Efficacy of human papillomavirus vaccines: a systematic quantitative review
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CRD summary
This review concluded that prophylactic vaccination can prevent infection with human papillomavirus (HPV) in women (nine to 26 years) who had not previously been infected with the vaccine HPV subtypes. Longer follow-up was required. These findings should be interpreted with caution as they were based a small number of studies that had varying clinical characteristics.

Authors' objectives
To compare the efficacy, safety and immunogenicity of vaccines against human papillomavirus (HPV) with placebo.

Searching
MEDLINE, EMBASE, LILACS and CANCERLIT were searched from January 1997 to September 2007. Search terms were reported. The Cochrane Library was searched and the reference lists of primary studies screened for additional studies. No language restrictions were applied.

Study selection
Double-blind randomised placebo-controlled trials of HPV vaccines based on the L1 virus-like particle (L1-VLP) in HPV seropositive (evidence of immune response to HPV) and HPV DNA (deoxyribonucleic acid) positive women (evidence of ongoing HPV infection) were eligible for inclusion in the review. Eligible vaccines were quadrivalent HPV 6, 11, 16, 18 vaccine (20/40/40/20μg, Gardasil), univalent HPV 16 vaccine (40μg, Merck) and bivalent HPV 16 and 18 vaccine (20μg, Ceravix, GlaxoSmithKline). Studies that did not describe the final histological or cytological diagnosis of participants were excluded. Eligible primary outcomes were incidence of cytologically and/or histologically proven cervical lesions. Secondary outcomes were vaccine safety and immunogenicity.

Half of the included studies compared HPV 16 and 18 vaccination with placebo (hepatitis A vaccine). The studies were all multicentre studies and most were conducted in more than one country (USA, Brazil, Canada and Costa Rica were included). Included women were between 15 and 26 years old. Primary study inclusion/exclusion criteria varied between the studies (further details in the review). Follow-up ranged from 12 to 48 months. Outcomes included incidence of lesions, which included high-grade squamous intraepithelial lesions (Hi-SIL; cervical intraepithelial neoplasia or CIN, grades II and III) and low-grade squamous intraepithelial lesions (Lo-SIL; CIN grades I). Half of the studies reported seroconversion rates. Safety assessments considered the number of injection site events, systemic events, serious events and deaths.

Four reviewers independently assessed studies for inclusion in the review; disagreements were resolved through consensus or the involvement of a fifth reviewer.

Assessment of study quality
Studies were assessed for methodological quality using criteria of allocation concealment, extent of blinding, compatibility of study groups at baseline, losses to follow-up, non-compliance, standardisation of outcome assessment and use of an intention-to-treat (ITT) analysis.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
Two reviewers extracted the number of participants reporting an outcome (disease or infection). Data were used to calculate odds ratios (ORs) with 95% confidence intervals (CIs) based on ITT values (all participants randomised regardless of their baseline HPV status or evidence of HPV associated disease). A primary study author was contacted for further information.
Methods of synthesis
Pooled odds ratios with 95% CIs were calculated using a random effects model. Statistical heterogeneity was assessed using $X^2$ and $I^2$ tests and defined as significant if $I^2$ was greater than 50%. A sensitivity analysis was performed to investigate the effects of study design and quality.

Results of the review
Six RCTs (n=47,236) were included in the review. Sample sizes ranged from 560 to 9,325 per treatment arm. Four trials were reported as having adequate concealment of allocation. All trials used computer-generated randomisation methods, justified sample sizes and reported losses to follow-up.

The pooled rate of lesions (cervical, vulval, vaginal and anogenital) was significantly reduced with vaccines in comparison with control (93%, 95% CI 87 to 96 for bivalent vaccines and 62%, 95% CI 27 to 70 for quadrivalent vaccines). Further subgroup analyses according to different vaccine types also favoured vaccines in comparison with control groups (further details reported in the review). No significant statistical heterogeneity was detected.

A significantly greater number of adverse events was identified in women treated with bivalent HPV vaccine in comparison with placebo (OR 1.35, 95% CI 1.05 to 1.73). Adverse events varied (further details reported in the review). No deaths were reported for bivalent vaccines. Two studies reported a total of nine deaths in the quadrivalent vaccine group in comparison with five deaths in the placebo control groups.

Three RCTs reported that seroconversion rates were significantly higher in participants who received bivalent vaccine in comparison with placebo (OR 0.19, 95% CI 0.05 to 0.75; no significant heterogeneity). One RCT that assessed a quadrivalent vaccine reported a similar finding (OR 0.16, 95% CI 0.10 to 0.26).

Differences in study quality and the vaccine type (univalent versus mutivalent) were not found to affect the review findings significantly.

Authors’ conclusions
Prophylactic vaccination can prevent infection with HPV in women aged nine to 26 years who had not previously been infected with the vaccine HPV subtypes. Longer follow-up was required to evaluate the incidence of cervical cancer and mortality.

CRD commentary
This review assessed a clearly defined review question. A range of databases was searched for eligible studies. No language restrictions were applied. It was unclear whether restrictions were placed on publication status and so there may have been a risk of publication bias. Multiple reviewers were involved in selecting eligible studies for inclusion in the review and extracting the study data; it was unclear whether similar precautions were taken to prevent the risk of reviewer error and bias during study validity assessment. Relevant quality criteria were assessed. Variations in the use of allocation concealment were not found to significantly affect the review findings. The reliability of the analyses was unclear given the small number of studies with in some cases heterogeneous characteristics (such as geographical variations in clinical practice) included in the analyses. Figures for pooled effect sizes also presented total effect sizes across different lesion types and included duplicate data entries. Statistical heterogeneity was reported for some outcomes. Further review limitations included a lack of long-term data with regard to assessing important final outcomes such as mortality and cancer incidence (this was acknowledged by the authors).

Overall, given that the review included only a small number of relatively short-term studies with varying clinical characteristics, the findings of the review should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further long-term randomised controlled trials were required to assess the prophylactic efficacy of HPV vaccines. Such studies should address effects in specific subgroups who may benefit.
from vaccination (including women over 26 years, boys and men). Studies should include outcomes such as vaccine efficacy in recurrent lesions, population satisfaction, quality of life and costs.

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