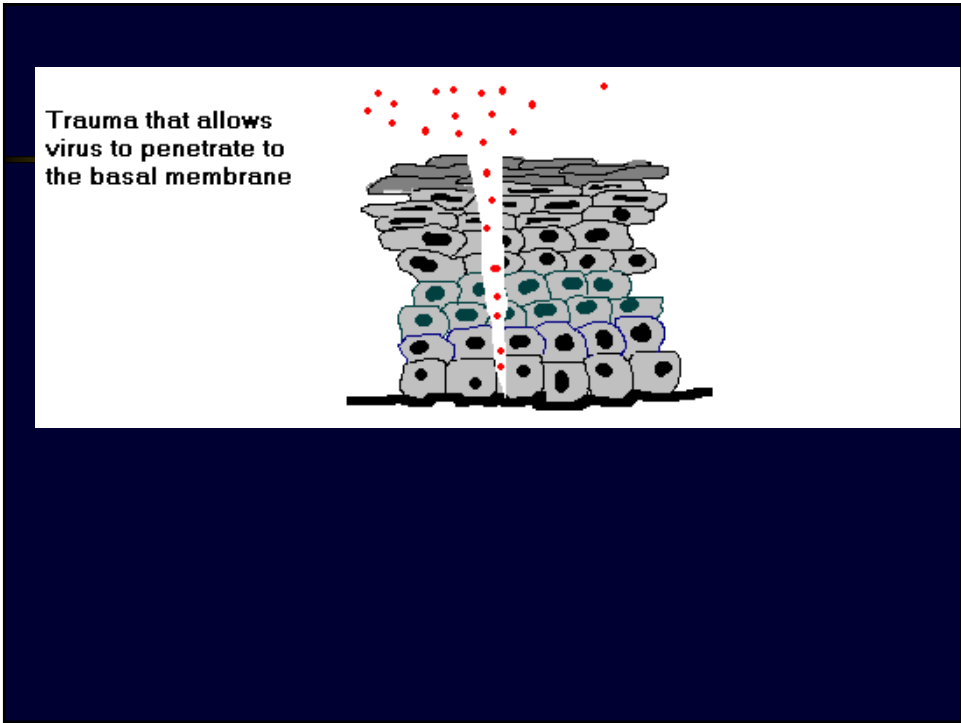
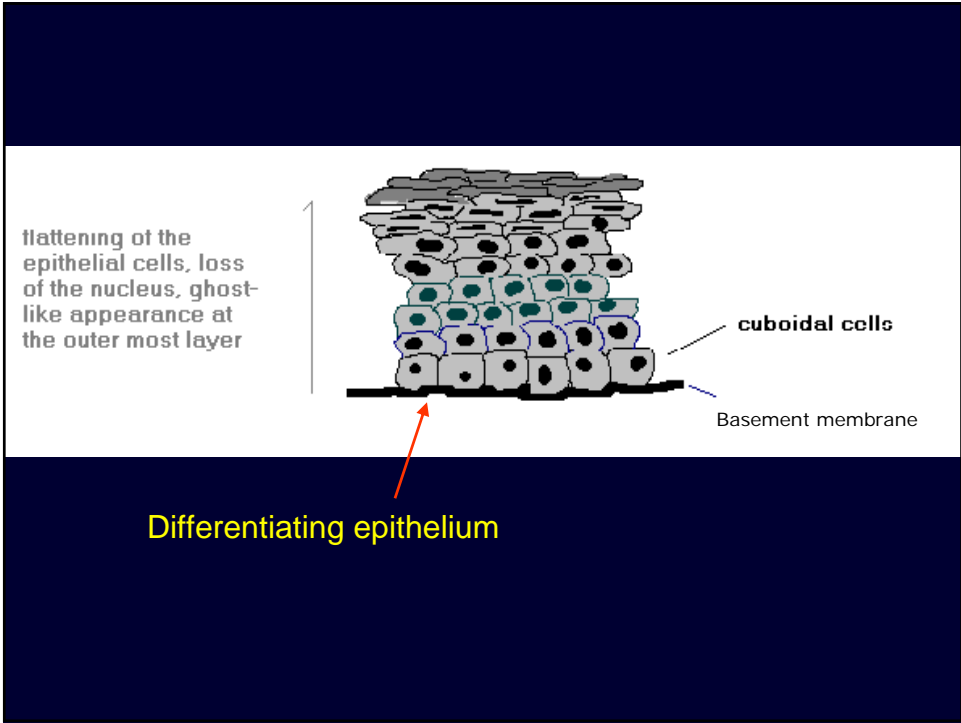


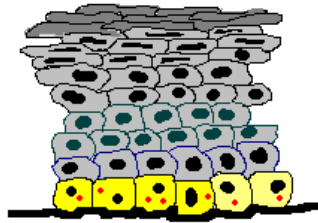
Human papillomavirus Infections,
Outcomes, Treatments and
Concerns

Dorothy Wiley, MPH, PhD
Associate Professor
Primary Care Division
University of California, Los Angeles School of Nursing
Los Angeles, California

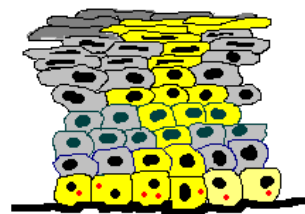
... were to build an HPV lesion...

- *You would need a few essential ingredients...*





Infection spreads
laterally at first



Infection and consequent
atypias begin to ascend

Screening versus diagnostic testing?

- Pap testing
- Excisional biopsy
- HPV (molecular) testing
 - Signal amplification tests
 - Product amplification (PCR)

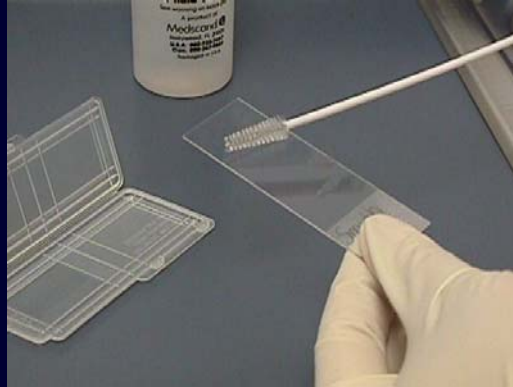
Pap test

- Assessment of exfoliated cells from the (hopefully) squamocolumnar junction of the cervix



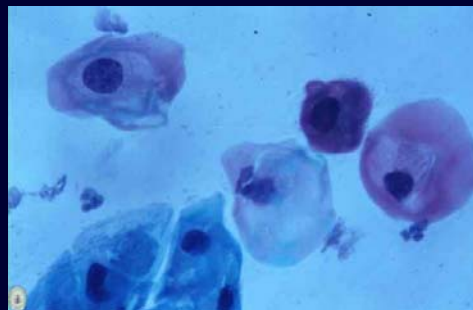
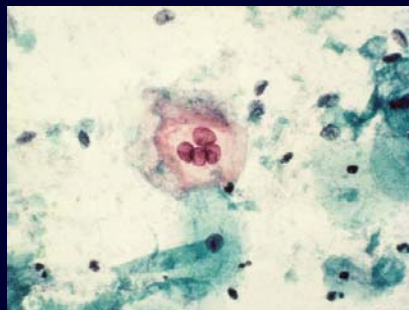
Pap test

- Brush or wooden “spatula” are used to scrape cells and place onto slide or into solution.



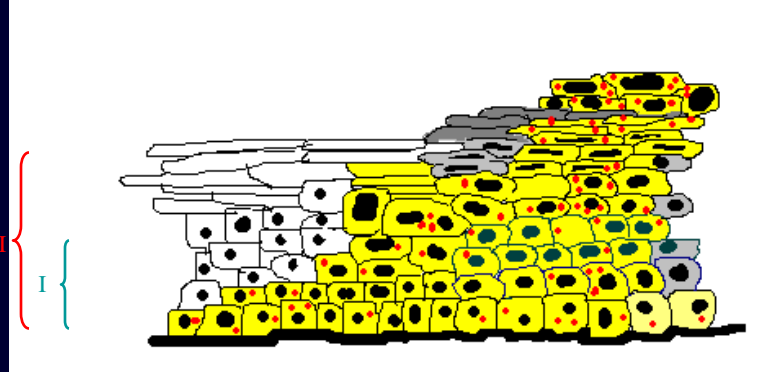
Pap test

- Specimens are prepared in the lab and cells are stained. The test name related to the staining procedure and named after Dr. Papanicolaou.



Must have mitosis in upper 2/3 of epithelium

III
III
I



Molecular testing

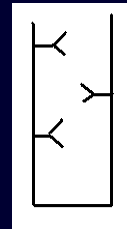
- Hybrid Capture II



Disrupt the DNA virus



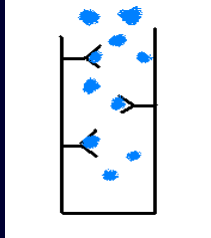
Add RNA probe to anneal to the disrupted DNA in the specimen



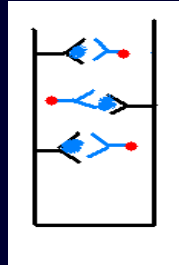
mAB(s) for the DNA-RNA hybrid (both)

Molecular testing

- Hybrid Capture II



Pass specimen through... DNA/RNA complexes (both) anneal to the mAbs



Wash and add a series of mAbs (not just one) that are tagged to amplify the SIGNAL

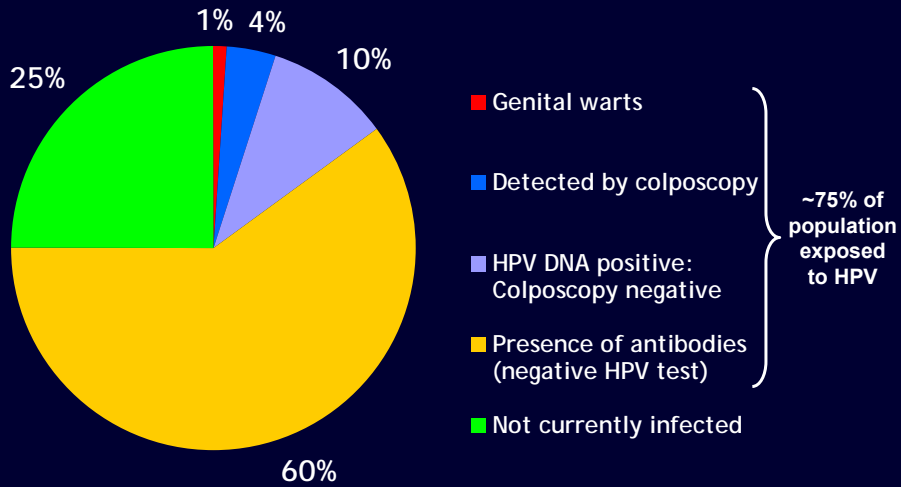
Read-out is optical density

Controversy: can this number reflect virus load?

PCR

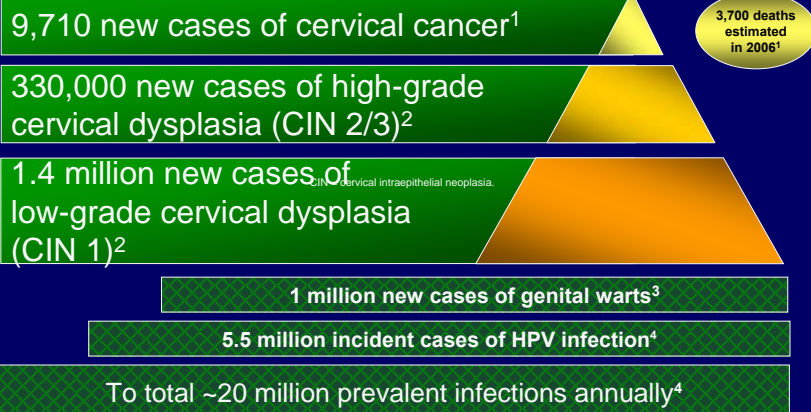
- Among “newly” developed assays - Not FDA approved for clinical use
 - Gravitt
 - Virus load
 - Roche Dot Blot Assay - “linear array”
 - Identifies up to 27 different HPVs

HPV Infection in the United States



Koutsky. *Am J Med.* 1997;102(5A):3.

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



CIN = cervical intraepithelial neoplasia.

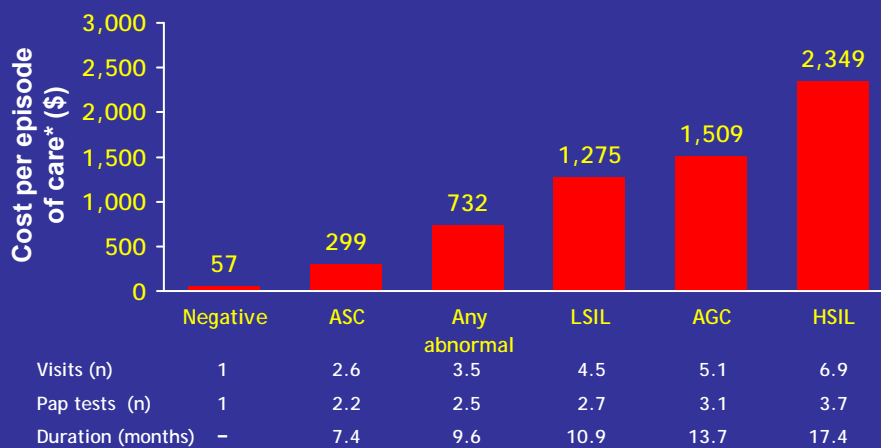
1. American Cancer Society. *Cancer Facts and Figures 2006*. Atlanta, Ga: American Cancer Society; 2006:4. 2. Schiffman M, Solomon D. Findings to date from the ASCUS-LSIL Triage Study (ALTS). *Arch Pathol Lab Med.* 2003;127:946-949. 3. Fleischer AB, Parrish CA, Glenn R, Feldman SR. Condylomata acuminata (genital warts): Patient demographics and treating physicians. *Sex Transm Dis.* 2001;28:643-647. 4. Cates et al. American Social Health Association Panel. *Sex Transm Dis.* 1999;26(suppl 4):52.

So, why do we care...

- Although the incidence and prevalence of HPV infection is high
 - Mortality is low
 - Morbidity is low relative to prevalence of infection
 - Most (men and) women spontaneously clear infection

19

Healthcare Costs of Cervical HPV



*Average age adjusted to the 1998 US female population; all cost estimates were converted to 2002 dollars. ASC = atypical squamous cells; AGC = atypical glandular cells; LSIL = low-grade squamous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion.

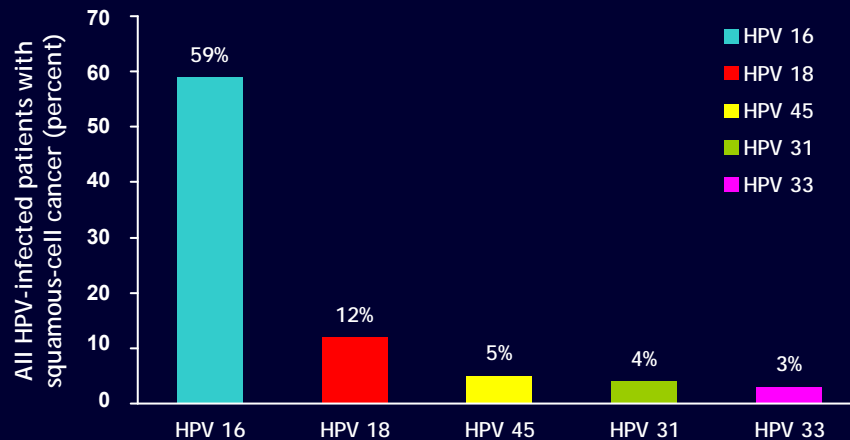
Insinga et al. *Am J Obstet Gynecol.* 2004;191:114.

Common HPV Types Associated With Benign and Malignant Disease

	HPV Types	Manifestations
Low-Risk	6, 11	Benign low-grade cervical changes Condylomata acuminata (genital warts)
High-Risk	16, 18, 31, 33, 45	Low-grade cervical changes High-grade cervical changes Cervical cancer Anogenital and other cancers

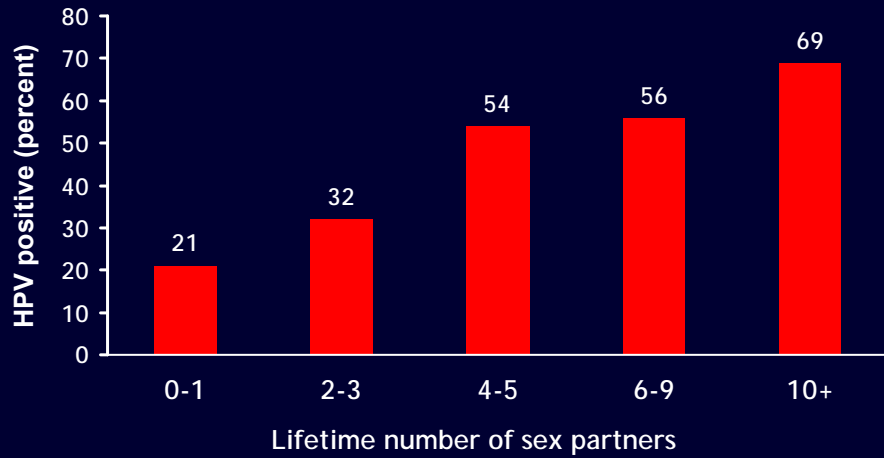
Cox. *Baillière's Clin Obstet Gynaecol.* 1995;9:1.
Munoz et al. *N Engl J Med.* 2003;348:518.

Most Prevalent HPV Types That Cause Cervical Cancer



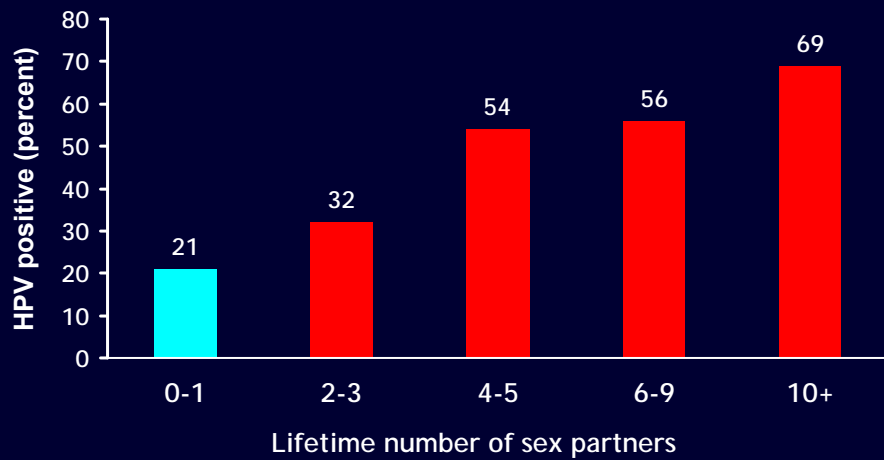
HPV DNA was detected in 1,739 of the 1,918 patients with cervical cancer.
Muñoz et al. *N Engl J Med.* 2003;348:518. Based on a worldwide survey.

HPV Infection in Young Women



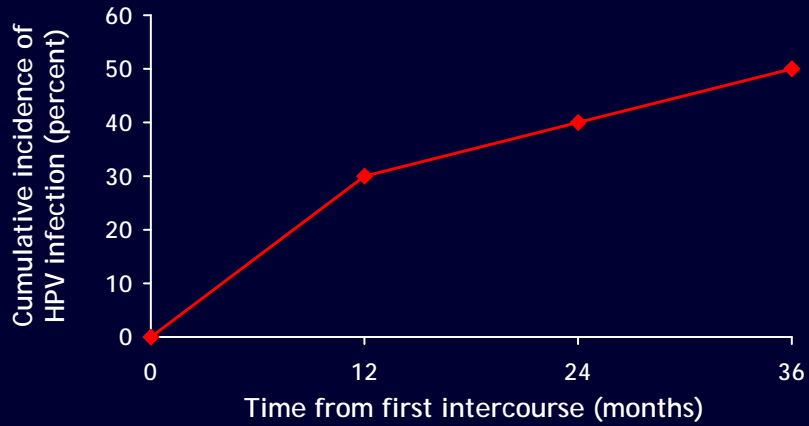
Ley et al. *J Natl Cancer Inst.* 1991;83:997.

HPV Infection in Young Women



Ley et al. *J Natl Cancer Inst.* 1991;83:997.

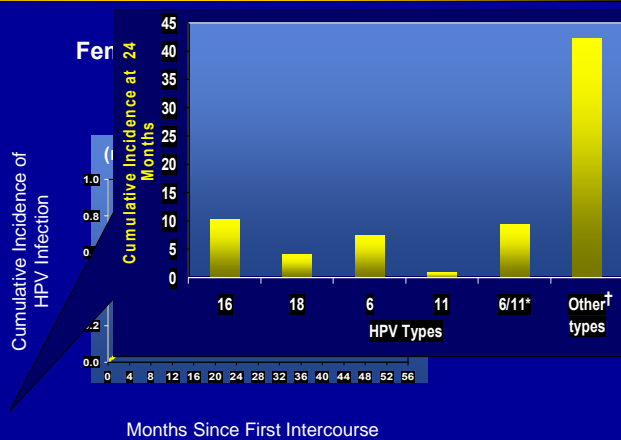
HPV Infection Among College-Age Women



Cumulative incidence of HPV infection from time of first sexual intercourse (n=94) among women in Washington State, 1990-2000.

Adapted from Winer et al. *Am J Epidemiol.* 2003;157:218.

... While the Prevalence of HPV Infection After Sexual Debut Is High



*Not all HPV-6/11 specimens were individually tested for HPV 6 and HPV 11 separately.

†Types 31, 45, 51, 52, 55, 58, 56, 33, 35, 39, 40, 42, 53, 54.

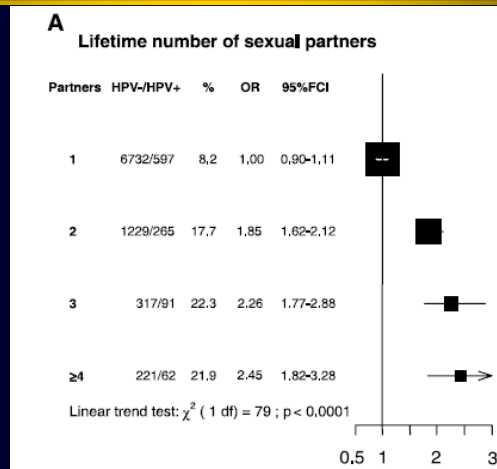
Adapted from Winer RL, Lee S-K, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. *Am J Epidemiol.* 2003;157:218-226, by permission of Oxford University Press.

Predictive Factors for HPV Infections: College Women

- Smoking
- Oral Contraceptive Use
- Report of new male sexual partner
 - In particular, 1 known for <8 months

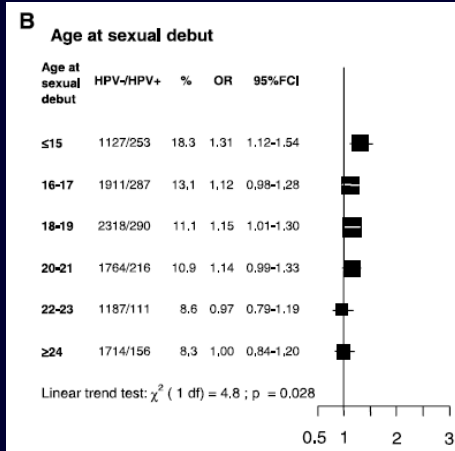
Internationally, only a modest increase in the odds testing HPV DNA+ when 3 or more (lifetime) male partners are reported by women

11,337 Women Enrolled in IARC Prevalence Study Group



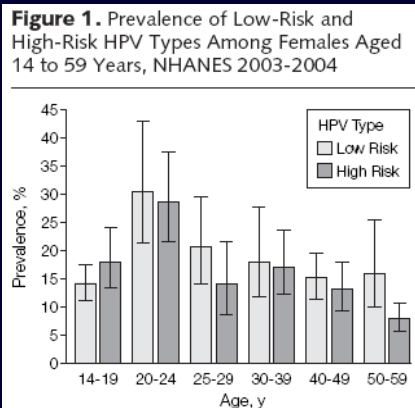
Vaccarella S, Franceschi S, Herrero R, Munoz N, Snijders PJ, Clifford GM, et al. Sexual behavior, condom use, and human papillomavirus: pooled analysis of the IARC human papillomavirus prevalence surveys. *Cancer Epidemiol Biomarkers Prev* 2006;15(2):326-33.

... and age at first "sexual debut" has a modest affect on the odds of testing HPV DNA+
 11,337 Women Enrolled in IARC Prevalence Study Group



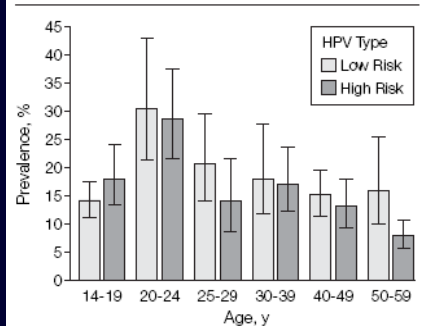
Vaccarella S, Franceschi S, Herrero R, Munoz N, Snijders PJ, Clifford GM, et al. Sexual behavior, condom use, and human papillomavirus: pooled analysis of the IARC human papillomavirus prevalence surveys. *Cancer Epidemiol Biomarkers Prev* 2006;15(2):326-33.

NHANES Data Still Support that HPV Infection is most common young adults



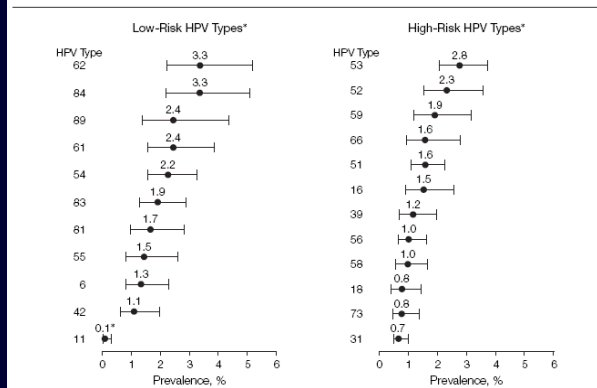
...but suggest that low-risk HPVs are as common as high-risk virus types

Figure 1. Prevalence of Low-Risk and High-Risk HPV Types Among Females Aged 14 to 59 Years, NHANES 2003-2004



...population-based data suggest the distribution of types may differ from our prior assumptions

Figure 2. Prevalence of HPV Types Among Females Aged 14 to 59 Years, NHANES 2003-2004



HPV indicates human papillomavirus; NHANES, National Health and Nutrition Examination Survey. Error bars indicate 95% confidence intervals.
 * HPV types with a relative SE of more than 30% are not presented, except for HPV-11, since it is a vaccine type.

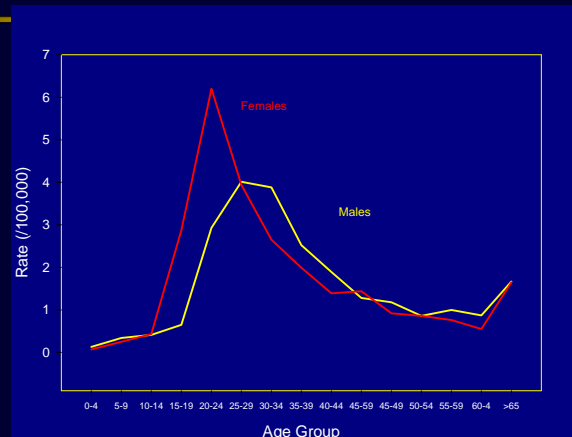
Epidemiology of Genital Warts

- One of the most common STDs
- ~1.4 million (1%) individuals in the United States¹ currently have genital warts
- Incidence of genital warts is underestimated²
- Annually, 500,000-1,000,000 new cases of genital warts occur in the United States³
- ~264,000 initial office visits for genital warts in the United States annually (NDTI)⁴

NDTI = National Disease and Therapeutic Index 2003.

1) Koutsky. *Am J Med.* 1997;102(5A):3. 2) Koshiol et al. *Sex Transm Dis.* 2004;31:748. 3) Strauss et al. *Int J Dermatol.* 1996;35:340. 4) CDC. STD Surveillance 2003.

HMO data suggest EGWs disproportionately affect young men and women and peak at different ages for each...



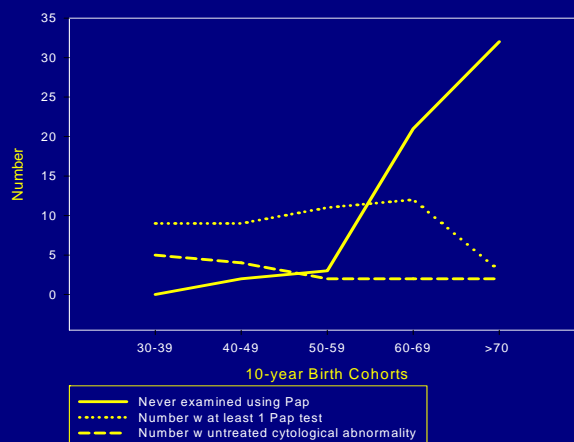
Insinga RP, Dasbach EJ, Myers ER. The health and economic burden of genital warts in a set of private health plans in the United States. *Clin Infect Dis* 2003;36(11):1397-403.

Epidemiology of Cervical Cancer

- Second most common cancer in women worldwide¹
 - Estimated 400,000-500,000 cases of cervical cancer diagnosed each year²
 - Surpassed only by breast cancer, domestically & internationally
- In the United States, the estimated incidence is ~8.0/100,000³
 - ~10,520 new cases and ~3,900 deaths annually³
 - Even though >50 million Pap smears are performed each year⁴
 - ~half of cervical cancer cases are attributable to one HPV Type
- Equal opportunity disease...
 - Half of the cases will occur in women never screened and an additional 10% in women not screened within the past 5 years⁵
- Cost of US cervical cancer screening programs, using Pap test, >\$5 billion annually⁶

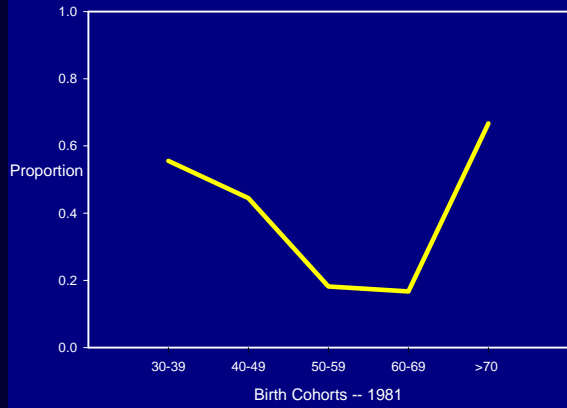
1. World Health Organization. *World Cancer Report 2003*.
 2. Kiviat et al. In: Holmes K, Mardh P, Sparling P et al. eds. *Sexually Transmitted Diseases*. 3rd ed. New York, NY: McGraw-Hill Inc; 1999:811.
 3. American Cancer Society. *Cancer Facts and Figures*. 2004.
 4. Sirovich and Welch. *J Gen Intern Med*. 2004;19:243.
 5. *NIH Consensus Statement. Cervical Cancer*. 1996;14:1.
 6. American Social Health Association. HPV: Get the Facts. 2005. Available at: <http://www.ashastd.org/hpvccro/background.html> Accessed March 3.

Patterns for Pap testing and Undertreatment of Pap test Abnormalities within Ten Years of Diagnosis of Cervical Cancer; 1981



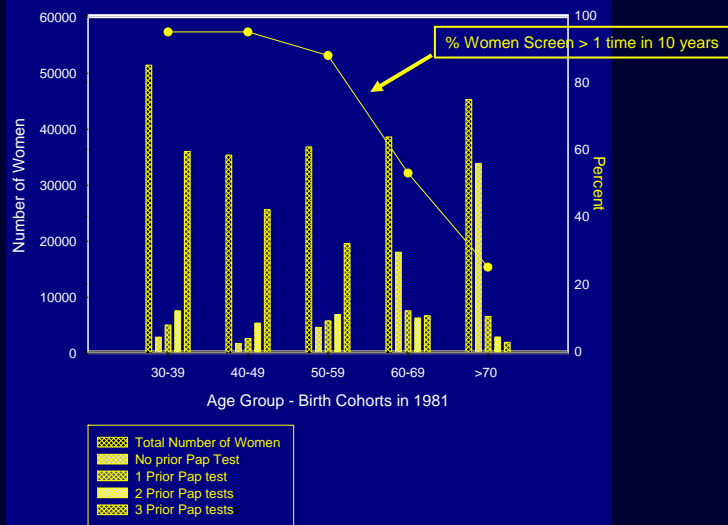
Stenkvist B, Bergstrom R, Eklund G, Fox CH. Papanicolaou smear screening and cervical cancer. What can you expect? *Jama* 1984;252(11):1423-6.

Proportion of Cervical Cancer Cases Diagnosed in 1981 Showing Undertreatment of Pap Test Abnormalities in Prior 10 years

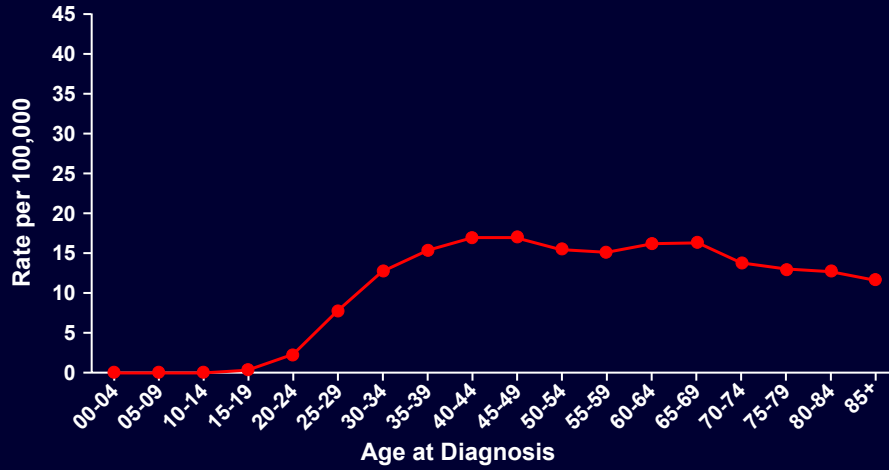


Stenkvist B, Bergstrom R, Eklund G, Fox CH. Papanicolaou smear screening and cervical cancer. What can you expect? *Jama* 1984;252(11):1423-6.

Number of Women Eligible, Showing None, One or Two Prior Pap tests in Prior 10 Years Swedish Registry in 1981

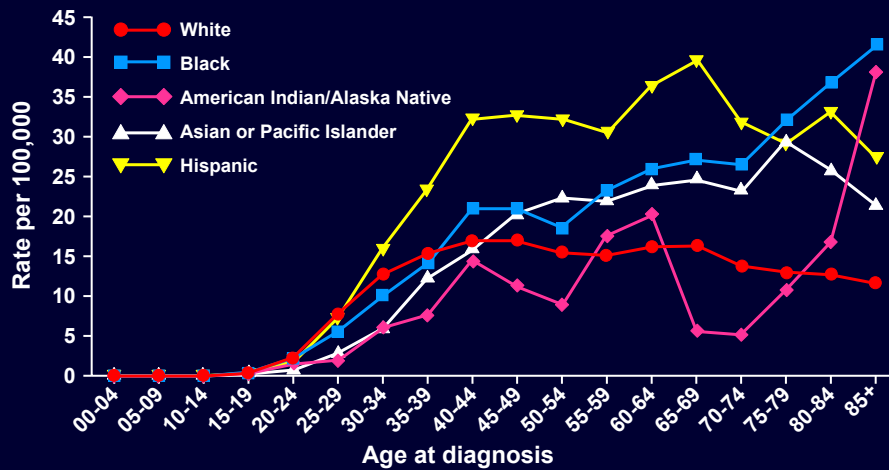


Cervical Cancer



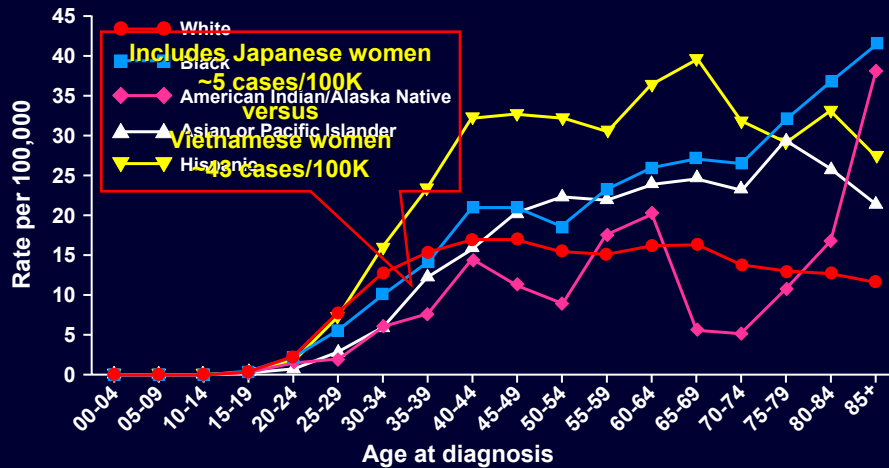
Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Databases: Incidence – SEER 11 Regs + AK Public-Use, Nov 2003 Sub for Expanded Races (1992-2001) and Incidence – SEER 11 Regs Public-Use, Nov 2003 Sub for Hispanics (1992-2001), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2004, based on the November 2003 submission

Cervical Cancer is Not an Equal Opportunity Disease



Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Databases: Incidence – SEER 11 Regs + AK Public-Use, Nov 2003 Sub for Expanded Races (1992-2001) and Incidence – SEER 11 Regs Public-Use, Nov 2003 Sub for Hispanics (1992-2001), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2004, based on the November 2003 submission

Cervical Cancer is Not an Equal Opportunity Disease



Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Databases: Incidence – SEER 11 Regs + AK Public-Use, Nov 2003 Sub for Expanded Races (1992-2001) and Incidence – SEER 11 Regs Public-Use, Nov 2003 Sub for Hispanics (1992-2001), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2004, based on the November 2003 submission

Cervical Cancer Rates Have Plummeted Since the 1930s

- Nearly 70% reduction; attributable to Pap test screening
- Still, approximately 10,000-12,000 incident US cases annually
- ~ 3,500 to 4,000 US women perish annually
- Almost all cervical cancers are due to HPVs

Transmission of HPV

- Intimate skin-to-skin contact with an infected partner is necessary for transmission¹
 - Intromissive intercourse is not strictly necessary^{1,2}
 - Men implicated in epidemiologic chain of the infection³
- Incubation period ranges from weeks to several months⁴
- Source contact usually has subclinical infection⁵
- Perinatal transmission can, in rare instances, cause recurrent respiratory papillomatosis in infants and young children⁶
- Condoms may not prevent HPV infection⁷
 - Condom usage should be encouraged to decrease the risk of HIV and other STDs

1) Schiffman and Kjaer. *J Natl Cancer Inst Monogr.* 2003;(31):14. 2) Marrazzo et al. *Am J Public Health.* 2001;91:947. 3) Castellsague et al. *Salud Publica Mex.* 2003;45(suppl 3):S345. 4) American Social Health Association. *HPV: Get the Facts.* 2005. 5) Koutsky et al. *Am J Med.* 1997;102(5A):3. 6) Armstrong et al. *Clin Infect Dis.* 2000;31:107. 7) Manhart and Koutsky. *Sex Transm Dis.* 2002;29:725. Wiley et al., *International J STD AIDS.* 2005; 16(3): 203-211

Factors Associated With Higher Risk of HPV Infection

Women

- Age^{1,2}
- Sexual behavior^{1,2}
 - Increased risk associated with >number of male sexual partners^{1,2,3}
 - Risk increases with earlier age of first sexual intercourse⁴
- Sexual history of the male partner^{1,2}
- Immunologic status⁵
 - HPV more likely in immunosuppressed women

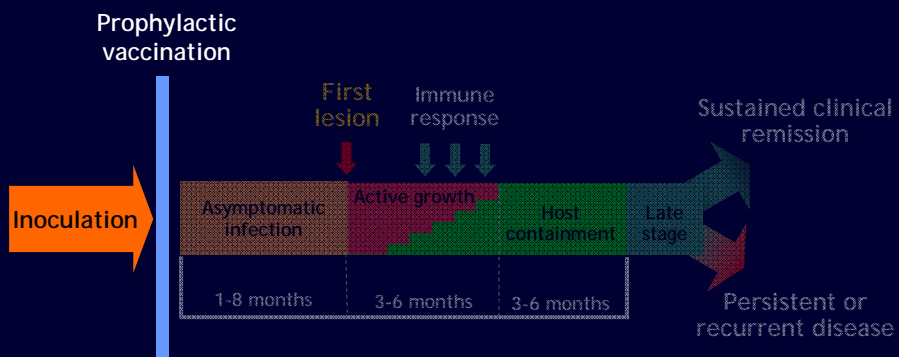
Men

- Lifetime number of sexual partners⁶
- Number of recent sexual partners⁶
- Uncircumcised⁶
- Same-sex encounters⁷

1) Ho et al. *N Engl J Med.* 1998;338:423. 2) Koutsky et al. *Am J Med.* 1997;102(5A):3. 3) Karlsson et al. *Sex Transm Dis.* 1995;22:119. 4) Moscicki et al. *JAI* 2001;285:2995. 5) World Health Organization. *IARC Monograph on the Evaluation of Carcinogenic Risks to Humans: Human Papillomaviruses.* 1995. 6) Schiffman and Kjaer. *J Natl Cancer Inst Monogr.* 2003;(31):14. 7.) Chin-Hong. *J Infect Dis.* 2004;190:2070.

Natural History of HPV Infection

Natural History of HPV Infection



Available at: <http://www.arhp.org/healthcareproviders/onlinepublications/clinicalproceedings.cfm?ID=149>
Accessed February 14, 2005.

Natural History of HPV Infection (cont'd)

- Most individuals will get HPV at some time
- In most cases, HPV either clears or becomes undetectable
- Persistence of high-risk HPV can lead to true precancer

HPV Infection

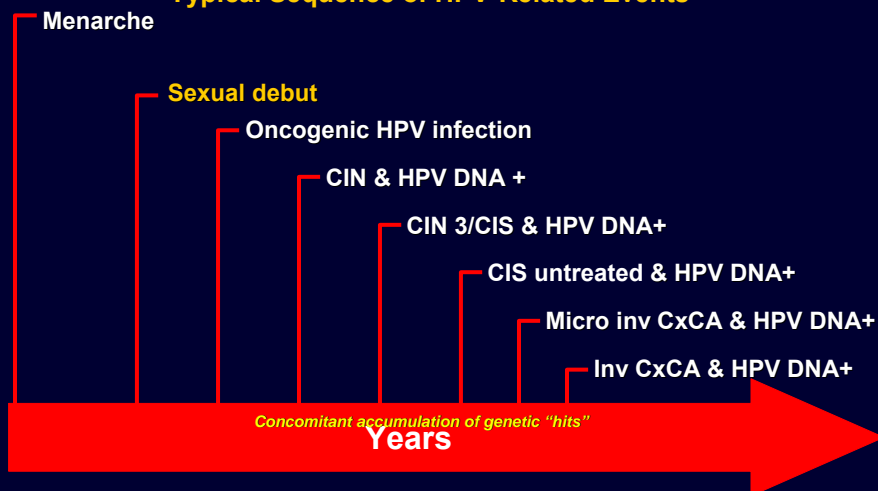


- Long persistence of HPV and CIN 3 are necessary for the accumulation of random mutations that lead to cancer

Koutsky et al. *Am J Med.* 1997;102(5A):3.
Schiffman and Kjaer. *J Natl Cancer Inst Monogr.* 2003;(31):14.

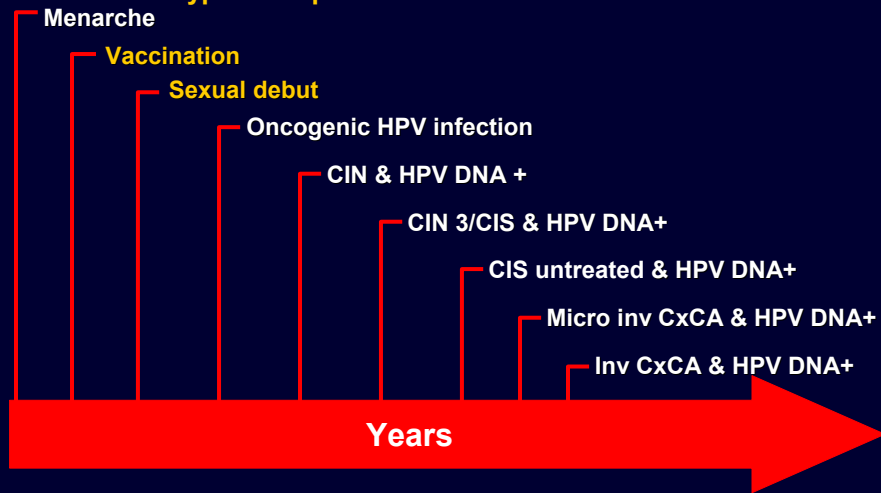
Natural History of Cervical Neoplasia

Typical Sequence of HPV-Related Events



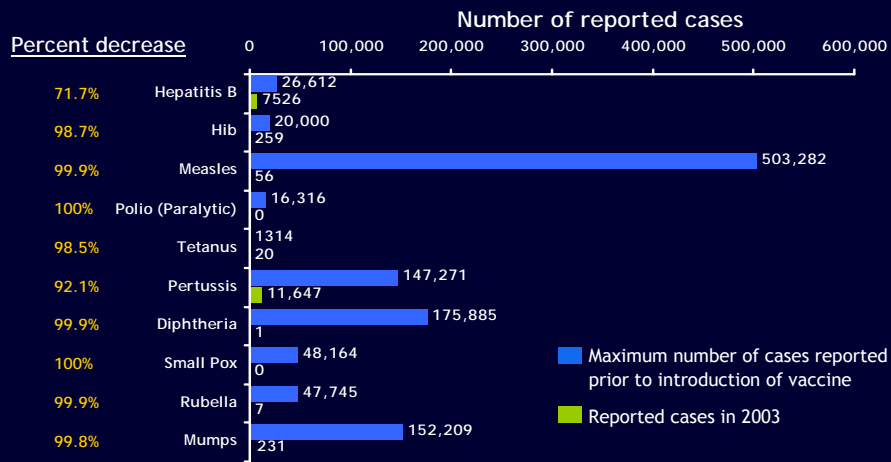
Natural History of Cervical Neoplasia

Typical Sequence of HPV-Related Events



The Future of Prevention: An Overview of HPV Vaccines

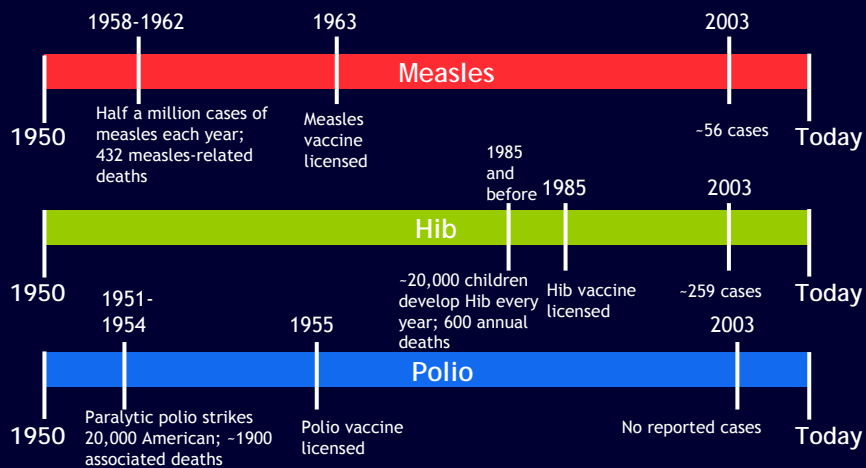
Impact of Routine Vaccination on Vaccine-Preventable Diseases in the US



Hib = *Haemophilus influenzae* type b

Adapted from Needle Tips and the Hepatitis B Coalition News, October 2004, Vol 14, No.3. Available at: <http://www.immunize.org/nslt.d/n31/n31.pdf> Accessed March 28, 2005.

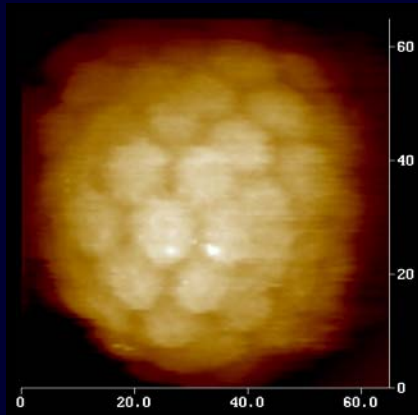
Vaccination Success Stories



Needle tips and the Hepatitis B coalition news. October 2004, Vol 14, No.3. Available at: <http://www.immunize.org/nslt.d/n31/n31.pdf>
 US Center for Disease Control and Prevention. ABCs of childhood vaccines. Available at: <http://www.cdc.gov/nip/vaccine/ABCs/default.htm> Screen Accessed March 30, 2005.

HPV Vaccine Trials

HPV, Cervical Cancer, and Vaccines



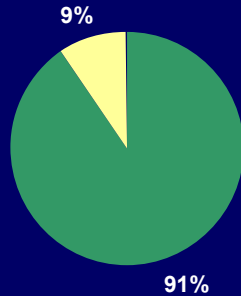
- Cervical cancer is a consequence of infection with human papillomavirus (HPV)
- Worldwide cervical cancer is a significant cause of death with >250,000 deaths/yr
- Clinical trials of subunit vaccines show promise for preventing HPV infection and sequelae

Courtesy of Dr Eliav Barr.

Ferlay J et al. GLOBOCAN 2002. Cancer Incidence, Mortality, and Prevalence Worldwide Version 2. IARC Cancer Base NO.5; 2004.

Lowy and Frazer. *J Natl Cancer Inst Monogr.* 2003;(31):114-116.

Prevalence of HPV in Sexually Active Women 18 to 26 Years of Age in National Longitudinal Study of Adolescent Health



■ PCR^a negative to all 4 vaccine types (6, 11, 16, 18)

■ PCR positive to at least 1 of the vaccine types (6, 11, 16, 18)

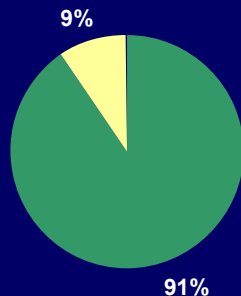
n=3,276 women 18 to 26 years of age

^aPCR = polymerase chain reaction.
Dempsey AF et al. *Vaccine*. 2008;26(8):1111-1117.

- Can we discern behavioral and socio-demographic characteristics to help us target "high risk" young adult females for vaccination?
 - 3,276 18 - 26 years
 - National Longitudinal Study of Adolescent Health
- Answer: probably not.
 - 0/3276 HPV 6, 11, 16, and 18 positive.
 - Coinfection with HPV 16/18 rare (0.4%).
 - Prevalence of *any* HPV infection - 27% using PCR assay.

55

Prevalence of HPV in Sexually Active Women 18 to 26 Years of Age in National Longitudinal Study of Adolescent Health



■ PCR^a negative to all 4 vaccine types (6, 11, 16, 18)

■ PCR positive to at least 1 of the vaccine types (6, 11, 16, 18)

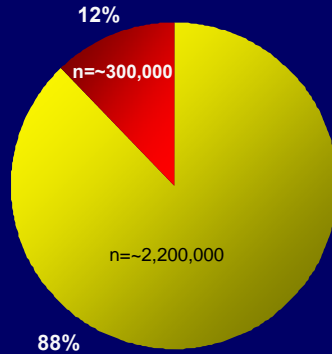
n=3,276 women 18 to 26 years of age

^aPCR = polymerase chain reaction.
Dempsey AF et al. *Vaccine*. 2008;26(8):1111-1117.

- Usual risk factors were associated with HPV positivity for HPV6, 11, 16 & 18
 - Sex partner > 2 years older
- However, in this sample, previously published data and these prevalence data show everyone would have benefited by vaccination
 - > 3 lifetime sex partners
 - ORadj=1.7 (1.0-2.7)
 - 0/3274 were positive for all 4 types
 - New sex partner last 12 months
 - ORadj=2.1 (1.3-3.2)

56

Estimated Population-Level Impact of Not Vaccinating Women With >3 Lifetime Sex Partners



- % *without* current infection HPV 6, 11, 16, and/or 18
- % *with* current infection HPV 6, 11, 16, and/or 18

- Of the estimated 2.5 million women with >3 sex partners:
 - 12% would already be currently infected with 1 or more HPV vaccine types.
 - 88% would not be currently infected with 6, 11, 16, and/or 18.
- The population-level impact of not vaccinating women with >3 lifetime sex partners means an estimated 2.2 million women who could potentially benefit would not be vaccinated.

Dempsey AF et al. *Vaccine*. 2008;26(8):1111–1117.

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Risk-Based Vaccination Strategies: Study Conclusion

- Risk-factor–based vaccination would cause HPV vaccines to be withheld from a large number of women without evidence of current infection.
- Identification of individuals based on either the presence or absence of risk factors does not appear to be a viable strategy for HPV catch-up vaccination of young adults.
- The ACIP does not recommend a risk-based immunization strategy for HPV vaccination.

Dempsey AF et al. *Vaccine*. 2008;26(8):1111–1117.

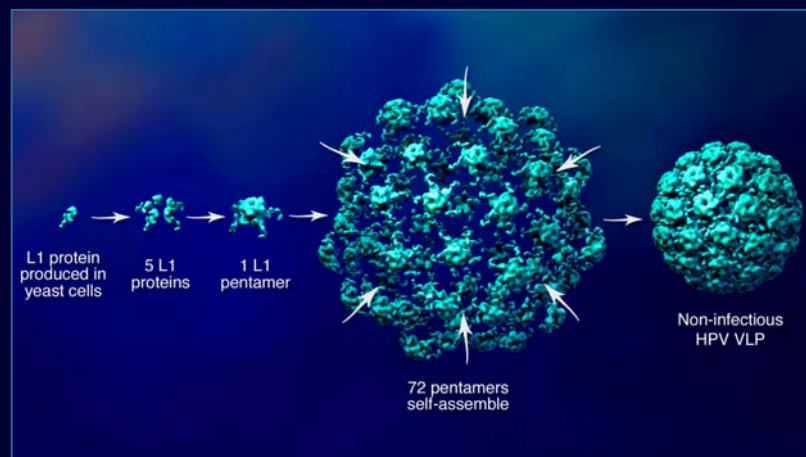
58

GARDASIL[®]: The First Cervical Cancer Vaccine in the United States

- 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).



Assembly of VLPs¹⁻³



1. Berzofsky JA, et al. *J Clin Invest.* 2004;114:450–462.
2. Kirnbauer R, et al. *Proc Natl Acad Sci USA.* 1992;89:12180–12184.
3. Modis Y, et al. *EMBO J.* 2002;21:4754–4762.

Prophylactic Efficacy: GARDASIL® Was 100% Efficacious Against HPV 16- and 18-related CIN 2/3 or AIS

Population	n	GARDASIL Cases	n	Placebo Cases	Efficacy	95% CI
Protocol 005*	755	0	750	12	100%	65.1–100
Protocol 007	231	0	230	1	100%	-3734.9–100
FUTURE I	2,200	0	2,222	19	100%	78.5–100
FUTURE II	5,301	0	5,258	21	100%†	80.9–100
Combined protocols	8,487	0	8,460	53	100%†	92.9–100

*Evaluated only the HPV 16 L1 VLP component of GARDASIL.

†P-values were computed for the prespecified primary hypothesis tests. All p-values were <0.001, supporting the following conclusions: efficacy against HPV 16/18-related CIN 2/3 is >0% (FUTURE II); and efficacy against HPV 16/18-related CIN 2/3 is >25% (combined protocols).

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Prophylactic Efficacy: GARDASIL® Was Efficacious Against HPV 6-, 11-, 16-, and 18-related Genital Warts

Population	n	GARDASIL Cases	n	Placebo Cases	Efficacy	95% CI
Protocol 007	235	0	233	3	100%	-139.5–100
FUTURE I	2,261	0	2,279	29	100%	86.4–100
FUTURE II	5,401	1	5,387	59	98.3%	90.2–100
Combined protocols	7,897	1	7,899	91	98.9%	93.7–100

- The efficacy of GARDASIL against HPV 6-, 11-, 16-, and 18-related VIN 1 or VaIN 1 was 100%.

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Prophylactic Efficacy: GARDASIL® Was Efficacious Against Persistent Vaccine-specific HPV Infections

Population	n	GARDASIL Cases	n	Placebo Cases	Efficacy	95% CI
Protocol 005	755	7 ^a	750	111	94%	88-98
Protocol 007	235	2 ^b	233	43	96%	83.3–99.5

^a Monovalent HPV16 VLP vaccine: 43% (3/7) HPV16 was detected at last visit prior to loss-to-follow up.

^b Quadrivalent HPV6, 11, 16, 18 vaccine: 50% (1/2) HPV16 was detected at last visit prior to loss-to-follow up; 50% (1/2) HPV18 detected at month 12 & 18 visit.

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General Population Impact: GARDASIL® Reduced HPV 16- and 18-related CIN 2/3 or AIS

HPV 16- or 18-related CIN 2/3 or AIS	N	GARDASIL or HPV 16 L1 VLP Cases	N	Placebo Cases	% Reduction	95% CI
Prophylactic Efficacy*	9,342	1	9,400	81	98.8%	93–100
HPV 16 and/or HPV 18 Positive at Day 1	--	121	--	120	--	--
General Population Impact†	9,831	122	9,896	201	39.0%	23–52

* Includes all subjects who received at least 1 vaccination and who were naïve (PCR (-) and sero (-)) to HPV 6, 11, 16, and/or 18 at Day 1. Case counting started at 1 Month Postdose 1.

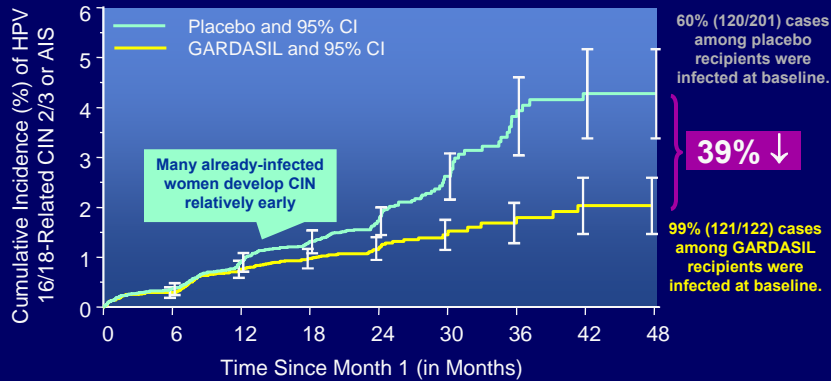
† Includes all subjects who received at least 1 vaccination (regardless of baseline HPV status at Day 1). Case counting started at 1 Month Postdose 1.

Note: Table does not include disease due to nonvaccine HPV types.

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General Population Impact: GARDASIL® Reduced the Likelihood of HPV 16/18-Related CIN 2/3 or AIS in 16- to 26-Year-Old Females Within 2 to 4 Years¹

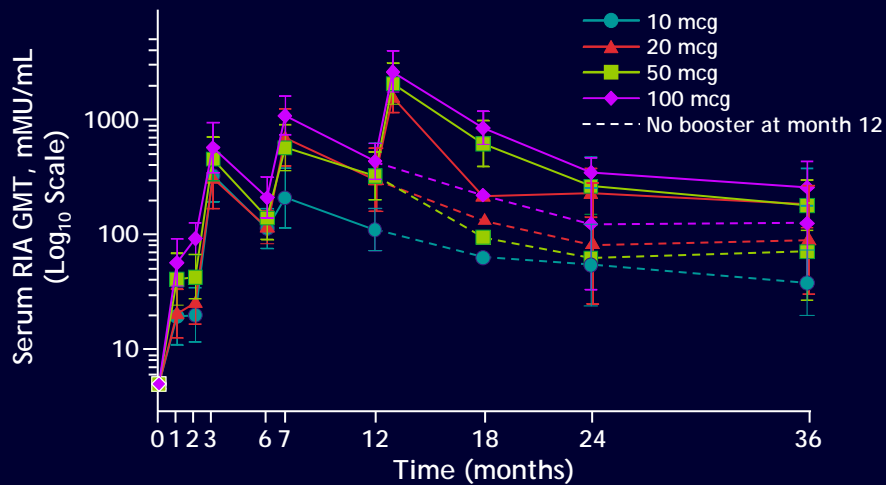
MITT-3 Population



With successive semi-annual visits and screening, the protective impact of the vaccine became more apparent.

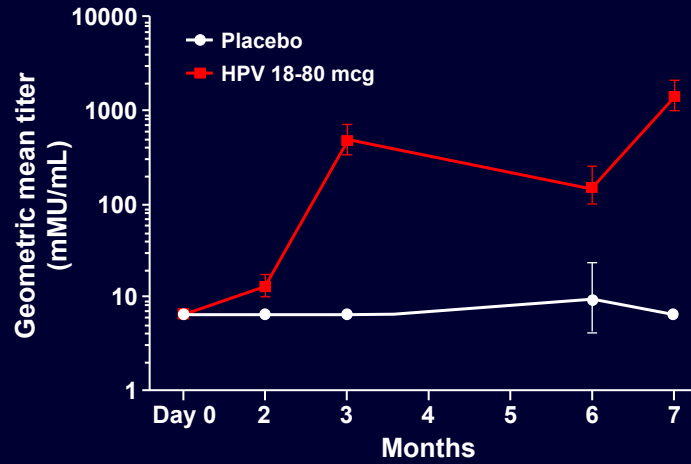
1. Data on file, MSD.

HPV 11 VLP Vaccine: Serologic Response



Fife et al. *Vaccine*. 2004;22:2943-2952.

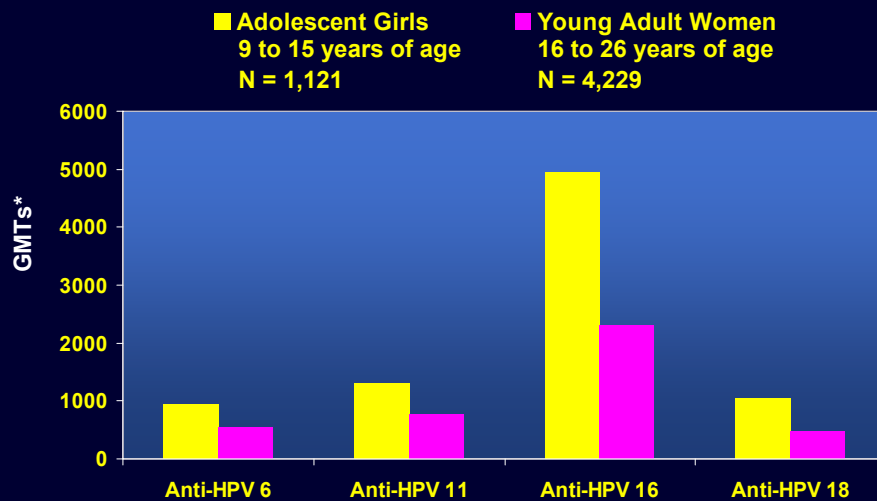
HPV 18 Serology/RIA Results



N = 37

Ault et al. *Vaccine*. 2004;22:3004-3007.

Bridging the Efficacy of GARDASIL® From Young Adult Women to Adolescent Girls



*GMT = Geometric mean titer in mMU/mL (mMU = milli-Merck units).

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Vaccine-related Experiences

Injection site (1 to 5 days postvaccination)			
	GARDASIL (N=5,088)	Placebo (Aluminum) (N=3,470)	Placebo (Saline) (N=320)
Pain	83.9%	75.4%	48.6%
Swelling	25.4%	15.8%	7.3%
Erythema	24.6%	18.4%	12.1%
Pruritus	3.1%	2.8%	0.6%
Systemic adverse event (1 to 15 days postvaccination)			
	GARDASIL (N=5,088)	Placebo (N=3,790)	
Fever	10.3%	8.6%	

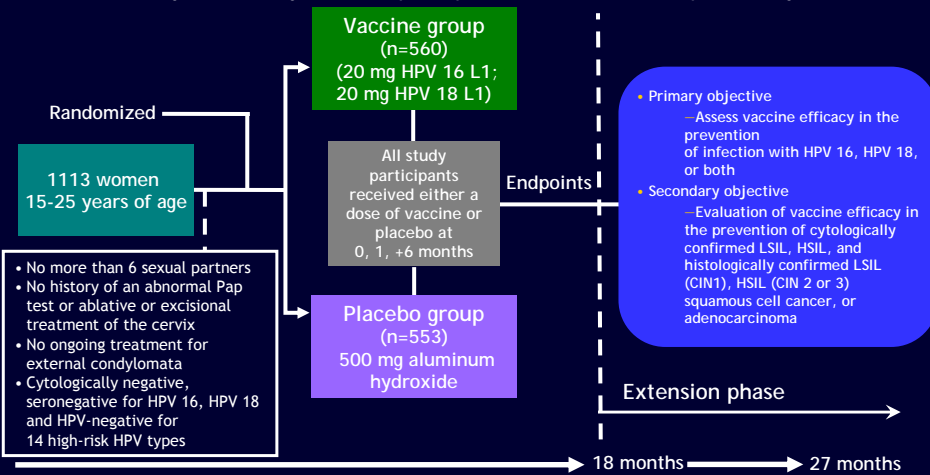
- Few subjects (0.1%) discontinued due to adverse experiences.

The vaccine-related adverse experiences that were observed among recipients of GARDASIL were at a frequency of at least 1.0% and also at a greater frequency than that observed among placebo recipients.

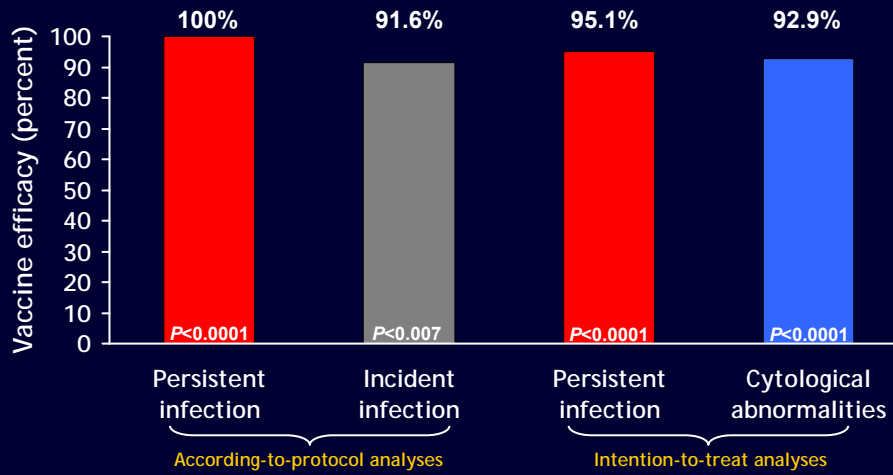
69

Trial of a Bivalent L1 VLP Vaccine in Prevention of HPV 16/18 Infection

Every 6 months participants were tested for cervical HPV DNA, cytology, and serum antibody levels; every 3 months, participants were tested for HPV presence by PCR



HPV 16/18 Vaccine Efficacy



Harper et al. *Lancet*. 2004;364:1757-1765.

Serious AEs in HPV 16/18 Study

	Vaccine group (n=531)	Placebo group (n=538)	P value
Serious adverse events			
Related to vaccination	0	0	-
During study*	22 (4.0%)	19 (3.5%)	0.636
Withdrawal from study			
Due to nonserious adverse event	0	3 (0.6%)	0.249
Due to serious adverse event	1 (0.1%)	0	0.497

*Participants who reported a serious adverse event during the entire study period (month 0-27).

Harper et al. *Lancet*. 2004;364:1757-1765.

Summary: Potential Benefits of HPV Vaccine

- Historically, vaccines have represented a cost-effective means to prevent disease induced by microbial agents and other pathogens
- Potential reduction in incidence of
 - Cervical cancer and its precursor lesions
 - Other associated cancers (anal, penile, vaginal, vulvar)
 - Genital warts

Lowy and Frazer. *J Natl Cancer Inst Monogr.* 2003;31:111-116.
US Center for Disease Control and Prevention. The ABCs of childhood vaccination. Risks of not vaccinating.
Available at: <http://www.cdc.gov/nip/vaccine/ABCs/2-ABCs-Risks.txt> Accessed March 30, 2005.

What about disease in teens?

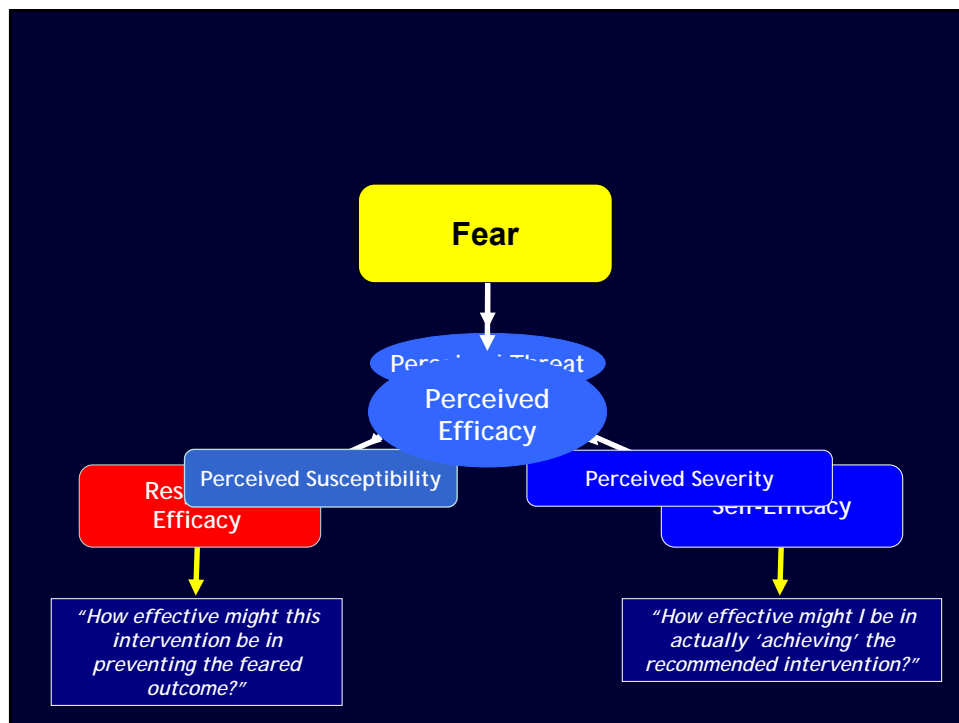
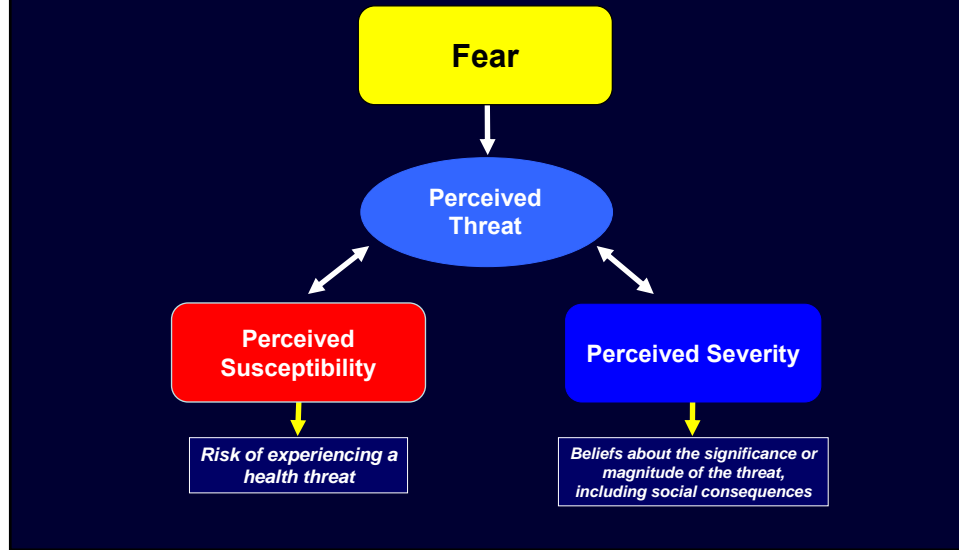
Incidence of Cervical Dysplasia in Adolescents

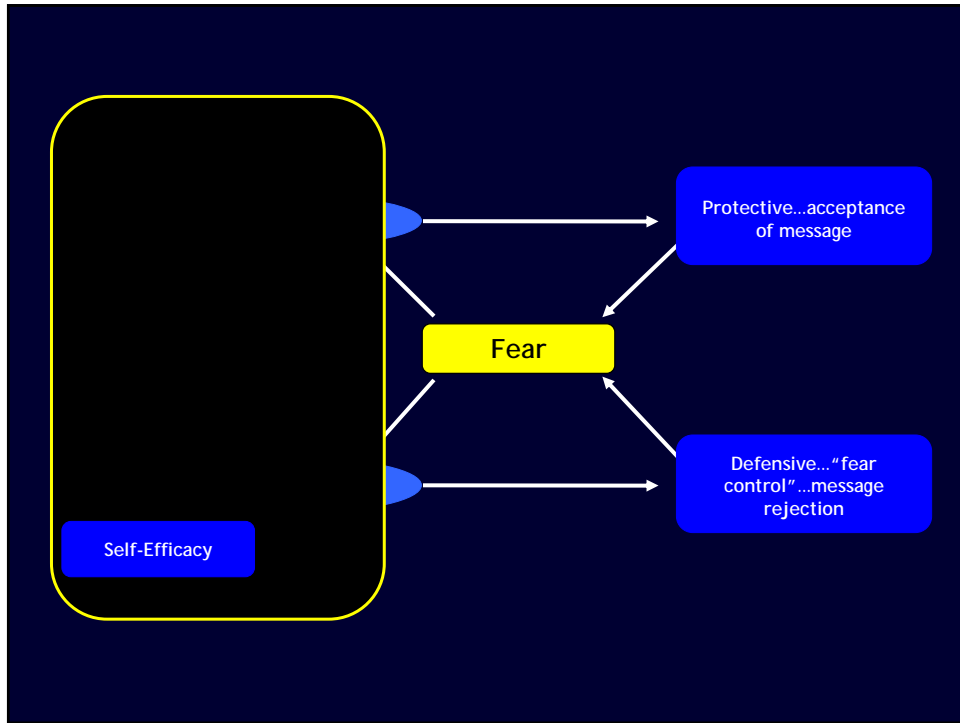
- Adolescents are at high risk for high-grade lesions
- Retrospective review of adolescents ≤ 18 years old
 - Median age in LSIL cohort (n=477) was 16.7
 - 199 (47.2%) had ASC-US, LSIL, or CIN 1
 - 77 (18.2%) had HSIL, CIN 2, CIN 3, or AIS
 - 146 (34.6%) had negative follow-up
 - Median age in HSIL cohort (n=55) was 16.9
 - 15 (27.3%) had ASC-US, LSIL, or CIN 1
 - 28 (50.9%) had HSIL, CIN 2, CIN 3, or AIS
 - 12 (21.8%) had negative follow-up

Wright et al. Paper presented at 2005 SGO Annual Meeting. Abstract 5.

Overcoming Barriers to Vaccine Acceptance

Extended Parallel Process Model





Barriers to Vaccine Acceptance

Individual and Family Issues

Barriers to Vaccine Acceptance

Individual and Family Issues: Lessons From HBV Vaccine Research

- Poor knowledge about Hepatitis B vaccines
 - 25% of clinic providers think adolescents lack knowledge
 - Caused, rather than prevented, disease
 - Serious side effects associated with vaccine
 - Only 47% of adolescents could correctly convey any correct information about vaccinations
 - 27% stated they knew nothing
 - 20% gave incorrect information
 - Only 20% of adolescents could correctly define a vaccination
 - No difference between groups previously vaccinated for HBV and those not

Slonim AB et al. *Journal of Adolescent Health*. 2005;36:178-186.

Barriers to Vaccine Acceptance

Lessons from HBV Vaccine Research

- Specific barriers to vaccination can be identified consistently by providers and adolescents alike
 - 94% of clinic providers: “adolescents don’t like getting shots”
 - Developmental norms
 - Idea of systems vs individual decision-making approach
 - 50% suggested “time constraints” were a barrier

Slonim AB et al. *Journal of Adolescent Health*. 2005;36:178-186.

Mrs. Smith, now that your daughter is 11, it's time for her to get vaccinated for HPV, a sexually transmitted infection.



Courtesy of Greg Zimet, PhD

I *HATE* shots!



Courtesy of Greg Zimet, PhD

She wants to go to the mall on Saturday...Susie's best friend just pierced her navel...what is it with those bare midriffs...you want me to argue with her to come to the clinic 3 times for 3 shots in how many months...?



Courtesy of Greg Zimet, PhD

Factors Affecting the Rate of Immunization Exemptions Among School-Age Children...

- Approximately 30% reduction of exemptions associated with number and type of procedures required to obtain an exemption
 - Dose response
- Administrative procedures required to obtain an exemption
 - Required annual renewal of exemption
 - Letter from parents for religious exemption
 - Signature of religious leader, school official, physician
 - Written information informing parents requesting exemption of the risks associated with nonparticipation

Salmon DA, Omer SB, Moulton LH, et al. *AJPH*. 2005;95:436-440.

Barriers to Vaccine Acceptance

Lessons from HBV Vaccine research

- Specific barriers to vaccination can be identified consistently by providers and adolescents alike
 - Surprisingly...
 - 56% of providers “little perceived threat”
 - 43% of providers “poor efficacy of the vaccine”

Slonim AB et al. *Journal of Adolescent Health*. 2005;36:178-186.

Barriers to HPV Vaccine Acceptance

Individual and Family Issues

- Poorly informed public
 - Many have not heard of HPV; for some, “disease” is the first knowledge
 - Link of HPV to Pap testing is not widely understood
 - Poor understanding of Pap testing results
- Information desired by women
 - What is HPV?
 - How do you get HPV?
 - How can HPV be prevented?
 - Information should be given before initiation of sexual activity of HPV
- Source of information
 - Those whose source was a doctor had greater knowledge of HPV
 - Doctors identified as a preferred source of information on HPV

Barriers to Vaccine Acceptance

Individual Issues: Attitudes Toward Vaccination

- Will desire for information translate into vaccine acceptance?
 - Stigma related to STI
 - Vaccine acceptance as acknowledgement of risky behavior
- Can we reframe the discussion to the relevant issue?
 - Describing HPV vaccines as a vaccine to prevent cervical cancer

Ms. Smith, I'd like you to get vaccinated against HPV, a very common infection, but one that can cause cancer or genital warts



Courtesy of Greg Zimet, PhD

Barriers to Vaccine Acceptance

Individual Issues: Research on Acceptability

- Small qualitative and quantitative studies suggest high levels of interest
 - Parents, young adults, adolescents
 - Nearly three-quarters of respondents in each study group suggested they would view vaccines positively
- The key determinants of intention to get vaccinated
 - Sexual transmission as mode is not a barrier
 - Recommendation by a provider is important
 - Cancer prevention is compelling
 - Prevention of warts may be more compelling for youth
 - Warts prevention may ↑ acceptability

Kahn et al. (2003), Boehner et al. (2003), Mays et al. (2004), Davis et al. (2004), Zimet et al. (2005)

Barriers to Vaccine Acceptance

Parental Issues



Courtesy of Greg Zimet, PhD

Barriers to Vaccine Acceptance

Parental Issues: Consent and Concerns

- Parental consent likely to be required
 - For some period of time after availability
 - Most adolescents look to their parents for healthcare decisions
- Potential parental concerns
 - Sexual nature of transmission
 - Approval of vaccine = approval of sex
 - Vaccination → early initiation of sex/reduced condom use
 - How to describe the vaccine to adolescent or preadolescent child

Barriers to Vaccine Acceptance

Provider Issues

How am I going to talk with Mrs. Smith and her 11 year old daughter about this new vaccine?



Courtesy of Greg Zimet, PhD

Barriers to Vaccine Acceptance

Provider Issues

- Parents look to healthcare providers for guidance...but
 - Will providers be willing to recommend HPV vaccine?
 - Will providers be comfortable recommending vaccination?
 - Do providers have the skills to talk about this kind of vaccine with parents and children?
- Potential concerns for healthcare providers
 - STI issue and communication
 - Anticipation of angry parent
 - Parents with antivaccination beliefs
 - How to describe the vaccine to adolescent or preadolescent child

Barriers to Vaccine Acceptance

Provider Issues: Research

- 2 studies
 - Positive disposition toward recommending STI vaccination
 - Mays et al. (2004) - study of pediatric nurse practitioners' willingness to recommend STI vaccines to parents of adolescents
 - Raley et al. (2004) - study of obstetricians' and gynecologists' willingness to recommend HPV vaccines for adolescents
- What are the key determinants of willingness to recommend vaccination?
 - Approval of professional organization (AAP and ACOG)
 - Older age of patient
 - Relative reluctance to vaccinate 11- to 13-year-olds

Barriers to Vaccine Acceptance

Summary

- Studies of individuals, parents, and providers all show
 - High levels of interest in an HPV vaccine for children
 - Parents are motivated by desire to protect their children
 - Parents and providers show a relative reluctance around vaccination of younger vs older adolescents

Barriers to Vaccine Acceptance

Other Issues to Consider

- Communicating risks associated with HPV infection
 - Infection is common but usually clears spontaneously
 - Warts are typically benign from a medical viewpoint
 - Stigmatizing and often of great concern
 - Cervical cancer is rare, but very serious
 - The communication challenge is to emphasize the severity of persistent high-risk HPV infection as a cause of cancer, while not invoking confusion, guilt, or psychological stress
- Anticipation of dissemination of information and misinformation regarding HPV and HPV vaccination
 - Internet information
 - Press coverage

Overcoming the Barriers

- Research is reassuring
 - Young women and parents of adolescents want to know more about HPV
 - Women desire and value information from healthcare providers
 - The majority of women and parents feel very positively about HPV vaccination for themselves and their children
 - For most, the STI issue is not a significant obstacle
 - Parents and patients look to their healthcare providers for vaccine recommendations
- Important to anticipate some opposition
 - From those who are broadly antivaccine
 - From those who have specific concerns about vaccination or preventive strategy for any STI



Warning: This vaccine may not protect you against HPV Types 1-5, 31, 33, 35, 52, 56, cp6108, is39,

Question and Answer Session
