

## HPV PP: grading of scientific evidence (Adolescent Girls)

**Question:** Is there evidence to support administration of the currently licensed HPV vaccines to young adolescent girls who are naïve to vaccine-related HPV types, to prevent cervical cancer later in life?

**Settings:** Global

**Conclusions:** Moderate quality of scientific evidence to support HPV vaccination of young adolescent girls to prevent cervical cancer later in life.

Quality assessment							Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations		
<b>Efficacy of HPV vaccination of young adolescent girls to prevent cervical cancer</b>								
7+ 4 <sup>1</sup>	RCTs	no serious	no serious	serious <sup>2</sup>	no serious	none	⊕⊕⊕○ MODERATE	CRITICAL
<b>Risk of serious adverse reactions following HPV immunization</b>								
3 <sup>3</sup>	RCTs	no serious	no serious	no serious	serious <sup>4</sup>	none	⊕⊕⊕○ MODERATE	CRITICAL

<sup>1</sup>7 RCT efficacy studies and 4 immunogenicity studies

The investigation by *SM Garland et al* which involved 5455 women between the ages of 16 and 24 years, studied the protective efficacy of the quadrivalent HPV vaccine against CIN 2/3 and AIS caused by HPV16 or HPV18. Among females naïve to HPV16 or HPV18 through to 1 month following the 3rd vaccine dose, protection against these combined endpoints was 100% (95% CI 94-100%) after a mean follow-up of 3 years. *The Future II Study Group* reporting on a second phase III study of 12,167 women aged 15-26, followed for a mean of 3 years after the first dose, found efficacy against CIN 2/3 and AIS caused by HPV-16 or HPV-18 of 98% (95% CI, 86-100%). In 2007, *the Future II Study Group* reported a combined analysis of these two phase III studies that included 17,622 females aged 15-26 years who were infected with one or more oncogenic vaccine-related HPV type at baseline. Following 3 doses and an average observation period of 3 years, the quadrivalent vaccine was 100% (95% CI 79-100%) effective against the combined endpoint of CIN 2/3 and AIS due to the HPV type or types for which the women were negative at enrolment. In a phase II study that was extended through to 5 years after enrolment, vaccine efficacy against the combined endpoint of CIN 1-3 or anogenital warts due to HPV 6,11,16 or 18 among women naïve to these 4 types at enrolment was 100% (95% CI 12- 100%) (*Villa LL et al, 2006*). A combined analysis of the above phase II trial of the quadrivalent vaccine, one phase II trial of a monovalent HPV 16 vaccine, and the two phase III trials of the quadrivalent vaccine mentioned above, reported an efficacy of 99% (95% CI 93-100%) for the composite endpoint of CIN2/3 or AIS after 3 years of follow-up among women naïve to the relevant HPV type at baseline who had received all 3 doses (*Ault KA, Future II, 2007*).

*Paavonen J et al* assessed the efficacy of the bivalent HPV vaccine in the prevention of vaccine-type CIN2+ in an interim analysis of a Phase III study that included 18,644 women aged 15-25 years. Following a mean follow-up period of 14.8 months the vaccine efficacy was 90% (97.9% CI 53-99%) in preventing CIN2+ due to HPV 16 or 18. These interim analyses were performed on a modified intention-to-treat basis, i.e. included women who had received ≥1 vaccine dose and who were naïve to either vaccine type 16 or 18 at baseline.

An extended phase II study conducted by *Harper DM et al.* included 776 females aged 15-25 years who were followed for 6.4 years after the first dose. The bivalent vaccine provided efficacy of 100% (95% CI 51-100%) against HPV 16/18-related CIN2+ among women who received at least one dose and were naïve to the relevant type at baseline. Also, high vaccine efficacy against CIN2+ caused by HPV 16/18 was reported in females aged 15-25 years who were naïve to 14 oncogenic HPV types at baseline (including HPV 16 and 18). In a *post hoc* analysis by *Harper DM* (in which the type-specific etiology of CIN2+ lesions that included multiple HPV types was classified according to the type of persistent infection before diagnosis, only lesions in which persistent HPV types 16 or 18 were found before diagnosis were classified as cases) 100% (95% CI 67-100%) effectiveness against CIN 2+ was found among the subset followed for 15 months after the first dose in the phase III trial.

Additionally, 100% effectiveness (95% CI 33-100%) was found among the smaller subset followed for 5.5 years after the first dose in a phase II trial.

*Block SL et al* compared the immunogenicity of the quadrivalent vaccine in females aged 10-15 years and 16-23 years. Following 3 doses, both groups showed  $\geq 99\%$  seroconversion against the 4 genotypes, including HPV 16 and 18, with higher geometric mean titres (GMTs) in the younger age group.

In a study of females aged 9-26 years, *Giuliano AR et al* reported that GMT responses to the quadrivalent vaccine virus-like particles (VLPs) was higher in younger females than in older females. *Reisinger KS et al* found  $\geq 99.5\%$  seroconversion rates following 3-doses of quadrivalent HPV vaccine in girls aged 9-15 years.

*Pedersen C et al* compared the immunogenicity of the bivalent vaccine in females aged 10-14 years and 15-25 years. Following 3 doses, both groups showed 100% seroconversion against HPV 16 and 18, with higher GMTs in the younger age group.

<sup>2</sup> Following HPV infection, the development of cervical cancer can take 20 years or more. The high-grade precancerous lesions (CIN 2/3 and/or AIS) usually develop in less than 5 years after infection and in clinical trials these lesions are widely accepted as clinical endpoints to infer vaccine efficacy against invasive cervical cancer. As most cervical cancers are caused by HPV genotypes 16 and 18 efficacy studies focus on prevention of lesions due to these two types.

In girls and young adolescent females the collection of cervical specimens is usually considered unethical or impractical. Therefore, the evidence for vaccine efficacy in this age group is indirect and based on the outcome of efficacy studies in females aged 15-25 years and on immunobridging studies that compare vaccine immunogenicity in females aged 9-13 years with immunogenicity in older females. Finally, unless vaccine immunogenicity/efficacy is found to be long-lasting, females who are vaccinated as girls may not be protected against oncogenic HPV types to which they are exposed many years later. As of early 2009, the reported immunogenicity and efficacy studies have followed cohorts for only 5-6 years.

<sup>3</sup> Three RCTs investigated safety and reactogenicity of HPV vaccines in young adolescent females: *Block SL et al* and *Reisinger KS et al* (quadrivalent vaccine), and *Pedersen C et al* (bivalent vaccine). Compared with recipients of placebo (in quadrivalent vaccine studies) or control Hepatitis A vaccine (in bivalent vaccine studies), HPV vaccine recipient were more likely to have local injection-site reactions, but were not significantly more likely to experience serious or systemic adverse events. These findings are consistent with large safety studies in older adolescent females and women (See WHO Background Paper for references).

<sup>4</sup> The short (2-3 years) post marketing surveillance periods of these vaccines do not permit final assessments of possible rare or long-term adverse effects.

## Bibliography:

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;356(19):1928-43.

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

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;196(10):1438-46.

Villa LL, Costa RL, Petta CA, Andrade RP, Paavonen J, Iversen OE, Olsson SE, Høye J, Steinwall M, Riis-Johannessen G, Andersson-Ellstrom A, Elfgrén 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;95(11):1459-66.

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;369(9576):1861-8.

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;369(9580):2161-70.

Harper DM, Gall S, Naud P, 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 published in *Gynecologic Oncology* 2008; 109:158.

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;110(3 Suppl 1):S11-7.

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;118(5):2135-45.

Giuliano AR et al. 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; 196(8):1153-1162.

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; 26(3):201-9.

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;40(6):564-71.