

# Comparative efficacy of Gag/Pol/Env vaccines derived from temporal isolates of SIVmne against cognate virus challenge

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AIDS Vaccine 07  
Seattle, 2007

# Differential Phenotypes of Temporal Isolates of HIV

- Viruses isolated early during the asymptomatic phase, are typically macrophage-tropic, slow replicating, minimally cytopathic, and non-syncytium inducing: M-tropic, slow-low/NSI phenotype
- Viruses emerge later are often able to infect CD4<sup>+</sup> T-cell lines, and replicate rapidly, cytopathic, and syncytium inducing: T-tropic, rapid-high/SI phenotype

# Questions

- Do vaccines derived from early or late isolates induce qualitatively different immune responses?
- Do these responses show differential protection against early or late virus isolates?

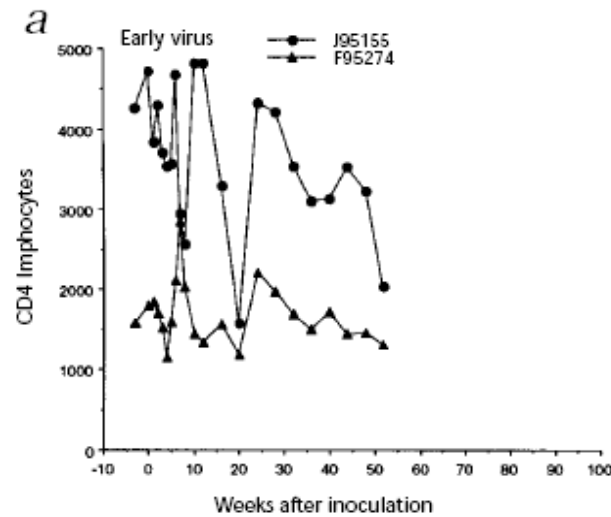
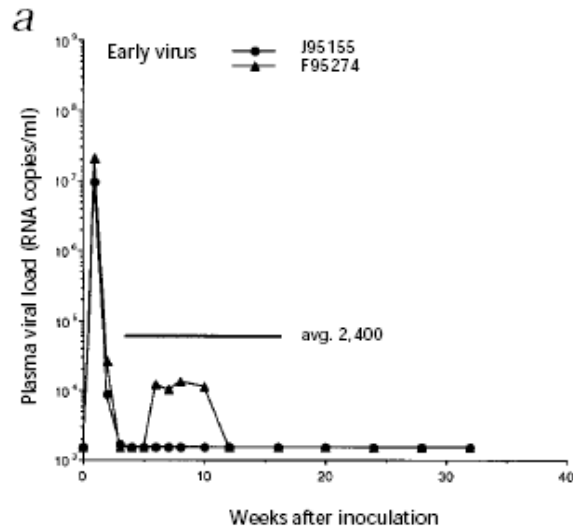
# Temporal Isolates of SIVmne

- Inoculum: SIVmne CL8 (molecular clone of E11S)
  - Slow replication kinetics
  - Macrophage tropic
  - Low cytopathicity
- Late (Wk 170) isolate: SIVmne 170
  - Rapid replication kinetics
  - Syncytium-forming
  - Highly cytopathic

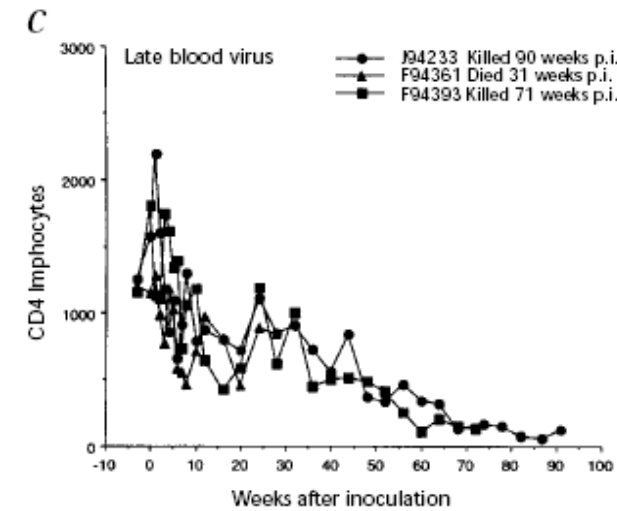
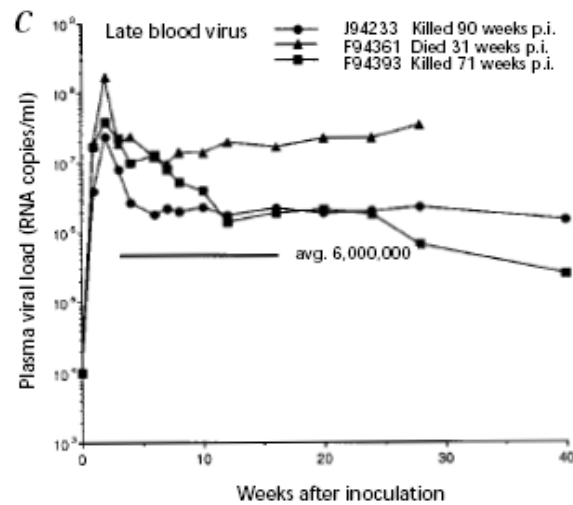
*Overbaugh J, Rudensey LM.. J Virol. 1992 Oct;66(10):5937-48.*

# Differential In Vivo Pathogenicity of Temporal Isolates of SIVmne

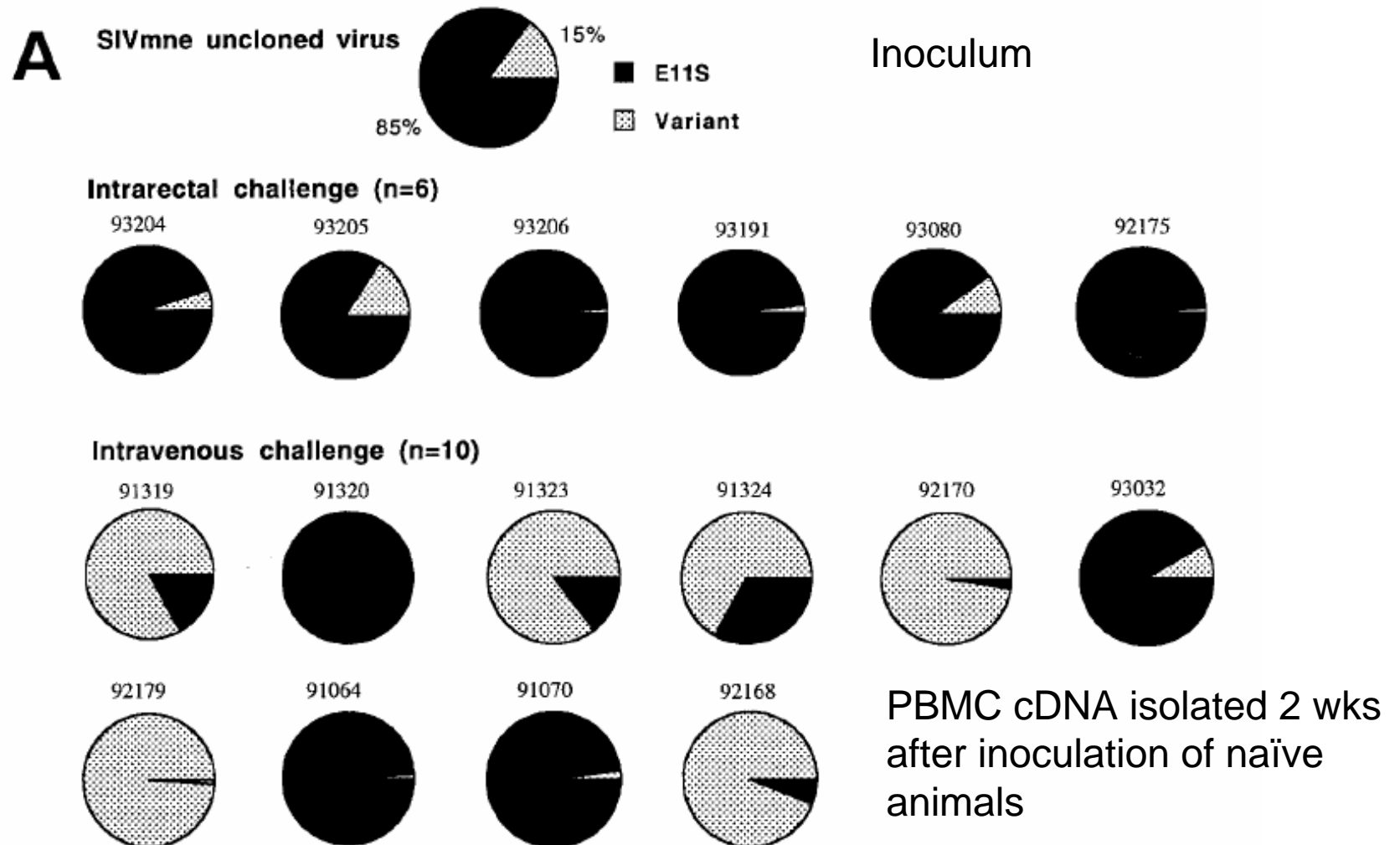
CL8



170



# Preferential Transmission or Amplification of E11S-like Viruses After Intrarectal Inoculation



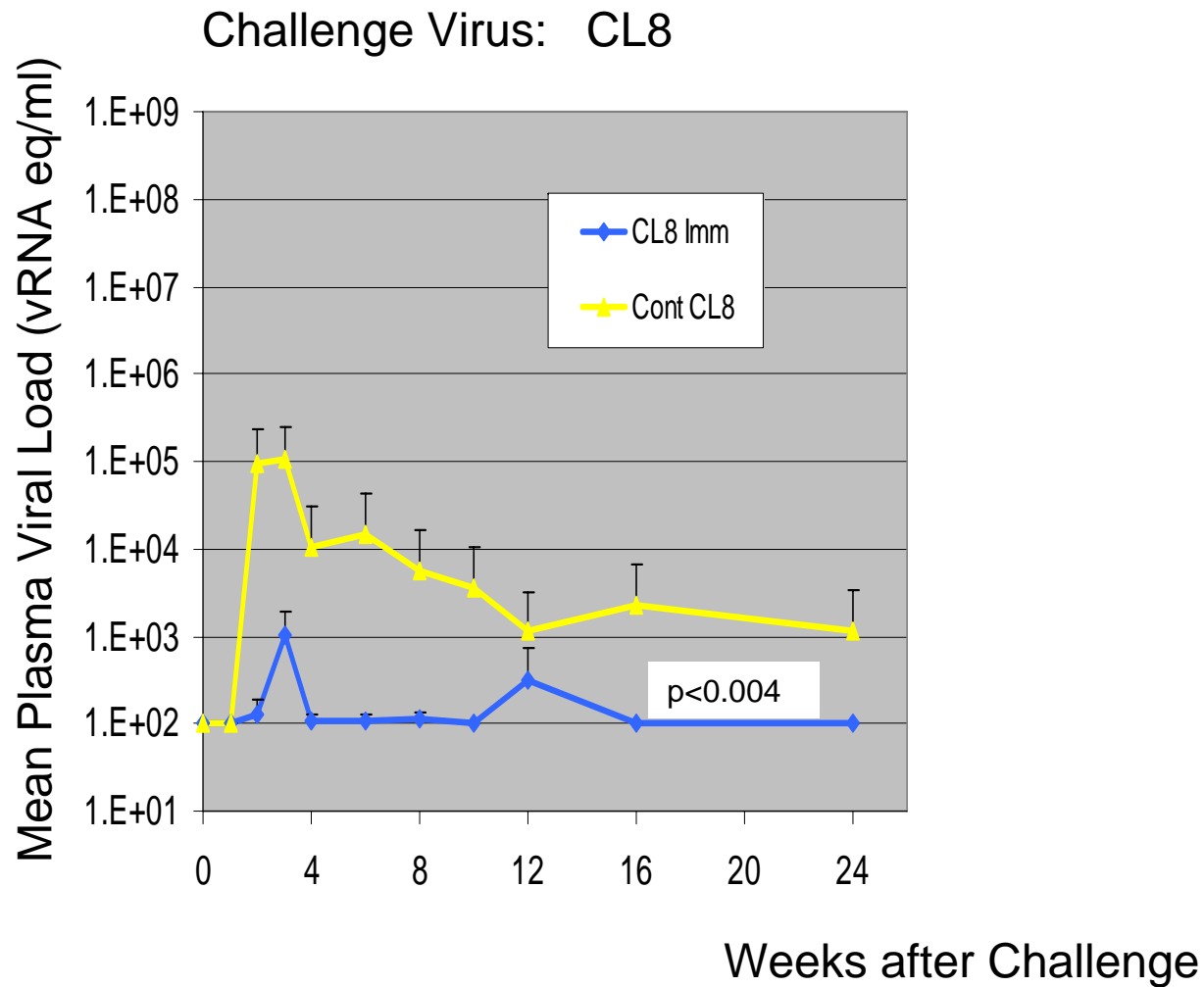
Polacino *et al. J. Virol.* 73:3134-3146, 1999

# Study Design

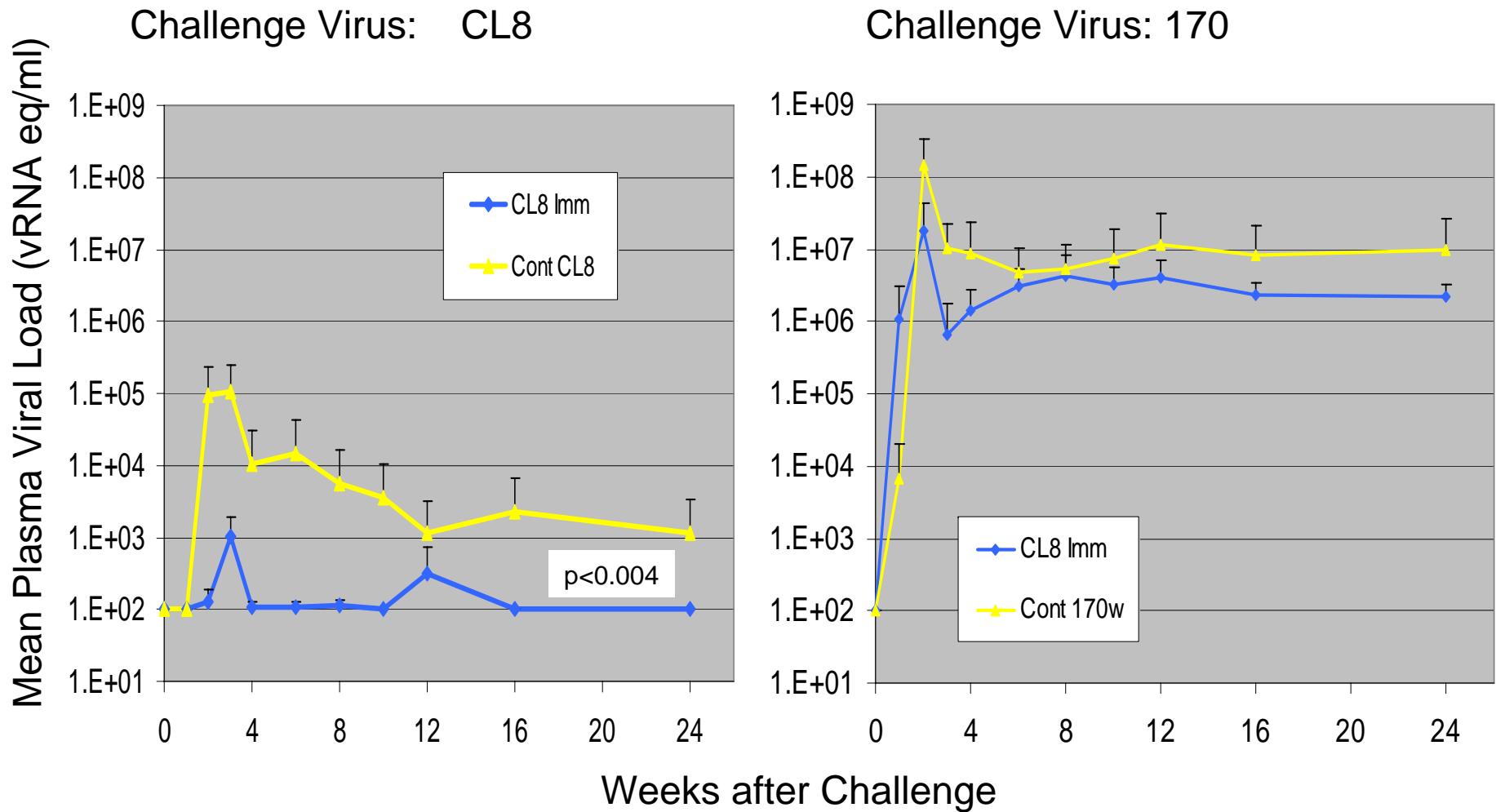
- Recombinant vaccinia virus priming (wk 0 and 8)
  - Each vaccinee receives two recombinants: one expressing Gag-Pol; the other, Env gp160
  - Two isolates: SIVmne CL8, or SIVmne 170
- A single booster immunization 10 or 12 mo later with the cognate recombinant proteins: Gag-Pol and Env
- N=16 vaccinees per arm; 16 naïve controls
- Four weeks after the booster immunization, animals were challenged intravenously with CL8, 170 or chimeric viruses between CL8 and 170, all at 20 50% animal-infectious doses ( $AID_{50}$ )



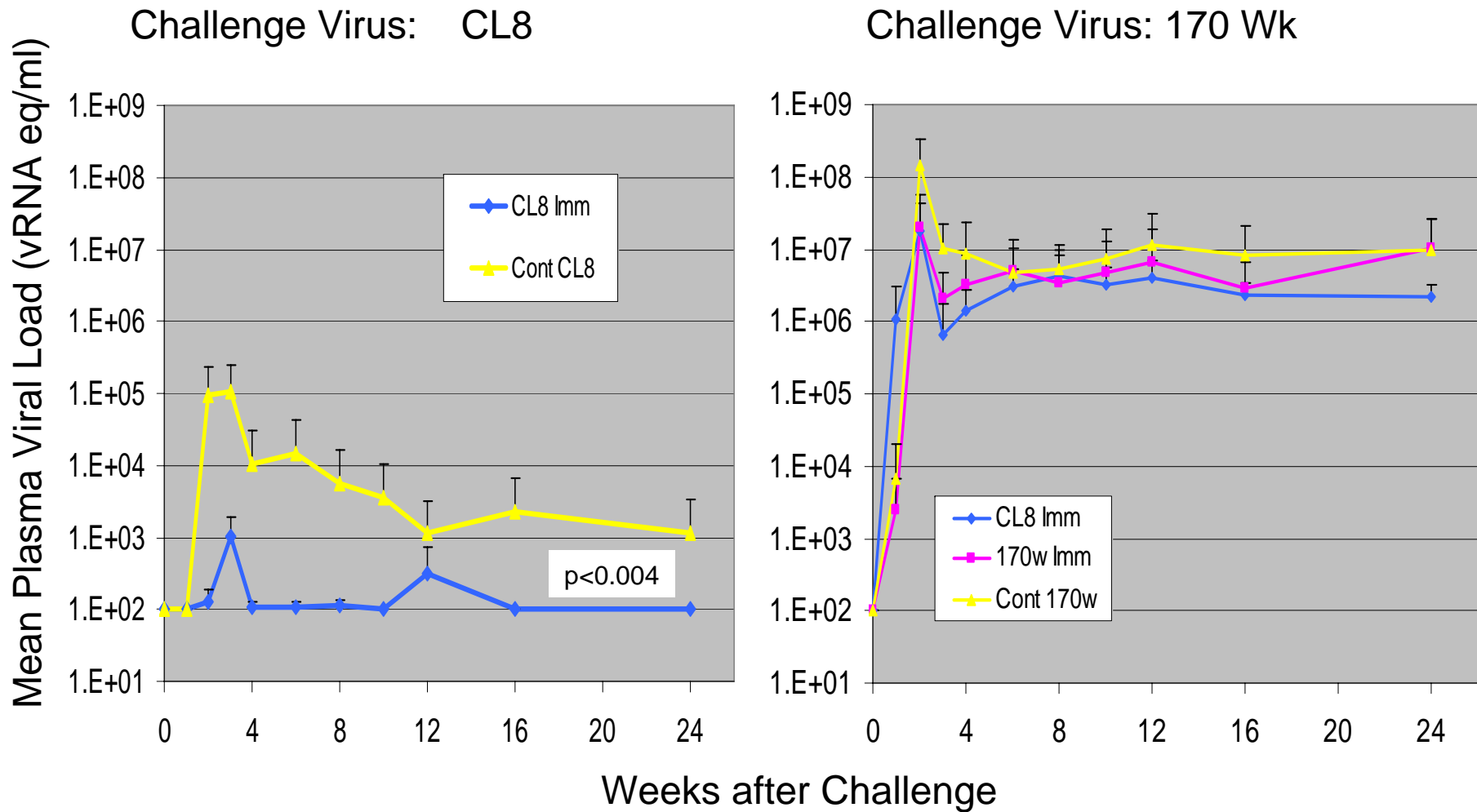
# CL8 Vaccines Protected Against Homologous CL8 Virus Challenge



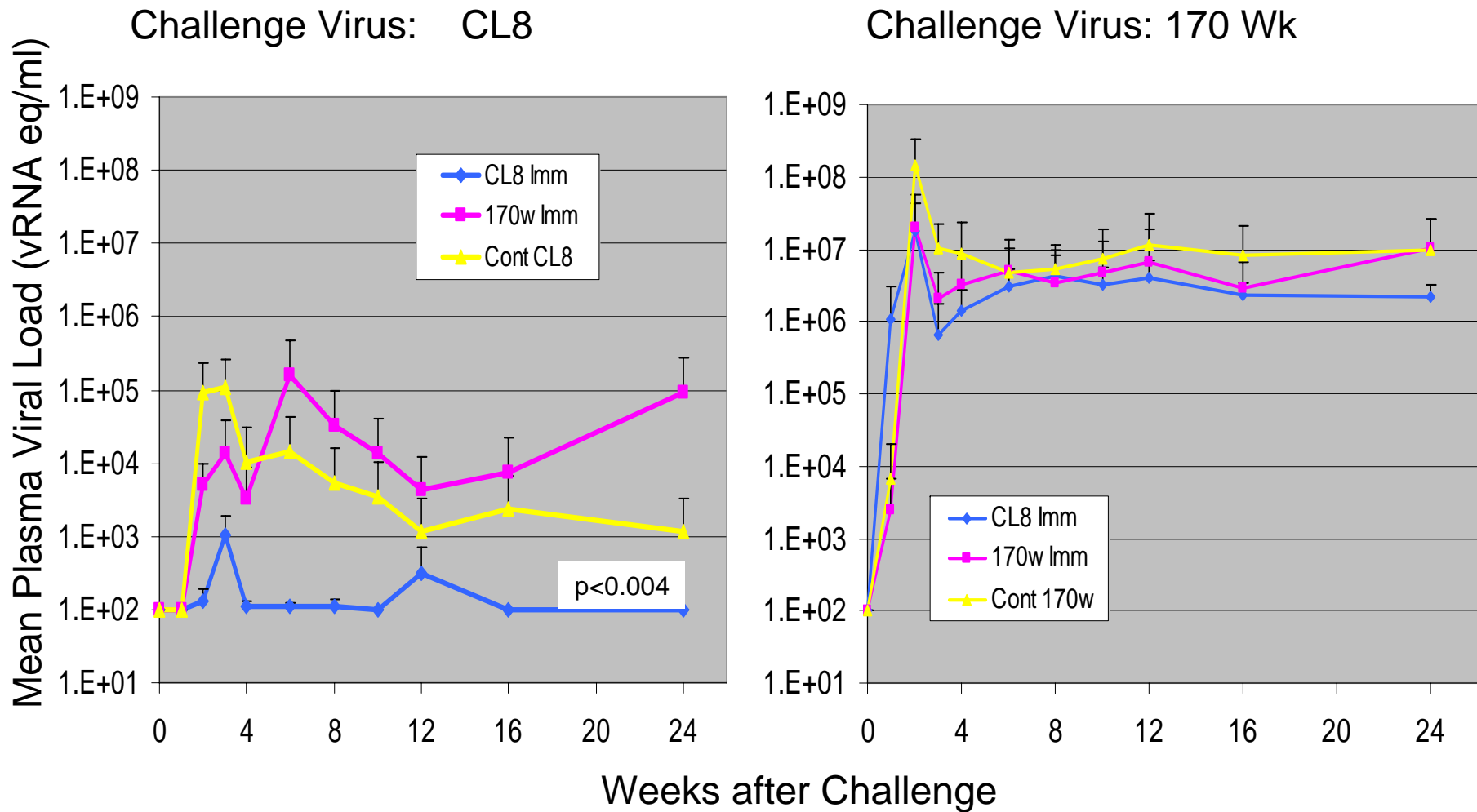
# CL8 Vaccines Failed to Protect Against SIVmne170 Challenge



# 170 Vaccines Failed to Protect Against Late Virus Challenge

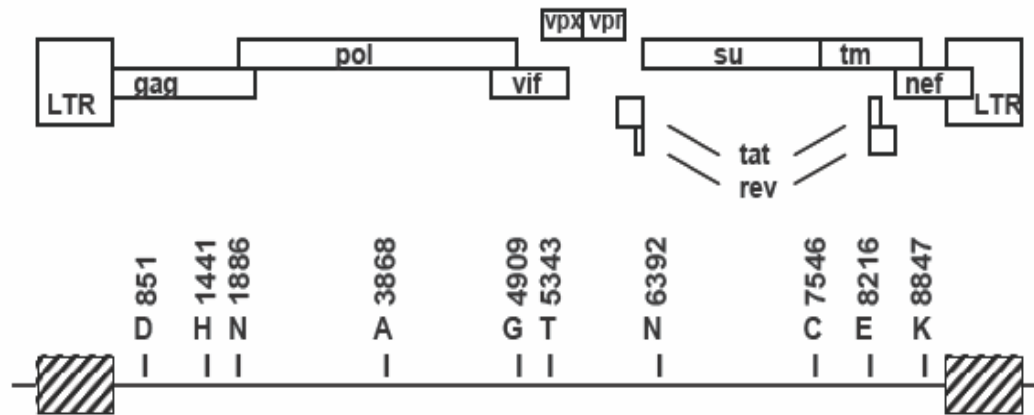


# 170 Vaccine Also Failed to Protect Against CL8 Challenge



# Chimeric Viruses Derived from Temporal Isolates of SIVmne

A

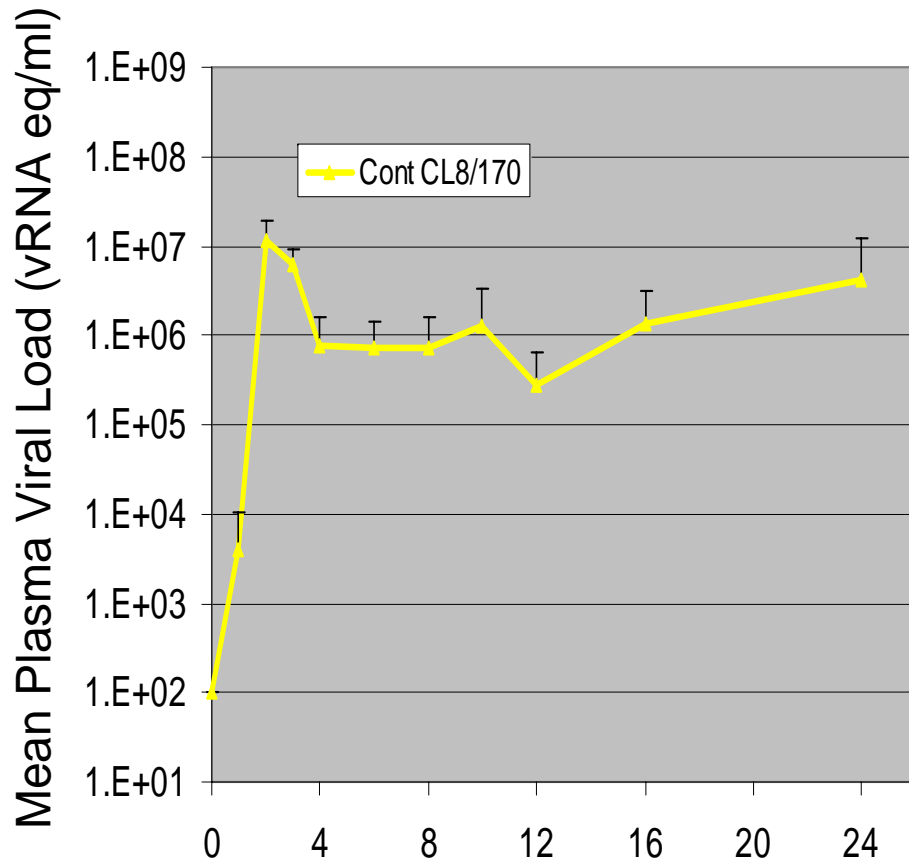


		Replication	Syncytia	Viability (%)
CL8		++	-	50 ± 2
8/170		++	+	19 ± 3
170/8		+++	-	9 ± 1
170		+++	+	10 ± 1

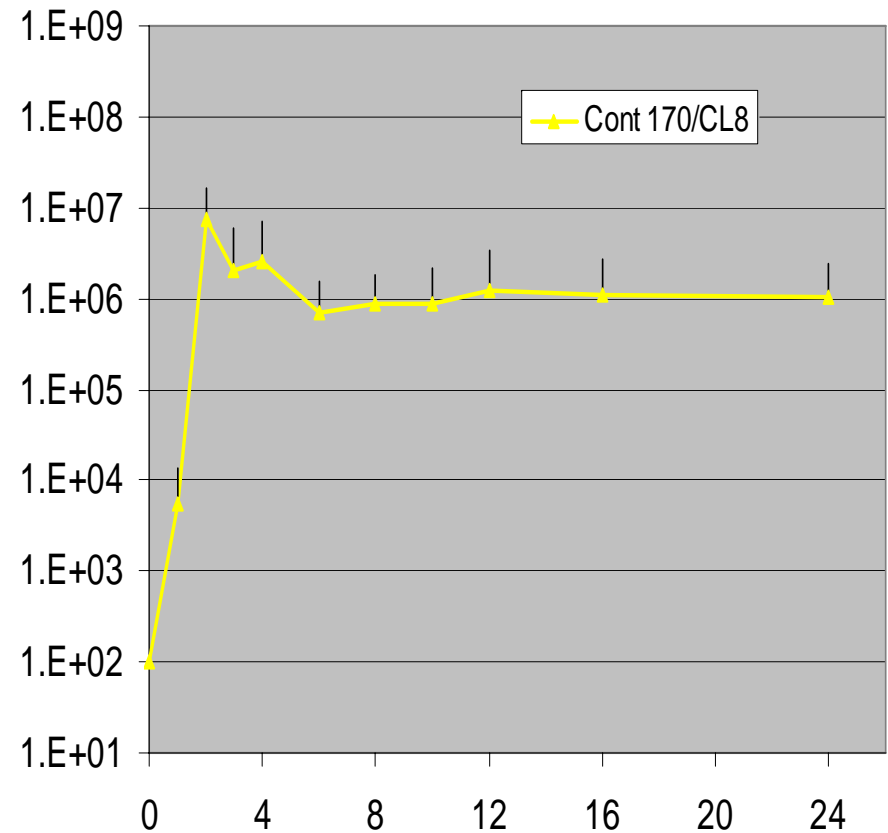
*Kimata and Overbaugh, J. Virol., 71:, 7629-7639, 1997.*

# Persistent and High Viral Load Following Infection with CL8 and 170 Chimeras

Challenge Virus: 170/8

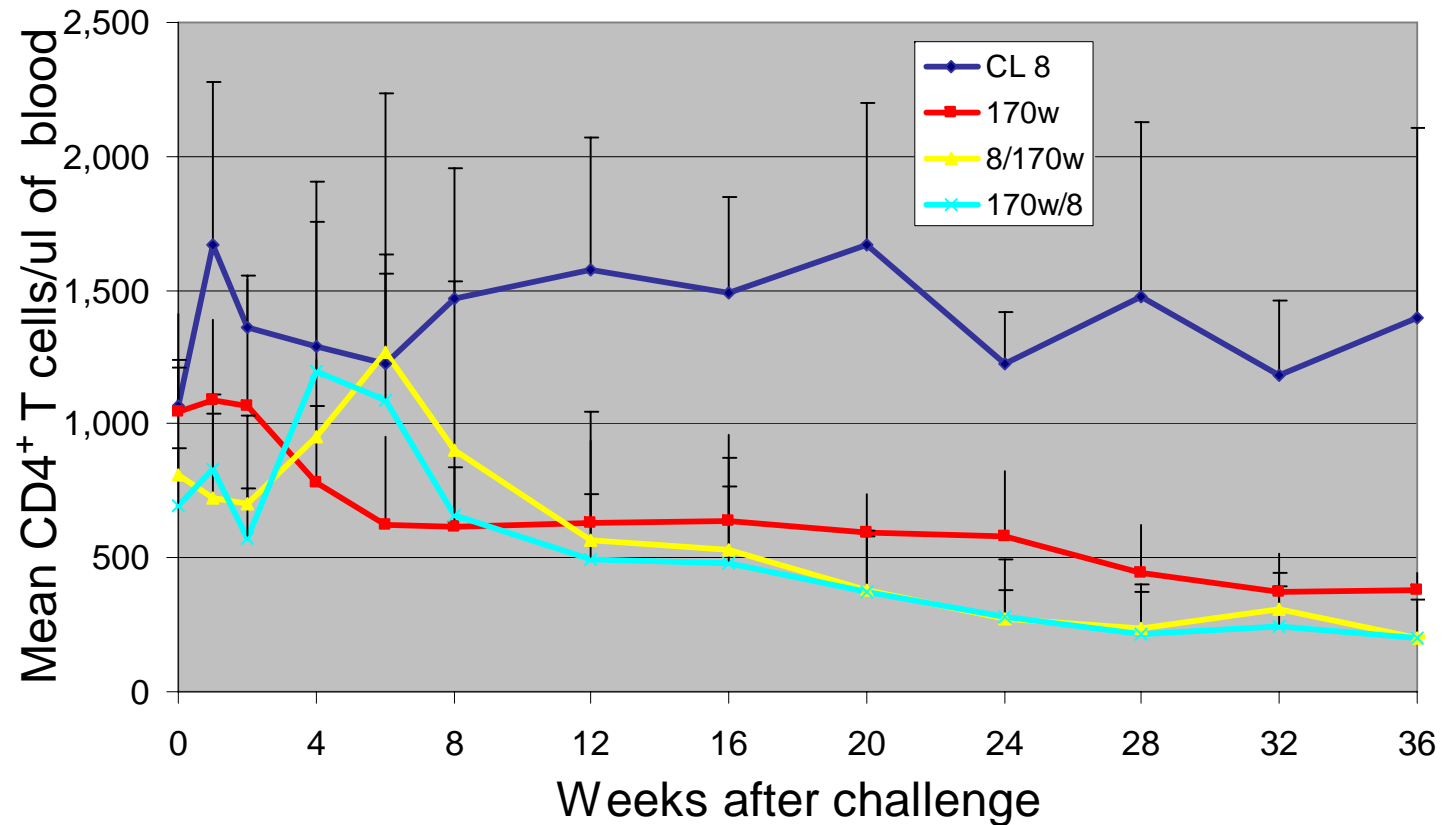


Challenge Virus: 8/170

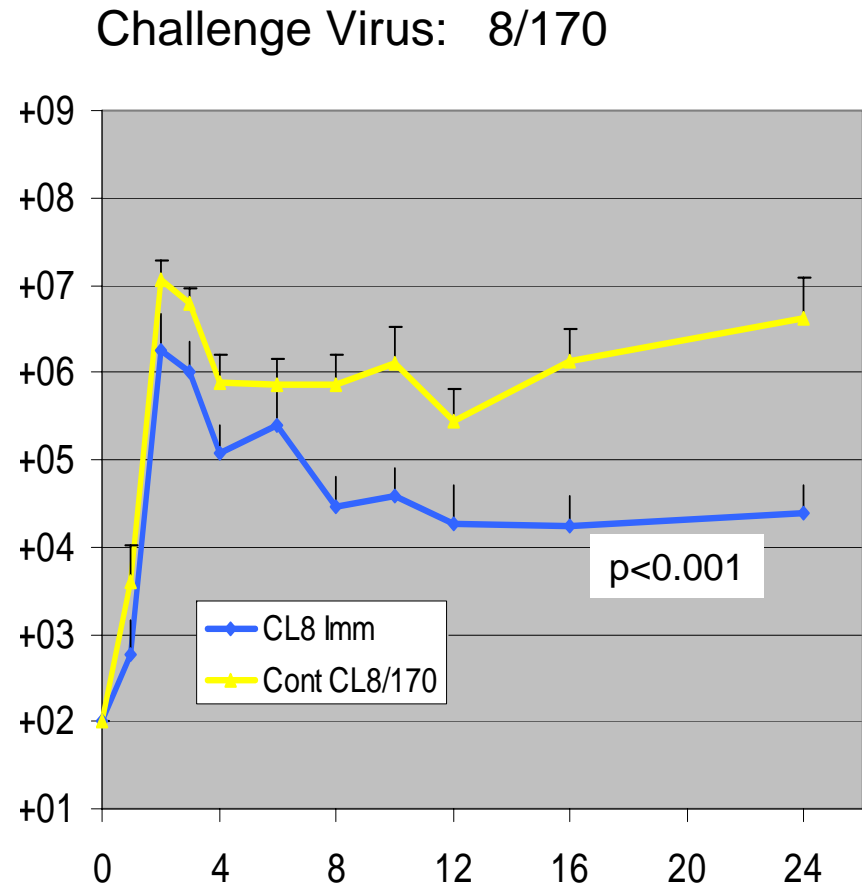
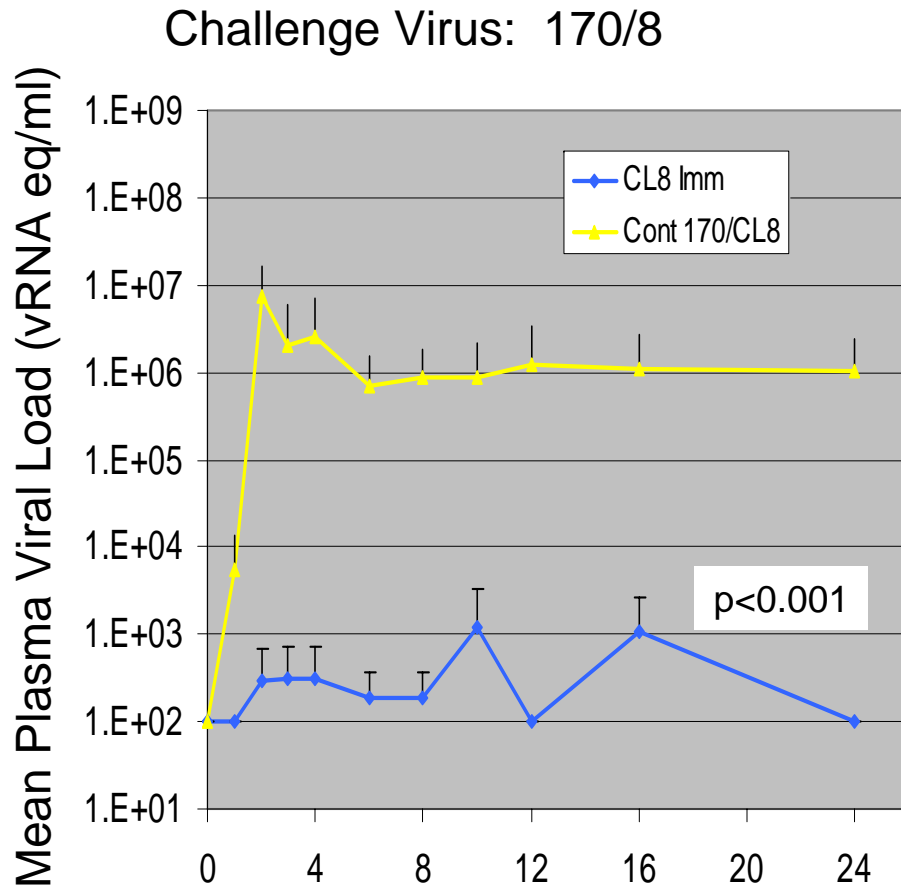


Weeks after Challenge

# Chimeric Viruses Are Pathogenic In Vivo

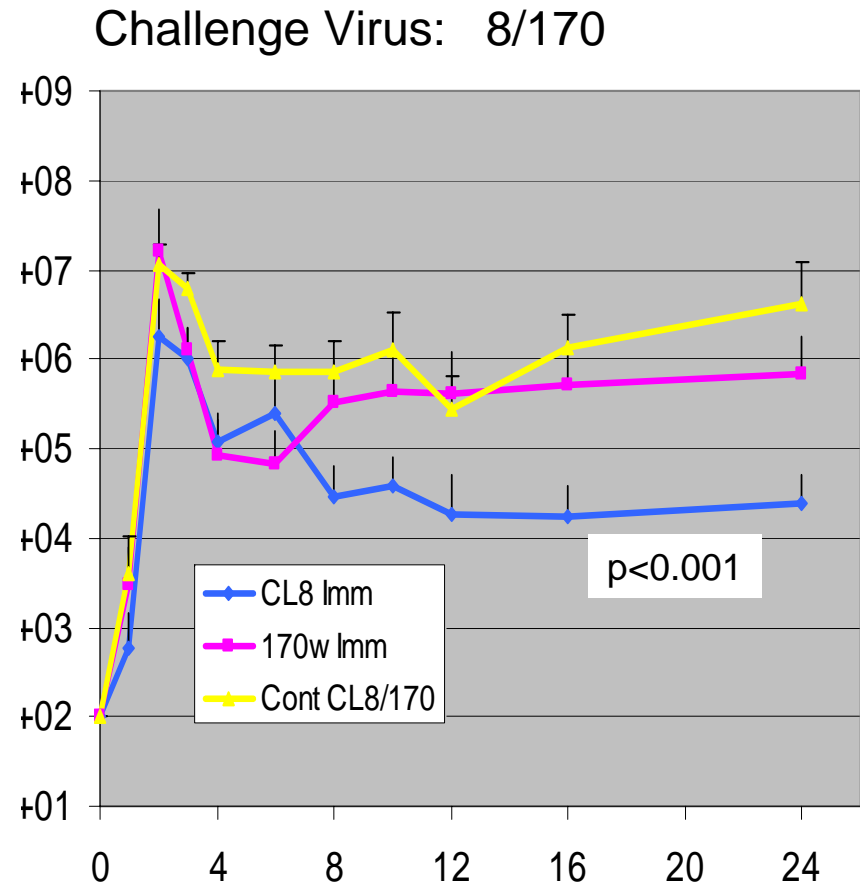
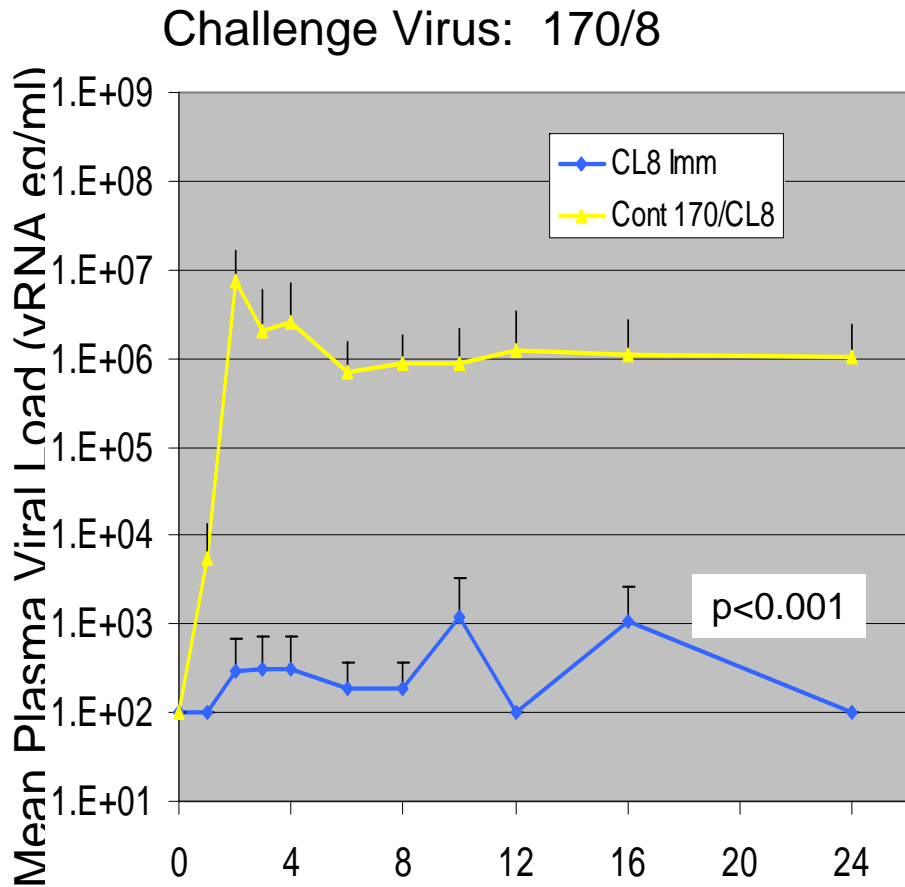


# CL8 Vaccines Control Infection by Chimeric Viruses 170/8 and 8/170



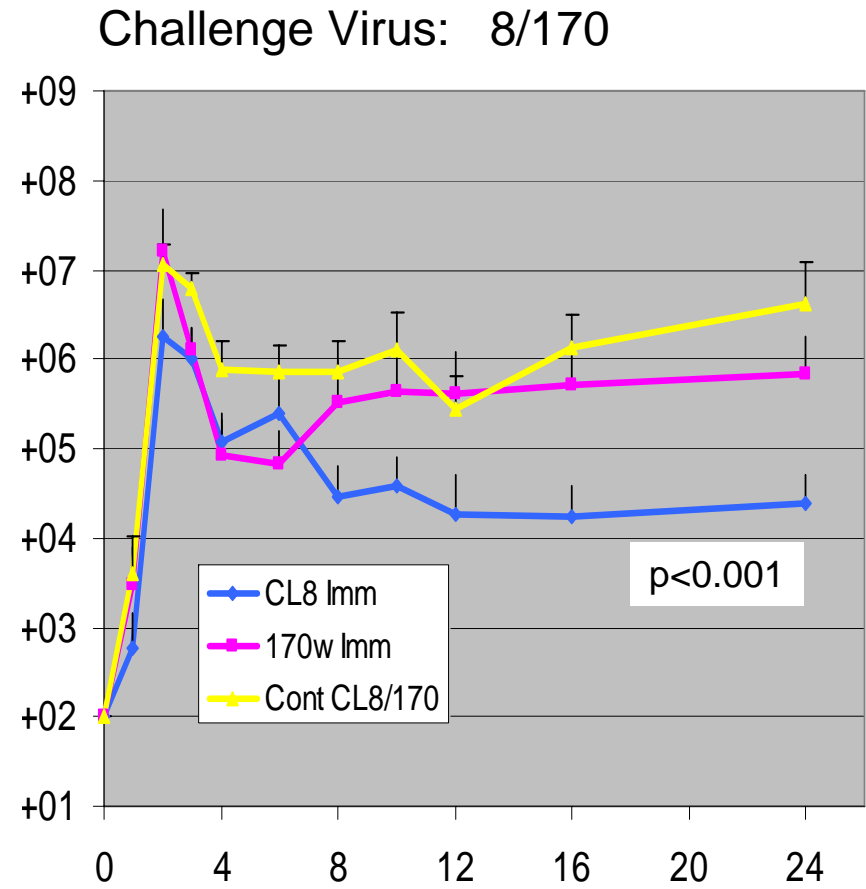
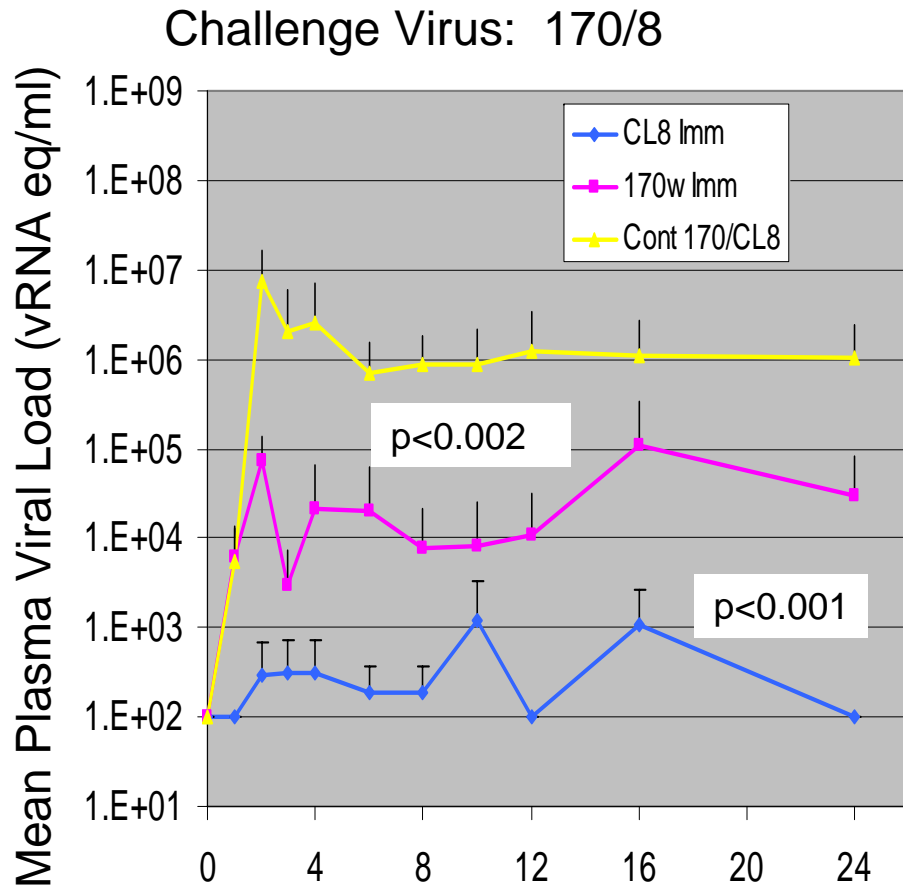
Weeks after Challenge

# 170 Vaccine Failed to Protect Against Chimera with Env from the Late 170 Isolate



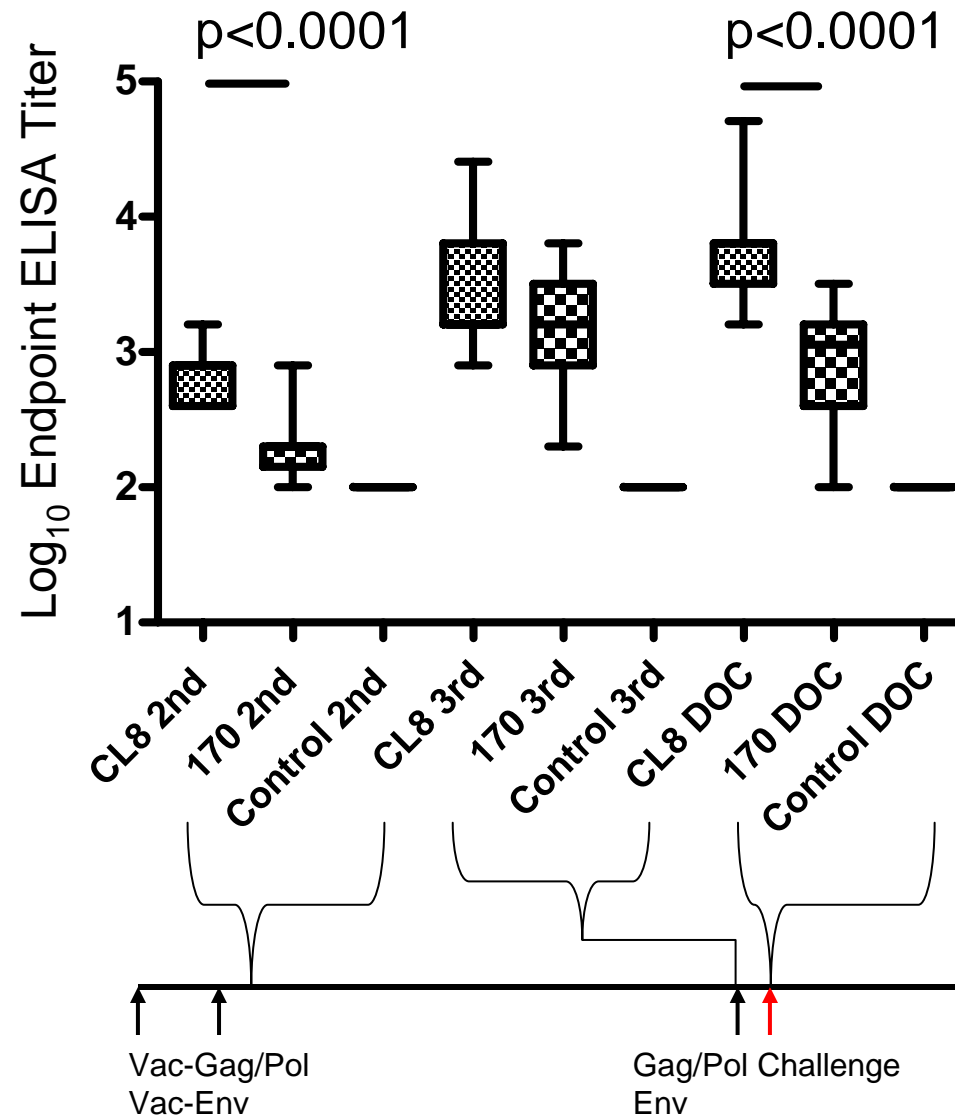
Weeks after Challenge

# Partial Control of CL8 Env Chimera (170/8) Infection by 170 Vaccines



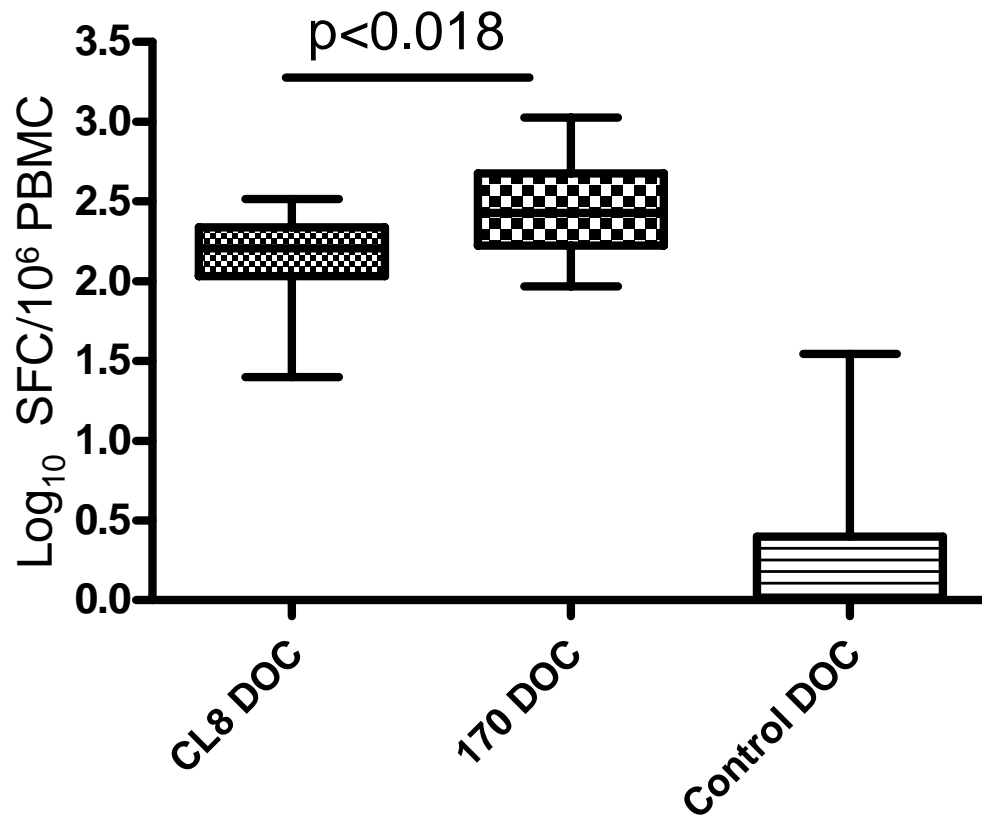
Weeks after Challenge

# SIV-Specific Antibody Response\* to Prime-Boost Immunization with SIVmne CL8 or 170 Vaccines



\*ELISA Antigen:  
SIVmne E11S

# SIV-Specific IFN- $\gamma$ <sup>+</sup> T-cell Response\* to SIVmne CL8 or 170 Vaccines on Day-of-Challenge



\*Stimulating Antigen: AT-2 inactivated SIVmne E11S

# Summary

- CL8 vaccines protected against CL8 challenge
- Not entirely because CL8 is “wimpy”: CL8 vaccines protected against 170/8 and 8/170 chimera, infection by which resulted in high and persistent plasma viral load
- Env-specific responses played a major role in protective immunity elicited by this vaccine regimen
- Neither CL8 nor 170 vaccine protected against the late isolate 170, possibly it represents escape variants
- Vaccines based on the late isolate 170 failed to protect against the homologous virus 170, or even the “wimpy” virus CL8

# Questions

- Vaccines: Are vaccines based on late HIV isolates relevant for protection against transmitted viruses?
- Model: Are challenge models based on late viral isolates relevant for vaccine evaluation?

# Acknowledgments

## University of Washington

Patricia Firpo

Brad Cleveland

Igor Klots

Jane Moon

Jennifer McKenna

Heather Mack

Modou Mbowe

Yongde Zhu

Dave Anderson

Kay Larsen

Barbra Richardson

## Fred Hutchinson Cancer

Research Institute

Julie Overbaugh

## Baylor College of Medicine

Jason Kimata

## National Cancer Institute

Raoul Benveniste

NIH R01 AI 047735