

**References Human papillomavirus vaccines: WHO position paper, May 2017**

(References with abstracts cited in the position paper in the order of appearance.)

**SAGE guidance for the development of evidence-based vaccine-related recommendations.**

[http://www.who.int/immunization/sage/Guidelines\\_development\\_recommendations.pdf](http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf), accessed February 2017.

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**WEEKLY EPIDEMIOLOGICAL RECORD, NO. 43, 24 OCTOBER 2014, 89, pp. 465–492. Human papillomavirus vaccines: WHO position paper, October 2014.**

(No abstract available.)

**SAGE meeting October 2016.**

[http://www.who.int/immunization/sage/meetings/2016/october/presentations\\_background\\_docs/en/](http://www.who.int/immunization/sage/meetings/2016/october/presentations_background_docs/en/), accessed February 2017

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**HPV vaccine background document.**

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(No abstract available.)

**Bruni L, et al. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. J Infect Dis, 2010;202(12):1789–1799.**

**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.

**Smith JS, et al. Age-specific prevalence of infection with human papillomavirus in females: a global review. J Adolesc Health. 2008;43:S5–S25. S25 e21–41.**

#### PURPOSE:

Global data on age-specific prevalence of human papillomavirus (HPV) infection overall, and for high-risk HPV types 16 and 18, are essential for the future implementation of HPV prophylactic vaccines for cervical cancer prevention.

#### METHODS:

A systematic review of peer-reviewed publications was conducted to summarize worldwide data on genital HPV-DNA prevalence in women. Studies with clear descriptions of polymerase chain reaction or hybrid capture detection assays were included.

#### RESULTS:

A total of 346,160 women were included in 375 studies. Of 134 studies with age-stratified HPV prevalence data (116 low sexual risk populations, 18 high sexual risk populations), over 50% were from Europe and the Middle East (38%) and North America (19%), with smaller proportions from Asia and Australia (21%), Central and South America (11%), and Africa (10%). Across all geographical regions, data on HPV prevalence were generally limited to women over 18 years of age. Consistently across studies, HPV infection prevalence decreased with increasing age from a peak prevalence in younger women (< or =25 years of age). In middle-aged women (35-50 years), maximum HPV prevalence differed across geographical regions: Africa (approximately 20%), Asia/Australia (approximately 15%), Central and South America (approximately 20%), North America (approximately 20%), Southern Europe/Middle East (approximately 15%), and Northern Europe (approximately 15%). Inconsistent trends in HPV prevalence by age were noted in older women, with a decrease or plateau of HPV prevalence in older ages in most studies, whereas others showed an increase of HPV prevalence in older ages. Similar trends of HPV 16 and/or 18 prevalence by age were noted among 12 populations with available data.

#### DISCUSSION:

Genital HPV infection in women is predominantly acquired in adolescence, and peak prevalence in middle-aged women appears to differ across geographical regions. Worldwide variations in HPV prevalence across age appear to largely reflect differences in sexual behavior across geographical regions. Further studies of HPV prevalence in adolescents are needed for all geographic regions.

**Smith JS, et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a metaanalysis update. *Int J Cancer*, 2007;121:621–632.**

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-analysis 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.

**Insinga RP, et al. Progression and regression of incident cervical HPV 6, 11, 16 and 18 infections in young women. *Infectious Agents and Cancer*, 2007; 2:15.**

#### 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.

**Smith JS, et al. Age-specific prevalence of human papillomavirus infection in males: a global review. J Adolesc Health, 2011;48(6):540–552.**

**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.

**Schim van der Loeff MF, et al. HPV and Anal Cancer in HIV-Infected Individuals: A Review. Curr**

### **HIV/AIDS Rep. 2014 Jul 3.**

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.

### **Vardas E, et al. External Genital Human Papillomavirus Prevalence and Associated Factors Among Heterosexual Men on 5 Continents. JID, 2011;203(1): 58–65.**

#### **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.

### **Olesen TB, et al. Human papillomavirus prevalence among men in sub-Saharan Africa: a systematic review and meta-analysis. Sex Transm Infect, 2014 May 7.**

#### **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. CLINICALTRIALS.GOV IDENTIFIER: NCT00932009.

#### **Walboomers JL, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J. Pathol, 1999;189:12–19.**

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.

#### **Bosch FX, et al. The causal relation between human papillomavirus and cervical cancer. J Clin Pathol, 2002;55(4):244–265.**

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.

#### **De Martel C, Plummer M, Vignat J and Franceschi S. Worldwide burden of cancer attributable to HPV by site, country and HPV type. IJC 2017 (in Press)**

HPV is the cause of almost all cervical cancer and is responsible for a substantial fraction of other

anogenital cancer and oropharyngeal cancer. Understanding the HPV-attributable cancer burden can boost programs of HPV vaccination and HPV-based cervical screening. Attributable fractions (AF) and the relative contributions of different HPV types were derived from published studies reporting on the prevalence of transforming HPV infection in cancer tissue. Maps of age-standardized incidence rates of HPV-attributable cancers by country from GLOBOCAN 2012 data are shown separately for the cervix, other anogenital tract, and head and neck cancers. The relative contribution of HPV16/18 and HPV6/11/16/18/31/33/45/52/58 was also estimated. 4.5% of all cancers worldwide (630,000 new cancer cases per year) are attributable to HPV: 8.6% in women and 0.8% in men. AF in women ranges from <3% in Australia/New Zealand and the USA to >20% in India and sub-Saharan Africa. Cervix accounts for 83% of HPV-attributable cancer, two-thirds of which occur in less developed countries. Other HPV-attributable anogenital cancer includes 8,500 vulva; 12,000 vagina; 35,000 anus (half occurring in men); and 13,000 penis. In the head and neck, HPV-attributable cancers represent 38,000 cases of which 21,000 are oropharyngeal cancers occurring in more developed countries. The relative contributions of HPV16/18 and HPV6/11/16/18/31/33/45/52/58 are 73% and 90%, respectively. Universal access to vaccination is the key to avoiding most cases of HPV-attributable cancer. The preponderant burden of HPV16/18 and the possibility of cross-protection emphasize the importance of the introduction of cheaper vaccines in less developed countries. This article is protected by copyright. All rights reserved.

**de Sanjose S, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. *Lancet Oncology*, 2010;11:1048–1056.**

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.

**Serrano B, et al. Human papillomavirus genotype attribution for HPVs 6,11,16,18,31,33,45,52 and 58 in female anogenital lesions. *EurJCancer*. 2015;51(13):1732-41.**

#### OBJECTIVE:

Human papillomavirus (HPV) vaccines can potentially control cervical cancer and help to reduce other HPV-related cancers. We aimed to estimate the relative contribution (RC) of the nine types (HPVs

16/18/31/33/45/52/58/6/11) included in the recently approved 9-valent HPV vaccine in female anogenital cancers and precancerous lesions (cervix, vulva, vagina and anus).

#### METHODS:

Estimations were based on an international study designed and coordinated at the Catalan Institute of Oncology (Barcelona-Spain), including information on 10,575 invasive cervical cancer (ICC), 1709 vulvar, 408 vaginal and 329 female anal cancer cases and 587 Vulvar Intraepithelial Neoplasia grade 2/3 (VIN2/3), 189 Vaginal Intraepithelial Neoplasia grade 2/3 (VaIN2/3) and 29 Anal Intraepithelial Neoplasia grade 2/3 (AIN2/3) lesions. Consecutive histologically confirmed paraffin-embedded cases were obtained from hospital pathology archives from 48 countries worldwide. HPV DNA-detection and typing was performed by SPF10-DEIA-LiPA25 system and RC was expressed as the proportion of type-specific cases among HPV positive samples. Multiple infections were added to single infections using a proportional weighting attribution.

#### RESULTS:

HPV DNA prevalence was 84.9%, 28.6%, 74.3% and 90.0% for ICC, vulvar, vaginal and anal cancers, respectively, and 86.7%, 95.8% and 100% for VIN2/3, VaIN2/3 and AIN2/3, respectively. RC of the combined nine HPV types was 89.5% (95% confidence interval (CI): 88.8-90.1)-ICC, 87.1% (83.8-89.9)-vulvar, 85.5% (81.0-89.2)-vaginal, 95.9% (93.0-97.9)-female anal cancer, 94.1% (91.7-96.0)-VIN2/3, 78.7% (71.7-84.2)-VaIN2/3 and 86.2% (68.3-96.1)-AIN2/3. HPV16 was the most frequent type in all lesions. Variations in the RC of HPVs 31/33/45/52/58 by cancer site were observed, ranging from 7.8% (5.0-11.4)-female anal cancer to 20.5% (16.1-25.4)-vaginal cancer.

#### CONCLUSIONS:

The addition of HPVs 31/33/45/52/58 to HPV types included in current vaccines (HPV16/18) could prevent almost 90% of HPV positive female anogenital lesions worldwide. Taking into account that most HPV-related cancers are ICC ones, the 9-valent HPV vaccine could potentially avoid almost 88% of all female anogenital cancers.

### **Greer CE, et al. Human papillomavirus (HPV) type distribution and serological response to HPV type 6 virus-like particles in patients with genital warts. J Clin Microbiol, 1995;33(8):2058–2063.**

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 seroresponse.

### **Sturegard E, et al. Human papillomavirus typing in reporting condyloma. Sex Transm Dis, 2013;40: 123–129.**

#### 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.

**Patel H, et al. Systematic review of the incidence and prevalence of genital warts. BMC Infectious Diseases, 2013;13:39.**

**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.

**International Human Papillomavirus Reference Center. Human papillomavirus reference clones. <http://www.hpvcenter.se/html/refclones.html>, accessed February 2017.**

(No abstract available.)

**Doorbar J et al. The biology and life-cycle of human papillomaviruses. Vaccine, 2012; 30S: F55-F70.**

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.

**International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans: human papillomaviruses. Vol. 90. Lyon, IARC, 2007.**  
**<http://monographs.iarc.fr/ENG/Monographs/vol90/mono90.pdf>, accessed February 2017.**

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**International Agency for Research on Cancer. IARC Working Group Report: Primary End-Points for Prophylactic HPV Vaccine Trials. Vol 7. Lyon, IARC, 2014.**  
**[http://www.iarc.fr/en/publications/pdfs-online/wrk/wrk7/Prophylactic\\_HPV\\_VaccineTrials.pdf](http://www.iarc.fr/en/publications/pdfs-online/wrk/wrk7/Prophylactic_HPV_VaccineTrials.pdf), accessed February 2017.**

(No abstract available.)

**Denny LA, et al. Human Papillomavirus, human immunodeficiency virus and immunosuppression. Vaccine, 2012;30S:F168-74.**

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.

**Plummer et al. Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob Health 2016; 4: e609–16.**

**BACKGROUND:**

Infections with certain viruses, bacteria, and parasites are strong risk factors for specific cancers. As new cancer statistics and epidemiological findings have accumulated in the past 5 years, we aimed to assess the causal involvement of the main carcinogenic agents in different cancer types for the year 2012.

**METHODS:**

We considered ten infectious agents classified as carcinogenic to human beings by the International Agency for Research on Cancer. We calculated the number of new cancer cases in 2012 attributable to infections by country, by combining cancer incidence estimates (from GLOBOCAN 2012) with estimates of attributable fraction (AF) for the infectious agents. AF estimates were calculated from the prevalence of infection in cancer cases and the relative risk for the infection (for some sites). Estimates of infection prevalence, relative risk, and corresponding 95% CIs for AF were obtained from systematic reviews and pooled analyses.

**FINDINGS:**

Of 14 million new cancer cases in 2012, 2·2 million (15·4%) were attributable to carcinogenic infections. The most important infectious agents worldwide were *Helicobacter pylori* (770 000 cases), human papillomavirus (640 000), hepatitis B virus (420 000), hepatitis C virus (170 000), and Epstein-Barr virus (120 000). Kaposi's sarcoma was the second largest contributor to the cancer burden in sub-Saharan Africa. The AFs for infection varied by country and development status—from less than 5% in the USA, Canada, Australia, New Zealand, and some countries in western and northern Europe to more than 50% in some countries in sub-Saharan Africa.

**Larson DA, Derkay CS. Epidemiology of recurrent respiratory papillomatosis. APMIS 2010;118:450–454.**

Recurrent respiratory papillomatosis (RRP) was first described in the 1800s, but it was not until the 1980s when it was convincingly attributed to human papilloma virus (HPV). RRP is categorized into juvenile onset and adult onset depending on presentation before or after the age of 12 years, respectively. The prevalence of this disease is likely variable depending on the age of presentation, country and socioeconomic status of the population being studied, but is generally accepted to be between 1 and 4 per 100 000. Despite the low prevalence, the economic burden of RRP is high given the multiple procedures required by patients. Multiple studies have shown that the most likely route of transmission of HPV in RRP is from mother to child during labor. Exceptions to this may include patients with congenital RRP who have been exposed in utero and adult patients who may have been exposed during sexual contact. Although cesarean section may prevent the exposure of children to the HPV virus during childbirth, its effectiveness in preventing RRP is debatable and the procedure itself carries an increased risk of complications. The quadrivalent HPV vaccine holds the most promise for the prevention of RRP by eliminating the maternal reservoir for HPV.

**Stanley MA. Epithelial cell responses to infection with human papillomavirus. Clin Microbiol Rev, 2012;25(2):215–222.**

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.

**Giuliano A et al. Incidence and clearance of genital human papillomavirus infection in men (HIM): a cohort study. *Lancet* 377(9769): 932-40, 2011.**

#### BACKGROUND:

Human papillomaviruses (HPVs) cause genital warts and cancers in men. The natural history of HPV infection in men is largely unknown, and that information is needed to inform prevention strategies. The goal in this study was to estimate incidence and clearance of type-specific genital HPV infection in men, and to assess the associated factors.

#### METHODS:

Men (aged 18-70 years), residing in Brazil, Mexico, and the USA, who were HIV negative and reported no history of cancer were recruited from the general population, universities, and organised health-care systems. They were assessed every 6 months for a median follow-up of 27.5 months (18.0-31.2). Specimens from the coronal sulcus, glans penis, shaft, and scrotum were obtained for the assessment of the status of HPV genotypes.

#### FINDINGS:

In 1159 men, the incidence of a new genital HPV infection was 38.4 per 1000 person months (95% CI 34.3-43.0). Oncogenic HPV infection was significantly associated with having a high number of lifetime female sexual partners (hazard ratio 2.40, 1.38-4.18, for at least 50 partners vs not more than one partner), and number of male anal-sexual partners (2.57, 1.46-4.49, for at least three male partners vs no recent partners). Median duration of HPV infection was 7.52 months (6.80-8.61) for any HPV and 12.19 months (7.16-18.17) for HPV 16. Clearance of oncogenic HPV infection decreased in men with a high number of lifetime female partners (0.49, 0.31-0.76, for at least 50 female partners vs not more than one partner), and in men in Brazil (0.71, 0.56-0.91) and Mexico (0.73, 0.57-0.94) compared with the USA. Clearance of oncogenic HPV was more rapid with increasing age (1.02, 1.01-1.03).

**Stanley MA, et al. Host responses to infection with human papillomavirus. *JC Curr Probl Dermatol*, 2014;45:58-74.**

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.

**WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention.** [http://apps.who.int/iris/bitstream/10665/94830/1/9789241548694\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/94830/1/9789241548694_eng.pdf), accessed February 2017.

(No abstract available.)

**WHO guidance note: comprehensive cervical cancer prevention and control: a healthier future for girls and women.** [http://apps.who.int/iris/bitstream/10665/78128/3/9789241505147\\_eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/78128/3/9789241505147_eng.pdf?ua=1), accessed February 2017.

(No abstract available.)

**WHO guidelines: use of cryotherapy for cervical intraepithelial neoplasia.** [http://whqlibdoc.who.int/publications/2011/9789241502856\\_eng.pdf?ua=1](http://whqlibdoc.who.int/publications/2011/9789241502856_eng.pdf?ua=1), accessed February 2017.

(No abstract available.)

**Gardasil 9. Food and Drug Administration.** <https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf>, accessed February 2017.

(No abstract available.)

**“ WHO/IVB Database, as of 31 March 2017 “.**

**Cervarix. Summary of Product Characteristics. European Medicines Agency.** [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/000721/WC500024632.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000721/WC500024632.pdf), accessed February 2017.

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**Gardasil. Summary of Product Characteristics. European Medicines Agency.**  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/000703/WC500021142.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000703/WC500021142.pdf), accessed February 2014.

(No abstract available.)

**Gardasil 9. Summary of Product Characteristics. European Medicines Agency.**  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/003852/WC500189111.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003852/WC500189111.pdf), accessed February 2017.

(No abstract available.)

**Giannini SL, et al. Enhanced humoral and memory B cellular immunity using HPV16/18 L1 VLP vaccine formulated with the MPL/aluminium salt combination (AS04) compared to aluminium salt only. Vaccine, 2006;24(33-34):5937–5949.**

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 TNF $\alpha$  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.

**Dauner JG, et al. Characterization of the HPV-specific memory B cell and systemic antibody responses in women receiving an unadjuvanted HPV16 L1 VLP vaccine. Vaccine, 2010;28(33):5407–5413.**

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.

**Safaeian M, et al. Durable antibody responses following one dose of the bivalent human papillomavirus L1 virus-like particle vaccine in the Costa Rica vaccine trial. *Cancer Prev Res*, 2013; 6:1242–1250.**

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.

**Zeybek B, Rodriguez A. Comparison of long term impact and clinical outcomes of reduced dose vs standard dose quadrivalent human papillomavirus vaccine in the United States: a database study. Paper presented at: 48th Annual Meeting of the Society of Gynecologic Oncology; March 12-15, 2017; National Harbor, MD**

**Summary:** Researchers conducted this study to investigate the long-term effects and clinical outcomes of varying human papillomavirus (HPV) vaccine doses in the U.S. population. Women who received two doses of the HPV vaccine, they found, exhibited higher prophylactic efficacy against abnormal high-grade cytology, high-grade histology, adenocarcinoma in situ, and invasive cervical cancer when compared to women who received a single dose. No additional protective effect was found, however, with a third dose of the HPV vaccine.

**Methods:**

Researchers extracted data from health insurance claims from the Clinformatics Data Mart (CDM) Database over a 9-year period (2006–2015) from all patients who had at least 1 dose of HPV vaccination. They excluded female patients outside the age range, who were not continuously enrolled for insurance, or had a prior record of cervical cytologic or histologic abnormality, and all male patients. Their final study cohort included females between ages 9 and 26 years with at least 1 dose of the HPV vaccine within a 3-year period and without a previous diagnosis of cervical dysplasia or cervical cancer. The follow-up period was at least 4 years and started either once patients reached 21 or once the last dose of vaccine was administered (age  $\geq 21$ ). Researchers used a  $\chi^2$  test to analyze categorical outcomes, ANOVA to analyze continuous outcomes, and Kaplan-Meier survival method to analyze time to event.

**Results:**

Final cohort included 11,335 women, out of whom 1,975 received 1 dose of the vaccine (group 1),

2,089 received 2 doses (group 2), and 7,271 received 3 doses (group 3). Mean age was  $21.51 \pm 2.67$  years in group 1,  $20.94 \pm 2.85$  in group 2, and  $20.33 \pm 2.85$  in group 3. Mean time interval to receive subsequent vaccine shots was  $5.25 \pm 4.85$  months in group 2 and  $8.04 \pm 4.07$  months in group 3. Researchers found that single-dose HPV-vaccinated women had a higher cumulative incidence of high-grade cytology or histology, adenocarcinoma in situ, and cervical cancer when compared to the 2-dose group ( $P=0.04$ ); however, they found no significant difference in clinical outcomes between the 2- and 3-dose vaccine groups ( $P=0.17$ ).

**Recommendations to assure the quality, safety and efficacy of recombinant human papillomavirus virus-like particle vaccines.**

[http://www.who.int/entity/biologicals/areas/vaccines/Annex\\_4\\_Recommendations\\_recombinant\\_human\\_papillomavirus\\_virus-like\\_particle\\_vaccines.pdf?ua=1](http://www.who.int/entity/biologicals/areas/vaccines/Annex_4_Recommendations_recombinant_human_papillomavirus_virus-like_particle_vaccines.pdf?ua=1), accessed February 2017.

(No abstract available.)

**WHO Human papillomavirus laboratory manual**

[http://apps.who.int/iris/bitstream/10665/70505/1/WHO\\_IVB\\_10.12\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/70505/1/WHO_IVB_10.12_eng.pdf), accessed March 2017.

(No abstract available.)

**Schiller JT, et al. A review of clinical trials of human papillomavirus prophylactic vaccines. *Vaccine*, 2012;30 Suppl 5:F123-38.**

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<sup>®</sup> (Merck & Co., Whitehouse Station, NJ USA) a quadrivalent vaccine containing VLPs of types 6, 11, 16 and 18 and Cervarix<sup>®</sup> (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<sup>®</sup> also demonstrated strong protection against genital warts and vulvar/vaginal neoplasia associated with the vaccine types. In other trials, Gardasil<sup>®</sup> 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<sup>®</sup> 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.

**Van Damme P, et al. Immunogenicity and safety of a 9-valent HPV vaccine. *Pediatrics*. 2015;136(1):e28–39.**

#### OBJECTIVES:

Prophylactic vaccination of youngwomen aged 16 to 26 years with the 9-valent (6/11/16/18/31/33/45/52/58) human papillomavirus (HPV) virus-like particle (9vHPV) vaccine prevents infection and disease. We conducted a noninferiority immunogenicity study to bridge the findings in young women to girls and boys aged 9 to 15 years.

#### METHODS:

Subjects (N = 3066) received a 3-dose regimen of 9vHPV vaccine administered at day 1, month 2, and month 6. Anti-HPV serologic assays were performed at day 1 and month 7. Noninferiority required that the lower bound of 2-sided 95% confidence intervals of geometric mean titer ratios (boys:young women or girls:young women) be >0.67 for each HPV type. Systemic and injection-site adverse experiences (AEs) and serious AEs were monitored.

#### RESULTS:

At 4 weeks after dose 3, >99% of girls, boys, and young women seroconverted for each vaccine HPV type. Increases in geometric mean titers to HPV types 6/11/16/18/31/33/45/52/58 were elicited in all vaccine groups. Responses in girls and boys were noninferior to those of young women. Persistence of anti-HPV responses was demonstrated through 2.5 years after dose 3. Administration of the 9vHPV vaccine was generally well tolerated. A lower proportion of girls (81.9%) and boys (72.8%) than young women (85.4%) reported injection-site AEs, most of which were mild to moderate in intensity.

#### CONCLUSIONS:

These data support bridging the efficacy findings with 9vHPV vaccine in young women 16 to 26 years of age to girls and boys 9 to 15 years of age and implementing gender-neutral HPV vaccination programs in preadolescents and adolescents.

**Naud PS, et al. Sustained efficacy, immunogenicity, and safety of the HPV-16/18 AS04-adjuvanted vaccine. *Hum Vaccin Immunother*. 2014 Aug; 10(8): 2147–2162.**

HPV-023 (NCT00518336; ClinicalTrial.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  $\geq$  ASC-US; 95.0% (68.0, 99.9; 1/18) against  $\geq$  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.

**Schwarz et al. 10-Year Follow-Up On Immunogenicity And Safety Of The Human Papillomavirus (HPV)-16/18 As04-Adjuvanted Vaccine Administered To 10–14-Year-Old Girls. Abstract at WSPID 2016, Rio de Janeiro, Brazil. <http://wspid.kenes.com/Documents/WSPID%20All%20Abstracts.pdf>,**

accessed April 2017.

**Background and aims:** This open-label extension study (HPV-025/NCT00877877) is a 10-year follow-up of the immunogenicity and safety after 3 doses of the HPV-16/18 AS04-adjuvanted vaccine administered to 10-14-year-old girls in a phase III, randomized, controlled, observer-blinded trial (NCT00196924). We present end-of-study results.

**Methods:** The study was approved by Institutional Review Boards/Ethical Committees. Written informed consents/assents were obtained from all participants/parents/guardians before enrolment. Humoral immune responses were determined by enzyme-linked immunosorbent assay. Serious adverse events (SAEs) were assessed throughout the follow-up.

**Results:** 10 years after the first vaccination, in the Month 120 according-to-protocol immunogenicity cohort (N=418), all subjects analyzed were seropositive for HPV-16 and HPV-18 antibodies. Geometric mean titers (GMTs) were 1589.9 EL.U/mL [95%CI: 1459.8-1731.6] for HPV-16 and 597.2 EL.U/mL [95%CI: 541.7-658.5] for HPV-18 in subjects seronegative at baseline for the type analyzed. HPV-16 GMT was 53.4-fold higher and HPV-18 GMT 26.3-fold higher than GMTs of the respective types after natural infection in 15-25-year-old women (NCT00122681). GMTs were 3.8-fold (HPV-16) and 2.5-fold (HPV-18) higher than GMTs of the respective types, 9.4 years after vaccination in 15-25-year-old women for whom vaccine efficacy was demonstrated (NCT00518336). During the 10-year follow-up, 99 out of 557 subjects in the HPV-025 total vaccinated cohort (17.8%, 95%CI: 14.7-21.2) reported 155 SAEs; none were vaccine-related, led to study withdrawals or were fatal to participants.

**Conclusions:** The HPV-16/18 AS04-adjuvanted vaccine induced a sustained serum antibody response up to 10 years after administration of the first dose in 10-14-year-old girls, and exhibited an acceptable safety profile.

**Joura EA. Introduction of Immune Memory Following Administration of the 9-valent HPV vaccine. European Research Organisation on Genital Infection and Neoplasia (EUROGIN) Salzburg, Austria. June 15-18, 2016. Presentation OC 06-02. Available at: <http://eurogin.com/2016/images/doc/eurogin-2016-abstracts-part-2.pdf>, , accessed April 2017.**

#### Background / Objectives

Duration of protection is an important parameter in the assessment of HPV vaccines. Vaccines that induce long term protection are generally characterized by the generation of immune memory. The pivotal efficacy study of the 9vHPV vaccine has shown high efficacy to prevent infection and disease due to the vaccine HPV types through at least 5 years. The purpose of this study is to assess the potential of the 9vHPV vaccine to induce HPV type specific immune memory.

#### Methods

This is an open-label extension of the pivotal efficacy study of 9vHPV vaccine (Protocol V503-001). A subset of subjects (N=150) initially randomized to 9vHPV vaccine and who received 3 dose regimen of 9vHPV vaccine in the base study were enrolled in the study extension and administered a 4th dose of 9vHPV vaccine at Month 60. HPV type specific serum antibody levels were measured pre-dose 4 and at 7 and 28 days post dose 4. Serum anti HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 antibody levels were assessed by competitive Luminex immunoassay (cLIA).

#### Results

Pre-dose 4 geometric mean titers (GMTs) were lower than GMTs at Month 7 (4 weeks post dose 3) for all 9 vaccine HPV types. Administration of a fourth dose resulted in a rapid increase of GMTs for all 9 HPV types. GMTs at 7 and 28 days post dose 4 were higher than GMTs at 4 weeks post dose 3 for all 9 HPV types.

#### Conclusion

A three-dose regimen of the 9vHPV vaccine induces high efficacy and stable antiHPV antibody levels for at least 5 years. Also, similar to what was previously observed with the quadrivalent HPV vaccine, administration of the 9vHPV vaccine induces robust immune memory. These findings suggest that the efficacy of the 9vHPV vaccine will be long lasting.

**Dillner J, et al. Four years efficacy of prophylactic human papillomavirus quadrivalent vaccine against low grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts: randomized controlled trial. BMJ, 2010;341:c3493.**

**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.

**Romanowski B. Long term protection against cervical infection with the human papillomavirus: review of currently available vaccines. Hum Vaccin, 2011;7(2):161–169.**

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.

**Garland SM, et al. Impact and Effectiveness of the Quadrivalent Human Papillomavirus Vaccine: A Systematic Review of 10 Years of Real-world Experience. Clin Infect Dis. 2016 Aug 15; 63(4): 519–527.**

Prophylactic human papillomavirus (HPV) vaccination programs constitute major public health initiatives worldwide. We assessed the global effect of quadrivalent HPV (4vHPV) vaccination on HPV infection and disease. PubMed and Embase were systematically searched for peer-reviewed articles from January 2007 through February 2016 to identify observational studies reporting the impact or effectiveness of 4vHPV vaccination on infection, anogenital warts, and cervical cancer or precancerous lesions. Over the last decade, the impact of HPV vaccination in real-world settings has become increasingly evident, especially among girls vaccinated before HPV exposure in countries with high vaccine uptake. Maximal reductions of approximately 90% for HPV 6/11/16/18 infection, approximately 90% for genital warts, approximately 45% for low-grade cytological cervical abnormalities, and approximately 85% for high-grade histologically proven cervical abnormalities have been reported. The full public health potential of HPV vaccination is not yet realized. HPV-related disease remains a significant source of morbidity and mortality in developing and developed nations, underscoring the need for HPV vaccination programs with high population coverage.

**Lehtinen et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol 2012; 13: 89–99.**

**Background** Cervical intraepithelial neoplasia grade 2 or greater (CIN2+) is the surrogate endpoint used in licensure trials of human papillomavirus (HPV) vaccines. Vaccine efficacy against CIN3+, the immediate precursor to invasive cervical cancer, is more difficult to measure because of its lower incidence, but provides the most stringent evidence of potential cancer prevention. We report vaccine efficacy against CIN3+ and adenocarcinoma in situ (AIS) in the end-of-study analysis of 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 receive an HPV-16/18 AS04-adjuvanted 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 patients and study investigators were masked to allocated vaccine. The primary endpoint of PATRICIA has been reported previously. In the present end-of-study analysis, we focus on CIN3+ and AIS in the populations of most clinical interest, the total vaccinated cohort (TVC) and the TVC-naïve. The TVC comprised all women who received at least one vaccine dose, approximating catch-up populations and including sexually active women (vaccine n=9319; control=9325). The TVC-naïve comprised women with no evidence of oncogenic HPV infection at baseline, approximating early adolescent HPV exposure (vaccine n=5824; control=5820). This study

is registered with ClinicalTrials.gov, number NCT00122681. Findings Vaccine efficacy against CIN3+ associated with HPV-16/18 was 100% (95% CI 85.5–100) in the TVC-naïve and 45.7% (22.9–62.2) in the TVC. Vaccine efficacy against all CIN3+ (irrespective of HPV type in the lesion and including lesions with no HPV DNA detected) was 93.2% (78.9–98.7) in the TVC-naïve and 45.6% (28.8–58.7) in the TVC. In the TVC-naïve, vaccine efficacy against all CIN3+ was higher than 90% in all age groups. In the TVC, vaccine efficacy against all CIN3+ and CIN3+ associated with HPV-16/18 was highest in the 15–17 year age group and progressively decreased in the 18–20 year and 21–25 year age groups. Vaccine efficacy against all AIS was 100% (31.0–100) and 76.9% (16.0–95.8) in the TVC-naïve and TVC, respectively. Serious adverse events occurred in 835 (9.0%) and 829 (8.9%) women in the vaccine and control groups, respectively; only ten events (0.1%) and five events (0.1%), respectively, were considered to be related to vaccination. Interpretation PATRICIA end-of-study results show excellent vaccine efficacy against CIN3+ and AIS irrespective of HPV DNA in the lesion. Population-based vaccination that incorporates the HPV-16/18 vaccine and high coverage of early adolescents might have the potential to substantially reduce the incidence of cervical cancer.

**Hildesheim A, et al. Efficacy of the HPV-16/18 vaccine: Final according to protocol results from the blinded phase of the randomized Costa Rica HPV-16/18 vaccine trial. Vaccine, 2014 Sep 3;32(39):5087–5097.**

#### 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.

**Roteli-Martins, et al. Sustained immunogenicity and efficacy of the HPV-16/18 AS04-adjuvanted vaccine: up to 8.4 years of follow-up. Human Vaccin Immunother, 2012;8:390–397.**

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<sup>®</sup>) 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.

**Einstein MH, et al. Comparison of the immunogenicity and safety of Cervarix<sup>TM</sup> and Gardasil<sup>R</sup> human papillomavirus (HPV) cervical cancer vaccines in healthy women aged 18-45 years. *Hum Vaccines* 2009;5(10):705–719.**

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.

**Einstein M. Comparison of long-term immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and HPV-6/11/16/18 vaccine in healthy women aged 18-45 years: End-of-study analysis of a Phase III randomized trial. *Hum Vaccin Immunother.* 2014 Dec; 10(12): 3435–3445.**

The observer-blind, randomized, age-stratified, head-to-head study (NCT00423046) comparing immunogenicity and safety of HPV-16/18 and HPV-6/11/16/18 vaccines in healthy women aged 18-45 y was completed. Five y after vaccination, in subjects from the Month 60 according-to-protocol cohort (seronegative and DNA negative for HPV type analyzed at baseline), serum neutralizing antibody (nAb) responses induced by HPV-16/18 vaccine remained 7.8-fold (18-26-y stratum), 5.6-fold (27-35-y stratum) and 2.3-fold (36-45-y stratum) higher than those induced by HPV-6/11/16/18 vaccine for HPV-16. For HPV-18, the fold differences were 12.1, 13.0 and 7.8, respectively. At Month 60, all (100%) subjects in HPV-16/18 vaccine group and the majority (95.7%-97.5%) in HPV-6/11/16/18 vaccine group were seropositive for HPV-16. For HPV-18, the majority (98.1%-100%) of subjects in HPV-16/18 vaccine group were seropositive; however, seropositivity rates in HPV-6/11/16/18 vaccine group decreased considerably (61.1%-76.9%) across the 3 age strata. In the total vaccinated cohort (received  $\geq 1$  dose regardless of baseline HPV serostatus and DNA status), geometric mean titers for anti-HPV-16 and anti-HPV-18 nAb were higher in HPV-16/18 vaccine group than in HPV-6/11/16/18 vaccine group. Based on the 5-y data, piece-wise and modified power-law models predicted a longer durability of nAb response for HPV-16/18 vaccine compared to HPV-6/11/16/18 vaccine. Beyond the differences apparent between the vaccines in terms of immunogenicity and modeled persistence of antibody responses, comparative studies including clinical endpoints would be needed to determine whether differences exist in duration of vaccine-induced protection.

**Joura EA, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. NEJM 2015;372(8):711-723.**

#### BACKGROUND:

The investigational 9-valent viruslike particle vaccine against human papillomavirus (HPV) includes the HPV types in the quadrivalent HPV (qHPV) vaccine (6, 11, 16, and 18) and five additional oncogenic types (31, 33, 45, 52, and 58). Here we present the results of a study of the efficacy and immunogenicity of the 9vHPV vaccine in women 16 to 26 years of age.

#### METHODS:

We performed a randomized, international, double-blind, phase 2b-3 study of the 9vHPV vaccine in 14,215 women. Participants received the 9vHPV vaccine or the qHPV vaccine in a series of three intramuscular injections on day 1 and at months 2 and 6. Serum was collected for analysis of antibody responses. Swabs of labial, vulvar, perineal, perianal, endocervical, and ectocervical tissue were obtained and used for HPV DNA testing, and liquid-based cytologic testing (Papanicolaou testing) was performed regularly. Tissue obtained by means of biopsy or as part of definitive therapy (including a loop electrosurgical excision procedure and conization) was tested for HPV.

#### RESULTS:

The rate of high-grade cervical, vulvar, or vaginal disease irrespective of HPV type (i.e., disease caused by HPV types included in the 9vHPV vaccine and those not included) in the modified intention-to-treat population (which included participants with and those without prevalent infection or disease) was 14.0 per 1000 person-years in both vaccine groups. The rate of high-grade cervical, vulvar, or vaginal disease related to HPV-31, 33, 45, 52, and 58 in a prespecified per-protocol efficacy population (susceptible population) was 0.1 per 1000 person-years in the 9vHPV group and 1.6 per 1000 person-years in the qHPV group (efficacy of the 9vHPV vaccine, 96.7%; 95% confidence interval, 80.9 to 99.8). Antibody responses to HPV-6, 11, 16, and 18 were noninferior to those generated by the qHPV vaccine. Adverse events related to injection site were more common in the 9vHPV group than in the qHPV group.

#### CONCLUSIONS:

The 9vHPV vaccine prevented infection and disease related to HPV-31, 33, 45, 52, and 58 in a susceptible population and generated an antibody response to HPV-6, 11, 16, and 18 that was

noninferior to that generated by the qHPV vaccine. The 9vHPV vaccine did not prevent infection and disease related to HPV types beyond the nine types covered by the vaccine. (Funded by Merck; ClinicalTrials.gov number, NCT00543543).

**Vesikari T, et al. A randomized, double-blind, phase III study of the immunogenicity and safety of a 9-valent human papillomavirus L1 virus-like particle vaccine (V503) versus Gardasil® in 9–15-year-old girls. *Pediatr Infect Dis J* 2015;34:992-998.**

#### BACKGROUND:

A 9-valent human papillomavirus (9vHPV) vaccine has been developed to prevent infections and diseases related to HPV 6/11/16/18 [as per the licensed quadrivalent HPV (qHPV) vaccine], as well as 5 additional oncogenic HPV types (HPV 31/33/45/52/58). Compared with the qHPV vaccine, the 9vHPV vaccine potentially increases the coverage of protection from 70% to 90% of cervical cancers. We compared the immunogenicity and safety of the 9vHPV vaccine versus the qHPV vaccine in 9-15-year-old girls.

#### METHODS:

Participants (n = 600) were randomized to receive 9vHPV or qHPV vaccines on day 1, month 2 and month 6. Serology testing was performed on day 1 and month 7. HPV type-specific antibody titers (anti-HPV 6/11/16/18/31/33/45/52/58) were determined by competitive Luminex immunoassay and expressed as geometric mean titers and seroconversion rates. Vaccine safety was also assessed.

#### RESULTS:

The HPV 6/11/16/18 immune responses elicited by the 9vHPV vaccine were comparable with those elicited by the qHPV vaccine. All participants (except 1 for HPV 45) receiving the 9vHPV vaccine seroconverted for HPV 31/33/45/52/58. The 9vHPV and qHPV vaccines showed comparable safety profiles, although the incidence of injection-site swelling was higher in the 9vHPV vaccine group.

#### CONCLUSIONS:

In addition to immune responses to HPV 31/33/45/52/58, a 3-dose regimen of the 9vHPV vaccine elicited a similar immune response to HPV 6/11/16/18 when compared with the qHPV vaccine in girls aged 9-15 years. The safety profile was also similar for the 2 vaccines.

**Randomized controlled trials of human papillomavirus vaccines: Systematic reviews prepared by Cochrane Response, London, UK.**

**[http://www.who.int/immunization/sage/meetings/2016/october/04\\_Clinical\\_trials\\_of\\_HPV\\_vaccines.pdf?ua=1](http://www.who.int/immunization/sage/meetings/2016/october/04_Clinical_trials_of_HPV_vaccines.pdf?ua=1), accessed February 2017.**

Background Human papilloma virus (HPV) is the most common viral infection of the reproductive tract and causes a range of conditions in females and males, including precancerous lesions that may progress to cancer. In this Targeted Update, we review and analyse evidence for the protection afforded by two doses of prophylactic HPV vaccines in younger females (9 to 15 years) compared with three doses in older females (16 to 26 years). Objectives To evaluate the effect of HPV vaccination in females, comparing younger versus older females, updating the systematic review by D'Addario et al. Search methods Searches were conducted from July 2013 to June 2016, and all relevant studies regardless of language or publication status were searched. We searched the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), published in The Cochrane Library; MEDLINE (PubMed); EMBASE (OVID). We searched the WHO International Clinical Trials Registry Platform and ClinicalTrials.gov, to identify ongoing trials. We searched the reference lists of relevant systematic reviews published within the search dates. We contacted the pharmaceutical industry for any potential relevant study through the WHO Initiative for Vaccines Research Department (IVR). Selection criteria Experimental studies with a non-randomised comparison of two doses of HPV vaccine in younger females (9 to 15 years) versus three doses in older females (15 to 26 years) were eligible for inclusion. Data collection and analysis Two review

authors independently assessed trial eligibility and risk of bias, and extracted data. Risk ratios (RR) with 95% confidence intervals (CI) were calculated for binary outcomes reported as ratios. For continuous data, where GMTs were reported, we presented the data as mean differences (95% CI) on the log scale and re-expressed as ratio of GMTs. The non-inferiority threshold for younger females (two doses) was 0.5 for the ratio of GMTs.

**Main Results** We included six studies (Canada1; Canada/Germany1; Mexico1; Mexico2; Multinational2; Multinational3) comparing 2 doses in girls with 3 doses in women. This update includes two additional trials to the previous review (Mexico2; Multinational3). Canada/Germany1, Mexico1, and Multinational2 assessed 2-valent vaccine, Canada1 and Mexico2 assessed 4-valent vaccine, and Multinational3 assessed 9-valent vaccine. Multinational3 provided no long-term follow up data past 7 months. All outcomes were downgraded for lack of randomised comparison. For some longer-term time points the quality of the evidence was downgraded for risk of bias for low sample size and loss to follow-up.

Two doses HPV vaccine in younger females versus three doses HPV vaccine in older females – all vaccines at 7 months

As in the D’Addario review, we analysed studies comparing two doses of HPV vaccine in younger females versus three doses in older females, reporting immunogenicity outcomes at 7 months, regardless of vaccine type. We added data from Mexico2 and Multinational3 to this comparison. For GMTs for HPV 6, 11, 16 and 18, there was very low-quality evidence of non-inferiority or higher GMTs for younger females (two doses) when compared with older females (three doses) at 7 months. There was high heterogeneity. One possible source of heterogeneity was Mexico2, which included both seronegative and seropositive participants at baseline. For GMTs for HPV 16 and HPV 18, additional possible sources of heterogeneity include the different types of vaccine used, different dose schedules in three dose arms (0,1,6 or 0,2,6), and different assays used to measure GMTs (lumindex or ELISA). For GMTs for HPV 31, 33, 45, 52, and 58, there was moderate-quality evidence of higher GMTs in younger females (2 doses) compared with older females (3 doses). For seropositivity to all HPV subtypes measured, there was moderate-quality evidence of no significant difference between younger (two doses) and older (three doses) at 7 months.

Two doses of 2-valent HPV vaccine in younger females versus three doses of 2-valent HPV vaccine in older females – multiple time points

There was low-quality (7 months) and very low-quality evidence (60 months) of non-inferiority for GMTs for HPV 16 and 18 in younger females (2 doses) when compared to older females (3 doses) of 2-valent vaccine. There was moderate-quality evidence of no significant difference in seropositivity for HPV 16 and 18 in younger versus older females at 7 and 12 months.

Two doses of 4-valent HPV vaccine in younger females versus three doses of 4-valent HPV vaccine in older females – multiple time points

There was low to moderate-quality evidence of non-inferior or higher GMTs for HPV 6, 11, 16 and 18 in younger females (2 doses) when compared to older females (3 doses) at 7 months, and very-low quality evidence at 36 months, with 4-valent vaccine. There was moderate-quality evidence of no significant difference in seropositivity for the same HPV subtypes in two-dose vaccinated younger females versus three-dose vaccinated older females at 7 and 12 months.

**Implications and conclusions** The evidence indicates that younger females (two doses) have noninferior or higher GMT responses than older females (3 doses) at 7 months, which appears to be sustained in longer-term follow-up (60 months with 2-valent and 36 months with 4-valent vaccines). No significant differences were detected in seropositivity between younger and older females at 7 months or with longer follow-up.

**D’Addario M, et al. HPV vaccines: systematic review of literature on alternative vaccination schedules. Report to WHO. Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland (24th June 2014). In: Evidence based recommendations on human papilloma virus (HPV) schedules: Background paper for SAGE discussions. Geneva: World Health Organization 2014: Annex 1**  
[http://www.who.int/immunization/sage/meetings/2014/april/1\\_HPV\\_Evidence\\_based\\_recommendationsWHO\\_with\\_Appendices2\\_3.pdf?ua=1](http://www.who.int/immunization/sage/meetings/2014/april/1_HPV_Evidence_based_recommendationsWHO_with_Appendices2_3.pdf?ua=1), accessed July 2014).

(No abstract available.)

**Grading of scientific evidence – table II: Immunogenicity of 2 vs. 3 doses of HPV vaccination in immunocompetent girls. Available at [http://www.who.int/immunization/position\\_papers/hpv\\_grad\\_immunogenicity\\_2vs3\\_immunocompetent.pdf](http://www.who.int/immunization/position_papers/hpv_grad_immunogenicity_2vs3_immunocompetent.pdf), accessed February 2017.**

(No abstract available.)

**Dobson SRM, et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. JAMA 2013;309(17):1793-1802.**

**IMPORTANCE:**

Global use of human papillomavirus (HPV) vaccines to prevent cervical cancer is impeded by cost. A 2-dose schedule for girls may be possible.

**OBJECTIVE:**

To determine whether mean antibody levels to HPV-16 and HPV-18 among girls receiving 2 doses was noninferior to women receiving 3 doses.

**DESIGN, SETTING, AND PATIENTS:**

Randomized, phase 3, postlicensure, multicenter, age-stratified, noninferiority immunogenicity study of 830 Canadian females from August 2007 through February 2011. Follow-up blood samples were provided by 675 participants (81%).

**INTERVENTION:**

Girls (9-13 years) were randomized 1:1 to receive 3 doses of quadrivalent HPV vaccine at 0, 2, and 6 months (n = 261) or 2 doses at 0 and 6 months (n = 259). Young women (16-26 years) received 3 doses at 0, 2, and 6 months (n = 310). Antibody levels were measured at 0, 7, 18, 24, and 36 months.

**MAIN OUTCOMES AND MEASURES:**

Primary outcome was noninferiority (95% CI, lower bound >0.5) of geometric mean titer (GMT) ratios for HPV-16 and HPV-18 for girls (2 doses) compared with young women (3 doses) 1 month after last dose. Secondary outcomes were noninferiority of GMT ratios of girls receiving 2 vs 3 doses of vaccine; and durability of noninferiority to 36 months.

**RESULTS:**

The GMT ratios were noninferior for girls (2 doses) to women (3 doses): 2.07 (95% CI, 1.62-2.65) for HPV-16 and 1.76 (95% CI, 1.41-2.19) for HPV-18. Girls (3 doses) had GMT responses 1 month after last vaccination for HPV-16 of 7736 milli-Merck units per mL (mMU/mL) (95% CI, 6651-8999) and HPV-18 of 1730 mMU/mL (95% CI, 1512-1980). The GMT ratios were noninferior for girls (2 doses) to girls (3 doses): 0.95 (95% CI, 0.73-1.23) for HPV-16 and 0.68 (95% CI, 0.54-0.85) for HPV-18. The GMT ratios for girls (2 doses) to women (3 doses) remained noninferior for all genotypes to 36 months. Antibody responses in girls were noninferior after 2 doses vs 3 doses for all 4 vaccine genotypes at month 7, but not for HPV-18 by month 24 or HPV-6 by month 36.

**CONCLUSIONS AND RELEVANCE:**

Among girls who received 2 doses of HPV vaccine 6 months apart, responses to HPV-16 and HPV-18 one month after the last dose were noninferior to those among young women who received 3 doses of the vaccine within 6 months. Because of the loss of noninferiority to some genotypes at 24 to 36 months in girls given 2 doses vs 3 doses, more data on the duration of protection are needed before reduced-dose schedules can be recommended.

**Romanowski B, et al. Sustained immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine administered as a two-dose schedule in adolescent girls: Five-year clinical data and modeling predictions from a randomized study. Human Vaccines & Immunotherapeutics 2016;12(1):20-9.**

In this randomized, partially-blind study ( clinicaltrials.gov ; NCT00541970), the licensed formulation of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine (20 µg each of HPV-16/18 antigens) was found highly immunogenic up to 4 y after first vaccination, whether administered as a 2-dose (2D) schedule in girls 9-14 y or 3-dose (3D) schedule in women 15-25 y. This end-of-study analysis extends immunogenicity and safety data until Month (M) 60, and presents antibody persistence predictions estimated by piecewise and modified power law models. Healthy females (age stratified: 9-14, 15-19, 20-25 y) were randomized to receive 2D at M0,6 (N = 240 ) or 3D at M0,1,6 (N = 239). Here, results are reported for girls 9-14 y (2D) and women 15-25 y (3D). Seropositivity rates, geometric mean titers (by enzyme-linked immunosorbent assay) and geometric mean titer ratios (GMRs; 3D/2D; post-hoc exploratory analysis) were calculated. All subjects seronegative pre-vaccination in the according-to-protocol immunogenicity cohort were seropositive for anti-HPV-16 and -18 at M60. Antibody responses elicited by the 2D and 3D schedules were comparable at M60, with GMRs close to 1 (anti-HPV-16: 1.13 [95% confidence interval: 0.82-1.54]; anti-HPV-18: 1.06 [0.74-1.51]). Statistical modeling predicted that in 95% of subjects, antibodies induced by 2D and 3D schedules could persist above natural infection levels for  $\geq 21$  y post-vaccination. The vaccine had a clinically acceptable safety profile in both groups. In conclusion, a 2D M0,6 schedule of the HPV-16/18 AS04-adjuvanted vaccine was immunogenic for up to 5 y in 9-14 y-old girls. Statistical modeling predicted that 2D-induced antibodies could persist for longer than 20 y.

**A phase III study of a 2-dose regimen of a multivalent human papillomavirus (HPV) vaccine (V503), administered to 9 to 14 year-olds and compared to young women, 16 to 26 years old (V503-010). Available: <https://clinicaltrials.gov/ct2/show/NCT01984697> [accessed 21-09-2016].**

(No abstract available.)

**Puthanakit T et al. Randomized Open Trial Comparing 2-Dose Regimens of the Human Papillomavirus 16/18 AS04-Adjuvanted Vaccine in Girls Aged 9-14 Years Versus a 3-Dose Regimen in Women Aged 15-25 Years. J Infect Dis. 2016 Aug 15;214(4):525-36.**

#### BACKGROUND:

This randomized, open trial compared regimens including 2 doses (2D) of human papillomavirus (HPV) 16/18 AS04-adjuvanted vaccine in girls aged 9-14 years with one including 3 doses (3D) in women aged 15-25 years.

#### METHODS:

Girls aged 9-14 years were randomized to receive 2D at months 0 and 6 (M0,6; (n = 550) or months 0 and 12 (M0,12; n = 415), and women aged 15-25 years received 3D at months 0, 1, and 6 (n = 482). End points included noninferiority of HPV-16/18 antibodies by enzyme-linked immunosorbent assay for 2D (M0,6) versus 3D (primary), 2D (M0,12) versus 3D, and 2D (M0,6) versus 2D (M0,12); neutralizing antibodies; cell-mediated immunity; reactogenicity; and safety. Limits of noninferiority were predefined as <5% difference in seroconversion rate and <2-fold difference in geometric mean antibody titer ratio.

#### RESULTS:

One month after the last dose, both 2D regimens in girls aged 9-14 years were noninferior to 3D in women aged 15-25 years and 2D (M0,12) was noninferior to 2D (M0,6). Geometric mean antibody titer ratios (3D/2D) for HPV-16 and HPV-18 were 1.09 (95% confidence interval, .97-1.22) and 0.85 (.76-.95) for 2D (M0,6) versus 3D and 0.89 (.79-1.01) and 0.75 (.67-.85) for 2D (M0,12) versus 3D. The safety profile was clinically acceptable in all groups.

#### CONCLUSIONS:

The 2D regimens for the HPV-16/18 AS04-adjuvanted vaccine in girls aged 9-14 years (M0,6 or M0,12) elicited HPV-16/18 immune responses that were noninferior to 3D in women aged 15-25 years.

**Lazcano-Ponce E, et al. Overcoming barriers to HPV vaccination: non-inferiority of antibody response to human papillomavirus 16/18 vaccine in adolescents vaccinated with a two-dose versus a three-dose schedule at 21 months. Vaccine 2014;32:725-732.**

For middle and low-income countries, the cost of HPV vaccines remains challenging. We conducted an open-label nonrandomized clinical trial evaluating immune response to the HPV-16/18 AS04-adjuvanted vaccine administered on a standard (months (M) 0-1-6) versus extended schedule (M 0-6-60) at 7, 21, 60, 72 and 120 months post-vaccination. Participants were females recruited in Morelos, Mexico: 474 girls aged 9-10 years and 500 women aged 18-24 years receiving a standard schedule, and 1026 girls aged 9-10 years receiving an extended schedule (currently the girls in the extended schedule had received only the first 2 doses). This report presents the interim analysis results for non-inferiority between the regimes conducted with the current available data at 21 months after the first dose, with serum antibodies assessed by ELISA. A pre-stated margin of non-inferiority was defined by post-vaccination geometric mean titer (GMT) ratio (upper 95% confidence interval [CI]  $\leq 2.0$ ) between the standard and the two-dose schedule in girls at month 21. Immune response to the vaccine was strongest in adolescent girls and in the 3-dose group. Statistical non-inferiority of the two-dose versus three-dose groups was demonstrated. At 21 months, comparing the adolescent 2-dose versus 3-dose groups, the GMT ratio and 95% CI were 1.66 (1.55-1.81) and 1.67 (1.51-1.86) for HPV16 and 18, respectively. The two-dose regimen was non-inferior when compared to the three-dose response in same-age girls and with women aged 18-24 years after 21 months of follow-up. The reduction in the number of doses from the current three-dose schedule may lower overall costs associated with the vaccination and increase accessibility and compliance with the recommended dosing of the HPV vaccine.

**Hernandez-Avila M, et al. Evaluation of the immunogenicity of the quadrivalent HPV vaccine using two versus three doses at month 21: an epidemiological surveillance mechanism for alternate vaccination schemes. Human Vaccines & Immunotherapeutics 2016;12(1)30-38.**

The cost of HPV vaccines and the need for 3 doses remains a barrier for their inclusion in routine vaccination schedules for girls in low and middle income countries. In a non-inferiority study, we aimed to compare the immunogenicity of a standard 3 doses and a 2 doses schedule. We enrolled 450 participants in an open-label non-randomized clinical trial to evaluate the immunogenicity induced at different ages by the licensed HPV6/11/16/18 quadrivalent vaccine in a 2 doses schedule (0-6 months, n = 150 girls aged 9-10 y) and 3 doses schedule (0, 2, and 6 months; n = 150 girls aged 9-10 y and n=150 women aged 18 to 24 years). To assess the antibody response, blood samples were obtained at Month 7 and 21 after the first vaccination from participants in all study groups. cLIA testing was performed at Merck Research Laboratories. Antibody levels were expressed as milli-Merck units (mMU) per ml. Primary outcome was non-inferiority (95% CI, lower bound  $>0.5$ ) of the geometric mean titers (GMT) ratios for HPV6, HPV11, HPV16 and HPV18 antibodies 7 and 21 months after the first dose among girls receiving 2 doses compared with young women and girls receiving 3 doses. All vaccinees were seropositive for both HPV16 and HPV18 antibodies at month 7. At month 21, 98.5 and 56.6% of women 18-24 y old were seropositive for HPV16 and 18, respectively. For girls in the three doses group, seropositivity rates were 99.3 and 86.3% for HPV16 and 18, respectively. For girls in the two doses group rates were 99.3 and 70.2% for HPV16 and 18, respectively. The two doses schedule was non-inferior compared to the 3 doses schedule in same-age girls and to the group of adult women after 21 months of the first vaccine dose. Our results are in agreement

with similar trials evaluating the immune response of a 2 doses schedule of both HPV vaccines, supporting the recent WHO recommendation as well as the Mexican policy to incorporate the 2 doses schedule for girls aged 9-11 y.

**Iversen OE, et al. Immunogenicity of the 9-Valent HPV Vaccine Using 2-Dose Regimens in Girls and Boys vs a 3-Dose Regimen in Women. JAMA. 2016 Dec 13;316(22):2411-2421.**

**IMPORTANCE:**

Human papillomavirus (HPV) infections cause anogenital cancers and warts. The 9-valent HPV vaccine provides protection against 7 high-risk types of HPV responsible for 90% of cervical cancers and 2 other HPV types accounting for 90% of genital warts.

**OBJECTIVE:**

To determine whether HPV type-specific antibody responses would be noninferior among girls and boys aged 9 to 14 years after receiving 2 doses of the 9-valent HPV vaccine compared with adolescent girls and young women aged 16 to 26 years receiving 3 doses.

**DESIGN, SETTING, AND PARTICIPANTS:**

Open-label, noninferiority, immunogenicity trial conducted at 52 ambulatory care sites in 15 countries. The study was initiated on December 16, 2013, with the last participant visit for this report on June 19, 2015. Five cohorts were enrolled: (1) girls aged 9 to 14 years to receive 2 doses 6 months apart (n = 301); (2) boys aged 9 to 14 years to receive 2 doses 6 months apart (n = 301); (3) girls and boys aged 9 to 14 years to receive 2 doses 12 months apart (n = 301); (4) girls aged 9 to 14 years to receive 3 doses over 6 months (n = 301); and (5) a control group of adolescent girls and young women aged 16 to 26 years to receive 3 doses over 6 months (n = 314).

**INTERVENTIONS:**

Two doses of the 9-valent HPV vaccine administered 6 or 12 months apart or 3 doses administered over 6 months.

**MAIN OUTCOMES AND MEASURES:**

The primary end point was prespecified as the antibody response against each HPV type assessed 1 month after the last dose using a competitive immunoassay. Each of the three 2-dose regimens was compared with the standard 3-dose schedule in adolescent girls and young women using a noninferiority margin of 0.67 for the ratio of the antibody geometric mean titers.

**RESULTS:**

Of the 1518 participants (753 girls [mean age, 11.4 years]; 451 boys [mean age, 11.5 years]; and 314 adolescent girls and young women [mean age, 21.0 years]), 1474 completed the study and data from 1377 were analyzed. At 4 weeks after the last dose, HPV antibody responses in girls and boys given 2 doses were noninferior to HPV antibody responses in adolescent girls and young women given 3 doses ( $P < .001$  for each HPV type). Compared with adolescent girls and young women who received 3 doses over 6 months, the 1-sided 97.5% CIs for the ratio of HPV antibody geometric mean titers at 1 month after the last dose across the 9 HPV subtypes ranged from 1.36 to  $\infty$  to 2.50 to  $\infty$  for girls who received 2 doses 6 months apart; from 1.37 to  $\infty$  to 2.55 to  $\infty$  for boys who received 2 doses 6 months apart; and from 1.61 to  $\infty$  to 5.36 to  $\infty$  for girls and boys who received 2 doses 12 months apart.

**CONCLUSIONS AND RELEVANCE:**

Among girls and boys aged 9 to 14 years receiving 2-dose regimens of a 9-valent HPV vaccine separated by 6 or 12 months, immunogenicity 4 weeks after the last dose was noninferior to a 3-dose regimen in a cohort of adolescent girls and young women. Further research is needed to assess persistence of antibody responses and effects on clinical outcomes.

**Kreimer AR, et al. Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV16/18 vaccine. J Natl Cancer Inst, 2011;103:1444–1451.**

#### 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.

**Basu P et al. Less than 3 doses of the HPV vaccine – Review of efficacy against virological and disease end points. Hum Vaccin Immunother 2016; 12:1394-1402.**

World Health Organization (WHO) recommended 2 doses of the Human Papillomavirus (HPV) vaccine for girls below 15 y on the basis of the immune-bridging studies demonstrating non-inferior immune response of 2 doses in the adolescent girls compared to 3 doses in the young adult women in whom the efficacy against disease is established. The biological nature of the antigens (virus-like particles) constituting the HPV vaccine is responsible for the vigorous antibody response that may make the third dose redundant. The protection offered by 2 doses has been demonstrated in non-randomized clinical trials to be comparable to that offered by 3 doses against incident and persistent infections of vaccine targeted HPV types. However, results emerging from the ecological and nested case-control studies embedded in the population based screening programs of different countries indicate reduced efficacy of 2 doses against virological and disease end points. Some recent studies observed the protective effect of single dose of the vaccine against incident and persistent infections of the vaccine targeted HPV types to be similar to 3 doses in spite of immunological inferiority. The sample size, duration of follow-ups and number of events were limited in these studies. Longer follow ups of the less than 3 doses cohorts in the ongoing studies as well as appropriately designed and ethically justifiable randomized studies are needed to establish the protection offered by the alternative schedules at least beyond 10 y of vaccination.

**Sankaranarayanan R. et al. Immunogenicity and HPV infection after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre prospective cohort study. Lancet Oncol 2016; 17: 67–77.**

#### BACKGROUND:

An increase in worldwide HPV vaccination could be facilitated if fewer than three doses of vaccine are as effective as three doses. We originally aimed to compare the immunogenicity and frequency of persistent infection and cervical precancerous lesions caused by vaccine-targeted HPV after

vaccination with two doses of quadrivalent vaccine on days 1 and 180 or later, with three doses on days 1, 60, and 180 or later, in a cluster-randomised trial. Suspension of the recruitment and vaccination due to events unrelated to our study meant that some enrolled girls could not be vaccinated and some vaccinated girls received fewer than the planned number of vaccinations by default. As a result, we re-analysed our data as an observational cohort study.

#### METHODS:

Our study was designed to be done in nine locations (188 clusters) in India. Participants were unmarried girls aged 10-18 years vaccinated in four cohorts: girls who received three doses of vaccine on days 1, 60, and 180 or later, two doses on days 1 and 180 or later, two doses on days 1 and 60 by default, and one dose by default. The primary outcomes were immunogenicity in terms of L1 genotype-specific binding antibody titres, neutralising antibody titres, and antibody avidity after vaccination for the vaccine-targeted HPV types 16, 18, 6, and 11 and incident and persistent infections with these HPVs. Analysis was per actual number of vaccine doses received. This study is registered with ISRCTN, number ISRCTN98283094; and with ClinicalTrials.gov, number NCT00923702.

#### FINDINGS:

Vaccination of eligible girls was initiated on Sept 1, 2009, and continued until April 8, 2010. Of 21 258 eligible girls identified at 188 clusters, 17 729 girls were recruited from 178 clusters before suspension. 4348 (25%) girls received three doses, 4979 (28%) received two doses on days 1 and 180 or later, 3452 (19%) received two doses at days 1 and 60, and 4950 (28%) received one dose.

Immune response in the two-dose HPV vaccine group was non-inferior to the three-dose group (median fluorescence intensity ratio for HPV 16 1·12 [95% CI 1·02-1·23] and for HPV 18 1·04 [0·92-1·19]) at 7 months, but was inferior in the two-dose default (0·33 [0·29-0·38] for HPV 16 and 0·51 [0·43-0·59] for HPV 18) and one-dose default (0·09 [0·08-0·11] for HPV 16 and 0·12 [0·10-0·14] for HPV 18) groups at 18 months. The geometric mean avidity indices after fewer than three doses by design or default were non-inferior to those after three doses of vaccine. Fewer than three doses by design and default induced detectable concentrations of neutralising antibodies to all four vaccine-targeted HPV types, but at much lower concentration after one dose. Cervical samples from 2649 participants were tested and the frequency of incident HPV 16, 18, 6, and 11 infections was similar irrespective of the number of vaccine doses received. The testing of at least two samples from 838 participants showed that there was no persistent HPV 16 or 18 infections in any study group at a median follow-up of 4·7 years (IQR 4·2-5·1).

#### INTERPRETATION:

Despite the limitations imposed by the suspension of the HPV vaccination, our findings lend support to the WHO recommendation of two doses, at least 6 months apart, for routine vaccination of young girls. The short-term protection afforded by one dose of HPV vaccine against persistent infection with HPV 16, 18, 6, and 11 is similar to that afforded by two or three doses of vaccine and merits further assessment.

**Markowitz LM et al. High effectiveness after vaccine type prevalence after 1, 2 and 3 doses of quadrivalent HPV vaccine, United States. HPV 2017, March 2, 2017.**

(No abstract available.)

**Gertig DM, Brotherton JM, Budd AC, et al. Impact of a population-based HPV vaccination program on cervical abnormalities: a data linkage study. BMC Med, 2013;11:227.**

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.

**Powell SE, Hariri S, Steinau M, et al. Impact of human papillomavirus (HPV) vaccination on HPV 16/18-related prevalence in precancerous cervical lesions. *Vaccine*, 2012;31:109–113.**

#### 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 screening. 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.

#### **Pollock et al. Reduction of low- and high-grade cervical abnormalities associated with high uptake of the HPV bivalent vaccine in Scotland. *British Journal of Cancer* (2014) 111, 1824–1830.**

#### BACKGROUND:

In Scotland, a national HPV immunisation programme began in 2008 for 12- to 13-year olds, with a catch-up campaign from 2008 to 2011 for those under the age of 18. To monitor the impact of HPV immunisation on cervical disease at the population level, a programme of national surveillance was established.

#### METHODS:

We analysed colposcopy data from a cohort of women born between 1988 and 1992 who entered the Scottish Cervical Screening Programme (SCSP) and were aged 20-21 in 2008-2012.

#### RESULTS:

By linking datasets from the SCSP and colposcopy services, we observed a significant reduction in diagnoses of cervical intraepithelial neoplasia 1 (CIN 1; RR 0.71, 95% CI 0.58 to 0.87;  $P=0.0008$ ), CIN 2 (RR 0.5, 95% CI 0.4 to 0.63;  $P<0.0001$ ) and CIN 3 (RR 0.45, 95% CI 0.35 to 0.58;  $P<0.0001$ ) for women who received three doses of vaccine compared with unvaccinated women.

#### CONCLUSIONS:

To our knowledge, this is one of the first studies to show a reduction of low- and high-grade CIN associated with high uptake of the HPV bivalent vaccine at the population level. These data are very encouraging for countries that have achieved high HPV vaccine uptake.

#### **Tabrizi SN, Brotherton JML, Kaldor JM, et al. Assessment of herd immunity and cross-protection after a human papillomavirus vaccination programme in Australia: a repeat cross-sectional study. *Lancet Infect Dis*, 2014; 14:958–966.**

#### 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.

**McCormack PL. Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine (Gardasil®): A Review of Its Use in the Prevention of Premalignant Anogenital Lesions, Cervical and Anal Cancers, and Genital Warts. *Drugs*, 2014;74(11):1253–1283.**

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.

**Muñoz N, et al. Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women. *J Nat Cancer Inst*, 2010;102(5):325–339.**

#### 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.

**Grading of scientific evidence – table IV: Protection against anogenital warts conferred by HPV vaccination in immunocompetent girls. Available at**

**[http://www.who.int/immunization/position\\_papers/hpv\\_grad\\_protection\\_warts\\_immunocompetent.pdf](http://www.who.int/immunization/position_papers/hpv_grad_protection_warts_immunocompetent.pdf)**

(No abstract available.)

**Bollerup S, et al. Significant reduction in the incidence of genital warts in young men 5 years into the danish human papillomavirus vaccination program for girls and women. Sex Transm Dis 2016;43:238e42.**

#### BACKGROUND:

Denmark introduced the quadrivalent human papillomavirus vaccine into the vaccination program for 12- to 15-year-old girls in 2008 to 2009. In 2012, the program was supplemented with a catch-up program for women aged up to 27 years. We evaluated the effectiveness of the Danish vaccination program on the nationwide incidence of genital warts (GWs), after the second catch-up by including information on both hospital treatments and on self-administered treatment with podophyllotoxin. Genital wart incidence was investigated in both sexes; however, the main focus was on potential herd protection of men.

#### METHODS:

Incident cases of GWs were identified from the Danish National Patient Register and through redemptions of prescription for podophyllotoxin in the Danish National Prescription Registry in 2006 to 2013. Age-specific incidence rates (IRs) were assessed, and estimated annual percentage change (EAPC) was calculated by Poisson regression.

#### RESULTS:

Genital wart incidence was either stable or increased in both sexes in 2006 to 2008. After introduction of the vaccination program, GW incidence decreased significantly in women aged 12 to 35 years and men aged 12 to 29 years, with rapid decrease among 16- to 17-year-olds (IR women, from 1071 to 58 per 100,000 person-years [EAPC, -55.1%; 95% confidence interval, -58.7 to -51.2];

IRmen, from 365 to 77 per 100,000 person-years [EAPC, -36.6%; 95% confidence interval, -40.5 to -32.5] in 2008-2013).

**CONCLUSIONS:**

We found a significantly decreasing incidence of GWs in women up to 35 years of age after the start of the humanpapillomavirus vaccination program. A similar pattern was observed for men aged 12 to 29 years, indicating substantial herd protection.

**Ali H, et al. Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data. BMJ, 2013;346:f2032.**

**BACKGROUND:** 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 wart 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.

**Garland SM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007;356:1928e43.**

**BACKGROUND:**

A phase 3 trial was conducted to evaluate the efficacy of a prophylactic quadrivalent vaccine in preventing anogenital diseases associated with human papillomavirus (HPV) types 6, 11, 16, and 18.

**METHODS:**

In this randomized, placebo-controlled, double-blind trial involving 5455 women between the ages of 16 and 24 years, we assigned 2723 women to receive vaccine and 2732 to receive placebo at day 1, month 2, and month 6. The coprimary composite end points were the incidence of genital warts, vulvar or vaginal intraepithelial neoplasia, or cancer and the incidence of cervical intraepithelial

neoplasia, adenocarcinoma in situ, or cancer associated with HPV type 6, 11, 16, or 18. Data for the primary analysis were collected for a per-protocol susceptible population of women who had no virologic evidence of HPV type 6, 11, 16, or 18 through 1 month after administration of the third dose.

#### RESULTS:

The women were followed for an average of 3 years after administration of the first dose. In the per-protocol population, those followed for vulvar, vaginal, or perianal disease included 2261 women (83%) in the vaccine group and 2279 (83%) in the placebo group. Those followed for cervical disease included 2241 women (82%) in the vaccine group and 2258 (83%) in the placebo group. Vaccine efficacy was 100% for each of the coprimary end points. In an intention-to-treat analysis, including those with prevalent infection or disease caused by vaccine-type and non-vaccine-type HPV, vaccination reduced the rate of any vulvar or vaginal perianal lesions regardless of the causal HPV type by 34% (95% confidence interval [CI], 15 to 49), and the rate of cervical lesions regardless of the causal HPV type by 20% (95% CI, 8 to 31).

#### CONCLUSIONS:

The quadrivalent vaccine significantly reduced the incidence of HPV-associated anogenital diseases in young women. (ClinicalTrials.gov number, NCT00092521 [ClinicalTrials.gov].).

**Giuliano AR, et al. Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. N Engl J Med 2011;364:401e11.**

#### BACKGROUND:

Infection with human papillomavirus (HPV) and diseases caused by HPV are common in boys and men. We report on the safety of a quadrivalent vaccine (active against HPV types 6, 11, 16, and 18) and on its efficacy in preventing the development of external genital lesions and anogenital HPV infection in boys and men.

#### METHODS:

We enrolled 4065 healthy boys and men 16 to 26 years of age, from 18 countries in a randomized, placebo-controlled, double-blind trial. The primary efficacy objective was to show that the quadrivalent HPV vaccine reduced the incidence of external genital lesions related to HPV-6, 11, 16, or 18. Efficacy analyses were conducted in a per-protocol population, in which subjects received all three vaccinations and were negative for relevant HPV types at enrollment, and in an intention-to-treat population, in which subjects received vaccine or placebo, regardless of baseline HPV status.

#### RESULTS:

In the intention-to-treat population, 36 external genital lesions were seen in the vaccine group as compared with 89 in the placebo group, for an observed efficacy of 60.2% (95% confidence interval [CI], 40.8 to 73.8); the efficacy was 65.5% (95% CI, 45.8 to 78.6) for lesions related to HPV-6, 11, 16, or 18. In the per-protocol population, efficacy against lesions related to HPV-6, 11, 16, or 18 was 90.4% (95% CI, 69.2 to 98.1). Efficacy with respect to persistent infection with HPV-6, 11, 16, or 18 and detection of related DNA at any time was 47.8% (95% CI, 36.0 to 57.6) and 27.1% (95% CI, 16.6 to 36.3), respectively, in the intention-to-treat population and 85.6% (97.5% CI, 73.4 to 92.9) and 44.7% (95% CI, 31.5 to 55.6) in the per-protocol population. Injection-site pain was significantly more frequent among subjects receiving quadrivalent HPV vaccine than among those receiving placebo (57% vs. 51%,  $P<0.001$ ).

#### CONCLUSIONS:

Quadrivalent HPV vaccine prevents infection with HPV-6, 11, 16, and 18 and the development of related external genital lesions in males 16 to 26 years of age. (Funded by Merck and others; ClinicalTrials.gov number, NCT00090285.).

**Howell-Jones et al. Declining Genital Warts in Young Women in England Associated With HPV 16/18 Vaccination: An Ecological Study. J Infect Dis 2013;208:1397–1403.**

#### 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.

**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. Clin Infect Dis, 2013; 57 (7): 929–934.**

#### 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.

**Szarewski et al. Efficacy of the HPV-16/18 AS04-adjuvanted vaccine against low-risk HPV types (PATRICIA randomized trial): an unexpected observation. The Journal of Infectious Diseases 2013;208:1391–6.**

#### 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.

**Miltz A, et al. Sytematic review and meta-analysis of l1-VLP-based Human Papillomavirus vaccine efficacy against anogenital pre-cancer in women with evidence of prior HPV exposure. Plos One, 2014;9; 3:e90348.**

#### 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 (Rixensart, 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.

**Lehtinen M. et al. Clinical trials of human papillomavirus vaccines and beyond. Clinical trials of human papillomavirus vaccines and beyond. Nature Reviews Clinical Oncology.2013. 10, 400-410.**

Human papillomavirus (HPV) is the most common sexually transmitted infectious agent; its 14 oncogenic types are causally associated with 5-10% of all cancers. The major structural HPV protein self-assembles into immunogenic virus-like particles. Two licensed HPV vaccines--the bivalent vaccine comprising HPV types 16 and 18, and the quadrivalent vaccine comprising HPV types 6, 11, 16 and 18--have proven to be safe and efficacious against 6-month-persistent cervical infections of HPV16 and HPV18 and associated precancerous lesions, and both have efficacies of 90-100%. Among baseline HPV-negative adolescent females, vaccine efficacies against the immediate precursor of cervical cancer (intraepithelial neoplasia grade 3) irrespective of HPV type are 93.2% and 43.0% for the bivalent and quadrivalent vaccines, respectively. The quadrivalent vaccine is efficacious (>75% vaccine efficacy) against any of the more-severe precursors of vulval, vaginal and anal cancers. A strong increase in vaccine efficacy with increasing severity of the precancerous lesion is explained by accumulation of the most-oncogenic HPV types 16 and 18 in these lesions. Therefore, prophylactic HPV vaccination will exceed the best results from screening for cancer. With the extremely efficacious prophylactic HPV vaccines, the focus of organized intervention (vaccination and screening) programmes should, however, shift from reducing the HPV disease burden to controlling the prevalence of oncogenic HPV (and nononcogenic HPV) types. Eradication of the major oncogenic HPV types should be pursued.

**Kojic EM, et al. Immunogenicity and Safety of a Quadrivalent Human Papillomavirus Vaccine in HIV-1-Infected Women. Clin Infect Dis 2014;59(1):127–135.**

#### 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.

**Kahn JA, et al. Immunogenicity and safety of human papillomavirus 6, 11, 16, 18 vaccine in HIV infected young women Clin Infect Dis, 2013;57(5):735–744.**

#### 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.

**Wilkin T, et al. Safety and immunogenicity of the quadrivalent human papillomavirus vaccine in HIV-1-infected men. J Infect Dis, 2010;202:1246–1253.**

**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.

**Levin MJ, et al. Safety and Immunogenicity of a Quadrivalent Human Papillomavirus (Types 6, 11, 16, and 18) Vaccine in HIV-Infected Children 7 to 12 Years Old. J Acquir Immune Defic Syndr, 2010; 55(2):197–204.**

**BACKGROUND:**

Quadrivalent human papillomavirus vaccine (QHPV) is > 95% effective in preventing infection with vaccine-type humanpapillomavirus. 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%  $\geq$  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.

**Grading of scientific evidence – table V: Safety of HPV vaccination in HIV infected girls. Available at [http://www.who.int/immunization/position\\_papers/hpv\\_grad\\_safety\\_hiv.pdf](http://www.who.int/immunization/position_papers/hpv_grad_safety_hiv.pdf), accessed February 2017.**

(No abstract available.)

**Weinberg A, et al. Humoral, mucosal, and cell-mediated immunity against vaccine and nonvaccine genotypes after administration of quadrivalent human papillomavirus vaccine to HIV-infected children. 2012;206:1309-1318.**

**OBJECTIVES:**

To characterize the immunogenicity of a quadrivalent human papillomavirus vaccine (QHPV) in human immunodeficiency virus (HIV)-infected children, we studied their immune responses to 3 or 4 doses.

**METHODS:**

HIV-infected children aged 7-12 years with a CD4 cell percentage of  $\geq$ 15% of lymphocytes, received 3 doses of QHPV with or without a fourth dose after 72 weeks. Type-specific and cross-reactive antibodies and cell-mediated immunity were measured.

**RESULTS:**

Type-specific antibodies to HPV6, 11, and 16 were detected in 100% and  $\geq$ 94% of children at 4 and 72 weeks, respectively, after the third QHPV dose. Corresponding numbers for HPV18 were 97% and 76%, respectively. A fourth QHPV dose increased seropositivity to  $\geq$ 96% for all vaccine genotypes. Four weeks after the third QHPV dose, 67% of vaccinees seroconverted to HPV31, an HPV16-related genotype not in the vaccine; 69% and 39% of vaccinees developed mucosal HPV16 and 18 immunoglobulin G antibodies, respectively; and 60% and 52% of vaccinees developed cytotoxic T lymphocytes (CTLs) for HPV16 and 31, respectively.

**CONCLUSIONS:**

Three QHPV doses generated robust and persistent antibodies to HPV6, 11, and 16 but comparatively weaker responses to HPV18. A fourth dose increased antibodies against all vaccine genotypes in an anamnestic fashion. CTLs and mucosal antibodies against vaccine genotypes, as well as cross-reactive antibodies and CTL against nonvaccine genotypes, were detected.

**Denny L, et al. Safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine in HIV-positive women in South Africa: a partially-blind randomized placebo-controlled study. Vaccine,**

**2013 Nov 19;31(48):5745-53.**

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<sup>+</sup> T-cell count and randomised (1:1) to receive HPV-16/18 vaccine (Cervarix®; GlaxoSmithKline Vaccines) or placebo (Al(OH)<sub>3</sub>) 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<sup>+</sup> T-cell responses, CD4<sup>+</sup> 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<sup>+</sup> T-cell responses in both HIV-positive and HIV-negative women. No impact of baseline CD4<sup>+</sup> 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<sup>+</sup> 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.

**Toft L, et al. Comparison of the immunogenicity and reactogenicity of Cervarix and Gardasil human papillomavirus vaccines in HIV-infected adults: a randomized, double-blind clinical trial. Hum Vaccine Immunother. 2014;209:1165-1173.**

**BACKGROUND:**

We compared the immunogenicity and reactogenicity of Cervarix or Gardasil human papillomavirus (HPV) vaccines in adults infected with the human immunodeficiency virus (HIV).

**METHODS:**

This was a double-blind, controlled trial randomizing HIV-positive adults to receive 3 doses of Cervarix or Gardasil at 0, 1.5, and 6 months. Immunogenicity was evaluated for up to 12 months. Neutralizing anti-HPV-16/18 antibodies were measured by pseudovirion-based neutralization assay. Laboratory tests and diary cards were used for safety assessment. The HPV-DNA status of the participants was determined before and after immunization.

**RESULTS:**

Ninety-two participants were included in the study. Anti-HPV-18 antibody titers were higher in the Cervarix group compared with the Gardasil group at 7 and 12 months. No significant differences in anti-HPV-16 antibody titers were found among vaccine groups. Among Cervarix vaccinees, women had higher anti-HPV-16/18 antibody titers compared to men. No sex-specific differences in antibody titers were found in the Gardasil group. Mild injection site reactions were more common in the Cervarix group than in the Gardasil group (91.1% vs 69.6%; P = .02). No serious adverse events occurred.

**CONCLUSIONS:**

Both vaccines were immunogenic and well tolerated. Compared with Gardasil, Cervarix induced superior vaccine responses among HIV-infected women, whereas in HIV-infected men the difference in immunogenicity was less pronounced.

**Faust H, et al. Human papillomavirus neutralizing and cross-reactive antibodies induced in HIV-**

**positive subjects after vaccination with quadrivalent and bivalent HPV vaccines. 2016;34:1559-1565.**

Ninety-one HIV-infected individuals (61 men and 30 women) were randomized to vaccination either with quadrivalent (Gardasil™) or bivalent (Cervarix™) HPV vaccine. Neutralizing and specific HPV-binding serum antibodies were measured at baseline and 12 months after the first vaccine dose. Presence of neutralizing and binding antibodies had good agreement (average Kappa for HPV types 6, 11, 16, 18, 31, 33 and 45 was 0.65). At baseline, 88% of subjects had antibodies against at least one genital HPV. Following vaccination with Cervarix™, all subjects became seropositive for HPV16 and 18. After Gardasil™ vaccination, 96% of subjects seroconverted for HPV16 and 73% for HPV18. Levels of HPV16-specific antibodies were <1 international unit (IU) in 87% of study subjects before vaccination but >10IU in 85% of study subjects after vaccination. Antibodies against non-vaccine HPV types appeared after Gardasil™ vaccination for >50% of vaccinated females for HPV 31, 35 and 73 and for >50% of Cervarix™-vaccinated females for HPV 31, 33, 35, 45, 56 and 58. Cross-reactivity with non-genital HPV types was also detected. In conclusion, HIV-infected subjects responded to HPV vaccination with induction of neutralizing antibodies against both vaccine and non-vaccine types.

**Grading of scientific evidence – table VI: Efficacy of HPV vaccination in HIV infected girls. Available at [http://www.who.int/immunization/position\\_papers/hpv\\_grad\\_efficiency\\_hiv.pdf](http://www.who.int/immunization/position_papers/hpv_grad_efficiency_hiv.pdf), accessed February 2017.**

(No abstract available.)

**MalagonT, et al. Cross-protective efficacy of two human papillomavirus vaccines: a systematic review and meta- analysis. Lancet Infect Dis, 2012;12:781–789.**

#### 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  $\chi^2$  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% [-71.2 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.

**Kemp TJ, et al. HPV16/18 L1 VLP vaccine induces cross-neutralising antibodies that may mediate cross-protection. *Vaccine* 2011;29(11):2011–2014.**

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.

**Draper E, et al. A randomized, observer-blinded immunogenicity trial of Cervarix and Gardasil human papillomavirus vaccines in 12-15 year old girls. *Plos One*, 2013;8:e61825.**

#### 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 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.

**Mesher D, et al. Population-level effects of human papillomavirus vaccination programs on infections with nonvaccine genotypes. *Emerg Infect Dis.* 2016;22(10):1732-40.**

We analyzed human papillomavirus (HPV) prevalences during prevaccination and postvaccination periods to consider possible changes in nonvaccine HPV genotypes after introduction of vaccines that confer protection against 2 high-risk types, HPV16 and HPV18. Our meta-analysis included 9 studies with data for 13,886 girls and women ≤19 years of age and 23,340 women 20-24 years of age. We found evidence of cross-protection for HPV31 among the younger age group after vaccine introduction but little evidence for reductions of HPV33 and HPV45. For the group this same age group, we also found slight increases in 2 nonvaccine high-risk HPV types (HPV39 and HPV52) and in 2 possible high-risk types (HPV53 and HPV73). However, results between age groups and vaccines used were inconsistent, and the increases had possible alternative explanations; consequently, these data provided no clear evidence for type replacement. Continued monitoring of these HPV genotypes is important.

**Das R, et al. Effectiveness, immunogenicity, and safety of Gardasil™ in pre-adolescents and adolescents- 10 years of follow-up. *EUROGIN* 2016.**  
**<http://eurogin.com/2016/images/doc/eurogin-2016-abstracts-part-2.pdf>, accessed February 2016.**

**Background / Objectives** Quadrivalent HPV vaccine has previously been shown to be effective, immunogenic, and safe in pre-adolescents and adolescents aged 9-15, through 8 years after vaccination. We describe final 10-year data for the long-term follow-up (LTFU) study of GARDASIL™ in this population. **Methods** In the base study of V501-Protocol 018, 1661 sexually naïve boys and girls were assigned to GARDASIL or placebo at day 1, months 2 and 6. At the end of the base study (month 30), the placebo group received GARDASIL™. Those vaccinated with GARDASIL™ in the base study are the early vaccination group (EVG). Those vaccinated with GARDASIL™ thereafter are the catch-up vaccination group (CVG). As this LTFU study does not have a placebo arm, effectiveness was estimated by calculating the incidence rate of the primary endpoints (HPV6/11/16/18 related disease or persistent infection) and comparing with rates from previous studies in young adults (aged 16-26). **Results** A total of 1245 subjects (821 in the EVG and 424 in the CVG) had visits in the LTFU study. The median follow-up time was 9.9 years in EVG and 7.4 years in the CVG. No cases of HPV 6/11/16/18-related disease were observed. Ten subjects were detected to have persistent infection of ≥6month duration with vaccine-type HPV (females: 0.3/100 person-years at risk in the EVG and CVG, males: 0.6/100 person-years at risk in the EVG and 0.4/100 person-years at risk in the CVG). Infection persisted for ≥12 months in only 2 of these subjects. Incidence of HPV 6/11/16/18 persistent infection in female and male placebo recipients from previous studies were 6/100 person-years at risk and 4/100 person years at risk respectively. For each of HPV types 6, 11 and 16, 89%-96% remained seropositive through 10-years post-vaccination. Lower anti-HPV 18 responses were seen over time, consistent with observations in other studies of GARDASIL™ but no cases of 273 persistent infection due to HPV type 18 were observed. No serious adverse events were reported between 8 and 10 years. **Conclusion** No breakthrough cases of cervical/genital disease related to HPV types 6, 11, 16, and 18 were observed among preadolescents and adolescents vaccinated with GARDASIL™ during 10 years of follow-up. Although 10 cases of persistent infection were detected, a majority (8/10) were of <12 months duration. Anti-HPV 6, 11, 16, and 18 antibody responses post-vaccination persisted over time. Additionally, the safety profile of GARDASIL™ during the LTFU period remained favorable.

**Grading of scientific evidence – table VII: Duration of protection conferred by HPV vaccination in**

immunocompetent females. Available at [http://www.who.int/immunization/position\\_papers/hpv\\_grad\\_duration\\_immunocompetent.pdf](http://www.who.int/immunization/position_papers/hpv_grad_duration_immunocompetent.pdf), accessed February 2017.

(No abstract available.)

**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\\_HP12\\_Mar\\_2014.pdf?ua=1](http://www.who.int/vaccine_safety/committee/topics/hpv/GACVS_Statement_HP12_Mar_2014.pdf?ua=1), accessed February 2017.

(No abstract available.)

**See No 3, 2016, 91, 21–32**

**Einstein MH, et al. Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 vaccine and HPV-6/11/16/18 vaccine: follow-up from months 12-24 in a phase III randomized study of healthy women aged 18-45 years. Hum Vaccin, 2011; 7: 1343–1358.**

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  $\geq 1$  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<sup>+</sup> 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.

**Grading of scientific evidence – table VIII: Safety of HPV vaccination in young females. Available at [http://www.who.int/immunization/position\\_papers/hpv\\_grad\\_safety.pdf](http://www.who.int/immunization/position_papers/hpv_grad_safety.pdf).**

(No abstract available.)

**Moreira ED, et al. Safety Profile of the 9-Valent HPV Vaccine: A Combined Analysis of 7 Phase III Clinical Trials. Pediatrics.2016;138(2).**

#### OBJECTIVES:

The overall safety profile of the 9-valent human papillomavirus (9vHPV) vaccine was evaluated across 7 Phase III studies, conducted in males and females (nonpregnant at entry), 9 to 26 years of

age.

#### METHODS:

Vaccination was administered as a 3-dose regimen at day 1, and months 2 and 6. More than 15 000 subjects received  $\geq 1$  dose of 9vHPV vaccine. In 2 of the studies, >7000 control subjects received  $\geq 1$  dose of quadrivalent HPV (qHPV) vaccine. Serious and nonserious adverse events (AEs) and new medical conditions were recorded throughout the study. Subjects testing positive for pregnancy at day 1 were not vaccinated; those who became pregnant after day 1 were discontinued from further vaccination until resolution of the pregnancy. Pregnancies detected after study start (n = 2950) were followed to outcome.

#### RESULTS:

The most common AEs ( $\geq 5\%$ ) experienced by 9vHPV vaccine recipients were injection-site AEs (pain, swelling, erythema) and vaccine-related systemic AEs (headache, pyrexia). Injection-site AEs were more common in 9vHPV vaccine than qHPV vaccine recipients; most were mild-to-moderate in intensity. Discontinuations and vaccine-related serious AEs were rare (0.1% and <0.1%, respectively). Seven deaths were reported; none were considered vaccine related. The proportions of pregnancies with adverse outcome were within ranges reported in the general population.

#### CONCLUSIONS:

The 9vHPV vaccine was generally well tolerated in subjects aged 9 to 26 years with an AE profile similar to that of the qHPV vaccine; injection-site AEs were more common with 9vHPV vaccine. Its additional coverage and safety profile support widespread 9vHPV vaccination.

### **Andrews N No increased risk of Guillain-Barré syndrome after human papilloma virus vaccine: A self-controlled case-series study in England. Vaccine. 2017 Mar 23;35(13):1729-1732.**

#### OBJECTIVE:

To investigate the risk of Guillain-Barré syndrome (GBS) after human papilloma virus (HPV) vaccine given to 12-18year old girls in England.

#### METHODS:

Hospital Episode Statistics (HES) were searched using data to March 2016 to identify incident cases of GBS in female patients aged from 11 to 20years eligible to have received the HPV vaccine since its introduction as a 3 dose schedule in September 2008. Diagnosis was confirmed by the case's general practitioner (GP) who also provided HPV vaccination dates. The risk of admission within 3months (primary risk window) 6 and 12months of any dose was assessed using the self-controlled case-series (SCCS) method in vaccinated girls with age, season and time-period adjustment. The risk before and after the change in 2012 from bivalent vaccine to quadrivalent vaccine was also assessed.

#### RESULTS:

A total 244 episodes were initially identified which reduced to 101 episodes in 100 girls when just including cases where the GP could be contacted, at least one vaccine dose was given, and GBS was confirmed or classed as probable. Nine, 14 and 24GBS admissions occurred within 3, 6, 12months of a dose respectively. The relative incidence (RI) for the 3month risk period was 1.04 (95% confidence interval 0.47-2.28), for the 6month period 0.83 (0.41-1.69) and for the 12month period 1.10 (0.57-2.14). When restricting to 79 confirmed cases the RI in the 3month risk period was 1.26 (0.55-2.92) and the RI 1.61 (0.39-6.54) for quadrivalent vaccine compared to 0.84 (0.30-2.34) for bivalent.

#### CONCLUSION:

We found no evidence of an increased risk of GBS following HPV vaccination in England and, based on the upper end of the 95% CI for the RI and the number of HPV vaccine doses given in England, can exclude a risk of about 1 per million doses.

### **Angelo MG, et al. Post-licensure safety surveillance for human papillomavirus-16/18-AS04-**

**adjuvanted vaccine: more than 4 years of experience. Pharmacoepidemiol Drug Saf, 2014;23(5):456–465.**

**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.

**Wacholder S, et al. Risk of miscarriage with bivalent vaccine against human papillomavirus (HPV) types 16 and 18: pooled analysis of two randomised controlled trials. BMJ, 2010 Mar 2;340:c712.**

**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.

**FDA Cervarix. Full prescribing information, 2009. Available at <http://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm186981.pdf>, accessed February 2017.**

(No abstract available.)

**Scheller NM, et al. Quadrivalent HPV Vaccination and the Risk of Adverse Pregnancy Outcomes. N Engl J Med 2017;376:1223-33.**

**Background** The quadrivalent human papillomavirus (HPV) vaccine is recommended for all girls and women 9 to 26 years of age. Some women will have inadvertent exposure to vaccination during early pregnancy, but few data exist regarding the safety of the quadrivalent HPV vaccine in this context. **Methods** We assessed a cohort that included all the women in Denmark who had a pregnancy ending between October 1, 2006, and November 30, 2013. Using nationwide registers, we linked information on vaccination, adverse pregnancy outcomes, and potential confounders among women in the cohort. Women who had vaccine exposure during the prespecified time windows were matched for propensity score in a 1:4 ratio with women who did not have vaccine exposure during the same time windows. Outcomes included spontaneous abortion, stillbirth, major birth defect, small size for gestational age, low birth weight, and preterm birth. **Results** In matched analyses, exposure to the quadrivalent HPV vaccine was not associated with significantly higher risks than no exposure for major birth defect (65 cases among 1665 exposed pregnancies and 220 cases among 6660 unexposed pregnancies; prevalence odds ratio, 1.19; 95% confidence interval [CI], 0.90 to 1.58), spontaneous abortion (20 cases among 463 exposed pregnancies and 131 cases among 1852 unexposed pregnancies; hazard ratio, 0.71; 95% CI, 0.45 to 1.14), preterm birth (116 cases among 1774 exposed pregnancies and 407 cases among 7096 unexposed pregnancies; prevalence odds ratio, 1.15; 95% CI, 0.93 to 1.42), low birth weight (76 cases among 1768 exposed pregnancies and 277 cases among 7072 unexposed pregnancies; prevalence odds ratio, 1.10; 95% CI, 0.85 to 1.43), small size for gestational age (171 cases among 1768 exposed pregnancies and 783 cases among 7072 unexposed pregnancies; prevalence odds ratio, 0.86; 95% CI, 0.72 to 1.02), or stillbirth (2 cases among 501 exposed pregnancies and 4 cases among 2004 unexposed pregnancies; hazard ratio, 2.43; 95% CI, 0.45 to 13.21). **Conclusions** Quadrivalent HPV vaccination during pregnancy was not associated with a significantly higher risk of adverse pregnancy outcomes than no such exposure. (Funded by the Novo Nordisk Foundation and the Danish Medical Research Council.).

**Goss MA, et al. No adverse signals observed after exposure to human papillomavirus type 6/11/16/18 vaccine during pregnancy: 6-year pregnancy registry data. Obstet Gynecol, 2014;123 Suppl 1:93S.**

**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.

**Noronha AS, et al. Systematic review of human papillomavirus vaccine coadministration. Vaccine 2014;32(23):2670–2674.**

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.

**Schilling A, et al. Coadministration of a 9-Valent Human Papillomavirus Vaccine With Meningococcal and Tdap Vaccines. Pediatrics. 2015 Sep;136(3):e563-72.**

**BACKGROUND:**

This study in 11- to 15-year-old boys and girls compared the immunogenicity and safety of GARDASIL 9 (9-valent human papillomavirus [9vHPV] vaccine) administered either concomitantly or nonconcomitantly with 2 vaccines routinely administered in this age group (Menactra [MCV4; *Neisseria meningitidis* serotypes A/C/Y/W-135] or Adacel [Tdap; diphtheria/tetanus/acellular pertussis]).

**METHODS:**

Participants received 9vHPV vaccine at day 1 and months 2 and 6; the concomitant group (n = 621) received MCV4/Tdap concomitantly with 9vHPV vaccine at day 1; the nonconcomitant group (n = 620) received MCV4/Tdap at month 1. Antibodies to HPV-, MCV4-, and Tdap-relevant antigens were determined. Injection-site and systemic adverse events (AEs) were monitored for 15 days after any vaccination; serious AEs were monitored throughout the study.

**RESULTS:**

The geometric mean titers for all HPV types in 9vHPV vaccine 4 weeks after dose 3, proportion of subjects with a fourfold rise or greater in titers for 4 N meningitidis serotypes 4 weeks after injection with MCV4, proportion of subjects with antibody titers to diphtheria and tetanus  $\geq 0.1$  IU/mL, and geometric mean titers for pertussis antigens 4 weeks after injection with Tdap were all noninferior in the concomitant group compared with the nonconcomitant group. Injection-site swelling occurred more frequently in the concomitant group. There were no vaccine-related serious AEs.

#### CONCLUSIONS:

Concomitant administration of 9vHPV vaccine with MCV4/Tdap was generally well tolerated and did not interfere with the antibody response to any of these vaccines. This strategy would minimize the number of visits required to deliver each vaccine individually.

#### **HUMAN PAPILLOMA VIRUS (HPV) VACCINATION: AN UPDATED SYSTEMATIC REVIEW OF COST-EFFECTIVENESS ANALYSES,**

[http://www.who.int/immunization/sage/meetings/2016/october/SAGE\\_yellow\\_book\\_october\\_2016.pdf?ua=1](http://www.who.int/immunization/sage/meetings/2016/october/SAGE_yellow_book_october_2016.pdf?ua=1) , assessed March 2017

(No abstract available.)

#### **Modelling estimates of the incremental effectiveness & cost-effectiveness of HPV vaccination.**

[http://www.who.int/immunization/sage/meetings/2016/october/07\\_Modelling\\_HP\\_vaccination\\_strategies.pdf?ua=1](http://www.who.int/immunization/sage/meetings/2016/october/07_Modelling_HP_vaccination_strategies.pdf?ua=1), accessed February 2017.

(No abstract available.)

#### **Fesenfeld et al. Cost-effectiveness of human papillomavirus vaccination in low and middle income countries: a systematic review. Vaccine. 2013 Aug 20;31(37):3786-804.**

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.

#### **WHO Guide to introducing HPV vaccine into national immunization programmes.**

<http://apps.who.int/iris/bitstream/10665/253123/1/9789241549769-eng.pdf?ua=1>, accessed February 2017.

(No abstract available.)

#### **Evidence to recommendation table. Assessment of gender-based immunization. Link to be provided.**

(No abstract available.)

**Evidence to recommendation table. Vaccination of multiple female age-cohorts. Link to be provided.**

(No abstract available.)

**Evidence to recommendation table on choice of vaccine. Link to be provided.**

(No abstract available.)

**WEEKLY EPIDEMIOLOGICAL RECORD, NO. 25, 18 JUNE 2010, 89, pp. 237–243. Monitoring the coverage and impact of human papillomavirus vaccine – report of WHO meeting, November 2009.**

(No abstract available.)

**IARC. Planning and Developing Population-Based Cancer Registration in Low- and Middle-Income Settings <http://www.iarc.fr/en/publications/pdfs-online/treport-pub/treport-pub43/index.php>, accessed February 2017.**

(No abstract available.)