

Frederick National Laboratory for Cancer Research



Immune Responses to Human Papillomavirus Vaccines: What We Have Learned

Ligia Pinto, PhD

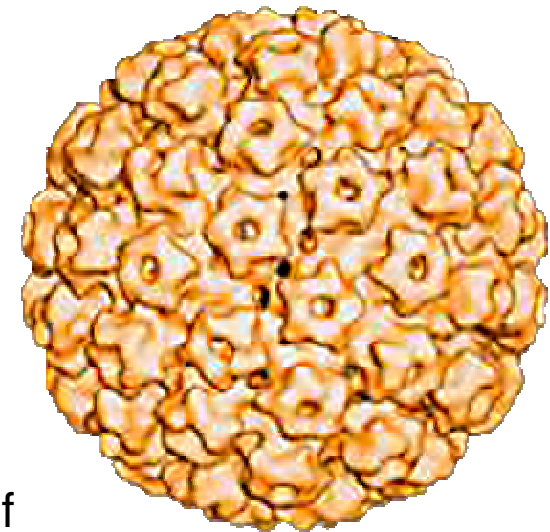
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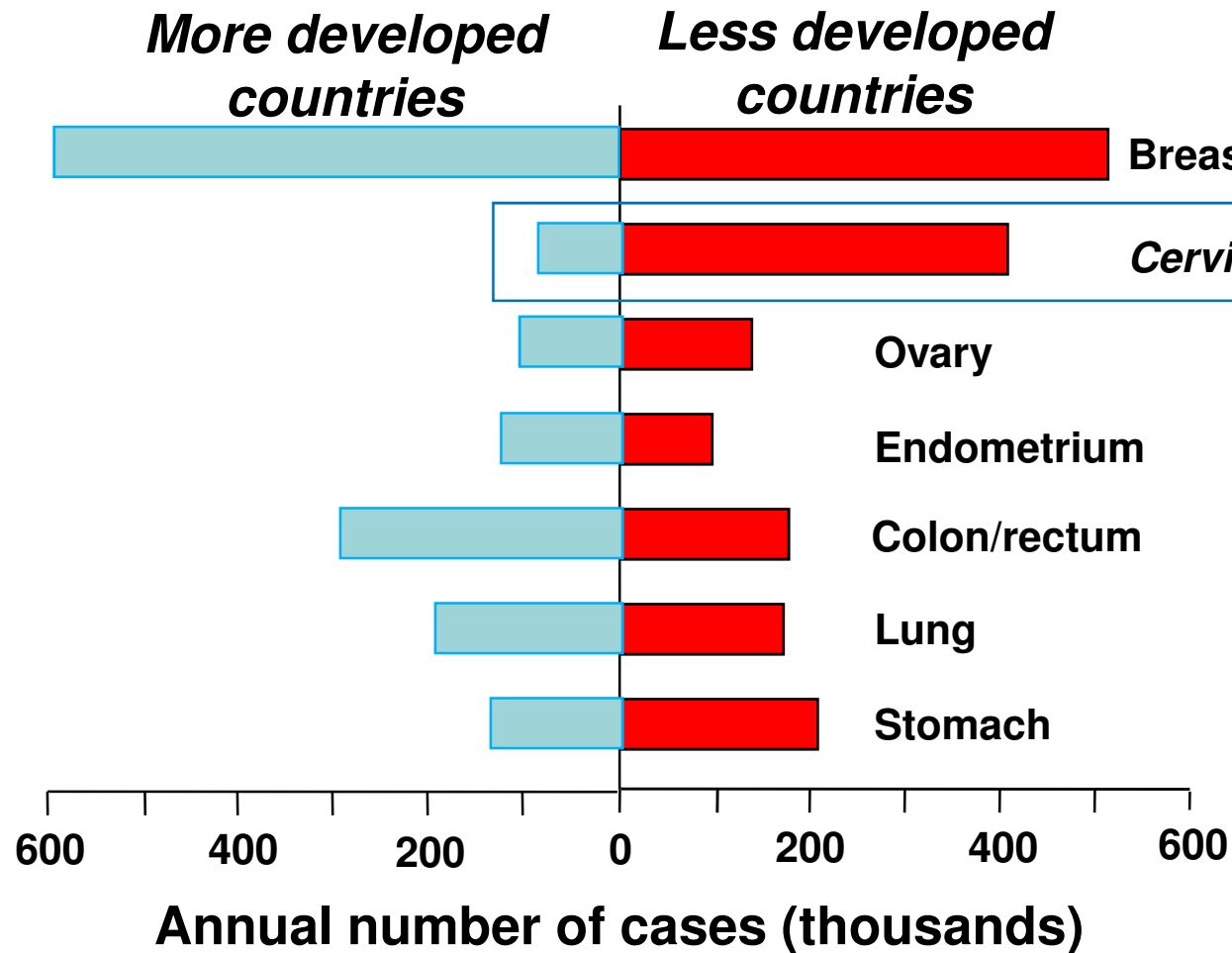
DEPARTMENT OF HEALTH AND HUMAN SERVICES • National Institutes of Health • National Cancer Institute

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- **Non-enveloped double-stranded DNA virus**
- **One of the most common sexually transmitted infections**
- **>100 types identified**
- **~30–40 mucosal**
 - ~15–20 **oncogenic** types
 - HPV 16 and HPV 18 types account for 70% of cervical cancer cases
 - Nononcogenic types
 - HPV 6 and 11 are most often associated with external anogenital warts

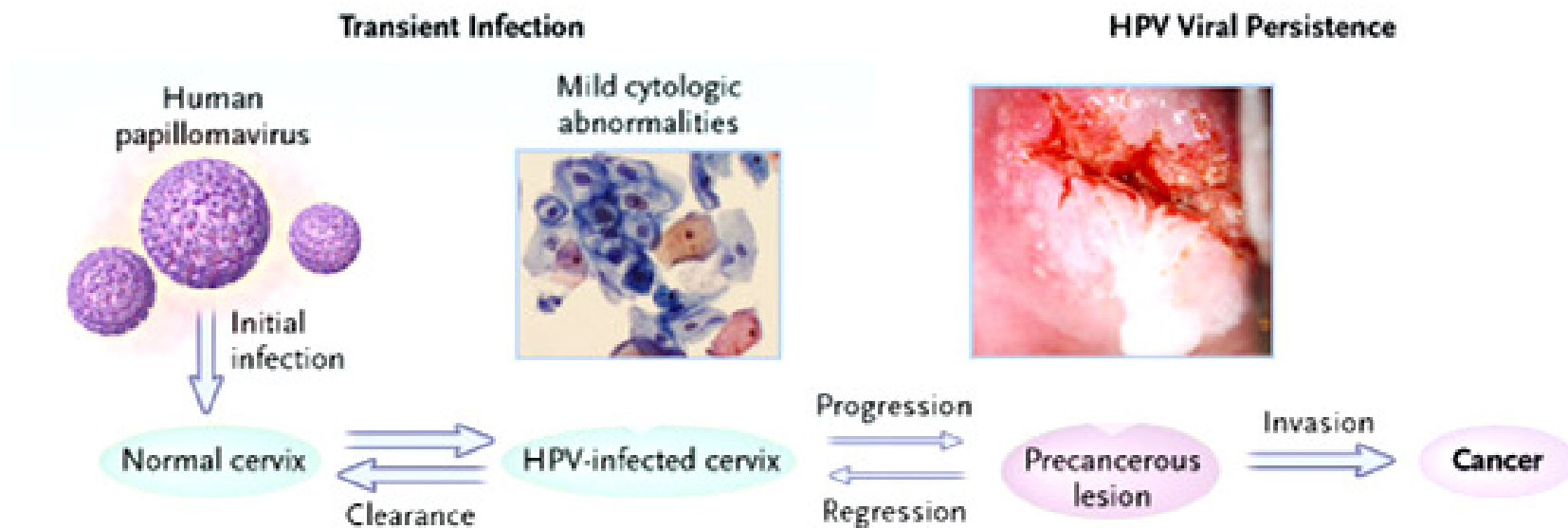


Most Common Cancers in Women



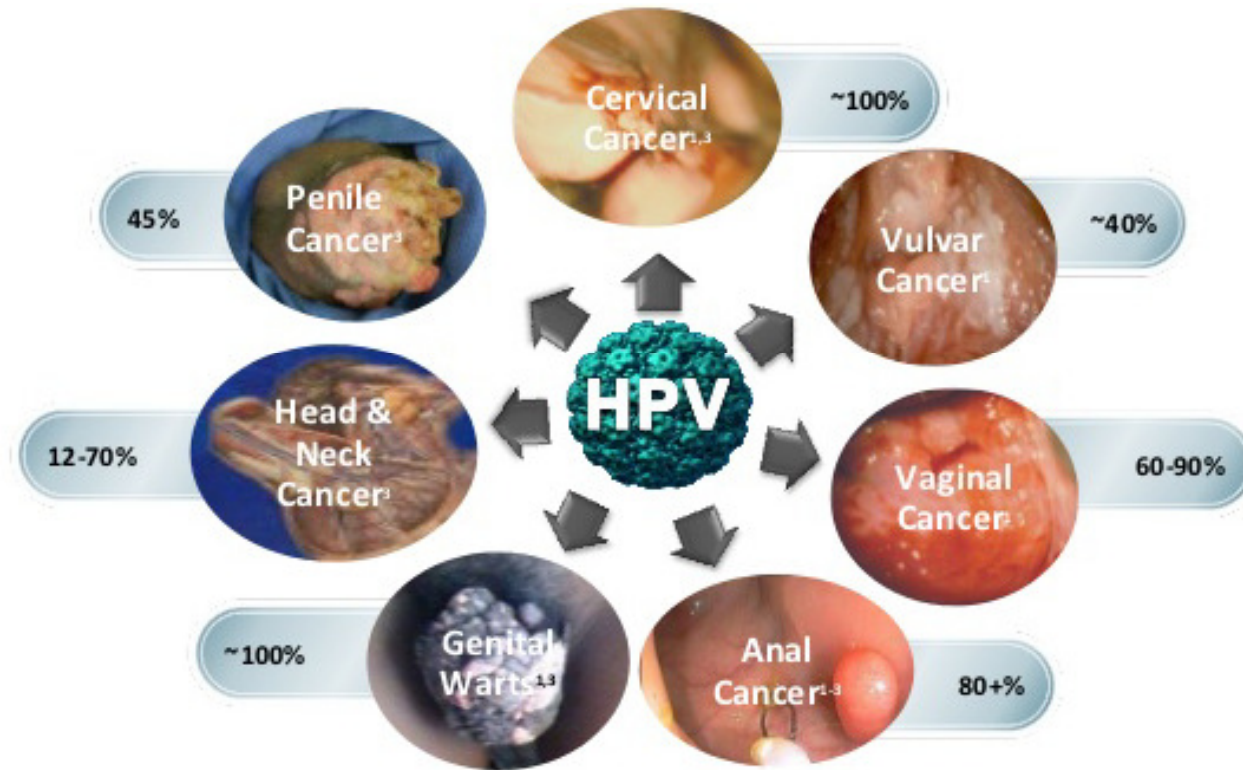
Adapted from Parkin et al, Eur J Cancer 2001; 37 S4

Cervical Pathogenesis



HPV persistence is the most important predictor of high grade cervical cancer precursors

HPV Causes More than Cervical Cancer



HPV Associated Cancers, both Sexes, US 2005-2009

	Average annual number of cases	HPV attributable	HPV 16/18 attributable
Cervix	11,279	10,150	7,470
Vagina	694	520	380
Vulva	3,039	2,100	1,480
Anus	3,084	2,810	2,450
Oropharynx	2,317	1,670	1,420
Total (Females)	21,342	17,250	13,200
Penis	1,003	630	450
Anus	1,687	1,540	1,400
Oropharynx	9,312	6,700	5,700
Total (Males)	12,002	8,800	7,550

Two Licensed Prophylactic HPV Vaccines (L1 Virus-Like Particles)

Manufacturer	Merck	GlaxoSmithKline
Trade name	Gardasil®	Cervarix™
HPV types	6, 11, 16, 18	16, 18
Adjuvant	AAHS	ASO4 Adjuvant (MPL + Alum)
Licensed	Female and males (ages 9-26yrs)	Females (ages 9-25yrs)
Expected coverage of protection	70% of Cervical Cancer 90% Genital Warts	70% of Cervical Cancer

3 intra-muscular injections over 6 months

HPV Prophylactic Efficacy Trials

Table 1

Proof-of-principle HPV VLP prophylactic efficacy trials

Study	Koutsky et al. (32)	Harper et al. (35)	Villa et al. (33)	Mao et al. (34)
HPV VLP type	16	16, 18	6, 11, 16, 18	16
Adjuvant	Alum	AS04	Alum	Alum
Sponsor	Merck	GSK	Merck	Merck
Trial site	United States	United States, Canada, Brazil	United States, European Union, Brazil	United States
Subject age	16–23	15–25	16–23	16–23
No. subjects (ATP)	1,533	721	468	1,505
Vaccination schedule (mo)	0, 2, 6	0, 1, 6	0, 2, 6	0, 2, 6
Follow-up (yr)	1.5	1.5	2.5	3.5
Persistent infections ^A	42/0 (100)	7/0 (100)	36/4 ^B (90)	111/7 ^C (94)
CIN1+ ^D	9/0 (100)	6/0 (100)	3/0 (100)	24/0 (100)

Shown are according-to-protocol (ATP) analyses for the HPV types included in the vaccines. ^AValues are shown as number of controls versus number of vaccinees with persistent infections; values in parentheses indicate percent efficacy. ^BTen of 36 controls and 3 of 4 vaccinees were HPV DNA positive only at the last visit. ^CNineteen of 111 controls and 7 of 7 vaccinees were HPV DNA positive only at the last visit. ^DValues are shown as number of controls versus number of vaccinees that were CIN1+; values in parentheses indicate percent efficacy. GSK, GlaxoSmithKline.

Two Prophylactic HPV Vaccines: Protection Beyond Cervical Cancer

	Gardasil (Quadrivalent)	Cervarix (Bivalent)
Cervix	High protection against HPV-infection and related disease	
Vagina/Vulva	Protection against HPV-infection and related disease	Not evaluated
Penis	Protection against HPV-infection	Not evaluated
Anus	Protection against HPV-infection and disease	Protection against HPV-infection
Oropharynx	Not evaluated	Protection against HPV infection

Evolution of Recommendations for HPV Vaccination in the US

Quadrivalent Vaccine

Routine: females 11 or 12yrs* and 13-26 yrs if not previously vaccinated

Quadrivalent or Bivalent

Routine: females 11 or 12yrs* and 13-26 yrs if not previously vaccinated

Quadrivalent

Maybe given males 9-26yrs*

Quadrivalent

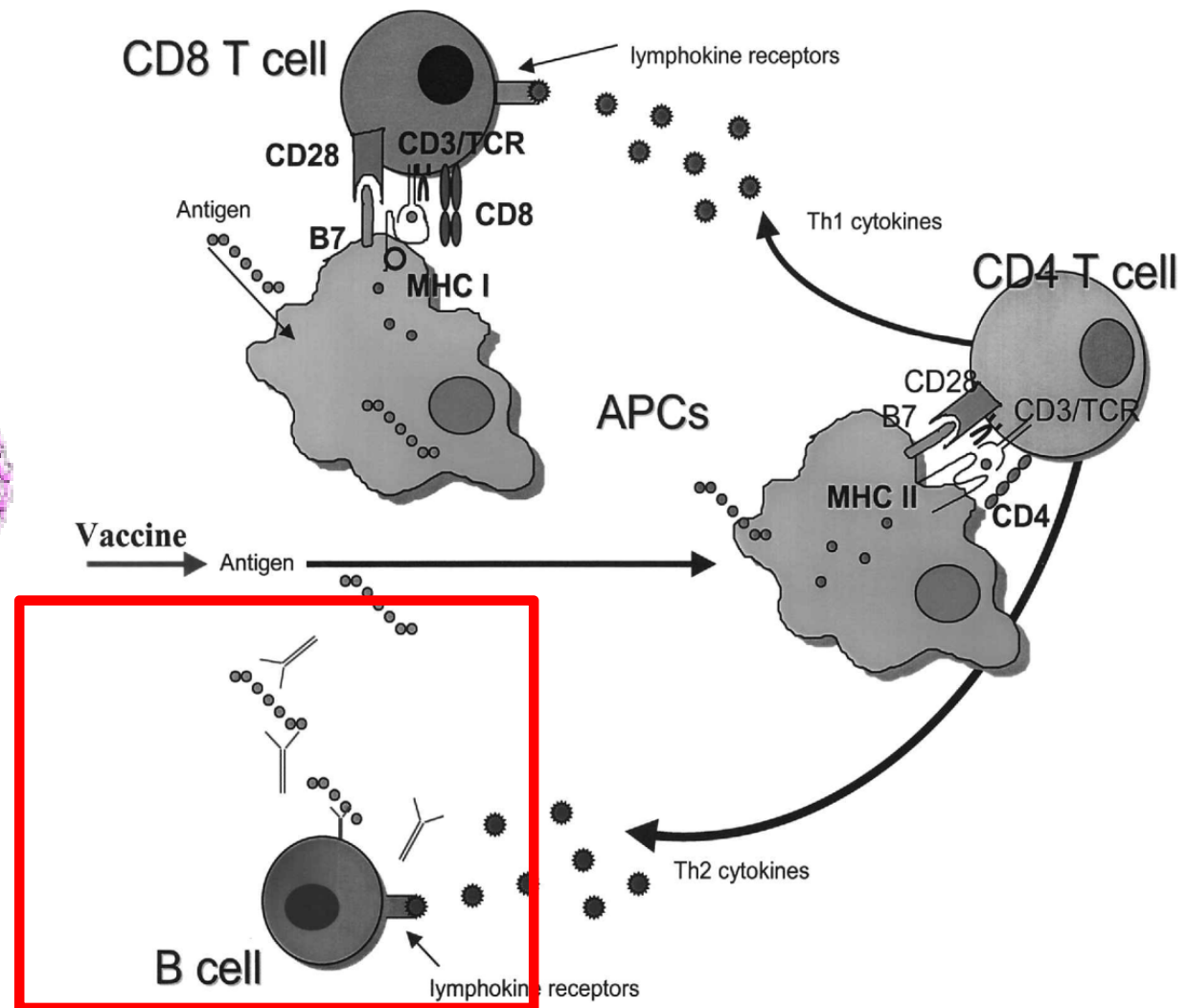
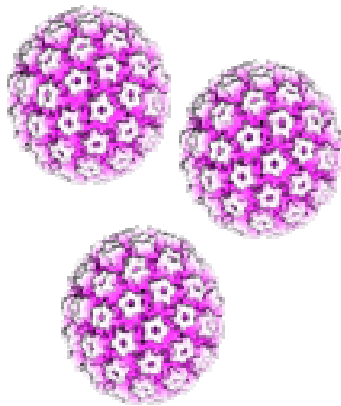
Routine: males 11 or 12yrs* and 13-21 yrs if not previously vaccinated
May be given, 22-26 yrs

WHO Advisory Group recommends a 2-dose schedule for girls, <15 years (0/6)

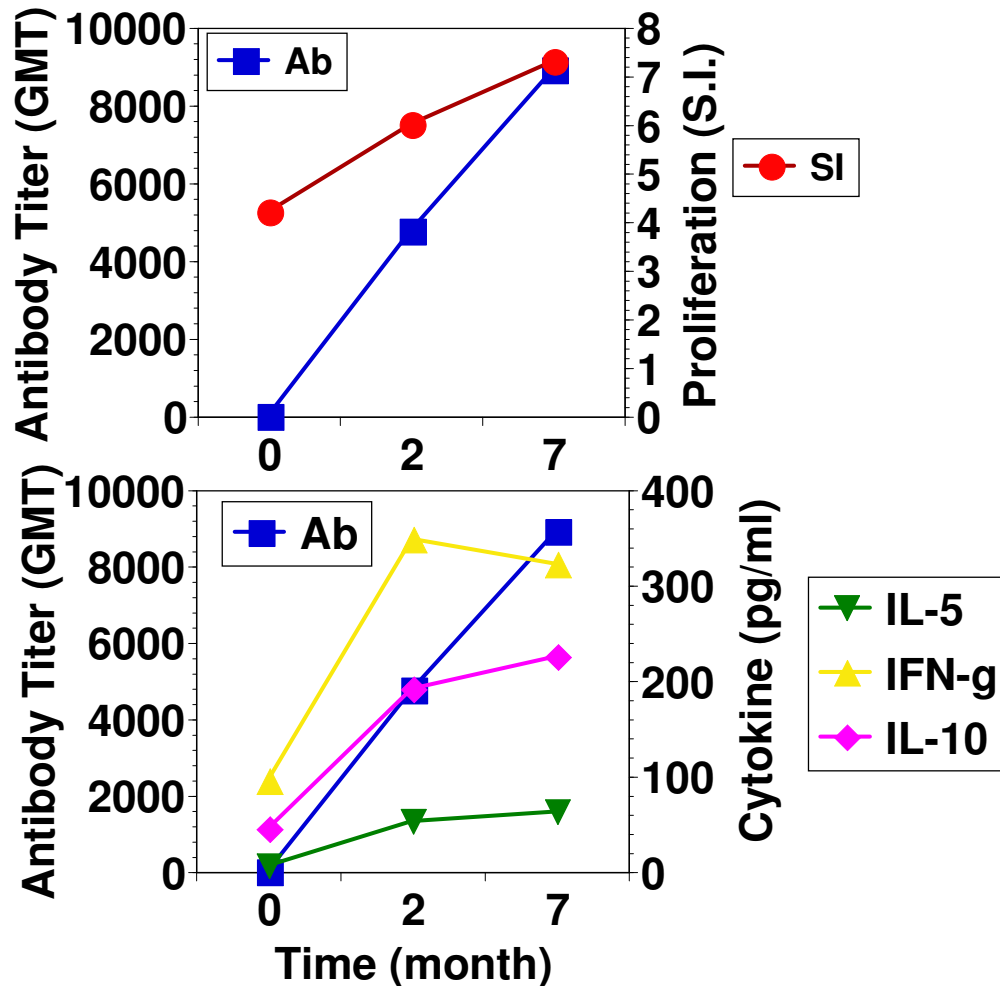
2006 2007 2008 2009 2010 2011 2012 2013 2014

Potential Mechanisms of Vaccine-Induced Protection Against Infection and Disease

- **Humoral Immunity :**
Neutralizing Antibodies
- **Cellular Immunity :**
CTL, T helper

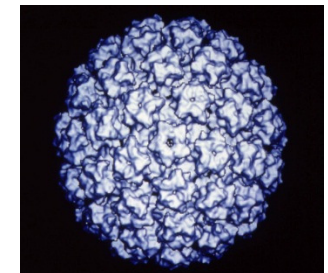


Cell-Mediated and Humoral Responses to HPV-16 L1 VLP vaccine



• Immune Response to Vaccination:

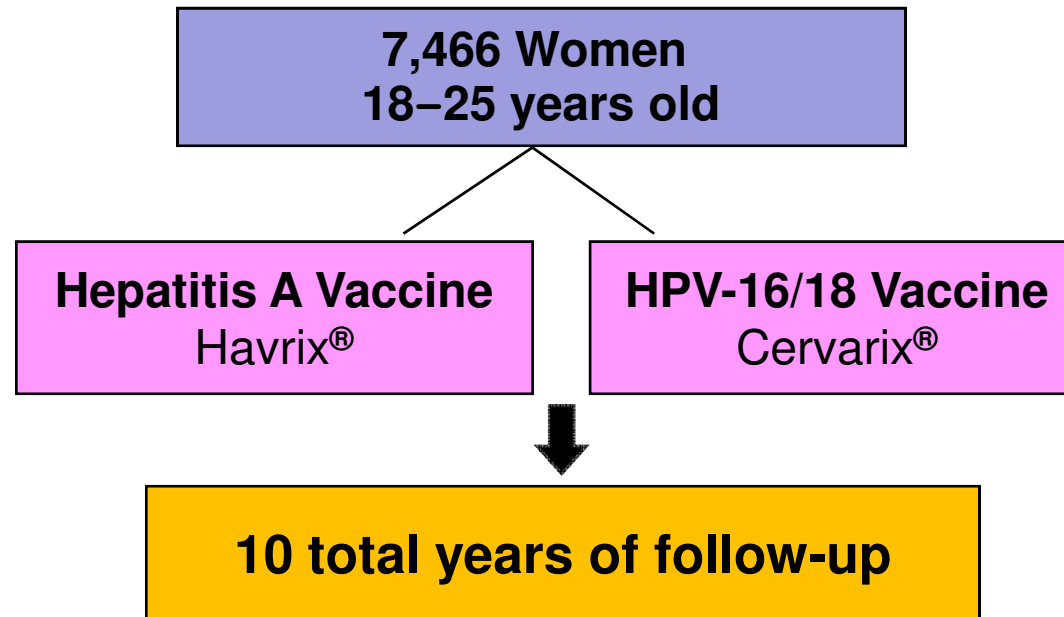
- Type-specific neutralizing antibodies
- T-cell proliferation (CD4+ and CD8+ T cells)
- Complex cytokine responses (Th1, Th2 and inflammatory cytokines)
- Innate immune responses (DC activation)



(Pinto et al, JID 2003; García-Piñeres et al, EJI 2006; García-Piñeres et al, CVI 2007, García-Piñeres et al, JI 2009)

NCI Costa Rican Vaccine Efficacy Trial: Immunity Studies

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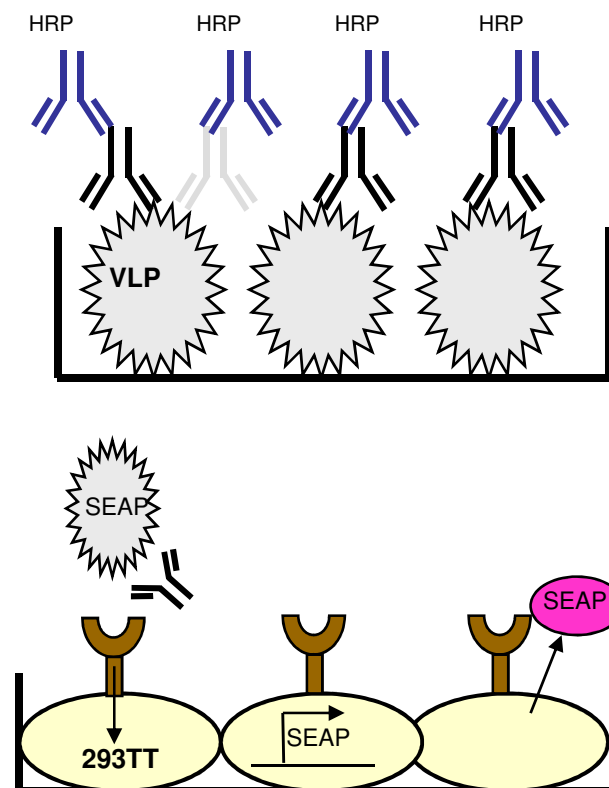


- **Optimization and validation of assays (serum and cervical secretions)**
- **Monitor antibody responses and duration of protection**
- **Understand immune mechanisms of protection and failure**
 - Cross-protection
 - Immunogenicity of less than three doses

Validated Assays for Measurement of Antibodies in Serum and Cervix

HPV Serology Assays

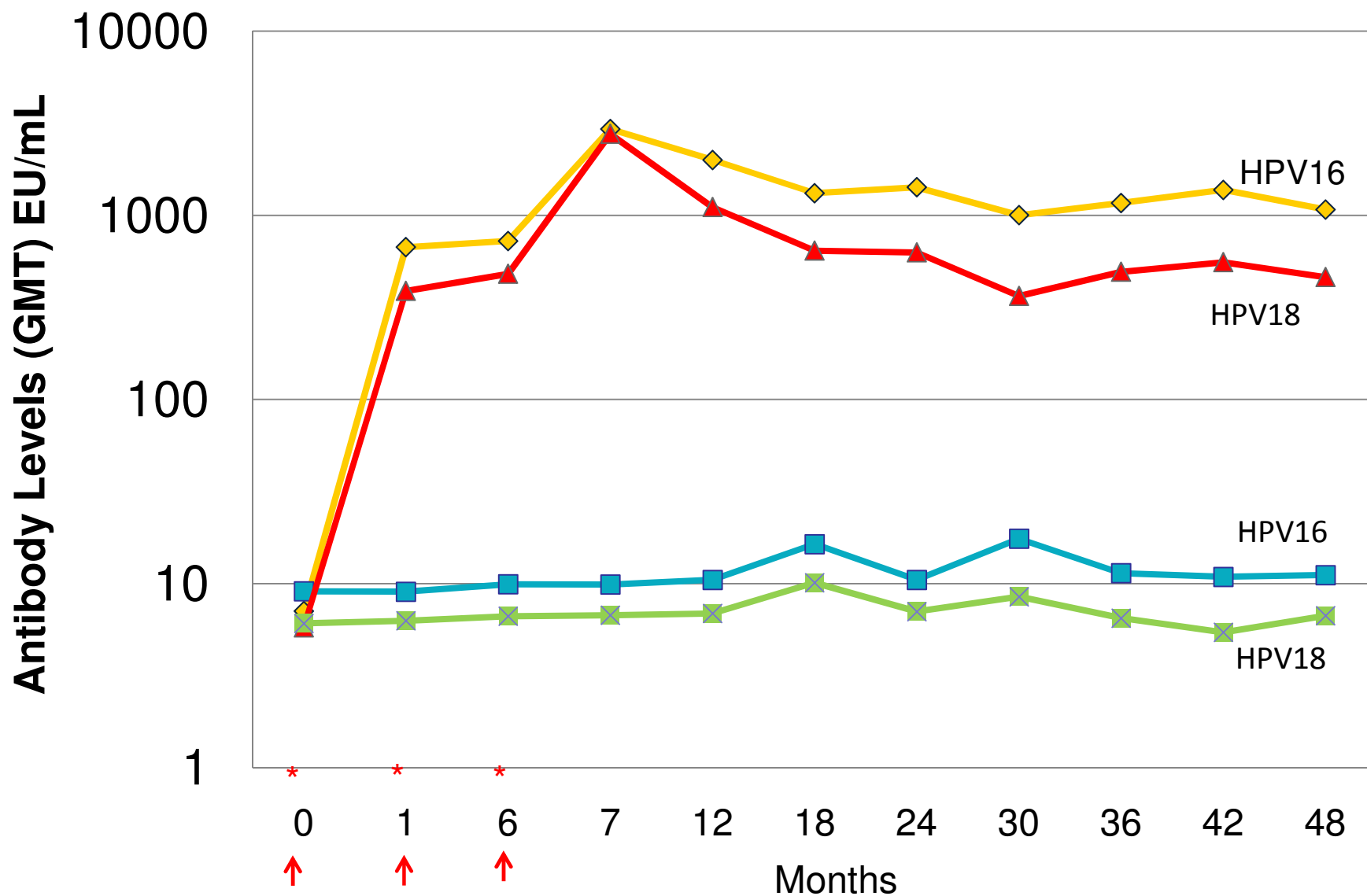
- **Quantity:**
 - HPV IgG ELISA
- **Quality/Function:**
 - Pseudovirion neutralization assay
 - ELISA antibody avidity assay
 - Memory B cell ELISPOT



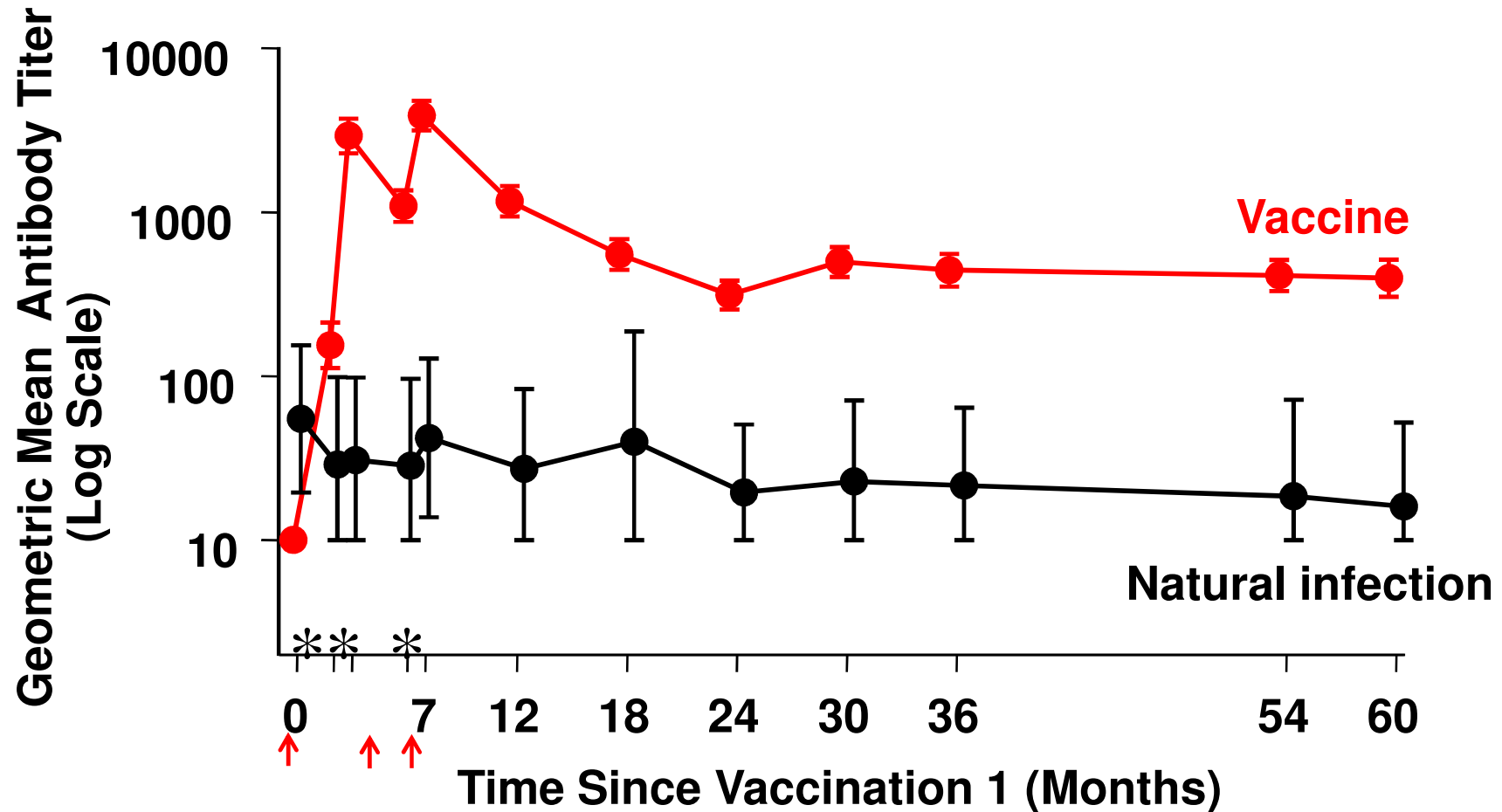
All assays used in-house produced HPV VLPs, standards, and controls

HPV-16/18 L1 VLP Vaccine Immunogenicity Study: Costa Rica Vaccine Trial

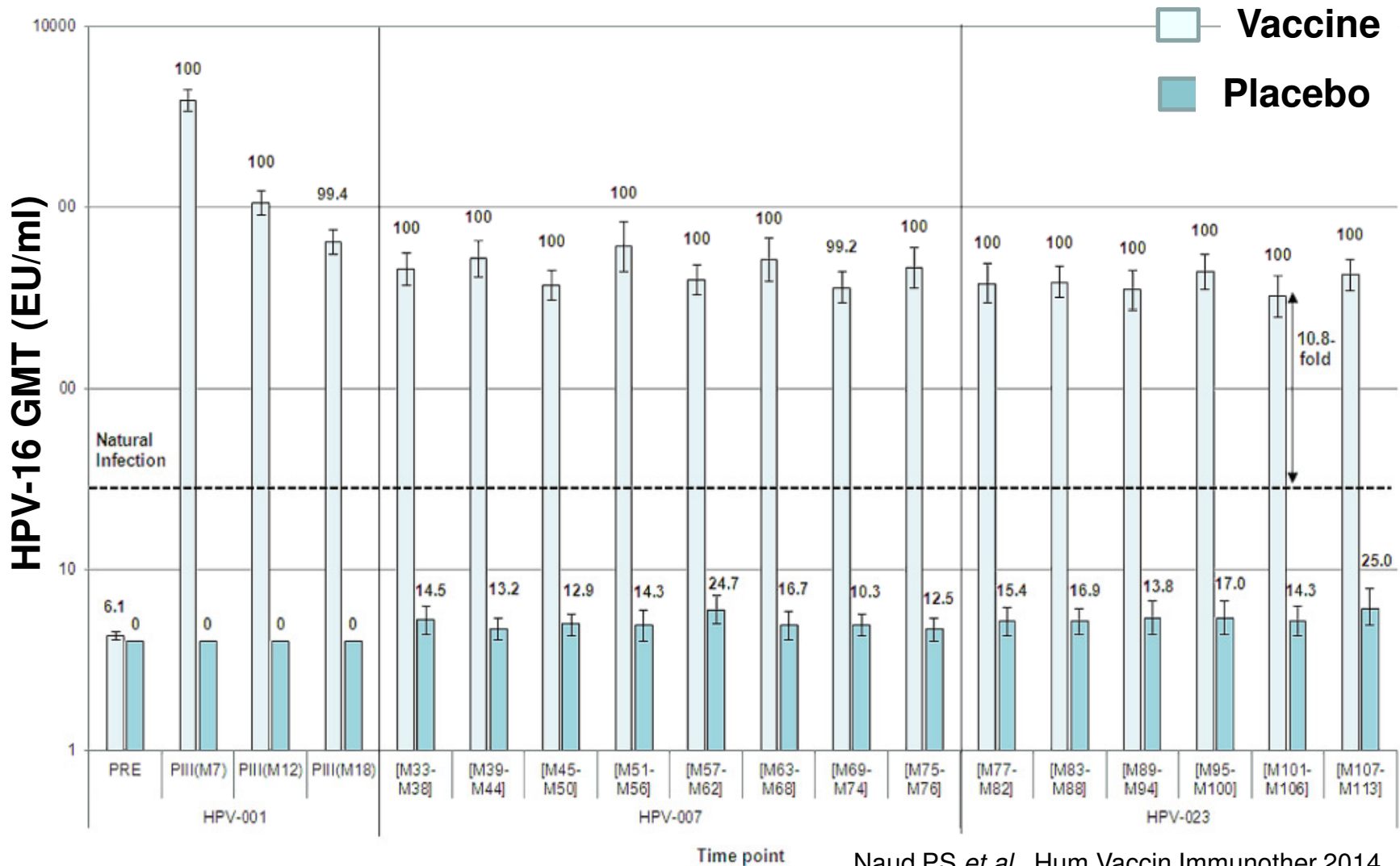
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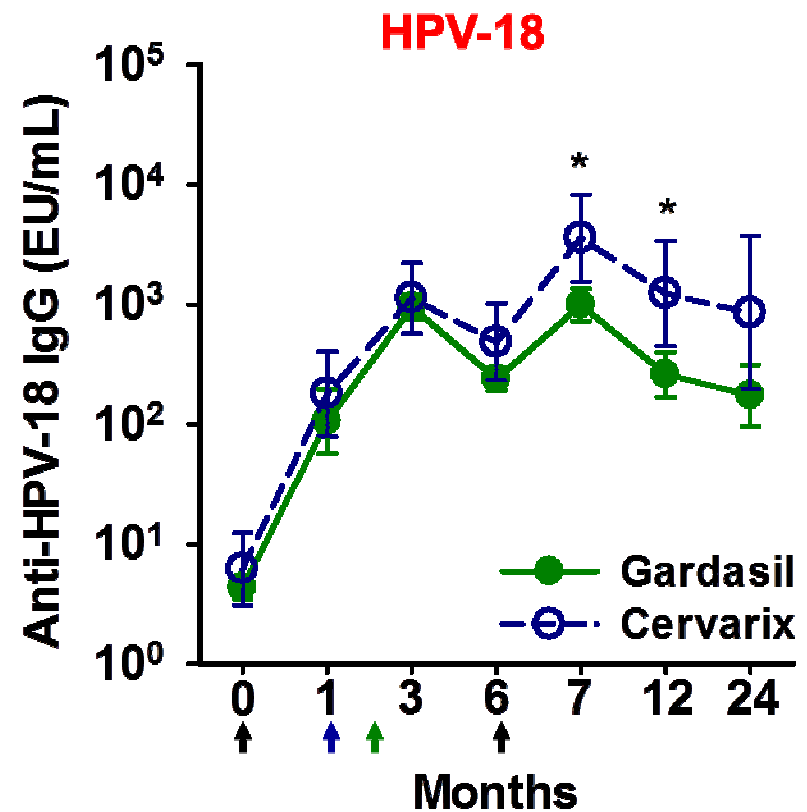
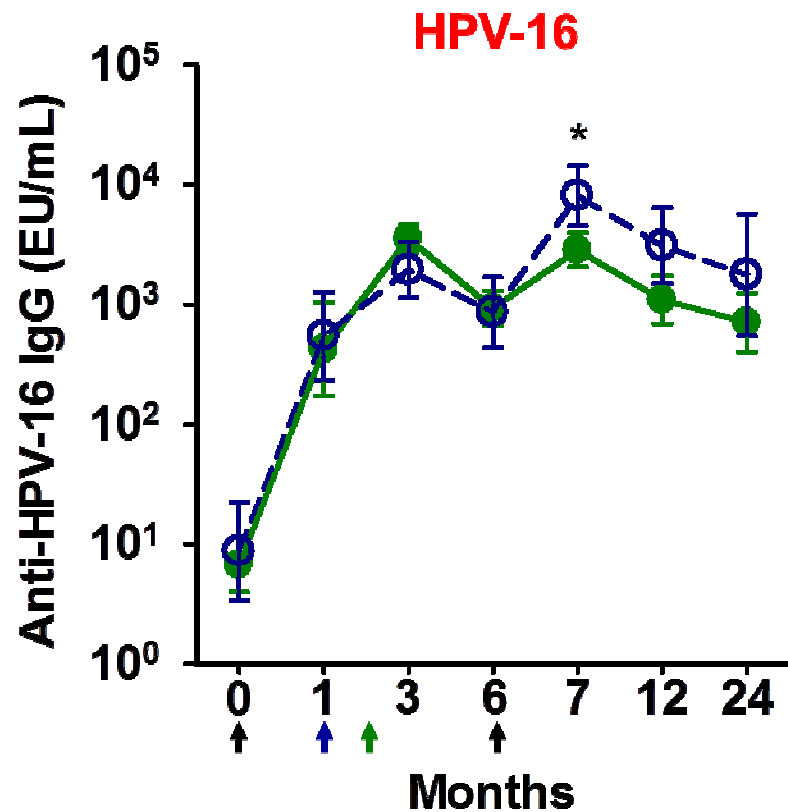
Anti HPV-16 Antibody Over 5 Years Follow-Up (Quadrivalent vaccine)



Durability of Antibody Response to 3 Doses of the Bivalent Vaccine: 9.4 yrs



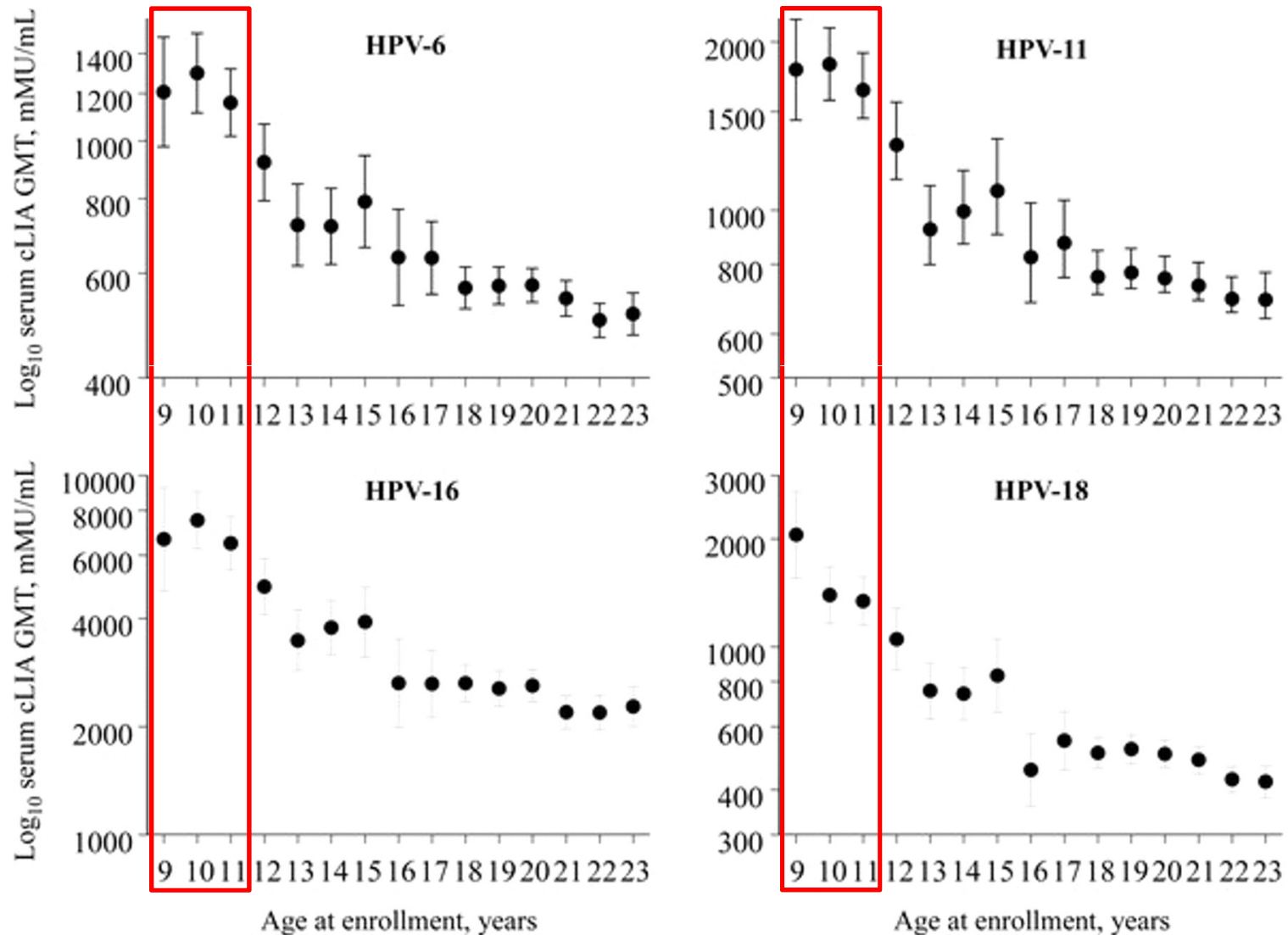
Antibody Titers in Gardasil® and Cervarix® Recipients



* $p < 0.05$, Mann-Whitney U test

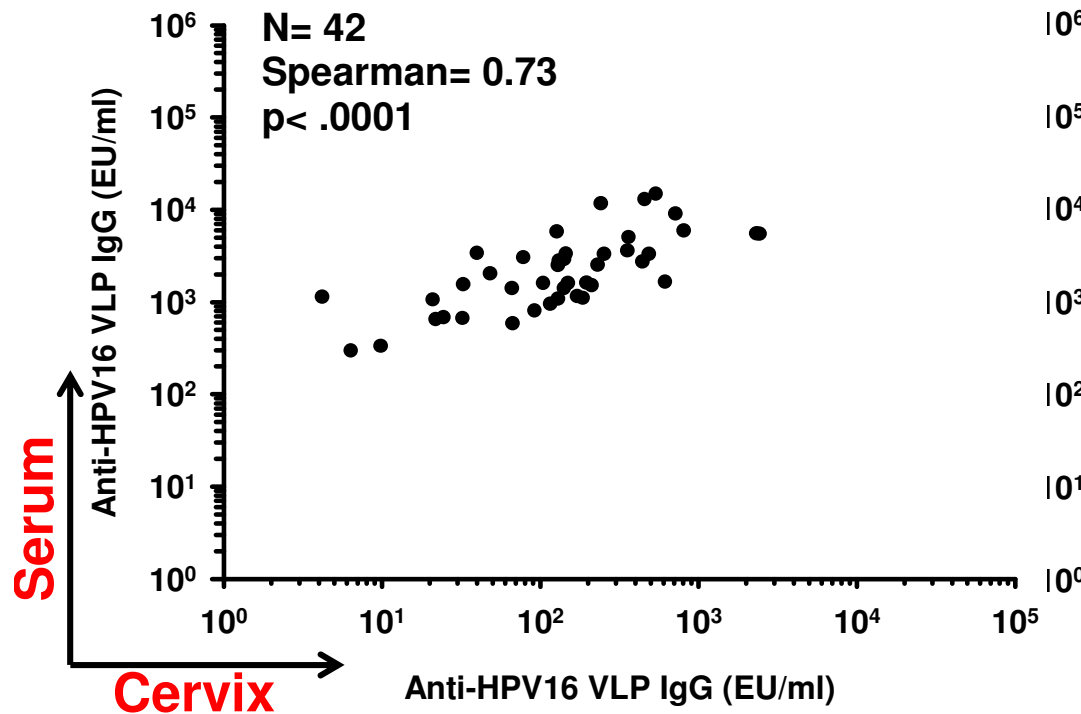
Herrin et al. Hum Vaccin Immunother . *In Press*

Influence of Age at Vaccination in Females (HPV Quadrivalent Vaccine)

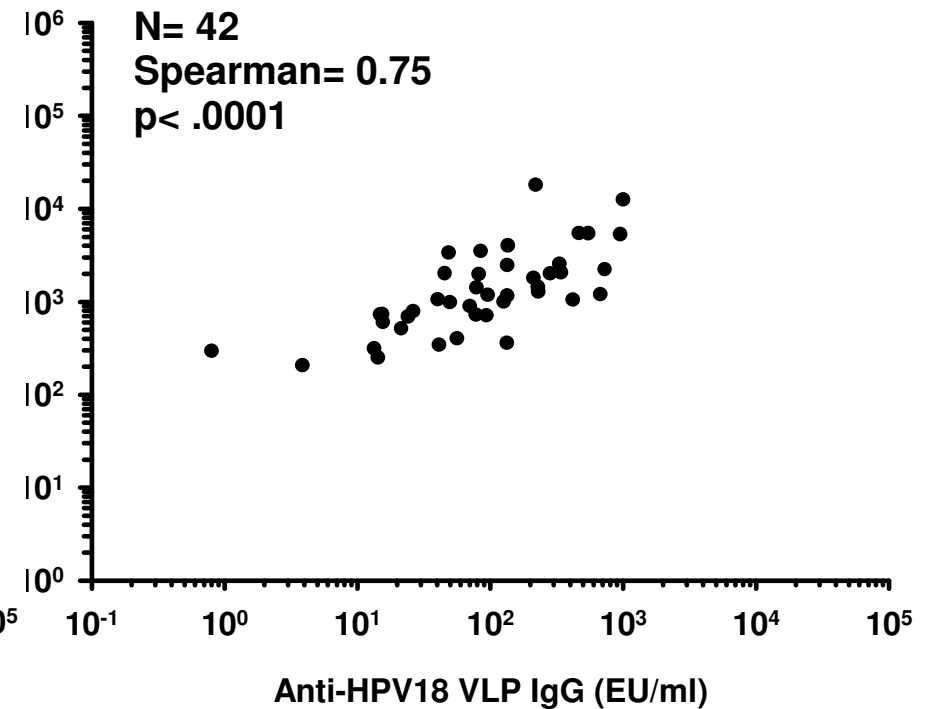


Levels of Antibodies in Serum Correlate Well with Levels in the Cervix

HPV-16



HPV-18



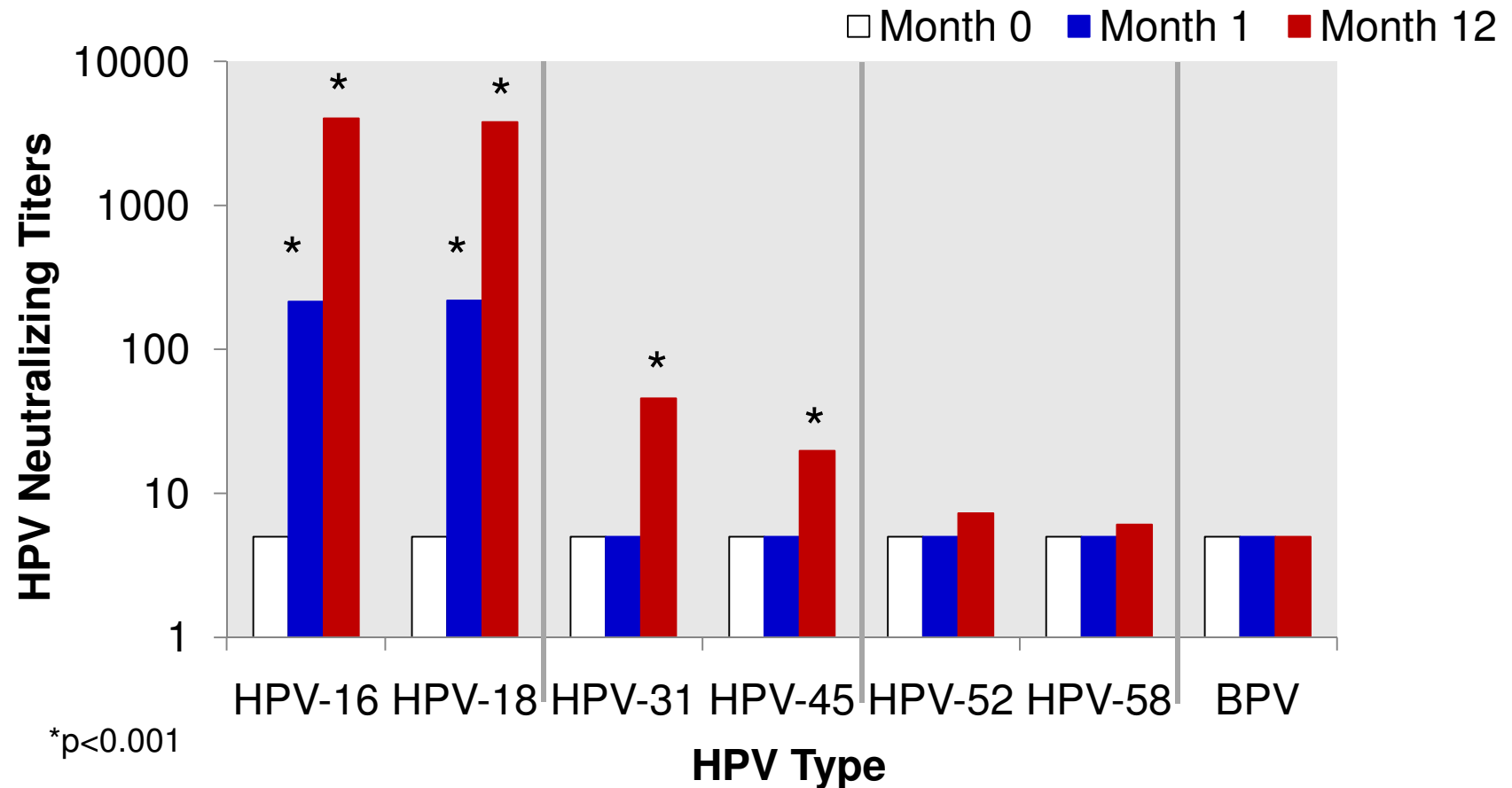
Cross-Protection Against Persistent Infection with Related High Risk HPV Types

Cervarix HPV16/18 Vaccine ATP analysis; >7,000 per arm: 3.5 yrs follow-up

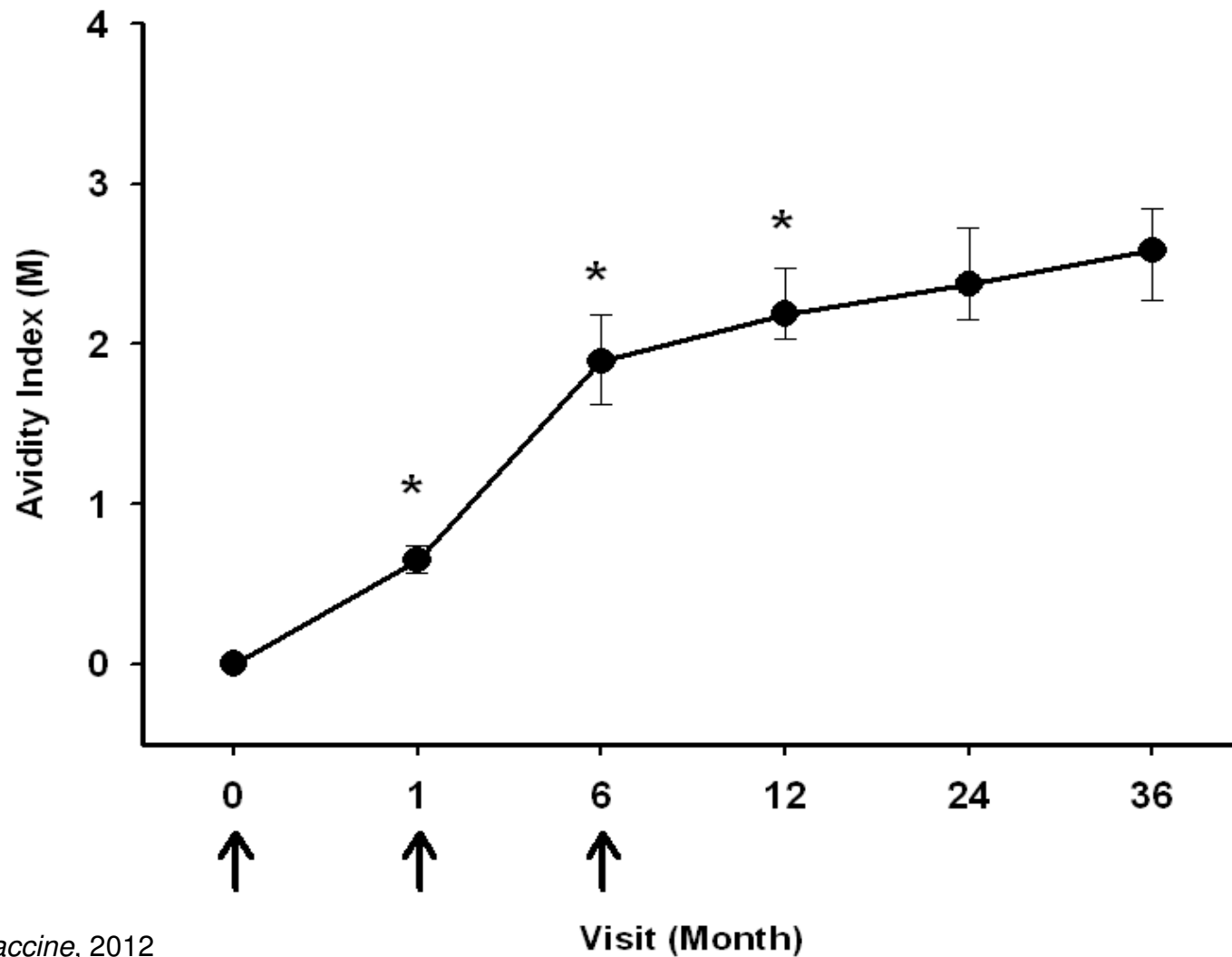
HPV Type	# Vaccine	# Placebo	Efficacy
31	21	102	79%
33	31	50	38%
45	10	27	76%
52	150	143	-5%
58	64	56	-15%
All of Above	255	336	24%

Protection Beyond Vaccine Types: HPV-16/18 L1 VLP Vaccine Induces Cross-Neutralizing Antibodies

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HPV-16 Antibody Avidity Increases after Vaccination over 36 Months of Follow-up



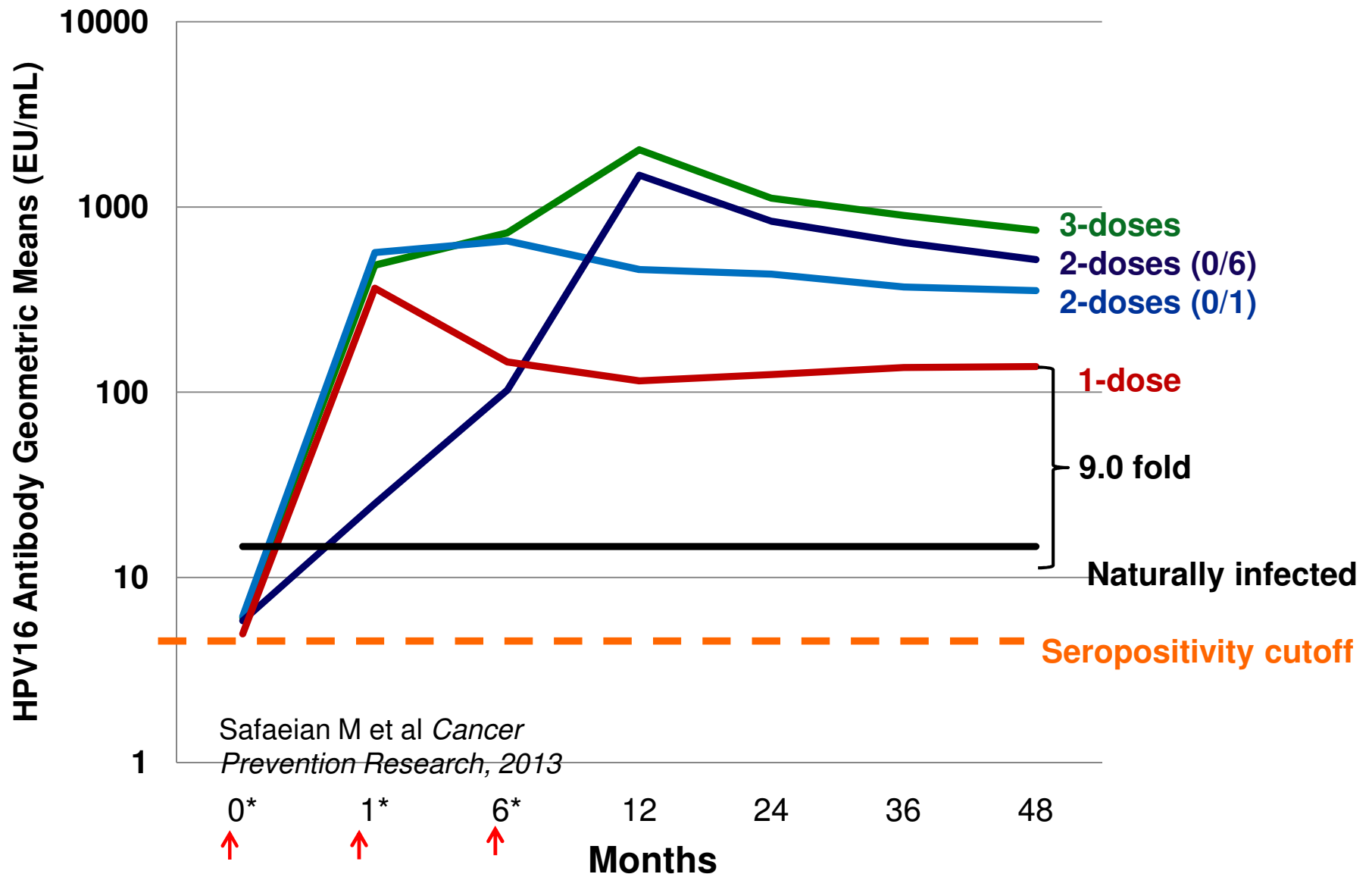
Kemp et al., *Vaccine*, 2012
Dauner et al., *Mol Cell Probes*, 2012

Vaccine Efficacy by Doses Received Costa Rican Vaccine Trial

# of Doses	Arm	# of Women	# of persistent HPV16/18 infections	HPV16/18 VE (95%CI)
3	Control	3010	133	81% (71% to 88%)
	HPV	2957	25	
2	Control	380	17	84% (50% to 96%)
	HPV	422	3	
1	Control	188	10	100% (67% to 100%)
	HPV	196	0	

HPV16 Antibody levels in Recipients of 1, 2 and 3 Doses of the bivalent HPV vaccine, Costa Rican Clinical Trial

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Summary

- High efficacy for preventing HPV infection
- Generally safe and tolerable
- High levels of immunogenicity
 - >99% seroconversion rates in 9-26 years old
 - Antibody titers higher than in natural infection
 - Antibodies decline over time after the 3rd dose, but plateau by 18 months
 - Stable antibody levels up to 9 years of follow-up
 - Induction of T cell immunity and DC activation
 - Non-inferiority of 2 doses, if given at 0, 6 month schedule
 - The minimum protective antibody threshold not known
- **Current HPV vaccines will not eliminate the need for cervical cancer screening**

There are Still Many Unanswered Questions

Vaccine Performance

- Duration of protection/boosting requirements
- Alternative vaccination schedules/doses/adjuvant
- Immunogenicity and Efficacy in Males

Immunological Mechanisms of Protection/Failure

- Correlates of Protection/Effector mechanisms (neutralizing antibodies)
- Determinants of long-term protection (B/T-cell memory)
- Epitopes
- Surrogates for evaluation of second generation vaccines

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For additional questions:

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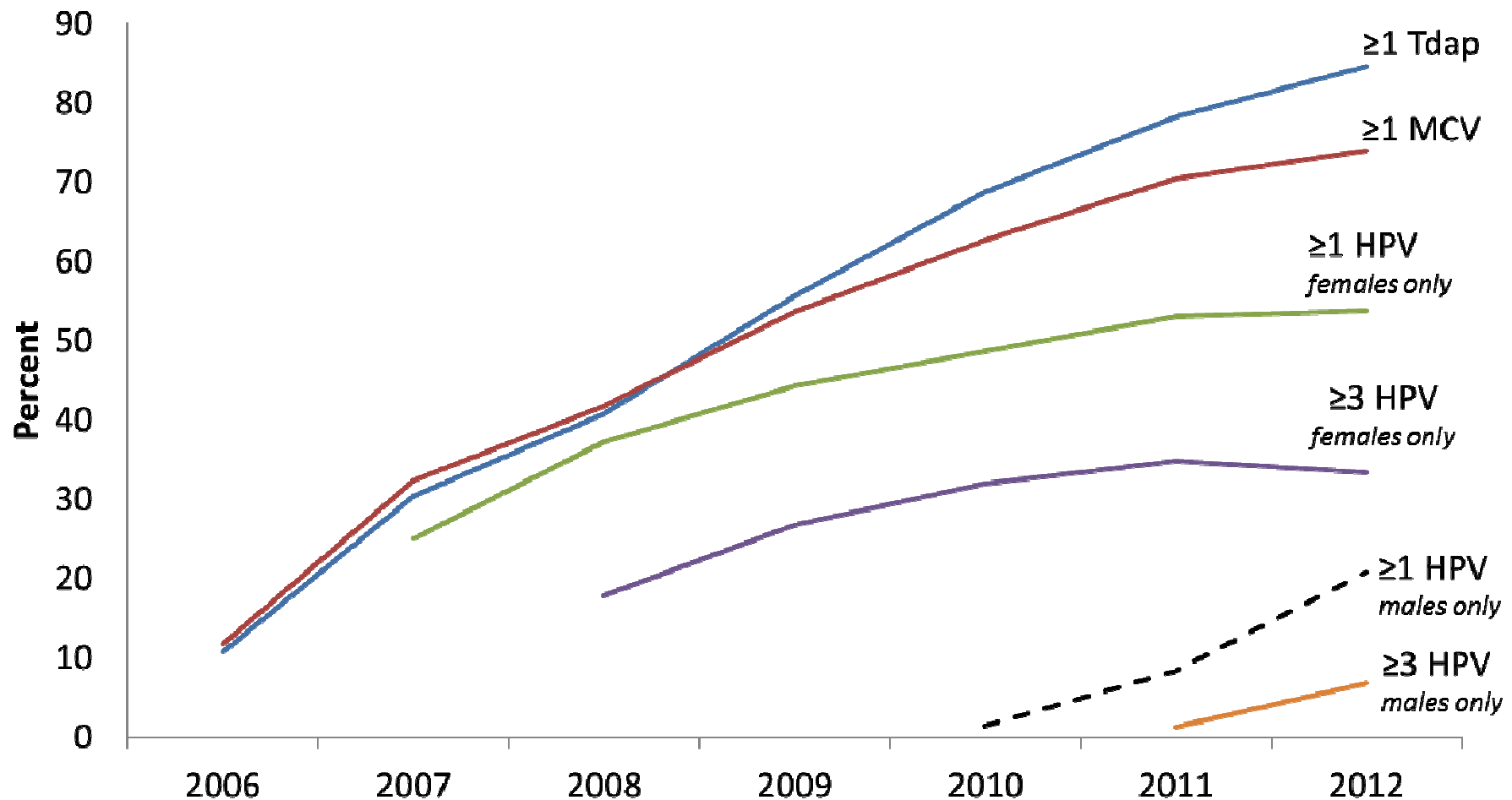
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Adolescent Vaccine (13-17 Years Old), United States, 2006-2012

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Centers for Disease Control and Prevention. National and State Vaccination Coverage Among Adolescents Aged 13–17 Years — United States, 2012. *MMWR*. 2013;62(34):685-693; NIS-Teen