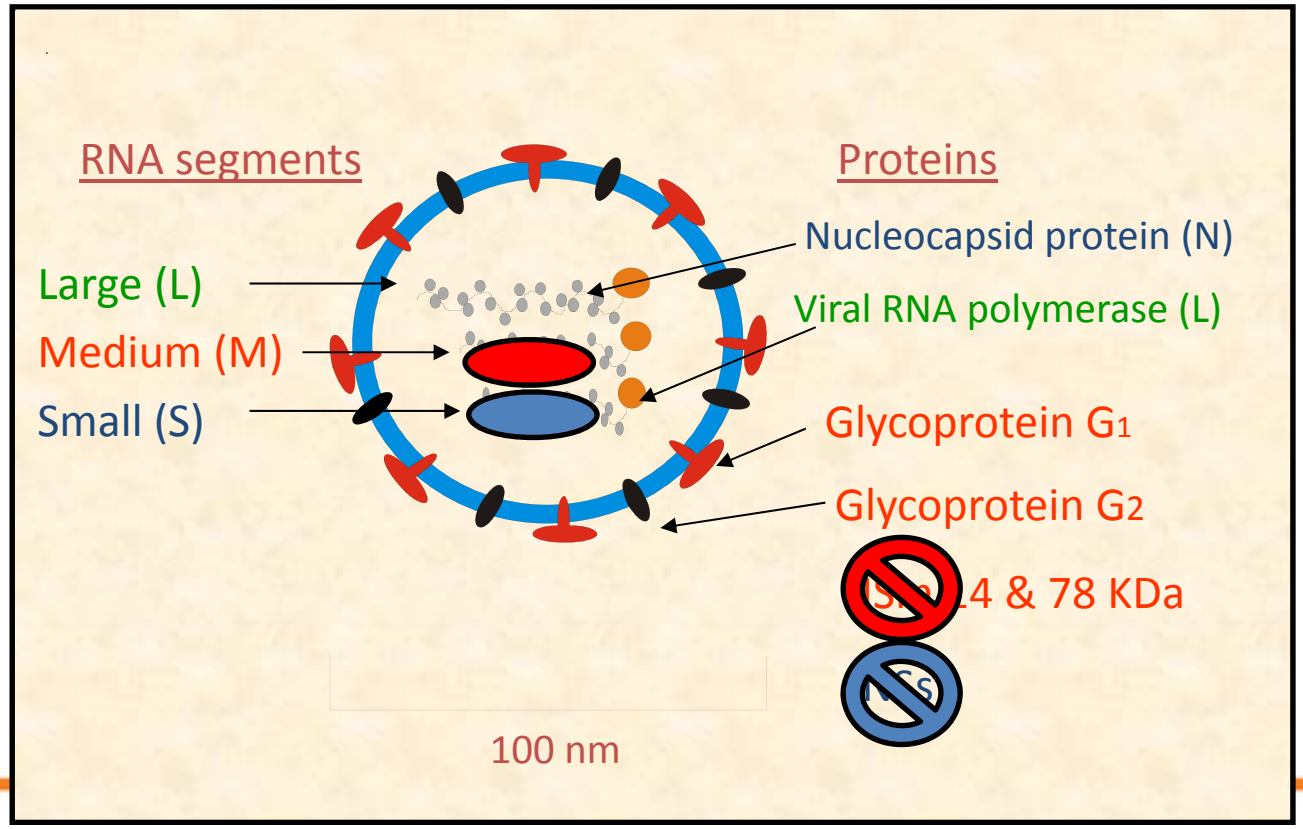
VACCINE	STRAIN	ADVANTAGES	DISADVANTAGES
Live attenuated	MP12	● Effective and good protective immunity ● Easy and safe to produce ● Better safety than Smithburn in most species and age groups	● Teratogenic for foetus ● Abortion in early pregnancy ● Not available commercially
Avirulent natural mutant	Clone 13	● Good protective immunity in sheep & cattle ● Safe in pregnant animals ● Safe in outbreak ● Produced as standard freeze-dried live vaccine ●More than 19 million doses used ● Safe, effective and easy to produce ● Possible DIVA (NSs ELISA?) ●Registered & used extensively in South Africa	●Only registered to date in South Africa & Namibia ●Large scale field data in other regions needed ●No evidence of DIVA to date
Recombinant Lumpy skin virus expressing RVF	LSD Neethling strain expressing RVF glycoproteins	● Dual vaccine ● Safe in all animals ● DIVA ● Long shelf life (LSD) ● More thermo-tolerant than others ● Efficacy shown in animal trials	● Only proof of concept to date ● Currently grown in primary cells ● Possible GMO regulation challenge (?)

RVFV Clone 13 deletion



Candidates evaluated in target animals (contd.)

VACCINE	STRAIN	ADVANTAGES	DISADVANTAGES
Recombinant-multiple deletion virus	● Reverse genetic generating RVF virus with double deletions in NSs & NSm *Bird et al., 2008*	● Less prone to reassortment ● Live vaccine ● DIVA: negative marker ● Easy and safe to produce	● No published proof of concept in target animals



Candidates not evaluated in target animals

VACCINE	STRAIN	ADVANTAGES	DISADVANTAGES
Avirulent (lab generated) reassortant	R566: deletion in the M and S segments	● Safer due to deletions in all 3 segments, may never reassort ● Protection in mice	● Never tested in target animals ● More stringent regulatory requirements for registration (?)
Virus-vectored RVF vaccines	Canarypox-expressing RVF proteins Heterologous virus expressing GP (Kortekaas *et al., 2010)*	● DIVA: Positive & Negative marker ● Live vaccine ● Replication deficient ● Multivalent: suitable where annual vaccination is a challenge ● Potential for improved thermostability	● No registered vaccine yet available ● No large scale field data yet available, although extensive analytical data generated
Virus like particle (VLP)	VLP made of envelop proteins (GP) *Naslund et al., 2009*	● Potentially very safe ● Immunity similar to live vaccine, but no replication ● DIVA	● No proof of concept in target animals ● Large scale production might be a challenge
DNA	DNA priming + inact. Vaccine *Lorenzo et al., 2009* cDNA encoding GP *Lagerqvist et al., 2009*	● DIVA ● Potentially long lasting immunity ● Ability to enhance and modulate induced immunity	● Only incomplete protection demonstrated in mice ● Production challenges ● Regulatory challenges (use in food animals)

Vaccination strategies to be considered

- ***Endemic regions***
  - Yearly vaccination
  - Multivalent or combination vaccine, consisting of RVF antigen & antigen of a vaccine likely to be used regularly
    - RVF+LSD; RVF+ s/g pox; RVF + CBPP
  - Thermostability
  - Use of sentinel animals: need for good diagnostics capability & effective
  - Emergency preparedness: Strategic reserve: Vaccine or antigen bank
- **Possible suitable candidates:**
  - Multivalents including a safe deleted RVFV vaccine

- ***Free regions/ Preventing epidemics***
  - Elimination of possible source of re-infection
  - Use of non-replicating antigen vaccine
  - Early and rapid onset of immunity, even in young animals
- DIVA
  - Positive marker: export of animals from endemic countries
  - Negative marker: for detecting infection
- **Possible suitable candidates:**
  - Replication deficient, deleted, marker vaccine

Suitable vaccination strategies more critical than improved vaccines

GALVmed
Protecting Livestock – Saving Human Life

GALVmed

Protecting livestock,
saving human life

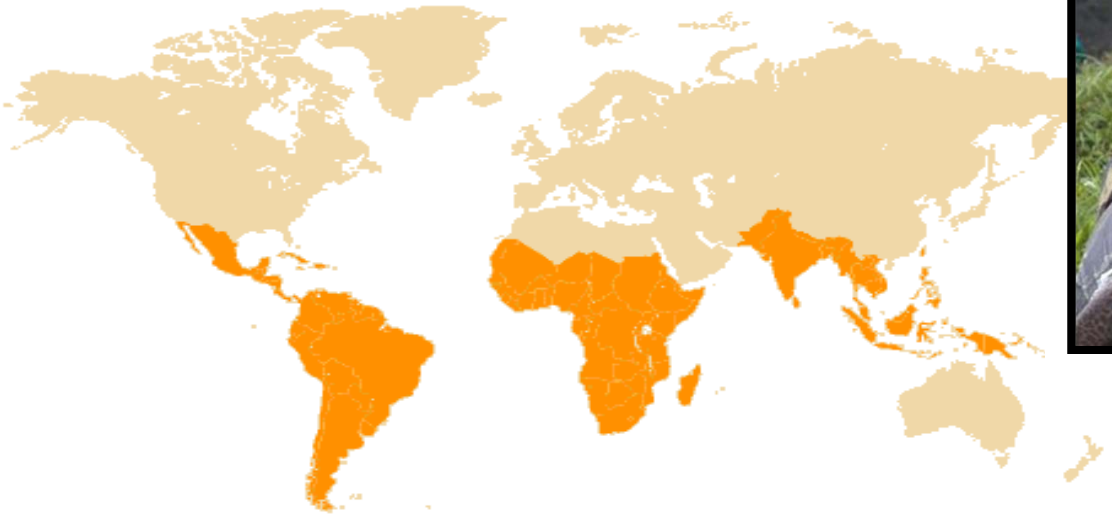
GALVmed RVF interventions





GALVmed - GLOBAL ALLIANCE LIVESTOCK VETERINARY MEDICINES

- An **Animal health Product development & access Partnership** organisation
- A not-for-profit **Public-Private Partnership** – registered charity
- Sponsored by the UK Department for International Development (**DFID**), and with projects funded by BMGF, DFID and EC.
- **Pro-poor focus:** working with key partners to make a **sustainable** difference in access to animal health products for poor livestock keepers



GALVmed RVF interventions

What are we trying to achieve?

	MA 6 - Rift Valley Fever
A	**Multivalent vaccine with LSD/Sheep & goat pox to increase uptake**
1	Process development of recombinant and/or combination vaccine
2	Vaccine safety and efficacy evaluation
3	Vaccine registration
B	**Monovalent emergency vaccine**
4	Field evaluation selected candidate
5	Facilitate registration
6	Support mechanisms for vaccine stockpiling at African level
C	**Pen side diagnostics**
7	Validate test according OIE procedures
8	Select manufacturing partners
9	Select distributing partners
10	Assay validation in one country
11	Start assay dissemination and distribution

Rift Valley Fever – Key achievements

Multivalent vaccine (RVF-LSD)

- *Focus on Combination RVF C13- LSD* (OBP - Registration trials):
  - PoC obtained. Registration trials ongoing

Monovalent vaccine (RVF C13)

- Field trials to facilitate registration in Kenya and Senegal
- Strategic reserve (vaccine bank)

Penside test:

- Prototype produced & under evaluation

- Market studies ongoing
- RVF access strategy

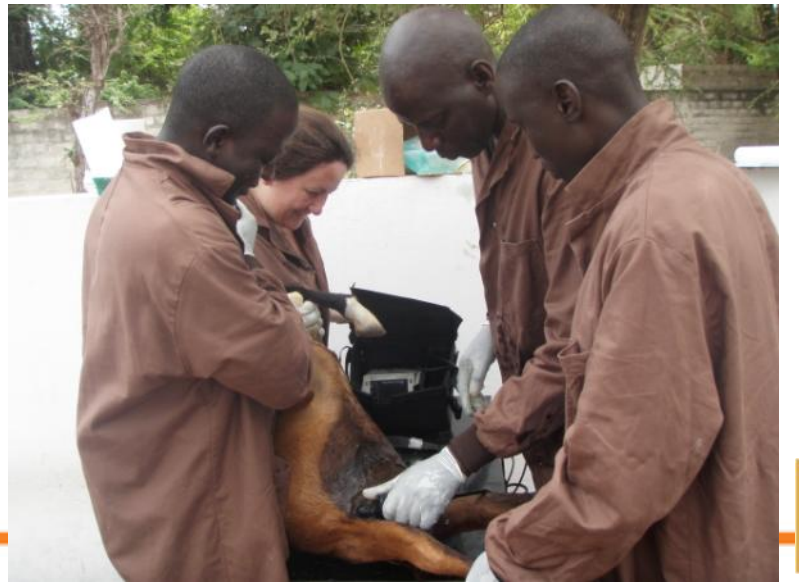
GALVmed
Protecting Livestock – Saving Human Life

RVF: Lab trial in Senegal

To date: no vaccination due to safety concern with Smithburn & limited efficacy of inactivated RVF vaccine

•Lab trial for safety, including pregnant animals, 42 goats and ewes.

• No differences for mean rectal temperatures, no clinical signs, and no injection site reactions. No evidence of transmission (control animals did not seroconvert).



GALVmed
Protecting Livestock – Saving Human Life

RVF: Field trial in Senegal

- Conducted in 3 sites with 267 sheep & goats.

- Animals were vaccinated in September 2011. So far, no adverse effect seen, good seroconversion.

- Animals were followed until October 2012 (last blood sampling). Samples being currently analysed.

Results to be used to facilitate registration in Senegal & hopefully other countries

RVF Clone 13 trial in Kenya

- In collaboration with CDC-Kenya, Vet services & OBP
- Field trial for registration
- 404 cattle, sheep and goats included in 3 separate sites, vaccinated in August 2011.
- (Please refer to poster)

GALVmed
Protecting Livestock – Saving Human Life

Progress up to date

Type	Products	Diseases	Progress on 5 September 2012				
			Exploratory	PoC	Development	Registration	Commercialisation
Vaccines	RVF Clone 13	RVF					
	Combination RVF-LSD	RVF, LSD, SP, GP					
	Recombinant RVF-LSD	RVF, LSD, SP, GP					
Diagnosis	RVF penside	RVF					

Completed | Ongoing | No-go

Availability strategy

Strategic reserve (Vaccine bank)

- Vaccine bank managed by vaccine manufacturer (EC-FMD vaccine bank model)
- Target Southern & Eastern Africa initially
  - SADC, EAC, COMESA, PANVAC, AU-IBAR partnership
  - Possibility of partnerships beyond Africa
- Stockpiling of frozen pre-lyophilization (stabilized bulk) vaccine antigen or bottled vaccine?
- Technical feasibility of the RVF Clone 13 strategic reserve *(Pretoria, December 2011)*
  - R&D activities identified
  - Size determination: risk mapping
  - Infrastructure of the bank
  - Policy aspects & countries participations

GALVmed
Protecting Livestock – Saving Human Life

GALVmed

Protecting livestock,
saving human life

Thank you!