Efficacy of HPV vaccination in adolescent girls

Population : Adolescent girls
Intervention: Primary HPV vaccination
Comparison: Placebo/ no vaccination
Outcome : HPV infection

What is the scientific evidence to support administration of the currently licensed HPV vaccines to young adolescent girls, naïve to vaccine-related HPV types, to prevent cervical cancer later in life?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		8/ RCT[1]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	Serious[2]	-1
		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			**3**
Summary of Findings	**Statement on quality of evidence**			**We are moderately confident in the estimate of effect on health outcome. The true effect is likely to be close to the estimate of the effect.**
	Conclusion			**We are moderately confident that administration of primary HPV vaccination to young adolescent girls prevents cervical cancer later in life.**

[1] End of study analyses of the phase III trials of prophylactic human papillomavirus (HPV) virus-like particle (VLP) vaccines were published by Schiller et al. in 2012. Both available vaccine formulations demonstrated high 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. 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 naive 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 naive 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 naive 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 naive 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. Sexually naive boys and girls aged 9 to 15 years (N = 1781) were assigned (2:1) to receive HPV4 vaccine or saline placebo at day 1 and months 2 and 6. At month 30, the placebo group (n = 482) received HPV4 vaccine following the same regimen and both cohorts were followed through month 96. Data showed that, when administered to adolescents, the HPV4 vaccine demonstrated durability in clinically effective protection and sustained antibody titers over 8 years (*Ferris et al.2014*).

[2] 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 2014, the reported immunogenicity and efficacy studies have followed cohorts for 9 years.

References

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