REVIEW

Impact of HPV vaccination on anogenital warts and respiratory papillomatosis

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ABSTRACT

Human papillomavirus (HPV), the most common sexually transmitted infection in the US and worldwide, can cause cancers, anogenital warts (AGW), and recurrent respiratory papillomatosis (RRP) in men, women, and children. Global incidence of AGW ranges from 160–289 cases per 100,000 person-years and peaks in young men and women in the third decade of life. RRP has an estimated incidence of 3 per 1 million person-years in children. Pre-licensure trial efficacy, modeling and time-trend ecological studies have shown a significant short-term impact of 4vHPV vaccine. In girls aged 15–19 years, a previously published meta-analysis indicated that genital warts decreased significantly by 31%; stratified analysis revealed more substantial reductions in populations with high ($\geq 50\%$) vs. low ($< 50\%$) vaccination coverage (61% vs. 14%). Longer-term monitoring will reveal whether this impact continues under 9vHPV programs, and whether current declines in AGW are mirrored by declines in RRP.

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Introduction

Genital human papillomavirus (HPV) is the most common sexually transmitted infection in the US and worldwide.¹ Although most infections are self-limited and/or asymptomatic, persistent HPV infection can cause cervical cancer in women, as well as anogenital and oropharyngeal cancer, condylomata or anogenital warts (AGW), and respiratory papillomatosis in men, women, and children. There are approximately 40 types of genital HPV which can be categorized by their epidemiologic association with cervical cancer.² High-risk types (e.g. types 16, 18, 31, 33, 45, 52, and 58) are carcinogenic; high-risk type infection has been linked to low- and high- grade epithelial cell abnormalities or precancers, as well as cancers.^{3,4} Low-risk types (e.g., types 6 and 11) can cause benign or low-grade cervical cell changes, AGW, and recurrent respiratory papillomatosis (RRP).⁵ This review focuses on the epidemiology of AGW and RRP and what is currently known about the impact of HPV vaccination on these two diseases.

Methods

We searched the PubMed English-language database for the 5 years prior to November 30, 2015 for studies regarding AGW and RRP epidemiology, and HPV vaccine impact on AGW and RRP including pre-vaccine licensure, modeling and post-vaccination population-level vaccine studies. The reference lists of studies identified within this time period in PubMed were manually reviewed to identify additional past references of interest for inclusion. Specific United States clinical guidelines for management and prevention of HPV (the 2015 Centers for Disease

Control (CDC) STD Treatment Guidelines, and current CDC Advisory Committee on Immunization Practices (ACIP) HPV vaccination guidelines) were also manually reviewed to identify key references pertaining to AGW and RRP epidemiology and HPV vaccine impact on AGW and RRP. The PubMed function “Cited by other PubMed Central articles” was utilized to identify additional references of interest, and titles and abstracts of those articles were reviewed for potential inclusion. Studies were included only if both authors agreed they were relevant for inclusion to this review after title and abstract review.

Global burden, natural history, and morbidity from disease

Anogenital warts

HPV types 6 and 11 account for almost 100% of AGW but 20–50% of lesions represent co-infections with low and high-risk HPV types.⁵ Global incidence and prevalence of AGW were estimated within a previously published systematic review of PubMed and EMBASE of all articles published from January 2001 through January 2012 plus manual review of bibliographies of selected references. Thirty-two studies met the inclusion criteria of original studies reporting AGW incidence, prevalence or self-reported history in the general adult (at least including ages 20 through 40 years) male, female or combined populations.⁶ Twelve studies were from Europe, 10 from North America (including Mexico), 4 from Asia, 3 from South America, 2 from Australia and 1 multiregional. Screening abstracts from relevant conferences yielded an additional 5 references: 3 from Europe and 1 each from Canada and Japan. Calculated global incidence

of AGW ranged from 160–289 cases per 100,000 person-years (median 194.5 per 100,000). Incidence peaked before 24 years of age in females and between 25 and 29 years of age among males. The reported incidence of recurrent AGW was as high as 110 per 100,000 among females and 163 per 100,000 among males. Overall prevalence of AGW based on retrospective administrative databases, medical chart reviews, or prospectively-collected physician reports ranged from 0.13% to 0.56%; prevalence ranged from 0.2% to 5.1% based on genital examinations.

Median time to wart development after incident infection with HPV 6 or 11 is 6–10 months (range up to 18 months) in men; women may have a shorter time to wart development (median time 2.9 months). Regression of warts is common even in the absence of treatment (e.g. 60% of women living with HIV/AIDS and 80% of HIV-negative women demonstrated regression in the first year after diagnosis).⁷ As mentioned above, AGW are often asymptomatic and may not be brought to medical attention (or removed) until they cause discomfort, pruritis or bleeding.⁸ The primary reason for treatment of AGW is symptom amelioration or cosmetic concerns (unless their appearance is suspicious for malignancy per clinician discretion), as many lesions if left untreated may self-resolve. Available therapies such as antimitotics (podofilox), immune enhancers (imiquimod), protein coagulants (trichloroacetic acid), surgical therapy and cryotherapy reduce but may not eradicate HPV infectivity. It is also unclear whether treatment reduces future HPV transmission.

Recurrent respiratory papillomatosis and vertically transmitted disease

Recurrent respiratory papillomatosis (RRP) is a condition of condylomatous lesions of the airway secondary to HPV infection and typically affects children or young adults. It is caused primarily by HPV 6 and 11 with less than 5% of cases caused by HPV 16 or other types.⁹ Disease occurring before the age of 14 years is classified as juvenile-onset (JORRP) while that occurring at older ages (probably via sexual contact) is classified as adult-onset. RRP has an estimated incidence of 3 per 1 million person-years in children, and a prevalence of 3 to 7 per 100,000 for both pediatric and adult disease.⁹

JORRP occurs secondary to vertical transmission from an HPV-infected mother to her neonate, and most cases manifest between the ages of 1 and 4 years.⁹ Offspring of women with genital warts are estimated to have over 200 times the risk of JORRP compared to those of women without genital warts. Specifically, 7 of 1000 neonates born to mothers with a history of genital warts developed disease, corresponding to a 231.4 (95% confidence interval 135.3, 395.9) times higher risk of disease relative to those neonates born to mothers without disease.¹⁰ Acquisition is via contact of the fetus with the mother's infected vaginal canal; caesarean delivery is not fully protective suggesting that infection can be perinatal as well.^{9,11} In adults, acquisition is typically via oral sex, although there are two case reports of healthcare workers who acquired laryngeal papillomas presumably through inhalation of aerosolized HPV 6/11 from laser ablation procedures.^{7,11} Factors including immunodeficiency or co-infection with herpesviruses impact development of RRP as well.¹¹

While RRP is rare, the morbidity can be significant.^{9,11} Patients typically present with hoarseness or stridor secondary to laryngeal papillomas, and disease may extend from the upper airway to the trachea and lungs. Papillomas are benign but can grow rapidly and may also undergo malignant transformation; they can cause airway obstruction, necessitating multiple surgical procedures. Young age at onset (<3 or 4 years) is associated with increased severity of disease as measured by number of required surgeries, presence and degree of airway obstruction, and/or severity of hoarseness. Nonsurgical therapies (interferon, cidofovir, celecoxib, photodynamic therapy and others) have not been shown to prevent the need for frequent surgical intervention. Disease course is highly variable and can either persist lifelong or have intermittent periods of remission.

Disease pathophysiology and mechanism of vaccine protection

HPV is highly infectious and is typically transmitted between persons via friction resulting in microabrasions during skin-to-skin contact, including sexual or birth canal contact. For example, approximately 60% of individuals exposed to anal warts in this way will develop clinical disease.^{12,13} Once epithelial infection occurs, viral replication occurs within the basal layer of epithelium for about three months. Infected basal cells then move gradually to the surface layer, eventually producing condylomata.¹⁴ Infection is exclusively intraepithelial; no viremia occurs and no antigen is presented in local lymph nodes. Recovery from infection and viral clearance is secondary to cell-mediated immunity and the recruitment and activation of cytotoxic effector cells.¹⁵

The mechanism of protection from HPV infection via vaccination is very different than the mechanism of recovery from HPV infection. All three currently licensed HPV vaccines—2vHPV, 4vHPV, and 9vHPV—are prophylactic, and following intramuscular administration, virus-neutralizing antibodies are generated to type-specific HPV L1 proteins.¹⁵ These serum antibodies are thought to transudate or exudate into relevant mucosal sites to block viral entry into mucosal basal squamous epithelial cells and thereby prevent new viral infections from the specific HPV L1 types found in vaccine.¹⁶ However, whether this hypothetical mechanism of action applies equally to all types of squamous epithelium (cervical, vaginal, vulvar, penile, urethral, and anal) is not known. All three vaccines contain high-risk HPV 16 and 18 virus-like particles (VLPs); 4vHPV also contains low-risk HPV 6 and 11 VLPs; 9vHPV contains additional high-risk HPV 31, 33, 45, 52, and 58 VLPs.^{3,4}

Studies looking at vaccine impact on incidence of anogenital warts

Pre-vaccine licensure trials

Two 4vHPV pre-vaccine licensure phase 3 trials examined vaccine efficacy against AGW. The FUTURE I/II Study was conducted in North America, Latin America, Europe, and the Asia Pacific region, and followed 16–26 year old women for 48 months following the start of a 3-dose vaccination series. Per-protocol susceptible population efficacy was based upon

comparison of the 2 cases of HPV6- and -11-related AGW that occurred in 6,718 vaccinated women compared to 186 cases that occurred in 6,647 controls, for a calculated vaccine efficacy of 98.9% (95% confidence interval (CI) 96.1–99.9%).¹⁷ The equivalent male study was conducted in 18 countries, and followed both heterosexual men aged 16–23 years and men-who-have-sex-with-men aged 16–26 years for an average of 2.9 years following the start of a 3-dose vaccination series. Per-protocol susceptible population efficacy was based upon comparison of the 3 cases of AGW that occurred in 1,397 vaccinated men compared to 28 cases that occurred in 1,408 controls, for a calculated vaccine efficacy of 89.4% (95% CI 65.5%–97.9%).¹⁸

The phase 2b-3 study of 9vHPV vaccine did not examine vaccine efficacy against AGW, as the study was designed to compare 9vHPV with 4vHPV vaccine effects, and the expectation was that the two vaccines would be similarly efficacious.¹⁹ Instead, the primary analysis of efficacy with respect to endpoints related to HPV 6 and 11 was designed to determine whether 9vHPV was non-inferior to 4vHPV with respect to immunogenicity at month 7 (1 month after dose 3 in the per-protocol population). According to geometric mean titers (GMT), anti-HPV-6 and anti-HPV-11 were both non-inferior (GMT ratio 1.02 (95% CI 0.99 – 1.06) and GMT ratio 0.80 (95% CI 0.77 – 0.83), respectively; neither lower boundary of the 95% CI of the GMT ratio was <0.67 which was the criterion for inferiority). Also, no statistically significant difference in seroconversion rates was seen.

Modeling studies

Based on pre-vaccine licensure trial estimates of vaccine efficacy, several modeling studies were published to predict when and what population reductions might occur with AGW.

An early dynamic population-based compartmental model was used to estimate the timing of reductions in AGW after onset of different 4vHPV vaccination strategies in the United States over a 100-year horizon. A 50% reduction in incident AGW was predicted in those 12 years and older, within 10 years, only if catch-up HPV vaccination programs through age 24 years were implemented together with universal vaccination programs for 12-year-old girls, boys, or both.²⁰ When the same model was applied using United Kingdom parameters, a 50% reduction in incident AGW was predicted in girls 12 years and older within 10 years, regardless of whether female-only vaccination programs universally implemented catch-up vaccination through age 24 years.²¹

A deterministic, dynamic population-based compartmental model was used to estimate the timing of reductions in AGW after onset of 4vHPV vaccination in the United States over a 25-year horizon. Fastest declines (within 3 years) were predicted for the youngest age group examined (15–19 year olds) if higher coverage (e.g., 70% of 12-year-old females receive all 3 doses) was achieved; with lower coverage (e.g. Twenty% of 12-year-old females received all 3 doses), a 50% reduction in AGW was not seen until year 18 of the model. The addition of a universal male vaccination program was predicted to have the greatest impact directly on reducing male AGW, and had relatively little impact on female AGW if higher coverage in a female-only vaccination program was achieved early.²²

An agent-based dynamic model was used to evaluate the potential impact of HPV vaccination on AGW over a 70 y horizon in Canada. This model predicted that 4vHPV vaccination programs would lead to a 50% decrease in AGW in males and females by 10 years, if 70% of 12-year-old girls were vaccinated.²³

Finally, a deterministic, dynamic population-based compartmental model was used to estimate relative reductions in AGW in the Australian heterosexual population over a ~50 y horizon, following introduction of male 4vHPV vaccination in 2013. Based on reductions in AGW that have already been seen since beginning a school-based 4vHPV vaccination program in 2007 in Australian 12 to 13-year-old girls with catch-up through age 26 years, this model predicts near elimination ($>90\%$ reduction) in AGW incidence in both sexes by year 2030 with implementation of a school-based male vaccination program in boys begun in 2013 combined with catch-up vaccination in boys aged 14–15 y. An 85% reduction in AGW incidence in females and 75% reduction in heterosexual males by 2050 was predicted even in the absence of a male vaccination program.²⁴

Model outcomes were most sensitive to changes in assumptions about vaccine uptake and duration of protection. In retrospect, most models underestimated the speed and degree to which HPV vaccination might impact AGW (see next section), probably because of underestimations of impact of partial dosing regimens of 4vHPV vaccine on AGW incidence, and because shorter durations of infectiousness and lower transmissibility of HPV types 6 and 11 may not have been fully accounted for.²⁵

Post-vaccination population-level surveillance studies

Eleven studies have been published on the population-level impact of 2vHPV and 4vHPV vaccination on AGW; no post-licensure studies have yet examined 9vHPV impact, which was only recently licensed by the US. Food and Drug Administration in December 2014. Ten studies focused on 4vHPV vaccine impact and one on 2vHPV.^{26–36} All studies were done in high-income countries (in order of publication: New Zealand, USA, Canada, Sweden, Australia, Denmark, England, and Germany). Study populations included clinic patients (STD clinics in Auckland, New Zealand and Australia; family planning programs in California), enrollees in health insurance plans (~100 private health plans in USA, 1 health insurer in Germany), all US. Armed Forces active duty service members, or entire geographic populations (Manitoba, Canada; Sweden; Denmark; England). Case definitions varied from simple utilization of clinical diagnosis to more complex combinations of diagnostic codes, treatment procedures, and/or prescriptions of specific medications used to treat AGW (imiquimod or podophyllo-toxin). Estimates of 3-dose vaccination coverage ranged from 15–84% for the youngest age group targeted in any country (usually 11–12 y old girls); delivery of vaccine was through a mixture of school-based programs (Australia, Canada, New Zealand, Sweden, and England), general practitioners/primary care providers/private providers, and community programs. Most cases included catch-up vaccination in older girls and women. Despite heterogeneity in vaccine implementation

programs, all published studies identified declines in AGW in girls in vaccine-eligible age range.

A definitive meta-analysis has been published on the basis of these 11 studies.³⁷ This study represents the single best summary of post-vaccination population-level surveillance studies on reductions in AGW. Researchers reached out to each study group to standardize the effect measure into a relative risk (RR) comparing pre- and post-vaccination periods for frequency (prevalence or incidence) of AGW diagnosis. Frequency of AGW diagnosis was estimated by number of cumulative cases divided by person-years for up to 3 years before vaccination (including the calendar year of HPV vaccination introduction, and 1-2 years after introduction for some studies where vaccination coverage was <15 % in those years) and up to 4 years post-vaccination introduction. Analysis was stratified by vaccine type, vaccination coverage (low <50 % or high $\geq$ 50 %), age (15-19, 20-24, 25-29, or 30-39 years), and gender (male or female).

For countries using 4vHPV, in girls aged 15-19 years, AGW decreased significantly by 31% (RR 0.69 [95% CI 0.60-0.79]); stratified analysis revealed more substantial reductions in populations with high vs. low vaccination coverage (61% vs. 14%). Furthermore, a dose-response association was found between population-level female vaccination coverage and AGW ($p = 0.0007$). In women 20-39 years and boys aged 15-19 years, non-significant decreases in AGW occurred (respectively 11%, RR 0.89 [95% CI 0.79-1.02] and 5%, RR 0.95 [95% CI 0.84-1.08]). However, stratified analysis revealed significant reductions in populations with high ($\geq$ 50 %) female vaccination coverage (32% in women 20-39 years, RR 0.68 [95% CI 0.51-0.89] and 34% in boys aged 15-19 years, RR 0.66 [95% CI 0.47-0.91]), consistent with catch-up vaccination and herd immunity effects predicted by dynamic models. Again, AGW reductions showed a significant dose-response association with increased population-level female vaccination coverage ($p = 0.05$ for women 20-39 years, $p = 0.005$ for boys aged 15-19 years). None of the studies of populations where vaccination coverage was lower than 50% demonstrated any significant effects on AGW in older women or young boys. No changes were found in men aged 20-39 years. Additional analysis pointed to both faster and broader age and gender impact in populations with high vaccination coverage (in countries with low vaccination coverage, declines were recorded only in 15-19 year old girls, and then only in the third year after vaccine implementation).³⁷

The study based in England's genitourinary medicine (GUM) clinics was the only one to examine 2vHPV impact on genital warts. Using the same methods to calculate RR, the meta-analysis identified a small but significant decrease in warts in girls aged 15-19 years and a small but significant increase in warts in boys aged 15-19 years. No significant effects were found in the older age groups.³⁷ The original study investigators had reviewed but discarded (1) untallied use of 4vHPV, (2) reductions in use of GUM clinics, and (3) decreases in sexual activity as explanations for these changes, and arrived instead at the conclusion that 2vHPV's prevention of HPV 16/18 acquisition decreased the number of clinical genital wart cases where HPV 16/18 either directly or synergistically contributed.³²

Potential vaccine impact on incidence and recurrence of respiratory papillomatosis

Studies have yet to examine the impact of HPV vaccination on overall incidence of RRP and JORRP. Impact on the former is already expected based on declines in genital wart acquisition. Impact on JORRP might be expected as vaccinated females reach childbearing age, because fewer women will carry the causative strains of HPV that could then be passed along to a fetus or neonate. Two additional strategies have been proposed to have more direct effects on JORRP incidence: (1) vaccination of neonates born to women with clinically diagnosed genital warts,³⁸ or (2) vaccination of pregnant women screened and infected with HPV 6/11, to boost maternal titers of neutralizing antibody and increase maternal transfer of antibody to the newborn.³⁹ These two strategies are based on previous studies indicating that antibody responses to HPV 6/11 are low or nonexistent in children who develop JORRP,⁴⁰ but in 4vHPV vaccinated women, HPV 6/11 titers in the newborn match maternal antibody titers.⁴¹ Transplacental transfer of antibody titers sufficient to protect newborn acquisition of HPV 6/11 is therefore possible. However, several factors are likely to discourage further research in the area of direct vaccination of newborns or pregnant women to prevent JORRP. These include: 1) already low odds of development of JORRP in infants born to women with genital warts; 2) lack of existing or planned trials to examine vaccine safety, immunogenicity, and efficacy in neonates or pregnant women; 3) absence of screening programs to identify maternal HPV 6/11 infection; and (4) gradual increases in HPV vaccine coverage rates in women of childbearing age, which are predicted to lead to eventual decreases in the pool of women who have infected maternal genital tracts leading to infant infection.

There is literature, however, regarding impact of HPV vaccine in prevention of disease recurrence in those with established RRP. A prospective study of patients with both juvenile and adult-onset RRP in Romania from 2009 to 2012 examined the clinical efficacy of quadrivalent vaccine on recurrence of papillomas.⁴² A total of 13 patients were included in the study, all of whom had recurrences after therapy with intralesional cidofovir injections. Patients received three doses of quadrivalent vaccine. Two patients (one with juvenile and one with adult-onset RRP; 15%, 95% CI 0.59-45.56) developed recurrent papillomas after the first vaccine dose; one month after the third vaccine dose, both patients required repeat papilloma surgery with no recurrences at 1 year of follow-up. While the authors acknowledged that additional larger studies are required to investigate the effect of vaccine on papilloma recurrence, the combination of surgery, antiviral therapy and vaccination might have a significant impact on disease outcomes.

A more recent retrospective chart review also assessed the effect of quadrivalent vaccine on the disease course of RRP.⁴³ Analysis was conducted on 20 patients receiving vaccine; inter-surgical interval (ISI) before and after vaccination and number of remissions (both partial and complete) were described. Complete or partial remission was achieved in 65% of patients; ISI increase of 4.2 months was noted in males (95% CI: 1.6-6.7, $P = 0.0048$) while nonsignificant ISI increase of 1.2 months was noted in females (95% CI: 3.1-5.4, $P = 0.51$). The authors

note that as RRP itself is characterized by spontaneous remission and recurrences, it was difficult to isolate treatment effects from natural disease course. Furthermore, patients were treated with other nonsurgical (antivirals, immunomodulatory agents) and surgical therapies, making it a challenge to establish causality. Randomized controlled trials would be needed to more accurately assess vaccine impact on disease. However, both of these studies show a practical need for development of therapeutic vaccines for RRP.

Conclusions/future thoughts

The results of pre-licensure trial efficacy, modeling, and time-trend ecological studies of 4vHPV vaccine programs all point to the significant impact 4vHPV has already had on the incidence and prevalence of AGW in both women and men in the short-term. The most significant declines have been identified in populations with early high vaccination coverage of pre-teen girls combined with catch-up vaccination of older girls and women (Australia, Canada, Denmark, and New Zealand), often through the use of school-based vaccination programs. The early impact on male AGW is thought to be substantive evidence supporting herd immunity, since vaccine implementation did not include male vaccination in the early years. Future examination of datasets monitoring RRP may also reveal time trends which already match current declines in AGW; impact on JORRP would be expected to increase as greater vaccine uptake is achieved in the cohort of women of childbearing age. Longer-term monitoring will be needed to understand whether these early declines continue under 9vHPV vaccination programs.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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