Cochrane review – Intervention Protocol CD009069

(http://summaries.cochrane.org/CD009069/GYNAECA_prophylactic-vaccination-against-human-papillomaviruses-to-prevent-cervical-cancer-and-its-precursors)

Suggested changes and clarifications

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> **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 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 The objective of this reviewis to summarise all available (published and unpublished) evidence by combining outcomes with similar definitions and times of measurement.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.

We agree to the points made above.

However, we think the paragraph warrants the following clarifications,

1. This Cochrane review is important in order to examine the validity and trustworthiness of the design of the clinical trials with regard to the choice of outcomes as well as the rigour with which these trials were conducted. Consequently, the reviewers will need to address certain problems and limitations in the design and conduct of the studies:
    - The documents we have obtained from the FDA indicate that there were changes in the protocol during the course of the trials and therefore during the approval process. These changes necessarily had a major impact on the quality of the reporting and redefinition of certain sub-groups in at least three instances[1].
    - The minutes from meetings of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) show that the decision to fast track the research led the American regulatory officials to choose outcomes that would allow them to evaluate **only** the specific effectiveness of the vaccination on lesions associated with HPV 16 and 18 and not its effectiveness on all HPV-associated lesions[2].
    - The criteria required to satisfy a fast track procedure were not fulfilled[3] but the fast tracking had an impact on the choice of outcomes[4].
    - The entries regarding the trials on clinictrials.gov indicate that their primary and secondary outcomes were not registered prospectively[5].

We believe that this Cochrane review should raise these issues with FDA officials[6] and scientific journals which have published results from the Phase III trials[7] because they have broken their own rules of proper scientific conduct.

2. This Cochrane review is important for thoroughly evaluating a potentially increased risk of the subsequent development of precancerous lesions in women who already have HPV infections targeted by the vaccination at the time they are vaccinated. This risk has not been sufficiently examined although existing evidence indicates the need for a thorough and careful examination of the possibility. This evidence includes:
    - Results submitted to VRBPAC in June, 2006[8]
    - The Australian study done by Brotherton et al[9].

   This Cochrane review is important to calculate and report the risk of subsequent development of precancerous lesions in women who already have HPV infections targeted by the vaccination at the time they are vaccinated, and the ways in which it must be communicated to vaccinated women and to vaccinated girls and their legal guardians.

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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.

These objectives seem entirely pertinent.
Nevertheless, it is essential that objectives specify explicitly that the effectiveness of vaccination will be evaluated with regard to all of the high-grade lesions; i.e., CIN2/3+, no matter the HPV types associated with them, and that the focus will be on young girls who were negative only for HPV-types targeted by the vaccines and not for 14 HPV types. This point is essential for methodological reasons, since analyzing the effectiveness of vaccination for young girls who were HPV-negative for 14 HPV types was post hoc and not in the protocols before the trials began. The value of these two analyses is therefore not equal.

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Types of studies

We will only consider randomised controlled trials (RCTs).

This point strikes us as essential. Moreover, it should be made clear that post hoc analyses of subgroups will be treated, if at all, separately.
Moreover, we believe that the Cochrane reviewers should clearly indicate how they will take into consideration unpublished results that the manufacturer possesses.

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Primary outcomes

1. Histologically confirmed high-grade cervical intraepithelial neoplasia (CIN2, CIN3 and adenocarcinoma in situ (AIS).
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.

We believe that primary outcome 1 must state explicitly that histological confirmation will focus specifically on "CIN2, CIN3 and AIS irrespective of HPV type".

We believe that primary outcome 4 (safety) must include:

- an analysis of the adequacy of the protocol planned for the studies on the safety and innocuousness of the vaccine as well as the effects of the placebo chosen to evaluate these aspects of the research
- a third point (iii) that encompasses an evaluation of the increase in the risk of CIN2/3 for women who were already infected by HPV types targeted by the vaccine

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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.

We believe that the secondary outcomes should include an HPV-specific analysis of the lesions found in the vaccinated population to clarify the possibility of viral replacement. It is essential to know whether during the Phase III trials, the efficacy of the vaccines against high-risk HPV 16 and 18 resulted in an increase in high-grade lesions associated with other high-risk HPV types.

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DECLARATIONS OF INTEREST

MA: has received travel grants fromMSD-Sanofi-Pasteur and GSK, (ceased in 2008). AB: no conflict of interest. PM-H: travel grants received fromGSKandMSD-Sanofi-Pasteur. LX: no conflict of interest. CS received travel grant from GSK. LM; no conflict of interest.

All of the research to date has been conducted by authors who have conflicts of interest with the vaccine manufacturer.

In December 2012, we alerted the Cochrane Gynecological and Orphan Cancer Group that the authors originally chosen for this Cochrane review also had conflicts of interest with the manufacturer. Some of these authors were dropped in December 2013. Nevertheless, the question remains, since certain authors did not step aside and state here that they have no conflicts of interest. We believe that the stated conflicts of interest in the protocol are incomplete for Marc Arbyn and Lauri E. Markowitz. As we previously pointed out in December 2012, these two authors have already made favorable pronouncements regarding the vaccine, which constitutes a clear bias.

> Marc Arbyn:
> "HPV vaccination will reduce the burden of cervical precancer and probably also of invasive cervical and other HPV-related disease in women."
> http://www.ncbi.nlm.nih.gov/pubmed/22623137
> Marc Arbyn (with Philippe Beutels):
> "Well-planned introduction of vaccination combined with an organized screening program and active surveillance are crucial for the program to achieve and monitor its desired aims. Such surveillance should include linkage between vaccination, screening and cancer registries." http://www.ncbi.nlm.nih.gov/pubmed/21051840

> Lauri E. Markowitz, Team Lead, Centers for Disease Control and Prevention (Atlanta, Georgia): "The CDC has approved these vaccines as safe and effective. Both vaccines were studied in thousands of people around the world, and these studies showed no serious safety concerns. Side effects reported in these studies were mild, including pain where the shot was given, fever, dizziness, and nausea. Vaccine safety continues to be monitored by CDC and the FDA. More than 46 million doses of HPV vaccine have been distributed in the United States as of June 2012." http://www.cdc.gov/std/hpv/stdfact-hpv-vaccine-young-women.htm.
> L. E. Markowitz also transmits his conclusions in the context of events like this (http://www.medscape.org/viewarticle/768633_sidebar2), sponsored by the manufacturer of the quadrivalent vaccine ("supported by an independent educational grant from Merck").

We believe that it is imperative for this information to appear in the declaration of interest for Marc Arbyn and Lauri Markowitz. We also think that this protocol must explicitly state what measures will be taken in order to limit, as much as possible, the influence of these conflicting ties on the analysis of the results.

[1] Statistical Data Analysis Plan (Protocol 015). V501 Reference P015V1. Appendix 3.11. Prepared by Lisa Lupinacci. 2003 July 21. P. 24.

Statistical Data Analysis Plan (Sudies 005, 007, 013, and 015). V501 Data Analysis Plan. Amendement 1. Prepared by Lisa Lupinacci.2005 Aug 04. P. 24

[2] Summary Minutes Vaccine and Related Biological Products Advisory Committee. Meeting #88 November 28-29, 2001.

[3] Tomljenovic L, Shaw CA, Too fast or not too fast: the FDA's approval of Merck's HPV vaccine Gardasil. J Law Med Ethics. 2012 Fall;40(3):673-81. doi: 10.1111/j.1748-720X.2012.00698.x.

[4] Vaccine and Related Biological Products Advisory Committee. Open Session (Minutes). 2001 Nov 29, pp 71-72, pp 119-127.

[5] Clincaltrials.gov Archive. History of NCT00365716. [homepage on the Internet]. No date [cited 2012 Feb 22]. Available from: http://clinicaltrials.gov/archive/NCT00365716. Clincaltrials.gov Archive. History of NCT00365378. [homepage on the Internet]. No date [cited 2012 Feb 22]. Available from: http://clinicaltrials.gov/archive/NCT00365378. Clincaltrials.gov Archive. History of NCT00092534. [homepage on the Internet]. No date [cited 2012 Feb 22]. Available from: http://clinicaltrials.gov/archive/NCT00092534. Clincaltrials.gov Archive. History of NCT00092521. [homepage on the Internet]. No date [cited 2012 Feb 22]. Available from: http://clinicaltrials.gov/archive/NCT00092521.

[6] FDA, HHS. 21 CFR § 314.126 Adequate and well-controlled studies**. Available from:** http://www.gpo.gov/fdsys/pkg/CFR-2010-title21-vol5/pdf/CFR-2010-title21-vol5-sec314-126.pdf.

[7] De Angelis C, Drazen JM, et al. Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors. N Engl J Med. 2004; 351:1250-1. Available from: http://www.nejm.org/doi/full/10.1056/NEJMe048225.

[8] VRBPAC. Background Document, Gardasil™ HPV Quadrivalent Vaccine May 18, 2006 VRBPAC Meeting. Table 19, 21, 25. Available from: http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4222B3.PDF

[9] Brotherton JM, Fridman M, May CL, Chappell G, Saville AM, Gertig DM. Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. Lancet. 2011 Jun 18;377(9783):2085-92.