

# Human Papillomavirus

Kathryn Thiessen, ARNP, ACRN  
The Kansas AIDS Education and Training  
Center

The University of Kansas School of  
Medicine – Wichita

# What is Genital HPV Infection

Human papillomavirus is the name of a group of viruses that includes more than 100 different strains or types.

More than 30 of these viruses are sexually transmitted, and they can infect the genital area of men and women

## Nearly 1 out of 4...

In the United States in 2000, there were almost 9.2 million sexually active young males and females 15 to 24 years of age estimated to be infected with HPV. This translates to nearly 1 out of 4 of all the 15 – 24 year olds in the country

80% of Sexually Active  
Women...

in the United States will have  
acquired a genital HPV infection  
by 50 years of age

## Easily Acquired...

According to a study in the American Journal of Epidemiology, HPV can be spread through sexual intercourse as well as genital-to-genital, hand-to-genital, and oral-to-genital contact

# HPV/Genital Warts

Each year in the United States,  
there are approximately 1 million  
new cases of genital warts

# HPV is often spread unknowingly

- HPV infection can be asymptomatic or subclinical in its manifestations
- Most people are unaware of their infection
- HPV is often underdiagnosed

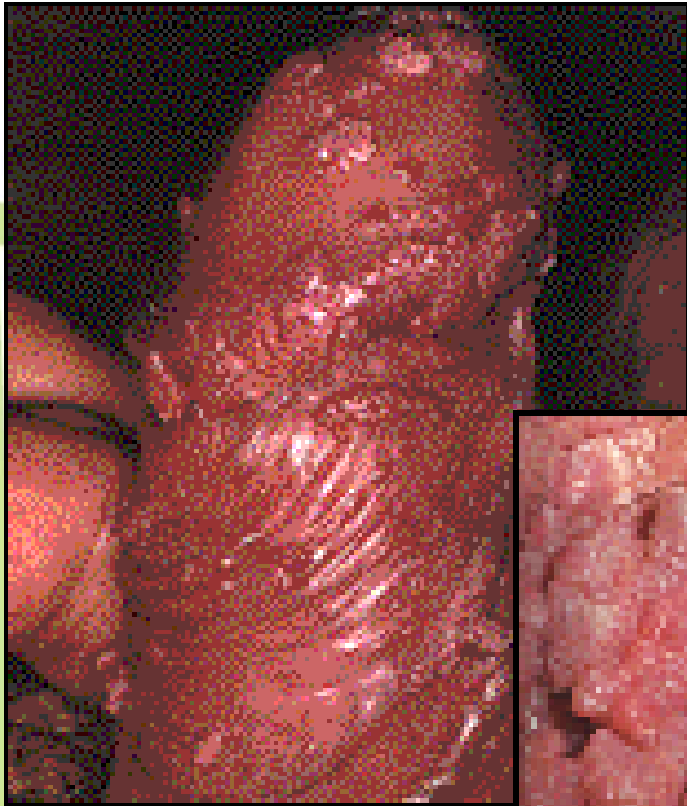
# How Common is HPV

- 20 million people are currently infected with HPV
- By age 50 at least 80% of women will have acquired genital HPV
- About 602 million Americans get a new genital HPV infection each year

# \$3 billion

- Recent estimates of total direct HPV-related costs in the United States among people 15 to 24 years of age: ~\$3 billion per year.
- Nearly all of this cost (\$2.7 billion, or 90%) is attributed to follow-up of abnormal Pap test results and treatment of cervical dysplasia (CIN)

# Papillomavirus



# HPV Basics

- The most common sexually transmitted disease
- 100 types
- 30 infect the genital skin
- Usually transient, but it may become persistent
- Peak age is the mid-20's

# Genital HPV Infection

- First infection is usually acquired soon after sexual encounter
  - Infection with multiple types is common
- Infection is usually transient and not associated with symptoms – 90% of infections clear within 2 years
- Persistent HPV infection is cause of cervical cancer as well as other anogenital cancers

# HPV Background

- Non enveloped DNA virus
- >100 different types
- ~40 types are sexually transmitted
  - “Low Risk” types: 6, 11, 42, 43,44
  - “High Risk” types:  
16,18,31,33,35,39,45,51,52,56,58
- Most common cervical dysplasia is from high-risk type HPV 16

## 30% Regress

Studies have found that up to 30% of genital warts cases spontaneously regress within 4 months

## 25% Recur

For those patients who undergo and respond to treatment, 25% of cases recur within 3 months of clearance

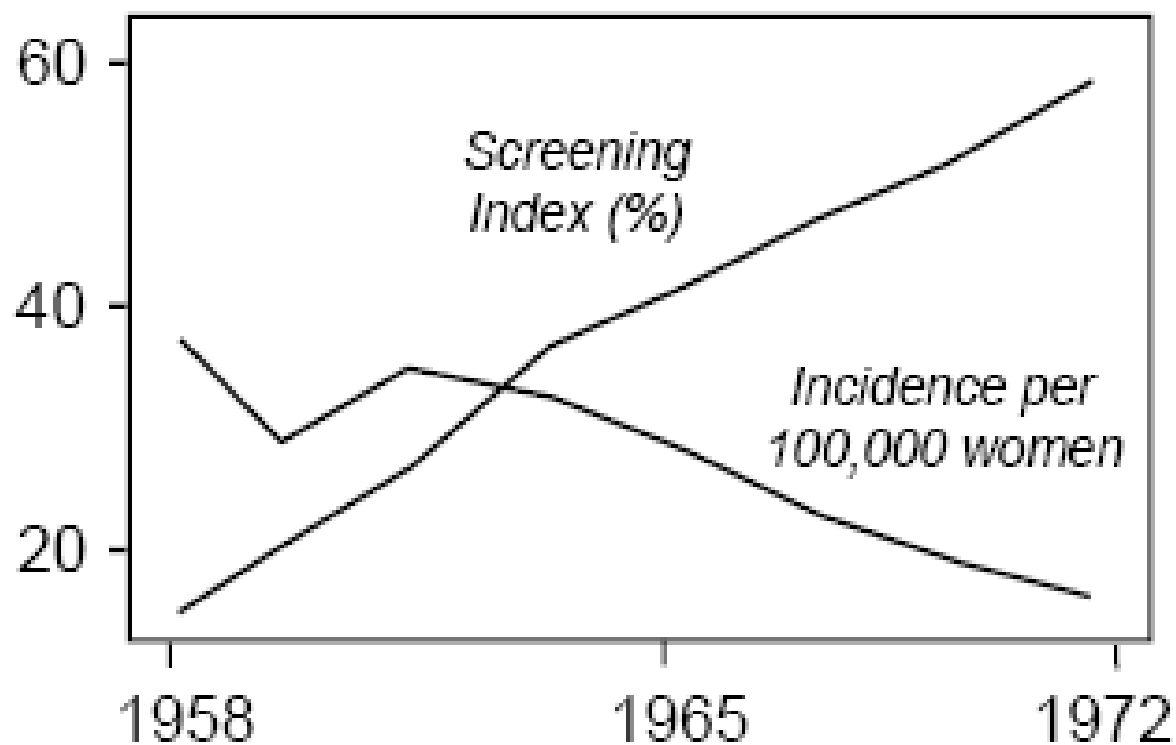
# HPV Testing and Primary Screening

- Combination of a Pap and an HPV test is more sensitive than a Pap alone
- Identifies women who possibly have long-term persistent infection or disease missed by the Pap
- Meaning of a positive test increases in seriousness with age, as does the risk of cervical cancer
- HPV DNA testing is not intended for women who are immunocompromised or HIV-positive

# PAP Definitions

- ASC-US = atypical squamous cells of undetermined significance
- LSIL = low grade squamous intraepithelial lesions (mild dysplasia, CIN I)
- CIN = cervical intraepithelial neoplasia

## Impact of Cytological Screening in the U.S.



# HPV Testing

- Only FDA-approved test for HPV DNA is the Hybrid Capture 2 by Digene
- May be performed off the residual solution of a liquid-based cytology sample
- Collected in a separate tube at the time of the PAP smear

# Differences in Detection

- Numerous studies have provided evidence that persistent high-risk HPV is necessary for the development of true cancer lesions
- Approximately half of women with ACS-US are not infected with HPV
- Most young women with LSIL PAP tests have high-risk HPV

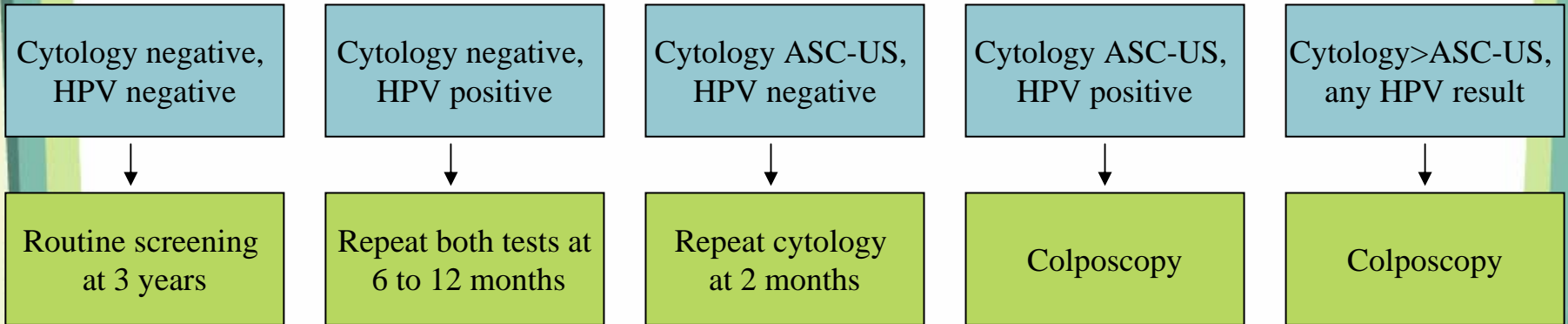
# Cost-Saving Recommendations

The American Society for Colposcopy and  
Cervical treatment recommends  
colposcopy for all women with LSIL  
without incurring the cost of an HPV test

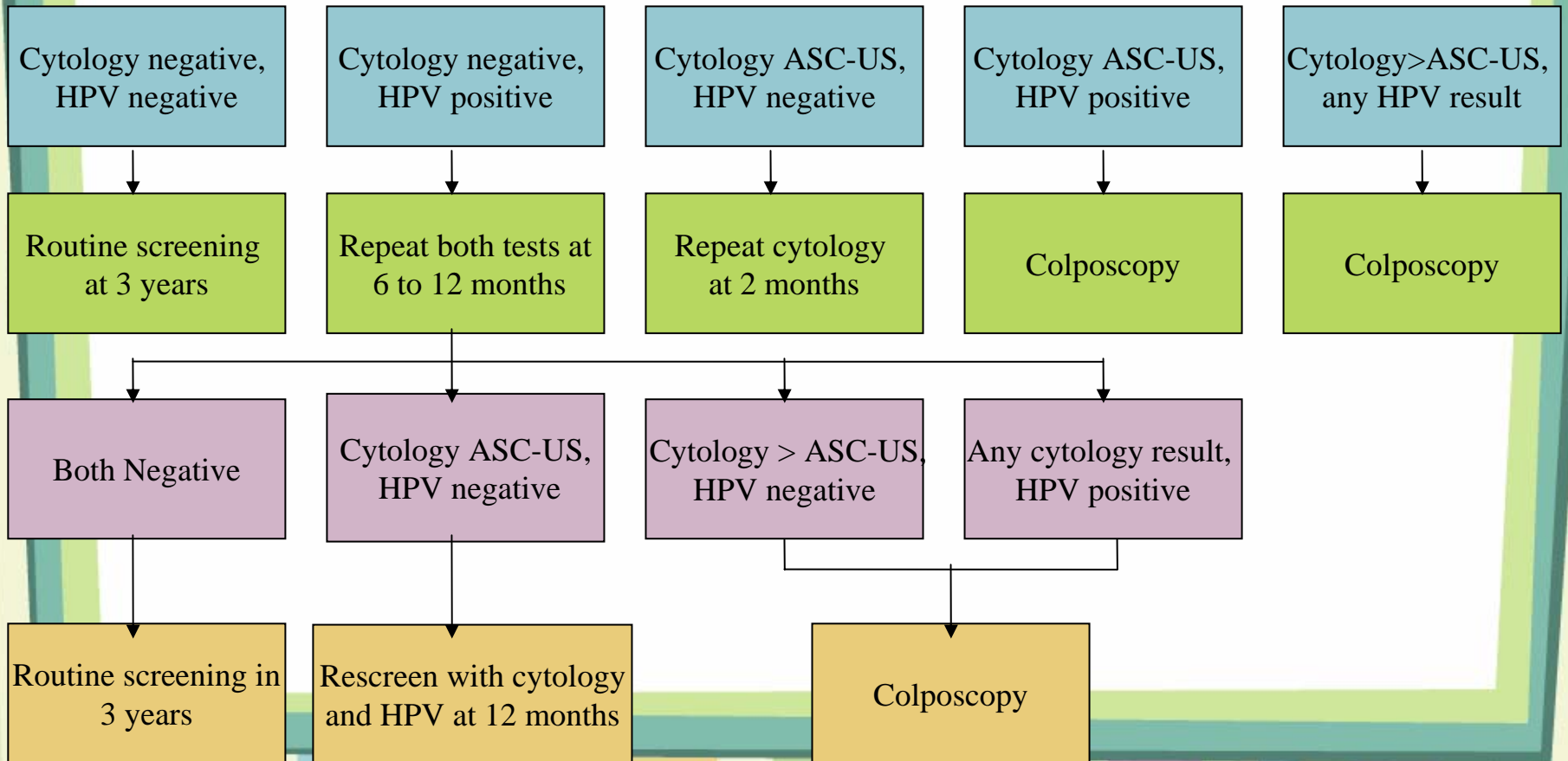
# ACOG Recommendations

- ACOG recommends the use of combined screening with a PAP test and an HPV test in women 30 and older
- If negative on both tests – rescreening no more frequent than every 3 years is suggested

# Algorithm for Cytology and HPV Test Results



# Algorithm for Cytology and HPV Test Results



# Treatment

- Primary goal for treatment of visible warts is the removal of symptomatic warts
- Therapy may reduce but probably does not eradicate infection with HPV
- Difficult to determine if treatment reduces transmission
  - No laboratory marker of infectivity
  - Variable results utilizing viral DNA



# Papillomavirus Treatment

## Patient-applied

Condylox (Podofilox) 0.5% solution or gel

Or

Aldara (Imiquimod) 5% cream

## Provider-administered

Cryotherapy

or

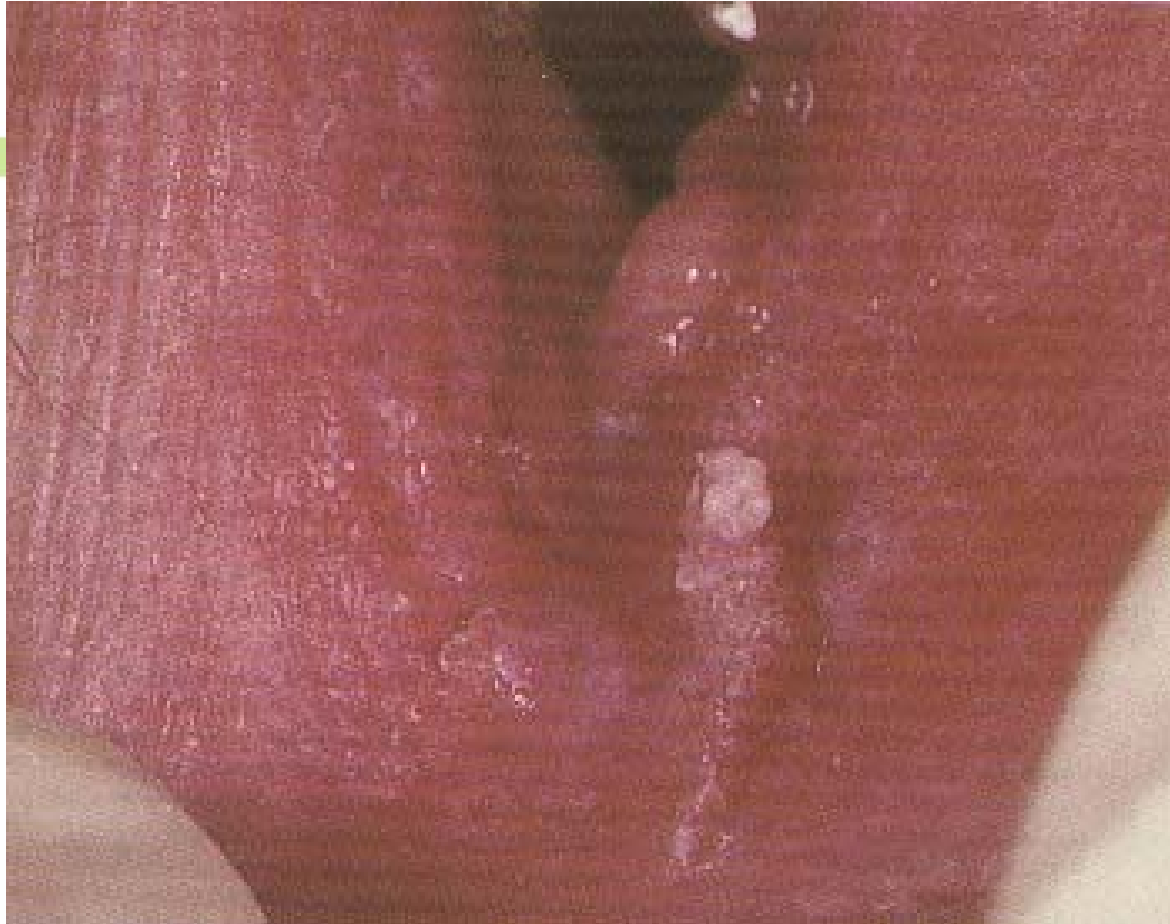
Podophyllin resin 10-25%

or

Trichloroacetic or Bichloroacetic acid 80-90%

or

Surgical removal





# HPV

## Treatment in Pregnancy

- Many specialists advocate wart removal due to possible proliferation and friability
- HPV types 6 and 11 can cause respiratory papillomatosis in infants and children
- Preventative value of cesarean section is unknown; may be indicated for pelvic outlet obstruction
- Topical creams/gels should not be used during pregnancy

# Causation of HPV-related disease

HPV types most often linked to high-grade cervical dysplasia (CIN 2/3) and Low-grade dysplasia (CIN 1)

# Cervical Cancer Screening Not Done

Half of women with a diagnosis of invasive cervical cancer have never been screened, and another 10% have not had a Pap test in more than 5 years

# Cervical Cancer Screening Today

- Evidence of a link between HPV and the development of cervical neoplasia and cancer was first noted in the 1970s
- FDA approved the use of HPV DNA testing in women 30 and older for primary cervical cancer screening
- The majority of women 30 and older who undergo regular screening by Pap have never heard of HPV

# High-Risk HPV

- Women who test positive for high-risk HPV are more likely to have persistent infection
- A positive test for high-risk HPV has greater positive predictive value for neoplasia in older women

# Physical

- Women diagnosed with cervical dysplasia may need:
  - Repeat Pap tests and HPV testing
  - Colposcopy
  - Cryotherapy
  - LEEP (loop electrosurgical excision procedure)
  - Laser therapy
  - Conization (cone biopsy)

# Emotional

- One or more of the following feelings were expressed in a clinical survey of respondents at diagnosis of an HPV-related disease
  - Anger 78%
  - Depression 76%
  - Guilt 60%
  - Shame 66%
  - Isolation 70%
  - Fear of rejection 70%

# Survival Rate

- The overall 5-year survival rate for women diagnosed with cervical cancer, regardless of stage, is 73%
- Women diagnosed with pre-invasive lesions have nearly a 100% survival rate

# HPV

- The majority of low-grade lesions regress without treatment
- Mean time to clearance of HPV infection is 8 or 9 months
- Clears in the majority of women within 24 months

# HPV

- Peak incidence of invasive cervical cancer is approximately 15 years later than the peak incidence of HPV infection
  - Occurs in the fourth and fifth decades
  - Cofactors are not well understood but include immunocompetence level and smoking



In the United States, an estimated 10 women die every day from cervical cancer---

more than 3,900 women a year

## Follow-up for CIN

HPV testing should be performed 6-12 months after cervical treatment



# Post-Test Counseling

- HPV may still go away on its own
- For safety, both tests will be repeated in 6-12 months. If the HPV test is still positive, cervix will be evaluated through a colposcope.

# Post-Test Counseling

- Most women have HPV at some point, yet few develop cancer
- The virus can be in the cells for a long time, and there is no way of knowing the time of original exposure
- Between 5% and 15% of women have high-risk HPV and a normal Pap result
- A positive result for high-risk HPV does not mean cancer will develop.

# How to Tell a Partner About a Positive HPV Test Result

- Most people have HPV at some point in their lives
- Men do not require screening since HPV rarely causes cancer on their genital skin
- The virus can stay around for years in the genital skin cells

# Is There a Vaccine to Prevent HPV and Cervical Cancer?

Not yet, but two HPV vaccines are in the final stages of clinical testing. If licensed by the **Food and Drug Administration (FDA)**, one of the vaccines may be available in the summer or fall of 2006. Both vaccines would be delivered through a series of three injections over a six-month period.

# Advisory Committee on Immunization Practices (ACIP)

- Provides guidance to Secretary, HHS and Director, CDC on vaccine preventable diseases in the US
- Develops recommendations and publishes written guidance for use of vaccines
- Makes recommendations for the Vaccines for Children (VFC) Program

# Rationale: Routine Vaccination of Females at 11-12 years

- Routine
  - Preventable infection, targeting 'high risk' groups not possible
  - Studies shows more impact if done routinely
- 11-12 years
  - More females vaccinated prior to sexual encounter than at older ages
  - Implementation advantages - consistent with young adolescent health care visit
  - Although duration of protection not known, no evidence of waning immunity; ongoing studies will monitor duration

# Vaccine Acceptability

- Multiple issues related to a vaccine for a sexually transmitted infection
- Acceptability high; providers and parents report higher intent to vaccinate older adolescents
- Education about HPV and vaccine can increase acceptability

# Potential Unintended Consequences of HPV Vaccine

- Increase in sexual risk unlikely
  - Research shows generally low levels of HPV knowledge
  - Multiple influences on adolescent sexual behavior
  - Fear of STD not apparent major motivation of abstinence
  - No evidence of behavioral changes in other similar fields

# Family Research Council and HPV Vaccines

- FRC welcomes the news that vaccines are in development for preventing HPV
- Media reports suggesting that FRC opposes all development or distribution of such vaccines are false
- While we welcome medical advances such as an HPV vaccine, it remains clear that practicing abstinence until marriage and fidelity within marriage is the single best way of preventing the full range of STD

# HPV Vaccine Initial Clinical Development Programs

| Vaccine/<br>Manufacturer | Efficacy Trials*       | Adolescent<br>Immunogenicity<br>Safety Trials |
|--------------------------|------------------------|---|
| Quadrivalent /<br>Merck  | Females<br>16 – 26 yrs | Females and<br>males 9 – 15 yrs               |
| Bivalent / GSK           | Females<br>15 – 25 yrs | Females<br>10 – 14 yrs                        |

\*endpoints include CIN 2/3

## What is the Difference Between the Two Vaccines?

- One vaccine would protect against four types of HPV, including two that cause most (70%) cervical cancers (types 16, 18), and two that cause most (90%) genital warts (types 6, 11). This vaccine is being tested in women and men.

## What is the Difference Between the Two Vaccines?

- The second vaccine would protect against the two types of HPV (16,18) that cause most (70%) cervical cancers. This vaccine is being tested in women.

## What is the Difference Between the Two Vaccines?

Both vaccines would prevent the cervical cell changes (found on PAP tests) that are caused by the targeted HPV types.

# Are the Vaccines Effective??

These vaccines have been found to be highly effective in preventing infection with the targeted types of HPV. They also have been found to be 100% effective in preventing the conditions caused by those HPV types.

# How Long Will the Vaccine Last? Will a Booster Be Needed?

- The length of protection (immunity) from a new vaccine is usually not known when a vaccine is first introduced. Research is being done to find out how long protection will last and if a booster vaccine is needed.
- So far, studies have followed up vaccinated persons for 2.5 to 4.5 years and have shown the vaccines to be effective

# What will the Vaccines NOT Protect Against?

- Because these vaccines will not protect against all types of HPV, they will not prevent all cases of cervical cancer or genital warts. About 30% of cervical cancers will not be prevented by these vaccines. And about 10% of genital warts will not be prevented by the vaccine that targets wart-causing HPV types. The vaccines will also not prevent other STIs. Finally, it is not known whether the vaccines will prevent other, less common cancers linked to HPV, such as anal cancer.

# Will Women Vaccinated Still Need Cervical Cancer Screening?

- Yes. There are a few reasons why women will still need regular cervical cancer screening.
  - First, the vaccine will **not** provide protection against all types of HPV that cause cervical cancer, so women will still be at risk for some cancers.
  - Second, some women may not get all required doses of the vaccine (or they may not get them at the right times), so they may not get the vaccine's full effects.

# PAP tests still needed

So, it will still be important for sexually active adults to reduce exposure to HPV and other STIs. It will also be important for women to continue getting screened for cervical cancer.

# PAP tests still needed

It is not yet known if screening guidelines for vaccinated women will change. The changes might address the age to start screening and how often to get screened.

# Are HPV Vaccines Safe?

- Tested in thousands of people
- Tested in women 9-26 y/o
- 1 vaccine also tested in men 9-15 y/o
- No serious side effects
- Brief soreness at injection site

# Are HPV Vaccines Safe?

Before any vaccine is licensed and made available to the American public, the FDA will have to approve it as safe and effective. The FDA is now reviewing one of the vaccines.

# Should girls/women be vaccinated and if so---when?

The vaccine would be most effective if given before girls become sexually active. It is not yet known what the best ages will be for them to get the vaccine.

# Should boys/men be vaccinated and if so---when?

- If the FDA licenses the HPV vaccine for boys as well as girls, the ACIP will consider whether boys should get the vaccine and what ages would be best.
- It is possible that the vaccine may be licensed for girls before it is licensed for boys.
- If the vaccine is recommended for boys and men, the vaccine would be most effective if given before boys become sexually active.

# How Much Will HPV Vaccine's Cost

The vaccine will cost \$300 – \$500 for three shots give over six months

Will likely be covered by insurance once approved, if insurance covers vaccines

## The Problem Is...

Those who most need the vaccine may not have private health insurance and would not be able to pay for the vaccine.

# Quadrivalent HPV Vaccine Summary

- High efficacy in 16 to 26 year-old females
  - HPV 16,18 related CIN 2/3 (100%)
  - HPV 6,11,16,18 related CIN (100%)
  - HPV 6,11,16,18 related external genital lesions (100%)

# Quadrivalent HPV Vaccine Summary

- Efficacy data available 2.5 – 4.5 years; duration of protection and need for booster unknown
- Limited or no efficacy in persons already infected
- Safe; side effects mainly local reactions

# Quadrivalent HPV Vaccine Summary

- >99% seroconversion rates in 9-26 year-olds
- Antibody titers decline over time after 3<sup>rd</sup> injection, but plateau by 18 months
- Antibody titers substantially higher than after natural infection; highest in those vaccinated at younger ages

# Vaccine Summary

- Two HPV vaccines are in development; FDA approval for the quadrivalent HPV vaccine may be in June 2006...possibly this week.
- If licensed, ACIP will consider recommendations for quadrivalent vaccine at the June 29-30 meeting
- Vaccines have high efficacy for prevention of HPV infection, cervical cancer precursor lesions, external genital lesions in females

# Vaccine Summary

- Recommendations need to take into consideration multiple factors, including epidemiology, acceptability, impact and cost effectiveness
- Vaccine would be most efficacious administered to young adolescent females

# HPV Summary

- The majority of low-grade lesions regress without treatment
- Mean time to clearance of HPV infection is 8 or 9 months
- Clears in the majority of women within 24 months

# HPV Summary

- Peak incidence of invasive cervical cancer is approximately 15 years later than the peak incidence of HPV infection
  - Occurs in the fourth and fifth decades
  - Cofactors are not well understood but include immunocompetence level and smoking