

HPV PP: Grading of scientific evidence (Booster)

Question: Is there evidence to support administration of a booster dose of HPV vaccine to ensure long term protection against cervical cancer?

Settings: Global

Conclusion: Low quality of scientific evidence that a booster dose of HPV vaccine is not required to ensure long term protection against cervical cancer.

Quality assessment							Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations		
Waning of protection over time against established histological outcomes								
5+2 ¹	RCT	serious ²	no serious	serious ³	no serious	none	⊕⊕○○ LOW	CRITICAL

¹5 RCTs and 2 modelling studies

An extended phase II study conducted by *Villa LL et al* reported that the quadrivalent vaccine provided efficacy of 100% (95% CI 12-100%) against CIN (any grade) or external anogenital or vaginal lesions related to HPV 6, 11, 16 or 18 for 5 years after the first dose in females aged 16-23 years who were naïve to the relevant types at baseline. In a combined analysis of phase II and phase III data from >20,000 females aged 15-26 years followed for a mean of 44 months, efficacy was high against CIN2/3 (98%, 95% CI 93-100%) and AIS (100%, 95% CI 31-100%) related to HPV 6,11,16,or 18 (*Haupt R*). *Olsson SE et al* found that among 241 females aged 16-23 this vaccine induced an anamnestic response typical of cellular immunity following a challenge dose 60 months after the primary course of vaccination. A lower proportion of females had sustained detectable antibodies against HPV 18 compared to the other types included in the vaccine, but this was not associated with reduced efficacy against clinical endpoints.

Harper DM et al. reported an extended phase II study which 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). A *post hoc* analysis of a phase III bivalent vaccine trial by *Harper DM*, where lesion type-specific etiology was classified according to the type of persistent infection before diagnosis, found 100% (95% CI 67-100%) effectiveness against CIN 2+ judged to be caused by HPV types 16 or 18 among women followed for 15 months after the first dose of the bivalent vaccine.

Recent modelling of long-term antibody persistence based on the above data through 6.4 years, predicted that with the bivalent HPV vaccine anti-HPV-16 and anti-HPV-18 antibodies will remain detectable for at least 20 years (*David MP et al*). *Fraser et al* modelled longevity of anti-HPV-16 antibodies based on 48 months following HPV-16 vaccination, and predicted that anti-HPV-16 levels will remain above those induced from natural infection for at least 12 years, and potentially for a lifetime depending on model assumptions.

² Information available only as abstracts (*Harper DM et al; David M-P et al*) or as a document prepared for ACIP (*Haupt R*) limits assessment of study quality.

³ As cervical cancer mostly occurs 20 years or more after HPV infection, current follow-up periods of 5-6.4 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. 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.

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