HPV vaccines

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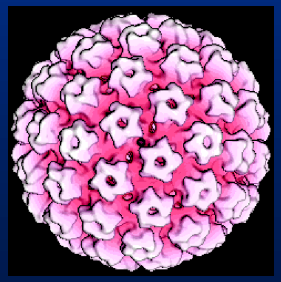
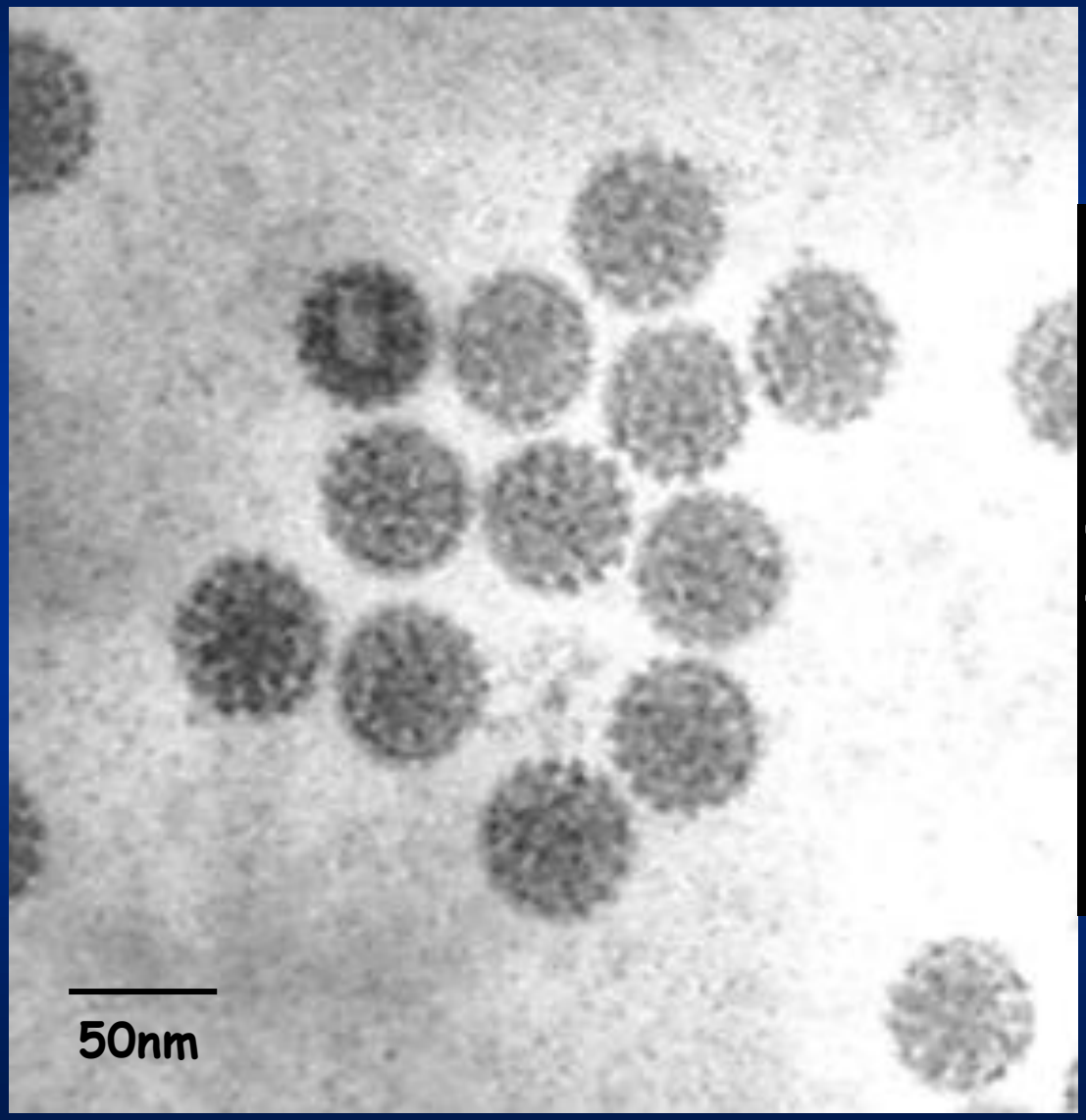
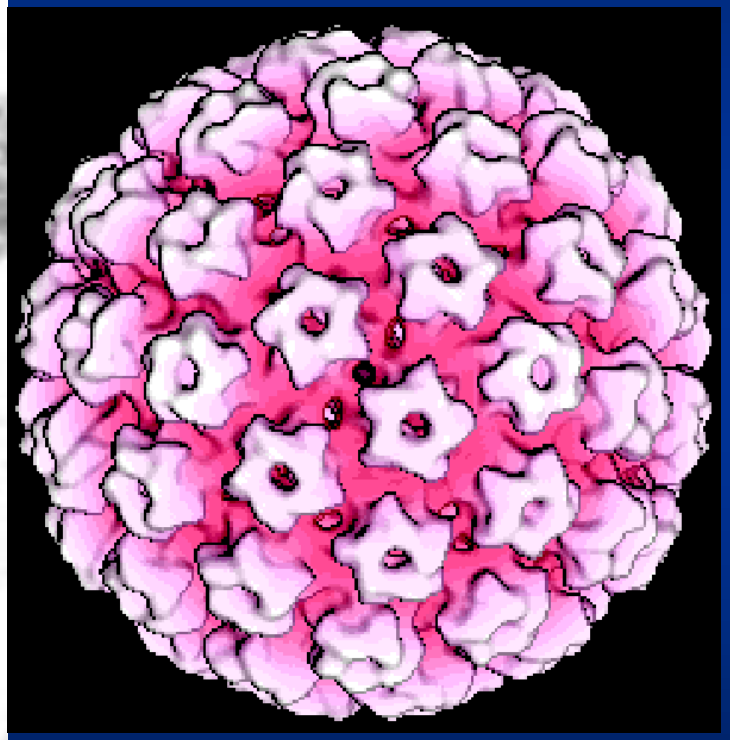


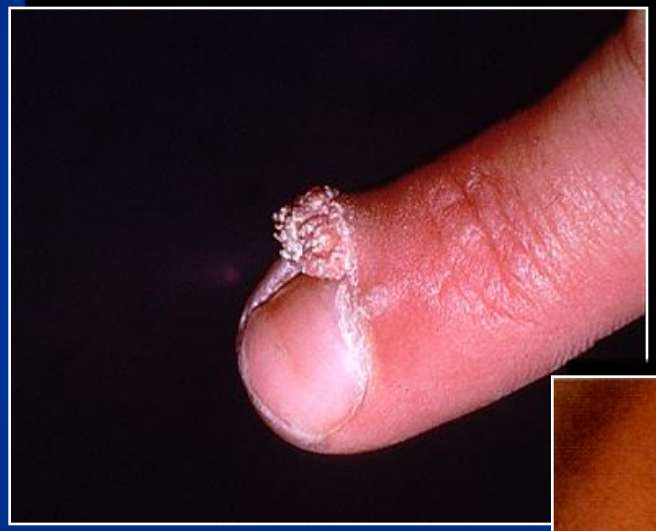
Human papillomavirus (HPV)



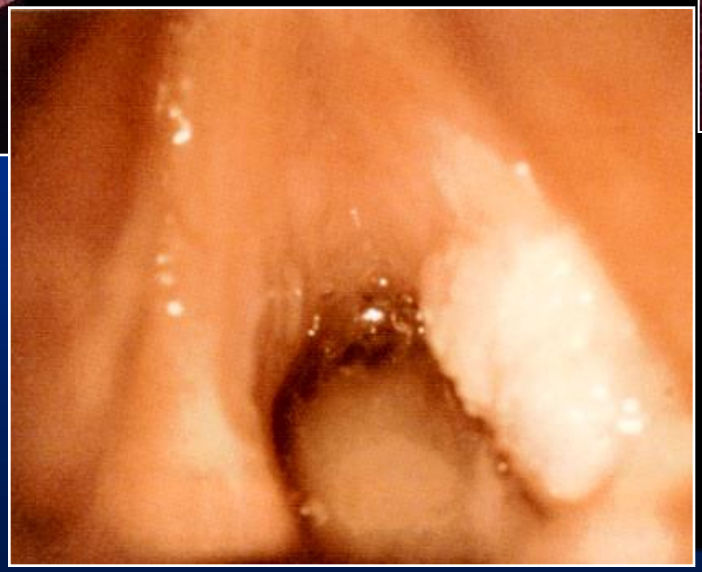


The humble wart

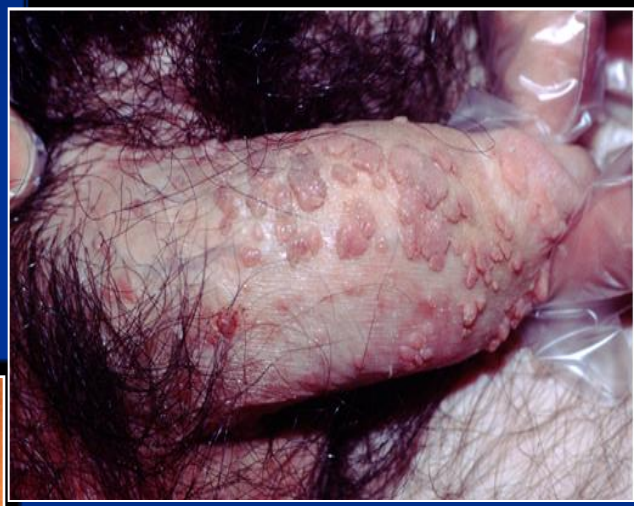
Common warts



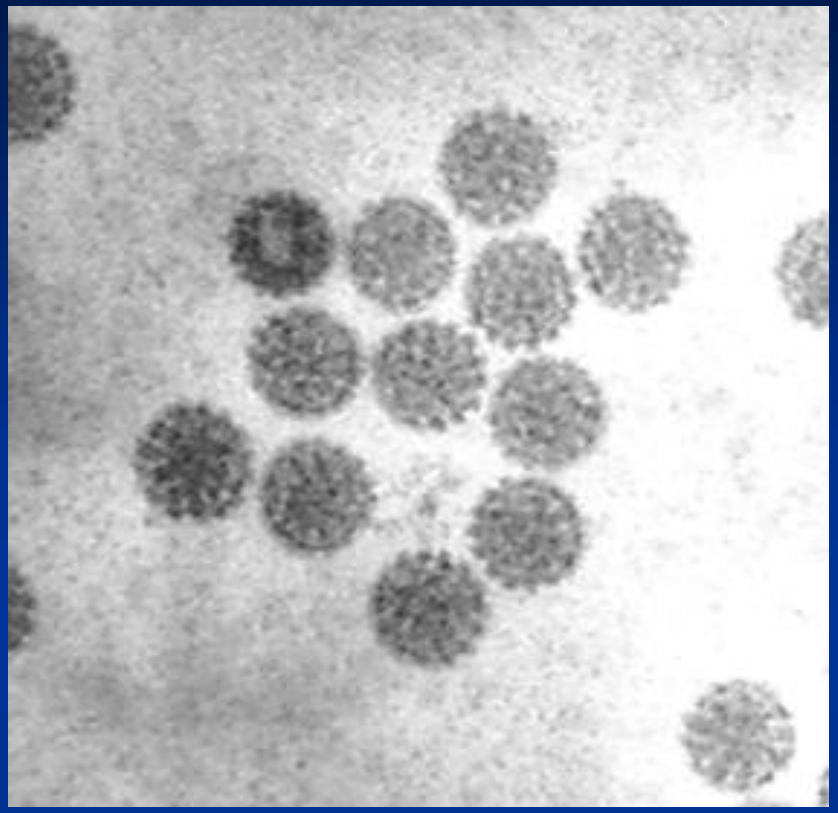
Laryngeal papillomas

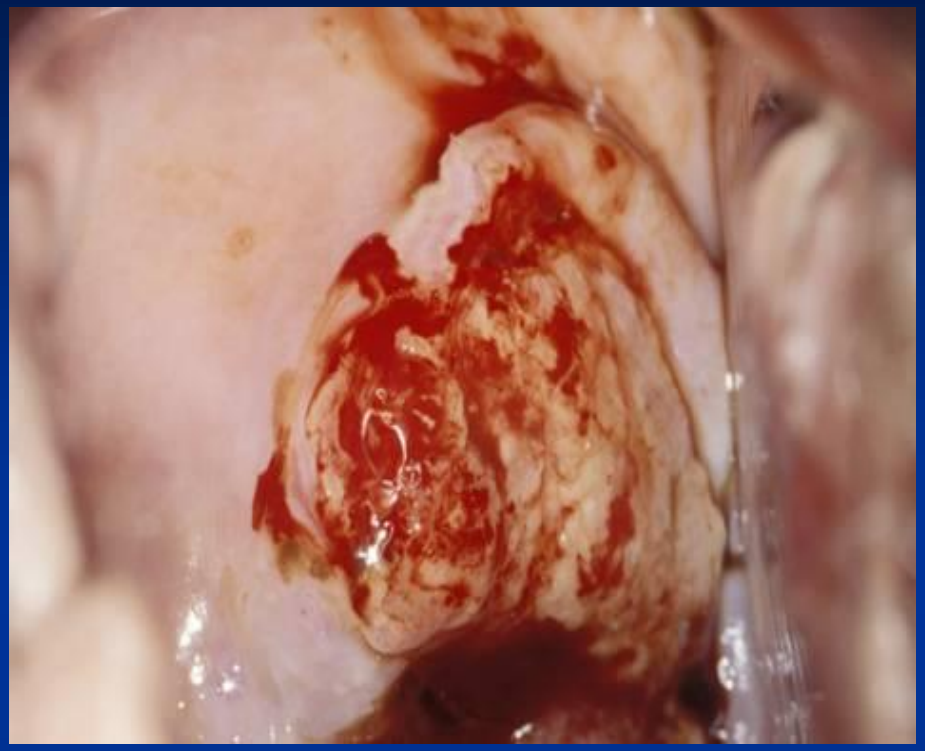


Condylomata acuminata



Luc Montagnier, Francoise Barre Sinoussi, Harald zur Hausen
Nobel Laureates in Medicine 2008





HPV

Cervical cancer

1983/1984

zur Hausen group detects HPV DNA in cervical cancers
new HPVs – HPV 16 and HPV 18

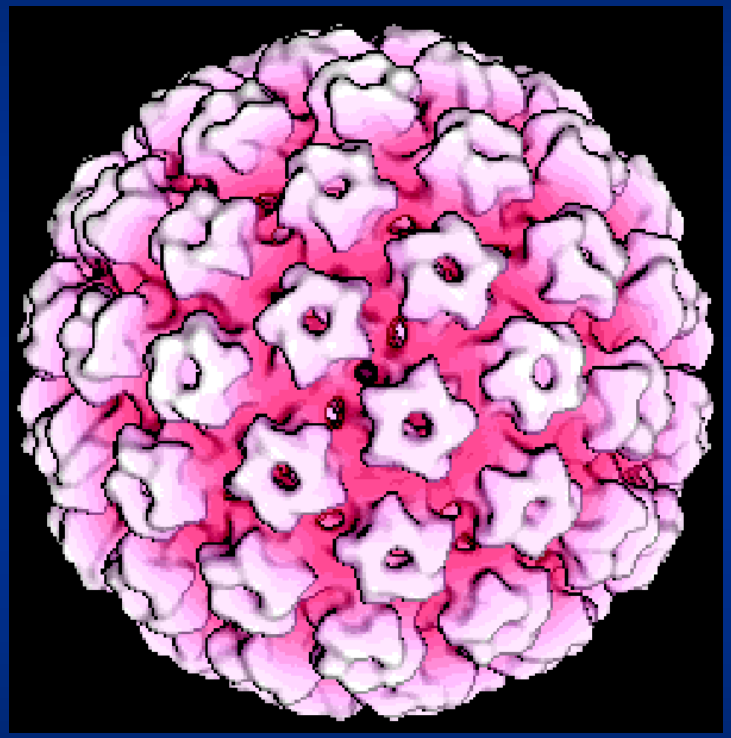
What are human papillomaviruses?

What diseases do they cause?

Prophylactic HPV vaccines

- Efficacy, Mechanism of Protection
- Who and when to immunise
- Implementation and Impact

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

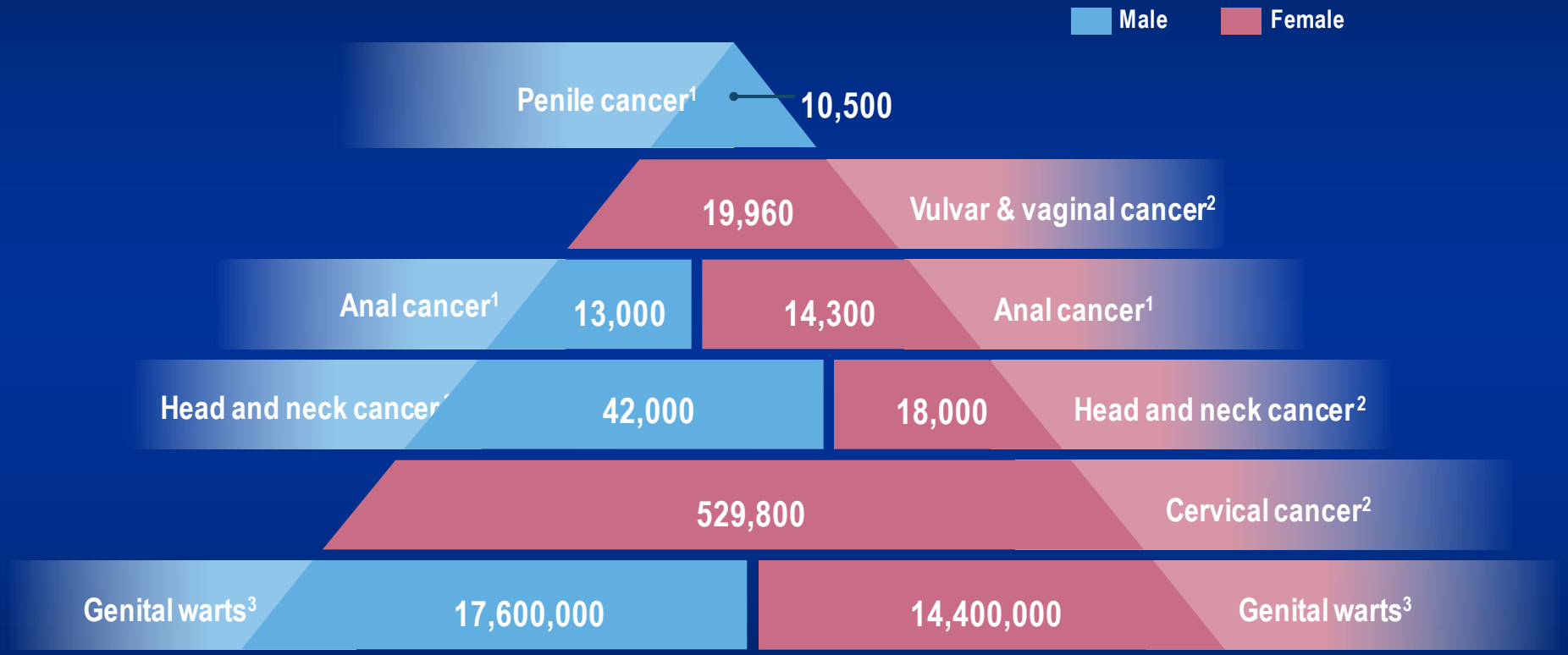
    16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59,68

    HPV 16,18 – most important

HPV associated benign and malignant disease is a global public health problem

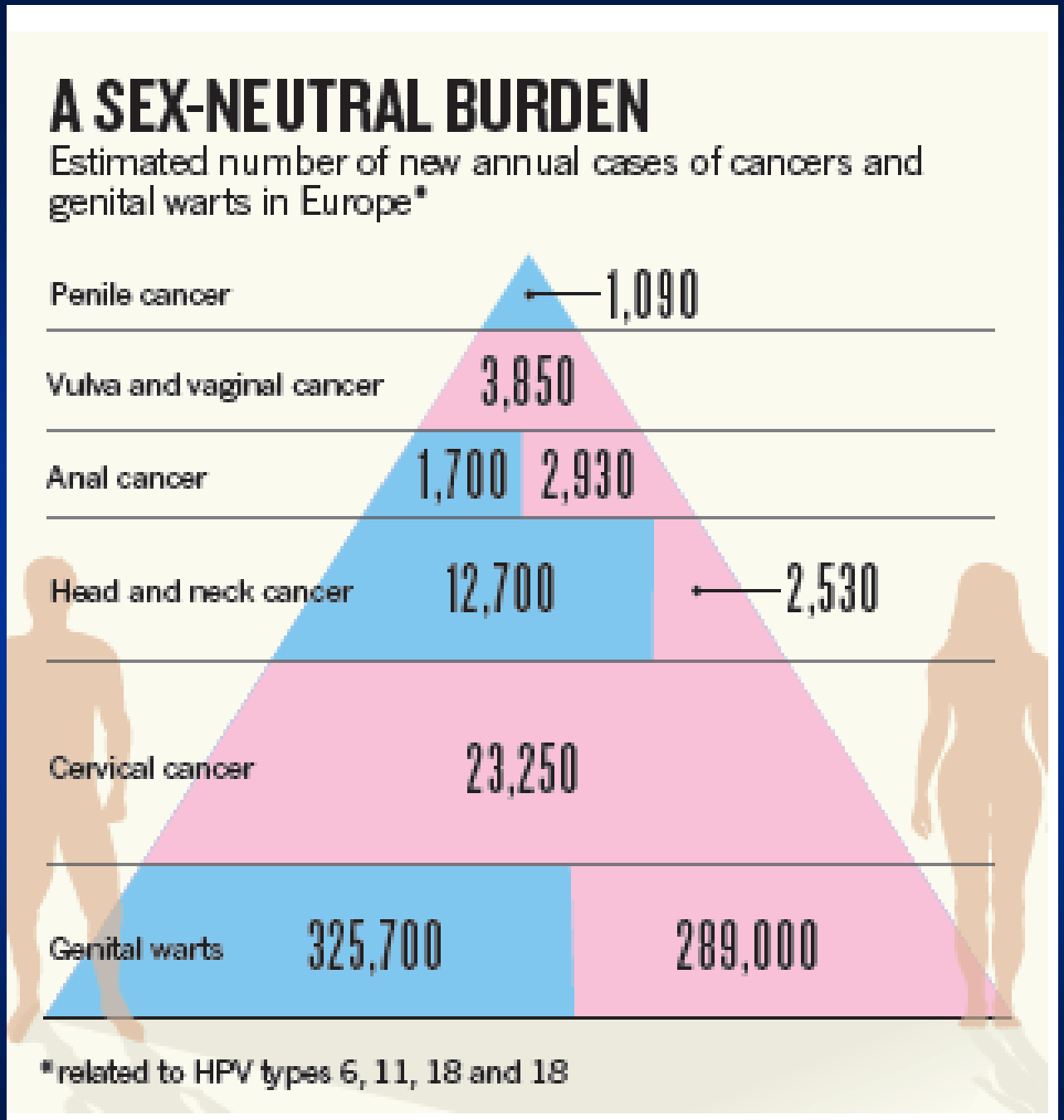
HPV Disease Burden Among Males and Females Globally

Estimated annual new HPV-related disease cases in males and females globally



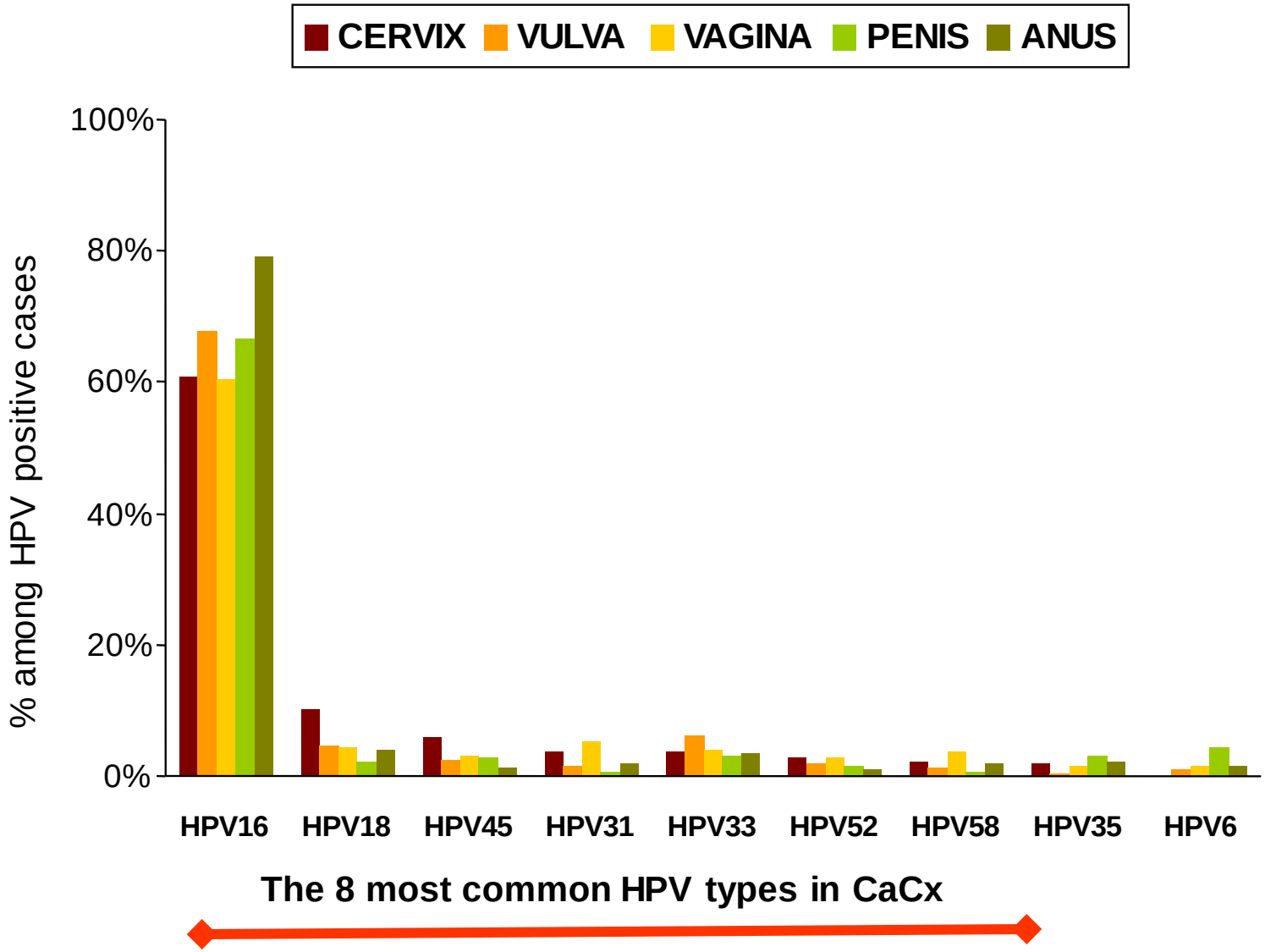
Published HPV prevalence rates were applied as follows: Parkin D et al. *Vaccine*. 2006 (penile, vulvar, anal, oropharyngeal, cervical cancers); De Vuyst H et al. *Int J Cancer*. 2009 (vaginal cancer); Guan P et al. *Int J Cancer*. 2012 (high- and low-grade cervical dysplasia); Greer CE et al. *J Clin 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*. 3. World Health Organization. Geneva, Switzerland: World Health Organization; 1999:1–22. 4. World Health Organization (WHO). Executive summary: the state of world health. 1995.



Stanley M 2012
Nature Outlook

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



De Sanjose et al 2010 Lancet Oncol. 2010;11:1048-56

What are human papillomaviruses?

What diseases do they cause?

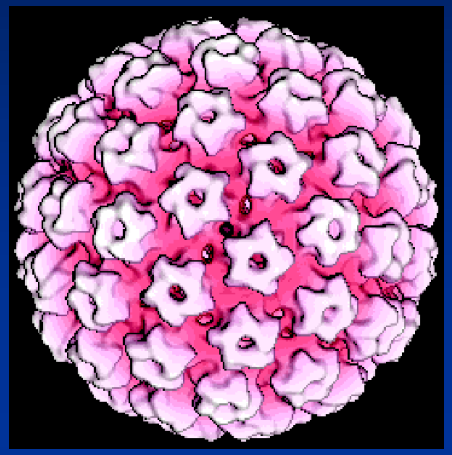
Prophylactic HPV vaccines

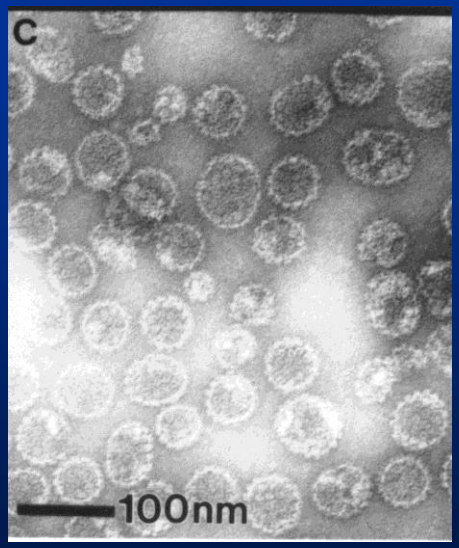
Efficacy. Mechanism of Protection

Who and when to immunise

Implementation and Impact

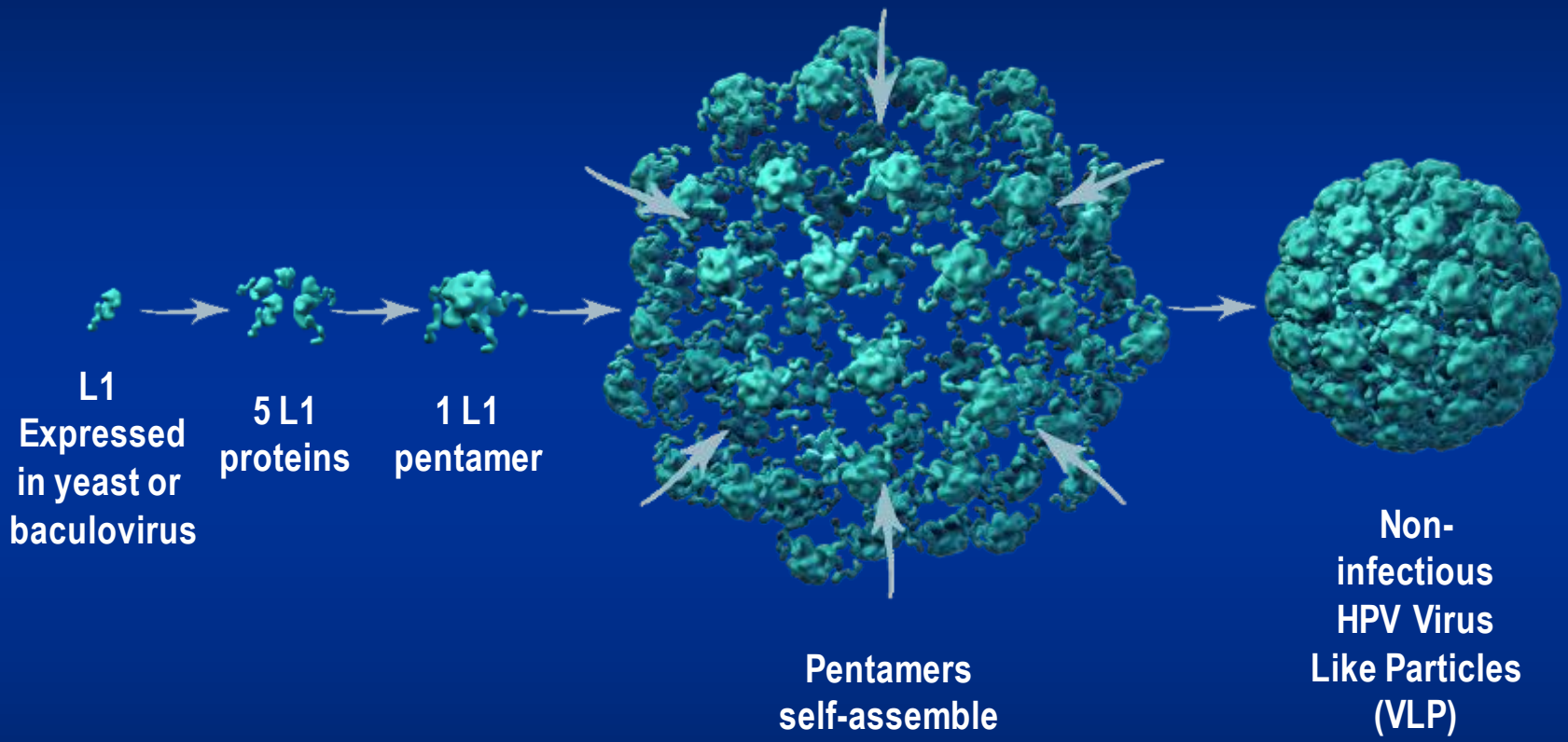
There are 2 virus capsid proteins L1 and L2





- 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

Virus-Like Particles (VLPs) in HPV vaccines are morphologically similar to wt virus



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

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

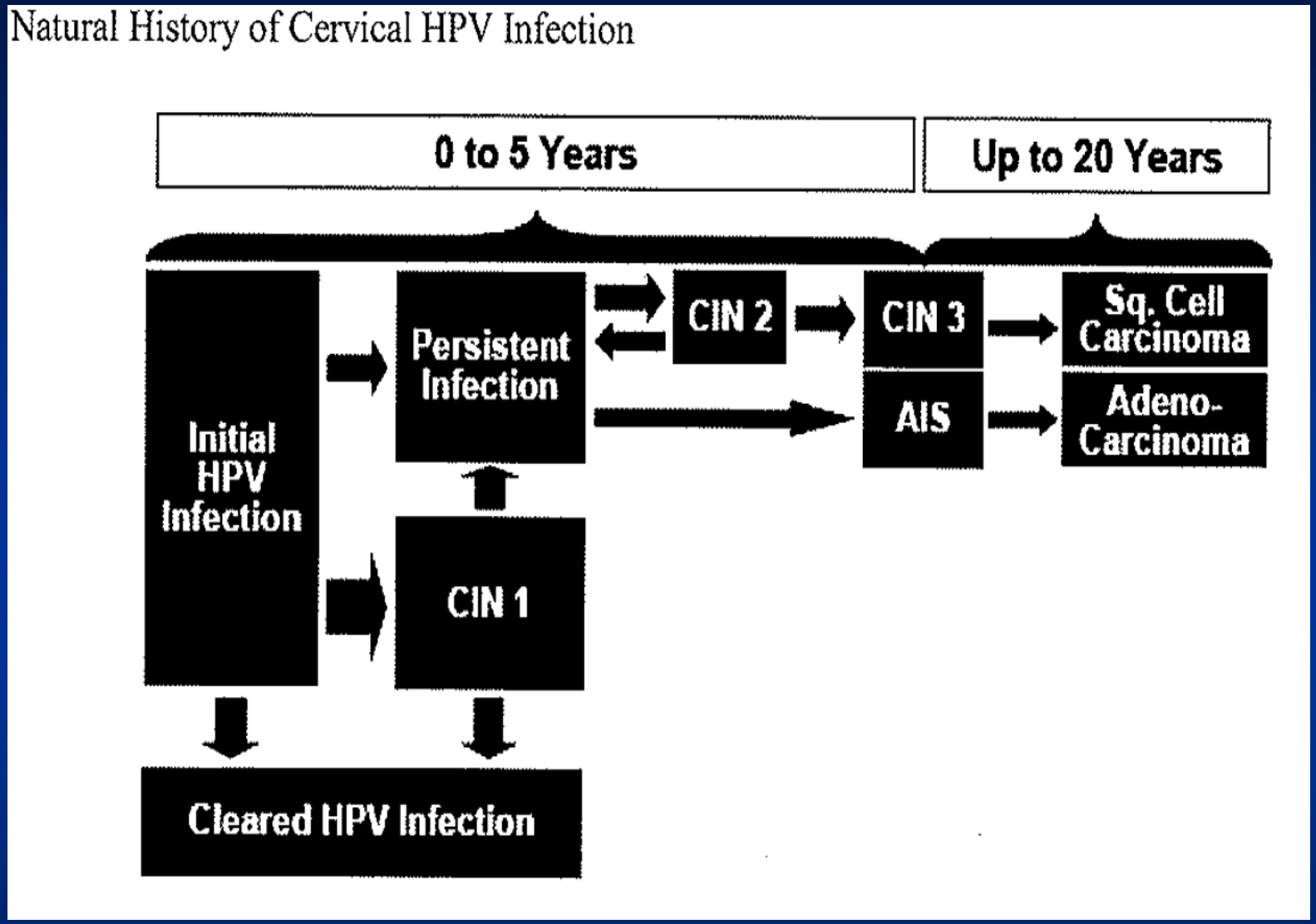
*MPL 3-O-deacylated-4'-monophosphoryl lipid A

In large randomised placebo controlled clinical trials

Both vaccines have been shown

- To be highly efficacious against HPV associated disease

- Well tolerated



Disease endpoints in HPV vaccine trials are high grade precancers caused by vaccine HPV types

A secondary endpoint is persistent infection with vaccine HPV types

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

mechanism of protection of HPV VLP vaccines

Assumption

mechanism of protection is neutralising antibody mediated

Evidence

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 1995

Antibody responses to HPV

Natural infection

- 70-80% women 20-30% men sero-convert
- Antibody response to HPV infection at the cervix is typically slow and weak
- Detectable serum neutralising antibody responses are to L1
- Antibody generated in natural infections is usually protective against subsequent incident infection

HPV L1 VLP vaccination

- In clinical trials 100% women and men sero-convert
- Peak antibody titres are 10-1000x greater than in natural infections
- Neutralising antibody persists for >9 years post immunisation
- No antibody threshold level for the protection provided by HPV vaccines has been identified
- **No immune correlate**

Safaeian etal. 2010 JNCI:102;165
Harper et al Lancet 2006, 367,1247.
Rowhani-Rahbar A et al. *Vaccine* 2009;27:5612-5619 Olsson et al. *Vaccine*. 2007

In contrast to natural infection
HPV VLP vaccines evoke high avidity antibody

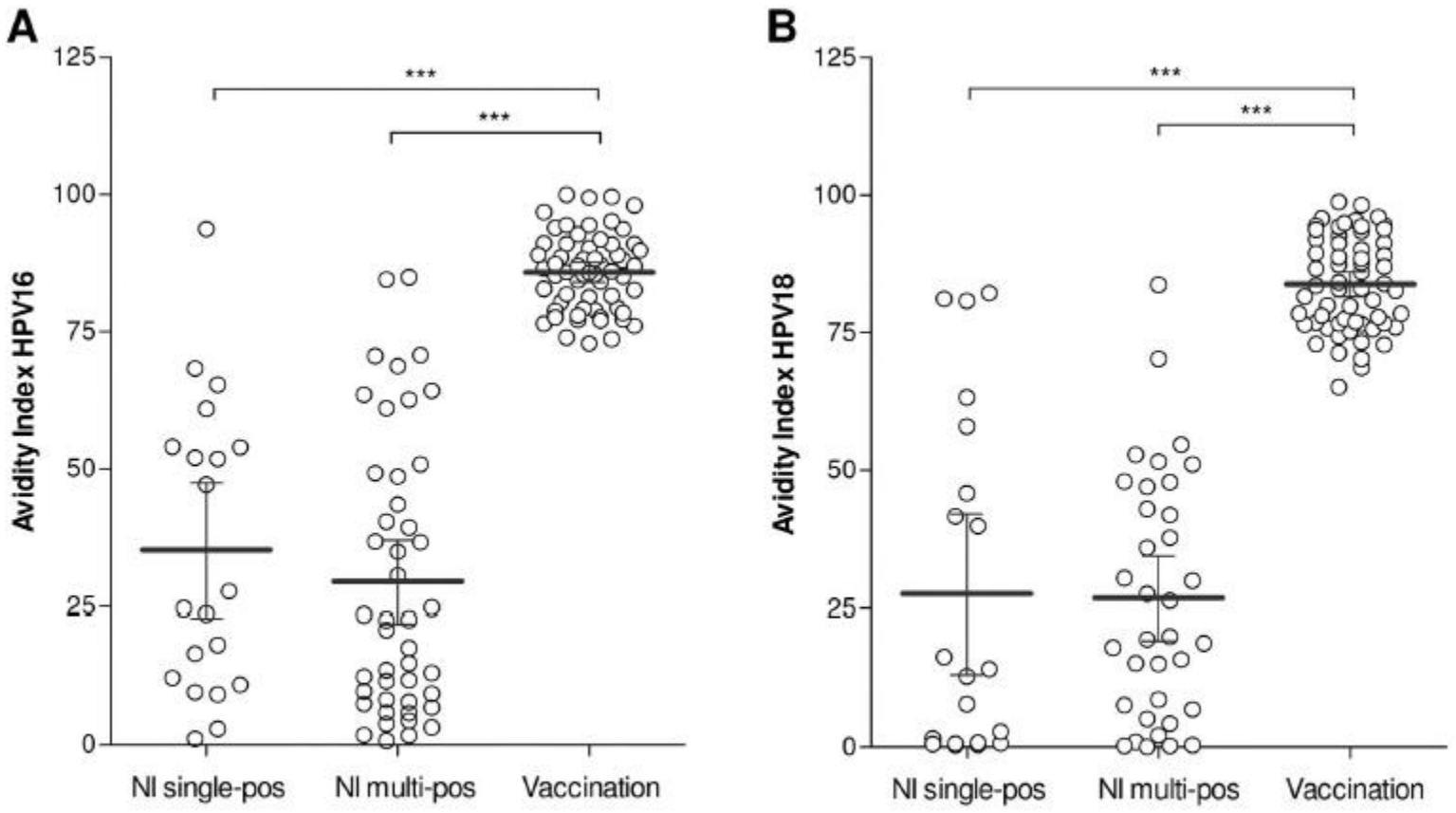


Figure 2. Antibody avidity after HPV infection and vaccination. Antibody avidity (%) for HPV16 (A) and HPV18 (B) of HPV-specific single-seropositive and multi-seropositive naturally derived antibodies and HPV vaccine-derived antibodies are shown. The dark grey line indicates the mean antibody avidity. *** $p<0.0001$.

doi: 10.1371/journal.pone.0074797.g002

Schernpenisse et al PLoS One. 2013;8(9)

Why are vaccine antibody responses so much stronger than natural infection

Route of Immunisation

Natural infection - poor access of virus to lymph nodes

intra-epithelial infectious cycle -no viraemia
infectious virus shed from mucosal surfaces[1]

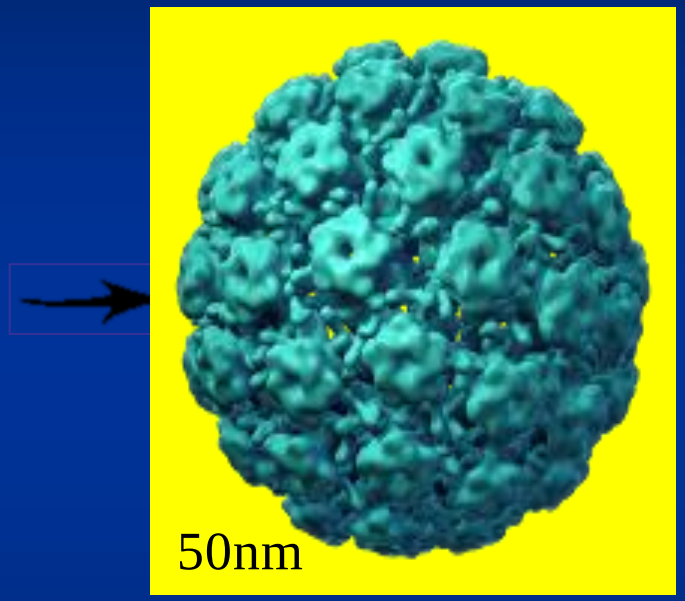
VLP vaccines delivered intramuscularly

rapid access of VLPs to blood vessels,
local lymph nodes, spleen (access to all B cell subsets)
avoids virus immune evasion strategies[1]

Optimal immunogen, Optimal immunisation schedule,

[1]*Stanley MA Vaccine 2006.*

VLPs are very immunogenic



Size

Enter lymphatics and blood vessels – easy access to lymph nodes

Geometry

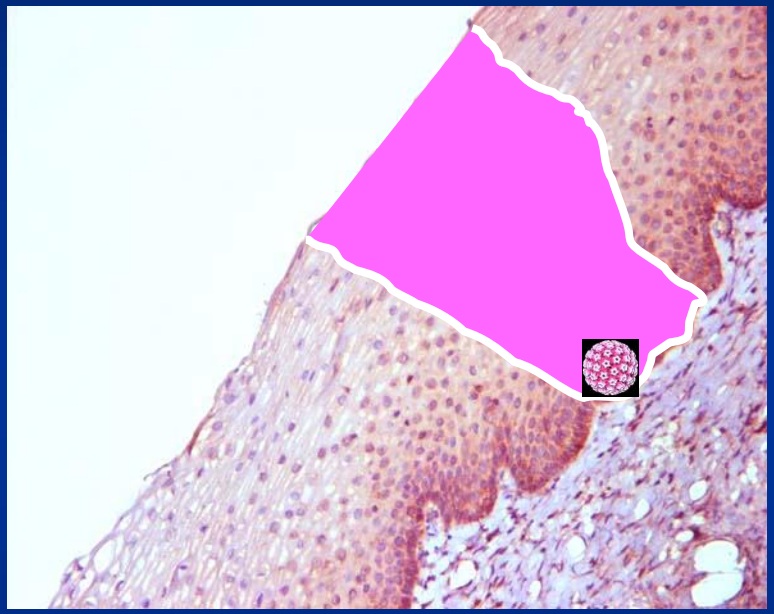
Regular repeat pentamer structure across the particle activate B cells and antigen presenting cells

induce robust antibody even in the absence of adjuvant (cross link B cell receptors, activate TLRs)

Evoke robust memory responses

Serological memory	persistence of antibody
Reactive memory	anamnestic or recall response

Epithelial microabrasion and wound healing are necessary for HPV infection



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

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

What are human papillomaviruses?

What diseases do they cause?

Prophylactic HPV vaccines

- Efficacy, Mechanism of Protection
- **Who and when to immunise**
- Implementation and Impact

Genital HPV infection is usually but not always sexually transmitted

Infection occurs early after the onset of sexual activity

Prophylactic vaccination will be most effective if vaccines are delivered before sexual activity

Recommended target age

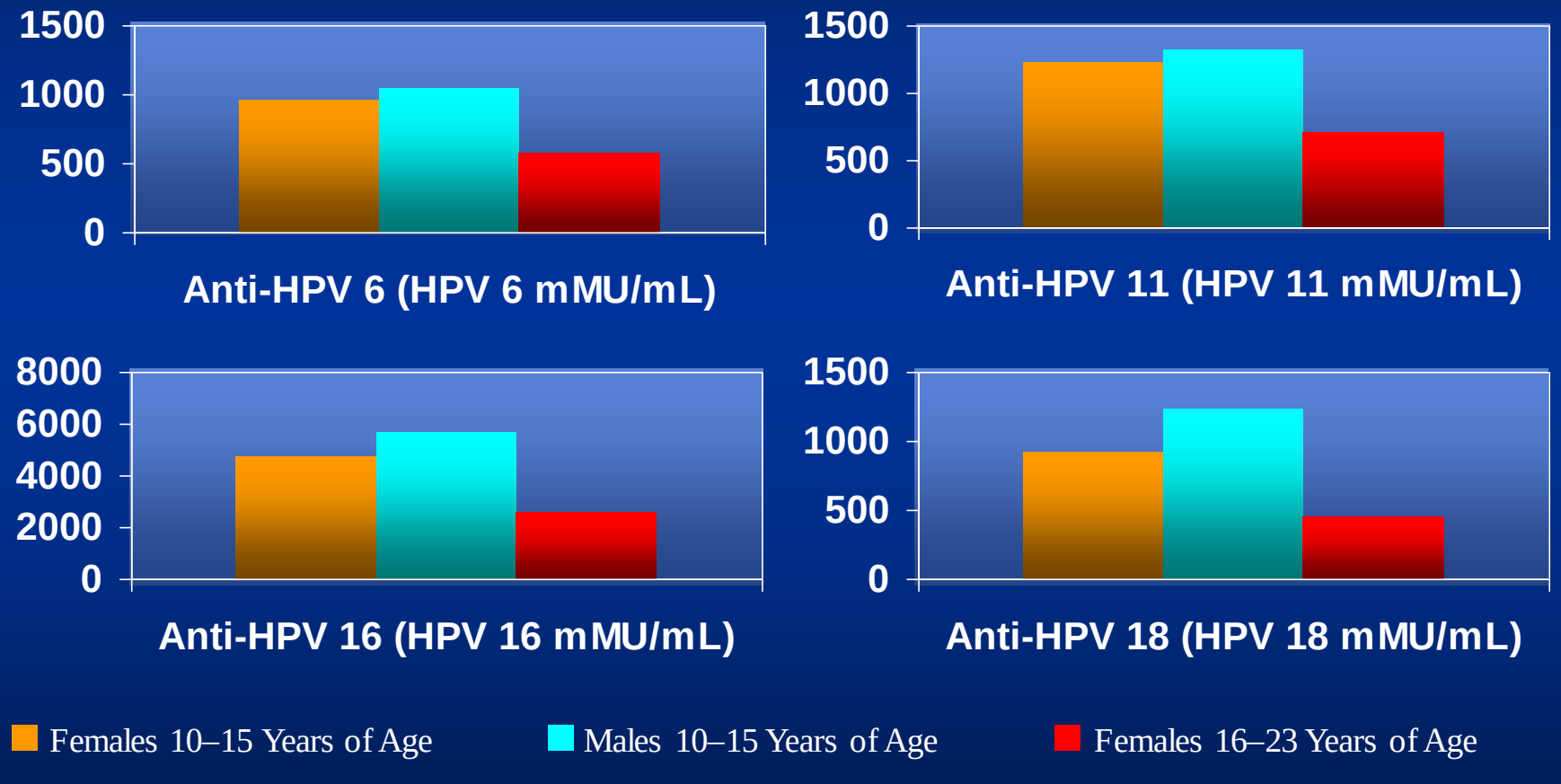
Country	Gender	Age
Australia[1]	F	12-13
Austria[2]	F/M	<9
Belgium[2]	F	12-18
Canada[3]	F	9-15
Denmark[2]	F	12
France[2]	F	14
Germany[2]	F	12-17
Greece[2]	F	12-15
Ireland[2]	F	12-13
Italy[2]	F	11
Latvia[2]	F	12
Luxemburg[2]	F	12

Country	Gender	Age
Netherlands[2]	F	12
Mexico[3]	F	9
Norway[2]	F	12
Panama[3]	F	10
Portugal[2]	F	13
Romania[2]	F	12
Slovenia[2]	F	11-12
Spain[2]	F	11-14
Sweden[2]	F	10-12
United Kingdom[2]	F	12
United States of America[3]	F/M	≤18

1. Garland SM, et al. *Prev Med* 2011;53 Suppl 1:S29–S35. **2.** Dorleans F, et al. *Euro Surveill* 2010;15(47):2–4. **3.** MMWR Morb Mortal Wkly Rep 2011;60:1382–1384.

Quadrivalent HPV Vaccine Phase III Adolescent Immunogenicity Study

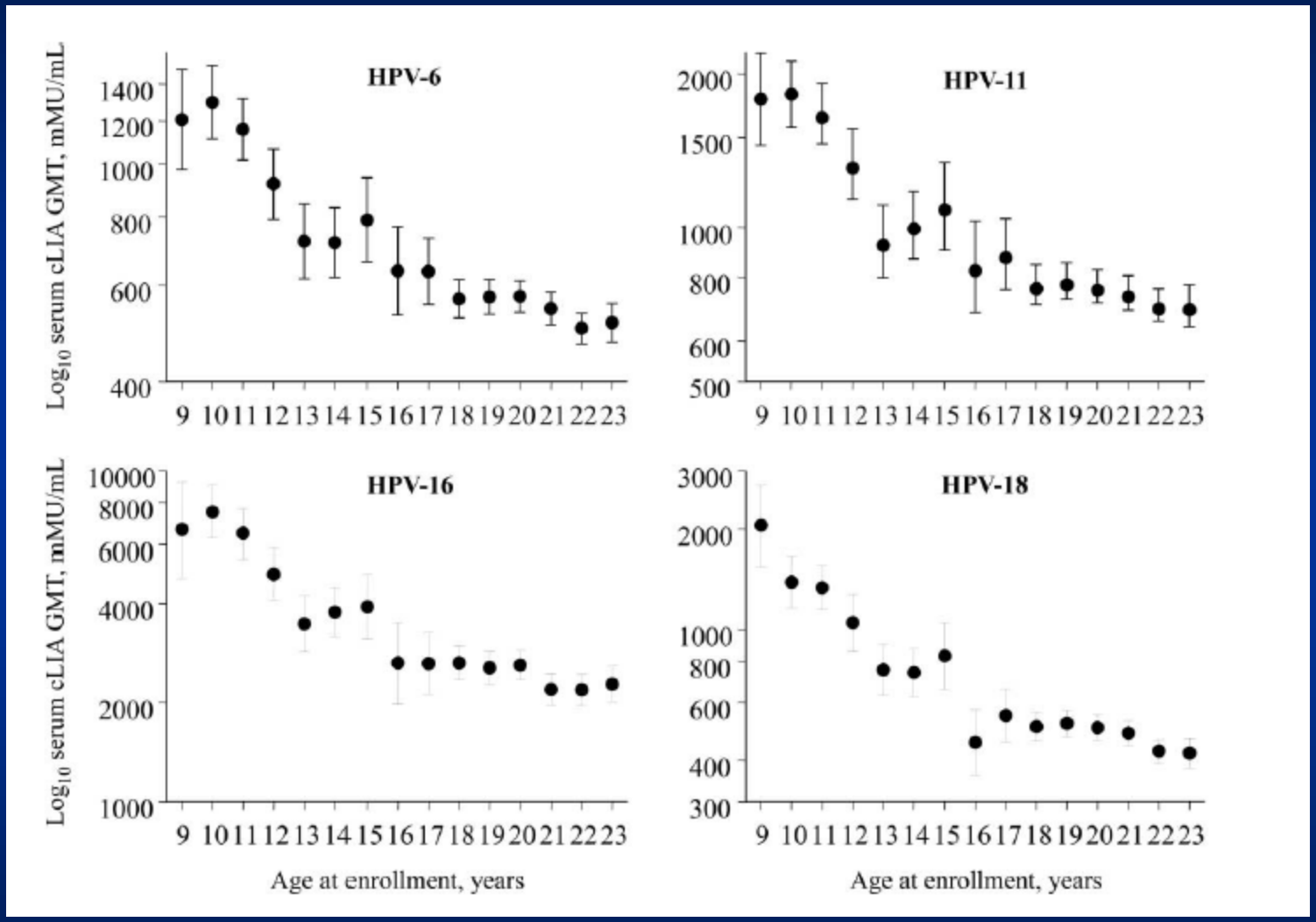
Neutralizing Anti-HPV GMTs at Month 7*



*GMT = geometric mean titers

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

Antibody responses in females by age group at month 7 post vaccination



Giuliano etal 2007 JID 196

Clinical trials: immunogenicity and safety of 2 dose regimen in adolescents

2 dose 0, 6 months adolescent (9-14 years)
versus
3 dose 0,1 or 2,6 months adult (15-23 years)

qHPV vaccine Dobson etal 2013 JAMA 309, 1973-1980
bHPV vaccine Romanowski etal 2011 Human Vaccines 7, 1374-1386

Immunogenicity
antibody concentrations (GMTs) were non inferior in the 2 dose group compared to 3 dose

Safety
Well tolerated

The immunogenicity data supports reduced/alternative schedules in 9-13 year olds

The antibody quantity and quality in 9-13 year olds after 2 vaccine doses at 0-6months is as good as that generated after 3 doses 0,2,6 months in 16-23 year olds in whom efficacy has been shown

There is no efficacy data for the 2 dose regimen in 9-13 year olds

The duration of protection is not known

There is no immune correlate

SAGE April 2014 meeting

"SAGE reiterated the importance of providing human papillomavirus immunization to girls as early as necessary, i.e. in girls aged 9 to 13 years prior to sexual debut, based on local data and patterns of sexual activity.

Upon review of the evidence, SAGE recommended a 2-dose schedule for girls, if vaccination is initiated prior to 15 years of age.

A 3-dose schedule remains necessary if immunization is initiated after the girls' 15th birthday.

The recommended minimal interval between the 2 doses is 6 months.

This interval may be extended to 12 months if this facilitates administration.
A 3-dose schedule (i.e. at 0, 1-2, and 6 months) remains recommended for immunocompromised individuals, including those known to be HIV-infected."

http://www.who.int/immunization/sage/meetings/2014/april/report_summary_april_2014/en/

What are human papillomaviruses?

What diseases do they cause?

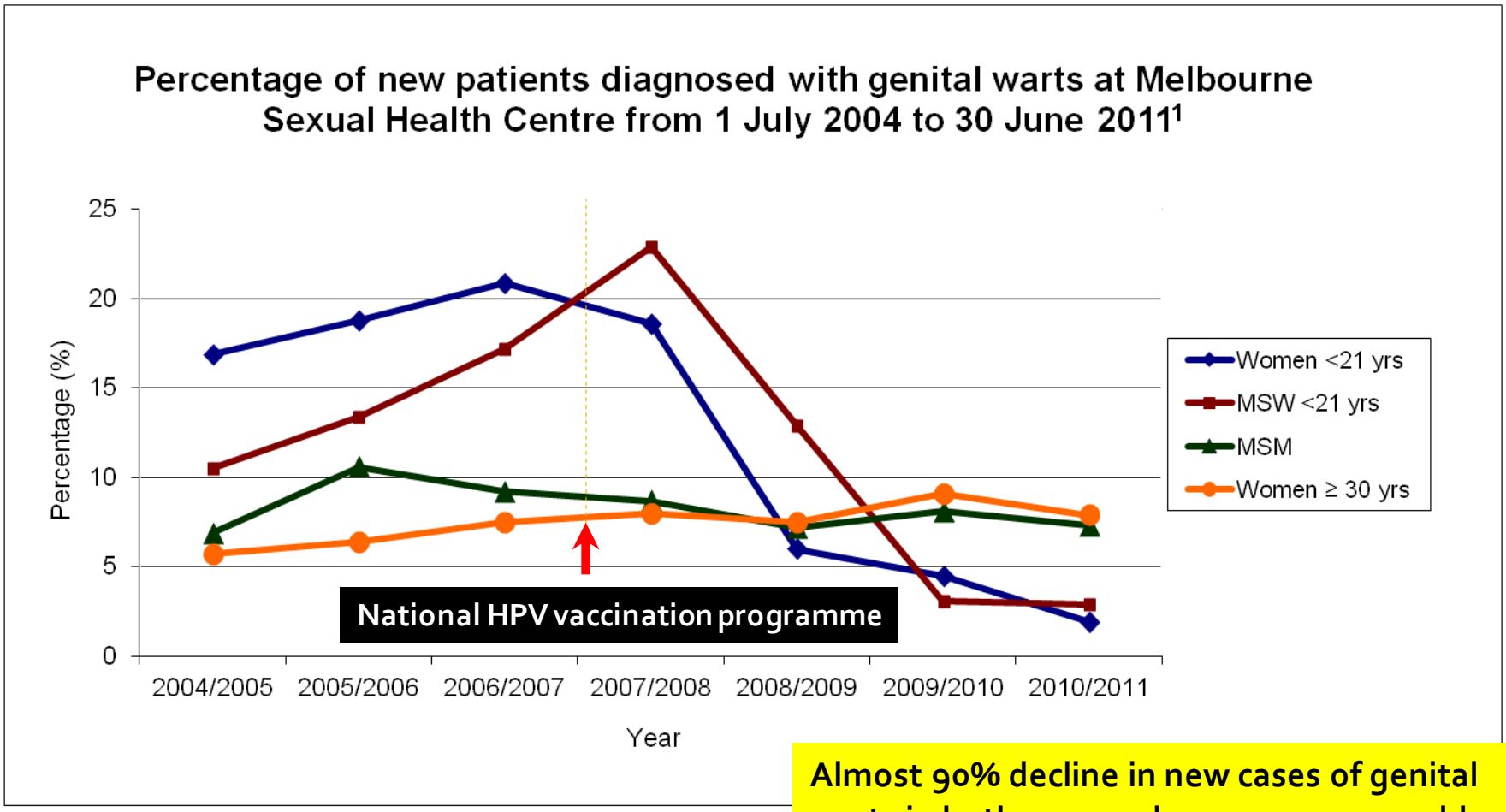
Prophylactic HPV vaccines

- Efficacy
- Who and when to immunise
- Implementation and Impact

The Australian National HPV vaccination program

- Funded by federal government, delivered by States and Territories
- quadrivalent HPV vaccine used.
- >7 million doses quadrivalent HPV vaccine distributed
- Commenced in April/July 2007 12-26 year old females
  12-13 yrs ongoing cohort 13-26 catch up
- School based 12-18 year olds
  GP/clinic based 18-26 year olds
- Overall coverage 70-80%

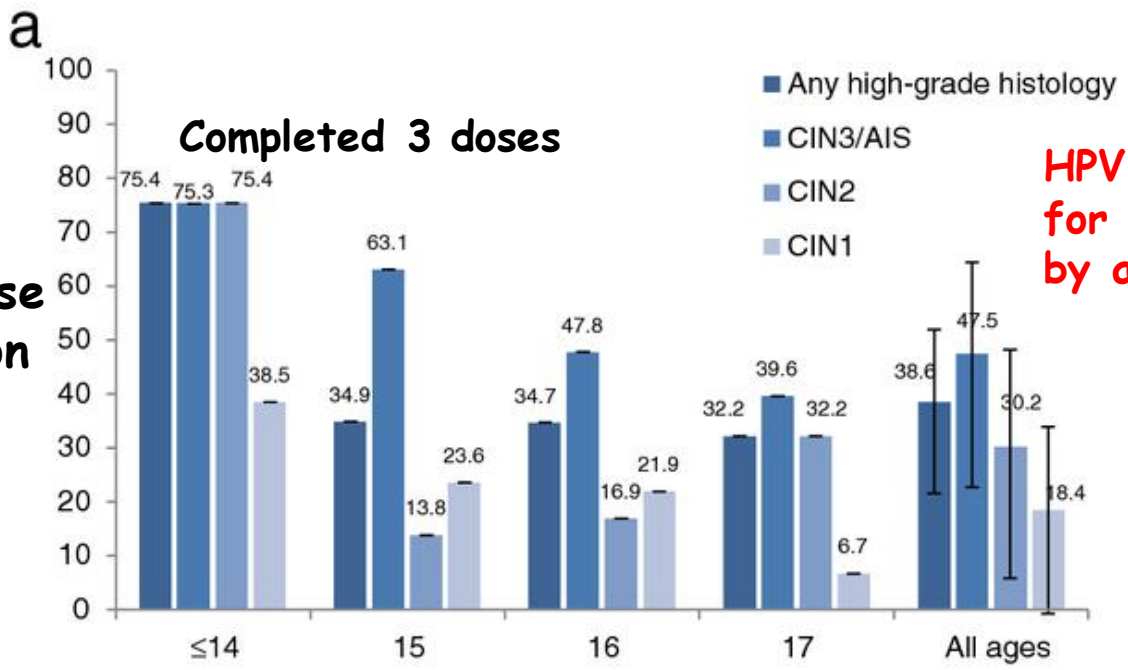
Australia: Near disappearance of genital warts after commencement of national HPV program

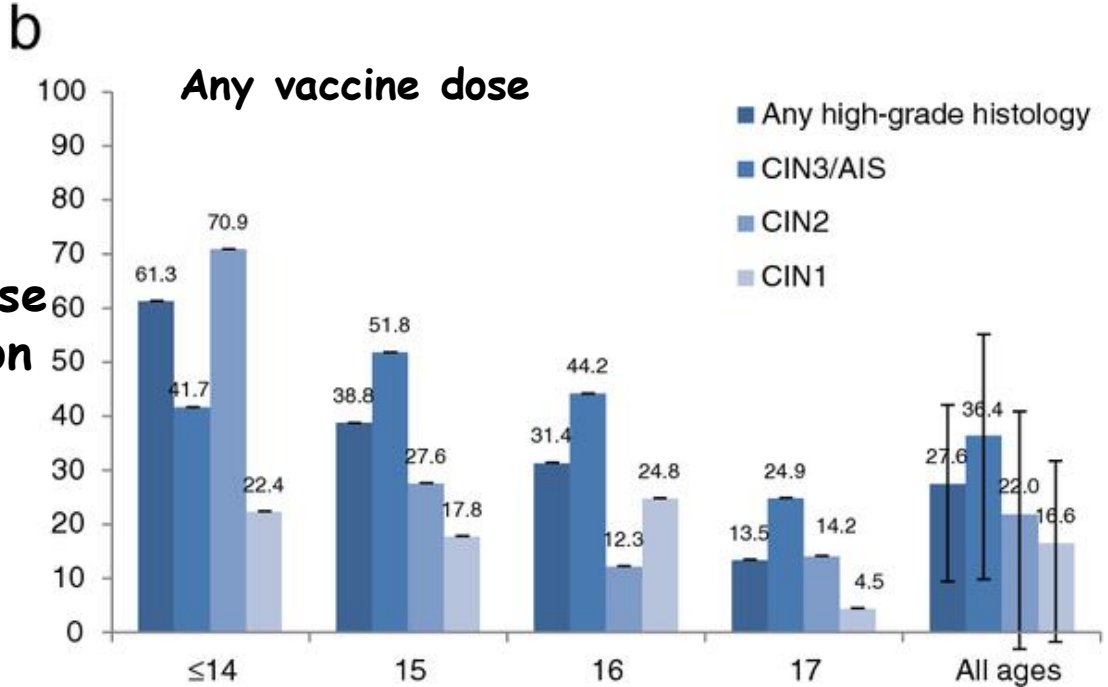


Almost 90% decline in new cases of genital warts in both men and women < 21 yrs old

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

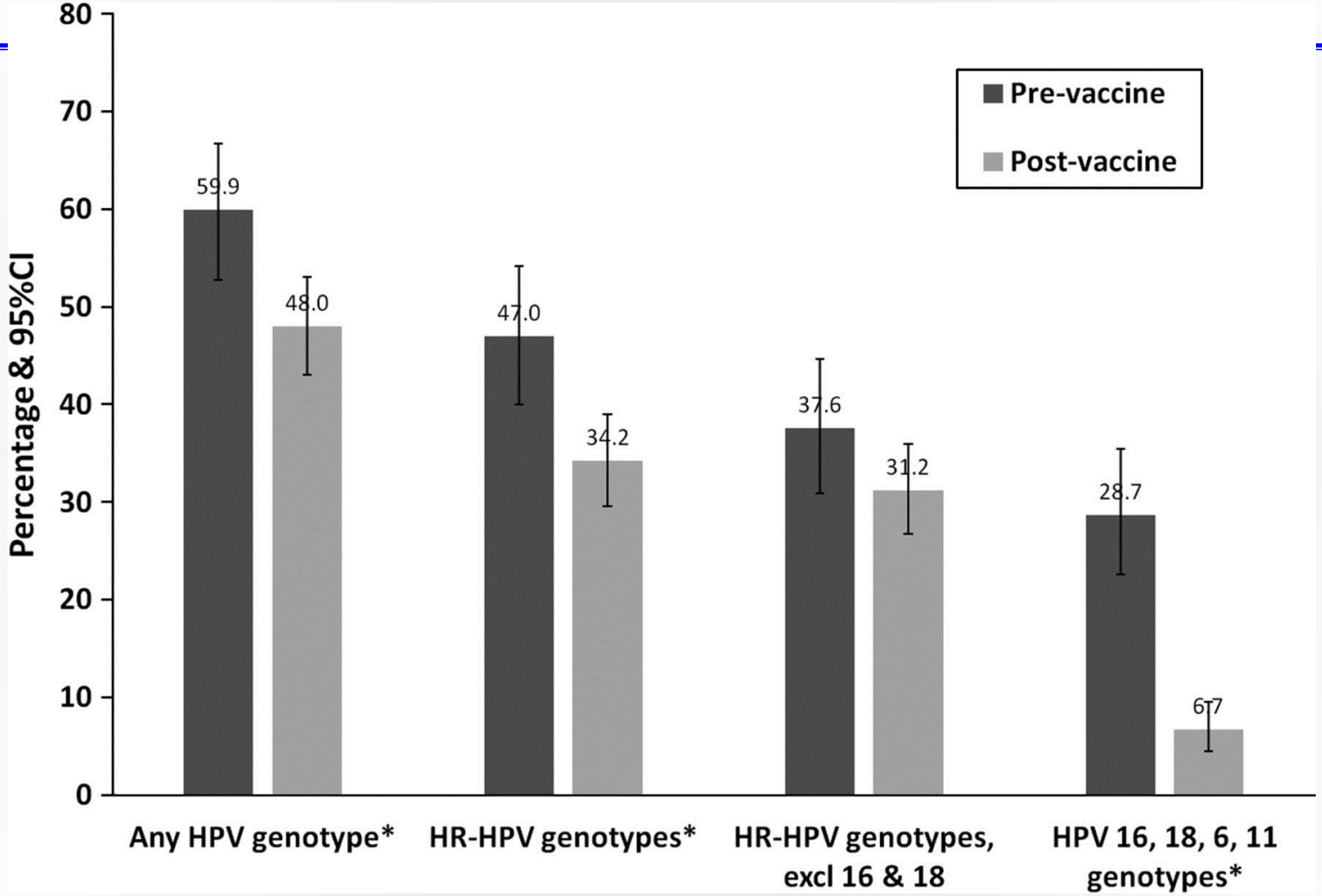
HPV vaccine effectiveness for CIN outcome to end 2011 by age of vaccination in 2007





Gertig et al 2013
BMC Med Oct 22 epub

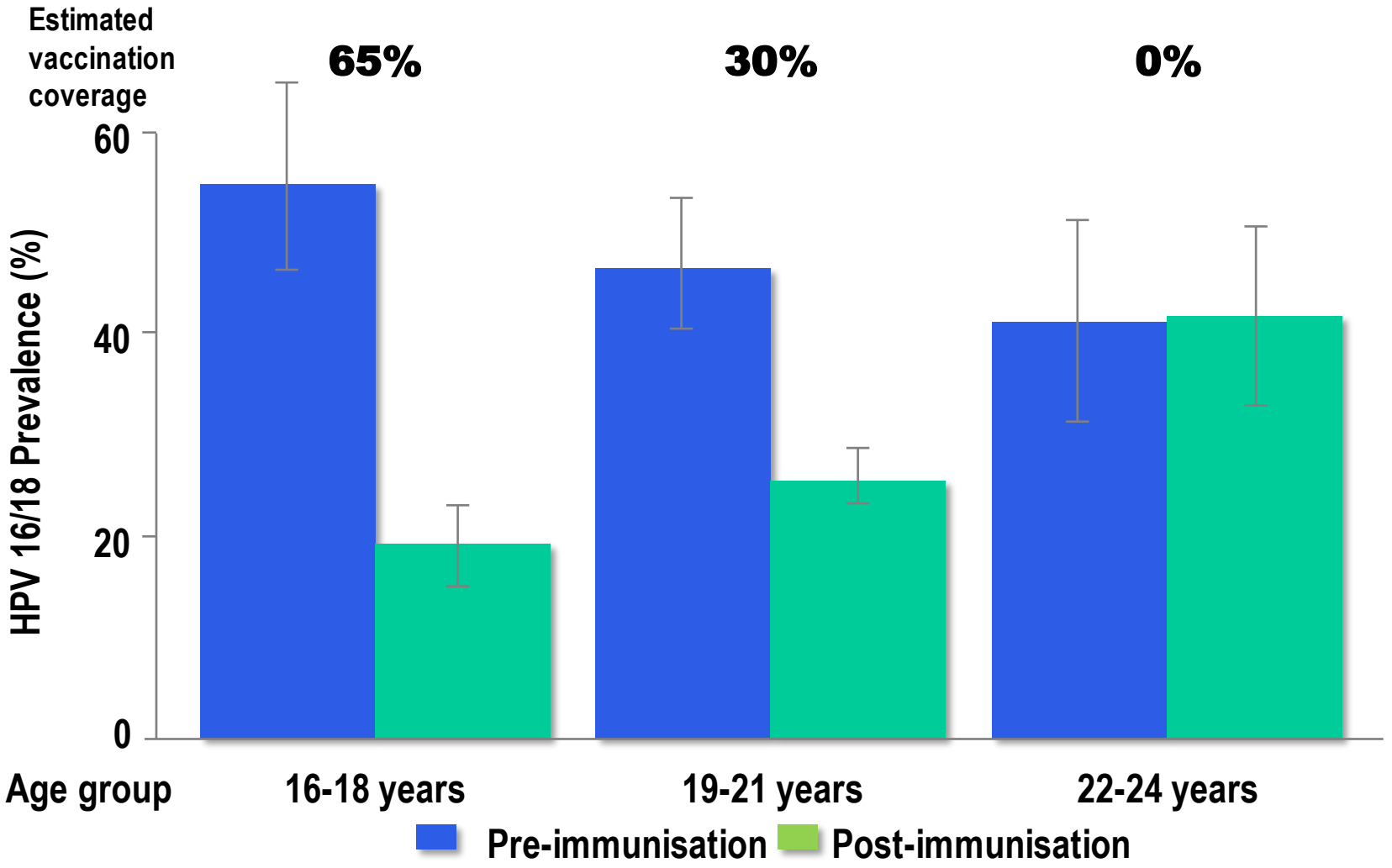
Differences in human papillomavirus (HPV) genoprevalence between prevaccine and postvaccine populations. *P < .05 for difference in percentages between groups.



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

The Journal of Infectious Diseases

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



HR 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.

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 Gardasil

Issues: cost

Efficacy of a novel nonavalent HPV VLP vaccine against HPV 31,33,45,52,58, in 16-23 year old women

Per Protocol Population			
	High Grade Disease CIN2/3		
	V503	Gardasil	
HPV 31/33/45/52/58 cervical/vulvar/vaginal	1	30	96.7 (80.9 , 99.8)
HPV 31/33/45/52/58 cervical	1	27	96.3% (79.5, 99.8)
HPV 31/33/45/52/58 vulvar/vaginal	0	3	100% (-71.5, 100)
	Persistent Infection		
HPV 31/33/45/52/58 cervical/vulvar/vaginal	35	810	96% (94.4, 97.2)

Joura etal Abstract SS8-4 Eurogin Florence November 5th 2013

Summary

Both qHPV and bHPV VLP vaccines are highly efficacious with a good safety profile

Population effectiveness against EGW demonstrated for qHPV
>90% reduction in incidence in <21yr old women 4 years post vaccine introduction with evidence for herd protection

50% reduction in abnormal smears and high grade CIN in <20years women 3 years post vaccine introduction (qHPV)

Duration of protection against disease caused by HPV 16/18 extends at least to 8 years (qHPV and bHPV)

The current assumption is that protection is effected by antibody

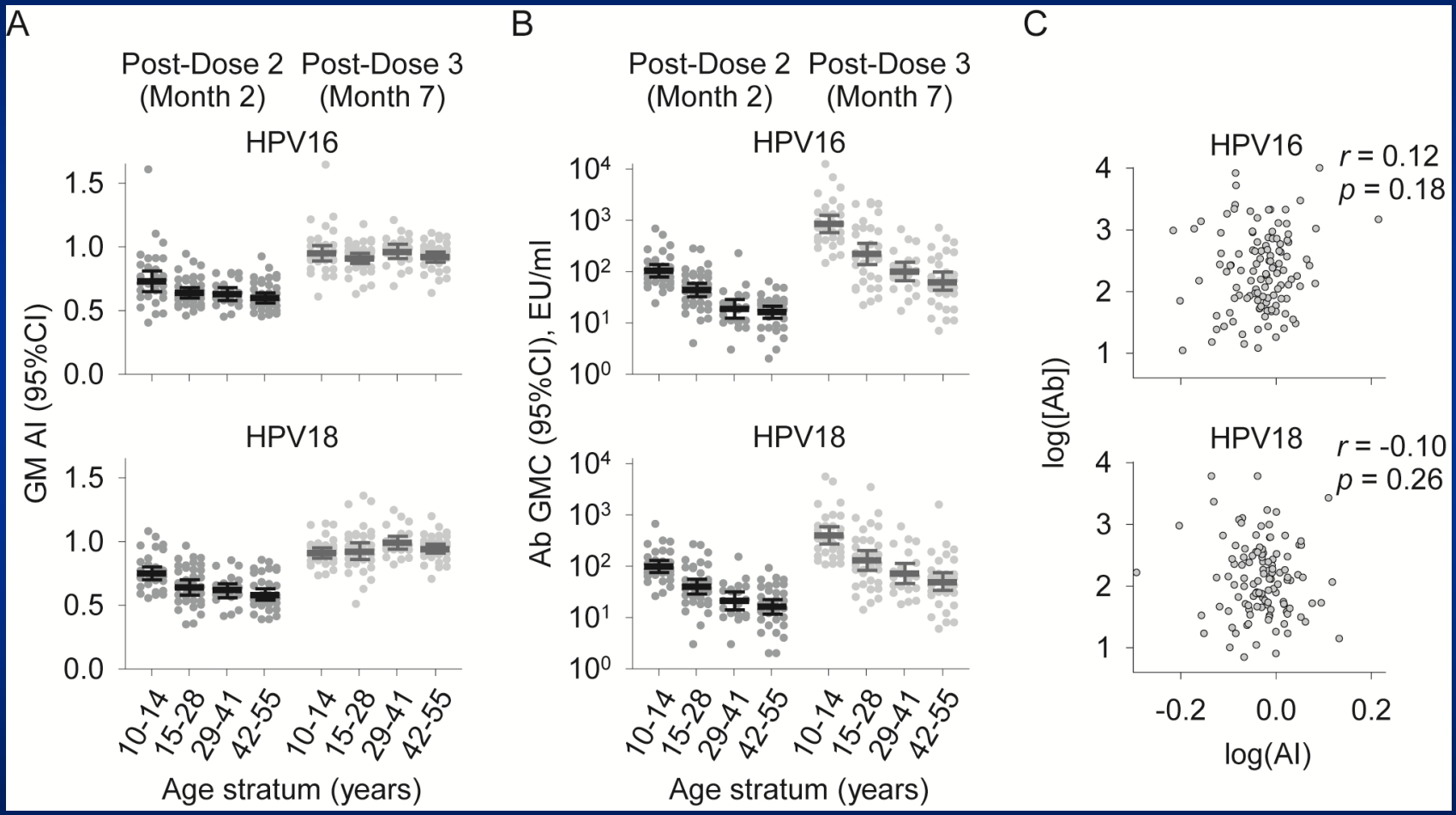
Emerging evidence shows that very low concentrations of antibody at or below current assay detection levels are protective

Immunogenicity and Safety Study of GlaxoSmithKline Biologicals' HPV-16/18 L1 AS04 Vaccine When Administered According to Alternative 2-dose Schedules in 9 - 14 Year Old Females
NCT01381575 Sponsor Glaxo Smith Kline

This study has been designed to evaluate the immunogenicity and safety of GSK Biologicals' HPV-16/18 vaccine when administered according to alternative 2-dose schedules (0,6 mths and 0,12 mths) in healthy 9-14 year old females as compared to the standard 3-dose schedule (0,1,6 mths) in 15-25 year old females

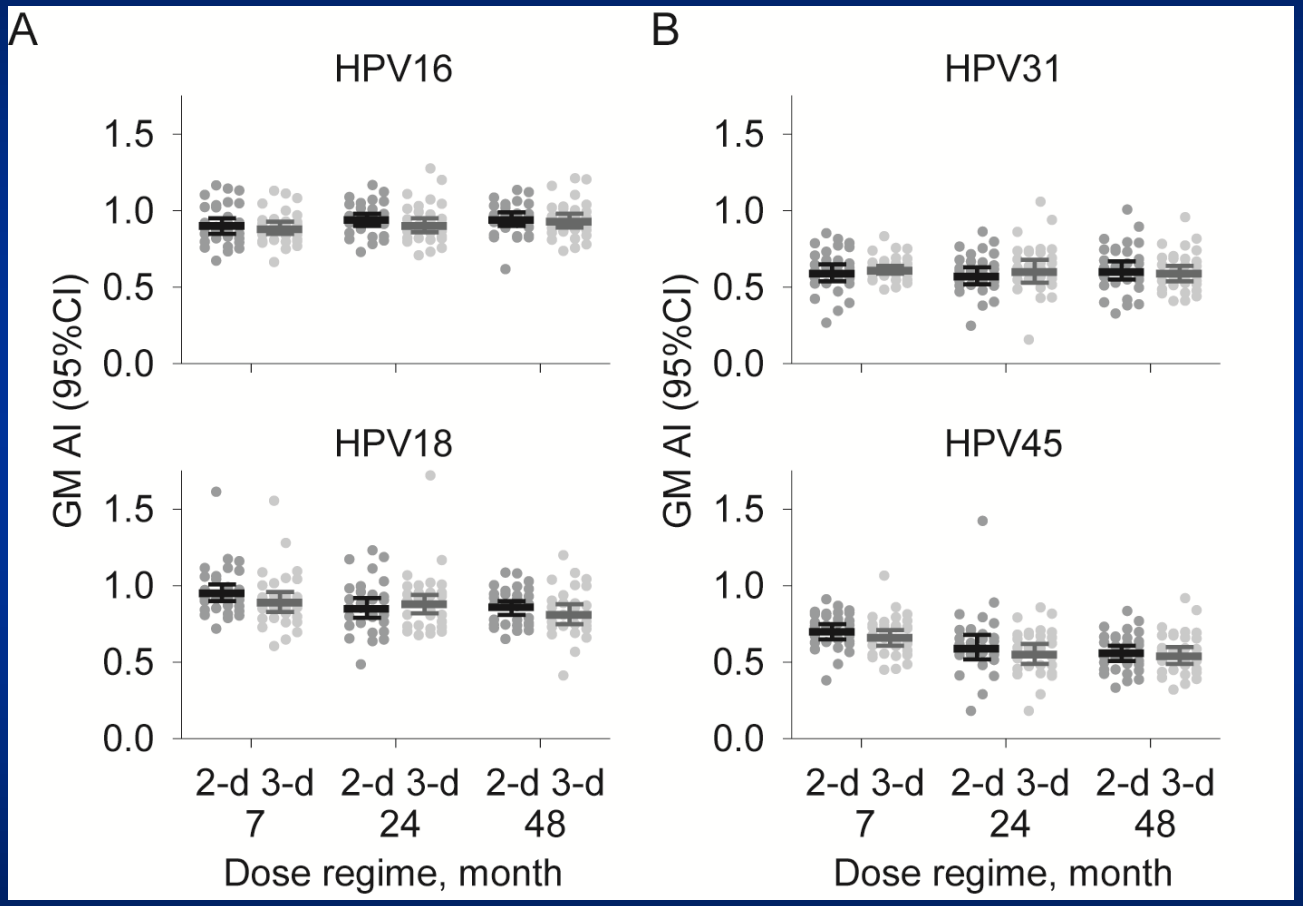
http://clinicaltrials.gov/ct2/show/NCT01381575

HPV-specific antibody avidities at Months 2 and 7 with a 0-1-6 month HPV-16/18 vaccination schedule



Boxus etal Vaccine 2014 epub

HPV-specific antibody avidities at Months 7, 24 and 48 with 0-6 or 0-1-6 month HPV-16/18 vaccination schedules



2 dose 10-14 year olds 3 dose 15-23 year old females clinical trial NCT00541970

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