Professor Margaret Stanley

University of Cambridge

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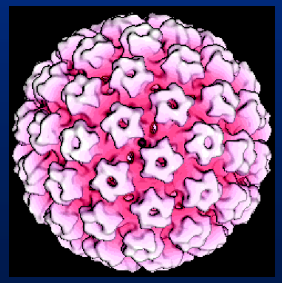
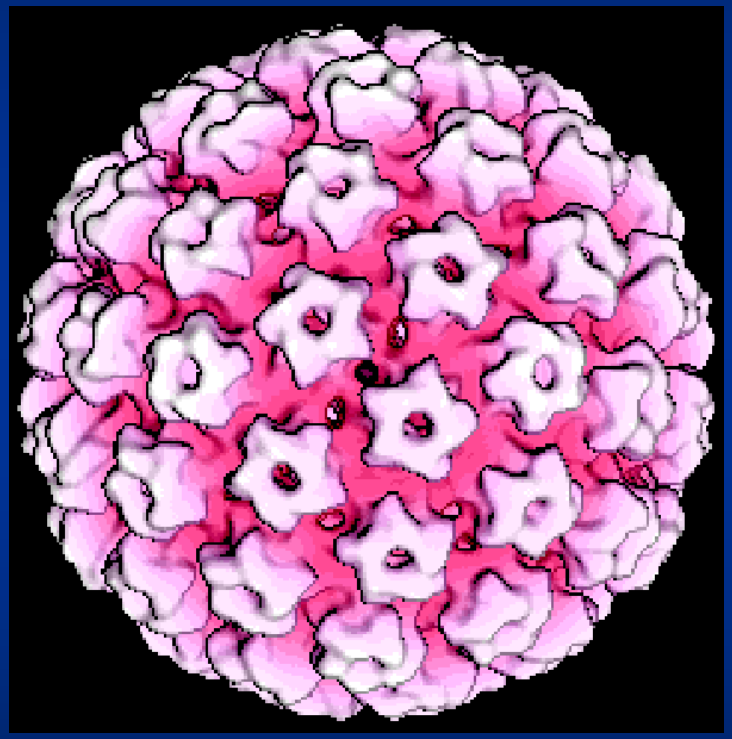
COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Margaret Stanley	Has acted as a consultant for SPMSD Lyon France, GSK Biologicals Rixensart Belgium and MSD Whitehouse Station USA
Date	**April 2013**

'Where to next with HPV vaccination? New strategies, new vaccines'.

Margaret Stanley
Department of Pathology
University of Cambridge
UK



HPV



- Non enveloped dsDNA virus, simple capsid of 2 proteins L1 and L2
- Common virus with >100 types identified
- Infects cutaneous and mucosal epithelia
- 30–40 infect the mucosal epithelia of women and men

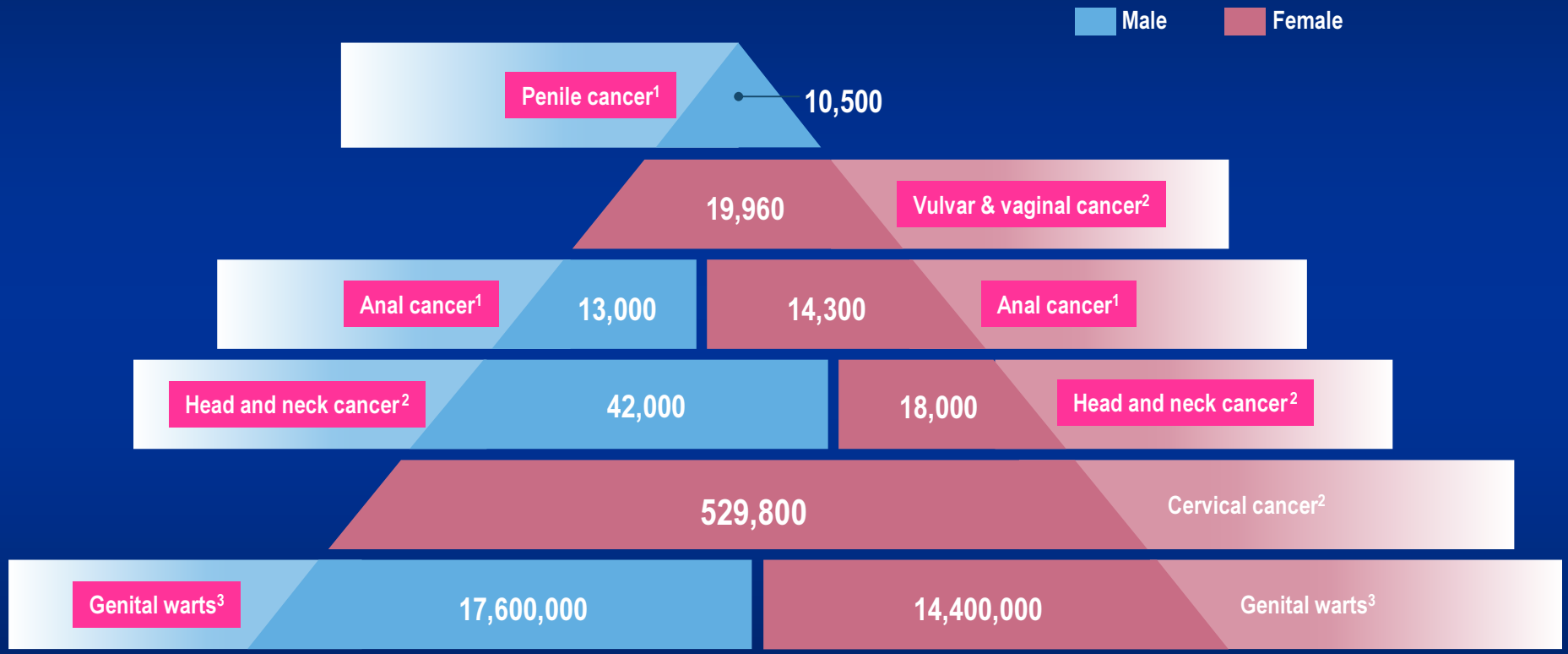
  2 groups
  - low risk types causing warts

    HPV 6,11
  - 13 high risk types causing cancer

    16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59,68

    HPV 16,18 – most important

Estimated annual global burden of HPV associated disease in men and women



Published HPV prevalence rates were applied as follows: Parkin D et al. *Vaccine*. 2006 (penile, vulvar, anal, cervical cancers); WHO/ICO 2010 (head and neck cancer); De Vuyst H et al. *Int J Cancer*. 2009 (vaginal cancer); Greer CE et al. *J Clin Microbiol.* 1995 (genital warts).

1. Parkin DM et al. *Vaccine*. 2006;24(Suppl 3):S3/11–S3/25. **2.** WHO/ICO Information Centre on HPV and Cervical Cancer (HPV Information Centre). Human Papillomavirus and Related Cancers in World. Summary Report 2010. http://www.who.int/hpvcentre/en/. Accessed June 21, 2012. **3**. World Health Organization (WHO). Executive summary: the state of world health. 1995. http://www.who.int/whr/1995/media_centre/executive_summary1/en/index3.html#. Accessed June 7, 2012.

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

Bivalent **Quadrivalent**

*MPL 3-O-deacylated-4'-monophosphoryl lipid A

Prophylactic HPV vaccines
Efficacy
Effectiveness

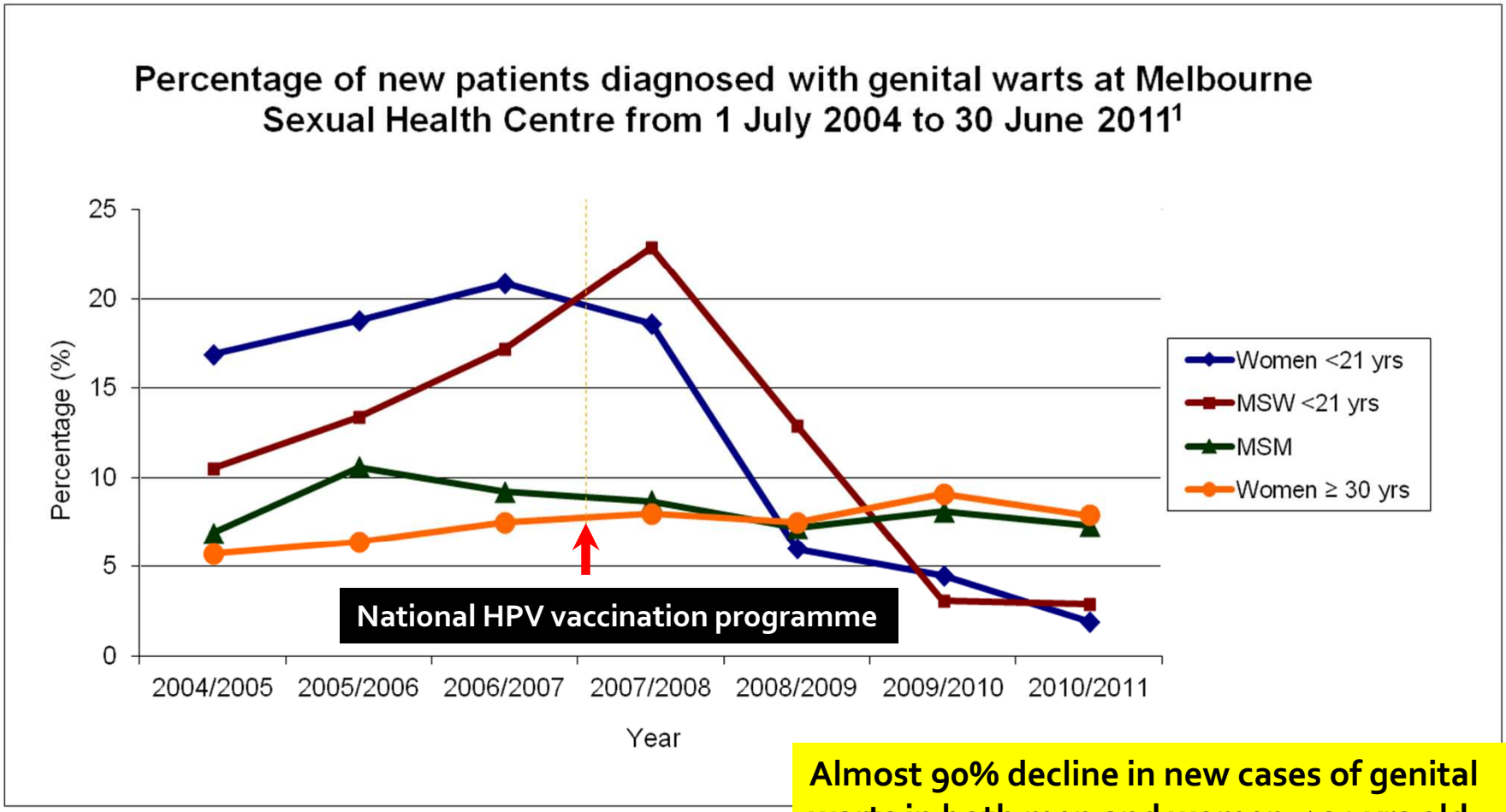
Phase III Randomised Control Trials (RCTs)
End of Study: Per Protocol Efficacy Populations

Vaccine	Quadrivalent	Bivalent
WOMEN		
Mean Follow up	42 months	42 months
Prophylactic Efficacy	*% 95%CI*	*% 95%CI*
HPV16/18 CIN2	100 (95,100)	95 (88,98)
HPV16/18 CIN3	97 (88,100)	92 (67,91)
HPV16/18 AIS	100 (31,100)	100 (-8,100)
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
WOMEN 25-45 yrs		
6/11/16/18 PI/CIN/VIN/VaIN	89 (78,95)	
MEN 16-23 yrs	36 months	
HPV 16/18/6/11 EGL (MSW)	90 (69,98)	No studies
HPV 16/18/6/11AIN (MSM)	78* (40,93)	No studies
	91+ (64,99)	

*pre-specified +post hoc analysis

DATA FROM Kjaer etal Cancer Prev Res 2009 2:868 Lehtinen Lancet Oncol 2012 13:89
Dillner et al 2010. BMJ 341:3493 Guiliano 2011 NEJM364:401 Palefsky 2011 365:401

Australia: Near disappearance of genital warts after commencement of national HPV program

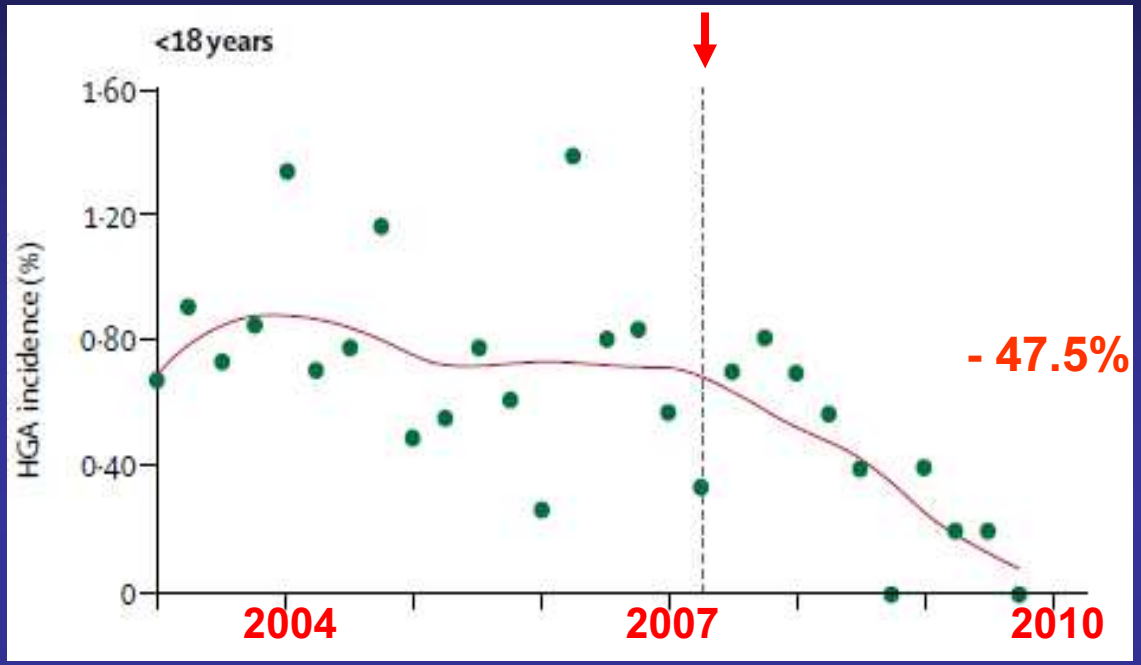


Almost 90% decline in new cases of genital warts in both men and women < 21 yrs old

1. Read et.al., *Sex Transm Infect 2011*; 87:544e547. doi:10.1136/sextrans-2011-050234

Start of vaccination programme (mid-2007)

Incidence of HGA/100 women tested in a 3 month period



- 47.5%

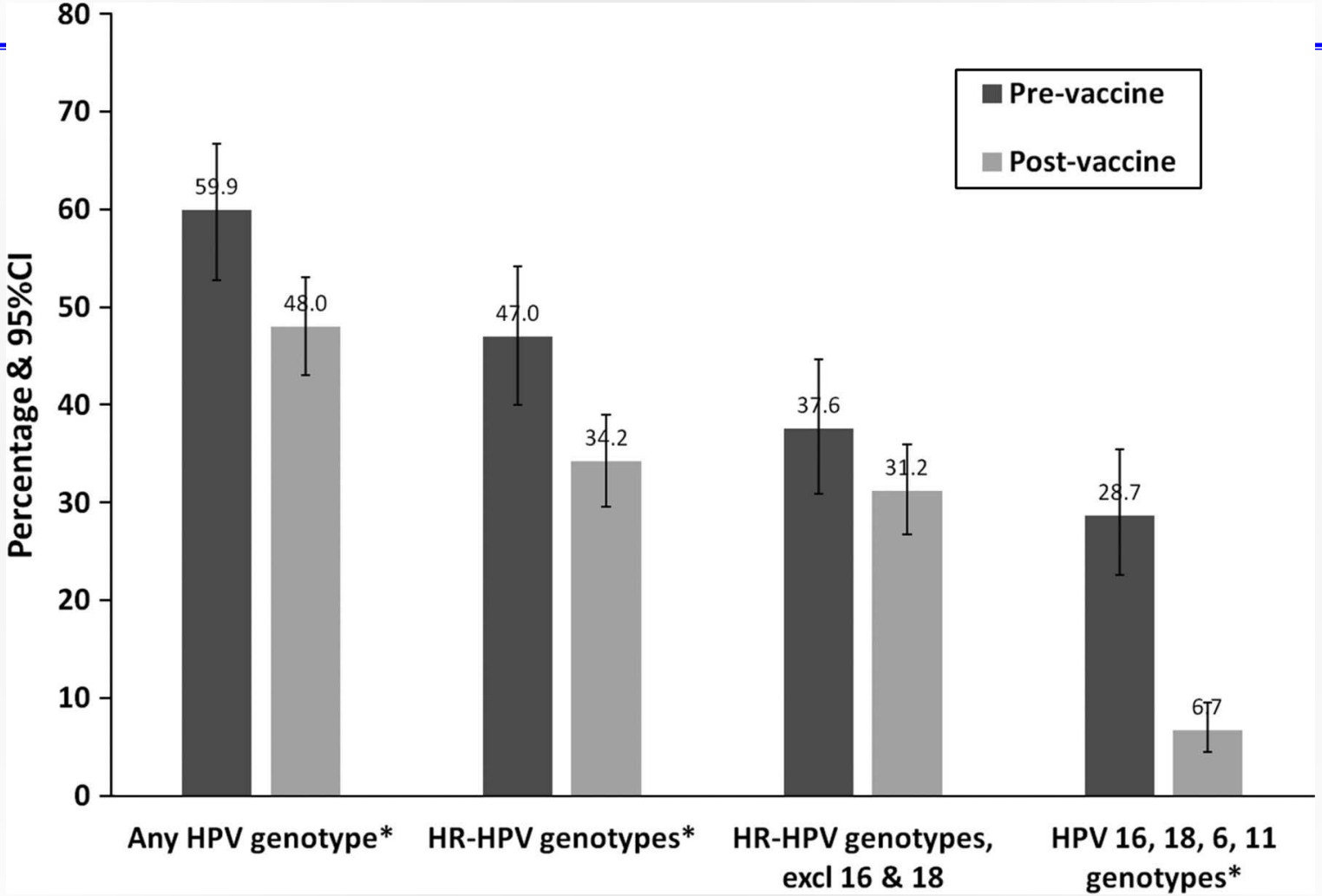
p=0.003

A relative reduction of ~50% of high grade abnormalities (HGA) was observed in women <18 years, post vaccination vs. pre vaccination, less than 3 years after the introduction and the trend continues.

Similar early trends have been observed in the US.

Brotherton J et al. Lancet 2011

Differences in human papillomavirus (HPV) genoprevalence between prevaccine and postvaccine populations. *P < .05 for difference in percentages between groups.



Tabrizi S N et al. J Infect Dis. 2012;206:1645-1651

The Journal of Infectious Diseases

Current issues

- Alternative immunisation schedules
- Gender neutral vaccination
- Next generation prophylactic vaccines

Why consider alternative dosing regimens?

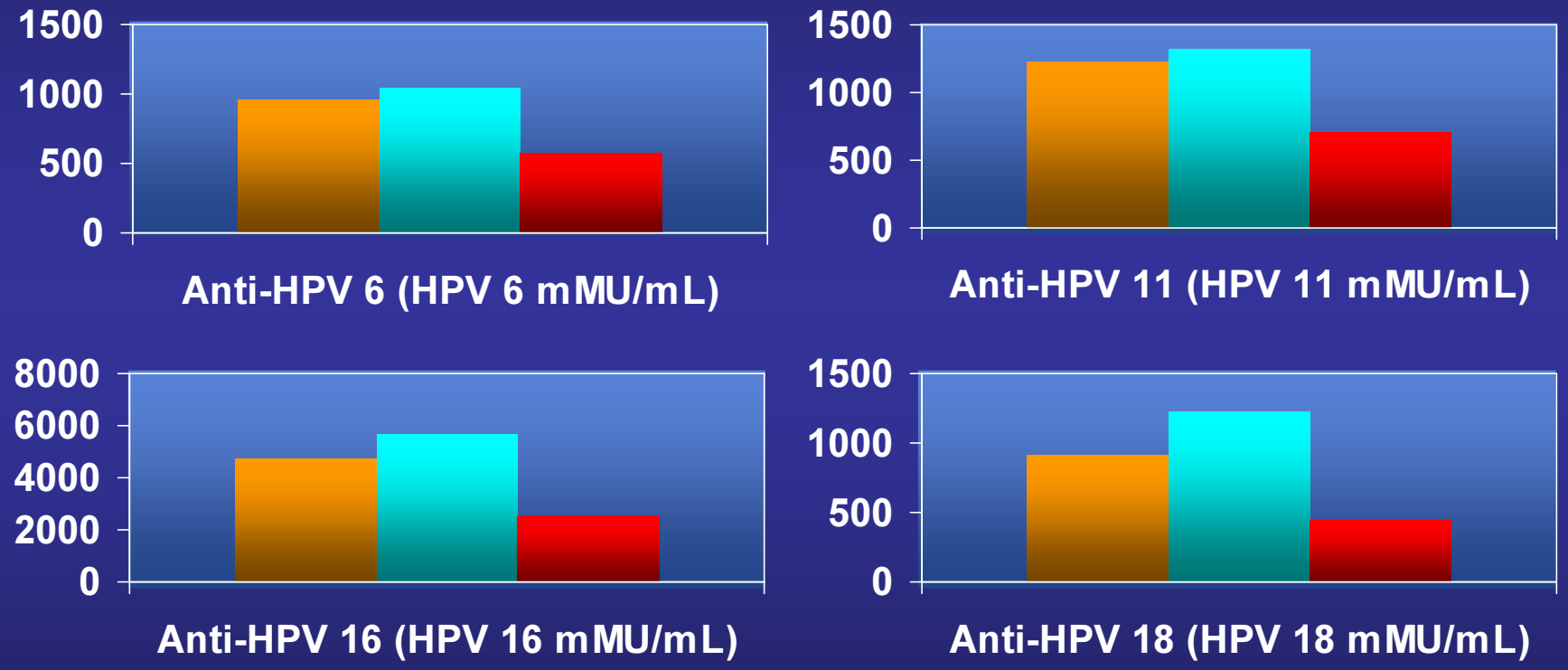
Cost Reduction
- administrative costs
- vaccine costs

Difficulty of delivering 3 doses over 6 months

Immunogenicity in young adolescents

Quadrivalent HPV Vaccine Phase III Adolescent Immunogenicity Study

Neutralizing Anti-HPV GMTs at Month 7*

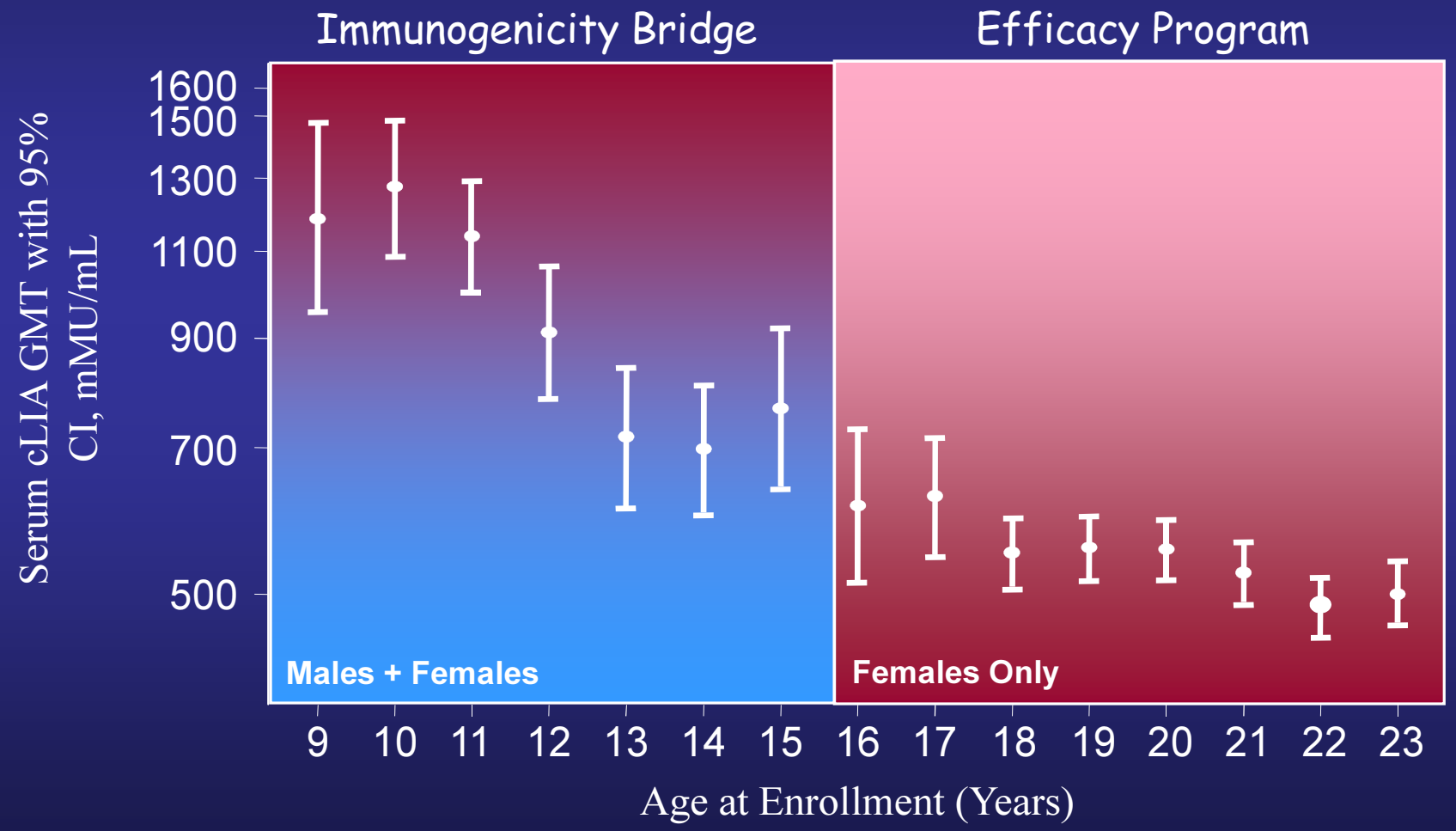


*GMT = geometric mean titers

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

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

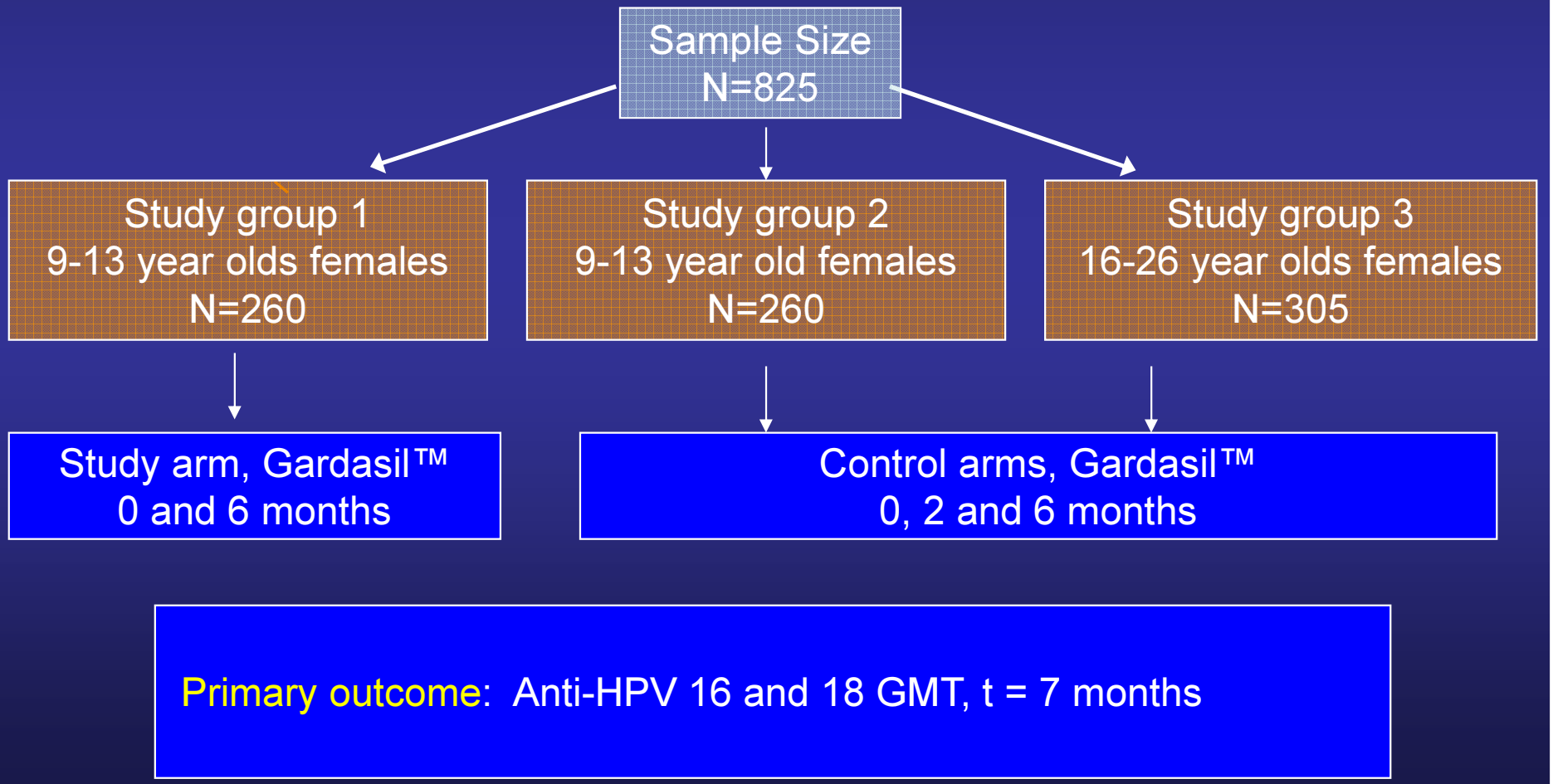
PPE population*
Neutralizing anti-HPV 6 GMTs at month 7

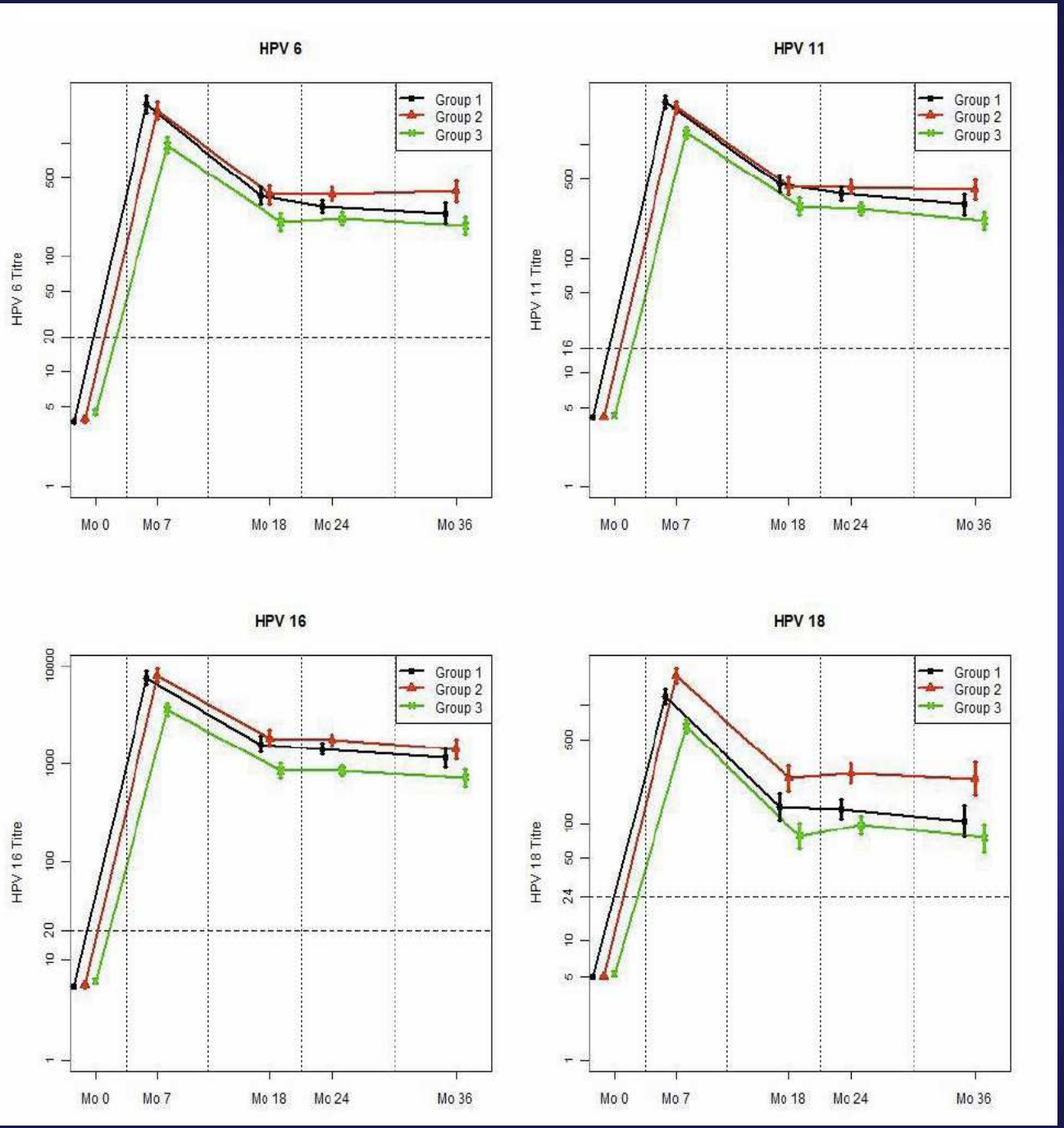


*Inclusive of five study protocols; all GMTs measured using cLIA

2 versus 3 dose HPV vaccine study Phase II post licensure
randomised control multicentre study (NCT00501137)
3 Canadian provinces PI Dr Simon Dobson BC

Trial design





GMTs
Group 1
2D 9-13yrs

Group 2
3D 9-13yrs

Group 3
3D 16-26yrs

Cervarix

	HPV type	Age yrs	Dose	GMT 95% CI	GMT ratio 3:2 95% CI
Month 7	HPV 16	15-25	3 dose n=111	10322 *8329,12792*	
		9-14	2 dose n=65	11067, *9190,13328*	0.93 0.68-1.28
	HPV 18	15-25	3 dose n=114	4262 *3572,5084*	
		9-14	2 dose n=64	5510 *4646,6535*	0.77 0.59-1.01
Month 24	HPV 16	15-25	3 dose n=101	1865 *1505,2311*	
		9-14	2 dose n=64	1702 *1416,2045*	1.10 0.81,1.49
	HPV 18	15-25	3 dose n=103	728 *588,900*	
		9-14	2dose n=63	702 *563,876*	1.04 0.75,1.43

Unresolved issues

Duration of protection: only data on duration comes from 3 dose regimens

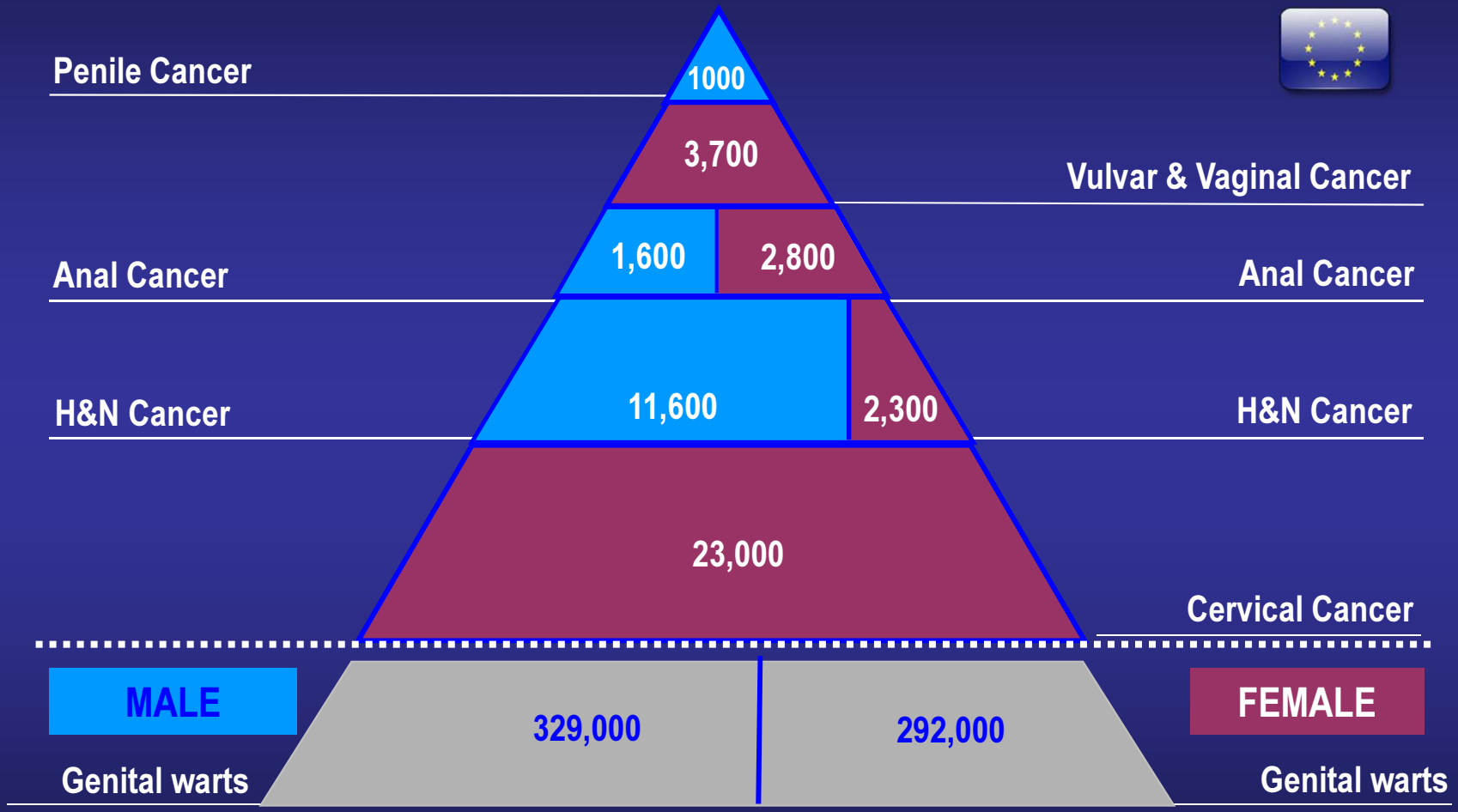
No immune correlate

Kinetics of antibody response in 2dose versus 3 dose poorly known

Rudimentary data on antibody affinity and avidity maturation

HPV vaccination in men

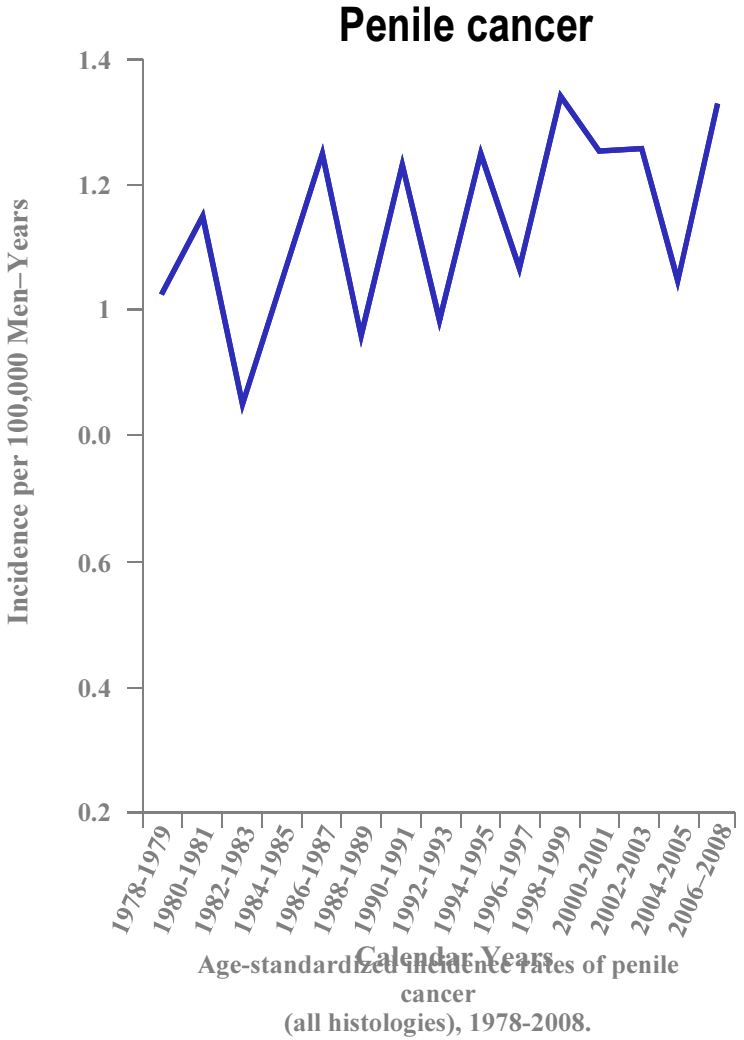
HPV is a Potent Carcinogen causing Multiple Related Cancers in Men and Women



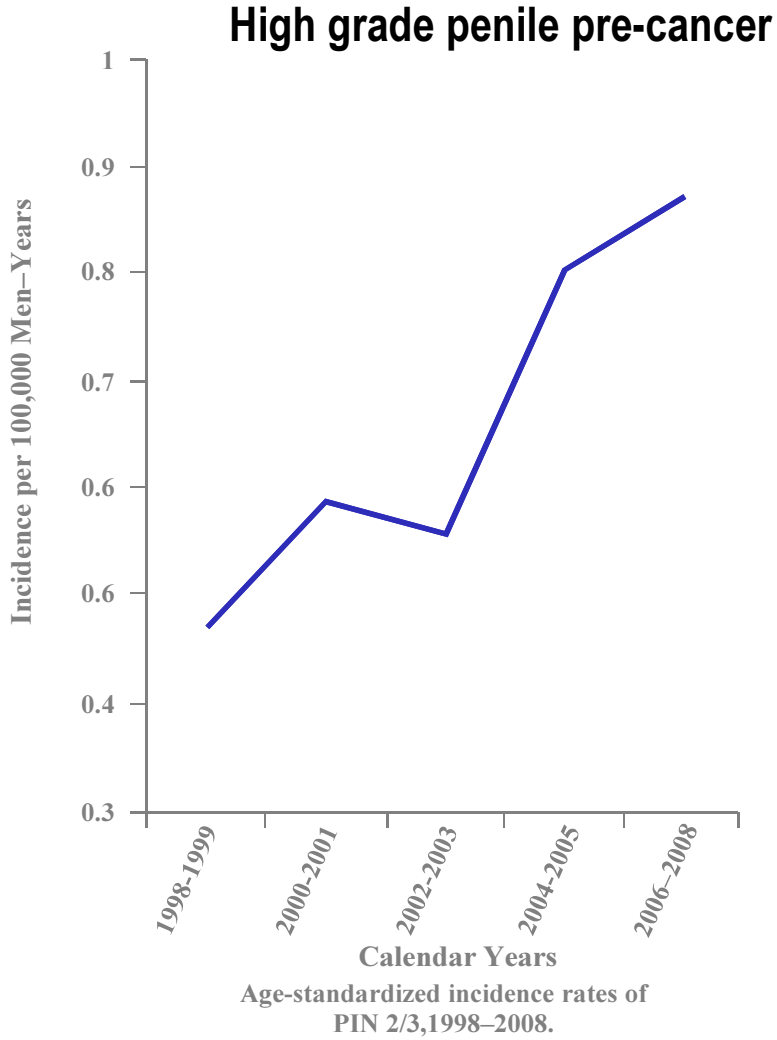
Annual new cancers and genital warts cases related to HPV 6,11,16 and/or 18 in Males and Females in Europe

Annual number of new cancer cases calculated based on crude incidence rates from IARC database (1998-2002) and population estimate Eurostat 2008; estimate Globocan 2008 for cervical cancer; published HPV prevalence rates were applied (for Europe, when available) Genital warts estimates based on incidence rates in UK, HPA 2007

Increasing Incidence of Penile Cancer and High-Grade PIN in Denmark



Age-standardized incidence rates of penile cancer (all histologies), 1978-2008.



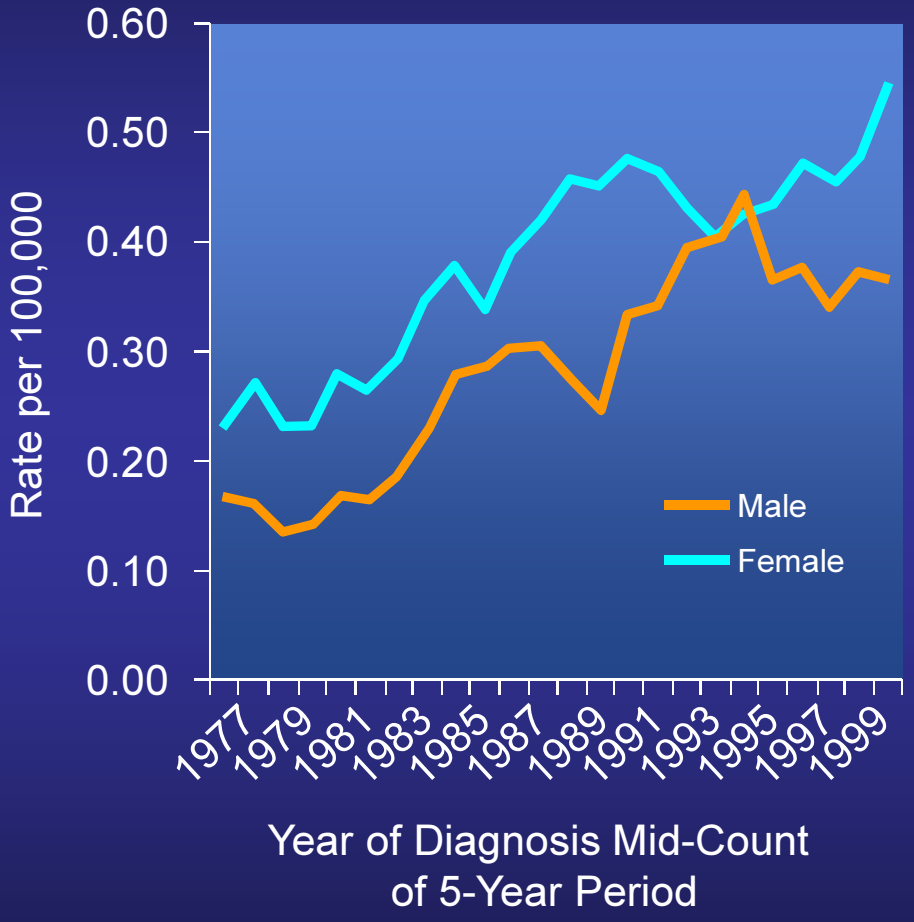
Age-standardized incidence rates of PIN 2/3,1998–2008.

CI=confidence interval; PIN=penile intraepithelial neoplasia.

Baldur-Felskov B et al. *Cancer Causes Control.* 2012;23:273–280.

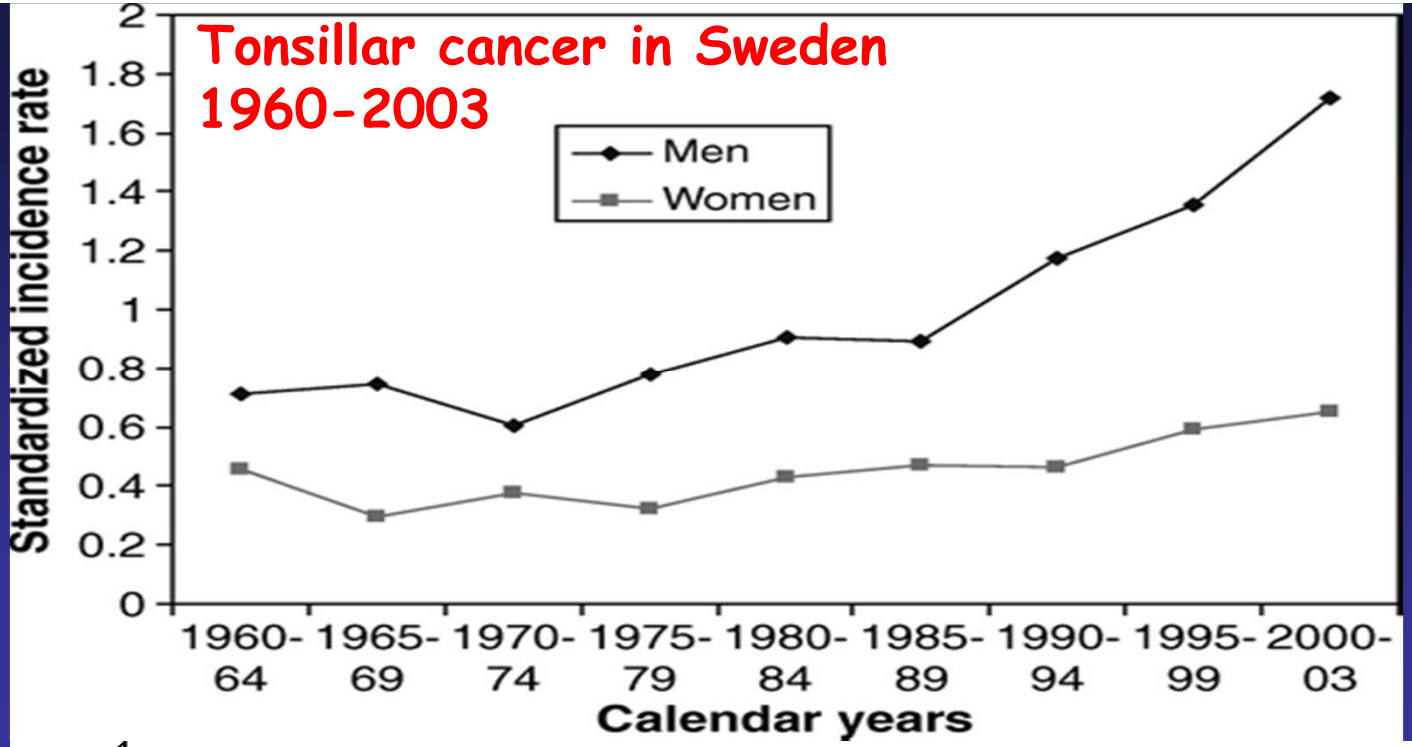
Increasing Incidence of Anal Cancer: Example of Scotland and England[1]

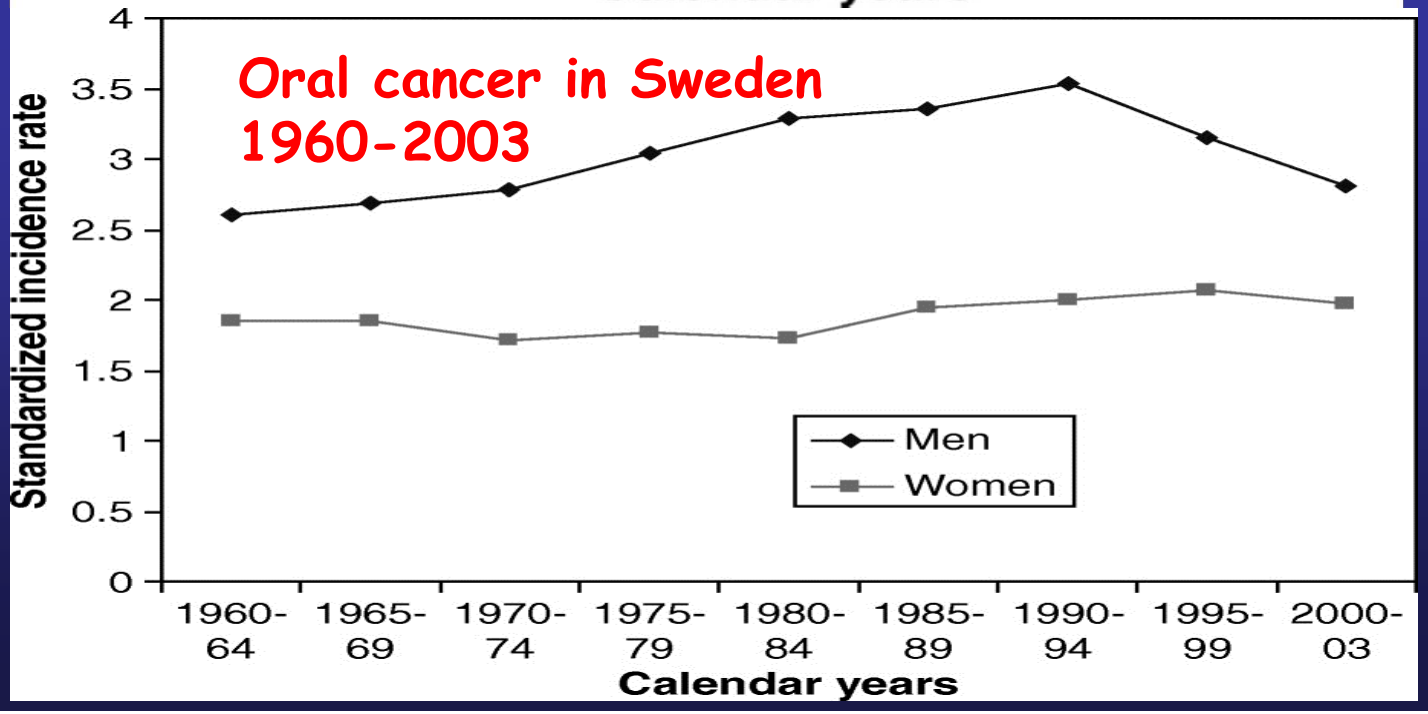
- Since the 1970s, the incidence of anal cancer in Scotland has more than doubled in both sexes.
- Incidence rates in England from 1986 to 2003 also nearly doubled in both men and women.



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.

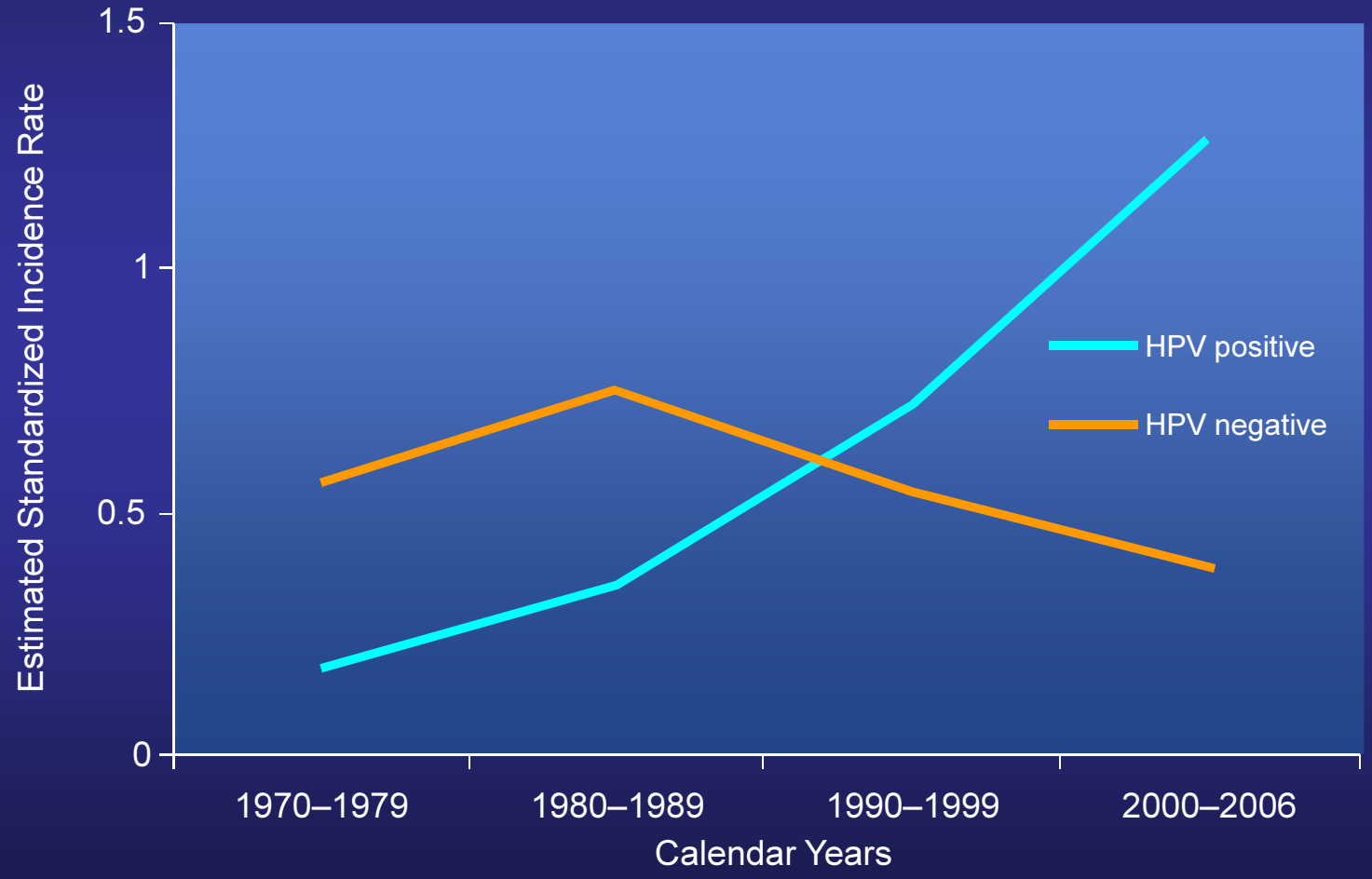




Hammarstedt etal
Acta
Otolaryngologica
2007, 9.988

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.

Estimated Cost Per QALY Gained of Male Vaccination

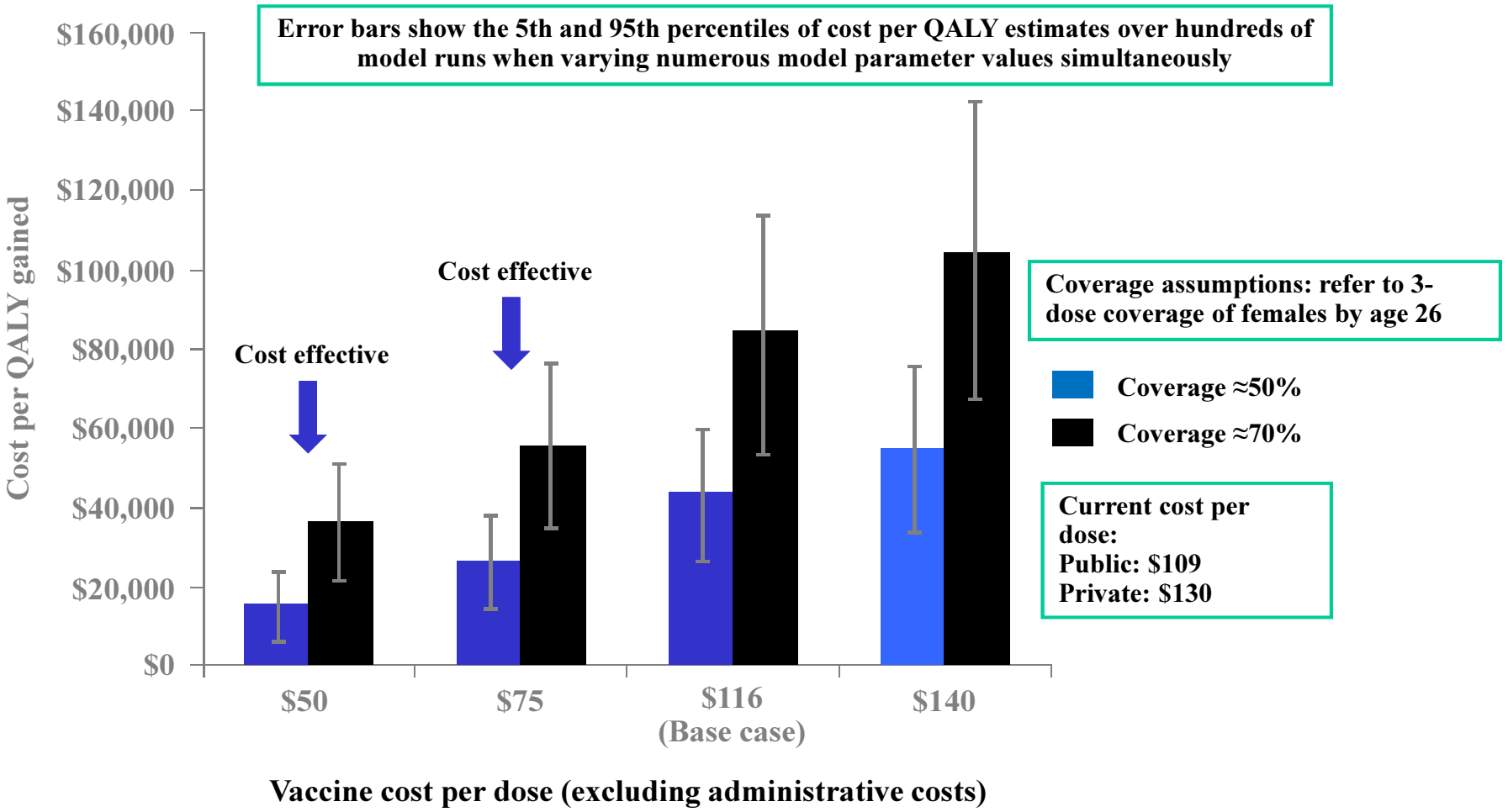
Outcomes		Female Coverage (3-dose)			
		20-45%	50%	70- 75%	80- 90%
Cervical	Taira, 2004	$41,000	-	$442,000	-
Cervical + Genital warts (M/F)	Elbasha, 2007	-	$24,000	$42,000	$128,000
	Jit (UK), 2008	-	-	-	. $1,000,000
Cervical + Genital warts (M/F) + Non-cervical cancers (M/F) RRP (M/F)	Kim, 2009	-	$62,000	$91,000	-
	Elbasha, 2010	$24,000	$27,000	-	$39,000
	Chesson, Preliminary	$24,000	$43,000	$84,000	$192,000

Base Case

Chesson H. ACIP February, 2011

Adapted from Chesson H. Presented at the Advisory Committee on Immunization Practices Meeting. February 24, 2011.

Cost Per QALY Gained Vaccinating 12-Yr-Old Boys, All HPV Outcomes—USA CDC Model



CDC=Centers for Disease Control and Prevention; QALY=quality-adjusted life year.

CDC Vaccine Price List: http://www.cdc.gov/vaccines/programs/vfc/cdc-vac-price-list.htm.

Adapted from Chesson H. Presented at the Advisory Committee on Immunization Practices Meeting. February 24, 2011.

The burden of HPV associated disease in men is equivalent to that in women in industrialised countries

High vaccine coverage (>70%) in women should give herd immunity for MSW
this makes male vaccination not cost effective if vaccine cost per dose is high

MSM are not protected in this scenario but targeting MSM for vaccination is likely to be ineffective, stigmatising, discriminatory

may threaten vaccine uptake in females

Next generation vaccines
broad protection
cheap

Polyvalent HPV VLP vaccines

MSD Merck is conducting phase III clinical trials of an nonavalent vaccine comprising L1 VLPs of types
6, 11, 16, 18, 31, 33, 45, 52, and 58

Advantages: Proven technology; potential for decreasing Cx Ca risk by 90% vs 70% for Garadsil

Issues: Increased cost of production. Large efficacy trials to demonstrate increased efficacy.

Courtesy Dr John Schiller NCI

Many Other 2nd Generation Candidates Are Being Developed

Protein:

- Alternative VLP production systems:
  E. coli, Pichia, Hansenula, Plants
- L1 pentameric subunits
- L2-polypeptides – many variations

Vectored:

- L1 recombinant AAV
- L1 recombinant Salmonella vaccine
- L1 recombinant Measles vaccine
- L1 AcHERV

Thank you

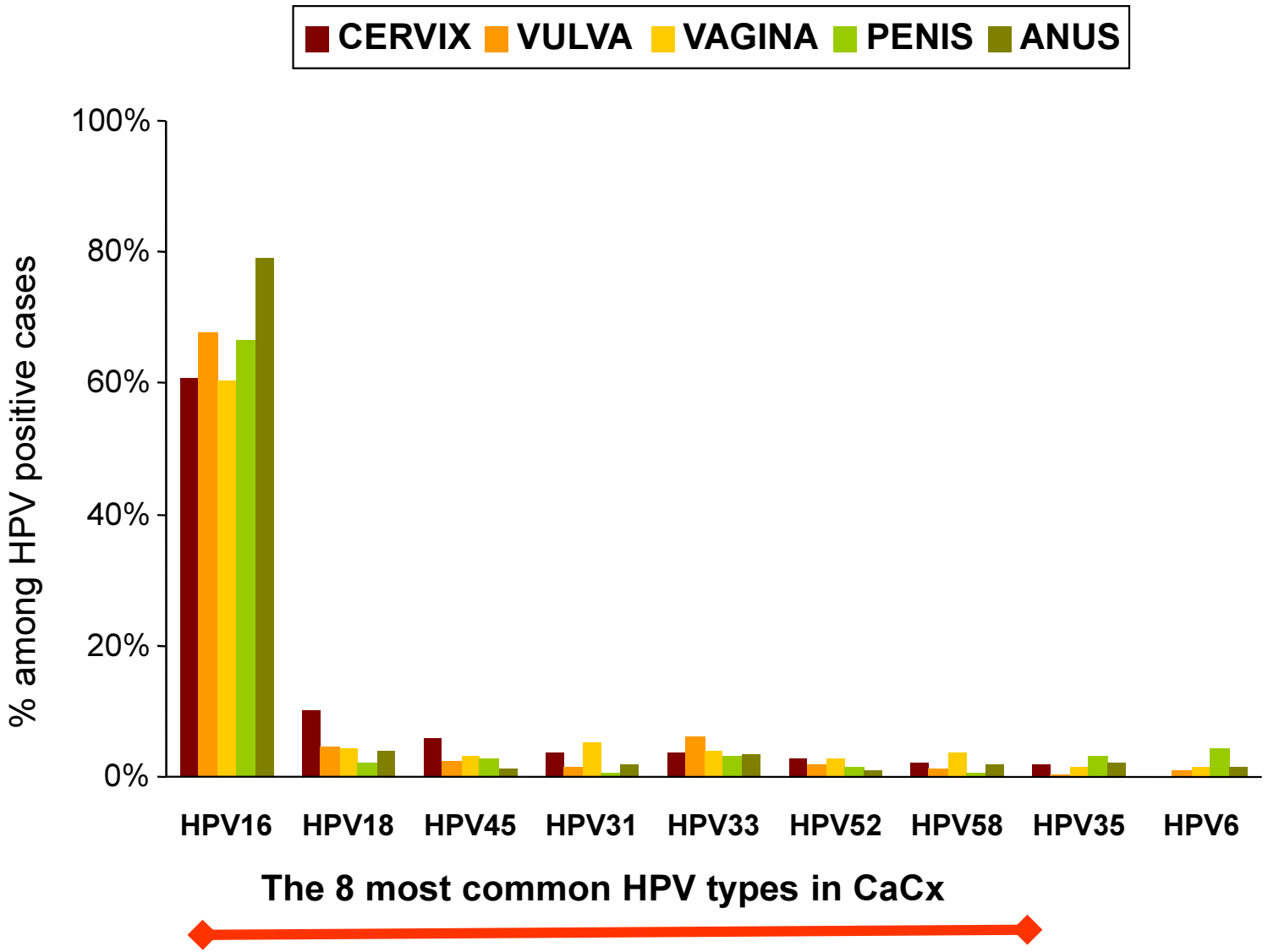
Using vaccine efficacy against persistent infection with data generated in the qHPV vaccine clinical trial in Australia

- models predict female-only vaccination will reduce HPV 6 incidence by:
  - 92%[1] and 80% in females and males, respectively
  - **97% and 95%** under female-plus-male vaccination
- Female-only vaccination is predicted to reduce HPV 16 incidence by:
  - 74%[2] and 42% in females and and males, respectively
  - compared to **81% and 73%** under female-plus-male vaccination.

1 Donovan et al Lancet Inf Dis 2011

2 Tabrizi et al JID 2012

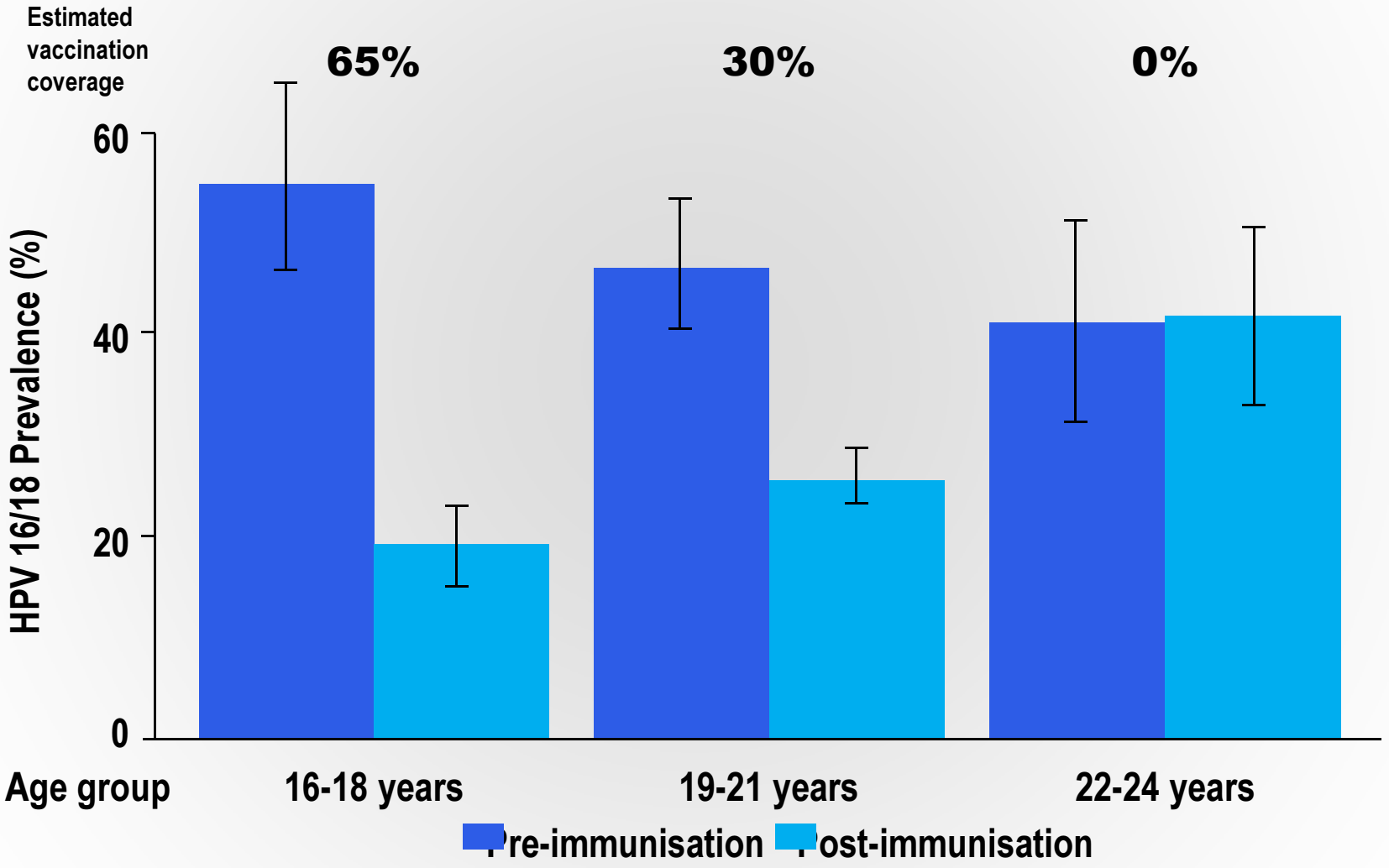
RELATIVE CONTRIBUTION of HPV 16,18,45,31,33,52,58,35 & 6



Courtesy Dr X Castellsague ICO

Updated: June 1st, 2010

HPV 16/18 Prevalence By Age: Pre- vs. Post-immunisation Amongst Those Testing HR HPV Positive (England)



HC2 positive tested by Linear Array (Howell-Jones et al, *Vaccine*, 2012). Luminex-based genotyping system.

Mesher D et al. Presented at the 28th International Papillomavirus Conference. San Juan, Puerto Rico. November 30 – December 6, 2012.

British HIV Association

BHIVA

19th Annual Conference of the British HIV Association (BHIVA)

16–19 April 2013

Manchester Central Convention Complex