Prophylactic HPV Vaccines

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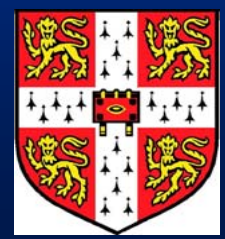
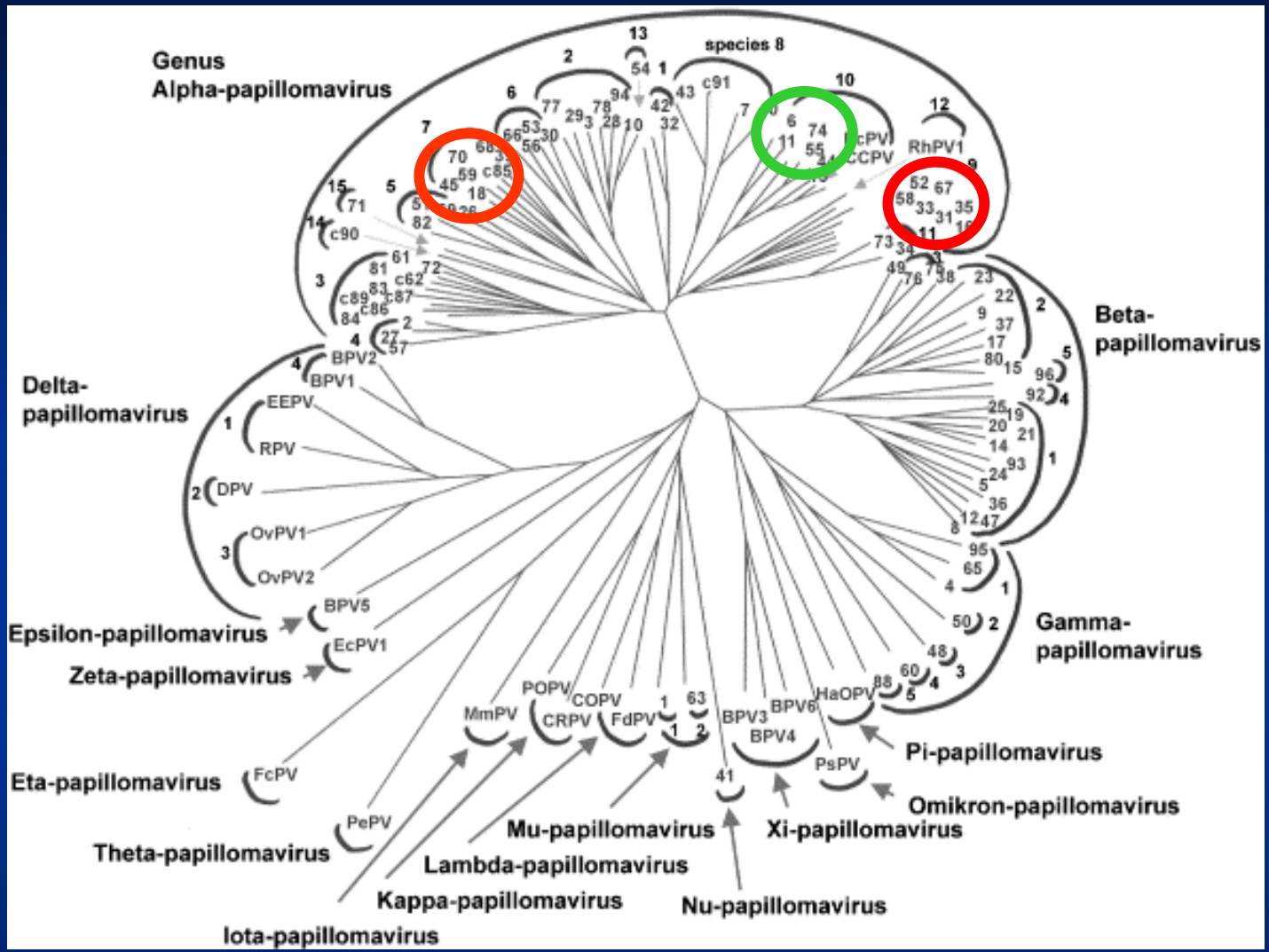




8kb double stranded DNA viruses, absolutely host and tissue specific,
Can't grow virus in tissue culture
Classified by genotype not serotype

Benign Mucosal HPV-Associated Disease

Laryngeal papillomas

HPV 6, 11

Condylomata acuminata

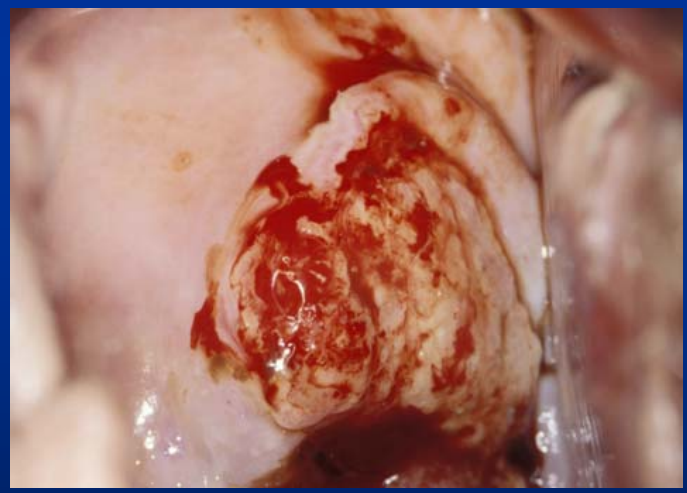
HPV 6, 11

Neoplastic HPV-Associated Genital Disease

Anogenital cancer and AIN

HPV 16, 18

Invasive cervical cancer and CIN



HPV 16, 31, 33, 35, 52, 58,
HPV 18, 39, 45, 59
HPV 56, 66. HPV 51

VIN (Vulval intra-epithelial neoplasia) and Vulval cancer

HPV 16,31, 33

ALL WORLD REGIONS COMBINED

WOMEN > 15: 2,013,133,000

N CASES per year: 469,723

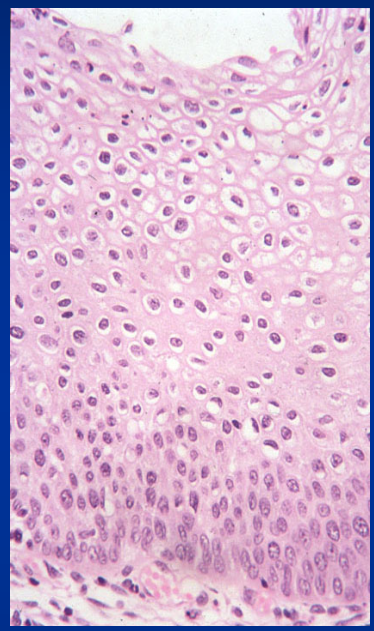
Infection with one of the high risk genital HPVs is the major risk factor for cervical cancer

- HrHPV DNA sequences are detected in 90-100% of cancers
- HrHPV DNA sequences are detected in 90% of high grade CIN or SIL
- Case control studies – OR's > 100
- Prospective studies – HrHPV infection causes CIN
- HrHPVs immortalise primary genital keratinocytes

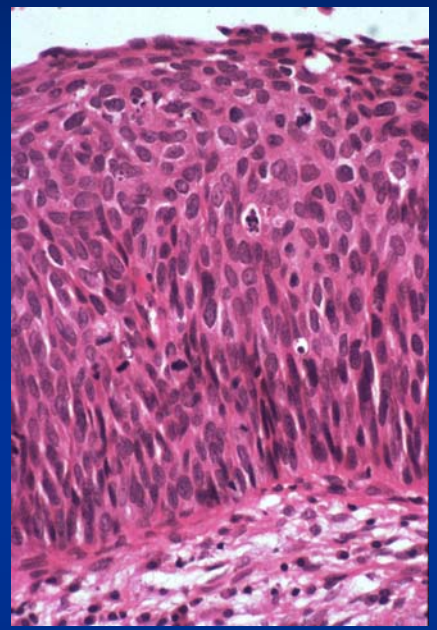
cervical intra-epithelial neoplasia-CIN

Normal

CIN 1



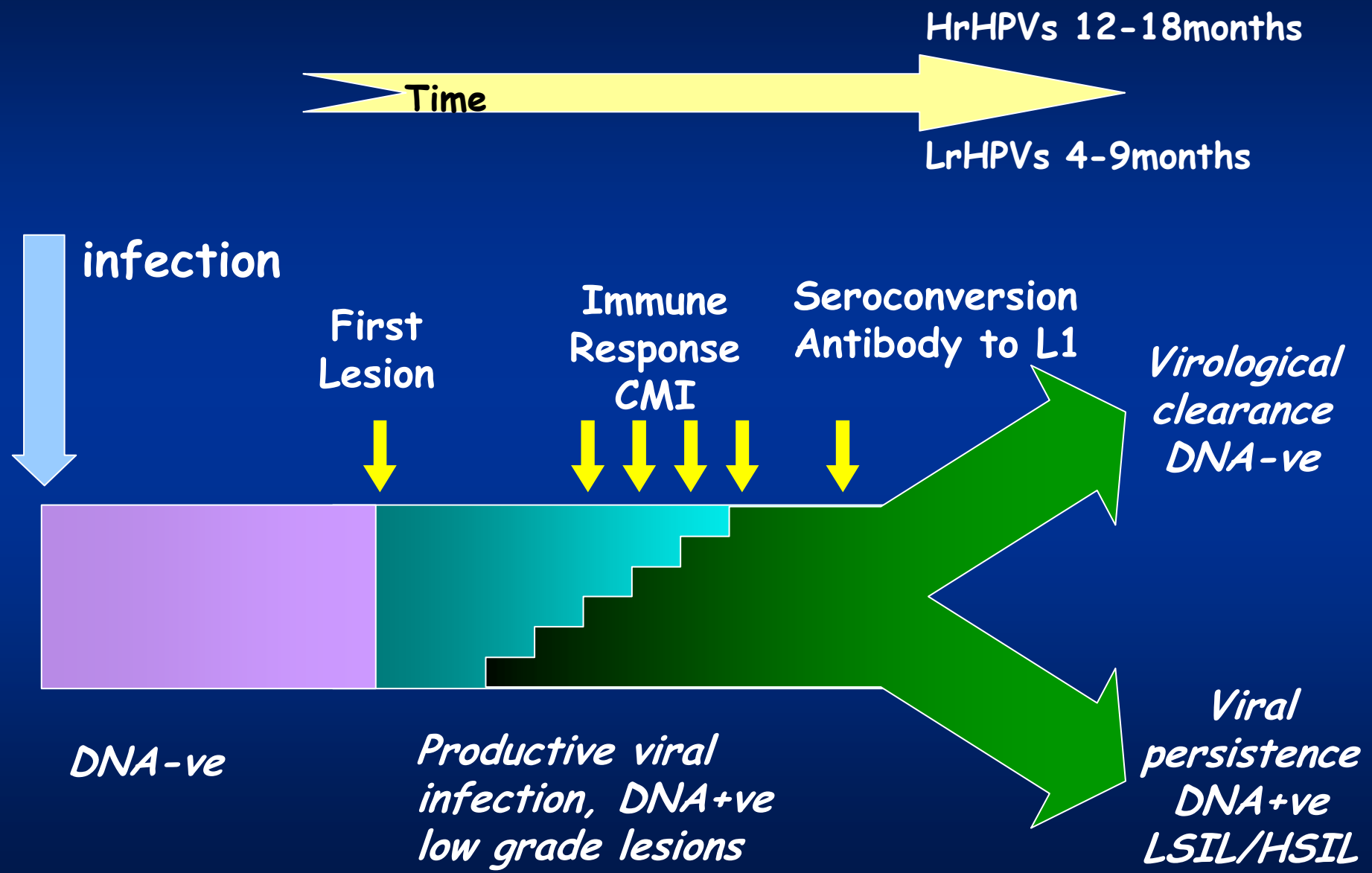
CIN 3



Transient genital HPV infections very common in young sexually active women
Most are subclinical and resolve
Most lesions are low grade CIN 1 and most resolve

A minority of women develop persistent infections with focally high levels of DNA
Some persistent infections with hrHPVs progress to CIN2/3
Some CIN2/3 progress to invasive carcinoma

Natural Course of Genital HPV Infection



Detectable Serum Antibodies to HPV: Limitations as Marker of Infection or Natural Immunity

- Antibody responses to HPV infection slow and weak and vary with HPV type[1]
  - In a study of 588 women with HPV 16, 18, and 6 infections, median time to seroconversion was ~12 months after incident infection.
  - Did not occur in all women
  - Only 54%–69% seroconverted within 18 months of incident infection.

1. Carter JJ, Koutsky LA, Hughes JP, et al. *J Infect Dis*. 2000;181:1911–1999.

Why are antibody responses so poor in natural HPV infections?

No viraemia

HPV does not lyse keratinocytes

- no inflammation
- no pro-inflammatory cytokines
- poor activation of Langerhans cells and stromal dendritic cells

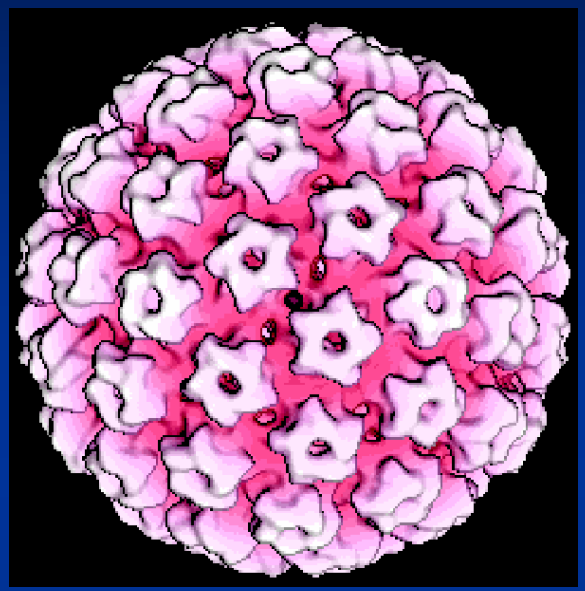
Free virus particles are shed from mucosal surfaces with poor exposure to APC

Why might vaccines generating neutralising antibody be effective prophylactically ?

Systemic immunisation with infectious CRPV

- did not induce visible papillomas
- generated serum neutralising antibody
- Immunised rabbits were protected against viral challenge

Shope RE 1937 Immunisation of rabbits to infectious papillomatosis J Exp Med 65 607-24

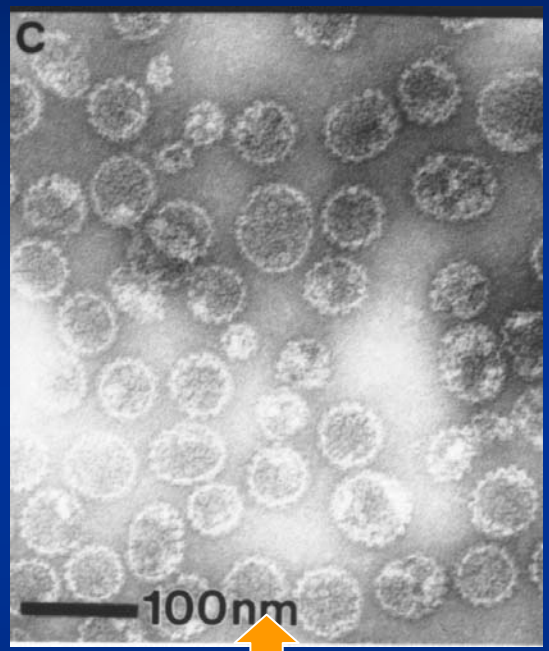


- Neutralising antibodies are directed against the L1 capsid protein

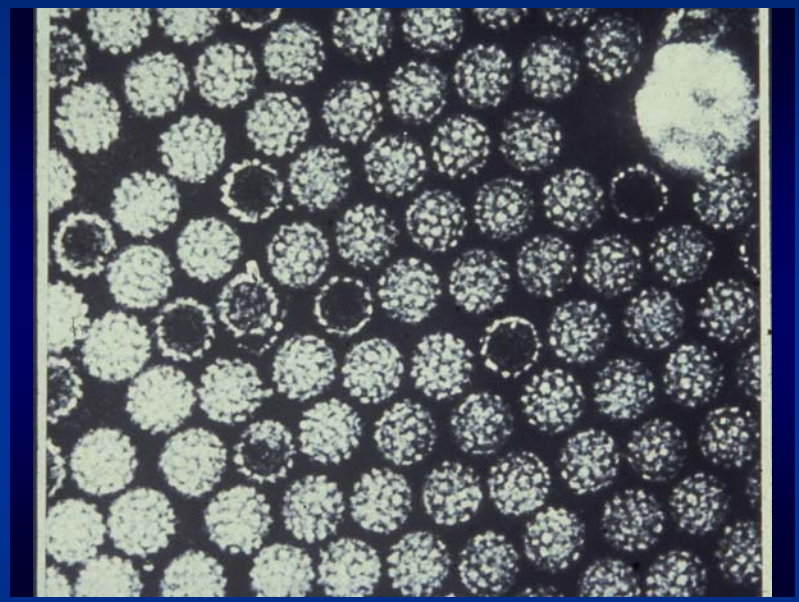
- Generation of neutralising antibody requires the tertiary or native structure of the protein

- these viruses cannot be grown in bulk in tissue culture

HPV 16 L1 VLPs -
Virus like particles



Virions



Express the L1 gene in a suitable vector (yeast, baculo-virus), the protein self assembles into a macromolecular structure – a virus like particle - that is geometrically and antigenically almost identical to the native virion

Vaccine profiles

	HPV 16/18 vaccine Cervarix	HPV 6/11/16/18 vaccine Gardasil
Manufacturer	GlaxoSmithKline	MSD
Volume	Per dose 0.5 mL	Per dose 0.5 mL
Adjuvant	AS04: $Al(OH)_3$ 500 μg MPL® 50 μg	Aluminium salt 225 μg
Antigens	L1 HPV 16 20 μg L1 HPV 18 20 μg	L1 HPV 6 20 μg L1 HPV 11 40 μg L1 HPV 16 40 μg L1 HPV 18 20 μg
Expression system	Hi-5 Baculovirus	Yeast
Schedule	Intramuscular 0, 1, 6 mths	Intramuscular 0, 2, 6 mths

Licence application made

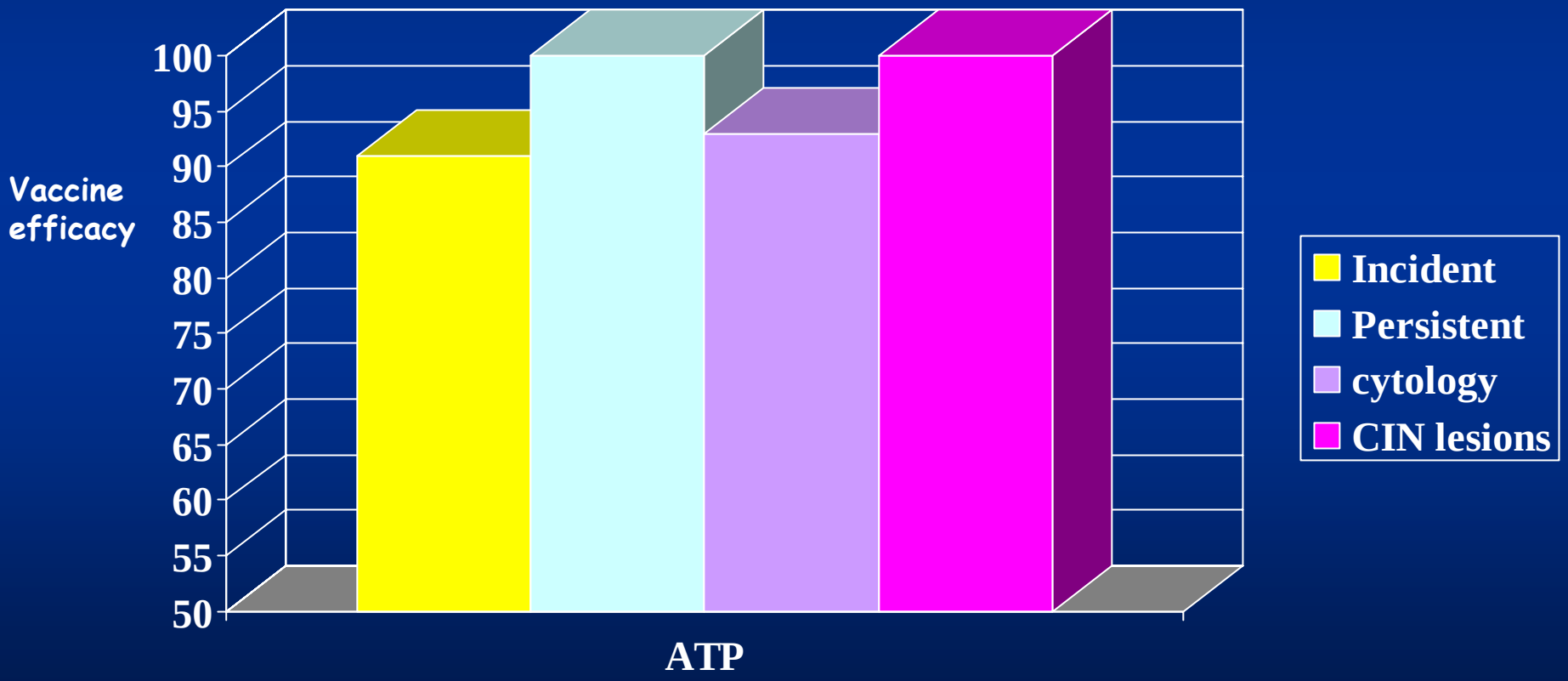
licensed

Bivalent Vaccine

Phase II Data

Efficacy data (HPV-001) Cervarix
HPV 16 and/or 18 Cervical Protection

Prevention of HPV-16/18 related infection & lesions



D. Harper *et al*, Lancet, 2004, 364 : 1757-65

Quadrivalent vaccine

Phase III Data

HPV 16/18-Related Cervical Cancer

HPV-Naïve MITT Population

Endpoint	HPV vaccine cases n=9342	Placebo cases n=9400	% Efficacy	95% C.I
HPV 16/18-related CIN 3 or AIS	0	52	100	93, 100
·HPV 16/18-related CIN3	0	47	100	92, 100
·HPV 16/18-related AIS	0	9	100	49, 100

Mean follow up 2 years

Subjects are counted once per applicable row.

www.fda.gov/ohrms/dockets/ac/06/slides/2006-4222s-index.htm

Gardasil efficacy against external genital disease

HPV type	Vaccine cases:2261	Placebo cases:2279
HPV 6	0	23
HPV 11	0	10
HPV 16	0	10
HPV 18	0	3

Mean 20 months follow up

www.fda.gov/ohrms/dockets/ac/06/slides/2006-4222s-index.htm

Some frequently asked questions

Immune correlates and duration of protection

Is there cross protection

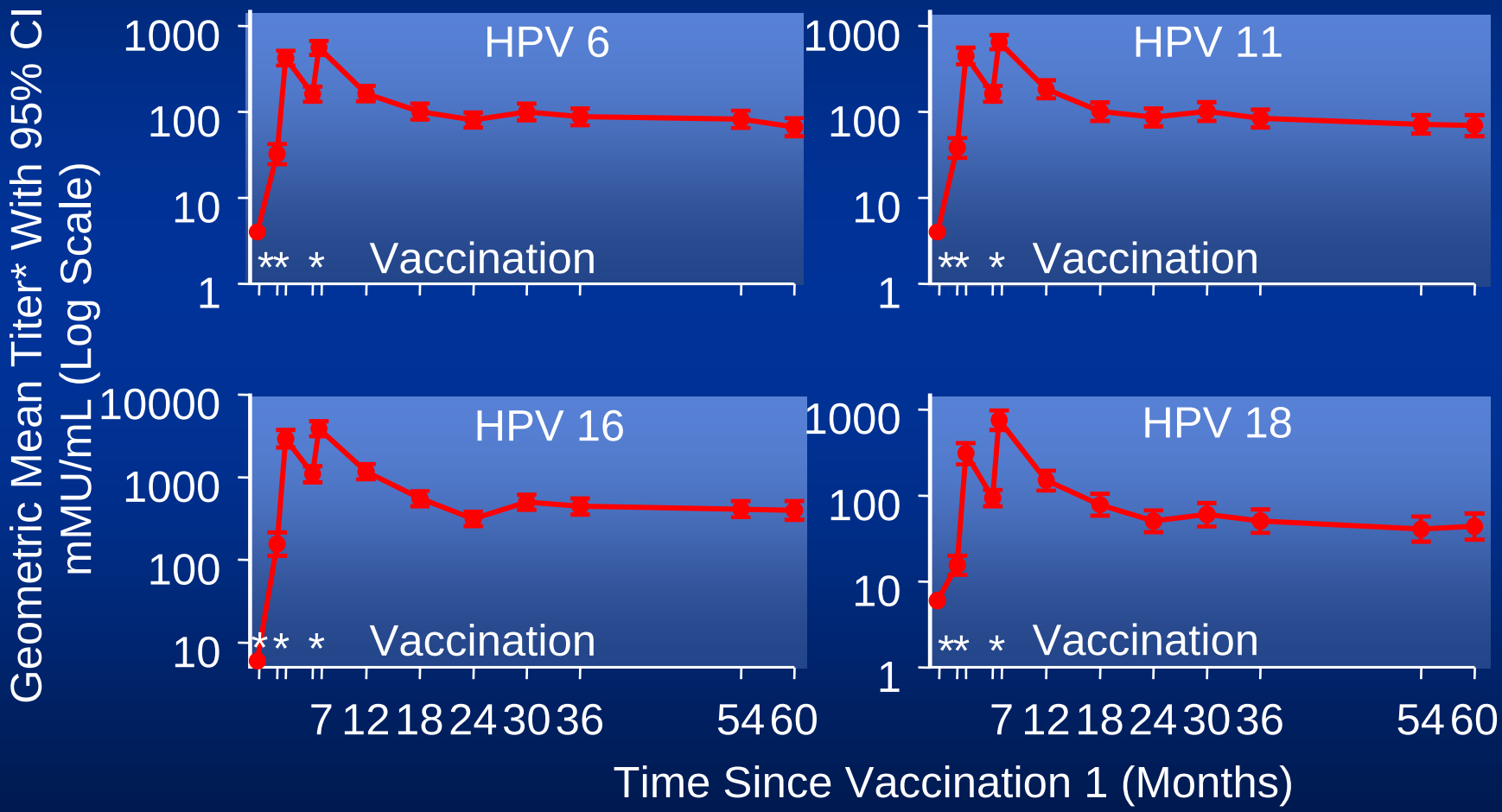
Who should we immunise

Must the vaccine be given pre-exposure to virus

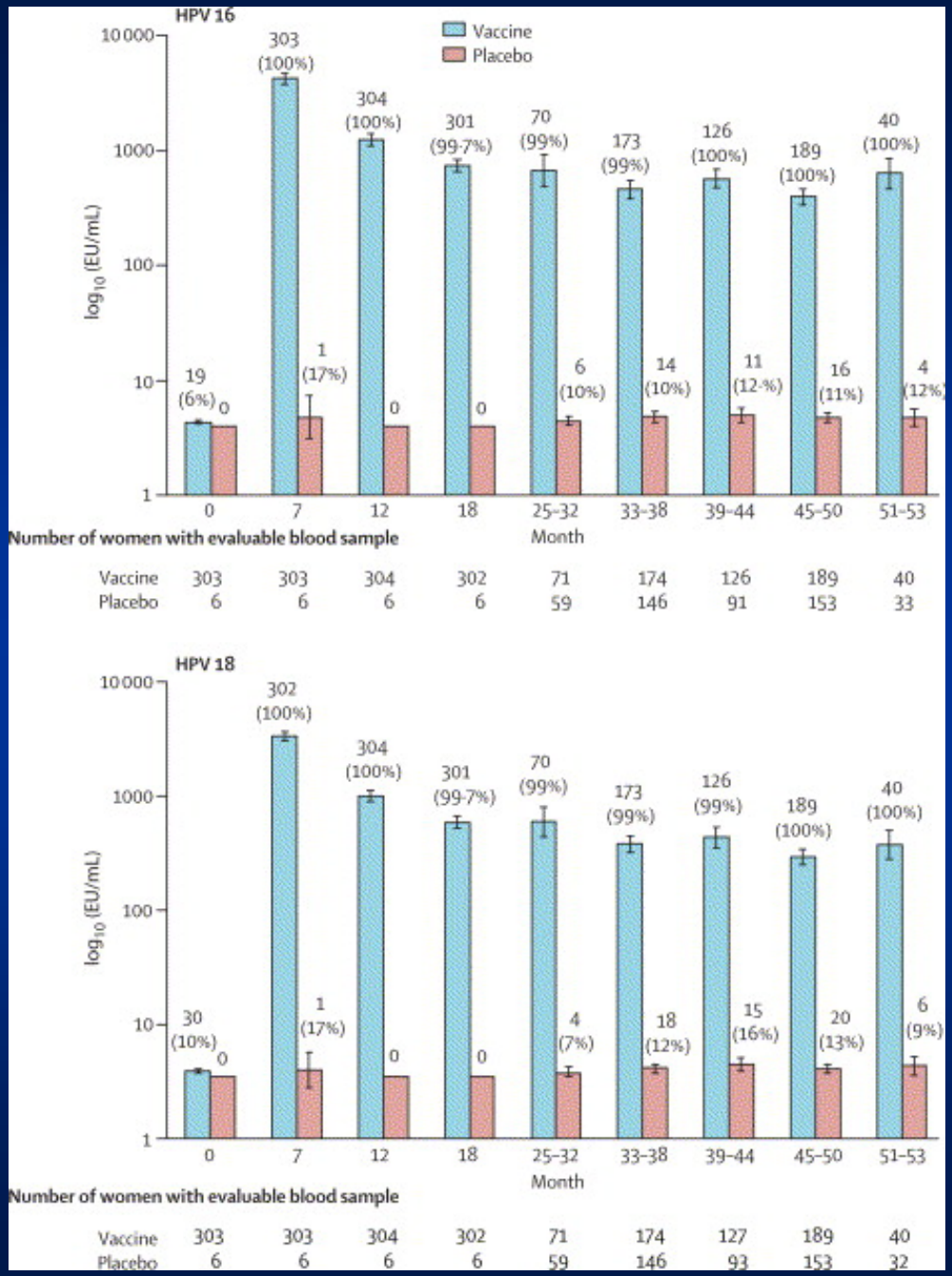
If we control types that are currently the most common, will other rarer types take their place

Quadrivalent HPV Vaccine
Anti-HPV Immunogenicity, Neutralizing Ab

In a double-blind, placebo-controlled, dose-ranging study of quadrivalent HPV (types 6, 11, 16, 18) L1 VLP vaccine.



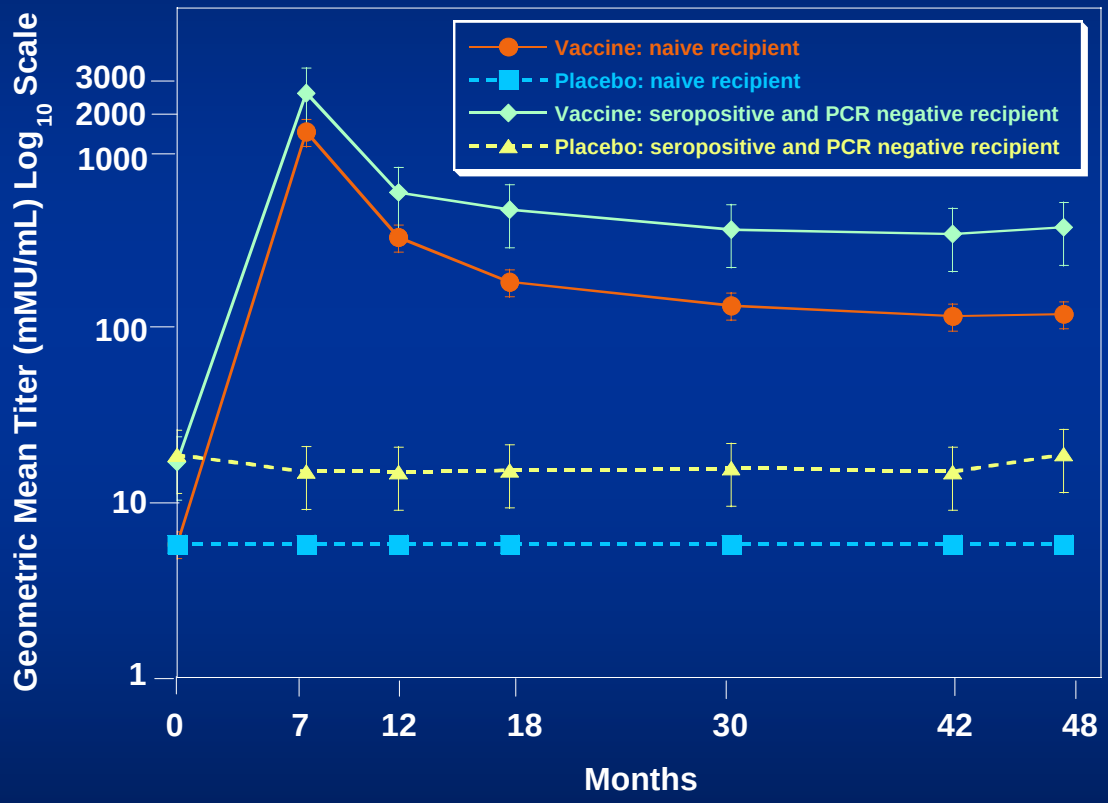
*cLIA=competitive Luminex immunoassay



Bivalent vaccine 5 year antibody concentration in vaccinees and placebos

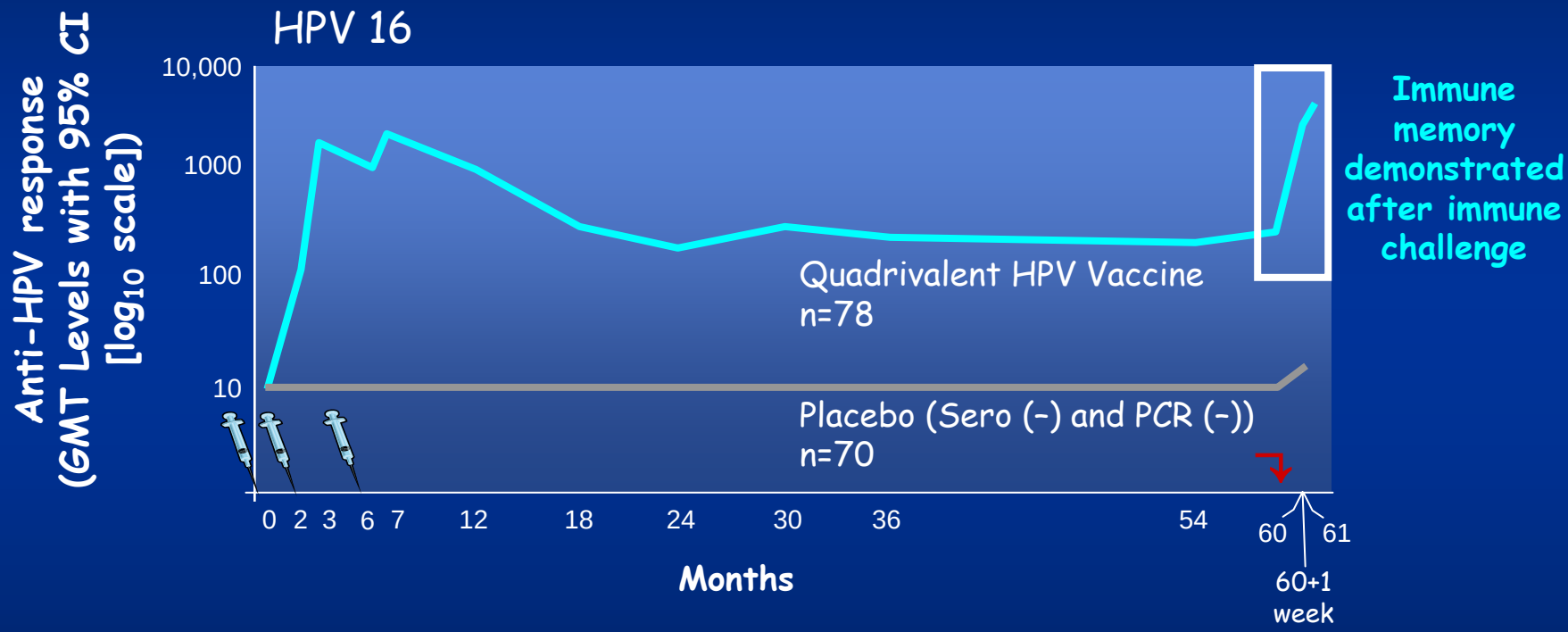
Harper et al 2006 Lancet 367 1247-55

Quadrivalent HPV Vaccine Yields Higher Neutralizing Anti-HPV Antibodies in Baseline Seropositive Subjects



- These results suggest that women who were baseline anti-HPV positive had developed a booster response to the vaccination.

Demonstration of Immune Memory with an Antigen Challenge at Month 60[1]



Vaccination on day 0, at two and six months
Immune challenge at 60 months

- **Similar results seen with HPV 18, 6, and 11**

*In subjects naïve to the relevant HPV type from day 1 through month 60

1. Data on file, MSD.

Is there cross-protection?

Some suggestion for cross-protection against infection against HPV 45 and 31 after vaccination with Cervarix

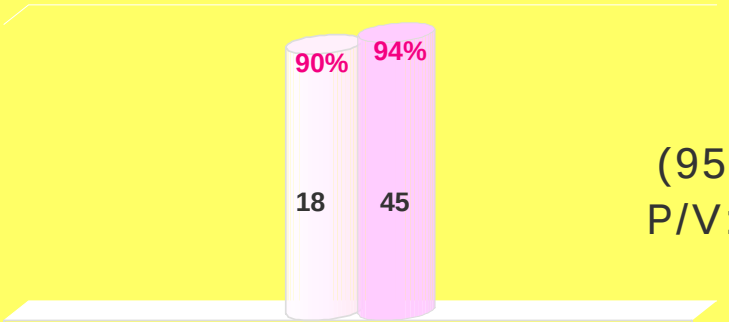
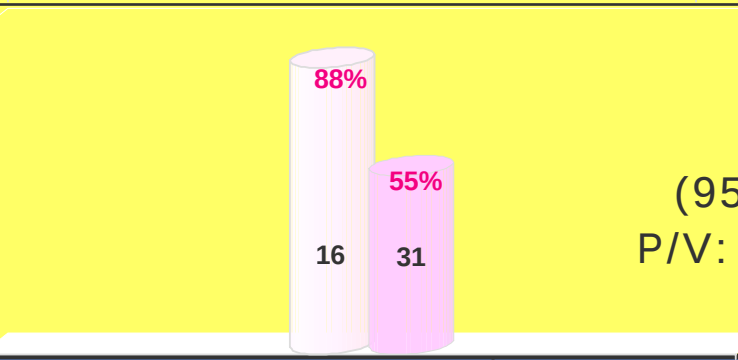
Harper etal Lancet April 6th 2006

Cross reacting and cross-neutralising antibodies to HPV 45,31,58 and 52 generated after immunisation with Gardasil

Titres of these cross-reacting antibodies are 1-2 logs lower than the dominant type specific neutralising antibody

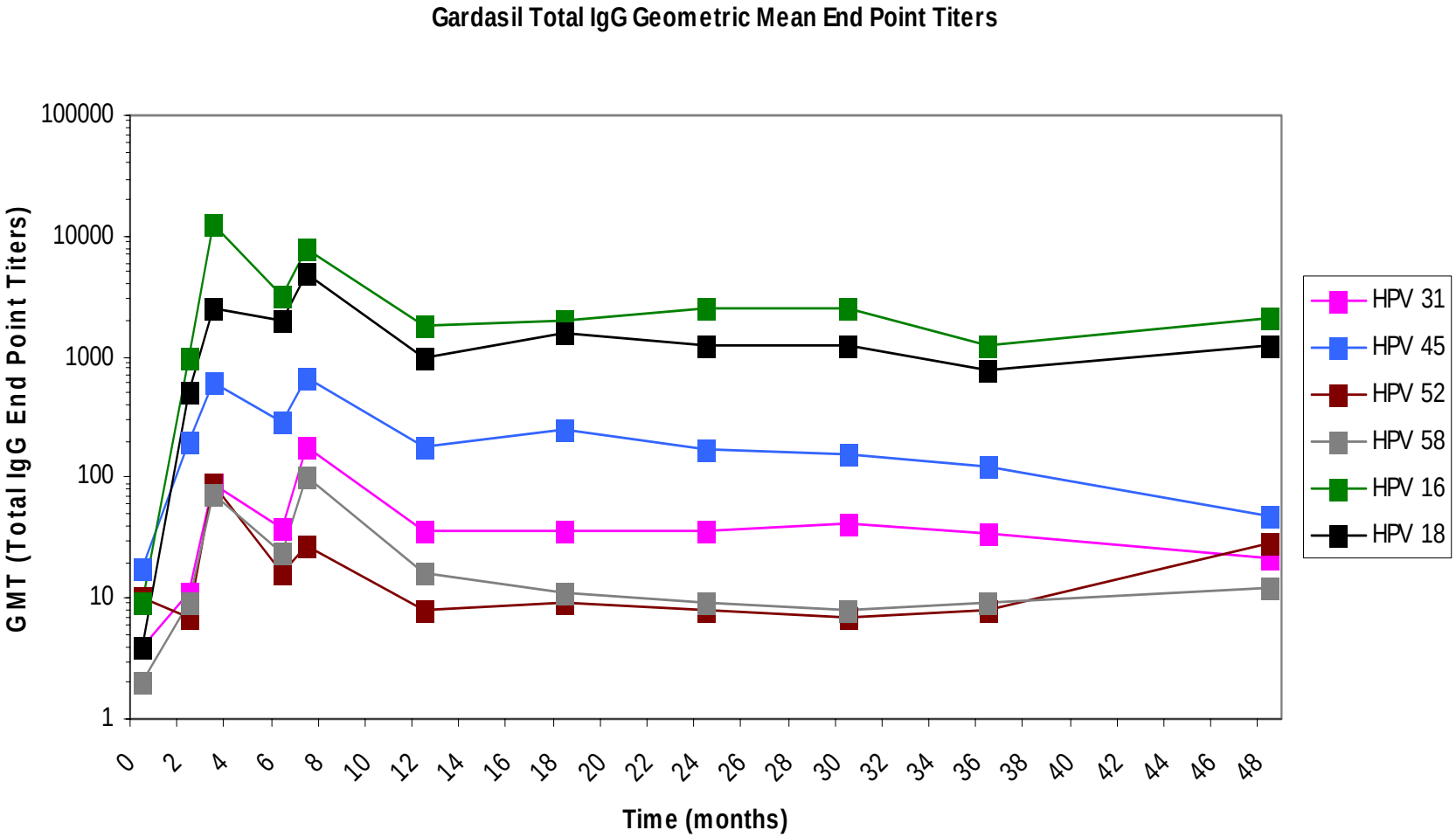
Smith JF et al IPV Prague Sept 3 2006
Abstract PL 1-6

Prevention of Other High Risk Incident HPV Infections

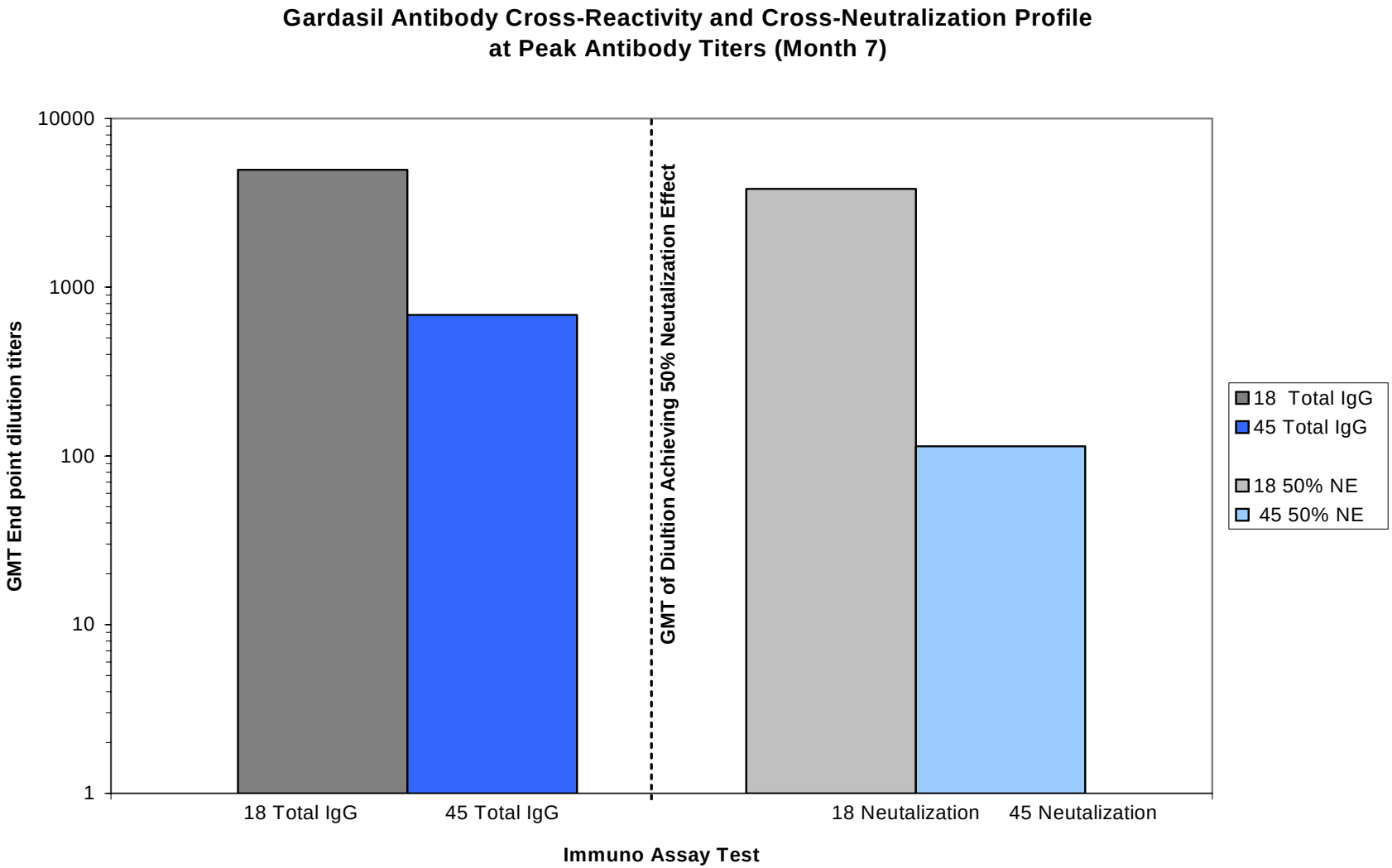
ITT Group	Bivalent Vaccine Cross Protection
HPV 45 (related HPV 18)	 **94%** (95% CI: 63-100 P/V: 17/1 events)
HPV 31 (related HPV 16)	 **55%** (95% CI: 12-78 P/V: 30/14 events)

Courtesy Dr Diane Harper

Evidence of Cross-Reacting Antibodies - GARDASIL™

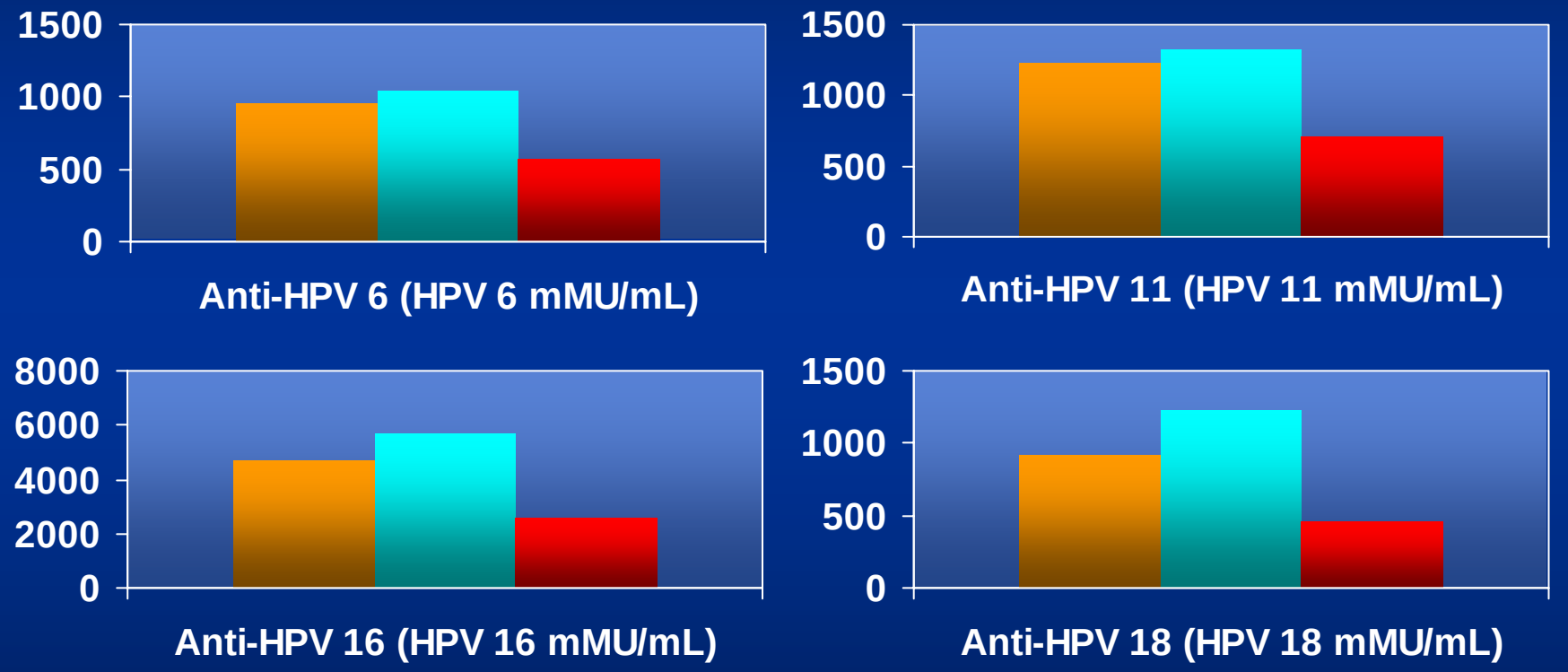


Evidence of Cross-Neutralization GARDASIL™



Quadrivalent HPV Vaccine Phase III Adolescent Immunogenicity Study

Neutralizing Anti-HPV GMTs at Month 7*

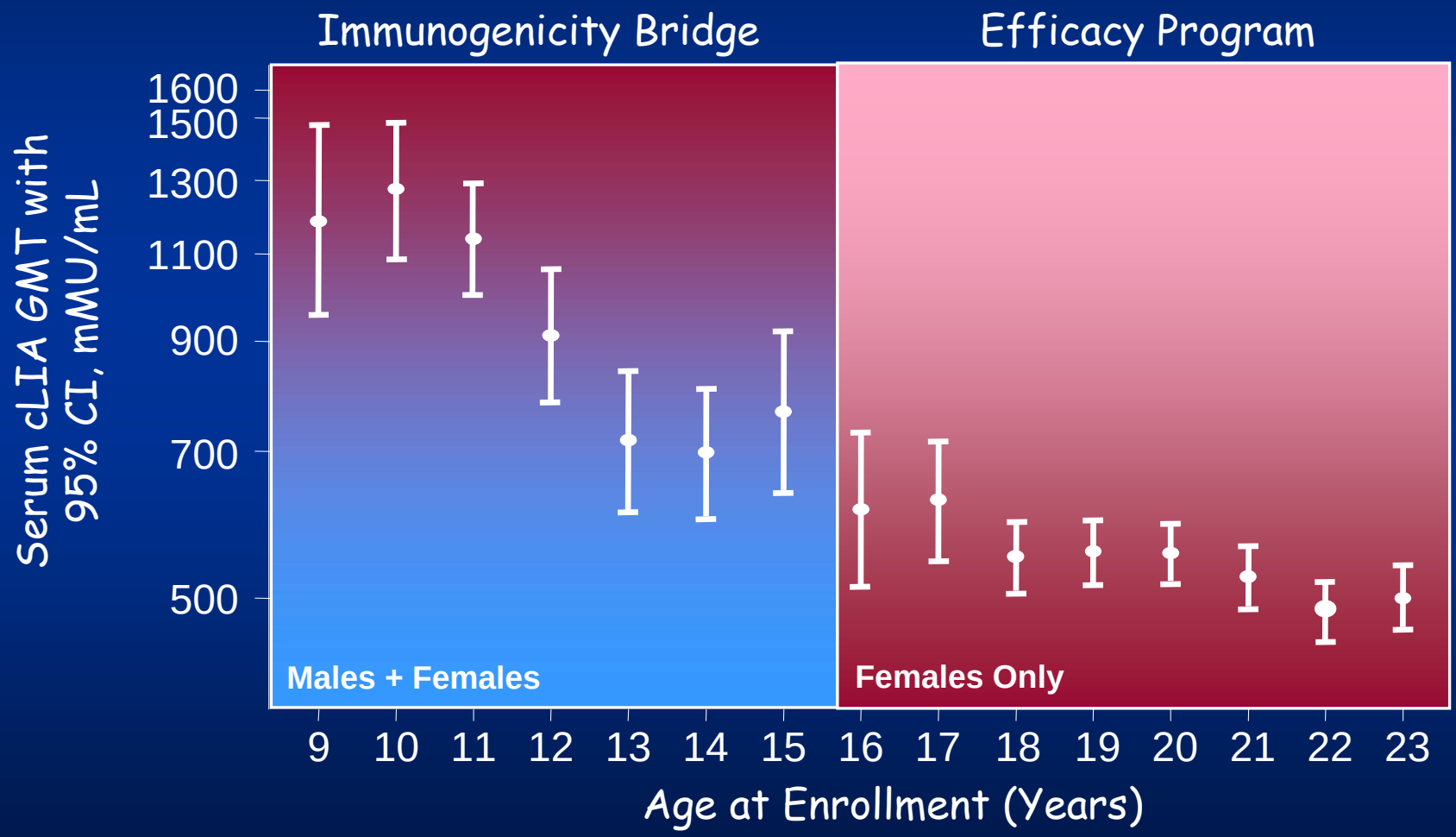


*GMT = geometric mean titers

1. Block SL, Nolan T, Sattler C, et al. *Pediatrics.* 2006: in press.

Age Specific Neutralizing HPV-6 Antibodies 1 Month Post-Vaccination[1]

PPE population*
Neutralizing anti-HPV 6 GMTs at month 7



*Inclusive of five study protocols; all GMTs measured using cLIA

1. Data on file, MSD.

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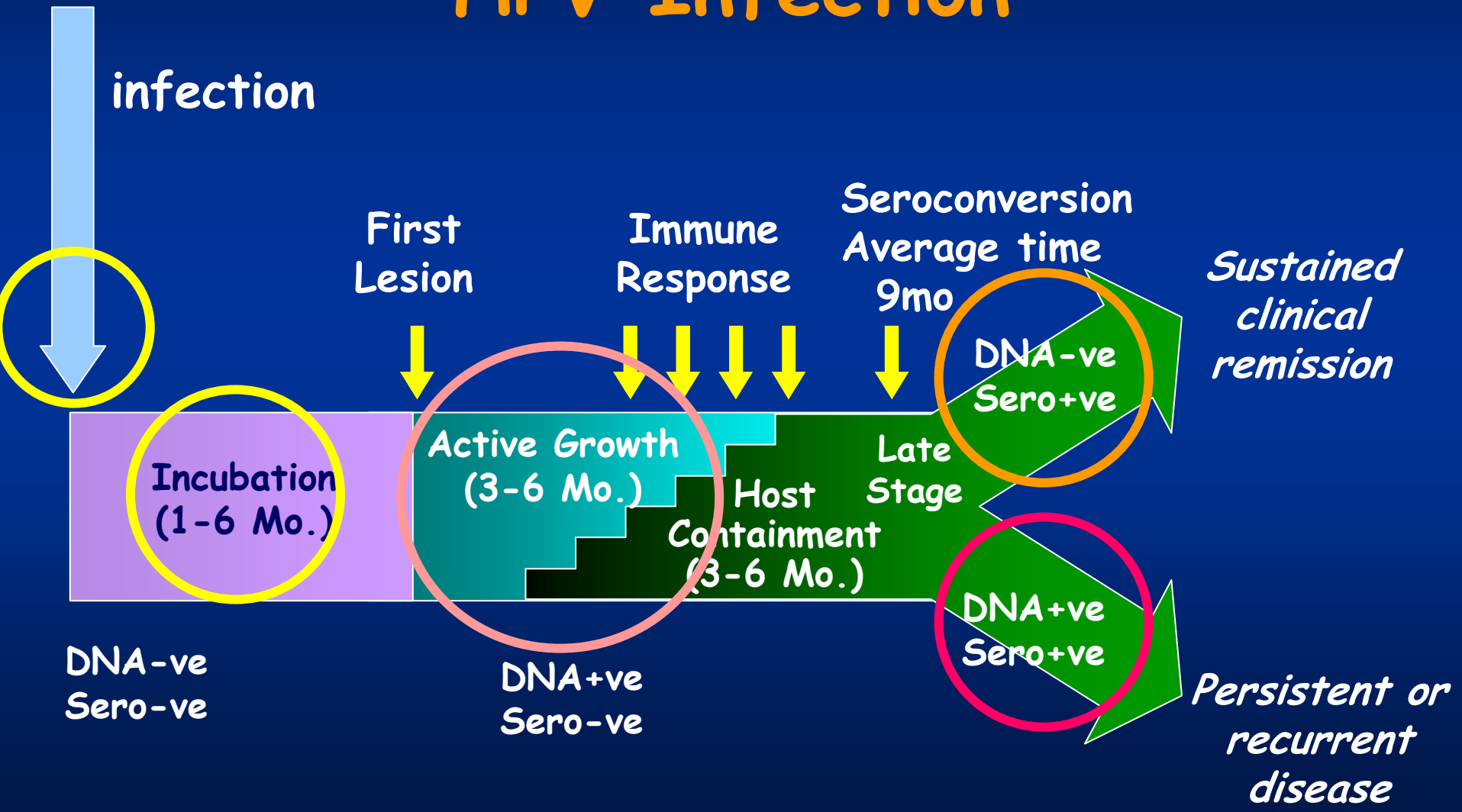
Natural Course of Genital HPV Infection



Prophylactic HPV L1 VLP vaccines

Efficacy	>90% for persistent infection 100% for disease (5 years post vaccination) in subjects naïve for vaccine HPV types
Immunogenic	high antibody concentrations up to 1000x > than in natural HPV infection
Duration of protection	vaccine induced antibody levels maintained over 5 years
Safe	no vaccine related serious adverse events identified in the trials to date (70,000 women)