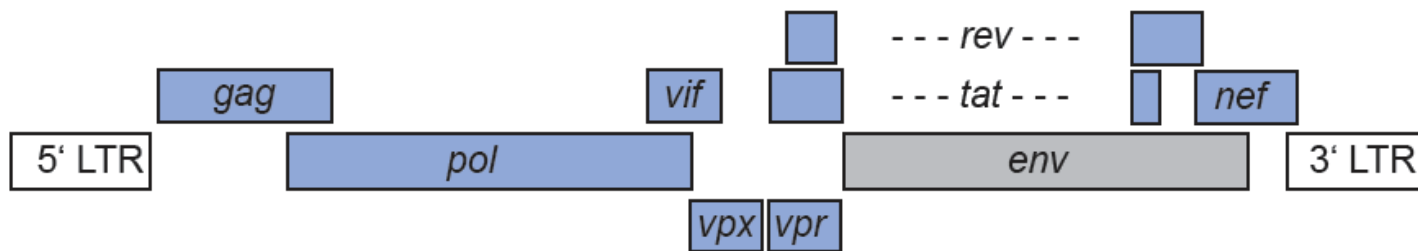
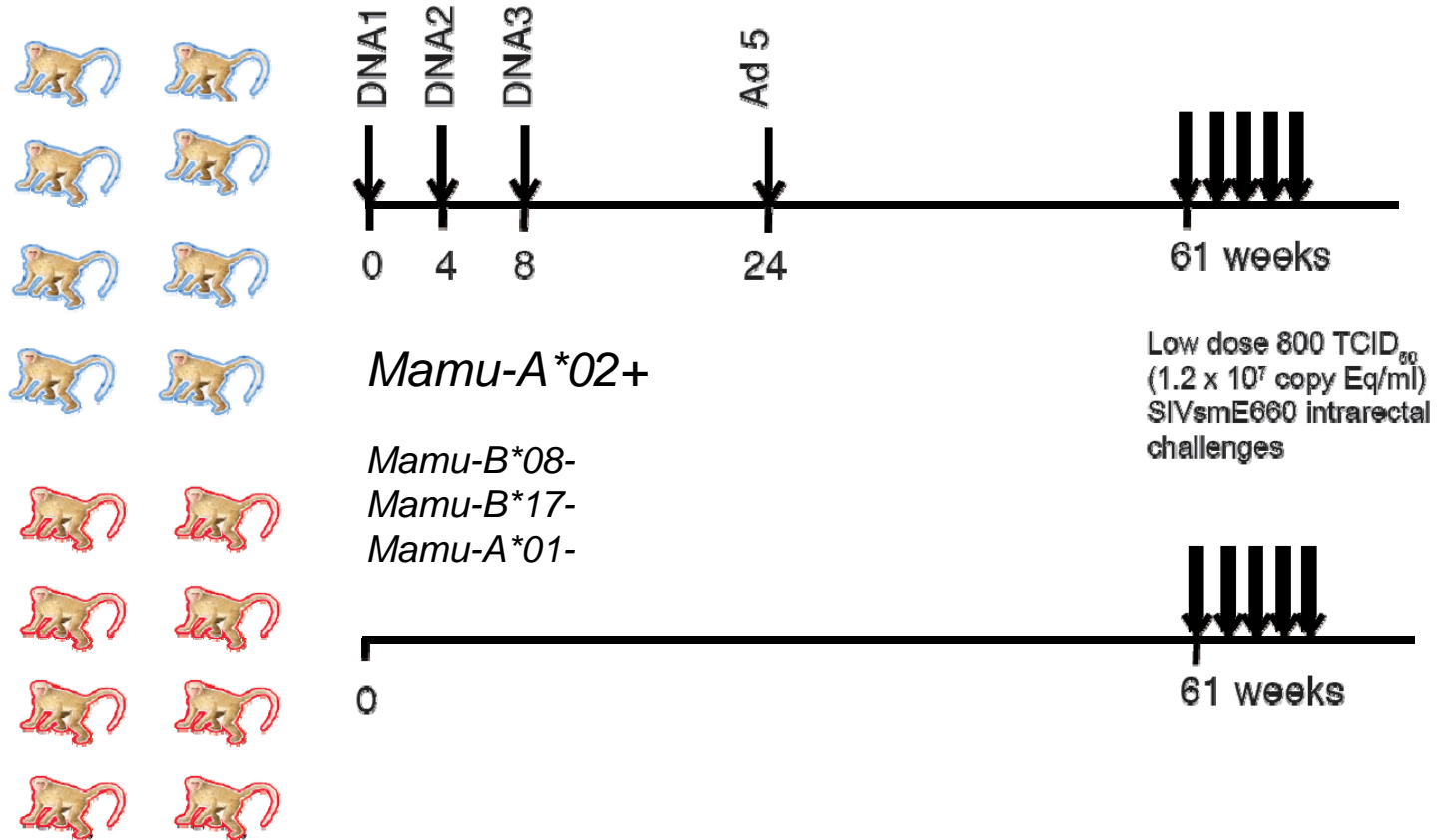


Vaccine-induced cellular immune responses reduce acute phase simian AIDS virus replication after Heterologous Low-Dose Mucosal Challenge.

Nancy A. Wilson, Brandon F. Keele, Jason S. Reed, Shari M. Piaskowski, Caitlin E. Mac Nair, Andrew Bett, Xiaoping Liang, Fubao Wang, Elizabeth Thoryk, Chanook D. Ahn, Masahiko Kaizu, Nicholas J. Maness, Matthew R. Reynolds, Thomas C. Friedrich, John T. Loffredo, Eva G. Rakasz, Stephen Erickson, David B. Allison, Michael Piatak, Jr., Jeffrey D. Lifson, John Shiver, Danilo R. Casimiro, George M. Shaw, Beatrice H. Hahn, **David I. Watkins**.

2008 AIDS Vaccine
Cape Town, South Africa
Late Breaker Abstract #148050
October 16, 2008

Vaccination scheme



SIVmac239 sequences

The Vaccine Engenders High Frequency T-Cell responses

	Gag	Nef	Tat	Rev	Vpr	Vpx	Vif	Env*	Pol	Total
r00061	3615			510			990	105	240	5460
r01099	2745	680		1000	303		733	1510	1130	8100
r02089	8683	218		1510	2493		1278	1943	4670	20793
r02103	3258	785			255	60	2675	163	328	7523
r02114	7183	385	1133	305	63		6565	3425		19058
r95116	6120			1495	143		1343	358	170	9628
r97112	5720	3365		920	725		2508	1515	8065	22818
r99063	3225	295		100			358	1235	288	5500
Average	5068	716	142	730	498	8	2056	1282	1861	12,360

*Env responses are primarily to Env RY8(788-795), a *Mamu-A*02* epitope that is encoded by an alternate reading frame on the Rev plasmid.

Vaccinees Recognized 11 – 34 Epitopes

	Gag	Nef	Tat	Rev	Vpr	Vpx	Vif	Env	Pol	Total
r00061	7			2			2	1	1	13
r01099	9	2		2	2		3	1	3	22
r02089	13	1		4	1		5	1	9	34
r02103	9	2			2	1	4	1	2	21
r02114	11	2	1	2	1		4	2		23
r95116	5			3	1		2	1	1	13
r97112	8	2		3	1		5	1	4	24
r99063	4	2		1			1	1	2	11
Average	8	1	0	2	1	0	3	1	3	20

A Heterologous Challenge

	Vaccine strain vs SIVsmE660
Protein	% aa difference
Tat	26
Rev	25
Nef	21.3
Vif	17
Env	-
Vpr	12
Pol	8.3
Pro	11.1
RT	6.2
Int	5.1
Gag	7.8
p15	5.2
p27	4.8
p18	15

- Animals were vaccinated using sequences from SIVmac239.
- Animals were challenged with a low dose of the swarm virus SIVsmE660.
- Strains in the same subtype can differ by as much as 20% in their Env sequence*.

**Gashen et al., Science 296 2354-2360 (2002)*

Challenge was heterologous and low dose to mimic human HIV infection

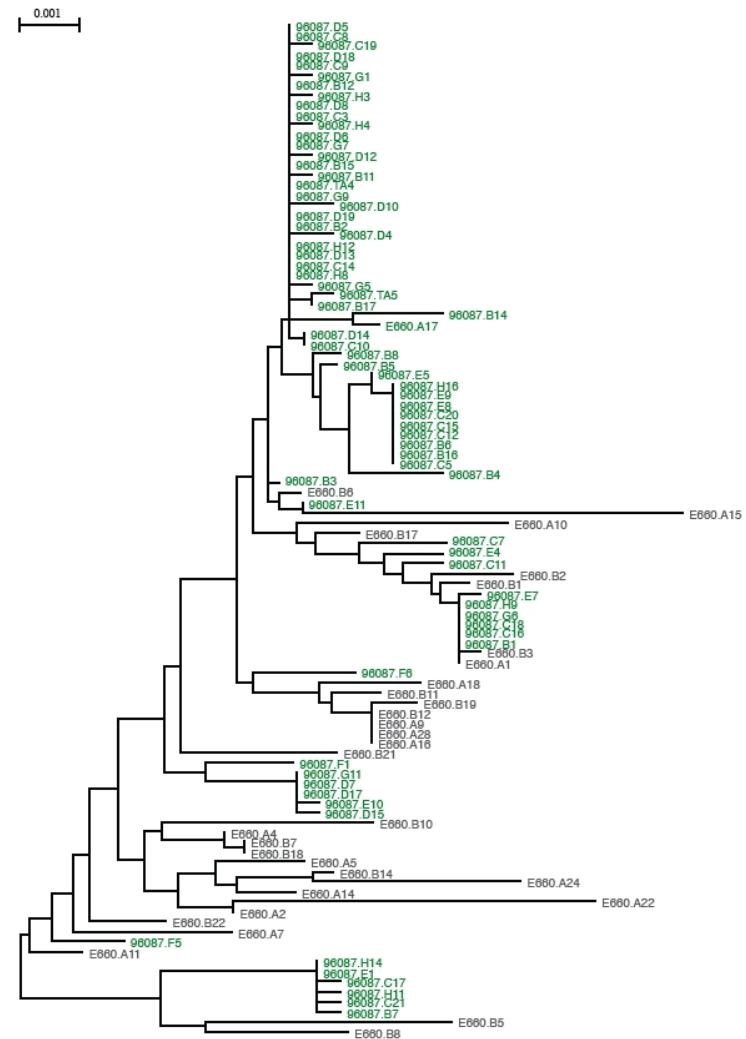
- Keele et al.* showed that the number of viral variants that cross a mucosal membrane is dose dependent.
- In humans, very few variants are present in the early acute phase.
- We titrated SIVsmE660 so that we had 1-3 viral variants cross the mucosal barrier.

**Keele, BF, et al. PNAS 104:7552-7557 (2008)*

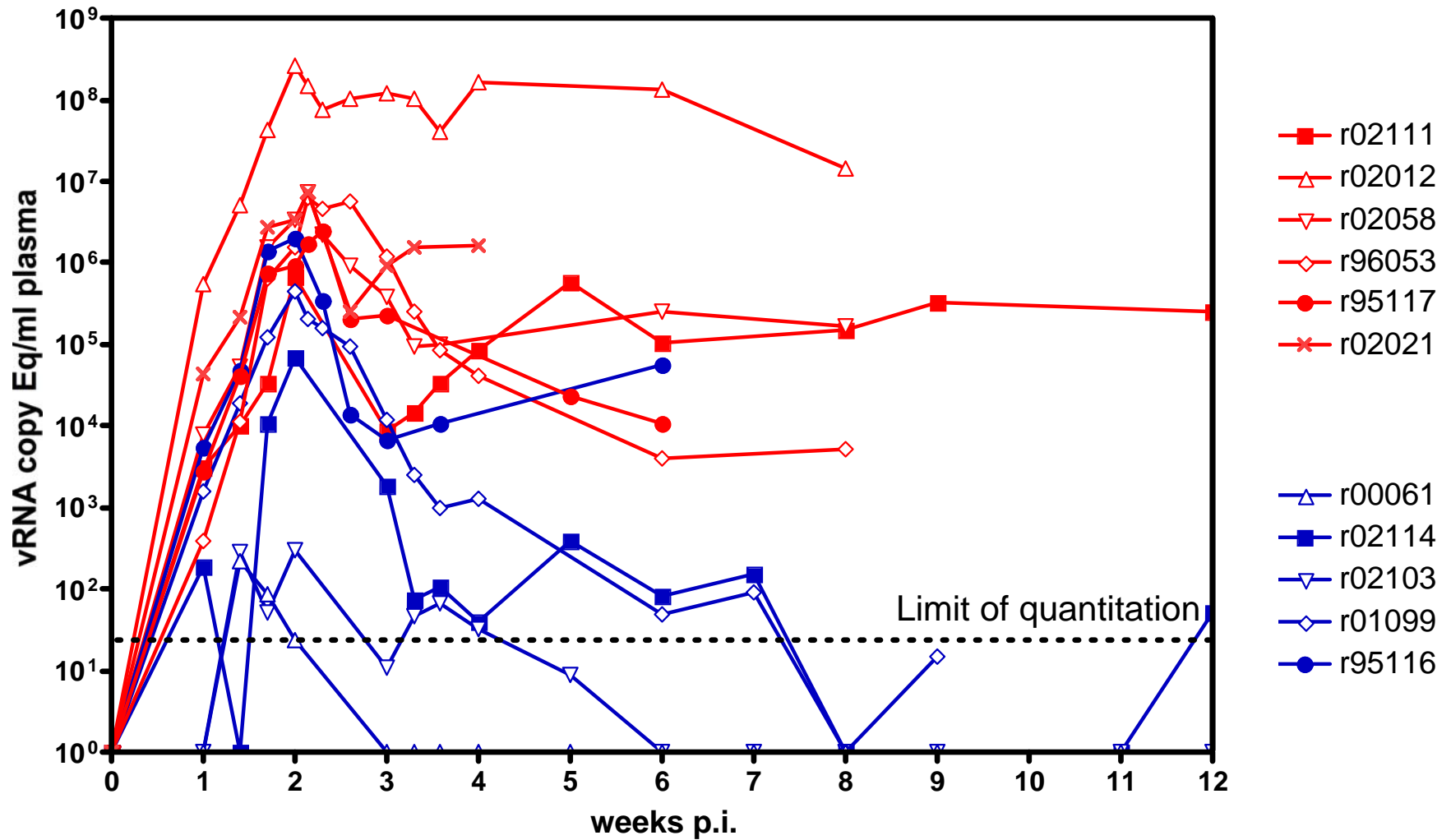
Number of variants that cross the mucosal barrier is dose dependent

400 TCID₅₀ – 1 variant

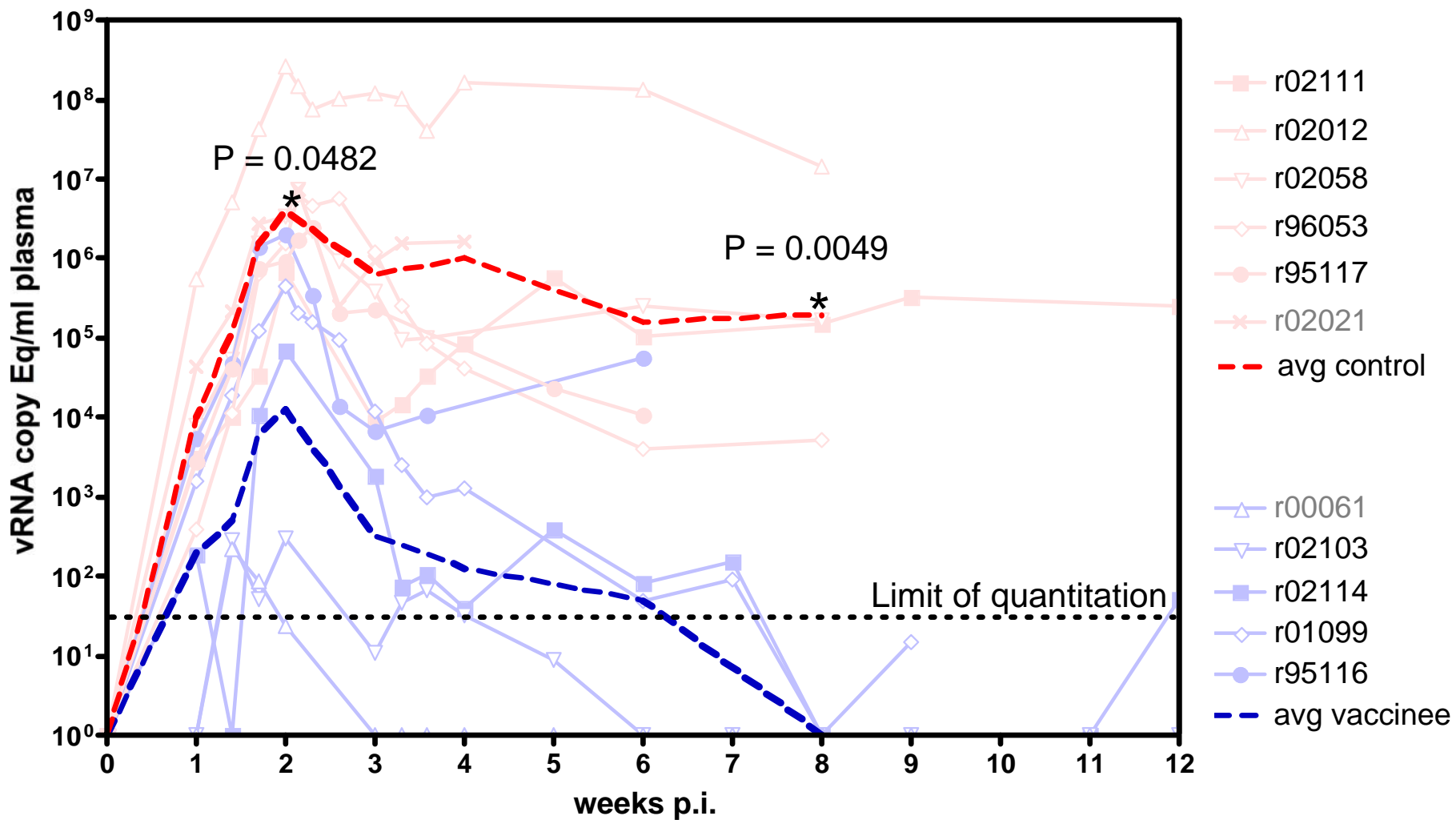
4,000 TCID₅₀ – 10 variants



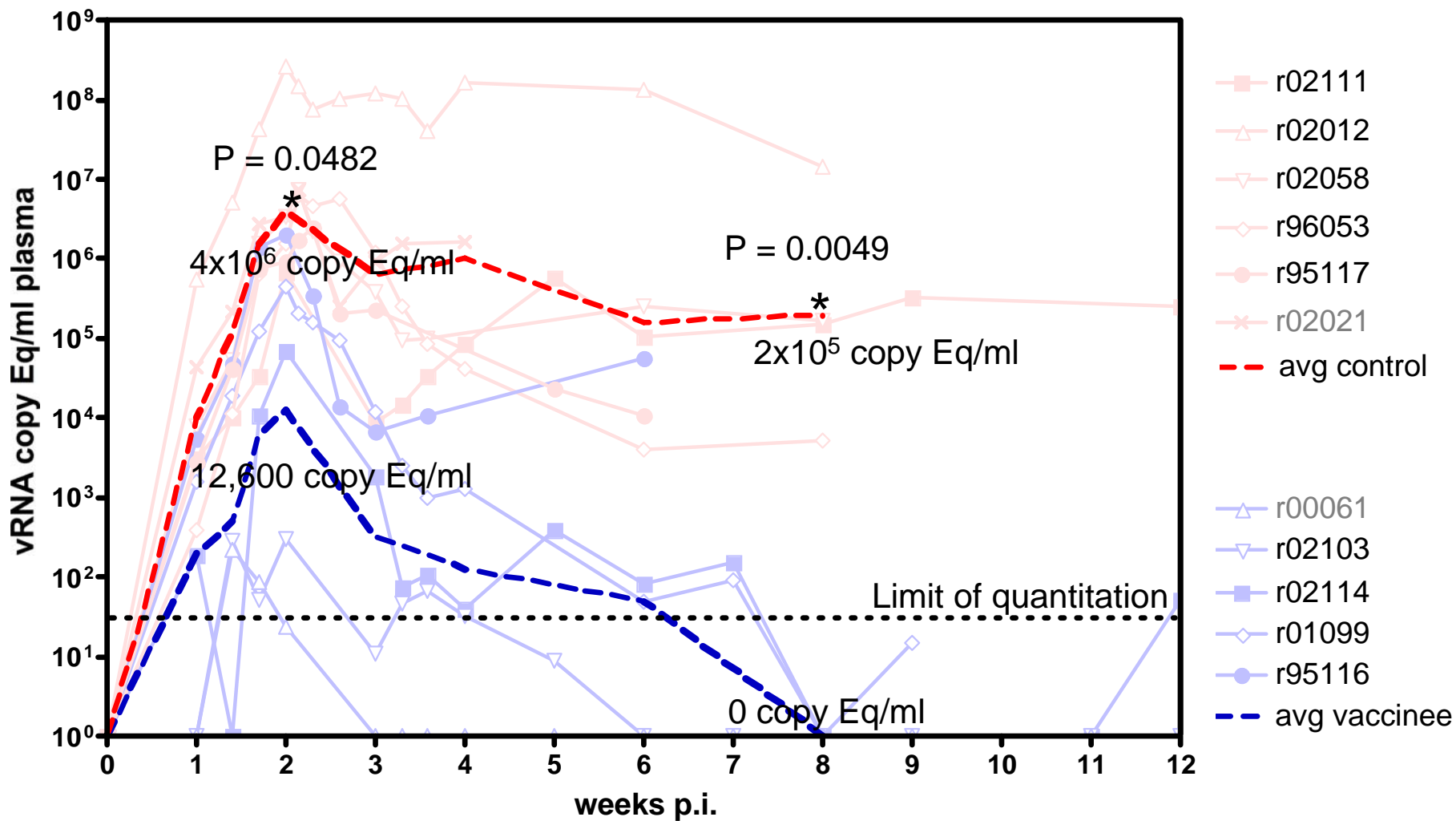
Vaccinees control viral load in the acute phase



Vaccinees control viral load in the acute phase



Vaccinees control viral load in the acute phase

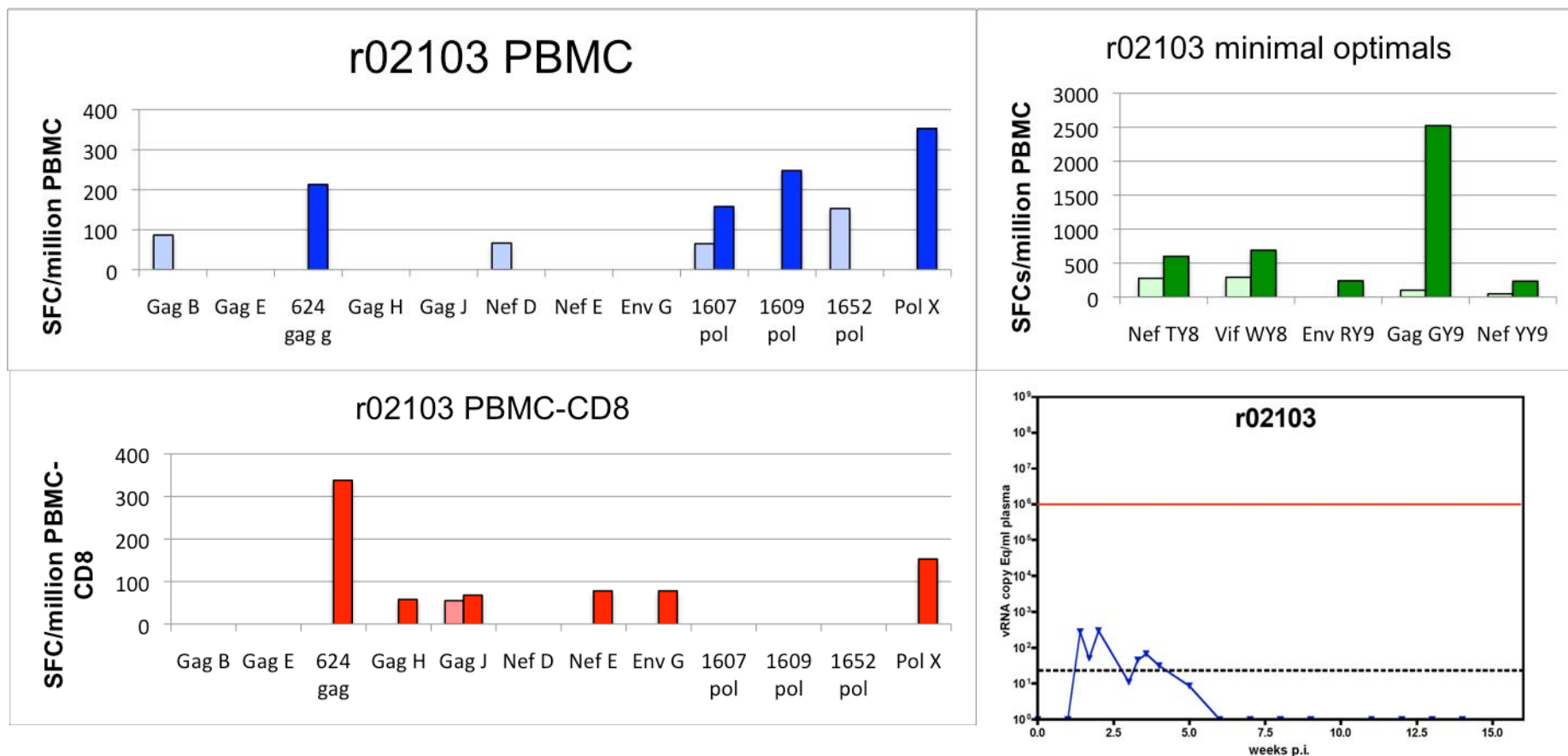


50% of Vaccine-Induced T-cell Responses were Expanded Post-Challenge

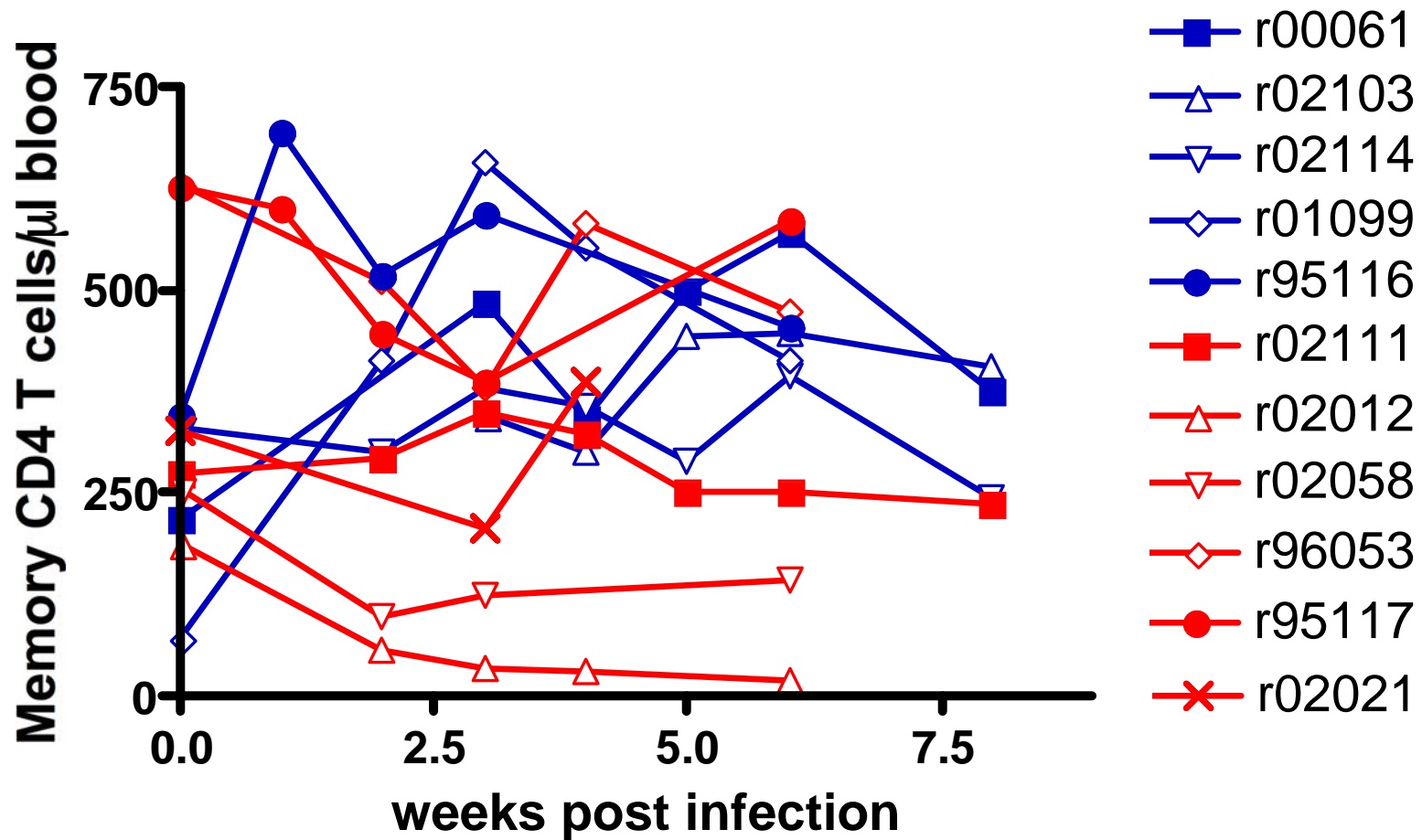
	Post Ad5	Post infection
r00061	13	9
r02103	21	12
r02114	23	14
r01099	22	11
r95116	13	9
r02089	34	-
r97112	24	-
r99063	11	-
Total	20	12

An animal with peak viremia of 302 viral Eq/ml has high frequency anamnestic responses

Assays done d21 post infection. Peak VL = 302



Preservation of CD4 Memory in **Vaccinees**



Summary

- We vaccinated 8 animals with all proteins in SIVmac239 except Envelope.
- To mimic HIV exposure, vaccinees and control animals were then challenged with repeated relevant mucosal doses with heterologous swarm virus SIVsmE660.
- 4/5 vaccinees controlled acute phase viral replication.

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