

14TH ANNUAL CONFERENCE
OF THE BRITISH HIV ASSOCIATION (BHIVA)



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University of York

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HYMS

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Human papillomavirus – prevention of infection and disease through vaccination

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Classification of human papillomaviruses (HPVs)

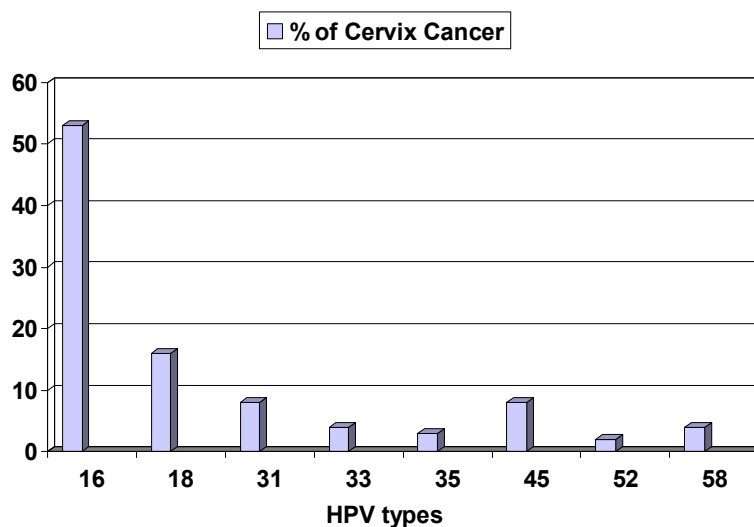
- **Mucosal / genital**

- Can be associated with invasive cancer - higher oncogenic risk (HR) - HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82, 83
- Very rarely associated with invasive cancer - lower oncogenic risk (LR) - HPV 6, 11, 42, 43, 44, 53, 54, 57, 66

- **Cutaneous**

- Classical cutaneous causing clinical lesions – HPV 1, 2, 3, 4, 7, etc
- Sub-clinical 'epidermodysplasia verruciformis' family – HPV 5, 8, 9, 12, 14, etc

HPV 16 & 18 occur in ~70% of cervical cancer cases worldwide

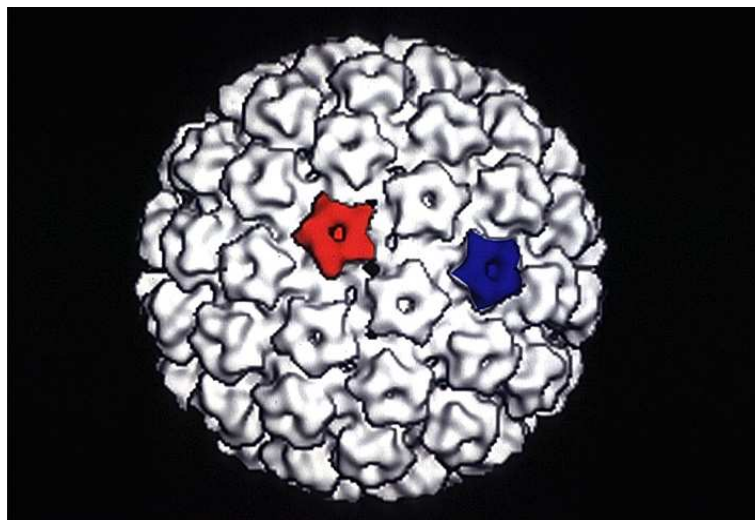


IARC series, Walboomers 1999

Critical breakthroughs on the path to a successful HPV virus-like particle prophylactic vaccine

- 1991 – Zhou et al describe production of virus-like particles (VLPs) from HPV 16 L1 & L2
- 1992 – Kirnbauer et al show that expression of L1 alone sufficient for VLP production
- 1994 – Rose et al show that VLP vaccination protects against viral challenge and induces neutralizing antibodies
- 1995 – Breitburd & Suzich show that in the rabbit CRPV model VLP vaccine-induced protection can be passively transferred by immunoglobulin

HPV 16 VLP composed of 72 capsomere subunits of L1 protein



Papillomavirus VLPs as vaccine immunogens

- LI protein in *in-vivo* conformation
- High potency antigen for induction of neutralising antibodies
- Vaccines induce B cell & CD4 cell memory
- VLPs of multiple genotypes can be combined as multivalent vaccines
- No safety issues to date

Virus-like particles as vaccines

- Hepatitis B vaccine is a VLP vaccine
- There are now 'second generation' Hepatitis B vaccines where the VLPs include additional inserts (pre-S1+2)
 - 'chimeric VLPs'
- Other viral VLP vaccines are in development – Norwalk virus, HEV, HCV, etc
- Immunization with papillomavirus VLPs with ordered array of antigens on their surfaces with antigen spacing of 60-85 Å produces optimal antibody induction

Major Pharma developing HPV VLP vaccines

- Merck / SPMSD - Gardasil™
 - A quadrivalent HPV 6, 11, 16, 18 LI VLP vaccine, alum adjuvanted, FDA license granted June 2006, ACIP recommended June 2006, EMEA license granted August 2006, available in UK from October 2006
- GSK - Cervarix™
 - A bivalent HPV 16, 18 LI VLP vaccine, AS04 adjuvanted, EMEA licence granted September 2007, FDA issued “complete response letter” December 2007 asking for more data

Prophylactic quadrivalent HPV (types 6, 11, 16, 18) LI VLP vaccine (Gardasil™) reduces CIN 2/3 risk

	Vaccine			Placebo			Vaccine efficacy (%)	Confidence Interval
	N	Cases	Rate ^{\$}	N	Cases	Rate ^{\$}		
PP	5301	0	0.0	5258	21	0.3	100	76, 100 [£]
MITT	5736	1	<0.1	5766	36	0.3	97	83, 100 [£]

^{\$}Rate = N/subject years at risk*100

[£]P<0.001

Conclusion: In this study, prophylactic quadrivalent HPV vaccination reduced CIN 2/3 through 2 years of follow-up.

Quadrivalent HPV (types 6, 11, 16, 18) VLP vaccine (Gardasil™) reduces VIN 2/3* and vulval warts* risk

	Vaccine		Placebo		Vaccine efficacy (%)	Confidence Interval
	N	Cases	N	Cases		
VIN 2/3	7899	0	7900	8	100	42, 100 [£]
Vulval warts	7899	2	7900	155	99	95, 100 [£]

*These are per protocol analyses and refer to HPV 6/11/16/18-associated VIN 2/3 and vulval warts

Conclusion: In this study, prophylactic quadrivalent HPV vaccination reduced VIN 2/3 and vulval warts through 3 years of follow-up.

Summary of Gardasil efficacy data (per protocol populations - pivotal trials)

Primary Endpoint	N	Efficacy (CI)	Follow-up
HPV 6/11/16/18-related ¹ infection or disease	552	96% (84-100)	5 years
HPV 6/11/16/18-related cervical lesions of any grade severity ¹	5,455	100% (87-100)	5 years
HPV 6/11/16/18-related vulvar and vaginal lesions and warts ¹	5,455	100% (88-100)	5 years
HPV 16/18-related high grade pre-cancerous lesions ¹	12,167	100% (76-100)	5 years

1.Villa, LL. Br J Cancer 2006;95:1459

Efficacy of Cervarix against HPV 16/18 infection – interim analysis of the phase 3 trial

- Mean 14.8 month follow-up of 18644 women
- Primary endpoint vaccine efficacy against HPV 16/18 CIN2+
- Vaccine efficacy (VE)
 - HPV 16/18: 90.4% (p<0.0001)
 - HPV 16: 93.3% (p=0.0005)
 - HPV 18: 83.3% (p=0.125)
- Overall vaccine efficacy lowered by two cases in the active arm where there were other HR HPVs in the Cx lesions as well as HPV 16/18
- Analyses based on persistent detection of HPV 16/18 prior to CIN2+ development show 100% VE
- No safety concerns
 - *Lancet 2007;369:2161*

Long term (6.4 yrs) follow-up of a Cervarix phase 2 study

- 776 women aged 15-25 yrs, in N America and Brazil, who were HPV 16/18 sero- and DNA-negative at entry, who completed initial phase 2, entered into extended follow-up, mean 6.4 yrs
- >98% of women (developed and) remained sero-positive for HPV 16/18 antibodies, both IgG and neutralizing
 - VE against HPV 16/18 CIN1+ 100% (95%CI 71-100%)
 - VE against HPV 16/18 CIN2+ 100% (95%CI 51-100%)
 - VE against HPV any CIN2+ 72%
 - No safety issues
- *Gynecol Oncol 2008;109:158-9*

Evidence of vaccine-induced cross-protection against related HPV types

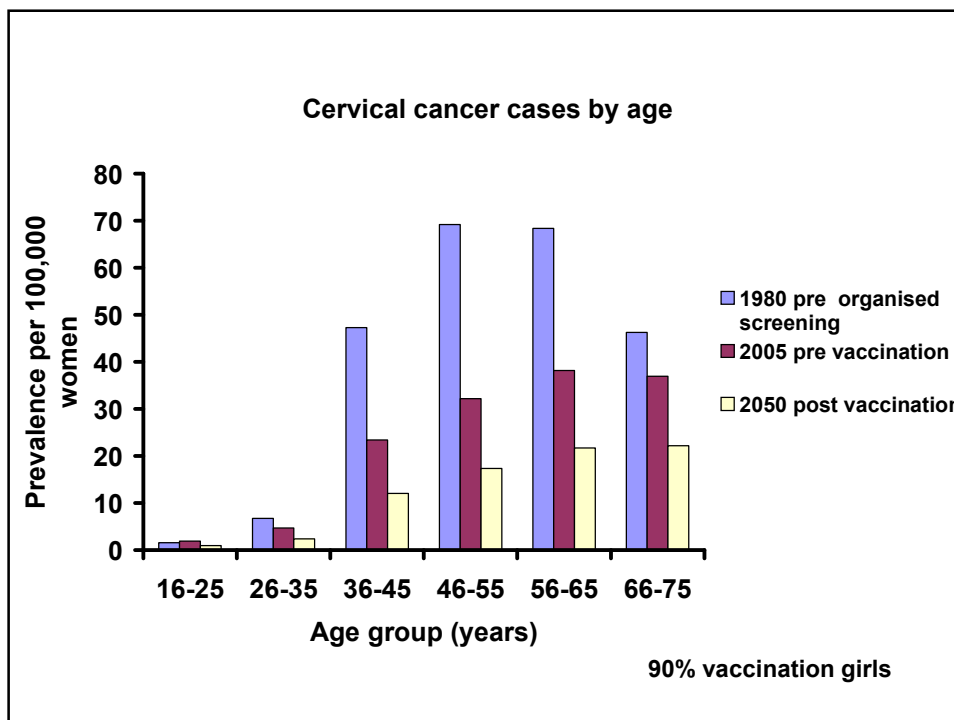
- Cervarix vaccine efficacy over 24 month follow up (n=776) against incident HPV 45 (94%) and HPV 31 (55%) infection observed. No data on protection against disease yet presented
 - *Lancet 2006;367:1247-55*
- Gardasil vaccine efficacy over 48 month follow up against infection (n=2072) or disease (CIN 2/3 or AIS, n=9232)
 - HPV 31/45: Inf. 45% Dis. 62%
 - HPV 31/33/45/52/58 Inf. 28% Dis. 43%
 - HPV 31/33/35/39/45/51/52/56/58/59 Dis. 38%
 - *Brown DA, ICAAC 2007, G-1720b*

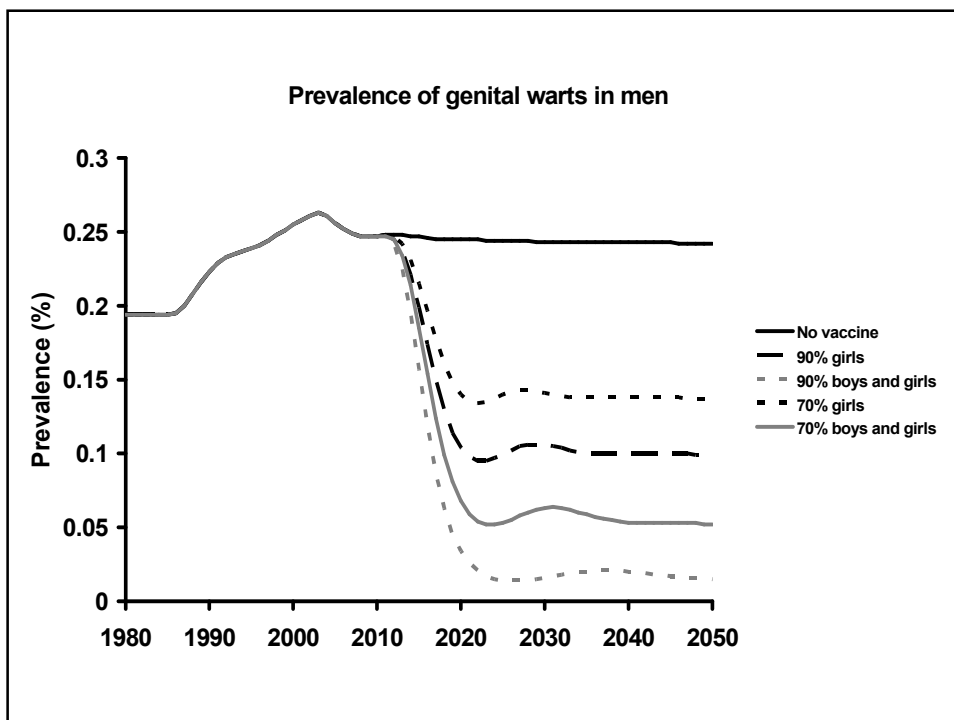
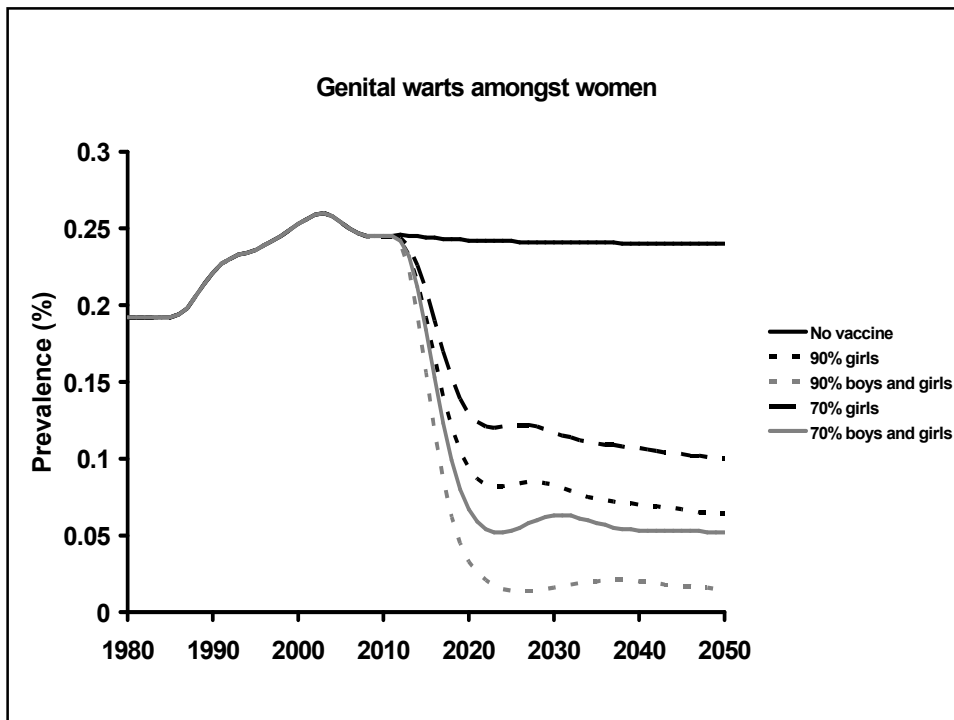
How do the vaccines compare? Pros / Cons?

- Both vaccines show astounding efficacy against the HPV types included in the vaccines
- Therefore Gardasil shows additional efficacy (compared to Cervarix) against HPV 6/11 disease, i.e. genital warts & HPV 6/11-related CIN / VIN / VAIN (proven); prevention of laryngeal papillomatosis highly likely
- Cervarix uses a new adjuvant – less long term safety data, appears to produce higher antibody levels, ??enhanced longevity of protection
- GSK is conducting a trial to compare the immunogenicity of Cervarix vs Gardasil against HPV 16,18,31,45

Effectiveness / cost-effectiveness of the 6/11 component of the quadrivalent vaccine

- Almost all GW are associated with HPV 6/11
- Direct costs of GW are ~£220 per episode, total UK episodes p.a. ~146,000, total costs ~ £32 million
- HPV 6/11 are also sole direct causes of juvenile & adult laryngeal papillomatosis; juvenile disease morbid and disabling, annual costs per case ~£20K
- HPV 6/11 are also associated with ~10% of LSIL
- Therefore a lower estimate of total annual costs of HPV 6/11 disease in the UK is ~£35 million





What plans have been made about introduction of an HPV vaccine in the UK?

- The DH has agreed to introduce HPV vaccination routinely for girls aged 12-13yrs in autumn 2008
- This will be a school-based vaccination programme and a catch-up component up to the age of 18 will also be delivered from 2009
- Cost-effectiveness studies of the two vaccines have been completed, independently peer-reviewed, and submitted to DH. These have quantified the additional benefit from using the HPV 6/11/16/18 vaccine
- Competitive tenders re the actual programme purchase costs of the two vaccines have been submitted (e.g. currently one shot of both Gardasil and Cervarix cost ~ £80), a decision as to which vaccine will be used is expected before the end of May 2008
- Specific educational materials have been designed and circulated

Do the new HPV vaccines have any effect on established infection?

- The mechanism of action of the HPV VLP vaccines through production of neutralising antibodies seems unlikely to be able to cause regression of infection
- In 2189 women aged 18-25 with HPV in Costa Rica receiving HPV 16/18 or Hepatitis A vaccine Hildesheim & Herrero compared regression at 6 & 12 months of
 - HPV 16/18
 - Non HPV 16/18 in clades A7/A9
 - Other HR HPV
 - LR HPV
 - HC2 +ve HPV
- **The HPV vaccine (Cervarix) had no effect on viral clearance**
 - JAMA 2007;298:743

Is the efficacy of the Cervarix (GSK) associated with the AS04 adjuvant?

- AS04 one of a series of proprietary adjuvants developed by GSK
- AS04 consists of MPL (monophosphoryl lipid A) + alum, which acts as a TLR4 agonist
- An RCT of Hepatitis B vaccines adjuvanted with (a) alum (Engerix B) given 0,1,6 months or (b) AS04 (Fendrix) given 0,6 months showed superior immunogenicity of Fendrix
 - *Boland G et al, Vaccine 2004;23:316*
- Cervarix vs alum-adjuvanted HPV 16/18 VLP vaccine showed increased frequency (~3 fold) of antigen-specific memory B cells
 - *Giannini SL et al, Vaccine 2006;24:5937*

Will the HPV vaccines be effective in the presence of HIV infection?

- Both Merck and GSK are conducting trials of the immunogenicity of their vaccines in HIV positive subjects
- Although there is no data, one might speculate that the apparent superior B cell priming associated with the AS04 adjuvant could result in Cervarix having better response rates in HIV infection or better persistence of responses in the face of T helper dysfunction
- Should we investigate the concept of 'specifically-tailored' vaccines in HIV infection?

The problem of HPV disease in MSM

- Gay men suffer a high rate of HPV diseases including ano-genital warts, anal intra-epithelial neoplasia, and anal cancer
- These conditions are increased in frequency in HIV positive MSM and are often more difficult to treat
- Part of the logic behind the DH's decision to vaccinate only girls is that heterosexually transmitted STDs can be prevented by vaccinating one sex only, which will induce herd (i.e. female) immunity. Vaccinating one sex only is more cost-effective than vaccinating both sexes
- Thus the population reservoir of male homosexually transmitted HPV is unlikely to be influenced by population-based female vaccination for the foreseeable future

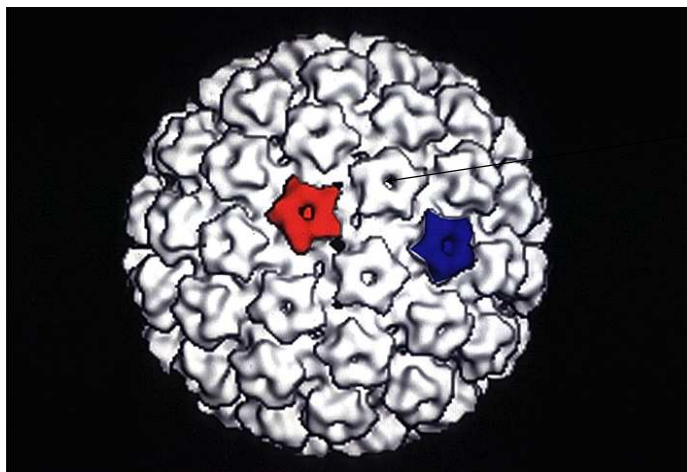
How could the problem of HPV disease in MSM be addressed?

- Vaccinate all boys aged 12 (unlikely in the UK)
- Develop effective screening and treatment for AIN
- Develop effective therapeutic HPV vaccines
- Try and identify gay men early in adolescence (before exposure to HPV 6/11/16/18) and vaccinate then.
- There are a number of difficulties with such a strategy
 - Investigating the cost-effectiveness – we would need data including the median time of HPV DNA- and sero-conversion after MSM sexual debut
 - Implementing such a strategy – where and how?

Papillomavirus L2 as a vaccine candidate

- HPV L2 is the minor capsid protein, with up to 72 L2 molecules per VLP
- We know that there are anti-L2 neutralizing monoclonal antibodies are that therefore L2 contains neutralizing epitopes
- The precise location of L2 has been difficult to demonstrate but some of the sequence must be surface exposed on the virion

Where is HPV L2?



Probably sits
in the top of
the centre
of the centre
of each
capsomere

HPV L2 is a potential prophylactic vaccine immunogen capable of cross-neutralization

- Immunization of animal models with various PV L2 proteins can produce HPV cross-neutralizing responses
- In a clinical trial of a HPV 16 L2E7E6 fusion protein cross-neutralizing responses to HPV 18 were induced
- A protective and broadly cross-neutralizing epitope at residues 17 to 36 has been described
 - Neutralised HPV 6, 11, 16, 18, 31, 45, 52, 58
 - *Gambhira et al, J Virol 2007;81:13927*
- A 20mer peptide would be a very attractive immunogen amenable to various vaccine delivery modalities and potentially low production costs



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