Epidemiology


Contribution over time of human papillomavirus (HPV) types in human cancers has been poorly documented. Such data is fundamental to measure current HPV vaccines impact in the years to come. We estimated the HPV type-specific distribution in a large international series of invasive cervical cancer (ICC) over 70 years prior to vaccination. Paraffin embedded ICC cases diagnosed between 1940 and 2007 were retrieved from eleven countries in Central-South America, Asia and Europe. Included countries reported to have low-medium cervical cancer screening uptake. Information on age at and year of diagnosis was collected from medical records. After histological confirmation, HPV DNA detection was performed by SPF-10/DEIA/LiPA25 (version1). Logistic regression models were used for estimating the adjusted relative contributions (RC) of HPV16 and of HPV18 over time. Among 4,771 HPV DNA positive ICC cases, HPV16 and HPV18 were the two most common HPVs in all the decades with no statistically significant variations of their adjusted-RC from 1940-59 to 2000-07 (HPV16-from 61.5 to 62.1%, and HPV18 from 6.9 to 7.2%). As well, the RC of other HPV types did not varied over time. In the stratified analysis by histology, HPV16 adjusted-RC significantly increased across decades in adenocarcinomas. Regarding age, cases associated to either HPV16, 18 or 45 were younger than those with other HPV types in all the evaluated decades. The observed stability on the HPV type distribution predicts a high and stable impact of HPV vaccination in reducing the cervical cancer burden in future vaccinated generations.


The causal role of human papillomavirus infections in cervical cancer has been documented beyond reasonable doubt. The association is present in virtually all cervical cancer cases worldwide. It is the right time for medical societies and public health regulators to consider this evidence and to define its preventive and clinical implications. A comprehensive review of key studies and results is presented.


BACKGROUND: Baseline information on human papillomavirus (HPV) prevalence and type distribution is highly desirable to evaluate the impact of prophylactic HPV vaccines in the near future. METHODS: A meta-analysis was performed of studies published between 1995 and 2009 that used polymerase chain reaction or Hybrid
Capture 2 for HPV detection in women with normal cytological findings. RESULTS: The analysis included 194 studies comprising 1,016,719 women with normal cytological findings. The estimated global HPV prevalence was 11.7% (95% confidence interval, 11.6%-11.7%). Sub-Saharan Africa (24.0%), Eastern Europe (21.4%), and Latin America (16.1%) showed the highest prevalences. Age-specific HPV distribution presented with a first peak at younger ages (<25 years) and, in the Americas and Africa, a rebound at older ages (≥45 years). Among the women with type-specific HPV data (n = 215,568), the 5 most common types worldwide were HPV-16 (3.2%), HPV-18 (1.4%), HPV-52 (0.9%), HPV-31 (0.8%), and HPV-58 (0.7%). CONCLUSIONS: Although the prevalence of HPV in women with normal cytological findings is high and variable across world regions, HPV types 16, 18, 31, 52, and 58 are consistently found among the 10 most common types in all of them. These results represent the most comprehensive assessment of HPV burden among women with normal cytological findings in the pre-HPV vaccination era worldwide.


BACKGROUND: Infections with certain viruses, bacteria, and parasites have been identified as strong risk factors for specific cancers. An update of their respective contribution to the global burden of cancer is warranted. METHODS: We considered infectious agents classified as carcinogenic to humans by the International Agency for Research on Cancer. We calculated their population attributable fraction worldwide and in eight geographical regions, using statistics on estimated cancer incidence in 2008. When associations were very strong, calculations were based on the prevalence of infection in cancer cases rather than in the general population. Estimates of infection prevalence and relative risk were extracted from published data. FINDINGS: Of the 12.7 million new cancer cases that occurred in 2008, the population attributable fraction (PAF) for infectious agents was 16.1%, meaning that around 2 million new cancer cases were attributable to infections. This fraction was higher in less developed countries (22.9%) than in more developed countries (7.4%), and varied from 3.3% in Australia and New Zealand to 32.7% in sub-Saharan Africa. Helicobacter pylori, hepatitis B and C viruses, and human papillomaviruses were responsible for 1.9 million cases, mainly gastric, liver, and cervix uteri cancers. In women, cervix uteri cancer accounted for about half of the infection-related burden of cancer; in men, liver and gastric cancers accounted for more than 80%. Around 30% of infection-attributable cases occur in people younger than 50 years. INTERPRETATION: Around 2 million cancer cases each year are caused by infectious agents. Application of existing public health methods for infection prevention, such as vaccination, safer injection practice, or antimicrobial treatments, could have a substantial effect on the future burden of cancer worldwide. FUNDING: Fondation Innovations en Infectiologie (FINOVI) and the Bill & Melinda Gates Foundation (BMGF).


BACKGROUND: Knowledge about the distribution of human papillomavirus (HPV) genotypes in invasive cervical cancer is crucial to guide the introduction of prophylactic vaccines. We aimed to provide novel and comprehensive data about the worldwide genotype distribution in patients with invasive cervical cancer. METHODS:
Paraffin-embedded samples of histologically confirmed cases of invasive cervical cancer were collected from 38 countries in Europe, North America, central South America, Africa, Asia, and Oceania. Inclusion criteria were a pathological confirmation of a primary invasive cervical cancer of epithelial origin in the tissue sample selected for analysis of HPV DNA, and information about the year of diagnosis. HPV detection was done by use of PCR with SPF-10 broad-spectrum primers followed by DNA enzyme immunoassay and genotyping with a reverse hybridisation line probe assay. Sequence analysis was done to characterise HPV-positive samples with unknown HPV types. Data analyses included algorithms of multiple infections to estimate type-specific relative contributions. FINDINGS: 22,661 paraffin-embedded samples were obtained from 14,249 women. 10,575 cases of invasive cervical cancer were included in the study, and 8977 (85%) of these were positive for HPV DNA. The most common HPV types were 16, 18, 31, 33, 35, 45, 52, and 58 with a combined worldwide relative contribution of 8196 of 8977 (91%, 95% CI 90-92). HPV types 16 and 18 were detected in 6357 of 8977 of cases (71%, 70-72) of invasive cervical cancer. HPV types 16, 18, and 45 were detected in 443 of 470 cases (94%, 92-96) of cervical adenocarcinomas. Unknown HPV types that were identified with sequence analysis were 26, 30, 61, 67, 69, 82, and 91 in 103 (1%) of 8977 cases of invasive cervical cancer. Women with invasive cervical cancers related to HPV types 16, 18, or 45 presented at a younger mean age than did those with other HPV types (50·0 years [49·6-50·4], 48·2 years [47·3-49·2], 46·8 years [46·6-48·1], and 55·5 years [54·9-56·1], respectively).INTERPRETATION: To our knowledge, this study is the largest assessment of HPV genotypes to date. HPV types 16, 18, 31, 33, 35, 45, 52, and 58 should be given priority when the cross-protective effects of current vaccines are assessed, and for formulation of recommendations for the use of second-generation polyvalent HPV vaccines. Our results also suggest that type-specific high-risk HPV-DNA-based screening tests and protocols should focus on HPV types 16, 18, and 45.


CONTEXT: Human papillomavirus (HPV) infection is the principal cause of a distinct form of oropharyngeal squamous cell carcinoma that is increasing in incidence among men in the United States. However, little is known about the epidemiology of oral HPV infection. OBJECTIVE: To determine the prevalence of oral HPV infection in the United States. DESIGN, SETTING, AND PARTICIPANTS: A cross-sectional study was conducted as part of the National Health and Nutrition Examination Survey (NHANES) 2009-2010, a statistically representative sample of the civilian noninstitutionalized US population. Men and women aged 14 to 69 years examined at mobile examination centers were eligible. Participants (N = 5579) provided a 30-second oral rinse and gargle with mouthwash. For detection of HPV types, DNA purified from oral exfoliated cells was evaluated by polymerase chain reaction and type-specific hybridization. Demographic and behavioral data were obtained by standardized interview. Statistical analyses used NHANES sample weights to provide weighted prevalence estimates for the US population. MAIN OUTCOME MEASURES: Prevalence of oral HPV infection. RESULTS: The prevalence of oral HPV infection among men and women aged 14 to 69 years was 6.9% (95% CI, 5.7%-8.3%) and of HPV type 16 was 1.0% (95% CI, 0.7%-1.3%). Oral HPV infection followed a bimodal pattern with respect to age, with peak prevalence among individuals aged 30 to 34 years (7.3%; 95% CI, 4.6%-11.4%) and 60 to 64 years.
Men had a significantly higher prevalence than women for any oral HPV infection (10.1% [95% CI, 8.3%-12.3%] vs 3.6% [95% CI, 2.6%-5.0%], P < .001; unadjusted prevalence ratio [PR], 2.80 [95% CI, 2.02-3.88]). Infection was less common among those without vs those with a history of any type of sexual contact (0.9% [95% CI, 0.4%-1.8%] vs 7.5% [95% CI, 6.1%-9.1%], P < .001; PR, 8.69 [95% CI, 3.91-19.31]) and increased with number of sexual partners (P < .001 for trend) and cigarettes smoked per day (P < .001 for trend). Associations with age, sex, number of sexual partners, and current number of cigarettes smoked per day were independently associated with oral HPV infection in multivariable models. CONCLUSION: Among men and women aged 14 to 69 years in the United States, the overall prevalence of oral HPV infection was 6.9%, and the prevalence was higher among men than among women.


Thirty-nine patients with condylomas (12 women and 27 men) attending a dermatology clinic were tested for genital human papillomavirus (HPV) DNA and for seroprevalence to HPV type 6 (HPV6) L1 virus-like particles. The L1 consensus PCR system (with primers MY09 and MY11) was used to determine the presence and types of HPV in sample specimens. All 37 (100%) patients with sufficient DNA specimens were positive for HPV DNA, and 35 (94%) had HPV6 DNA detected at the wart site. Three patients (8%) had HPV11 detected at the wart site, and one patient had both HPV6 and -11 detected at the wart site. Thirteen additional HPV types were detected among the patients; the most frequent were HPV54 (8%) and HPV58 (8%). Baculovirus-expressed HPV6 L1 virus-like particles were used in enzyme-linked immunosorbent assays to determine seroprevalence among the patients with warts. Seronegativity was defined by a control group of 21 women who were consistently PCR negative for HPV DNA. Seroprevalence was also determined for reference groups that included cytologically normal women who had detectable DNA from either HPV6 or HPV16 and women with HPV16-associated cervical intraepithelial neoplasia. Among the asymptomatic women with HPV6, only 2 of 9 (22%) were seropositive, compared with 12 of 12 (100%) female patients with warts. A similar trend in increased HPV6 seropositivity with increased grade of disease was found with the HPV16 DNA-positive women, whose seroprevalence increased from 1 in 11 (9%) in cytologically normal women to 6 in 15 (40%) among women with cervical intraepithelial neoplasia 1 or 3. However, only 4 of 25 (16%) male patients were seropositive. No factors examined, such as age, sexual behavior, or a history of warts, were found to definitively account for the gender difference in seropositive.


BACKGROUND: We describe type-specific progression, regression and persistence of incident human papillomavirus (HPV)-6-11-16 and -18 infections, along with type distribution in cervical intra-epithelial neoplasia (CIN) lesions. METHODS: The study population consisted of 16-23 year-old women undergoing Pap testing and cervical swab polymerase chain reaction testing for HPV DNA at approximate 6 month
intervals for up to 4 years in the placebo arm of a clinical trial of an HPV 16-vaccine. HPV types in incident infections were correlated with types in lesion biopsy specimens. RESULTS: 56.7% of CIN-1 and nearly one-third of CIN-2/3 lesions following incident HPV-6-11-16 or -18 infections did not correlate with the incident infection HPV type. Cumulative 36-month progression rates to CIN-2/3 testing positive for the relevant HPV type were highest for HPV-16 infections (16.5%), followed by HPV-18 (8.2%). Overall, 26.0% of CIN-1, 50.0% of CIN-2 and 70.6% of CIN-3 biopsies tested positive for HPV-6-11-16-18 infections. CONCLUSION: Women with a given HPV type may often be co-infected or subsequently infected with other types which may lead to subsequent cervical lesions. This issue has been addressed in this study reporting data for the natural history of HPV-6-11-16 and -18 infections and is a relevant consideration in designing future studies to evaluate the incidence/risk of CIN following other type-specific HPV infections.


BACKGROUND: We performed a systematic review and meta-analysis to summarise the available data on the prevalence of human papillomavirus (HPV) among men in sub-Saharan Africa. METHODS: PubMed and Embase were searched up to 10 March 2014. Random effects meta-analyses were used to calculate a pooled prevalence of any HPV and high-risk (HR) HPV. RESULTS: A total of 11 studies comprising 9342 men were identified. We found that HPV is very common among men in sub-Saharan Africa, the prevalence of any HPV ranging between 19.1% and 100%. Using random effects meta-analysis, the pooled prevalence of any HPV was 78.2% (95% CI 54.2 to 91.6) among HIV-positive and 49.4% (95% CI 30.4 to 68.6) among HIV-negative men (p=0.0632). When restricting the analyses to PCR-based studies, the pooled prevalence of any HPV was 84.5% (95% CI 74.2 to 91.2) among HIV-positive and 56.4% (95% CI 49.7 to 62.9) among HIV-negative men (p<0.0001). Of the HPV types included in the nine-valent HPV vaccine, the most common HR HPV types were HPV16 and HPV52, and HPV6 was the most common low-risk HPV type. When examining the prevalence of HPV in relation to age no clear trend was observed. CONCLUSIONS: The prevalence of HPV is high among men in sub-Saharan Africa, which could contribute to the high rates of penile and cervical cancer in this part of the world. Implementation of the prophylactic HPV vaccines could potentially help prevent this large burden of HPV and HPV-associated disease in sub-Saharan Africa. CLINICALTRIALSGOV IDENTIFIER: NCT00932009.


BACKGROUND: Anogenital warts (AGWs) are a common, highly infectious disease caused by the human papillomavirus (HPV), whose high recurrence rates contribute to direct medical costs, productivity loss and increased psychosocial impact. Because of the lack of a systematic review of the epidemiology of AGWs in the literature, this study reviewed the published medical literature on the incidence and
prevalence of AGWs. METHODS: A comprehensive literature search was performed on the worldwide incidence and prevalence of AGWs between 2001 and 2012 using the PubMed and EMBASE databases. An additional screening of abstracts from relevant sexual health and infectious disease conferences from 2009 to 2011 was also conducted. Only original studies with general adult populations (i.e., at least including ages 20 through 40 years) were included. RESULTS: The overall (females and males combined) reported annual incidence of any AGWs (including new and recurrent) ranged from 160 to 289 per 100,000, with a median of 194.5 per 100,000. New AGW incidence rates among males ranged from 103 to 168 per 100,000, with a median of 137 per 100,000 and among females from 76 to 191 per 100,000, with a median of 120.5 per 100,000 per annum. The reported incidence of recurrent AGWs was as high as 110 per 100,000 among females and 163 per 100,000 among males. Incidence peaked before 24 years of age in females and between 25 and 29 years of age among males. The overall prevalence of AGWs based on retrospective administrative databases or medical chart reviews or prospectively collected physician reports ranged from 0.13% to 0.56%, whereas it ranged from 0.2% to 5.1% based on genital examinations. CONCLUSIONS: The literature suggests that AGWs are widespread and the prevalence depends on study methodology as suggested by higher rates reported from routine genital examinations versus those from treatment records. However, there remains a need for more population-based studies from certain regions including Africa, Latin America and Southern Asia to further elucidate the global epidemiology of this disease.


HIV infection is one of the strongest risk factors for anal squamous cell cancer (ASCC). Most ASCC are caused by HPV, and most HPV-associated ASCC are caused by HPV-16. Anal HPV infections are very common in men who have sex with men (MSM), and nearly universal among HIV-infected MSM. High-grade anal intraepithelial neoplasia (HGAIN), the precursor for ASCC, is present in about 30% of HIV+ MSM, but neither the progression rate to ASCC nor the regression rate are known. The incidence rate of ASCC among HIV-infected people has risen in the first decade after cART became available, but appears to be plateauing recently. Anal cytology has poor sensitivity and specificity. High resolution anoscopy (HRA) is advocated by some as a screening tool in high-risk groups, but is cumbersome and time-consuming and it is unknown whether HRA followed by treatment of HGAIN prevents ASCC. More research is needed on progression and regression rates of HGAIN, on effective therapy of HGAIN, and on biomarkers that predict HGAIN or anal cancer. HPV vaccination and earlier start of cART may prevent most anal cancers in the long run.


PURPOSE: Global data on age-specific prevalence of human papillomavirus (HPV) infection in males, especially for oncogenic HPV types 16 and 18, are essential for future efforts to prevent HPV-related diseases, including expanded access to HPV prophylactic vaccines for boys and young men. METHODS: A systematic review of peer-reviewed publications was conducted to summarize worldwide data on genital
HPV-DNA prevalence in men. Studies using polymerase chain reaction or hybrid capture detection assays were included. RESULTS: Approximately 6,600 abstracts were identified. Of them, 64 reported age-specific HPV prevalence and were included in the review. Of these, 38 were from populations at high risk of HPV infections, such as sexually transmitted infection clinic attendees, human immunodeficiency virus-positive males, and male partners of women with HPV infection or abnormal cytology. The largest proportions of studies were from Europe (38%) and North America (25%), with smaller proportions from Central and South America (19%), Asia (11%), and Africa (5%). Across all regions, data on HPV prevalence were generally limited to men >18 years of age. HPV prevalence was high among sexually active men in all regions but with considerable variation, from 1% to 84% among low-risk men and from 2% to 93% among high-risk men. Peak HPV prevalence spanned a wide range of ages and was generally not concentrated in the younger age groups. Age-specific prevalence curves were relatively flat or declined only slightly following peak prevalence. CONCLUSIONS: Genital HPV infection in men varies widely, both between and within high- and low-risk groups and by geographic region. Compared with that in women, HPV prevalence in men seems to peak at slightly older ages and remains constant or decreases slightly with increasing age, suggesting persistent HPV infection or a higher rate of reinfection.


Data on human papillomavirus (HPV) type distribution in invasive and pre-invasive cervical cancer is essential to predict the future impact of HPV16/18 vaccines and HPV-based screening tests. A meta-analyses of HPV type distribution in invasive cervical cancer (ICC) and high-grade squamous intraepithelial lesions (HSIL) identified a total of 14,595 and 7,094 cases, respectively. In ICC, HPV16 was the most common, and HPV18 the second most common, type in all continents. Combined HPV16/18 prevalence among ICC cases was slightly higher in Europe, North America and Australia (74-77%) than in Africa, Asia and South/Central America (65-70%). The next most common HPV types were the same in each continent, namely HPV31, 33, 35, 45, 52 and 58, although their relative importance differed somewhat by region. HPV18 was significantly more prevalent in adeno/adenosquamous carcinoma than in squamous cell carcinoma, with the reverse being true for HPV16, 31, 33, 52 and 58. Among HSIL cases, HPV16/18 prevalence was 52%. However, HPV 16, 18 and 45 were significantly under-represented, and other high-risk HPV types significantly over-represented in HSIL compared to ICC, suggesting differences in type-specific risks for progression. Data on HPV-typed ICC and HSIL cases were particularly scarce from large regions of Africa and Central Asia.


BACKGROUND: Monitoring of condylomas is an early evidence of population effectiveness of human papillomavirus (HPV) vaccination programs. If reporting could include HPV typing, the contribution by vaccine HPV types to condyloma burden could be monitored. METHODS: A sentinel site for reporting of condyloma including HPV typing was established at the Centre for Sexual Health in Malmö,
Sweden. In 2006 to 2009, when there were few HPV vaccines, 621 subjects with condyloma were reported and HPV genotyped. RESULTS: Ninety-four percent of the condylomas contained genital HPV types. Thirty-five different genital HPV types were identified, with HPV6 (62%), HPV16 (13%), and HPV11 (10%) being the most common. At least 1 of the 4 HPV types in the HPV6/11/16/18 vaccine was detected in 77%. High-risk HPV types were more common in females (45%) than among males (27%) (odds ratio, 1.9; confidence interval, 1.3-2.8). Extended testing among subjects initially negative for HPV found 21 patients with cutaneous types of HPV, including a novel type (HPV153). CONCLUSIONS: This report provides a baseline distribution of HPV types in condylomas before the introduction of an HPV vaccination program in this population. Human papillomavirus typing is feasible in routine condyloma reporting.


BACKGROUND: We examined the baseline prevalence of penile, scrotal, and perineal/perianal human papillomavirus (HPV) in heterosexual men (HM). We also evaluated baseline characteristics of HM to assess factors associated with prevalent HPV detection. METHODS: We tested serum samples from 3463 HM aged 16-24 years with 1-5 lifetime female sexual partners for antibodies to HPV 6, 11, 16, and 18. We collected baseline swab specimens for the detection of DNA of HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 from 3 areas: penile, scrotal, and perineal/perianal. Risk factors for prevalent HPV DNA detection were evaluated. RESULTS: The prevalence of any tested HPV type was 18.7% at the penis, 13.1% at the scrotum, 7.9% at the perineal/perianal region, and 21.0% at any site. Having >3 lifetime female sexual partners had the greatest impact on HPV prevalence: odds ratio (OR) 3.2 (95% confidence interval (CI) 2.1-4.9) for HPV 6, 11, 16, and 18; and OR 4.5 (95% CI 3.3-6.1) for all HPV types tested. HPV DNA detection was highest in Africa. Neither condom usage nor circumcision was associated with HPV DNA prevalence. CONCLUSION: Genital-HPV DNA detection is common in young, sexually active HM. We found HPV to be most prevalent in African men and least prevalent in men from the Asia-Pacific region. Increased numbers of sexual partners was an important risk factor for HPV DNA prevalence.


A recent report that 93 per cent of invasive cervical cancers worldwide contain human papillomavirus (HPV) may be an underestimate, due to sample inadequacy or integration events affecting the HPV L1 gene, which is the target of the polymerase chain reaction (PCR)-based test which was used. The formerly HPV-negative cases from this study have therefore been reanalyzed for HPV serum antibodies and HPV DNA. Serology for HPV 16 VLPs, E6, and E7 antibodies was performed on 49 of the 66 cases which were HPV-negative and a sample of 48 of the 866 cases which were HPV-positive in the original study. Moreover, 55 of the 66 formerly HPV-negative biopsies were also reanalyzed by a sandwich procedure in which the outer sections in a series of sections are used for histological review, while the inner sections are assayed by three different HPV PCR assays targeting different open reading frames (ORFs). No significant difference was found in serology for HPV 16 proteins between the cases that were originally HPV PCR-negative and -
positive. Type-specific E7 PCR for 14 high-risk HPV types detected HPV DNA in 38 (69 per cent) of the 55 originally HPV-negative and amplifiable specimens. The HPV types detected were 16, 18, 31, 33, 39, 45, 52, and 58. Two (4 per cent) additional cases were only HPV DNA-positive by E1 and/or L1 consensus PCR. Histological analysis of the 55 specimens revealed that 21 were qualitatively inadequate. Only two of the 34 adequate samples were HPV-negative on all PCR tests, as against 13 of the 21 that were inadequate (p < 0.001). Combining the data from this and the previous study and excluding inadequate specimens, the worldwide HPV prevalence in cervical carcinomas is 99.7 per cent. The presence of HPV in virtually all cervical cancers implies the highest worldwide attributable fraction so far reported for a specific cause of any major human cancer. The extreme rarity of HPV-negative cancers reinforces the rationale for HPV testing in addition to, or even instead of, cervical cytology in routine cervical screening.

Pathogen, Disease, Screening, and Treatment

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The vast majority of women infected with human immunodeficiency virus (HIV) will be co-infected with human papillomavirus (HPV). The interaction between the two sexually transmitted infections appears to be related to the alteration in cell-mediated immunity in HIV infected persons, increased susceptibility, and possibly reactivation of latent HPV infection. Linkage studies of HIV/AIDS and Cancer registries have indicated a 2- to 22-fold increase in cervical cancer in HIV-positive women compared to HIV-negative women. Data on the prevalence of HPV types in invasive cervical carcinoma (ICC) suggest that the proportion of infection with types HPV16/18 (responsible for over 70% of all cervical cancers) is similar in HIV-negative and HIV-positive women. The biological interaction between HIV and HPV needs further elucidation, although there is some evidence that the presence of HPV infection may be associated with increased HIV transmission. Adolescents perinatally infected by HIV are known to have higher rates of HPV infection and also have been shown to seroconvert in response to HPV vaccination with the quadrivalent vaccine, albeit to lower titers than HIV-negative individuals. Anal cancer incidence is greatly increased in HIV-positive individuals, particularly in HIV-positive men who have sex with men. Screening for anal cancer precursors is feasible and effective; however, the impact on reduction of anal cancer remains to be demonstrated. There are ongoing studies on the safety, immunogenicity, and efficacy of current HPV vaccines in HIV-positive individuals and mature data are awaited. Male circumcision may be another approach to prevention of HPV transmission, which also requires further study. This article forms part of a special supplement entitled "Comprehensive Control of HPV Infections and Related Diseases" Vaccine Volume 30, Supplement 5, 2012.


Human papillomaviruses (HPVs) comprise a diverse group, and have different epithelial tropisms and life-cycle strategies. Many HPVs are classified as low-risk, as
they are only very rarely associated with neoplasia or cancer in the general population. These HPVs typically cause inapparent/inconspicuous infections, or benign papillomas, which can persist for months or years, but which are eventually resolved by the host's immune system. Low-risk HPVs are difficult to manage in immunosuppressed people and in individuals with genetic predispositions, and can give rise to papillomatosis, and in rare instances, to cancer. The high-risk HPV types are, by contrast, a cause of several important human cancers, including almost all cases of cervical cancer, a large proportion of other anogenital cancers and a growing number of head and neck tumours. The high-risk HPV types constitute a subset of the genus Alphapapillomavirus that are prevalent in the general population, and in most individuals cause only inconspicuous oral and genital lesions. Cancer progression is associated with persistent high-risk HPV infection and with deregulated viral gene expression, which leads to excessive cell proliferation, deficient DNA repair, and the accumulation of genetic damage in the infected cell. Although their life-cycle organisation is broadly similar to that of the low-risk HPV types, the two groups differ significantly in their capacity to drive cell cycle entry and cell proliferation in the basal/parabasal cell layers. This is thought to be linked, at least in part, to different abilities of the high- and low-risk E6 proteins to modulate the activity of p53 and PDZ-domain proteins, and the differential ability of the E7 proteins to target the several different members of the retinoblastoma protein family. This article forms part of a special supplement entitled "Comprehensive Control of HPV Infections and Related Diseases" Vaccine Volume 30, Supplement 5, 2012.


BACKGROUND: Genital human papillomavirus (HPV) infection is highly prevalent in sexually active young women. However, precise risk factors for HPV infection and its incidence and duration are not well known. METHODS: We followed 608 college women at six-month intervals for three years. At each visit, we collected information about lifestyle and sexual behavior and obtained cervicovaginal-lavage samples for the detection of HPV DNA by polymerase chain reaction and Southern blot hybridization. Pap smears were obtained annually. RESULTS: The cumulative 36-month incidence of HPV infection was 43 percent (95 percent confidence interval, 36 to 49 percent). An increased risk of HPV infection was significantly associated with younger age, Hispanic ethnicity, black race, an increased number of vaginal-sex partners, high frequencies of vaginal sex and alcohol consumption, anal sex, and certain characteristics of partners (regular partners having an increased number of lifetime partners and not being in school). The median duration of new infections was 8 months (95 percent confidence interval, 7 to 10 months). The persistence of HPV for > or =6 months was related to older age, types of HPV associated with cervical cancer, and infection with multiple types of HPV but not with smoking. The risk of an abnormal Pap smear increased with persistent HPV infection, particularly with high-risk types (relative risk, 37.2; 95 percent confidence interval, 14.6 to 94.8). CONCLUSIONS: The incidence of HPV infection in sexually active young college
women is high. The short duration of most HPV infections in these women suggests that the associated cervical dysplasia should be managed conservatively.


BACKGROUND: Oncogenic human papillomavirus (HPV) has been hypothesised as a risk factor for oesophageal squamous cell carcinoma (OSCC), but aetiological research has been limited by the varying methodology used for establishing HPV prevalence. The aims of this systematic review and meta-analysis were to estimate the prevalence of HPV DNA detected in OSCC tumours and the influence of study characteristics. METHODS: Study-level estimates of overall and type-specific HPV prevalence were meta-analysed to obtain random-effects summary estimates. RESULTS: This analysis included 124 studies with a total of 13 832 OSCC cases. The average HPV prevalence (95% confidence interval) among OSCC cases was 0.277 (0.234, 0.320) by polymerase chain reaction; 0.243 (0.159, 0.326) by in situ hybridisation; 0.304 (0.185, 0.423) by immunohistochemistry; 0.322 (0.154, 0.490) by L1 serology; and 0.176 (0.061, 0.292) by Southern/slot/dot blot. The highest HPV prevalence was found in Africa and Asia, notably among Chinese studies from provinces with high OSCC incidence rates. CONCLUSIONS: Future research should focus on quantifying HPV in OSCC cases using strict quality control measures, as well as determining the association between HPV and OSCC incidence by conducting large, population-based case-control studies. Such studies will provide a richer understanding of the role of HPV in OSCC aetiology.


Human papillomavirus (HPV) causes papillomas (warts) on the skin and respiratory mucosal surfaces (laryngeal and oral papillomas) in addition to condyloma acuminata (anogenital warts). HPV has become one of the most common sexually transmitted diseases in adults. Vertical transmission from mother to infant during birth is well recognized. Laryngeal papillomas are the most common tumors of the larynx in children worldwide, and recurrent lesions are common occurrences. Anogenital warts in children are problematic in that child sexual abuse is a potential means of acquisition, but many cases are acquired perinatally. Postnatal acquisition by nonsexual means also can occur. The likelihood of sexual abuse as the mode of acquisition increases with increasing age in childhood. The virus infects primarily epithelial cells, where it can exist as a long-term latent infection that can reactivate or
persist actively (even subclinically), with resultant accumulation of host chromosomal mutations. The latter accounts for the oncogenic potential of a number of HPV types, and childhood infections may lead to neoplasia later in life. Regression of papillomas over the course of months to years is the usual natural course. Numerous treatments are available, but most do not prevent persistent infection or problematic recurrences. Multivalent HPV vaccines have been developed, and early results of clinical trials appear to be very promising.


Viral infections in pregnancy are a major cause of morbidity and mortality for both mother and fetus. Viral STIs occur as surface infection and then gradually infect immunologically protected sites. Therefore, these are asymptomatic, hidden and hence underdiagnosed, persistent and difficult to treat. HSV, HPV, HBV, HIV and CMV (cytomegalovirus) are the common ones. Most of these are transmitted during intrapartum period. Proper screening, identification and treatment offered during prenatal period may help in preventing their complications. Twenty five percent of women with a history of genital herpes have an outbreak at some point during the last month of pregnancy. Acyclovir is the accepted efficacious and safe therapy for HSV in pregnancy. Globally, HPV infection is the most common sexually transmitted infection. Neonatal transmission can occur in the absence of clinically evident lesions. HPV 6 or 11 may lead to Juvenile Onset Recurrent Respiratory Papillomatosis (JORRP). TCA, liquid nitrogen, laser ablation or electrocautery can be used to treat external genital HPV lesions at any time during pregnancy. Cesarean section is recommended only if the lesions are obstructing the birth canal. Mother to child transmission (MTCT) in HIV accounts for 15-30% during pregnancy and delivery, and a further 5-20% of transmission occurs through breastfeeding. HBV infection during pregnancy does not alter the natural course of the disease. In women who are seropositive for both HBsAg and HBeAg, vertical transmission is approximately 90%. Pregnancy is not a contraindication for HBV vaccination. Cytomegalovirus (CMV) is the most common intrauterine infection. Cytomegalic inclusion disease (CID) is the most severe form of congenital CMV infection. Treatment is supportive.


Human papillomavirus (HPV) infections of cutaneous and genital mucosae are very common but the majority of individuals clear the infection without overt clinical disease. Those who develop lesions, also in most cases, mount an effective cell-mediated immune response and the lesions regress. The increased prevalence of HPV infections in individuals with a range of immunodeficiencies, including immunosuppression as a consequence of HIV infection, demonstrates the central importance of the CD4 T cell population in the control of established HPV infections. Failure to induce an effective immune response is related to inefficient activation of innate immunity and ineffective priming of the adaptive immune response; this defective immune response facilitates viral persistence, a key feature of high-risk HPV infection. This milieu becomes operationally HPV antigen tolerant, and the host's defences become irrevocably compromised. HPV antigen-specific effector cells are poorly recruited to the infected focus, and their activity is downregulated; neoplastic HPV-containing cervical keratinocytes expressing high levels of E6 and E7 oncoproteins are not killed in this immunosuppressive, tolerant milieu, and
progression to high-grade disease and cancer can result. Highly efficacious prophylactic HPV L1 virus-like particle (VLP) vaccines circumvent viral epithelial evasion strategies since they are delivered by intramuscular injection. The stromal dendritic cells of the muscle that encounter the highly immunogenic repeat structure of the VLP then migrate with their cargo to the lymph node, initiating an immune cascade that results in a robust T cell-dependent B cell response, which generates high levels of L1-specific serum neutralizing antibodies and immune memory.


Human papillomavirus (HPV) infection of the genital tract is common in young sexually active individuals, the majority of whom clear the infection without overt clinical disease. Most of those who do develop benign lesions eventually mount an effective cell-mediated immune (CMI) response, and the lesions regress. Regression of anogenital warts is accompanied histologically by a CD4(+) T cell-dominated Th1 response; animal models support this and provide evidence that the response is modulated by antigen-specific CD4(+) T cell-dependent mechanisms. Failure to develop an effective CMI response to clear or control infection results in persistent infection and, in the case of the oncogenic HPVs, an increased probability of progression to high-grade intraepithelial neoplasia and invasive carcinoma. Effective evasion of innate immune recognition seems to be the hallmark of HPV infections. The viral infectious cycle is exclusively intraepithelial: there is no viremia and no virus-induced cytolysis or cell death, and viral replication and release are not associated with inflammation. HPV globally downregulates the innate immune signaling pathways in the infected keratinocyte. Proinflammatory cytokines, particularly the type I interferons, are not released, and the signals for Langerhans cell (LC) activation and migration, together with recruitment of stromal dendritic cells and macrophages, are either not present or inadequate. This immune ignorance results in chronic infections that persist over weeks and months. Progression to high-grade intraepithelial neoplasia with concomitant upregulation of the E6 and E7 oncoproteins is associated with further deregulation of immunologically relevant molecules, particularly chemotactic chemokines and their receptors, on keratinocytes and endothelial cells of the underlying microvasculature, limiting or preventing the ingress of cytotoxic effectors into the lesions. Recent evidence suggests that HPV infection of basal keratinocytes requires epithelial wounding followed by the reepithelization of wound healing. The wound exudate that results provides a mechanistic explanation for the protection offered by serum neutralizing antibody generated by HPV L1 virus-like particle (VLP) vaccines.


WHO guidelines: Treatment of cervical intraepithelial neoplasia 2-3 and adenocarcinoma in situ: cryotherapy, large loop excision of the transformation zone,
and cold knife conisation. 104.

*WHO guidelines: use of cryotherapy for cervical intraepithelial neoplasia. 2011

*WHO Human Papillomavirus Laboratory Manual (WHO/IVB/10.12)”

Vaccines

Product monographs

Vaccine immunogenicity, efficacy and effectiveness

Humoral memory to an antigen (Ag) is maintained for several decades in the form of memory B cells and serum Ab. In fact, plasma cells (PCs) that secrete Ab are known to be long-lived and could be solely responsible for maintaining the long-lived Ab titers. Alternatively, it has been proposed that the PC compartment is maintained for long periods by the differentiation of memory cells into long-lived PCs as a result of nonspecific stimulation. This model predicts accelerated decay of PC numbers in the absence of memory cells for the same Ag. To address this prediction, we have developed a mouse model system that combined the ability to deplete B cells with the ability to detect Ag-specific memory and PCs. After establishing an immune response, we depleted Ag-specific memory B cells with an anti-hCD20 mAb and determined the effect on the PC compartment over 16 weeks. Using a combination of surface markers, we demonstrated that memory B cells remained depleted over the course of the experiment. However, despite this absence of memory cells for an extended duration, PC numbers in spleen and bone marrow did not decline, which indicates that the PC compartment does not require a significant contribution from memory B cells for its maintenance and instead that PCs are sufficiently long-lived to maintain Ab titers over a long period without renewal. This observation settles an important controversy in B cell biology and has implications for the design of vaccines and for B cell depletion therapy in patients.

OBJECTIVE: To measure the effect on genital warts of the national human papillomavirus vaccination programme in Australia, which started in mid-2007. DESIGN: Trend analysis of national surveillance data. SETTING: Data collated from eight sexual health services from 2004 to 2011; the two largest clinics also collected self reported human papillomavirus vaccination status from 2009. PARTICIPANTS: Between 2004 and 2011, 85,770 Australian born patients were seen for the first time; 7686 (9.0%) were found to have genital warts. MAIN OUTCOME MEASURE: Rate ratios comparing trends in proportion of new patients diagnosed as having genital warts in the pre-vaccination period (2004 to mid-2007) and vaccination period (mid-2007 to the end of 2011). RESULTS: Large declines occurred in the proportions of under 21 year old (92.6%) and 21-30 year old (72.6%) women diagnosed as having genital warts in the vaccination period-from 11.5% in 2007 to 0.85% in 2011 (P<0.001) and from 11.3% in 2007 to 3.1% in 2011 (P<0.001), respectively. No significant decline in wart diagnoses was seen in women over 30 years of age. Significant declines occurred in proportions of under 21 year old (81.8%) and 21-30 year old (51.1%) heterosexual men diagnosed as having genital warts in the vaccination period-from 12.1% in 2007 to 2.2% in 2011 (P<0.001) and from 18.2% in 2007 to 8.9% in 2011 (P<0.001), respectively. No significant decline in genital wart diagnoses was seen in heterosexual men over 30 years of age. In 2011 no genital warts diagnoses were made among 235 women under 21 years of age who reported prior human papillomavirus vaccination. CONCLUSIONS: The significant declines in the proportion of young women found to have genital warts and the absence of genital warts in vaccinated women in 2011 suggests that the human papillomavirus vaccine has a high efficacy outside of the trial setting. Large declines in diagnoses of genital warts in heterosexual men are probably due to herd immunity.


BACKGROUND: There has been a rapid decline in the number of young heterosexuals diagnosed with genital warts at outpatient sexual health services since the national human papillomavirus (HPV) vaccination program started in Australia in 2007. We assessed the impact of the vaccination program on the number of in-patient treatments for genital warts. METHODS: Data on in-patient treatments of genital warts in all private hospitals were extracted from the Medicare website. Medicare is the universal health insurance scheme of Australia. In the vaccine period (2007-2011) and pre-vaccine period (2000-2007) we calculated the percentage change in treatment numbers and trends in annual treatment rates in private hospitals. Australian population data were used to calculate rates. Summary rate ratios of average annual trends were determined. RESULTS: Between 2000 and 2011, 6,014 women and 936 men aged 15-44 years underwent in-patient treatment for genital warts in private hospitals. In 15-24 year old women, there was a significant decreasing trend in annual treatment rates of vulval/vaginal warts in the vaccine period (overall decrease of 85.3% in treatment numbers from 2007 to 2011) compared to no significant trend in the pre-vaccine period (summary rate ratio (SRR) = 0.33, p < 0.001). In 25-34 year old women, declining trends were seen in both vaccine and pre-vaccine periods (overall decrease of 33% vs. 24.3%), but the
rate of change was greater in the vaccine period (SRR = 0.60, p < 0.001). In 35-44 year old women, there was no significant change in both periods (SRR = 0.91, p = 0.14). In 15-24 year old men, there was a significant decreasing trend in annual treatment rates of penile warts in the vaccine period (decrease of 70.6%) compared to an increasing trend in the pre-vaccine period (SRR = 0.76, p = 0.02). In 25-34 year old men, there was a significant decreasing trend in annual treatment rates of penile warts in the vaccine period (decrease of 70.6%) compared to an increasing trend in the pre-vaccine period (SRR = 0.76, p = 0.02). In 35-44 year old men there was no significant change in rates of penile warts both periods, but the rate of change was greater in the vaccine period (SRR = 0.70, p = 0.02).

CONCLUSIONS: The marked decline in in-patient treatment of vulval/vaginal warts in the youngest women is probably attributable to the HPV vaccine program. The moderate decline in in-patient treatments for penile warts in men probably reflects herd immunity.


BACKGROUND: Approximately 90% of genital warts (GWs) are caused by human papillomavirus (HPV) types 6 and 11. Denmark has provided the quadrivalent HPV vaccine to all 12-year-old girls since 2009 and catch-up vaccination to girls up to 15 years since 2008, with up to 80% to 85% vaccine coverage. We determined the incidence of GWs in Denmark since 1996, focusing on the period after licensing of HPV vaccination (October 2006). METHODS: From the Danish National Patient Register, we identified all hospitalizations and outpatient consultations for GWs between January 1995 and July 2011. Poisson regression was used to estimate average annual percentage changes. RESULTS: The overall incidence of GWs in women increased significantly until 2007, followed by an average yearly decline of 3.1% (95% confidence interval [CI], -5.5 to -0.7). In men, the incidence increased by 6.2% per year from 2004 (95% CI, 4.6-7.8). Stratifying on age, a significant decline was seen only for young women, particularly those aged 16 to 17 years, in whom GWs were virtually eliminated (average annual percentage change, -45.3%; 95% CI, -55.8 to -33.3). The incidences of genital Chlamydia, syphilis, and gonorrhea were stable or increased during the study period. CONCLUSIONS: The incidence of GWs decreased substantially among women with high HPV vaccine coverage, pointing to the effect of the national HPV vaccination program.


Aim of this investigator-initiated study was to evaluate and compare the titres of neutralizing and cross-neutralizing antibodies (NAbs) induced by the bivalent (Cervarix®) and quadrivalent (Gardasil®) HPV vaccines in a cohort of girls aged 11-13 years from organized vaccination programmes. To this aim, HPV16 and HPV18 NAbs were measured by pseudovirion-based neutralization assays in serum collected at 1-6 months after the third vaccine dose in 107 girls vaccinated with Cervarix® and 126 vaccinated with Gardasil®, while HPV31 and HPV45 cross-NAbs were tested in the first 50 consecutive girls of both vaccine groups. The results of this study demonstrated that all vaccinated girls developed HPV16 and HPV18 NAbs, with the exception of two Gardasil® vaccinees with undetectable HPV18
NAbs. Geometric mean titles (GMTs) of both HPV16 and HPV18 NAbs were significantly higher in Cervarix® than in Gardasil® vaccinees [HPV16 NAb GMT 22,136 (95% CI, 18,811-26,073) vs 5092 (4230-6151), respectively; P<0.0001; HPV18 NAb GMT 11,962 (9536-14,363) vs 1804 (1574-2110), respectively; P<0.0001]. Cross-NAbs to HPV31 and HPV45 were detected more frequently Cervarix® (HPV31 NAb positivity rates 92.7% and 36%, respectively; P<0.05) than in Gardasil® vaccinees (HPV45 NAb positivity rates 56% and 6%, respectively; P<0.0001). The titres of cross-NAbs against HPV31 and HPV45 were also significantly higher in Cervarix® than in Gardasil® vaccinees [HPV31 NAb GMT 157.2 (95% CI, 92-269) vs 13.0 (6.5-25.8), respectively; P<0.0001; HPV45 NAb GMT 4.7 (2.1-10.2) vs 1.3 (0.3-3.1), respectively; P<0.01]. In conclusion, in adolescent girls vaccinated within organized vaccination programmes, HPV vaccines drive the generation not only of NAbs to HPV vaccine types, but also of cross-NAbs. The bivalent vaccine induced significantly higher HPV16 and HPV18 NAb titres and more frequently and at higher titre HPV31 and HPV45 cross-NAbs than the quadrivalent vaccine.

*Blomberg M et al., Strongly Decreased Risk of Genital Warts After Vaccination Against Human Papillomavirus: Nationwide Follow-up of Vaccinated and Unvaccinated Girls in Denmark.Clinical Infectious Diseases, DOI: 10.1093/cid/cit436

BACKGROUND: A reduction in the incidence of genital warts (GWs) is one of the first markers of the effectiveness of vaccination against human papillomavirus (HPV) at the population level. The aim of this cohort study was to use individual information on HPV vaccination status to assess the effect on risk of GWs. METHODS: Population-based registries were used to identify all girls in the birth cohorts 1989-1999 in Denmark, and information about HPV vaccination was obtained for the period 2006-2012. The cohort was linked to incident cases of GWs, and vaccinated and unvaccinated girls were compared using Cox proportional hazards models. RESULTS: A total of 248 403 girls were vaccinated. The relative risk of GWs among girls who had received at least 1 dose of vaccine compared with unvaccinated girls was 0.12, 0.22, 0.25, and 0.62 for those born in 1995-1996, 1993-1994, 1991-1992, and 1989-1990, respectively (P for trend < .0001). No GWs occurred among vaccinated girls in the youngest birth cohort (1997-1999). CONCLUSIONS: The strong, highly significant reduction in the occurrence of GWs among vaccinated girls indicates an early and marked population effect of the national HPV vaccination program and may forecast a similar effect on cervical precancerous lesions.


We tested the ability of vaccination with virus-like particles (VLPs) to protect domestic rabbits against papillomas induced by the cottontail rabbit papillomavirus (CRPV). A recombinant baculovirus system that expressed only the L1 major papillomavirus structural protein or L1 plus the minor L2 protein was used in insect cells as the source of VLPs. Groups of 10 rabbits were immunized with native or denatured VLPs from CRPV or type 1 bovine papillomavirus by using Freund's adjuvant. Alum was used as the adjuvant for an additional group immunized with CRPV L1-L2 VLPs. Animals were challenged with 5 x 10(10) and 2 x 10(11) particles on opposing flanks. No protection was seen in rabbits immunized with native or denatured bovine papillomavirus L1-L2 or with denatured CRPV L1-L2. In these
groups, the lower and higher challenge doses resulted in 27 of 30 animals with extensive papillomas, with each of the remaining animals having a smaller number of persistent papillomas. Progression to carcinoma developed in 20 rabbits. Animals inoculated with native CRPV VLPs composed of L1 alone or L1-L2 developed many fewer lesions; the lower and higher challenge doses resulted in 17 of 29 and 5 of 29 rabbits, respectively, with no lesions, and the remainder developed only one to eight papillomas, which all regressed except for those on 1 rabbit. None developed cancer within 1 year of infection. Rabbits vaccinated with native CRPV VLPs developed high-titer antibodies in an enzyme-linked immunosorbent assay based on native VLPs, and passive transfer of serum or immunoglobulin G from rabbits immunized with CRPV VLPs protected against CRPV challenge. We conclude that native VLPs can induce antibody-mediated, type-specific protection against experimental papillomavirus infection.


BACKGROUND: Endemic malaria and helminth infections in sub-Saharan Africa can act as immunological modulators and impact responses to standard immunizations. We conducted a cohort study to measure the influence of malaria and helminth infections on the immunogenicity of the bivalent HPV-16/18 vaccine. METHODS: We evaluated the association between malaria and helminth infections, and HPV-16/18 antibody responses among 298 Tanzanian females aged 10-25 years enrolled in a randomized controlled trial of the HPV-16/18 vaccine. Malaria parasitaemia was diagnosed by examination of blood smears, and helminth infections were diagnosed by examination of urine and stool samples, respectively. Geometric mean antibody titres (GMT) against HPV-16/18 antibodies were measured by enzyme-linked immunosorbent assay. RESULTS: Parasitic infections were common; one-third (30.4%) of participants had a helminth infection and 10.2% had malaria parasitaemia. Overall, the vaccine induced high HPV-16/18 GMTs, and there was no evidence of a reduction in HPV-16 or HPV-18 GMT at Month 7 or Month 12 follow-up visits among participants with helminths or malaria. There was some evidence that participants with malaria had increased GMTs compared to those without malaria. CONCLUSIONS: The data show high HPV immunogenicity regardless of the presence of malaria and helminth infections. The mechanism and significance for the increase in GMT in those with malaria is unknown.


Human papillomavirus (HPV)-specific antibodies are proposed to be the correlate of protection afforded by HPV L1 virus-like particle (VLP) vaccines. Previous studies have characterized the systemic antibody response to immunization in terms of both the quantity and the ability to neutralize HPV. Here, we have adapted a generalized memory B cell ELISPOT to the HPV16 system and expanded the analysis of the systemic antibody response to include an avidity measurement of HPV L1 VLP-specific antibodies. We show the results of the memory B cell ELISPOT significantly correlated with IgG and neutralizing antibody titers, but not with the avidity measurement. This is the first comprehensive study to correlate a variety of humoral aspects potentially associated with protective immunity following vaccination with a HPV16 L1 VLP vaccine.


In developing countries, risk of human papillomavirus (HPV) infection may be increased by the high prevalence of human immunodeficiency virus (HIV) infection. We evaluated the safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine in HIV-infected women in South Africa. Asymptomatic HIV-positive women aged 18-25 years (N=120) were stratified by CD4⁺ T-cell count and randomised (1:1) to receive HPV-16/18 vaccine (Cervarix®; GlaxoSmithKline Vaccines) or placebo (Al[OH]3) at 0, 1 and 6 months (double-blind). HIV-negative women (N=30) received HPV-16/18 vaccine (open label). Anti-HPV-16/18 antibody and CD4⁺ T-cell responses, CD4⁺ T-cell count, HIV viral load, HIV clinical stage and safety were evaluated for 12 months. The safety and reactogenicity profile of the HPV-16/18 vaccine was comparable in HIV-positive and HIV-negative women. Irrespective of baseline HPV status, all HIV-positive and HIV-negative women who received the HPV-16/18 vaccine were seropositive for both HPV-16 and HPV-18 after the second vaccine dose (month 2) and remained seropositive for both antigens at month 12. Anti-HPV-16/18 antibody titres at month 12 remained substantially above levels associated with natural infection. The HPV-16/18 vaccine induced sustained anti-HPV-16/18 CD4⁺ T-cell responses in both HIV-positive and HIV-negative women. No impact of baseline CD4⁺ T-cell count or HIV viral load was observed on the magnitude of the immune response in HIV-positive women. In HIV-positive women, CD4⁺ T-cell count, HIV viral load and HIV clinical stage were unaffected by HPV-16/18 vaccine administration. In conclusion, the HPV-16/18 AS04-adjuvanted vaccine appears immunogenic and well-tolerated in women with HIV infection. Study ID: 107863/NCT00586339.


OBJECTIVES: To evaluate the prophylactic efficacy of the human papillomavirus (HPV) quadrivalent vaccine in preventing low grade cervical, vulvar, and vaginal intraepithelial neoplasias and anogenital warts (condyloma acuminata). DESIGN:
Data from two international, double blind, placebo controlled, randomised efficacy trials of quadrivalent HPV vaccine (protocol 013 (FUTURE I) and protocol 015 (FUTURE II)). The trials were to be 4 years in length, and the results reported are from final study data of 42 months’ follow-up. SETTING: Primary care centres and university or hospital associated health centres in 24 countries and territories around the world. PARTICIPANTS: 17 622 women aged 16-26 years enrolled between December 2001 and May 2003. Major exclusion criteria were lifetime number of sexual partners (>4), history of abnormal cervical smear test results, and pregnancy. INTERVENTION: Three doses of quadrivalent HPV vaccine (for serotypes 6, 11, 16, and 18) or placebo at day 1, month 2, and month 6. MAIN OUTCOME MEASURES: Vaccine efficacy against cervical, vulvar, and vaginal intraepithelial neoplasia grade I and condyloma in a per protocol susceptible population that included subjects who received all three vaccine doses, tested negative for the relevant vaccine HPV types at day 1 and remained negative through month 7, and had no major protocol violations. Intention to treat, generally HPV naive, and unrestricted susceptible populations were also studied. RESULTS: In the per protocol susceptible population, vaccine efficacy against lesions related to the HPV types in the vaccine was 96% for cervical intraepithelial neoplasia grade I (95% confidence interval 91% to 98%), 100% for both vulvar and vaginal intraepithelial neoplasia grade I (95% CIs 74% to 100%, 64% to 100% respectively), and 99% for condyloma (96% to 100%). Vaccine efficacy against any lesion (regardless of HPV type) in the generally naive population was 30% (17% to 41%), 75% (22% to 94%), and 48% (10% to 71%) for cervical, vulvar, and vaginal intraepithelial neoplasia grade I, respectively, and 83% (74% to 89%) for condyloma. CONCLUSIONS: Quadrivalent HPV vaccine provided sustained protection against low grade lesions attributable to vaccine HPV types (6, 11, 16, and 18) and a substantial reduction in the burden of these diseases through 42 months of follow-up. TRIAL REGISTRATIONS: NCT00092521 and NCT00092534.


Cervical cancer is an important public health problem worldwide, and especially in developing countries. The link between cervical cancer and oncogenic human papillomavirus (HPV) infection has been clearly established. Furthermore, non-oncogenic HPV are responsible for the majority of genital warts. Two prophylactic HPV vaccines are available, which have the potential of considerably reducing HPV-related morbidity and mortality. Both vaccines are based on virus-like particles of the L1 capsid protein, and are highly efficacious and immunogenic if given before exposure to HPV, i.e. to adolescent girls between 9 and 13 years of age in a three-dose schedule. This review describes the immunology of natural HPV infections and the immune response evoked through vaccination. The current duration of protection is 8.4 years with the bivalent vaccine (HPV16/18) and 5 years with the quadrivalent vaccine (HPV6/11/16/18). Research is on-going to evaluate the efficacy of the current vaccines in a two-dose schedule, as compared to the recommended three-dose schedule. To increase the protection, the development and testing of a nine-valent prophylactic HPV vaccine (HPV6/11/16/18/31/33/45/52/58) is being undertaken. Research is also directed towards therapeutic vaccines and the development of a prophylactic L2 vaccine.
BACKGROUND: The current generation of Human Papillomavirus (HPV) vaccines, Cervarix® and Gardasil®, exhibit a high degree of efficacy in clinical trials against the two high-risk (HR) genotypes represented in the vaccines (HPV16 and HPV18). High levels of neutralizing antibodies are elicited against the vaccine types, consistent with preclinical data showing that neutralizing antibodies can mediate type-specific protection in the absence of other immune effectors. The vaccines also confer protection against some closely related non-vaccine HR HPV types, although the vaccines appear to differ in their degree of cross-protection. The mechanism of vaccine-induced cross-protection is unknown. This study sought to compare the breadth and magnitudes of neutralizing antibodies against non-vaccine HPV types elicited by both vaccines and establish whether such antibodies could be detected in the genital secretions of vaccinated individuals. METHODS AND FINDINGS: Serum and genital samples were collected from 12-15 year old girls following vaccination with either Cervarix® (n = 96) or Gardasil® (n = 102) HPV vaccine. Serum-neutralizing antibody responses against non-vaccine HPV types were broader and of higher magnitude in the Cervarix®, compared to the Gardasil®, vaccinated individuals. Levels of neutralizing and binding antibodies in genital secretions were closely associated with those found in the serum (r = 0.869), with Cervarix® having a median 2.5 (inter-quartile range, 1.7-3.5) fold higher geometric mean HPV-specific IgG ratio in serum and genital samples than Gardasil® (p = 0.0047). There was a strong positive association between cross-neutralizing antibody seropositivity and available HPV vaccine trial efficacy data against non-vaccine types. CONCLUSIONS: These data demonstrate for the first time that cross-neutralizing antibodies can be detected at the genital site of infection and support the possibility that cross-neutralizing antibodies play a role in the cross-protection against HPV infection and disease that has been reported for the current HPV vaccines. TRIAL REGISTRATION: ClinicalTrials.gov NCT00956553.
low levels of neutralizing antibodies would be sufficient to protect at the site of infection in the absence of other immune effectors but the coincidence with HPV types reported from efficacy studies is intriguing. The utility of neutralizing antibodies as surrogate markers of protection remains to be determined.


This observer-blind study compared the prophylactic human papillomavirus (HPV) vaccines, Cervarix (GlaxoSmithKline) and Gardasil (Merck), by assessing immunogenicity and safety through one month after completion of the three-dose vaccination course. Women (n = 1106) were stratified by age (18-26, 27-35, 36-45 years) and randomized (1:1) to receive Cervarix (Months 0, 1, 6) or Gardasil (Months 0, 2, 6). At Month 7 after first vaccination, all women in the according-to-protocol cohort who were seronegative/DNA negative before vaccination for the HPV type analyzed had seroconverted for HPV-16 and HPV-18 serum neutralizing antibodies, as measured by pseudovirion-based neutralization assay (PBNA), except for two women aged 27-35 years in the Gardasil group who did not seroconvert for HPV-18 (98%). Geometric mean titers of serum neutralizing antibodies ranged from 2.3-4.8-fold higher for HPV-16 and 6.8-9.1-fold higher for HPV-18 after vaccination with Cervarix compared with Gardasil, across all age strata. In the total vaccinated cohort (all women who received at least one vaccine dose, regardless of their serological and DNA status prior to vaccination), Cervarix induced significantly higher serum neutralizing antibody titers in all age strata (p < 0.0001). Positivity rates for anti-HPV-16 and -18 neutralizing antibodies in cervicovaginal secretions and circulating HPV-16 and -18 specific memory B-cell frequencies were also higher after vaccination with Cervarix compared with Gardasil. Both vaccines were generally well tolerated. The incidence of unsolicited adverse events was comparable between vaccinated groups. The incidence of solicited symptoms was generally higher after Cervarix, injection site reactions being most common. However, compliance rates with the three-dose schedules were similarly high (>or= 84%) for both vaccines. Although the importance of differences in magnitude of immune response between these vaccines is unknown, they may represent determinants of duration of protection against HPV-16/18. Long-term studies evaluating duration of efficacy after vaccination are needed for both vaccines.

*Erickson BK, Landers EE, Huh WK. Update on Vaccination Clinical Trials for HPV-Related Disease. Clinical Therapeutics 2014;36(1):8–16.

BACKGROUND: Cervical cancer remains a major cause of cancer death in women worldwide. Moreover, human papillomavirus (HPV)-related disease of the urogenital tract (including preinvasive and invasive cervical, vaginal, vulvar, penile, and anal disease) remains a major cause of morbidity and mortality in the United States and internationally. OBJECTIVE: The goal of this article was to review the vaccines available as well as the major Phase III trials of the quadrivalent and bivalent vaccines for the prevention of HPV-related genital tract disease. METHODS: A literature search was performed through PubMed using the terms "HPV vaccination"
and limited to clinical trials over the last 6 years. The most relevant and largest scale trials were included in this report. RESULTS: Prophylactic vaccination has emerged as an important tool that holds promise in decreasing the burden of HPV disease. However, HPV vaccination is known to be largely type-specific. Vaccination is most effective when administered at a younger age and before sexual activity and exposure to HPV. Large trials have been conducted and show efficacy of both the bivalent (HPV types 16 and 18) and quadrivalent (HPV types 6, 11, 16, and 18) vaccine in the prevention of preinvasive lesions and infection with these HPV types.

CONCLUSIONS: Future directions include development of more affordable vaccines with extended HPV-type coverage as well as implementation of feasible worldwide vaccination programs.


BACKGROUND: We present a long-term safety, immunogenicity, and effectiveness study of a quadrivalent human papillomavirus (HPV4) vaccine. METHODS: Sexually naive boys and girls aged 9 to 15 years (N = 1781) were assigned (2:1) to receive HPV4 vaccine or saline placebo at day 1 and months 2 and 6. At month 30, the placebo group (n = 482) received HPV4 vaccine following the same regimen and both cohorts were followed through month 96. Subjects ≥16 years were eligible for effectiveness evaluations. The primary objective was to evaluate the long-term anti-HPV6/11/16/18 serological levels. The secondary objective was to estimate vaccine effectiveness against HPV6/11/16/18-related persistent infection or disease.

RESULTS: For each of the HPV4 vaccine types, vaccination-induced anti-HPV response persisted through month 96. Among 429 subjects who received HPV4 vaccine at a mean age of 12, none developed HPV6/11/16/18-related disease or persistent infection of ≥12 months’ duration. Acquisition of new sexual partners (among those ≥16 years) was ~1 per year. Subjects receiving HPV4 vaccine at month 30 (mean age 15 years) had a similar baseline rate of seropositivity to ≥1 of the 4 HPV types to those vaccinated at day 1 (mean age 12 years; 1.9% [9 of 474] vs 1.7% [20 of 1157]); however, 4 of the 9 subjects vaccinated at the later age were seropositive to 3 vaccine types, indicating previous HPV exposure. No new significant serious adverse events were observed for 8 years postvaccination in both genders. CONCLUSIONS: When administered to adolescents, the HPV4 vaccine demonstrated durability in clinically effective protection and sustained antibody titers over 8 years.


BACKGROUND: Australia was one of the first countries to introduce a publicly funded national human papillomavirus (HPV) vaccination program that commenced in April 2007, using the quadrivalent HPV vaccine targeting 12- to 13-year-old girls on an ongoing basis. Two-year catch-up programs were offered to 14- to 17-year-old girls in schools and 18- to 26-year-old women in community-based settings. We present data from the school-based program on population-level vaccine effectiveness against cervical abnormalities in Victoria, Australia. METHODS: Data for women age-eligible for the HPV vaccination program were linked between the Victorian Cervical Cytology Registry and the National HPV Vaccination Program Register to create a cohort of screening women who were either vaccinated or
unvaccinated. Entry into the cohort was 1 April 2007 or at first Pap test for women not already screening. Vaccine effectiveness (VE) and hazard ratios (HR) for cervical abnormalities by vaccination status between 1 April 2007 and 31 December 2011 were calculated using proportional hazards regression. RESULTS: The study included 14,085 unvaccinated and 24,871 vaccinated women attending screening who were eligible for vaccination at school, 85.0% of whom had received three doses. Detection rates of histologically confirmed high-grade (HG) cervical abnormalities and high-grade cytology (HGC) were significantly lower for vaccinated women (any dose) (HG 4.8 per 1,000 person-years, HGC 11.9 per 1,000 person-years) compared with unvaccinated women (HG 6.4 per 1,000 person-years, HGC 15.3 per 1,000 person-years) HR 0.72 (95% CI 0.58 to 0.91) and HR 0.75 (95% CI 0.65 to 0.87), respectively. The HR for low-grade (LG) cytological abnormalities was 0.76 (95% CI 0.72 to 0.80). VE adjusted a priori for age at first screening, socioeconomic status and remoteness index, for women who were completely vaccinated, was greatest for CIN3+/AIS at 47.5% (95% CI 22.7 to 64.4) and 36.4% (95% CI 9.8 to 55.1) for women who received any dose of vaccine, and was negatively associated with age. For women who received only one or two doses of vaccine, HRs for HG histology were not significantly different from 1.0, although the number of outcomes was small. CONCLUSION: A population-based HPV vaccination program in schools significantly reduced cervical abnormalities for vaccinated women within five years of implementation, with the greatest vaccine effectiveness observed for the youngest women.


An effective virus-like particle (VLP) based prophylactic vaccine designed to protect against persistent infection with human papillomavirus (HPV) types 16 and 18 and subsequent lesion development will need to induce a strong humoral and cellular immune response capable of providing long-term protection. Our objective was to evaluate the ability of an HPV16/18 L1 VLP vaccine formulated with the AS04 adjuvant system (3-O-desacyl-4′-monophosphoryl lipid A (MPL) and aluminium salt) to induce an immune response of higher magnitude and persistence compared to a vaccine formulated with aluminium salt only. We demonstrated that MPL adsorbed onto aluminium salt retains its capacity to activate an innate immune response as assessed by the production of TNFalpha by human monocytes (U937). In addition, vaccination of mice, monkeys or human subjects with AS04 formulations induced higher total anti-L1 VLP16 and L1 VLP18 antibody responses (1.6-8.5-fold) than the aluminium salt only formulations. The enhanced antibody response induced by the AS04 vaccine formulation (1.6-4.1-fold) in monkeys and humans was shown to be targeted to functional neutralising L1 VLP16 and L1 VLP18 epitopes as assessed by V5/J4 specific ELISAs or HPV16 and HPV18 pseudo-neutralization assays. The enhanced immune profile observed with the AS04 formulation in terms of both total, V5/J4 specific and neutralizing antibodies was shown to persist for at least 3.5-year post-vaccination in human subjects. Finally, using the newly developed B cell ELISPOT assay we also demonstrated that the AS04 formulation elicited an increased frequency (2.2-5.2-fold) of HPV L1 VLP specific memory B cells when compared with the aluminium salt only formulations. These data strongly support the
role of the AS04 adjuvant, which includes the immunostimulant MPL, in triggering a persistent vaccine-induced immune response of high quality.


Background. No immunogenicity data has been reported after a single dose of the quadrivalent HPV vaccine (qHPV-Gardasil®) and no data are available on co-administration of this vaccine with the HAV/HBV vaccine (Twinrix-Junior®). Two pre-licensure studies reported similar anti-HPV but lower anti-HBs titers when co-administering HPV and HBV vaccines. Objectives. To assess the immunogenicity of the qHPV and HAV/HBV vaccine when co-administered (Group-Co-adm) or given one month apart (Group-Sep) and to measure the persistence of HPV antibodies three years post-second dose of qHPV vaccine in both study groups. Methods. 416 9-10 year-old girls were enrolled. Vaccination schedule was 0-6 months. Anti-HAV and anti-HBs were measured in all subjects 6 months post-first dose and 1 month post-second dose. Anti-HPV were measured 6 months post-first dose in Group-Co-adm and in all subjects 1 and 36 months post-second dose. Results. Six months post-first dose: 100% of subjects had detectable anti-HAV and 56% and 73% had detectable anti-HBs in Group-Co-adm and Group-Sep, respectively. In Group-Co-adm 94, 100, 99 and 96% had detectable antibodies to HPV 6, 11, 16 and 18, respectively. One month post-second dose of qHPV and HAV/HBV vaccine, in both study groups 99.5-100% of subjects had an anti-HAV titer ≥ 20IU/L, 97.5-97.6% an anti-HBs level ≥ 10IU/L, and 100% had an anti-HPV titer ≥ 3LU. Thirty-six months post-second dose of qHPV all but four subjects (99%) had antibodies to HPV18 and 100% had antibodies to HPV6, 11 and 16. The great majority (97-100%) had an anti-HPV titer ≥ 3 LU. Post-second dose administration of qHPV and HAV/HBV, no meaningful difference was observed in the immune response in the two study groups to any component of vaccines. Conclusions. The results indicate that qHPV and HAV/HBV can be given during the same vaccination session. Two doses of of qHPV and HAV/HBV vaccines induce a strong immune response. Three years post-second dose of qHPV, the great majority of subjects had antibodies to HPV types included in the vaccine. A two-dose schedule for pre-adolescents might be a reasonable alternative to the currently approved three-dose schedules.


*Harper et al. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. Lancet 2006;367:1247.

BACKGROUND: Effective vaccination against HPV 16 and HPV 18 to prevent cervical cancer will require a high level of sustained protection against infection and precancerous lesions. Our aim was to assess the long-term efficacy, immunogenicity, and safety of a bivalent HPV-16/18 L1 virus-like particle AS04 vaccine against incident and persistent infection with HPV 16 and HPV 18 and their associated
cytological and histological outcomes. METHODS: We did a follow-up study of our multicentre, double-blind, randomised, placebo-controlled trial reported in 2004. We included women who originally received all three doses of bivalent HPV-16/18 virus-like particle AS04 vaccine (0.5 mL; n=393) or placebo (n=383). We assessed HPV DNA, using cervical samples, and did yearly cervical cytology assessments. We also studied the long-term immunogenicity and safety of the vaccine. FINDINGS: More than 98% seropositivity was maintained for HPV-16/18 antibodies during the extended follow-up phase. We noted significant vaccine efficacy against HPV-16 and HPV-18 endpoints: incident infection, 96.9% (95% CI 81.3-99.9); persistent infection: 6 month definition, 94.3 (63.2-99.9); 12 month definition, 100% (33.6-100). In a combined analysis of the initial efficacy and extended follow-up studies, vaccine efficacy of 100% (42.4-100) against cervical intraepithelial neoplasia (CIN) lesions associated with vaccine types. We noted broad protection against cytohistological outcomes beyond that anticipated for HPV 16/18 and protection against incident infection with HPV 45 and HPV 31. The vaccine has a good long-term safety profile. INTERPRETATION: Up to 4.5 years, the HPV-16/18 L1 virus-like particle AS04 vaccine is highly immunogenic and safe, and induces a high degree of protection against HPV-16/18 infection and associated cervical lesions. There is also evidence of cross protection.


BACKGROUND: A community-based randomized trial was conducted in Costa Rica to evaluate the HPV-16/18 AS04-adjuvanted vaccine (NCT00128661). The primary objective was to evaluate efficacy of the vaccine to prevent cervical intraepithelial neoplasia 2 or more severe disease (CIN2+) associated with incident HPV-16/18 cervical infections. Secondary objectives were to evaluate efficacy against CIN2+ associated with incident cervical infection by any oncogenic HPVs and to evaluate duration of protection against incident cervical infection with HPV-16/18. Vaccine safety and immunogenicity over the 4-year follow-up were also evaluated. METHODS: We randomized (3727 HPV arm; 3739 control arm), vaccinated (HPV-16/18 or Hepatitis A) and followed (median 53.8 months) 7466 healthy women aged 18-25 years. 5312 women (2635 HPV arm; 2677 control arm) were included in the according to protocol analysis for efficacy. The full cohort was evaluated for safety. Immunogenicity was considered on a subset of 354 (HPV-16) and 379 (HPV-18) women. HPV type was assessed by PCR on cervical specimens. Immunogenicity was assessed using ELISA and inhibition enzyme immunoassays. Disease outcomes were histologically confirmed. Vaccine efficacy and 95% confidence intervals (95%CI) were computed. RESULTS: Vaccine efficacy was 89.8% (95% CI: 39.5-99.5; N=11 events total) against HPV-16/18 associated CIN2+, 59.9% (95% CI: 20.7-80.8; N=39 events total) against CIN2+ associated with non-HPV-16/18 oncogenic HPVs and 61.4% (95% CI: 29.5-79.8; N=51 events total) against CIN2+ irrespective of HPV type. The vaccine had an acceptable safety profile and induced robust and long-lasting antibody responses. CONCLUSIONS: Our findings confirm the high efficacy and immunogenicity of the HPV-16/18 vaccine against incident HPV infections and cervical disease associated with HPV-16/18 and other oncogenic HPV types. These results will serve as a benchmark to which we can compare future
findings from the ongoing extended follow-up of participants in the Costa Rica trial.
TRIAL REGISTRATION: Registered with clinicaltrials.gov: NCT00128661.


BACKGROUND: Diagnoses of genital warts (GW) in genitourinary medicine (GUM) clinics have been increasing in England for many years. In 2008, an HPV immunization program began with a bivalent vaccine (Cervarix). This was expected to markedly reduce infections and disease due to human papillomavirus (HPV) 16/18 but not HPV 6/11 infections or disease. However, from 2009 to 2011 there were decreases in reported diagnoses of GW in young females at GUM clinics.

METHODS: Using data from GUM clinics and a sample of general practices (GPs) throughout England, we analyzed rates of GW diagnoses by age, year of diagnosis, and estimated immunization coverage. RESULTS: The overall reduction in GW diagnoses at GUM clinics between 2008 and 2011 was 13.3% among 16- to 19-year-old females, with the greatest decline of 20.8% in 17-year-olds. Declines were positively associated with estimated immunization coverage. A similar pattern was seen in GP diagnoses, but not among older women, and for other GUM consultations. CONCLUSIONS: Several factors might contribute to declines in GW. However, the size and pattern of the declines strongly suggest that we are observing an unexpected, moderately protective effect of HPV 16/18 vaccination against GW.


BACKGROUND: The objective of this study was to determine whether the 3-dose quadrivalent human papillomavirus (HPV) vaccine series (HPV-6, -11, -16, -18) is immunogenic and safe in young women infected with human immunodeficiency virus (HIV). METHODS: We enrolled 99 women aged 16-23 years in a phase 2, open-label, multicenter trial, conducted from 2008 to 2011 by the Adolescent Medicine Trials Network for HIV/AIDS Interventions. Outcome measures were immunogenicity 4 weeks after dose 3, measured by (1) geometric mean titers (GMTs) and (2) seroconversion rates for HPV-6, -11, -16, and -18, among those seronegative and HPV DNA negative for each type. Immune responses were compared to those of a historical comparison group of HIV-negative women (n = 267) using univariate methods. Clinical and laboratory adverse events were assessed after each dose. RESULTS: The mean age of subjects was 21.4 years; 80% were non-Hispanic black, 69 were not taking antiretroviral therapy (ART), and 30 were taking ART. No differences in GMTs were noted among participants taking ART vs the comparison group, but GMTs were lower in participants not taking ART vs the comparison group for HPV-16 (2393 vs 3892 milli-Merck units per milliliter [mMU/mL], P = .012) and HPV-18 (463 vs 801 mMU/mL, P = .003). Seroconversion rates were 100% for HPV-6, -11, -16, and -18 among participants taking ART. Rates ranged from 92.3% (for HPV-18) to 100.0% (for HPV-6) among participants not taking ART. One severe adverse event (fatigue) was noted. CONCLUSIONS: In a sample of HIV-infected women who were HPV DNA and HPV seronegative, immune responses to HPV vaccination were generally robust and the vaccine was well tolerated.

BACKGROUND: In 2008, a national human papillomavirus (HPV) immunisation programme began in Scotland for 12-13 year old females with a three-year catch-up campaign for those under the age of 18. Since 2008, three-dose uptake of bivalent vaccine in the routine cohort aged 12-13 has exceeded 90% annually, while in the catch-up cohort overall uptake is 66%. METHODS: To monitor the impact of HPV immunisation, a programme of national surveillance was established (pre and post introduction) which included yearly sampling and HPV genotyping of women attending for cervical screening at age 20. By linking individual vaccination, screening and HPV testing records, we aim to determine the impact of the immunisation programme on circulating type-specific HPV infection particularly for four outcomes: (i) the vaccine types HPV 16 or 18 (ii) types considered to be associated with cross-protection: HPV 31, 33 or 45; (iii) all other high-risk types and (iv) any HPV. RESULTS: From a total of 4679 samples tested, we demonstrate that three doses (n=1100) of bivalent vaccine are associated with a significant reduction in prevalence of HPV 16 and 18 from 29.8% (95% confidence interval 28.3, 31.3%) to 13.6% (95% confidence interval 11.7, 15.8%). The data also suggest cross-protection against HPV 31, 33 and 45. HPV 51 and 56 emerged as the most prevalent (10.5% and 9.6%, respectively) non-vaccine high-risk types in those vaccinated, but at lower rates than HPV 16 (25.9%) in those unvaccinated. CONCLUSIONS: This data demonstrate the positive impact of bivalent vaccination on the prevalence of HPV 16, 18, 31, 33 and 45 in the target population and is encouraging for countries which have achieved high-vaccine uptake.


Human papillomavirus (HPV) L1 VLP-based vaccines are protective against HPV vaccine-related types; however, the correlates of protection have not been defined. We observed that vaccination with Cervarix™ induced cross-neutralizing antibodies for HPV types for which evidence of vaccine efficacy has been demonstrated (HPV31/45) but not for other types (HPV52/58). In addition, HPV31/45 cross-neutralizing titers showed a significant increase with number of doses (HPV31, p<0.001; HPV45, p<0.001) and correlated with HPV16/18 neutralizing titers, respectively. These findings raise the possibility that cross-neutralizing antibodies are effectors of cross-protection observed for the HPV16/18 vaccine.


BACKGROUND: Women infected with human immunodeficiency virus (HIV) are disproportionately affected by human papillomavirus (HPV)-related anogenital disease, particularly with increased immunosuppression. AIDS Clinical Trials Group protocol A5240 was a trial of 319 HIV-infected women in the United States, Brazil, and South Africa to determine immunogenicity and safety of the quadrivalent HPV vaccine in 3 strata based on screening CD4 count: >350 (stratum A), 201-350 (stratum B), and ≤200 cells/µL (stratum C). METHODS: Safety and serostatus of HPV types 6, 11, 16, and 18 were examined. HPV serological testing was performed
using competitive Luminex immunoassay (HPV-4 cLIA). HPV type-specific seroconversion analysis was done for participants who were seronegative for the given type at baseline. RESULTS: Median age of patients was 36 years; 11% were white, 56% black, and 31% Hispanic. Median CD4 count was 310 cells/µL, and 40% had undetectable HIV-1 load. No safety issues were identified. Seroconversion proportions among women at week 28 for HPV types 6, 11,16, and 18 were 96%, 98%, 99%, and 91%, respectively, for stratum A; 100%, 98%, 98%, and 85%, respectively, for stratum B, and 84%, 92%, 93%, and 75%, respectively, for stratum C. CONCLUSIONS: The quadrivalent HPV vaccine targeted at types 6, 11, 16, and 18 was safe and immunogenic in HIV-infected women aged 13-45 years. Women with HIV RNA load >10 000 copies/mL and/or CD4 count <200 cells/µL had lower rates of seroconversion rates. Clinical Trials Registration. NCT00604175.


BACKGROUND: Three-dose regimens for human papillomavirus (HPV) vaccines are expensive and difficult to complete, especially in settings where the need for cervical cancer prevention is greatest. METHODS: We evaluated the vaccine efficacy of fewer than three doses of the HPV16/18 vaccine Cervarix in our Costa Rica Vaccine Trial. Women were randomly assigned to receive three doses of the HPV16/18 vaccine or to a control vaccine and were followed for incident HPV16 or HPV18 infection that persisted in visits that were 10 or more months apart (median follow-up 4.2 years). After excluding women who had no follow-up or who were HPV16 and HPV18 DNA positive at enrollment, 5967 women received three vaccine doses (2957 HPV vaccine vs 3010 control vaccine), 802 received two doses (422 HPV vs. 380 control), and 384 received one dose (196 HPV vs. 188 control). Reasons for receiving fewer doses and other pre- and post-randomization characteristics were balanced within each dosage group between women receiving the HPV and control vaccines. RESULTS: Incident HPV16 or HPV18 infections that persisted for 1 year were unrelated to dosage of the control vaccine. Vaccine efficacy was 80.9% for three doses of the HPV vaccine (95% confidence interval [CI] = 71.1% to 87.7%; 25 and 133 events in the HPV and control arms, respectively), 84.1% for two doses (95% CI = 50.2% to 96.3%; 3 and 17 events), and 100% for one dose (95% CI = 66.5% to 100%; 0 and 10 events). CONCLUSION: Four years after vaccination of women who appeared to be uninfected, this nonrandomized analysis suggests that two doses of the HPV16/18 vaccine, and maybe even one dose, are as protective as three doses.


BACKGROUND: More than 90% of genital warts (GW) cases are caused by human papillomavirus (HPV) types 6 and 11. The introduction of HPV vaccines necessitates the estimation of the population-based incidence of GW immediately before and after vaccination uptake. METHODS: Incidence proportions were calculated using the entire population aged 10–44 years living in Sweden during 2006–2010. The Prescribed Drug Register and the National Patient Register were used to define GW episodes. Time trends were estimated using Poisson regression. RESULTS: In 2010, age-stratified incidence proportions of GW were highest for 20-year-old women (956
cases/100 000), while the incidence proportion among males was greatest at the slightly older age of 24 years (1137 cases/100 000). Crude rates were marginally higher among males than among females during 2006–2007 and appeared to later diverge. Between 2008 and 2010, the overall incidence appeared to increase among males, and the incidence among females declined. Females aged 17 and 18 years had a >25% decline in GW rates between 2006 and 2010, with significant decreases through the age of 25 years. CONCLUSIONS: This study provides a reasonable estimation of the incidence of GW in the Swedish population by use of register data, with results comparable to those from previous smaller studies. There was a downward trend of GW incidence among younger females between 2006 and 2010.


BACKGROUND: Quadrivalent human papillomavirus vaccine (QHPV) is >95% effective in preventing infection with vaccine-type human papillomavirus. The safety and immunogenicity of QHPV are unknown in HIV-infected children. METHODS: HIV-infected children (N = 126)-age > 7 to < 12 years, with a CD4% ≥ 15-and on stable antiretroviral therapy if CD4% was < 25-were blindly assigned to receive a dose of QHPV or placebo (3:1 ratio) at 0, 8, and 24 weeks. Adverse events were evaluated after each dose. Serum antibody against QHPV antigens was measured by a competitive Luminex immunoassay 1 month after the third QHPV dose. RESULTS: The safety profile of QHPV was similar in the 2 study arms and to that previously reported for QHPV recipients. QHPV did not alter the CD4% or plasma HIV RNA. Seroconversion to all 4 antigens occurred in >96% of QHPV recipients and in no placebo recipients. Geometric mean titer was >27 to 262 times greater than the seropositivity cutoff value, depending on the antigen, but was 30%-50% lower against types 6 and 18 than those of age-similar historical controls. CONCLUSIONS: QHPV was safe and immunogenic in this cohort of HIV-infected children. Efficacy trials are warranted.


BACKGROUND: Previous analyses from a randomized trial in women aged 24-45 have shown the quadrivalent HPV vaccine to be efficacious in the prevention of infection, cervical intraepithelial neoplasia (CIN) and external genital lesions (EGL) related to HPV 6/11/16/18 through 4 years. In this report we present long term follow-up data on the efficacy, safety and immunogenicity of the quadrivalent HPV vaccine in adult women. METHODS: Follow-up data are from a study being conducted in 5 sites in Colombia designed to evaluate the long-term immunogenicity, effectiveness, and safety of the qHPV vaccine in women who were vaccinated at 24 to 45 years of age (in the original vaccine group during the base study [n=684]) or 29 to 50 years of age (in the original placebo group during the base study [n=651]). This analysis summarizes data collected as of the year 6 post-vaccination visit relative to day 1 of the base study (median follow-up of 6.26 years) from both the original base study and the Colombian follow-up. RESULTS: There were no cases of HPV 6/11/16/18-related CIN or EGL during the extended follow-up phase in the per-protocol population. Immunogenicity persists against vaccine-related HPV types, and
no evidence of HPV type replacement has been observed. No new serious adverse experiences have been reported. CONCLUSIONS: Vaccination with qHPV vaccine provides generally safe and effective protection from HPV 6-, 11-, 16-, and 18-related genital warts and cervical dysplasia through 6 years following administration to 24-45 year-old women. TRIAL REGISTRATION: Clinicaltrials.govNCT00090220.


BACKGROUND: The extent of cross-protection is a key element in the choice of human papillomavirus (HPV) vaccine to use in vaccination programmes. We compared the cross-protective efficacy of the bivalent vaccine (HPV 16 and 18; Cervarix, GlaxoSmithKline Biologicals, Rixensart, Belgium) and quadrivalent vaccine (HPV 6, 11, 16, and 18; Gardasil, Merck, Whitehouse Station, NJ, USA) against non-vaccine type HPVs. METHODS: We searched Medline and Embase databases, conference abstracts, and manufacturers’ websites for randomised clinical trials assessing the efficacy of bivalent and quadrivalent vaccines against persistent infections (lasting ≥6 months) and cervical intraepithelial neoplasia (CIN) associated with the non-vaccine type HPVs (types 31, 33, 45, 52, and 58). We included studies of participants who were HPV DNA negative before vaccination for all HPV types assessed. We assessed heterogeneity in vaccine efficacy estimates between trials with I(2) and χ(2) statistics. FINDINGS: We identified two clinical trials (Females United to Unilaterally Reduce Endo/Ectocervical Disease [FUTURE] I and II) of the quadrivalent vaccine and three (Papilloma Trial Against Cancer In Young Adults [PATRICIA], HPV007, and HPV-023) of the bivalent vaccine. Analysis of the most comparable populations (pooled FUTURE I/II data vs PATRICIA) suggested that cross-protective vaccine efficacy estimates against infections and lesions associated with HPV 31, 33, and 45 were usually higher for the bivalent vaccine than the quadrivalent vaccine. Vaccine efficacy in the bivalent trial was higher than it was in the quadrivalent trial against persistent infections with HPV 31 (77·1% [95% CI 67·2 to 84·4] for bivalent vaccine vs 46·2% [15·3 to 66·4] for quadrivalent vaccine; p=0·003) and HPV 45 (79·0% [61·3 to 89·4] vs 7·8% [67·0 to 49·3]; p=0·0003), and against CIN grade 2 or worse associated with HPV 33 (82·3% [53·4 to 94·7] vs 24·0% [-7·2 to 67·2]; p=0·02) and HPV 45 (100% [41·7 to 100] vs 51·9% [-1717·8 to 82·6]; p=0·04). We noted substantial heterogeneity between vaccine efficacy in bivalent trials against persistent infections with HPV 31 (I(2)=69%, p=0·04) and HPV 45 (I(2)=70%, p=0·04), with apparent reductions in cross-protective efficacy with increased follow-up. INTERPRETATION: The bivalent vaccine seems more efficacious against non-vaccine HPV types 31, 33, and 45 than the quadrivalent vaccine, but the differences were not all significant and might be attributable to differences in trial design. Efficacy against persistent infections with types 31 and 45 seemed to decrease in bivalent trials with increased follow-up, suggesting a waning of cross-protection; more data are needed to establish duration of cross-protection. FUNDING: Public Health Agency of Canada.


The fact that you can vaccinate a child at 5 years of age and find lymphoid B cells and antibodies specific for this vaccination 70 years later remains an immunologic enigma. It has never been determined how these long-lived memory B cells are
maintained and whether they are protected by storage in a special niche. We report that, whereas blood and spleen compartments present similar frequencies of IgG(+) cells, antismallpox memory B cells are specifically enriched in the spleen where they account for 0.24% of all IgG(+) cells (ie, 10-20 million cells) more than 30 years after vaccination. They represent, in contrast, only 0.07% of circulating IgG(+) B cells in blood (ie, 50-100,000 cells). An analysis of patients either splenectomized or rituximab-treated confirmed that the spleen is a major reservoir for long-lived memory B cells. No significant correlation was observed between the abundance of these cells in blood and serum titers of antivaccinia virus antibodies in this study, including in the contrasted cases of B cell-depleting treatments. Altogether, these data provide evidence that in humans, the two arms of B-cell memory--long-lived memory B cells and plasma cells--have specific anatomic distributions--spleen and bone marrow--and homeostatic regulation.


BACKGROUND: Human papillomavirus (HPV) vaccination was introduced into the routine immunization schedule in the United States in late 2006 for females aged 11 or 12 years, with catch-up vaccination recommended for those aged 13-26 years. In 2010, 3-dose vaccine coverage was only 32% among 13-17 year-olds. Reduction in the prevalence of HPV types targeted by the quadrivalent vaccine (HPV-6, -11, -16, and -18) will be one of the first measures of vaccine impact. METHODS: We analyzed HPV prevalence data from the vaccine era (2007-2010) and the prevaccine era (2003-2006) that were collected during National Health and Nutrition Examination Surveys. HPV prevalence was determined by the Linear Array HPV Assay in cervicovaginal swab samples from females aged 14-59 years; 4150 provided samples in 2003-2006, and 4253 provided samples in 2007-2010. RESULTS: Among females aged 14-19 years, the vaccine-type HPV prevalence (HPV-6, -11, -16, or -18) decreased from 11.5% (95% confidence interval [CI], 9.2-14.4) in 2003-2006 to 5.1% (95% CI, 3.8-6.6) in 2007-2010, a decline of 56% (95% CI, 38-69). Among other age groups, the prevalence did not differ significantly between the 2 time periods (P > .05). The vaccine effectiveness of at least 1 dose was 82% (95% CI, 53-93). CONCLUSIONS: Within 4 years of vaccine introduction, the vaccine-type HPV prevalence decreased among females aged 14-19 years despite low vaccine uptake. The estimated vaccine effectiveness was high.


Quadrivalent human papillomavirus (HPV) [types 6, 11, 16, 18] recombinant vaccine (Gardasil®; Silgard®)) is composed of virus-like particles formed by self-assembly of recombinant L1 capsid protein from each of HPV types 6, 11, 16 and 18. It is indicated for use from the age of 9 years as a two- or three-dose vaccination course.
over 6 months for the prevention of premalignant anogenital lesions, cervical and anal cancers, and genital warts caused by the vaccine HPV types. In placebo-controlled trials, quadrivalent HPV vaccine provided high-level protection against infection or disease caused by the vaccine HPV types over 2-4 years in females aged 15-45 years who were negative for the vaccine HPV types, and provided a degree of cross-protection against certain non-vaccine HPV types. The vaccine also provided high-level protection against persistent infection, anogenital precancerous lesions and genital warts caused by the vaccine HPV types over 3 years in susceptible males aged 16-26 years. Protection has been demonstrated for up to 8 years. In subjects who were negative for the vaccine HPV types, high seroconversion rates and high levels of anti-HPV antibodies were observed in females of all age ranges from 9 to 45 years and in males aged 9-26 years. The vaccine was generally well tolerated and was usually predicted to be cost effective in girls and young women. Therefore, quadrivalent HPV vaccine offers an effective means to substantially reduce the burden of HPV-related anogenital disease in females and males, particularly cervical cancer and genital warts.


BACKGROUND: It is unclear whether L1-VLP-based human papillomavirus (HPV) vaccines are efficacious in reducing the likelihood of anogenital pre-cancer in women with evidence of prior vaccine-type HPV exposure. This study aims to determine whether the combined results of the vaccine trials published to date provide evidence of efficacy compared with control (hepatitis A vaccine/placebo). METHODS: A systematic review and meta-analysis was conducted. Randomized-controlled trials (RCTs) were identified from MEDLINE, Embase, Web of Science, PubMed, Cochrane Central Register of Controlled Trials and references of identified studies. The bivalent vaccine containing HPV-16 and 18 VLPs from GlaxoSmithKline Biologicals (Rixenstart, Belgium), the quadrivalent vaccine containing HPV-6, 11, 16, and 18 VLPs from Merck & Co., Inc., (Whitehouse Station, NJ USA), and the HPV-16 monovalent vaccine from Merck Research Laboratories (West Point, PA USA) were evaluated. FINDINGS: Three RCT reports and two post-trial cohort studies were eligible, comprising data from 13,482 women who were included in the vaccine studies but had evidence of HPV infection at study entry. Data on efficacy was synthesized using the Mantel-Haenszel weighted fixed-effect approach, or where there was heterogeneity between studies, the DerSimonian and Laird weighted random-effect approach. The mean odds ratio (OR) and 95% confidence interval (CI) for the association between Cervarix, Gardasil and HPV-16 monovalent vaccine and HPV-associated cervical intraepithelial neoplasia grade 3 or worse was 0·90 (95% CI: 0·56, 1·44). For the association between Gardasil and HPV-associated vulval/vaginal intraepithelial neoplasia grades 2-3, the overall OR and 95% CI was 2·25 (95% CI: 0·78, 6·50). Sample size and follow-up were limited. CONCLUSIONS: There was no evidence that HPV vaccines are effective in preventing vaccine-type HPV associated pre-cancer in women with evidence of prior HPV exposure. Small effects of vaccination however cannot be excluded and a longer-term benefit in preventing re-infection remains possible.

BACKGROUND: Vaccines are now available for the prevention of HPV-16/18-related cervical infections and pre-cancers, primarily targeting adolescent girls. Since the risk of HPV exposure potentially persists throughout a woman's sexual life, vaccine-derived immunity should be long-term. The current study, HPV-024 (NCT00546078, http://clinicaltrials.gov), assessed the immune memory in North American women who received three doses of HPV-16/18 AS04-adjuvanted vaccine 7 years earlier in HPV-001 (NCT00689741). METHODS: Women vaccinated in HPV-001 received a 4th dose of the HPV-16/18 vaccine (024-4DV group, N=65). Post 4th dose immune responses were compared with post 1st dose immune responses in cross-vaccination controls (024-3DV group, N=50). Reactogenicity was compared between the 4th dose and the 1st dose administration. RESULTS: Pre 4th dose, 100% of subjects in the 024-4DV group remained seropositive for anti-HPV-16/18 antibodies (ELISA). Compared to pre 4th dose, GMTs for anti-HPV-16 and anti-HPV-18 antibodies were respectively 9.3-fold and 8.7-fold higher at day 7, and 22.7-fold and 17.2-fold higher at month 1. Compared to post 1st dose, GMTs for anti-HPV-16 and anti-HPV-18 were respectively 80.5-fold and 205.4-fold higher at day 7, and 11.8-fold and 20.5-fold higher at month 1. Furthermore, 68.2% and 77.3% of women had HPV-16/18 specific memory B-cells, respectively, pre 4th dose, rising to 100% one month post 4th dose vaccination. The 4th dose was generally well tolerated. CONCLUSION: A 4th dose of HPV-16/18 AS04-adjuvanted vaccine triggered a rapid and strong anamnestic response in previously vaccinated women, demonstrating vaccine-induced immune memory.


BACKGROUND: The impact of the prophylactic vaccine against human papillomavirus (HPV) types 6, 11, 16, and 18 (HPV6/11/16/18) on all HPV-associated genital disease was investigated in a population that approximates sexually naive women in that they were "negative to 14 HPV types" and in a mixed population of HPV-exposed and -unexposed women (intention-to-treat group). METHODS: This analysis studied 17 622 women aged 15-26 years who were enrolled in one of two randomized, placebo-controlled, efficacy trials for the HPV6/11/16/18 vaccine (first patient on December 28, 2001, and studies completed July 31, 2007). Vaccine or placebo was given at day 1, month 2, and month 6. All women underwent cervicovaginal sampling and Papanicolaou (Pap) testing at day 1 and every 6-12 months thereafter. Outcomes were any cervical intraepithelial neoplasia; any external anogenital and vaginal lesions; Pap test abnormalities; and procedures such as colposcopy and definitive therapy. Absolute rates are expressed as women with endpoint per 100 person-years at risk. RESULTS: The average follow-up was 3.6 years (maximum of 4.9 years). In the population that was negative to 14 HPV types, vaccination was up to 100% effective in reducing the risk of HPV16/18-related high-grade cervical, vulvar, and vaginal lesions and of HPV6/11-related genital warts. In the intention-to-treat group, vaccination also statistically significantly reduced the risk of any high-grade cervical lesions (19.0% reduction; rate vaccine = 1.43, rate placebo = 1.76, difference = 0.33, 95% confidence interval
[CI] = 0.13 to 0.54), vulvar and vaginal lesions (50.7% reduction; rate vaccine = 0.10, rate placebo = 0.20, difference = 0.10, 95% CI = 0.04 to 0.16), genital warts (62.0% reduction; rate vaccine = 0.44, rate placebo = 1.17, difference = 0.72, 95% CI = 0.58 to 0.87), Pap abnormalities (11.3% reduction; rate vaccine = 10.36, rate placebo = 11.68, difference = 1.32, 95% CI = 0.74 to 1.90), and cervical definitive therapy (23.0% reduction; rate vaccine = 1.97, rate placebo = 2.56, difference = 0.59, 95% CI = 0.35 to 0.83), irrespective of causal HPV type. CONCLUSIONS: High-coverage HPV vaccination programs among adolescents and young women may result in a rapid reduction of genital warts, cervical cytological abnormalities, and diagnostic and therapeutic procedures. In the longer term, substantial reductions in the rates of cervical, vulvar, and vaginal cancers may follow.


HPV-023 (NCT00518336; ClinicalTrials.gov) is a long-term follow-up of an initial double-blind, randomized (1:1), placebo-controlled study (HPV-001, NCT00689741) evaluating the efficacy against human papillomavirus (HPV)-16/18 infection and associated cyto-histopathological abnormalities, persistence of immunogenicity, and safety of the HPV-16/18 AS04-adjuvanted vaccine. Among the women, aged 15-25 years, enrolled in HPV-001 and who participated in the follow-up study HPV-007 (NCT00120848), a subset of 437 women from five Brazilian centers participated in this 36-month long-term follow-up (HPV-023) for a total of 113 months (9.4 years). During HPV-023, anti-HPV-16/18 antibodies were measured annually by enzyme-linked immunosorbent assay (ELISA) and pseudovirion-based neutralisation assay (PBNA). Cervical samples were tested for HPV DNA every 6 months, and cyto-pathological examinations were performed annually. During HPV-023, no new HPV-16/18-associated infections and cyto-histopathological abnormalities occurred in the vaccine group. Vaccine efficacy (VE) against HPV-16/18 incident infection was 100% (95%CI: 66.1, 100). Over the 113 months (9.4 years), VE was 95.6% (86.2, 99.1; 3/50 cases in vaccine and placebo groups, respectively) against incident infection, 100% (84.1, 100; 0/21) against 6-month persistent infection (PI); 100% (61.4, 100; 0/10) against 12-month PI; 97.1% (82.5, 99.9; 1/30) against ≥ ASC-US; 95.0% (68.0, 99.9; 1/18) against ≥ LSIL; 100% (45.2, 100; 0/8) against CIN1+; and 100% (-128.1, 100; 0/3) against CIN2+ associated with HPV-16/18. All vaccinees remained seropositive to HPV-16/18, with antibody titers remaining several folds above natural infection levels, as measured by ELISA and PBNA. There were no safety concerns. To date, these data represent the longest follow-up reported for a licensed HPV vaccine.


Human papillomavirus (HPV) vaccination is recommended in early adolescence, at an age when other vaccines are also recommended. Administration of multiple vaccines during one visit is an opportunity to improve uptake of adolescent vaccines. We conducted a systematic review of safety and immunogenicity of HPV vaccines coadministered with other vaccines. Our review included 9 studies, 4 of quadrivalent HPV vaccine and 5 of bivalent HPV vaccine; coadministered vaccines included: meningococcal conjugate, hepatitis A, hepatitis B, combined hepatitis A and B,
tetanus, diphtheria, acellular pertussis, and inactivated poliovirus vaccines. Studies varied in methods of data collection and measurement of immunogenicity and safety. Noninferiority of immune response and an acceptable safety profile were demonstrated when HPV vaccine was coadministered with other vaccines.


AIM: To review cases of genital warts diagnosed at Auckland Sexual Health Service (ASHS) and to document any change following the introduction of the human papillomavirus (HPV) vaccination. The national HPV immunisation programme, using the quadrivalent vaccine Gardasil, commenced on 1 September 2008. The publically funded programme provides for the ongoing vaccination of girls in year 8 with an initial catch-up programme for young women born after 1 January 1990 until the end of 2010. Monitoring rates of diagnosis of genital warts should provide the earliest clinical indicator of a population response to the vaccine. METHOD: The proportion of new clients attending ASHS who were diagnosed with genital warts from 1 January 2007 to 31 December 2008 was compared to the proportion diagnosed from 1 January 2009 to 30 June 2010. RESULTS: 40,793 new clients attended the ASHS between 2007 and June 2010 and genital warts were diagnosed in 3125 (7.7%). Genital warts were diagnosed in 9.2% of new clients in 2007 decreasing to 6.6% for the first 6 months of 2010. Analysis of the subgroup of clients under the age of 20 years, found genital warts in males decreased from 11.5% in 2007 to 6.9% in 2010 while in females the rates decreased from 13.7% to 5.1% over the same time period. In comparison, the rates decreased from 7.5% in 2007 to 5.9% in 2010 for females aged 20 years and over. Thus there was evidence of a significant difference, in the pre to post vaccination era, in the proportion of female clinic visits for genital warts in those aged less than 20 years and those aged 21 years or older (p=0.02) and further a borderline significant difference for males aged less than 20 years (p=0.05). CONCLUSION: A significant decline in the incidence of genital warts in the target population suggests an early response to the HPV vaccination programme with some evidence of an effect for males aged less than 20 years.


OBJECTIVE: In the quadrivalent (types 6/11/16/18) HPV vaccine (GARDASIL/SILGARD) clinical program, 73% of women aged 16-26 were naïve to all vaccine HPV types. In these women, prophylactic administration of the vaccine was highly effective in preventing HPV 6/11/16/18-related cervical disease. Of the remaining women, 15% of had evidence of past infection with one or more vaccine HPV types (seropositive and DNA negative) at the time of enrollment. Here we present an analysis in this group of women to determine the efficacy of the HPV 6/11/16/18 vaccine against new cervical and external anogenital disease related to the same vaccine HPV type which had previously been cleared. Vaccine tolerability in this previously infected population was also assessed. METHODS: 18,174 women were enrolled into 3 clinical studies. The data presented comprise a subset of these
subjects (n = 2,617) who were HPV seropositive and DNA negative at enrollment (for >or=1 vaccine type). In each study, subjects were randomized in a 1:1 ratio to receive HPV 6/11/16/18 vaccine or placebo at day 1, month 2 and month 6 (without knowledge of baseline HPV status). Procedures performed for efficacy data evaluation included detailed genital examination, Pap testing, and collection of cervicovaginal and external genital specimens. Analyses of efficacy were carried out in a population stratified by HPV serology and HPV DNA status at enrollment.

RESULTS: Subjects were followed for an average of 40 months. Seven subjects in the placebo group developed cervical disease, and eight subjects developed external genital disease related to a vaccine HPV type they had previously encountered. No subject receiving HPV 6/11/16/18 vaccine developed disease to a vaccine HPV type to which they were seropositive and DNA negative at enrolment.

CONCLUSIONS: These results suggest that natural HPV infection-elicited antibodies may not provide complete protection over time, however the immune response to the HPV 6/11/16/18 vaccine appears to prevent reinfection or reactivation of disease with vaccine HPV types. Vaccine-related adverse experiences were higher among subjects receiving vaccine, mostly due to increased injection site adverse experiences.


BACKGROUND: The duration of protection afforded by vaccines represents a critical test of their utility as public health interventions. Some vaccines induce long-term immunity, while others require booster doses. Vaccines that induce long-term protection are usually characterized by the generation of immune memory. Recent trials of a quadrivalent (types 6, 11, 16, 18) human papillomavirus (HPV) vaccine have demonstrated high efficacy through 5 years of follow-up. We evaluated the extent to which the vaccine is able to generate HPV type-specific immune memory.

METHODS: A total of 552, 16-23-year-old women were enrolled in a double-blind, placebo-controlled study. At enrollment, subjects were randomized in a 1:1 ratio to receive three-dose regimens of quadrivalent HPV vaccine or placebo with 3 years' follow-up. A subset of 241 subjects (n=114 in the quadrivalent HPV vaccine group and n=127 in the placebo group) underwent 2 further years of follow-up. All extension subjects received quadrivalent HPV vaccine at month 60 to examine the extent of immune memory in response to the primary vaccination series.

RESULTS: Serum anti-HPV levels declined post-vaccination, but reached a plateau at month 24 that remained stable through month 60. Administration of a challenge dose of vaccine induced a classic anamnestic response, with anti-HPV levels 1 week post-challenge reaching levels observed 1 month following the completion of the three-dose primary series. At 1 month post-challenge, anti-HPV responses were higher than those observed 1-month post-dose 3.

DISCUSSION: A three-dose regimen of quadrivalent HPV vaccine induces high efficacy and stable anti-HPV levels for at least 5 years. Vaccination also induces robust immune memory. These findings suggest that the efficacy of this vaccine will be long lasting.

BACKGROUND: The human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine was immunogenic, generally well tolerated, and effective against HPV-16 or HPV-18 infections, and associated precancerous lesions in an event-triggered interim analysis of the phase III randomised, double-blind, controlled PAPilloma TRial against Cancer In young Adults (PATRICIA). We now assess the vaccine efficacy in the final event-driven analysis. METHODS: Women (15-25 years) were vaccinated at months 0, 1, and 6. Analyses were done in the according-to-protocol cohort for efficacy (ATP-E; vaccine, n=8093; control, n=8069), total vaccinated cohort (TVC, included all women receiving at least one vaccine dose, regardless of their baseline HPV status; represents the general population, including those who are sexually active; vaccine, n=9319; control, n=9325), and TVC-naive (no evidence of oncogenic HPV infection at baseline; represents women before sexual debut; vaccine, n=5822; control, n=5819). The primary endpoint was to assess vaccine efficacy against cervical intraepithelial neoplasia 2+ (CIN2+) that was associated with HPV-16 or HPV-18 in women who were seronegative at baseline, and DNA negative at baseline and month 6 for the corresponding type (ATP-E). This trial is registered with ClinicalTrials.gov, number NCT00122681. FINDINGS: Mean follow-up was 34.9 months (SD 6.4) after the third dose. Vaccine efficacy against CIN2+ associated with HPV-16/18 was 92.9% (96.1% CI 79.9-98.3) in the primary analysis and 98.1% (88.4-100) in an analysis in which probable causality to HPV type was assigned in lesions infected with multiple oncogenic types (ATP-E cohort). Vaccine efficacy against CIN2+ irrespective of HPV DNA in lesions was 30.4% (16.4-42.1) in the TVC and 70.2% (54.7-80.9) in the TVC-naive. Corresponding values against CIN3+ were 33.4% (9.1-51.5) in the TVC and 87.0% (54.9-97.7) in the TVC-naive. Vaccine efficacy against CIN2+ associated with 12 non-vaccine oncogenic types was 54.0% (34.0-68.4; ATP-E). Individual cross-protection against CIN2+ associated with HPV-31, HPV-33, and HPV-45 was seen in the TVC. INTERPRETATION: The HPV-16/18 AS04-adjuvanted vaccine showed high efficacy against cervical intraepithelial neoplasia 2+ (CIN2+) that was associated with HPV-16 or HPV-18 in women who were seronegative at baseline, and DNA negative at baseline and month 6 for the corresponding type (ATP-E). This trial is registered with ClinicalTrials.gov, number NCT00122681. FINDINGS: Mean follow-up was 34.9 months (SD 6.4) after the third dose. Vaccine efficacy against CIN2+ associated with HPV-16/18 was 92.9% (96.1% CI 79.9-98.3) in the primary analysis and 98.1% (88.4-100) in an analysis in which probable causality to HPV type was assigned in lesions infected with multiple oncogenic types (ATP-E cohort). Vaccine efficacy against CIN2+ irrespective of HPV DNA in lesions was 30.4% (16.4-42.1) in the TVC and 70.2% (54.7-80.9) in the TVC-naive. Corresponding values against CIN3+ were 33.4% (9.1-51.5) in the TVC and 87.0% (54.9-97.7) in the TVC-naive. Vaccine efficacy against CIN2+ associated with 12 non-vaccine oncogenic types was 54.0% (34.0-68.4; ATP-E). Individual cross-protection against CIN2+ associated with HPV-31, HPV-33, and HPV-45 was seen in the TVC. INTERPRETATION: The HPV-16/18 AS04-adjuvanted vaccine showed high efficacy against CIN2+ associated with HPV-16/18 and non-vaccine oncogenic HPV types and substantial overall effect in cohorts that are relevant to universal mass vaccination and catch-up programmes. FUNDING: GlaxoSmithKline Biologicals.


BACKGROUND: Vaccination against human papillomavirus (HPV) types 16 and 18 is recommended for girls aged 11 or 12 years with catch-up vaccination through age 26 in the U.S. Cervical intraepithelial neoplasia (CIN) grade 2 or 3 and adenocarcinoma in situ (CIN2+) are used to monitor HPV vaccine impact on cervical disease. This report describes vaccination status in women diagnosed with CIN2+ and examines HPV vaccine impact on HPV 16/18-related CIN2+. METHODS: As part of a vaccine impact monitoring project (HPV-IMPACT), females 18-31 years with CIN2+ were reported from pathology laboratories in CA, CT, NY, OR, TN from 2008 to 2011. One diagnostic block was selected for HPV DNA typing with Roche Linear Array. Demographic, abnormal Papanicolaou (Pap) test dates and vaccine status information were collected. The abnormal Pap test immediately preceding the CIN2+ diagnosis was defined as the ‘trigger Pap’. RESULTS: Among 5083 CIN2+ cases reported to date, 3855 had vaccination history investigated; 1900 had vaccine history documented (vaccinated, with trigger Pap dates, or unvaccinated). Among women
who initiated vaccination >24 months before their trigger Pap, there was a significantly lower proportion of CIN2+ lesions due to 16/18 compared to women who were not vaccinated (aPR=.67, 95% CI:.48-.94). Among the 1900 with known vaccination status, 20% initiated vaccination on/after their trigger Pap, Women aged 21-23 years were more likely to initiate vaccination on/after the trigger Pap compared to 24-26 year olds (29.0% vs. 19.6%, p=.001), as were non-Hispanic blacks compared to non-Hispanic whites (27.3% vs. 19.0%, p=.001) and publicly compared to privately insured women (38.1% vs. 17.4%, p<.0001). CONCLUSION: We found a significant reduction in HPV 16/18-related lesions in women with CIN2+ who initiated vaccination at least 24 months prior to their trigger Pap. These preliminary results suggest early impact of the HPV vaccine on vaccine-type disease, but further evaluation is warranted.


Two vaccines against HPV are commercially available: an HPV-16/18 (bivalent) and an HPV-6/11/16/18 (quadrivalent) vaccine. Vaccination programs have been and will be implemented before the full duration of protection is known. Whether booster doses will be required is also unknown at this time. Meanwhile, predictions rely upon phase III studies and mathematical modelling. In a head to head study, the bivalent vaccine induced a higher, more sustained immune response than the quadrivalent vaccine. Immunogenicity of the bivalent vaccine against HPV-16 and HPV-18 has been demonstrated up to 8.4 years. For the quadrivalent vaccine, immunogenicity data up to 5 years show that the immune response against HPV-18 wanes after approximately 4 years. Efficacy against infection and cervical lesions associated with HPV-16/18 has been shown up to 8.4 and 5 years with the bivalent and quadrivalent vaccine, respectively. Cross-protection against non-vaccine types appears stronger with the bivalent vaccine. However, both vaccines may provide sufficient immunogenicity to confer long-term protection. Ongoing monitoring is essential.


This randomized, partially-blind study (ClinicalTrials.gov registration number NCT00541970) evaluated the immunogenicity and safety of 2-dose (2D) schedules of the HPV-16/18 AS04-adjuvanted vaccine. Results to month (M) 24 have been reported previously and we now report data to M48 focusing on the licensed vaccine formulation (20 µg each of HPV-16 and -18 antigens) administered at M0,6 compared with the standard 3-dose (3D) schedule (M0,1,6). Healthy females (age stratified: 9-14, 15-19, 20-25 years) were randomized to receive 2D at M0,6 (n = 240) or 3D at M0,1,6 (n = 239). In the according-to-protocol immunogenicity cohort, all initially seronegative subjects seroconverted for HPV-16 and -18 antibodies and remained seropositive up to M48. For both HPV-16 and -18, geometric mean antibody titer (GMT) ratios (3D schedule in women aged 15-25 years divided by 2D schedule in girls aged 9-14 years) at M36 and M48 were close to 1, as they were at M7 when non-inferiority was demonstrated. The kinetics of HPV-16, -18, -31, and -45 antibody responses were similar for both groups and HPV-16 and -18 GMTs were substantially higher than natural infection titers. The vaccine had a clinically acceptable safety profile in both groups. In summary, antibody responses to a 2D
A 2D schedule could facilitate implementation of HPV vaccination programs and improve vaccine coverage and series completion rates.


Prophylactic human papillomavirus (HPV) vaccines are now available and vaccination programs are being widely implemented, targeting adolescent girls prior to sexual debut. Since the risk of HPV exposure persists throughout a woman’s sexual life, the duration of protection provided by vaccination is critical to the overall vaccine effectiveness. We report the long-term efficacy and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine (Cervarix (®) ) up to 8.4 y after the first vaccine dose. In an initial placebo-controlled study performed in US, Canada and Brazil, women aged 15-25 y with normal cervical cytology, HPV-16/18 seronegative by ELISA, DNA-negative for 14 oncogenic HPV types by PCR, received either the HPV-16/18 vaccine or placebo (n = 1,113). Subjects were followed up to 6.4 y after the first dose (n = 776). We report an additional 2-y follow-up for women enrolled from the Brazilian centers from the initial study (n = 436). During the current follow-up study (HPV-023, NCT00518336), no new infection or lesions associated with HPV-16/18 occurred in the vaccine group. Vaccine efficacy over the entire follow-up (up to 8.4 y) was 95.1% (84.6, 99.0) for incident infection, 100% (79.8, 100) for 6-mo persistent infection, 100% (56.1, 100) for 12-mo persistent infection and 100% (< 0, 100) for CIN2+ associated with HPV-16/18. All women in the vaccine group remained seropositive to both HPV-16/18, with antibody titers for total and neutralizing antibodies remaining several-folds above natural infection levels. The safety profile was clinically acceptable for both vaccine and control groups. This is, to date, the longest follow-up study for a licensed cervical cancer vaccine.


We conducted an extended follow-up study (March 2006-May 2008) to assess the longer term efficacy of a prophylactic monovalent human papillomavirus (HPV) type 16 L1 virus-like particle vaccine in women (n=290) who had enrolled in a randomized controlled trial of this vaccine (October 1998-November 1999) in Seattle and remained HPV-16 DNA negative during the course of that trial. During the extended follow-up period, in the per-protocol susceptible population, none of the vaccine recipients was found to be infected with HPV-16 or developed HPV-16-related cervical lesions; among placebo recipients, 6 women were found to be infected with HPV-16 (vaccine efficacy [VE]=100%; 95% confidence interval [CI]: 29-100%) and 3 women developed HPV-16-related cervical lesions (VE=100%; 95% CI: <0-100%). Approximately 86% of vaccine recipients remained HPV-16 competitive Luminex immunoassay seropositive at an average of 8.5 years of follow-up. During the combined original trial and extended follow-up period, in the intention-to-treat population, 20 and 22 women developed any cervical lesion regardless of HPV type among the vaccine and placebo recipients, respectively (VE=15%; 95% CI: <0-56%). The results suggest that this monovalent HPV-16 vaccine remains efficacious through 8.5 years after its administration.

The Costa Rica HPV16/18 Vaccine Trial (CVT) showed that four-year vaccine efficacy against 12-month HPV16/18 persistent infection was similarly high among women who received one, two, or the recommended three doses of the bivalent HPV16/18 L1 virus-like particle (VLP) vaccine. Live-attenuated viral vaccines, but not simple-subunit vaccines, usually induce durable lifelong antibody responses after a single dose. It is unclear whether noninfectious VLP vaccines behave more like live-virus or simple-subunit vaccines in this regard. To explore the likelihood that efficacy will persist longer term, we investigated the magnitude and durability of antibodies to this vaccine by measuring HPV16- and HPV18-specific antibodies by VLP-ELISA using serum from enrollment, vaccination, and annual visits through four years in four vaccinated groups; one-dose (n = 78), two-doses separated by one month (n = 140), two doses separated by six months (n = 52), and three scheduled doses (n = 120, randomly selected). We also tested enrollment sera from n = 113 HPV16- or HPV18 L1-seropositive women prevaccination, presumably from natural infection. At four years, 100% of women in all groups remained HPV16/18 seropositive; both HPV16/18 geometric mean titers (GMT) among the extended two-dose group were non-inferior to the three-dose group, and ELISA titers were highly correlated with neutralization titers in all groups. Compared with the natural infection group, HPV16/18 GMTs were, respectively, at least 24 and 14 times higher among the two-dose and 9 and 5 times higher among one-dose vaccinees. Antibody levels following one-dose remained stable from month 6 through month 48. Results raise the possibility that even a single dose of HPV VLPs will induce long-term protection.


BACKGROUND: Infection with human papillomavirus (HPV) 16 or HPV18 elicits an antibody response, but whether the elicited antibodies protect women against subsequent infection by a homologous HPV type compared with seronegative women is unknown. METHODS: Study participants were women aged 18-25 years at enrollment in the control group of the ongoing National Cancer Institute-sponsored, community-based, randomized HPV16/18 Costa Rica Vaccine Trial. At enrollment, 2813 participants were negative for cervical HPV16 DNA and 2950 for HPV18 DNA. Women were interviewed regarding sociodemographic data and medical and health history. Medical and pelvic examinations were conducted for all consenting sexually experienced women. Serum samples taken at enrollment were tested for total HPV16/18 antibodies with a polyclonal enzyme-linked immunosorbent assay, and cervical specimens were tested for type-specific HPV DNA over 4 years of follow-up. Using Poisson regression, we compared rate ratios of newly detected cervical HPV16 or HPV18 infection among homologous HPV-seropositive and HPV-seronegative women, adjusting for age, education, marital status, lifetime number of sexual partners, and smoking. RESULTS: There were 231 newly detected HPV16 infections during 5886 person-years among HPV16-seronegative women compared with 12 newly detected HPV16 infections during 581 person-years among HPV16-seropositive women with the highest HPV16 sero-levels. There were 136 newly detected HPV18 infections during 6352 person-years among HPV18-seronegative women compared with six new infections detected during 675 person-years among
HPV18 seropositives with the highest sero-levels. After controlling for risk factors associated with newly detected HPV infection, having high HPV16 antibody titer at enrollment was associated with a reduced risk of subsequent HPV16 infection (women in the highest tertile of HPV16 antibody titers, adjusted rate ratio = 0.50, 95% confidence interval = 0.26 to 0.86 vs HPV16-seronegative women). Similarly, having high HPV18 antibody titer at enrollment was associated with a reduced risk of subsequent HPV18 infection (women in the highest tertile of HPV18 antibody titers, adjusted rate ratio = 0.36, 95% confidence interval = 0.14 to 0.76 vs HPV18-seronegative women). CONCLUSION: In this study population, having high antibody levels against HPV16 and HPV18 following natural infection was associated with reduced risk of subsequent HPV16 and HPV18 infections.


End of study analyses of the phase III trials of prophylactic human papillomavirus (HPV) virus-like particle (VLP) vaccines in young women are now largely completed. Two distinct vaccines were evaluated, Gardasil® (Merck & Co., Whitehouse Station, NJ USA) a quadrivalent vaccine containing VLPs of types 6, 11, 16 and 18 and Cervarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium), a bivalent vaccine containing VLPs of types 16 and 18. Both vaccines exhibited excellent safety and immunogenicity profiles. The vaccines also demonstrated remarkably high and similar efficacy against the vaccine-targeted types for a range of cervical endpoints from persistent infection to cervical intraepithelial neoplasia grade 3 (CIN3) in women naïve to the corresponding type at the time of vaccination. However, protection from incident infection or disease from non-vaccine types was restricted, and the vaccines had no effect on prevalent infection or disease. Gardasil® also demonstrated strong protection against genital warts and vulvar/vaginal neoplasia associated with the vaccine types. In other trials, Gardasil® protected mid-adult women from incident infection and CIN caused by the vaccine types and protected men for incident infection, genital warts and anal intraepithelial neoplasia by the vaccine types. Cervarix® protected against vaccine-targeted anal infections in women in an end of study evaluation. For practical reasons, efficacy studies have not been conducted in the primary target populations of current vaccination programs, adolescent girls and boys. However, immunogenicity bridging studies demonstrating excellent safety and strong immune responses in adolescence, coupled with the documentation of durable antibody responses and protection in young adults, leads to an optimistic projection of the effectiveness of the vaccines in adolescent vaccination programs. Taken together, the excellent clinical trial results strongly support the potential of the vaccines as high value public health interventions and justify their widespread implementation to prevent anogenital HPV infections and their associated neoplasia. This article forms part of a special supplement entitled "Comprehensive Control of HPV Infections and Related Diseases" Vaccine Volume 30, Supplement 5, 2012.


Infection of mucosal epithelium by papillomaviruses is responsible for the induction of genital and oral warts and plays a critical role in the development of human cervical and oropharyngeal cancer. We have employed a canine model to develop a
systemic vaccine that completely protects against experimentally induced oral mucosal papillomas. The major capsid protein, L1, of canine oral papillomavirus (COPV) was expressed in Sf9 insect cells in native conformation. L1 protein, which self-assembled into virus-like particles, was purified on CsCl gradients and injected intradermally into the foot pad of beagles. Vaccinated animals developed circulating antibodies against COPV and became completely resistant to experimental challenge with COPV. Successful immunization was strictly dependent upon native L1 protein conformation and L1 type. Partial protection was achieved with as little as 0.125 ng of L1 protein, and adjuvants appeared useful for prolonging the host immune response. Serum immunoglobulins passively transferred from COPV L1-immunized beagles to naive beagles conferred protection from experimental infection with COPV. Our results indicate the feasibility of developing a human vaccine to prevent mucosal papillomas, which can progress to malignancy.


In the Phase III PATRICIA study (NCT00122681), the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine (Cervarix®, GlaxoSmithKline Biologicals) was highly efficacious against HPV-16/18 infections and precancerous lesions in women HPV-16/18 deoxyribose nucleic acid (DNA) negative and seronegative at baseline. We present further data on vaccine efficacy (VE) against HPV-16/18 in the total vaccinated cohort including women who may have been exposed to HPV-16/18 infection before vaccination. In women with no evidence of current or previous HPV-16/18 infection (DNA negative and seronegative), VE was 90.3% (96.1% confidence interval: 87.3-92.6) against 6-month persistent infection (PI), 91.9% (84.6-96.2) against cervical intraepithelial neoplasia (CIN)1+ and 94.6% (86.3-98.4) against CIN2+ [97.7% (91.1-99.8) when using the HPV type assignment algorithm (TAA)]. In women HPV-16/18 DNA negative but with serological evidence of previous HPV-16/18 infection (seropositive), VE was 72.3% (53.0-84.5) against 6-month PI, 67.2% (10.9-89.9) against CIN1+, and 68.8% (-28.3-95.0) against CIN2+ [88.5% (10.8-99.8) when using TAA]. In women with no evidence of current HPV-16/18 infection (DNA negative), regardless of their baseline HPV-16/18 serological status, VE was 88.7% (85.7-91.1) against 6-month PI, 89.1% (81.6-94.0) against CIN1+ and 92.4% (84.0-97.0) against CIN2+ [97.0% (90.6-99.5) when using TAA]. In women who were DNA positive for one vaccine type, the vaccine was efficacious against the other vaccine type. The vaccine did not impact the outcome of HPV-16/18 infections present at the time of vaccination. Vaccination was generally well tolerated regardless of the woman's HPV-16/18 DNA or serological status at entry.


BACKGROUND: Public Health England has reported a decrease of up to 20.8% in new diagnoses of external genital warts (GWs) among women aged <19 years since the national vaccination program with the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine began in 2008. A post hoc analysis of the phase III PATRICIA (PAPilloma TRIal against Cancer In young Adults) trial (NCT00122681) was performed to ascertain whether protection against low-risk HPV types was apparent.
METHODS: Vaccine efficacy (VE) at 48 months was assessed against 6-month persistent infection (6MPI) with low-risk HPV types in the total vaccinated cohort (TVC) and in the TVC naive (for 25 HPV types tested) populations. RESULTS: In the TVC naive cohort, VE against 6MPI (95% confidence interval) was 34.5% (11.3 to 51.8) for HPV-6/11, 34.9% (9.1 to 53.7) for HPV-6, 30.3% (-45.0 to 67.5) for HPV-11, and 49.5% (21.0 to 68.3) for HPV-74. CONCLUSIONS: The HPV-16/18 AS04-adjuvanted vaccine appears to have moderate efficacy against persistent infections with a number of low-risk HPV types (HPV-6/11/74), which are responsible for the majority of external GWs, and recently, antibody and cell-mediated immune response to HPV-6/11 have been observed. These findings may help to explain the decrease in external GW diagnoses seen in England.


BACKGROUND: After the introduction of a quadrivalent human papillomavirus (HPV) vaccination programme in Australia in April, 2007, we measured the prevalence of vaccine-targeted and closely related HPV types with the aim of assessing direct protection, cross-protection, and herd immunity. METHODS: In this repeat cross-sectional study, we recruited women aged 18-24 years who attended Pap screening between October, 2005, and July, 2007, in three major metropolitan areas of Australia to form our prevaccine-implementation sample. For our postvaccine-implementation sample, we recruited women aged 18-24 years who attended Pap screening in the same three metropolitan areas from August, 2010, to November, 2012. We compared the crude prevalence of HPV genotypes in cervical specimens between the prevaccine and the postvaccine implementation groups, with vaccination status validated against the National HPV Vaccination Program Register. We estimated adjusted prevalence ratios using log linear regression. We estimated vaccine effectiveness both for vaccine-targeted HPV types (16, 18, 6, and 11) and non-vaccine but related HPV types (31, 33, and 45). FINDINGS: 202 women were recruited into the prevaccine-implementation group, and 1058 were recruited into the postvaccine-implementation group. Crude prevalence of vaccine-targeted HPV genotypes was significantly lower in the postvaccine-implementation sample than in the prevaccine-implementation sample (58 [29%] of 202 vs 69 [7%] of 1058; p<0.0001). Compared with the prevaccine-implementation sample, adjusted prevalence ratios for vaccine-targeted HPV genotypes were 0.07 (95% CI 0.04-0.14; p<0.0001) in fully vaccinated women and 0.65 (0.43-0.96; p=0.03) in unvaccinated women, which suggests herd immunity. No significant declines were noted for non-vaccine-targeted HPV genotypes. However, within the postvaccine-implementation sample, adjusted vaccine effectiveness against vaccine-targeted HPV types for fully vaccinated women compared with unvaccinated women was 86% (95% CI 71-93), and was 58% (26-76) against non-vaccine-targeted but related genotypes (HPV 31, 33, and 45). INTERPRETATION: 6 years after the initiation of the Australian HPV vaccination programme, we have detected a substantial fall in vaccine-targeted HPV genotypes in vaccinated women; a lower prevalence of vaccine-targeted types in unvaccinated women, suggesting herd immunity; and a possible indication of cross-protection against HPV types related to the vaccine-targeted types in vaccinated women. FUNDING: Australian National Health and Medical Research Council and Cancer Council Victoria.

BACKGROUND: We evaluated the efficacy of the human papillomavirus HPV-16/18 AS04-adjuvanted vaccine against non-vaccine oncogenic HPV types in the end-of-study analysis after 4 years of follow-up in PATRICIA (PApilloma TRIal against Cancer In young Adults). METHODS: Healthy women aged 15-25 years with no more than six lifetime sexual partners were included in PATRICIA irrespective of their baseline HPV DNA status, HPV-16 or HPV-18 serostatus, or cytology. Women were randomly assigned (1:1) to HPV-16/18 vaccine or a control hepatitis A vaccine, via an internet-based central randomisation system using a minimisation algorithm to account for age ranges and study sites. The study was double-blind. The primary endpoint of PATRICIA has been reported previously; the present analysis evaluates cross-protective vaccine efficacy against non-vaccine oncogenic HPV types in the end-of-study analysis. Analyses were done for three cohorts: the according-to-protocol cohort for efficacy (ATP-E; vaccine n=8067, control n=8047), total vaccinated HPV-naïve cohort (TVC-naïve; no evidence of infection with 14 oncogenic HPV types at baseline, approximating young adolescents before sexual debut; vaccine n=5824, control n=5820), and the total vaccinated cohort (TVC; all women who received at least one vaccine dose, approximating catch-up populations that include sexually active women; vaccine n=9319, control=9325). Vaccine efficacy was evaluated against 6-month persistent infection, cervical intraepithelial neoplasia grade 2 or greater (CIN2+) associated with 12 non-vaccine HPV types (individually or as composite endpoints), and CIN3+ associated with the composite of 12 non-vaccine HPV types. This study is registered with ClinicalTrials.gov, number NCT00122681. FINDINGS: Consistent vaccine efficacy against persistent infection and CIN2+ (with or without HPV-16/18 co-infection) was seen across cohorts for HPV-33, HPV-31, HPV-45, and HPV-51. In the most conservative analysis of vaccine efficacy against CIN2+, where all cases co-infected with HPV-16/18 were removed, vaccine efficacy was noted for HPV-33 in all cohorts, and for HPV-31 in the ATP-E and TVC-naïve. Vaccine efficacy against CIN2+ associated with the composite of 12 non-vaccine HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), with or without HPV-16/18 co-infection, was 46·8% (95% CI 30·7-59·4) in the ATP-E, 56·2% (37·2-69·9) in the TVC-naïve, and 34·2% (20·4-45·8) in the TVC. Corresponding values for CIN3+ were 73·8% (48·3-87·9), 91·4% (65·0-99·0), and 47·5% (22·8-64·8). INTERPRETATION: Data from the end-of-study analysis of PATRICIA show cross-protective efficacy of the HPV-16/18 vaccine against four oncogenic non-vaccine HPV types-HPV-33, HPV-31, HPV-45, and HPV-51-in different trial cohorts representing diverse groups of women. FUNDING: GlaxoSmithKline Biologicals.


BACKGROUND: Human immunodeficiency virus type 1 (HIV-1)-infected men are at increased risk for anal cancer. Human papillomavirus (HPV) vaccination may prevent anal cancer caused by vaccine types. METHODS: AIDS Malignancy Consortium Protocol 052 is a single-arm, open-label, multicenter clinical trial to assess the safety
and immunogenicity of the quadrivalent HPV (types 6, 11, 16, and 18) vaccine in HIV-1-infected men. Men with high-grade anal intraepithelial neoplasia or anal cancer by history or by screening cytology or histology were excluded. Men received 0.5 mL intramuscularly at entry, week 8, and week 24. The primary end points were seroconversion to vaccine types at week 28, in men who were seronegative and without anal infection with the relevant HPV type at entry, and grade 3 or higher adverse events related to vaccination. RESULTS: There were no grade 3 or greater adverse events attributable to vaccination among the 109 men who received at least 1 vaccine dose. Seroconversion was observed for all 4 types: type 6 (59 [98%] of 60), type 11 (67 [99%] of 68), type 16 (62 [100%] of 62), and type 18 (74 [95%] of 78). No adverse effects on CD4 counts and plasma HIV-1 RNA levels were observed. CONCLUSIONS: The quadrivalent HPV vaccine appears safe and highly immunogenic in HIV-1-infected men. Efficacy studies in HIV-1-infected men are warranted. Clinical trials registration. NCT 00513526.

Vaccine Safety


PURPOSE: The purpose of this study is to further evaluate the safety of the human papillomavirus (HPV)-16/18-AS04-adjuvanted vaccine (HPV-16/18-vaccine Cervarix®, GlaxoSmithKline, Belgium) through a pooled analysis of data from 42 completed/ongoing clinical studies. METHODS: Unsolicited adverse events (AEs) were reported for 30 days after each dose. Medically significant conditions, serious AEs (SAEs), potential immune-mediated diseases (pIMDs) and pregnancy outcomes were captured until study completion. Events leading to subject withdrawal were reviewed. Relative risks compared incidences of spontaneous abortion and pIMDs in controlled studies. RESULTS: Thirty one thousand one hundred seventy-three adolescent girls/women received HPV-16/18-vaccine alone (HPV group), 2166 received HPV-16/18-vaccine coadministered with another vaccine and 24 241 were controls. Mean follow-up was 39 months (range 0-113.3). Incidences of unsolicited AEs reported within 30 days after any dose were similar between HPV and Control groups (30.8%/29.7%). During the entire study period, reports of medically significant conditions (25.0%/28.3%) and SAEs (7.9%/9.3%) were also similarly distributed between groups. Deaths were rare: HPV (alone/coadministered) n = 25, controls n = 20 (n = 18 in blinded groups). pIMDs within 1 year were reported by 0.2% of HPV-16/18 vaccinees and controls. For each pIMD event category, no increased relative risks were reported for HPV-16/18 vaccinees versus controls. Coadministration did not change the overall safety profile. Pregnancy outcomes and withdrawal rates were similar between groups. CONCLUSIONS: Analysis of safety data arising from 57 580 subjects and 96 704 HPV-16/18-vaccine doses shows that the incidences and distribution of AEs were similar among HPV-16/18-vaccine recipients and controls. No new safety signals were identified. The data confirm previous findings that HPV-16/18-vaccine has an acceptable benefit-risk profile in adolescent girls and adult women.

*Angelo MG, Zima J, Tavares Da Silva F, Baril L, Arellano F. Post-licensure safety surveillance for human papillomavirus-16/18-AS04-adjuvanted vaccine: more than 4 years
PURPOSE: To summarise post-licensure safety surveillance over more than 4 years of routine use of the human papillomavirus-16/18-AS04-adjuvanted vaccine (HPV-16/18 vaccine: Cervarix®, GlaxoSmithKline, Belgium). METHODS: We describe global post-licensure passive surveillance data based on routine pharmacovigilance from 18 May 2007 until 17 November 2011 and enhanced surveillance implemented during the 2-year national immunisation programme in the UK (school years 2008-2010). RESULTS: Spontaneous reports from countries worldwide showed a similar pattern for the most frequently reported adverse events after HPV-16/18 vaccination. No patterns or trends were observed for potential immune-mediated diseases after vaccination. Observed incidences of Bell's palsy and confirmed Guillain-Barré syndrome were within the expected range in the general population. Outcomes of pregnancy in women who were inadvertently exposed to HPV-16/18 vaccine during pregnancy, were in line with published reports for similar populations. Enhanced surveillance of adverse events in the UK triggered a review of cases of anaphylaxis, angioedema and syncope reports, leading to an update to the prescribing information. CONCLUSION: Collaborative partnerships between industry and national regulatory agencies facilitated rapid notification and transfer of safety information, allowing for rapid responses in the event of a safety signal of adverse event of concern. More than 4 years of post-licensure experience may provide confidence to providers and the public about the safety profile of HPV-16/18 vaccine in routine use. The safety profile appears to be consistent with pre-licensure data reporting that HPV-16/18 vaccine has an acceptable benefit-risk profile in adolescent girls and women.


OBJECTIVE: To assess the risk of serious adverse events after vaccination of adolescent girls with quadrivalent human papillomavirus (qHPV) vaccine. DESIGN: Register based cohort study. SETTING: Denmark and Sweden, October 2006 to December 2010. PARTICIPANTS: 997,585 girls aged 10-17, among whom 296,826 received a total of 696,420 qHPV vaccine doses. MAIN OUTCOME MEASURES: Incident hospital diagnosed autoimmune, neurological, and venous thromboembolic events (53 different outcomes) up to 180 days after each qHPV vaccine dose. Only events with at least five vaccine exposed cases were considered for further assessment. Rate ratios adjusted for age, country, calendar year, and parental country of birth, education, and socioeconomic status were estimated, comparing vaccinated and unvaccinated person time. For outcomes where the rate ratio was significantly increased, we regarded three criteria as signal strengthening: analysis based on 20 or more vaccine exposed cases (reliability), rate ratio 3.0 or more (strength), and significantly increased rate ratio in country specific analyses (consistency). We additionally assessed clustering of events in time and estimated rate ratios for a risk period that started on day 181. RESULTS: Among the 53 outcomes, at least five vaccine exposed cases occurred in 29 and these were analysed further. Whereas the rate ratios for 20 of 23 autoimmune events were not significantly increased, exposure to qHPV vaccine was significantly associated with Behcet's syndrome, Raynaud's disease, and type 1 diabetes. Each of these three
outcomes fulfilled only one of three predefined signal strengthening criteria. Furthermore, the pattern of distribution in time after vaccination was random for all three and the rate ratios for these outcomes in the period from day 181 after vaccination were similar to the rate ratios in the primary risk period. The rate ratios for five neurological events were not significantly increased and there were inverse associations with epilepsy (rate ratio 0.66, 95% confidence interval 0.54 to 0.80) and paralysis (0.56, 0.35 to 0.90). There was no association between exposure to qHPV vaccine and venous thromboembolism (0.86, 0.55 to 1.36). CONCLUSIONS: This large cohort study found no evidence supporting associations between exposure to qHPV vaccine and autoimmune, neurological, and venous thromboembolic adverse events. Although associations for three autoimmune events were initially observed, on further assessment these were weak and not temporally related to vaccine exposure. Furthermore, the findings need to be interpreted considering the multiple outcomes assessed.


OBJECTIVE: An observational safety study of the quadrivalent human papillomavirus vaccine (HPV4) in women was conducted. This report presents findings from autoimmune surveillance. Design. Subjects were followed for 180 days after each HPV4 dose for new diagnoses of 16 prespecified autoimmune conditions. SETTING: Two managed care organizations in California. Subjects. Number of 189,629 women who received ≥1 dose of HPV4 between 08/2006 and 03/2008. OUTCOME: Potential new-onset autoimmune condition cases amongst HPV4 recipients were identified by electronic medical records. Medical records of those with ≥12-month health plan membership prior to vaccination were reviewed by clinicians to confirm the diagnosis and determine the date of disease onset. The incidence of each autoimmune condition was estimated for unvaccinated women at one study site using multiple imputations and compared with that observed in vaccinated women. Incidence rate ratios (IRR) were calculated. Findings were reviewed by an independent Safety Review Committee (SRC). RESULTS: Overall, 1014 potential new-onset cases were electronically identified; 719 were eligible for case review; 31-40% were confirmed as new onset. Of these, no cluster of disease onset in relation to vaccination timing, dose sequence or age was found for any autoimmune condition. None of the estimated IRR was significantly elevated except Hashimoto's disease [IRR=1.29, 95% confidence interval: 1.08-1.56]. Further investigation of temporal relationship and biological plausibility revealed no consistent evidence for a safety signal for autoimmune thyroid conditions. The SRC and the investigators identified no autoimmune safety concerns in this study. CONCLUSIONS: No autoimmune safety signal was found in women vaccinated with HPV4.


In this observer-blind study (NCT00423046), women (N=1,106), stratified by age (18-26, 27-35, 36-45 y), were randomized (1:1) to receive the HPV-16/18 vaccine (Cervarix®, GlaxoSmithKline Biologicals, Months 0, 1, 6) or the HPV-6/11/16/18
vaccine (Gardasil® Merck & Co., Inc., Months 0, 2, 6). Month 7 results were previously reported; we now report Month 24 results. In the according-to-protocol cohort for immunogenicity (seronegative and DNA-negative at baseline for HPV type analyzed), seropositivity rates of neutralizing antibodies (nAbs) [pseudovirion-based neutralization assay] were, across all age strata, 100% (HPV-16/18 vaccine) and 97.5-100% (HPV-6/11/16/18 vaccine) for HPV-16, and 99.0-100% (HPV-16/18 vaccine) and 72.3-84.4% (HPV-6/11/16/18 vaccine) for HPV-18. Corresponding geometric mean titers (GMTs) were 2.4-5.8-fold higher for HPV-16 and 7.7-9.4-fold higher for HPV-18 with the HPV-16/18 vaccine versus the HPV-6/11/16/18 vaccine; HPV-16 and HPV-18 GMTs were significantly higher with the HPV-16/18 vaccine than the HPV-6/11/16/18 vaccine (p< 0.0001) in the total vaccinated cohort (received ≥1 vaccine dose, irrespective of baseline sero/DNA-status). Similar results were obtained using enzyme-linked immunosorbent assay (ELISA). Positivity rates and GMTs of antigen-specific IgG antibodies in cervicovaginal secretions (ELISA) were not significantly different between vaccines. At Month 24, CD4⁺ T-cell responses for HPV-16 and HPV-18 were higher with the HPV-16/18 vaccine; memory B-cell response was higher for HPV-18 with the HPV-16/18 vaccine and similar between vaccines for HPV-16. Both vaccines were generally well tolerated. Although an immunological correlate of protection has not been defined, differences in the magnitude of immune response between vaccines may represent determinants of duration of protection.


OBJECTIVE: To present a combined analysis of the pregnancy outcomes for women aged up to 45 years enrolled in five phase III clinical studies of the prophylactic quadrivalent human papillomavirus 6/11/16/18 vaccine. METHODS: Twenty thousand five hundred fifty-one women aged 15-45 years received quadrivalent HPV vaccine or placebo at day 1 and months 2 and 6. Urine pregnancy tests were performed immediately before each injection; participants testing positive were not vaccinated. Women who became pregnant after enrollment were discontinued from further vaccination until resolution of pregnancy. All pregnancies were followed for outcomes. RESULTS: During the studies, 1,796 vaccine and 1,824 placebo recipients became pregnant, resulting in 2,008 and 2,029 pregnancies with known outcomes. No significant differences were noted overall for the proportions of pregnancies resulting in live birth, fetal loss, or spontaneous abortion. A total of 40 neonates born to vaccinated women and 30 neonates born to women given placebo
had one or more congenital anomalies (P=.20). The anomalies were diverse and consistent with those most commonly observed in the general population. The vaccine was well tolerated among women who became pregnant. CONCLUSION: Administration of quadrivalent human papillomavirus vaccine to women who became pregnant during the phase III clinical trials did not appear to negatively affect pregnancy outcomes. The vaccine is a U.S. Food and Drug Administration pregnancy category B medication (animal studies revealed no evidence of fetal harm, but there are no adequate and well-controlled studies in pregnant women); however, vaccination is not recommended during pregnancy. Postlicensure surveillance is ongoing. CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, www.clinicaltrials.gov, NCT00092521, NCT00092534, NCT00092495, NCT00092547 and NCT00090220. LEVEL OF EVIDENCE: II.


BACKGROUND: In 7 large managed care organizations (MCOs), we performed a post-licensure safety assessment of quadrivalent human papillomavirus vaccine (HPV4) among 9-26 year-old female vaccine recipients between August 2006 and October 2009. METHODS: Sequential analyses were conducted weekly to detect associations between HPV4 exposure and pre-specified outcomes. The pre-specified outcomes identified by ICD-9 codes using computerized data at the participating MCOs included: Guillan-Barré Syndrome (GBS), stroke, venous thromboembolism (VTE), appendicitis, seizures, syncope, allergic reactions, and anaphylaxis. For rare outcomes, historical background rates were used as the comparison group. For more common outcomes, a concurrent unexposed comparison group was utilized. A standardized review of medical records was conducted for all cases of GBS, VTE, and anaphylaxis. RESULTS: A total of 600,558 HPV4 doses were administered during the study period. We found no statistically significant increased risk for the outcomes studied. However, a non-statistically significant relative risk (RR) for VTE ICD-9 codes following HPV4 vaccination of 1.98 was detected among females age 9-17 years. Medical record review of all 8 vaccinated potential VTE cases in this age group revealed that 5 met the standard case definition for VTE. All 5 confirmed cases had known risk factors for VTE (oral contraceptive use, coagulation disorders, smoking, obesity or prolonged hospitalization). CONCLUSIONS: In a study of over 600,000 HPV4 vaccine doses administered, no statistically significant increased risk for any of the pre-specified adverse events after vaccination was detected. Further study of a possible association with VTE following HPV4 vaccination is warranted.

*Global Advisory Committee on Vaccine Safety Statement on the continued safety of HPV vaccination
http://www.who.int/vaccine_safety/committee/topics/hpv/GACVS_Statement_HPV_12_Mar_2014.pdf?ua=1


INTRODUCTION: Human papillomavirus (HPV) 6/11/16/18 vaccine (qHPV vaccine) is a quadrivalent vaccine for the prevention of cervical, vulvar, and vaginal cancers;
their respective precancers; and genital warts caused by these vaccine types. As of December 2012, more than 50 million doses of qHPV vaccine have been distributed in the United States where the majority of exposures occurred. Because the vaccine is recommended for women of childbearing age, Merck and Co, Inc established the Pregnancy Registry for qHPV vaccine in 2006. A 6-year summary of the safety profile of pregnancy exposures and outcomes to the qHPV vaccine is presented. METHODS: Enrollment criteria to the registry included an identifiable patient and health care provider from the United States, France, or Canada exposed within 1 month before the date of onset of the last menstrual period or at any time during pregnancy. Outcomes of interest were pregnancy outcomes and birth defects. Prospectively reported cases (reported before the outcome of the pregnancy was known) were used for rate calculations because retrospectively reported cases (reported after the outcome is known) are considered to be inherently biased toward abnormal outcomes. The Metro Atlanta Congenital Defects Program methodology is used to compare and define birth defects and estimate rates. RESULTS: For the 1,573 prospective reports with known natural pregnancy outcomes, 1,452 (92%) were live births. Of 1,460 neonates, 1,381 (95%) were born without birth defects. The prevalence of major birth defects was 2.5 per 100 live-born neonates (95% confidence interval [CI] 1.7-3.4) and compares favorably with the observed Metro Atlanta Congenital Defects Program rate of 2.67 per 100. The overall rate of spontaneous abortion was 6.7 per 100 outcomes (95% CI 5.5-8.2). There were 12 fetal deaths (0.8/100 outcomes, 95% CI 0.4-1.4) not clustered around a specific abnormality. CONCLUSION: This is likely the largest HPV vaccine pregnancy registry to date. Rates of spontaneous abortions and major birth defects were not greater than the Metro Atlanta Congenital Defects Program unexposed population rates. Analysis of 6 years of pregnancy registry data shows no adverse signals. The qHPV vaccine is not recommended for use in pregnant women.


OBJECTIVES: The aim of this study was to investigate whether the quadrivalent human papillomavirus (HPV) vaccine Gardasil is associated with a change in the risk of autoimmune disorders (ADs) in young female subjects. DESIGN: Systematic case-control study of incident ADs associated with quadrivalent HPV vaccination in young women across France. PARTICIPANTS AND SETTING: A total of 113 specialised centres recruited (from December 2007 to April 2011) females aged 14-26 years with incident cases of six types of ADs: idiopathic thrombocytopenic purpura (ITP), central demyelination/multiple sclerosis (MS), Guillain-Barré syndrome, connective tissue disorders (systemic lupus erythematosus, rheumatoid arthritis/juvenile arthritis), type 1 diabetes mellitus and autoimmune thyroiditis. Control subjects matched to cases were recruited from general practice. ANALYSIS: Multivariate conditional logistic regression analysis; factors included age, geographical origin, smoking, alcohol consumption, use of oral contraceptive(s) or vaccine(s) other than Gardasil received within 24 months before the index date and personal/family history of ADs. RESULTS: Overall, 211 definite cases of ADs were matched to 875 controls. The adjusted odds ratio (OR) for any quadrivalent HPV vaccine use was 0.9 [95% confidence interval (CI) 0.5-1.5]. The individual ORs were 1.0 (95% CI 0.4-2.6) for ITP, 0.3 (95% CI 0.1-0.9) for MS, 0.8 (95% CI 0.3-2.4) for connective disorders and 1.2 (95% CI 0.4-3.6) for type 1 diabetes. No exposure to
HPV vaccine was observed in cases with either Guillain-Barré syndrome or thyroiditis. CONCLUSIONS: No evidence of an increase in the risk of the studied ADs was observable following vaccination with Gardasil within the time periods studied. There was insufficient statistical power to allow conclusions to be drawn regarding individual ADs.


OBJECTIVE: To assess the safety of the quadrivalent human papillomavirus vaccine (HPV4) in females following routine administration. DESIGN: In a cohort of vaccinated females, we compared the risk of emergency department visits and hospitalizations during the interval soon after vaccination with risk during a comparison interval more remote from vaccination. SETTING: Kaiser Permanente in California. PARTICIPANTS: All females who received the HPV4 vaccine. MAIN EXPOSURE: One or more doses of HPV4 between August 2006 and March 2008. MAIN OUTCOME MEASURES: Outcomes were emergency department visits and hospitalizations, grouped into predefined diagnostic categories. Within diagnostic groups, we used odds ratios (ORs) to estimate whether each subject had any outcome in postvaccination risk intervals (days 1-60, days 1-14, and day 0), compared with a control interval distant in time from vaccination. RESULTS: One hundred eighty-nine thousand six hundred twenty-nine females received at least 1 dose and 44 001 received 3 HPV4 doses. Fifty categories had significantly elevated ORs during at least 1 risk interval. Medical record review revealed that most diagnoses were present before vaccination or diagnostic workups were initiated at the vaccine visit. Only skin infections during days 1 to 14 (OR, 1.8; 95% CI, 1.3-2.4) and syncope on day of vaccination (OR, 6.0; 95% CI, 3.9-9.2) were noted by an independent Safety Review Committee as likely associations with HPV4.

CONCLUSIONS: The quadrivalent human papillomavirus vaccine was associated with same-day syncope and skin infections in the 2 weeks after vaccination. This study did not detect evidence of new safety concerns among females 9 to 26 years of age secondary to vaccination with HPV4.


Vaccination to prevent human papillomavirus (HPV)-related infection leading to cancer, particularly cervical cancer, is a major public health breakthrough. There are currently two licensed HPV vaccines, both of which contain recombinant virus-like particles of HPV types 16 and 18 (which account for approximately 70 % of cervical cancer). One vaccine also protects against HPV types 6 and 11, which cause genital warts. The safety profile of both vaccines was assessed extensively in randomised controlled clinical trials conducted prior to licensure and has been further elucidated following licensure from surveillance and specific studies in large populations. This review aims to examine current evidence regarding the safety of HPV vaccines. In summary, both vaccines are associated with relatively high rates of injection site reactions, particularly pain, but this is usually of short duration and resolves spontaneously. Systemic reactions have generally been mild and self-limited. Post vaccination syncope has occurred, but can be avoided with appropriate care. Serious vaccine-attributable adverse events, such as anaphylaxis, are rare, and although not recommended for use in pregnancy, abnormal pregnancy outcomes
following inadvertent administration do not appear to be associated with vaccination. HPV vaccines are used in a three-dose schedule predominantly in adolescent females: as such case reports linking vaccination with a range of new onset chronic conditions, including autoimmune diseases, have been made. However, well-conducted population-based studies show no association between HPV vaccine and a range of such conditions. Whilst this reassuring safety profile affirms the positive risk benefit of vaccination, as HPV vaccine use expands into more diverse populations, including males, ongoing safety assessment using well-conducted studies is appropriate.


OBJECTIVE: To assess whether vaccination against human papillomavirus (HPV) increases the risk of miscarriage. DESIGN: Pooled analysis of two multicentre, phase three masked randomised controlled trials SETTING: Multicentre trials in several continents and in Costa Rica. PARTICIPANTS: 26 130 women aged 15-25 at enrolment; 3599 pregnancies eligible for analysis. INTERVENTIONS: Participants were randomly assigned to receive three doses of bivalent HPV 16/18 VLP vaccine with AS04 adjuvant (n=13 075) or hepatitis A vaccine as control (n=13 055) over six months. MAIN OUTCOME MEASURES: Miscarriage and other pregnancy outcomes. RESULTS: The estimated rate of miscarriage was 11.5% in pregnancies in women in the HPV arm and 10.2% in the control arm. The one sided P value for the primary analysis was 0.16; thus, overall, there was no significant increase in miscarriage among women assigned to the HPV vaccine arm. In secondary descriptive analyses, miscarriage rates were 14.7% in the HPV vaccine arm and 9.1% in the control arm in pregnancies that began within three months after nearest vaccination. CONCLUSION: There is no evidence overall for an association between HPV vaccination and risk of miscarriage. TRIAL REGISTRATION: Clinical Trials NCT00128661 and NCT00122681.

Cost-effectiveness


BACKGROUND: The decrease in human papillomavirus (HPV) vaccine prices may allow upscale already started vaccination programmes but the advantages of different options are unclear. METHODS: Using a mathematical model of HPV16 and 18 transmission and data on vaccination coverage from Italy, we compared 3 options to upscale an already started programme targeting 11-year old girls (coverage 65%): a) coverage improvement (from 65% to 90%); b) addition of 11-year-old boys (coverage 65%); or c) 1-year catch-up of older girls (coverage 50%). RESULTS: The reduction of cervical HPV16/18 infection as compared to no vaccination (i.e. effectiveness against HPV16/18) increased from 76% to 98% with coverage improvement in girls and to 90% with the addition of boys. With higher coverage in girls, HPV16/18 infection cumulative probability by age 35 decreased
from 25% to 8% with a 38% increase in vaccine number. The addition of boys decreased the cumulative probability to 18% with a 100% increase in the number of vaccinees. For any coverage in girls, the number of vaccinees to prevent 1 woman from being infected by HPV16/18 by age 35 was 1.5, whereas it was 2.7 for the addition of boys. Catch-up of older girls only moved forward the vaccination effectiveness by 2-5 years. CONCLUSIONS: Increasing vaccination coverage among girls is the most effective option for decreasing HPV16/18. If not achievable, vaccinating boys is justifiable if vaccine cost has at least halved, because this option would almost double the number of vaccinees.


BACKGROUND: The quadrivalent and bivalent human papillomavirus (HPV) vaccines are now licensed in several countries. We compared the cost-effectiveness of the HPV vaccines to provide evidence for policy decisions. METHODS: We developed HPV-ADVISE, a multi-type individual-based transmission-dynamic model of HPV infection and disease (anogenital warts, and cervical, anogenital and oropharyngeal cancers). We calibrated the model to sexual behavior and epidemiologic data from Canada, and estimated quality-adjusted life-years (QALYs) lost and costs ($CAN 2010) from the literature. Vaccine-type efficacy was based on a systematic literature review. The analysis was performed from the healthcare provider perspective, and costs and benefits were discounted at 3%. Predictions are presented using the median [10th;90th percentiles] of simulations. RESULTS: Under base-case assumptions (vaccinating 10-year-old girls, 80% coverage, $95/dose), using the quadrivalent and bivalent vaccines is estimated to cost $15,528 [12,056;19,140] and $20,182 [15,531;25,240] per QALY-gained, respectively. At equal price, the quadrivalent vaccine is more cost-effective than bivalent under all scenarios investigated, except when assuming longer duration of protection for the bivalent and minimal anogenital warts burden. Under base-case assumptions, the maximum additional cost per dose for the quadrivalent vaccine to remain more cost-effective than the bivalent is $32 [17;46] (using a $40,000/QALY-gained threshold). Results were most sensitive to discounting, time-horizon, differences in durations of protection and anogenital warts burden. CONCLUSIONS: Vaccinating pre-adolescent girls against HPV is predicted to be highly cost-effective. If equally priced, the quadrivalent is the most economically desirable vaccine. However, ultimately, the most cost-effective HPV vaccine will be determined by their relative price.


BACKGROUND: With promising efficacy results from randomized control trials of human papillomavirus (HPV) vaccines and the availability of new screening paradigms, policymakers are being asked to make recommendations and decisions regarding the optimal strategies to reduce HPV infection and disease. Such decisions are increasingly being made with significant input from mathematical and economic models. The demand for modeling has resulted in the publication of numerous mathematical models looking at the cost-effectiveness of HPV vaccination. OBJECTIVE: To review published models that have been used to evaluate the cost-effectiveness of HPV vaccination in developed countries and highlight points of
consensus and disagreement in methods and findings. METHODS: This review consists of cost-effectiveness studies published in the peer-reviewed literature before August 2008. RESULTS: Despite variations in methods, modeling studies are producing consistent conclusions: (1) vaccinating young girls against HPV is likely to be cost-effective; (2) vaccinating boys will most likely not be cost-effective in countries that can reach high coverage rates in girls, and (3) results are most sensitive to the duration of vaccine protection. However, results from analyses examining the effectiveness and cost-effectiveness of vaccinating boys when coverage rates are low (< or = 80%) and catch-up strategies have reached conflicting conclusions.


Our aim was to examine the potential incremental impact of vaccinating boys against human papillomavirus (HPV) on vaccine-type infection in females and males, using an individual-based HPV transmission-dynamic model. Under base assumptions (vaccine efficacy = 99%, duration of protection = 20 years, coverage = 70%), vaccinating 12-year-old boys, in addition to girls, resulted in an incremental reduction in HPV-16/18 (HPV-6/11) incidence over 70 years of 16% (3%) in females and 23% (4%) in males. The benefit of vaccinating boys decreased with improved vaccination coverage in girls. Given the important predicted herd immunity impact of vaccinating girls under moderate to high vaccine coverage, the potential incremental gains of vaccinating boys are limited.


BACKGROUND: Increasingly, countries have introduced female vaccination against human papillomavirus (HPV), causally linked to several cancers and genital warts, but few have recommended vaccination of boys. Declining vaccine prices and strong evidence of vaccine impact on reducing HPV-related conditions in both women and men prompt countries to reevaluate whether HPV vaccination of boys is warranted. METHODS: A previously-published dynamic model of HPV transmission was empirically calibrated to Norway. Reductions in the incidence of HPV, including both direct and indirect benefits, were applied to a natural history model of cervical cancer, and to incidence-based models for other non-cervical HPV-related diseases. We calculated the health outcomes and costs of the different HPV-related conditions under a gender-neutral vaccination program compared to a female-only program. RESULTS: Vaccine price had a decisive impact on results. For example, assuming 71% coverage, high vaccine efficacy and a reasonable vaccine tender price of $75 per dose, we found vaccinating both girls and boys fell below a commonly cited cost-effectiveness threshold in Norway ($83,000/quality-adjusted life year (QALY) gained) when including vaccine benefit for all HPV-related diseases. However, at the current market price, including boys would not be considered 'good value for money.' For settings with a lower cost-effectiveness threshold ($30,000/QALY), it would not be considered cost-effective to expand the current program to include boys, unless the vaccine price was less than $36/dose. Increasing vaccination coverage to 90% among girls was more effective and less costly than the benefits achieved by vaccinating both genders with 71% coverage. CONCLUSIONS: At the anticipated
tender price, expanding the HPV vaccination program to boys may be cost-effective and may warrant a change in the current female-only vaccination policy in Norway. However, increasing coverage in girls is uniformly more effective and cost-effective than expanding vaccination coverage to boys and should be considered a priority.


INTRODUCTION: The objective of this study was to estimate the cost-effectiveness of adding human papillomavirus (HPV) vaccination of 12-year-old males to a female-only vaccination program for ages 12-26 years in the United States. METHODS: We used a simplified model of HPV transmission to estimate the reduction in the health and economic burden of HPV-associated diseases in males and females as a result of HPV vaccination. Estimates of the incidence, cost-per-case, and quality-of-life impact of HPV-associated health outcomes were based on the literature. The HPV-associated outcomes included were: cervical intraepithelial neoplasia (CIN); genital warts; juvenile-onset recurrent respiratory papillomatosis (RRP); and cervical, vaginal, vulvar, anal, oropharyngeal, and penile cancers. RESULTS: The cost-effectiveness of male vaccination depended on vaccine coverage of females. When including all HPV-associated outcomes in the analysis, the incremental cost per quality-adjusted life year (QALY) gained by adding male vaccination to a female-only vaccination program was $23,600 in the lower female coverage scenario (20% coverage at age 12 years) and $184,300 in the higher female coverage scenario (75% coverage at age 12 years). The cost-effectiveness of male vaccination appeared less favorable when compared to a strategy of increased female vaccination coverage. For example, we found that increasing coverage of 12-year-old girls would be more cost-effective than adding male vaccination even if the increased female vaccination strategy incurred program costs of $350 per additional girl vaccinated. CONCLUSIONS: HPV vaccination of 12-year-old males might potentially be cost-effective, particularly if female HPV vaccination coverage is low and if all potential health benefits of HPV vaccination are included in the analysis. However, increasing female coverage could be a more efficient strategy than male vaccination for reducing the overall health burden of HPV in the population.


The World Health Organization recommends establishing that human papillomavirus vaccination is cost-effective before vaccine introduction. We searched Pubmed, Embase and the Cochrane Library to 1 April 2012 for economic evaluations of human papillomavirus vaccination in low and middle income countries. We found 25 articles, but almost all low income countries and many middle income countries lacked country-specific studies. Methods, assumptions and consequently results varied widely, even for studies conducted for the same country. Despite the heterogeneity, most studies conclude that vaccination is likely to be cost-effective and possibly even cost saving, particularly in settings without organized cervical screening programmes. However, study uncertainty could be reduced by clarity about vaccine prices and vaccine delivery costs. The review supports extending vaccination to low income settings where vaccine prices are competitive, donor funding is available, cervical cancer burden is high and screening options are limited.
Approximately 70% of cases of cervical cancer worldwide are caused by genotypes 16 and 18 of human papillomavirus (HPV), which is sexually transmitted. With the availability of an effective vaccine against these HPV types, there is real hope for reducing the global burden of cervical cancer in developing countries. Stakeholders faced with decisions about where to invest money to improve health must consider the burden of disease caused by cervical cancer relative to other priorities and the comparative benefits of different interventions. We conducted a series of analyses to obtain information for agencies drafting immunisation policy recommendations, financing coordination mechanisms, and country decision-makers on the benefits, cost requirements and cost-effectiveness of the HPV16,18 vaccine. We found that making an HPV16,18 vaccine accessible to 70% of young adolescent girls in 72 of the poorest countries, China, Thailand, and all of Latin America and the Caribbean, could prevent the future deaths of more than four million women vaccinated over the next decade. Provided the cost per vaccinated girl is less than $10-$25, adolescent HPV16,18 vaccination would be cost-effective even in relatively poor countries. Concerns about financial costs and affordability highlight the need for lowering vaccine prices, cost-efficient mechanisms for delivery of vaccinations to adolescents, and creative sources of financing.

BACKGROUND: Introduction of human papillomavirus (HPV) vaccination in settings with the highest burden of HPV is not universal, partly because of the absence of quantitative estimates of country-specific effects on health and economic costs. We aimed to develop and validate a simple generic model of such effects that could be used and understood in a range of settings with little external support. METHODS: We developed the Papillomavirus Rapid Interface for Modelling and Economics (PRIME) model to assess cost-effectiveness and health effects of vaccination of girls against HPV before sexual debut in terms of burden of cervical cancer and mortality. PRIME models incidence according to proposed vaccine efficacy against HPV 16/18, vaccine coverage, cervical cancer incidence and mortality, and HPV type distribution. It assumes lifelong vaccine protection and no changes to other screening programmes or vaccine uptake. We validated PRIME against existing reports of HPV vaccination cost-effectiveness, projected outcomes for 179 countries (assuming full vaccination of 12-year-old girls), and outcomes for 71 phase 2 GAVI-eligible countries (using vaccine uptake data from the GAVI Alliance). We assessed differences between countries in terms of cost-effectiveness and health effects.

FINDINGS: In validation, PRIME reproduced cost-effectiveness conclusions for 24 of 26 countries from 17 published studies, and for all 72 countries in a published study of GAVI-eligible countries. Vaccination of a cohort of 58 million 12-year-old girls in 179 countries prevented 690,000 cases of cervical cancer and 420,000 deaths during their lifetime (mostly in low-income or middle-income countries), at a net cost of US$4 billion. HPV vaccination was very cost effective (with every disability-adjusted life-year averted costing less than the gross domestic product per head) in 156 (87%) of 179 countries. Introduction of the vaccine in countries without national HPV vaccination at present would prevent substantially more cases of cervical cancer.
cancer than in countries with such programmes, although the disparity has narrowed since 2012. If 71 phase 2 GAVI-eligible countries adopt vaccination according to forecasts, then in 2070 GAVI Alliance-funded vaccination could prevent 200,000 cases of cervical cancer and 100,000 deaths in some of the highest-burden countries. INTERPRETATION: Large between-country disparities exist for HPV vaccination, with countries with the most to gain yet to introduce national HPV vaccination. Support from the GAVI Alliance could help to reduce such disparities, but a substantial burden will remain even after presently projected vaccine introductions. FUNDING: WHO.


BACKGROUND: Two-dose human papillomavirus (HPV) vaccine schedules may provide short-term protection but their long-term population impact is unknown.

METHODS: Two models of HPV transmission and associated cervical disease (squamous and glandular, neoplasia and cancer) were fitted to data from England and Canada on HPV epidemiology, sexual behaviour, cervical screening outcomes and cervical cancer incidence. RESULTS: Models suggest that at 40-80% coverage, if two-dose schedules protect vaccinees for 20 years, then the benefits of the third dose are small. If two doses protect for 10 years, then the third dose may prevent as many cancers as the first two. At 80% coverage, numbers needed to receive a third dose to prevent an additional cancer are 5900-110,000 (England), 3000-5100 (Canada) with 20 years two-dose protection, and 2000-5300 (England), 760-950 (Canada) with 10 years two-dose protection. CONCLUSION: Results enable decision makers to quantify risks associated with two-dose schedules despite remaining uncertainties in vaccine duration and cross-protection.


BACKGROUND: The World Health Organization (WHO) recommends that the cost effectiveness of introducing human papillomavirus (HPV) vaccination is considered before such a strategy is implemented. However, developing countries often lack the technical capacity to perform and interpret results of economic appraisals of vaccines. To provide information about the feasibility of using such models in a developing country setting, we evaluated models of HPV vaccination in terms of their capacity, requirements, limitations and comparability.

METHODS: A literature review identified six HPV vaccination models suitable for low-income and middle-income country use and representative of the literature in terms of provenance and model structure. Each model was adapted by its developers using standardised data sets representative of two hypothetical developing countries (a low-income country with no screening and a middle-income country with limited screening). Model predictions before and after vaccination of adolescent girls were compared in terms of HPV prevalence and cervical cancer incidence, as was the incremental cost-effectiveness ratio of vaccination under different scenarios. RESULTS: None of the models perfectly reproduced the standardised data set provided to the model developers. However, they agreed that large decreases in type 16/18 HPV prevalence and cervical cancer incidence are likely to occur following vaccination. Apart from the Thai model (in which vaccine and non-vaccine HPV types were combined), vaccine-
type HPV prevalence dropped by 75% to 100%, and vaccine-type cervical cancer incidence dropped by 80% to 100% across the models (averaging over age groups). The most influential factors affecting cost effectiveness were the discount rate, duration of vaccine protection, vaccine price and HPV prevalence. Demographic change, access to treatment and data resolution were found to be key issues to consider for models in developing countries. CONCLUSIONS: The results indicated the usefulness of considering results from several models and sets of modelling assumptions in decision making. Modelling groups were prepared to share their models and expertise to work with stakeholders in developing countries. Please see related article: http://www.biomedcentral.com/1741-7007/9/55.


Low- and middle-income countries need to consider economic issues such as cost-effectiveness, affordability and sustainability before introducing a program for human papillomavirus (HPV) vaccination. However, many such countries lack the technical capacity and data to conduct their own analyses. Analysts informing policy decisions should address the following questions: 1) Is an economic analysis needed? 2) Should analyses address costs, epidemiological outcomes, or both? 3) If costs are considered, what sort of analysis is needed? 4) If outcomes are considered, what sort of model should be used? 5) How complex should the analysis be? 6) How should uncertainty be captured? 7) How should model results be communicated? Selecting the appropriate analysis is essential to ensure that all the important features of the decision problem are correctly represented, but that the analyses are not more complex than necessary. This report describes the consensus of an expert group convened by the World Health Organization, prioritizing key issues to be addressed when considering economic analyses to support HPV vaccine introduction in these countries.


We assessed the cost-effectiveness of including boys vs girls alone in a pre-adolescent vaccination programme against human papillomavirus (HPV) types 16 and 18 in Brazil. Using demographic, epidemiological, and cancer data from Brazil, we developed a dynamic transmission model of HPV infection between males and females. Model-projected reductions in HPV incidence under different vaccination scenarios were applied to a stochastic model of cervical carcinogenesis to project lifetime costs and benefits. We assumed vaccination prevented HPV-16 and -18 infections in individuals not previously infected, and protection was lifelong. Coverage was varied from 0-90% in both genders, and cost per-vaccinated individual was varied from IUSD 25 to 400. At 90% coverage, vaccinating girls alone reduced cancer risk by 63%; including boys at this coverage level provided only 4% further cancer reduction. At a cost per-vaccinated individual of USD 50, vaccinating girls alone was <USD 200 per year of life saved (YLS), while including boys ranged from USD 810-18,650 per YLS depending on coverage. For all coverage levels, increasing coverage in girls was more effective and less costly than including boys in the vaccination programme. In a resource-constrained setting such as Brazil, our
results support that the first priority in reducing cervical cancer mortality should be to vaccinate pre-adolescent girls.

*Kim SY, Sweet S, Chang J, Goldie SJ. Comparative evaluation of the potential impact of rotavirus versus HPV vaccination in GAVI-eligible countries: a preliminary analysis focused on the relative disease burden.-BMC Infect Dis 2011;11:174

BACKGROUND: Immunization policymakers at global and local levels need to establish priorities among new vaccines competing for limited resources. However, comparison of the potential impact of single vaccination programs is challenging, primarily due to the limited number of vaccine analyses as well as their differing analytic approaches and reporting formats. The purpose of this study is to provide early insight into how the comparative impact of different new vaccines could be assessed in resource-poor settings with respect to affordability, cost-effectiveness, and distributional equity. METHODS: We compared the health, economic, and financial consequences of introducing the two vaccines in 72 GAVI-eligible countries using a number of different outcome measures to evaluate affordability, cost-effectiveness, and distributional equity. We use simple static models to standardize the analytic framework and improve comparability between the two new vaccines. These simple models were validated by leveraging previously developed, more complex models for rotavirus and human papillomavirus (HPV). RESULTS: With 70% coverage of a single-age cohort of infants and pre-adolescent girls, the lives saved with rotavirus (~274,000) and HPV vaccines (~286,000) are similar, although the timing of averted mortality differs; rotavirus-attributable deaths occur in close proximity to infection, while HPV-related cancer deaths occur largely after age 30. Deaths averted per 1000 vaccinated are 5.2 (rotavirus) and 12.6 (HPV). Disability-adjusted life years (DALYs) averted were ~7.15 million (rotavirus) and ~1.30 million (HPV), reflecting the greater influence of discounting on the latter, given the lagtime between vaccination and averted cancer. In most countries (68 for rotavirus and 66 for HPV, at the cost of I$25 per vaccinated individual) the incremental cost per DALY averted was lower than each country’s GDP per capita. Financial resources required for vaccination with rotavirus are higher than with HPV since both genders are vaccinated. CONCLUSIONS: While lifesaving benefits of rotavirus and HPV vaccines will be realized at different times, the number of lives saved over each target populations’ lifetimes will be similar. Model-based analyses that use a standardized analytic approach and generate comparable outputs can enrich the priority-setting dialogue. Although new vaccines may be deemed cost-effective, other factors including affordability and distributional equity need to be considered in different settings. We caution that for priority setting in an individual country, more rigorous comparisons should be performed, using more comprehensive models and considering all relevant vaccines and delivery strategies.


BACKGROUND: In November 2011, the GAVI Alliance made the decision to add HPV vaccine as one of the new vaccines for which countries eligible for its funding (less than $1520 per capita income) could apply to receive support for national HPV vaccination, provided they could demonstrate the ability to deliver HPV vaccines. This paper describes the data and analysis shared with GAVI policymakers for this decision regarding GAVI HPV vaccine support. The paper reviews why strategies
and costs for HPV vaccine delivery are different from other vaccines and what is known about the cost components from available data that originated primarily from HPV vaccine delivery costing studies in low and middle income-countries.

METHODS: Financial costs of HPV vaccine delivery were compared across three sources of data: 1) vaccine delivery costing of pilot projects in five low and lower-middle income countries; 2) cost estimates of national HPV vaccination in two low income countries; and 3) actual expenditure data from national HPV vaccine introduction in a low income country. Both costs of resources required to introduce the vaccine (or initial one-time investment, such as cold chain equipment purchases) and recurrent (ongoing costs that repeat every year) costs, such as transport and health personnel time, were analyzed. The cost per dose, cost per fully immunized girl (FIG) and cost per eligible girl were compared across studies. RESULTS: Costs varied among pilot projects and estimates of national programs due to differences in scale and service delivery strategy. The average introduction costs per fully immunized girl ranged from $1.49 to $18.94 while recurrent costs per girl ranged from $1.00 to $15.69, with both types of costs varying by delivery strategy and country. Evaluating delivery costs along programme characteristics as well as country characteristics (population density, income/cost level, existing service delivery infrastructure) are likely the most informative and useful for anticipating costs for HPV vaccine delivery. CONCLUSIONS: This paper demonstrates the importance of country level cost data to inform global donor policies for vaccine introduction support. Such data are also valuable for informing national decisions on HPV vaccine introduction.


INTRODUCTION: Human papillomavirus (HPV) is one of the world’s most common sexually transmitted infections, and has been associated with a number of cervical and non-cervical diseases, including cancer. HPV vaccines have been licensed for use in females for some time, but the quadrivalent vaccine has only recently become licensed for use in males. Many countries have adopted a vaccination programme for adolescent females based on results of cost-effectiveness analyses. However, given the new indications for use of the vaccine in males, decision makers require information on the cost effectiveness of vaccinating males in order to make policy decisions on whether or not to fund such programmes. OBJECTIVE: Our objective was to conduct a qualitative systematic review to update a previously conducted review of HPV vaccine studies. METHODS: Articles were obtained from an extensive literature search to determine the cost effectiveness of implementing an HPV vaccination programme with routine cervical cancer screening. A total of 29 studies were included in this review. Seventeen of the included articles looked only at cervical disease outcomes, and 12 studies also included non-cervical disease outcomes. Four studies explored the economic impact of vaccinating both boys and girls. One study focused on a population of men who have sex with men (MSM). RESULTS: While different model structures, input parameters and baseline assumptions were used, the consistent message in studies that focused on female-only vaccination programmes was that routine vaccination of females is cost effective compared with cervical cancer screening alone. DISCUSSION: Based on the currently available literature, it appears that the addition of boys to a vaccination programme generally exceeds traditional cost-effectiveness thresholds. The MSM population represents a potential additional target for routine HPV vaccination;
however, more cost-effectiveness studies are required before making such a policy change.


Mathematical models of HPV vaccine effectiveness and cost-effectiveness have produced conflicting results. The aim of this study was to use mathematical models to compare and isolate the impact of the assumptions most commonly made when modeling the effectiveness of HPV vaccines. Our results clearly show that differences in how we model natural immunity, herd immunity, partnership duration, HPV types, and waning of vaccine protection lead to important differences in the predicted effectiveness of HPV vaccines. These results are important and useful to assist modelers/health economists in choosing the appropriate level of complexity to include in their models, provide epidemiologists with insight on key data necessary to increase the robustness of model predictions, and help decision makers better understand the reasons underlying conflicting results from HPV models.


Monitoring vaccine impact and Other Resources


*WHO's conclusions regarding appropriate HPV vaccine impact monitoring were published in the 2010 WER (see http://www.who.int/wer/2010/wer8525.pdf?ua=1) and the publication http://whqlibdoc.who.int/hq/2010/WHO_IVB_10.05_eng.pdf?ua=1).