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Fact Sheet

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HPV — The Most Common Sexually Transmitted Virus

Human papillomavirus (HPV) is a common infection that affects skin and mucous membranes. Some types cause common skin warts in areas such as the hands or feet. Some types cause warts in the genital areas. Certain high-risk types can cause cancers of the cervix, vagina, vulva, penis, anus, and throat. More than 150 viral types of HPV have been identified — about 40 of these are associated with sexually transmitted infections, and people may be infected with more than one type at a time (NCI, 2012; Gillison et al., 2012; Schiffman & Castle, 2003; Wiley et al., 2002). HPV has affected humans for thousands of years — ancient Greek and Roman medical records described genital lesions consistent with genital warts and associated them with sexual activity (Jay & Moscicki, 2000).

Today HPV is the most common sexually transmitted infections in the U.S. — yet in 2000 70 percent of Americans had never heard of it and 89 percent had never discussed HPV with their health care provider (CDC, 2011a; KFF, 2000). More recent studies confirm that knowledge of HPV is still low for all groups, regardless of gender, urban/rural location, and ethnicity (Friedman and Shepeard, 2007. In 2005, 60 percent of women had never heard of HPV. Of those who had heard of HPV, less than half knew that it can cause cervical cancer (Tiro et al, 2007). Up to 20 million Americans are currently infected with sexually transmitted HPVs, and approximately 6.2 million Americans acquire sexually transmitted HPV annually (Cates, 1999; CDC, 2011a). The highest rates of new genital HPV infections — approximately 74 percent of annual infections — occur among young adults between the ages of 15 and 24. About one in four of all young adults in America have HPV at any given time (Dunne et al., 2007; Weinstock et al., 2004). HPV is also prevalent among people with immunosuppressive disorders, such as HIV (Koutsky & Kiviat, 1999). HPV is believed to be widespread across racial groups and to have very little variation in prevalence across regions in the U.S. (CDC, 2000). HPV is so common, in fact, that it is considered a virtual marker for having had sex (Boonstra, 2004). In fact, the lifetime risk for contracting HPV is at least 50 percent for all sexually active women and men (CDC, 2011a).

Transmission

HPV is transmitted by direct skin-to-skin contact with an infected individual. Transmission is usually from vaginal, oral, or anal sexual contact and can occur whether or not warts or other symptoms are present (McDermott-Webster, 1999). Unprotected penetrative intercourse with multiple partners is the greatest behavioral risk for contraction of HPV (Kjaer et al., 2001; Winer et al., 2003).

The virus can also be transmitted from mother to infant during childbirth — also known as vertical transmission (Puranen, 1997). In one of the largest studies to look at both oral and genital HPV infections in newborns, research showed that the vertical transmission rate was less than one percent (Smith et al., 2004). The development of recurrent respiratory papillomatosis (warts in the respiratory tract) is one potential consequence of vertical transmission (Smith et al., 2004; Kashima et al, 1996). It is estimated that about 2,000 out of every four million newborns are infected (Jay & Moscicki, 2000). This is a serious, and potentially fatal, condition that may require frequent laser surgery to prevent obstruction of the infant's airways (NIAID, 2004).

Some research also suggests that genital HPV can be transmitted through nonsexual routes, via fomites

— inanimate objects such as towels or underwear — but more research must be conducted to examine these modes of transmission (Carson, 1997; Keller et al., 1995; Stevens-Simon et al., 2000).

Natural History

Although there is currently no "cure" for genital HPV infection, most cases are transient and clear themselves without medical intervention (Brown et al., 2005; CDC, 2011; Elfgren et al., 2000; Ho et al., 1998). It is estimated that approximately 90 percent of HPV infections are cleared by the body's immune system within two years (CDC, 2011a). The viral type of HPV is a major determinant in the duration of infection, with types 16, AE7, 61, 18, and 73 having the longest average duration (Elfgren et al., 2000; Ho et al., 1998; Muñoz et al., 2004; Richardson et al., 2003; Woodman et al., 2001). Other factors associated with the persistence of HPV infections are age (older than 30 years), infection with multiple HPV types, and a compromised immune system (CDC, 2011a; Hildesheim et al., 1994; Ho et al., 1995; Moscicki et al., 1998).

Subclinical Manifestations of HPV

Most HPV infections are subclinical (no visible signs or symptoms), and many people with HPV never know they have it (Verdon, 1997). HPV targets the deep, basal level of the skin and most often causes no clinical or microscopic changes in the cells of the skin (Keller et al., 1995; Verdon, 1997). In some cases, subclinical HPV may cause cellular changes that are only detectable using clinical instruments or the study of cervical cells. These changes may be, in rare instances, the precursor to cancer cells (Lytwyn & Sellors, 1997).

Changes related to HPV infections that cannot be seen with the naked eye may be identified using a variety of clinical tools:

- A hand lens or colposcope may be used to magnify cervical and vaginal tissue (Verdon, 1997).
- Pap tests may reveal precancerous conditions of the cervix that are caused by HPV. (Some experts also recommend anal Pap tests for men at increased risk of anal cancer — men who have sex with men and men who are HIV positive) (CDC, 2011a; Gilden, 2005; Tuller, 2003).
- HPV testing of samples taken with a cervical swab can detect high-risk types of HPV.

In March 1999, the U.S. Food and Drug Administration (FDA) approved the Hybrid Capture II HPV test — a DNA-based technology that can detect 13 high-risk types of HPV (those associated with an increased risk of cancer) ("HPV DNA Tests", 2000). HPV tests are not recommended for women under the age of 30 unless they have atypical or unclear Pap test results. This is because HPV is very common; cervical cancer is rare at this age; and most HPV infections go away by themselves without causing any health problems. For women age 30 or older, HPV tests can be done at the same time as a Pap test. If both test results are normal, a woman has a very low risk of developing cervical cancer. She will not need a Pap and HPV test for five years. Some women age 30 or older see this choice as more appealing than having a Pap test more frequently (ACOG, 2009 and 2012).

Clinical Manifestations of HPV

In some instances HPV infection can lead to clinical manifestations that can be seen with the "naked" eye. Clinical manifestations can appear as classical warts, or as a variety of lesions on the cervix, vagina, vulva, penis, anus throat.

Genital Warts

Genital warts (condylomata acuminata) are the most common clinical manifestation of genital HPV. In more than 90 percent of cases, they are caused by HPV types 6 and 11, which are considered low-risk types because they are not associated with increased risk of cancer (Jay & Moscicki, 2000; Moscicki, 2005; Wiley, 2002).

It is estimated that one percent of the sexually active American population has genital warts, and women and men have similar rates of infection (Cockerell, 1995; Jay & Moscicki, 2000; Moscicki, 2005). Between half a million and one million cases are diagnosed annually (Moscicki, 2005).

Genital warts usually start as small bumps that appear in the anogenital area. They may be single or clusters and have a cauliflower-like appearance as they grow larger. In women, genital warts may appear on the vulva, in the vagina, on the cervix, groin, or in the anal area. In men, they appear on

the foreskin, head or shaft of the penis, groin, and in the anal area, urethra, and scrotum (ASHA, 2006; Cockerell, 1995). Rarely, warts may also develop in the mouth or throat of a person who has had sexual contact with an infected person (Koutsky & Kiviat, 1999).

Genital warts usually are painless, but they may cause itching or irritation (Cockerell, 1995). Genital warts are very contagious, with an estimated rate of infection between 60 and 75 percent from unprotected exposure (NIAID, 2004; Soper, 2002). The incubation period for genital warts is usually between three weeks and six months, but it may last for years after exposure (ASHA, 1998; ASHA, 2006).

Treating Genital Warts

Because there is no cure for HPV infections, the purpose of treatment is to control outbreaks of warts. Although genital warts often fade away by themselves, they sometimes need to be treated. There are a variety of options to treat warts, including several chemicals that can be applied directly to genital warts:

- biochloroacetic acid (BCA)
- trichloroacetic acid (TCA)
- podofilox
- imiquimod

BCA and TCA are chemicals that must be applied by a clinician. Podofilox and imiquimod are two treatments that can be prescribed for use at home. Podofilox is a self-applied cream or gel that destroys wart tissue. Imiquimod, also a self-applied cream, is an immune system modulator. It works by boosting the immune system to fight HPV infection. Some of these treatments can cause local discomfort, and some cannot be used during pregnancy (ASHA, 2006; Holmes et al., 2008).

A clinician can also remove genital warts with cryotherapy (freezing off), electrocautery therapy (burning off), laser therapy, or surgery (ASHA, 2006).

HPV and Cancer

It is estimated that in 2012 there will be about 12,170 new cases of invasive cervical cancer in the United States, which will result in about 4,220 deaths (ACS, 2012). Worldwide, about 530,000 new cases are diagnosed each year. Cervical cancer is the third most common type of cancer among women worldwide and one of the leading causes of cancer-related mortality in women in the developing world. It was responsible for 275 000 deaths in 2008, about 88 percent of which occur in developing countries (Ferlay et al., 2010). The median age of diagnosis for cervical cancer for all races is 48 years (Howlander et al., 2011). Sixty percent of all women diagnosed with cervical cancer are younger than age 50 (ACS, 2011).

Due largely to routine screening using Pap tests, the number of deaths attributed to cervical cancer in the United States dropped almost 70 percent between 1955 and 1992, and the death rate continues to drop nearly three percent annually (ACS, 2011). The five-year survival rate for patients diagnosed with localized disease is 91 percent. The overall five-year survival rate for all stages of cervical cancer is about 70 percent (ACS, 2012).

African-Americans experience a disproportionate number of deaths from cervical cancer — due mainly to underscreening in this population. From 2003–2007, the death rate was 4.4 per 100,000 for African-American women, compared to 2.2 per 100,000 for white women. Latinas and Native Americans also have cervical cancer death rates that are above average (Howlander et al., 2011).

Since the late 1800s, researchers have suspected that cervical cancer was sexually transmitted. Medical reports noted that nuns and virgins were not likely to have cervical cancer, and that women who were married to men who traveled a great deal or who had previous wives who died of cervical cancer were more likely to develop cervical cancer ("The Cervical Cancer Virus," 1995). Today, 15–20 types of HPV have been classified as oncogenic, and the DHHS has added HPV to the list of cancer-causing agents (Janicek & Averette, 2001; Kay, 2005; Muñoz et al., 2003; Schiffman & Castle, 2003; Wiley et al., 2002). Large studies have found that HPV is present in more than 99 percent of cervical cancer tumors (Clifford et al., 2003; Walboomers et al., 1999). HPV 16 and 18 are responsible for about 70 percent of all cervical cancers. Other HPV types are associated with the remaining 30 percent of cases (Bosch & deSanjosé, 2003; Clifford et al,, 2003; Shah, 1997).

Most HPV infections never lead to the development of cervical cancer — even in the absence of medical intervention — and appropriate management of precancerous cervical lesions detected by Pap tests has greatly reduced the rate of invasive cervical

cancer (Ho et al., 1998; NCI, 1999a). Only one out of 1,000 women with HPV develops invasive cervical cancer (ACOG, 2000).

HPV appears to be necessary, but not sufficient, to the development of cervical cancer. Besides HPV type, researchers believe there are several cofactors that may contribute to the development of cervical cancer. These may include alcohol consumption, smoking, diet, familial history, HIV infection, hormonal factors — including multiple pregnancies and the use of both oral contraceptives and DES, low socioeconomic status, the presence of other sexually transmitted infections, such as chlamydia and/or herpes simplex virus 2, and having an uncircumcised male partner (ACS, 2011; Anttila et al., 2001; Moscicki, 2005; NCI, 1999b).

Certain high risk HPV types are also now considered to be a cause of many cancers of the vagina, vulva, anus, penis, and throat. Although each of these cancers occurs less frequently than cervical cancer, taken together they equal more than the number of cases of cervical cancer in the U.S. (ACS, 2012). The average age for diagnosis of these cancers is significantly later than for cervical cancer. The median age of diagnosis for vaginal cancer is 68 years and 68 years for vulvar cancer. Anal cancer is typically diagnosed at 61 years of age for women and 57 years for men, and the average age of diagnosis for cancer of the penis is 68 years (Howlander et al., 2011). The mean age for diagnosis of HPV-related throat cancer is 61.

As is the case with cervical cancer, HPV 16 and HPV 18 are most often associated with vaginal, vulvar, anal, and penile cancers (Chaturvedi et al., 2008; Eng & Butler, 1997). HPV is also associated with 20 percent of oropharyngeal (primarily the tongue and tonsils) cancers and 90 percent of skin cancers in immunocompromised patients (González et al., 2002; Ryerson et al., 2008). Men are three times more likely than women to develop throat cancers (Ryerson et al., 2008).

Prevention — Vaccination, Safer-Sex Practices, and Pap Tests

Over the last few years, there have been great strides in the development and testing of vaccines against HPV: (Austell, 2000).

Gardasil®

Gardasil®, a prophylactic, quadravalent (HPV types 6, 11, 16, and 18) vaccine manufactured by Merck and Co., Inc., was approved June 8, 2006, by the U.S. Food and Drug Administration. Given in three injections over a six-month period, clinical trials have shown this vaccine to be both safe and effective (Koutsky et al., 2002; Mao et al., 2006; Skjeldestad et al., 2005; Villa et al., 2005).

Follow-up studies (3.5 years after vaccination) have shown an effectiveness rate of 94 percent against persistent HPV 16 infection (Mao et al., 2006). These studies have also found a 100 percent effectiveness rate in preventing the development of high-grade (CIN 2–3), pre-cancerous cervical lesions related to HPV 16 and 18 — which cause 70 percent of all cervical cancers (Koutsky et al., 2002; Mao et al., 2006; Muñoz et al., 2010; Villa et al., 2005). Gardisil also protects against the two types of HPV that cause genital warts and protects against cancers of the anus in women and men (CDC 2011a) and researchers are optimistic that it protects against HPV-related throat cancers as well (Gillison, 2012).

Except for local irritation at the injection site, side effects in the study group were similar to the placebo group (Kahn, 2005). An Institute of Medicine (IOM) review of the scientific evidence on adverse events associated with vaccines covered by the National Vaccine Injury Compensation Program (VICP) found that “evidence favors acceptance of a causal relationship” between HPV vaccine and anaphylaxis, but the evidence is “not firm enough to be described as convincing” (IOM, 2011).

Cervarix™

Cervarix™, a three-dose bivalent (HPV types 16 and 18) prophylactic vaccine manufactured by GlaxoSmithKline (GSK) was approved in October, 2009 (GSK, 2009).

Studies showed the vaccine to be safe and 100 percent effective in preventing HPV type 16 and 18 infections, and nearly 100 percent immunogenic over a period of 4.5 years that have been measured so far (Harper et al., 2004; Harper et al., 2006). No serious adverse events related to the vaccine were reported during these studies (Kahn, 2005). Preliminary results of phase III clinical trials showed detectable HPV 16 and 18 antibody levels six months following the completion of the vaccination

series to be at least 16 to 26 times higher than antibody levels seen after natural infection (GSK, 2006; Schwarz et al., 2006). Cervarix also protects against cancer of the anus and is presumed to protect against HPV-related cancers of the throat (Gillison, 2012; Kreimer et al., 2011).

Social Acceptance of STI Vaccines for the Young

Because HPV types 16 and 18 are responsible for nearly 70 percent of all cervical cancers, as well as many anal, penile, and some oropharyngeal cancers, the development of these HPV vaccines has the enormous potential to improve the reproductive health and well-being of women and men. And because prophylactic HPV vaccines are only effective in individuals not currently infected by the virus, it will be important for the vaccine to be administered to women and men *before* they become sexually active.

In 2003, nearly 28 percent of young women in the ninth grade, and more than 37 percent of young men in the ninth grade had had sexual intercourse (Grunbaum et al., 2004). To reach these young people before they become sexually active, the FDA approved Gardasil for girls and women from nine to 26 years old, and the Center for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) has recommended that the vaccine be *routinely* administered to girls and women starting at age 11 and 12 and up to age 26. The vaccines are also available to boys and men of the same ages (Associated Press, 2006; CDC, 2011a; FDA, 2006). Initial testing was done mostly on women 15–26 years of age.

One study estimated that the vaccination of 12-year-old girls could potentially reduce the number of HPV 16- and 18-related cervical cancer cases by more than 95 percent. The vaccination of both young boys and girls could further reduce the number of cervical cancer cases by an additional three percent (Taira et al., 2004). Protecting men from genital warts could also potentially break the chain of transmission of genital warts (Bor, 2006).

The young target age of vaccination has led many researchers, health care providers, parents, and the patients themselves to consider the unique issues related to the acceptance of an STI, or more specifically an HPV vaccine. Some of the many potential barriers to vaccination include the belief that young children already receive too many vaccinations, concern that immunization might lead to risky sexual behavior, concern about vaccine safety, a reluctance to immunize against an STI, and a reluctance to talk with young children about STIs and sexuality, (Kahn et al., 2005; Mays et al., 2004). These potential barriers were very similar to those observed upon the development and approval of Hepatitis B vaccines — the first vaccines developed to reduce the risk of contracting a virus that can cause cancer (Rosenthal et al., 1995).

When individuals and parents learn about the connection between HPV and cervical cancer their reluctance to vaccinate dissipates. Surveys of young adults have shown HPV and general STI vaccination acceptance rates between 74 and 89 percent (Boehner et al., 2003; Kahn et al., 2003). Surveys of parents have shown HPV vaccine acceptance rates between 73 and 84 percent (Davis et al., 2004; Mays et al., 2004). Vaccinating young children opens the door to parent-child and provider-child communication. The HPV vaccine presents a unique opportunity to both introduce young children to sexuality education and educate them about healthy sexual expression.

Cost

Parents and providers are also concerned about the costs associated with the HPV vaccines. The retail cost of HPV vaccines is about $130 a dose — $390 for the full, three-shot series. Most insurance plans cover the cost. The Vaccines for Children (VFC) program may be able to help cover the cost for those who are uninsured or those whose insurance does not cover the cost. Children younger than 19 years old are VFC-eligible if they have no insurance, are eligible for Medicaid, or are American Indian or Alaskan Native (CDC, 2011b).

HPV-vaccine manufacturers also help women and men who cannot afford their vaccines. GlaxoSmithKline has its Vaccine Access Program (1-877-822-2911), which serves low-income women and men who are 19–25 and too old for the VFC program. Merck has its Vaccine Patient Assistance Program (1-800-293-3881), which helps women and men over 19 who do not have insurance or cannot afford to pay for vaccination (NCI, 2012).

While the potential cost of the vaccine is high, it is not comparable to the total cost of HPV and cervical cancer in the United States. In 2000, the total cost attributed to HPV among women and men between the ages of 15 and 24 years was approximately $3 billion (Chesson et al., 2004). A cost-study analysis of women's health plan enrollees determined that

the average per-woman cost associated with the screening and treatment of cervical HPV-related diseases was $26,415 (Insinga et al., 2004). Vaccines will not eliminate the total cost of screening or treatment, but they do have the potential to significantly reduce it.

Ongoing Prevention

Vaccine boosters might be necessary. Until other vaccines are developed that will protect against *all* oncogenic HPV types, women will need to continue to practice safer sex *and* receive regular Pap tests.

Abstinence and lifelong monogamy will continue to be the most effective ways to avoid HPV infection entirely. Even if Gardasil and Cervarix are 100 percent effective, they only prevent HPV types that cause 70 percent of cervical cancers. Women will still need screening to protect themselves against the other 30 percent. For most sexually active women, the most important preventive measure to protect themselves from developing cervical cancer will continue to be regular Pap tests (Janicek & Averette, 2001). Avoiding skin-to-skin contact with someone with HPV is the most effective, but not always practical, strategy to prevent HPV infection. And although condoms may not entirely eliminate the risk of transmitting HPV, they are recommended for risk reduction (ASHA, 2001; Winer, et al., 2006). A recent study published in the *New England Journal of Medicine,* showed that women whose partners used condoms consistently and correctly during vaginal intercourse over a period of eight months were 70 percent less likely to acquire a new HPV infection than women whose partners used condoms less than five percent of the time (Winer et al., 2006).

Because HPV may shed beyond the covered area, however, condoms do not provide as complete protection as they do for some other pathogens, such as HIV and gonorrhea (Stone et al., 1999). The claims of condom-use opponents who suggest that condom use leads to increased numbers of HPV infections are false and alarmist. Condom use cannot be blamed for the high prevalence of HPV infection or the incidence of cervical cancer among women in the U.S. In fact, two Dutch studies found that condom use promotes the regression of HPV lesions in women and men, as well as the clearance of HPV in women (Hogewoning et al., 2003; Bleeker et al., 2003).

While HPV is endemic among sexually active women and men in the U.S., it is reassuring to know that vaccines are now available, that these infections most often remain asymptomatic, that their symptoms, if they occur, are usually manageable, and that condom use is likely to reduce the risk of infection. Sexually active women should also be sure to have routine Pap tests as well.

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