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REVIEW ARTICLE

# Quadrivalent human papillomavirus (HPV) vaccine: a review of safety, efficacy, and pharmacoeconomics

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## SUMMARY

***What is known and background:*** **The introduction of vaccines has lead to a significant reduction in morbidity and mortality from diseases such as measles, rubella and poliomyelitis, as well as the eradication of smallpox (Ertl HC, Xiang Z (1996) *The Journal of Immunology*, 156, 3579–3582). A recent vaccine approved by the Food and Drug Administration (FDA) is the recombinant quadrivalent human papillomavirus (HPV) vaccine (Merck, Gardasil®). Concerns raised with this preventive measure include safety and efficacy issues as well as the financial implications. Furthermore, the use of the vaccine in women outside the currently approved age ranges and in adolescent boys and men has also been a source of debate.**

***Objective:*** **A review of two licensed HPV vaccines (Gardasil, Merck and Cervarix, GalxoSmithKline) in the light of these issues.**

***Methods:*** **Literature searches were conducted using the MEDLINE (1966 – December 2008) and PubMed databases in addition to the Centers for Disease Control and Prevention website. Bibliographies of selected references were also evaluated for relevant articles. Published guidelines and press releases were utilized as were the manufacturer's package inserts. The collection of information for this review was limited to the most recently available human data.**

***Results and discussion:*** **The HPV quadrivalent vaccine has been effective in the management of HPV by preventing vaccine subtype-related persistent infection and precancerous lesions as evidenced by numerous clinical trials. It is also regarded as a generally safe and well-tolerated vaccine, based on an assessment of reported adverse events submitted through governmental databases and analyzed by independent researchers. The majority of adverse events were non-serious and the vaccine has not been conclusively implicated with serious events. The FDA continues to focus on routine post-marketing surveillance monitoring of reported adverse events. The bivalent vaccine has also been shown to be effective in reported trials. Its adverse effect profile also appears acceptable.**

***What is new and conclusion:*** **The HPV vaccines appear safe and effective. Additional clinical research on the vaccines on women outside the currently approved age ranges and in males is necessary. Studies on longer-term outcomes, including cervical cancer and the emergence of new viral genotypes are also necessary.**

*Keywords*: **adverse events, and pharmacoeconomics, Centers for Disease Control and Prevention, human papillomavirus virus, safety, vaccine**

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## INTRODUCTION

The human papillomavirus (HPV) is a sexually transmitted infection affecting nearly 20 million Americans with an estimated 50% of cases occurring in adolescent females aged 15–34 years (1–3). Causing significant morbidity and mortality if left untreated, certain HPV subtypes may be

oncogenic, resulting in cervical cancer and, although less common, various anogenital cancers. Each year nearly 12 000 women are diagnosed with cervical cancer, with approximately 4000 deaths caused by this disease according to the 2005 cancer data (4). In 2006, the Food and Drug Administration (FDA) approved the quadrivalent recombinant HPV vaccine, Gardasil® (Merck & Co., Whitehouse Station, NJ, USA), which targets subtypes 16 and 18, accounting for nearly 70% of all cervical cancer cases, and types 6 and 11, which are responsible for nearly 90% of anogenital warts (5, 6). The National Cancer Institute states that complete vaccination may reduce the mortality rate of cervical cancer by as much as two-thirds (7). However, a vaccine with limited valency may affect overall efficacy, resulting in a potential increase in disease and morbidity caused by the omission of commonly implicated HPV serotypes. Preferential inclusion of the most prominent subtypes in vaccine coverage should remain a therapeutic strategy, as HPV subtype distribution varies with geographic location. In addition, other prevalent subtypes should be considered to maximize coverage and minimize potential disease progression. Due to global differences in HPV subtype distributions epidemiological studies should continue since particular subtypes may not remain permanently silent, but may be a factor in the development of various carcinomas. Limited vaccine valency may possibly permit less common subtypes to proliferate, potentially allowing persistence of infection and progression of precancerous lesions (8).

Although the quadrivalent HPV vaccine has been incorporated into the Routine Pediatric and Adolescent Immunization Schedule, its use continues to be associated with controversies. Concerns over the safety of the vaccine have risen in response to published reports of adverse events including Guillain-Barré Syndrome (GBS), blood clots and death. The use of the vaccine in non-approved patient populations, and its true cost-effectiveness, have also been causes of public concern (9). To date, the quadrivalent vaccine has been approved for use in 112 countries worldwide, including the United Kingdom and 41 other European countries; however, approval for use in Japan has not yet been granted (10).

## SAFETY DATA

Prior to approval, the quadrivalent HPV vaccine was studied extensively in a number of clinical trials that included over 21 000 young girls and adolescent women between the ages of 9 and 26 years (11). During these trials, fever, nausea, dizziness, injection-site pain, swelling, erythema, pruritis and bruising were noted as the most commonly reported adverse events (12). The Centers for Disease Control and Prevention (CDC) and FDA continue to monitor the safety of the vaccine via three mechanisms: the Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD) Project and the Clinical Immunization Safety Assessment (CISA) network. The VAERS system reports healthcare professional and patient-reported claims of potential side effects following vaccine administration. This information is then utilized by the VSD project, a network link between the CDC and eight healthcare organizations, to assist with identifying possible patterns in VAERS reports and evaluate immunization safety. The CISA Network, a project between six academic research centers in the United States, conducts independent research on vaccine-associated health risks (11).

Through 31 December, 2008, more than 23 million doses of the quadrivalent HPV vaccine were distributed in the United States with 11 916 VAERS documented reports of adverse events following vaccination. Overall, 94% of the documented adverse events were considered 'non-serious', whereas the remaining 6%, which encompassed those that lead to hospitalization, permanent disability, life-threatening illness and death, were deemed 'serious.' Events such as fainting, syncope, pain and swelling at the injection site, headache, nausea and fever were identified as non-serious adverse events, wheras events such as GBS, blood clots, allergic shock, nervous system damage and death were identified as serious. GBS typically occurs in 1–2 out of every 100 000 people during their teenage years and can be caused by a number of factors including infections. As of April 2008, there have been 31 GBS reports through the VAERS system post-quadrivalent HPV vaccine administration; however, only 10 cases have been confirmed. These reported GBS cases correlate with an incidence rate that does not exceed what would typically be expected in the general population of young

adolescent females, independent of vaccination. Reports of blood clots in the heart, lungs and legs are rare, and the majority of incidents reported occurred in individuals at an increased risk of blood clots, such as those taking oral contraceptives. Although 23 deaths have been reported among females who received the vaccine, death certificate evaluations have not provided common patterns that readily implicate the vaccine as the causative agent (11).

Safety information pertaining to the quadrivalent HPV vaccine was presented at the October 2008 Advisory Committee on Immunization Practices (ACIP) meeting. The CDC concluded, after an evaluation of VAERS data, that the submitted information did not find a link between the vaccine and serious adverse events claims. Information reported to the VSD project was also unable to definitively correlate the vaccine with blood clots, allergic reactions, stroke, seizure and/or GBS reported events. In addition, the CISA reported no link implicating the vaccine with central or peripheral nervous system disorders, including transverse myelitis and GBS, respectively. A Merck-sponsored registry of women inadvertently administered the HPV vaccine during pregnancy did not recognize any links with birth defects, miscarriages or infant/fetal deaths; and although identified as a pregnancy category B, HPV vaccine administration is not recommended during pregnancy and should be deferred until post-partum (12, 13).

All events reported as 'serious' and attributed to the HPV vaccine have been analyzed by medical professionals; however, no common medical patterns have been identified to associate the vaccine as the underlying cause. After analyzing all available data, the quadrivalent HPV vaccine is still CDC and FDA recommended for routine administration; however, vigilant safety monitoring continues through independent and government-sponsored databases and research.

Currently, the quadrivalent HPV vaccine is a three-dose, intramuscular vaccine administered on a 0-, 2- and 6-month schedule. It is approved by the FDA for the prevention of cervical, vulvar and vaginal cancers caused by HPV types 16 and 18, genital warts caused by HPV types 6 and 11, and precancerous or dysplastic lesions caused by HPV types 6, 11, 16 and 18 in girls and young women ages 9 through 26 years as well as for the prevention of genital warts caused by HPV types 6 and 11 in boys and men ages 9 through 26 years (12). In addition, the manufacturer Merck & Co has submitted information to the FDA seeking to extend the indication to women 27 through 45 years of age. In January of 2009, the FDA issued a complete response letter, it's second, concerning this extended indication. The response letter requested additional information from a 48-month trial that is currently ongoing. A response from the manufacturer is anticipated in late 2009 (14).

In December 2008 Merck & Co, also submitted information to the FDA seeking approval for use in boys/young men ages 9–26 years to prevent genital warts and other lesions (15, 16). It is believed that in addition to providing active protection to young males, protection would be extended to females via herd immunity. This concept may be beneficial in situations of low female vaccination rates (17–19). While trials have demonstrated a positive immunologic response after quadrivalent HPV vaccine administration in sexually active 11- to 15-year-old boys, conclusive efficacy trials are limited. In late 2008, an interim analysis of an ongoing efficacy trial consisting of nearly 3400 heterosexual males aged 16–23 years, and approximately 600 men who have sex with men ages 16–26 years was presented. The interim report (mean duration = 29 months) demonstrated that the quadrivalent HPV vaccine was 90·4% effective in reducing external genital lesions ($P < 0{\cdot}001$) and 89·4% effective in preventing genital warts ($P$ value not reported). More injection-site events were reported among patients in the vaccine group compared with those in the placebo group, and there were no reports of serious adverse events. This trial is ongoing, initially designed as a 36-month follow-up study. Any additional results will be submitted to the FDA once available (15).

Although efficacy trials are underway in males, there is currently limited long-term efficacy data available. The European Commission, Mexico and Australia have licensed the quadrivalent vaccine for men; and in October 2009 the FDA expanded the labelling indications of the quadrivalent HPV vaccine to include the prevention of HPV types 6 and 11-related genital warts in males aged 9–26 years (12).

## CLINICAL TRIALS DATA

The Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE I) study was

a phase III, randomized, double-blind, placebo-controlled, international trial that assessed the incidence of genital warts, vulvar or cervical intraepithelial neoplasia (CIN) or cancer, and the incidence of CIN, adenocarcinoma *in situ* (AIS) or cancer associated with HPV type 6, 11, 16 or 18. A total of 5455 women aged 16–24 years with no history of genital warts or abnormal cervical cytology screenings and ≤4 lifetime sexual partners were assigned to active vaccine ($n$ = 2723) or placebo ($n$ = 2732) and were monitored for up to an average of 3 years after vaccination. Vaginal, vulvar, perineal and perianal intraepithelial lesions or warts were prevented via the HPV vaccine, showing 100% effectiveness against the four HPV subtypes, compared with 60 placebo-related cases (95% CI, 94–100). Analyses conducted on the per-protocol, susceptible population showed that the vaccine was also 100% effective ($n$ = 2241) in preventing CIN (grades 1–3) or AIS compared with the 65 cases ($n$ = 2258) in the placebo group (95% CI, 94–100). Analyses conducted on the unrestricted susceptible population (USP) [negative polymerase chain reaction (PCR) and serologic testing at enrollment] yielded a 95% vaccine efficacy rate for any grade external anogenital or vaginal lesions (four vaccine-treated cases vs. 81 placebo-treated cases), 98% efficacy for all grades of cervical lesions (two vaccine-treated cases vs. 89 placebo-treated cases), 91% efficacy for high grade vulvar or vaginal lesions (one vaccine-treated case vs. 11 placebo-treated cases) and 100% efficacy for AIS (zero vaccine-treated cases vs. 6 placebo-treated cases) (20).

The intention-to-treat (ITT) population analysis, regardless of baseline HPV status, yielded a combined vaccine efficacy rate of 73% (95% CI, 58–83) for all stages of external anogenital or vaginal lesions, and a combined efficacy of 55% (95% CI, 40–66) for all stages of cervical lesions. Overall, no cancer related to the vaccine-related HPV types was observed. A second ITT analysis was performed to evaluate the vaccine efficacy against all anogenital disease, including the HPV subtypes not covered by the vaccine. There were 104 vaccine-treated cases with anogenital lesions compared with 157 placebo-treated cases, corresponding to a 34% reduction (95% CI, 15–49) and an observed incidence of 344 vaccine-treated cases of vaginal lesions vs. 421 placebo-treated cases, correlating with a reduction of 20% (95% CI, 8–31). Seroconversion was observed in 99·5% of subjects 1 month after the third vaccination. The vaccine population had more administration-related adverse events, with the most common event being pain at the injection site (risk difference of 10 percentage points; 95% CI, 7·8–12·1). Also, more common among the vaccine-treated subjects were erythema, pruritis and swelling at the injection site, while serious adverse events were similar among both treatment groups (20).

The landmark FUTURE II trial consisted of 12 167 women aged 15–26 years from 13 countries, with otherwise normal Papanicolaou (Pap) tests. The HPV vaccine prevented 98% of HPV (16/18)-related high-grade cervical lesions in the 10 565 women (87%) in the per-protocol susceptible population ($P < 0{\cdot}001$). One vaccine-treated patient and 42 placebo-treated patients in the per-protocol susceptible population had a subsequent diagnosis of cervical AIS associated with HPV-16, 18 or both. Patients in the unrestricted population ($n$ = 11 508), consisting of those with a negative PCR and serological assays to the relevant HPV types at enrollment, had a reported treatment efficacy of approximately 95%. CIN (grade 2 or 3) or AIS was found in three vaccine-treated patients and 62 placebo-treated patients. The ITT analysis of all randomized women ($n$ = 12 167), regardless of baseline HPV status or cervical neoplasia, yielded a vaccine efficacy of 44%, with high-grade cervical disease related to HPV-16 or 18 occurring in 83 vaccine patients and 148 placebo patients (21).

An analysis of six phase II and III studies involving 12 343 patients categorized as virginal 9- to 15-year-old girls and boys, and sexually active women aged 9–26 years was conducted by Giuliano *et al*. The analysis combined the immunogenicity databases of the six studies to determine if an effect existed between subjects' baseline characteristics and vaccine-induced immune response. Overall, 96% of patients completed the three-dose series. At month 7, the geometric mean titers (GMTs) decreased as the age at first vaccination increased for each of the four HPV types. The anticipated decreases in month 7 antibodies to HPV-6, 11, 16 and 18 natural log titers associated with increases in subject age at enrollment were 0·024, 0·023, 0·045 and 0·043, respectively; corresponding to reductions in the 7-month antibodies to the subtype's GMTs by 2·4%, 2·3%, 4·6% and

4·4% respectively. While no baseline factor served as a predictive feature of changes in month 7 GMTs across all HPV types, the various HPV types were influenced by different baseline characteristics such as race/ethnicity, geographical region, body mass index, hormonal contraceptive use and lactation status. Prophylactic vaccine administration to subjects aged 16–26 years was 100% effective in preventing HPV-16 and HPV-18 associated CIN (grade 2 or 3) or AIS (22).

Another clinical trial evaluated 1781 sexually naïve males and females aged 9–15 years to assess the tolerability and immunogenicity through 18 months after enrollment, along with immune response among preadolescent and adolescent males and females via anti-HPV GMTs and seroconversion rates at month 7. Immunogenicity comparisons between males and females were compared via a non-inferiority analysis for each HPV type (6, 11, 16, 18) in the per-protocol populations, including 948, 949, 944 and 952 patients respectively. For each HPV type, ≥99·5% of patients had seroconverted at month 7, regardless of gender, with males having higher observed GMTs for all vaccine types. The fold-difference (males divided by females) in GMT parameters for the four types were 1·3 (95% CI, −1·0–1·0; $P < 0·001$), 1·1 (95% CI, 0·9–1·4; $P < 0·001$), 1·4 (95% CI, 1·1–1·8; $P < 0·001$) and 1·5 (95% CI, 1·2–1·9; $P < 0·001$) respectively. This analysis illustrated that the anti-HPV GMTs in males were non-inferior to females over the study period. The persistence of immunogenicity at month 18 (time interval: 1-year post-third vaccine) demonstrated that ≥91·5% of all per-protocol patients remained seropositive; however, the GMT levels were approximately four to seven times lower than the values at month 7. Whereas the GMT response at month 7 remained higher among males compared with females, the GMT parameter among males at month 18 all remained higher compared with females, except for the anti-HPV 11-type GMT response. Injection site adverse events were more common among those receiving the vaccine (75·3%) compared with those receiving placebo (50·0%) with a significantly higher proportion of vaccine patients reporting erythema, pain and swelling on days 1–5 among all vaccinations compared with placebo (20·3% vs. 13·2%, 73·2% vs. 45·4% and 20·7 vs. 7·7%, respectively; $P < 0·001$ for all comparisons). All serious adverse events ($n = 5$) were reported by vaccine patients; however, none were determined to be vaccine related (23).

Barr *et al*. used data obtained from five, phases II and III clinical trials and extracted data specific to North American women ($n = 5996$). The data were analyzed with respect to baseline characteristics and vaccine efficacy to determine the clinical impact of the vaccine among women with ongoing or previous HPV infection. Among the USP, there were no vaccine-related occurrences of CIN 2/3 or AIS due to HPV-16 or 18 compared with 35 cases among the 2116 placebo patients. Prophylactic efficacy analyses were conducted on an USP and ITT analyses were conducted on all North American subjects receiving at least 1 dose and having at least 1 post-enrollment visit (data from four trials). The USP group (seronegative and PCR-negative at day 1) did not have any HPV-16 or 18-related CIN 2/3 or AIS cases ($n = 2100$) compared with the placebo group which had 35 observed cases ($n = 2116$), yielding a 100% reduction (95% CI, 89·0–100·0). There were also no observed CIN (any grade) or AIS cases in the vaccine group ($n = 2111$) related to the four HPV types compared with 69 cases in the placebo group ($n = 2127$ population), yielding a 100% reduction (95% CI, 94·6–100·0). USP data analysis from three trial protocols resulted in two vaccine cases of genital lesions related to the four HPV types in 1329 susceptible patients and 36 placebo cases in the 1327 susceptible patients, resulting in a 94·5% reduction (95% CI, 78·7–99·4). The ITT population had 19 observed cases of HPV-16 or 18-related CIN 2/3 or AIS ($n = 2313$ population) compared with 57 cases in the placebo group ($n = 2356$), resulting in a 66·4% reduction (95% CI, 42·7–81·1); whereas there were 30 cases of CIN (any grade) or AIS in the treatment group ($n = 2313$) and 108 cases in the placebo group ($n = 2356$), resulting in a reduction of 72·1% (95% CI, 57·9–82·0). Endpoint data from three protocols resulted in 20 observed cases of genital lesions in the treatment group ($n = 1348$) and 47 cases in the placebo group ($n = 1350$), correlating with a 57·7% reduction (95% CI, 27·3–76·3) (24).

The ITT population's overall reduction in endpoints (regardless of causal HPV type) for CIN 2/3 or AIS, CIN (any grade) or AIS, or genital lesions was 33·0% (95% CI, 8·9–51·0), 17·4%, (95% CI, 1·4–30·9) and 34·2 (95% CI, <0·0–57·7) respectively. The vaccine demonstrated a clinical benefit which

appeared to be similar across all age ranges and sexual behaviour patterns. It was noted, however, that the benefit of the vaccine was lowest among abnormal Pap screening results, as many of the women already had HPV disease present at vaccine initiation, and the vaccine does not alter the course of infection or pre-existing disease (24).

## PHARMACOECONOMIC CONSIDERATIONS

Routine administration of vaccines in many situations is a cost-effective strategy to minimize preventable diseases and decrease disease complications. The administration of the quadrivalent HPV vaccine is recommended at the preadolescent visit of young girls and as a catch up vaccine for girls/young women ages 13–26 years not previously vaccinated against HPV (25). The inclusion of this vaccine as a component of the Recommended Pediatric and Adolescent Immunization Schedule makes it mandatory for certain individuals to receive it. All immigrants entering the US have been required to have all CDC-recommended vaccines that are administered to existing citizens; however the HPV vaccine is no longer included as part of this mandate (26). These requirements have also raised concerns over the cost of the vaccine and its cost-effectiveness for inclusion in routine vaccination schedules.

Further contributing to the cost-effectiveness debate, Kim *et al.* used projection models to synthesize epidemiologic and demographic data to compare health and economic outcomes of females vaccinated with the quadrivalent HPV vaccine either at 12 years of age or in a catch-up program (to 18, 21 or 26 years of age). The study found a correlation between age at vaccination with quality-adjusted life year (QALY), concluding that as the age at vaccination increased so did the cost per QALY gained. The cost effectiveness ratio was $43 600/QALY for 12-year-old girls, $97 300/QALY for 18-year-old adolescents, $120 400/QALY for 21-year-old women and $152 700/QALY for 26-year-old women. The authors note that a number of assumptions were required to generate these results, notably duration of immunity (27). These data may be viewed as a potential reason for not including the HPV vaccine in the recommended schedule. In addition, these results may be a factor in FDA deliberations in broadening the indications of the vaccine to women beyond 26 years of age.

In a follow-up statement to Kim *et al.*, the CDC acknowledge their findings stating the results were aligned with their original recommendation that 11- to 12-year-old girls should receive the quadrivalent HPV vaccine. The statement also recognized that although not as cost-effective in the 13- to 26-year cohort, this patient population may experience vaccine benefits overall. The ACIP acknowledges the pharmacoeconomic analysis by Kim *et al.* as important information and has utilized it in their deliberations pertaining to the expanded indication to women >27 years; however, the ACIP is not considering adjustments to their current position concerning the vaccine administration in females 13–26 years of age (28).

## BIVALENT HPV VACCINE OVERVIEW

A bivalent HPV vaccine (Cervarix®; GlaxoSmithkline Biologicals, Rixensart, Belgium), administered intramuscularly as a three-dose series, targets subtypes 16 and 18, the two most commonly associated subtypes implicated in cervical cancer cases. The vaccine provides long-term protection against these subtypes by maintaining high and sustained levels of antibodies (29). To date, the bivalent vaccine is approved in 97 countries worldwide, including the 27 union states of the European Union; with licensing applications submitted in more than 20 additional countries including Japan (30). In October 2009, the FDA approved the use of Cervarix® for the prevention of cervical cancer, CIN and AIS due to HPV types 16 and 18 in females ages 10 through 25 years (31). In addition, in 2008 the United Kingdom's Department of Health selected the bivalent vaccine as the vaccine of choice for their national HPV immunization programme (32).

Overall, the bivalent vaccine has been reported to be effective and generally well tolerated. The most commonly reported adverse events include pain, redness and swelling at the injection site, fatigue, fever, headache, itching, rash and gastrointestinal events (29). The safety of the vaccine was analyzed in 11 trials consisting of approximately 30 000 women aged 10–72 years. Participants received either the bivalent vaccine or placebo with no differences observed in serious adverse events between the treatment groups during and post-vaccination (33).

The efficacy of the vaccine is believed to be proportional to the extent and duration of antibodies it stimulates. An extended follow-up study consisting of more than 700 women aged 15–25 years demonstrated that the bivalent vaccine maintained high levels of antibodies (11 times higher than with natural infection) against HPV types 16 and 18 for up to 6·4 years. The manufacturer states that the impact on antibodies is due in part to the vaccine adjuvant, AS04 (33). In addition to showing 100% efficacy in preventing pre-cancerous lesions secondary to HPV subtypes 16 and 18, it demonstrated 60% and 78% efficacy in preventing incident infections secondary to subtypes 31 and 45 respectively (34).

The bivalent vaccine was directly compared with the quadrivalent vaccine in a trial of women 18–45 years of age to evaluate the impact of therapy on neutralizing antibodies and memory B cells. The trial found that the bivalent vaccine resulted in neutralizing antibody levels >2 times and >6 times higher than the levels observed with the quadrivalent vaccine for HPV subtypes 16 and 18, respectively ($P < 0{\cdot}0001$). In addition, the bivalent vaccine resulted in nearly three times as many memory B cells for HPV subtypes 16 and 18 compared with the quadrivalent vaccine. Although these results show that the administration of the bivalent vaccine resulted in a significantly higher immune response compared with the quadrivalent vaccine, the true clinical significance of these results is not yet known (35).

The most recent information concerning the efficacy of the bivalent vaccine is from PApilloma TRIal against Cancer In young Adults (PATRICIA), a phase III, multi-center, double-blind, randomized study which included 18 644 women between the ages of 15 and 25. In the according-to-protocol cohort, the vaccine provided 92·9% protection against cervical pre-cancers (CIN 2+) associated with HPV subtypes 16 or 18 and 92·0% ($P < 0{\cdot}0001$), 51·9% ($P = 0{\cdot}0332$) and 100% ($P = 0{\cdot}0619$) protection against CIN 2+ associated with HPV subtypes 31, 33 and 45 respectively. In the total vaccinated cohort, the vaccine provided 68·4% ($P = 0{\cdot}0005$), 49·8% ($P = 0{\cdot}0239$) and 100% ($P = 0{\cdot}0312$) protection against CIN 2+ associated with HPV 31, 33 and 45 respectively. In addition, the reported rates of serious adverse events were similar among the treatment and control groups (30, 36). GlaxoSmithKline has subsequently submitted the data from PATRICIA to supplement what has already been presented as part of the original Biologics License Application to the FDA (37).

## CONCLUSION

Vaccines play a key role in disease prevention and in the stability and maintenance of public health. Vaccinations have resulted in a significant decline and eradication of some vaccine preventable diseases. The HPV vaccines (Gardasil® Cervarix®) have been shown to be effective in preventing pre-cancerous lesions and are regarded by health professionals as generally safe and well-tolerated. The majority of adverse events reported have been non-serious in nature and oftentimes self-limiting, potentially contributing to the notion that the benefits of vaccination outweigh the potential risks. Continued monitoring of adverse events with the quadrivalent vaccine, particularly serious events, is a focus of the FDA and the collected data will be routinely analyzed forthwith. Currently, there is ongoing research and analysis with the quadrivalent HPV vaccine that may potentially broaden the pool of individuals being advised to receive the preventive measure. Quadrivalent or bivalent vaccine selection for drug formulary coverage may be influenced by ongoing research and continued data analysis, especially in regards to long-term maintenance of antibody proliferation as well as adverse events. In addition, the benefits and potential limitations related to vaccine valency should be considered if one agent is to be granted preferential status. Furthermore, the overall pharmacoeconomic impact of a particular vaccine may differ based upon the characteristics of the patient population, necessitating evaluation in product selection. Research should continue in these and other areas in order to identify and improve vaccines that are able to reduce morbidity and mortality for diseases that remain a public health concern. Studies on longer-term outcomes, including cervical cancer and the emergence of new viral genotypes are also necessary.

## CONFLICT OF INTEREST STATEMENT

The authors, Thomas C. Pomfret PharmD, BCPS, James M. Gagnon Jr, PharmD, BCPS and Angela T.

Gilchrist PharmD, BCPS, do not have any conflicts of interest with respect to the agents discussed within this manuscript.

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