

Key references with PubMed-abstracts, where available, to the HPV Position Paper

These references are listed according to their respective numbers in the position paper. Reference 1 offers an extensive review of HPV vaccines. The reference lists of this background paper are extracted and presented at (*link to comprehensive ref list*). Additionally, references from the grade tables are placed here.

1) **Human papillomavirus (HPV) vaccine, Background paper, September 2008. Geneva, WHO, 2008** (<http://www.who.int/immunization/documents/positionpapers/en/index.html>).

2) **Human papillomavirus and HPV vaccines: technical information for policy-makers and health professionals. Geneva, WHO, 2007** (http://whqlibdoc.who.int/hq/2007/WHO_IVB_07.05_eng.pdf, accessed 25 September 2008).

3) **Smith JS, Melendy A, Rana RK, Pimenta JM. Age-specific prevalence of infection with human papillomavirus in females: a global review. J Adolesc Health. 2008 Oct;43(4 Suppl):S5-25, S25.e1-41.**

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.

4) Ault KA; Future II Study Group. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. Lancet. 2007 Jun 2;369(9576):1861-8.

BACKGROUND: Cervical cancer and its obligate precursors, cervical intraepithelial neoplasia grades 2 and 3 (CIN2/3), and adenocarcinoma in situ (AIS), are caused by oncogenic human papillomavirus (HPV). In this combined analysis of four clinical trials we assessed the effect of prophylactic HPV vaccination on these diseases. **METHODS:** 20,583 women aged 16-26 years were randomised to receive quadrivalent HPV6/11/16/18 vaccine (n=9087), its HPV16 vaccine component (n=1204), or placebo (n=10 292). They underwent periodic Papanicolaou testing, with colposcopy or biopsy for detected abnormalities. The primary composite endpoint was the combined incidence of HPV16/18-related CIN2/3, AIS, or cervical cancer. These trials are registered at ClinicalTrials.gov, numbers NCT00365378, NCT00365716, NCT00092521, and NCT00092534. **FINDINGS:** Mean follow-up was 3.0 years (SD 0.66) after first dose. In women negative for HPV16 or HPV18 infection during the vaccination regimen (n=17 129, per protocol), vaccine efficacy was 99% for the primary endpoint (95% CI 93-100), meeting the statistical criterion for success. In an intention-to-treat analysis of all randomised women (including those who were HPV16/18 naive or HPV16/18-infected at day 1), efficacy was 44% (95% CI 31-55); all but one case in vaccine recipients occurred in women infected with HPV16 or HPV18 before vaccination. In a second intention-to-treat analysis we noted an 18% reduction (95% CI 7-29) in the overall rate of CIN2/3 or AIS due to any HPV type. **INTERPRETATION:** Administration of HPV vaccine to HPV-naive women, and women who are already sexually active, could substantially reduce the incidence of HPV16/18-related cervical precancers and cervical cancer.

5) Stanley M, Lowy DR, Frazer I. Chapter 12: Prophylactic HPV vaccines: underlying mechanisms. Vaccine. 2006 Aug 31;24 Suppl 3:S3/106-13.

Human papillomavirus virus-like particles (HPV VLP) can be generated by the synthesis and self-assembly in vitro of the major virus capsid protein L1. HPV L1 VLPs are morphologically and antigenically almost identical to native virions, and this technology has been exploited to produce HPV L1 VLP subunit vaccines. The vaccines elicit high titres of anti-L1 VLP antibodies that persist at levels 10 times that of natural infections for at least 48 months. At present the assumption is that the protection achieved by these vaccines against incident HPV infection and HPV-associated ano-genital pathology is mediated via serum neutralising Immunoglobulin G (IgG). However, since there have been very few vaccine

failures thus far, immune correlates of protection have not been established. The available evidence is that the immunodominant neutralising antibodies generated by L1 VLPs are type-specific and are not cross-neutralising, although highly homologous HPV pairs share minor cross-neutralisation epitopes. Important issues remaining to be addressed include the duration of protection and genotype replacement.

6) Olsson SE, Villa LL, Costa RL, Petta CA, Andrade RP, Malm C, Iversen OE, Høye J, Steinwall M, Riis-Johannessen G, Andersson-Ellstrom A, Elfgren K, von Krogh G, Lehtinen M, Paavonen J, Tamms GM, Giacoletti K, Lupinacci L, Esser MT, Vuocolo SC, Saah AJ, Barr E. Induction of immune memory following administration of a prophylactic quadrivalent human papillomavirus (HPV) types 6/11/16/18 L1 virus-like particle (VLP) vaccine. *Vaccine*. 2007 Jun 21;25(26):4931-9.

BACKGROUND: The duration of protection afforded by vaccines represents a critical test of their utility as public health interventions. Some vaccines induce long-term immunity, while others require booster doses. Vaccines that induce long-term protection are usually characterized by the generation of immune memory. Recent trials of a quadrivalent (types 6, 11, 16, 18) human papillomavirus (HPV) vaccine have demonstrated high efficacy through 5 years of follow-up. We evaluated the extent to which the vaccine is able to generate HPV type-specific immune memory. **METHODS:** A total of 552, 16-23-year-old women were enrolled in a double-blind, placebo-controlled study. At enrollment, subjects were randomized in a 1:1 ratio to receive three-dose regimens of quadrivalent HPV vaccine or placebo with 3 years' follow-up. A subset of 241 subjects (n=114 in the quadrivalent HPV vaccine group and n=127 in the placebo group) underwent 2 further years of follow-up. All extension subjects received quadrivalent HPV vaccine at month 60 to examine the extent of immune memory in response to the primary vaccination series. **RESULTS:** Serum anti-HPV levels declined post-vaccination, but reached a plateau at month 24 that remained stable through month 60. Administration of a challenge dose of vaccine induced a classic anamnestic response, with anti-HPV levels 1 week post-challenge reaching levels observed 1 month following the completion of the three-dose primary series. At 1 month post-challenge, anti-HPV responses were higher than those observed 1-month post-dose 3. **DISCUSSION:** A three-dose regimen of quadrivalent HPV vaccine induces high efficacy and stable anti-HPV levels for at least 5 years. Vaccination also induces robust immune memory. These findings suggest that the efficacy of this vaccine will be long lasting.

7) Merck USA. GARDASIL® human papillomavirus quadrivalent (Types 6, 11, 16, and 18) vaccine, Recombinant: GARDASIL® full prescribing information, 2007. Whitehouse Station, NJ, 2007

(http://www.merck.com/product/usa/pi_circulars/g/gardasil_pi.pdf accessed 25 September 2008). http://www.merck.com/product/usa/pi_circulars/g/gardasil/gardasil_pi.pdf

8) GlaxoSmithKline Australia. Cervarix® product information: human papillomavirus vaccine type 16 and 18 (Recombinant AS04 adjuvanted), 2007. Boronia, Victoria, Australia, 2007

(http://www.gsk.com.au/resources.ashx/vaccineproductschilddataproinfo/94/FileName/7A14FBAEA16635A2DD7A68ED78E8FDDC/P1_Cervarix.pdf, accessed 15 May 2008).

9) Villa LL. Overview of the clinical development and results of a quadrivalent HPV (types 6, 11, 16, 18) vaccine. Int J Infect Dis. 2007 Nov;11 Suppl 2:S17-25

BACKGROUND: Human papillomaviruses (HPVs) play an obligatory role in cervical cancer development. Thus, immunization of women using a prophylactic vaccine against the most common high-oncogenic risk types (e.g., HPV 16 and 18) and HPV 6 and 11, which contribute to development of low-grade cervical lesions and cause most anogenital warts, represents a logical primary prevention strategy. **PERSPECTIVES:** At the time of licensure, Phase II/Phase III studies showed that administration of a quadrivalent HPV (types 6, 11, 16, 18) vaccine to young women (16 to 26 years) naïve to the vaccine HPV types resulted in 100% efficacy against HPV 16- and 18-related precancerous cervical lesions, 100% efficacy against HPV 16- and 18-related high-grade vulvar/vaginal neoplasias, 95% efficacy against HPV 6, 11, 16, or 18-related cervical intraepithelial neoplasia/adenocarcinoma in situ, and 99% efficacy against HPV 6, 11, 16, or 18-related genital lesions. The quadrivalent HPV vaccine is highly immunogenic in adolescent males and females, and long-term follow up of young women did not detect evidence of waning immunity through 5 years.

CONCLUSIONS: The quadrivalent vaccine is generally well tolerated. The efficacy and safety of the quadrivalent vaccine is continuing to be investigated in young men and mid-adult women. Nordic cancer registries are providing ongoing long-term pharmacovigilance.

10) Pedersen C, Petaja T, Strauss G, Rumke HC, Poder A, Richardus JH, Spiessens B, Descamps D, Hardt K, Lehtinen M, Dubin G; HPV Vaccine Adolescent Study Investigators Network. Immunization of early adolescent females with human papillomavirus type 16 and 18 L1 virus-like particle vaccine containing AS04 adjuvant. J Adolesc Health. 2007 Jun;40(6):564-71.

PURPOSE: In female individuals 15-25-years of age, the AS04-containing human papillomavirus (HPV)-16/18 vaccine is highly immunogenic and provides up to 100% protection against HPV-16/18 persistent infection and associated cervical lesions up to 4.5 years. Optimal cervical cancer prevention will require prophylactic vaccination against oncogenic HPV 16 and 18 before the onset of sexual activity in early adolescent girls. To establish the feasibility of vaccination in girls 10-14 years of age, we compared the immunogenicity and safety in early adolescent female individuals to those 15-25 years in whom vaccine efficacy has been demonstrated. **METHODS:** We enrolled 773 female participants aged 10-14 years and 15-25 years to receive the HPV-16/18 L1 VLP AS04 vaccine, which was administered at months 0, 1, and 6. Serum samples were collected at months 0 and 7; antibodies to HPV 16 and 18 VLPs were measured by enzyme-linked immunosorbent assay. Vaccine safety was assessed at 7 or 30 days after each dose; serious adverse events were recorded during the entire study period. **RESULTS:** Both age groups achieved 100% seroconversion for HPV 16 and 18. Participants in the group aged 10-14 years were not only noninferior to those 15-25 years in terms of HPV 16 and 18 seroconversion rates but also had approximately twice as high geometric mean titers. The vaccine was generally safe and well tolerated. **CONCLUSIONS:** These findings suggest that HPV vaccination during early adolescence is generally safe, well tolerated, and highly immunogenic. The observed higher antibody titers in the group 10-14 years of age are likely

to result in longer antibody persistence. Overall, these data support the implementation of prophylactic HPV vaccination in this age group.

11) Weinberg A, et al. Safety and immunogenicity of a quadrivalent vaccine to prevent human papillomavirus (HPV) in HIV-infected children: IMPAACT P1047. Poster 619a presented at the 15th Conference on Retroviral and Opportunistic Infections, 3–6 February, 2008, Boston, USA.

12) Pagliusi SR, Teresa Aguado M. Efficacy and other milestones for human papillomavirus vaccine introduction. Vaccine. 2004 Dec 16;23(5):569-78.

Last year, the World Health Organization (WHO) convened a gathering of experts, including scientists, national regulatory authorities, industry representatives, epidemiologists and government officials from both developed and developing countries to discuss appropriate endpoint measurements for HPV vaccine efficacy and effectiveness trials. The consultation also considered the regulatory requirements and public health issues that vaccine candidates should address before deployment, particularly in developing countries. This report summarizes the discussions and the conclusions reached over the course of the consultation. The general consensus of the consultation was that it would be desirable to have a globally-agreed, measurable efficacy endpoint for considering deployment of HPV vaccines in public health settings. After hearing from experts about virological and clinical endpoints to be considered, requirements of regulatory authorities of various countries and endpoints used to measure efficacy and effectiveness for another known cancer vaccine (hepatitis B), the experts agreed that ethical and time considerations make it necessary to use a surrogate endpoint, and not invasive cervical cancer, to define efficacy of HPV vaccines. While regulatory authorities of each country ultimately will determine the endpoints required for licensure, the consultation recommended that the endpoint for efficacy in population-based studies be, based on current knowledge, histologically-classified cervical intraepithelial neoplasias (CIN) of moderate or high-grade, as well as cancer. Since persistent infection with the same high-risk type is considered a predictor for moderate or high-grade cervical dysplasias and cancer, they might represent a useful endpoint in future vaccine efficacy studies. Indeed, if vaccines prove to be effective against transient or persistent HPV infections, it is likely that they will protect women against cervical cancer. The consultation recognized that in the context of many developing countries, efficacy alone might not provide enough information for countries to decide whether or not to adopt HPV vaccines as a public health prevention tool against cervical cancer. The consultation unanimously agreed that additional clinical bridging studies as well as studies to clarify local epidemiology should be conducted in certain developing countries to determine the potential impact of vaccination. Such countries should also undertake targeted interventions to ensure acceptability and programmatic feasibility of the vaccination. Recognizing that upon vaccine introduction it will be some years before a reduction in cervical cancer is detectable at the population level, the consultation stressed the importance of maintaining existing cervical screening programmes while such long-term studies are conducted. The following paper explains the background and rationale behind these conclusions and elaborates on specific considerations for vaccine study and introduction in developing countries.

13) FUTURE II Study Group. Prophylactic efficacy of a quadrivalent human papillomavirus (HPV) vaccine in women with virological evidence of HPV infection. J Infect Dis. 2007 Nov 15;196(10):1438-46.

BACKGROUND: A quadrivalent (types 6, 11, 16, and 18) human papillomavirus (HPV) L1 virus-like-particle (VLP) vaccine has been shown to be 95%-100% effective in preventing cervical and genital disease related to HPV-6, -11, -16, and -18 in 16-26-year-old women naive for HPV vaccine types. Because most women in the general population are sexually active, some will have already been infected with > or =1 HPV vaccine types at the time vaccination is offered. Here, we assessed whether such infected women are protected against disease caused by the remaining HPV vaccine types. **METHODS:** Two randomized, placebo-controlled trials of the quadrivalent (types 6, 11, 16, and 18) HPV vaccine enrolled 17,622 women without consideration of baseline HPV status. Among women infected with 1-3 HPV vaccine types at enrollment, efficacy against genital disease related to the HPV vaccine type or types for which subjects were naive was assessed. **RESULTS:** Vaccination was 100% effective (95% confidence interval [CI], 79%-100%) in preventing incident cervical intraepithelial neoplasia 2 or 3 or cervical adenocarcinoma in situ caused by the HPV type or types for which the women were negative at enrollment. Efficacy for preventing vulvar or vaginal HPV-related lesions was 94% (95% CI, 81%-99%). **CONCLUSIONS:** Among women positive for 1-3 HPV vaccine types before vaccination, the quadrivalent HPV vaccine protected against neoplasia caused by the remaining types. These results support vaccination of the general population without prescreening.

14) Paavonen J, Jenkins D, Bosch FX, Naud P, Salmerón J, Wheeler CM, Chow SN, Apter DL, Kitchener HC, Castellsague X, de Carvalho NS, Skinner SR, Harper DM, Hedrick JA, Jaisamrarn U, Limson GA, Dionne M, Quint W, Spiessens B, Peeters P, Struyf F, Wieting SL, Lehtinen MO, Dubin G; HPV PATRICIA study group. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. Lancet. 2007 Jun 30;369(9580):2161-70.

BACKGROUND: The aim of this interim analysis of a large, international phase III study was to assess the efficacy of an AS04 adjuvanted L1 virus-like-particle prophylactic candidate vaccine against infection with human papillomavirus (HPV) types 16 and 18 in young women. **METHODS:** 18,644 women aged 15-25 years were randomly assigned to receive either HPV16/18 vaccine (n=9319) or hepatitis A vaccine (n=9325) at 0, 1, and 6 months. Of these women, 88 were excluded because of high-grade cytology and 31 for missing cytology results. Thus, 9258 women received the HPV16/18 vaccine and 9267 received the control vaccine in the total vaccinated cohort for efficacy, which included women who had prevalent oncogenic HPV infections, often with several HPV types, as well as low-grade cytological abnormalities at study entry and who received at least one vaccine dose. We assessed cervical cytology and subsequent biopsy for 14 oncogenic HPV types by PCR. The primary endpoint--vaccine efficacy against cervical intraepithelial neoplasia (CIN) 2+ associated with HPV16 or HPV18--was assessed in women who were seronegative and DNA negative for the corresponding vaccine type at baseline (month 0) and allowed inclusion of lesions with several oncogenic HPV types. This interim event-defined analysis was triggered when at least

23 cases of CIN2+ with HPV16 or HPV18 DNA in the lesion were detected in the total vaccinated cohort for efficacy. Analyses were done on a modified intention-to-treat basis. This trial is registered with the US National Institutes of Health clinical trial registry, number NCT00122681. FINDINGS: Mean length of follow-up for women in the primary analysis for efficacy at the time of the interim analysis was 14.8 (SD 4.9) months. Two cases of CIN2+ associated with HPV16 or HPV18 DNA were seen in the HPV16/18 vaccine group; 21 were recorded in the control group. Of the 23 cases, 14 (two in the HPV16/18 vaccine group, 12 in the control group) contained several oncogenic HPV types. Vaccine efficacy against CIN2+ containing HPV16/18 DNA was 90.4% (97.9% CI 53.4-99.3; $p < 0.0001$). No clinically meaningful differences were noted in safety outcomes between the study groups. INTERPRETATION: The adjuvanted HPV16/18 vaccine showed prophylactic efficacy against CIN2+ associated with HPV16 or HPV18 and thus could be used for cervical cancer prevention.

15) Villa LL, Costa RL, Petta CA, Andrade RP, Paavonen J, Iversen OE, Olsson SE, Høye J, Steinwall M, Riis-Johannessen G, Andersson-Ellstrom A, Elfgren K, Krogh G, Lehtinen M, Malm C, Tamms GM, Giacoletti K, Lupinacci L, Railkar R, Taddeo FJ, Bryan J, Esser MT, Sings HL, Saah AJ, Barr E. High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up. *Br J Cancer*. 2006 Dec 4;95(11):1459-66.

Human papillomavirus (HPV) causes cervical, vulvar, and vaginal cancers, precancerous dysplasia, and genital warts. We report data for the longest efficacy evaluation to date of a prophylactic HPV vaccine. In total, 552 women (16-23 years) were enrolled in a randomised, placebo-controlled study of a quadrivalent HPV 6/11/16/18 L1 virus-like-particle vaccine with vaccination at months 0, 2, and 6. At regular intervals through 3 years, subjects underwent gynaecologic examination, cervicovaginal sampling for HPV DNA, serum anti-HPV testing, and Pap testing, with follow-up biopsy as indicated. A subset of 241 subjects underwent two further years of follow-up. At 5 years post enrollment, the combined incidence of HPV 6/11/16/18-related persistent infection or disease was reduced in vaccine-recipients by 96% (two cases vaccine versus 46 placebo). There were no cases of HPV 6/11/16/18-related precancerous cervical dysplasia or genital warts in vaccine recipients, and six cases in placebo recipients (efficacy = 100%; 95% CI:12-100%). Through 5 years, vaccine-induced anti-HPV geometric mean titres remained at or above those following natural infection. In conclusion, a prophylactic quadrivalent HPV vaccine was effective through 5 years for prevention of persistent infection and disease caused by HPV 6/11/16/18. This duration supports vaccination of adolescents and young adults, which is expected to greatly reduce the burden of cervical and genital cancers, precancerous dysplasia, and genital warts.

16) Smith JF, Brownlow M, Brown M, Kowalski R, Esser MT, Ruiz W, Barr E, Brown DR, Bryan JT. Antibodies from women immunized with Gardasil cross-neutralize HPV 45 pseudovirions. *Hum Vaccin*. 2007 Jul-Aug;3(4):109-15.

Human papillomavirus (HPV) types 6, 11, 16 and 18 L1 virus-like particles (VLPs) have been used to generate the prophylactic quadrivalent vaccine, Gardasil. There is a high degree of L1 homology between HPV types and it is likely that there is a substantial degree of surface exposed viral epitope similarity. An investigation of vaccine-induced antibody binding and

neutralization was undertaken focusing on A7 species members, HPV 18 and 45. Polyclonal sera from Gardasil recipients and from HPV 18 L1 VLP recipients were evaluated. Vaccine-induced antibodies were found to cross-neutralize HPV 45 pseudovirions (PsV) in vitro. Examination of a panel of monoclonal antibodies made against L1 VLPs revealed the presence of conformational, neutralizing epitopes on the surface of VLPs that may be shared between HPV 18 and HPV 45. These data demonstrate that Gardasil(r) immunization induces antibodies capable of neutralizing HPV 18 PsV and HPV 45 PsV in vitro.

17) Harper DM, et al. Sustained immunogenicity and high efficacy against HPV 16/18 related cervical neoplasia: long-term follow-up through 6.4 years in women vaccinated with Cervarix (GSK's HPV 16/18 AS04 candidate vaccine). Presented at the Meeting of the Society for Gynecologic Oncology, Tampa, Florida, USA, March 9–12, 2008. Abstract in Gynecologic Oncology, 2008, 109:158.

18) Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, Tang GW, Ferris DG, Steben M, Bryan J, Taddeo FJ, Railkar R, Esser MT, Sings HL, Nelson M, Boslego J, Sattler C, Barr E, Koutsky LA; Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I Investigators. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med. 2007 May 10;356(19):1928-43.

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.

19) The FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med. 2007 May 10;356(19):1915-27

BACKGROUND: Human papillomavirus types 16 (HPV-16) and 18 (HPV-18) cause approximately 70% of cervical cancers worldwide. A phase 3 trial was conducted to evaluate a quadrivalent vaccine against HPV types 6, 11, 16, and 18 (HPV-6/11/16/18) for the prevention of high-grade cervical lesions associated with HPV-16 and HPV-18. **METHODS:** In this randomized, double-blind trial, we assigned 12,167 women between the ages of 15 and 26 years to receive three doses of either HPV-6/11/16/18 vaccine or placebo, administered at day 1, month 2, and month 6. The primary analysis was performed for a per-protocol susceptible population that included 5305 women in the vaccine group and 5260 in the placebo group who had no virologic evidence of infection with HPV-16 or HPV-18 through 1 month after the third dose (month 7). The primary composite end point was cervical intraepithelial neoplasia grade 2 or 3, adenocarcinoma in situ, or cervical cancer related to HPV-16 or HPV-18. **RESULTS:** Subjects were followed for an average of 3 years after receiving the first dose of vaccine or placebo. Vaccine efficacy for the prevention of the primary composite end point was 98% (95.89% confidence interval [CI], 86 to 100) in the per-protocol susceptible population and 44% (95% CI, 26 to 58) in an intention-to-treat population of all women who had undergone randomization (those with or without previous infection). The estimated vaccine efficacy against all high-grade cervical lesions, regardless of causal HPV type, in this intention-to-treat population was 17% (95% CI, 1 to 31). **CONCLUSIONS:** In young women who had not been previously infected with HPV-16 or HPV-18, those in the vaccine group had a significantly lower occurrence of high-grade cervical intraepithelial neoplasia related to HPV-16 or HPV-18 than did those in the placebo group.

20) Palefsky J, Giuliano A, on behalf of the male quadrivalent HPV vaccine efficacy trial study group. Efficacy of the quadrivalent HPV vaccine against HPV 6/11/16/18-related genital infection in young men. Abstract of presentation at the European Research Organization on Genital Infection and Neoplasia (EUROGIN) International Multidisciplinary Conference, 13 November 2008.

http://www.eurogin.com/2008/EUROGIN2008_Abstracts.pdf

21) Giuliano A, Palefsky J, on behalf of the male quadrivalent HPV vaccine efficacy trial study group. The efficacy of quadrivalent HPV (types 6/11/16/18) vaccine in reducing the incidence of HPV infection and HPV-related genital disease in young men. Abstract of presentation at the European Research Organization on Genital Infection and Neoplasia (EUROGIN) International Multidisciplinary Conference, 13 November 2008.

http://www.eurogin.com/2008/EUROGIN2008_Abstracts.pdf

22) Harper DM. Impact of vaccination with Cervarix (trade mark) on subsequent HPV-16/18 infection and cervical disease in women 15-25 years of age. Gynecol Oncol. 2008 Sep;110(3 Suppl 1):S11-7.

Cervical cancer of both squamous and adenocarcinoma types is considered virtually 100% attributable to human papillomavirus (HPV) infection. HPV-16 and -18 are the predominant types worldwide accounting for over 70% of all cervical cancer. Persistent oncogenic HPV infection has been confirmed as one key determinant in the development of cervical precancer (cervical intraepithelial neoplasia [CIN] 2+) and cervical cancer. The impact of prophylactic HPV vaccination on the reduction of virological and cytohistological outcomes related to HPV-16 and -18 has been evaluated in clinical trials with the HPV-16/18 AS04-adjuvanted cervical cancer vaccine (Cervarix[®]) through a Phase IIb study with a long-term follow-up of efficacy up to 5.5 years, and a large Phase III trial in women 15-25 years of age. These individual studies include populations with different underlying risk factors, each of which shows high efficacy against both HPV-16/18 persistent infections and CIN2+. When the two studies are combined and the respective populations are evaluated, vaccine efficacy against HPV-16 and -18-related CIN2+ remains at 100%. As this vaccine is used over time in universal prophylactic HPV-16/18 vaccination of girls and women, reductions in cervical cancers at both the individual and public health levels will be appreciated.

23) Garland S. Safety of quadrivalent human papillomavirus (HPV) (types 6, 11, 16, 18) L1 virus-like particle (VLP) vaccine in pregnant women. Abstract presented at the 35th Annual Scientific Meeting of the Infectious Diseases Society for Obstetrics and Gynecology, Seattle, Washington, USA, 12–14 August 2008.

24) Kim JJ, Brisson M, Edmunds WJ, Goldie SJ. Modeling cervical cancer prevention in developed countries. Vaccine. 2008 Aug 19;26 Suppl 10:K76-86.

Cytology-based screening has reduced cervical cancer mortality in countries able to implement, sustain and financially support organized programs that achieve broad coverage. These ongoing secondary prevention efforts considerably complicate the question of whether vaccination against human papillomavirus (HPV) types 16 and 18 should be introduced. Policy questions focus primarily on the target ages of vaccination, appropriate ages for a temporary "catch-up" program, possible revisions in screening policies to optimize synergies with vaccination, including the increased use of HPV DNA testing, and the inclusion of boys in the vaccination program. Decision-analytic models are increasingly being developed to simulate disease burden and interventions in different settings in order to evaluate the benefits and cost-effectiveness of primary and secondary interventions for informed decision-making. This article is a focused review on existing mathematical models that have been used to evaluate HPV vaccination in the context of developed countries with existing screening programs. Despite variations in model assumptions and uncertainty in existing data, pre-adolescent vaccination of girls has been consistently found to be attractive in the context of current screening practices, provided there is complete and lifelong vaccine protection and widespread vaccination coverage. Questions related to catch-up vaccination programs, potential benefits of other non-cervical cancer outcomes and inclusion of boys are subject to far more uncertainty, and results from these analyses have reached conflicting conclusions. Most analyses find that some catch-up vaccination is warranted but becomes increasingly unattractive as the catch-up age is extended, and vaccination of boys is unlikely to be cost-effective if reasonable levels of coverage are achieved in girls or coverage among girls can be improved. The objective of this review is to highlight points of consensus and qualitative

themes, to discuss the areas of divergent findings, and to provide insight into critical decisions related to cervical cancer prevention.

25) Kim JJ, Andres-Beck B, Goldie SJ. The value of including boys in an HPV vaccination programme: a cost-effectiveness analysis in a low-resource setting. *Br J Cancer*. 2007 Nov 5;97(9):1322-8

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

26) Insinga RP, Dasbach EJ, Elbasha EH, Puig A, Reynales-Shigematsu LM. Cost-effectiveness of quadrivalent human papillomavirus (HPV) vaccination in Mexico: a transmission dynamic model-based evaluation. *Vaccine*. 2007 Dec 21;26(1):128-39.

We examined the potential health outcomes and cost-effectiveness of quadrivalent human papillomavirus (HPV) 6/11/16/18 vaccination strategies in the Mexican population using a multi-HPV type dynamic transmission model. Assuming similar cervical screening practices, with or without vaccination, we examined the incremental cost-effectiveness of vaccination strategies for 12 year-old females, with or without male vaccination, and temporary age 12-24 catch-up vaccination for females or both sexes. The most effective strategy therein was vaccination of 12-year-olds, plus a temporary 12-24-year-old catch-up program covering both sexes; whereby HPV 6/11/16/18-related cervical cancer, high-grade cervical precancer, and genital wart incidence was reduced by 84-98% during year 50 following vaccine introduction. Incremental cost-effectiveness ratios in the primary analyses ranged from approximately 3000 dollars (U.S.) per quality-adjusted life year (QALY) gained for female vaccination strategies to approximately 16000 dollars /QALY for adding male vaccination with catch-up.

27) Barnabas RV, Laukkanen P, Koskela P, Kontula O, Lehtinen M, Garnett GP. Epidemiology of HPV 16 and cervical cancer in Finland and the potential impact of vaccination: mathematical modelling analyses. *PLoS Med*. 2006 May;3(5):e138. *PLoS Medicine* Vol. 3, No. 5, e138 doi:10.1371/journal.pmed.0030138

BACKGROUND: Candidate human papillomavirus (HPV) vaccines have demonstrated almost 90%-100% efficacy in preventing persistent, type-specific HPV infection over 18 mo in clinical trials. If these vaccines go on to demonstrate prevention of precancerous lesions in phase III clinical trials, they will be licensed for public use in the near future. How these vaccines will be used in countries with national cervical cancer screening programmes is an important question. **METHODS AND FINDINGS:** We developed a transmission model of HPV 16 infection and progression to cervical cancer and calibrated it to Finnish HPV 16 seroprevalence over time. The model was used to estimate the transmission probability of the virus, to look at the effect of changes in patterns of sexual behaviour and smoking on age-specific trends in cancer incidence, and to explore the impact of HPV 16 vaccination. We estimated a high per-partnership transmission probability of HPV 16, of 0.6. The modelling analyses showed that changes in sexual behaviour and smoking accounted, in part, for the increase seen in cervical cancer incidence in 35- to 39-y-old women from 1990 to 1999. At both low (10% in opportunistic immunisation) and high (90% in a national immunisation programme) coverage of the adolescent population, vaccinating women and men had little benefit over vaccinating women alone. We estimate that vaccinating 90% of young women before sexual debut has the potential to decrease HPV type-specific (e.g., type 16) cervical cancer incidence by 91%. If older women are more likely to have persistent infections and progress to cancer, then vaccination with a duration of protection of less than 15 y could result in an older susceptible cohort and no decrease in cancer incidence. While vaccination has the potential to significantly reduce type-specific cancer incidence, its combination with screening further improves cancer prevention. **CONCLUSIONS:** HPV vaccination has the potential to significantly decrease HPV type-specific cervical cancer incidence. High vaccine coverage of women alone, sustained over many decades, with a long duration of vaccine-conferred protection, would have the greatest impact on type-specific cancer incidence. This level of coverage could be achieved through national coordinated programmes, with surveillance to detect cancers caused by nonvaccine oncogenic HPV types.

28) Techakehakij W, Feldman RD. Cost-effectiveness of HPV vaccination compared with Pap smear screening on a national scale: a literature review. Vaccine. 2008 Nov 18;26(49):6258-65.

Recommendations for worldwide use of human papillomavirus (HPV) vaccine are increasing. This study conducted a systematic review of articles related to cost-effectiveness analysis of wide-range HPV vaccination programs compared with Pap smear screening published before August 2007. Eight articles were identified using predefined inclusion and exclusion criteria. After excluding two outliers, the range of incremental cost-effectiveness ratios (ICERs) from six articles is between \$16,600 and \$27,231 per quality-adjusted life year (QALY) gained. The World Health Organization's guideline that compares incremental cost-effectiveness ratios (ICERs) with per capita Gross Domestic Product (GDP) was used to determine whether nation-wide application of HPV vaccine would be cost-effective. The HPV vaccination program is cost-effective in only 46 countries where per capita GDP is high. Further cost-effectiveness studies in developing and third-world countries are needed for making policy decisions.

29) Goldie SJ, O'Shea M, Diaz M, Kim SY. Benefits, cost requirements and cost-effectiveness of the HPV16,18 vaccine for cervical cancer prevention in developing countries: policy implications. *Reprod Health Matters*. 2008 Nov;16(32):86-96.

Approximately 70% of cases of cervical cancer worldwide are caused by genotypes 16 and 18 of human papillomavirus (HPV), which is sexually transmitted. With the availability of an effective vaccine against these HPV types, there is real hope for reducing the global burden of cervical cancer in developing countries. Stakeholders faced with decisions about where to invest money to improve health must consider the burden of disease caused by cervical cancer relative to other priorities and the comparative benefits of different interventions. We conducted a series of analyses to obtain information for agencies drafting immunisation policy recommendations, financing coordination mechanisms, and country decision-makers on the benefits, cost requirements and cost-effectiveness of the HPV16,18 vaccine. We found that making an HPV16,18 vaccine accessible to 70% of young adolescent girls in 72 of the poorest countries, China, Thailand, and all of Latin America and the Caribbean, could prevent the future deaths of more than four million women vaccinated over the next decade. Provided the cost per vaccinated girl is less than \$10-\$25, adolescent HPV16,18 vaccination would be cost-effective even in relatively poor countries. Concerns about financial costs and affordability highlight the need for lowering vaccine prices, cost-efficient mechanisms for delivery of vaccinations to adolescents, and creative sources of financing.

30) Block SL, Nolan T, Sattler C, Barr E, Giacoletti KE, Marchant CD, Castellsagué X, Rusche SA, Lukac S, Bryan JT, Cavanaugh PF Jr, Reisinger KS; Protocol 016 Study Group. Comparison of the immunogenicity and reactogenicity of a prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in male and female adolescents and young adult women. *Pediatrics*. 2006 Nov;118(5):2135-45.

OBJECTIVE: Prophylactic vaccination of 16- to 23-year-old females with a quadrivalent human papillomavirus (types 6, 11, 16, 18) L1 virus-like particle vaccine has been shown to prevent type-specific human papillomavirus infection and associated clinical disease. We conducted a noninferiority immunogenicity study to bridge the efficacy findings in young women to preadolescent and adolescent girls and boys, who represent a primary target for human papillomavirus vaccination. **METHODS:** We enrolled 506 girls and 510 boys (10-15 years of age) and 513 females (16-23 years of age). Participants were vaccinated on day 1, at month 2, and at month 6, and serology testing was performed on day 1 and at months 3 and 7 on blinded samples. Neutralizing antibody concentrations were determined using type-specific immunoassays and summarized as geometric mean titers and seroconversion rates. Vaccine tolerability also was assessed. **RESULTS:** By month 7, seroconversion rates were \geq 99% for all 4 human papillomavirus types in each group. By month 7, compared with women, anti-human papilloma virus geometric mean titers in girls or boys were noninferior and were 1.7- to 2.7-fold higher. Most ($> 97\%$) injection-site adverse events were mild to moderate in intensity. Significantly more boys (13.8%) and girls (12.8%) than women (7.3%) reported fevers ≥ 37.8 degrees C within 5 days of vaccination. Most (96.4%) fevers were mild (< 39 degrees C). **CONCLUSIONS:** Noninferior immunogenic responses to all 4 human papillomavirus types in the quadrivalent vaccine permit the bridging of efficacy data that were generated in young women to girls. The results in boys lend support for the implementation of

gender-neutral human papillomavirus vaccination programs. This vaccine generally was well tolerated.

31) Giuliano AR, Lazcano-Ponce E, Villa L, Nolan T, Marchant C, Radley D, Golm G, McCarroll K, Yu J, Esser MT, Vuocolo SC, Barr E. Impact of baseline covariates on the immunogenicity of a quadrivalent (types 6, 11, 16, and 18) human papillomavirus virus-like-particle vaccine. J Infect Dis. 2007 Oct 15;196(8):1153-62. Epub 2007 Sep 17.

BACKGROUND: The quadrivalent (types 6, 11, 16, and 18) human papillomavirus (HPV) L1 virus-like-particle vaccine was 95%-100% effective in preventing cervical and genital disease related to HPV-6, -11, -16, and -18. Vaccine efficacy is thought to be mediated by humoral immunity. Here, we analyze the effect of the baseline characteristics of subjects on vaccine-induced immune responses. **METHODS:** Immunogenicity data from 12,343 subjects 9-26 years old randomized to quadrivalent HPV vaccine or placebo in phase 2/3 studies were analyzed. Covariates examined were day 1 HPV serostatus, age, race/ethnicity, region of residence, lactation status, hormonal contraceptive usage, smoking status, Pap test diagnosis, immunosuppressant or anti-inflammatory agent use, and number of sex partners. Anti-HPV responses were summarized as serum anti-HPV-6, -11, -16, or -18 geometric mean titers 1 month after dose 3. **RESULTS:** Age at vaccination initiation was inversely proportional to the vaccine-induced anti-HPV response. Vaccination of subpopulations of subjects who were seropositive at day 1 to a vaccine HPV type resulted in more robust anti-HPV responses to that type, compared with those in subjects who were seronegative at baseline. Anti-HPV responses were comparable among the remaining demographic subgroups. **CONCLUSIONS:** The immunogenicity of quadrivalent HPV vaccine was comparable among subjects with differing baseline characteristics. These data support vaccination with quadrivalent HPV vaccine across a broad range of baseline subject characteristics.

32) Reisinger KS, Block SL, Lazcano-Ponce E, Samakoses R, Esser MT, Erick J, Puchalski D, Giacoletti KE, Sings HL, Lukac S, Alvarez FB, Barr E. Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: a randomized controlled trial. Pediatr Infect Dis J. 2007 Mar;26(3):201-9.

OBJECTIVE: Administration of a quadrivalent HPV-6/11/16/18 vaccine to 16- to 26-year-old women was highly effective in preventing HPV-6/11/16/18-related cervical/vulvar/vaginal precancerous lesions and genital warts. As the risk of acquiring HPV significantly rises after sexual debut, HPV vaccines should have the greatest benefit in sexually naive adolescents. We evaluated the tolerability and immunogenicity of quadrivalent vaccine in males and females 9 to 15 years of age through 18 months postenrollment. **METHODS:** In this randomized, double-blind trial, 1781 sexually naive children were assigned (2:1) to quadrivalent HPV-6/11/16/18 vaccine or saline placebo administered at day 1 and months 2 and 6. Serum neutralizing anti-HPV-6/11/16/18 responses were summarized as geometric mean titers (GMTs) and seroconversion rates. Primary analyses were done per-protocol (subjects received 3 doses, had no major protocol violations and were HPV type-specific seronegative at day 1). Adverse experiences were collected by diary card. **RESULTS:** At month 7, seroconversion rates were \geq 99.5% for the 4 vaccine-HPV-types. GMTs and seroconversion rates in boys were noninferior to those in girls ($P < 0.001$). At month 18, \geq 91.5% of vaccine recipients were seropositive, regardless of gender. A higher proportion of vaccine recipients (75.3%) than placebo recipients (50.0%) reported one or more injection-site adverse experiences following any vaccination. Rates of fever were similar between

vaccination groups. No serious vaccine-related adverse experiences were reported.

CONCLUSIONS: In 9- to 15-year-old adolescents, the quadrivalent vaccine was generally well tolerated and induced persistent anti-HPV serologic responses in the majority of subjects for at least 12 months following completion of a three-dose regimen. The vaccine durability supports universal HPV vaccination programs in adolescents to reduce the burden of clinical HPV disease, particularly cervical cancer and precancers.

33) Dillner J. On behalf of the Quadrivalent HPV Vaccine Phase IIb/III Investigators. Efficacy of quadrivalent HPV vaccination against condylomata and low-grade cervical, vulvar, and vaginal intraepithelial neoplasias. In: Proceedings of the New Strategies of Cervical Cancer Prevention: the Reality of HPV Vaccines Conference. Monte Carlo, Monaco, European Research Organization on Genital Infection and Neoplasia (EUROGIN), 2007. <http://www.eurogin.com/2007/abstractPart1.pdf>

34) Lehtinen M, et al. Immunogenicity and safety of human papillomavirus (HPV)-16/18 ASO4 adjuvanted vaccine in healthy males aged 10-18 years. Presented at the 13th International Conference on Infectious Diseases, Kuala Lumpur, Malaysia, June 19-22, 2008. http://ww2.isid.org/Downloads/13th_ICID

35) Taira AV, Neukermans CP, Sanders GD. Evaluating human papillomavirus vaccination programs. Emerg Infect Dis. 2004 Nov;10(11):1915-23.

Human papillomavirus (HPV) has been implicated as the primary etiologic agent of cervical cancer. Potential vaccines against high-risk HPV types are in clinical trials. We evaluated vaccination programs with a vaccine against HPV-16 and HPV-18. We developed disease transmission models that estimated HPV prevalence and infection rates for the population overall, by age group, by level of sexual activity within each age group, and by sex. Data were based on clinical trials and published and unpublished sources. An HPV-16/18 vaccine for 12-year-old girls would reduce cohort cervical cancer cases by 61.8%, with a cost-effectiveness ratio of 14,583 dollars per quality-adjusted life year (QALY). Including male participants in a vaccine rollout would further reduce cervical cancer cases by 2.2% at an incremental cost-effectiveness ratio of 442,039 dollars/QALY compared to female-only vaccination. Vaccination against HPV-16 and HPV-18 can be cost-effective, although including male participants in a vaccination program is generally not cost-effective, compared to female-only vaccination.

36) Elbasha EH, Dasbach EJ, Insinga RP. Model for assessing human papillomavirus vaccination strategies. Emerg Infect Dis. 2007 Jan;13(1):28-41.

We present a transmission dynamic model that can assess the epidemiologic consequences and cost-effectiveness of alternative strategies of administering a prophylactic quadrivalent (types 6/11/16/18) human papillomavirus (HPV) vaccine in a setting of organized cervical cancer screening in the United States. Compared with current practice, vaccinating girls before the age of 12 years would reduce the incidence of genital warts (83%) and cervical cancer (78%) due to HPV 6/11/16/18. The incremental cost-effectiveness ratio (ICER) of augmenting this strategy with a temporary catch-up program for 12- to 24-year-olds was US \$4,666 per quality-adjusted life year (QALY) gained. Relative to other commonly accepted healthcare programs, vaccinating girls and women appears cost-effective. Including men and boys in the program was the most effective strategy, reducing the incidence of genital warts,

cervical intraepithelial neoplasia, and cervical cancer by 97%, 91%, and 91%, respectively. The ICER of this strategy was \$45,056 per QALY.

37) Kulasingam S, Connelly L, Conway E, Hocking JS, Myers E, Regan DG, Roder D, Ross J, Wain G. A cost-effectiveness analysis of adding a human papillomavirus vaccine to the Australian National Cervical Cancer Screening Program. Sex Health. 2007 Sep;4(3):165-75.

BACKGROUND: The cost-effectiveness of adding a human papillomavirus (HPV) vaccine to the Australian National Cervical Screening Program compared to screening alone was examined. **METHODS:** A Markov model of the natural history of HPV infection that incorporates screening and vaccination was developed. A vaccine that prevents 100% of HPV 16/18-associated disease, with a lifetime duration of efficacy and 80% coverage offered through a school program to girls aged 12 years, in conjunction with current screening was compared with screening alone using cost (in Australian dollars) per life-year (LY) saved and quality-adjusted life-year (QALY) saved. Sensitivity analyses included determining the cost-effectiveness of offering a catch-up vaccination program to 14-26-year-olds and accounting for the benefits of herd immunity. **RESULTS:** Vaccination with screening compared with screening alone was associated with an incremental cost-effectiveness ratio (ICER) of \$51 103 per LY and \$18 735 per QALY, assuming a cost per vaccine dose of \$115. Results were sensitive to assumptions about the duration of vaccine efficacy, including the need for a booster (\$68 158 per LY and \$24 988 per QALY) to produce lifetime immunity. Accounting for herd immunity resulted in a more attractive ICER (\$36 343 per LY and \$13 316 per QALY) for girls only. The cost per LY of vaccinating boys and girls was \$92 052 and the cost per QALY was \$33 644. The cost per LY of implementing a catch-up vaccination program ranged from \$45 652 (\$16 727 per QALY) for extending vaccination to 14-year-olds to \$78 702 (\$34 536 per QALY) for 26-year-olds. **CONCLUSIONS:** These results suggest that adding an HPV vaccine to Australia's current screening regimen is a potentially cost-effective way to reduce cervical cancer and the clinical interventions that are currently associated with its prevention via screening alone.

38) Haupt R. Gardasil update: End-of-study (16-26 year olds), Adult women (24-45 year olds). Presentation to the US Advisory Committee on Immunization Practices, Atlanta, USA, February 27, 2008. <http://www.cdc.gov/vaccines/recs/acip/>

39) David M-P, Hardt K, Tibaldi F, Dubin G, Descamps D, Van Herck K, and Van Damme P. Modelling of long-term persistence of anti-HPV-16 and anti-HPV-18 antibodies induced by an ASO4-adjuvanted cervical cancer vaccine. Abstract presented at EUROGIN, Nice, France, November 2008. http://www.eurogin.com/2008/EUROGIN2008_Abstracts.pdf

40) Fraser C, Tomassini JE, Xi L, Golm G, Watson M, Giuliano AR, Barr E, Ault KA. Modeling the long-term antibody response of a human papillomavirus (HPV) virus-like particle (VLP) type 16 prophylactic vaccine. Vaccine. 2007 May 22;25(21):4324-33. Epub 2007 Mar 12.

The duration over which antibody responses persist following HPV vaccination is unknown. To estimate the longevity of responses induced by HPV-16 vaccination, two models were fitted to serum anti-HPV-16 levels measured during a 48-month study period. The first was a conventional model of antibody decay and the second was a modified model that accounts for

long-lived immune memory. Using the antibody decay model, it was estimated that following administration of a three-dose regimen of HPV-16 vaccine in women aged 16-23 years, anti-HPV-16 levels will remain above those induced naturally by HPV-16 infection for 12 years, and above detectable levels for 32 years in 50% of vaccinees. With the modified model, which fitted the data better ($p < 0.001$), it was estimated that near life-long persistence of anti-HPV-16 following vaccination is expected at titer levels above those associated with reduction of natural HPV-16 infection in 76% of these subjects, and above detectable levels in 99% of these subjects.

41) World Health Organization. Guidelines to assure the Quality, safety and efficacy of recombinant Human Papillomavirus virus-like particle vaccines (adopted 2006), In: WHO Expert Committee on Biological Standardization. Who Technical Report Series (in press). Electronic version available at http://www.who.int/biologicals/publications/trs/areas/vaccines/human_papillomavirus/en/index.html