Benefits and harms of the human papillomavirus vaccines: systematic review of industry and non-industry study reports

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Summary

We present the protocol for a systematic review evaluating the evidence of benefits and harms of the human papillomavirus (HPV) vaccines: Cervarix, Gardasil 4, Gardasil 9 and experimental HPV vaccines.

The review will facilitate open science by providing a publicly accessible synthesis with previously confidential industry submissions to regulators (i.e., clinical study reports) and (where possible) reports from non-industry HPV vaccines trials.

To minimise reporting bias, we will construct exhaustive study programmes (via registries, databases and correspondences with manufacturers, regulators, trial authors and funders) of the vaccines. We will include randomized phase II, III and IV industry clinical study reports and non-industry clinical trials of healthy participants of both sexes and of all ages.

The primary outcomes are all-cause mortality; mortality from and incidence of invasive cervical cancer; incidence of histologically confirmed cervical intraepithelial neoplasia (i.e., CIN2+: CIN2, CIN3 and adenocarcinoma in situ [AIS]); mortality from and incidence of other HPV related cancers; serious adverse events; and new onset diseases. The risk of bias for included studies will be assessed on an outcome level with the Cochrane risk of bias tool. The risk of bias results will be used to generate sensitivity and subgroup analyses (e.g., low vs. high or unclear risk of bias).

The review's results will be disseminated through publication in an open-access medical journal and the research data, including clinical study reports and other relevant regulatory documents, will be placed in an open repository.

Background

Human papillomaviruses (HPV) are the most common sexually transmissible infections in humans (1). Over 150 different strains of HPV exist. HPV infections are mainly transmitted sexually and are estimated to be associated with 5% of all cancers and responsible for more than 70% of cervical cancer cases worldwide (2,3).

Globally, cervical cancer is the second leading female-specific cancer after breast cancer. In Africa, cervical cancer is number one. Before the introduction of the HPV vaccines in 2006, especially high-income countries had invested in cervical cancer screening programmes that lowered cervical cancer rates. From the mid 1990s to the 2010s, the global annual death rate of cervical cancer declined by 200,000 deaths (from 470,000 to 270,000, 43%) (4,5). By 2014, the world's high-income countries accounted worldwide for 70% of women vaccinated against HPV strains and for 14% of annual cervical cancer cases (6).

Recently, other cancers in both males and females have been linked to HPV (7). In the United States, it is estimated that almost 50% of males have the HPV infection, causing 9000 annual HPV-related cancers (i.e., approximately 90% of anal, 70% of oropharyngeal, and 60% of penile cancers) (8).

The current consensus is that HPV vaccination protects against HPV infection, that the vaccines generally are safe and that they provide cost benefit gains (9–11). The World Health Organization (WHO) states that, "*Clinical trial results show that vaccines are safe and very effective in preventing infection with HPV 16 and 18*" (12).

As of June 30, 2015, the producers of Cervarix and Gardasil are estimated to have sold 57 million and 190 million doses, respectively (13) for approximately 25 billion USD in total (14). Recently, the United States recommended a two dose schedule of Gardasil 9 (instead of a three dose schedule) (15), and some suggested that even one dose might suffice (16).

Despite the vaccines' success, critics of the underlying trials imply that current vaccine policies may, to some extent, be based on assumptions or extrapolations of effectiveness and underestimation of harms (17,18).

In 2004, two years before the regulatory approval of the HPV vaccines, the WHO stated that, "…a study endpoint of [cervical] cancer can be ethically impracticable," given that it could take decades before HPV infection would cause cervical cancer. Hence, a surrogate outcome for cervical cancer (i.e., cervical intraepithelial neoplasia grade two or more, CIN2+: CIN2, CIN3 and adenocarcinoma in situ [AIS]) was accepted as the primary outcome (19). The European Medicines Agency (EMA) noted, however, "…that a vaccine to be licensed based on data using high-grade dysplasia [CIN2+] endpoint could only be promoted as a vaccine against dysplasia's [sic], not as a cancer vaccine" (19).

There is uncertainty about the transformation rate from CIN2+ to cervical cancer. Around 70% of CIN2+ cases are estimated to regress spontaneously (20,21), and CIN2+ development can be caused by non-vaccine HPV serotypes (22,23). Thus, the HPV vaccines' effect on mortality and incidence of cervical

cancer have been established and approved in an implicit manner. The public often confuse benefits on surrogate outcomes and relative risk improvements with benefits on mortality and absolute risk reductions (24).

Critics claim that Cervarix and Gardasil are unlikely to prevent cervical cancer and reduce cancer mortality in high-income countries because of their cervical screening programmes (25). In the United States, the annual cervical cancer incidence is 7 in 100,000 women (in comparison, the annual breast cancer incidence is 124 in 100,000) (26). Some estimate that 0.15% (i.e., 1 in 667) of individuals infected with high-risk HPV serotypes will develop cancer and that the vaccines merely provide an absolute cancer risk reduction of 0.1-0.7% (i.e., from 1 in 667 to 1 in 674-714) (17). However, no risk reduction estimate exists of HPV vaccination by itself, since cervical screening is recommended for all HPV vaccine recipients (27), although they seem less inclined to attend subsequent cervical screenings (28). This has likely been caused by powerful marketing campaigns presenting HPV vaccines as proven anti-cancer vaccines (29,30).

Regarding harms, the HPV vaccines seem to have a higher rate of serious adverse events reported compared to other vaccines (17). HPV vaccines are designed to maintain a high antibody level for a long time using immunogenic adjuvants, which possibly moves the vaccines out of the conventional vaccine paradigm (31,32).

The HPV vaccine adjuvants and other non-HPV vaccines (for example, the hepatitis A vaccine, Havrix) were often used as controls in pivotal randomized clinical trials (for example, the trials FUTURE I, II, III, and PATRICIA). This could have masked differences between the HPV vaccines and their control arms in relation to harms (18).

Recently, some nations have become concerned with the HPV vaccines' harms profile. For example, in Japan in 2013, the Ministry of Health, Labour and Welfare announced that the HPV vaccines would no longer be recommended for girls aged 12 to 16 due to concerns over harms (33). The Global Advisory Committee on Vaccine Safety subsequently complained to the Japanese ombudsman, but the ombudsman refuted the complaint stating, "…*there is no compelling reason for Japan to recommend vaccination*" (17).

Somewhat similar concerns have been raised in India (a pilot introduction project was stopped in 2010), Australia, UK, France (where the state Compensation Committee concluded that there was an association between Gardasil and autoimmunity), Ireland and Denmark (33–35).

Despite the uncertainty in the published evidence of the HPV vaccines' benefits and harms, no independent systematic review of the HPV vaccines exists.

Aims and objectives

We want to perform a systematic review evaluating the evidence of benefits and harms of the HPV vaccines using exhaustive study programmes, clinical study reports and unpublished data. The primary reasons why we want to use these sources are:

Firstly, manufacturers fund and perform most randomized clinical trials (and their follow-ups)—the most reliable form of evidence (24)—of vaccines and other drugs, but more than half of registered interventional trials (i.e., half of the study programmes) remain unpublished and the results that are readily available are often incomplete, subject to cherry-picking, and inconsistent (24,36–40). Less than a third of vaccine trials are published two years after completion (41).

Secondly, published manufacturer-sponsored studies tend to overestimate intervention effects and underestimate harms, which reduces the usefulness of traditional systematic reviews (42,43).

Thirdly, a systematic review's robustness relies upon the researchers' access to all clinical trial information (not just the published trials) and they ought to know the whole study programmes to minimise reporting bias (44).

Finally, when independent researchers have reviewed and reconstructed study programmes and included clinical study reports of interventions, this has often led to substantially different results than those the industry published, both for benefits and harms (14,38,39,44–50).

Given the scale and importance of the HPV vaccination programmes and the public resources spent on the vaccines, independent scrutiny of all available data is needed. Up until recently, this has not been possible except for published data, but changes in the EMA's policy on data access have enabled access to clinical study reports (46).

How we will conduct the review

We will base our review on a construction of the HPV vaccines' study programmes and include industry and non-industry study reports.

We will construct the study programmes via cross-referencing from public/industry registers, study databases, manufacturer submissions and correspondence with manufacturers, regulators and trial authors.

We are retrieving clinical study reports and other parts of manufacturers' submissions from the regulators and will also include post-trial observational studies, due to the latency of cervical cancer and some of the suspected harms (13,25). The main advantage of using clinical study reports (as opposed to published reports) is that they are at reduced risk of reporting bias. A clinical study of 1,000 pages may be condensed to a 10 page published report.

We will assess and extract data in duplicate (according to the extraction design of the 2014 Cochrane neuraminidase inhibitor review (49)) and perform meta-analyses where appropriate. We will assess the reliability of the studies with the Cochrane risk of bias tool (24).

The review's results will be disseminated through publication in an open-access medical journal. Deposition of research data, including clinical study reports and other relevant regulatory documents, will be available in an open repository so that anyone can assess or replicate our work.

Inclusion criteria

We will include industry clinical study reports of randomized clinical phase II/III/IV trials and their post-trial observational data, non-industry reports, and periodical safety update reports. We will include the most clinically relevant outcomes of the HPV vaccines using unmodified intention to treat analyses.

Type of participants

Males and females of any age.

Type of intervention

Human papillomavirus vaccines: Cervarix, Gardasil 4, Gardasil 9 and experimental HPV vaccines.

Types of comparator

- Placebo (saline carrier solution)
- Standard care
- Adjuvants
- Non-HPV vaccines

Primary outcomes

1) All-cause mortality.
2) Mortality from invasive cervical cancer irrespective of HPV-type.
3) Incidence of invasive cervical cancer irrespective of HPV-type.
4) Incidence of histologically confirmed cervical intraepithelial neoplasia (i.e., AIS, CIN3 and CIN2) irrespective of HPV-type.
5) Mortality from and incidence of other HPV related cancers (i.e., vaginal, vulvar, anal, oropharyngeal and penile cancer) irrespective of HPV-type.
6) Serious adverse events (i.e., events in total, events per type and organ system and event related attrition).
7) New onset diseases (i.e., chronic or auto-immune disease).

Secondary outcomes

1) Medically significant conditions (i.e., events prompting emergency room or physician visits not related to common diseases).
2) Solicited and unsolicited general symptoms (for example, fatigue or myalgia).
3) Referral for invasive procedures (i.e., colposcopy, loop electrosurgical excision procedure (LEEP) etc.)

Outcomes not considered due to low clinical relevance

- Cytological outcomes (i.e., low/high-grade squamous intraepithelial lesion, L/HSIL)
- Serological outcomes (i.e., geometric mean titres, GMT)
- Virological outcomes (i.e., antigen titres)
- Local adverse events (i.e., redness, swelling etc.)

Search strategy

Industry trials: We will search for trials according to the search design of the 2014 Cochrane neuraminidase inhibitor review because of its similar approach (45). We are currently retrieving clinical study reports and other parts of manufacturers' submissions from the regulators. An additional feature of the proposed design is the inclusion of post-trial observational studies (because of the latency of some proposed harms and cervical cancer). Currently, we hold 18 previously confidential industry clinical study reports consisting of approximately 25,000 pages. Additional clinical study reports are pending the EMA's assessment for commercially sensitive information prior to their release.

Non-industry trials: We will search for trials in registries and databases. We will request report summaries (i.e., detailed reports made by the trial authors for the trial funders) or the most detailed reports available from the trial authors.

Data lock: We will request and receive data until the 1st of July 2017, where we will lock our data and begin analyses.

Selection of studies

Two researchers will apply the inclusion criteria for the trials and post-trial observational studies with any disagreements to be resolved by discussion (with a third review author arbitrating if required).

Data extraction and management

We will construct study programmes and assess the completeness of identified trials. We will assess/extract data in double (according to the extraction design of the 2014 Cochrane neuraminidase inhibitor review (45)). We will perform a meta-analysis if the study reports are complete.

Assessment of the reliability of included studies

We will use the Cochrane risk of bias tool (24). The tool is based on seven bias domains: sequence generation and allocation concealment (both within the domain of selection bias or allocation bias), blinding of participants and personnel (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and an auxiliary domain: "other bias."

Data analysis

Measures of treatment effect

For binary outcomes, we will use risk ratios (RRs) as the measure of treatment effect. We will also use average control event rates and pooled RRs to calculate risk differences (RD) and its reciprocal, the number needed to vaccinate (NNV). For time to event outcomes, we will use hazard ratios to estimate relative risks to compare treatment groups.

Dealing with missing data

We have a comprehensive strategy for dealing with data that are missing at the trial level (i.e., we plan to obtain clinical study reports of unpublished trials), and at the outcome level (clinical study reports generally include comprehensive data on all planned outcomes). The purpose of this review is to provide as complete a picture as possible of a trial programme, without reliance on the published literature.

Assessment of heterogeneity

We will use Tau^2 (inverse variance method) and the I^2 statistic to estimate between-study variance as measures of the level of statistical heterogeneity and the Chi^2 test to test for heterogeneity.

Data synthesis
We will use the random-effects approach of DerSimonian and Laird where Tau^2 is estimated using the inverse variance method.

Subgroup analysis and investigation of heterogeneity
If there is evidence of heterogeneity and sufficient studies we will conduct meta-regression, and subgroup analyses to investigate potential sources of heterogeneity. Factors to potentially investigate include gender, age group, sexual history, health status (whether or not participants are immune-compromised), initial HPV status, and control treatment (saline placebo vs. adjuvant containing placebo).

Sensitivity analysis
We will use the alternative profile likelihood random-effects method of meta-analysis as a sensitivity analysis to supplement our primary analyses using the method of DerSimonian and Laird when there is heterogeneity and a small number of studies. We will also consider the alternative, a fixed-effect method, if we have sparse outcome data, a situation where random-effects methods are not recommended.

Scale and impact
Given its methodology and focus, our systematic review will be the first independent and thorough assessment based on the underlying clinical study reports and unpublished data from the HPV vaccine trials.

Our review will likely be of great interest to both the general public and health care providers given the scale and importance of the HPV vaccination programmes, public resources spent on the vaccines and the relevance of these studies in underpinning a public health intervention that is recommended to millions of healthy people. To address the public, we will work with the news and media to ensure an accurate dissemination of our results.

We anticipate that our research will help increase public trust in medical research. Such trust is at the heart of public health interventions, particularly for childhood vaccine recommendations, as the scientifically unfounded MMR vaccination scare story shows (52).

Finally, we welcome comments and suggestions on our protocol.

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