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Rift Valley Fever: Preventing epizootics and epidemics by livestock vaccination

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Layout

- Current RVF distribution and vaccination adoption
- Epidemiological situation of RVF and control approaches
- Expected characteristics of the RVF vaccine
- Current & known candidate vaccines
- Vaccination strategies to be considered
- Way forward: research areas

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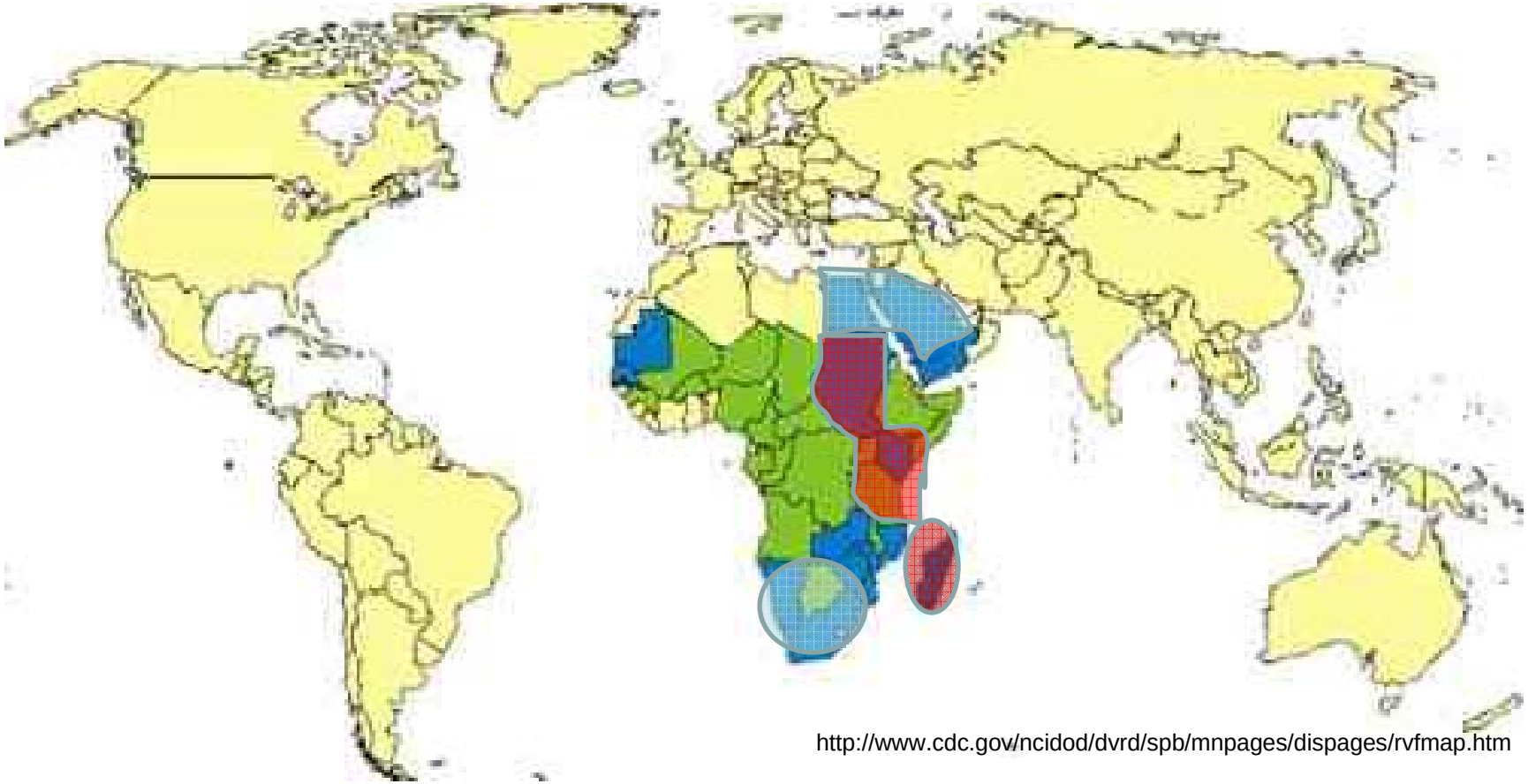
RVF distribution and Vaccination



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

Yearly or regular Outbreak-associated

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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 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

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

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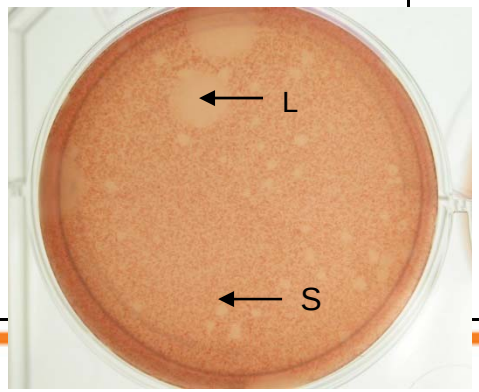
RVF Vaccines currently produced

VACCINE	STRAIN	ADVANTAGES	DISADVANTAGES
Inactivated (OBP, VSVRI) 	Pathogenic outbreak strains	■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 (?)

Epidemiology of Rift Valley Fever

Climatic factors
(heavy rainfall
associated with ENSO)

Human irrigation
practices

Endemic Cycle

Dry
Season

Temporary ponds

Rainy
Season

?

Floodwater *Aedes*
Neomelaniconion
Aedimorphus

Amplification

Epidemic Cycle

Floodwater *Aedes*
+ others ie *Culex* spp.
+ direct transmission
(aerosol, contact)

From: EFSA RVF risk assessment report 2005

Courtesy Prof. Dirk Pfeiffer

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Characteristics for the RVF vaccine

- **Generic characteristics**
  - **Safety**
    - Safe to produce (safe to all operators during production and evaluation)
    - Safe to all physiological stages (pregnancy, young 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

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Vaccine development

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 (*Hunter et al., 2001)* ■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 – ■Safe, effective and easy to produce ■Possible DIVA (NSs ELISA?)	■Under registration process ■No large scale field data yet available, although extensive analytical data generated
Avirulent (lab generated) reassortant	R566	■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 (?)
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 ■GMO regulation (?)

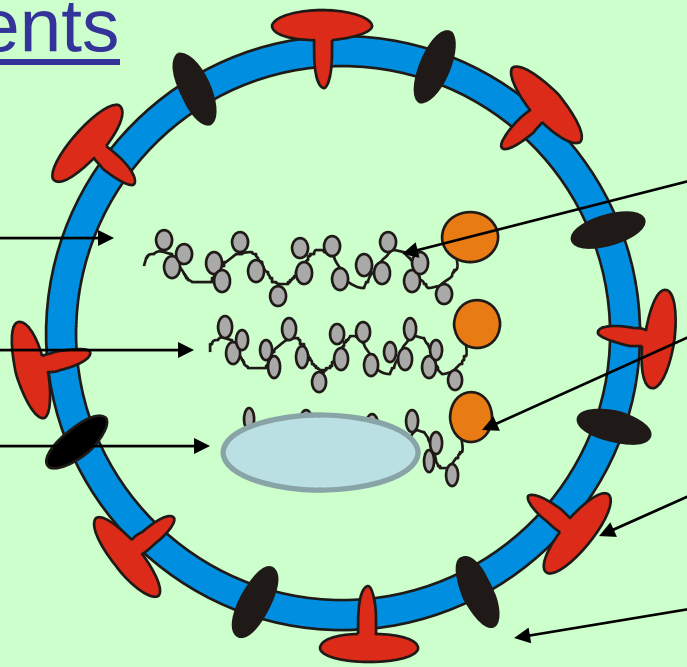
RVFV Clone 13 deletion

RNA segments

Large (L)

Medium (M)

Small (S)



Proteins

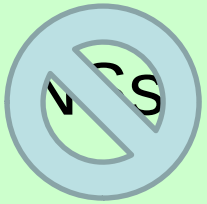
Nucleocapsid protein (N)

Viral RNA polymerase (L)

Glycoprotein G_1

Glycoprotein G_2

NS 14 & 78 KDa



100 nm

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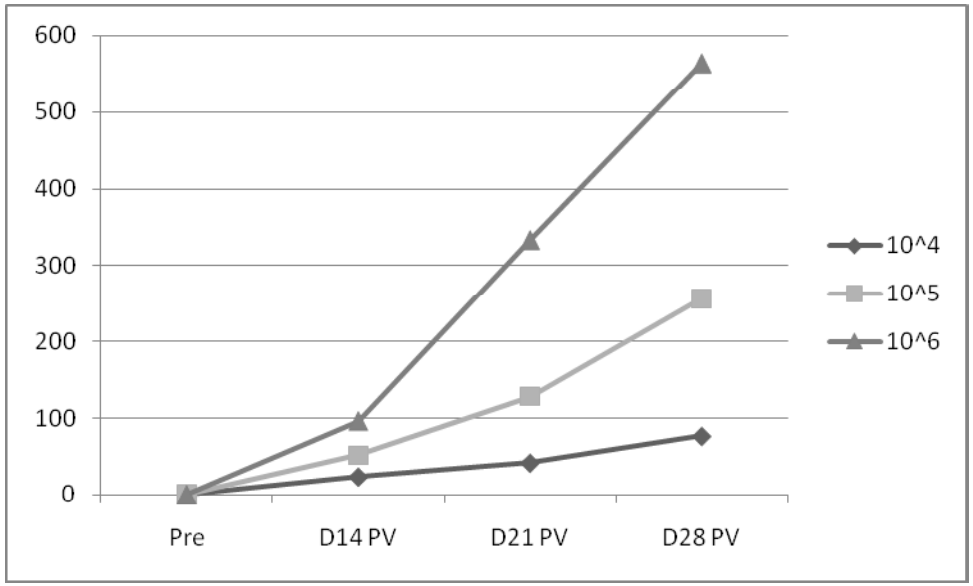
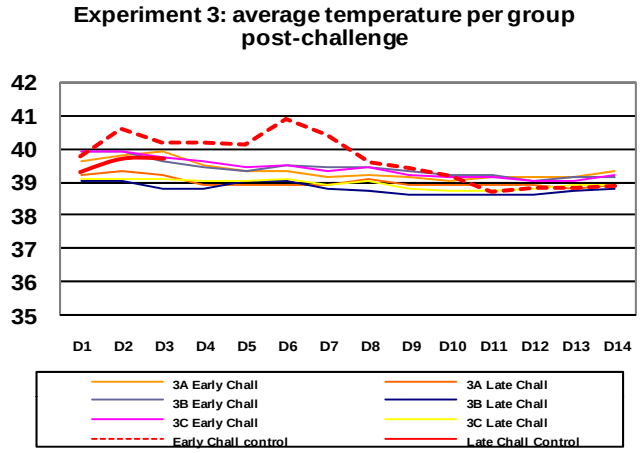
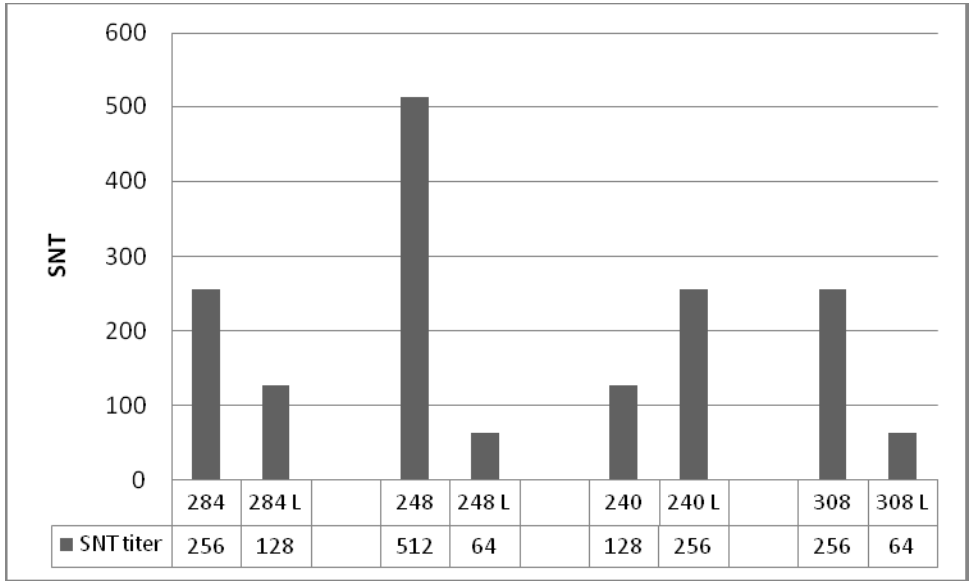
RVF Clone 13

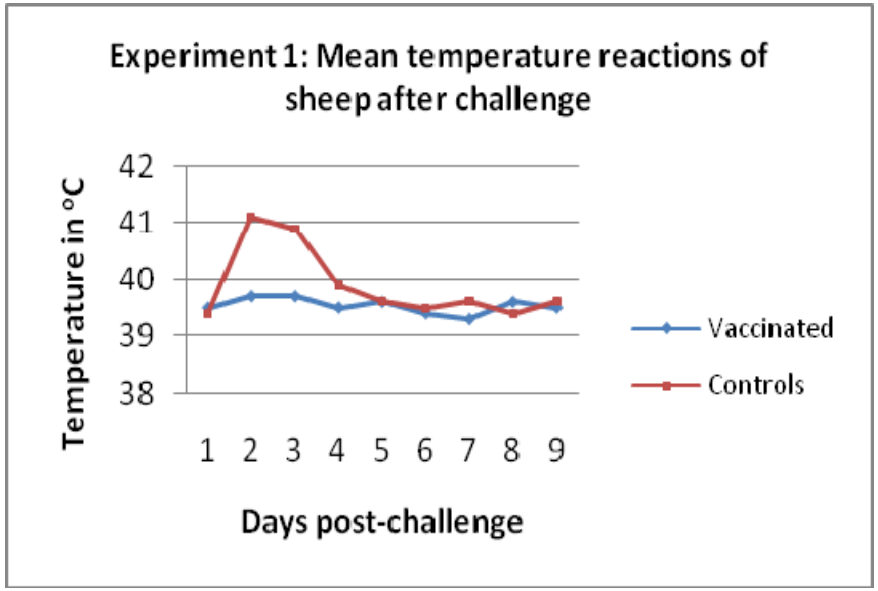
- Parent strain (74HB59)isolated in Central African Republic from non-fatal human case (Muller et al., 1995)
- Highly attenuated natural RVF mutant (avirulent)
  - 70% deletion (549 nucleotides) within NSs segment
- NSs associated with virulence:
  - Deletions results in high interferon production (Bouloy et al., 2001)
- Avirulent
  - No teratogenicity
  - Can be used in all physiological stages & ages
  - Live vaccine: long lasting immunity
  - Suitable for most susceptible species
  - Possible DIVA by RT-PCR (Garcia et al. 2001) and ELISA
  - Cheap (live vaccine)
- Possible challenges
  - Risk of reassortment with wildtype in an outbreak
    - In vaccinated animals the possible reassortant will not replicate highly due to the build up of immunity; limited viraemia

Clone 13 Sheep Efficacy data



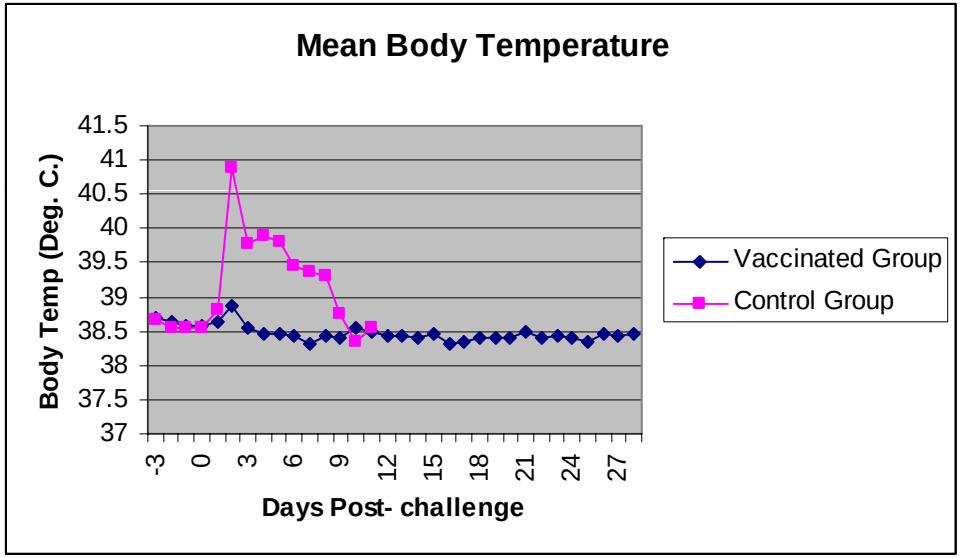






Clone 13 Calves efficacy data

Mean Body Temperature for each group through the viral challenge phase. DPC: Days post-challenge.



Clinical course for the unvaccinated control group

Animal ID	Peak Fever	Day PC	Duration of fever	Euthanasia
1367	41.2	3	8 days (2-9)	9
1402	41.4	2	1 day (2)	3
1404	41.0	2	7 days (2–8)	11
1405	41.3	2	1 day (2)	3
1406	40.4	2	3 days (2-4)	11

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RVF 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
  - Policy & Role of veterinary services

- **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

Key challenges in developing new RVF vaccine

•BSL3 to 4 stables for animal work, with lab capacity (Serology, Virus isolation, Virus titration)
•Staff Vaccinated against RVF
•Challenge model:
  •Assessing: pregnancy, teratogenicity, parturition
  •Oestrus synchronization of dams
  •Synchronized artificial insemination

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Some focus areas for further research

- **Endemic poor regions**
  - GALVmed approach: multivalent RVF + x
    - Funding available
  - Solid protective immunity after Single vaccination:
    - Replicating safe antigen vaccine
  - Thermo-tolerant
  - Vaccine that prevent transmission
  - Safe on pregnant and young animals
- *Examples: Clone 13, R566, Capripox expressing RVF,*

Key challenge is to devise vaccination strategies that work, more than the need for a suitable vaccine

- **Free countries/preventing introduction**
  - Non-replicating or mutant that would not reassort
  - Prevention of transmission
  - DIVA
  - Early onset of protective immunity
  - Antigen capable of long term storage
  - Appropriate vaccine delivery systems
- *Example: replication-deficient vectored vaccines, inactivated and adjuvanted vaccines*

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Thank you

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Protéger Le Bétail, C'est Sauver Des Vies Humaines

GALV*med*, une alliance mondiale à but non-lucratif présentement financée par la fondation Bill & Melinda Gates (BMGF) et le département britannique pour le développement international (DFID), travaille sans relâche avec ces principaux partenaires dans l'établissement des voies et moyens pouvant permettre l'accès aux vaccins et autres produits de santé animale aux éleveurs pauvres de notre planète. GALV*med* compte ainsi accomplir sa mission de la manière suivante:

- *En développant, en enregistrant auprès des autorités du médicament et en mettant en circulation différents vaccins, produits pharmaceutiques et testes diagnostiques durant les dix prochaines années*
- *En créant des partenariats avec des institutions des pays en développement visant à soutenir la recherche, la production et le lancement de nouveaux produits au service des éleveurs démunis*
- *En sensibilisant les différents partenaires sur les liens entre l'élevage et la pauvreté dans l'éradication de l'extrême pauvreté ainsi que de la faim*
- *En facilitant le dialogue et la collaboration dans les efforts visant au développement des nouveaux vaccins, produits pharmaceutiques et systèmes de diagnostique*