Licensure Pathways for vaccines for Emerging Infectious Diseases: considerations relevant for Rift Valley Fever

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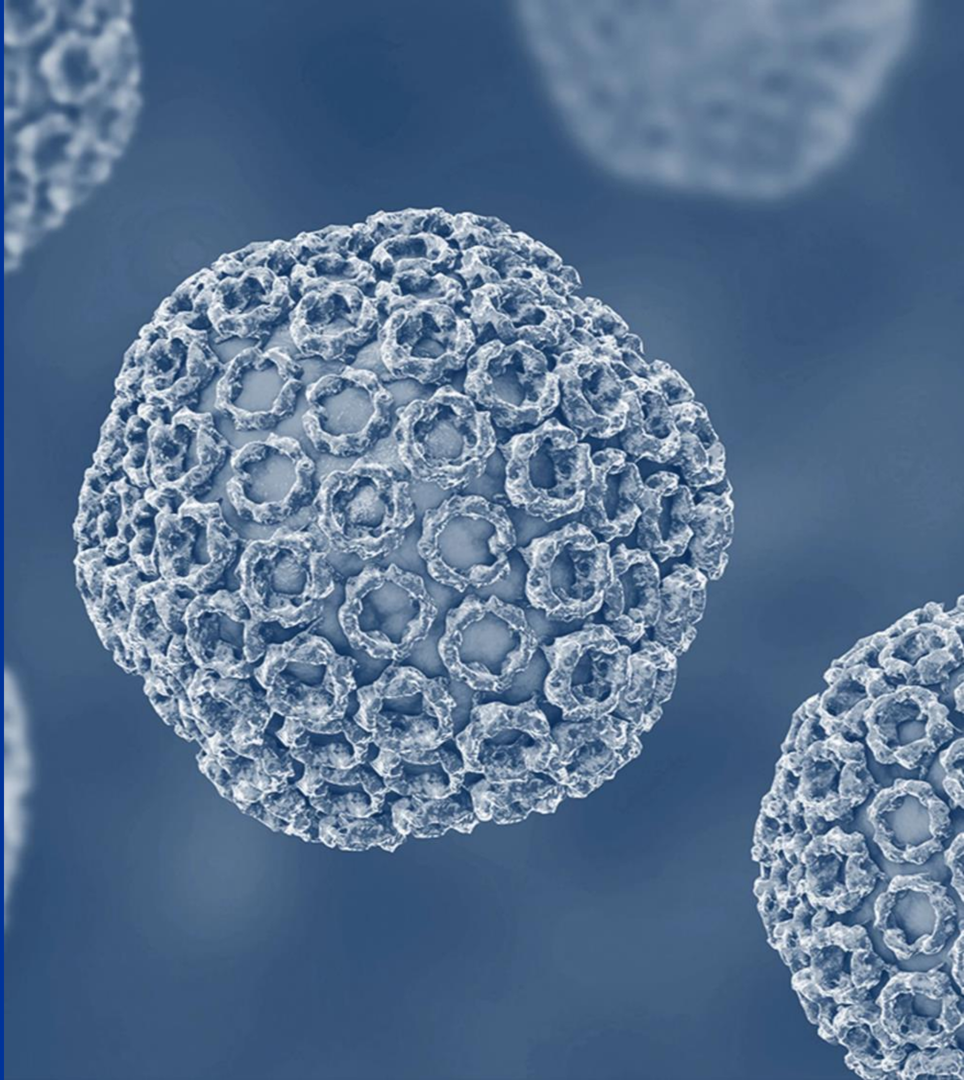
Dr. Marco Cavaleri

Head **of** Public Health Threats Department

Chair of the Emergency Task Force, EMA



Approval pathways for vaccines in the EU

- **Full approval** based on efficacy (e.g. rotavirus vaccines) or immunological data (e.g. flu vaccines, MenB vaccines)
- **Conditional marketing approval** (e.g. COVID-19 vaccines during Pandemic)
- **Approval under exceptional circumstances** (e.g. smallpox vaccine)
- **Art. 58 Scientific Opinion (now M4ALL)** for use outside of EU (e.g. malaria vaccine)

Clinical requirements for authorisation of a vaccine

Clinical Efficacy studies feasible:

- Absolute protective efficacy of vaccines by comparing the reduction in the incidence of the infectious disease in question vs. the incidence in a group that receives placebo in a prospective individually randomised and double-blind trial

- Case definitions to be used for the primary analysis and any alternative case definitions for secondary analyses usually comprise clinical signs and/or symptoms typical of the infectious disease together with laboratory confirmation of the aetiology

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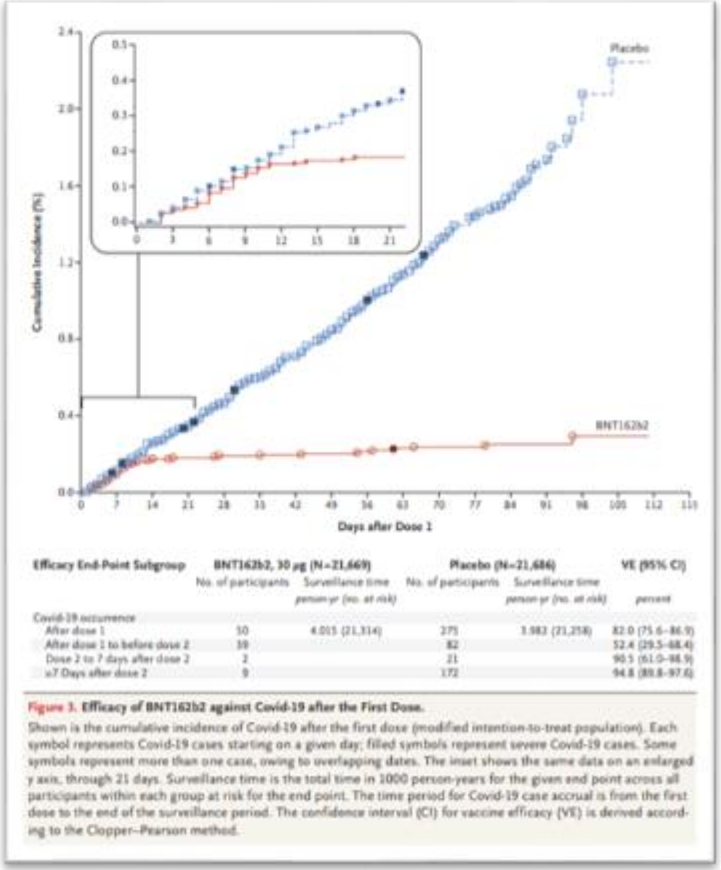
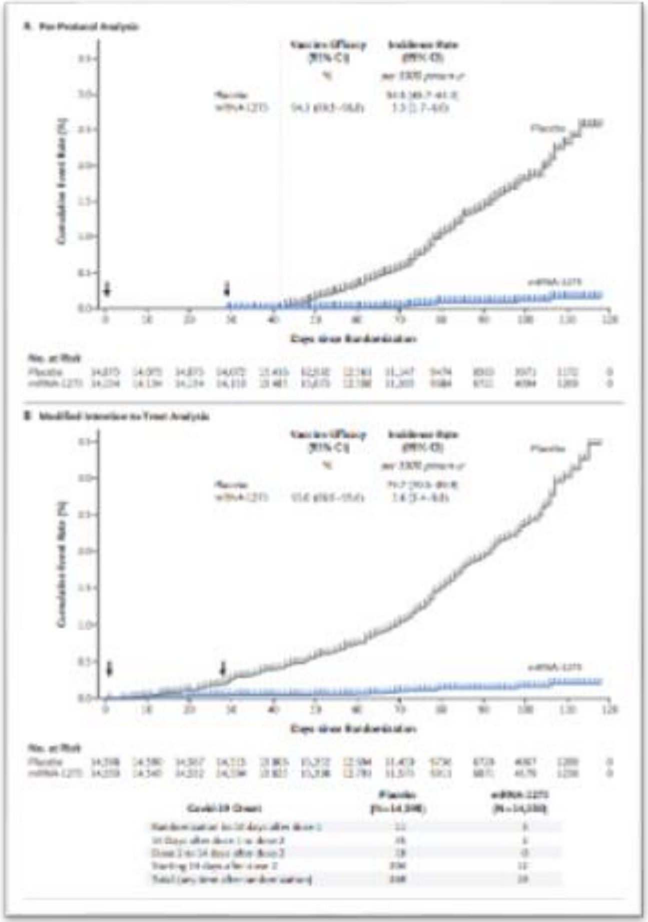
COVID-19 vaccines clinical efficacy data



[Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine | New England Journal of Medicine]



[Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine | New England Journal of Medicine]

Clinical requirements for authorisation of a vaccine

Clinical Efficacy studies not required:

- Well-established **Immune Correlate of Protection** (ICP): comparative study recommended for safety and to contextualize immunogenicity in case of unexcepted low or high results

- Efficacy can be inferred by comparing immune responses to a licensed vaccine with proven efficacy and/or effectiveness using an immune marker likely to predict protection **(immunobridging)**:

    - comparison based on statistical hypothesis testing (NI or SUP)
    - Immune parameter responsible for efficacy & platform, e.g. Neut Abs
    - Seroconversion and GMTs normally considered as primary endpoints

Clinical requirements for authorisation of a vaccine

Demonstrating Clinical Efficacy is not feasible:

- The disease occurs at too low a rate for a study to be performed in a reasonable timeframe or it occurs in unpredictable short-lived outbreaks (e.g. Filoviruses, MERS, Nipah, Zika, West Nile Virus).

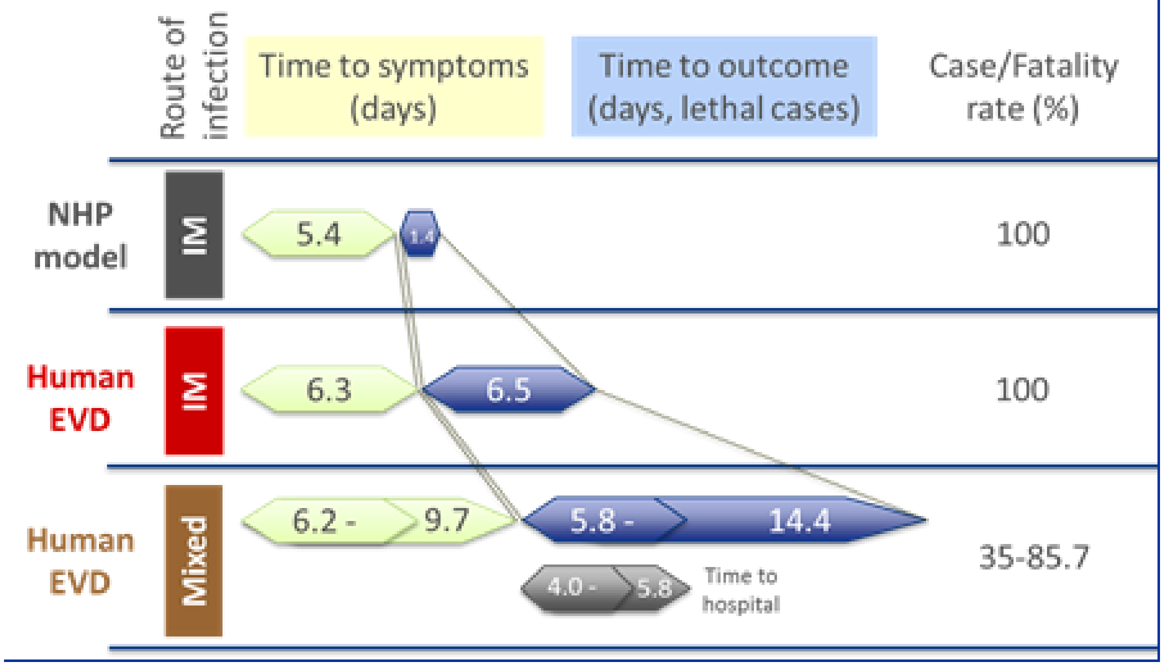
  ✓ **Alternative approaches to establish efficacy**:

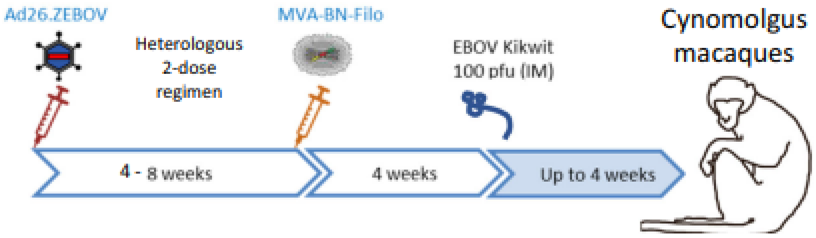
  ✓ Appropriate animal models of infection with extrapolation to humans based on immunobridging either via logistic regression or definition of putative immune correlate of protection

  ✓ Controlled Human Infection Models (CHIMs)

- Post-approval efficacy/effectiveness studies or other confirmatory studies needed.

Ebola Virus cynomolgus macaques model of infection

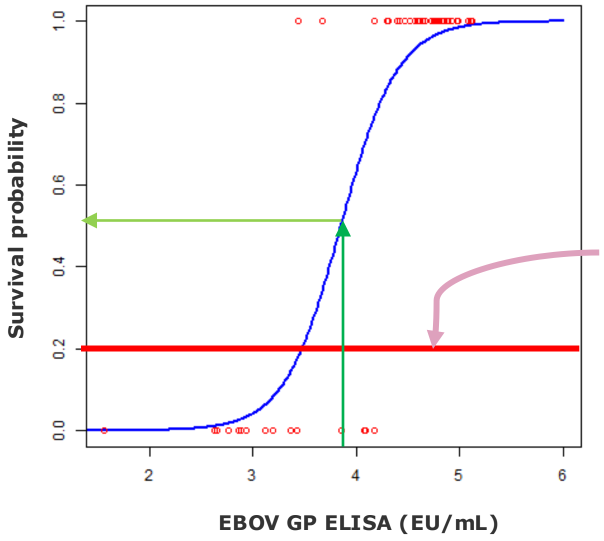




[Nonhuman primate to human immunobridging to infer the protective effect of an Ebola virus vaccine candidate (nature.com)]

Ebola vaccine Ad26-MVA
Immunobridging approach from NHP model

Logistic regression model established from NHP challenge studies



- NHP logistic regression model to determine survival probability in NHP model with **human antibody concentrations measured in clinical trials**
- **Comparison** NHP and human responses possible by use of **same assay at same lab** (EBOV GP FANG ELISA)
- Calculate mean survival probability and **95% confidence interval** using double-bootstrap method
- Protective effect demonstrated if lower limit of 95% CI above **pre-specified success criterion of 20%** (endorsed by EMA)

- NHP model >100x lethal dose by IM injection[1]:
  - *Model can provide* evidence of ***protective effect***
  - *Model* does ***not*** provide a ***direct quantification*** of vaccine effectiveness in humans

[1]CEPI Meeting report: Ebola vaccines regulatory science meeting, 22 Mar 2017, Washington DC; http://docplayer.net/57061912-Cepi-ebola-vaccines-regulatory-science-meeting.html

[Pre-existing chikungunya virus neutralizing antibodies correlate with risk of symptomatic infection and subclinical seroconversion in a Philippine cohort | Elsevier Enhanced Reader]

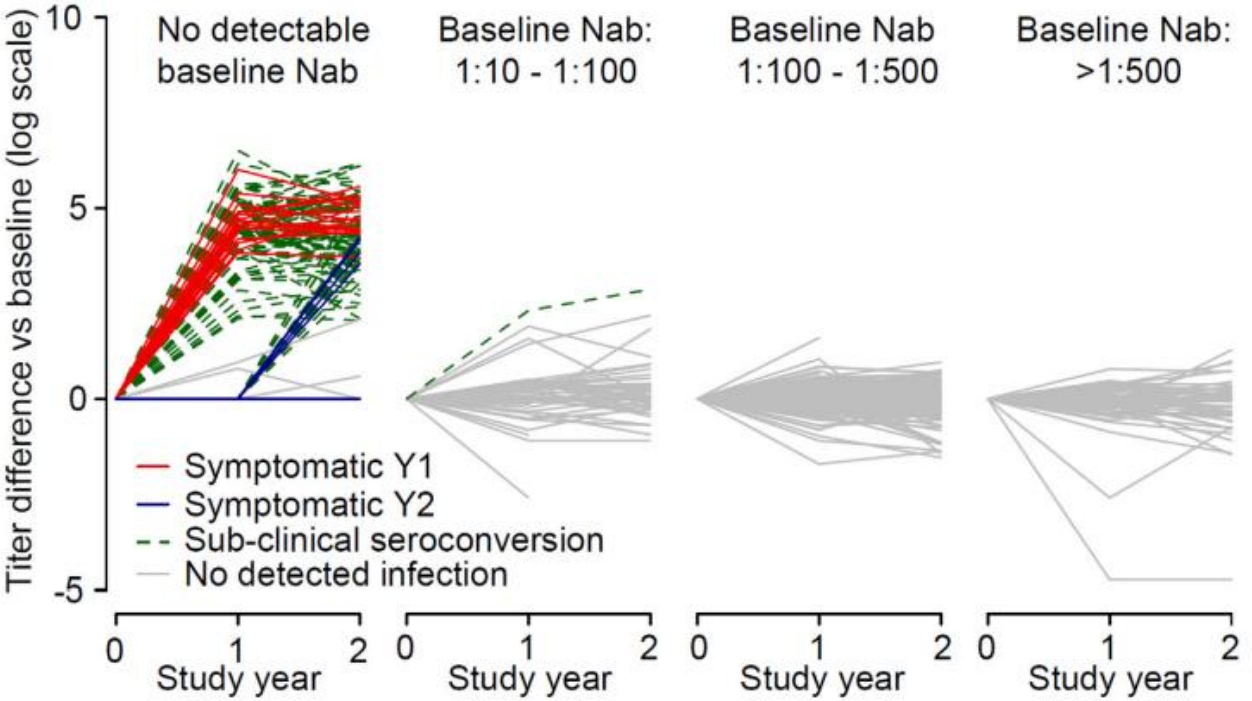
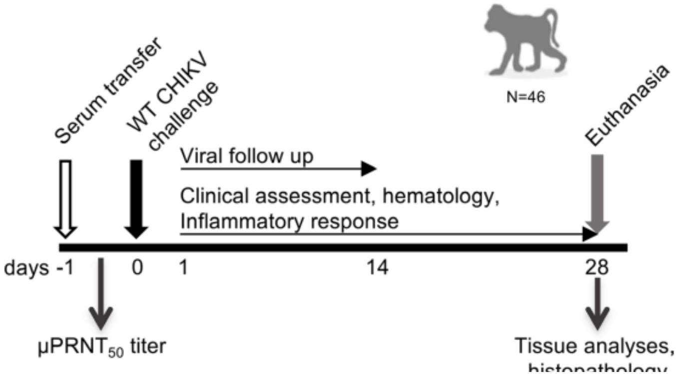


Figure 2. Changes in CHIKV PRNT80 titer (log scale) from baseline to 12 months (study year 1) and 24 months (study year 2) for each cohort participant according to baseline CHIKV PRNT80 titer group: no detectable NAb (<1:10), low titer (1:10 to <1:100), medium titer (1:100–1:500), high titer (>1:500). Red and blue solid lines indicate symptomatic infections, green dotted lines indicate subclinical seroconversions, and gray solid lines indicate no infections/seroconversions. CHIKV, chikungunya virus; PRNT80, 80% plaque reduction neutralization test; NAb, neutralizing antibody.



Effectiveness of CHIKV vaccine VLA1553 demonstrated by passive transfer of human sera

Pierre Roques,[1] Andrea Fritzer,[2] Nathalie Dereuddre-Bosquet,[1] Nina Wressnigg,[2] Romana Hochreiter,[2] Laetitia Bossevot,[1] Quentin Pascal,[1] Fabienne Guehenneux,[3] Annegret Bitzer,[2] Irena Corbic Ramljak,[2] Roger Le Grand,[1] Urban Lundberg,[2] and Andreas Meinke[2]

[1]Université Paris-Saclay, INSERM, CEA, Center for Immunology of Viral, Auto-Immune, Hematological and Bacterial diseases (IMVA-HB/IDMIT), Fontenay-aux-Roses, France. [2]Valneva Austria GmbH, Campus Vienna Biocenter 3, Vienna, Austria. [3]Valneva SE, Saint Herblain, France.

Table 2. Peak viremia for animals with different $\mu PRNT_{50}$ titer thresholds.

		$\mu PRNT_{50} \geq 50$ (*n* = 13)	$\mu PRNT_{50} \geq 100$ (*n*=4)	$\mu PRNT_{50} \geq 150$ (*n* = 2)
Peak viremia (copies/mL) Day 2–6	Geometric mean	941.1	16.3	10
	[95% CI]	[100, 8846]	[4, 77]	[10, 10]
Number of NHPs with detected CHIKV RNA	Not detected	4 (30.8%)	3 (75.0%)	2 (100%)
	Detected	9 (69.2%)	1 (25.0%)	0 (0.0%)

The geometric mean for the peak viremia (copies/mL) is shown for each group of animals assigned to the 3 $\mu PRNT_{50}$ thresholds. Numbers of animals with or without detectable CHIKV RNA were calculated for the 3 $\mu PRNT_{50}$ thresholds. Therefore, animals with an $\mu PRNT \geq 150$ are included in the $\mu PRNT_{50} \geq 100$ and $\mu PRNT_{50} \geq 50$ columns, and animals with an $\mu PRNT \geq 100$ are included in the $\mu PRNT_{50} \geq 50$ column. Peak copies/mL values reported as 0 were set to 10 for this summary.

jciinsight-7-160173.pdf (nih.gov)

EMA

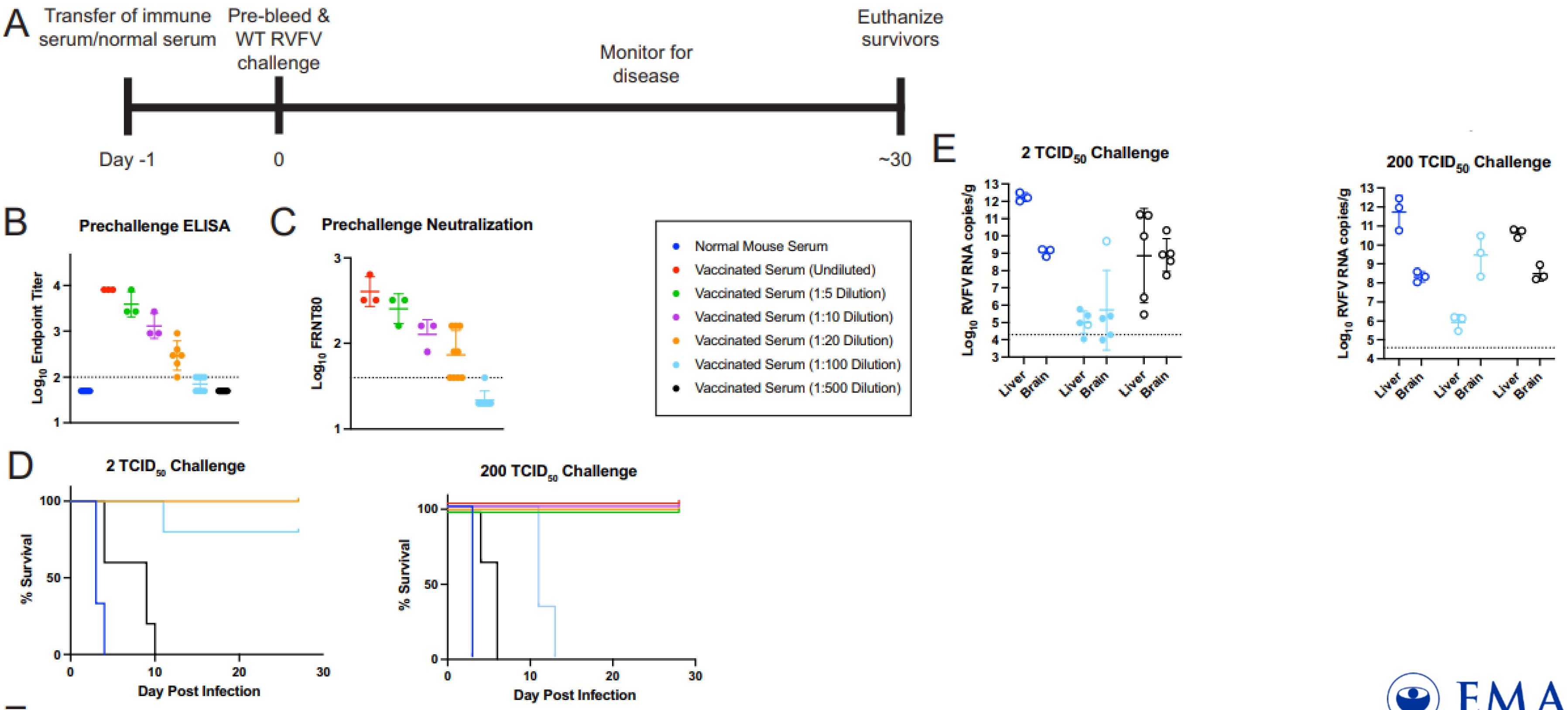
A Review of Nonhuman Primate Models of Rift Valley Fever Virus Infection: Progress, Challenge Strains, and Future Directions

Table 1. Overview of RVFV studies reported in rhesus macaques.

Publication	Challenge Dose	Challenge Route [1]	Number [2]	Outcomes
Findlay et al., 1931 [64]	Unknown	Unknown	Unknown	• Fever and leucopenia.
Findlay, 1932 [65]	Unknown	i.p.	10	• Viremia and fever.
		i.c.	1	• Viremia and fever.
		s.c.	1	• Viremia.
		i.n.	2	• Viremia and fever.
Findlay et al., 1936 [66]	Unknown	i.c.	3	• Viremia and encephalitis, resulting in being culled.
		i.p.	5	• Viremia and encephalitis in 2 animals [4].
		i.n.	2	• Viremia, fever and encephalitis.
Smithburn et al., 1948 [67]	Unknown	s.c.	6	• Viremia and fever, dependent on mosquito homogenate inoculum.
Miller et al., 1963 [68]	2820 $MIPLD_{50}$ [5]	Aerosol	4	• Viremia and temperature elevation.
	275 $MIPLD_{50}$	Aerosol	4	• Viremia and temperature elevation.
	145 $MIPLD_{50}$	Aerosol	4	• Viremia and temperature elevation.
	76 $MIPLD_{50}$	Aerosol	4	• Viremia and temperature elevation.
Easterday, 1965 [69]	Unknown	Unknown	Unknown	• Viremia and febrile.
Peters et al., 1986 [70]	4.2 $\log_{10}$ pfu	i.v.	4	• Non-clinically ill. All viremic for 3 days.
Peters et al., 1988 [71]	5.3 $\log_{10}$ pfu	s.c.	3	• One animal non-viremic, two animals viremic (days 1–3).
	4.7 $\log_{10}$ pfu	i.v.	4	• Three animals showed transient viremia; one ill with haemorrhagic diathesis and culled on day 7.
	4.1 $\log_{10}$ pfu	i.v.	3	• All were viremic, with one ill with haemorrhagic signs but recovered.
	4.8 $\log_{10}$ pfu	i.v.	5	• Viremic from day 1 up to day 4. One animal culled on day 3.
Morrill et al., 1989 [72]	10^5 pfu	i.v.	17	• All developed high viremia peaking at 48 h. $n = 3$ monkeys developed severe clinical signs: anorexia, cutaneous hemorrhage, epistaxis, and vomiting. One died on day 8 and two culled on days 6 and 15. Of the $n = 14$ which survived, 50% had a clinical illness (cutaneous rash, vomiting, or anorexia), and 7 had no evidence apart from brief pyrexia.
Morrill et al., 1989 [75]	5.0 $\log_{10}$ pfu	i.v.		• Report from monkeys used above.
Cosgriff et al., 1989 [74]	5.0 $\log_{10}$ pfu	i.m. [3]		• Report based on the data from monkeys used above.
Morrill et al., 1990 [73]	10^5 pfu	i.v.		• Report based on the data from monkeys used above.
Morrill et al., 1991 [76]	10^5 pfu	i.v.	3	• All viremic with a peak after 24–48 h. One animal showed clinical signs characterised by petechia in the axillary and inguinal area alongside a temperature increase.
Morrill et al., 2003 [77]	5.0 $\log_{10}$ pfu	i.v.	4	• All control monkeys challenged with virulent RVFV had detectable viremia for 3–5 days, and 75% (3/4) had poor appetite or anorexia, mild to moderate petechiation in the axillary and inguinal regions, and reduced activity from day 3 to 5.
Smith et al., 2011 [80]	7 $\log_{10}$ pfu	i.v.	4	• All developed viremia, peaking on day 2. None presented with clinical illness.
Morrill et al., 2011 [78]	~10^5 pfu	Aerosol	4	• All showed elevated temperatures and viremia.
Morrill et al., 2011 [79]	3×10^6 pfu	i.v.	3	• Reduced activity during the first 2 days. Viremia started at 24 h and continued to day 3.
	~5×10^5 pfu	Aerosol	5	• All showed viremia on days 3 and 4. One monkey had a mild transient elevation in rectal temperature coinciding with the recovery of the virus from the oropharyngeal swab.
Hartman et al., 2014 [81]	5.04 or 5.67 $\log_{10}$ pfu	Aerosol	2	• Biphasic fever, but no other clinical signs indicative of disease.
Bian et al., 2023 [82]	N/A	N/A	N/A	• Immunogenicity study, no challenge.

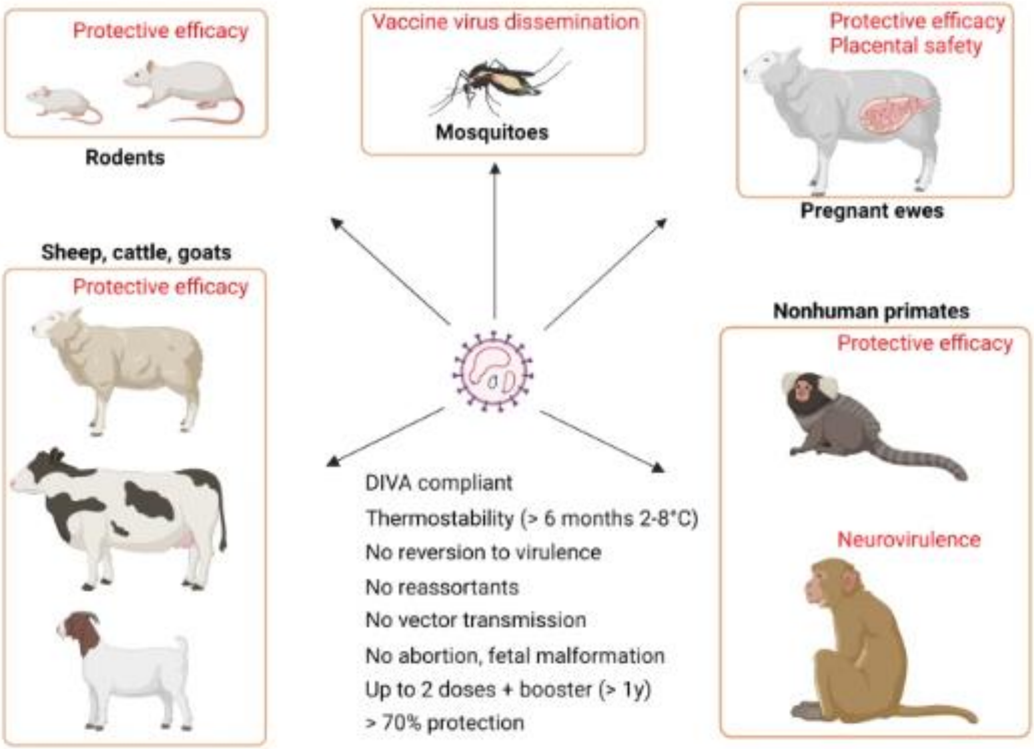
[1] i.p., intraperitoneal; i.c., intracranial; s.c., subcutaneous; i.n., intranasal; i.v, intravenous; s.c., subcutaneous. [2] Number of animals in untreated control groups. [3] Presumed error in the manuscript. [4] Animals with encephalitis received starch via the i.c. route alongside i.p. RVFV challenge. [5] $MIPLD_{50}$, mouse intraperitoneal lethal dose of 50%.

Immune correlates of protection following Rift Valley fever virus vaccination



Learnings from Animal vaccines

Fig. 4: Schematic of the effective vaccine design for Rift Valley fever (RVF) vaccine.



Summary

- Different options to be considered for generating evidence on benefit- risk including feasibility of individual randomised studies during outbreaks
- Clinical immunogenicity could derive pivotal evidence when an immune correlate of protection is established
- Use of animal challenge models that mimic human infection and disease can be used to determine putative correlates of protection or to infer protection in humans following immunobridging to human immunogenicity
- Safety to be tailored to the specific vaccine platforms, e.g. neurovirulence and genetic stability for live attenuated virus vaccines
- Post-authorisation effectiveness studies are to be required in case of approval based on animal models or immune markers
- Timely discussion with regulators, e.g. Emergency Task Force (ETF) at EMA is crucial to ensure successful development

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Marco.Cavaleri@ema.Europa.eu

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