

2012

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### Recommended Citation

Ragan, Kathleen (2012) "Public Health Impact of the HPV Vaccinations: A Research Update," *The Corinthian*: Vol. 13, Article 3.  
Available at: <http://kb.gcsu.edu/thecorinthian/vol13/iss1/3>

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**Public Health Impact of the HPV Vaccinations: A Research Update**

**Kathleen Ragan**

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In recent years, a large volume of medical and public health literature has been dedicated to the sexually transmitted infection Human Papillomavirus (HPV). The purpose of this paper is to provide a comprehensive assessment of recent empirical investigations which assess the public health impact of HPV and recent HPV vaccinations.

**Epidemiologic Assessment**

Human Papillomavirus is the most common sexually transmitted infection in the United States (U.S.; Weinstock, Berman, & Cates, 2004). It is estimated that 20 million people are currently infected with HPV and that an additional 6 million new infections occur every year (Centers for Disease Control and Prevention [CDC], 2009). Human Papillomavirus is a small DNA virus that replicates in squamous epithelial cells found on the skin, cervix, vagina, anus, vulva, head of the penis, mouth, and throat (Widdice & Kahn, 2006). It is passed from person-to-person via sexual intercourse or skin-to-skin contact and can infect both men and women (Baseman & Koutsky, 2005). In most cases, infections with HPV are not serious and are usually asymptomatic, transient, and resolve without treatment (Baseman & Koutsky, 2005). However, in some individuals HPV infections result in genital warts, cervical abnormalities, and/or various cancers (CDC, 2009; Worden et al., 2008). Since there are often no signs or symptoms of infection many individuals are unaware of their possible transmission to others (CDC, 2009). It is estimated that 80% of sexually active women will have acquired HPV by the age of 50 with a high prevalence occurring from ages 14-19 (Datta et al., 2008; Myers, McCrory, Nanda, Bastian, & Matchar, 2000). According to Manhart and colleagues (2006) the prevalence of infection among women aged 18-25 increases from 14.3% among those with one lifetime sexual partner to 31.5% with more than three partners.

There are more than 100 different strains of HPV and many differ in terms of the epithelium they infect. Some infect cutaneous sites whereas others infect mucosal surfaces (Trottier & Franco, 2006). Over 40 strains are sexually transmitted and can cause genital warts, cervical abnormalities, and/or cancer of the oral cavity, oropharynx, anus, vulva, penis and vagina (CDC, 2009). The

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incidence of HPV-associated cancers/year is as follows: 12,000 cervical, 4,400 anal, 2,700 vulvar, 1,000 vaginal, and 1,000 penile (CDC, 2009). The strains of HPV that cause cervical cancer differ from those that cause genital warts (Munoz, Bosch, & deSanjose, 2003). Strains 16 and 18 are considered high risk and have been detected in 99.7% of cervical cancer cases. Strains 6 and 11 are considered low risk and account for 90% of genital wart cases. Most genital infections will naturally clear without medical intervention (Munoz et al., 2003). However, women who do not clear high risk strains are at an increased risk for cervical cancer.

Human Papillomavirus causes cells on or around the cervix to become abnormal and may progress to pre-cancerous stages (Collins, Mazloomzadeh, & Winter, 2002). Many women may develop mild cytologic abnormalities causing atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesions (LGSIL) as detected on a Papanicolaou (Pap) test (Munoz et al., 2003). In the U.S., approximately 4% to 5% of all cervical cytology results are ASC-US (Munoz et al., 2003). These abnormal cells may clear without treatment and most high-risk HPV infections do not result in cancer (Munoz et al., 2003). Persistent infection is associated with adaptations that can result in pre-cancer cells. True pre-cancer cell changes are called high grade squamous intraepithelial lesions (SIL). Pap tests are used to identify cervical cancer precursors that can be treated before progression to cervical cancer occurs. The American Congress of Obstetricians and Gynecologists (ACOG) recommends women start having Pap tests approximately three years after the onset of vaginal intercourse but no later than age 21 (ACOG, 2003).

Selected strains of HPV can also cause genital warts. There is an estimated 1 million new cases of genital warts each year in the U.S. (Kodner & Nasraty, 2004). Genital warts are usually soft, flesh-colored growths that can be raised or flat, small or large, alone or in clusters. They sometimes disappear without treatment or may need to be removed by burning, freezing, laser or surgical procedures. However, they can return after treatment because the viral infection may be persistent. It is estimated that 25% of cases reoccur within three months (Kodner & Nasraty, 2004).

The high prevalence rates of HPV-related strains have generated public health interest in primary prevention methods focused upon risk reduction. Transmission of HPV can be reduced through the correct and consistent use of physical barriers such as male latex condoms (Winer et al., 2006). While HPV can occur in areas that are not covered or protected by a condom, the use of condoms has been associated with decreases in HPV-related problems. A study conducted by Winer and colleagues (2006) assessed the relationship between HPV infection and vaginal intercourse among 82 university students over an eight month period. Results indicated that the participants who used condoms on

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all sexual occasions exhibited an incidence of genital HPV of 37.8/100 patient-years, whereas participants who used male condoms less than 5% of the time had a rate of 89.3/100 patient-years.

According to the CDC (2010a):

Condom use may reduce the risk for HPV-associated diseases (e.g., genital warts and cervical cancer) and may mitigate the other adverse consequences of infection with HPV; condom use has been associated with higher rates of regression of cervical intraepithelial neoplasia (CIN) and clearance of HPV infection in women, and with regression of HPV-associated penile lesions in men.

In 2006, Merck Pharmaceuticals introduced a new vaccine titled Gardasil® that helps to protect against HPV strains 6, 11, 16, and 18. The prophylactic vaccine is made from non-infectious HPV L1 proteins and is administered through a series of three intramuscular injections (.5-ml doses) over a six month period (0, 2, and 6 months; CDC, 2007). Currently, the vaccine is licensed for females and males ages 9 to 26 and costs \$360 for the full series (Food and Drug Administration [FDA], 2010; Harris, 2006). A second vaccine, Cervarix®, was submitted to the FDA in 2008 and is currently available as a bivalent vaccine that protects against HPV 16 and 18 (Lowy & Schiller, 2006). The public health benefits of the vaccines would be expected to significantly reduce HPV-related morbidity and mortality and reduce the overall economic burden upon health care systems (De Melo-Martin, 2006). The vaccines represent a major step toward the prevention of HPV and cervical cancer but should not be used as a replacement for other prevention strategies such as cervical cancer screenings or protective sexual behaviors.

The prevalence of HPV infection is high among college women and young adults 20 to 24 years of age (Dunne, Unger, & Sternberg, 2007; Winer, Lee, & Hughes, 2003). College women have a high risk of acquiring HPV when compared to the general population because of their high-risk sexual behaviors (Dunne et al., 2007; Winer et al., 2003). Dinger and Parsons (1999) studied college students living in residence halls and in fraternity/sorority housing at a northwestern university. Results indicated that 39.4% of students living in fraternity/sorority housing reported having 6 or more sexual partners compared to 22.8% of students living in residence halls. In addition, 15% of students living in fraternity/sorority housing reported more than 20 acts of sexual intercourse prior to the study compared to 5% of students living in residence halls. According to the CDC (1997), only 29.6% of sexually active students reported that they or their partner used condoms during their last act of sexual intercourse.

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## Barriers to Vaccination Acceptance

Recent studies have begun to focus upon the examination of potential barriers to mandatory HPV vaccination as well as overall acceptance of the vaccine by target populations. A solid understanding of potential barriers is crucial for health care providers to enable them to effectively assist parents and adolescents in their decisions regarding the vaccines (Zimet, 2009). Research indicates that school-entry requirements of vaccinations have proven to be a very efficacious method of protecting a large majority of school children from vaccine-preventable diseases (Hinman, Orenstein, Williamson, & Darrington, 2002). Though the school-entry requirements for childhood vaccines vary from state to state, every state offers parents the option to opt-out for medical reasons and some allow exceptions based on religious or philosophical beliefs (Zimet, 2009). Studies also demonstrate that increased outbreaks of preventable diseases occur when vaccination requirements are relaxed (Feikin et al., 2000; Omer et al., 2006; Thompson et al., 2007). Controversy surrounding the quadrivalent HPV vaccine received increased media attention when several states proposed legislative efforts that would mandate HPV vaccination for girls entering middle school (Zimet, 2009).

On February 2, 2007 Texas became the first state to mandate HPV vaccination, requiring all girls to receive Gardasil® before entering 6th grade (Cook, 2008). By March 2007, legislation had been introduced in 41 states and the District of Columbia to “require, fund, or educate the public about the HPV [v]accine” (Cook, 2008, p. 213-214). Of these, 24 states required vaccination for enrollment in school, while the remaining 17 proposed policies that were centered upon funding the vaccine or sponsoring education-based programs (Cook, 2008).

Many parents view the efforts as an infringement upon their rights and are weary of the safety and efficacy of the vaccine (Cook, 2008). Dissent regarding school-entry vaccination requirements is centered upon the following key arguments (a) currently, long-term safety and accessibility issues have not been empirically assessed (b) fear that vaccination will promote increased sexual activity among young girls and adolescents and (c) the vaccination will provide a false sense of reduced susceptibility from other sexually transmitted infections (Blumenthal, Heyman, Trocola, & Slomovitz, 2008).

Although few laws pertaining to school-entry requirements have been enacted, research suggests that HPV vaccination utilization remains higher than comparable non-mandated vaccines for preventable communicable diseases (Jain, Stokley, & Yankey, 2008; Zimet, 2009).

In 2007, approximately 25% of 13-17 year old girls in the U.S. received at least one dose of HPV vaccine and an estimated 68% of first dose

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recipients received at least two doses at the time of follow-up (Jain et al., 2008). In contrast, a United Kingdom (U.K.) study of 2,817 girls attending 36 schools found that nearly 71% received the first dose and 97% of first dose recipients received the second (Brabin et al., 2008). Australian studies yield similar results of high vaccine acceptance, with 3-dose uptake at 75 - 80% (Garland, 2008).

Another Australian study conducted by Fairley and colleagues (2009) examined proportions of new clients presenting with genital warts beginning in 2004 before vaccination programs were implemented in 2007 (Fairley et al., 2009). In 2007, school-based and general practice programs began offering free quadrivalent vaccination for school girls aged 12-18 years and women less than 26 years of age. In the period from 2004 – 2007, there was an increase in new clients presenting with genital warts of 1.8% (95% CI 0.2% - 3.4%) per quarter in women under 28 years of age. In comparison, there was a decrease of 25.1% (95% CI 30.5% - 19.3%) in the proportion of women under 28 years presenting with warts per quarter in 2008. The average quarterly change for heterosexual men was a decrease of 5% (95% CI 0.5% -- 9.4%;  $p = .031$ ). These findings demonstrate that Australian and U.K. school-based vaccination approaches are more effective than the U.S. clinic based-approach (Zimet, 2009).

Worldwide acceptance of the vaccines is increasing. As of September 2008, over 100 countries had licensed the quadrivalent vaccine and over 75 countries had licensed the bivalent vaccine (Irwin, 2008). Unfortunately, there is a vast amount of misunderstanding and misperception regarding HPV and cervical cancer. In general, young women, parents, and health care providers appear to be interested in vaccines that prevent HPV, but there are varying degrees of acceptance among the populations (Zimet, 2005). Recent studies of physician attitudes regarding vaccination recommendations have revealed that acceptance rates of physicians generally increased with the girl's age (Mays & Zimet, 2004; Raley, Followwill, Zimet, & Ault, 2004; Riedesel et al., 2005). In 2005, Daley and colleagues (2006) conducted a national assessment of vaccination-related attitudes among 294 U.S. pediatricians. Results indicated that pediatricians believed that if a future vaccination was developed and endorsed by a health-related organization, they would increasingly be willing to recommend the vaccine to girls and boys based upon age. Vaccination recommendation rates ranged from 46% (ages 10 to 12) to 89% (ages 16 to 18) in girls as well as 37% (ages 10 to 12) to 82% (ages 16 to 18) in boys. In addition, only 11% of participants believed that the vaccine would encourage sexual behavior among their patients (Daley et al., 2006). Other factors that could influence acceptance beliefs include the potential economic and personal benefits associated with decreased health care costs and stress due to abnormal Pap results (Blumenthal et al., 2008; Harper, 2004).

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Studies reveal that sexually active college students ages 20 to 24 often lack knowledge regarding HPV and become more aware only after being diagnosed with HPV infection by a health care provider (Vail-Smith & White, 1992; Yacobi, Tennant, Ferrante, Pal, & Roetzheim, 1999). Previous studies have shown that 85% of college women have heard of HPV but are unaware of the infectivity and overall prevalence of the virus (Vail-Smith & White, 1992; Yacobi et al., 1999). A study by Lambert (2001) focused on college women's knowledge of HPV. The women were given a pre-questionnaire, participated in a brief HPV-focused educational intervention, and were reevaluated 3 months later. Results showed that the women answered 45% of the HPV questions correctly pre-intervention and 78% correctly post-intervention. These findings suggest that targeted intervention efforts may increase general knowledge in specific populations potentially leading to adoption of preventative methods such as receiving a vaccine.

Only 30% of women participants in two U.K. studies, as well as 13% of adolescents in a Canadian study, had prior knowledge of HPV (Dell, Chen, Ahmad, & Stewart, 2000; Pitts & Clark, 2002; Waller et al., 2003). Additional research has shown that even among those who had prior knowledge of HPV, many misunderstandings concerning infection, cervical cancer screening, and Pap smears exist (Zimet, 2005). One investigation indicated that 86% of women interested in learning about the virus believed that HPV-related educational materials should be distributed to individuals before they initiate sexual activity (Holcomb, Bailey, Crawford, & Ruffin, 2004). Another study of male and female university students revealed that 74% of participants were willing to receive the vaccine (Boehner, Howe, Bernstein, & Rosenthal, 2003). There were no differences in acceptance rates based on gender or motivation for vaccination (i.e., as an STI vaccine versus a reproductive health vaccine). Overall, this study suggests that HPV vaccination is generally viewed as positive by young men and women.

One important public health aspect of HPV for collegiate students is the availability of the vaccinations within their health centers. A study conducted in 2001 by Koumans and colleagues (2005) at the CDC assessed 910 colleges and universities nationally. Findings indicated that 60% of colleges and universities host a student health center/health services. Butler (2009) assessed the availability of the vaccine within 358 colleges and universities with student health centers nationally. Results indicated that 72.3% currently offer at least one form of the vaccine to their student population. Demographic characteristics (size of college/university, geographic region, as well as non-faith-based affiliation) were all significant factors in predicting vaccine availability. In addition, health center institutional complexity and formalization were also significant predictors.

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### **Age of Vaccination**

The 2009 Youth Risk Behavior Survey reported that 65.0% of 12th grade females had sexual intercourse; 52.5% of 11th grade; 39.6% of 10th grade; and 29.3% of 9th grade (CDC, 2010b). The median prevalence of having ever had sexual intercourse was 48.2% across state surveys (data ranged from 39.0% to 61.0%). More surprisingly, 5.9% of students nationwide reported having had sexual intercourse before the age of 13 and 8.8% of sexually active 9th graders reported having had 4 or more lifetime sex partners. Based upon these statistics, it is clear that HPV educational programs need to target younger populations and their parents in order to increase vaccination in adolescents before initial sexual activity which would greatly decrease their overall risk of cervical cancer (Blumenthal et al., 2008).

Promotion of early vaccination is also important because data shows that the efficacy and potential benefit of the vaccines is not as clear for women older than 19 years as it is for adolescents under the age of 19 (Saslow et al., 2007). However, females over the age of 19 who have not yet engaged in sexual intercourse would still greatly benefit from the vaccine, and women aged 19 to 26 could still benefit if they have not been exposed to all HPV vaccine types. The American Cancer Society (ACS) guidelines suggest that the three primary factors to consider when recommending age to vaccinate are duration of protection, age for optimal efficacy, and feasible plans for distribution (Saslow et al., 2007). Since the vaccines are relatively new, duration studies are limited and only include data from 3.5 to 5 years. The lower age limit for efficacy studies is 16 years of age for Gardasil® and 15 years of age for Cervarix®.

### **Differences between Specific Populations and Geographic Regions**

Another barrier to global vaccination utilization rates is that vaccine acceptance rates appear to differ among specific populations. One study revealed that Latina immigrants unanimously agreed upon acceptance while African Americans were more skeptical and cited concerns about effectiveness, side effects, and potential for an increase in sexual activity (Scarinci, Garc'es-Palacio, & Partridge, 2007). A study in Mexico examined the effect of HPV education on vaccine acceptance (Lazcano-Ponce et al., 2001). After participants were educated about the preventative factors of the vaccine regarding cervical cancer, 84% of the women stated they would allow their teenage daughter to be vaccinated. The effect of brief educational efforts is demonstrated in another study which found that acceptance of the vaccine among parents of 10 to 15-year-old children rose from 55% to 75% after they read an information sheet about HPV and vaccination; parents in opposition to the vaccine cited sexual

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disinhibition as a barrier (Davis, Dickman, Ferris, & Dias, 2004).

A separate review of studies of HPV beliefs in the United States found that only 6 - 12% of parents were concerned that vaccination would lead to increased sexual activity (Brewer & Fazekas, 2007). Furthermore, a study of parental acceptance in California found that 75% of parents would be likely to vaccinate a daughter before the age of 13 (Constantine & Jerman, 2007). In comparing non-Hispanic parents to other populations, Hispanic parents were more likely to accept vaccination, whereas African American and Asian-American parents were less likely. An investigation in England conducted by Marlow, Waller, and Wardle (2007) revealed that 75% of mothers with children in primary and secondary school settings were acceptant of vaccination. In addition, mothers were found to be more acceptant of the vaccine if they were categorized into the following traits (a) experienced cancer in their family, (b) had older daughters, (c) had perceived approval from their spouse/significant other, and (d) viewed vaccine acceptance as normative.

### **Health System Disparities**

Other concerns are that current social and economic disparities within the health care system have led to poor and minority populations being disproportionately affected by cervical and other HPV-related cancers (Zimet, 2009). In 2003, researchers from the International Agency for Research on Cancer conducted a meta-analysis of 57 studies which assessed the relationship between social inequality and cervical cancer risk (Parikh, Brennan, & Boffetta, 2003). Results of the investigation revealed:

An increased risk of approximately 100 percent between high and low social class categories for the development of invasive cervical cancer.

This increased risk was apparent in all geographic regions, although it was stronger in Africa, Asia and Latin America and the Caribbean than in Europe (Parikh, Brennan, & Boffetta, 2003, p. 687).

One of the most significant health disparities associated with cervical cancer is the lack of screening. Cervical screening is a highly effective prevention strategy that enables women to detect precancerous cervical abnormalities early on (Erdman, 2009). According to Erdman (2009), "social health disparities are unjust ... because they result from government action that adversely affects the health risks and outcomes of groups already disadvantaged by virtue of their underlying social position" (p. 370 ). Governments all over the world are failing to implement health measures for underserved populations, thus creating health disparities and placing already disadvantaged populations at increased risk (Erdman, 2009). General Comment No. 14 from the United Nations Committee on Economic, Cultural, and Social Rights (CECSR)

explicitly states:

Inappropriate health resource allocation can lead to discrimination that may not be overt. For example, investments should not disproportionately favour expensive curative health services which are often accessible only to a small, privileged fraction of the population, rather than primary and preventive health care benefiting a far larger part of the population (2000).

Increasing the availability of cancer screening programs for disadvantaged populations should be a high priority if the ultimate goal is to prevent worldwide HPV prevalence.

### **Male Vaccination**

Other policies and health measures that would facilitate an overall HPV prevalence decrease are those directed specifically at males. If only women are vaccinated, statistics indicate that 75% of HPV cases caused by the four strains that the vaccine prevents would be prevented, whereas more than 90% of cases would be prevented if both males and females are vaccinated (Cook, 2008). These statistics suggest that vaccinating males would be a very effective preventative method in terms of decreasing HPV prevalence, but some researchers are concerned with the cost-effectiveness of male vaccination programs. Furthermore, until more research is conducted that links HPV to cancer in men, acceptance and advocacy of male vaccination is unlikely.

Recent research conducted by Worden and colleagues (2008) shows a possible link between HPV and cancer of the tongue and tonsils in men. In their study, biopsies from 27 out of 42 (64.3%) oral cancer male and female patients tested positive for HPV16. Positive HPV16 results were associated with younger age (median, 55 v 63 years;  $p = .016$ ), nonsmoking status ( $p = .037$ ), and, most importantly, sex (22 of 30 males [73.3%] versus 5 of 12 females [41.7%];  $p = .08$ ). These results suggest that men with HPV infections have an increased risk for oral cancer. The team suggests that vaccinating both male and female adolescents should be considered because of the high risk of HPV associated cancers in men. Current estimates from the ACS report that HPV DNA is present in about one-third of oropharyngeal cancer cases and about one-half of tonsil cancer cases (ACS, 2010). Considering that men accounted for more than two-thirds (20,100) of the estimated 28,500 Americans who contracted oral cancer in 2009, HPV vaccines for males could prove to be a very effective preventative method (ACS, 2010).

Other researchers are focusing on the effectiveness of HPV vaccination regarding the prevention of anal cancer in men (Lindsey, DeCristofaro, & James, 2009). The HPV quadrivalent vaccine Gardasil® may also prove to be effective

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for preventing anal cancer because the same four strains (types 6, 11, 16, and 18) that are the most common precursors to the development of cervical cancer are also responsible for causing 80% of anal cancers (Lindsey et al., 2009). Therefore, anal cancer could become a vaccine-preventable disease if the HPV vaccine is effective for men (Lindsey et al., 2009). In a recent study of more than 4,000 males ages 16-26, sponsored by Merck & Co., Gardasil® was found to be 90.4% efficacious against HPV 6, 11, 16, and 18-related external genital lesions (EGL; Merck & Co, Inc., 2009). Proponents of male vaccination argue that it will also provide herd immunity which will ultimately significantly reduce the risk of cervical cancer in unvaccinated women (Nath & Thappa, 2009). Future research is needed to assess the causal role of HPV in various cancers as well as the potential beneficial outcomes associated with large-scale vaccination efforts in both male and female populations.

### **Efficacy**

Efficacy analyses of the quadrivalent vaccine found that it was 98.2% (CI = 93.5% - 99.8%) effective in protecting against HPV 16- or 18-related CIN 2/3 or AIS and 96.0% (CI = 92.3% - 98.2%) effective in protecting against any CIN attributed to HPV 6, 11, 16 or 18 (FDA, 2010). Vaccine efficacy against HPV 6- and 11-related external genital warts was 99.0% (CI = 96.2% - 99.9%) and 100% (CI = 55.5 - 100.0) against HPV 16- or 18-related VIN 2/3.

The bivalent vaccine Cervarix® has also been proven to be highly effective (Harper et al., 2006). After investigators conducted a combined analysis, the results revealed that vaccine efficacy was 100% (95% CI, 42.4% -100%) in preventing HPV16 or HPV18-related CIN in a study of women aged 15 to 25 years who received the recommended 3-dose vaccination regimen and participated in a 4.5 year (44 to 53 months) follow-up. In addition, other studies have found the bivalent HPV types 16, 18 vaccine to be more than 90% efficacious against incident infection, 100% efficacious against persistent infection and 90.4% to 100% efficacious against HPV types 16, 18-related CIN (Harper et al., 2004; Harper et al., 2006; Paavonen et al., 2007). Furthermore, research shows the vaccine has more than 98% seropositivity after 4.5 years and that cross-protection exists with the bivalent HPV types 16, 18 vaccine against incident infection with HPV types 45 and 31 (Harper et al., 2006).

### **Adverse Effects**

The future of HPV vaccination programs lies within current and developing research studies. While research supporting the effectiveness of the vaccines is the primary focus, reports on adverse effects of the vaccines

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will also play an important role in whether overall acceptance from the general population, as well as from healthcare providers, increases or decreases. In studies assessing the Cervarix® vaccine, vaccine recipients reported more overall adverse events (injection site and systemic) when compared to placebo recipients (92% versus 88% respectively; Villa et al., 2005). Investigators of school-based vaccination programs in New South Wales have recently estimated the rate of post-Gardasil® vaccine anaphylaxis to be 2.6/ 100,000 doses administered (95% CI 1.0 - 5.3 per 100,000; Brotherton et al., 2008). In comparison, one case of anaphylaxis was identified in a 2003 meningococcal C vaccination program (anaphylaxis rate of 0.1/100,000 doses administered; 95% CI 0.003 -- 0.7). Overall research results revealed that the estimated rate of anaphylaxis following HPV vaccination was significantly higher than the rate following comparable school-based vaccination programs.

Other research suggests that the immuno-stimulatory properties of the Gardasil® vaccine may influence the occurrence and severity of CNS demyelination in patients with known multiple sclerosis, however no direct conclusions have been made regarding recommendations for the immunization of these persons (Sutton, Lahoria, Tan, Clouston, & Barnett, 2009). Two post-vaccination cases of status epilepticus with myoclonus (repeated and prolonged seizures and loss of consciousness) in Spain have recently been reviewed by the Committee for Medicinal Products for Human Use (CHMP) and have been determined to be unlikely associated with the Gardasil® vaccine (European Medicines Agency [EMA], 2009). The EMA has also issued a report concerning the unexpected deaths of two females in the European Union (EU), stating that both occurred post-Gardasil® vaccination, but the causes of death could not be identified (EMA, 2008).

As of December 31, 2008, more than 23 million quadrivalent HPV doses had been distributed in the U.S. (Slade et al., 2009). Postlicensure data from the U.S. Vaccine Adverse Event Reporting System (VAERS) for the 2.5 years following Gardasil® licensure has recently been released and analyzed. At the time of release, VAERS had received 12,424 reports of adverse events following immunization (AEFI) yielding a report rate of 53.9/100,000 doses. Reports were submitted by the following: manufacturer (68%), providers (17%), “others” (11%), patients or parents (4%), and state health clinics (1%). Due to insufficient information, 7,561 (89%) of the manufacturer reports could not be further reviewed. Gardasil® was the only vaccine identified in 80% of reports (9,910 of 12,424). Females accounted for 97% (12,039 of 12,424) of reports, and of the 47 reports on male vaccine recipients, 53% (25 of 47) were classified as unintentional and 36% (17 of 47) as off-label use. The majority (61%) of the 9,396 reports (77%) listing dose information occurred after the first dose with 25% reported after the second dose, 13% after the third dose, and 1% reported

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after inadvertently receiving 4 or more doses. There was an average of 3.7 codes per report (range, 2--10; 46,932 codes for 12,424 reports) with the most frequently reported AEFIs including syncope (n = 1,847, 15%), dizziness (n = 1,763, 14%), nausea (n = 1,170, 9%), headache (n = 957, 8%), and injection site reactions (n = 926, 7.5%).

Of the 32 total reports of death, 20 (62.5%) had information available to permit further evaluation. Seventy percent of cases (14 reports) were after quadrivalent HPV alone, and the mean age was 18 years (median, 17 years; range, 12-26 years); no clustering of age was determined. Causes of death were generally classified as the following: unexplained (4), diabetic ketoacidosis (2), prescription drug abuse (1), juvenile amyotrophic lateral sclerosis (1), meningoencephalitis (1), influenza B viral sepsis (1), pulmonary embolism (3), cardiac-related deaths (6), and idiopathic seizure disorder (2).

Although data suggests no major complications during pregnancy, the vaccines are not currently approved for pregnant women (Dawar, Dobson & Deeks, 2007). Data from 1,901 women who became pregnant during the Gardasil® trials indicates similar results of pregnancy related adverse effects among vaccine and placebo recipients (4.2% and 4.3%, respectively; Merck Frost Canada, Ltd., 2006). Persons concerned with the safety of the vaccine can be reassured by the CDC who continues to monitor vaccine-related side effects and currently maintains that the vaccination is safe and effective for the recommended populations (CDC, 2010c).

### Future Directions

With the help of recent funding from the Bill & Melinda Gates Foundation along with the National Institutes of Health (NIH), Richard Schlegel, a primary researcher behind the development of Cervarix®, and his team now have \$3.5 million to use towards the creation of a new vaccine that will be both preventative and therapeutic (Bloom, 2005). The team also plans to combat transportation issues with the current vaccine formula (which must be kept frozen) by developing a powder formula which can be easily transported to developing countries and reconstituted with water. Researchers estimate that the development of a more inclusive prophylactic vaccine could potentially lead to a 70% or more reduction of cervical cancer risk (Saslow et al., 2007). According to Saslow and colleagues (2007):

Ultimately, cervical cancer rates will depend on (1) the degree of vaccination coverage of the at-risk population; (2) the number of carcinogenic HPV types targeted by the prophylactic vaccine; (3) the durability of protection; and (4) whether the medical community and

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the public continue to follow recommended screening guidelines (p. 18).

The possibility of continued protection from a HPV vaccine booster shot is being researched, but the reduction of HPV incidence will depend upon the percent of the population receiving the booster shot as well as the efficacy of the booster (Saslow et al., 2007).

An assessment of the cost-effectiveness of Gardasil® by Kulasingam and colleagues (2008) estimated that the vaccination of 100,000 girls would result in a reduction of 400 cases of cervical cancer, 6,700 cases of cervical intraepithelial neoplasia, and 4,750 cases of genital warts, suggesting that the addition of HPV vaccine programs to current screening measures could prove to be a cost-effective way to aid in the reduction of cervical cancer rates. In addition, investigators at Stanford University estimated that if the Gardasil® vaccine were implemented nationally in the U.S. to all 12 year old girls, 1,340 cancer-related deaths could be prevented over the target population's lifetime (Sanders & Taira, 2003). Researchers assessed factors such as lowered estimates of vaccine efficacy (40%) and potentially required reoccurring booster shots and concluded that the vaccine would be cost-effective even under these circumstances.

According to Insinga, Glass, and Rush (2004), annual costs in 1998 for cervical HPV-related disease in the U.S. are estimated to total about \$3.4 billion including the following expenditures (a) \$2.1 billion for routine screening (b) \$300 million for false positives (c) \$600 million for treatment of cervical pre-cancerous conditions and (d) and \$350 million for treatment of invasive cancer. Estimates indicated that this value had grown to \$5 billion by 2005 (Insinga, 2006). In addition, HPV-related health care costs were greater for HPV than other sexually transmitted infections including Hepatitis B, genital herpes, and Chlamydia (Insinga et al., 2004). A recent assessment by the ACS indicated that about 30 women/day were diagnosed with cervical cancer in the United States in 2008 and the cost of cervical cancer screening and treatment is estimated to be as high as \$6 billion/year in the U.S. (Saslow et al., 2007).

### **Conclusion**

A systematic review of the available literature reveals that HPV and the accompanying vaccinations have significant public health implications in the U.S. and abroad. Additional research is needed to assess the epidemiological impact of large-scale vaccine implementation including the prevention of HPV-related illnesses as well as the potential negative effects associated with vaccination. As findings of ongoing empirical assessments become available,

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additional HPV-related health policies will be needed to ensure that the best evidence-based public health practices are enacted.

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