Epidemiology of RVF: potential risks for introduction into Europe

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RIFT VALLEY FEVER: HISTORY

- 1910-12: DISEASE COMPATIBLE WITH RVF DESCRIBED IN LAMBS (EUROPEAN BREED) IN RIFT VALLEY, KENYA
- 1930: VIRUS FIRST ISOLATED IN OUTBREAK OF SHEEP DISEASE IN RIFT VALLEY, KENYA

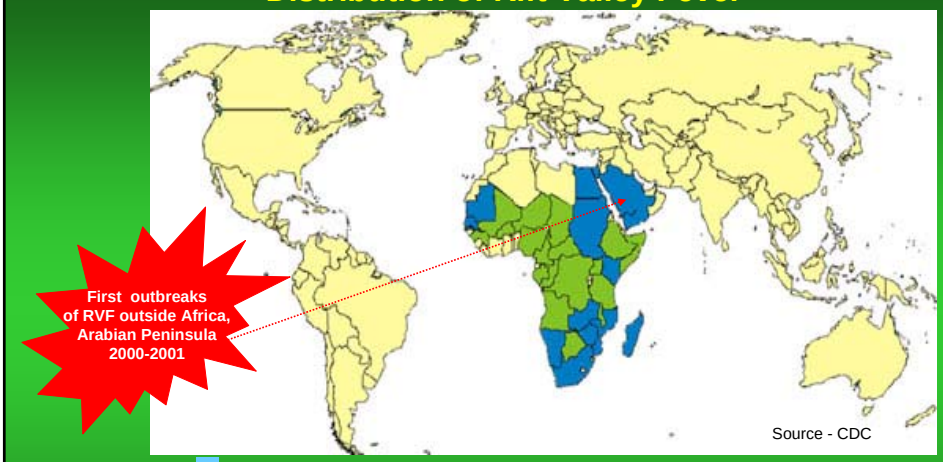
DAUBNEY

- SUBSEQUENT RECOGNITION OF PRESENCE OF VIRUS IN MANY SUB-SAHARAN COUNTRIES
- 1944: ISOLATION OF RVF VIRUS IN SEMLIKI FOREST UGANDA (NO LIVESTOCK OR HUMANS IN VICINITY) – HENCE RVF ASSUMED TO BE ENDEMIC IN FORESTS WITH SPREAD TO GRASSLANDS AFTER HEAVY RAINS
- 1950-1: LARGE OUTBREAK IN SOUTH AFRICA – ASSOCIATED WITH PANS & VLEIS (DAMBOS) - OCULAR LESIONS RECOGNIZED
- 1976: LARGE OUTBREAK IN SOUTH AFRICA – FATAL HUMAN DISEASE RECOGNIZED FOR FIRST TIME

RIFT VALLEY FEVER: HISTORY

- 1977-8: APPEARANCE OF RVF BEYOND SUB-SAHARAN AFRICA - IN EGYPT - >200,000 HUMAN INFECTIONS – 598 DEATHS
- 1979: RECOGNITION OF RVF IN MADAGASCAR
- 1987: LARGE OUTBREAKS IN MAURITANIA/SENEGAL – MANY HUMAN DEATHS
- 1997-8: LARGE OUTBREAK N-E KENYA/SOMALIA/TANZANIA - >300 HUMAN DEATHS
- 2000-1: APPEARANCE OF RVF BEYOND AFRICAN REGION IN SAUDI ARABIA & YEMEN – >200 DEATHS
- 2006-7: LARGE OUTBREAK N-E KENYA/SOMALIA/TANZANIA
- 2007: OUTBREAK IN SUDAN

Distribution of Rift Valley Fever

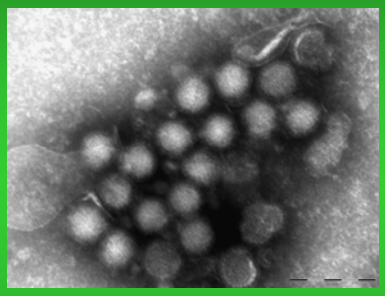


Countries with endemic disease and major outbreaks of RVF

Countries known to have sporadic cases, periodic virus isolation, or serological evidence of RVF

Rift Valley fever virus

- Bunyaviridae
- Phlebovirus
- 80-110 nm
- 3-segmented (L, M, S)
- Single-stranded, negative sense RNA genome
- Single serotype



RVF virus particles

Susceptibility of vertebrates to RVFV

Extremely susceptible (70-100% †)	Highly susceptible (20-70% †)	Moderately susceptible	Resistant (Inapparent infection	Refractory (Not susceptible)
New-borne lambs*	Sheep	Cattle	Equines	Birds
New-borne kids	Calves	Goats	Pigs	Reptiles
Puppies	Certain rodents	Camels	Dogs	Amphibians
Kittens		African buffalo	Cats	
Mice		Asian buffalo	African monkeys	
Hamsters		South American monkeys	Rabbits	
Certain other rodents		Asian monkeys	Guinea pigs	
		Baboons	Certain other rodents	
		Humans		

*There is much genetic variation, some breeds of sheep and goats may be classified in the moderately or resistant groups. *The EFSA Journal* 2005, 238, 1-128.

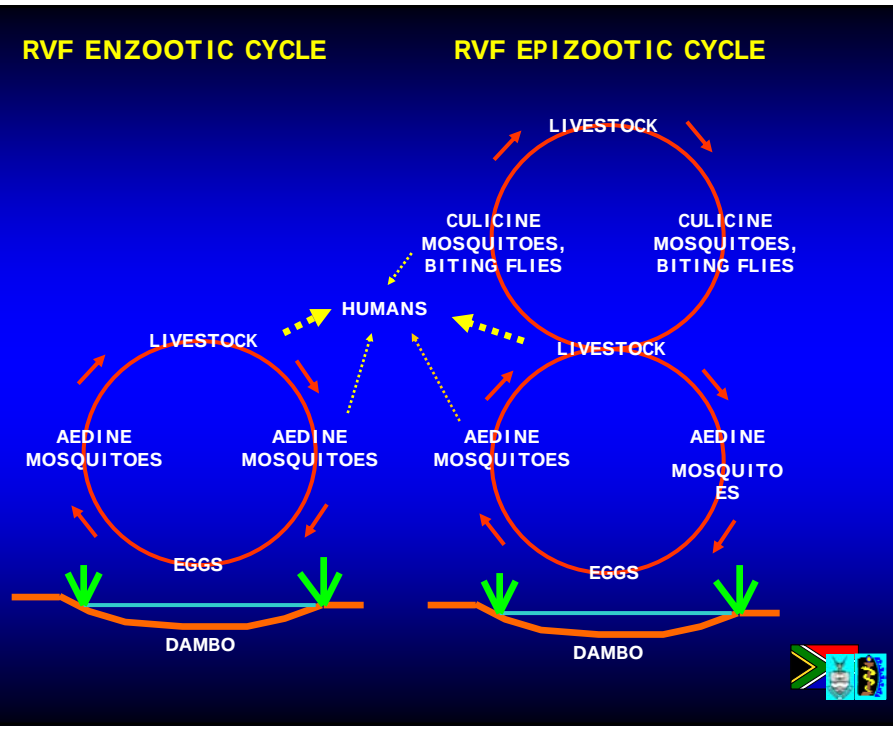
VECTORS OF RVF

ENZOOTIC (ENDEMIC) VECTORS = FLOODWATER-BREEDING AEDES MOSQUITOES (I.E. ONLY CERTAIN SPECIES OF AEDES)

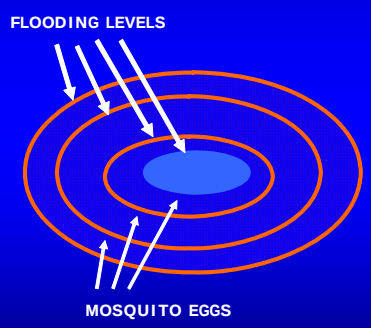
- EGGS LAID IN MUD AT THE EDGE OF WATER IN FLOODED DAMBOS
- NB EGGS REQUIRE DRYING BEFORE THEY WILL HATCH WHEN THE DAMBOS BECOME FLOODED AGAIN
- EGGS CAN SURVIVE FOR YEARS IN DRY MUD
- TRANSOVARIAL TRANSMISSION OF VIRUS OCCURS IN A LOW PROPORTION OF INFECTED AEDES MOSQUITOES
- INFECTED EGGS = MECHANISM FOR PERPETUATION OF VIRUS
- INFECTED EGGS HATCH AND ADULT AEDES EMERGE AFTER FLOODING TO TRANSMIT INFECTION TO LIVESTOCK
- LIFE CYCLE RAPIDLY COMPLETED – 10-20 DAYS

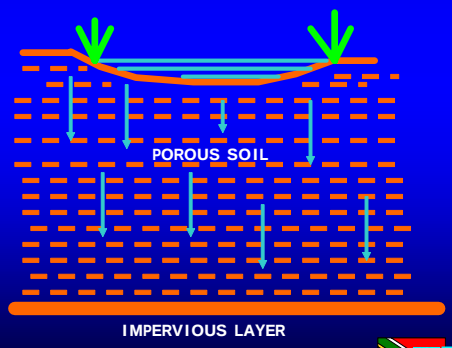
EPIZOOTIC (EPIDEMIC) VECTORS = CULICINE MOSQUITOES, BITING FLIES

ACQUIRE VIRUS BY TAKING BLOODMEALS FROM INFECTED (VIRAEMIC) LIVESTOCK AND SUSTAIN THE OUTBREAK BY TRANSMITTING INFECTION



DRAIANAGE/DRYING OR FLOODING OF DAMBOS:
EFFECTS ON FLOODWATER-BREEDING AEDES MOSQUITOES





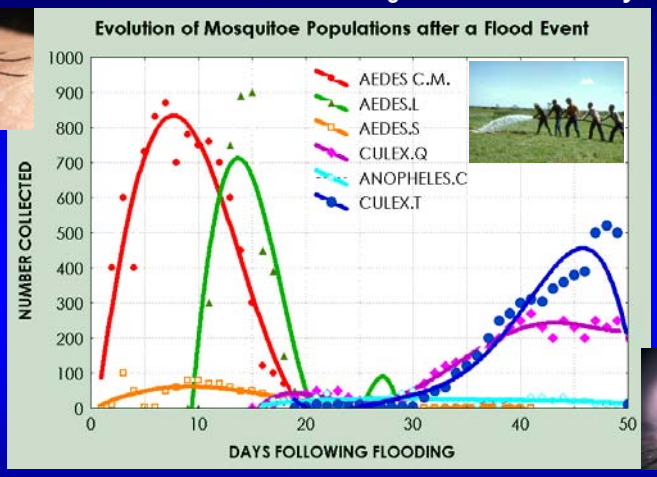
OBSERVATIONS IN KENYA
Linthicum/Davies/Bailey

VECTOR POPULATION AND RAINFALL DYNAMICS

Linthicum et al, 1983

Studies based on artificial flooding of a dambo in Kenya

Aedes spp.



Culex spp.

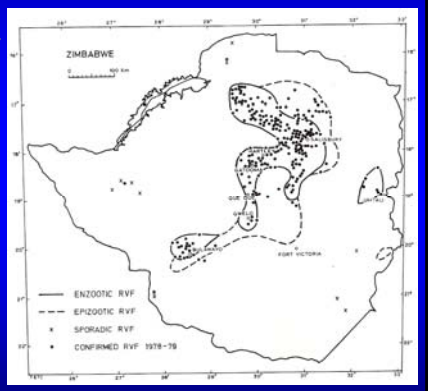
RESULTS:

- TRANSOVARIAL TRANSMISSION OF VIRUS DEMONSTRATED BY ISOLATION OF VIRUS FROM HATCHING AEDES
- ENDEMIC/ENZOOTIC AEDINE MOSQUITO VECTORS RAPIDLY REPLACED (20 DAYS) BY EPIDEMIC/EPIZOOTIC CULICINE VECTORS

RVF OBSERVATIONS IN ZIMBABWE 1955-1979

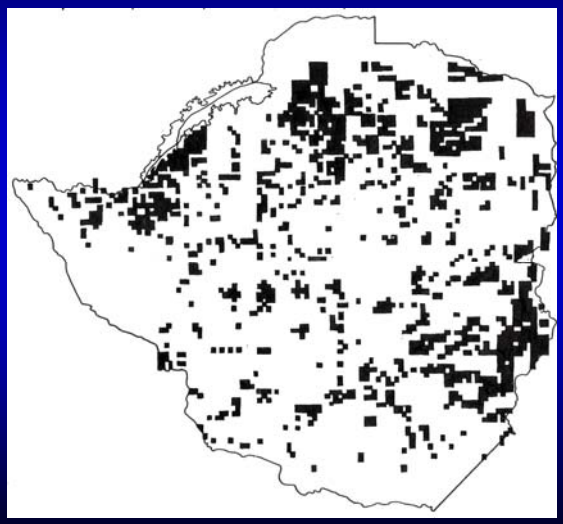
16,892 SERA, 4,002 VIROLOGICAL SPECIMENS FROM 2,354 LOCATIONS TESTED:

- RVF ENDEMIC IN SAVANAH/GRASSLANDS MAINLY ON CENTRAL WATERSHED PLATEAU
- LOW LEVEL OF VIRUS ACTIVITY TRIGGERED BY RAINS EVERY YEAR – ONLY DETECTED BY INTENSIVE MONITORING
- EPIDEMICS OCCUR IN SAME AREAS AS ENDEMIC VIRUS ACTIVITY – TRIGGERED BY EXCEPTIONAL RAINS
- ENDEMICITY PROBABLY ASSOCIATED WITH TRANSOVARIAL TRANSMISSION OF VIRUS IN FLOODWATER-BREEDING AEDES MOSQUITOES AS EARLIER DEMONSTRATED IN SOUTH AFRICA (1959) AND LATER IN KENYA (1985)



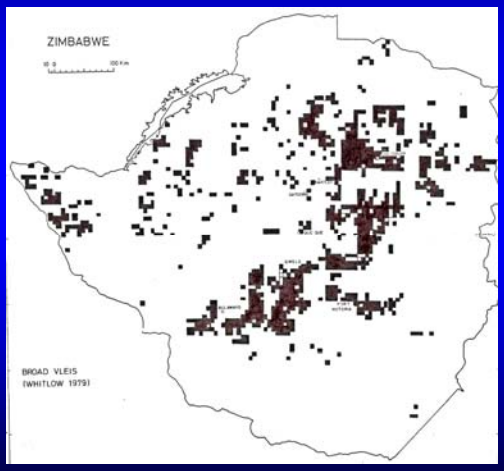
ZIMBABWE – CLOSED (CANOPY) FOREST - FROM AERIAL PHOTOGRAPHS

DISTRIBUTION OF FOREST DOES NOT CORRESPOND WITH RVF ENDEMICITY = MIRROR IMAGE



ZIMBABWE – DISTRIBUTION OF BROAD VLEIS (DAMBOS)

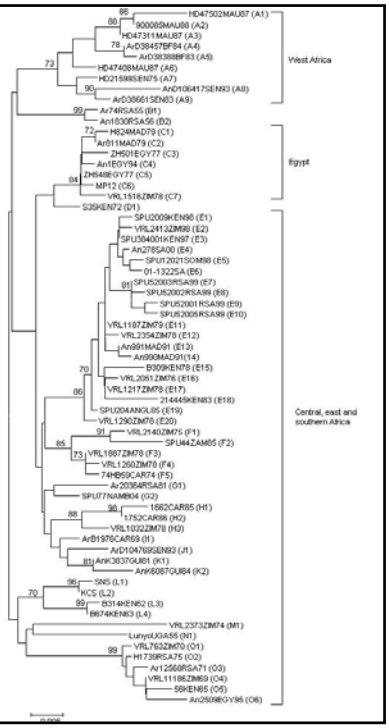
DISTRIBUTION OF BROAD VLEIS (DAMBOS) CORRESPONDS WITH AREAS OF RVF ENDEMICITY



RVF VIRUS PHYLOGENY

- VIRUS REMARKABLY STABLE GENETICALLY AND ANTIGENICALLY
- FOLLOWING HEAVY RAINS OUTBREAKS ASSOCIATED EITHER WITH A SINGLE GENETIC VARIANT OF VIRUS (= EPIDEMIC SPREAD)
  OR
  WITH SIMULTANEOUS EMERGENCE OF MULTIPLE VARIANTS FROM ENDEMIC FOCI

(unpublished information NICD)



RVF in animals

- abortions
- high fatality in young animals
- vomiting, diarrhoea, jaundice
- necrotic hepatitis with or without a haemorrhagic state


Aborted ovine fetuses


Necrotic hepatitis

RVF in humans

- Usually uncomplicated acute febrile illness but
  - hepatocellular failure
  - acute renal failure
  - hemorrhagic manifestations
  - retinitis, meningoencephalitis
  - death associated with hepatorenal failure, shock, severe anaemia

  occur in small proportion of patients.


Petechial rash and hemorrhage on arm

RVF HUMAN DISEASE

- INFECTED BY CONTACT WITH DISEASED ANIMAL TISSUES

OR

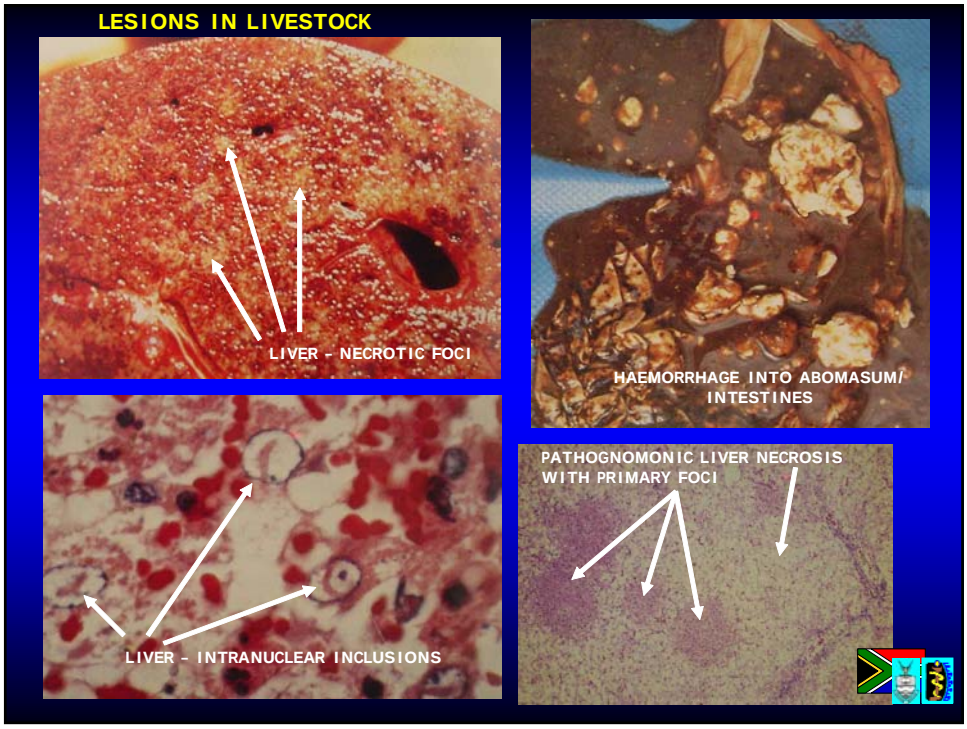
- MOSQUITO BITE – LESS COMMON IN SUB-SAHARAN AFRICA WHERE THE VECTORS ARE SYLVATIC (DO NOT ENTER DWELLINGS)

- INCUBATION PERIOD ‹1 WEEK
- =80% OF INFECTIONS SUBCLINICAL OR MILD
- ‹0.5% FATAL HAEMORRHAGIC FEVER/ENCEPHALITIS
- ~5% OCULAR SEQUELAE

CLINICAL SIGNS IN LIVESTOCK

- YOUNG ANIMALS:
- SUDDEN ONSET OF HIGH FEVER
- ACUTE PROSTRATION, COLLAPSE & DEATH

- ADULTS:
- ABORTIONS THE MOST IMPORTANT SIGN
- DYSTOCIA, SOME TERATOLOGY, HYDROPS AMNII
- ANOREXIA, DYSGALACTIA, NASAL AND LACHRYMAL DISCHARGES
- SALIVATION, 'VOMITING', LYMPHADENITIS
- COLIC, JAUNDICE, HAEMORRHAGIC ENTERITIS



Clinical features of RVF in 165 patients admitted to the Gizan hospital, Saudi Arabia, 2000

- Pallor (33.3%)
- Dehydration (24.8%)
- CNS abnormality (24.8%)
- Hepatomegaly (12.7%)
- Splenomegaly (12.1%)
- Jaundice (6%)
- Ecchymosis (4.8%)
- Petechiae (3.6%)
- Ascites (2.4%)
- Nausea and/or vomiting (91.5%)
- Fever and or chills (73.9%)
- Abdominal pain (46.1%)
- Diarrhea (43%)
- Headache (40.6%)
- Myalgia (40.0%)
- CNS symptoms (30.3%)
- Oliguria and/or anuria (21.2%)
- Bleeding (17.0%)
- Jaundice (10.9%)

– Source Al-Hazmi et al. CID, 2003

RVF epidemic in the Gizan region of Saudi Arabia, 2000

- The overall case-fatality 17% (87 of 516 case patients died)
- ~ 20. 000 people might have been infected, with the majority of the infections being subclinical or mild in persons who did not seek care
- The Gizan region: a rural area, main occupation – animal husbandry
- Climate favoring breeding of mosquitoes
- RVFV isolation from *Culex (Culex) tritaeniorhynchus* and *Aedes vexans arbiensis;* subsequently demonstrated to transmit the virus *in vivo,* both mosquito species were feed readily on humans and sheep
- Note – that *Culex (Culex) tritaeniorhynchus* is present in Turkey

Results of prospective study in 165 RVF patients admitted to the special RVF unit at of the Gizan regional hospital:

- Hepatocellular failure = 124 (75.2%)
- Acute renal failure = 68 (41.2%)
- Hemorrhagic manifestations = 32 (19.4%)
- Retinitis = 16 (9.7%)
- Meningoencephalitis = 7 (4.2%)
- Case-fatality = 56 (33.8%)
  - Possible contributory factors: subclinical liver diseases including schistosomiasis and chronic hepatitis
  - Exposure: 60% patients had direst contact either with infected and sick relatives or with sick, aborted, or dead animals; 31.5% slept in the open air most of the time; 80% had frequently sustained mosquito bites

Recognition of RVF outbreak - concurrent and interrelated features allowing for making fairly accurate tentative diagnosis:

- Unusually heavy and persistent rainfall resulting in flooding over a wide area and subsequent massive build up in vector competent populations;
- sudden simultaneous and multifocal onset of abortions among sheep, goats, cattle or camels and high mortality rate particularly in newborn lambs, kids and calves over a wide area;
- other severe, often haemorrhagic clinical signs and gross and histological lesions, especially in livers of young animals or aborted foetuses;
- usually benign febrile illness among people involved in handling the blood, tissues, secretions or excretions of infected animals, especially after abortion, or involved in slaughtering and autopsying of infected animals.

Recognition of RVF outbreak

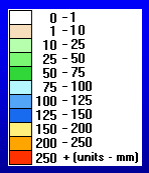
- Clinical, pathological, histological and laboratory diagnosis can be relatively simple when veterinary, medical, and laboratory personnel receive regular and continuous training and when suitably equipped laboratory facilities are available;
- During RVF epizootics isolation of the virus from animals and mosquito vectors is not difficult: high-level viremia and high virus concentrations in various tissues, high-level of virus amplification in competent vectors, high virus stability, high susceptibility of different *in vitro* and *in vivo* isolation systems;
- Infection with RVFV induces rapid production of class-specific immunoglobulins. They are easily detectable at the early stage of infection that allows rapid diagnosis on a single serum sample;
- During the long inter-epidemic periods RVFV is maintained silently within the cryptic cycle and only sporadic, small and local epizootics may occur. Therefore, unless very intensive and well-designed surveillance activities are in place virus activity usually remains undetected.

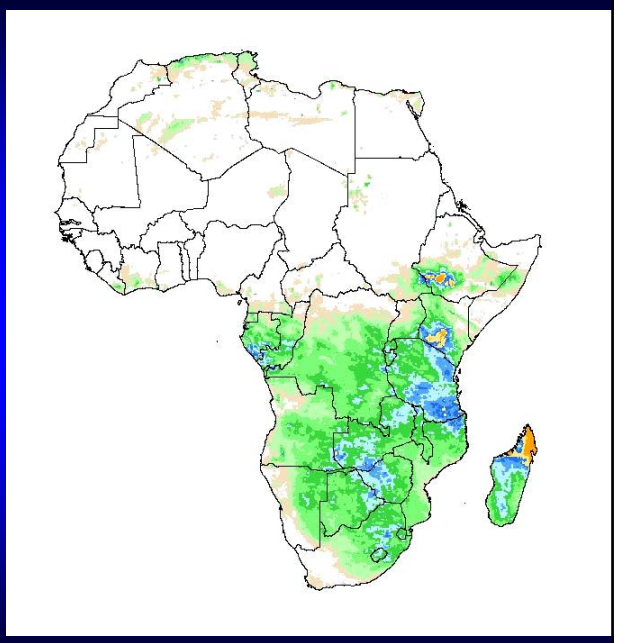
Recognition of RVF outbreak

- Note that:
  - The South African outbreaks of 1950-1951 and the Egyptian outbreaks of 1977-1978 were not recognized as RVF until several months had elapsed with the deaths of thousand of animals, and in the Egyptian outbreaks, of many deaths in humans.
  - In both these instances, delays occurred because the disease was previously unknown in those geographical areas and the possibility of RVF was not at first a consideration

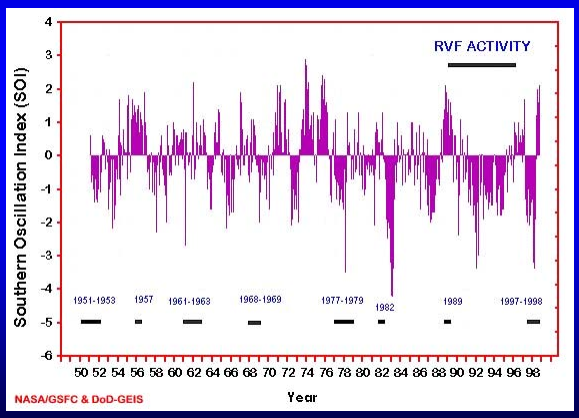
REMOTE SENSING (SATELLITE IMAGING) AND PREDICTION OF RVF OUTBREAKS

eg RFE (Rainfall Estimate) imaging

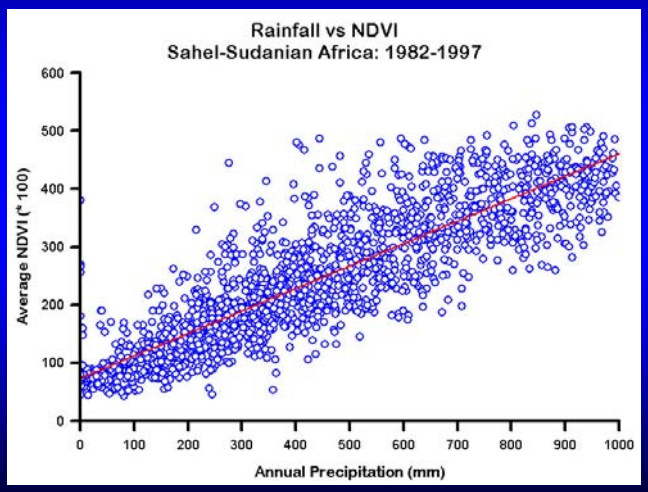




RAINFALL CORRELATES WITH RVFV ACTIVITY



RAINFALL ALSO CORRELATES WITH NORMALIZED DIFFERNCE VEGETATION INDEX (NDVI)

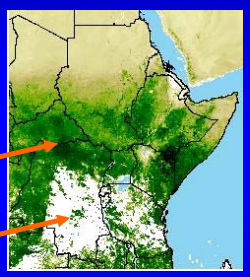


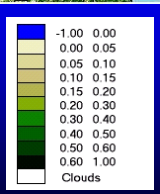
RELEVANCE OF REMOTE SENSING (NDVI) TO 2006-07 EAST AFRICAN RVF OUTBREAK

Current January 2007 vs Previous January

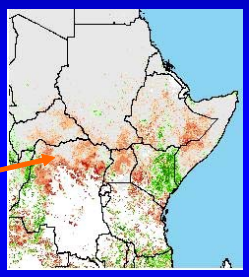
NDVI: green indicates recent heavy rains

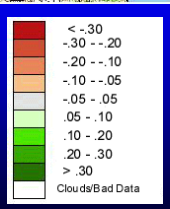
cloud cover



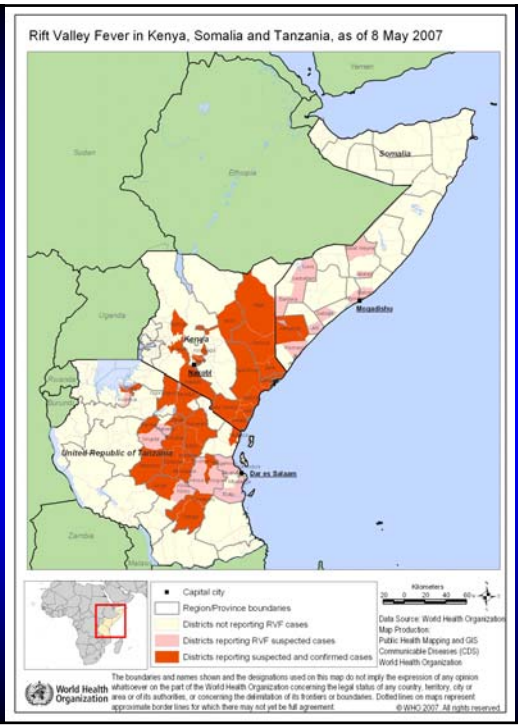


dry





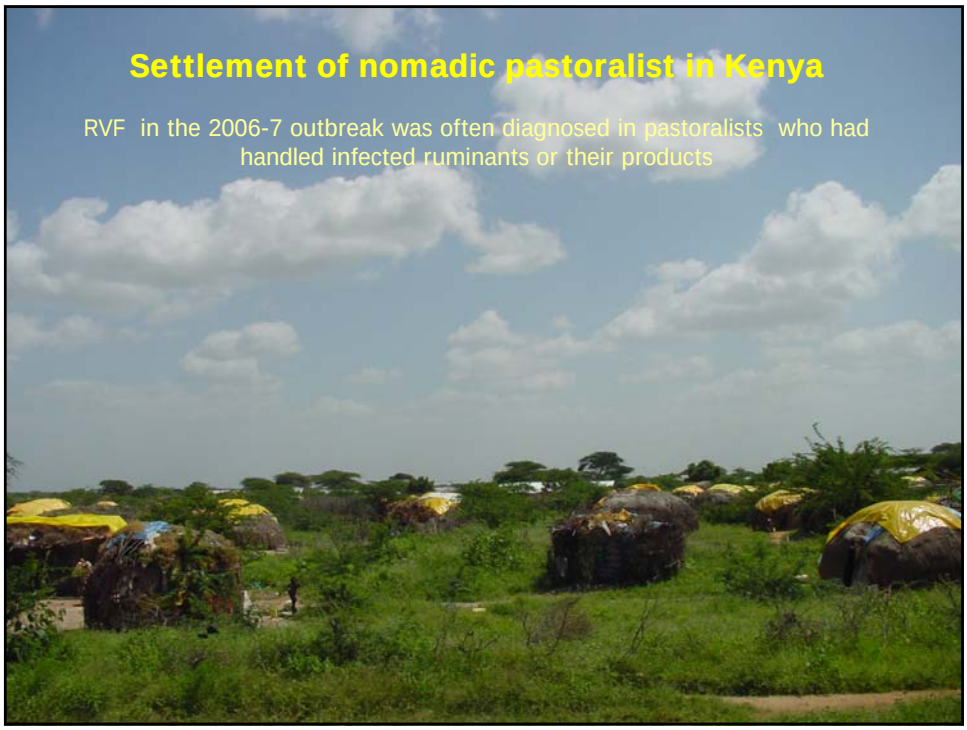
KENYA
SOMALIA
TANZANIA
RVF
AFFECTED
DISTRICTS
2007



RAINFALL ESTIMATES & NDVI DO NOT GIVE SUFFICIENT 'LEAD TIME'

HENCE ATTEMPT TO DERIVE LONGER TERM FORECASTS USING 'EL NINO SOUTHERN OCEANS OSCILLATIONS' (ENSO) PHENOMENON


Flooded areas in Garissa district, North-eastern Province of Kenya – an epicentre of the 2006-7 RVF outbreak


Settlement of nomadic pastoralist in Kenya
RVF in the 2006-7 outbreak was often diagnosed in pastoralists who had handled infected ruminants or their products

Viral loads in fatal cases of RVF – Kenya 2006-07

Case No.	Infectious virus particles/ml (Log_{10})	Days post-onset
1	7.8	3
2	6.8	3
3	5.8	7
4	5.8	3
5	1.3	3
6	5.8	4
7	1.8	-
8	5.3	-
9	4.8	3
10	4.3	3
11	5.3	-
12	7.0	-
13	6.5	-
14	4.5	1
15	5.5	-
Mean [Range]	5.2 [1.3 – 7.8]	2.9 [1-7]

Fatal RVF cases (n = 15) had 3-logs > $TCID_{50}$/mL serum concentrations ($10^{5.2}$) compared to 36 non-fatal cases ($10^{2.3}$).

Severe weakened RVF patient.
Garissa Provincial Hospital,
Northeastern province of Kenya, 2006

ALERT

An outbreak of Rift Valley fever (RVF) occurred in a disease-free buffalo breeding project in the Nkomazi State Veterinary area, Ehlanzeni district, Mpumalanga province from 14 January 2008

Directorate of Animal Health, Mpumalanga

•14, 25, 27, 30 January 2008: Abortions and deaths in buffalo.

•28 Jan 2008: State vet performs necropsy.

•1 Feb 2008: State vet develops fever, myalgia and photosensitivity 4 days after PM exposure on buffalo calf - RVF confirmed by RT- PCR, seroconversion, and virus isolation.

Buffalo calf died of RVF

Female buffalo stillbirth, hemorrhages of enlarged liver

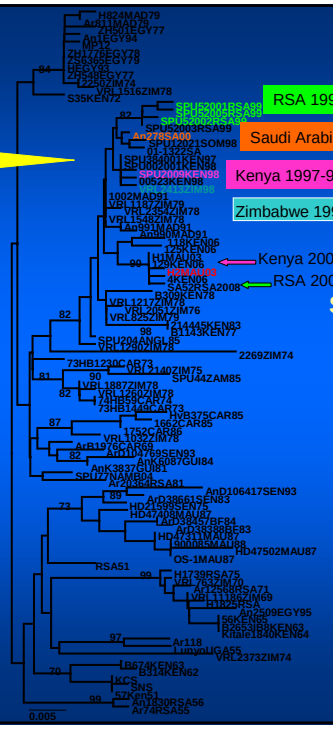
Faculty of Veterinary Medicine, Onderstepoort, RSA, 2008:

4 vet students and one technologist became infected with RVFV after post mortem exposure to Bela Bela calves: febrile illness with mild hepatic dysfunction, biphasic illness + encephalitis in one student .

Malelane Buffalo Research Station, Mpumalanga, RSA, 2008:

Farm worker acquired RVFV infection after handling liver at post mortem on buffalo calf.

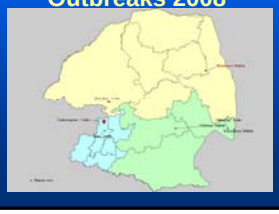
Genetic relation of RVFV causing the 2008 outbreak in RSA



RVF outbreaks in RSA

- **1951- 53: 100 000 sheep deaths, 500 000 abortions**
- **1974-6: livestock,** Free State, N Cape and southern Transvaal, **10 000 human cases, 7 deaths**
- **1989: dairy herd,** Empangeni KZN
- **1999: captive buffalo**, near Skukuza KNP

Outbreaks 2008



Summary of confirmed human cases

- 1 vet, 5 vet students, 2 post mortem technologists,
- 11 farm workers
- Incubation:2-5 days, with biphasic illness in 3 patients
- Fever and myalgia in all
- Encephalitis in 2 patients

EXTENSION/DISSEMINATION OF RVF INFECTION TO RECEPTIVE AREAS

MECHANISMS:

- TRANSLOCATION OF INFECTED VECTORS (eg AIR CURRENTS, EGGS IN MUD ON MIGRATING BIRDS?)
- TRANSLOCATION OF VIRAEMIC ANIMALS – eg ARABIAN PENINSULA (1997-2000?)
- SIMILAR INTRODUCTIONS LIKELY TO OCCUR IN INDIAN OCEAN ISLANDS: eg COMORES 2007
- VIRUS ALREADY PRESENT IN MADAGASCAR

RECEPTIVE AREAS:

- IRRIGATED LANDS, DAMS etc
- ANYWHERE WITH POTENTIAL FOR HIGH VECTOR POPULATIONS

PREVENTION/CONTROL IN LIVESTOCK

- ROUTINE VACCINATION – ESPECIALLY EXOTIC BREEDS - WEANERS
- RAINFALL RSSD PREDICTIONS TO DRIVE COST-EFFECTIVE VACCINATION STRATEGIES???
- SMITHBURN MLVV – LIFELONG IMMUNITY BUT ONLY PARTIALLY ATTENUATED – SOME ABORTIONS – THEREFORE VACCINATE WEANERS – ANNUALLY
- INACTIVATED VACCINE EXPENSIVE AND REQUIRES 2 DOSES – PLUS BOOSTERS
- NEED FOR SAFE AND POTENT NEW VACCINES – HUMAN AND VETERINARY!

CONFIRMED RVF: ACTION TO TAKE

- DEFINE INFECTED AREAS/TARGET POPULATIONS
- INSTITUTE CLINICAL/SEROLOGICAL SURVEILLANCE
- SURVEY FLOOD ZONES – ANALYSE REMOTE SENSING AND WEATHER DATA – ESTIMATE POTENTIAL FOR SPREAD
- STOP SLAUGHTER, CONSUMPTION AND MOVEMENT OF ANIMALS – INCREASE HUMAN AWARENESS – STOP UNPROTECTED HANDLING OF DISEASED ANIMALS/TISSUES

VECTOR CONTROL – ADULT INSECTICIDES, LARVICIDES, REPELLANTS, NETS

- VACCINATION NOT USUALLY AN OPTION:
  1) MLV VACCINE ONLY PARTIALLY ATTENUATED,
  2) KILLED VACCINES REQUIRES MULTIPLE DOSES,
  3) NEEDLE PROPOGATION OF OUTBREAK!

Risk assessment of RVF introduction and its persistence in EU

– The EFSA Journal 1-128, 2005

- **Aerial movement of RVFV infected vectors presents the greatest hazard to the EU countries.**
  - from Africa to the islands of Sicily, Cyprus, Crete and Turkey (*Culex (Culex) tritaeniorhynchus) – likely by air currents from Egypt driven by the Eastern Mediterranean Convergence Zone system*
- **The greatest danger – establishment of a cryptic focus of RVFV activity.**
  - *Aedes* spp. which potentially is capable of transovarial transmission is widely distributed in the EU countries
  - high risk vector habitat areas for the primary *Aedes* vectors (poorly draining soils susceptible to flooding, with high clay content) which might serve as emergence sites: Turkey, Greece, Italy, Spain, Portugal, and France.

Mosquito vectors of RVFV with known distribution in Europe

- *Aedes vexans vexans*
- *Ochlerotatus caspius s.l.*
- *Culex thelleri*
- *Culex pipiens*
- *Culex perexiguus/univittatus*

Obstacles to prevention and control of RVF

- Cryptic cycle of RVFV not fully understood.
- Surveillance systems in endemic areas need to be improved and/or implemented.
- Zoonotic in nature – requires countermeasures to prevent the disease in both animals and humans…but no RVF vaccines licensed in EU.
- No specific drugs available for treatment.
- No rapid, pen-side or field-based diagnostic assay available. Diagnostic capacity restricted…delay in outbreak recognition allows sufficient time for the disease wider spread.

Obstacles to prevention and control of RVF

- The probability of early detection and rapid response of control measures if RVFV is introduced into the EU is likely low.
- Field vets are not accustomed to the clinical signs of RVF …not unreasonable to expect a long delay between the first cases of the disease and a positive diagnosis.
- Restrictions in the ability to receive and handle specimens once RVF has been diagnosed …requirements for high biocontainment facility and vaccinated laboratory staff.
- Any vaccination programme incorporating a live, attenuated animal vaccine may result in accidental exposure of the filed workers to that vaccine

Desired Vaccine Profile

- Highly efficacious: prevents virus amplification in all target hosts, one dose, quick onset of immunity, ≥one year duration of immunity
- Safe: no reversion to virulence, non-abortogenic, all species, pure, no vector transmission
- DIVA compatible
- Manufacturing method yields high number of doses
- No maternal Ab interference
- Mass vaccination compatible
- Rapid speed of production and scale-up,
- Cost-effective
- Short withdrawal period for food consumption
  - promising vaccines: mutated strain MP12; clone 13; strain R566 (mutated L & M segment of MP12, and S segment from clone 13)

Desired Vaccine Profile

- A highly efficacious vaccine specifically designed for the control and eradication of RVF has yet to be developed for veterinary use
- The efficacy and safety profiles of vaccines available in Africa are inadequate
- There are no marker vaccines to differentiate infected from vaccinated animals (DIVA)

Desired Diagnostic Assay Profile

- Highly accurate and rapid tests for antigen, nucleic acid, IgG and IgM detection
- DIVA compatible
- Field validated
- Easy to perform
- Scalable
- Cost-effective

Conclusion

- The rapid global spread of arboviruses in the last decade (e.g. WNV, BTV), and including the expansion of RVFV from Africa to the Arabian Peninsula illustrate the natural ability of arboviruses to establish themselves in new ecosystems where adequate climatic conditions and breeding habitats can support maintenance of their biological vectors and large numbers of susceptible vertebrate hosts prevail .
- The EU is vulnerable to a natural RVF outbreak (high amplifying potential of domestic and wild ruminant species and most likely existence of mosquito multi-species potential for the virus vectoring).
- The epidemiology of RVF should it be introduced in EU is difficult to predict …but there is no reason to believe that the spread of RVFV would be slower, less dramatic, or more controllable than during large outbreaks of the disease in endemic regions.

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