

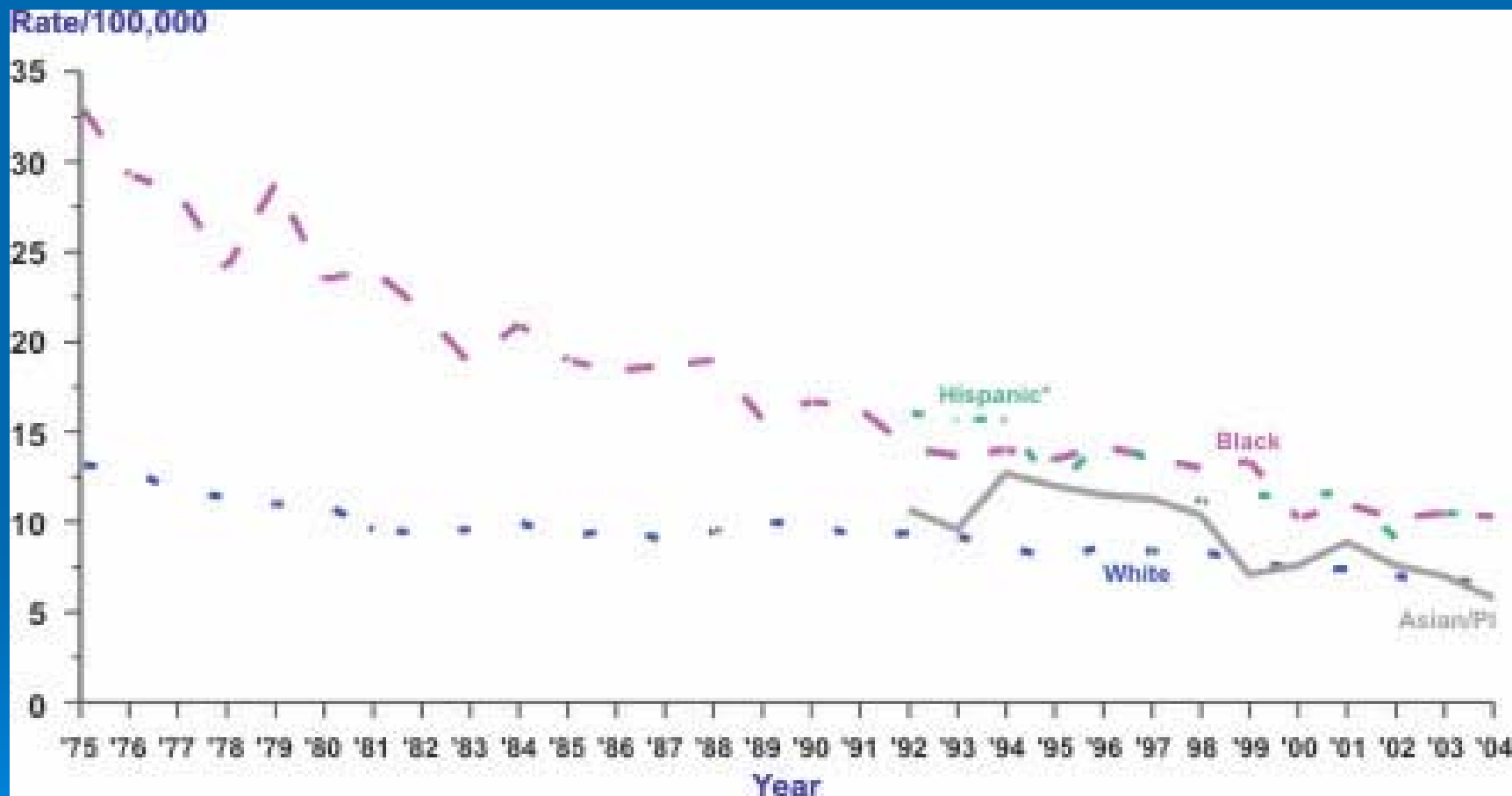
UPDATE ON CERVICAL
CANCER:
ROLE OF VACCINATION
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INTRODUCTION

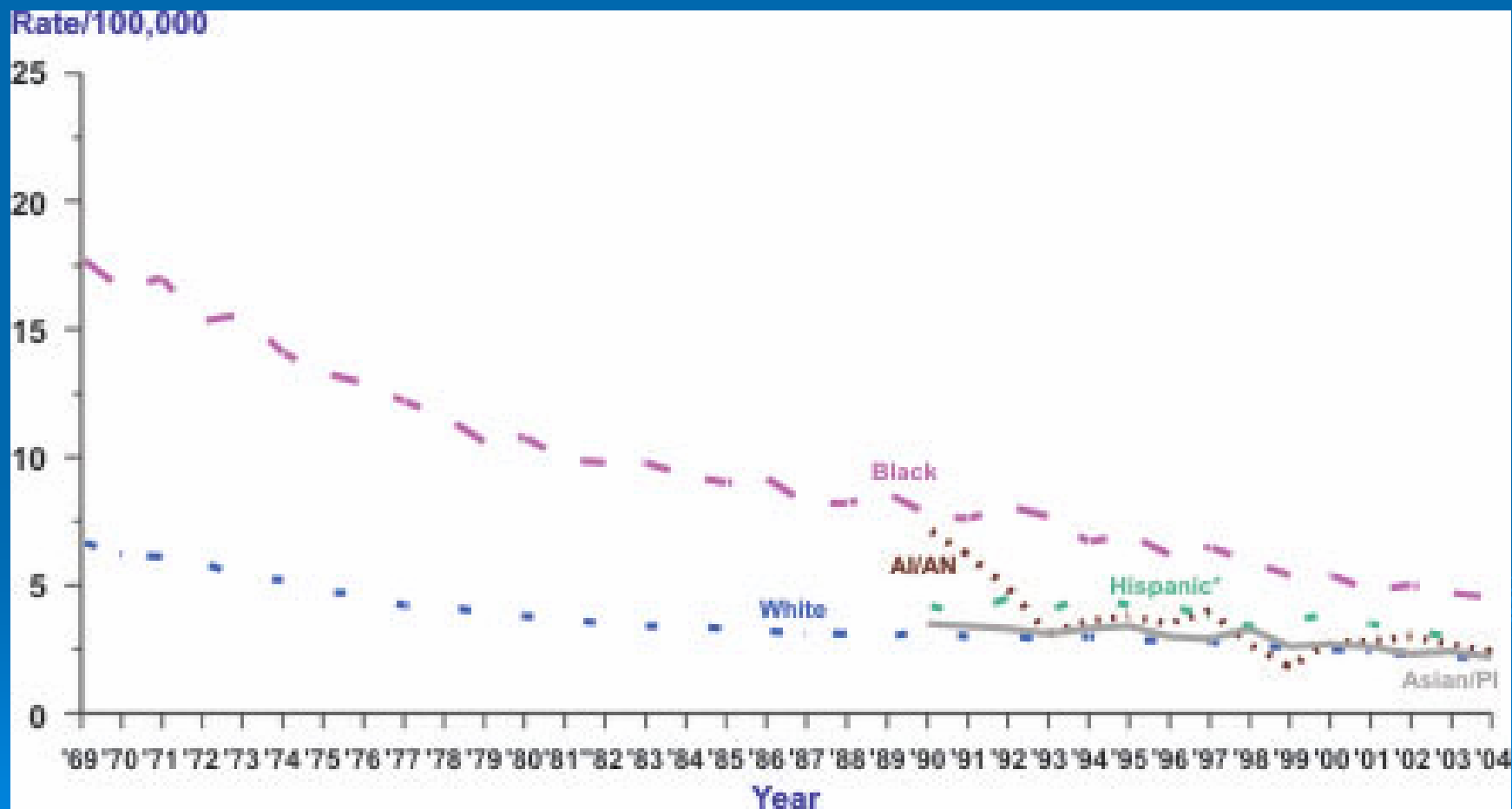
- Cervical cancer once claimed the lives of more American women than any other type of cancer.
- In 2007, cervical cancer in the USA developed in an estimated 11,150 women and caused death in 3600 women.
- HPV is the leading cause of cervical cancer
- Positive impact of screening programs in the last 40 years on both incidence and mortality across the board.

CERVICAL CANCER INCIDENCE RATES 1975-2004



SEER DATA BASE. Accessed online October 2008

CERVICAL CANCER MORTALITY RATES 1969-2004



SEER DATABASE. Accessed online October 2008

HPV STORY

- Human papillomaviruses (HPV) are highly prevalent, tissue-specific, DNA viruses that infect epithelial cells
- Persistent viral infection with oncogenic types of HPV leads to cancer of the cervix, anus, vagina, vulva, penis, mouth, and sinuses
- Cervical cancer is the second most common malignant disease in women worldwide and has a bimodal onset in the third and sixth decades of life

HPV subtypes

- High Grade lesions : 65% due to HPV 16, 18, 45, and 31.
- Low grade lesions: 50% due to HPV 16, 18, 45, and 31, 12% by HPV 6 and 11
- Up to 40 percent of patients are infected with more than one HPV type.
- HPV 16 and HPV 18 are associated with approximately 50 and 20 percent of cervical cancers, respectively

HPV subtypes

- The first peak of oncogenic HPV infection occurs between the ages of 15 to 25 years, with a secondary peak in the sixth decade of life.
- It is estimated that targeted HPV protection with the bivalent or quadrivalent vaccine would prevent half of the high-grade precancerous lesions (CIN 2 or 3) and two thirds of the invasive cancers.
- The quadrivalent vaccine would also prevent most genital warts

SCREENING

- Use of cervical cytology has reduced the incidence of cervical cancer by 70 percent.
- However, cervical cancer remains a leading cause of death in countries without screening programs.
- Vaccines that prevent these persistent HPV infections have the potential to further reduce the burden of disease

UTILIZATION OF SCREENING

- Today, as many as 82% of women in the U.S. have been screened with a Pap test in the past three years.
- Despite this, U.S. screening programs are not reaching all women in the U.S.
- It is estimated that half of the women diagnosed with cervical cancer have never been screened for cervical cancer, and an additional 10% have not been screened in the previous 5 years.

UTILIZATION OF SCREENING

- Cervical cancer disproportionately affects women of lower socioeconomic status, without regular access to health care, who are uninsured, and who are recent immigrants.
- These populations stand to benefit most from HPV vaccination.

MAGNITUDE OF THE PROBLEM!!!

- Approximately 20 million people are currently infected with genital human papillomavirus (HPV) in the United States (U.S.).
- As many as half of these infections are among adolescents and young adults, ages 15 through 24 years of age.

HPV induced malignancies

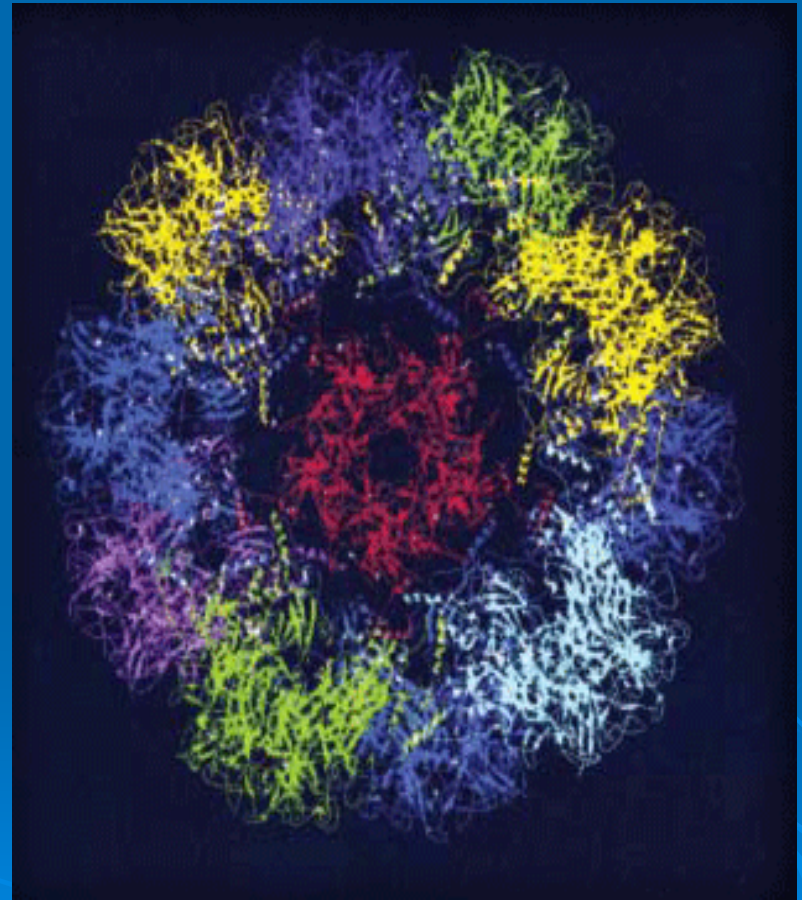
- Infection with high-risk "oncogenic" types of human papillomavirus (HPV) is the cause of:
 - 100% of cervical cancers (HPV-16 & 18 accounting for 70%),
 - 90% of anal cancers,
 - 40% of vulvar and vaginal cancers,
 - 12% of oropharyngeal cancers,
 - 3% of oral cancers.

HUMAN PAPILLOMA VIRUS

- Other, non-oncogenic HPV types can cause genital warts and, rarely, respiratory tract warts in children.

QUADRIVALENT HPV VACCINE

- Discovery of HPV L1 with or without L2 protein.
- Can self assemble in to Virus-like particles (VLPs) when expressed from a suitable expression system (yeast and baculovirus)
- FDA approval of quadrivalent HPV vaccine in 2006



MECHANISM OF ACTION

- Virus like particles (VLPs) composed of HPV L1 proteins
- VLPs are geometrically and antigenically similar to native virion
- Unable to produce infections
- Induce high levels of systemic anti HPV L1 Ig G antibodies as well as immune memory cells.
- Protection is type specific but cross reactivity may occur (shared cross neutralisation epitopes)
- Ig A inductions at mucosal surfaces do NOT play a role.

Stanley M et al., Vaccine 2006, Roden RB, Virology 2000, Olsson SE, et al., Vaccine 2007, Giannini SL, Vaccine 2006

QUADRIVALENT HPV VACCINE

- This prophylactic vaccine works by preventing four HPV types: HPV 16 and 18, which cause 70% of cervical cancers, and HPV 6 and 11, which cause 90% of genital warts.

QUADRIVALENT VACCINE EFFICACY

➤ Trials:

- Villa LL et al, Lancet Onc 2005
- Villa LL et al, Vaccine 2006

➤ Vaccine type:

- HPV 6/11/16/18 VLP
- L1 capsid component

➤ Concentration: 20ug for HPV 6,16 & 18, 40ug for HPV 11

QUADRIVALENT VACCINE EFFICACY

- Vaccine administered at : 0, 2, 6 months
- Sites: US, Europe, Brazil
- End points:
 - Primary: seroconversion
 - Secondary composite: 6 months; Persistent HPV Infection OR CIN histology
- Trial size:
 - Total: 552 women (277 vaccines, 275 placebo)
 - Age range: 16-26

QUADRIVALENT VACCINE EFFICACY

- Overall protection against persistent HPV 16/18 infection (>4 months) occurred in 89 percent of women who received vaccination and follow up visits according to protocol, with 100 percent, 86 percent, and 89 percent efficacy for HPV 6, 16, and 18, respectively.
- There were no cases of HPV 11 infection reported.
- Protection against CIN caused by HPV 6/11/16/18 occurred in 100 percent of all participants who were not infected with these types at first vaccination while seven cases occurred in the placebo group.

QUADRIVALENT VACCINE EFFICACY

- Protection against all external genital warts caused by HPV 6/11 occurred in 100 percent of all participants with four cases occurring in the placebo group.
- After three vaccine doses, seroconversion rates were 94, 96, 100, and 76 percent for HPV types 6, 11, 16, and 18 at month 36, respectively

QUADRIVALENT VACCINE EFFICACY

- Two hundred forty-one of these study participants were subsequently enrolled in an extension trial to obtain an additional two years of follow-up data.
- The combined incidence of HPV 6/11/16/18-related persistent infection or disease was reduced by 96 percent in vaccine recipients (two cases in the vaccine group versus 46 in the placebo group).

FUTURE II TRIAL

- Double blind placebo controlled study
- 12,000 females (age 15-26), < or = 4 lifetime partners
- 11% had baseline abnormal cytology on pap smears
- The primary composite end point was CIN 2 or 3, adenocarcinoma in situ, or cervical cancer related to HPV-16 or HPV-18.
- The mean duration of follow-up was three years.

FUTURE II TRIAL

- Highly immunogenic
- All individuals vaccinated seroconverted
- High titers of neutralizing antibodies
- Persist for at least 5 years
- Optimal immune responses to HPV-VLPs around puberty
- Immune memory generation

FUTURE II TRIAL

- Vaccine efficacy for CIN2 or 3 disease due to all HPV types was significantly lower (44 percent) in the overall population of women who had undergone randomization, which included participants with baseline or incident HPV infection by one month after the last dose of vaccine.

FUTURE I TRIAL

- Similar design to Future II
- 5455 women aged 16 to 24 years
- Assess the efficacy of quadrivalent vaccine to prevent HPV-related anogenital disease
- As noted in the FUTURE II trial, vaccine efficacy was lower when women with baseline HPV infection were included in the intent-to-treat analysis
- Bottom line: should be used for prophylaxis not treatment of existing HPV

VACCINE INDICATIONS

- The quadrivalent HPV vaccine, Gardasil®, is developed to protect against most cervical cancers and genital warts.
- The three-dose vaccine is routinely recommended for 11 and 12 year old girls.
- The vaccine series can be started at 9 years of age.
- Catch-up vaccination is recommended for 13 through 26 year old females who have not yet received or completed the vaccination series.

HPV VACCINE SPECIAL SITUATIONS

- The HPV vaccine can be given to females who:
 - Are lactating,
 - Have minor acute illnesses,
 - Have an equivocal or abnormal Pap test, a positive Hybrid Capture II® high risk test, or genital warts,
 - Are immunocompromised, either from disease or medication.

SPECIAL SITUATIONS

- The HPV vaccine should not be given to females who:
 - Are pregnant.
 - Have a history of immediate hypersensitivity to yeast or to any vaccine component.
 - Have moderate or severe acute illnesses. In these cases, girls/women should wait until the illness improves before getting vaccinated.

HPV VACCINE SAFETY

- The HPV vaccine has been studied in thousands of females (9 through 26 years of age) in many countries around the world, including the U.S.
- These studies found that the HPV vaccine was safe and caused no serious side effects.
- The most common adverse event was injection site pain. This reaction was common but mild.
- Since vaccine licensure, there have been reports of syncope after vaccination, more common in adolescents.
- Providers should consider a 15-minute waiting period for vaccine recipients following vaccination.

HPV Vaccine Efficacy and Antibody Response

- Efficacy has mainly been studied in young women (16 through 26 years of age) who previously had not been exposed to the targeted HPV types.
- These clinical trials demonstrated nearly 100% vaccine efficacy in preventing cervical precancers, vulvar and vaginal precancers, and genital warts caused by the four vaccine types.
- In women already infected with a targeted HPV type, the vaccine did not prevent disease from that HPV type but did protect against other vaccine types.

HPV Vaccine Efficacy and Antibody Response

- Immunogenicity studies also have been conducted in girls, ages 9 to 15 years of age.
- Over 99% of vaccinated girls in these studies developed antibodies after vaccination.
- Titers were higher in these young girls, compared to older females in the efficacy trials (ages 16 through 26 years of age).

Duration of Vaccine Protection

- Studies suggest that vaccine protection is long-lasting.
- Current studies (with about five years of follow-up data) indicate that the vaccine is effective for at least five years, with no evidence of waning immunity.

HPV Vaccine Administration

- The vaccine should be delivered through a series of three intra-muscular injections over a six-month period. The second and third doses should be given two and six months after the first dose.
- The vaccine can be administered at the same visit as other age-appropriate vaccines, such as Tdap, Td, MCV4, influenza, and hepatitis B vaccines.
- Providers should consider a 15-minute waiting period for vaccine recipients following vaccination.

POST VACCINATION...

- It is important to get all three doses of the vaccine to get its full benefits.
- Women will still need regular cervical cancer screening, beginning at age 21 or three years after initiating sexual activity, since the vaccine will not protect against all HPV types that cause cervical cancer.
- The vaccine will not prevent other sexually transmitted infections (STIs) so use of protective devices is encouraged.

OTHER
ISSUES/FUTURE
DIRECTIONS...



ADOLESCENT MALES

- While it is possible that vaccinating males with the quadrivalent vaccine may offer direct health benefits to males and indirect health benefits to females, there are currently no efficacy data available to support use of the HPV vaccine in males.
- Male HPV vaccination for female cervical cancer prevention is not cost effective
- Efficacy studies in males are ongoing. Information should be available within the next few years.

FUTURE DIRECTIONS

- Epidemiological studies to track effect of vaccination on other cancers e.g. head and neck cancers
- May take a long time to appreciate the full benefit.

TAKE HOME MESSAGE

- Persistent infection with hr-HPV types leads to cervical cancer
- Multicenter, double-blind, placebo-controlled trials for both quadrivalent and bivalent HPV vaccines demonstrate efficacy against incident and persistent HPV infection and abnormal cervical cytology and histology.

TAKE HOME MESSAGE

- Bivalent HPV 16/18 L1 vaccine has been submitted to the FDA for approval;
- Quadrivalent HPV 6/11/16/18 L1 VLP vaccine is available for use and distribution.
- The quadrivalent vaccine also prevents most genital warts.
- Both vaccines have an excellent safety profile.

TAKE HOME MESSAGE

- Immunization with HPV vaccine, as suggested by the ACIP and ACOG
- The currently suggested immunization schedule is in girls and women 9 to 26 years of age.
- Quadrivalent HPV 6/11/16/18 L1 VLP vaccine (Gardasil™) is administered in three doses at 0, 2, and 6 months.
- The duration of immunity is unknown.

TAKE HOME MESSAGE

- Cytologic screening is recommended for any woman who has been sexually active for three or more years or is 21 years of age.
- Clinicians need to be aware that HPV immunization is NOT effective in clearing cytologically evident disease or infection.
- A preventive health care visit in which vaccination is discussed or offered represents an ideal opportunity to offer Pap screening to sexually active patients as well.

TAKE HOME MESSAGE

- HPV vaccine is a major advance in the prevention of cervical cancer, but it will not replace the need for other preventive strategies, such as cervical screening.

THANK YOU

