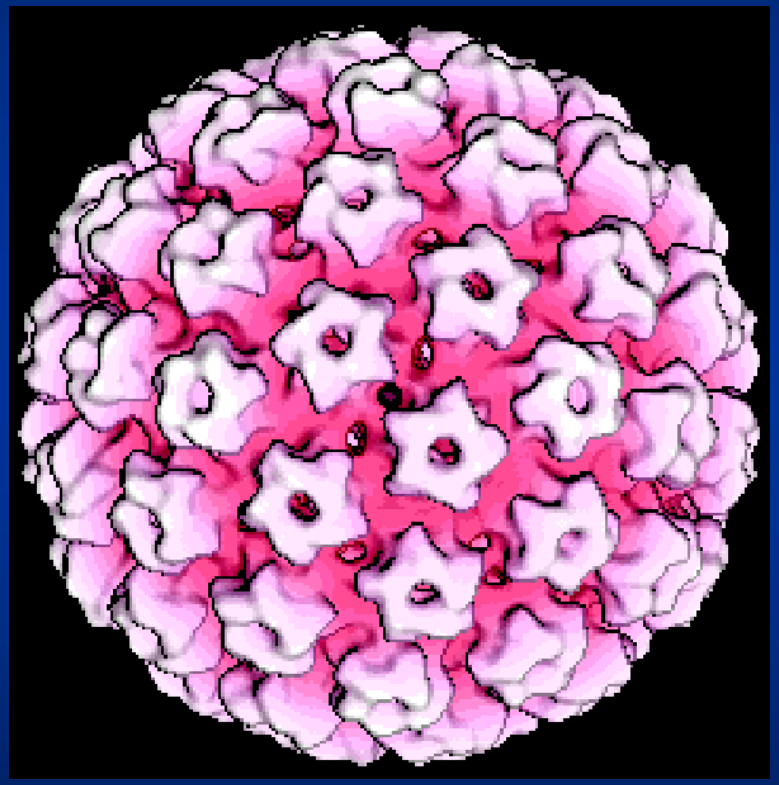
HPV VLP Vaccine Development and Impact

Margaret Stanley
Department of Pathology
Cambridge

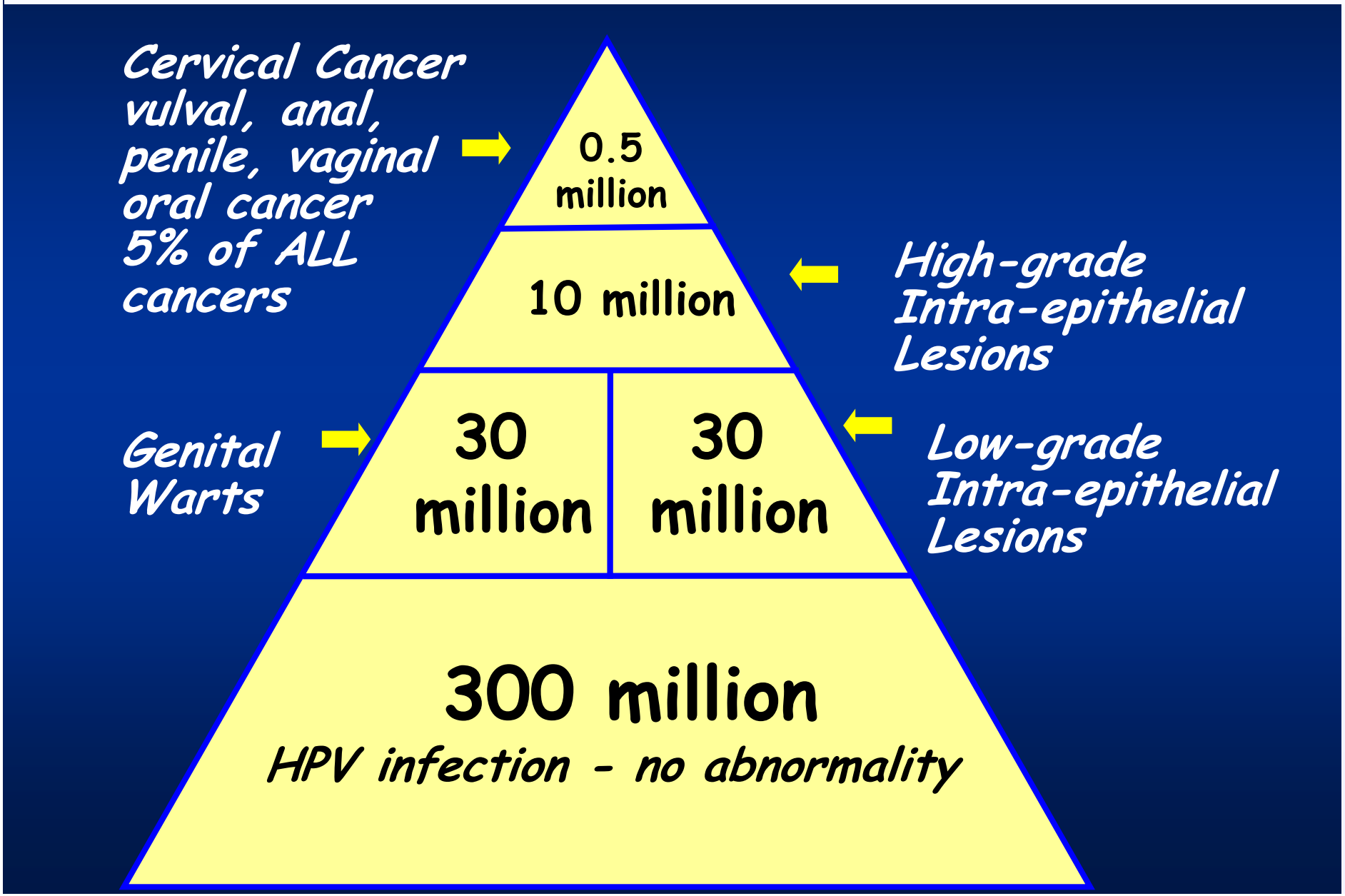
What is HPV?



- Non enveloped dsDNA virus
- Infectious cycle only in squamous epithelia
- Common virus with >100 types identified
- 30–40 infect the genital area of women and men
- 2 groups
  - low risk types causing warts
    HPV 6,11
  - high risk types causing cancer
    15 oncogenic types
    HPV 16,18 – most important

Burden of Disease

WORLDWIDE ESTIMATES ON THE BURDEN OF HPV INFECTION & RELATED GENITAL DISEASES IN WOMEN



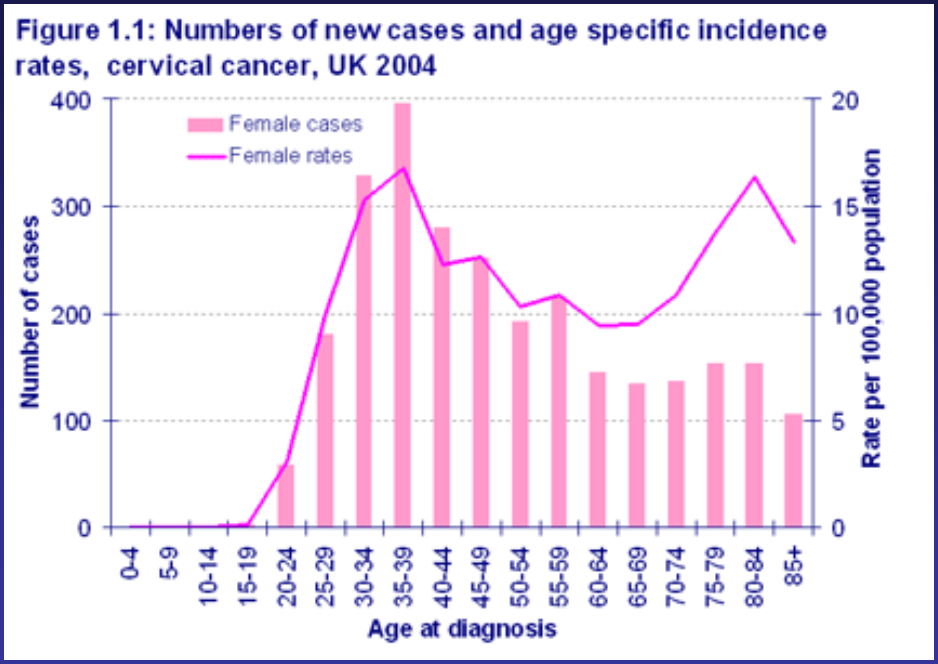
Global Burden of Cervical Cancer[a]

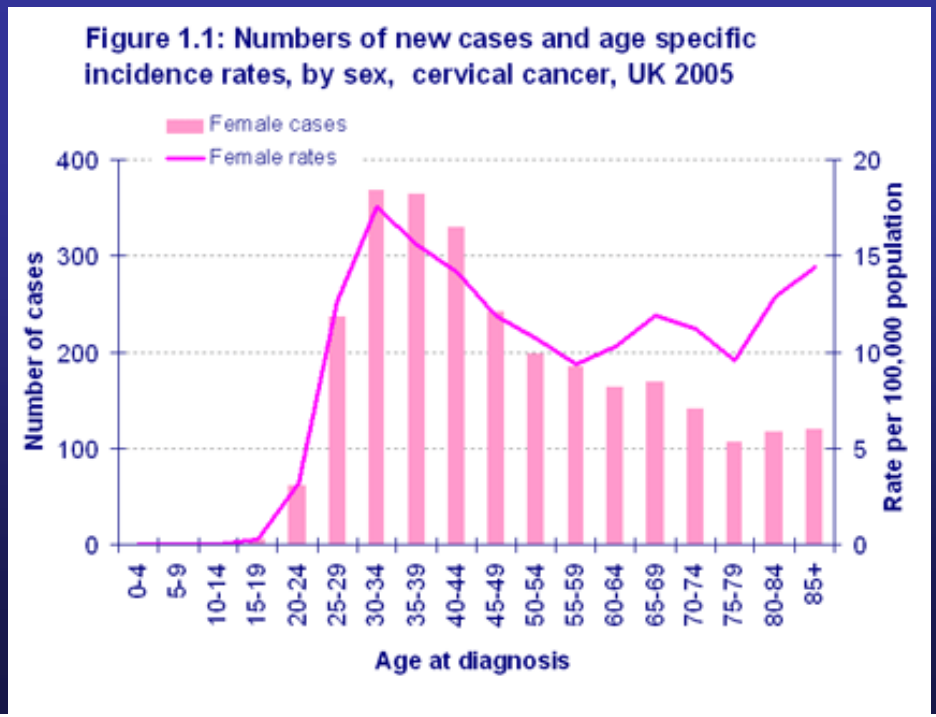
2008 estimated cervical cancer incidence[1]

- Total worldwide incidence[a] = **529,409**
  - More developed countries = **76,507**
  - Less developed countries = **452,902**
- Third to breast and colorectal cancer as the leading cause of cancer in women
- Fourth most common cause of overall female cancer-related mortality worldwide

[a]Incidence for Melanesia (724), Micronesia (24), and Polynesia (48) not shown on maps. More developed countries defined as North America, Japan, Europe, and Australia/New Zealand.

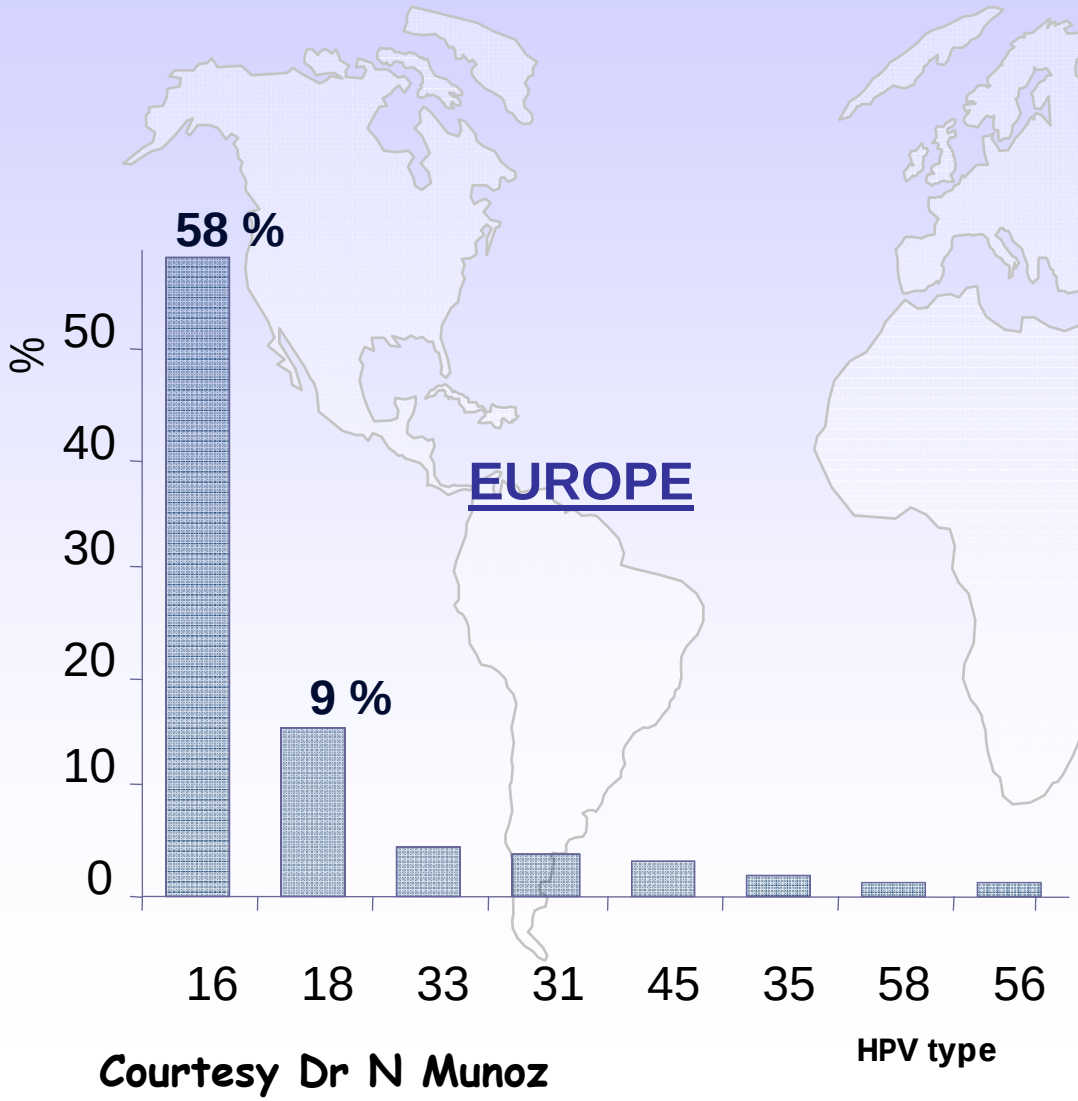
1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM. GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr

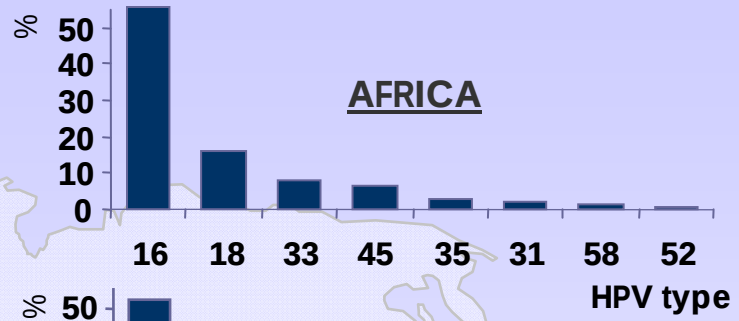


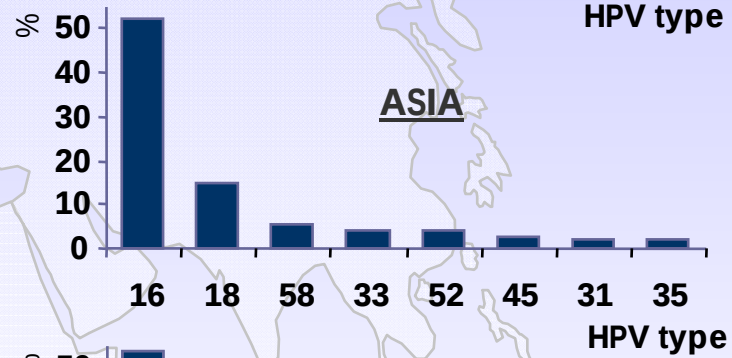


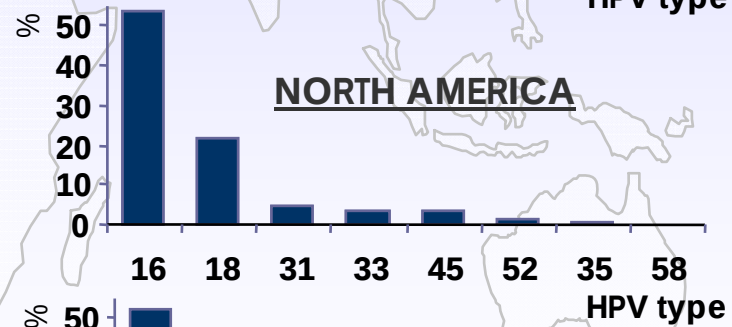
Screening has little impact on CaCx incidence in women under 35 years of age

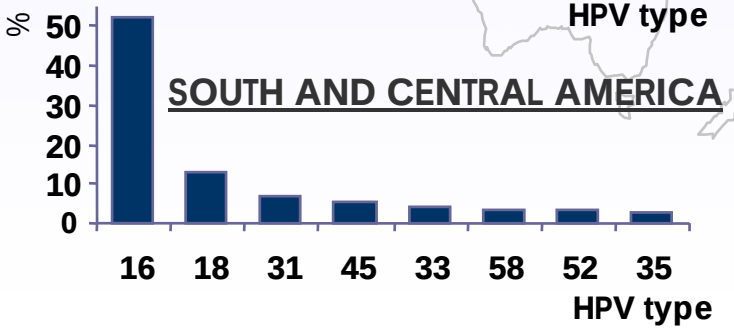
Contribution of HPV types to Cervical Cancer











SOURCE: SMITH JS ET AL. 2007

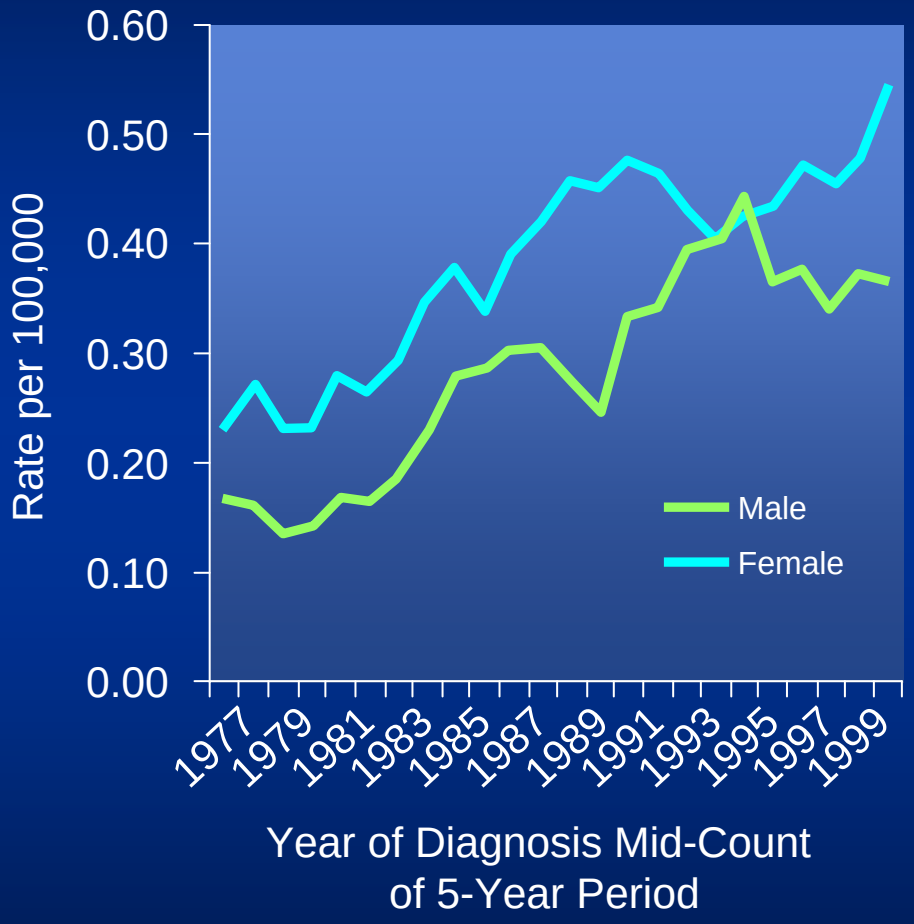
PREVALENCE OF HPV IN GENITAL CANCERS

	Vulvar cancer	VIN	Vaginal cancer	VAIN	Anal cancer	AIN
N of subjects	1873	1197	136	289	955	1280
HPV DNA	40.4 %	84.0 %	69.9 %	93.6 %	84.3 % male/female	92.7 %

De Vuyst H et al 2008
De Sanjose et al for the IARC Monograph

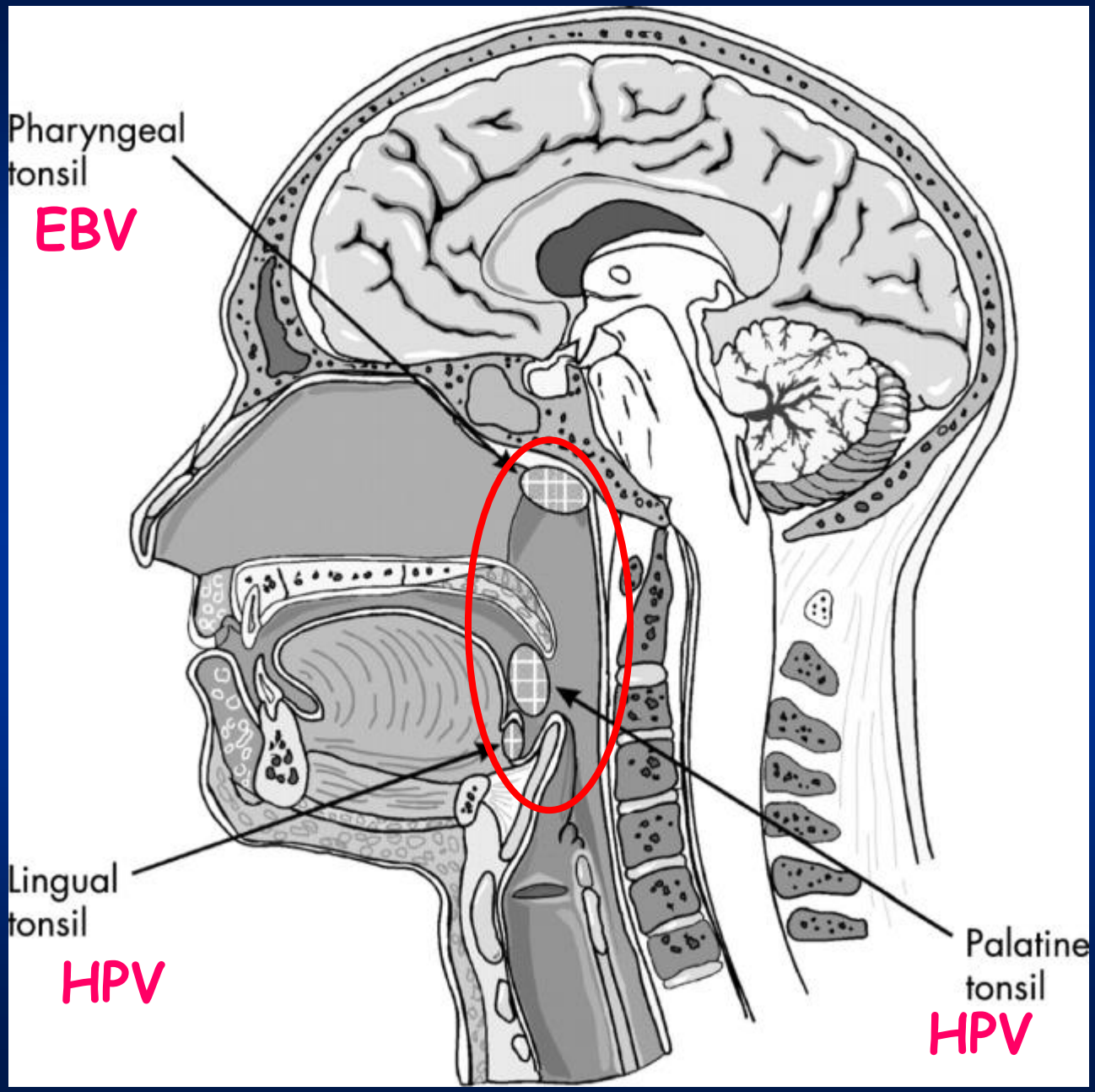
Increasing Incidence of Anal Cancer: Example of Scotland and England[1]

- Since the 1970s, the incidence of squamous anal carcinoma in Scotland has more than doubled in both sexes.
- Incidence rates in England from 1986 to 2003 also nearly doubled in both men and women.



Age-standardized incidence rates of squamous cell carcinoma of the anus by year of diagnosis (5-year moving averages) and sex; Scotland, 1975–2002.

1. Brewster DH et al. *Br J Cancer*. 2006;95:87–90.



Epithelium Covering Waldeyers Ring

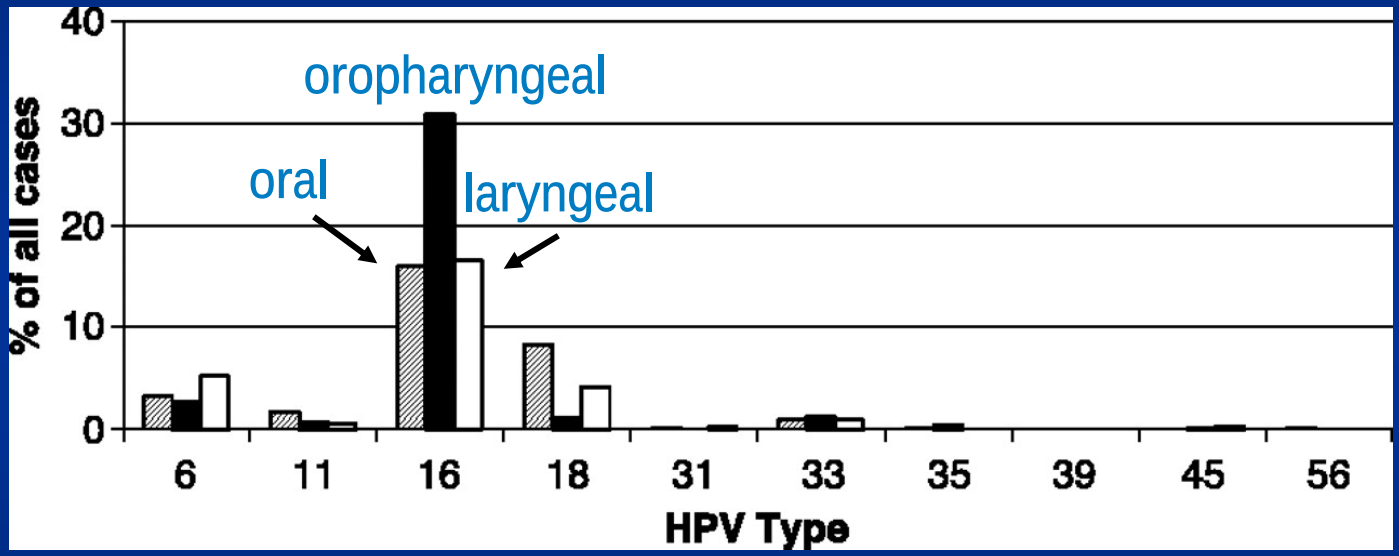
A viral target

HPV DNA in head and neck cancers

Anatomical Site	%age cancers with HPV DNA
Tonsillar Cancers	~60%[1]
Oropharyngeal Cancers	~35%[2]
Laryngeal Cancers	~25%[2]
Oral cavity	~25%[2]

1. Klussmann et al Med Microbiol Immuno 2003
2. Kreimer et al Cancer Epidemiology 2005

Figure 1. Type-specific prevalence of HPV in 2,642 oral cavity SCCs, 969 oropharyngeal SCCs, and 1,435 laryngeal SCCs

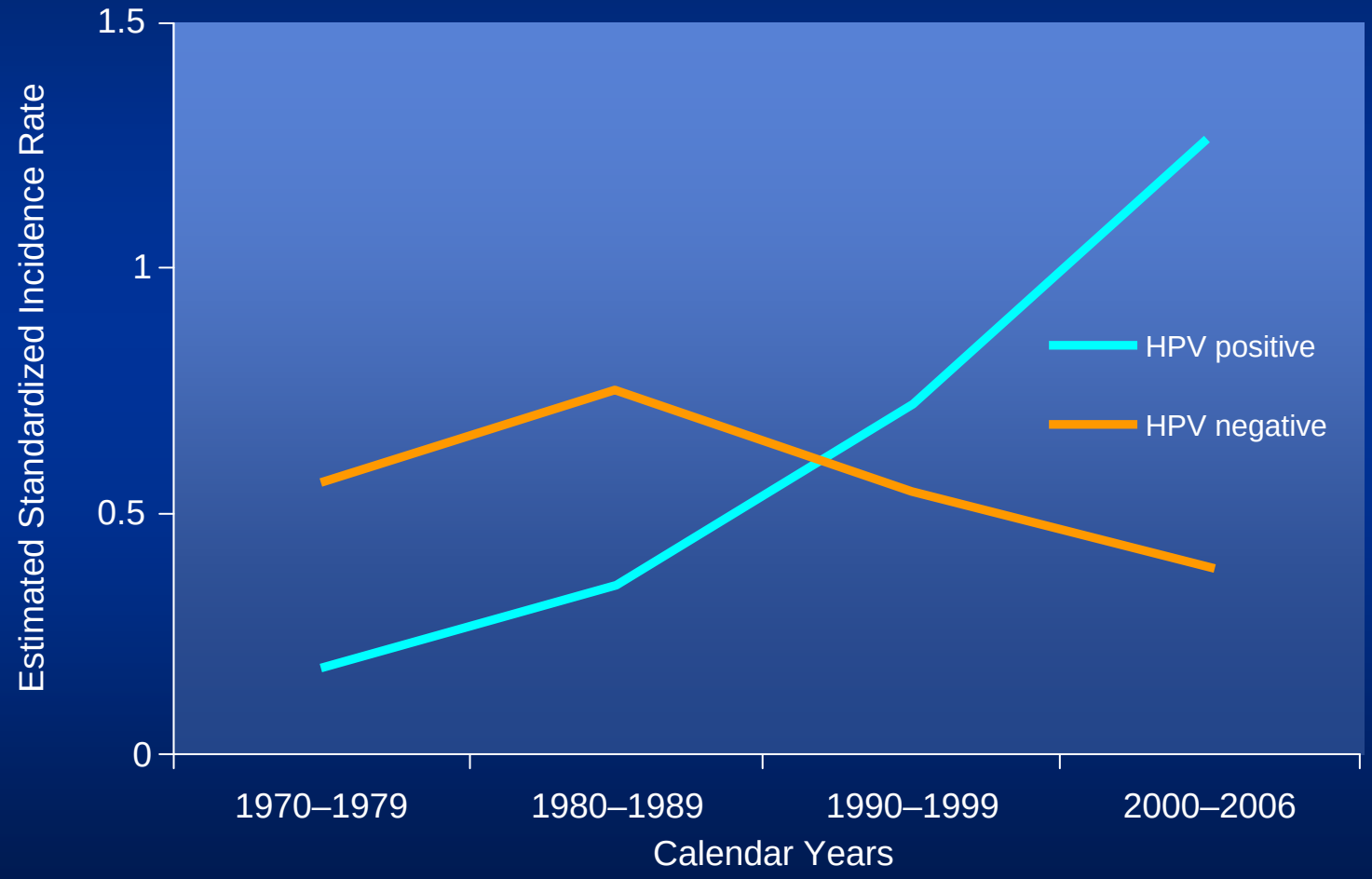


Kreimer, A. R. et al. Cancer Epidemiol Biomarkers Prev 2005;14:467-475

Cancer Epidemiology Biomarkers & Prevention
AACR

Increasing Incidence of HPV-Related Tonsillar Cancer in Sweden[1]

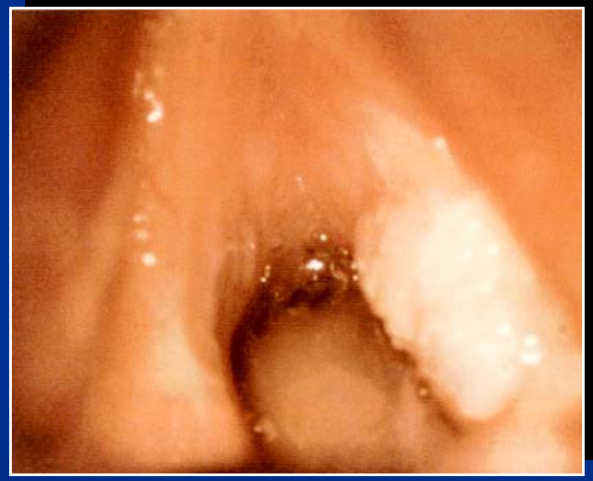
Study of all patients (N=120) diagnosed with tonsillar SCC in the County of Stockholm, Sweden, during 2003–2007



1. Näsman A et al. *Int J Cancer*. 2009;125:362–366.

Benign Mucosal HPV-Associated Disease

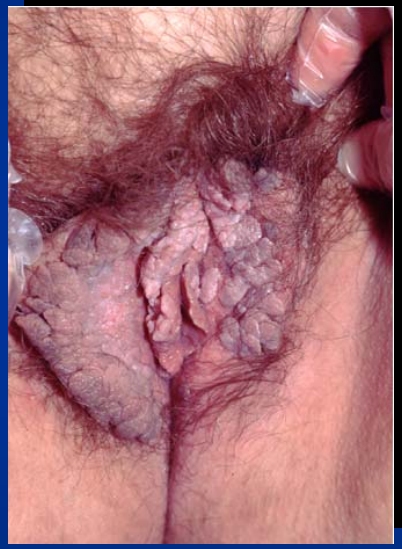
Laryngeal papillomas



HPV 6, 11

Rare: 4.3/100,000 children
Morbidity: >4-6 surgical interventions/child/annum
Mortality: 4-5/year in the UK

Genital warts



HPV 6, 11

Common: 93,000 new cases in 2009 in the UK
Costs: £20-30 million/year for management in GUM clinics

Incidence and Impact of RRP in Children and Adults

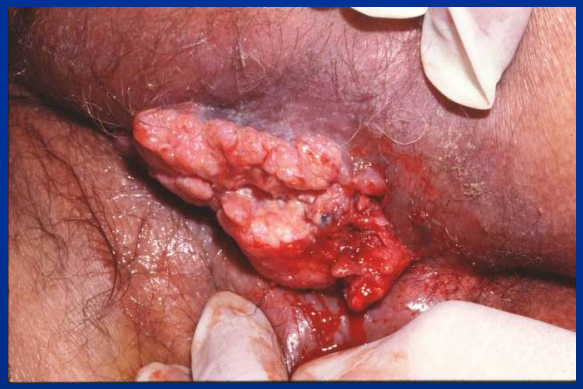
United States Cases	Childhood-Onset RRP (≤12 years at diagnosis)	Adult-Onset RRP (>12 years at diagnosis)
Most common age at diagnosis[1]	2 to 4 years	20 to 40 years
Cases[2] New/year Active	 2354 5970	 3623 9015
Surgical procedures/ year[2]	16,597	9284
Annual costs*,[2]	$109 million	$42 million

*In 1994 US dollars
CI = confidence interval

1. Larson DA, Derkay CS. Epidemiology of recurrent respiratory papillomatosis. *APMIS*. 2010;118:450-4. 2. Derkay CS. *Arch Otolaryngol Head Neck Surg*. 1995;121:1386–1391.

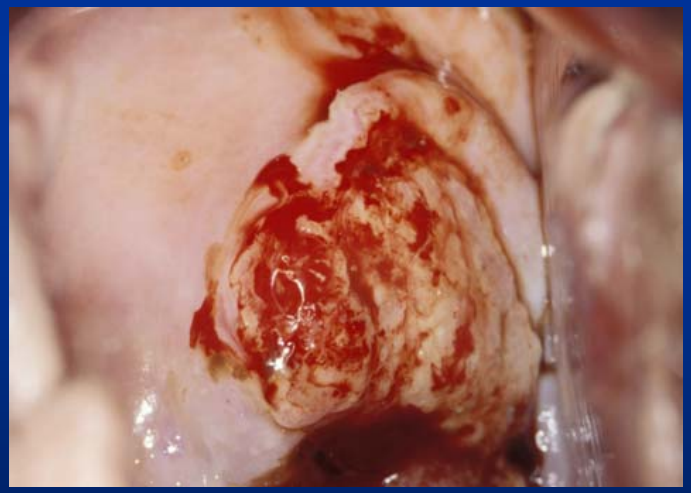
Neoplastic HPV-Associated Genital Disease

Anogenital cancer and AIN



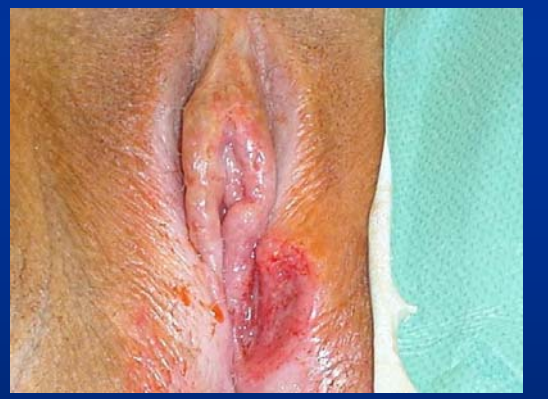
HPV **16**, 18, 31, 33

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



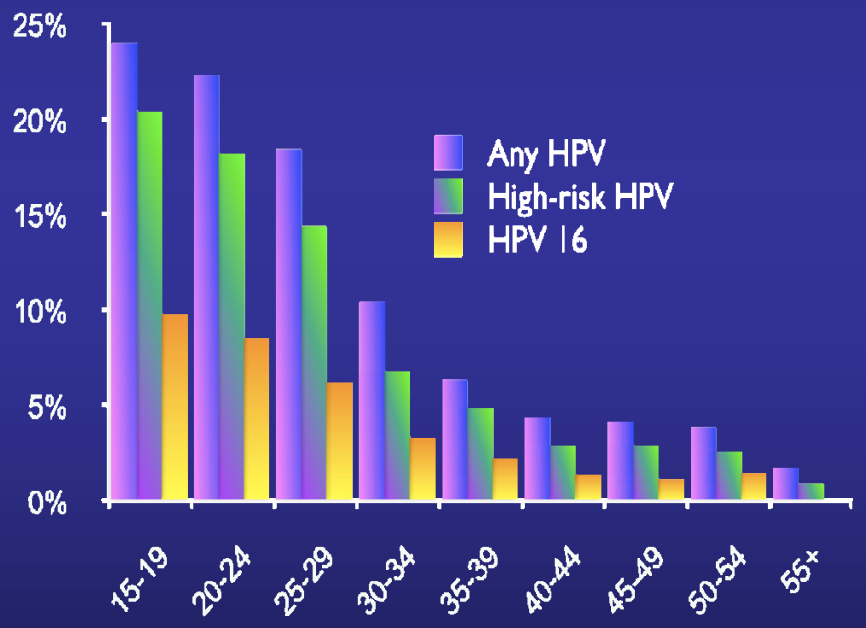
HPV **16**, 31, 33

Prophylactic HPV vaccines

Genital HPV: age related prevalence

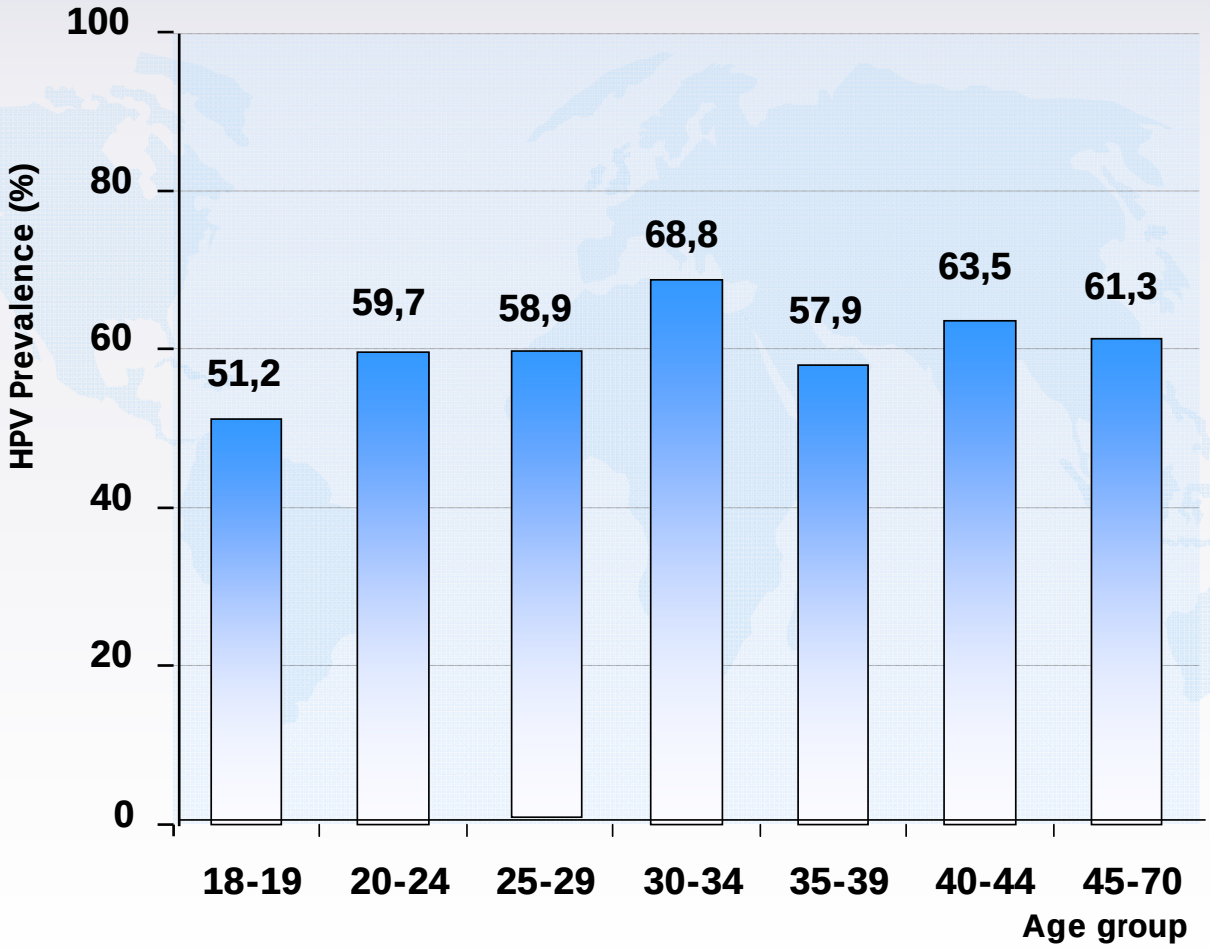
- 50-80% of all sexually active women acquire genital HPV in their lives
- Most common among young adults age 18-28[2]

HPV prevalence in Manchester[3]



1. Centers for Disease Control and Prevention. CDC Fact Sheet. Genital HPV Infection. Content Reviewed: May 2004. Technical Update: December 2, 2004. Centers for Disease Control Web site. Available at: http://www.cdc.gov/std/HPV/hpv.pdf. Accessed January 2005
2. Koutsky L. Epidemiology of Genital Human Papillomavirus Infection. *Am J Med* 1997;102:3-8
3. Peto J et al Brit J Cancer 2005

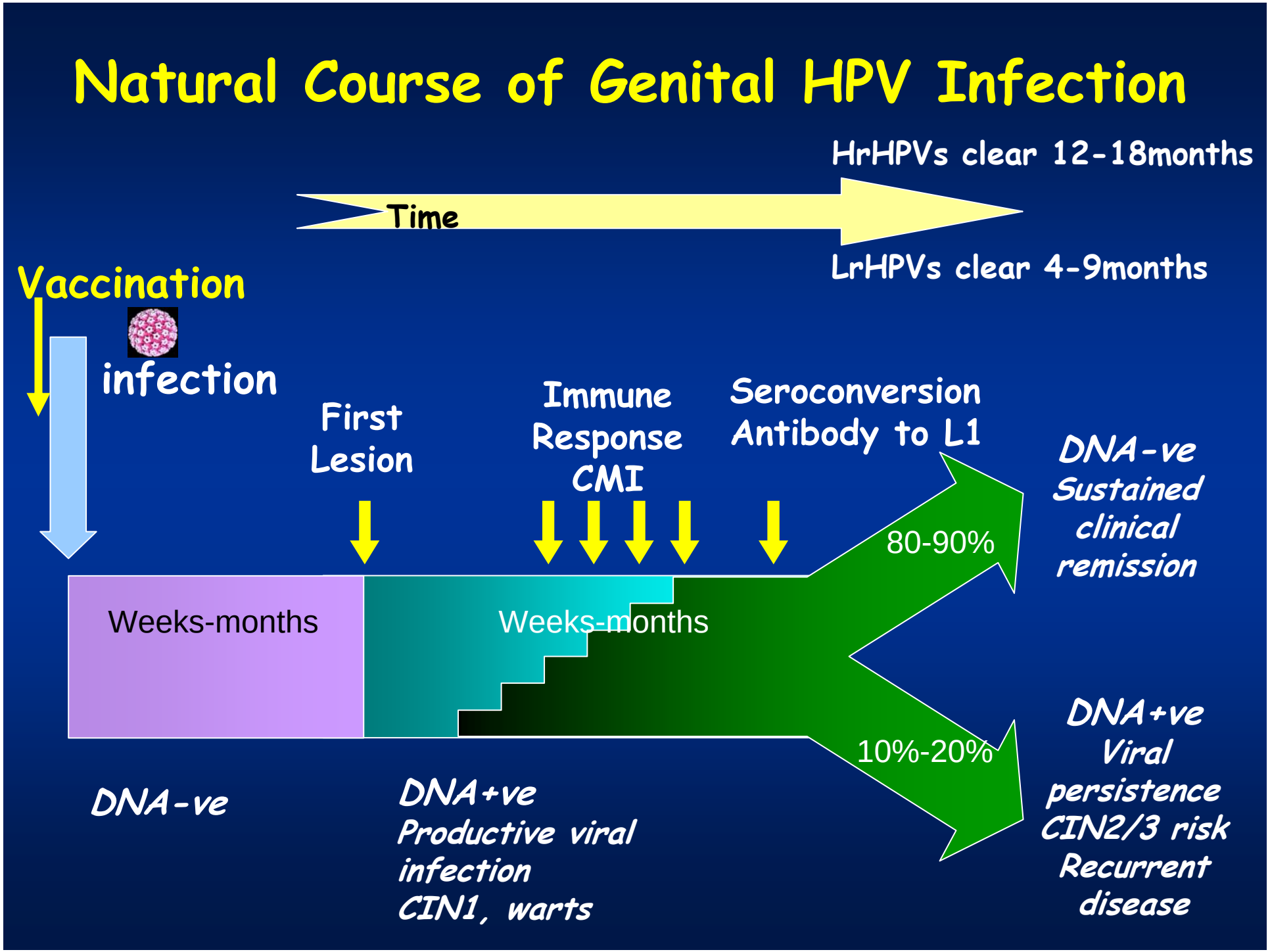
HPV PREVALENCE (ANY TYPE) BY AGE GROUP AMONG MEN RESIDING IN BRAZIL, MEXICO, AND THE US AND PARTICIPATING IN THE HIM STUDY



Source: Adapted from Giuliano A, et al. CEBP 2008

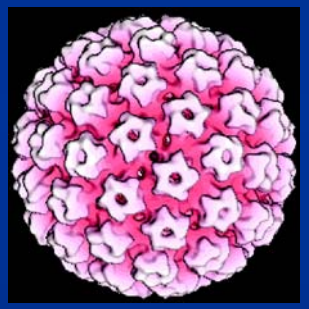
Bosch FX, et al. Vaccine, Vol. 26 Supplement 9, 2008 In press

Natural Course of Genital HPV Infection



Antibody response to Genital HPV infection in women

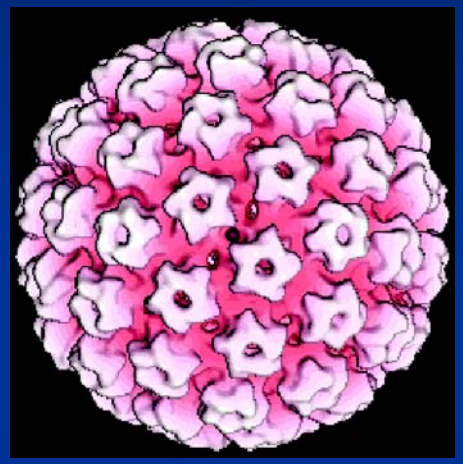
Detectable serum neutralising antibody responses are to L1

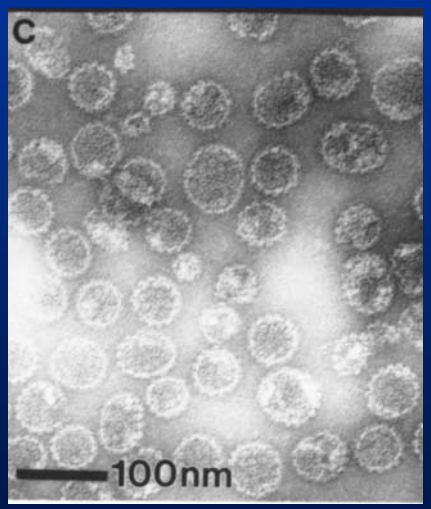


- These are mainly type specific
- Antibody response to HPV infection at the cervix is typically slow and weak
- 50-70% women with incident infection sero-convert
- Antibody persists for 10 Years*
- Antibody generated in natural infections is protective+

*Galloway IPV Montreal 2010 +Hildesheim IPV Montreal

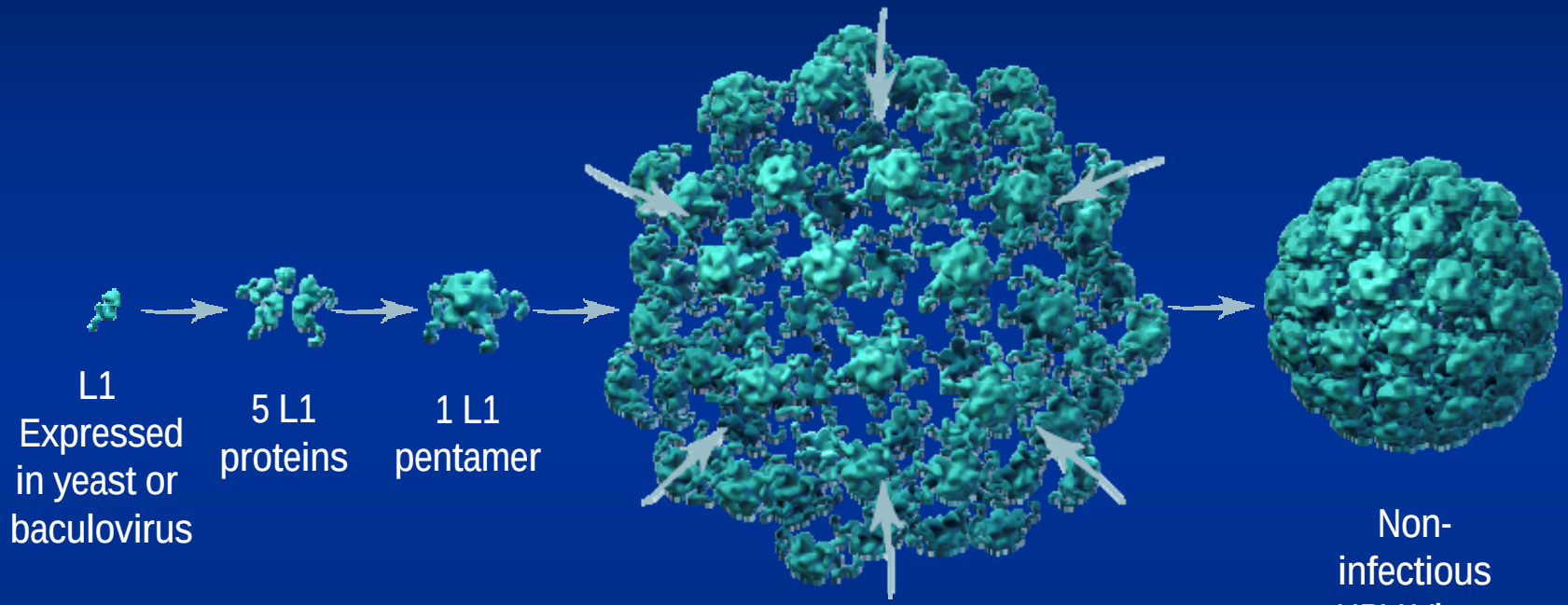
There are 2 virus capsid proteins L1 and L2
Each virus shell consists of 72 pentamers, each one made of 5 L1 molecules
L2 sits in the centre of each pentamer





- Neutralising antibodies are directed against the HPV L1 capsid protein in the native conformation
- HPV cannot be grown in bulk in culture so traditional virus vaccines made from live or killed virus are not possible
- Prophylactic HPV vaccines are sub unit protein vaccines comprised of the L1 protein assembled into virus like particles (VLPs), empty protein shells almost identical to the virus particle

The Virus-Like Particles (VLPs) in HPV vaccines aim to mimic the human papillomavirus



Gardasil SmPC. EMEA, 2007. - Kirnbauer R, Booy F, Cheng N, et al. Proc Natl Acad Sci USA. 1992;89:12180–12184. - Modis Y, Trus BL, Harrison SC. The EMBO Journal. 2002;21:4754–4762. - Stanley M, Lowy DR, Frazer I. Vaccine 2006; 24 suppl 3 : S106-13

Does neutralising IgG generated after immunisation with papillomavirus L1 VLPs provide protection?

Most convincing evidence is from preclinical experiments in dogs and rabbits

- passive transfer of purified IgG from hyperimmune donors immunised with L1 VLPs completely protects naive recipients from viral challenge

  Breitburd et al J Virol 1996
  Suzich et al PNAS 1995

- Only animals immunised with *intact* VLPs generate neutralising antibody

GARDASIL™: The First Cervical Cancer Vaccine

- HPV types 6, 11, 16, 18[1]
- Recombinant vaccine (does not contain live virus)[1]
- Manufactured in Saccharomyces cerevisiae[1]
  - Yeast-derived vaccines given to millions of children and adults[2]
- Proprietary aluminum adjuvant 225 µg per dose[1]
- Each 0.5-mL injection volume contains HPV types 6/11/16/18 (20/40/40/20 µg, respectively)[1]
- Intramuscular administration[1]
- 0-, 2-, 6-month dosing regimen[1]

1. GARDASIL Worldwide Product Circular. Merck & Co., Inc., Whitehouse Station, NJ, USA. 2. Unger ER, Barr E. Human papillomavirus and cervical cancer [conference summary]. *Emerg Infect Dis* [serial on the Internet]. 2004 Nov [Cited October 19, 2006]. Available from http://www.cdc.gov/ncidod/EID/vol10no11/04-0623_09.htm. Accessed April 26, 2007.

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 sulphate® 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

HPV vaccines
Phase III randomised control trials
Per Protocol Populations

- Women 15-26 years of age
  40,000 women in total in these trials

- <4-5 lifetime sex partners

- HPV DNA negative and sero-negative for the HPV types in the vaccine at trial entry through to 6 or 7 months post first dose

- Cohorts in the trials of the 2 vaccines differ in baseline prevalence of HPV infection

- Inclusion and exclusion criteria

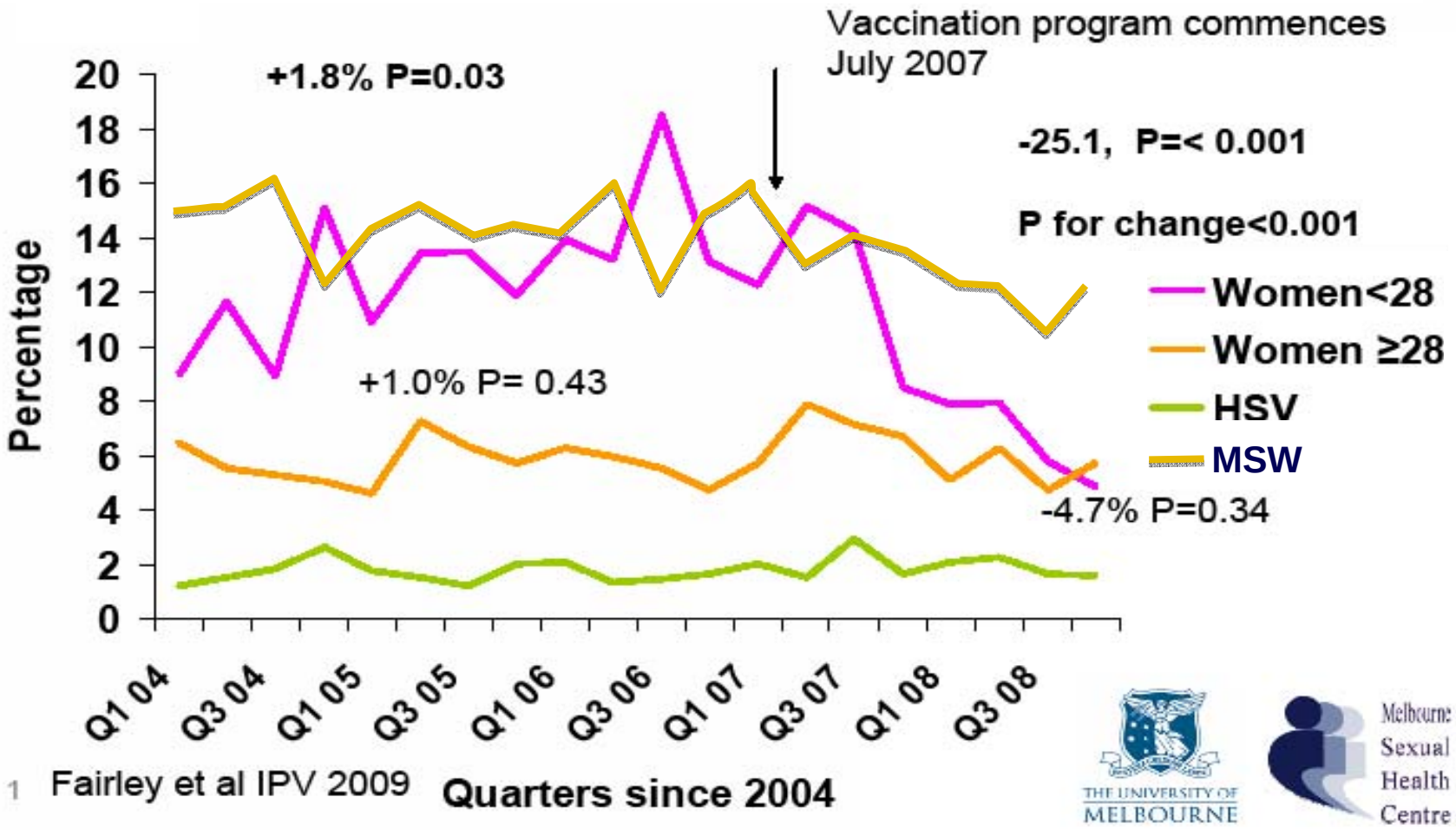
Phase III Randomised Control Trials (RCTs)
End of Study: Per Protocol Efficacy Populations

Vaccine	Quadrivalent	Bivalent
Mean Follow up	42 months	34.9months
Prophylactic Efficacy	*% CI*	*% CI*
HPV16/18 CIN2/3	98%* (94,100)	93%* (79.9,98.3)
	100%+	98%+ (88.4,100)
HPV16/18 AIS	100% (31,100)	Not reported
HPV 16/18 VIN3/VaIN3	100% (83,100)	Not reported
HPV6/11/16/18 VIN1/VaIN1	100% (86,100)	Not a target
EGL	99% (97,100)	Not a target
Cross protection	Demonstrated	Demonstrated
Tolerability	Well tolerated	Well tolerated
Therapeutic efficacy	None	None

*pre specified +post hoc analysis

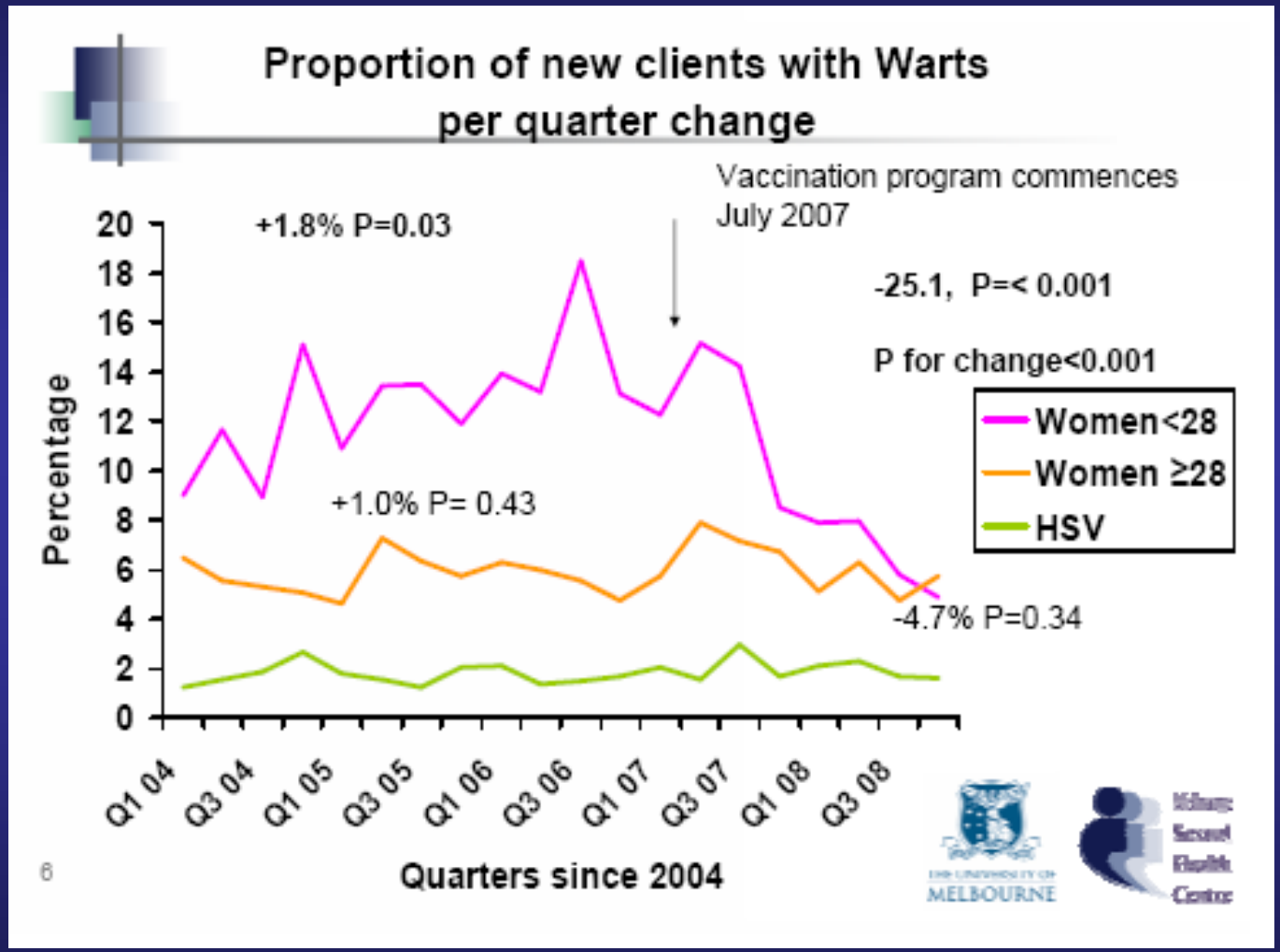
Kjaer etal Cancer Prev Res 2009 2:868 Paavonen etal 2009 Lancet 371:314
Dillner et al 2010. BMJ 341:3493

Proportion of new clients with warts per quarter change Melbourne Sexual Health clinic



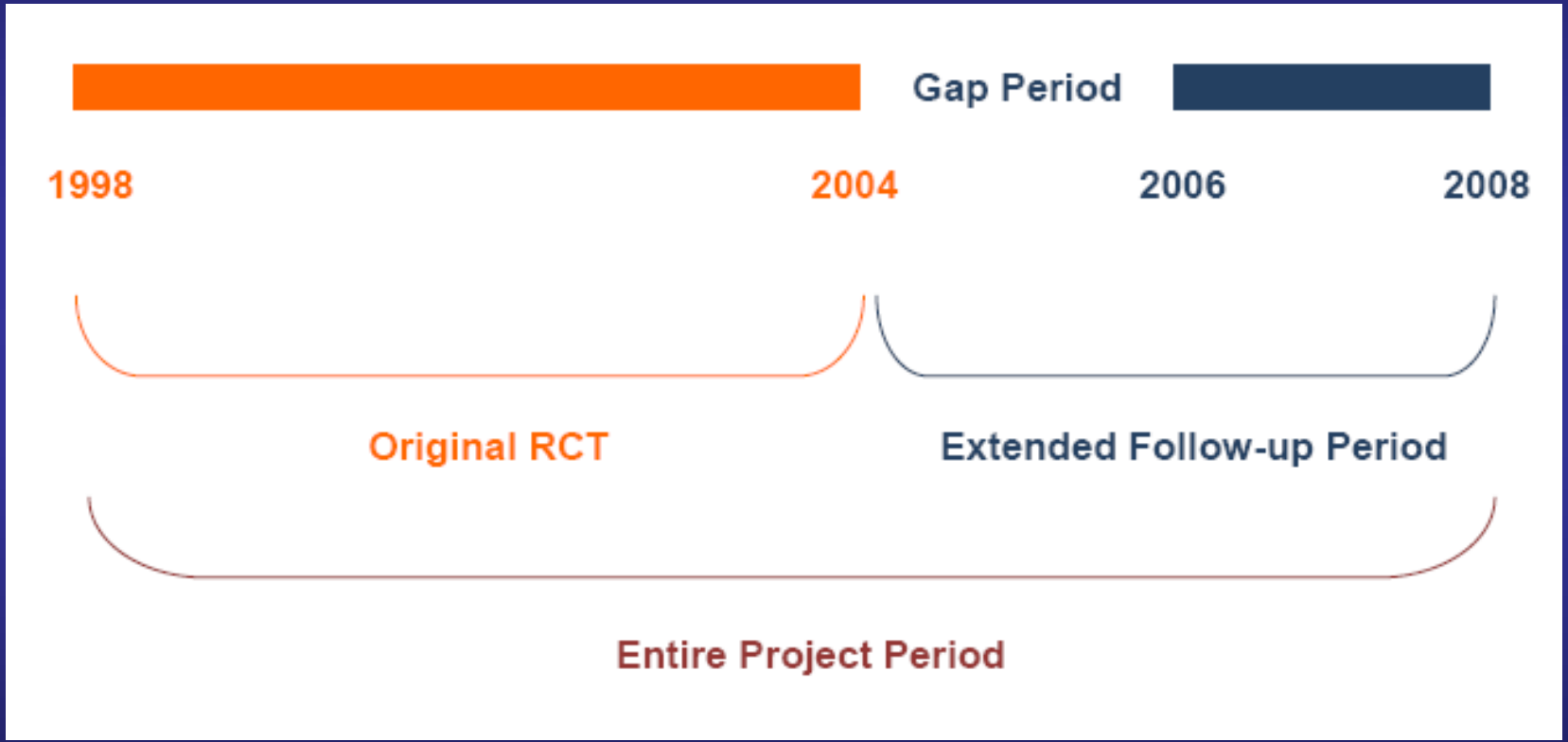
Fairley CK, Hocking JS, Gurrin LC, Chen MY, Donovan B, Bradshaw CS.
Sex Transm Infect. 2009;85:499-502

Incidence of EGW in young women before and after introduction of the quadrivalent vaccine



Fairchild etal Sex Trans Inf. 2009 85:499

Long-term Efficacy of a Prophylactic HPV-16 Vaccine (9.5 years)



P005 extended study follow-up average 8.5 years N=290
(maximum follow-up = 9.5 years)

Adapted from Ali Rowhani-Rahbar et al IPC 2009 Sweden Malmo

Long-term Efficacy of a Prophylactic HPV-16 Vaccine (9.5 years)

Extended Follow-up Period

	Vaccine		Placebo		Efficacy %
	Cases	Rate*	Cases	Rate*	95% CI
CIN-1 +	0	0	3	0.7	100 (<0-100)
CIN-2 +	0	0	3	0.7	100 (<0-100)

Entire Project Period

CIN-1 +	0	0	8	0.9	100 (43-100)
CIN-2 +	0	0	7	0.8	100 (32-100)

* Per 100 Person-years

P005 extended study follow-up average 8.5 years

(maximum follow-up = 9.5 years)

Rowhani-Rahbar A etal 2009 Vaccine 27:561

HPV L1 VLPs are very immunogenic

- Peak antibody concentrations are 50-10000x those in natural infections
- Neutralising antibody persists for 5years at least post immunisation
- Both type specific and cross neutralising antibodies are generated
- An antibody threshold level for protection has not been identified for HPV

  No immune correlate

Harper et al Lancet 2006, 367,1247. Villa LL, et al. *Br J Cancer*. 2006;95:1459–1466. Olsson et al. *Vaccine*. 2007. Smith JF etal Hum Vaccine 2007 3, 109

Natural infection - poor access of virus to lymph nodes

intra-epithelial infectious cycle -no viraemia

infectious virus shed from mucosal surfaces[1]

VLP vaccines delivered intramuscularly

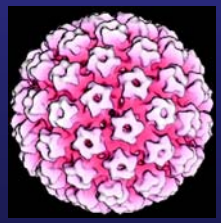
rapid access of VLPs to blood vessels and local lymph nodes[1]

VLPs are very immunogenic even without adjuvant

strongly activate innate and adaptive immunity[2,3]

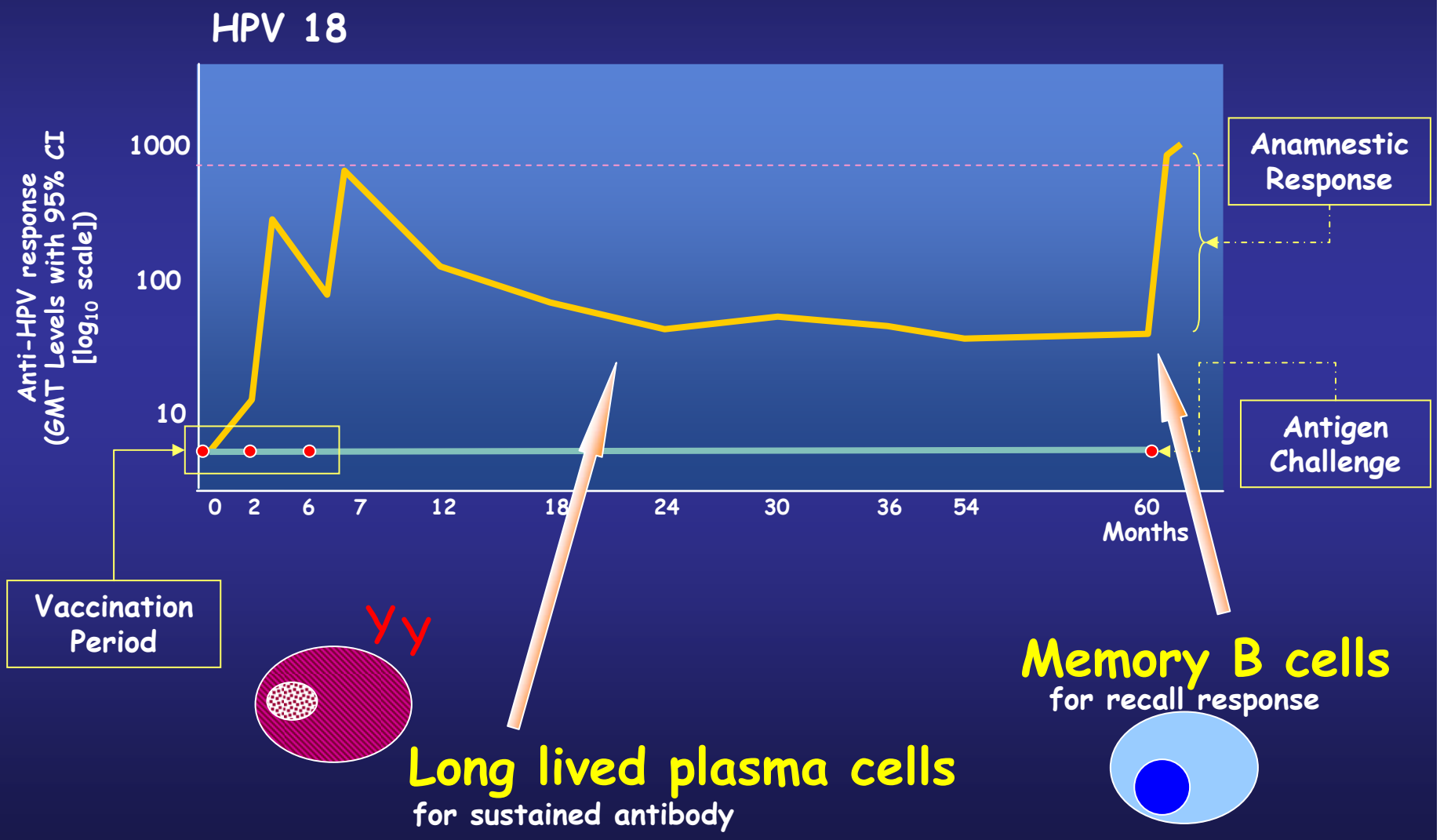
display many neutralising epitopes

induce good T cell helper responses for B cells important for robust antibody and B cell memory responses



[1]Stanley MA Vaccine 2006. [2]Yan etal Immunol Cell Biol 2005; 83;83. [3]Querec etal Nat Immunol 2009 10:116

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



[1] Olsson SE et al Vaccine 25 (2007) 4931–49391

Inconvenient facts about the HPV antibody response

- Very low levels of antibody are protective against disease in natural infections of animals

- In animals immunisation with L1 either as protein (VLPs), DNA or via recombinant vector induces very variable antibody concentrations but is always protective against disease

- Low levels of antibody protect against disease in natural genital infections in women

- There is no immune correlate for HPV L1 VLP vaccines

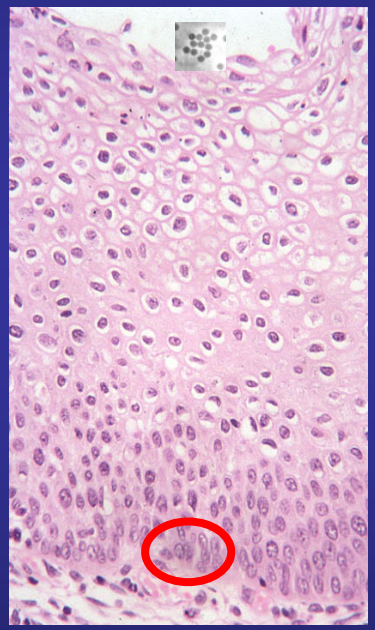
- Current methods for antibody measurement are not standardised

- They do not measure antibody affinity or avidity

How does serum neutralising antibody protect against HPV infection

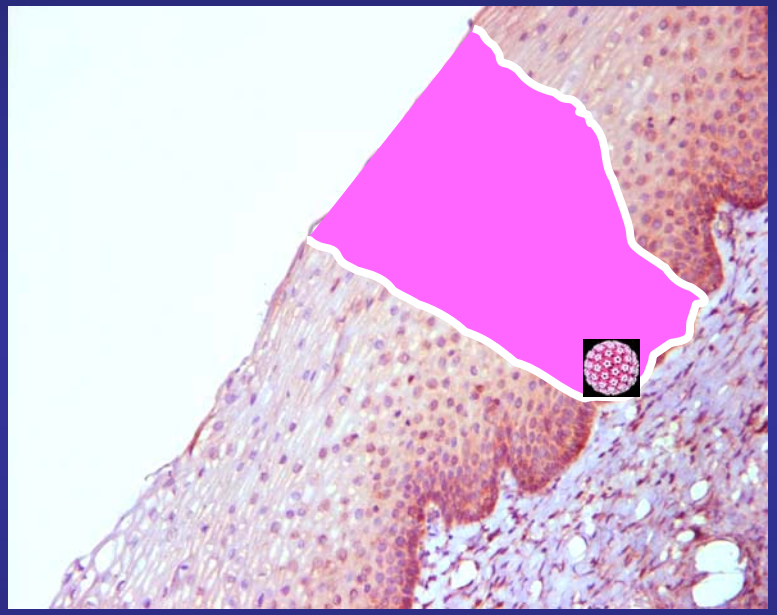
How does HPV infect the basal epithelial cell?

How and when does antibody prevent this?



Epithelial microabrasion and wound healing are necessary for HPV infection

Viral entry is slow
Minimum 14-20 hours

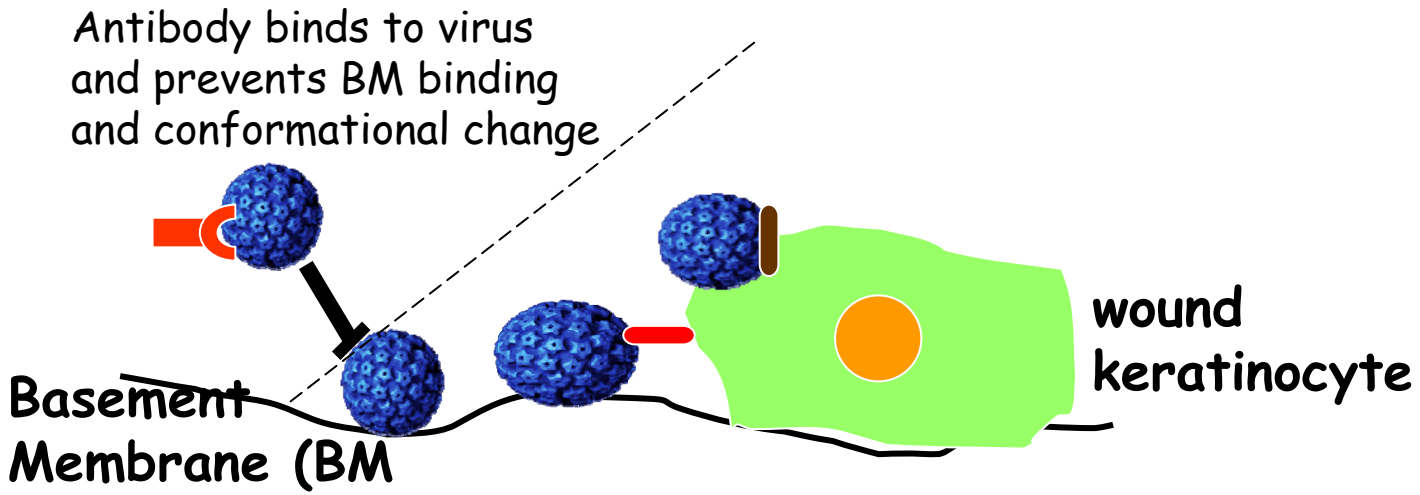


cervix
vagina
vulva
penile shaft
peri-anal skin

Microtrauma to the epithelium exposes the basement membrane to which HPV binds before entering the wound keratinocyte[1,2]
Microwounding will result in serous exudation
rapid access of serum IgGs to the virus particles
rapid encounter with the circulating B memory cells

[1]Roberts J etal Nature Med 13:857, Kines etal 2009 PNAS 106,20458

Neutralisation after HPV 16L1 VLP immunisation



HPV 16 L1 antibodies that prevent conformational change neutralise at very low concentrations (10^{-12}M)

Very low levels of antibody are needed to prevent HPV infection

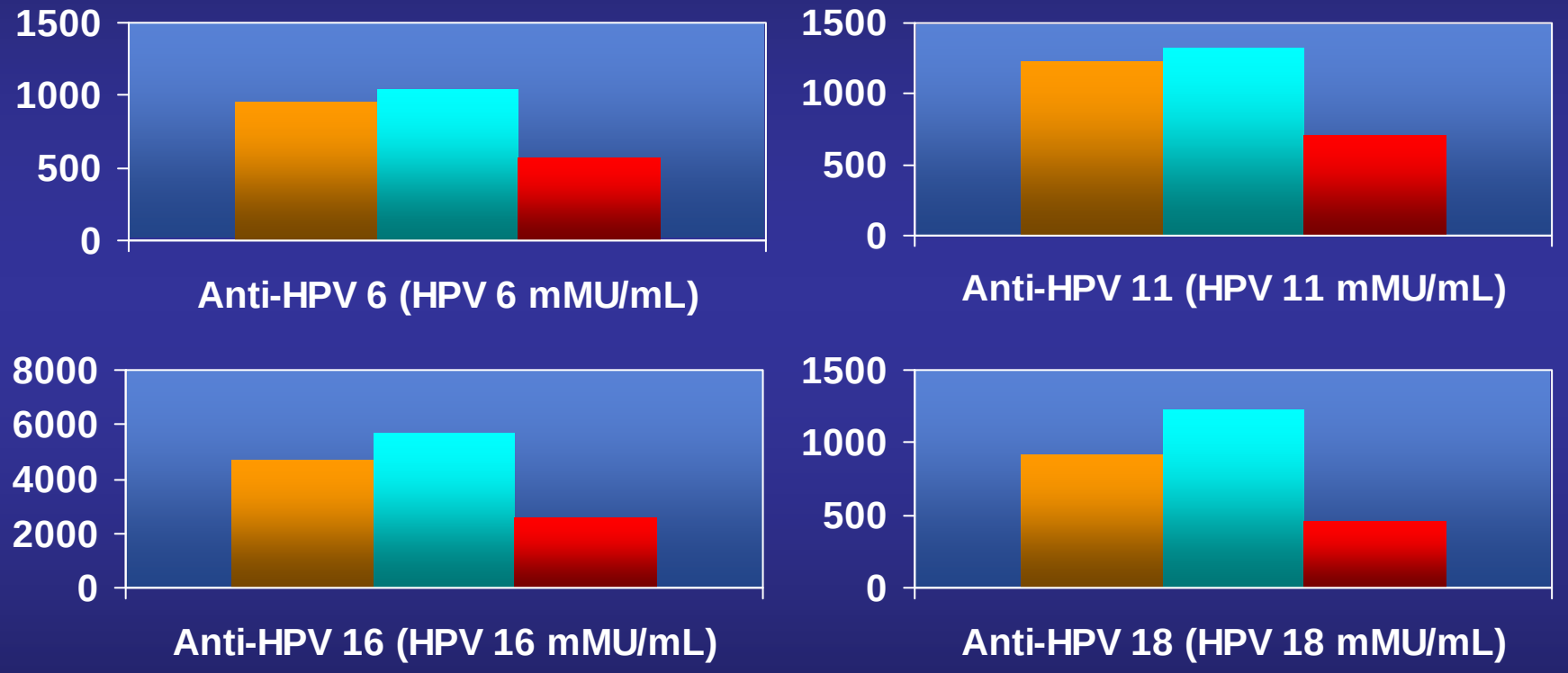
Alternate Schedules for HPV Vaccines

Immunogenicity Bridging Data

- Gardasil approval for girls aged 9-15 was based on immunogenicity bridging data as it was not possible to conduct efficacy evaluations (ie cervical specimens) in this population
- Bridging studies showed that girls aged 9-15 had antibody geometric mean titres (GMTs) 2-3x higher than GMTs in the population from which efficacy was established using tests for cervical HPV infections
- To date there are no efficacy studies from these bridging participants

Quadrivalent HPV Vaccine Phase III Adolescent Immunogenicity Study

Neutralizing Anti-HPV GMTs at Month 7*



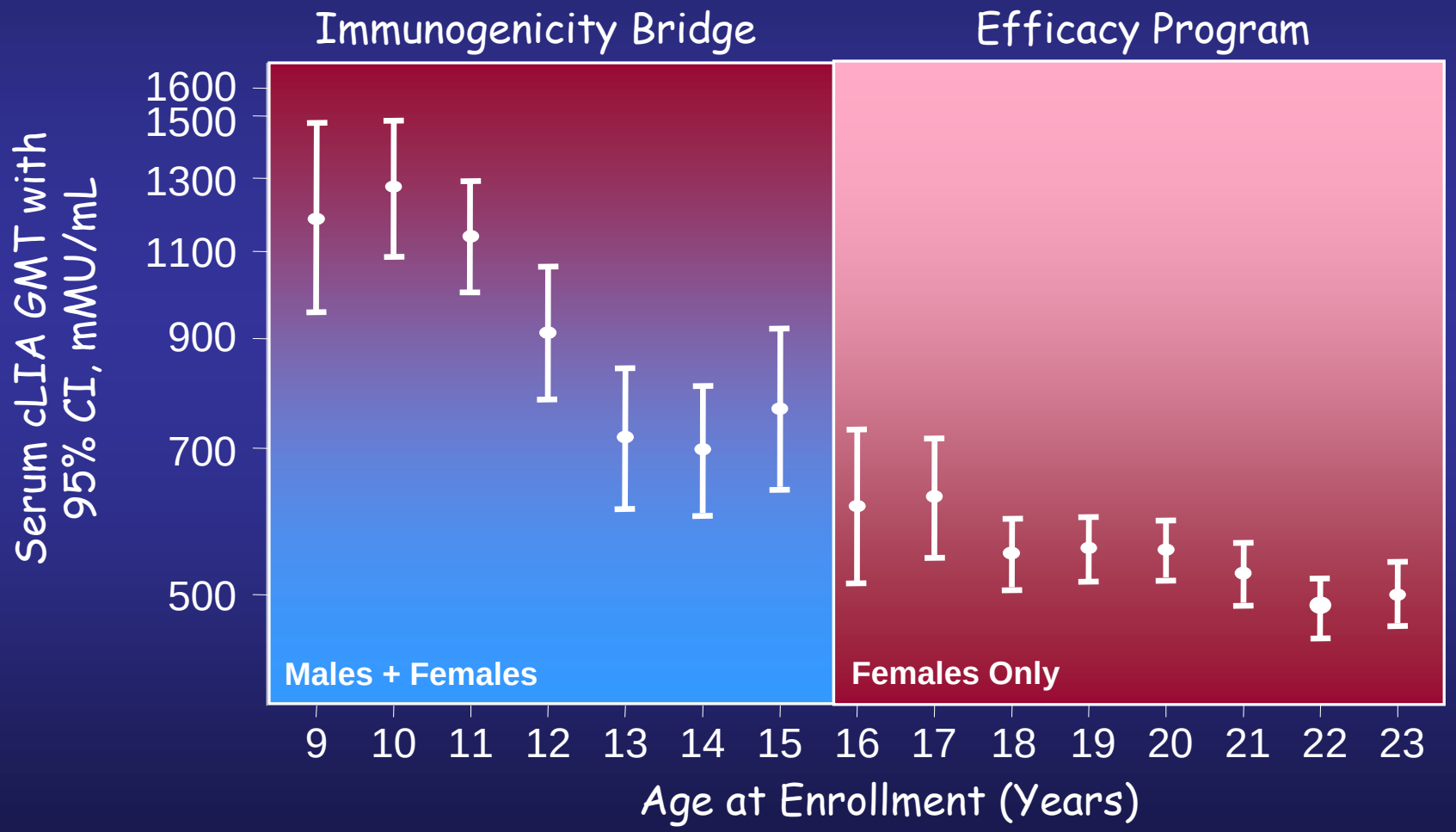
*GMT = geometric mean titers

1. Block SL, Nolan T, Sattler C, et al. *Pediatrics*. 2006:118,2135.

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

Block SL, Nolan T, Sattler C, et al. *Pediatrics*. 2006:118,2135

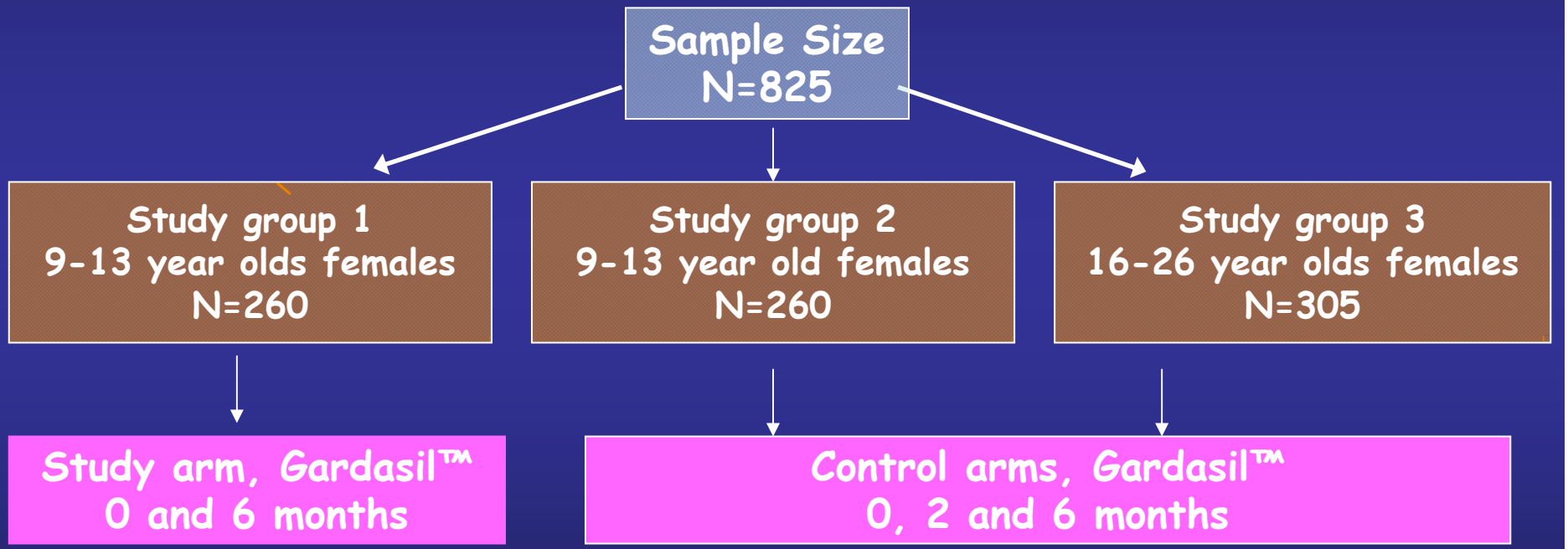
Alternate Schedules for HPV Vaccines

- Quebec: Program for girls in Grade 4, given at 0, 6, +/- 60 months
- Mexico: Program for girls aged 12, given at 0, 6 +/- 60
- Canada 2 versus 3 dose HPV vaccine study in 9-13 year old females

  Includes three Canadian jurisdictions

  British Columbia, Quebec, Halifax

Trial design



Primary outcome: Anti-HPV 16 and 18 GMT, t = 7 months

Conclusions at 7 months

Following a 2 dose regimen in 9-13 year old girls, antibody responses to HPV-16,-18,-6,-11 were **non-inferior** at month 7, as compared to 3-dose regimens in young adult women **and** 9-13 year old girls

Dobson etal 2010 IPV Montreal

Men

Men – Protocol 020
Study Design and Populations

- Randomized, double-blind, placebo-controlled, international, multicenter study
- 3 doses of GARDASIL™ or placebo at 0/2/6 months
- 36 month follow-up for each subject
- Enrolled subjects:
  - Heterosexual men (MSW)
    - 16-23 year old
    - N=3463
  - Men having sex with men (MSM)
    - 16-26 year old
    - N=602

Gardasil efficacy in men – PPE group

MSW

Endpoint:	6/11/16/18 external genital warts	
Vaccine Efficacy:	90.6%	95% CI 70,98

MSM

Endpoint:	6/11/16/18 related AIN	
Vaccine efficacy		
Prespecified analysis	77.5	95% CI 40,93
Post hoc type assignment analysis	91.1	95% CI 64,99

Palefsky et al IPV Montreal 2010

MSW men wo have sex with women
MSM men who have sex with men

Vaccine Impact

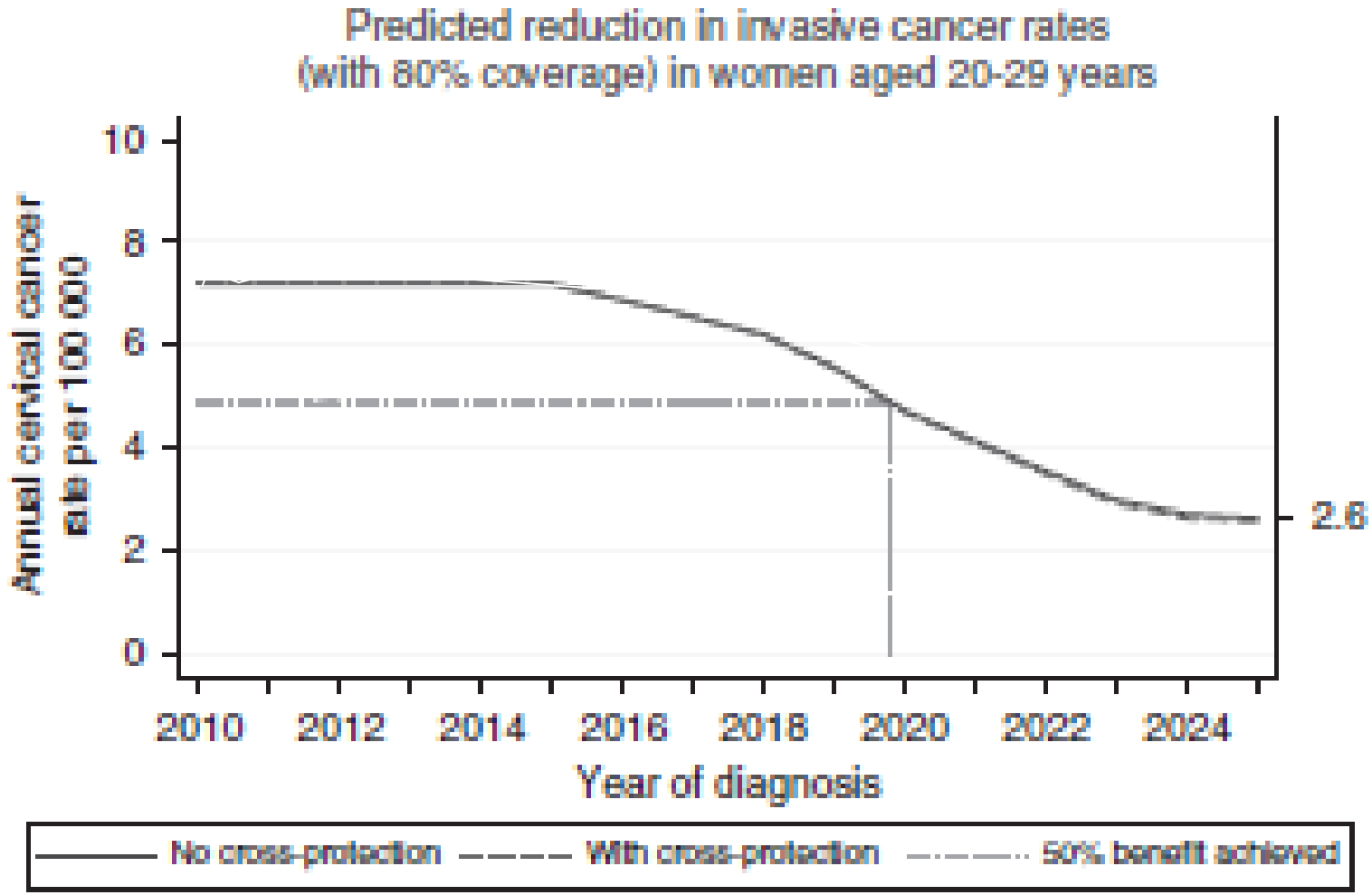
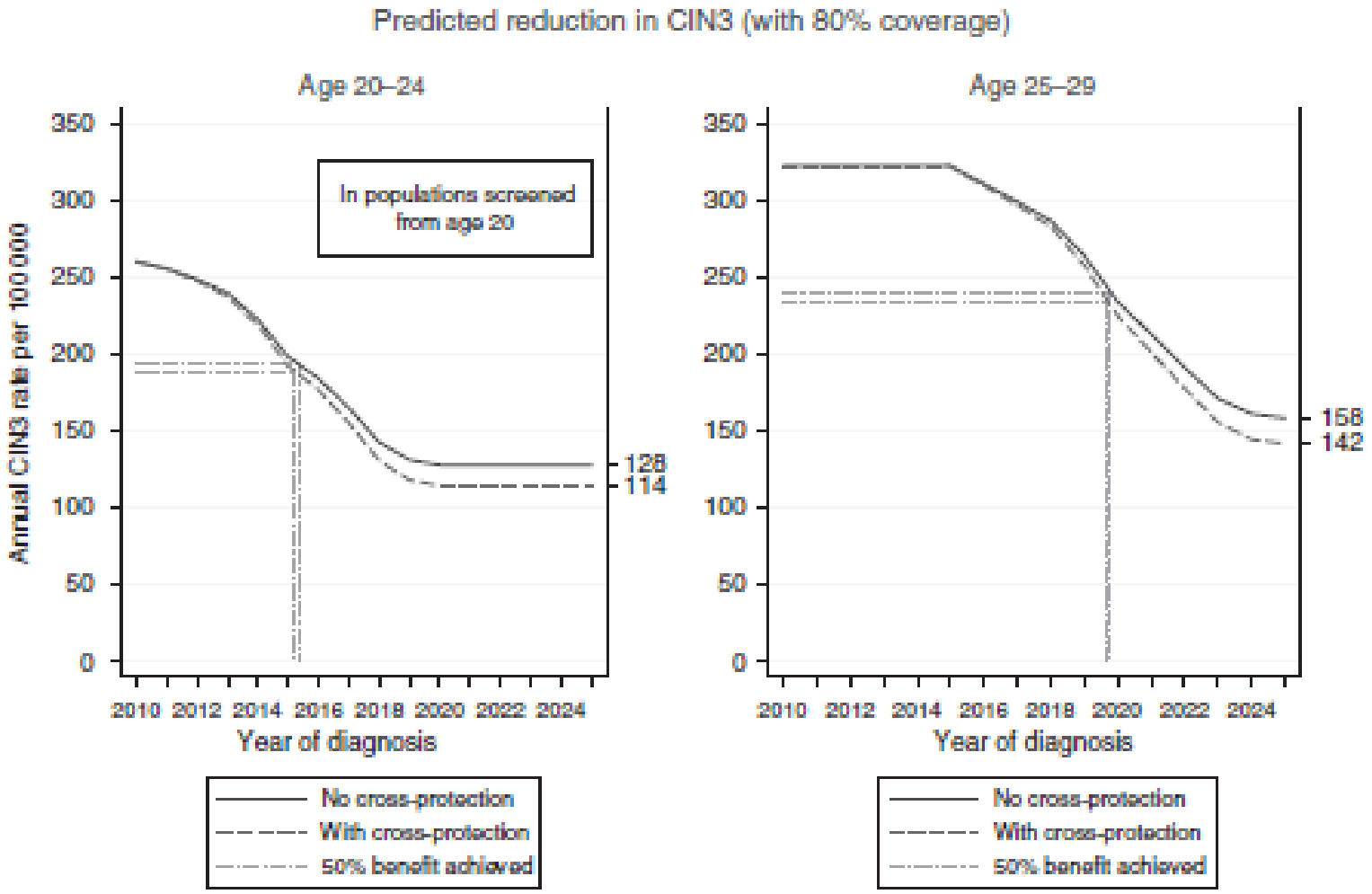


Figure 1 Predicted reduction in invasive cancer rates (with 80% coverage) in women aged 20–29 years.

Cuzick etal 2010 BJC 102, 933



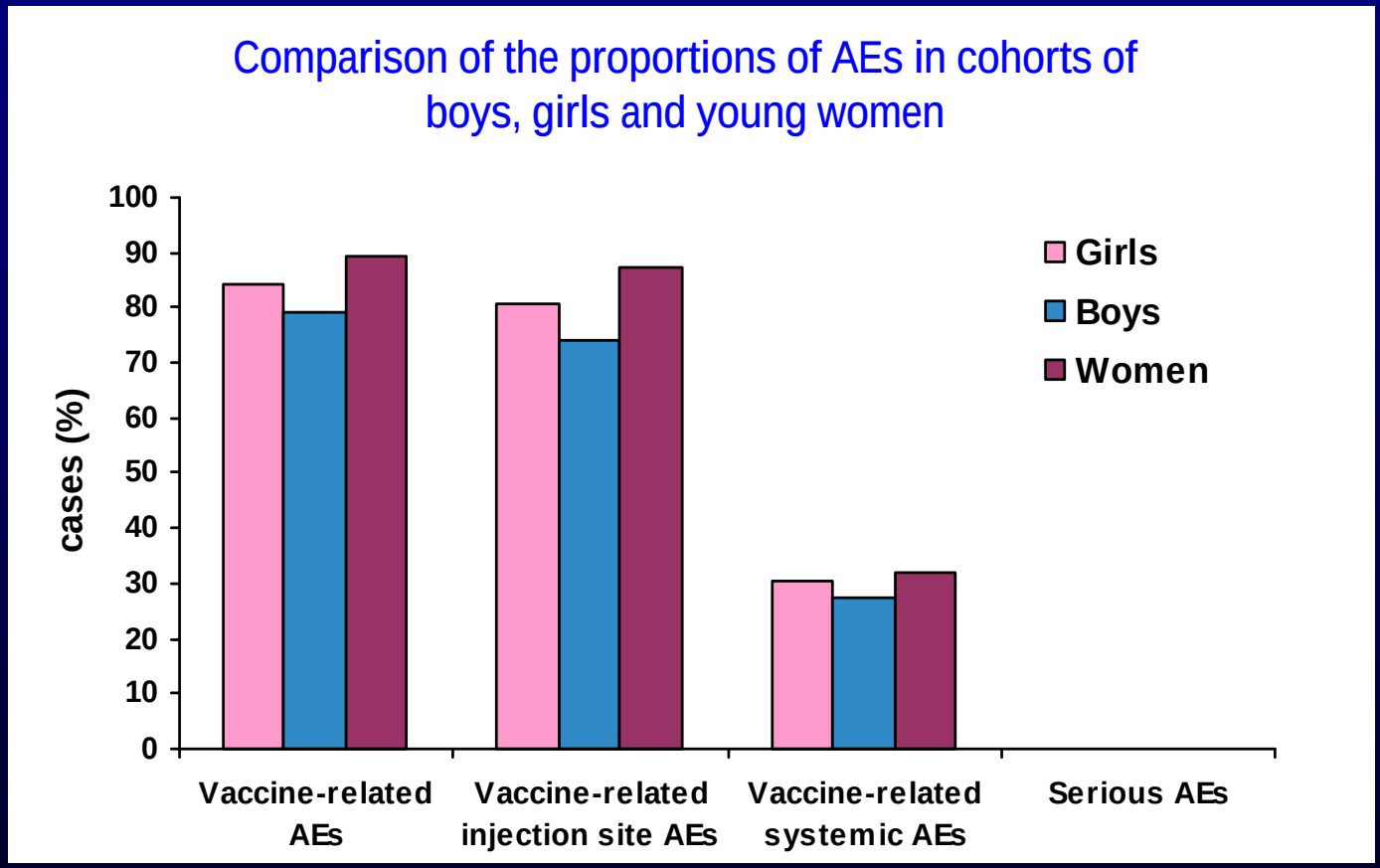
Cuzick etal 2010 BJC 102, 933

Successful Vaccine Implementation

- successful immunisation programme
  publicly funded
  effective immunisation infrastructure
  strategy that achieves high population coverage
- The general public is convinced that they work and are safe

Backup

Safety Profile of Gardasil in Girls and Boys Compared to Young Women



AE: adverse events
Per protocol population; injection of Gardasil or placebo at day 0, month 2 month 6
AE summary study period 1–15 days after receipt of dose
Population analysed: Girls (n = 501) ;Boys (n = 500); Women (n = 497)

Block SL *et al. Pediatrics* 2006;118:2135–2145.

Evidence from the randomized control trials and the post vaccine surveillance to date

- the VLP vaccines have a very good safety profile
- injection site reactions, pain, swelling, etc are the most commonly reported but serious adverse events are no more frequent in vaccinees than in the unvaccinated population in that age range

Clear statements regarding HPV vaccine safety have been made by both the US FDA

www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/ucm179549.htm

and European EMEA

www.emea.europa.eu/humandocs/PDFs/EPAR/gardasil/Gardasil_press_release.pdf,
www.emea.europa.eu/humandocs/PDFs/EPAR/cervarix/H-721-en6.pdf