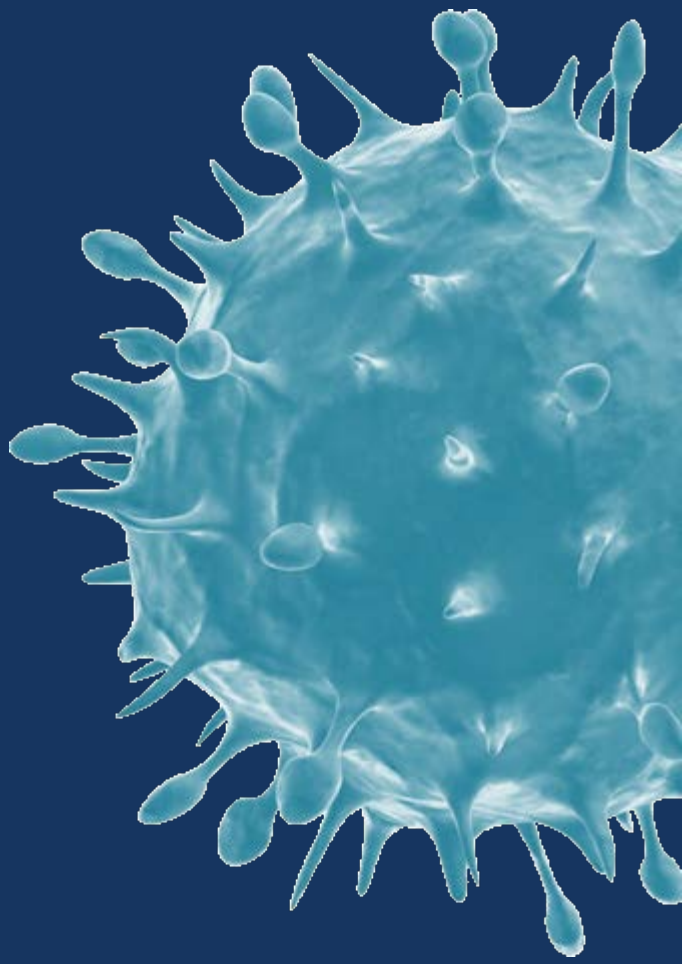
Human T cell and Antibody Responses to GEN-003, a Novel HSV-2 Therapeutic Vaccine



Jessica Baker Flechtner, PhD

International Herpesvirus Workshop; Poster 2_09
Kobe, Japan 19-23 July 2014

Prior Vaccine Candidates Did Not Meet Clinical Endpoints

Company	Type	Formulation	Indication	Outcome
GSK	DISC*	gH deletion virus	Therapy	No difference from placebo
Chiron	Subunit	gB2 + gD2 + MF59	Therapy	No effect on recurrence rate, Shortened symptom duration
Chiron	Subunit	gB2 + gD2 + MF59	Prophylaxis	No difference from placebo
GSK	Subunit	gD2 + alum + MPL	Prophylaxis	No difference from placebo

*Disabled Infectious Single Cycle virus

Recombinant gD Vaccine for the Prevention of HSV-2

EDITORIAL

Editorials represent the opinions of the authors and THE JOURNAL and not those of the American Medical Association.

JAMA, July 28, 1999—Vol 281, No. 4 **379**

Herpes Simplex Virus Vaccines—Why Don't Antibodies Protect?

John R. Mascola, MD

MOST EFFECTIVE VIRAL VACCINES WORK, AT LEAST in part, by inducing antibodies capable of neutralizing the invading virus.[1-3] Examples among licensed human vaccines include measles, pother by preventing infection (sterilizing immunity) or by ameliorating HSV-2–related disease, thereby making the infected individual less contagious. The article by Corey et al[8] describes 2 well-executed placebo-controlled multicenter clinical trials designed to test the efficacy of a recombinant subunit vaccine containing 2 major HSV-2 surface pro-

"It appears that effective protection against HSV-2 will require more than serum neutralizing antibodies."

Herpevac Clinical Trial

NEWS OF THE WEEK

IMMUNOLOGY

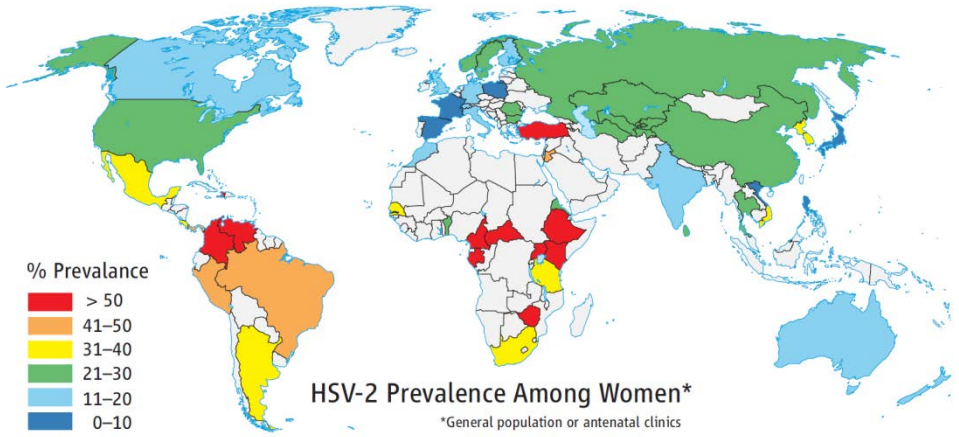
Painful Failure of Promising Genital Herpes Vaccine

A vaccine designed to ward off genital herpes has failed in a large clinical trial, abruptly ending the product's seemingly promising future. After 8 years of study in more

Rixensart, Belgium, the vaccine contains a protein from HSV-2 mixed with a novel adjuvant, or immune system stimulator, triggering antibodies that researchers hoped could

the new negative data. "The inconsistency between the trials is really quite disconcerting," says Corey.

When NIAID and GSK revealed on



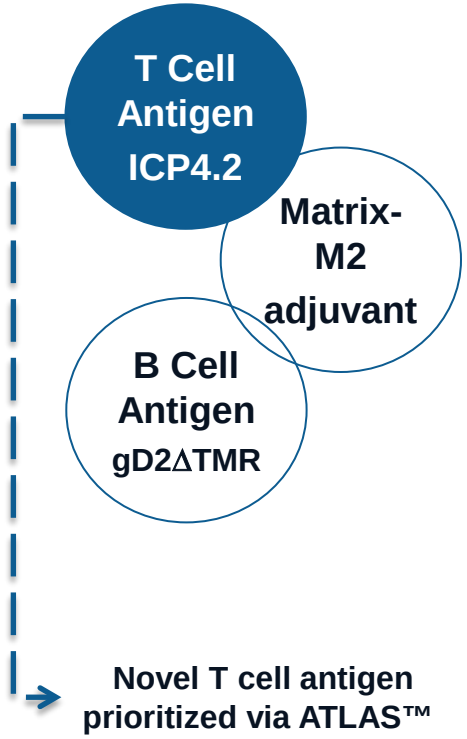
15 OCTOBER 2010 VOL 330 **SCIENCE** www.sciencemag.org

Published by AAAS

"…antibodies…alone are not the answer. Next generation vaccines…should also dispatch killer cells to clear cells that HSV-2 manages to infect."

GEN-003: A Novel Therapeutic Vaccine Candidate

GEN-003



GEN-003 Proposition

- Reduce viral shedding and transmission risk
- Ameliorate symptoms
- Convenient dosing regimen
- Novel mechanism of action

Trial Design and Objectives

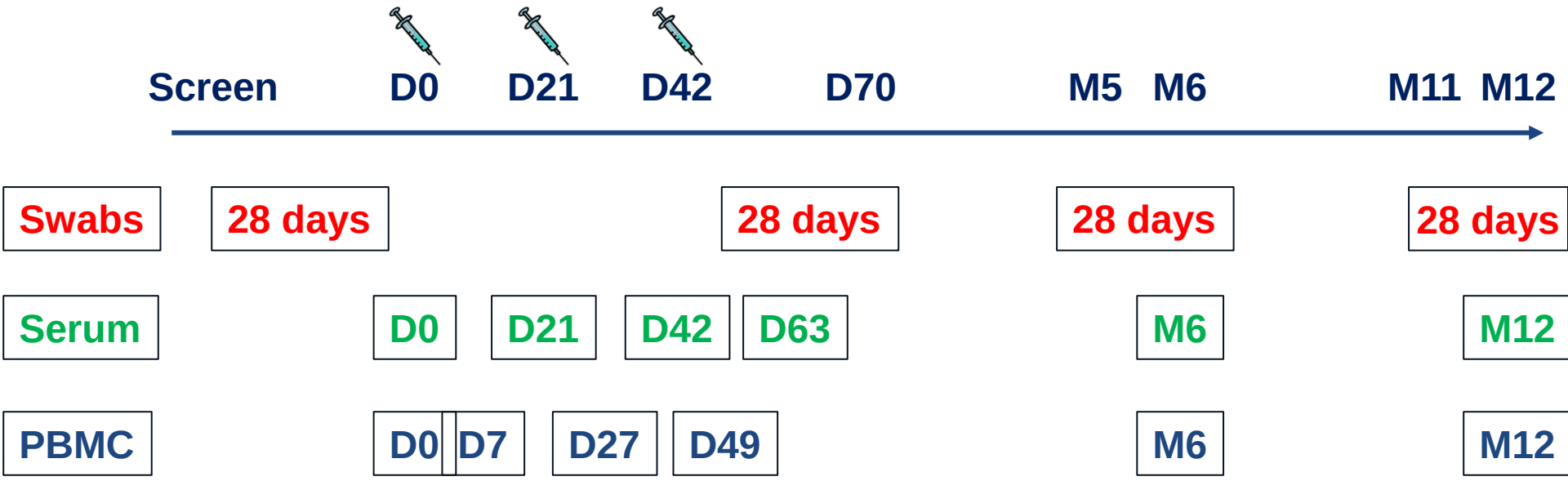
- **Patients: 143 with HSV-2 infections**
  - Moderate-to-severe infections (3-9 outbreaks/year)

- **Design:**
  - Double-blind, placebo-controlled
  - ~30 subjects in each of 5 groups:
    - Placebo
    - Proteins only
    - GEN-003 (10 µg per protein + 50 µg adjuvant)
    - GEN-003 (30 µg per protein + 50 µg adjuvant)
    - GEN-003 (100 µg per protein + 50 µg adjuvant)

- **Endpoints:**
  - Safety, tolerability, immune response
  - Viral shedding rate
  - Genital lesion rate

Immunogenicity Assays and Sample Collection

- **T cell Responses – PBMC IFNγ ELISpot**
- **Antibody Responses –**
  - IgG ELISA
  - Colorimetric Neutralization assay



Demographics of Study Participants

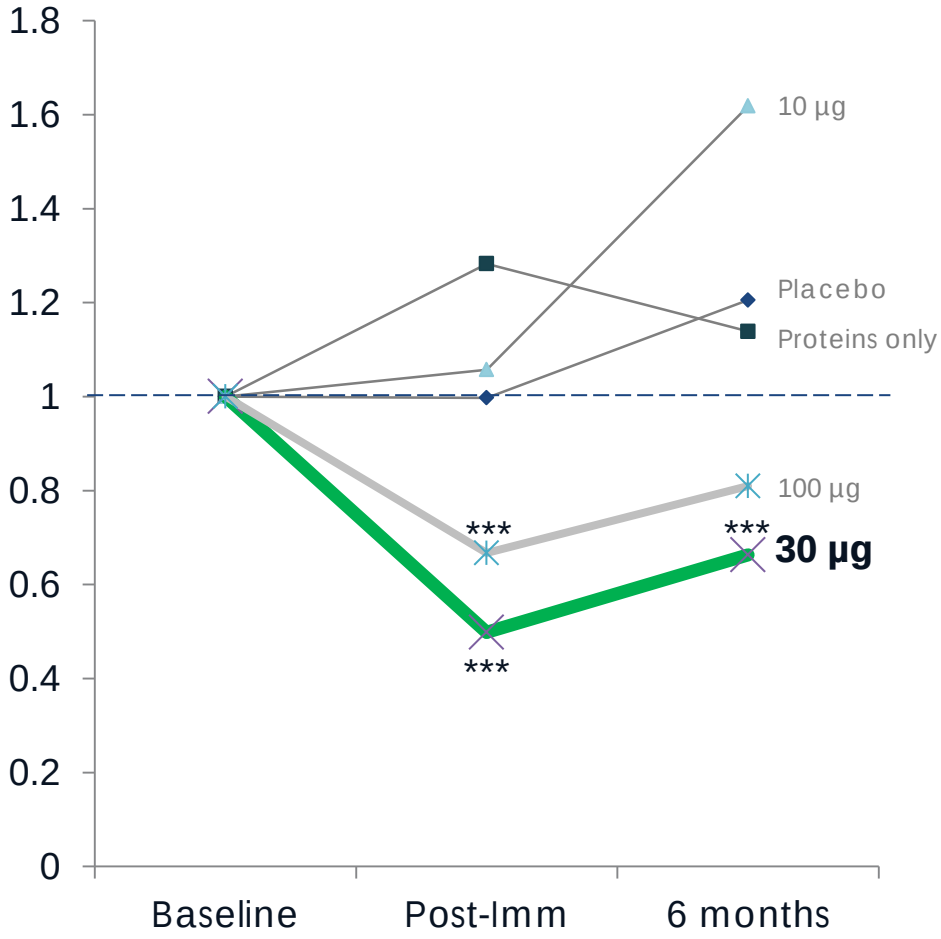
	Placebo	Proteins Only	GEN-003			Overall
			10µg	30µg	100µg	
N	28	28	31	29	27	143
No. of women (%)	17 (61)	17 (61)	21 (68)	18 (62)	15 (56)	88 (62)
Mean Age (Range)	37 (23-50)	36 (20-47)	36 (24–49)	38 (22–50)	37 (24-50)	37 (22-50)
Race n (%)						
White	17 (61)	15 (54)	23 (74)	16 (55)	17 (63)	88 (62)
Black	10 (26)	8 (29)	5 (16)	10 (35)	8 (30)	41 (29)
Asian	-	1 (4)	-	1 (3)	-	2 (1)
Multiracial	-	3 (11)	3 (10)	-	1 (4)	7 (5)
Other	1 (4)	1 (4)	-	2 (7)	-	4 (3)
Mean years since diagnosis (range)	9 (1-26)	9 (0-24)	10 (1-33)	10 (1-25)	10 (2-33)	10 (0-33)
Mean lesion episodes in last 12 months* (range)	5 (3-8)	5 (3-9)	5 (3-8)	5 (3-9)	5 (3-9)	5 (3-9)
#HSV-1 positive^ (%)	11 (39)	16 (57)	15 (48)	5 (17)	14 (52)	61 (43)

*subject reported

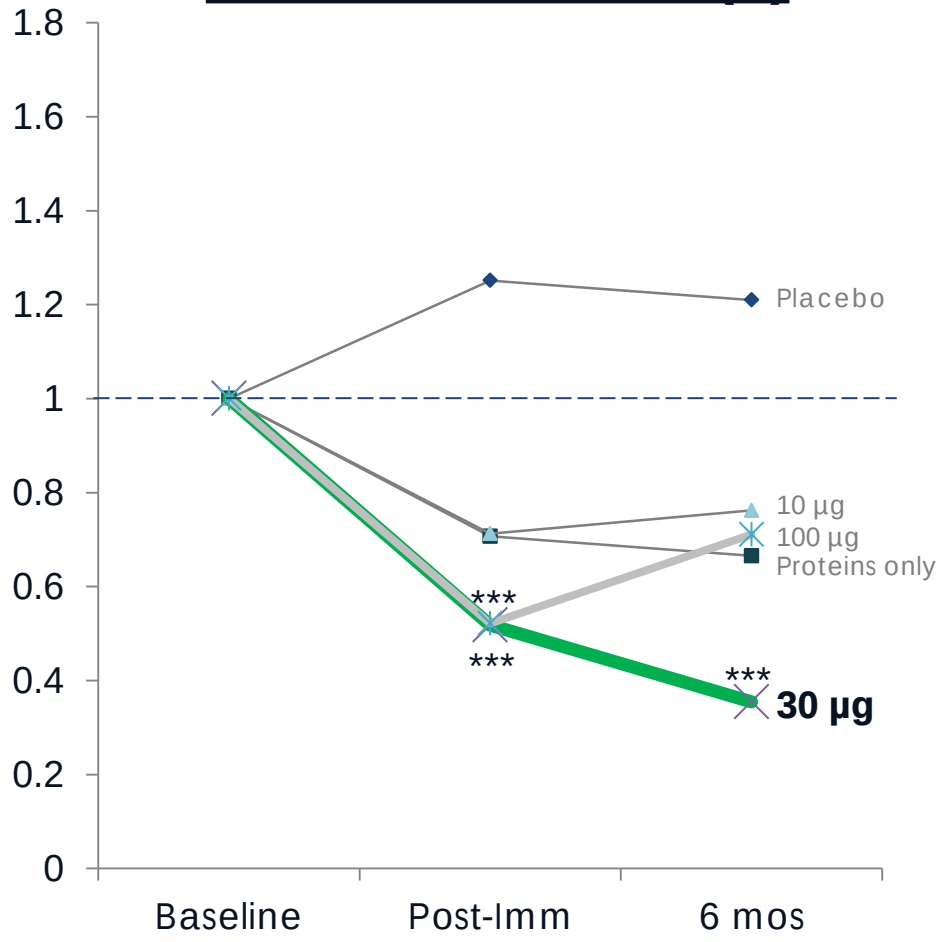
^seropositive; genital HSV-1 infection excluded

GEN-003: Statistically Significant, Durable Impact on HSV-2

Viral Shedding Rate (a)



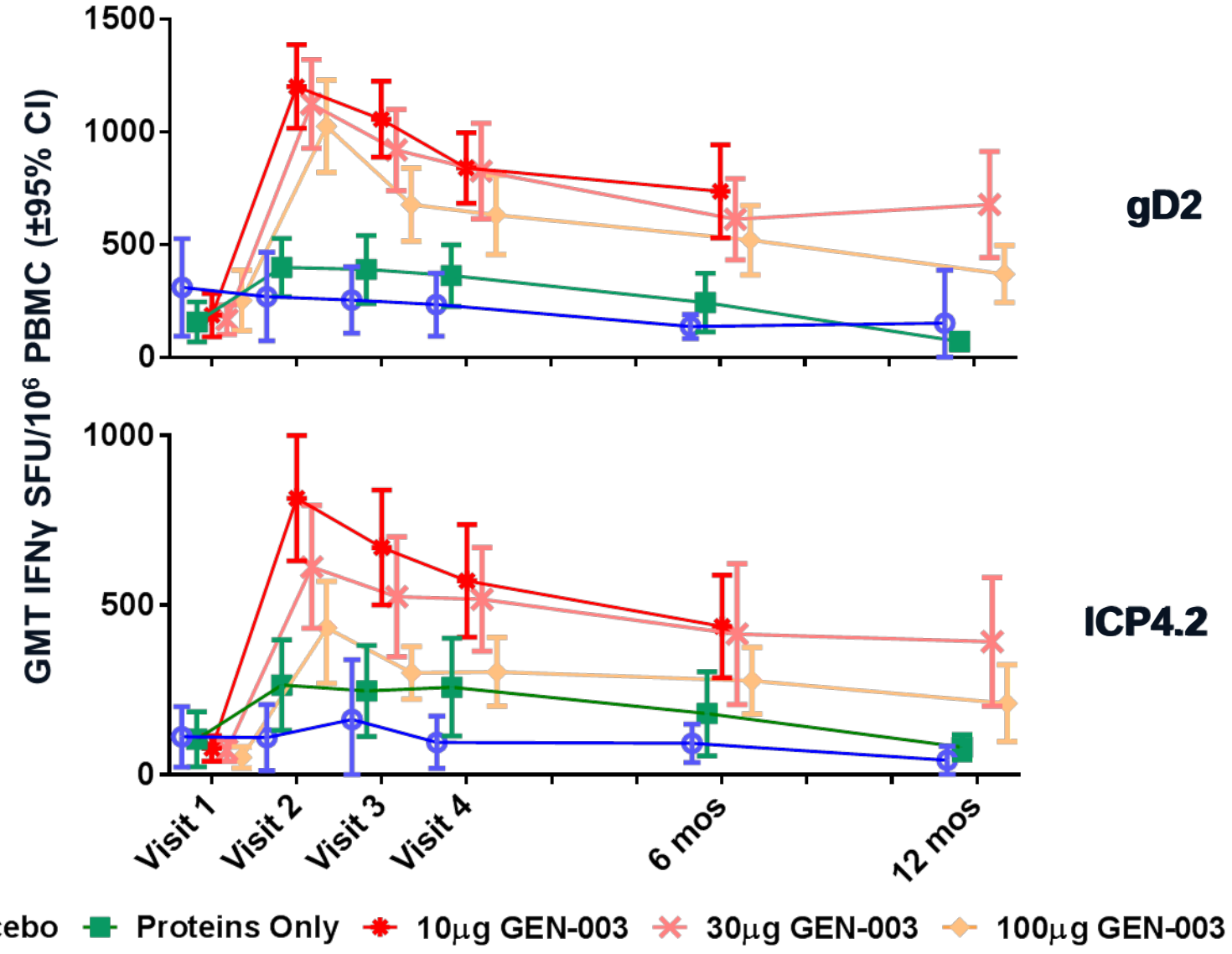
Genital Lesion Rate (a)



(a) Normalized so that rate at baseline = 1

***** = p<0.001 Poisson Mixed Model Analysis**

T cell Responses are Durable and Adjuvant-Dependent

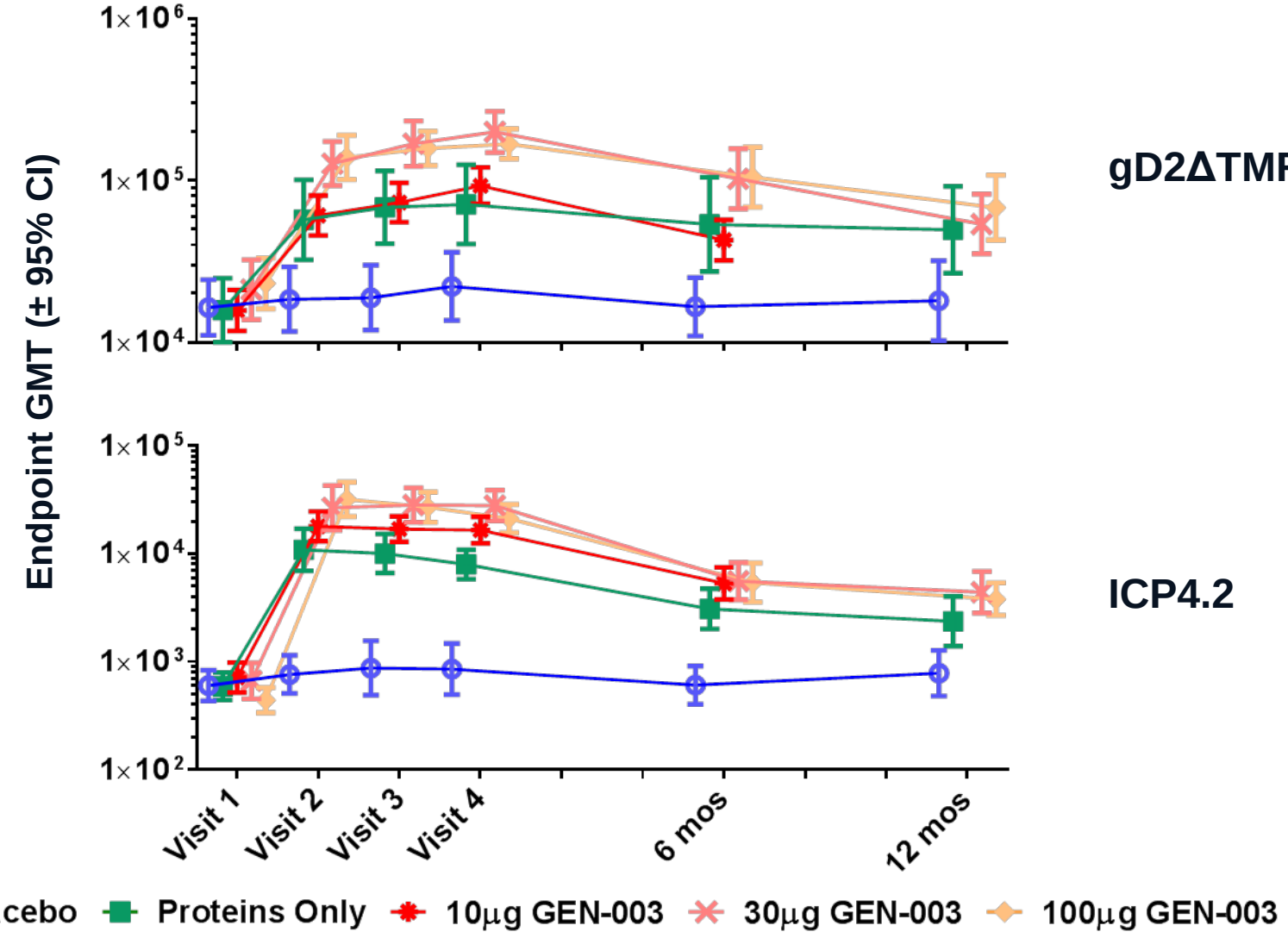


At Effective Dose, 80-90% of Subjects Defined as Responders

			IFNγ ELISpot Responders* (%)				
			D7	D28	D49	6 mos	12 mos
gD2	GEN-003	10μg	80	84	93	72	NT
		30μg	79	81	68	80	77
		100μg	70	59	52	50	50
		Proteins Only	54	60	46	39	14
		Placebo	0	0	0	0	0
ICP4.2	GEN-003	10μg	96	92	91	80	NT
		30μg	85	88	91	85	82
		100μg	85	78	78	77	63
		Proteins Only	50	64	54	44	21
		Placebo	0	0	0	5	0

*3.5-fold increase over baseline, based on a natural history study
NT = not tested

IgG Titers are Dose-Dependent and Long-Lived, with a Modest Adjuvant Benefit

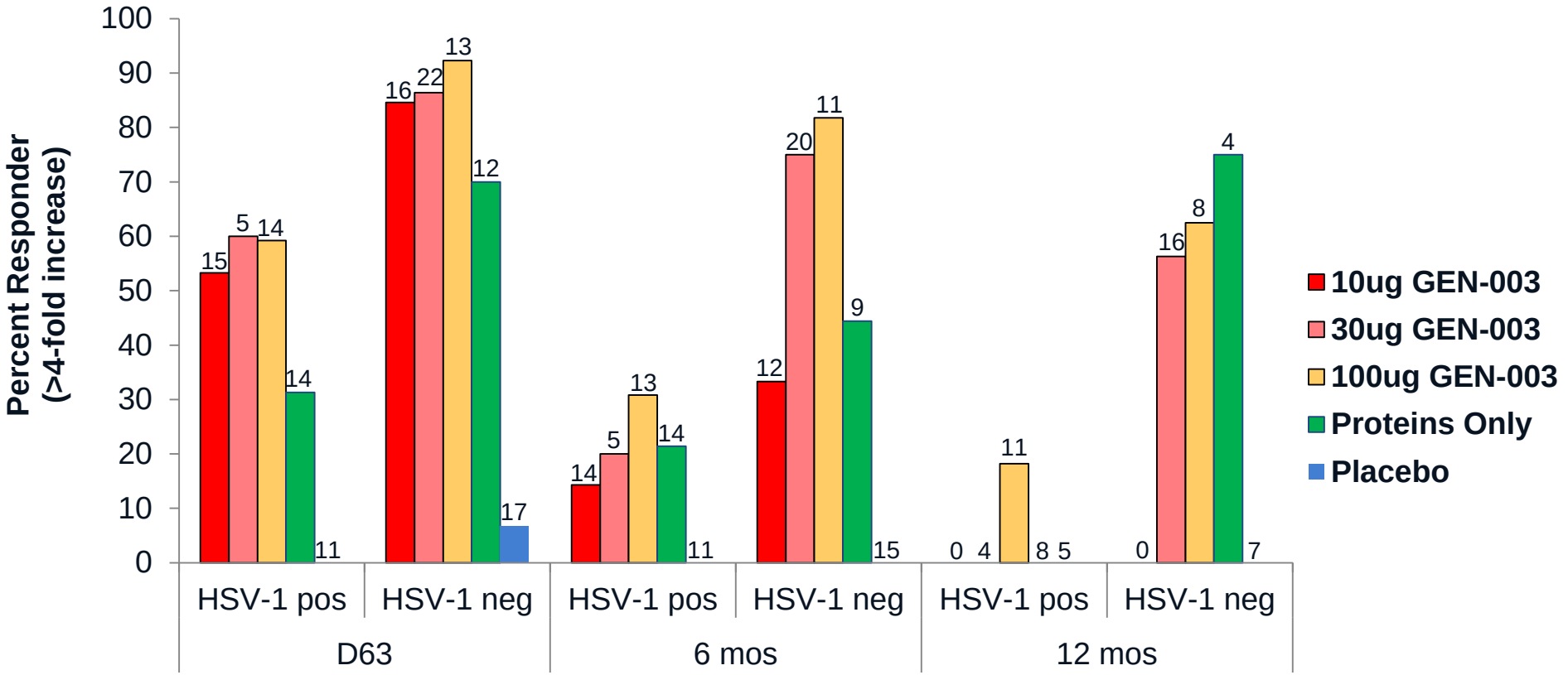


IgG Responders Increase with Increasing Dose

			IgG ELISA Responders* (%)				
			D21	D42	D63	6 mos	12 mos
gD2ΔTMR	GEN-003	10μg	39	54	32	23	NT
		30μg	66	75	82	64	45
		100μg	56	89	81	54	37
		Proteins Only	41	43	46	30	25
		Placebo	4	0	4	0	0
ICP4.2	GEN-003	10μg	100	100	100	85	NT
		30μg	100	100	100	80	90
		100μg	100	100	100	96	95
		Proteins Only	89	89	89	52	58
		Placebo	4	7	8	4	8

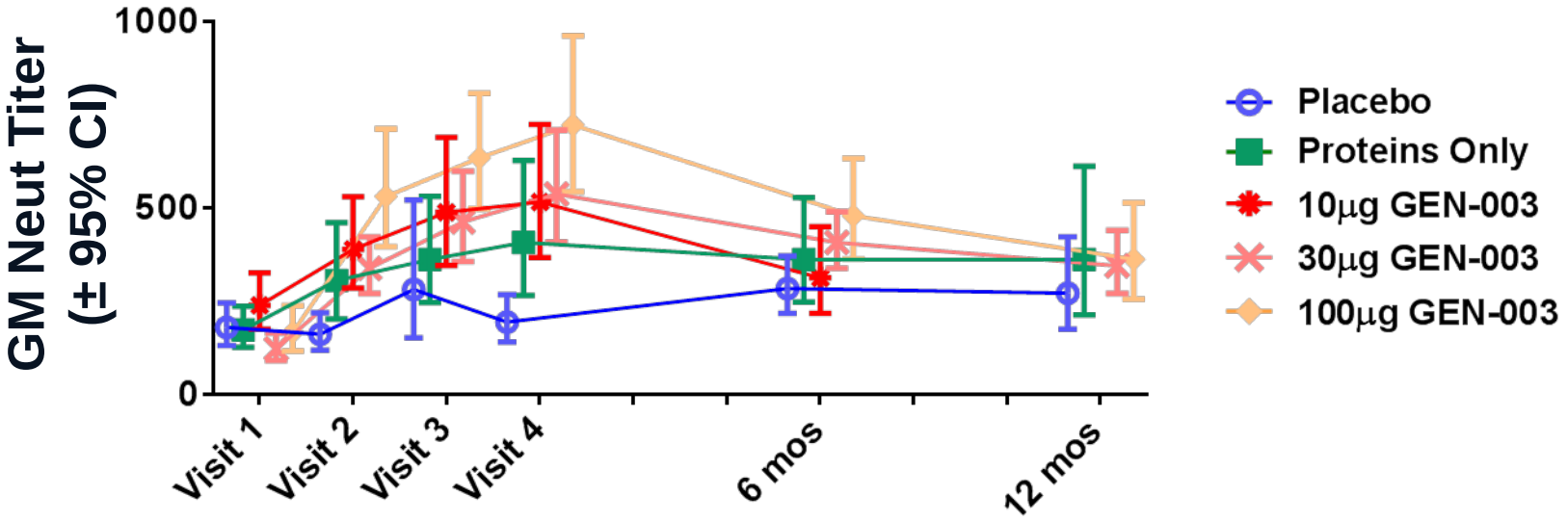
*4-fold increase over baseline
NT = Not Tested

Magnitude and Durability of gD2 IgG Responses Are Influenced by HSV-1 Serostatus



Numbers above bars indicate subject N

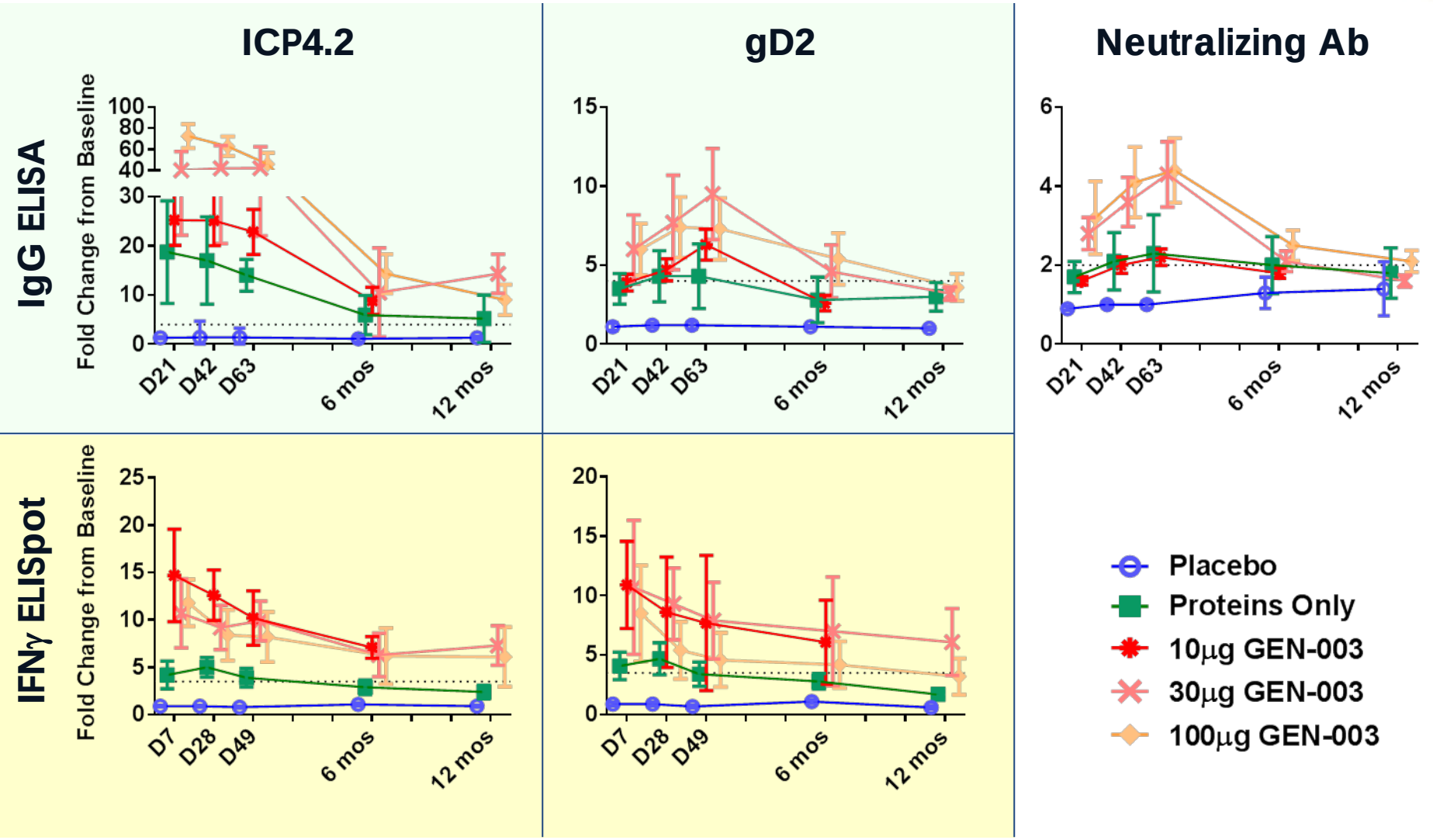
50% Neutralization Titers are Dose-Dependent



		Neutralizing Ab Responders* (%)				
		D21	D42	D63	6 mos	12 mos
Neuts GEN-003	10μg	23	50	43	32	NT
	30μg	72	89	93	40	25
	100μg	70	96	89	67	37
Proteins Only		30	43	44	30	33
Placebo		0	0	4	12	25

*2-fold increase over baseline

Fold Change From Baseline Analysis



Conclusions

- Immune responses are detectable at baseline and increase with immunization
  - T cell responses are highest after 1st dose
  - Ab responses are maximal after the 3rd dose for gD2 and neuts, 1st dose for ICP4.2
- All responses remain significantly above baseline at 12 months
- Matrix M-2 is critical for potentiating the T cell response, less important for antibody responses
- Fold change from baseline for antibody and T cell responses were greatest against ICP4.2, likely due to the higher baseline responses to gD2
- HSV-1 serostatus impacted the magnitude and duration of gD2 IgG titers but not other measures of immunity

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