Rift Valley fever:
Unanswered questions and unmet needs

Jeroen Kortekaas, 11th EPIZONE meeting
September 20th, Paris, France

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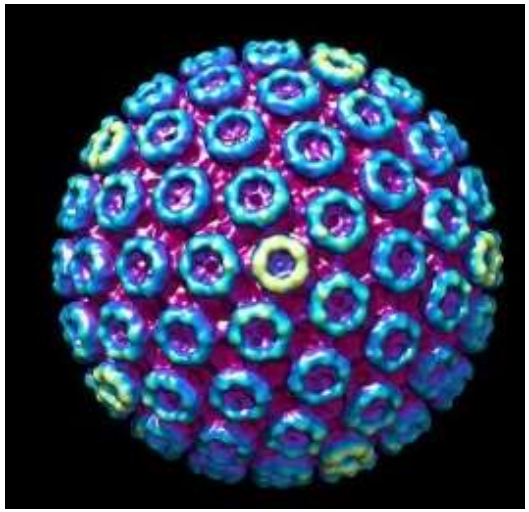
Presentation objectives

- Introduction of the Order Bunyavirales
- Rift Valley fever:
  - Susceptible species
  - Molecular virology
  - History
  - Epidemiology
  - Pathology
  - Vaccines



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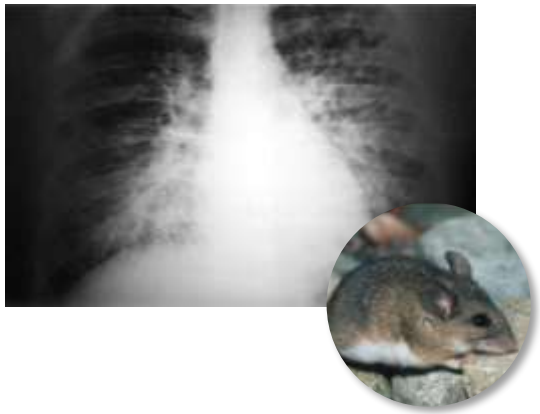
The order Bunyavirales

- Largest group of RNA viruses affecting mammals
- Nine families:
  - Feraviridae
  - Fimoviridae
  - Jonviridae
  - Phasmaviridae
  - Tospoviridae
  - Nairoviridae
  - Peribunyaviridae
  - Hantaviridae
  - Phenuiviridae



Rift Valley fever: Susceptible species













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Biosafety level-3

Laboratory

Animal facility

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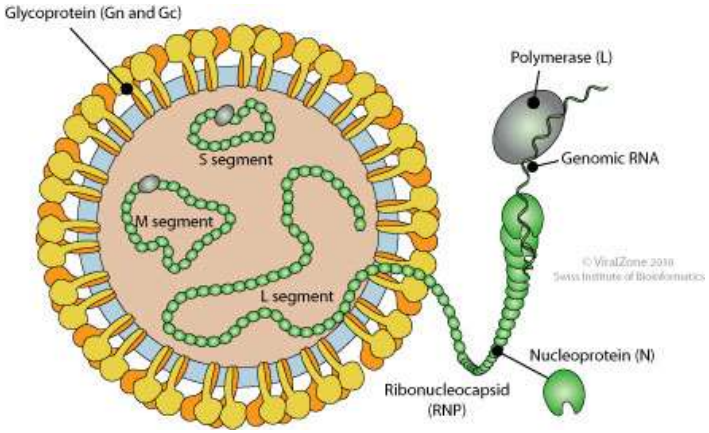
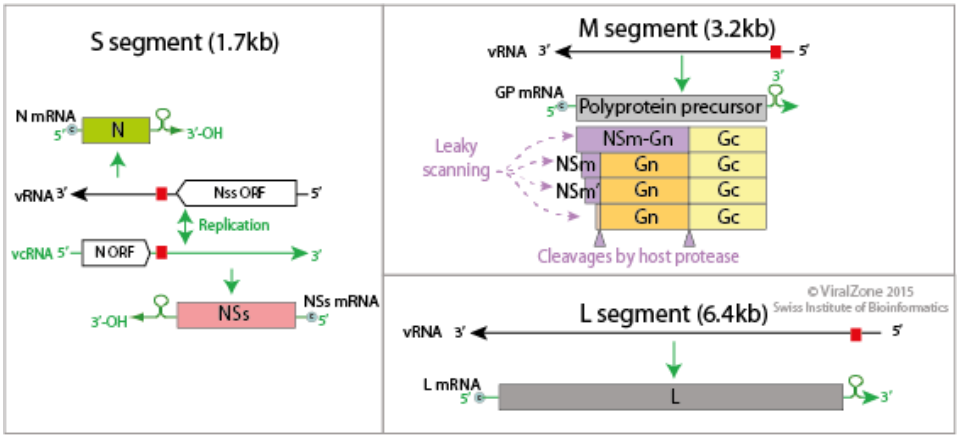
The RVFV virion

- Enveloped virus with icosahedral symmetry (90-110 nm)
- Segmented single-strand negative-sense RNA genome
  - Large (L), Medium (M), Small (S)
  - One serotype
  - NSs is the major virulence determinant





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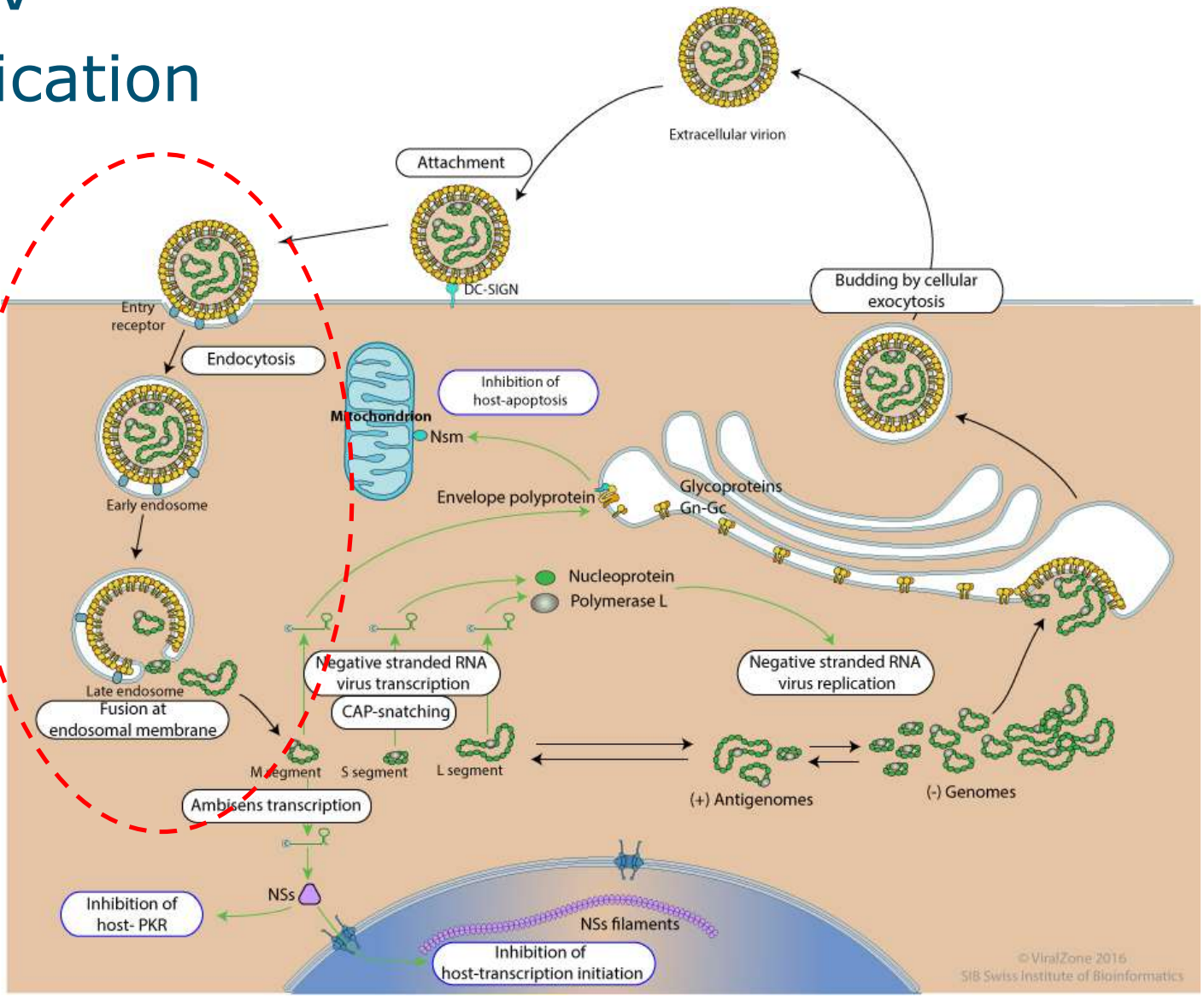
RVFV replication



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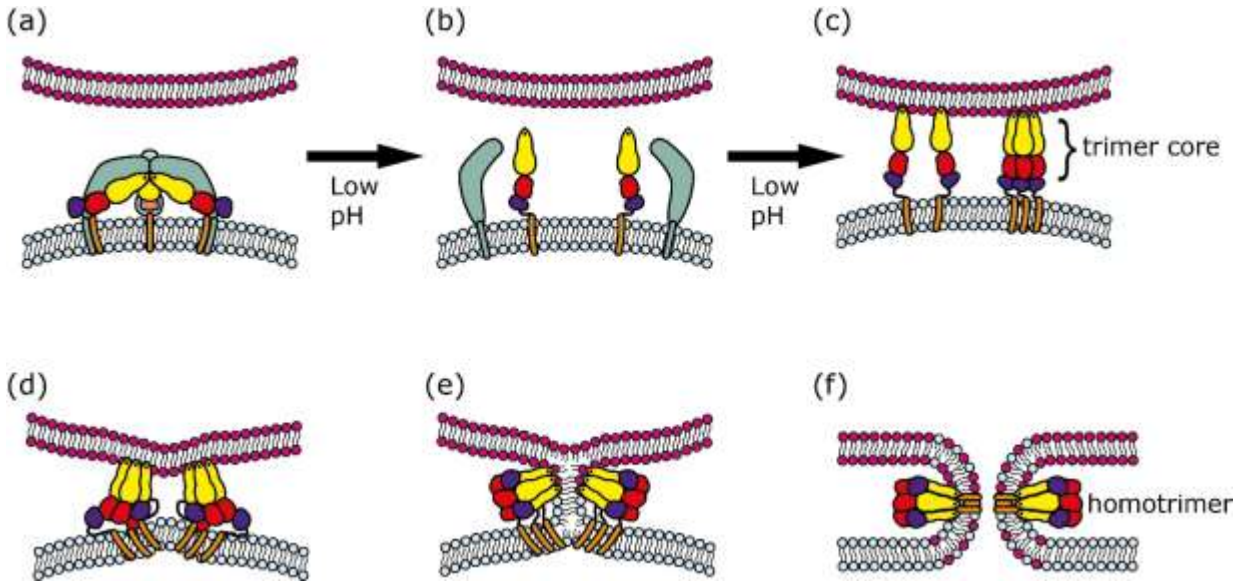
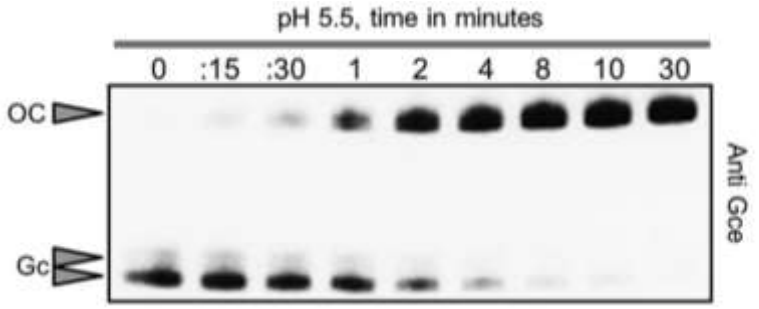
Class II fusion proteins (alphaviruses)



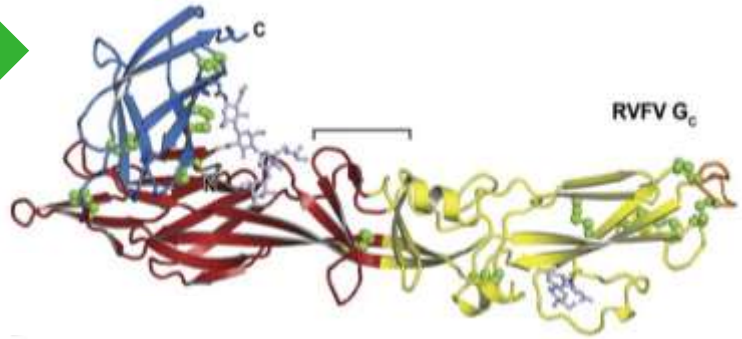
Kielian *et al.*, Viruses 2010

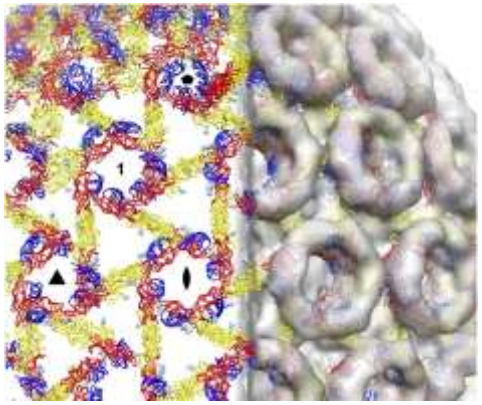
RVFV Gc is a class-II fusion protein

De Boer *et al*.,
J Virol 2012



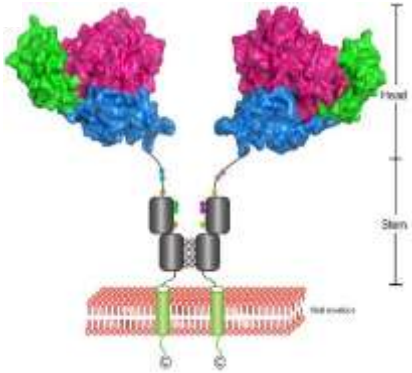
Dessau and Modis
PNAS 2013

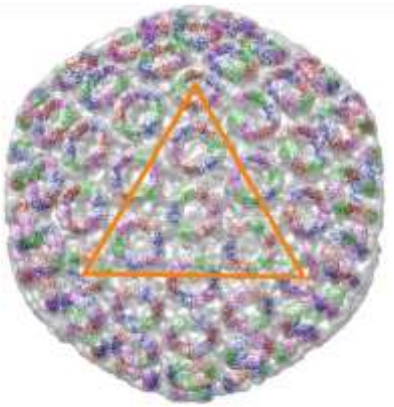




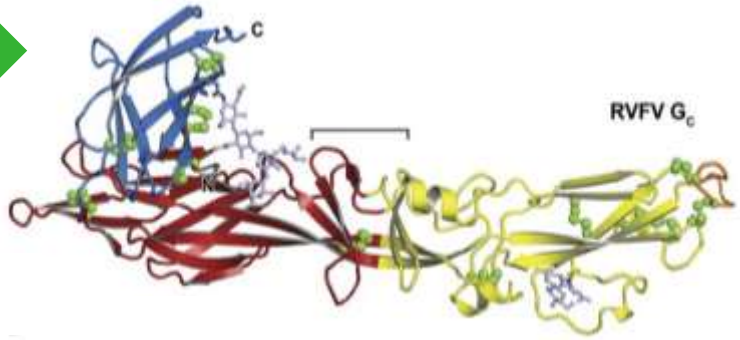
Structure of Gn (ectodomain)

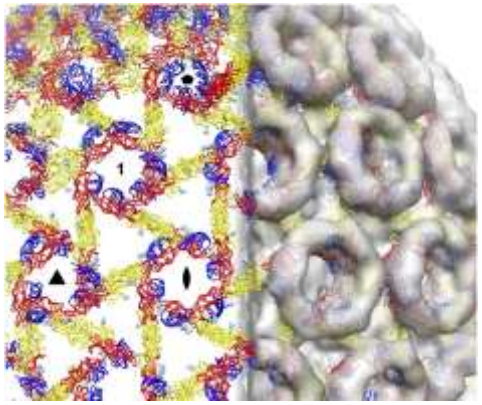
Yan Wu et al. PNAS 2017





Dessau and Modis PNAS 2013





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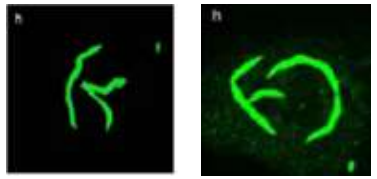
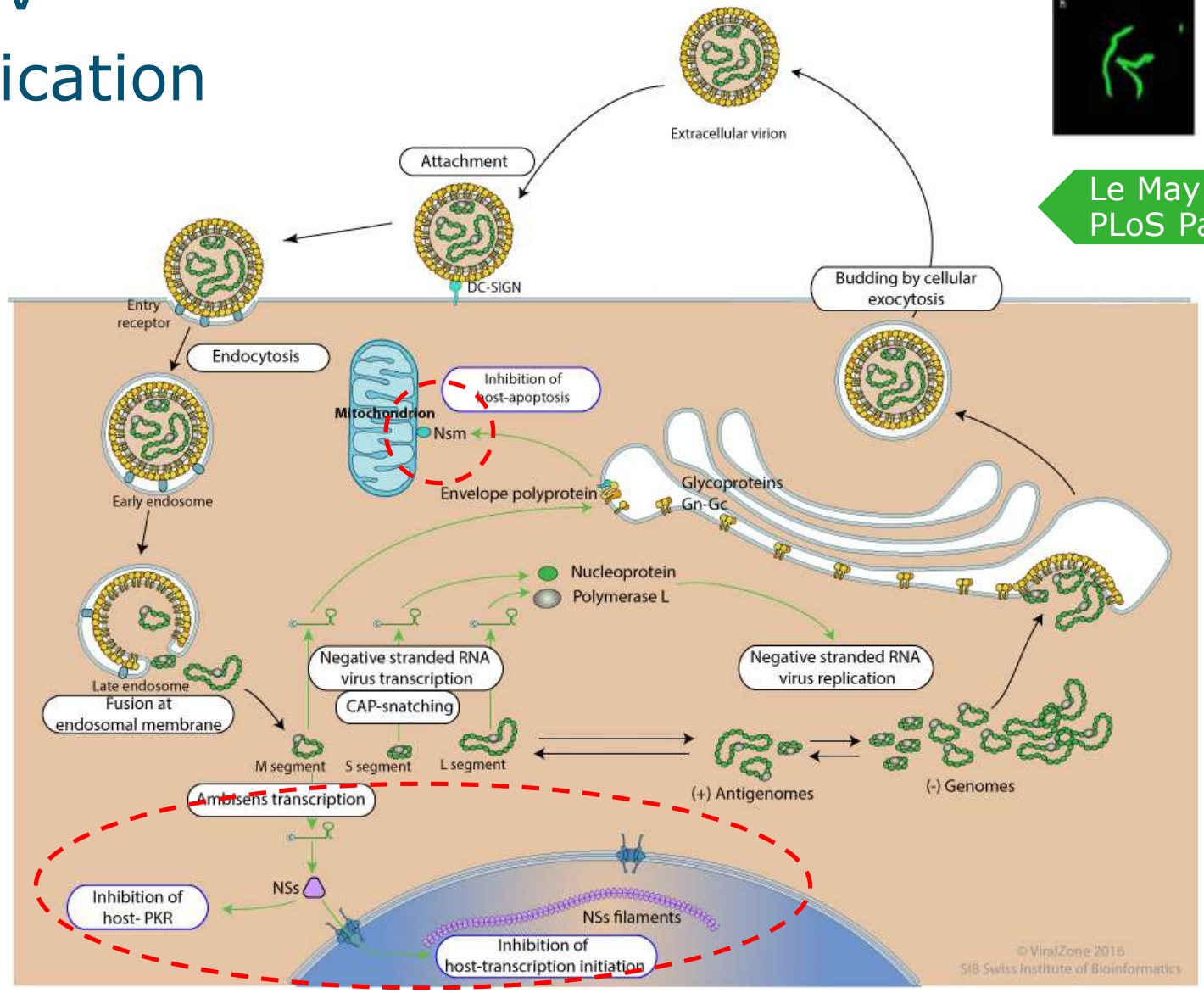
RVFV replication



Le May *et al.*, PLoS Path 2008



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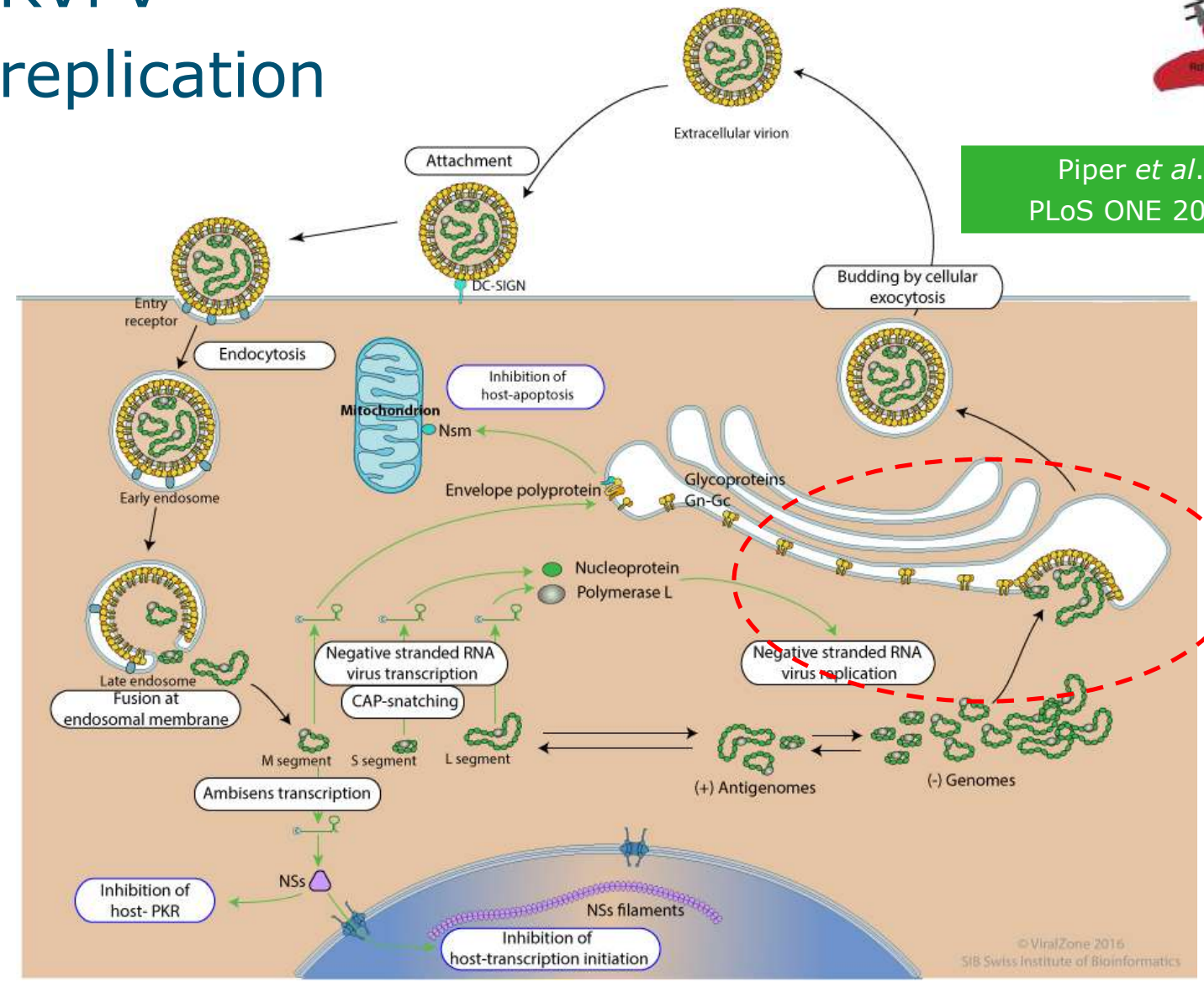
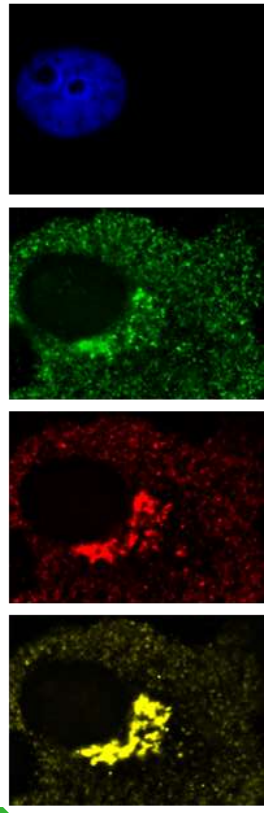
RVFV replication

Piper *et al.*, PLoS ONE 2011



10 hpi



S

M

L

Wichgers Schreur *et al.*, PLoS Path 2016

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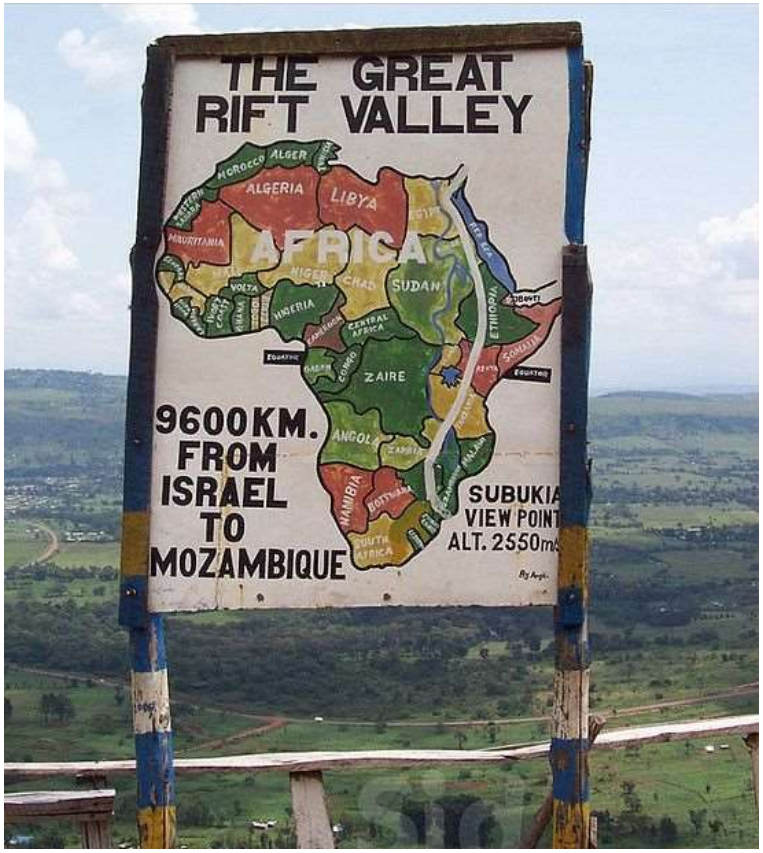
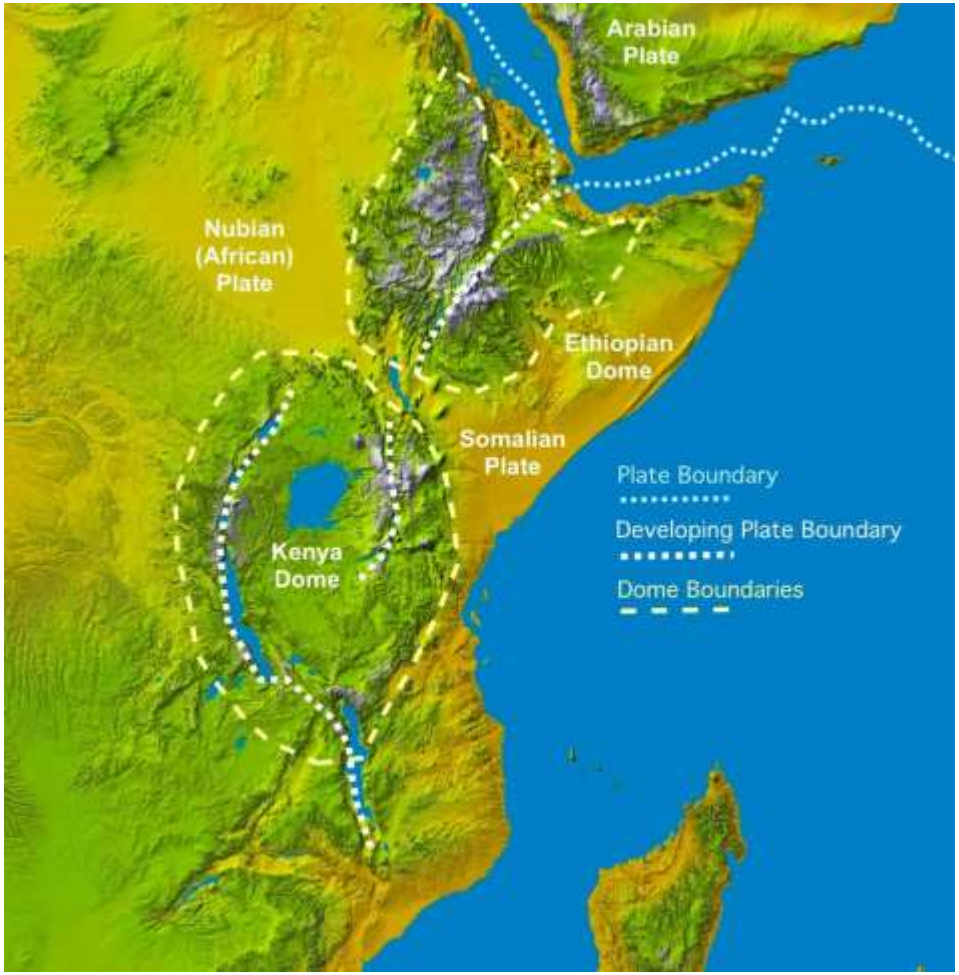
The Great Rift Valley





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History

- 1930: Virus isolated during outbreak among European-breed sheep in the Rift Valley, Kenya
  - 3500 lambs and 1200 ewes died from acute necrosis of the liver, also cattle and goats affected
  - Mosquito transmission suggested

Robert Daubney

Virus circulation between <1930-1950

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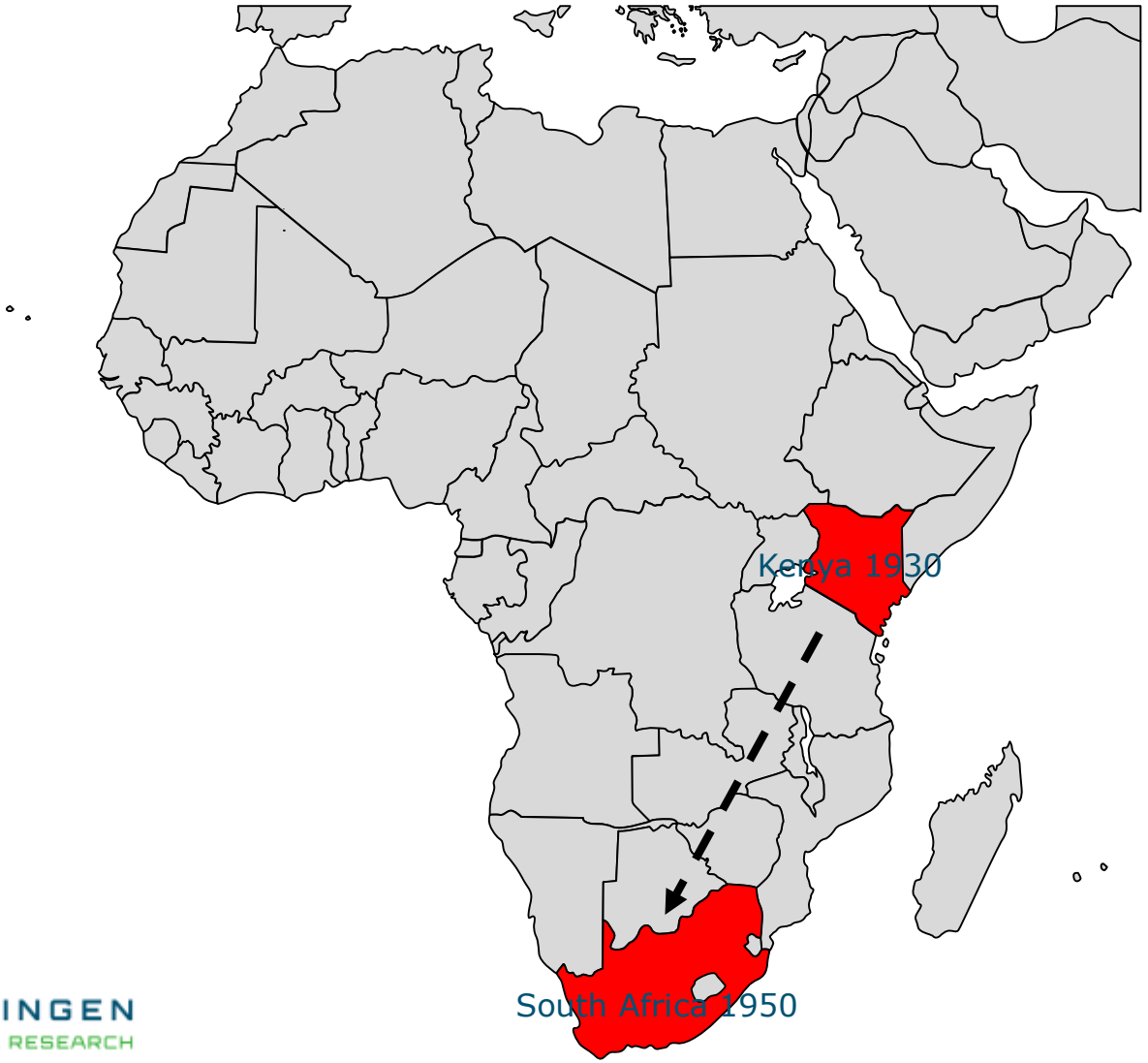
First incursion South Africa



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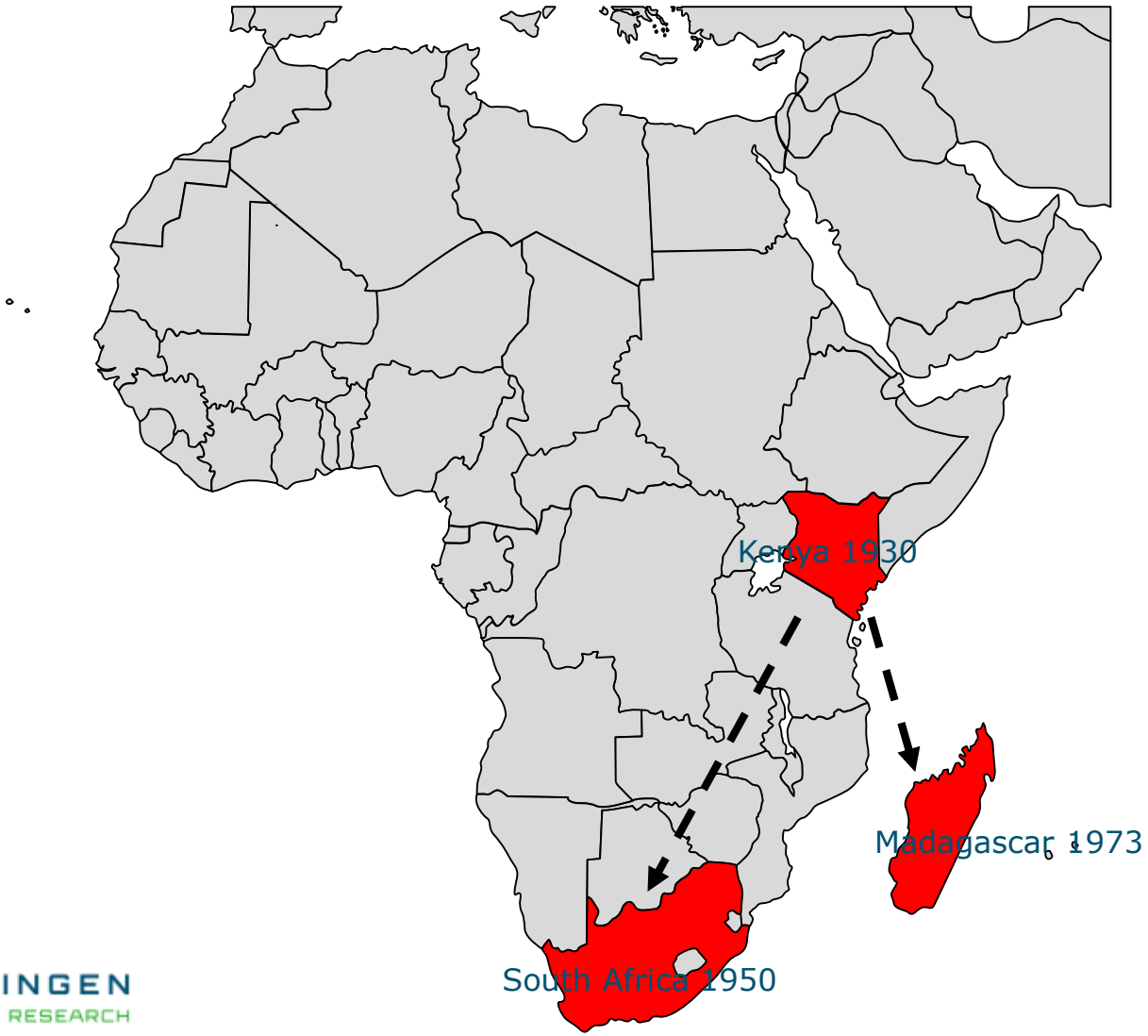
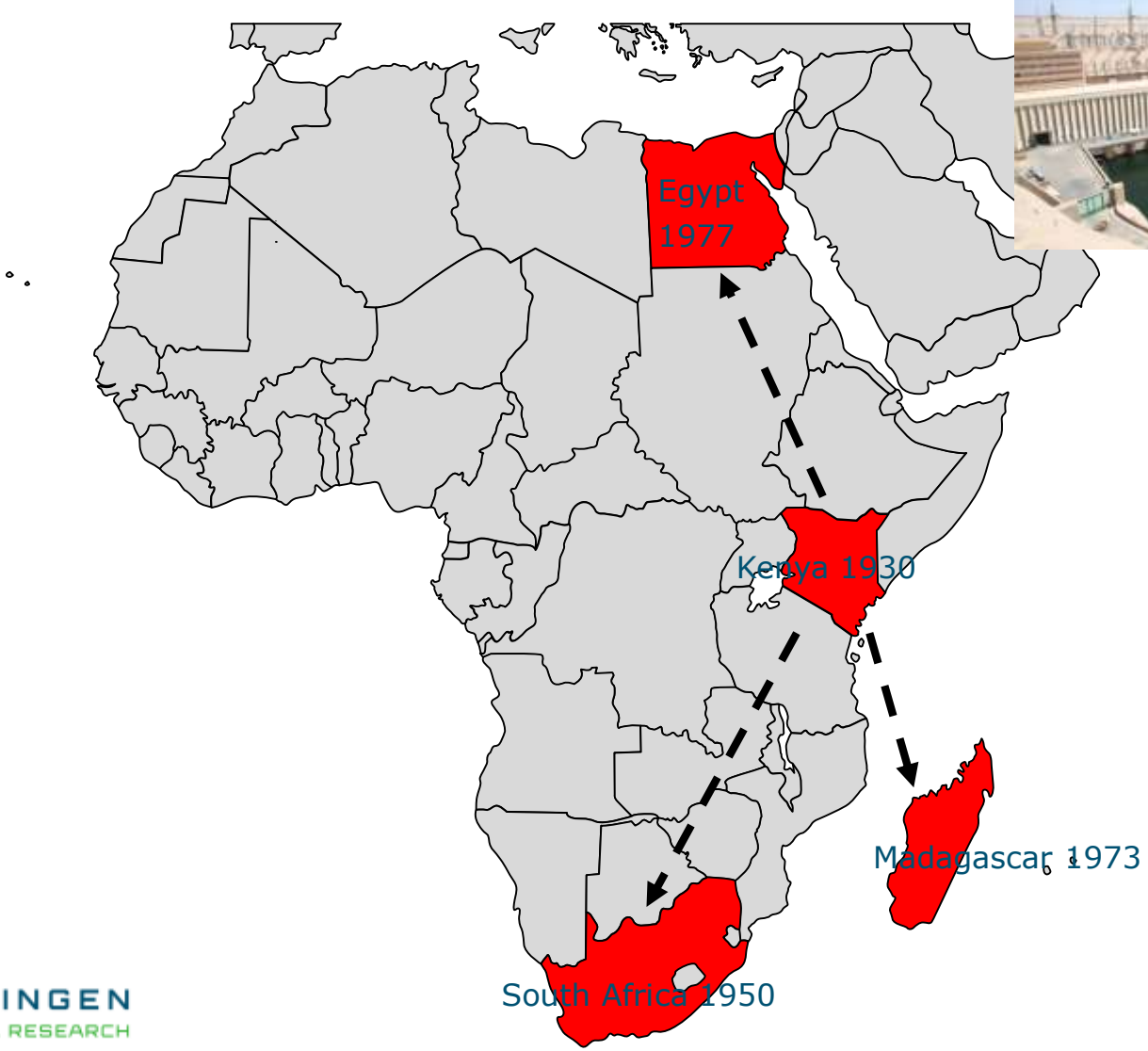
First incursion Madagascar



First incursion Egypt



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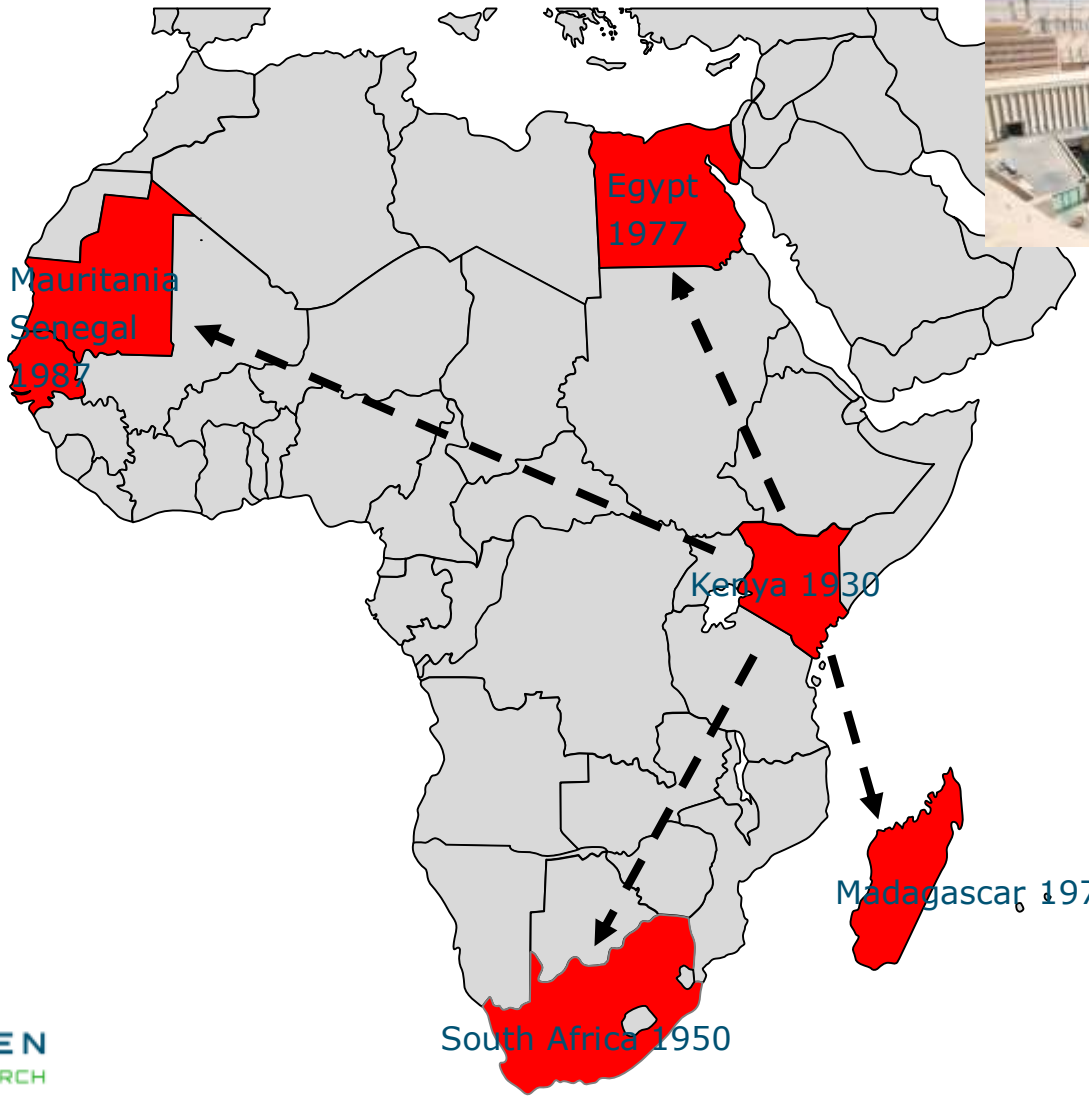
First incursion Mauritania and Senegal



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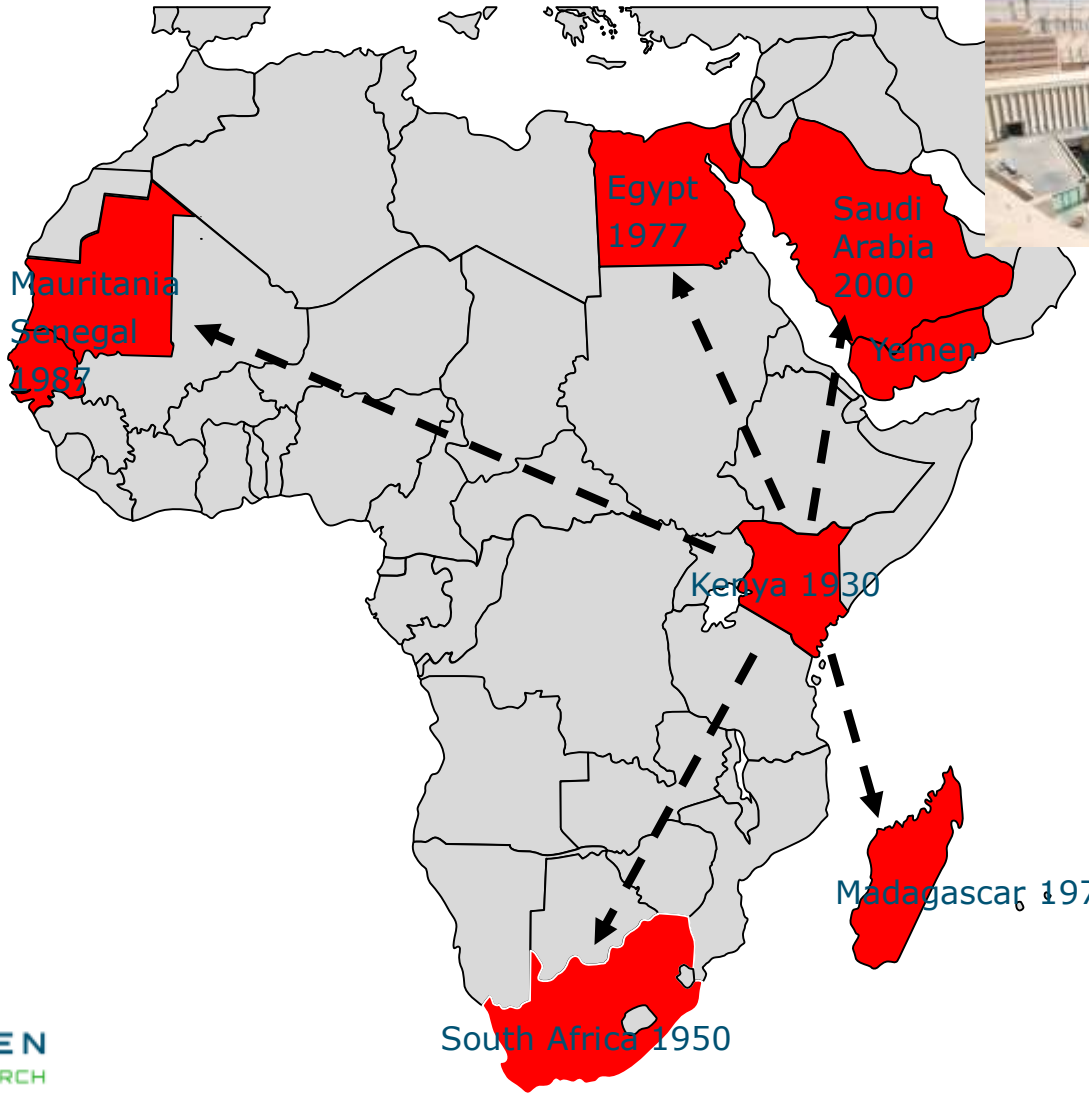
First incursions Saudi Arabia and Yemen



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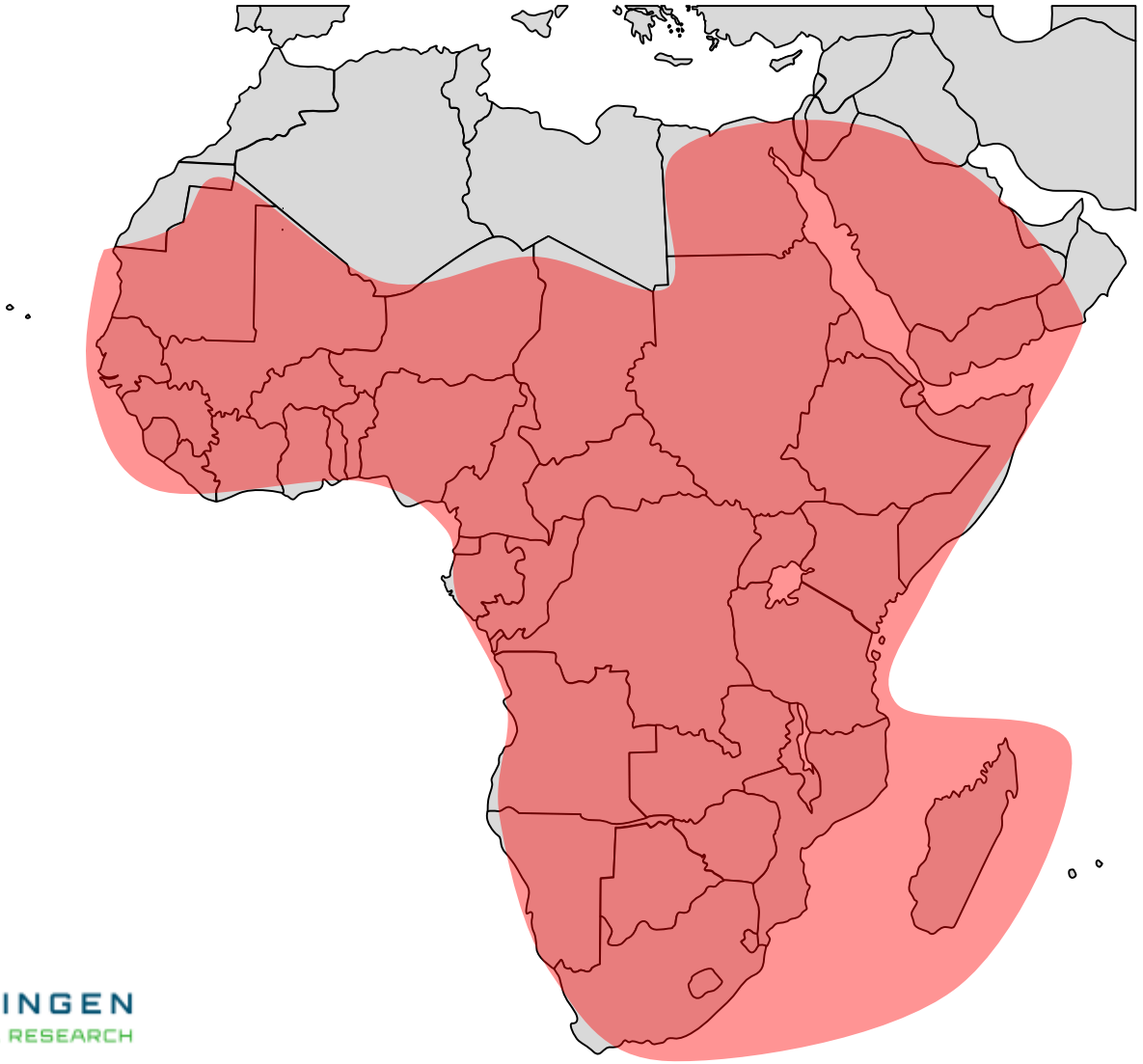
Current situation



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RVFV in Turkey?

Trop Anim Health Prod
DOI 10.1007/s11250-017-1359-8

REGULAR ARTICLES

The first serological evidence for Rift Valley fever infection in the camel, goitered gazelle and Anatolian water buffaloes in Turkey

Sibel Gür[1] · Mehmet Kale[2] · Nural Erol[3] · Orhan Yapici[4] · Nuri Mamak[5] · Sibel Yavru[4]

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JOURNAL OF VIROLOGY, Mar. 2007, p. 2805–2816
0022-538X/07/$08.00+0 doi:10.1128/JVI.02095-06

Vol. 81, No. 6

Complete Genome Analysis of 33 Ecologically and Biologically Diverse Rift Valley Fever Virus Strains Reveals Widespread Virus Movement and Low Genetic Diversity due to Recent Common Ancestry▽

Brian H. Bird,[1,3] Marina L. Khristova,[2] Pierre E. Rollin,[1] Thomas G. Ksiazek,[1] and Stuart T. Nichol[1]*

Special Pathogens Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases,[1] and Biotechnology Core Facility Branch,[2] Centers for Disease Control and Prevention, 1600 Clifton Road MS G-14, Atlanta, Georgia 30329, and University of California, Davis, School of Veterinary Medicine, Davis, California 95616[3]

CDC

CENTERS FOR DISEASE™
CONTROL AND PREVENTION

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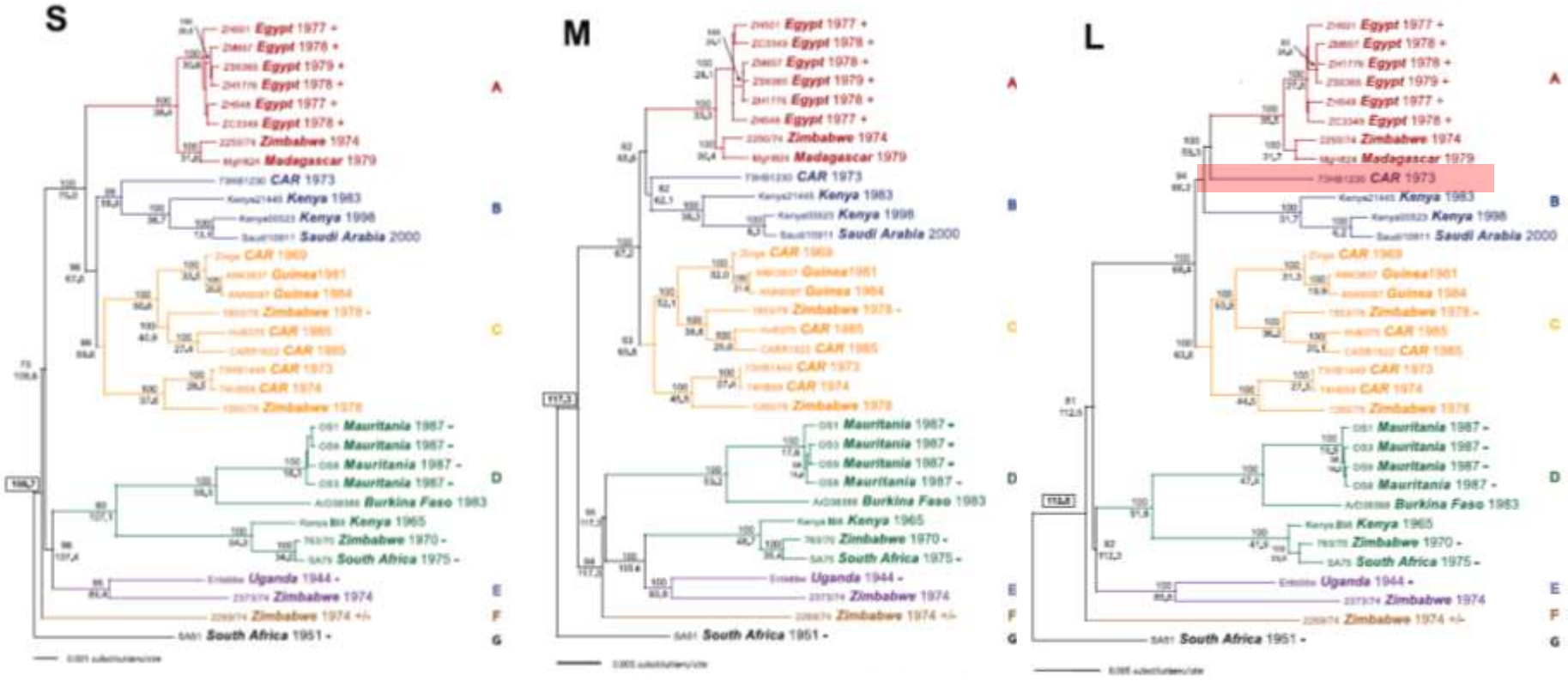
Widespread virus movement, few reassortment events



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RVFV isolated from 30 species, 10 genera

Aedes

Culex

Anopheles

Rift Valley Fever Virus (Family Bunyaviridae, Genus Phlebovirus). Isolations from Diptera Collected during an Inter-Epizootic Period in Kenya

K. J. Linthicum; F. G. Davies; A. Kairo; C. L. Bailey

The Journal of Hygiene, Vol. 95, No. 1. (Aug., 1985), pp. 197-209.

Aedes mcintoshi

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Medical and Veterinary Entomology

Medical and Veterinary Entomology (2017), doi: 10.1111/mve.12254

Rift Valley fever virus and European mosquitoes: vector competence of *Culex pipiens* and *Stegomyia albopicta* (=*Aedes albopictus*)

M. BRUSTOLIN[1], S. TALAVERA[1], A. NUÑEZ[1], C. SANTAMARÍA[1], R. RIVAS[1], N. PUJOL[1], M. VALLE[1], M. VERDÚN[1], A. BRUN[2], N. PAGÈS[1†], and N. BUSQUETS[1]

[1]IRTA, Centre de Recerca en Sanitat Animal, (CReSA, IRTA-UAB), Bellaterra, Spain and [2]Centro de Investigación en Sanidad Animal, Instituto Nacional de Investigación Agraria y Alimentaria (INIA-CISA), Valdeolmos, Madrid, Spain

Vmerge
Emerging viral vector-borne diseases

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Transmission of RVFV from European breed lambs to *Culex pipiens* mosquitoes

Culex

Vloet et al., submitted

Vmerge
Emerging viral vector-borne diseases

Ministry of Economic Affairs

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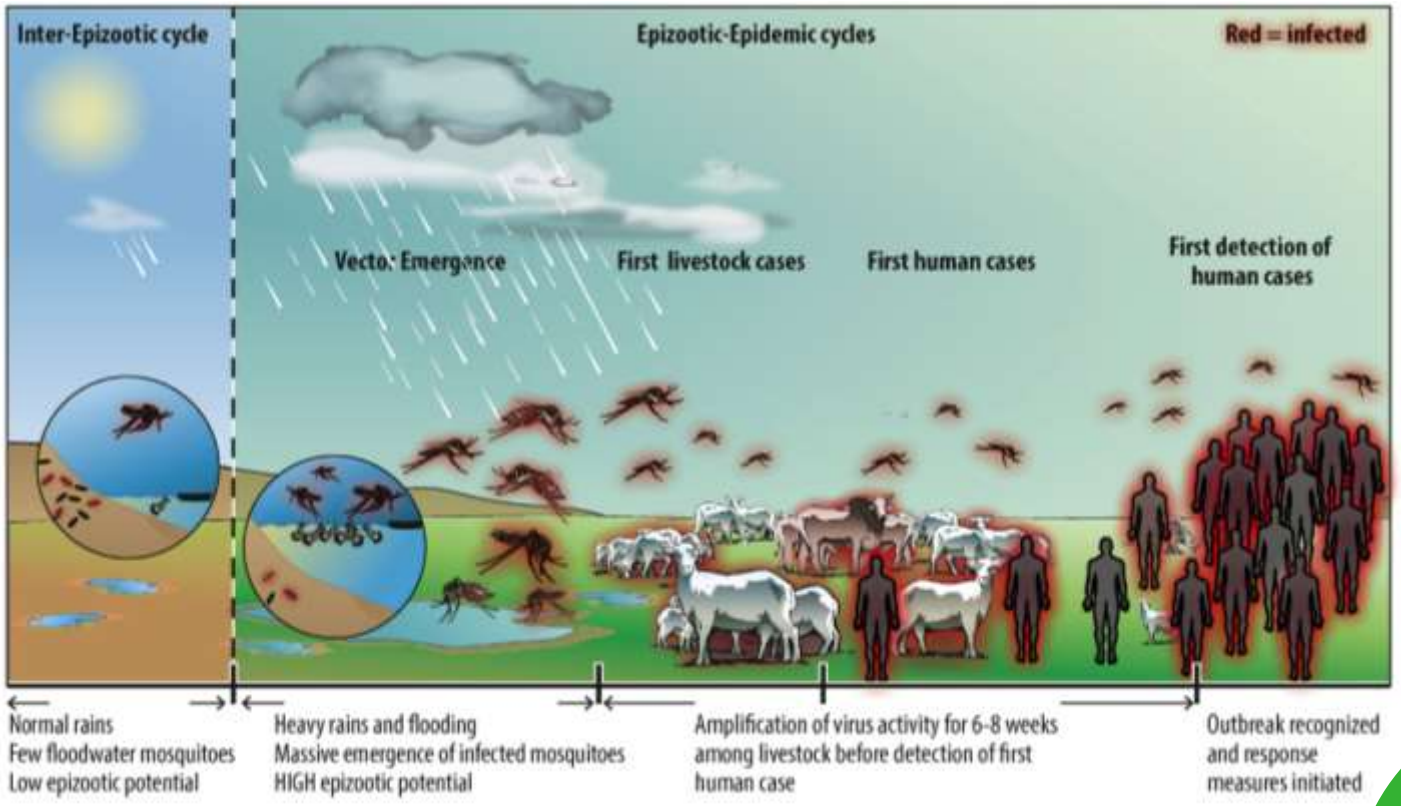
Ecology



Bird & McElroy
Antiviral Res
2016

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Rift Valley fever animal models @WBVR

a

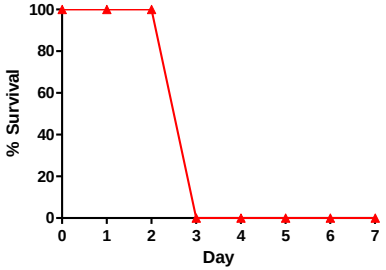
Mice

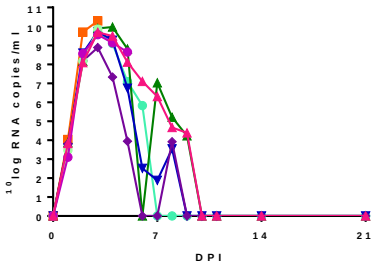
b

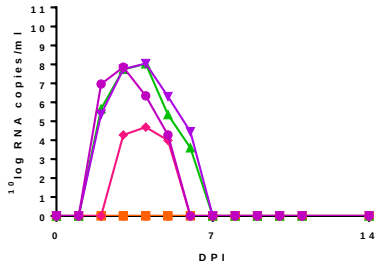
Sheep

c

Cattle







~20% Fatality

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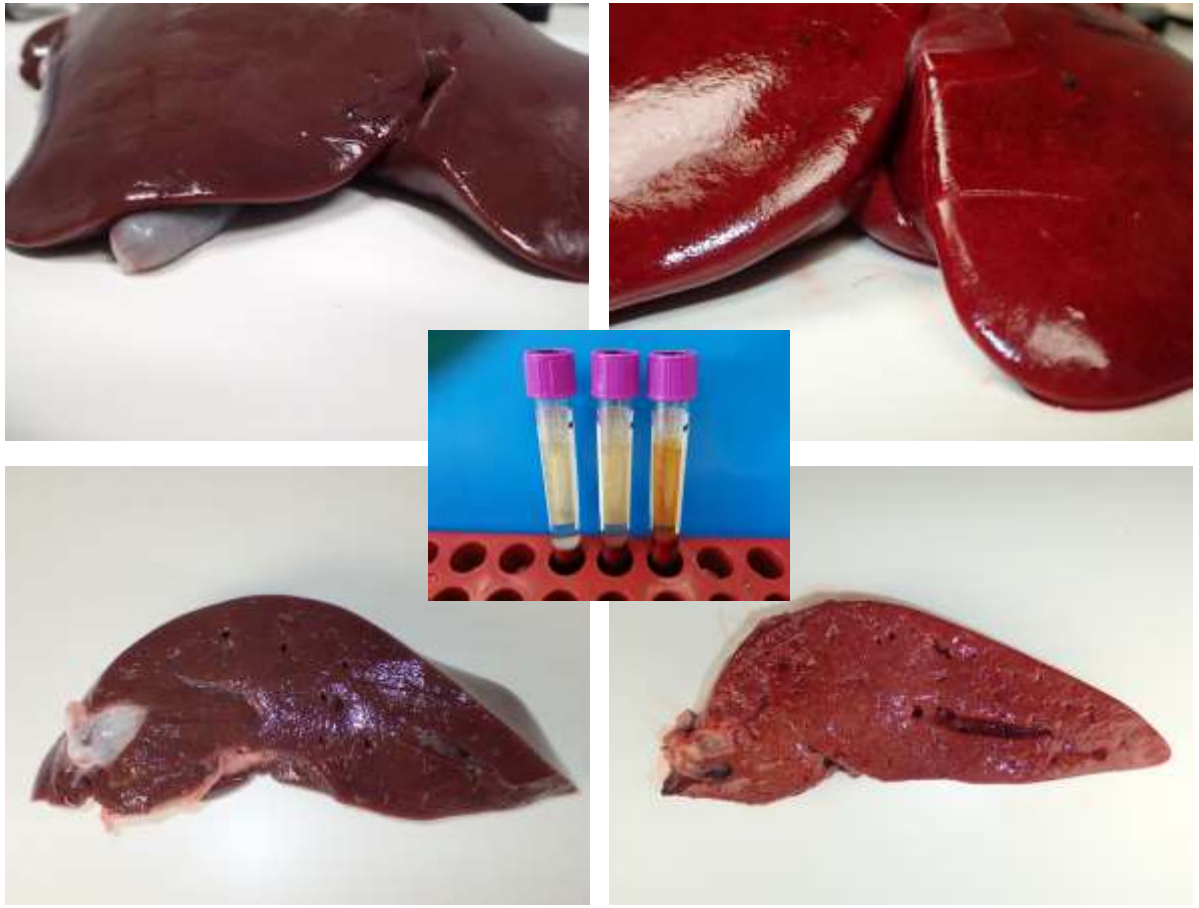
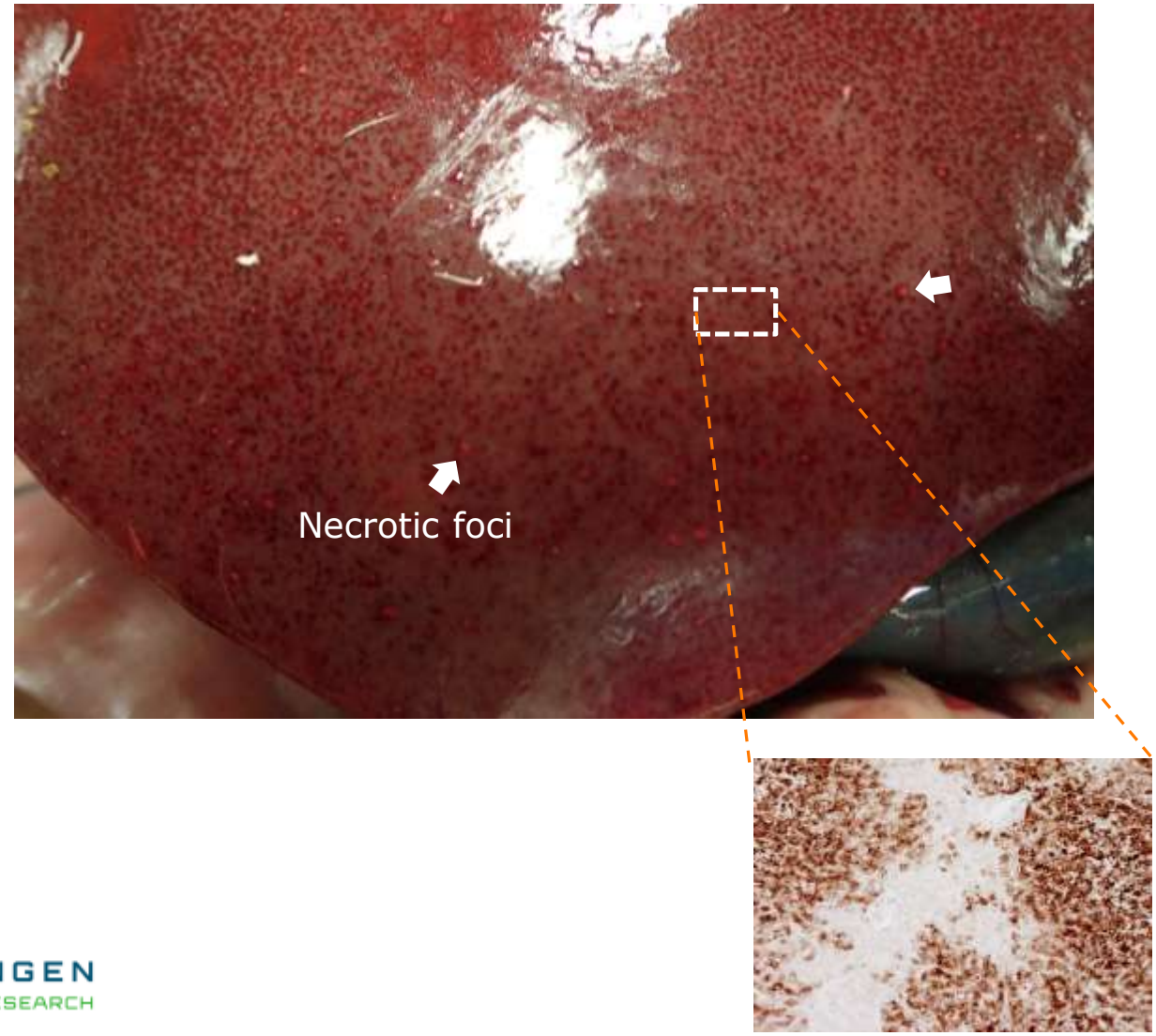
Liver: The major target organ



Fatal cases



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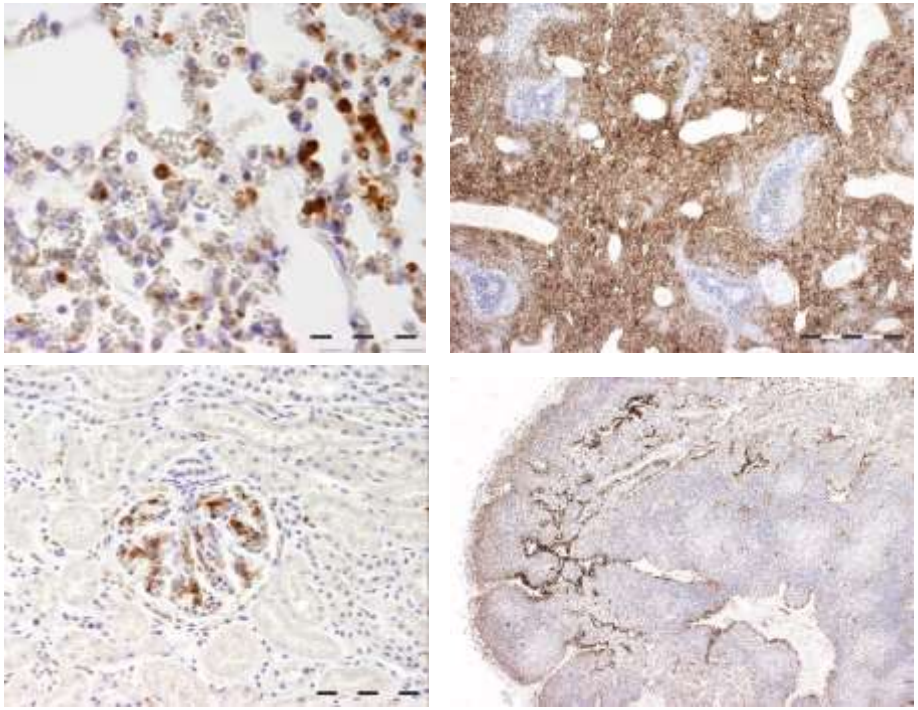
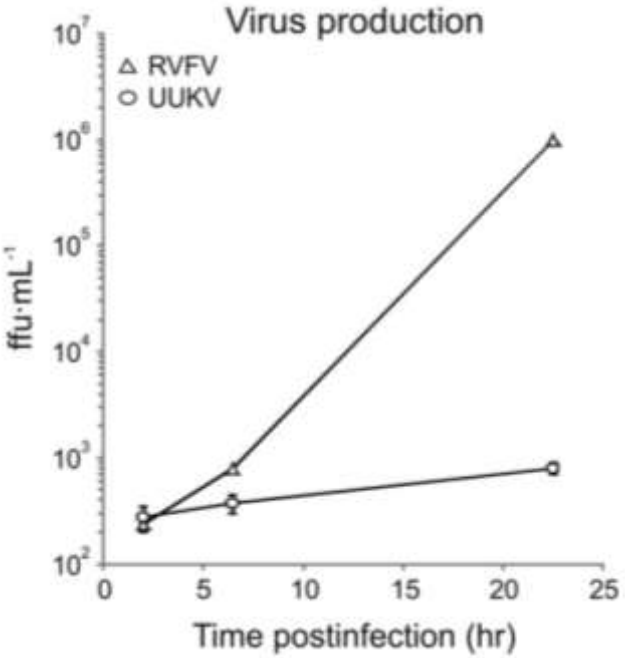
Mononuclear phagocytic cells





Lozach et al., Cell Host & Microbe 2011

Commercially available RVF vaccines

- Inactivated vaccine: Requires booster and yearly re-vaccinations

- Smithburn vaccine: Highly effective, but not safe for pregnant animals

ONDERSTEPOORT
BIOLOGICAL PRODUCTS

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Clone 13

Bouloy *et al*, 1995-2014

- Plaque-purified from a human case
- 70% deletion NSs gene
- Shown to be safe in mice, sheep and cattle
- Highly effective in sheep and cattle
- Since 2010, more than 19 million doses used in the field
- Registered in South Africa, Namibia and Botswana

ONDERSTEPOORT
BIOLOGICAL PRODUCTS

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National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

CENTRAL VETERINARY INSTITUTE
WAGENINGEN UR

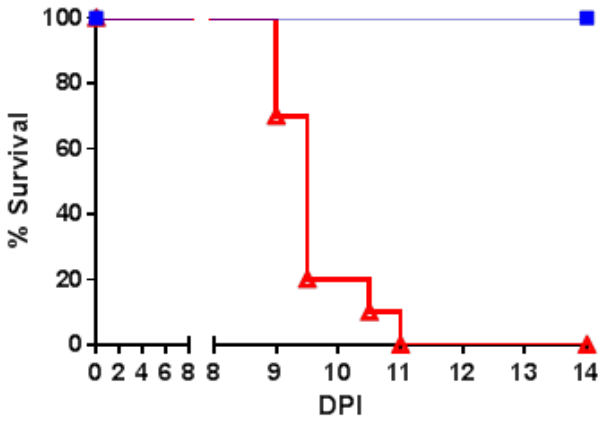
MSD

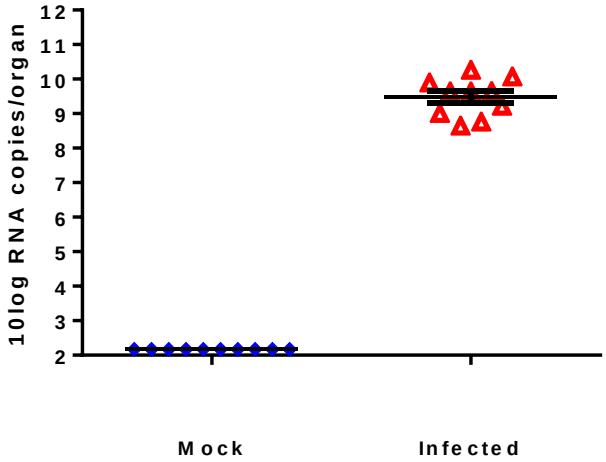
Universiteit Utrecht

CASTELLUM

A public-private partnership to protect humans and animals from emerging zoonoses

Clone 13 is neurovirulent in mice after intranasal administration



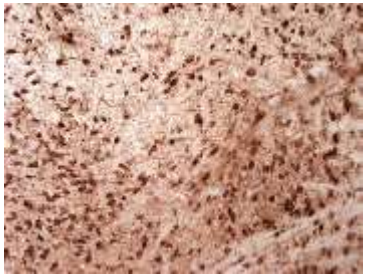


Clone 13

Negative control

Cerebellum

Hippocampus



Cerebral cortex

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Clone 13 is safe for lambs

- No viremia
- No disease
- No dissemination
- No shedding
- No spreading

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Fetal malformations and stillbirths after inoculation of an overdose of Clone 13

Makoschey et al., PLoS Negl Trop Dis. 2016

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Next-generation vaccines

- MP-12
- MP-12ΔNSm
- ZH501ΔNSs-ΔNSm (DDvax)
- ChAdOx-1-GnGc
- RVFV-4s

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SCIENTIFIC REPORTS

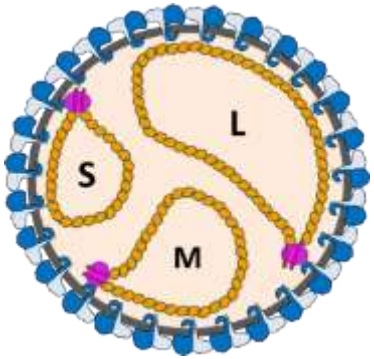
OPEN

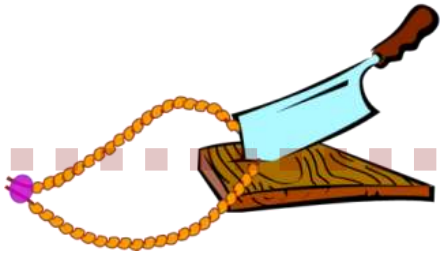
Chimpanzee Adenovirus Vaccine Provides Multispecies Protection against Rift Valley Fever

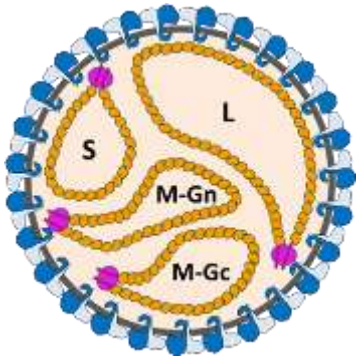
Received: 23 September 2015
Accepted: 08 January 2016
Published: 05 February 2016

George M. Warimwe[1,2], Joseph Gesharisha[3], B. Veronica Carr[4], Simeon Otieno[3], Kennedy Otingah[3], Danny Wright[1], Bryan Charleston[4], Edward Okoth[3], Lopez-Gil Elena[5], Gema Lorenzo[5], El-Behiry Ayman[6], Naif K. Alharbi[1,7], Musaad A. Al-dubaib[6], Alejandro Brun[5], Sarah C. Gilbert[1], Vishvanath Nene[3] & Adrian V. S. Hill[1]

Four-segmented RVFV

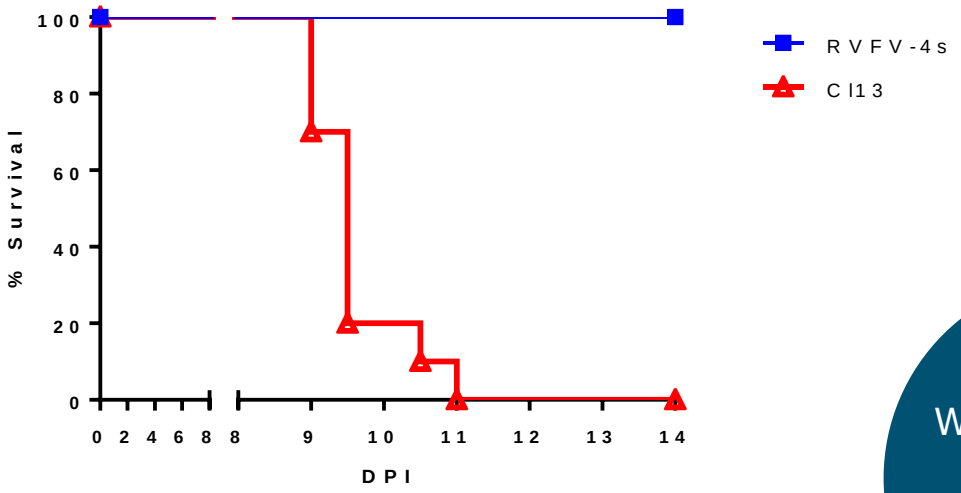






(ΔNSs)

Intranasal



Wichgers Shreur *et al.*, Vaccine 2014,2017

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Efficacy and safety of RVFV-4s

Sterile immunity, single vaccination

Wichgers Shreur *et al.*, Vaccine 2015

Overdose is safe for fetus

Wichgers Shreur *et al.*, Vaccine 2017

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Major conclusions

- RVFV has affected millions of animals and tens- to hundreds of thousands of humans in single outbreaks
- RVFV has a demonstrated ability to spread across large geographical areas
- Susceptible livestock, wildlife and mosquito species are globally prevalent
- Outbreaks are difficult to predict
- Vaccines (human and veterinary) and diagnostics to control large future outbreaks are not (readily) available

Unaswered questions and unmet needs

- Unanswered questions (a few of many):
  - Epidemiology: Transmission and sylvatic cycle
  - Immunology: Role of immune cells
  - Pathogenesis: Severe cases

- Unmet needs:
  - More and better diagnostic capablility
  - Vaccine that optimally combines efficacy with safety
  - Vaccine stockpile or incentive to vaccinate (combination vaccines!)

No longer neglected...

WHO publishes list of top emerging diseases likely to cause major epidemics

WHO HQ SHOC Room
WHO /Christopher Black

10 December 2015 -- A panel of scientists and public health experts convened by WHO met in Geneva this week to prioritise the top five to ten emerging pathogens likely to cause severe outbreaks in the near future, and for which few or no medical countermeasures exist. These diseases will provide the basis for work on the WHO Blueprint for R&D preparedness to help control potential future outbreaks.

The initial list of disease priorities needing urgent R&D attention comprises: Crimean Congo haemorrhagic fever, Ebola virus disease and Marburg, Lassa fever, MERS and SARS coronavirus diseases, Nipah and Rift Valley fever. The list will be reviewed annually or when new diseases emerge.

CEPI | New vaccines for a safer world

Coalition for Epidemic Preparedness Innovations (CEPI)

Call for proposals (CfP)
Topic: Platform technologies to enable rapid vaccine development for epidemic prone infections

Reference number: CEPI-CfP-002-platforms

ZAPI
Zoonoses Anticipation and Preparedness Initiative

http://www.zapi-imi.eu/

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