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Rift valley fever: Next generation vaccines for an old foe

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CDC Rift Valley fever Vaccine Initiative

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Viral Special Pathogens Branch

- **Focus on viral hemorrhagic fevers** (>35 viruses, 5 Families)
  - BSL-4, BSL-3+, BSL-2 labs

- **Diagnostics – Outbreak Response**
  - Serology, molecular, Next-Gen sequencing

- **Epidemiology**

- **Laboratory Science**
  - molecular biology, pathogenesis, immunology, vaccines and anti-viral therapeutic drugs

- **Ecology**
  - Uganda (Ebola, Marburg)
  - South America (hantaviruses)
  - Eastern and Southern Africa (RVF)
Rift Valley fever virus

- Mosquito-borne RNA virus (*Bunyaviridae*)
  - *(Aedes* sp. mosquitoes most important)

- Endemic throughout Africa and parts of Arabian Peninsula

- Outbreaks linked to extensive rainfall – mosquito abundance

- Outbreaks are extensive
  - humans (10s to 100s thousands)
  - livestock (millions)

- Threat of introduction into Middle East, Europe or US
  - Many competent mosquito vectors in North America

- Potential bioterrorism threat
RVF disease

- **Humans**
  - Majority: self limiting febrile illness
  - ~1-2% of cases
    - ACUTE: hepatitis > hemorrhagic syndrome
      - (10-20% case fatality)
    - DELAYED: encephalitis, retinitis, blindness

- Direct contact with infected livestock is the key risk factor for severe and lethal disease
RVF disease

- **Livestock**
  - Sheep, cattle, goats
  - Camelids
  - Abortion storms
    - near 100% sheep and cattle
  - High newborn mortality
    - 80-100%
  - Adult mortality
    - 5-20%

- Wildlife: Cape Buffalo transient viremia, many other species IgG positive

- *Horses, swine, poultry unaffected*
Current status of RVF vaccines

• No commercially available human or livestock vaccines for use in the U.S. and Europe

• Exciting time in RVFV vaccine research
  – Recombinant MLAV, VLP, VRP, Paramyxovectored, Pox virus vectored etc.

• A couple of livestock vaccines in limited use in Africa (OBP, South Africa):  
  – Inactivated vaccine
  – Live attenuated vaccines: Smithburn strain
    • Abortions, teratology, other fetal abnormalities
    • No capacity to differentiate vaccinated from naturally infected animals
    • Clone 13 LAV may be an improvement with fewer adverse effects
CDC RVF vaccine development strategy

- Virus amplification in livestock leads to explosive outbreaks and is needed to get spillover into humans
- Disease in livestock precedes disease in humans by ~ 1 month
- Significantly easier to get vaccines approved for livestock than humans
- One Health – good livestock vaccines should indirectly reduce or prevent human disease
- Vaccine design should allow for further development in humans
  - (FDA animal rule)
...or why is CDC working on a livestock vaccine ???
Don’t you work on people diseases???

One Health – good livestock vaccines should indirectly reduce or prevent human disease

Bird and Nichol
Ideal RVF vaccine properties

• Precise identity and excellent purity
• Safety – No post-vax disease; no abortions or fetal abnormalities (Historically this has been a BIG problem)
• Single dose, rapid and long lasting protection
  - best achieved with live attenuated vaccine
• Multiple attenuating lesions/ absence of reversion
• Inexpensive (*produced at high titers = cheap/dose*)
• Differentiate infected from vaccinated animals
  - DIVA
Towards rational vaccine design

• Reverse genetics approach
  – Generation of precisely engineered infectious virus from plasmid DNA
  – Identify and knock out critical virus virulence genes
  – Use these modified viruses as vaccine candidates
Genome composition
triptite ss(-) RNA

L segment ~6404nt

M segment ~3885nt

S segment ~1689
Major RVFV virulence factors

Δ-NSm virus attenuated in rats
LD$_{50}$ $\uparrow$ ~3 logs
Bird et. al., 2007

Deletion of 70% NSs ORF attenuated in mice
LD$_{50}$ $\uparrow$ ~4 logs
Muller et. al. 1995

L segment ~6404nt

Polymerase

M segment ~3885nt

S segment ~1689nt

Δ∆ ∆∆

-NSm virus attenuated in mice LD$_{50}$ $\uparrow$ ~4 logs

Bird et. al., 2007

Deletion of 70% NSs ORF attenuated in mice LD$_{50}$ $\uparrow$ ~4 logs

Muller et. al. 1995

Δ∆ ∆∆
Generation of ΔNSs-ΔNSm vaccine

BSR-T7 cell
or VERO + pT7

wtRVFV

Δ/Δ Vax

RVFL

RVFS

RVFM

ΔNSm-M

ΔNSs-S

ΔNSm-M

ΔNSs-S

L

M

S
Rodent results (~6yrs)

• Excellent safety with either candidate when given at doses up to 10,000x LD$_{50}$ of virulent virus (LD$_{50}$ = < 1.0 PFU)

• Complete protection from up to 10,000x LD$_{50}$ dose of virulent virus 28 days post-vax
  Robust IgG response >1:6400
  • PRNT$_{80}$ >1:1256

• Rapid protection up to 100% within 48 hours post-vaccination in mice
Rodent results

- Excellent safety with either candidate when given at doses up to 10,000x LD$_{50}$ of virulent virus

- Complete protection from up to 10,000x LD$_{50}$ dose of virulent virus 28 days post-vax
  Robust IgG response >1:6400
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BUT WHAT ABOUT A RELEVANT HOST???????
Vaccine Sheep Trial

Bird et al., Journal of Virology 2011

Deltamune Pty. Ltd. South Africa

• Safety and Efficacy Trial
  • timed pregnant ewes
  • $1.0 \times 10^4$ PFU SC
  • N=29 vaccinates, N=3 sham controls
  • Vacc. at day 42 gestation:
    • (fetus most sensitive to teratogenesis, MP12/Smithburn)
Δ/Δ Vaccine Trial Timeline

Dr. Barbara Knust

Day of Pregnancy

Pregnancy Dx U/S
N=32 selected

Timed Preg
N=54
Safety 1: Vax early gestation: N=29 + 3 shams

Vaccine Trial Timeline

Day of Pregnancy

Timed Preg

Vaccination 10^4 PFU SC

0 42 90 121 142/D+1 +5

U/S
Safety 1: Vax early gestation: N=29 + 3 shams

Vaccine Trial Timeline

Day of Pregnancy

Timed Preg

Vaccination 10^4 PFU SC

U/S

U/S Preg Dx

0 42 90 121 142/D+1 +5
Safety 2: NO CHALLENGE, Monitor through full-term N=20

Safety 1: Vax early gestation: N=29 + 3 shams

Vaccine Trial Timeline

Day of Pregnancy

0 42 90 121 142/D+1 +5

Timed Preg

Vaccination 10^4 PFU SC

Lambs born

U/S

U/S Preg Dx
Safety 1: Vax early gestation: N=30 + 3 shams

Safety 2: NO CHALLENGE, Monitor through full-term N=20

Vaccination 10^4 PFU SC

Challenge 10^6 PFU IV rRVFV

Lambs born
Safety and Immunogenicity post-Vaccination

All vaccinated animals (N=29) seroconverted
No fever detected post-vaccination
No other adverse events detected
No seroconversion in contact controls (N=3)
**EFFICACY**

- **Challenge (n=9) at Day 121 pregnancy or 82 days post-vax**

  - No abortion or viremia in vaccinated animals
    - Vacc. ewes: NO viremia or fever; day 1 to 14
    - Lambs born to vacc ewes: virus neg. (blood, liver, brain)

- All shams (n=3) aborted by day 6 PC
EFFICACY

- Challenge (n=9) at Day 121 pregnancy or 82 days post-vax
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  - All shams (n=3) aborted by day 6 PC
Differentiating Infected from Vaccinated Animals

Built into vaccine design
- 3-way ELISA assay
  - recombinant proteins

**Vax animals:**
- NP + only

**Infected animals:**
- NP+
- NSs+
- NSm+
Ideal RVF vaccine properties

Precise identity and excellent purity

– generated from plasmid DNA of 100% exact sequence

Safety - $\Delta/\Delta$ NOT a Select Agent, RSA and CDC IBC = BSL-2, awaiting more broad NIH RAC classification

– NO adverse events in rodents (n~350)
– NO adverse event in adult or pregnant sheep (n=42 total)

Single dose rapid protection

– Mice 100% protection by 48-72 hrs

Multiple attenuating lesions/ avoid reversion

– 2 complete virus gene deletions

Differentiate infected from vaccinated animals

– DIVA based on vaccine lacking NSs and NSm genes

Excellent “Environmental containment”

– Does not infect mosquito vectors (Crabtree et al, PLoS NTD 2012); no viremia in vaccinates

Inexpensive

– $\Delta/\Delta$ grows $>10^7$ pfu/ml in routine VERO cell culture
Lake Naivasha, Kenya
Site of first reported RVF outbreak 1930