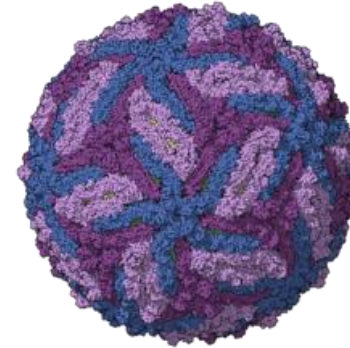
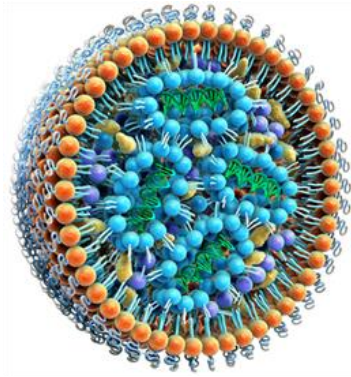




mRNA Vaccines Against Flaviviruses

WHO/MPP mRNA Technology Transfer Programme

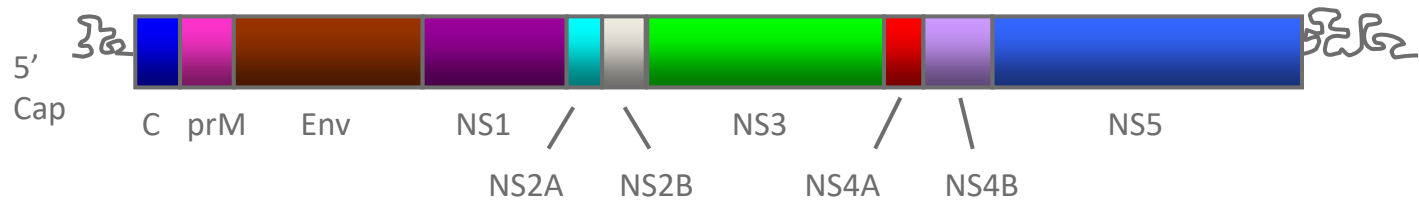
April 20th, 2023

Justin Richner

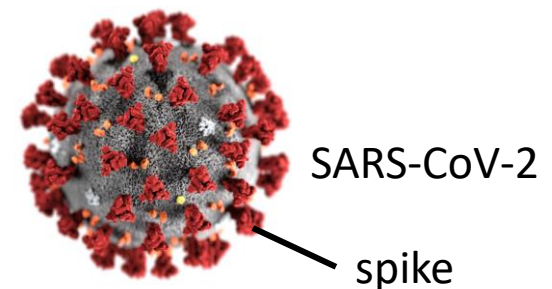
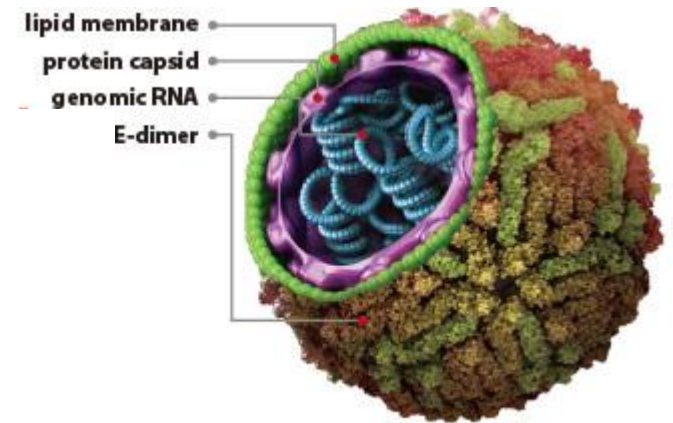
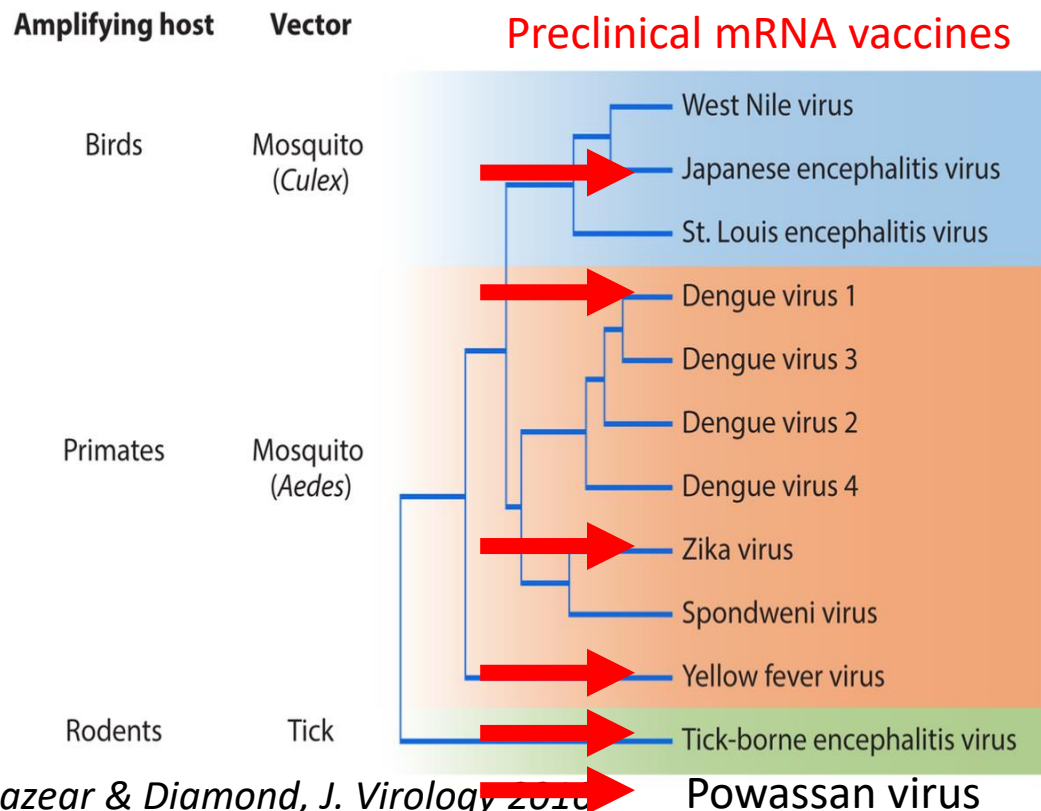


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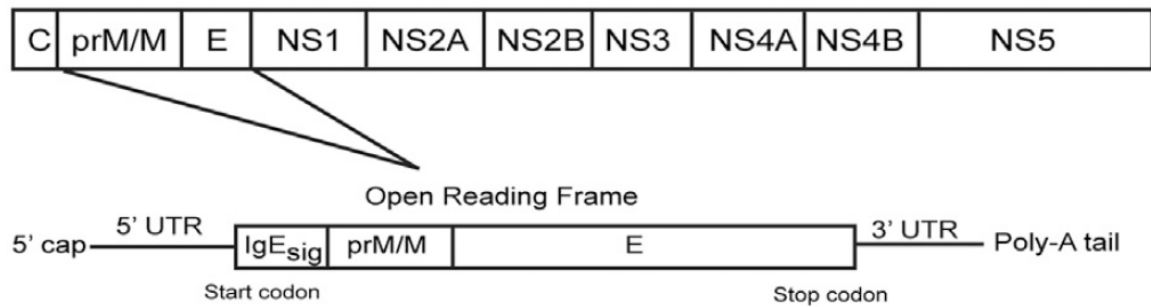
Flavivirus Family



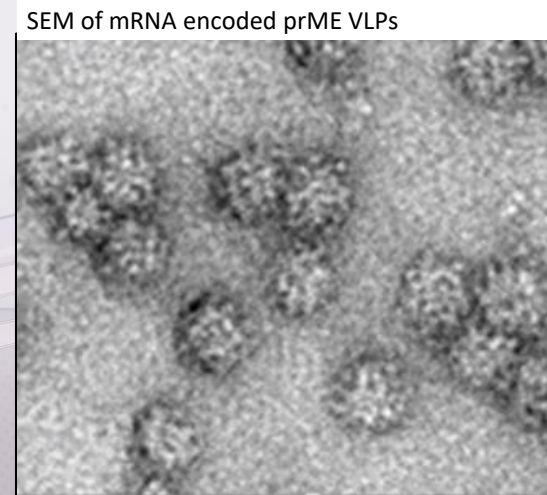
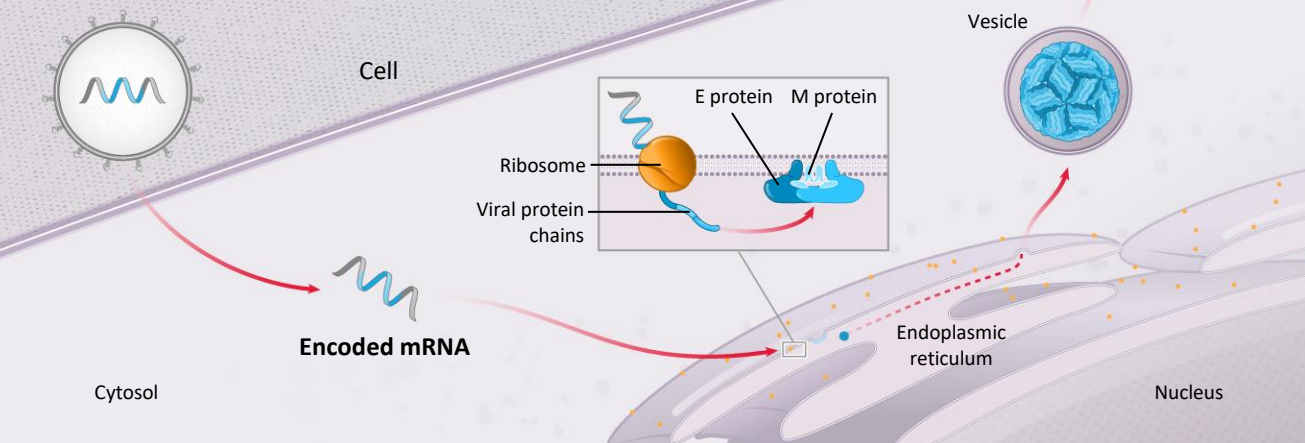
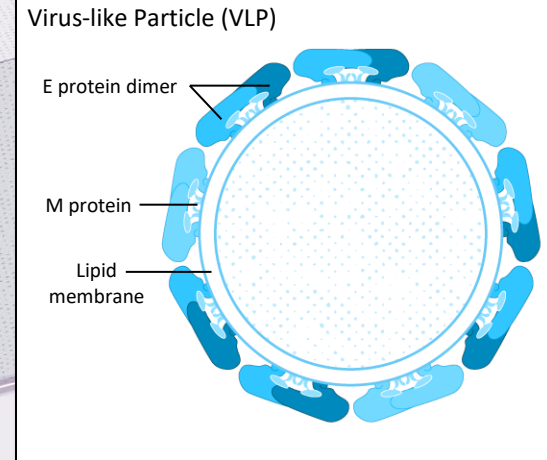
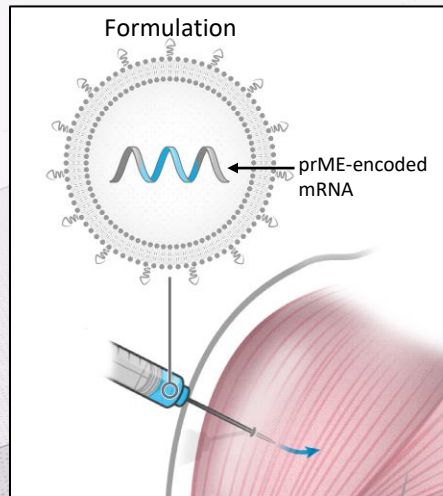
- Enveloped, (+) ssRNA genome (10-13 kb)
- Single ORF proteolytically cleaved to individual proteins



prM-ENV mRNA vaccines:



prM and ENV self-assemble
into a Viral-like particle (VLP)



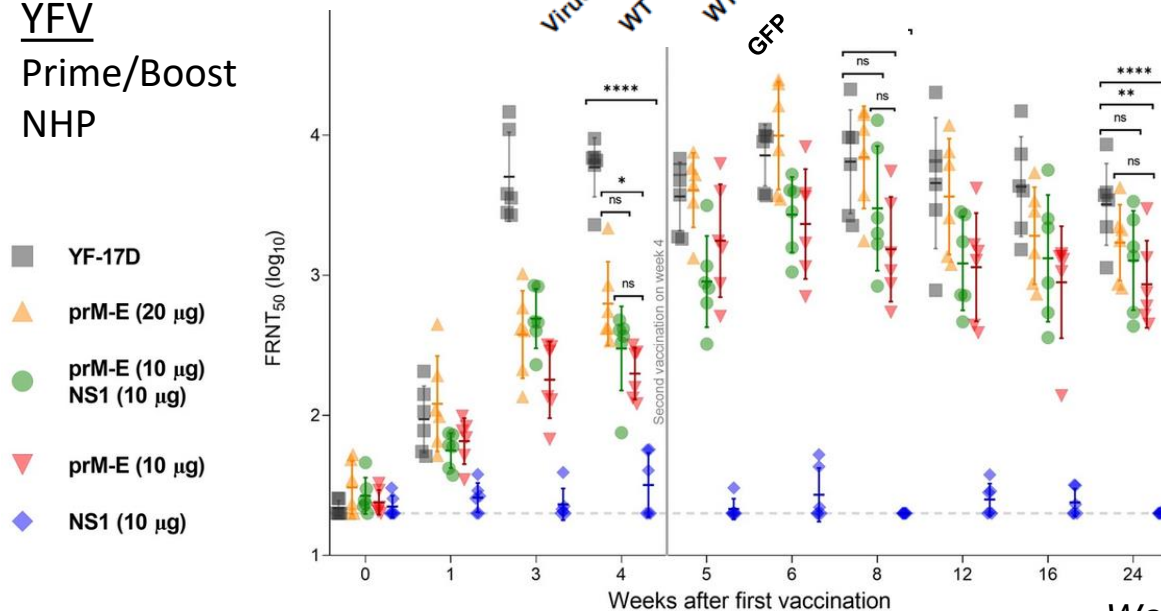
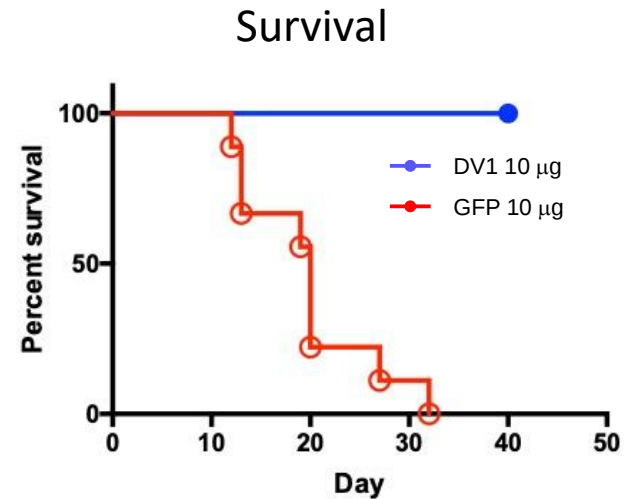
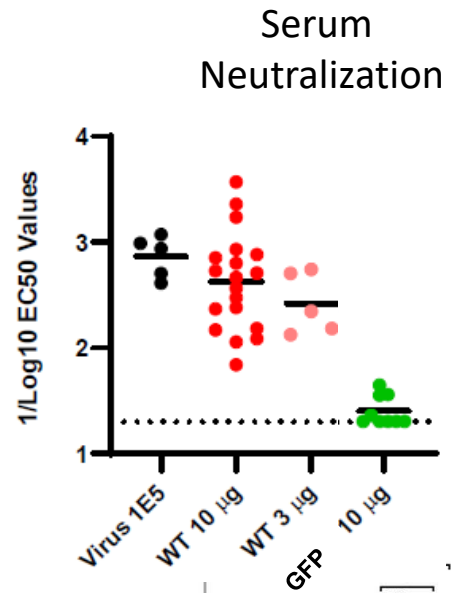
*prM-ENV mRNA-LNP Vaccines Elicit
Neutralizing, Protective Humoral Immunity*

DENV - 1

Prime/Boost

Mouse

YFV
Prime/Boost
NHP



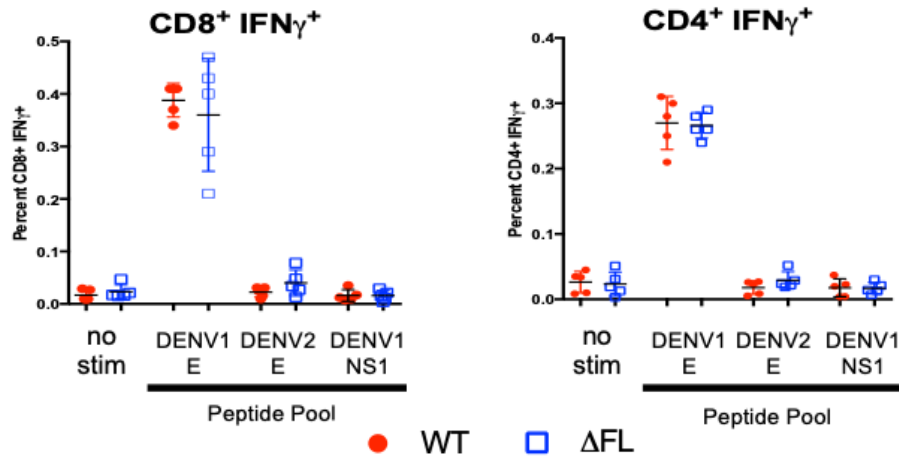
Similar findings for:

- Zika virus
- Powassan virus
- Japanese Encephalitis virus

mRNA-LNP vaccines elicit cellular immunity

DENV-1 prM-ENV

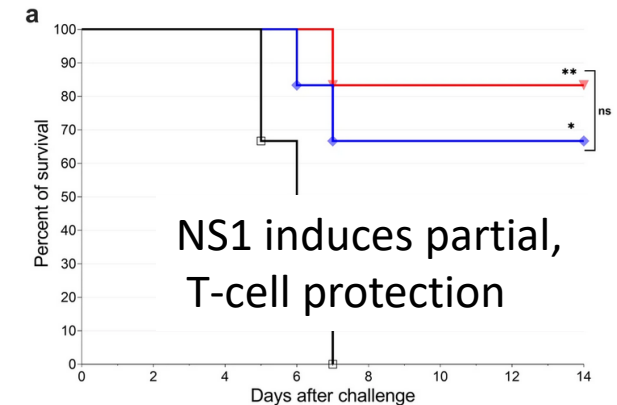
Mouse - Prime/Boost



YFV:

Mouse – Prime/Boost

Splenocyte Adoptive Transfer

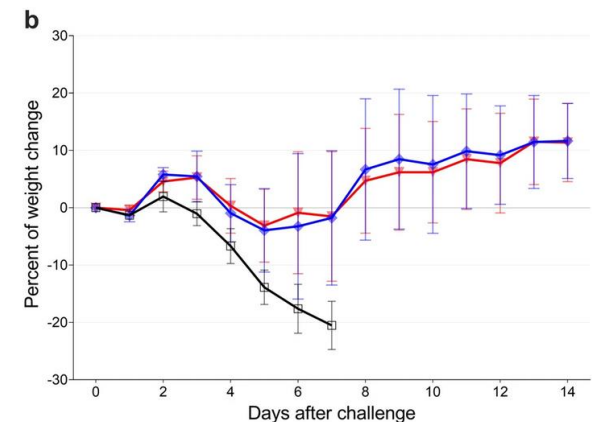
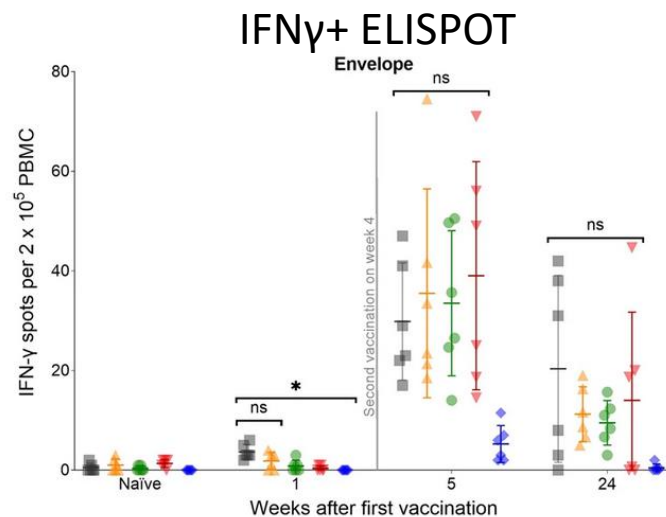


YFV:

NHP - Prime/Boost

- YF-17D
- ▲ prM-E (20 μ g)
- prM-E (10 μ g)
NS1 (10 μ g)
- ▼ prM-E (10 μ g)
- ◆ NS1 (10 μ g)

NS1 induces vascular leakage



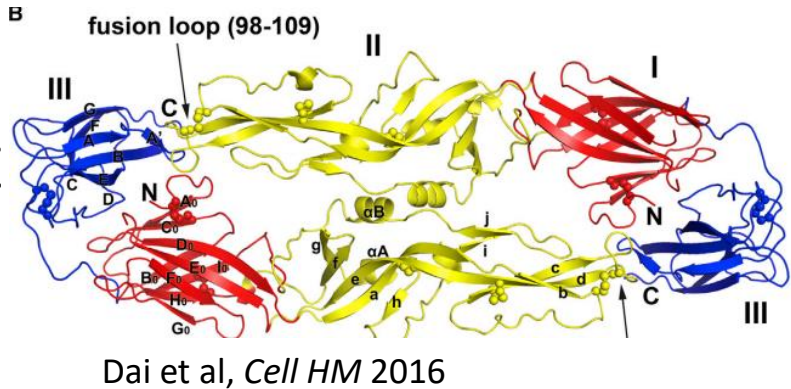
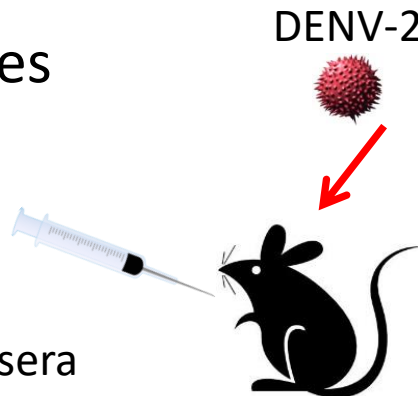
Potential Advantages of mRNA Vaccines

- 1.) Avoid SAE associated with live-attenuated viruses
- 2.) Engineer epitopes to ablate ADE

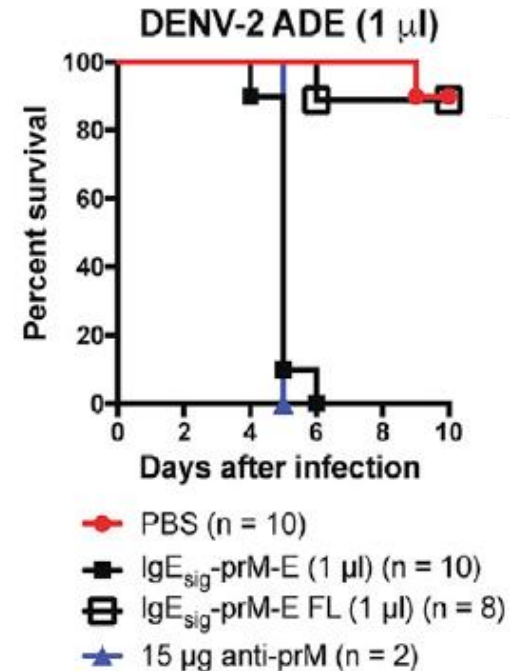
- Preexisting DENV or ZIKV immunity can enhance DENV
- Antibodies targeting the highly conserved fusion loop epitope primarily drive ADE

- ZIKV prM-E Δ FL mRNA vaccines
 - Equivalent Neut titers to WT vaccine
 - Lower ADE inducition

Passive transfer of immune sera
from Zika vaccinated mice



Dai et al, *Cell HM* 2016



Richner et al 2017

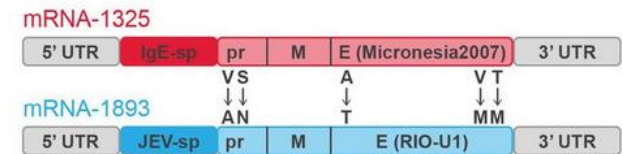
Challenges of mRNA Flavivirus Vaccines:

Antigen Expression/Optimization

- Expression of envelope in native confirmation is inefficient
- Zika virus mRNA vaccine phase I clinical data

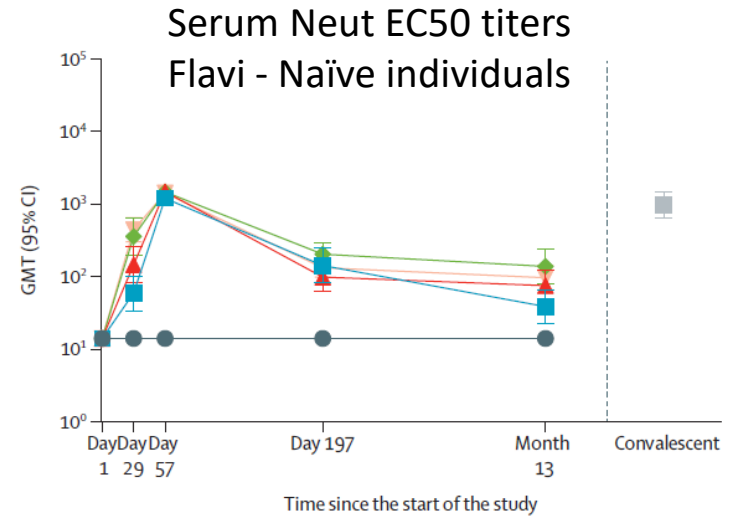
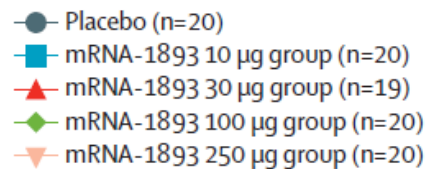
– mRNA-1325:

- Low ENV expression and low VLP secretion
- 10, 25, 50 ug prime/boost – low neutralization titers (<50)



– mRNA-1893:

- 10-250 ug prime/boost
- Neutralizing Ab response (100% - D57)
- Durable immunity



• DENV Vaccine:

- Antigen optimization required for efficient expression *Essink et al 2023*
- Elicit balanced neutralizing response against all four serotypes



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National Institute of
Allergy and
Infectious Diseases

R01AI150672

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