

Vaccines Against STD's

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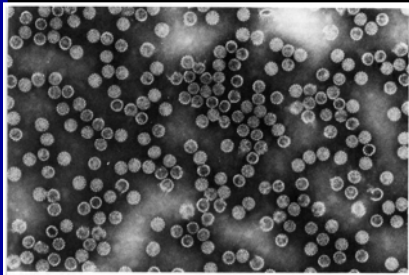
STD Vaccines

- What we have
 - Cervical cancer (HPV16 and 18)
 - Genital warts (HPV6 and 11)
 - Hepatitis B
- What we may have soon
 - Genital herpes (HSV-2)
- What we don't have (and why)
 - Syphilis
 - Gonorrhea
 - Chlamydia
 - Chancroid
 - trichomonas

Antiviral Vaccine Trials at the University of Utah

- Merck 015 (FUTURE II) Trial
 - 11,000 subjects worldwide
- Utah site: 45 enrolled and vaccinated subjects
 - 0, 2, and 6 months
- Herpevac (genital herpes vaccine)
 - 7700 young women vaccinated
 - 331 subjects enrolled and vaccinated at our site
 - Results available in 2010

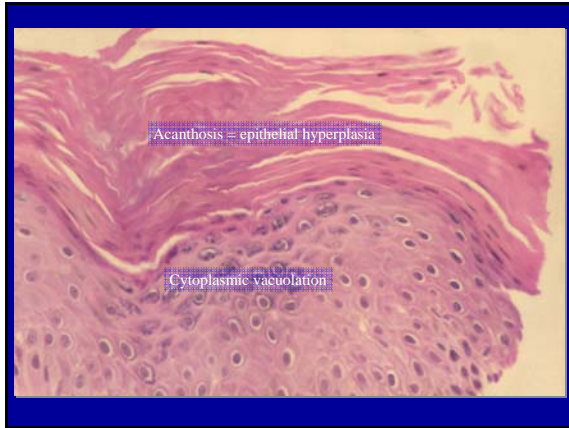
The Human Papilloma Virus



Shah, KV. Sexually Transmitted Diseases, 1990

HPV Serotypes

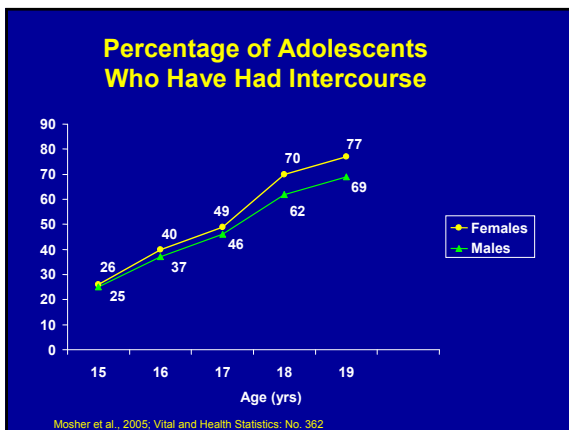
HPV-1	Deep plantar warts
HPV-2	Common warts
HPV-3	Flat warts in normal individuals and in patients with epidermodysplasia verruciformis (EV)
HPV-4	Deep plantar warts and common warts
HPV-5	Pityriasis-like macular lesions in EV patients
HPV-6	Genital and respiratory tract papillomas and some genital cancers
HPV-7	Common warts EV patients and in butchers
HPV-8	Macular lesions in EV patients
HPV-9	Macular lesions in EV patients
HPV-10	Flat warts
HPV-11	Genital and respiratory tract papillomas and some genital cancers
HPV-12	Macular lesions in EV patients
HPV-13	Oral focal epithelial hyperplasia
HPV-14	Macular lesions in EV patients
HPV-15	Macular lesions in EV patients
HPV-16	Genital tract cancers and few genital tract papillomas
HPV-17	Macular lesions in EV patients
HPV-18	Genital tract cancers
HPV-19 to HPV-25	Macular lesions in EV patients



Risk Factors for HPV Infection

Women	Men
<ul style="list-style-type: none"> • Young age (peak age group 20-24 years of age)¹ • Lifetime number of sex partners² • Early age of first sexual intercourse³ • Male partner sexual behavior³ • Smoking⁴ • Oral contraceptive use⁴ • Uncircumcised male partners⁵ 	<ul style="list-style-type: none"> • Young age (peak age group 25-29 years of age)¹ • Lifetime number of sex partners⁶ • Being uncircumcised⁶

1. *Clin Infect Dis.* 2003;36:1397-1403.
 2. *J Infect Dis.* 1996;174:679-689.
 3. *Eur J Cancer Prev.* 2000;9:5-14.
 4. *Am J Epidemiol.* 2003;157:218-226.
 5. *Arch Pathol Lab Med.* 2003;127:930-934.
 6. *Sex Transm Infect.* 2002;78:215-218.

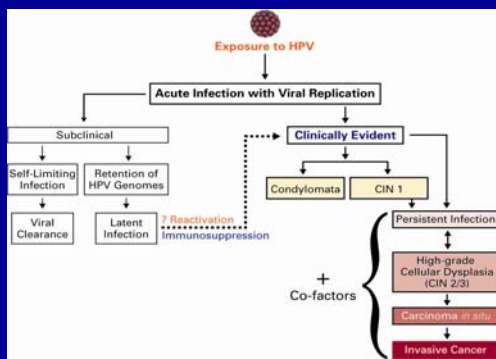


HPV Clearance

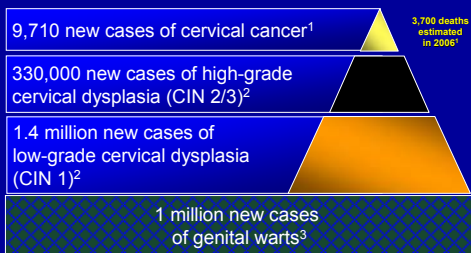
- In women 15-25 years of age, ~80% of HPV infections are transient.¹
 - Gradual development of cell-mediated immune response presumed mechanism²
- In a study of 608 college women, 70% of new HPV infections cleared within 1 year and 91% within 2 years.³
 - Median duration of infection = 8 months³
 - Certain HPV types are more likely to persist (e.g., HPV 16 and HPV 18).

1. Meijer CJJM et al. *Histopathology*, 1998;33:83-86.
 2. Schiffman M, Kiger SK. *J Natl Cancer Inst Monogr*, 2003;31:14-19.
 3. Ho GYF et al. *N Engl J Med*, 1998;338:423-428.

Natural History of HPV Infection



Estimated Annual Burden of HPV-Related Diseases in the United States



CIN = cervical intraepithelial neoplasia.
 1. American Cancer Society, *Cancer Facts and Figures 2006*. Atlanta, Ga: American Cancer Society, 2006;4. 2. Schiffman M, Solomon D. Findings to date from the ASCUS-LSIL Triage Study (ALTS). *Arch Pathol Lab Med*, 2003;127:386-393.
 3. Fleischer AB, Parrish CA, Glenn R, Feldman SR. Condyloblastoma acuminata (genital warts): Patient demographics and treatment outcomes. *Sex Transm Dis*, 2011;29:64-67.

Colposcopic Appearance of the Normal Cervix¹



¹ Selbors JW, Sankaranarayanan R, eds. Lyon, France. International Agency for Research on Cancer, 2003. Reprinted from Colposcopy and Treatment of Cervical Intraepithelial Neoplasia: A Beginner's Manual. With permission of the International Agency for Research on Cancer, World Health Organization.

Cervical Intraepithelial Neoplasia (CIN)¹



¹ Selbors JW, Sankaranarayanan R, eds. Lyon, France. International Agency for Research on Cancer, 2003. Reprinted from Colposcopy and Treatment of Cervical Intraepithelial Neoplasia: A Beginner's Manual. With permission of the International Agency for Research on Cancer, World Health Organization.

Invasive Cervical Carcinoma¹



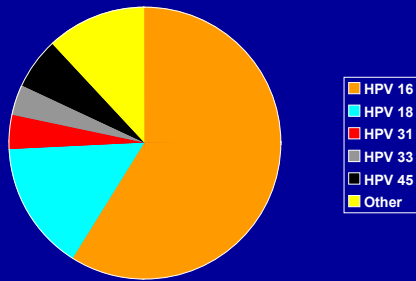
¹ Selbors JW, Sankaranarayanan R, eds. Lyon, France. International Agency for Research on Cancer, 2003. Reprinted from Colposcopy and Treatment of Cervical Intraepithelial Neoplasia: A Beginner's Manual. With permission of the International Agency for Research on Cancer, World Health Organization.

Cervical Adenocarcinoma¹

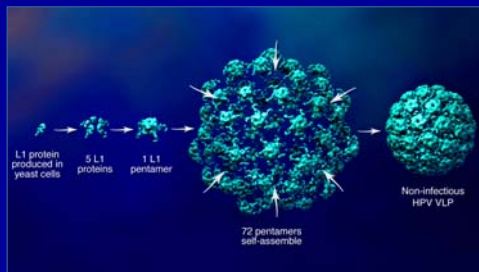


1. Selbros JW, Sarkararayanan R, eds. Lyon, France: International Agency for Research on Cancer, 2003. Reprinted from *Colposcopy and Treatment of Cervical Intraepithelial Neoplasia: A Beginner's Manual*. With permission of the International Agency for Research on Cancer, World Health Organization.

Prevalent HPV Types in Squamous Cell Cervical Cancer



Assembly of VLPs¹⁻³



1. Barzofsky JA, et al. *J Clin Invest*. 2004;114:450-462.
2. Kimmbauer R, et al. *Proc Natl Acad Sci USA*. 1992;89:12180-12184.
3. Modis Y, et al. *EMBO J*. 2002;21:4764-4762.

L1 VLPs Mimic the HPV Virion

Noninfectious HPV VLP Infectious HPV

Capsid proteins: L1

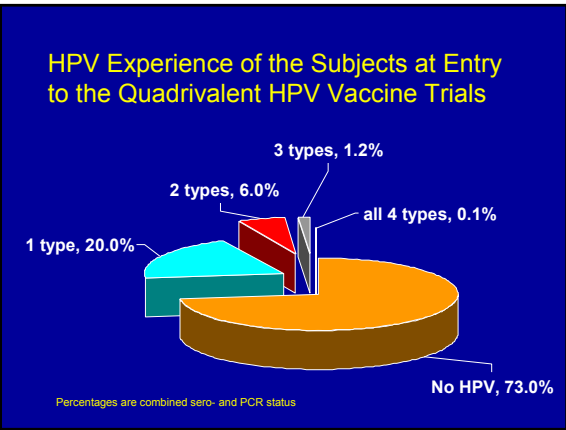
Lacks L2 protein
Lacks viral DNA

L2
Viral DNA

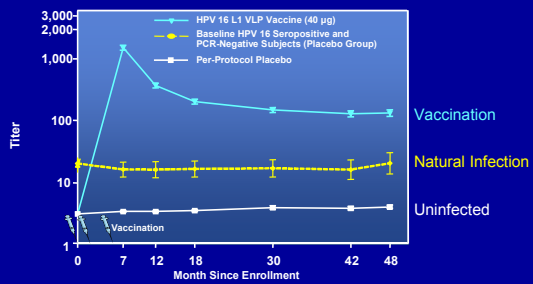
1. Stanley M. Vaccine 2006;24(Suppl 1):S16-S22.
2. Berzofsky JA, et al. J Clin Invest. 2004;114:450-462.
3. Baker TS, et al. Biophys J. 1991;60:1445-1456.
4. Chen XB, et al. Adv Cell. 2000;6:557-567.

The Merck Quadrivalent HPV Vaccine

- Quadrivalent human papillomavirus 6/11/16/18 L1 virus-like particle (VLP) vaccine VLPs are produced in *Saccharomyces cerevisiae*
 - The L1 proteins self-assemble into VLPs.
 - Purified VLPs are adsorbed on aluminum-containing adjuvant.
 - The adjuvant is amorphous aluminum hydroxyphosphate sulfate (225 µg per dose).
- Each 0.5-mL dose contains HPV Types 6/11/16/18 (20/40/40/20 µg L1 protein, respectively).



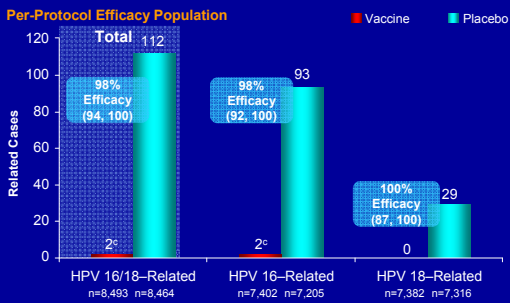
Immunogenicity of the HPV Vaccine



HPV Vaccine Clinical Trials: Per-Protocol Efficacy (PPE) Population

- Primary analysis of efficacy conducted in PPE population:
 - Received all 3 vaccinations within 1 year of enrollment
 - Did not have major deviations from the study protocol
 - Were naïve to the relevant HPV type(s)
- Efficacy measurements started after Month 7 visit.

Vaccine Efficacy Against HPV 16 or 18 Related CIN^a 2/3 or AIS



^aCIN = cervical intraepithelial neoplasia. ^bAIS = adenocarcinoma in situ. ^cOne case was a coinfection with HPV 52, the other was a coinfection with HPV 51 and 24.

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are needed to see this picture.

All CIN2/3 due to *any* HPV serotype, intent-to-treat analysis
NEJM 2007; 356: 1915-27.

Genital Warts: Female



Flat Cervical Wart



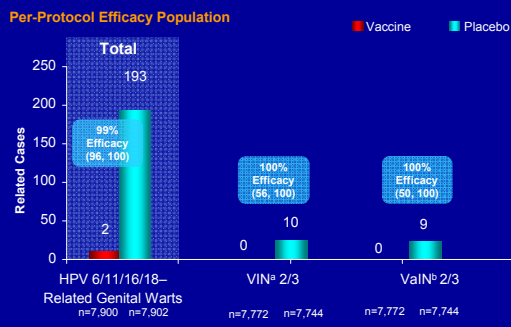
Genital Wart: Male



Genital Wart: Male



Vaccine Efficacy Against HPV 6/11/16/18-Related External Genital Lesions



HPV Quadrivalent Vaccine in Males: EUROGIN Meeting 2008

- Tested in asymptomatic young men ages 16-26
 - 3400 heterosexual males
 - 600 MSM
 - Mean followup 29 months
 - 5 or fewer lifetime partners
- 90.4% effective
 - 3 cases of genital warts in the vaccine group
 - 31 cases in the placebo group, 28 were genital warts, 3 were HPV-related intraepithelial neoplasia
- Vaccine was 86% effective against persistent HPV infection

http://www.merck.com/newsroom/press_releases/research_and_development/2008_1113.html

Glaxo HPV 16/18 Vaccine (Cervarix)

- Similar to the current (Merck) vaccine
 - HPV16 and HPV18 VLP's included
 - Prevents precancerous cervical lesions
- Differences
 - The adjuvant (AS04), contains an aluminum salt and monophosphoryl lipid A
 - Does not protect against genital wart strains
- Application to the U.S. FDA in 2007. Approval not expected until later this year.
 - Already approved in Europe and Australia

Genital Herpes Vaccine

- gD2 subunit vaccine
- Effective only in HSV-1 and HSV-2 seronegative women
 - Efficacy about 70% in preventing genital herpes disease in this group
- No efficacy in men or in HSV+ women

Stanberry et. al. NEJM 2002; 347:1652.

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TIFF (Uncompressed) decompressor
are needed to see this picture.

Herpevac Phase 3 Clinical Trial

- Jointly sponsored by NIH and GlaxoSmithKline
- gD2-based vaccine
- Double-blind, controlled (hep A vaccine)
- >8000 young women enrolled
 - HSV-1 and HSV-2 seronegative
- Results should be known in 2010

Syphilis Vaccine Efforts

- Treponema pallidum has been very difficult to culture
- Theoretically, a vaccine should be possible since immunity is acquired
 - Historically only 1/3 of patients with syphilis develop tertiary disease. The rest clear the infection.
 - Inoculation of prisoners with T. pallidum: Sing Sing prison, 1950s
 - 11/11 patients with untreated early syphilis developed skin lesions at site of inoculation
 - 0/5 patients with untreated late latent syphilis developed lesions

Chlamydia vaccine efforts

- The disease may be partially immunopathologic
 - Vaccination with killed Chlamydia led to severe trachoma after subsequent reinfection
- At least one vaccine candidate in preclinical development (Emergent Biosolutions)
- Some success with vaccine candidates in animal models
 - Subunit vaccines

Gonorrhea vaccine

- Subunit vaccines focusing on pili (attachment structures)
 - Limited by antigenic variation
- No clinical trials



STD Vaccines: Conclusions

- HPV vaccines
 - Quadrivalent (Gardasil, Merck)
 - Approved and available
 - Prevents cervical lesions and genital warts
 - Bivalent (Cervarix, Glaxo)
 - Not yet approved in the U.S.
 - Does not cover genital warts
- Genital herpes (HSV-2)
 - Phase 3 clinical trial being concluded
- Chlamydia, gonorrhea, chancroid
 - Not available anytime soon...

Questions? Comments?

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