Cancer Screening and Prevention:

Eliminating Deaths from Cervical Cancer

Learning Objectives

- Participant will understand the evolution of cervical cytology screening as well as current evidence-based guidelines
- Participant will gain knowledge about HPV, its relationship to cervical cancer, and indications for HPV testing
- Participant will be introduced to the HPV vaccine, including current recommendations for its use

History of the Conventional Pap Smear

- Developed by Dr. George N. Papanicolaou in 1940's
- Most common cancer screening test
- Critical aspect of annual gynecologic examination

Ferris et al. *Modern Colposcopy.* 2004: 2-4, 49.
Photo accessed from http://www.cytology-iac.org/Cytopaths/1998/cytoFall98.htm

Screening with the Conventional Pap Smear

- Sample collected undergoes cytologic evaluation
- Limitations
  - Screening test, not diagnostic
  - 7-10% of women screened will need further evaluation
  - Low sensitivity, high specificity

Cervical Cytology Screening. ACOG Practice Bulletin No. 45. 2003; 102:417-27.

Sources of Error with the Conventional Pap Smear

- Sampling / preparation errors[1]
  - Cells not collected on sampling device
  - Collected cells not transferred to slide
  - Poorly preserved cells

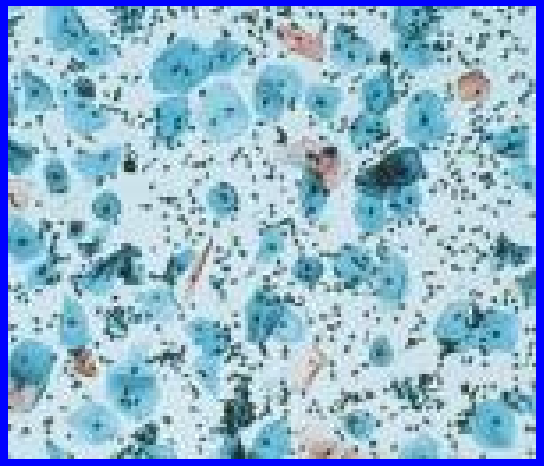
2/3 of false negatives

- Screening / interpreting errors[2,3]
  - Abnormal cells missed by cytologist
  - Cells incorrectly classified

1/3 of false negatives

1. Hutchinson ML. et al. Am J Clin Pathol. 1994; 101:215-219.
2. Linder J. et al. Arch Pathol Lab Med. 1998; 122: 139-144.
3. Agency for Health Care Policy and Research. Evaluation of Cervical Cytology. 1999.

Thin-Layer Preparations



- Reduce Sampling Errors
  - Virtually all of the sample is collected into the vial
  - Randomized, representative sample
- Reduce Screening Errors
  - Thin, uniform layer of cells
  - “Satisfactory, but limited” specimens greatly reduced
  - Screening errors reduced by 50%

Linder J. et al. Arch Pathol Lab Med. 1998; 122: 139-144.

Collection Devices

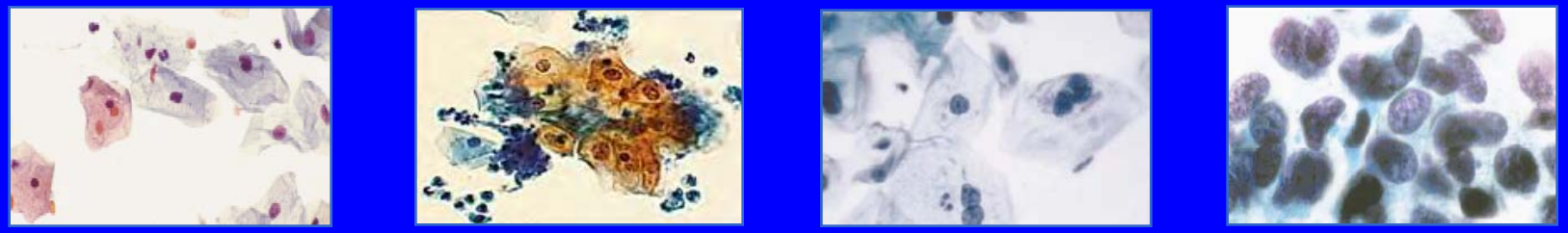
Spatula &
Endocervical Brush

Broom Device

Cervical Cytology Screening. ACOG Practice Bulletin No. 45. 2003; 102:417-27.
All pictures accessed from http://www.clinilab.fr/cytopathologie.html

Cervical Cytology Terminology

Normal[1] | ASCUS[2] | LSIL[3] | HSIL[3]



- Atypical squamous cells (ASC)[4]
  - Atypical squamous cells of undetermined significance (ASC-US)
  - Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesions (ASC-H)
- Squamous intraepithelial lesions (SIL)[4]
  - Low-grade SIL (LSIL): Mild dysplasia, cervical intraepithelial neoplasia 1 (CIN 1)
  - High-grade SIL (HSIL): Moderate and severe dysplasia (CIN 2/3) carcinoma in situ (CIS)
- Atypical glandular cells (AGC)[4]

1. Spitzer M, Johnson C. Philadelphia, Pa: WB Saunders Co; 2002:41–72. Reprinted with the permission of Elsevier.
2. Apgar BS, Zoschnick L. *Am Fam Physician.* 2003;68:1992–1998. Reprinted with the permission of the AAFP.
3. Cannistra SA, Niloff JM. *N Engl J Med.* 1996;334:1030–1038. Images reproduced courtesy of Dr. Graziella Abu-Jawdeh.
4. Solomon D, Davey D, Kurman R, et al, for the Forum Group Members and the Bethesda 2001 Workshop. *JAMA*. 2002;287:2114–2119.

Cervical Cancer Screening Guidelines

- From ACS, USPSTF, and ACOG
- Account for technologic innovations in cervical cancer screening
  - Thin-layer liquid-based cytology
  - HPV DNA testing
- Specifies screening intervals, start and stop rules

Cervical Cytology Screening. ACOG Practice Bulletin No. 45. 2003; 102:417-27.

Cervical Cancer Screening Guidelines Summary

How often

- Adults
  - Annually with conventional paps and every 2 years with liquid-based cytology
  - ≥30 with 3 consecutive negatives may change to every 2-3 years
    - GUIDANCE BY HPV STATUS!!
- Adolescents
  - First screen 3 years after onset of sexual intercourse or at age 21
  - Those who do not need screening should still get appropriate contraceptive services, STD screening and other preventive health care
- Exclusions:
    - DES exposure
    - Immunocompromised
    - HIV

Cervical Cytology Screening. ACOG Practice Bulletin No. 45. 2003; 102:417-27.

Cervical Cancer Screening Guidelines Summary

When To Stop

- Women >70 years with:
  - At least 3 consecutive documented, satisfactory negative smears[1]
  - No abnormal/positive cytology within past ten years[1]
- After hysterectomy
  - If hysterectomy performed for benign disease and cervix was removed[2]
  - Negative history of abnormal paps[2]
- Exclusions[2]:
  - History of cervical cancer
  - DES exposure
  - Immunocompromised
  - Positive HPV DNA test

1. American Cancer Society. Cancer facts & figures 2003.

2. Cervical Cytology Screening. ACOG Practice Bulletin No. 45. 2003; 102:417-27.

High-Risk HPV Testing
ACOG Guidelines

Two Indications:

- Primary screening after age 30
  - If both Pap and HPV test negative
    - Re-screen no more frequently than every 3 years
- Triage of minimally abnormal Paps
  - ASC-US
    - Only need to do colposcopy if HPV +

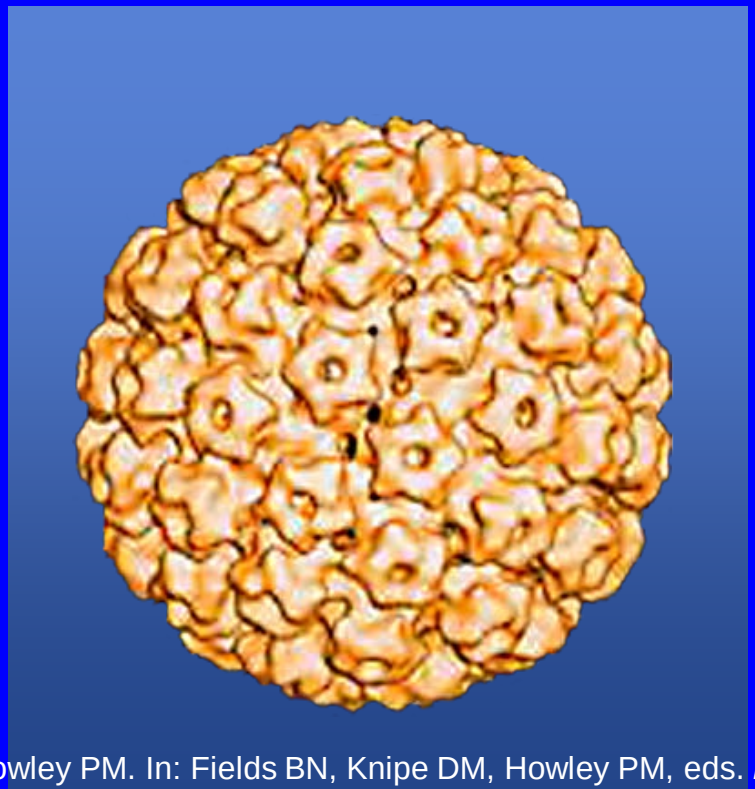
Cervical Cytology Screening. ACOG Practice Bulletin No. 45. 2003; 102:417-27.

HPV & Cervical Cancer

HPV is the Underlying Cause of Cervical Cancer

- NIH Consensus Conference on Cervical Cancer, 1996
- World Health Organization/European Research Organization on Genital Infection and Neoplasia, 1996
- Journal of the National Cancer Institute
  - Schiffman et al., 1993
  - Franco et al., 1995
  - Bosch et al., 1995

Human Papillomavirus (HPV)



- Over 100 types identified[2]
  - 30–40 anogenital[2,3]
  - 15-20 oncogenic types[2,3]
  - 30-35 types sexually transmitted
- Disease Burden
  - 20,000,000 current cases in US[6]
  - 6,200,000 new annual cases[5]
  - 80% of women will have acquired HPV infection by age 50[5]
  - 50% of college students are infected[4]

1. Howley PM. In: Fields BN, Knipe DM, Howley PM, eds. *Fields Virology.* 4th ed. Philadelphia, Pa: Lippincott-Raven; 2001:2197–2229. Picture reprinted with the permission of Lippincott-Raven.
2. Schiffman M, Castle PE. *Arch Pathol Lab Med*. 2003;127:930–934.
3. Wiley DJ, Douglas J, Beutner K, et al. *Clin Infect Dis*. 2002;35(suppl 2):S210–S224.
4. Winer RL et al. *Am J Epidemiol*. 2003; 157:218-226.
5. Centers for Disease Control and Prevention. Rockville, Md: CDC National Prevention Information Network; 2004.
6. Cates W Jr, and the American Social Health Association Panel. *Sex Transm Dis*. 1999;26(suppl):S2–S7.

Common HPV Types Associated With Benign and Malignant Disease

	HPV Types	Manifestations
Low-Risk	**HPV 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81**	**Benign low-grade cervical changes** **Condylomata acuminata (Genital warts)**
High-Risk	**HPV 16, 18, -31, -33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82**	**Low-grade cervical changes** **High-grade cervical changes** **Cervical cancer** **Anogenital and other cancers**

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

Human Papillomavirus

- Cancer of cervix uteri 100%
- Cancer of anus (squamous cell) 90%
- Cancer of vulva, vagina 40%
- Cancer of penis 40%
- Cancer of oro-pharynx 15-30%
- Cancer of mouth 3%
- Cancer of oesophagus .
- Cancer of skin .
- Cancer of X,Y,Z.... .

Parkin DM et al. *CA Cancer J Clin* 2005; 55:74-108.

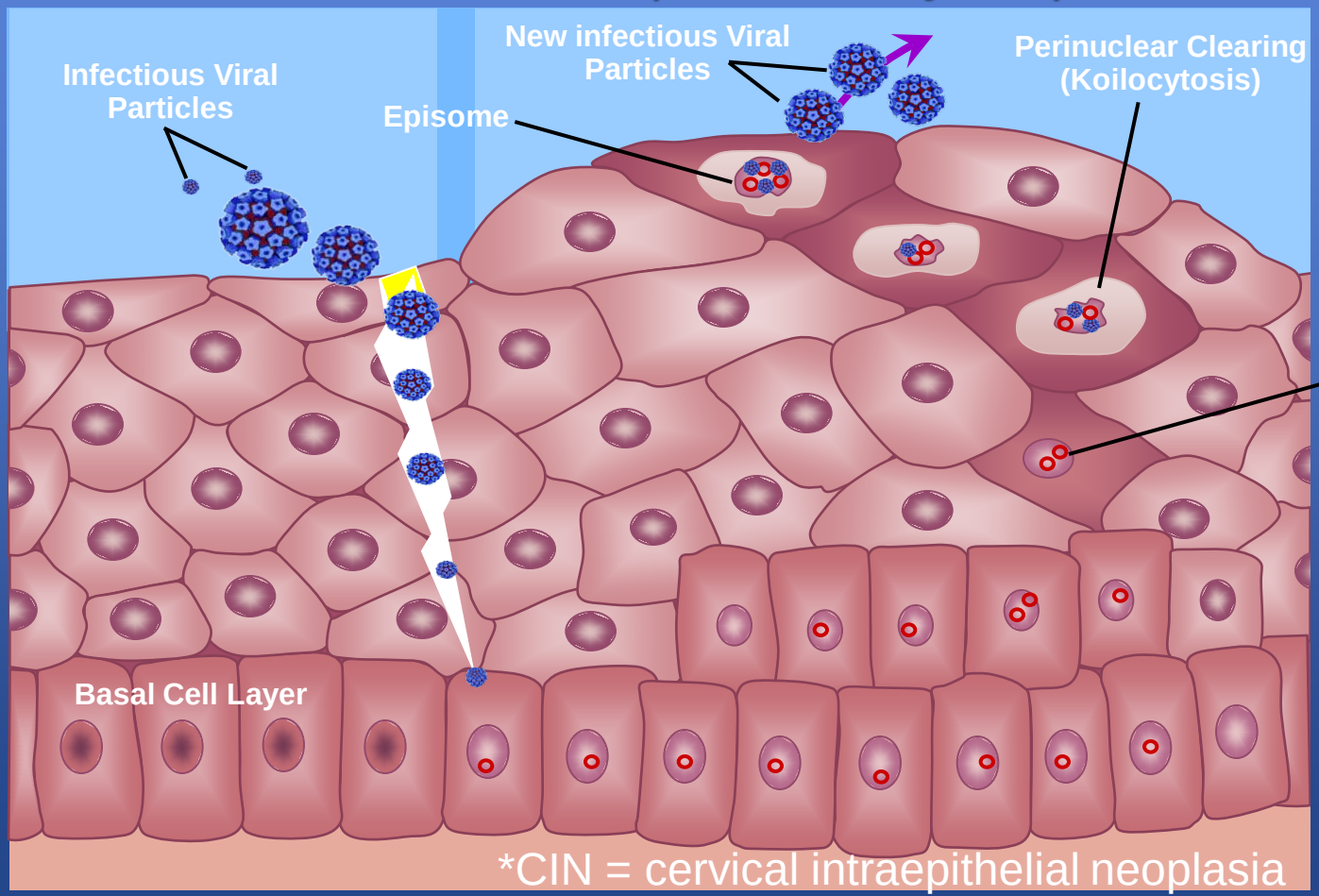
Natural History of HPV Infections

- HPV is sexually transmitted
  - Asymptomatic
  - No treatment for HPV infection
    - Cervical changes and warts CAN be treated
  - Transient or persistent

- HPV is a necessary cause of cervical cancer
  - HPV is present in over 99.7% of cervical cancers
  - High risk types (16, 18) associated with cancer and precancerous lesions
  - Low risk types (6, 11) are associated with external genital warts and abnormal Pap tests

Human Papillomavirus. ACOG Practice Bulletin No. 61. 2005; 105: 905-18.

Biology of HPV Infection: Low-Grade Lesions



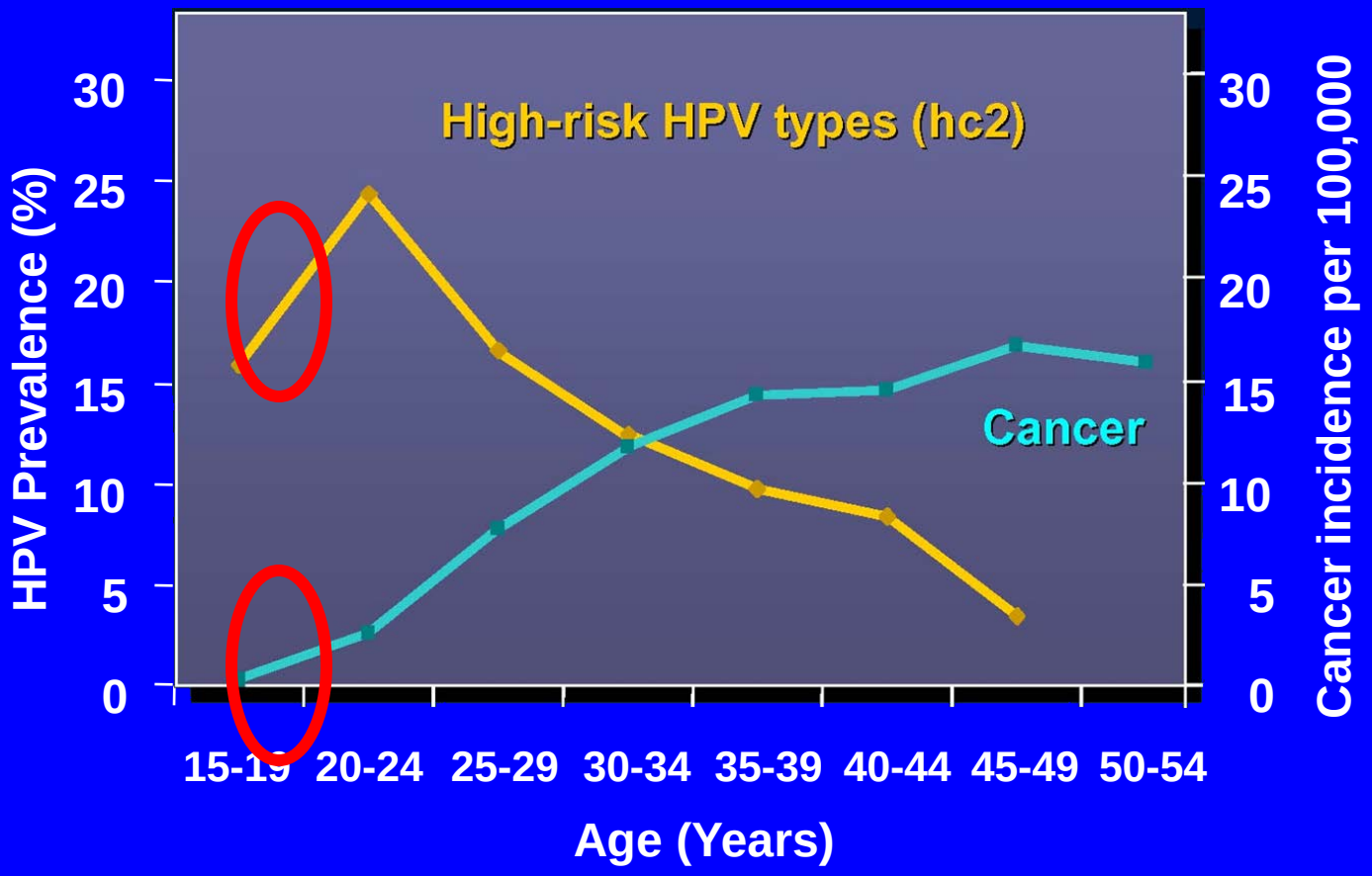
1. Goodman A, Wilbur DC. *N Engl J Med*. 2003;349:1555–1564.
2. Doorbar J. *J Clin Virol*. 2005;32(suppl):S7–S15.
3. Bonnez W. American Society for Microbiology Press; 2002:557–596.

Co-factors for HPV Infection

- Smoking
- HIV infection and other host immune factors
- Parity
- Oral contraceptive use

Ferris et al. *Modern Colposcopy.* 2004.

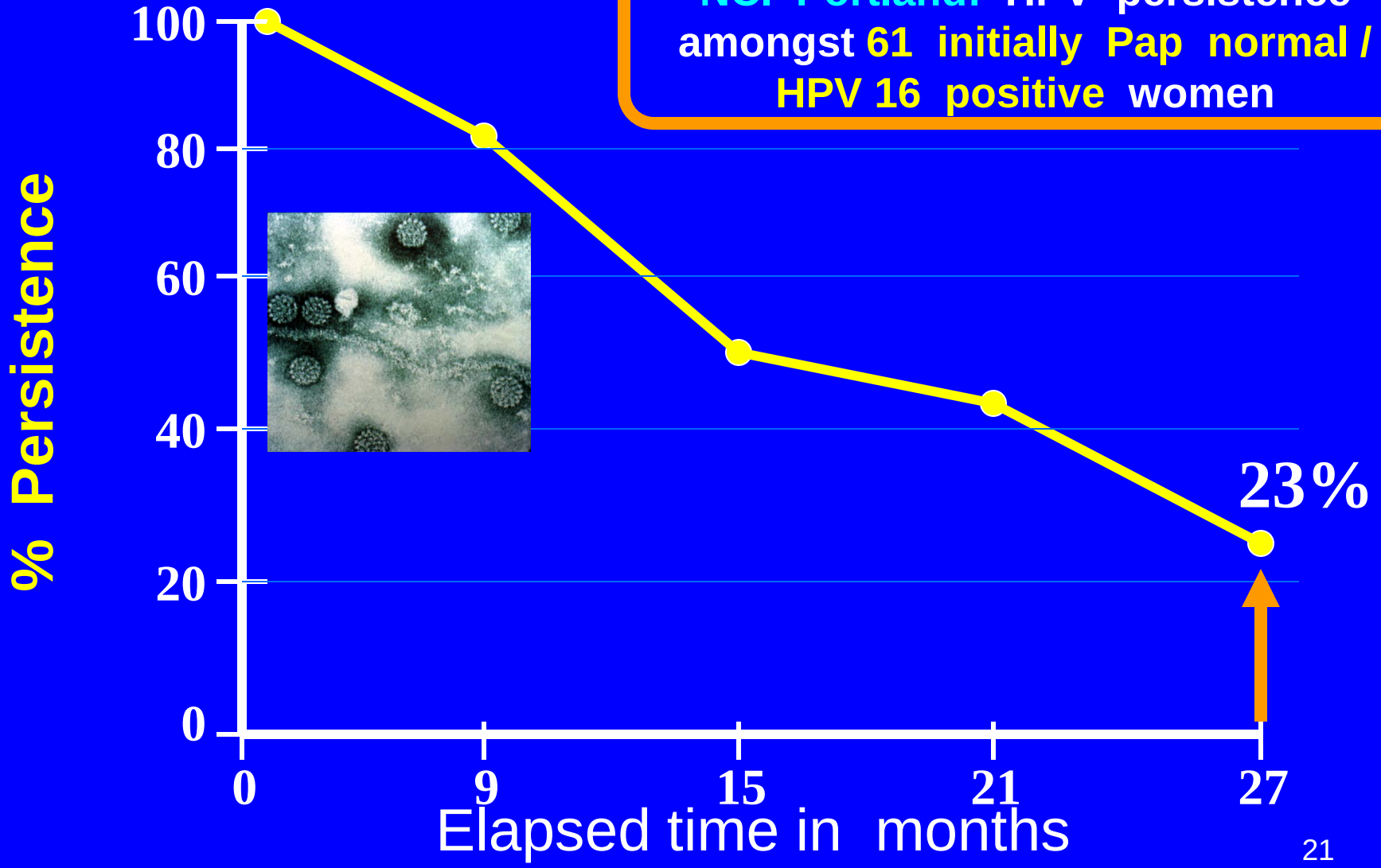
HPV Prevalence and Cervical Cancer - Incidence by Age [1,2]



1. Sellors et al. *CMAJ*. 2000;163:503.
2. Ries et al. Surveillance, Epidemiology and End Results (SEER) Cancer Stats NCI, 1973-1997. 2000.

Most HPV infections are transient

NCI Portland: HPV persistence amongst 61 initially Pap normal / HPV 16 positive women



Schiffman M ASCCP 2002 Biennial Orlando, Fl.

HPV and Anogenital Warts

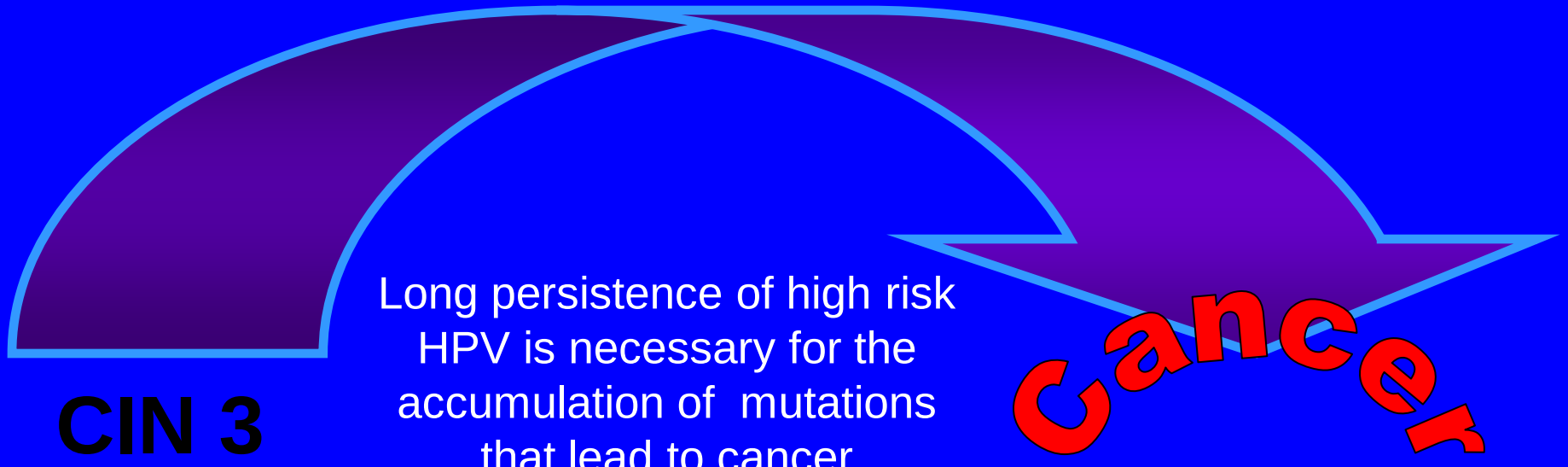
Images top left and top right: Reprinted with permission from NZ DermNet (www.dermnetnz.org).

- HPV 6 and 11 responsible for over 90% of anogenital warts[1]
- Infectivity upon exposure is over 75%[2]
- Spontaneous regression can occur in up to 30% women within 4 months[3]
- Treatment can be painful and embarrassing[4]
  - Topical and surgical therapies[5]
- Recurrence rates vary greatly[5]
  - As low as 5% with podofilox or laser treatment
  - As high as 65% with other treatments

1. Jansen KU, Shaw AR. Annu Rev Med. 2004;55:319–331.
2. Soper DE. *Novak's* Gynecology. 2002:453–470.
3. Lacey CJN. *J Clin Virol*. 2005;32(suppl):S82–S90.
4. Maw RD, Reitano M, Roy M. *Int J STD AIDS.* 1998;9:571–578.
5. Kodner CM, Nasraty S. *Am Fam Physician.* 2004;70:2335–2342.

HPV Infections: Summary

- Most will acquire HPV at some time
- Most will clear HPV, but some do not
- Persistence of low-risk HPV can lead to anogenital warts
- Persistence of high-risk HPV can lead to pre-cancer



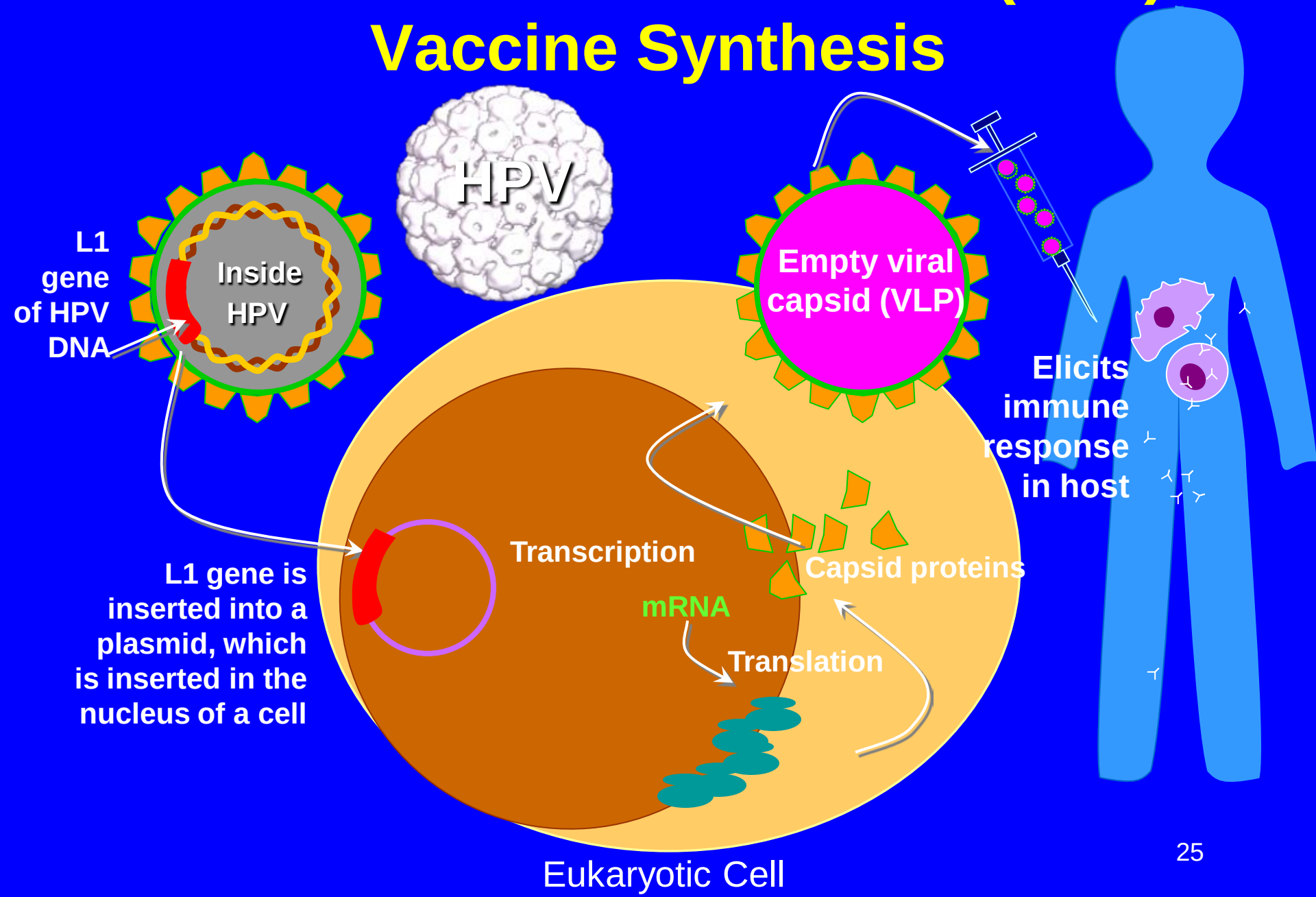
HPV Vaccine

Gardasil ® (Merck)

- Quadrivalent vaccine against types 16, 18, 6, 11
- FDA approved for use in females 9-26 years of age
- Prophylactic, not therapeutic
- Virus-like particles (VLP)
- Highly effective
- Safe, few serious adverse side effects
- Requires 3 injections
- Expensive ($360 + administrative fees)

Smith, RA et al. *Cancer.* 2003;53(1): 27-43.

HPV L1 Virus-Like-Particle (VLP) Vaccine Synthesis



Characteristics of Women who Participated in the Phase III Quadrivalent HPV Vaccine Trials

Day 1 Characteristics	Total (N=20887)	Asia Pacific (N=748)	Europe (N=9181)	Latin America (N = 5666)	North America (N=5292)
Percent of total	**100%**	**4%**	**44%**	**27%**	**25%**
Mean Age	20	21	20	21	20
Non-virgin	94%	96%	92%	99%	93%
Mean Age at Sexual Debut (y)	17	18	17	17	17
Med. Lifetime # of Sex Partners	2	2	2	2	2
Past Pregnancy	23%	25%	7%	51%	16%
Using Hormonal Contraception	58%	50%	68%	46%	55%
Chlamydia (+)	4%	3%	3%	7%	3%
LSIL or HSIL	6%	5%	6%	7%	7%
HPV 6, 11, 16, or 18 (+)	27%	16%	25%	32%	25%

Prevention of HPV16/18-Related Precancerous Cervical Lesions (CIN2/3) in a Susceptible Population

HPV16 and/or HPV18 negative at enrollment
Mean 25 months of follow-up (starting 1 month postdose 1)

Endpoint	Vaccine Cases† (N=9,342)	Placebo Cases† (N=9,400)	Vaccine Efficacy (95% CI)
HPV 16/18-related CIN 2/3 or AIS	**1**	**81**	**99% (93, 100)**
HPV 16/18-related CIN 2	1	55	98%
HPV 16/18-related CIN 3/AIS	0	52	100%

† **Subjects are counted once per row. Subjects may be counted in >1 row.**

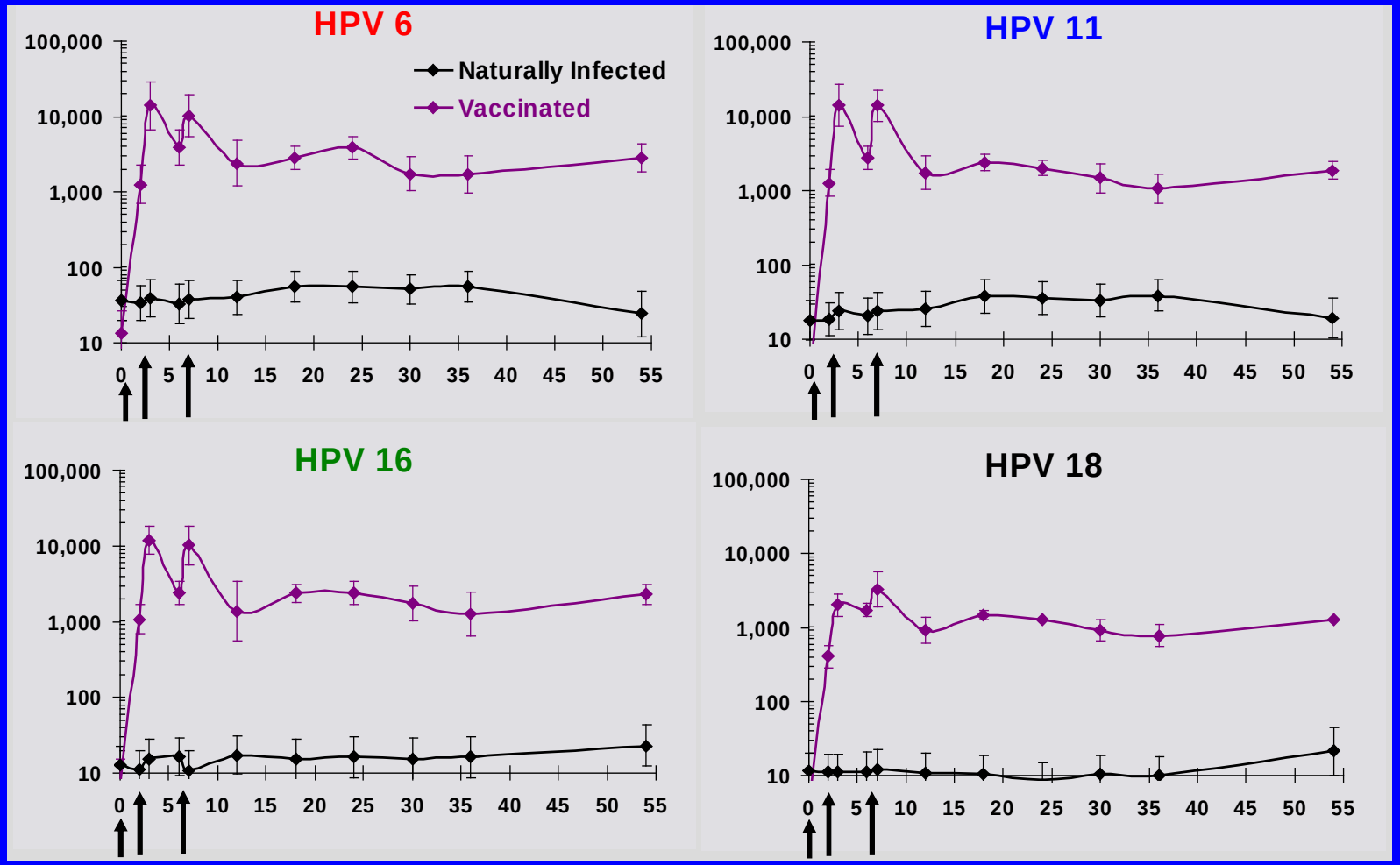
Prevention of HPV6/11/16/18-Related Genital Warts, and Precancers of the Vagina and Vulva in a Susceptible Population

HPV6, 11, 16 and/or HPV18 negative at enrollment
Mean 26 months of follow-up (starting 1 month postdose 1)

Endpoint	Vaccine Cases† (N = 2620)	Placebo Cases† (N = 2628)	Vaccine Efficacy (95% CI)
HPV 6/11/16/18- Lesions of the Vagina and Vulva	**3**	**59**	**95% (84, 99)**
Genital warts and other minor lesions of the vagina and vulva	3	53	94%
Precancer of the vagina or vulva (VIN 2/3 or VaIN 2/3)	0	9	100%

† **Subjects are counted once per row. Subjects may be counted in more than one row.**

Total HPV 6, 11,16, & 18 IgG Antibody Titers from the Quadrivalent and Natural Infection Titers



HPV VACCINE: ADVERSE EVENTS (CDC/ACIP-6/07)

- 5 million doses distributed, 3/07
- 87% in HPV alone; 70% ages 9-26
- Vomitting/syncope/fever/nausea/pain at injection site
- 1763 adverse events 33/100k reported

94 SAEs – 1.8/100k: 4 deaths, 13 GBS

RECOMMEND: OBSERVE X 15 MIN.

HPV Vaccine
ACOG Recommendations

Continued screening with Pap tests is mandatory

VACCINATE

- Females 9-26 years old, regardless of sexual activity
  - Potential benefit diminishes with age & increasing number of sexual partners

Special populations

- Previous CIN, abnormal cervical cytology or genital warts
  - Vaccine may be less effective
- Immunocompromised
  - Vaccine may be less effective

Human Papillomavirus Vaccination. ACOG Committee Opinion No. 344. 2006; 108: 699-705.

HPV Vaccine
ACOG Recommendations

Continued screening with Pap tests is mandatory

NOT CURRENTLY RECOMMENDED

(Awaiting more evidence)

- Women over age 26
- Pregnant women (Category B)
  - If pregnancy diagnosed during the vaccine schedule, give remaining vaccine post-partum
- Men

Human Papillomavirus Vaccination. ACOG Committee Opinion No. 344. 2006; 108: 699-705.

HPV Vaccine
Important Considerations

Continued screening with Pap tests is mandatory

- Vaccine is most effective if administered before sexual debut
  - Vaccine may be less effective in sexually active women
- HPV testing prior to initiating vaccine is not recommended
- Vaccine is not a treatment for current HPV infection, genital warts, or CIN

Human Papillomavirus Vaccination. ACOG Committee Opinion No. 344. 2006; 108: 699-705.

HPV Vaccine Counseling Points

- Vaccine administration will not cause HPV
  - Virus-like particle vaccine (not a live virus)
- HPV vaccines appear to be safe in the vast majority
  - Few major adverse events but limited data
- Most side effects are minor
  - Injection site reaction
- HPV vaccines are potentially effective in preventing cervical and other HPV-related cancers
  - Sexually active women may still contract HPV genotypes not covered by the vaccine

Continued screening with Pap tests is mandatory

Human Papillomavirus Vaccination. ACOG Committee Opinion No. 344. 2006; 108: 699-705.

Vaccine Specifics

- Dosage Schedule
  - 3 separate 0.5-mL doses at 0, 2 months, 6 months
  - Evidence suggests adequate immune response if all 3 doses given within 12 months
- Ordering
  - Through Merck
    - www.MerckVaccines.com
    - 1-877-VAX-MERCK
    - Vaccine Patient Assistance Program
  - Vaccines for Children Program
    - http://www.cdc.gov/nip/vfc/provider/provider_home.htm
- Storage
  - Refrigerated at 2-8°C (36-46°F)
- Consent
  - Currently in NYS, minors need parental consent
- Adverse event reporting
  - http://vaers.hhs.gov/

Human Papillomavirus Vaccination. ACOG Committee Opinion No. 344. 2006; 108: 699-705.

2006 ASCCP GUIDELINES AJOG, OCTOBER, 2007

- Last consensus report – 2001
- Why now?
  - 90% use of Liquid based cytology
  - Increased use of LEEP as office-based modality
  - ALTS trial results and clinical adoption
  - Widespread use of Hybrid Capture II HPV
  - FDA approval of “HPV-DNA Pap” for >30
  - Need for modification in special populations
  - Adolescents; Postmenopausal; Pregnant
  - Cytologic results have different risks for CIN2/3

  GUIDELINES ARE NO SUBSITUTE FOR CLINICAL JUDGMENT

-

2006 ASCCP GUIDELINES

- SPECIAL POPULATIONS: <20 YO
  - Have more minor cytology abns, higher rate of HPV (+); low risk for invasive cancer
  - Most HPV infections clear in 2 years
  - DON'T do reflex HPV testing in <20 for ASCUS or LSIL Paps
  - "See and treat" LEEPs are acceptable for HSIL but not in adolescents

2006 ASCCP GUIDELINES

- SPECIAL POPULATION: PREGNANT
  - Treatment only for invasive cancer
  - No Endocervical curettage
  - Colposcopic referral to those experienced with pregnancy evaluations
- SPECIAL POPULATION: POSTMENO.
  - Because both HPV (+) and CIN 2/3 decline with age in women with LSIL, reflex HPV acceptable after LSIL Pap in PM women

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Questions?

Program sponsored by
The American College of Obstetricians and Gynecologists District II/NY

with the generous support of

New York State Department of Health
Bureau of Chronic Disease Services
Cancer Services Program
and the Governor's Office

Case # 1

28 yr old female with post coital bleeding

- Pelvic exam reveals normal appearing cervix
- Pap smear results LSIL

What should you do?

Case # 2

45 year old female

- Asymptomatic
- Routine pap results ASC-US

What should you do?

Case # 2, continued

- Repeat pap at 12 months reveals ASC-US
- Do you perform an HPV test again?

What should you do?

Case # 3

35 year old female

- Asymptomatic
- Pap reveals AGC

What should you do?