Rift Valley Fever: key immunological considerations for vaccine development

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April 2023

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Rift Valley fever virus

First Identified in the 1930's

- Rift Valley of Kenya

Livestock pathogen

- Cattle, goats, sheep

Transmission to humans

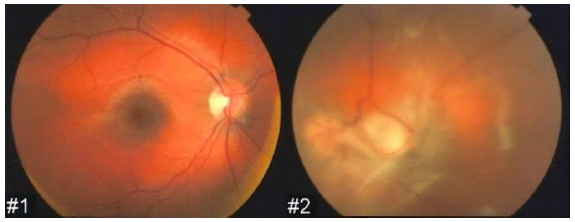
- Mosquito: arbovirus
- Contact with blood/bodily fluids of affected livestock

Blue= endemic

Green= seropositive reports

https://www.cdc.gov/vhf/rvf/index.html

Human disease manifestations



Retinitis

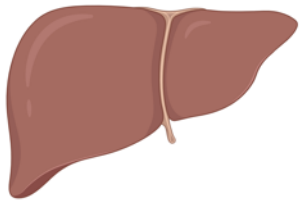
3-6 days post infection

Days post-initial symptom onset

7 14 21 28

Self-limiting febrile illness >80%

Hepatitis

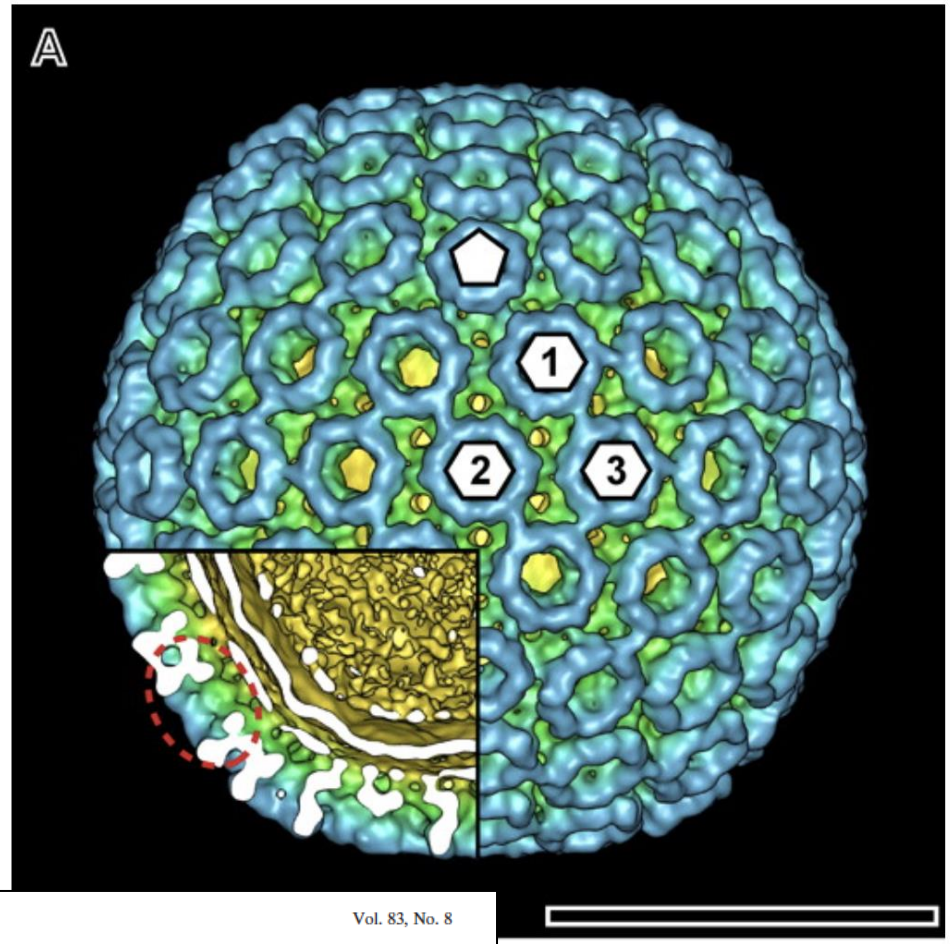


Encephalitis

Overall mortality: 1-3%
Up to 60% of adults seropositive in endemic areas

What are the key viral antigenic targets for a RVFV mRNA vaccine?

- Surface glycoproteins Gn/Gc
  - Target of neutralizing antibodies
- Nucleocapsid protein and the polymerase protein
  - Inside the virion
  - Intracellularly expressed
- Non-structural proteins NSm and NSs
  - Virulence factors

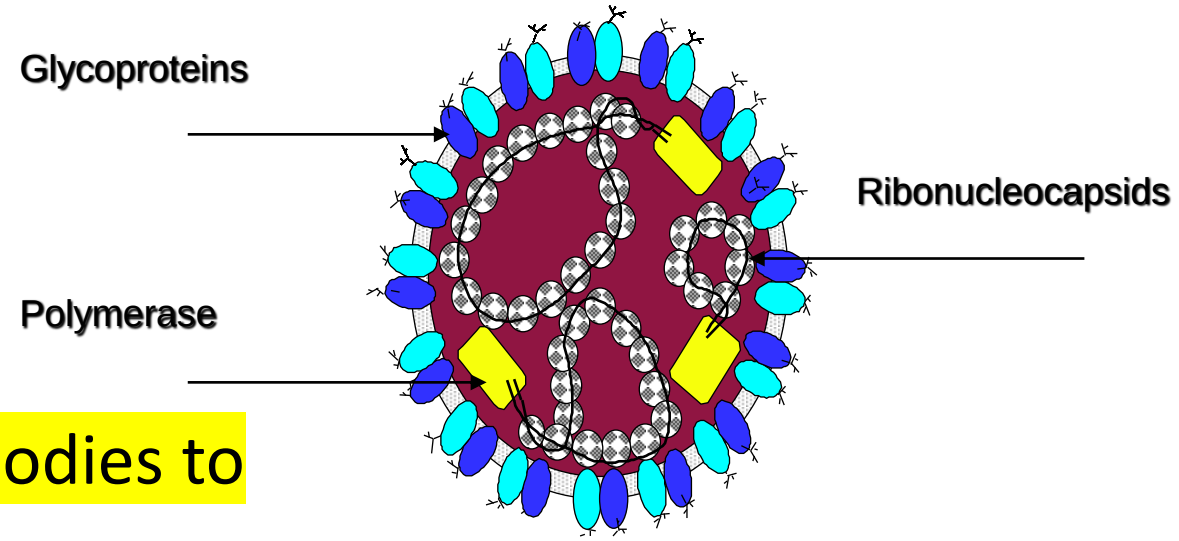


JOURNAL OF VIROLOGY, Apr. 2009, p. 3762–3769 Vol. 83, No. 8
0022-538X/09/$08.00+0 doi:10.1128/JVI.02483-08

Electron Cryo-Microscopy and Single-Particle Averaging of Rift Valley Fever Virus: Evidence for G_N-G_C Glycoprotein Heterodimers[▽]

Juha T. Huiskonen,[1,2*] Anna K. Överby,[3] Friedemann Weber,[3] and Kay Grünewald[1]

RVFV potential immune correlates



- Neutralization- functional ability of antibodies to block virus entry
  - Antibodies are directed against the viral surface glycoprotein (mostly Gn)
  - Plaque reduction neutralization titer: PRNT
  - Focus reduction neutralization titer: FRNT
  - Expressed as 50% or 80% reduction
- ELISA- quantitation of antibodies that bind to viral proteins
- Cellular immune assays- measure the ability of T cells to recognize viral proteins
  - Measured by the release of cytokines from the T cells, e.g. IFN-γ

Natural infection induces sustained RVFV humoral response

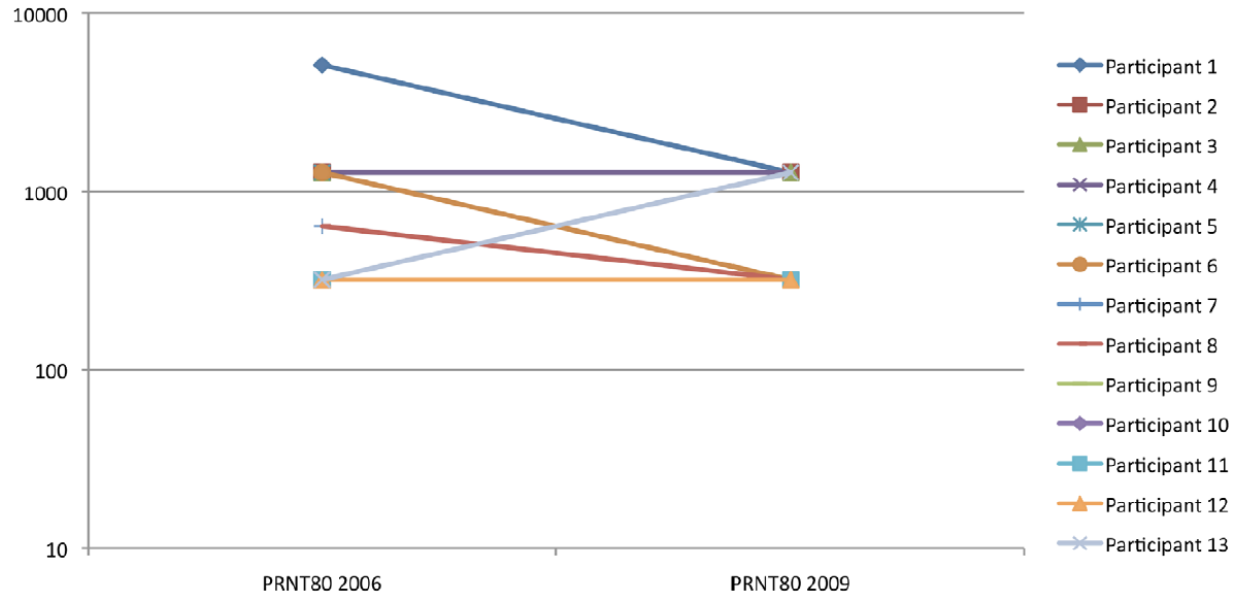
- Two villages in Kenya
- Sampled 3 years apart
- 13 individuals who were positive in 2006 also sampled in 2009
- All with PRNT80 over 100
- One with increased titer between sampling suggesting re-exposure

OPEN ACCESS Freely available online

PLoS NEGLECTED TROPICAL DISEASES

Postepidemic Analysis of Rift Valley Fever Virus Transmission in Northeastern Kenya: A Village Cohort Study

A. Desirée LaBeaud[1,2*], Samuel Muiruri[3], Laura J. Sutherland[2], Saidi Dahir[3], Ginny Gildengorin[1], John Morrill[4], Eric M. Muchiri[3], Clarence J. Peters[4], Charles H. King[2]



2011

Natural infection induces long-lived robust immune responses

- Two cohorts in Kenya
- Longitudinal data in 5 individuals
- High titer virus neutralizing antibodies
- IgG1 predominant
- Gn/Gc specific T cell function also noted

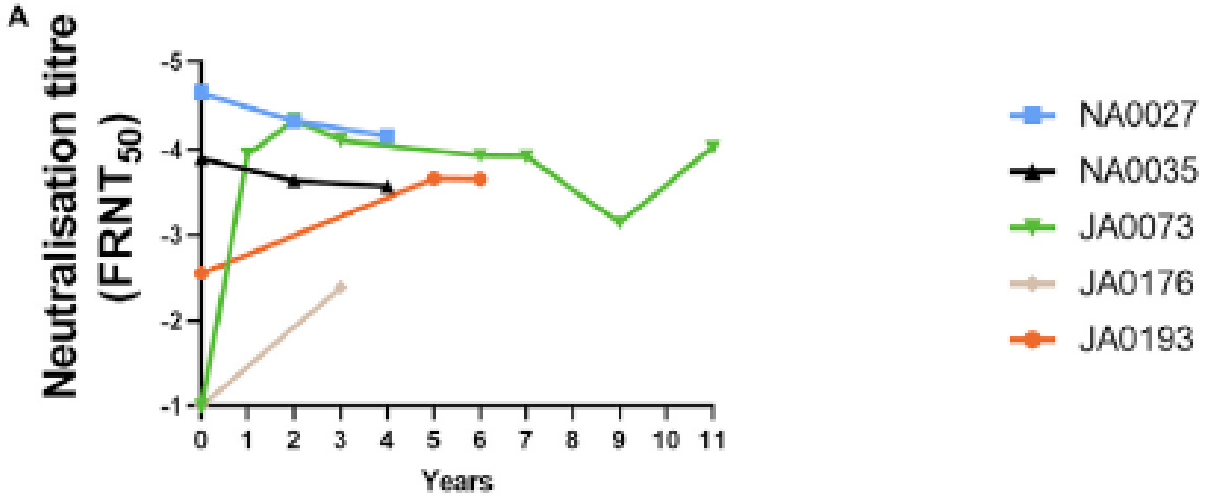
iScience

CellPress
OPEN ACCESS

Article

Naturally Acquired Rift Valley Fever Virus Neutralizing Antibodies Predominantly Target the Gn Glycoprotein

Daniel Wright,[1,2,7,*] Elizabeth R. Allen,[3] Madeleine H.A. Clark,[4] John N. Gitonga,[1] Henry K. Karanja,[1] Ruben J.G. Hulswit,[3] Iona Taylor,[2] Sumi Biswas,[2] Jennifer Marshall,[2] Damaris Mwololo,[5] John Muriuki,[5] Bernard Bett,[5] Thomas A. Bowden,[3] and George M. Warimwe[1,6]

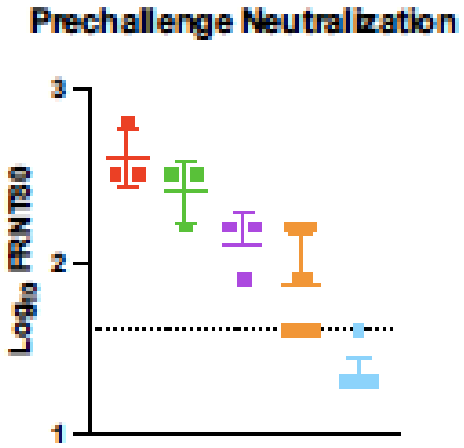


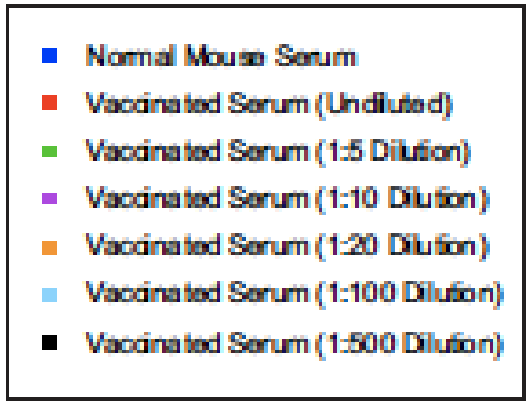
2020

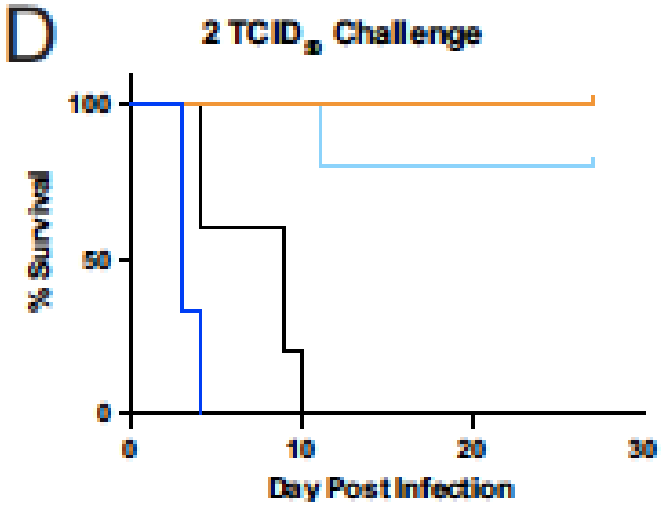
Immune correlates of protection

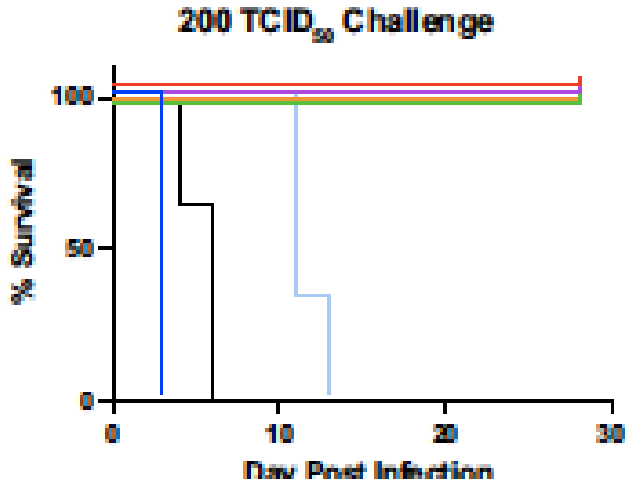
- Not clearly defined for humans
- Often associated with neutralizing antibodies
- Very little data on human cellular immunity and no established correlates for cellular immunity
- Pre-clinical data in mice, hamsters, rhesus macaques
  - Passive transfer experiments
  - PRNT or FRNT levels correlates with protection from challenge

Immune correlates of protection-mice









ARTICLE OPEN

Check for updates

Immune correlates of protection following Rift Valley fever virus vaccination

Joshua D. Doyle[1,2,3], Dominique J. Barbeau[1,2], Haley N. Cartwright[1,2] and Anita K. McElroy[1,2,3]✉

2022

- Naïve mice administered different amounts of immune serum from mice vaccinated with live attenuated DelNSs RVFV
- FRNT80 measure in mice 24 hours after transfer then mice challenged with WT RVFV
- Note differences in protection based upon challenge dose
- GMT $FRNT_{80}$ >=74 was 100% protective at both challenge doses

Immune correlates of protection- NHPs

Table 2. Protection against RVFV infection by passive antiserum

Experiment no.	Antibody dose[a]	Pre-infection PRNT[b]	N	Viremia[c] Day 1	Day 2	Day 3	Day 4	Day 5	PRN_{80} Day 21–25	Day 31
5, 6[d]	0	<10 (<10)	9	1.5 ±0.8 (5)	4.0 ±1.4 (9)	3.6 ±2.2 (6)	1.2 ±1.2 (1)	<0.7 (0)	940 (320–2,560)	1,110 (320–5,120)
5[d]	0.5	63 (40–80)	3	<0.7 (0)	<0.7 (0)	<0.7 (0)	<0.7 (0)	<0.7 (0)	63 (40–80)	—
5[d]	0.1	20 (20)	3	<0.7 (0)	<0.7 (0)	<0.7 (0)	<0.7 (0)	<0.7 (0)	508 (160–1,280)	—
6[d]	0.05	<10 (<10)	4	<0.7 (0)	<0.7 (0)	<0.7 (0)	<0.7 (0)	<0.7 (0)	538 (320–1,280)	2,150 (640–5,120)
6[d]	0.025	<10 (<10)	4	<0.7 (0)	<0.7 (0)	<0.7 (0)	<0.7 (0)	<0.7 (0)	1,080 (640–1,280)	2,560 (1,280–5,120)
2, 3[e]	0	<10 (<10)	7	2.8 ±2.1 (5)	5.6 ±1.2 (7)	4.9 ±0.9 (7)	3.3 ±1.4 (6)	1.7 0.7 (1/3)[f]	⩾160 (⩾160)	⩾160 (⩾160)

[a] ml/kg given i.m. on day −2; serum PRN_{80} 1:2,560
[b] Geometric mean titer or GMT (range)
[c] GMT ± SEM of $\log_{10}$ PFU/ml serum; number viremic in parenthesis
[d] s.c. inoculation with 6.0 $\log_{10}$ PFU of ZH501 $FRhL_2 spleen_1 serum_1 spleen_1$ on day 0
[e] i.v. inoculation with 4.1–4.7 $\log_{10}$ PFU of ZH501 $FRhL_2$ on day 0
[f] Only 3 monkeys sampled on day 5

Experimental Rift Valley fever in rhesus macaques

C. J. Peters, D. Jones, R. Trotter, J. Donaldson, J. White, E. Stephen, and T. W. Slone, Jr.

Disease Assessment and Pathology Divisions, U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, Maryland, U.S.A.

Accepted December 12, 1987

- Rhesus macaques given 0.5 ml/kg down to 0.025 ml/kg of immune serum with a starting PRNT80 of 1:2560
- Challenged with WT ZH501
- Animals were protected from disease and had undetectable viremia following any dose of antibody

Does vaccination induce sufficient immunity? How long will vaccine mediated immunity last? Will boosters be necessary?

- Likely depends upon the platform and immunogen
- Lessons learned from prior vaccines
  - Formalin inactivated vaccine
  - MP-12- live attenuated
  - ChAdOx
  - DDVax (University of California Davis and Colorado State)-NHP data
  - RVFV-4S (Wageningen Bioveterinary Research)- NHP data

Formalin inactivated vaccine

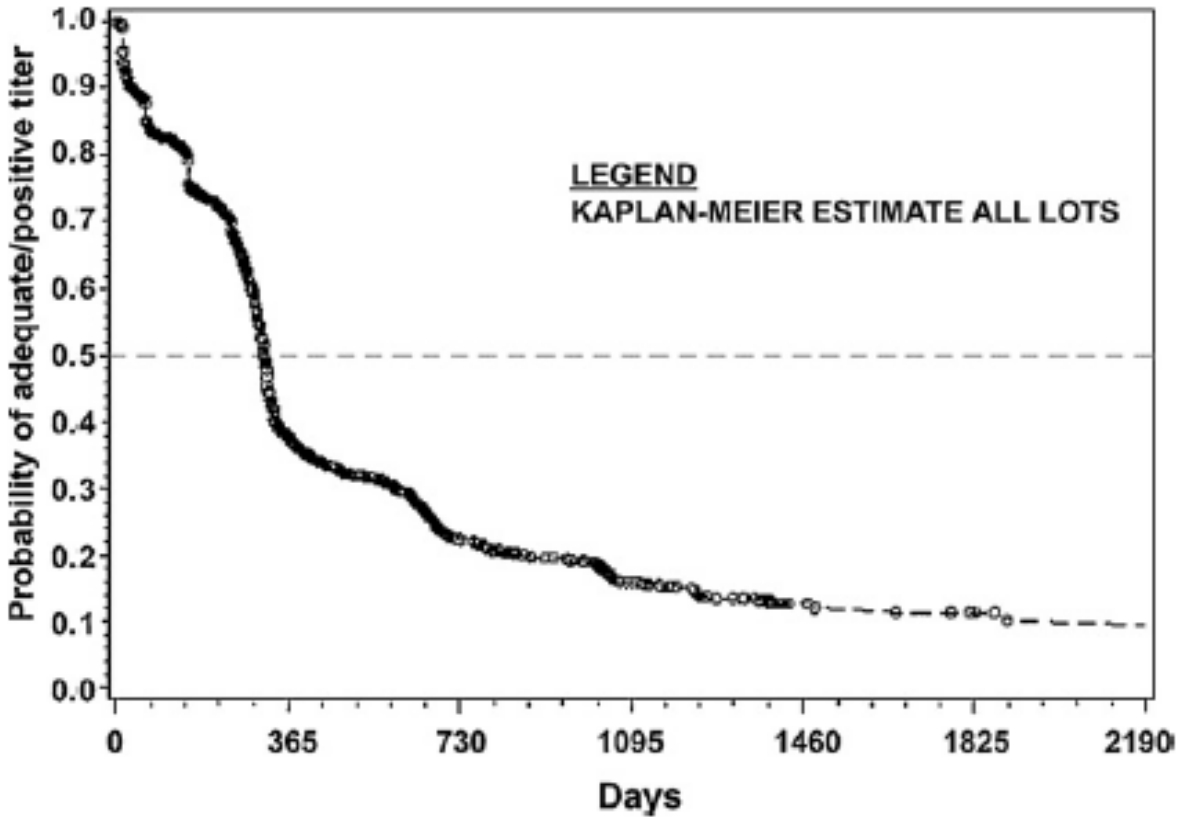


Fig. 1. Kaplan–Meier analysis of RVF loss of titer ($PRNT_{80}$) < 1:40 after primary dose 3 for subjects negative at baseline. Kaplan–Meier estimate for half-life of the $PRNT_{80}$ was 315 days (95% CI 308–321 days) from dose 3 of the primary series.

Immunogenicity and safety of an inactivated Rift Valley fever vaccine in a 19-year study☆

Janice M. Rusnak[a,*], Paul Gibbs[b], Ellen Boudreau[c], Denise P. Clizbe[c], Phillip Pittman[c]

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[b] Department of Statistics, USAMRIID, 1425 Porter Street, Fort Detrick, MD 21702, United States
[c] Medical Division, USAMRIID, 1425 Porter Street, Fort Detrick, MD 21702, United States

- First vaccine tested in humans
- 1860 subjects
- 3 dose primary series (0,14,28d)
- Estimated that >= 1:40 was protective
- Required boosting to maintain titers over time

MP-12- mutagenized live attenuated

Rift Valley fever MP-12 vaccine Phase 2 clinical trial: Safety, immunogenicity, and genetic characterization of virus isolates

Phillip R. Pittman[a,*], Sarah L. Norris[a], Elizabeth S. Brown[b], Manmohan V. Ranadive[c], Barbara A. Schibly[c], George E. Bettinger[d], Nandadeva Lokugamage[d], Lawrence Korman[a], John C. Morrill[d], Clarence J. Peters[d]

[a] U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), 1425 Porter Street, Fort Detrick, Frederick, MD 21702-5011, United States
[b] ClinicalRM, USAMRIID, 1425 Porter Street, Fort Detrick, Frederick, MD 21702-5011, United States
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[d] University of Texas Medical Branch, Galveston, TX 77555, United States

Table 2
Long-term immunogenicity of RVF MP-12, by subject.

Subject no.	Day 28		Month 12	Year 2	Year 3	Year 4	Year 5
	$PRNT_{80}$	$PRNT_{50}$	$PRNT_{80}$	$PRNT_{80}$	$PRNT_{80}$	$PRNT_{80}$	$PRNT_{80}$
001	1:120	1:320	1:60	1:30	1:20	1:30	1:15
002	1:240	1:640	1:120	–	–	–	–
003	1:480	1:960	1:240	1:120	1:320	1:120	1:60
004	1:10	1:30	<1:10	–	–	–	–
005	1:640	1:960	1:640	1:240	1:320	1:120	1:120
007	1:480	1:1280	1:240	1:120	–	1:60	–
008	1:960	1:1280	1:960	–	–	–	–
009	1:1280	1:1920	1:320	1:240	1:320	–	1:120
011	1:960	1:1920	1:240	1:120	1:320	–	1:120
012	1:120	1:640	1:320	1:120	–	–	–
014	1:960	1:1920	1:120	1:60	1:80	1:60	1:60
015	1:240	1:640	1:60	1:60	1:80	1:60	1:30
016	1:60	1:480	1:40	–	–	–	–
019	1:1280	1:3840	1:240	1:120	–	–	–
020	1:240	1:640	1:80	1:60	1:20	1:30	1:30
021	1:1280	1:3840	1:240	–	–	–	–
023	1:240	1:640	1:80	–	–	–	–
026	1:1920	1:3840	1:1280	1:480	1:1280	1:480	1:480
029	1:960	1:2560	1:640	1:240	–	–	–

Notes: PRNT, plaque reduction neutralization titer (80% and 50%). $PRNT_{50}$ values are provided for day 28 for comparison to $PRNT_{80}$ values at the same time point. – Denotes missing data for subjects who did not return for a follow-up visit.

- Single dose $1x10^5$ PFU
- 62 subjects in Phase I and Phase II
- Estimated that >= 1:20 was protective

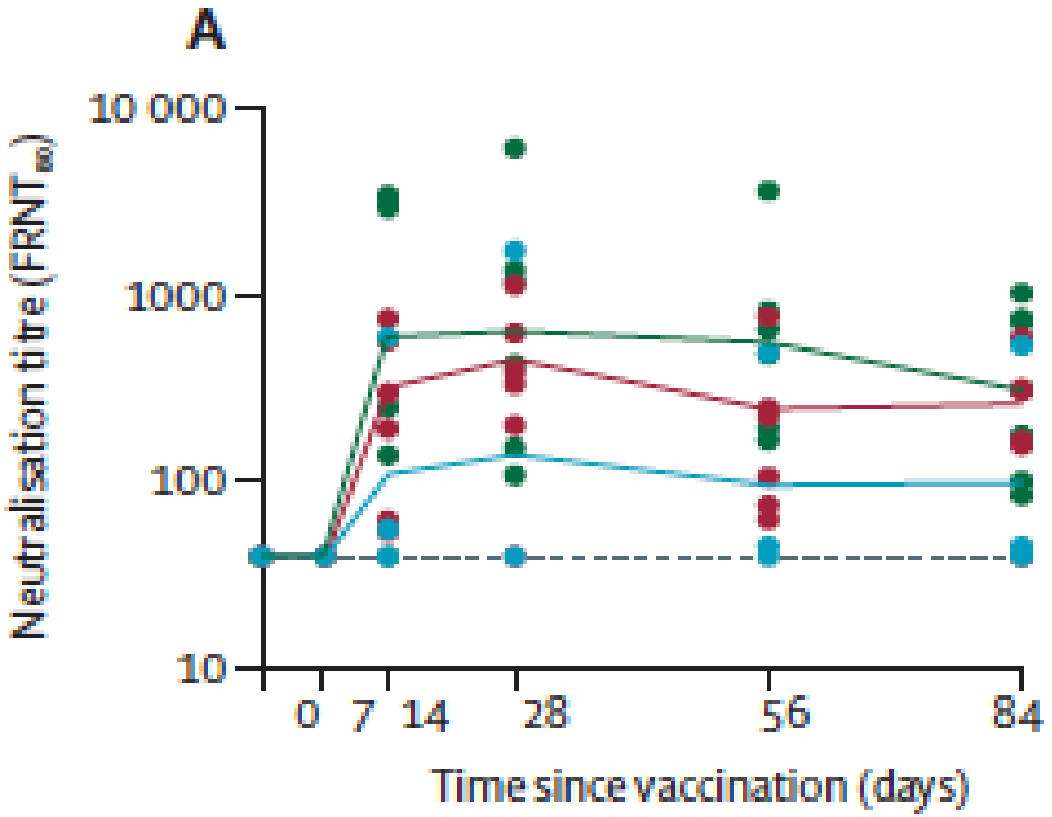
18/19 seroconverted

8/9 maintained >= 1:20 out to 5 years

ChAdOx1 RVFV vaccine

Safety and immunogenicity of a ChAdOx1 vaccine against Rift Valley fever in UK adults: an open-label, non-randomised, first-in-human phase 1 clinical trial

Daniel Jenkin, Daniel Wright*, Pedro M Folegatti, Abigail Platt, Ian Poulton, Alison Lawrie, Nguyen Tran, Amy Boyd, Cheryl Turner, John N Gitonga, Henry K Karanja, Daisy Mugo, Katie J Ewer, Thomas A Bowden, Sarah C Gilbert, Bryan Charleston, Pontiano Kaleebu, Adrian V S Hill, George M Warimwe*



- Chimpanzee adenovirus vectors RVFV Gn/Gc
- Single dose $5x10^9$-$5x10^{10}$
- 15 subjects
- 12/15 seroconverted
- FRNT stable out to 3 months
- Phase I in Uganda recently completed

Summary- a RVFV mRNA vaccine?

- Gn/Gc most likely antigen
- Neutralizing antibodies are easy to measure and correlate well with protection in pre-clinical models
- Defining the true protective neutralization titer in human efficacy studies still needs to be done- tough given the sporadic nature of RVFV emergence in resource limited locations
  - WHO/CEPI sponsored international standards will help to coordinate this amongst groups
- Unknowns:
  - Will mRNA vaccination induce sufficient magnitude of neutralizing antibodies?
  - Will an mRNA vaccination induce durable immunity?
  - Will route or dose of exposure affect vaccine efficacy in humans?