UTMB
The University of Texas Medical Branch

Rift Valley Fever in the USA
Appearance and Recovery

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FAZD CENTER
National Center for Foreign Animal and Zoonotic Disease Defense

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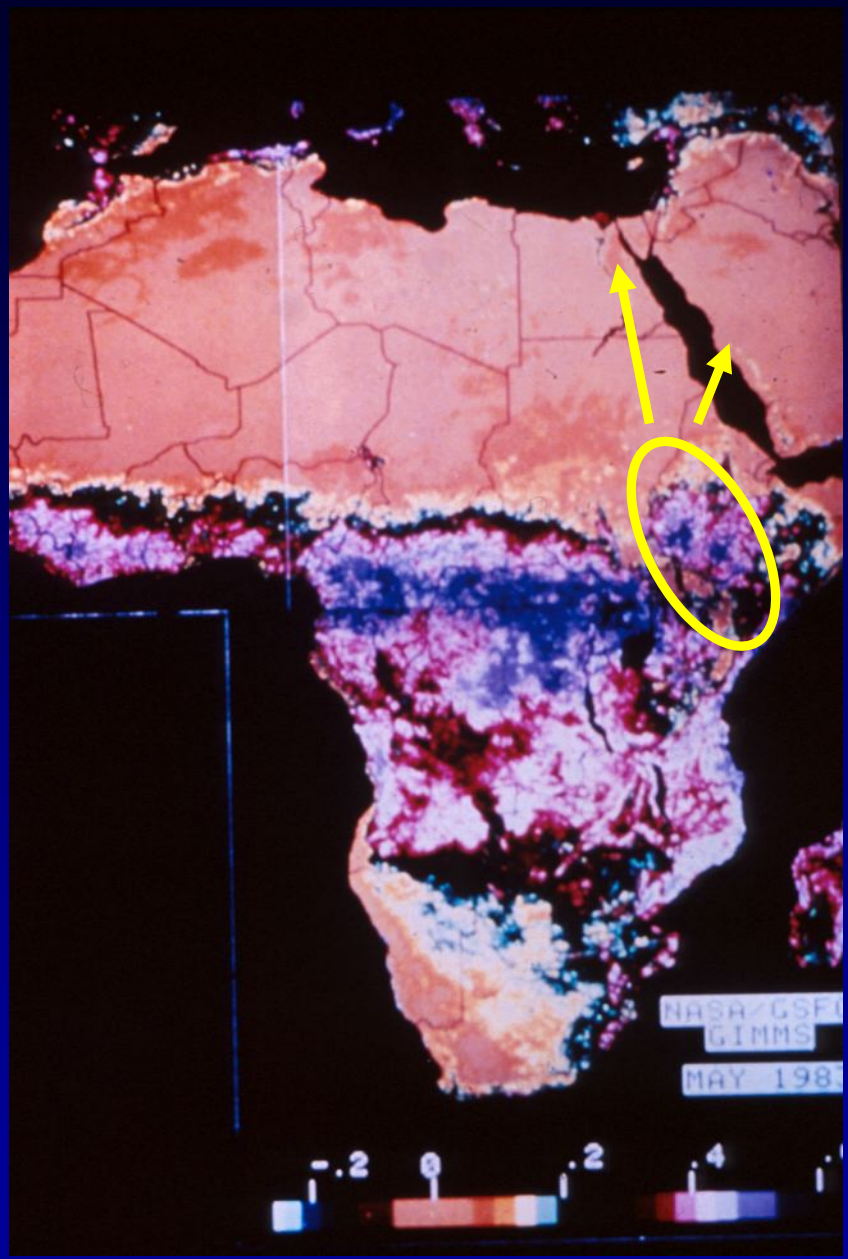
National Institutes of Health

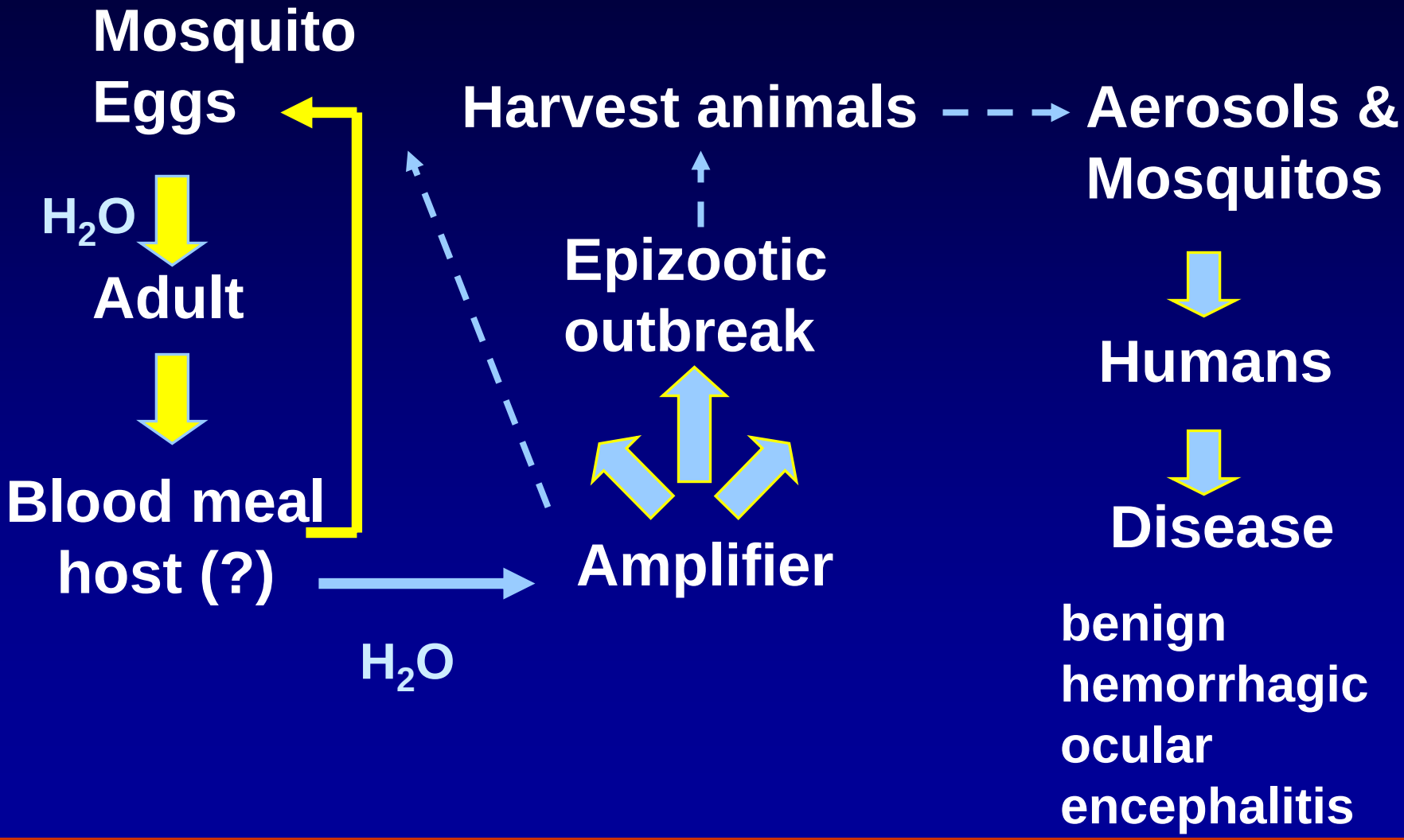


RIFT VALLEY FEVER

Endemic and intermittently epidemic throughout sub-Saharan Africa with distant spread to Egypt and Arabia

Rift Valley Fever

"Arbo-cycle"



Evaluation of pathways for release of Rift Valley fever virus into domestic ruminant livestock, ruminant wildlife, and human populations in the continental United States.

Kasari, T. et.al. USDA/APHIS JAVMA 232514-529 (2008)

- **Entry of infected persons**
- **Mechanical transport of infected insect vectors**
- **Importation of infected animals**
- **Intentional dissemination of live virus**

RVFV IN ANIMALS

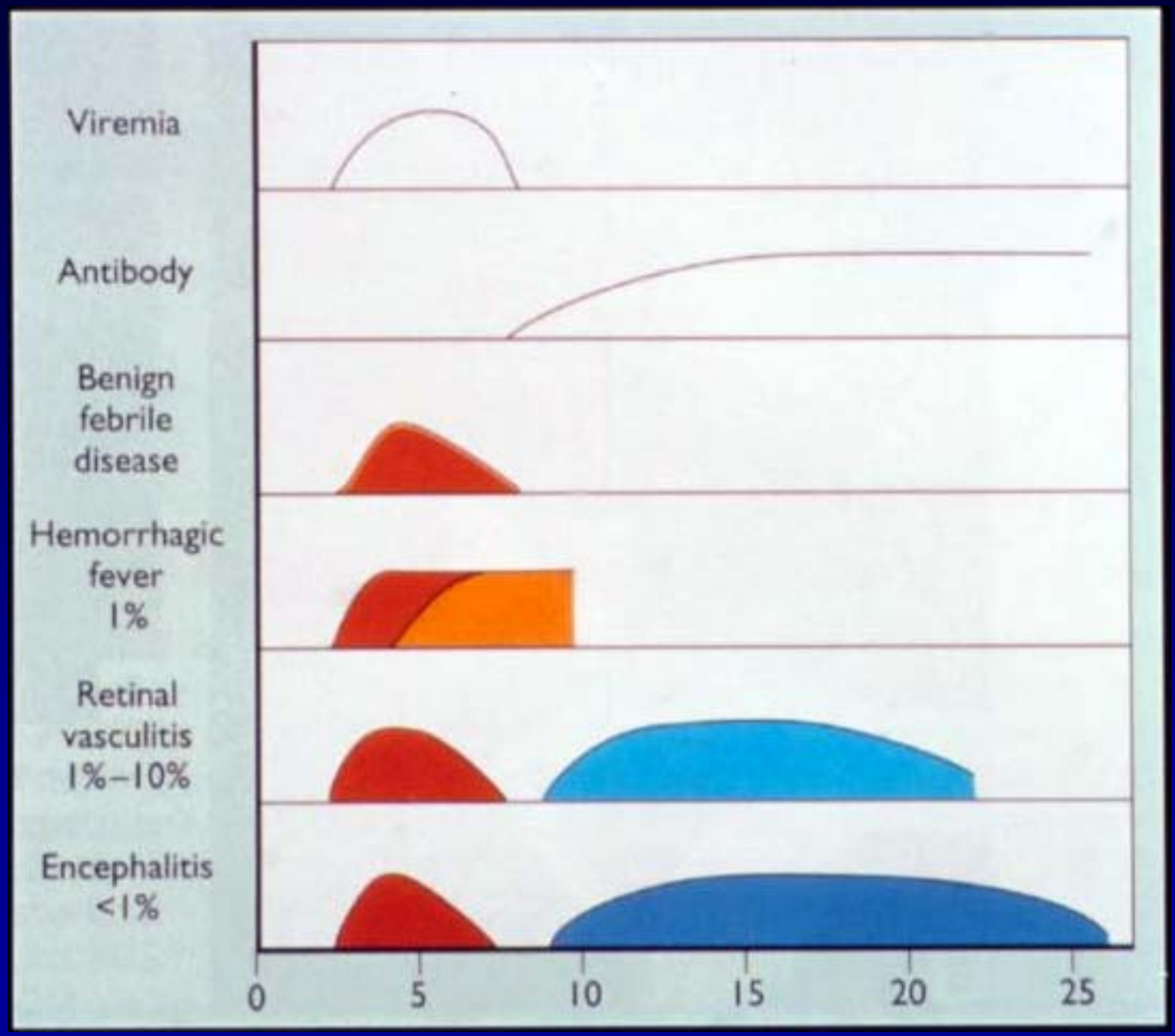
- SHEEP: ~20-30% mortality, abortion
- CATTLE: ~10-15% mortality, abortion
- GOATS: ~5-10% mortality, abortion

Amplifier

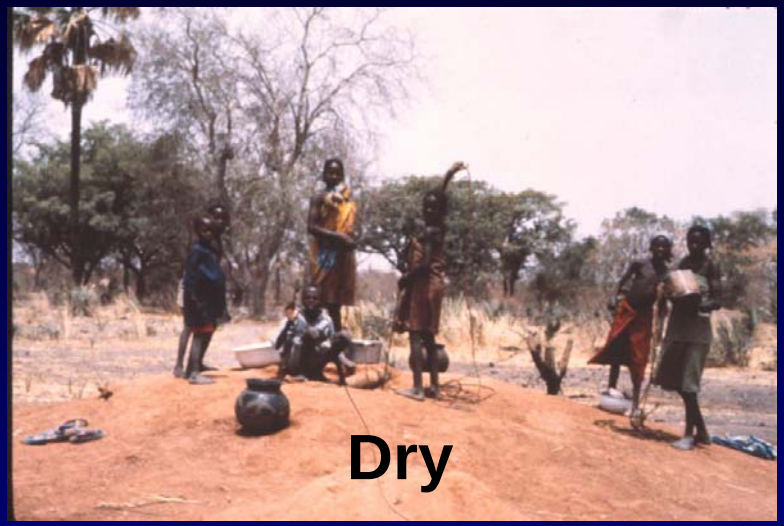
- CAMELS: survive, low viremia, abortion (?)
- WATER BUFFALO: survive, low viremia
- AFRICAN BUFFALO: survive, abortion
- OTHER AFRICAN UNGULATES: Antibody only

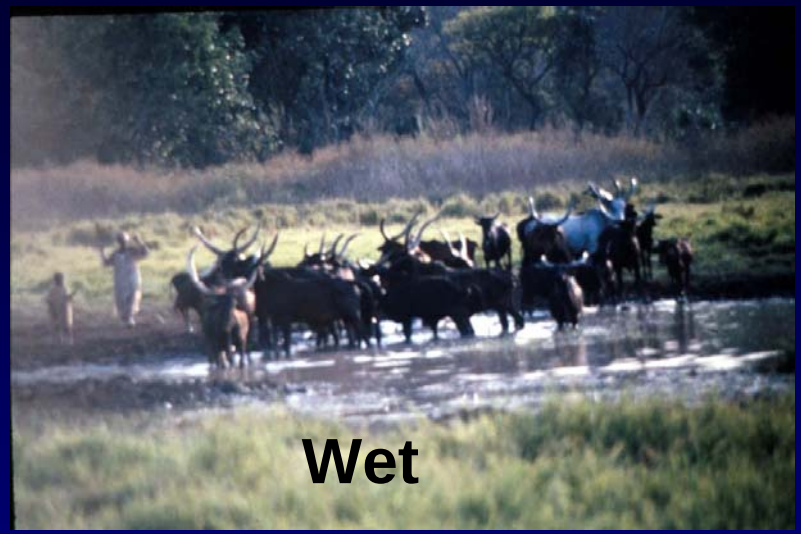
Mortality depends on breeds, other health and stress factors
Infections of adult animals ends in death if viremia high.
Immature animals have higher viremias and mortality.
Abortion seems to be a complication of most viremic infections.

CLINICAL SCHEMA RVF
Human Infection



The Milieu of RVFV





Zagazig Hospital, Egypt

Only 2 known autopsies of encephalitis victims

National Veterinary Stockpile Countermeasures Working Group Report Rift Valley Fever*

September 7, 2006

- **The United States is vulnerable to a natural or intentional RVF outbreak.**
- **There is no reason to believe that the spread of RVFV would be slower, less dramatic, or more controllable than that of West Nile virus.**
- **Every region of the U.S. has a competent vector for RVFV**

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*Sponsored by USDA/ARS

Available Tools*

- **No effective drugs**
- **No commercial vaccines available in N.A.**
- **No commercial pen-side tests (*regional and then national lab testing)***
- **There are numerous laboratory Dx tests – "tangled web of bench scientists" (*unvalidated and difficult to deploy*)**

*NVSC Working Report - Sep, 2006

Diagnosis of RVFV

- **Unfamiliar clinical signs?**
- **Tests**
  - **PCR (acute illness)**
  - **IgM and IgG ELISA (prevalence)**
  - **Inhibition ELISA (for wildlife)**
- **Transport & handling samples once diagnosed (select agent)**

Response Needs

- Strategy to contain outbreak
- Protect responders
  - Select agent, highly infectious
  - Vaccine or drug (rapid onset)
- Vector control (insecticides)
- Carcass disposal (de-population)

FAZD CENTER

National Center for Foreign Animal and Zoonotic Disease Defense

NATIONAL CENTER FOR FOREIGN ANIMAL & ZOONOTIC DISEASE DEFENSE

FY2007 Mission

- Protect against the introduction of high-consequence foreign animal and zoonotic diseases into the United States
- Emphasis on prevention, surveillance, intervention and recovery

Impact and Relevance

- New methods for rapid and accurate detection of foot and mouth disease, Rift Valley fever, avian influenza, and brucellosis
- Vaccines and antiviral agents against introduced diseases
- Decision tools for assessment of consequences of options to prevent/curtail disease spread
- Education and Outreach

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Major Partners

- Texas A&M University
- Univ. of California at Davis
- Univ. of Southern California
- Univ. of Texas Medical Branch
- Univ. of Maryland

- Plumb Island Animal Disease Center
- National Laboratories

Customers

- DHS Chief Veterinary Officer
- DHS Preparedness Directorate
- DHS NBACC
- USDA
- CDC
- NIAID
- State Emergency Response Agencies
- Agricultural Industry

Diagnostics for RVFV @ UTMB

Acute diagnostics

- Liver, serum, abortuses
- Virus isolation
- Immunoassays
- RT-PCR
  - Primers designed
  - 8 RVFV strains for test
  - Collaborations in Kenya & South Africa

Serological tests

- ELISA preferred
- Rec N Antigen (UCDavis)
- Irradiated virus available
- MAb hybridomas from mice, humans
- Human immune plasma
- Animals in So. Africa

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"Good News" about RVFV

- **Serologically "conserved"**
  - **Diagnostic test(s) are feasible**
- **Vaccine**
  - **Experimental killed vaccine (humans)***
    - **Limited availability**
    - **3 injections, 28 days**
    - **Circulating antibody lasts < 1 year**
    - **Anecdotally efficacious**

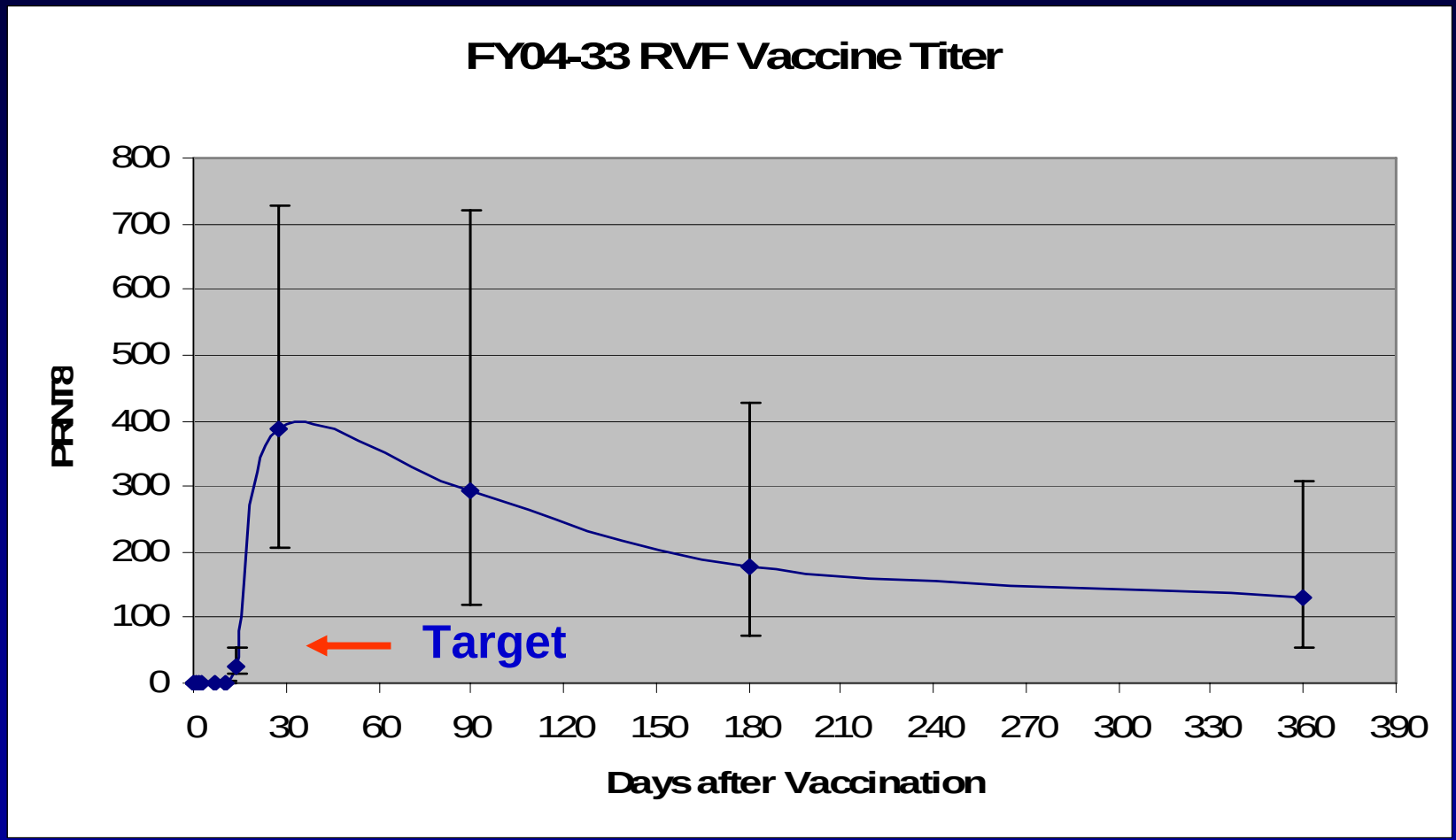
***USAMRIID**

MP-12 RVFV Experimental Vaccine (live, attenuated-USAMRIID)

- **Stable lyophilized (18 yrs, -30C)**
- **Immunizes humans & animals**
- **No phenotypic/genomic reversion**
- **Tested in 62 volunteers, no SAE***
- **Single inoculation**
- **Rapid, Ab in 7-10 days**
- **Lasting (Ab at 1 year post vaccination)**
- **Anecdotally efficacious**

***Serious Adverse Effects**

Overall antibody response to RVF MP12 vaccine



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Amino acid changes in virus isolates from human isolates

Amino acid changes in virus isolates from human vaccines

Volunteer number	Number of isolates	Mutation number and amino acid change									
		S1427	S1469	M2520	M3773	L127	L711	L2181	L3465	L3879	L4749
FY04-33-0005	1				Silent				Silent		Silent
FY04-33-0007	1			Phe→Leu				Glu▸Asp			
FY04-33-0014	1		Gly→Glu			Val▸Iso					
FY04-33-0021	4						Asn▸Lys			Silent	
FY04-33-0026	2	Asn→Ser									

No mutations in attenuating sites
No reversions to wild type detected

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MP-12 Veterinary Vaccine

- Protects animals from virulent RVFV
- No apparent reversion to virulence
- No abortions in USA studies
- Vaccinated pregnant sheep carried to term, lamb protected vs challenge
- Not DIVA competent
- UTMB collaborating with major animal health vaccine manufacturer

- DHS/FAZD developing deletion based vaccine
  - Virtually eliminates reversion to virulence
  - Potentially DIVA competent

MP-12 Manufacture Human Vaccine

- Genetics of Virulence
- New MRC-5 Master Cell Bank
- New Virus Seed
- Monkey Neurovirulence on Production Virus Seed
- Optimize MP-12 Production Methods
- Develop Downstream Processing Steps
- Qualify Process 10L (3 x 10^6 doses)
- Assemble IND Documentation

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