## Duration of protection conferred by HPV vaccination in immunocompetent females

**Population :** Immunocompetent females
**Intervention:** 3 doses of HPV vaccination
**Comparison:** Placebo/ no vaccination
**Outcome :** Cervical cancer

*In immunocompetent females, what is the evidence to ensure long term protection against cervical cancer following a three -dose HPV vaccination schedule?*

| | | | Rating | Adjustment to rating |
|---|---|---|---|---|
| **Quality Assessment** | No. of studies/starting rating | | 13/ RCTs[i] | 4 |
| | Factors decreasing confidence | Limitation in study design | None serious | 0 |
| | | Inconsistency | None serious | 0 |
| | | Indirectness | Serious[ii] | -2 |
| | | Imprecision | None serious | 0 |
| | | Publication bias | None serious | 0 |
| | Factors increasing confidence | Large effect | Not applicable | 0 |
| | | Dose-response | Not applicable | 0 |
| | | Antagonistic bias and confounding | Not applicable | 0 |
| | **Final numerical rating of quality of evidence** | | | **2** |
| **Summary of Findings** | **Statement on quality of evidence** | | | **Our confidence in the estimate of the effect on the health outcome is limited.** |
| | **Conclusion** | | | **Low quality of scientific evidence that HPV vaccine confers long term protection against cervical cancer in immunocompetent females. The need for a booster dose will have to be assessed once more long-term data on efficacy against cervical cancer becomes available.** |

**References**


Ferris,D, Samakoses, R., Block, S.L, et al, Long Term Study of a Quadrivalent Human Papilloma Virus Vaccine, Pediatrics 2014, 134: e657-e665

Naud PS, Roteli-Martins CM, De Carvlho NS et al. Sustained efficacy, immunogenicity and safety of the HPV-16/18 ASO4 adjuvanted vaccine: Final analysis of a long-term follow-up study up to 9.4 years post-vaccination. Human Vaccines & Immunotherapeuthics 2014; 10(8)

Nygard M. Long-term immunogenicity, safety, and effectiveness of GARDASIL in the Nordic countries. ESPID, May 28-June 1, 2013. Milan, Italy. Abstract 1249.

Romanowski B. Long term protection against cervical infection with the human papillomavirus: review of currently available vaccines. Hum Vaccin. 2011 Feb;7(2):161-9.

Roteli-Martins, C.M., Naud, P., De Borba, P. 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

Rowhani-Rahbar, A., Alvarez, F.B., Bryan, J.T. et al. Evidence of immune memory 8.5 years following administration of a prophylactic human papillomavirus type 16 vaccine. J Clin Virol. 2012; 53: 239–243

[i] In 2011, Romanowski et al evaluated the long term protection induced by the available vaccines against cervical infection with HPV. The systematic review summarizes the findings of 9 large RCTs conducted in various settings, on continued efficacy and immunogenicity of bivalent and quadrivalent HPV vaccines (HPV-010, HPV-001/007/023, HPV-14, HPV-013/025, HPV-012, PATRICIA, V501-007, FUTURE I and FUTURE 2). Clinical efficacy against infection and cervical lesions associtated with HPV-16/18 has been demonstrated up to 8.4years with the bivalent vaccine and up to 5 years with the quadrivalent vaccine.

Recent publications of the findings from these completed or ongoing trials support these findings.

Ferris et al. assessed, vaccination-induced anti-HPV response persisted through month 96 for each of the quadrivalent HPV vaccine types as well as vaccine effectiveness against HPV6/11/16/18-related persistent infection or disease. For each of the vaccine types, vaccination-induced anti-HPV response persisted through month 96. Among 429 subjects who received vaccine at a mean age of 12, none developed HPV6/11/16/18-related disease or persistent infection of ≥12 months' duration.

Naud et al. assessed no new HPV-16/18-associated infections and cyto-histopathological abnormalities during the study period in the vaccine group. The mean follow-up time since first vaccination was 107 months (8·9 y [SD: 0.4]), with a maximum duration of 113 months (9·4 y). A total of 399 women were included in the according-to-protocol (ATP) efficacy cohort and 304 in the ATP immunogenicity cohort.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% (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.

Roteli-Martins et al. reports on the long-term efficacy and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine up to 8.4 y after the first vaccine dose(n = 436). 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). 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.

Rowhani-Rahbar et al. suggests that following an antigen challenge to women who had received the monovalent HPV-16 vaccine 8.5 years earlier through administration of the quadrivalent HPV-06/11/16/18 a heightened immune response was observed indicating that the administration of the 3-dose regimen of the monovalent HPV-16 vaccine had produced memory lymphocytes, characterized by high antibody levels. The results of this study add to the existing body of knowledge that prophylactic HPV vaccines may generate long-term immune memory.

[ii] As cervical cancer mostly occurs 20 years or more after HPV infection, current follow-up periods of up to 9.4 years are too short to directly evaluate efficacy against cervical cancer. Although CIN grade 2 and 3 (but not CIN 1) have a high probability of progressing to cervical cancer, they are precancerous lesions and therefore indirect measures of the outcome of invasive cervical cancer. Adolescent girls under 15 years of age are considered the primary target for large-scale HPV vaccination, but were not included in efficacy trials due to concerns about cervical sampling in children and young adolescents and low chance of finding lesions. However, the demonstration that the immune response in adolescent females <15 years was stronger than that of older females in whom the vaccine has been proven to be efficacious supports the likelihood that the vaccines may be efficacious in young adolescent females, but also add to the indirectness of the scientific evidence. Anamnestic responses are considered a marker of long-term cellular immunity, but are not a definitive measure of long-term protection against disease. No immune correlate of protection has been established for HPV vaccines, and it is unknown whether higher antibody levels will result in a longer duration of protection.