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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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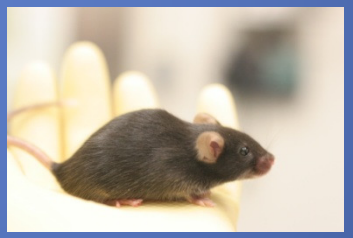
Viral Special Pathogens Branch

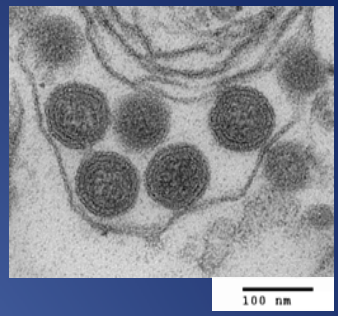
Centers for Disease Control and Prevention

Viral Special Pathogens Branch

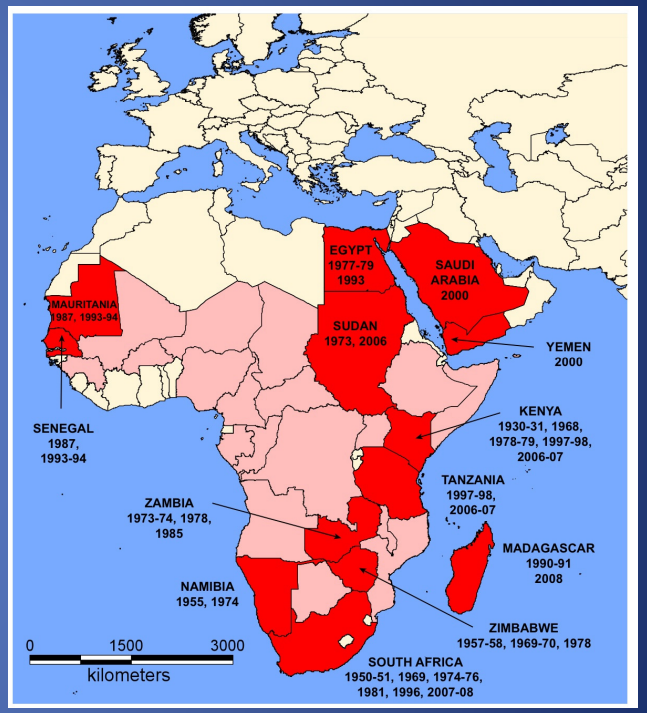
- Focus on viral hemorrhagic fevers (>35 viruses, 5 Families)
  - BSL-4, BSL-3+, BSL-2 labs
- Diagnostics – Outbreak Response
  - Serology, molecular, Next-Gen sequencing
- Epidemiology
- Laboratory Science
  - molecular biology, pathogenesis, immunology, vaccines and anti-viral therapeutic drugs
- Ecology
  - 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

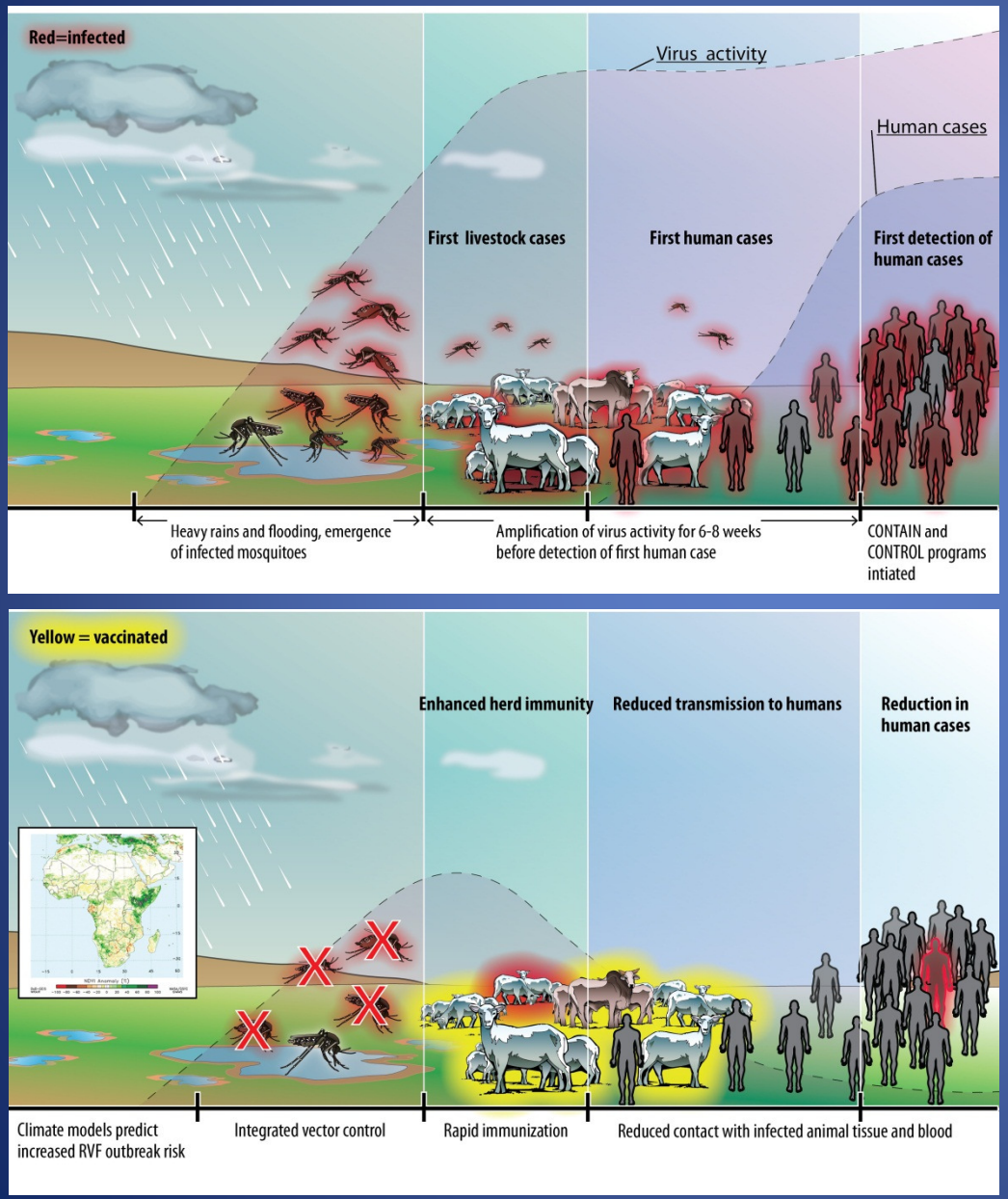
- Exciting time in RVFV vaccine research
  - Recombinant MLAV, VLP, VRP, Paramyxo vectored, Pox virus vectored etc.

- 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
*Curr Opinion in Virol,*2012

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

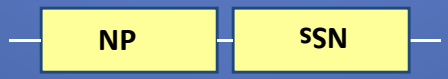
Genome composition

tripartite ss(-) RNA

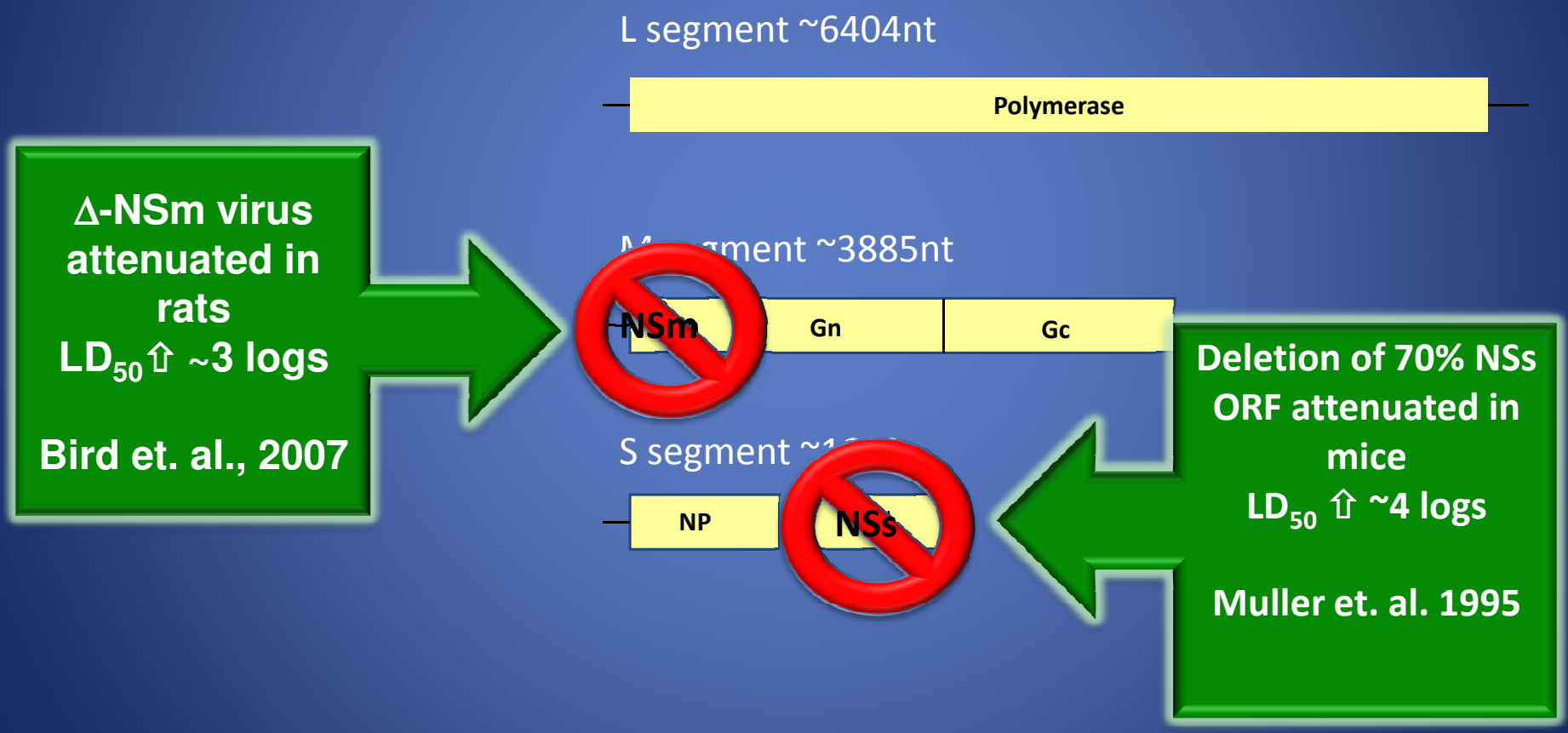
L segment ~6404nt

M segment ~3885nt

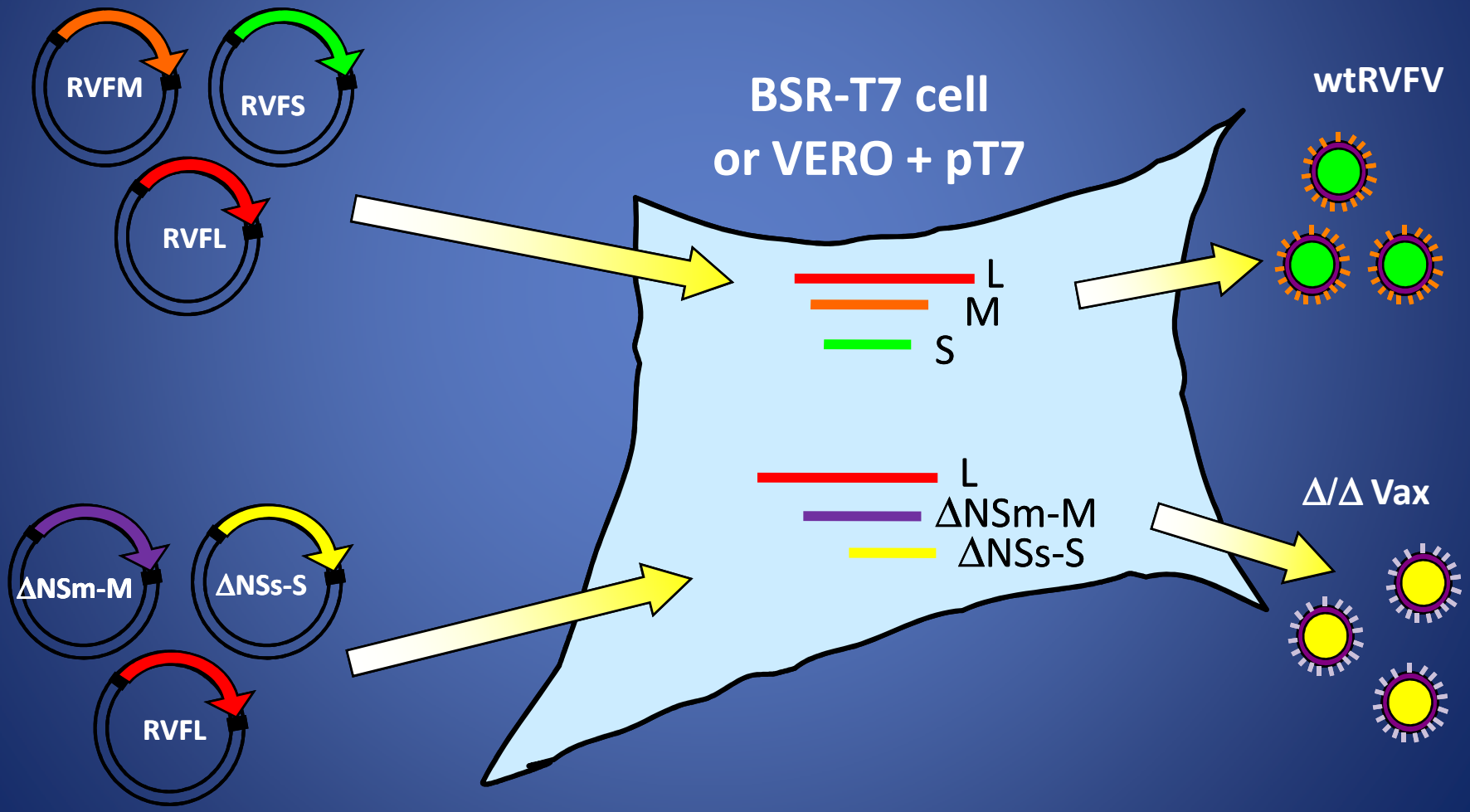
S segment ~1689



Major RVFV virulence factors

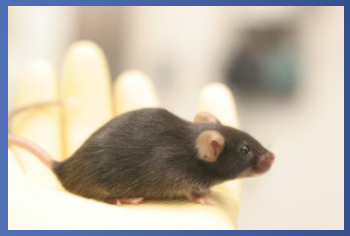


Generation of ΔNSs-ΔNSm vaccine



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*

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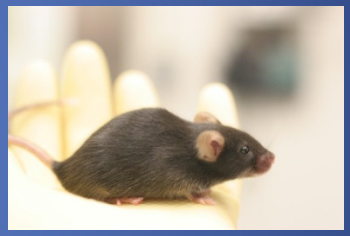

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BUT WHAT ABOUT A RELEVANT HOST?????

Δ/Δ Vaccine Sheep Trial

Bird et al., Journal of Virology 2011

Deltamune Pty. Ltd. South Africa

- Safety and Efficacy Trial
  - timed pregnant ewes
  - $1.0x10^4$ 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

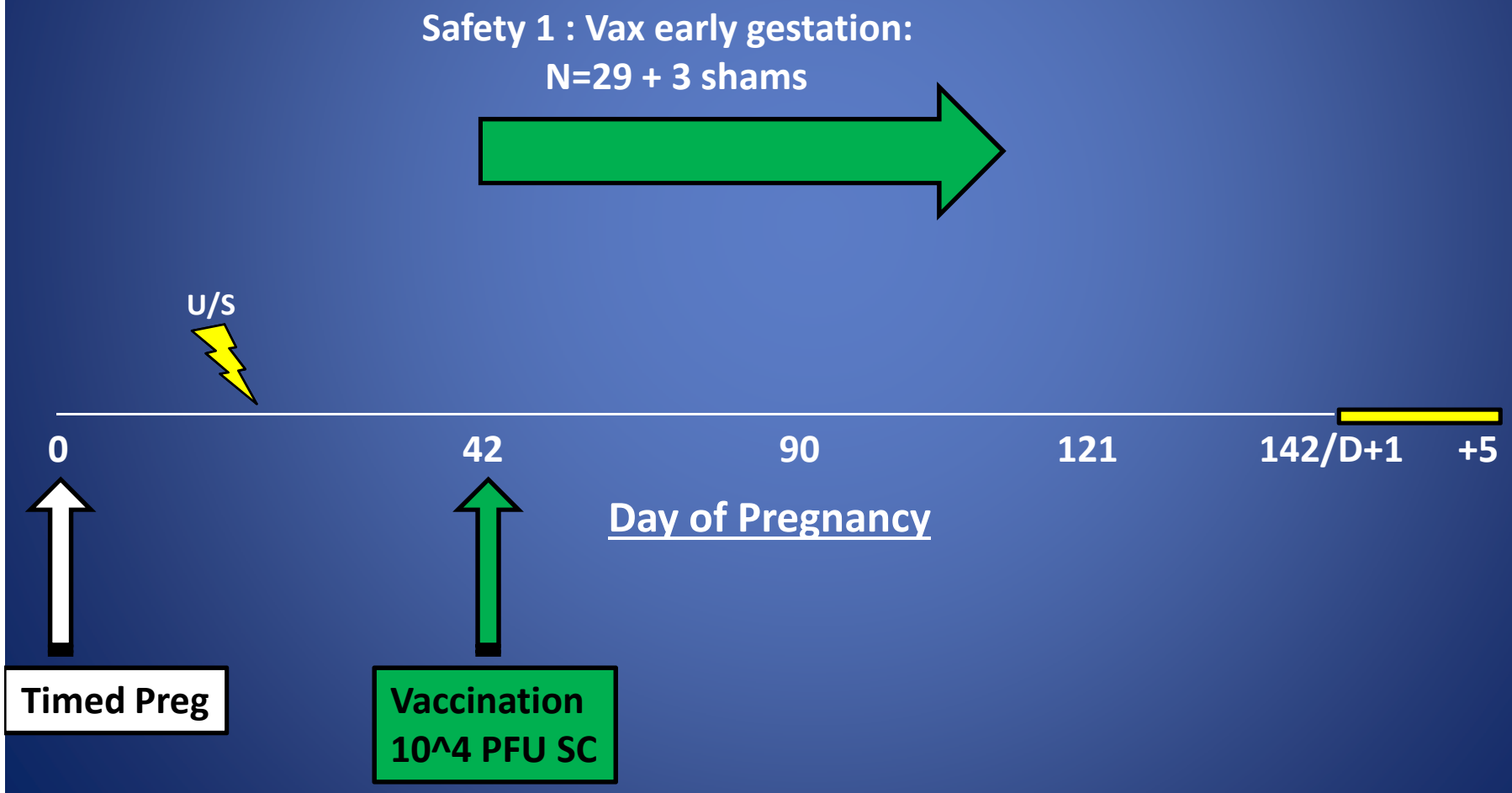
Pregnancy Dx U/S
N=32 selected

0 42 90 121 142/D+1 +5

Day of Pregnancy

Timed Preg
N=54

Δ/Δ Vaccine Trial Timeline



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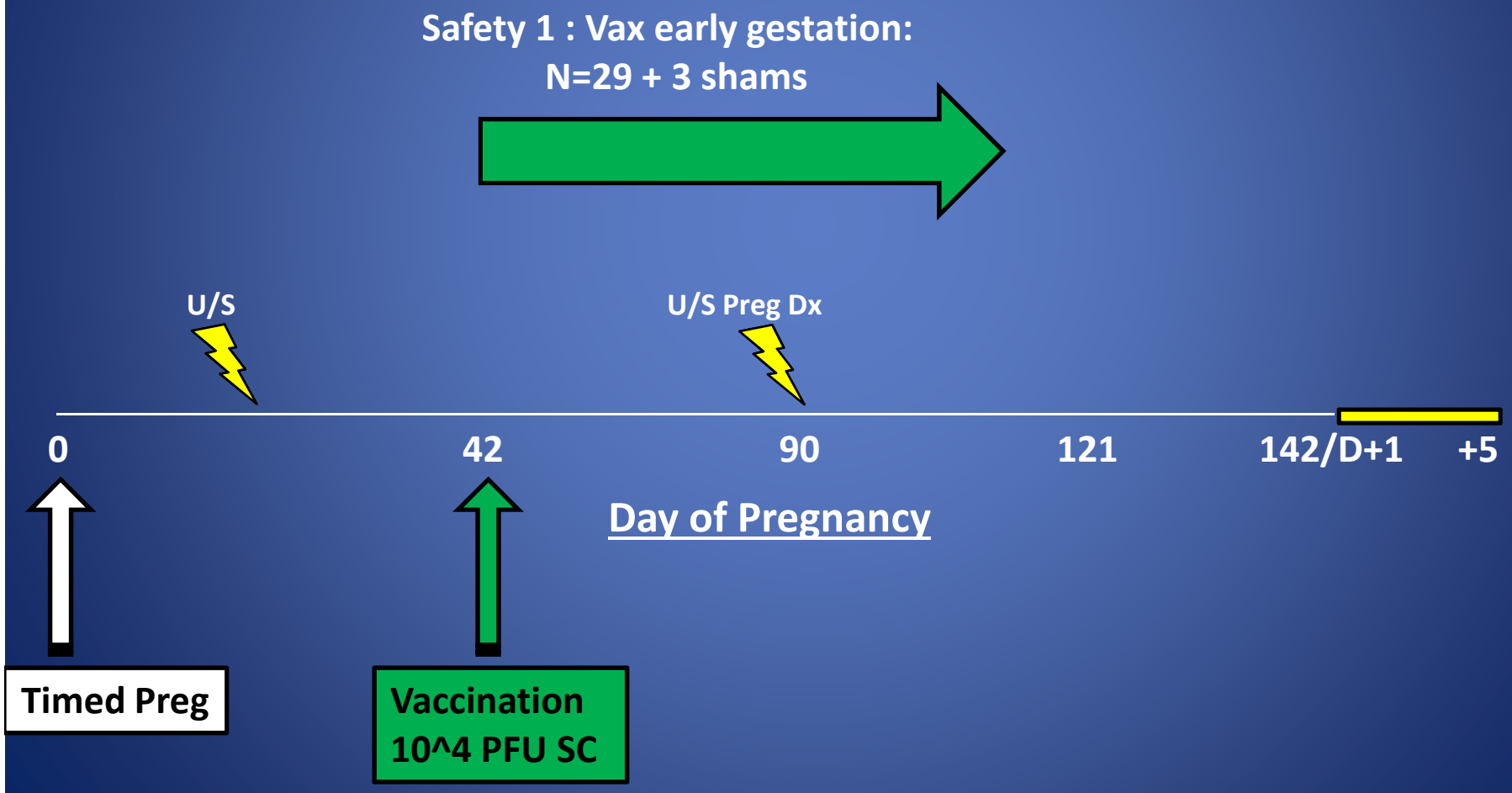

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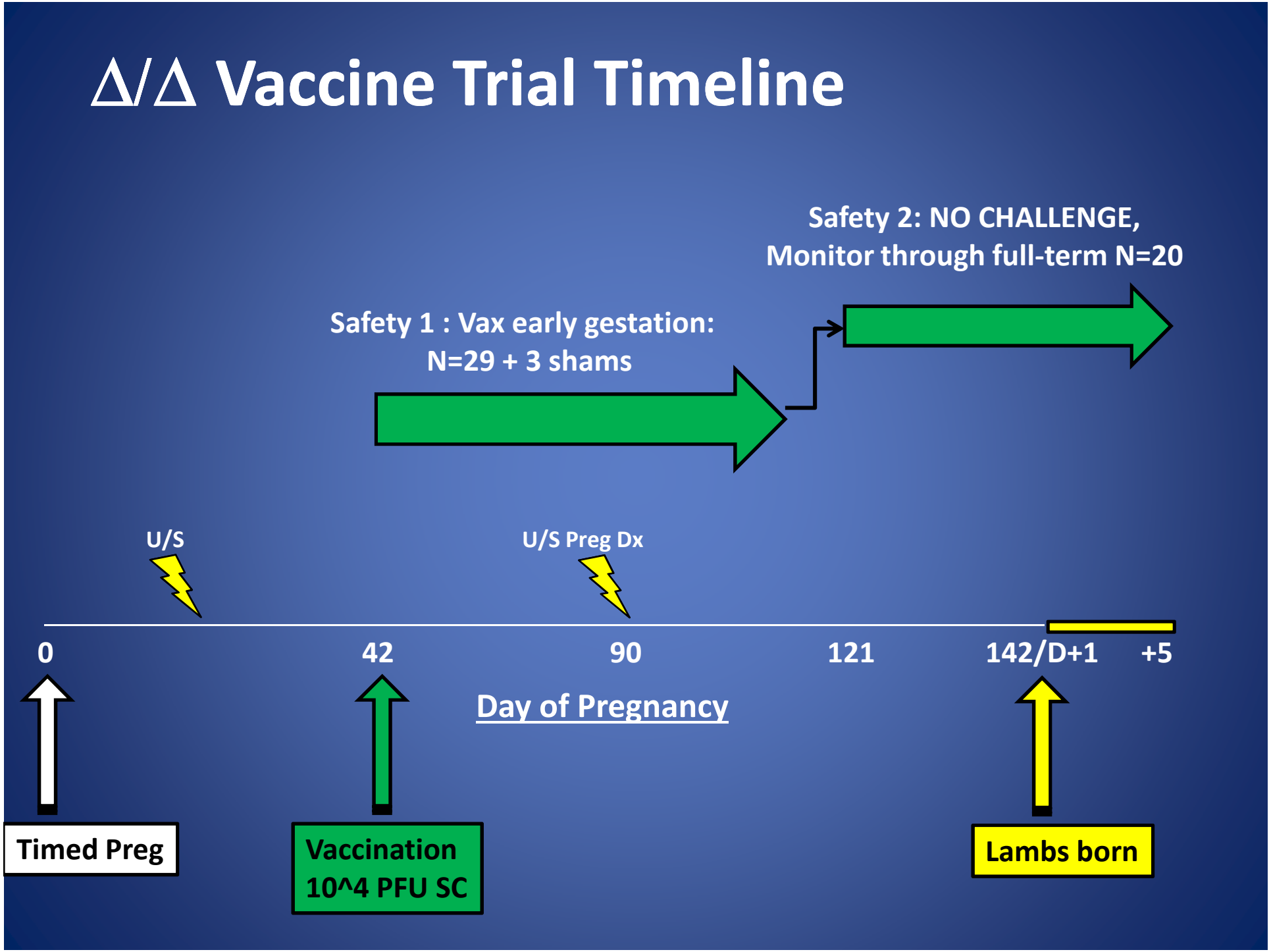

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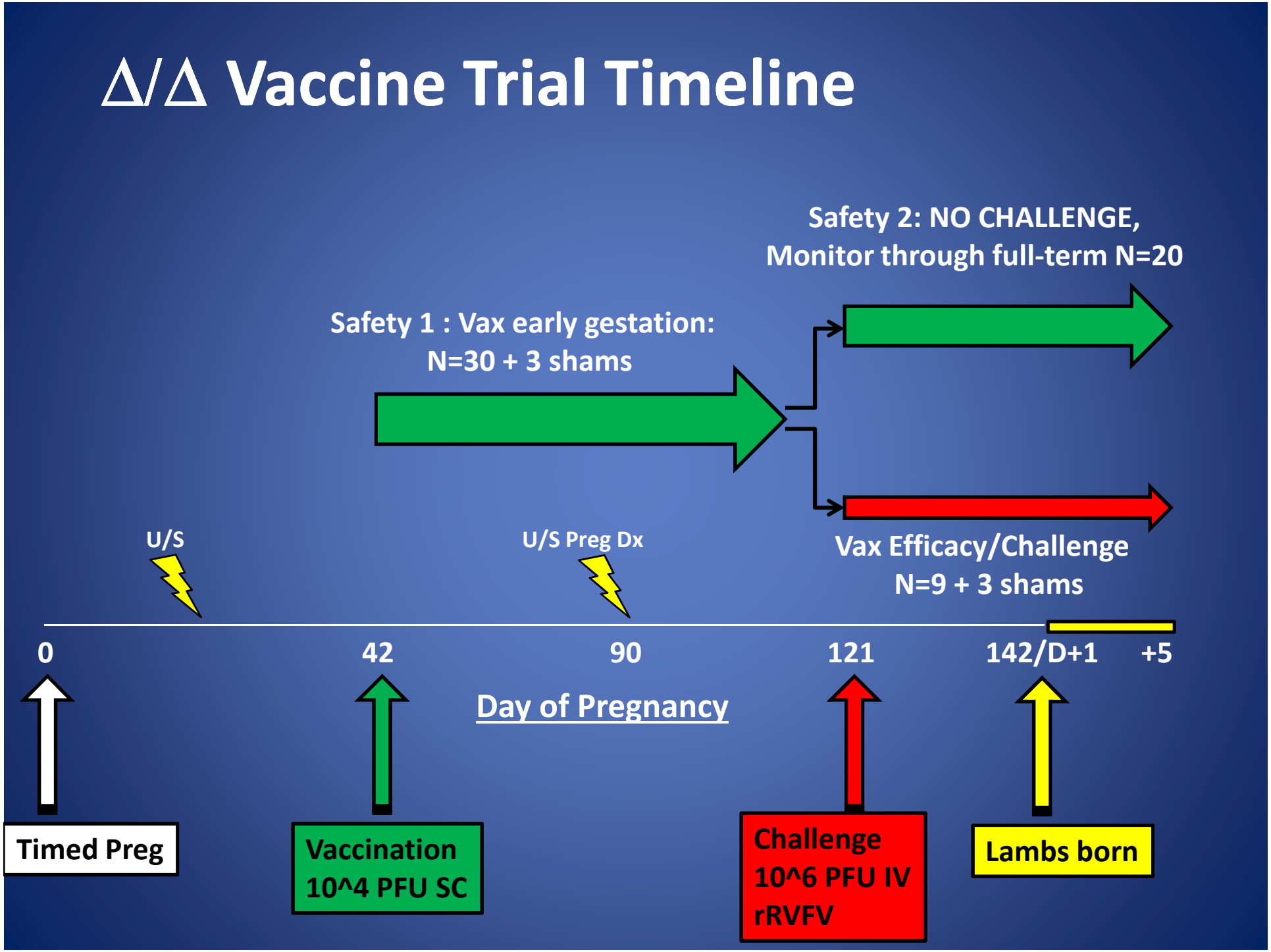
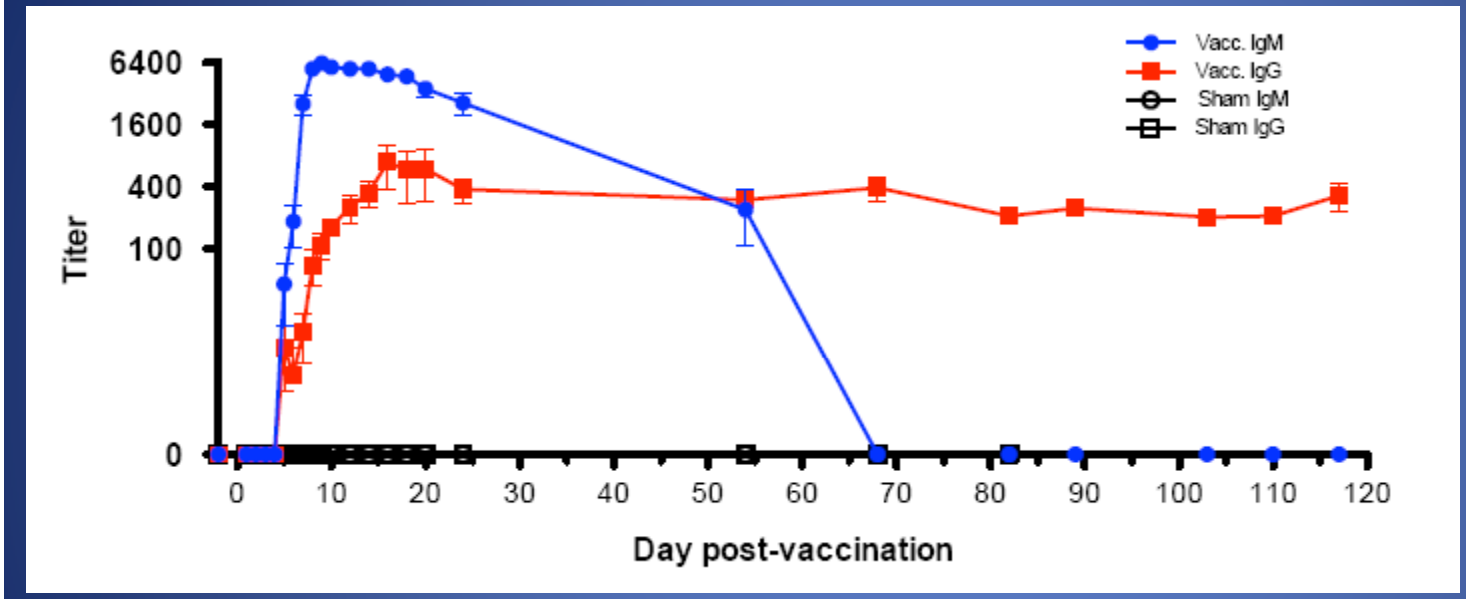


Δ/Δ Safety and Immunogenicity post-Vaccination

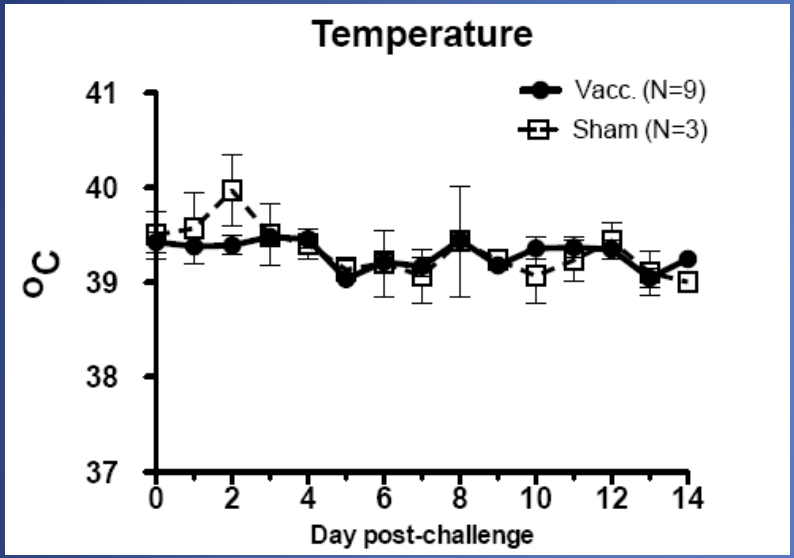


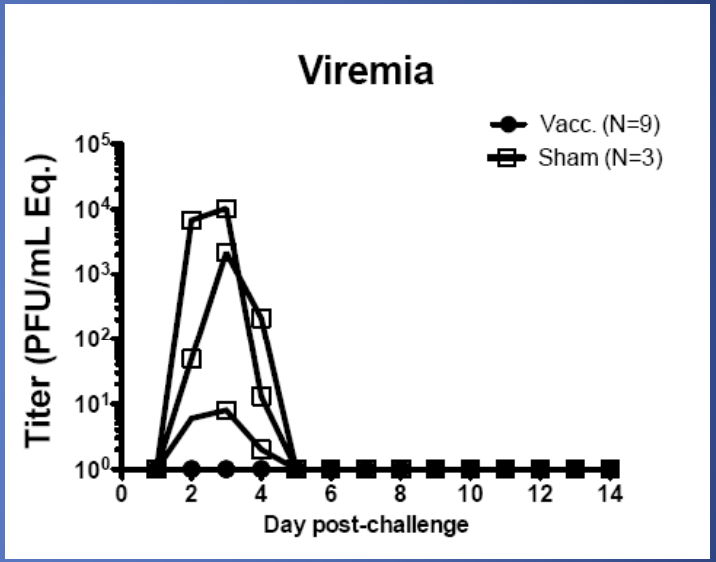
Shelley Campbell

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

Δ/Δ 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

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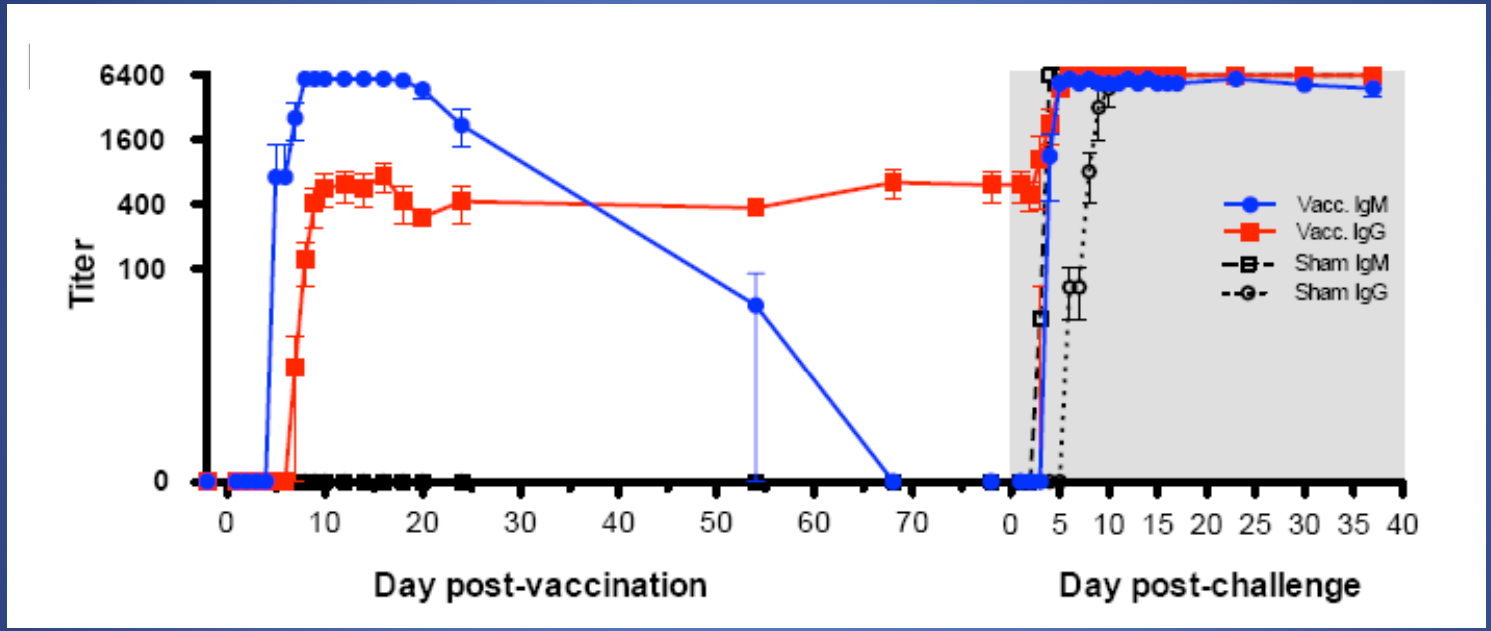

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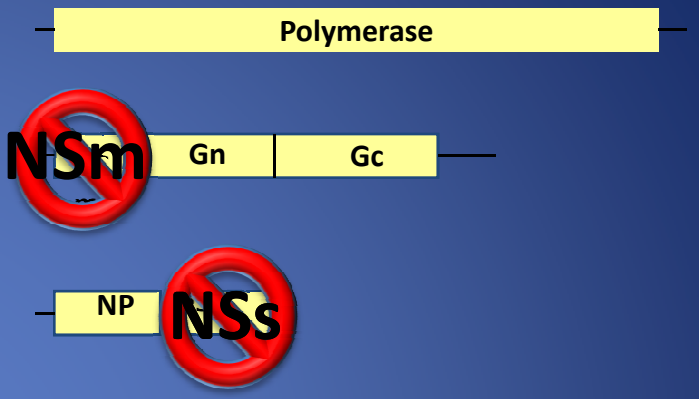
Differentiating Infected from Vaccinated Animals



Built into vaccine design

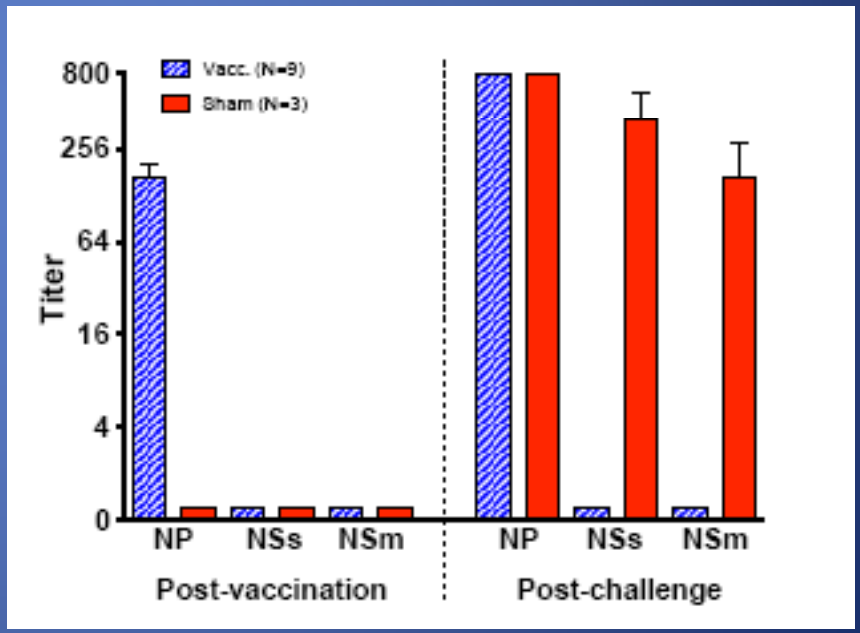
- 3-way ELISA assay
  - recombinant proteins

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 - *Δ/Δ 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

- *Δ/Δ grows > 10^7 pfu/ml in routine VERO cell culture*

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

DELTAMUNE

César Albariño

Stuart Nichol

Hannes Swart

Louis Maartens

Roelf Greyling

Baltus Erasmus

Kimberly Dodd


Lake Naivasha, Kenya
Site of first reported RVF outbreak 1930