Design and evaluation of vaccines against hemorrhagic fevers using the MVA-VLP platform

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Office of Regulated Nonclinical Studies I

- The University of Texas Medical Branch (UTMB) Office of Regulated Nonclinical Studies (ORNcS) was established under the direction of the Executive Vice President and Provost/Dean of the School of Medicine

- Provides the regulatory infrastructure and oversight to support regulated studies performed under Quality Management Systems (QMS) utilizing the GLP regulations as a reference standard.

- ORNcS contains two branches
  - a regulatory science branch and
  - a regulatory operations branch that operate in parallel to support the conduct and oversight of regulated studies.

Office of Regulated Nonclinical Studies II

- The regulatory operations branch provides the independent QAU support including:
  - Critical Phase Inspections
  - Laboratory/Equipment Audits
  - Data/Study Report Audits
  - Host External Audits

- The scientific branch provides oversight for the planning and conduct of regulated studies under the direction of a Study Director.
  - Study director is assigned by ORNcS Scientific Director.
    - All studies run in accordance to the Study Protocol, SOPs and Quality Agreements.
    - Study Director with previous GLP experience
    - One Study Coordinator
    - Five technical staff
    - Two Biomedical Equipment Specialists
    - Partner with UTMB's Animal Resource Center's (ARC) Preclincial Services Group.

Robert E. Shope, MD Laboratory

John Sealy Pavilion
for Infectious Diseases Research

Completed mid-2003

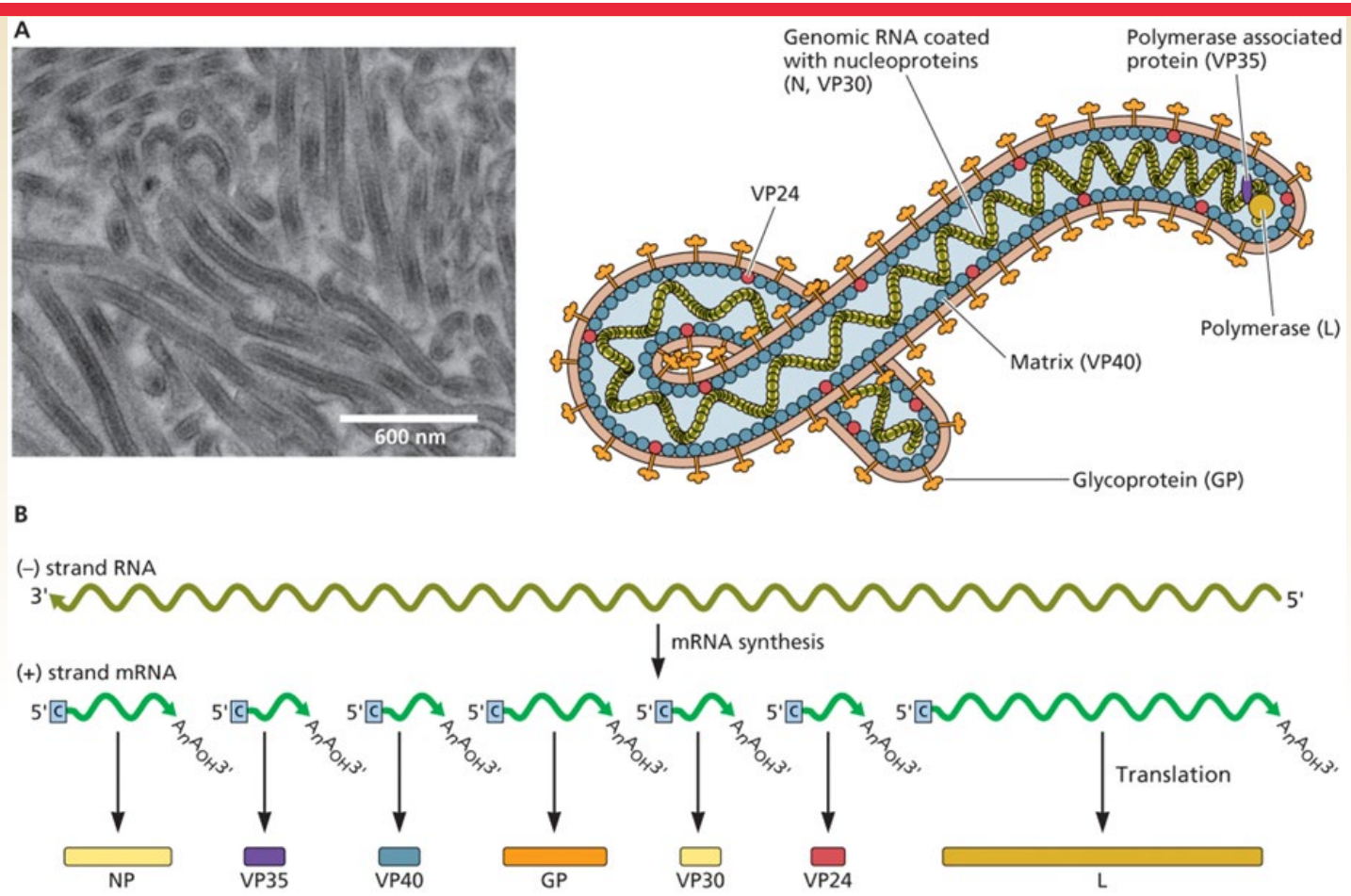
The Shope BSL-4, dedicated on November 17, 2003 is the first BSL-4 laboratory on a university campus in the US

Galveston National Laboratory (GNL)

- A National Biocontainment Laboratory within NIAID's Biodefense Laboratory Network
- Completed in 2008
- $176.6 million
  - $115.1 Million – NIAID Grants
  - $57.0 Million – Tuition Revenue Bonds (approved by Texas Legislature)
  - $4.5 Million - Philanthropy/UTMB Funds

Family Filoviridae

- Enveloped viruses with (–) strand RNA genomes.
- Filamentous morphology
- Three genera
  - Ebolavirus
    - Ebola virus (EBOV)
      - 12/19/2019 Ervebo approved
        - rVSV-EBOV
      - 12/21/2020 Ebanga approved
        - mAb to GP
      - 10/14/2020 - Inmazeb approved
        - mixture of three mAbs to GP
    - Sudan virus (SUDV)
    - Bundibugyo virus (BDBV)
    - Tai Forest virus (TAFV)
    - Reston virus (RESTV)
    - Bombali virus (BOMV)
  - Marburgvirus
    - Marburg Virus (MARV)
    - Ravin Virus (RAVV)
  - Cuevavirus
    - Lloviu cuevavirus (LLOV),



Filovirus Disease in Humans

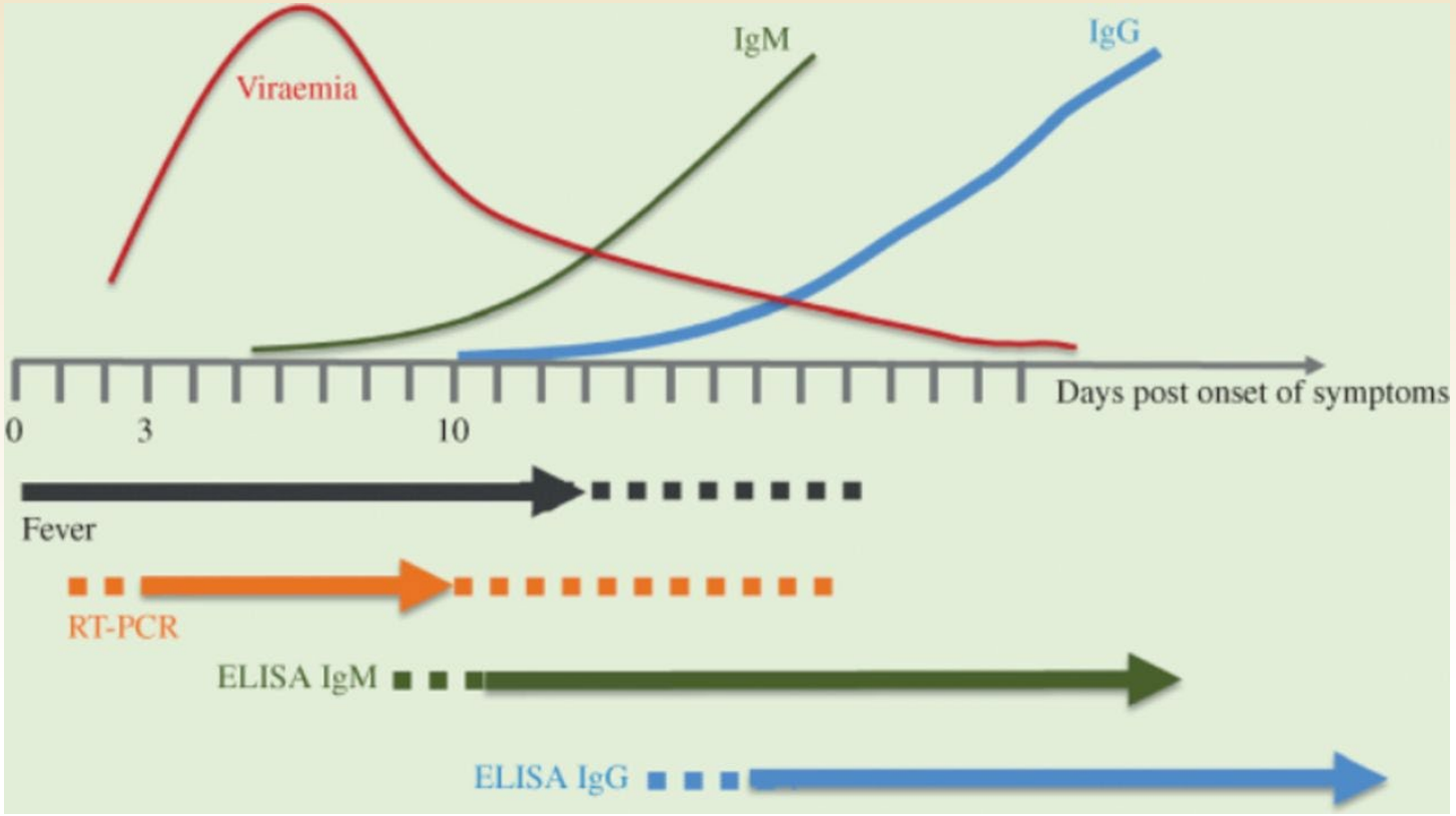
Primary signs and symptoms of Ebola disease often include some or several of the following:

- •Fever
- •Aches and pains, such as severe headache and muscle and joint pain
- •Weakness and fatigue
- •Sore throat
- •Loss of appetite
- •Gastrointestinal symptoms including abdominal pain, diarrhea, and vomiting
- •Unexplained hemorrhaging, bleeding or bruising

Other symptoms may include red eyes, skin rash, and hiccup

Symptoms may appear anywhere from 2 to 21 days after contact with an ebolavirus, with an average of 8 to 10 days

Virus and persist in the eye and testes

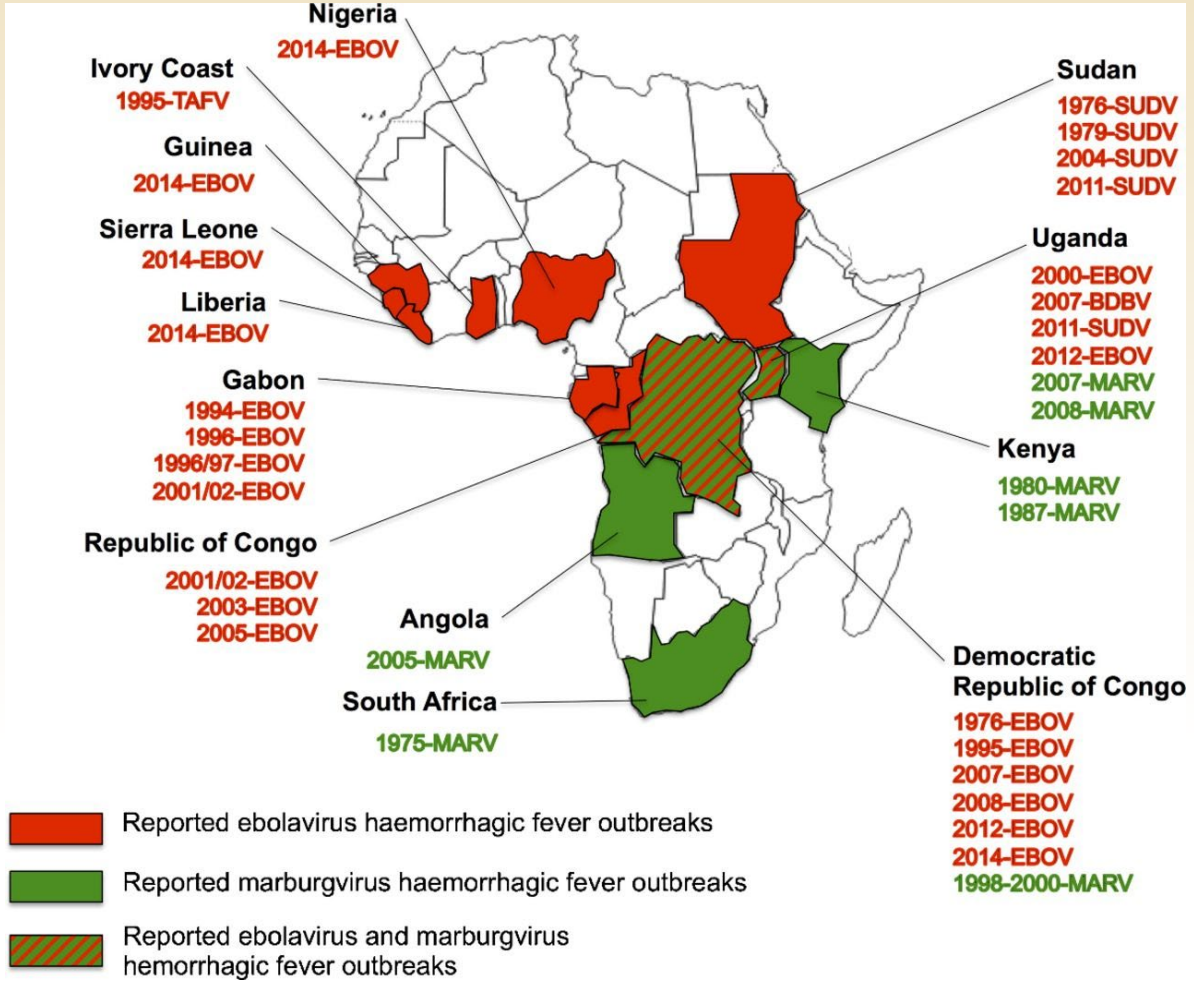


Emperador DM, Mazzola LT, Wonderly Trainor B, *et al*
Diagnostics for filovirus detection: impact of recent outbreaks on the diagnostic landscape
BMJ Global Health 2019;**4**:e001112

Filovirus Outbreaks

Factors like population growth, encroachment into forested areas, and direct interaction with wildlife (such as bushmeat consumption) may contribute to the introduction of filoviruses into human populations.

Once a person is infected, filoviruses can spread from person-to-person through direct contact with an infected person's body fluids. Those at highest risk of infection are caretakers and healthcare providers who do not use appropriate personal protective equipment.



utmb Health

Emperador DM, Mazzola LT, Wonderly Trainor B, et alDiagnostics for filovirus detection: impact of recent outbreaks on the diagnostic landscapeBMJ Global Health 2019;4:e001112

Filovirus Outbreaks

In Uganda, from 20 September 2022 to 11 January 2023, Uganda health authorities declared an outbreak of Sudan virus, following laboratory confirmation of a patient.

A total of 164 cases (142 confirmed, 22 probable) with 77 deaths (55 among confirmed cases and 22 among probable cases) were reported during the outbreak,

Equatorial Guinea and the United Republic of Tanzania have been responding to separate outbreaks of Marburg virus disease (MVD) since early February and late March 2023, respectively.

In Equatorial Guinea, from 13 February to 1 May 2023, 17 laboratory-confirmed cases and 23 probable cases have been reported. Among the laboratory-confirmed cases, there are 12 deaths (Case Fatality Ratio (CFR) 75%).

In the United Republic of Tanzania, between 16 March to 30 April 2023, a cumulative total of nine cases including eight laboratory-confirmed cases and one probable case have been reported. A total of six deaths (CFR 66.7%) have been reported, including one probable case and five among the confirmed cases.

Filovirus Animal Models

Table 1 Animal models for studying filovirus infections

Filovirus species	Immuno-competent mouse	Immuno-compromised mouse	Guinea pig	Syrian hamster	Ferret	NHP
EBOV	+	+	+	+	+	+
MARV	+	+	+	+	-	+
RAVV	+	+	+	-	-	+
SUDV	-	+	+	-	+	+
TAFV	-	-	-	-	-	-
BDBV	-	-	-	-	+	+

NHP: Non-human primate; EBOV: Ebola virus; MARV: Marburg virus; RAVV: Ravn virus; SUDV: Sudan virus; TAFV: Tai Forest virus; BDBV: Bundibugyo virus; "+": Available; "-": Not available.

Require adaptation by serial passage

Siragam V, Wong G, Qiu XG. Animal models for filovirus infections. Zool Res. 2018 Jan 18;39(1):15-24. doi: 10.24272/j.issn.2095-8137.2017.053. PMID: 29511141; PMCID: PMC5869237.

Filovirus Animal Models

Table 2 Advantages and disadvantages of animal models for filovirus infections

Animal models	Advantages	Disadvantages
Mice	Low cost, easy to use Transgenic and knockout models are available	Only i.p. infection is 100% lethal Mouse-adapted variants needed
Guinea pigs	Low cost, larger animals to study disease progression and easy to use	Transgenic and knockout models are not available Lack of immunological tools and reagents to evaluate cell-mediated responses to vaccines and therapeutics Guinea pig-adapted variants needed
Syrian Hamsters	An alternative to guinea pigs Elegant model to compare differences in immune responses to EBOV infection	Mouse-adapted variants needed Lack of commercially available reagents and host genomic information Transgenic and knockout models are available
Ferrets	Small body size, low cost Closely resembles to human filoviral disease Can use clinical isolates to study pathogenesis	Limited availability of ferret-specific reagents Ferret immune responses are poorly understood Transgenic and knockout models are available
NHPs	Gold standard model to evaluate filovirus infections and closely recapitulate human disease	Animals are expensive, ethical considerations and extensively husbandry requirements needed Transgenic and knockout models are not available

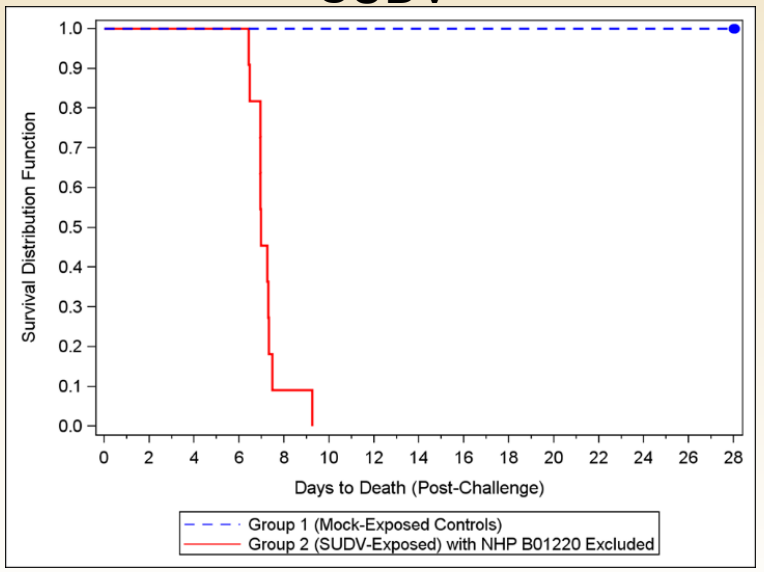
NHPs: Non-human primates.

Siragam V, Wong G, Qiu XG. Animal models for filovirus infections. Zool Res. 2018 Jan 18;39(1):15-24. doi: 10.24272/j.issn.2095-8137.2017.053. PMID: 29511141; PMCID: PMC5869237.

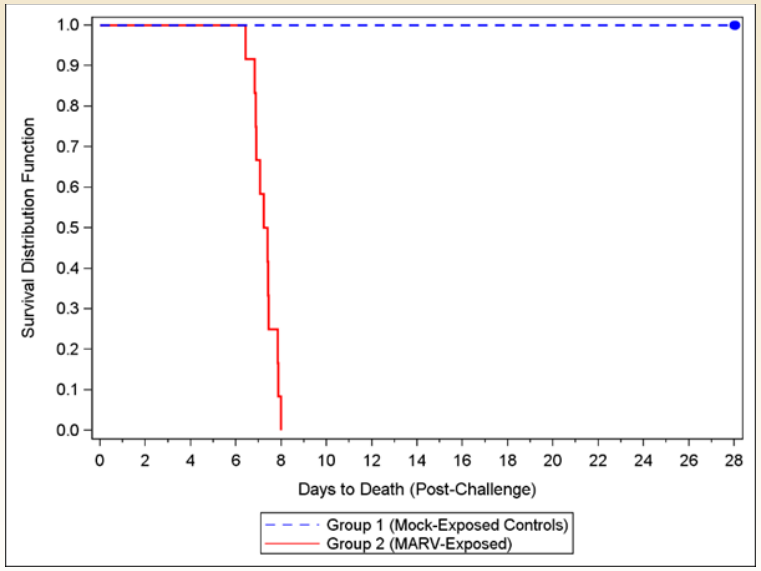
Natural History - NHP

- Challenge with 1000 PFU via IM injection
  - Uniformly lethal with death occurring with 8-9 days
- Disease presentation begins on Days 5-6
  - Lethargy
  - Inappetence
  - Hunched posture
  - Petechia
  - Loss of diurnal rhythm/fever prior to euthanasia

SUDV



MARV



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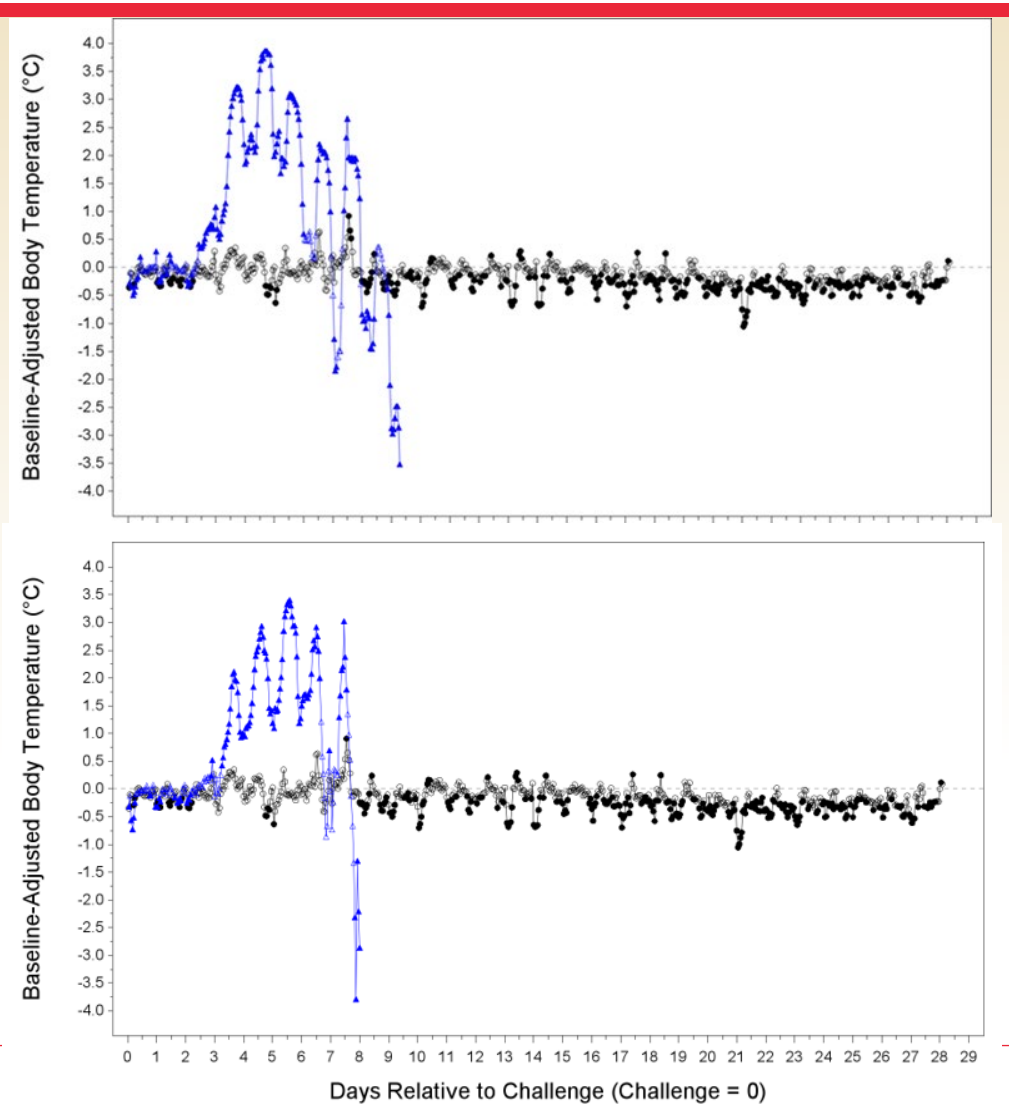
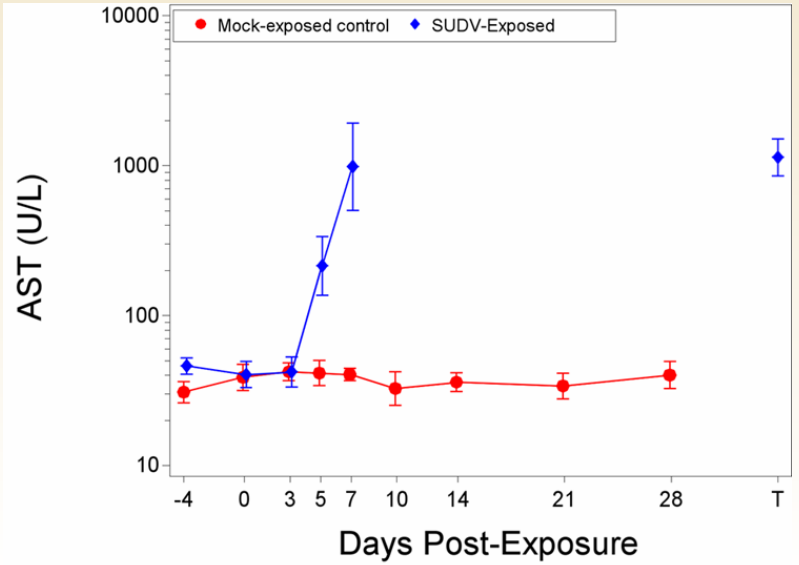


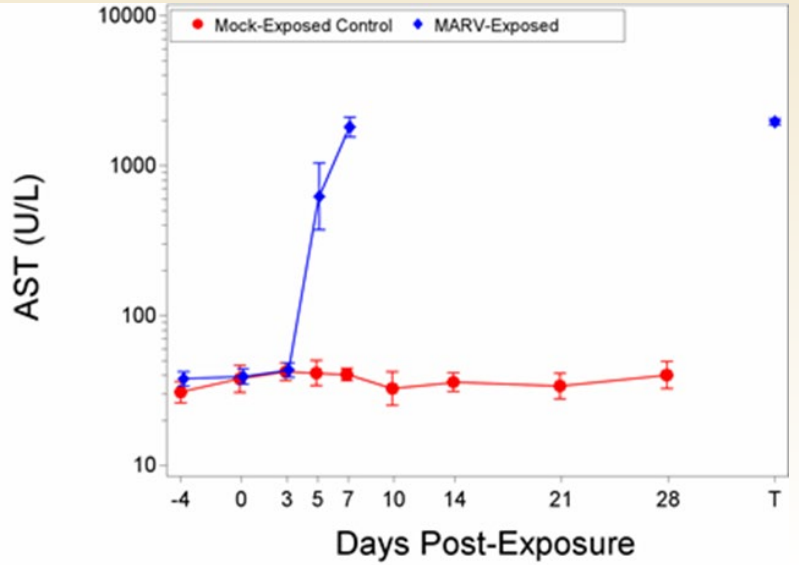
Natural History - NHP

- Increases in liver enzymes
- Hematological changes
  - ↓ Lymphocytes
  - ↑ Neutrophiles
  - ↓ Platelets
- Increases clotting time
  - Intrinsic
  - Extrinsic

SUDV



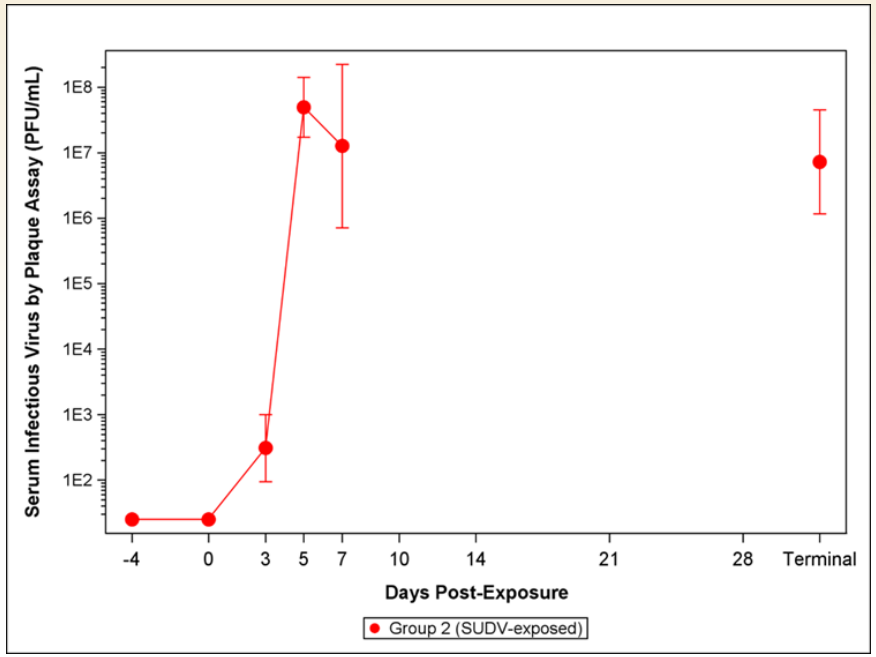
MARV



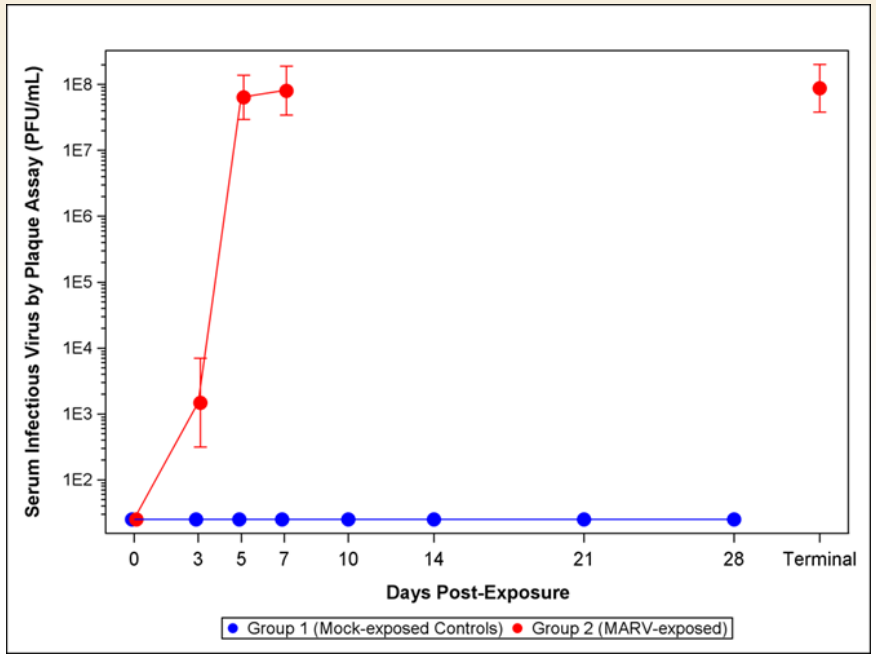
Natural History - NHP

- Viremia can be seen as early as Day 3
  - Reaches ~10^8 PFU/mL by on Day 5

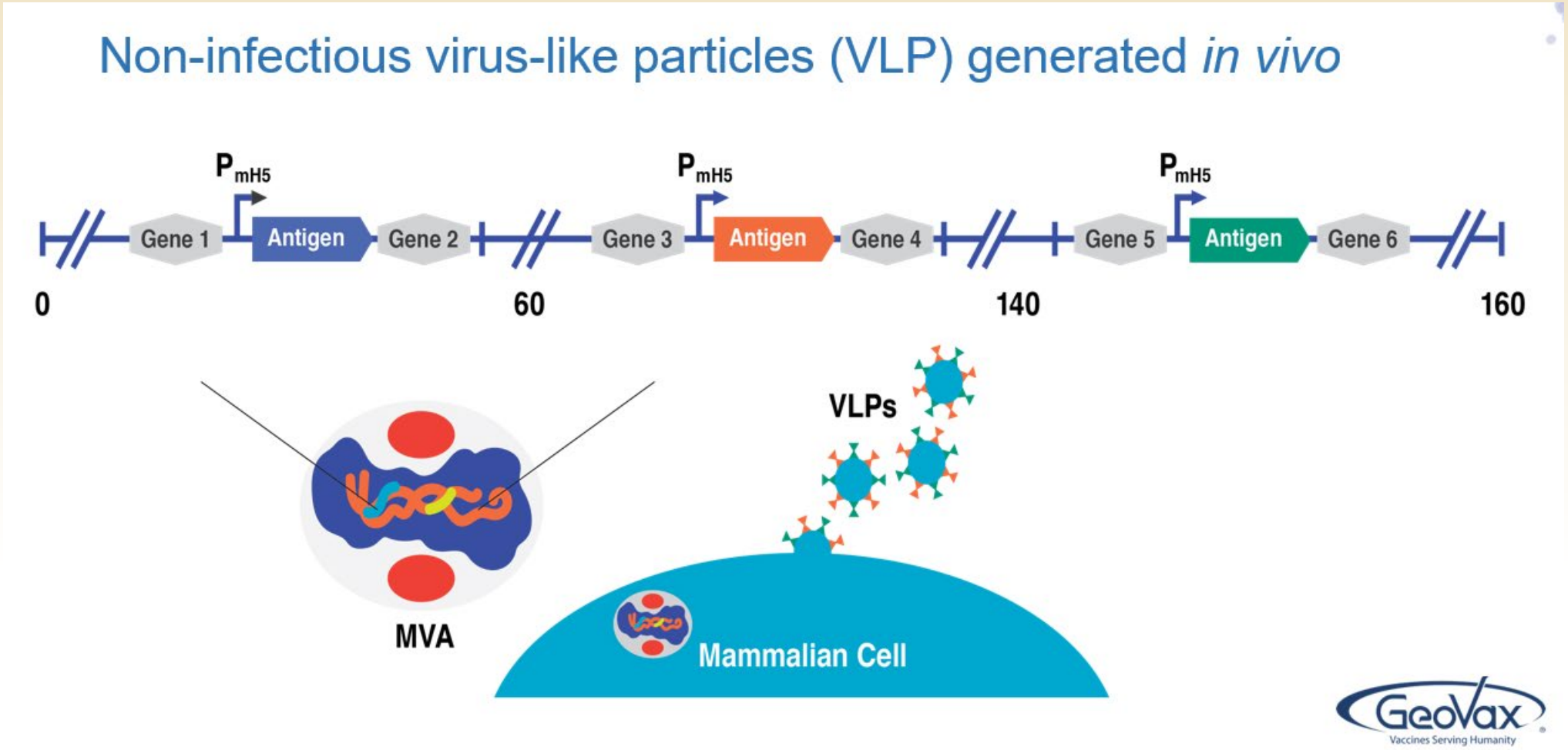
SUDV



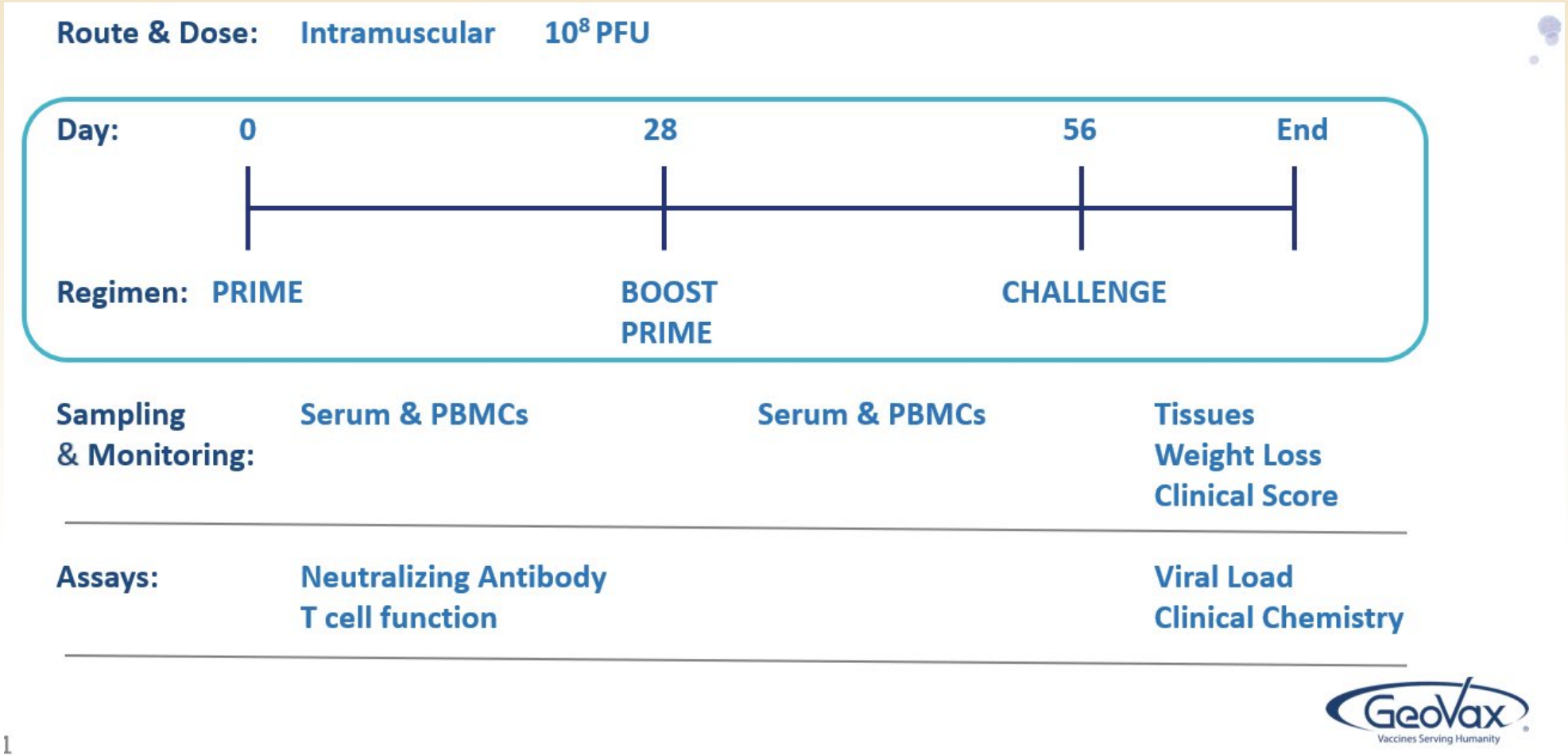
MARV



GeoVax MVA-VLP Vaccine Platform



Immunization Regimen



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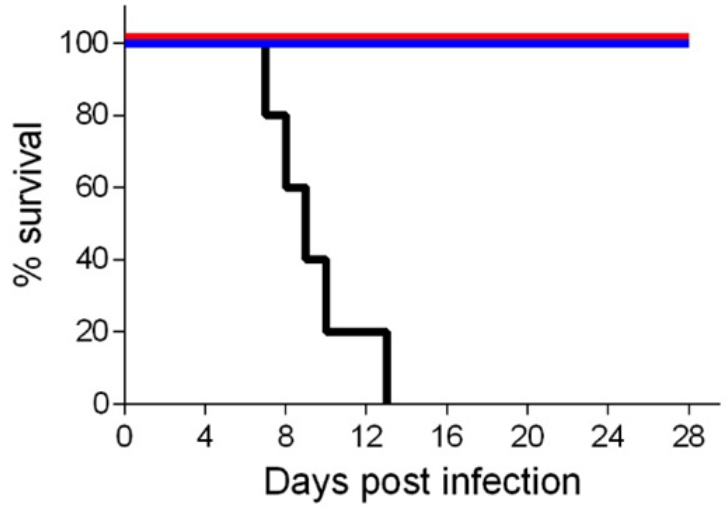
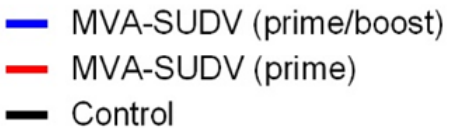
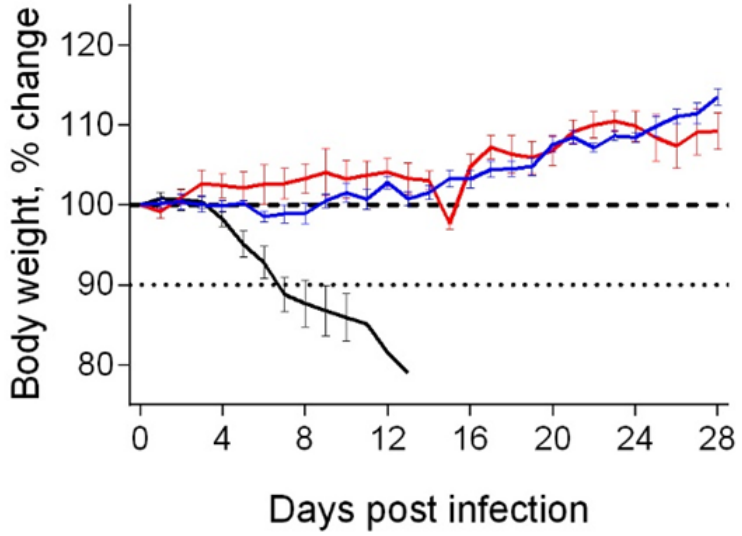
MVA-VLP-SUDV Vaccine Efficacy - GPs



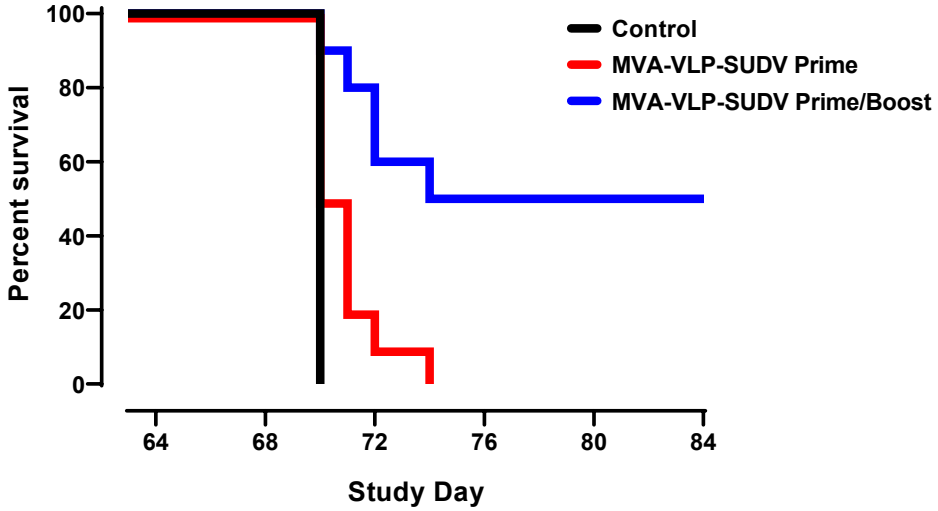


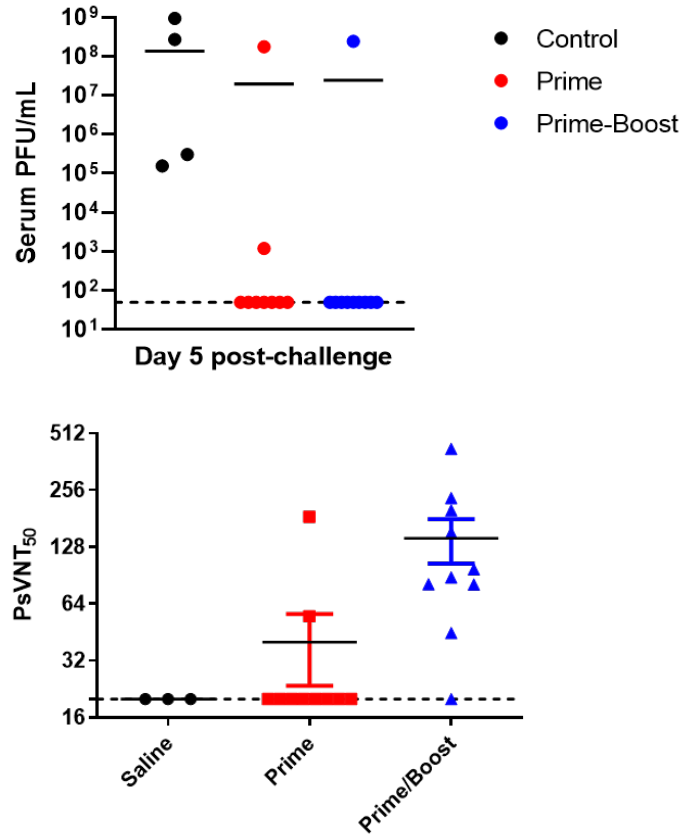


Malherbe DC, Domi A, Hauser MJ, Meyer M, Gunn BM, Alter G, Bukreyev A, Guirakhoo F. Modified vaccinia Ankara vaccine expressing Marburg virus-like particles protects guinea pigs from lethal Marburg virus infection. NPJ Vaccines. 2020 Sep 2;5(1):78. doi: 10.1038/s41541-020-00226-y. PMID: 32922962; PMCID: PMC7468113.

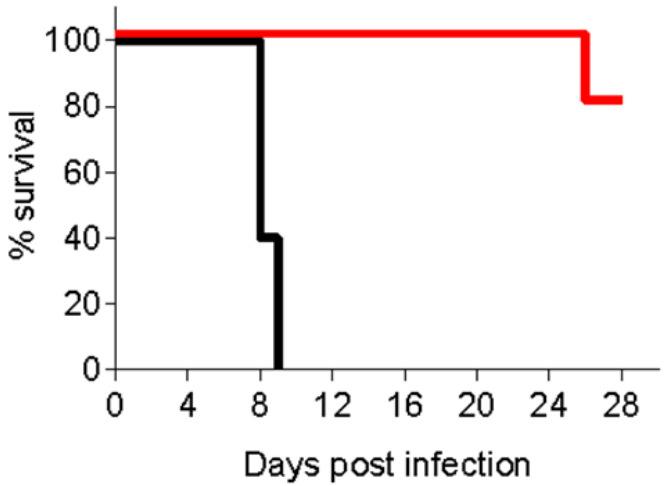
MVA-VLP-SUDV vaccine efficacy - NHPs

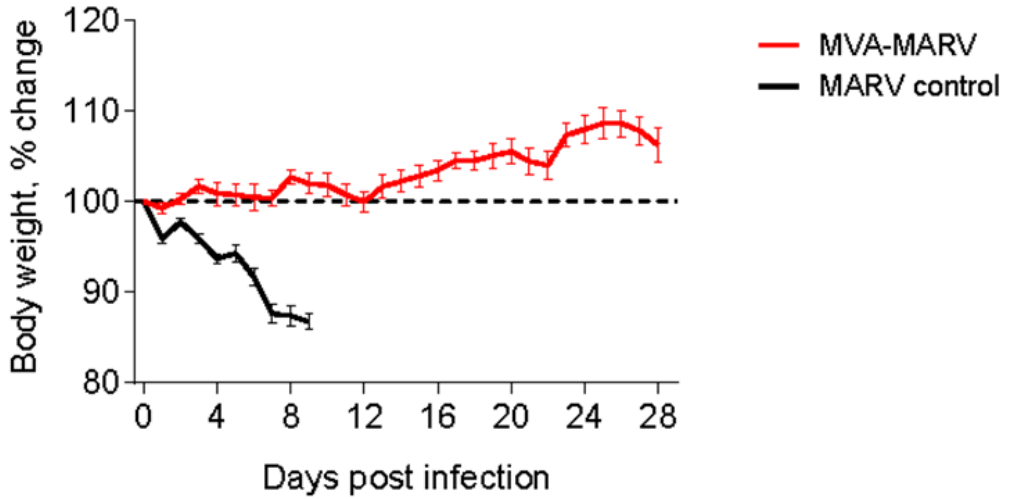
- Controls died on Day 7 post-challenge
- NHPs in the Prime Group died between Days 7 and 11
- 50% of NHPs in the Prime/Boost Group lived to the end of the study.
- Very low neutralizing titers in the Prime-only group.





MVA-VLP-MARV Vaccine Efficacy - GPs





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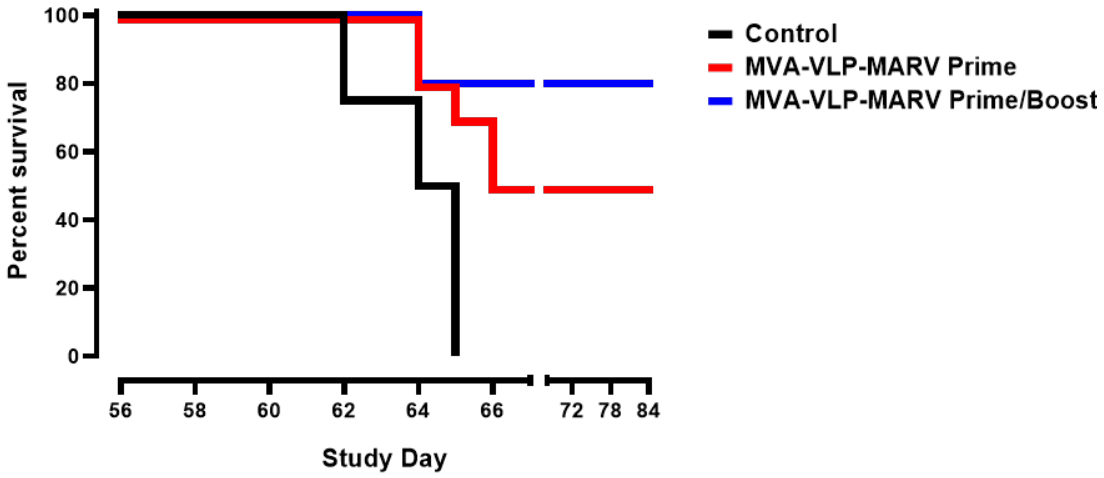
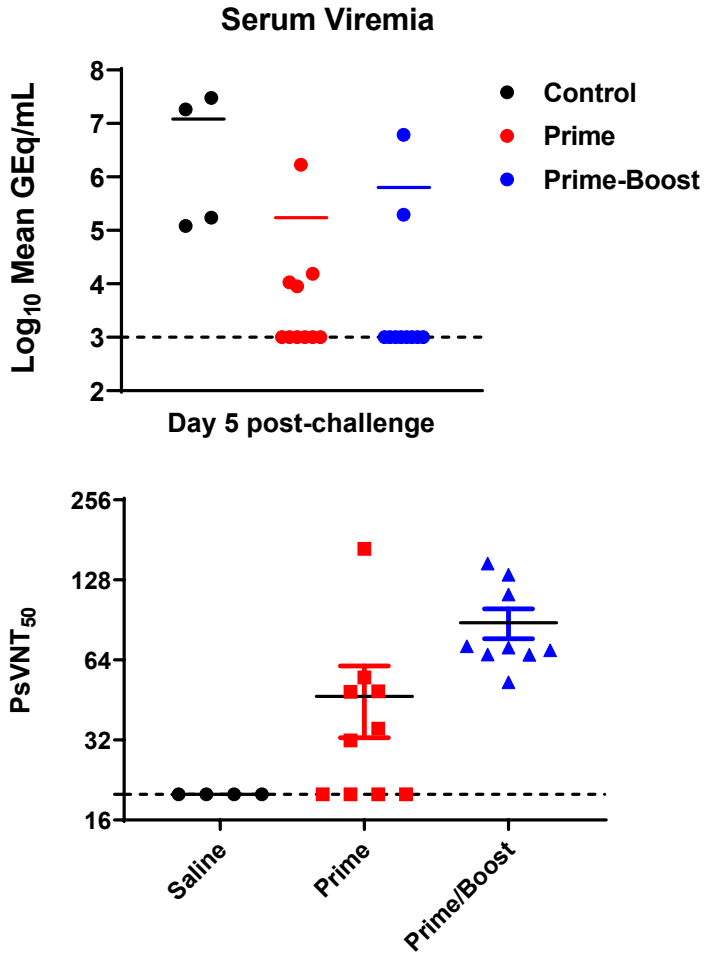
Marburg Virus: MVA-VLP-MARV Vaccine

- Same study design applied to Marburg virus
  - 50% Survival in Prime Group
  - 80% Survival in Prime/Boost Group
  - Demonstrates the platform is effective





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- BARDA (Battelle Flow-Through) HHSO100201700011I/75A50119F33009
    - Natural History Studies in NHP Models of Filovirus Infection

Vaccine Studies

- NIAID (Battelle Flow -Through) HHSN272201800013I / 75N93019F00131 / TOV2
    - Immunogenicity and Efficacy Testing of Medical Countermeasures (Vaccines and Other Biologics) Against BSL-4 Pathogens in NHPs

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Questions