Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors

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Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors

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DECLARATIONS OF INTEREST

MA: has received travel grants from MSD-Sanofi-Pasteur and GSK, (ceased in 2008).
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MS: has received sponsorship, research grants and consultation fees in his name, his company's name (Communications Actions-Santé Inc) or through HPV2010 or the Institut National de Santé Publique du Quebec from: Abbott Molecular, Beckton-Dickinsson, Copan, Digene-Qiagen, Genomica, Gen-Probe, Greiner Bio-One, GSK Biologicals, Graceway Pharma, Hologic, IncellDX, Innogenetics NV, Laboratoire Biron, Marubeni, Merck Sharp & Dohme, MTM Laboratories, Neodiagnostics, Roche Molecular Systems and Wamex.
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LK: none known.
AH: has not received any support from companies. He is the principle investigator in an HPV vaccine trial in Costa-Rica sponsored by the National Cancer Institute (NCI). Vaccines for this trial were provided free of charge by GSK under a clinical trial agreement with the NCI. GSK paid the regulatory costs associated with the trial under their FDA IND.

Additional comments

The authors of this systematic review are recognised experts in the field of cervical cancer screening and HPV vaccination and have contributed substantially to the bulk of knowledge on the pathogenesis of HPV-induced carcinogenesis, or are involved in the development of guidelines on cervical cancer prevention. The co-authorship is balanced, with certain co-authors having a conflict of interest and others explicitly not having a conflict of interest. Given the scientific weight of authors, it seems realistic that manufacturers owning the data of trials will be willing to provide additional requested non-published information. The reader should be aware that the authors have thorough knowledge of the field and that this could potentially generate a bias. However, the second author, AB (statistical advisor of the Gynaecological Cancer Cochrane Group), is not an HPV expert and his methodological expertise offers a certain degree of protection against possible bias from pre-knowledge.

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Abstract

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the immunogenicity, clinical efficacy, and safety of prophylactic HPV vaccines in females. The assessment of clinical efficacy will address protection against HPV infection (for homologous and heterologous HPV types), against re-infection, against cervical cancer and its precursors (high-grade CIN (grade 2 or grade 3), adenocarcinoma in situ) in women previously not exposed to HPV infection (negative at enrolment for both HPV DNA and antibodies against the vaccine HPV types). We will assess clinical effectiveness by evaluating outcomes in all women, irrespective of the HPV DNA or serology status at enrolment. Evaluation by fine age and time since sexual debut categories is also planned.

BACKGROUND

Description of the condition

Association between human papillomavirus (HPV) infection and cervical cancer and other HPV-related cancers and their precursors—The development of cervical cancer passes through a number of phases: (a) infection of the cervical epithelium with certain human papillomavirus (HPV) types; (b) persistence of the HPV infection; (c) progression to precancerous lesions (cervical intraepithelial neoplasia (CIN) and (d) eventually invasion. All phases are reversible, except for the last one (Bosch 2002;

Castellsague 2006; IARC 2007). Recently, an IARC (International Agency for Research on Cancer) expert group reviewed the carcinogenicity of human papilloviruses and confirmed that for 12 HPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) sufficient evidence exists that they are causally linked with the development of cervical cancer (Bouvard 2009). Type HPV 68 is considered as probably carcinogenic (Schiffman 2009). The HPV type 16, in particular, has a high potential for malignant transformation of infected cervical cells (Schiffman 2005). The HPV types 16 and 18 jointly cause 70% of all the cervical cancers worldwide (Munoz 2004). Moreover, HPV type 16 is also linked with rarer types of cancer, namely cancer of the vulva and vagina in women, penis cancer in men and anus, oropharynx and larynx cancer in women and men (Cogliano 2005; IARC 2007). IARC 2007

The main route of HPV transmission is sexual. Infection with HPV usually occurs soon after the onset of sexual activity (Winer 2003; Winer 2008). The prevalence of HPV infection generally peaks in late teenage or early twenties and declines thereafter (De Sanjose 2007). Human papillomavirus infection usually clears spontaneously, in particular in women younger than 30 years. Human papillomavirus infection can result in intraepithelial neoplastic cellular lesions which are identifiable by cytological examination (ASCUS, LSIL, HSIL, see list of abbreviations in Appendices) and which can be confirmed histologically (CIN1-3)*. These lesions generally regress, but the probability of regression decreases, and the likelihood of progression to cancer increases with the duration of HPV infection and the severity of the lesion. From historical data, it has been estimated that CIN3 incurs a probability of progressing to invasive cancer of 12% to 30%; whereas for CIN2 this probability is substantially less (McCredie 2008; Ostor 1993).The natural history of HPV infection to invasive cancer takes a minimum of 10 years and a median of approximately 25 to 30 years (IARC 2007).

A World Health Organization (WHO) expert group accepted a reduction in the incidence of high-grade CIN (CIN2+) and cervical adenocarcinoma (AIS) or worse as an acceptable surrogate outcome of HPV vaccination trials, since the reduction of the incidence of invasive cervical cancer would require large and lengthy studies which are unlikely to be undertaken (Pagliusi 2004). The low-risk HPV types 6 and 11 cause approximately 90% of genital warts in women and men (Lacey 2006). They occur in low-grade dysplastic cervical lesions but are not associated with cervical cancer (IARC 2007). Moreover, HPV types 6 and 11 cause recurrent respiratory papillomatosis, a rare but very serious disease of the upper airways often requiring repetitive surgical interventions (Lacey 2006).

The recognition of the strong causal association between HPV infection and cervical cancer has resulted in the development of HPV assays to detect cervical cancer precursors (Iftner 2003), and even vaccines that prevent HPV infection (prophylactic vaccines) or that treat HPV-induced lesions (therapeutic vaccines) (Frazer 2004; Galloway 2003; Schneider 2003). Therapeutic vaccines are still in very early experimental phases and are not further considered in this review.

* Throughout this review, we will use the 2001 Bethesda System to define cytologically defined neoplastic lesions of the cervical epithelium (Solomon 2002) and the CIN

nomenclature to define histologically confirmed cervical intraepithelial neoplasia (Richart 1973).

Burden of cervical cancer—Cervical cancer is the second most common cancer in women worldwide (Ferlay 2004). It is estimated that in 2002, approximately 493,000 women developed cervical cancer and that 273,000 died from the disease (Ferlay 2004). Eighty-three per cent of cervical cancer cases occur in developing countries. Cervical cancer is the predominant female cancer in Sub-Saharan Africa, Central America and South-Central Asia, where a woman's risk of developing this disease by age 65 years ranges between 2.1% and 3.2%. In many developed countries, the incidence of, and mortality from, squamous cervical cancer has dropped substantially over the last decades as a consequence of widespread screening (Arbyn 2009; Arbyn 2009a; Bray 2005a; IARC 2004). For instance, In the USA and North and West-Europe, the cumulative risk of cervix uteri cancer up to age 65 years is 0.7% or lower (Ferlay 2004). However, approximately 52,000 and 13,000 cases are reported each year in Europe and the USA, respectively (Ferlay 2004). Moreover, the incidence of adenocarcinoma of the cervix is less affected by cytological screening (Bray 2005; Smith 2000). In contrast to many other malignancies, cervical cancer primarily affects younger women, with the majority of cases appearing between the ages of 35 and 50 years (Yang 2004). In Europe, approximately 40% of women with cervical cancer die from the disease within five years of diagnosis (Sant 2009).

Description of the intervention

In this review, we will only study prophylactic HPV vaccines composed of virus-like particles of the L1 protein, which is the major protein of the capsid of the HPV virus.

To date, three prophylactic HPV vaccines have been developed and clinically evaluated in randomised controlled trials (RCTs): a monovalent HPV16 vaccine (manufactured by Merck, Sharpe & Dome (Merck), Whitehouse Station, NJ, USA); a quadrivalent vaccine, containing the L1 protein of HPV6, HPV11, HPV16 and HPV18 (Gardasil®, produced by the same manufacturer); and a bivalent vaccine containing L1 of HPV types 16 and 18 (Cervarix®, produced by GlaxoSmithKline (GSK), Rixensart, Belgium) (Koutsky 2002). The vaccine produced by Merck contains amorphous aluminium hydroxyphosphate sulphate as an adjuvant, whereas the GSK vaccine contains aluminium salt and ASO4 or monophosphoryl lipid A, which is an immunostimulating molecule (WHO 2009). More details about prophylactic HPV vaccines used are described in Appendix 1.

Animal experiments have shown that neutralising antibodies, elicited by vaccination with papillomavirus VLPs, prevent type-specific infection and subsequent lesions after viral challenge (Breitburd 1995;Ghim 2000; Stanley 2006). Vaccination by intramuscular injection of L1 VLPs in humans has been demonstrated to be highly immunogenic and well-tolerated in phase I trials. (Ault 2004; Brown 2001; Evans 2001; Harro 2001;).

Why it is important to do this review

Several phase II and III studies have been conducted to date and numerous reviews have tried to summarise the results (Arbyn 2007; Ault 2007; Harper 2009; Initiative 2009; Kahn

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2009; Kjaer 2009; Koutsky 2006; Medeiros 2009; Rambout 2007; Szarewski 2010). However, none of the reviews combined information on all the available endpoints. This is due to incomplete reporting of data, use of different assays, analyses of different per protocol or intention-to-treat groups, outcome definitions, lumping of different outcomes, and reporting at variable time points in the scientific literature. Previous reports have also not comprehensively evaluated the impact of vaccination by fine categories of age and time since sexual debut, have not systematically evaluated evidence for cross-protection against HPV types phylogenetically related to HPV-16/18, and have not specifically addressed the question of whether vaccination protects against re-infection among younger and older individuals known to be infected at vaccination and who subsequently clear their infections.

The objective of this review is to summarise all available (published and unpublished) evidence by combining outcomes with similar definitions and times of measurement. We will request missing outcomes or outcome data missing at specific time points.

OBJECTIVES

To evaluate the immunogenicity, clinical efficacy, and safety of prophylactic HPV vaccines in females. The assessment of clinical efficacy will address protection against HPV infection (for homologous and heterologous HPV types), against re-infection, against cervical cancer and its precursors (high-grade CIN (grade 2 or grade 3), adenocarcinoma in situ) in women previously not exposed to HPV infection (negative at enrolment for both HPV DNA and antibodies against the vaccine HPV types). We will assess clinical effectiveness by evaluating outcomes in all women, irrespective of the HPV DNA or serology status at enrolment. Evaluation by fine age and time since sexual debut categories is also planned.

METHODS

Criteria for considering studies for this review

Types of studies—We will only consider randomised controlled trials (RCTs).

Types of participants—We will include studies that enrol only females, without any age restriction. However, if possible, study participants will be distinguished by age group, sexual history and initial HPV status.

We will not include studies with male participants or special target groups such as immunocompromised patients.

Types of interventions

Intervention: Vaccination with prophylactic HPV vaccines containing virus like particles composed of the L1 capsid protein of HPV16 (monovalent vaccine), HPV16 and HPV18 (bivalent vaccine), or HPV6, HPV11, HPV16 and HPV18 (quadrivalent vaccine) (see Appendix 1). All vaccines are administered by intramuscular injection over a period of six months. The monovalent and quadrivalent vaccines are injected at zero, two and six months, whereas the bivalent vaccine is administered at zero, one and six months.

Comparison: Administration of placebo containing no active product or only the adjuvant of the HPV vaccine without L1 VLP, or another nonHPV vaccine.

In comparisons of bivalent and quadrivalent vaccines, participants who receive the bivalent vaccine will constitute the experimental group and participants who receive the quadrivalent vaccine will be considered as the comparison group.

Types of outcome measures

Primary outcomes

1. Histologically confirmed high-grade cervical intraepithelial neoplasia (CIN2, CIN3 and adenocarcinoma in situ).
2. Invasive cervical cancer.
3. Immunogenicty:
    - i. percentage of women vaccinated who have seroconverted after the third dose of vaccine;
    - ii. mean antibody level in International Units (IU) observed after completion of vaccine administration.
4. Safety:
    - i. immediate and short term adverse events (observed within four weeks after administration):
        - a. local adverse effects (redness, swelling, pain, itching at the injection place);
        - b. mild systemic effects;
        - c. severe systemic effects;
    - ii. serious adverse events observed after four weeks of administration of the vaccine during the trial;
    - iii. pregnancy outcomes observed during the trials, in particular occurrence of congenital anomalies.

Secondary outcomes

1. Incident infection with vaccine HPV types (HPV6, HPV11, HPV16 and HPV18, separately and jointly) and with hrHPV types other than HPV16/18.
2. Persistent infection with vaccine HPV types and hrHPV types other than HPV16/18.
3. Evolution over time of the geometric mean titres of antibodies against the vaccine HPV types.

Search methods for identification of studies

We will search for papers in all languages and undertake translations, if necessary.

Electronic searches—We will retrieve published studies from the Cochrane Gynaecological Cancer Review Group's Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, latest issue), MEDLINE and EMBASE. We have provided the search strategy for MEDLINE in Appendix 2; we will design a similarly structured search strategy to run in EMBASE and to search CENTRAL.

We will save the search string for MEDLINE in *My NCBI*, an electronic search tool developed by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine, which saves searches and automatically retrieves newer references not picked-up at previous searches. We will also set up an auto-alert in EMBASE.

We will use the 'related articles' feature in PubMed, departing from the original included studies; similarly, we will use Scopus to retrieve articles which cite the originally included studies.

We will search databases from 2002 (the year of publication of the results of the first phase II trial) until the present day.

Searching other resources

Websites of regulatory authorities responsible for approval of HPV vaccines for human use: We will consult the websites of the US Food & Drug Administration (FDA) and the European Medicine Agency (EMEA) to retrieve additional data not included in published scientific articles. In particular, we will verify the European Public Assessment Reports (EPAR) established by the Committee for Medicinal Products for Human Use (CHMP) of EMEA for the two HPV vaccines authorised in the European Union:

- http://www.emea.europa.eu/humandocs/Humans/EPAR/cervarix/cervarix.htm;
- http://www.emea.europa.eu/humandocs/Humans/EPAR/gardasil/gardasil.htm.,

We will retrieve data provided by the FDA via the following sites:

- for the quadrivalent vaccine: http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094042.htm;
- for the bivalent vaccine: http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm186957.htm.

Registries of randomised trials: We will search the following registries for ongoing trials: www.metaregister.com, www.controlled-trials.com/rct, www.clinicaltrials.gov and www.cancer.gov/clinicaltrials.

International public health organisations: We will contact international public health organisations that have investigated questions on HPV vaccine efficacy and safety or that have formulated recommendations on the use of HPV vaccines, to retrieve key documents. Concerned organisations include: the World Health Organization (WHO, Geneva), the US Centers for Disease Control and Prevention (CDC, Atlanta), the European Centre for Disease Prevention and Control (ECDC, Stockholm), and the International Agency for Research on Cancer (IARC, Lyon).

Handsearching: We will handsearch the citation lists of included studies.

In addition, we will search the abstracts of the latest conferences of relevant scientific societies related to vaccination, virology (in particular the Papillomavirus Society), paediatrics, and gynaecology for new or pending information not yet published in peer-reviewed journals.

Correspondance: We will contact the principal investigators of included studies and manufacturers of prophylactic HPV vaccines (MSD, USA) and GSK (Rixensart, Belgium) to obtain available data already published but not sufficiently detailed in published reports. We will develop data sheets to record commonly defined, and timed and efficacy outcomes stratified by age group, sexual history and initial HPV status. We will complete these sheets with data extracted from published reports and we will request any missing data from data owners.

In addition, we will request information on pending or planned relevant trials from principal investigators and researchers of the vaccine manufacturers.

Data collection and analysis

Selection of studies—We will download all titles and abstracts retrieved by electronic searching to a bibliographic database stored in Reference Manager. We will add any references we obtain by handsearching and remove duplicates.

Two review authors (MA and AB) will independently verify inclusion and exclusion of eligible studies and we will discuss any disagreements. In case of doubt, we will read the full report. If no consensus can be reached, we will consult with other review authors. We will document reasons for exclusion.

Data extraction and management—For included studies, we will extract the following study characteristics and outcome data.

- Study identification: first author, year of publication, journal, trial number.
- Geographical area where the study was conducted.
- Period when study was conducted.
- Inclusion and exclusion criteria.
- Characteristics of included participants (total number enrolled, number of drop-outs, age, continent, ethnic origin, comorbidity, contraceptive use, number of previous sexual partners, obstetric and gynaecological antecedents, smoking history).
- Initial HPV status (presence or absence of hrHPV DNA; presence or absence of DNA of the vaccine HPV types; serological status (presence of antibodies against vaccine HPV types) at enrolment). Differences in efficacy outcomes by initial HPV status will reflect protection in women or girls previously exposed, or not exposed to prior HPV infection.

- Study design:
    - phase of the randomised trial (II or II);
    - type of vaccine evaluated (monovalent, bivalent, or quadrivalent);
    - control group: type of placebo or other vaccine administered;
    - time points (mean duration of follow-up after first dose) at which outcomes were collected and reported;
    - study size at enrolment and at subsequent time points of follow-up;
    - loss to follow-up according to reason for drop-out and trial arm, number of doses received, other protocol violations used to assess HPV status (group tests, type-specific tests);
    - methods used to assess HPV serology;
    - scheduling of screen tests (HPV tests, cytology);
    - diagnostic algorithms used to confirm outcomes;
    - definition of study groups on which per-protocol and intention-to-treat analyses were applied;
    - risk of bias in study design (see below: Assessment of risk of bias in included studies).
- Outcomes, subdivided by the association with vaccine HPV types and all hrHPV types:
    - outcome definition (including diagnostic criteria and assays);
    - unit of measurement; for scales: upper and lower limits, with indication whether high or low score is good;
    - results: number of participants allocated to each intervention group; number of missing values and absolute values required to compute effect measures (see Types of outcome measures).
- Involvement of manufacturers.

We will extract data on outcomes as follows.

- For dichotomous outcomes, we will extract the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed at endpoint in order to estimate a risk ratio (RR) or risk difference (RD). Where possible, we will also extract the number of person-years at risk in order to compute incidence rates and incidence rate ratios or differences.
- For time to event data, the review authors will extract the log of the hazard ratio (log(HR) and its standard error (SE) from trial reports. If these are not reported, or computable from other reported statistics, we will use Adobe Photoshop (Adobe 2007) to prepare digital prints of the published Kaplan-Meier survival curves (or its complement, the cumulative incidence curve) and note the minimum and maximum

duration of follow-up in order to estimate the log (HR), using the methods proposed by Parmar 1998.

- For continuous outcomes, the review authors will extract the final value and standard deviation (SD) of the outcome of interest and the number of participants assessed in each treatment arm at the end of the considered follow-up, in order to estimate the mean difference (MD) between treatment arms and its SE, if trials measured outcomes on the same scale; otherwise we will compute standardised mean differences (SMD).

Two review authors (MA, AB) will independently extract data onto a data abstraction form specially designed for the review. We will resolve differences between review authors by discussion or by appeal to a third review author (PMH) if necessary.

Assessment of risk of bias in included studies—We will assess the risk of bias in included RCTs using The Cochrane Collaboration's tool and the criteria specified in chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). This will include assessment of:

- the method used for randomisation to generate the sequence of participants allocated to the treatment arms;
- allocation concealment;
- blinding (of participants, healthcare providers and outcome assessors);
- reporting of incomplete outcome data for each outcome;
- selective reporting of outcomes;
- other possible sources of bias.

Two review authors (MA, AB) will independently apply the risk of bias tool and we will resolve differences by discussion or by appeal to a third review author (PMH). We will present results in both a risk of bias graph and a risk of bias summary. We will interpret the results of meta-analyses in the light of the findings with respect to risk of bias.

Measures of treatment effect

- We will compute RRs from the proportions or rates among trial participants showing effects in the treatment arms for the dichotomous variables. For vaccine efficacy (VE), we will also express treatment effects as VE = (1-RR)*100, where a high level of protection will yield values approximating 100%.
- We will assess time to development of infections or lesions using HRs.
- We will assess the evolution of the serologic response to immunisation by MD or SMD in antibody level (preferentially expressed in IU) of type-specific antibodies at different time points, as well as the ratio of the mean antibody level of type specific antibodies in women who have been vaccinated versus women in the control group who are seropositive because of a natural infection. We will make a

distinction between overall antibody titres and virus-neutralising antibody titres, if possible.

Dealing with missing data—We will contact study authors or data owners to request data on the outcomes that were not reported.

We will not impute missing outcome data.

If data are reported for grouped end points, we will contact trial authors or data owners to request data on the separated outcomes. We will use a grid of commonly defined and timed outcomes for this purpose. In addition, we will solicit results stratified by initial HPV status, age and sexual history if these have not been reported.

Assessment of heterogeneity—We will assess heterogeneity between studies by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials which cannot be ascribed to sampling variation (Higgins 2003), by a formal statistical test of the significance of the heterogeneity (Deeks 2001) and, if possible, by subgroup analyses. If there is evidence of substantial heterogeneity, we will investigate and report the possible reasons.

We will avoid heterogeneity caused by combining data series from participants with different initial HPV status (presence of HPV DNA, anti-HPV antibodies). We will investigate age group and sexual history as potential sources that could explain possible heterogeneity.

Assessment of reporting biases—We will examine funnel plots corresponding to meta-analysis of the primary outcome to assess the relation between sample size and treatment effects. When there is evidence of small study effects, we will consider publication bias as only one of a number of possible explanations. If these plots suggest that treatment effects may not be sampled from a symmetric distribution, as assumed by the random-effects model, we will perform sensitivity analyses using fixed-effect models.

Data synthesis—If sufficient clinically similar studies are available, we will pool the results in meta-analyses.

- For dichotomous outcomes, we will pool RRs, VEs or RDs.
- For time-to-event data, we will pool HRs.
- For continuous outcomes, we will pool the MD or SMD between treatment arms.

We will apply random-effects models with inverse variance weighting for all meta-analyses of RRs, HRs and SMDs using the Review Manager (RevMan) 5 facility (DerSimonian 1986).

For cluster RCTs, if the analysis accounts for the cluster design then we will extract a direct estimate of the desired treatment effect e.g. RR plus 95% confidence interval (CI). If the analysis does not account for the cluster design, we will extract the number of clusters randomised to each intervention, the average cluster size in each intervention group and the

outcome data, ignoring the cluster design, for all women in each group. Next, using an external estimate of the intracluster coefficient (ICC), we will estimate a design effect. Hence, the variance of the effect estimate will be inflated. It will then be possible to enter the data into RevMan (Cochrane Editorial software package) and combine the cluster randomised trials with individually randomised trials in the same meta-analysis, using the generic inverse variance method of meta-analysis.

Subgroup analysis and investigation of heterogeneity—We will base particularly important subgroup analyses on separation of participants being initially hrHPV DNA negative, HPV16/18 DNA negative, or HPV16/18 DNA positive. If possible, we will further subdivide these subgroup analyses by initial serological status (presence of antiHPV16/18 antibodies). When published data are not clearly separated by initial HPV status, we will request them from the owners of the databases. Age group and previous sexual experience are particularly important stratifying covariates, which we will request from data owners if insufficiently reported and which we will use for meta-regression.

We will consider a particularly interesting subgroup analysis depending on available data, and we will base this on participants having received only two doses of vaccine. This subgroup analysis could be added to results from planned trials evaluating efficacy of reduced number of administrations (Eggertson 2007).

We will attempt to project reported study outcomes to the nearest multiple of 12 months to account for differences in the timing of reporting.

Type of vaccine and certain other study covariates (see Data extraction and management) may be considered as objects for subgroup meta-analysis or meta-regression (Sharp 1998; Thompson 1999).

Sensitivity analysis—We will perform sensitivity analyses excluding studies at moderate or high risk of bias (see: Assessment of risk of bias in included studies).

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Internal sources

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Appendix 1. Characteristics of currently licensed prophylactic HPV vaccines

	Monovalent vaccine	Bivalent vaccine	Quadrivalent vaccine
Manufacturer	Merck, Sharp & Dome (Merck & Co, Whitehouse Station, NJ, USA)	GlaxoSmithKline (GSK, Rixensart, Belgium)	Merck, Sharp & Dome (Merck & Co, Whitehouse Station, NJ, USA)
Antigens	HPV16 (40 μg)	L1VLPs of HPV16 (20μg) and HPV18 (20 μg)	L1 VLPs of HPV6 (20 μg), HPV11 (40 μg), HPV16 (40 μg) and HPV18 (20 mg)
Vaccination schedule	3 doses: at day 1, month 2 and month 6	3 doses: at day 1, month 1 and month 6	3 doses: at day 1, month 2 and month 6
Adjuvant	225 μg amorphous aluminium hydroxyl-phosphate sulphate	ASO4: 500 μg Aluminium hydroxide, 50 μg 3-deacylated monophosphoryl lipid A (MPL)	225 μg amorphous aluminium hydroxyl-phosphate sulphate
Trade name	Not commercialised	Cervarix	Gardasil, Silgard
Produced by recombinant technology using	Saccharomyces cerevisae (baker's yeast)	Baculovirus in Trichoplusia in insect cells	Saccharomyces cerevisae (baker's yeast)

Adapted from WHO 2009.

Appendix 2. MEDLINE Search strategy

The following search strategy will by used to retrieve references in MEDLINE (Ovid):

1. exp Papillomavirus Infections/
2. exp Papillomaviridae/
3. HPV*.mp.
4. human papillomavirus*.mp.
5. human papilloma virus*.mp.
6. or/1-5

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7. exp Papillomavirus Vaccines/
8. gardasil.mp.
9. cervarix.mp.
10. vaccin*.mp.
11. immuni*.mp.
12. or/7-11
13. 6 and 12
14. randomized controlled trial.pt.
15. controlled clinical trial.pt.
16. randomized.ab.
17. placebo.ab.
18. drug therapy.fs.
19. randomly.ab.
20. trial.ab.
21. groups.ab.
22. or/14-21
23. 13 and 22
24. (animals not (humans and animals)).sh.
25. 23 not 24
26. limit 25 to yr = “2002-2011”

key:

mp = title, original title, abstract, name of substance word, subject heading word, unique identifier

pt = publication type

ab = abstract

sh = subject heading

Appendix 3. List of abbreviations

AGC: atypical glandular cells

AGUS: atypical glandular cells of undetermined significance

AIS: adenocarcinoma in situ

ASC: atypical squamous cells (comprises ASC-US and ASC-H)

ASC-H: atypical squamous cells, HSIL cannot be ruled out

ASC-R: atypical squamous cells favouring a benign reactive process squamous cells of undetermined significance

ASC-US: atypical squamous cells of undetermined significance

ASCUS: atypical squamous cells of undetermined significance (comprises ASC-R, ASC-US and ASC-H)

CDC: Centre for Disease Control

CGIN: cervical glandular intraepithelial neoplasia

CHMP: Committee for Medicinal Products for Human Use

CI: (95 %) confidence interval

CIN: cervical Intra-epithelial neoplasia

CIS: carcinoma in situ

CISA: Clinical Immunization Safety Assessment

DNA: Desoxyribo-nucleic acid

EC: endocervical curettage

ECDC: European Centre for Disease Control

EMEA: European Medicines Agency

EPAR: European Public Assessment Reports

FDA: Food and Drugs Agency

GSK: GlaxoSmithKline

HC: hybrid capture

HPV: human papillomavirus

HR: hazard ratio

hrHPV: high-risk HPV type

HSIL: high-grade squamous intraepithelial lesion

IARC: International Agency for Research on Cancer

lrHPV: low-risk HPV type

LSIL: low-grade squamous intraepithelial lesion

MCO: managed care organizations

MSD: Merck-Sharp & Dome

NCBI: National Center for Biotechnology Information

ITT: intention-to-treat

PCR: polymerase chain reaction

PP: per-protocol

RCT: randomised controlled trial

RD: risk difference

RR: risk ratio

TBS: The Bethesda System

UK: United Kingdom

USA: United States of America

VAERS: Vaccine Adverse Event Reporting System

VE: vaccine efficacy

VLP: virus-like particles

VSD: Vaccine Safety Datalink

WHO: World Health Organization

HISTORY

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* *Indicates the major publication for the study*

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