



HPV vaccine and cervical cancer prevention

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Introduction of new vaccines into national
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Outline of presentation

- Cervical cancer
- Human papillomavirus (HPV)
- HPV vaccines
- Public health considerations

Cervical cancer worldwide

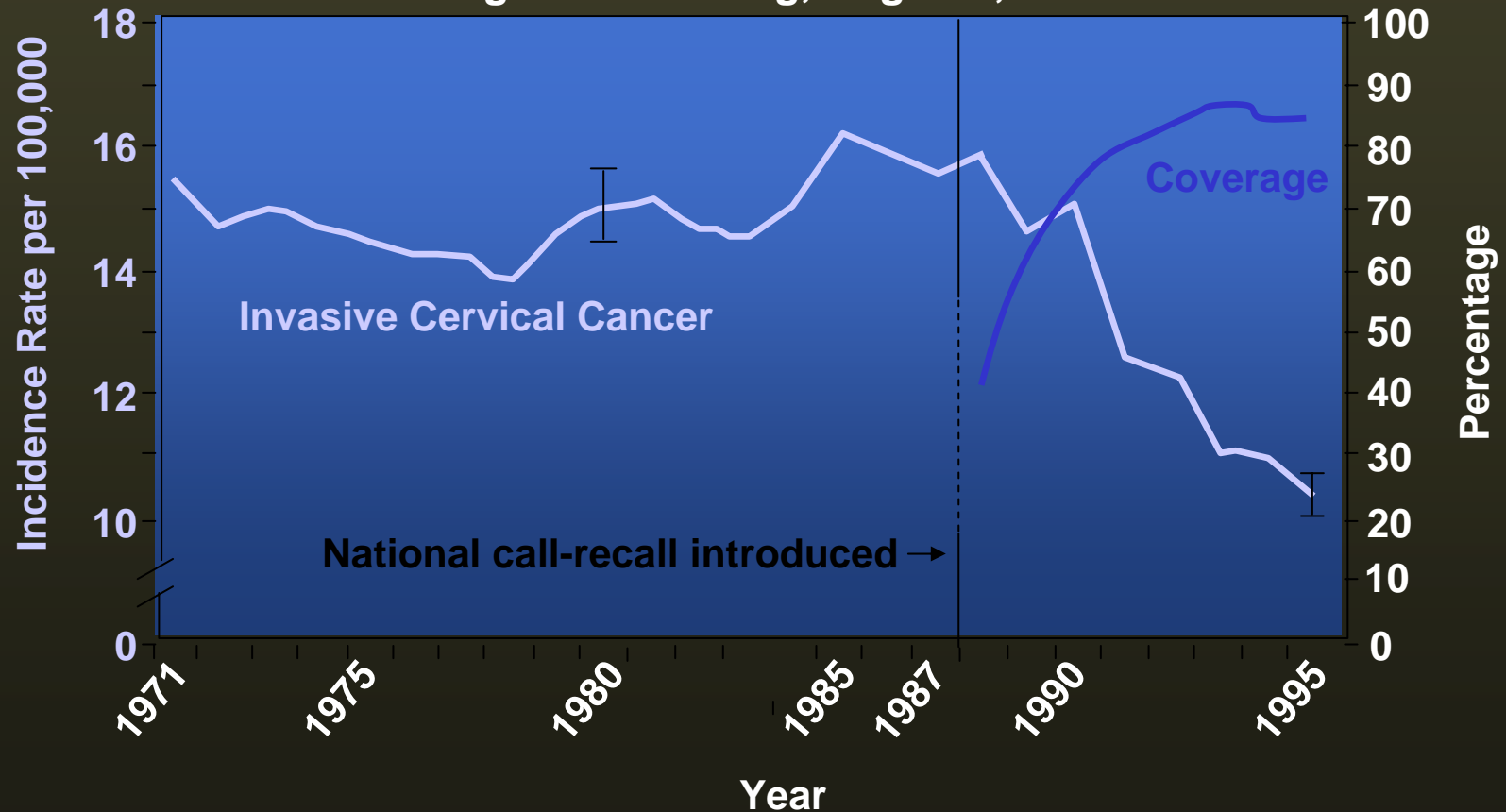
- 493,000 women affected each year
- 274,000 deaths annually
- Cervical cancer is the second largest cause of cancer deaths in women worldwide
- 80% are in developing countries (>90% by 2020)
- Cervical cancer is a global public health problem that disproportionately affects poor women in developing countries
- Cervical cancer is the first cause of cancer in African women
- 6742 new cases annually in South Africa
- 3681 deaths annually in South Africa

Cervical cancer screening

- Incidence and mortality of cervical cancer much reduced in industrialised countries by screening based on cervical cytology (Pap smears) - less impact on adenocarcinoma
- Screening programmes difficult to implement in low-resource settings
- “Opportunistic” screening is not very effective; should be well organised programmes with high coverage (call/recall system)

Improvements in Screening Coverage Can Reduce the Incidence of Cervical Cancer

Age-standardized incidence of invasive cervical cancer and coverage of screening, England, 1971–1995

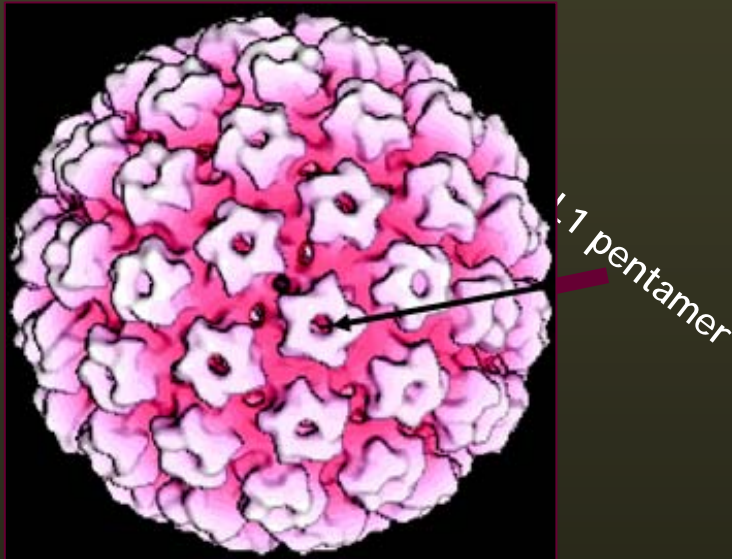


Quinn M, Babb P, Jones J, Allen E. *BMJ*. 1999;318:904-908.
Adapted with permission from the BMJ Publishing Group.

Cervical cancer and Human Papillomavirus

- 1980s → discovery of link between cervical cancer and HPV - Prof. Harald Zur Hausen (Heidelberg, Germany) got the Nobel Prize for this last year
- Chronic infection with high-risk or oncogenic HPV types are essential for the development of cervical cancer
- Oncogenic HPV detected in more than 99% of cervical cancers

Cervical cancer is caused by a virus called the Human Papillomavirus



The rosette-like surface structures (arrowed) are pentamers each consisting of five molecules of L1; one molecule of L2 fits into the centre of each pentamer

- Small, double-stranded DNA viruses that infect the epithelium.
- Icosohedral viral capsid is composed of two proteins, L1 and L2.
- More than 100 HPV types identified based on the genetic sequence of the outer capsid protein L1.
- Most HPV types infect cutaneous epithelium.
- 40 types infect the mucosal epithelium.

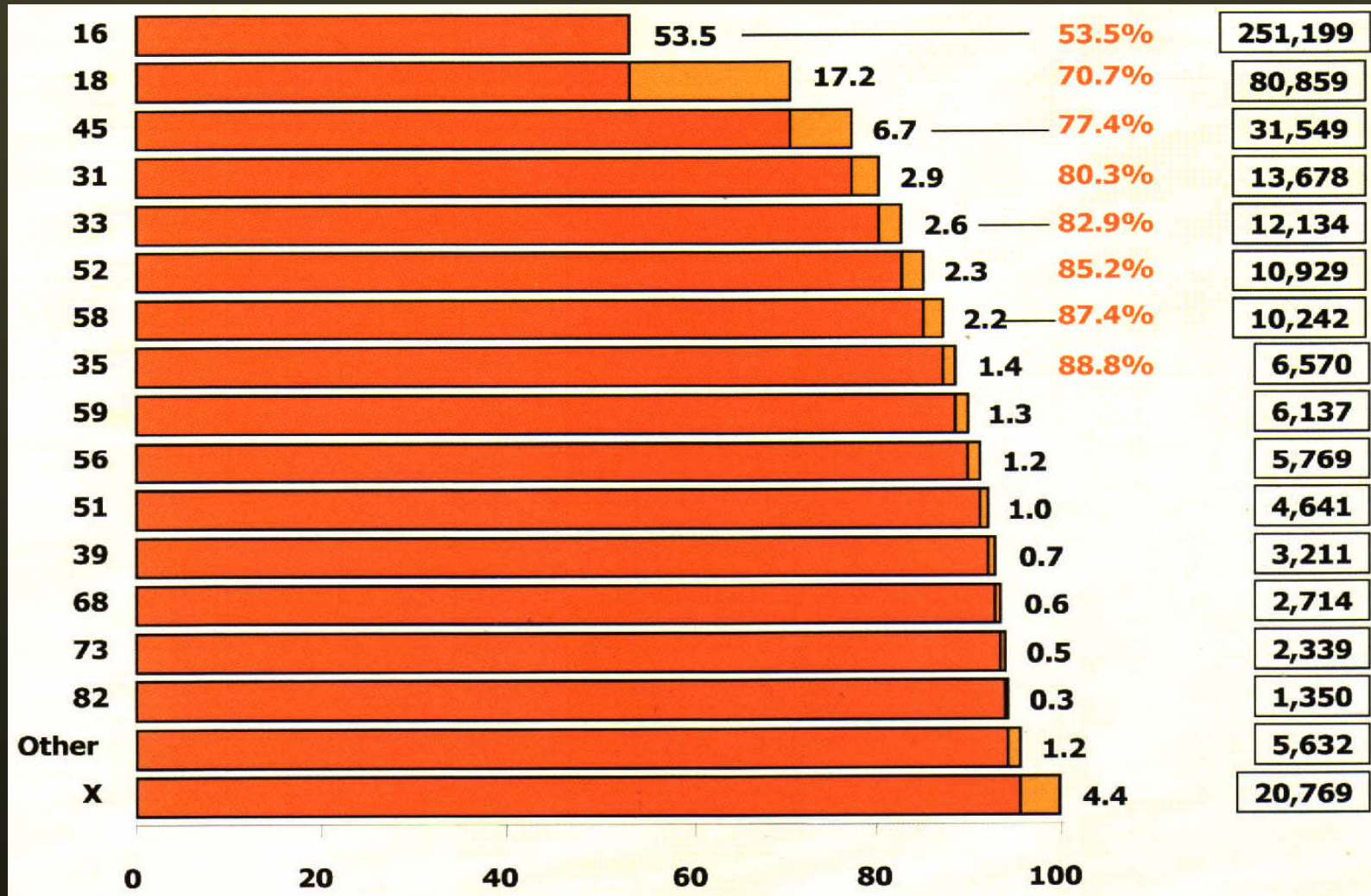
HPV genotypes

- High risk or oncogenic HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82
→ 16 and 18 cause 70% of cervical cancer
- 3 HPV types classified as probable high-risk types: 26, 53, 66
- Low risk or non-oncogenic types: 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, CP6108
→ 6 and 11 cause genital warts

Estimates of global burden of HPV associated cancer

- 100% cervical cancers
- 90% anal cancers
- 40% of cancers of the vulva, vagina and penis
- 12% of cancers of the oropharynx
- 3% of cancers of the mouth

HPV genotype distribution in cervical cancer: worldwide estimates (N=469,723)



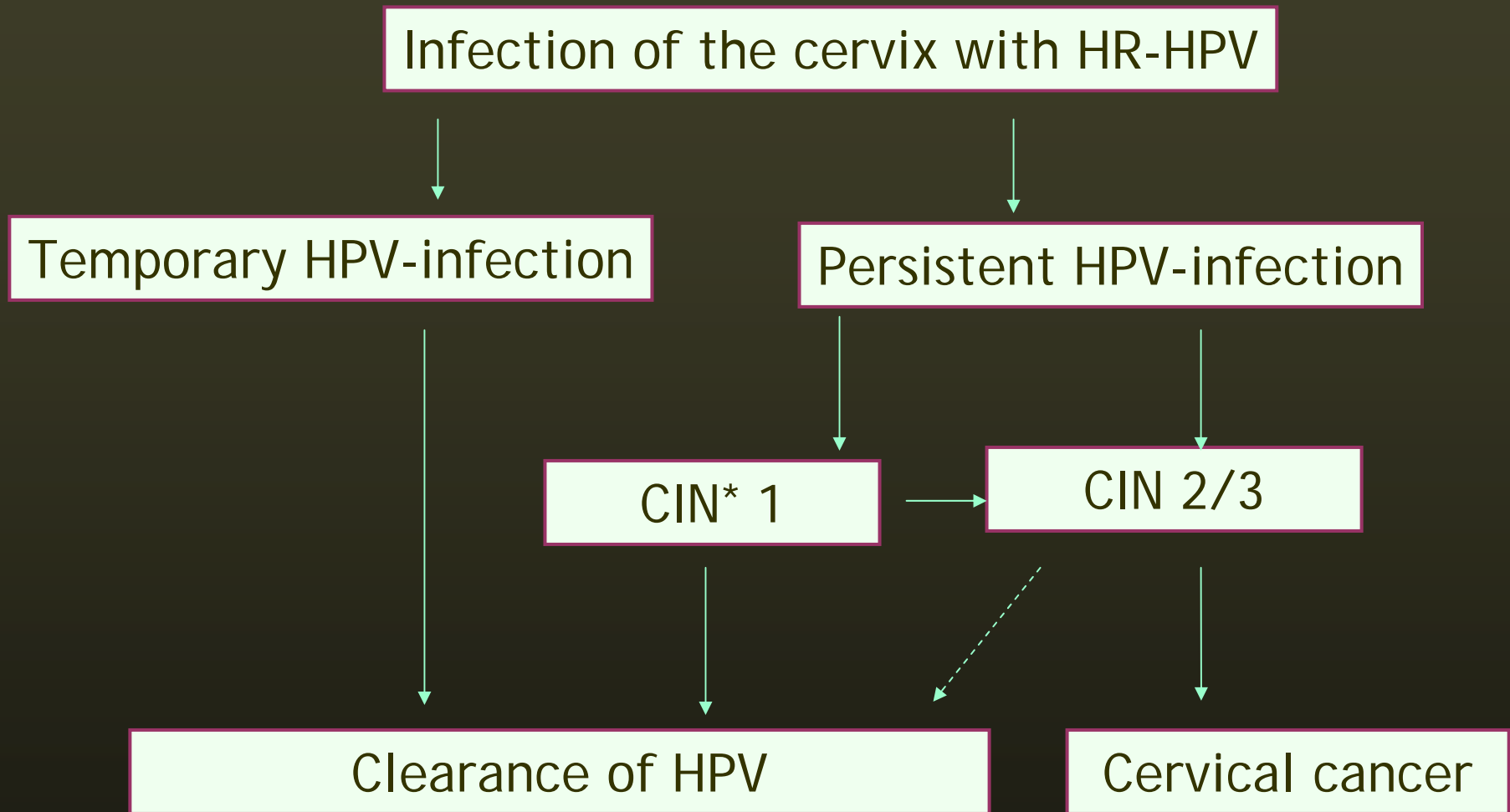
HPV infection and cervical cancer

- Almost all Cervical Cancer is due to high-risk HPV
- Up to 80% of women will acquire an HPV infection in their lifetime^{1,2} and 50% of these infections will be with a high-risk HPV type³
- HPV infection often acquired within 2-5 years after sexual debut
- Most infections are asymptomatic and are cleared within 2 years
- Only a fraction of women (chronically) infected with high-risk HPV will develop cervical cancer, most infections resolve spontaneously

1. Bosch FX, de Sanjose S. *J Natl Cancer Inst Monogr* 2003; 3-13

2. Brown DR, et al *J Infect Dis* 2005; 191: 182-192 3. Baseman JG, Koutsky LA. *J Clin Virol* 2005;32 Supp I: S16-24

Natural history of HPV infection

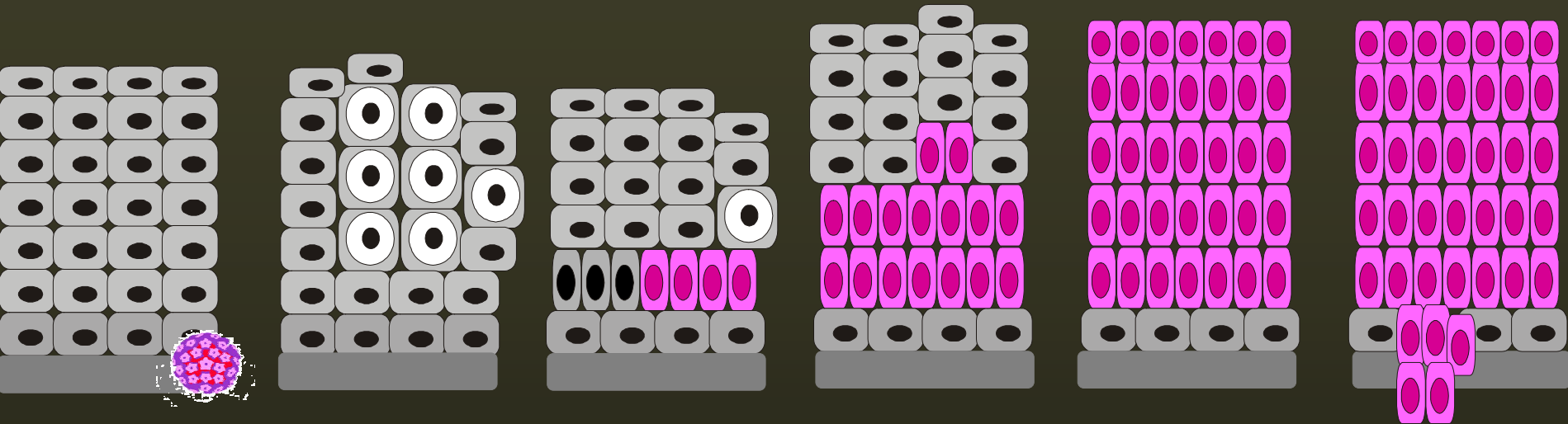


*CIN: cervical intraepithelial neoplasia

Progression to Cervical Cancer

Within months after sexual debut

Years



Normal epithelium

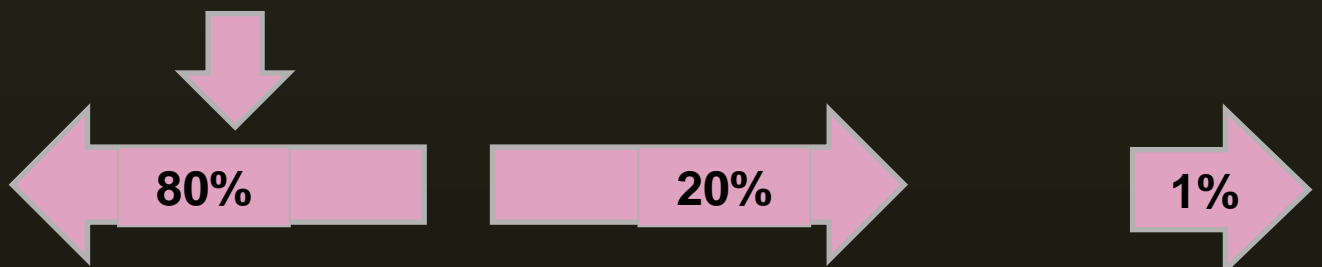
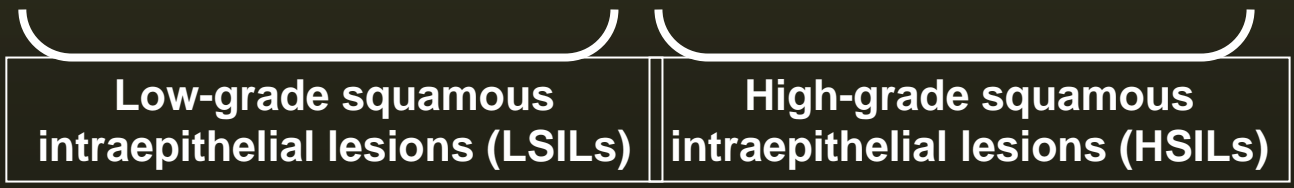
HPV infection; koilocytosis

CIN I

CIN II

CIN III

Carcinoma



Antibody responses are relatively poor after natural HPV infection

- Only 50-60% of women develop serum antibodies to HPV after natural infection
- No viraemia
- HPV does not induce cell death
 - no inflammation
 - no pro-inflammatory cytokines
 - downregulation of antiviral pathways in the cell
 - poor activation of epithelial antigen presenting cells (APC)
 - free virus particles are shed from mucosal surfaces with poor exposure to APCs

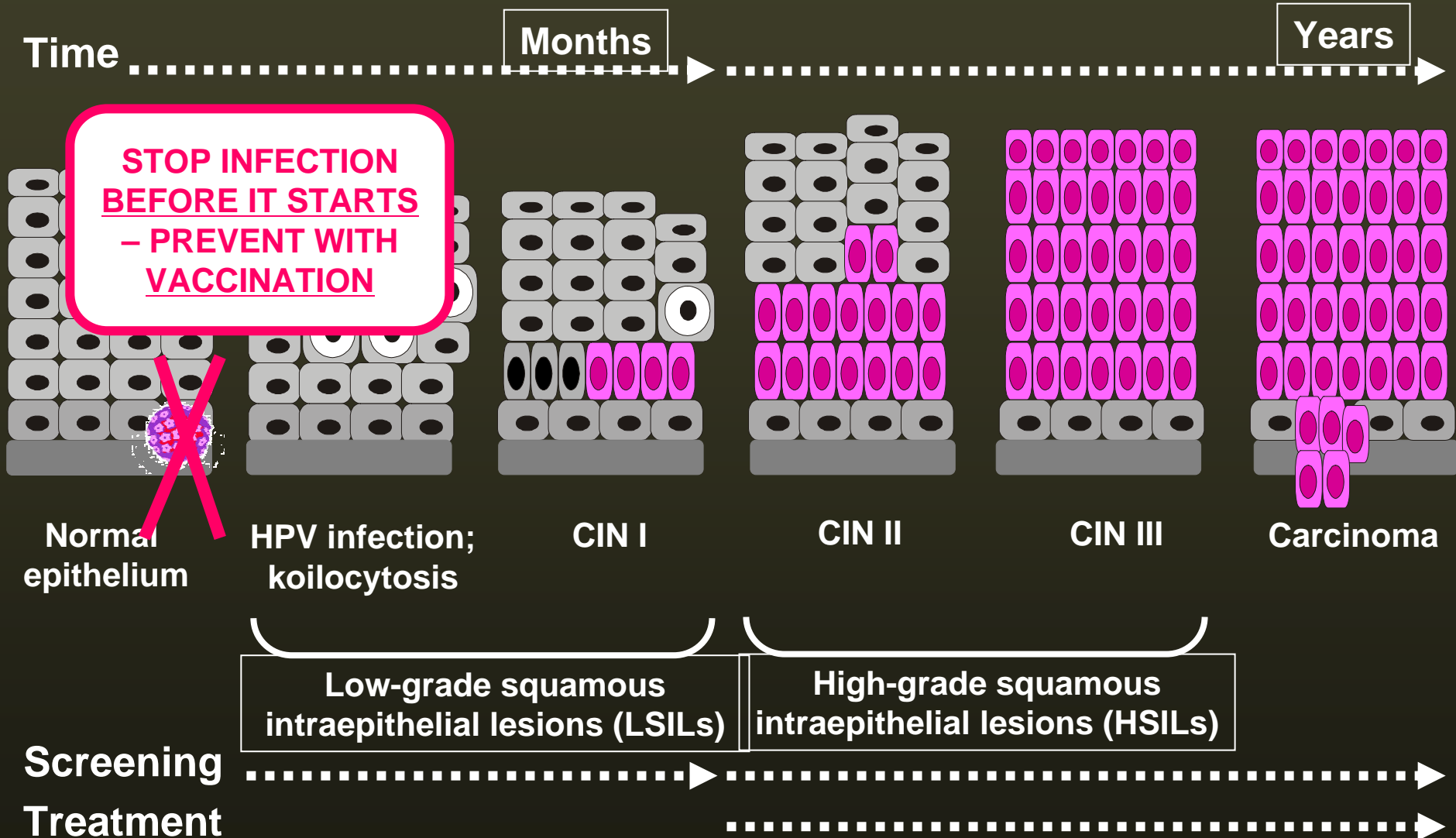
Risk factors

- Persistent infection with high risk (oncogenic) HPV is the necessary cause of cervical cancer
- Factors that could be adding to the risk of persistent HPV infection and cervical cancer:
 - Smoking
 - High parity
 - Long-term use of oral contraceptives
 - Immuno-suppression

HPV and HIV

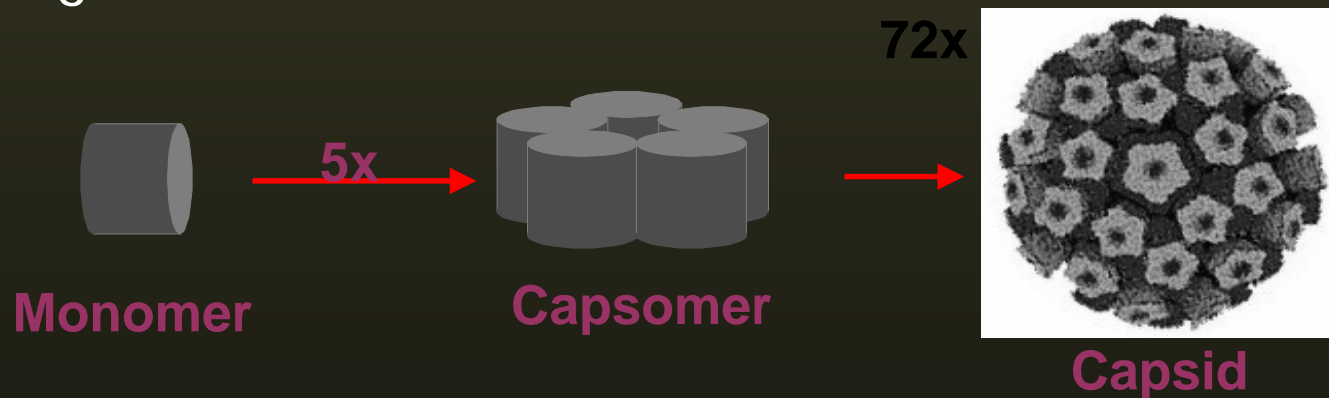
- Prevalence of HPV infection much higher in HIV infected women
- Higher HPV viral load in HIV infected women
- Infection with multiple HPV genotypes is more common in HIV positive women
- HIV positive women at greater risk of lower genital tract cytological/histological abnormalities and (pre) cancers including vulvar and anal cancers.
- HIV positive women with invasive cervical cancer almost 5-10 years younger than HIV sero-negative women.

Role of vaccination



Human Papillomavirus-Like Particles as HPV Vaccines

- Prophylactic vaccines are based on recombinant L1 proteins self-assembled into VLPs.
- L1 is expressed in yeast or baculovirus expression systems, and the protein self-assembles into virus-like-particles (VLP).
- VLPs are non-infectious (contain no DNA) and non-oncogenic.



- Safe, immunogenic and well tolerated

Quadrivalent vaccine

- Produced in Yeast
- HPV types 6, 11, 16, 18,
- Protects against cervical Neoplasia caused by HPV 16 and 18 – some cross protection against other HPV types
- Protects against genital warts caused by HPV 6 and 11
- Adjuvant: aluminium hydroxyphosphate sulphate
- Schedule 0, 2, 6 months
- Intramuscular injection
- Liquid, storage 2°C – 8°C; must not be frozen

Bivalent vaccine

- Baculovirus expression system
- HPV types 16,18
- Protects against cervical Neoplasia caused by HPV 16 and 18 – some cross protection against other HPV types
- Does not prevent genital warts
- Adjuvant: ASO4 (aluminium hydroxide and 3-deacylated monophosphoryl lipid A)
- Schedule: 0, 1, 6 months
- Intramuscular injection
- Liquid, storage 2°C – 8°C; must not be frozen

HPV vaccines: Immunogenicity/safety

- Both vaccines are highly immunogenic and produce high levels of antibodies that are substantially greater than those produced during natural infections
- Antibody levels after vaccination inversely related to age
- Antibody levels in young adolescents in bridging studies (9-14 years old) higher than in adolescents/young adults (15-25 years old)

HPV vaccines: Immunogenicity/safety

- Duration of protection up till 6.4 years
- Experimental booster after 5 years showed immunologic memory
- Safety profile (adverse events):
 - Mild local reactions: pain, swelling
 - Fever, nausea
 - No differences in the proportion of women developing a serious adverse event in the vaccine or placebo group

Bivalent HPV vaccine

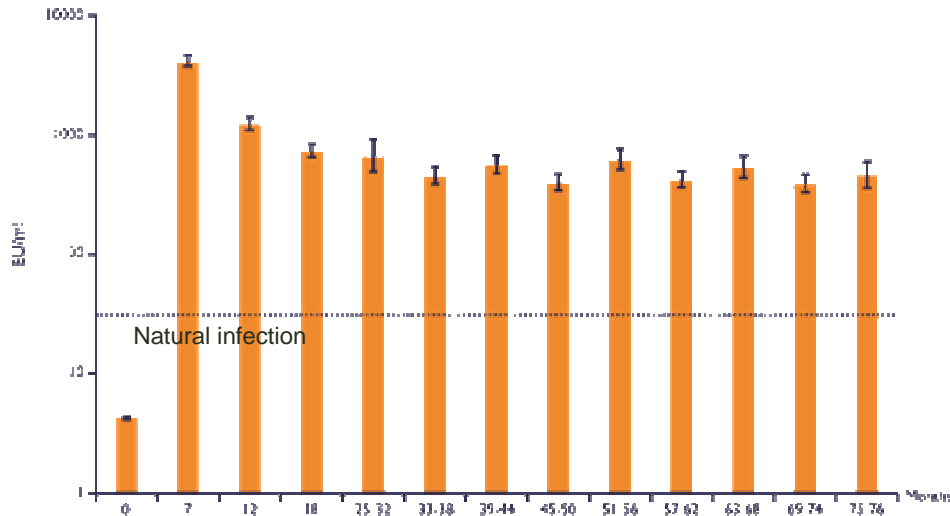
Protection against HPV 16/18 CIN 2/3+

776 women, 15-25 years of age at time of vaccination

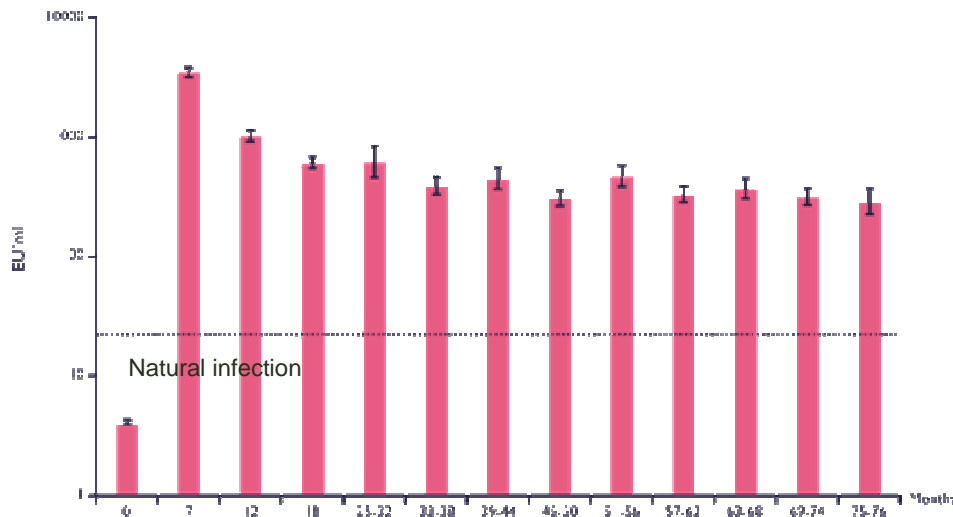
HPV 16/18 related CIN2+	Bivalent vaccine	Control	Vaccine efficacy
	n	n	%
27 months ¹	0	3	100
4.5 years ²	0	5	100
5.5 years ³	0	7	100
6.4 years ⁴	0	9	100

1. Harper et al. 2004. Lancet 364: 1757.
2. Harper et al. 2006. Lancet 367: 1247-1255.
3. Presentation Gall 2007, AACR, abstract 4900
4. Presentation Harper 2008, SGO.

ELISA titers through 6.4 years after bivalent HPV vaccination



More than 98% of women remain seropositive for both HPV-16 and 18 up to 6.4 years



Bivalent vaccine

Cross protection against 6 months persistent infection - phase III study

Causal HPV type	Vaccine		Placebo		Efficacy
	N	Cases	N	Cases	
Type 45	6734	10	6747	25	59.9
Type 31	6615	47	6667	74	36.1
Type 33	6702	31	6736	49	36.5
Type 52	6532	79	6573	116	31.6
Type 58	6688	43	6734	33	-31.4

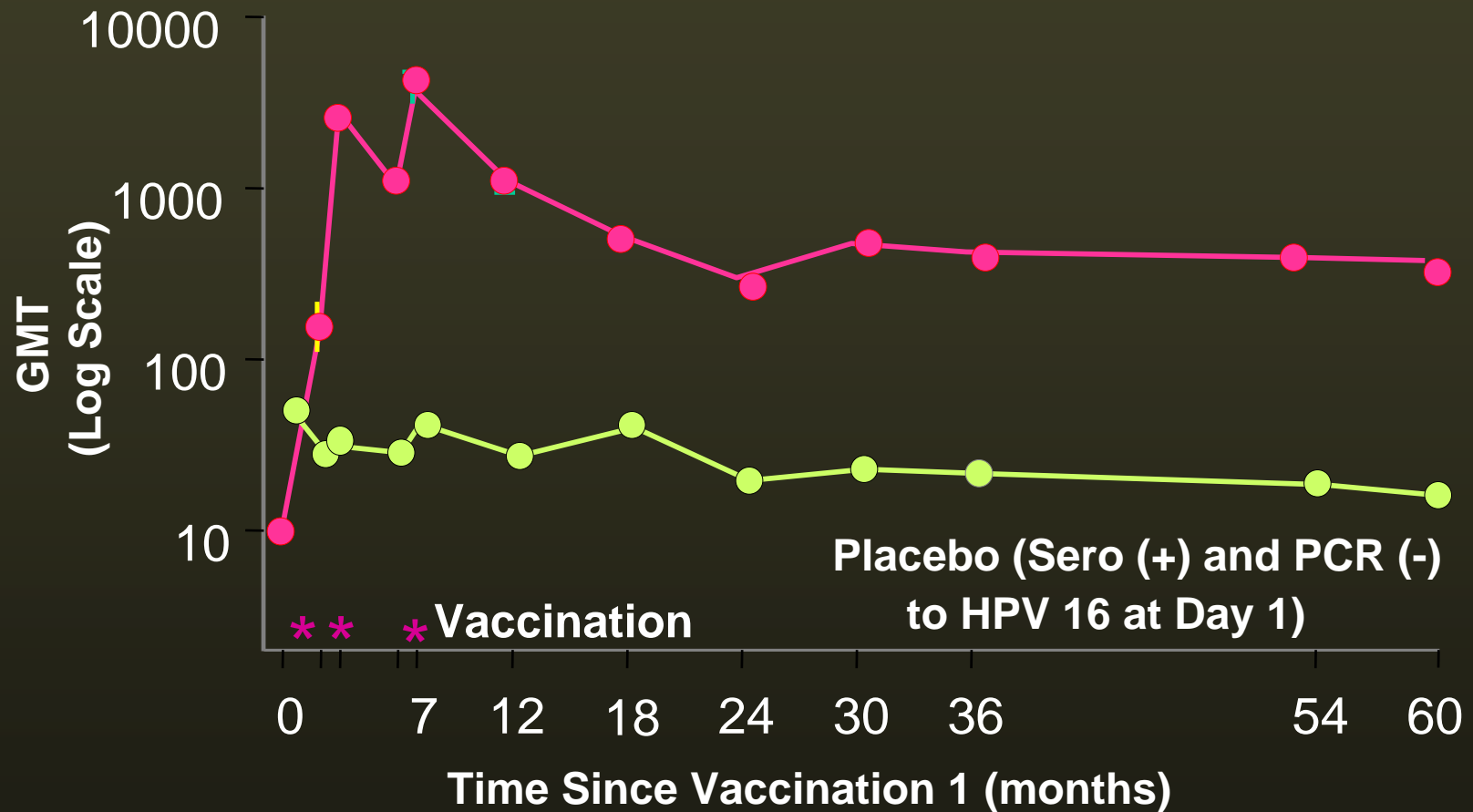
Quadrivalent HPV vaccine efficacy

CIN & AIS

Per-protocol population (protocols 007, 013, 015)
End-of-study data, mean follow-up 44 months

Endpoint	Vaccine	Placebo	
	N=9075	N=9075	% Efficacy
HPV 6/11/16/18 related CIN or AIS	9	225	96
By Type			
HPV 6-related	0	47	100
HPV 11-related	0	12	100
HPV 16-related	8	137	94
HPV 18-related	1	61	98
By Disease			
CIN 1	7	170	96
CIN 2/3	2	110	98
AIS	0	7	100

Quadrivalent vaccine: Five-year duration of antibody titers against HPV type 16



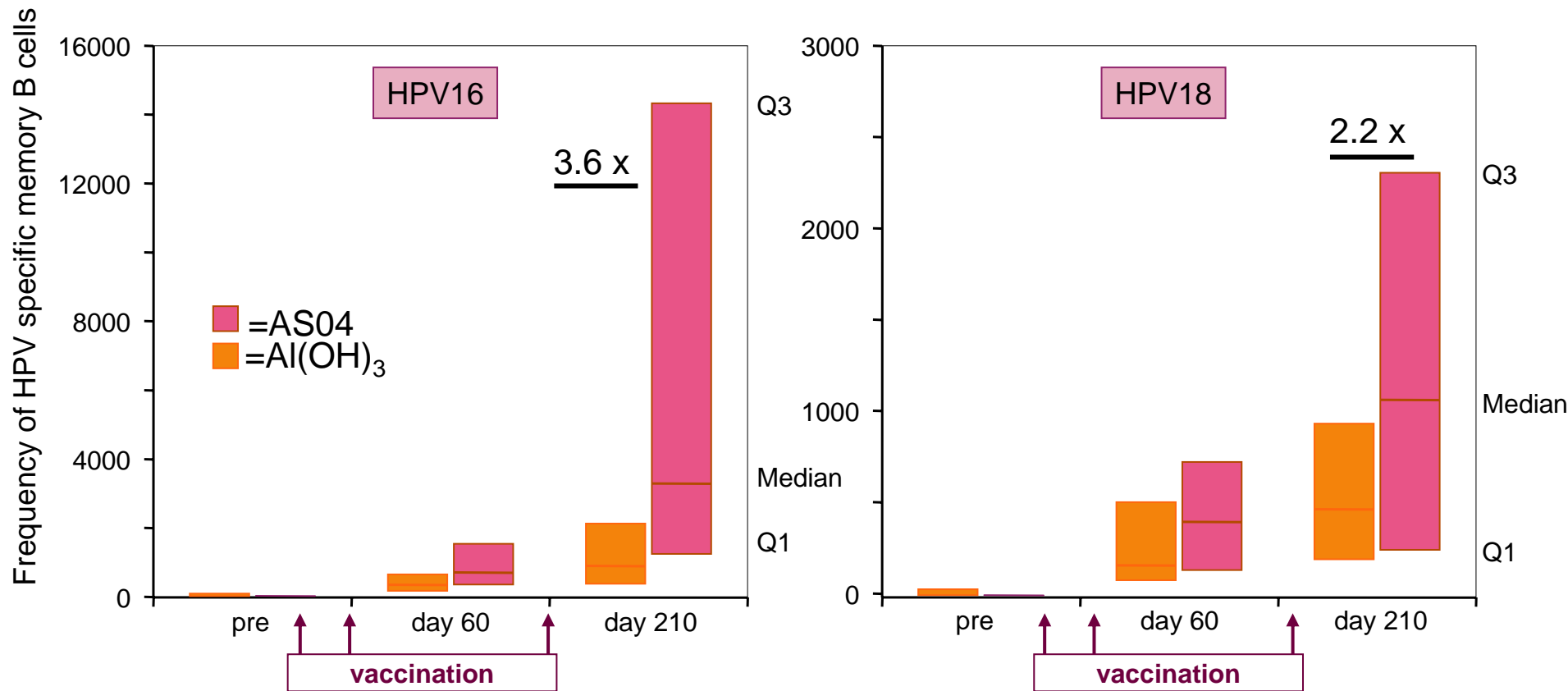
Quadrivalent vaccine

Cross protection against CIN 2/3 and AIS

	Vaccine	Placebo	
Causal HPV types	N=4616	N=4680	Efficacy
31, 45	11	27	59%
31,33,45,52,58	44	66	33%
31,33,35,39,45,51,52,56,58,59	62	93	33%

Adjuvants

HPV vaccine candidate formulated with AS04 induces higher frequency of memory B cells as compared to the same vaccine formulated with **Al(OH)₃**



statistically significant ($p < 0.05$, Wilcoxon's test)

Giannini et al., *Vaccine* 2006; 24: 5937

Slide from Dr. Benninghoff

Public health considerations

- The risk for HPV infection starts from the first sexual encounter and lasts throughout a woman's life^{1,2}
- Prophylactic vaccine, not therapeutic → optimal if used before sexual debut

Public health considerations

- Ideal age group to vaccinate: 10-13 year old girls – not a standard target population (=adolescent vaccination).
- Implement vaccination in a one year cohort every year, e.g. 10, 11 or 12 years old; can be implemented for girls in last year of primary school/first year of secondary school.
- Catch-up vaccination in older adolescents and adult women?
 - Not recommended in a public health programme
 - Could be considered through private sector

Public health considerations

- Will targeting young adolescent girls for a vaccine to protect from a STI be a problem; communicate on HPV vaccine as a cancer prevention vaccine.
- Vaccinate both sexes?
 - Only modest benefit of male vaccination on herd immunity if coverage of females is sufficiently high (also not cost-effective now)
 - Vaccinating males could provide benefits against HPV-related penile, anal, head and neck cancers in males

Public health considerations

- Vaccine will impact on cancers caused by HPV types in vaccine but there is still need for a cervical screening programme to deal with HPV types not in the vaccine (simplified screening programme to be developed).

South Africa

- Bivalent and quadrivalent vaccines licensed in South Africa since March 2008
- Support for HPV vaccine
- National screening policy since 2000 → but difficulties in implementing
- Optimal target population: 9-15 year old girls, with a preference towards 9 years
- 95.5% of school aged children are enrolled in primary schools in SA → possibility for school based vaccination
- Communication as vaccine for cervical cancer prevention as opposed to focusing on the fact that HPV is sexually transmitted

Source: Harries *et al.*, Vaccine 27 (2009)

Study in Western Cape Province

Conclusions

- Cervical cancer is caused by a persistent oncogenic HPV infection.
- Immunogenic and safe prophylactic HPV vaccines are available.
- Prophylactic vaccine → optimal if used before sexual debut.
- Interaction between different disciplines: sexual and reproductive health, adolescent health, EPI and cancer control programmes.



Saving children's life through immunisation