Efficacy and safety of prophylactic vaccines against cervical HPV infection and diseases among women: a systematic review & meta-analysis

Lu B, Kumar A, Castellsague X, Giuliano AR

CRD summary
This well-conducted review found that prophylactic human papilloma virus vaccines were safe, generally well-tolerated and efficacious in preventing persistent infections and cervical diseases among young females. Long-term efficacy and safety data were required. The conclusions' appear reasonable, but the potential for missed data should be borne in mind.

Authors' objectives
To determine the efficacy and safety of prophylactic human papilloma virus (HPV) vaccines for cervical cancer precursor events in women.

Searching
MEDLINE and The Cochrane Library were searched to July 2009. Search terms were reported. Conference abstracts from International Papillomavirus Society (IPVS) were handsearched from 2006 to 2009. Bibliographies of identified trials were checked for additional relevant studies. Only trials published in English were included.

Study selection
Randomised controlled trials (RCTs) of L1 virus-like particle-based HPV vaccines conducted in women that reported prophylactic efficacy against HPV infection or diseases of interest were eligible for inclusion. Trials that reported therapeutic vaccination or ad hoc subgroup analyses of existing RCTs were excluded. The primary endpoint was high-grade cervical lesions or worse (CIN2+), including Cervical Intraepithelial Neoplasia (CIN) grade 2-3, Adenocarcinoma in Situ (AIS) and cervical carcinoma. Secondary endpoints were type-specific persistent infections, CIN 1 or worse (CIN1+), adverse events and vaccine-related adverse events.

Included studies assessed quadrivalent, bivalent and monovalent vaccines. Most studies used placebo as the comparator; one study used placebo plus hepatitis B vaccine and one used hepatitis A vaccine. Proprietary adjuvant was used with each type of vaccine. Treatment regimens were administered in a three-dose regimen within a six-month time period. In most trials the mean age of participants was approximately 20 years; one trial included older females (mean age 34 years). Most participants had two or fewer lifetime sexual partners, used hormonal contraceptives and had normal cytology at enrolment. Reported mean trial duration ranged from 26.4 to 41 months; two trials had an extended follow-up of 53 and 60 months.

Two reviewers independently selected trials for inclusion in the review.

Assessment of study quality
Two reviewers independently assessed the validity of the included trials according to criteria of allocation concealment, blinding, drop-outs/loss to follow-up, expected efficacy and performance of sample size calculation. Discrepancies were resolved by consensus or in consultation with a third reviewer.

Data extraction
Two reviewers independently extracted data to calculate relative risks (RRs) along with associated 95% confidence intervals (CIs) onto a standardised data extraction form. Efficacy was estimated as [1-RR] and expressed as a percentage. Populations were categorised as intention-to-treat (ITT), modified ITT and per protocol population. Where both interim and final analyses were reported, data were used from the final analyses with complete follow-up. Discrepancies were resolved by consensus or in consultation with a third reviewer.

Methods of synthesis
Summary relative risks and 95% CIs were estimated using a fixed-effect model. Statistical heterogeneity was assessed using Cochrane's Q and I². Sensitivity analyses that used key methodological quality domains and study characteristics
were planned a priori to explore possible sources of heterogeneity. Publication bias was assessed using the Begg and Egger funnel plot method.

**Results of the review**

Seven RCTs reported in 13 publications were included in the review (43,283 participants, range 552 to 18,644). All trials reported adequate allocation concealment and blinding and reported drop-outs/loss to follow-up and sample size calculation. Expected efficacy ranged from 0.70 to 0.90. All trials were industry funded.

- **HPV-16**: Statistically significant reductions in risks of CIN2+ (RR 0.47, 95% CI 0.36 to 0.61, I²=87%; four RCTs), CIN1+ (RR 0.43, 95% CI 0.33 to 0.58, I²=76%; four RCTs) and persistent infection of at least six months (RR 0.15, 95% CI 0.10 to 0.23, I²=23%; two RCTs) were associated with HPV-16 was found with prophylactic vaccine use compared with controls in ITT cohorts.

- **HPV-18**: Significant reductions in risks of CIN2+ (RR 0.16, 95% CI 0.08 to 0.34, I²=9%; three RCTs), CIN1+ (RR 0.22, 95% CI 0.10 to 0.44, I²=0%; three RCTs) and persistent infection of at least six months (RR 0.24, 95% CI 0.14 to 0.42, I²=0%; two RCTs) were associated with HPV-18 compared to control in ITT cohorts.

- **HPV-31, 33, 45, 52 and 58**: Reductions in risks of CIN2+ (RR 0.79, 95% CI 0.67 to 0.92, I²=74%; two RCTs) and persistent infection of at least six months (RR 0.77, 95% CI 0.72 to 0.83, I²=66%; two RCTs) associated with non-vaccine oncogenic HPV types (31, 33, 45, 52 and 58) were found compared with control in ITT cohorts.

When cross-protection against six-month persistent infection was examined by HPV type, a significant reduction in risk was found for HPV-31 (RR 0.47 95% CI 0.40 to 0.55, I²=94%; two RCTs), HPV-33 (RR 0.65, 95% CI 0.53 to 0.80, I²=16%; two RCTs) and HPV-45 (RR 0.50, 95% CI 0.39 to 0.64, I²=94%; two RCTs). No significant between-group differences were found for risk of persistent infection of at least six months with HPV-52 and HPV-58.

Exclusion of the FUTURE trials increased efficacy estimates and reduced observed heterogeneity. Per protocol population cohort analyses showed larger effect sizes than the ITT analyses.

- **Adverse events**: No significant between-group differences were found for participants who experienced one or more serious adverse events or vaccine-related serious adverse events.

The funnel plot indicated no significant publication bias for the primary endpoint (CIN2+) associated with HPV-16/18 in ITT cohorts (p=0.60).

- **Authors' conclusions**: Virus-like particle-based prophylactic HPV vaccines were efficacious in preventing persistent infections and cervical diseases associated with vaccine HPV types among young females and were safe and generally well tolerated. Long-term efficacy and safety data were required.

- **CRD commentary**: The review question was supported by clearly defined inclusion criteria. Electronic databases and conference abstracts from a relevant source were searched. Inclusion was restricted to published trials in English, which raised the possibility of language and publication biases. Publication bias was analysed, but the small number of included trials made this difficult to assess. Appropriate steps were taken to reduce the likelihood of reviewer error and bias during study selection, data extraction and trial quality assessment. Trial quality was assessed using relevant criteria and the overall methodological quality was considered to be good.

Trials were pooled using standard meta-analytic techniques. Exploration of possible sources of heterogeneity were performed. The authors acknowledged that the population related to young females with limited sexual exposure to HPV and so may not be generalisable to other population groups. They also acknowledged that the included trials did not provide long-term data on efficacy and safety.

The authors’ conclusions appear to follow from the results presented, but the possibility that relevant trials were missed should be borne in mind.
Implications of the review for practice and research

**Practice:** The authors stated that vaccination of adolescent girls prior to sexual debut appeared to be an effective public health measure for the prevention of cervical diseases and cancer.

**Research:** The authors stated that further research was required on the long-term effect of prophylactic vaccines and further data was needed on pregnancy outcomes and long-term follow-up of live births during trial regimen for a full assessment of vaccine safety. The authors indicated that due to the common use of composite endpoints the prophylactic efficacy against anogenital warts and vulvar and vaginal diseases associated with vaccine HPV remained unclear.

**Funding**
None reported.

**Bibliographic details**
Lu B, Kumar A, Castellsague X, Giuliano AR. Efficacy and safety of prophylactic vaccines against cervical HPV infection and diseases among women: a systematic review & meta-analysis. BMC Infectious Diseases 2011; 11(13)

**PubMedID**
21226933

**DOI**
10.1186/1471-2334-11-13

**Original Paper URL**
http://www.biomedcentral.com/1471-2334/11/13/abstract/

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adolescent; Adult; Drug-Related Side Effects and Adverse Reactions; Female; Humans; Papillomaviridae /genetics /isolation & purification /physiology; Papillomavirus Infections /drug therapy /epidemiology /prevention & control /virology; Papillomavirus Vaccines /adverse effects /therapeutic use; Pregnancy; Randomized Controlled Trials as Topic; Uterine Cervical Neoplasms /drug therapy /epidemiology /prevention & control /virology; Young Adult

**AccessionNumber**
12011001427

**Date bibliographic record published**
03/08/2011

**Date abstract record published**
15/02/2012

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.