HPV vaccine efficacy in preventing persistent cervical HPV infection: A systematic review and meta-analysis

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Abstract

Introduction: We performed a pooled analysis of randomised clinical trials (RCT) on HPV vaccine efficacy in preventing cervical persistent infection.

Methods: We carried out a bibliographic search on electronic databases and we selected RCT to perform the meta-analyses.

Results: We selected five studies. The first meta-analysis, including all studies, showed an important reduction of the risk of infection from HPV 16 in vaccinated cohort [RR 0.10 (95% CI: 0.07–0.15)]. The second and third meta-analyses, including only studies on bivalent and tetravalent vaccines, showed a RR of 0.13 (95% CI: 0.09–0.20) for HPV 16 infections and a RR of 0.22 (95% CI: 0.13–0.38) for HPV 18 ones.

Discussion: HPV vaccine efficacy in preventing persistent infection is high but there is the need for further studies on the duration of immunization and long-term vaccine efficacy.

Keywords: HPV vaccine; Efficacy; Meta-analysis

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1. Introduction

Human Papillomavirus (HPV) is an epitheliumtropic DNA virus belonging to the Papovaviridaevirus family and it is responsible for one of the commonest sexually transmitted...
infection. In the USA about 75% of individuals from 15 to 50 years of age are infected with genital HPV during their lifetime; 60% of them present with a transient infection, 10% with a persistent infection, 4% with mild cytological signs and 1% with clinical lesions [1]. In the USA 20 million people are actually affected by HPV and 6.2 million are newly infected each year [2].

The prevalence of infection differs greatly worldwide. Genital HPV infection affects 440 million people worldwide [1] with the highest prevalence proportion being observed in Sub-Saharan Africa [3]. In Italy the prevalence of HPV anogenital infections ranges from 8.8% [4] to 15.9% [5].

Among the over 100 HPV types infecting humans, the HPV type 16 is the most diffuse [3–5].

HPV is responsible of a wide spread infection with different modes of transmission. Anogenital infections, which are the commonest, are sexually transmitted but can also be carried by fomites or medical instruments [6] or digitally from one epithelium site to another [7]. The infection is transmitted precociously after the beginning of sexual intercourse and it is widely spread among women from 25 to 30 years of age. Some studies reported a second peak in the prevalence of infection among women over 55 years of age [8].

Well-known risk factors for anogenital HPV infection are multiple sexual partners, a new sexual partner, the partner’s previous sexual history and young age [2].

HPV could even cause oral and skin infections, transmitted by oral–genital intercourses [9] and contact or wounds with contaminated materials [10,11].

Actually, the natural history of HPV infections is not clearly understood. It appears that the majority of infections are transient and asymptomatic, but HPV could lead to benign proliferations (warts, epithelial cysts, hyperkeratosis, anogenital, oro-laryngeal and -pharyngeal papillomas, etc.) or to invasive malignancy.

Over the past 20 years, scientific evidence clearly supported the hypothesis that persistent infection with one of the 15 cancerogenic HPV types is the fundamental cause of cervical cancer [12]. HPV DNA is detected in approximately 99.7% of cervical cancers [13,14] being HPV 16 and HPV 18 associated with about 60% and 10% of them, respectively [15,16]. HPV infection is also associated with cancers of the anus, head and neck and it is related to recurrent respiratory papillomatosis in children [1]. HPV 6 and 11 are associated with squamous-cell carcinoma of the larynx and some tumours of the vulva, the penis and the anus, as well as with about 90% of genital warts [17].

About 500,000 cases of cervical cancer occur yearly and over 80% of these are in developing countries. Deaths related to cervical cancer are around 250,000 per year [1].

Prophylactic HPV vaccines, which are subunit vaccines, have been developed to reduce HPV-related cervical cancer burden. There are two different vaccines: the first one is a tetravalent vaccine composed by virus-like particles (VLPs) of HPV 16, HPV 18, HPV 6 and HPV 11; the second one is a bivalent vaccine composed by VLPs of HPV16 and HPV 18. Both vaccines are “prophylactic”, since they immunize the individual against the contraction of the HPV, but they do not eradicate a pre-existing infection. Both the bivalent and the tetravalent vaccines are in ongoing phase 3 clinical trials that investigate their long-term efficacy [18].

The aim of our study was to review the scientific literature regarding HPV vaccine efficacy in preventing cervical persistent infection and to perform a pooled analysis of studies whose results could be combined. The main reason to do that is to have an estimate of HPV vaccine efficacy across studies to be used in a preliminary health technology assessment of this vaccine.

2. Methods

2.1. Identification of relevant studies

The electronic medical databases used for the search were PubMed, Embase and Cochrane Library.

On Medline, we used the key words “Papillomavirus”, “Vaccine”, “Randomized”, “Randomised”, “Controlled” and “Trial” applying the following algorithm: (Papillomavirus OR HPV) AND Vaccine AND (randomized or controlled or randomised) AND trial.

On Embase we computed the search with the algorithm “((HPV or papillomavirus) and vaccine and trial and (randomized or randomised or controlled)).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name)”.

In the Cochrane Library we restricted our search to the Cochrane Central Register of Controlled Trials and we used the key words “HPV Vaccine” and “papillomavirus vaccine” linked by the Boolean operator OR.

The identification of relevant studies was carried out from 1990 until 15 July 2007 and it was not restricted to English language.

We only selected randomised clinical trials (RCT) on HPV vaccine efficacy in preventing cervical persistent infection. Therefore, we only chose studies carried out on women.

We excluded RCT that only evaluated vaccine immunogenicity, safety and tolerability. We further excluded RCT that tested HPV vaccine efficacy in preventing cervical carcinoma and virus infection/neoplasia of sites other than the cervix.

2.2. Quality assessment and data extraction

The studies were reviewed by two different researchers to assess their quality, according to the JADAD scale [19].

To perform the meta-analysis we extracted data related to persistent infections in vaccinated and control groups. Data extraction was performed independently by two different researchers and was restricted to per-protocol groups, constituted by women HPV DNA negative and seronegative at
the enrollment and who completed the third dose vaccination (for the vaccination treatment group). Extracted data regarded persistent infection, defined by the HPV DNA detection in two or more consecutive visits performed at a defined time apart. Whereas studies reported 6- and 12-month definition of persistent infection, we drew data on 6-month definition of persistent infection. Data extraction was carried out choosing the longest follow up time results; we retrieved also data on follow up times.

2.3. Statistical analysis

Meta-analyses were performed including studies with JADAD score ≥3. We carried out three different analyses: the first one, including all selected studies, evaluated vaccine efficacy in preventing HPV 16 cervical persistent infections; the second and the third ones included only studies on bivalent and tetravalent vaccines and investigated vaccine efficacy in preventing HPV 16 and HPV 18 cervical persistent infections, respectively.

In order to assess vaccine efficacy versus placebo we used the relative risk (RR) measure.

We computed the Chi-square test to evaluate studies heterogeneity, thus using the random effect model when the test highlighted differences between studies and the fixed effect model when no significant differences were shown. Funnel plots were used in order to control for the presence of publication bias.

Meta-analysis was performed using the software RevMan 4.2 for Windows.

We finally performed a meta-regression analysis to assess the influence of follow up time on vaccine efficacy estimate, using Stata 8.0.

3. Results

3.1. Identification of relevant studies

We found 79 articles in Medline, 126 articles on Embase and 30 articles in the Cochrane Library. Some of them were overlapping: PubMed and Cochrane articles were all overlapping but one which was reported in Embase database. Forty-two articles were overlapping between PubMed and Embase. Overall we retrieved 163 articles.

We excluded 63 studies as they were not randomised clinical trials but review, notes or comment about HPV vaccines and attendant clinical trials, 48 studies as they analysed different topics or concerns in relation to cervical carcinoma and HPV infection. Eighteen studies were eliminated since they regarded the therapeutical employ of HPV vaccines.

Of the remaining 34 studies we excluded those which investigated HPV vaccine efficacy in preventing cervical intraepithelial neoplasia and cancer, high-grade vulvae and vaginal lesions and anogenital diseases (7) and those regarding HPV vaccine immunogenicity only (18). In the case of studies that provided up-dated results from previous studies, we chose the most recent one. Those were the cases of Villa’s three articles [20–22] and Harper’s two ones [23,24]. Concerning the papers written by Koutsky et al. [25] and Mao et al. [26] we selected only the last one since they were carried out on the same population and Mao et al. presented up-dated results.

For our analysis we finally selected five studies [22,24,26–28].

3.2. Quality assessment and data extraction

Each study was a randomised clinical trial, double-blinded and placebo control.

The characteristics of each study are shown in Table 1. The five selected studies analysed different types of anti-HPV vaccines: one investigated the tetravalent vaccine, two the bivalent vaccine and two the monovalent anti-HPV 16 vaccine.

In each study genital HPV infection was assured by testing HPV DNA with polymerase chain reaction (PCR) but follow up time was different between studies (36 months in Brown’s work, 48 months in Mao’s, 5 years in Villa’s, 4.5 years in Harper’s and 18 months in Paavonen’s).

Table 1

<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment in study</th>
<th>Alternative treatment</th>
<th>Type of patients</th>
<th>Intervention group (N)</th>
<th>Control group (N)</th>
<th>HPV infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>[27]</td>
<td>HPV 16 L1 vaccine</td>
<td>Placebo or HPV 11 vaccine</td>
<td>Women 16–23</td>
<td>82</td>
<td>167</td>
<td>Vaccinated patients: 0/66. Control group: 15/129</td>
</tr>
</tbody>
</table>
Each study was judged of good or optimal quality, according to JADAD scale.

### 3.3. Statistical analysis

The first meta-analysis (Fig. 1) showed an important reduction of the HPV 16 persistent infection risk; the relative risk was 0.10 (95% CI: 0.07–0.15) with a 10-fold decrease in the risk of becoming persistent infected in the vaccinated group. The heterogeneity test did not highlight differences between the studies ($p = 0.12$).

The second meta-analysis [22,24,28] (Fig. 2) showed a pooled relative risk of 0.13 (95% CI: 0.09–0.20) with no heterogeneity between the studies ($p = 0.18$) thus indicating an about eightfold decrease of risk of persistent infection from HPV 16 for women vaccinated with bivalent and tetravalent vaccines. The third meta-analysis [22,24,28] (Fig. 3) showed a pooled relative risk of 0.22 (95% CI: 0.13–0.38) with no heterogeneity between studies ($p = 0.48$) being a 4.5-fold reduction of risk of persistent infection from HPV 18 in vaccinated women. The funnel plots related to the three meta-analyses are shown in Figs. 4–6.

Meta-regression was performed only in relation to the first meta-analysis since the few number of RCT included in the second and third meta-analyses. It showed a statistical significant inverse correlation between time of follow up and...
4. Discussion

Cervical cancer is the second most common cancer in women worldwide and the first in most developing countries, where 80% of all cases occur [1]. Screening with cervical cytology (the “Pap test”), as a principle cancer screening tool, helped to reduce the incidence and the mortality for cervical cancer. However, a prophylactic vaccine against the most common HPV types could substantially reduce the burden of HPV-related cervical diseases. The two different types of vaccine, developed up to now, have been shown to be safe and to induce high titers of neutralising antibodies that prevent HPV infection. Vaccine efficacy in preventing persistent HPV infection and HPV-associated diseases ranges from 90% to 100%, according to the scientific literature.

The tetravalent vaccine provided immunization for up to 5 years [22] and the bivalent one demonstrated proven immunization up to 4.5 years [24]. However, if vaccines require a booster dose is not actually known, even if it is believable that protective effectiveness is long lasting. On 8 June 2006, the U.S. Food and Drug Administration (FDA) approved the tetravalent vaccine for use in girls and women from 9 to 26 years of age and the Advisory Committee on Immunization Practices recommended routine vaccination of girls when they reached 11–12 years of age [29].

Since the FDA’s approval of the vaccine, an analysis of the health, social, economical and organizational impacts of the HPV vaccine’s introduction should be carried out.

On 20 September 2006, the European Commission approved to commercially produce the tetravalent vaccine [30]. In the session of 11 January 2007, the Higher Health Council in Italy established that the vaccine should be given to teenage women since sexual intercourse is unlikely before this age [31]. Vaccination could be given to 12-year-old females as their immune response is better at this age and teenagers are attending secondary compulsory schools. On 24 January 2007, the Italian Minister of Health announced the initiation of a national vaccination campaign, which will involve 12-year teenagers. Nevertheless the Higher Health Council has expressed the need to evaluate the opportunity to start the vaccination program in other cohorts such as those of women who are 25 years of age, as well as potentially other age groups. However, further studies on vaccine efficacy and health impact on these specific cohorts are necessary to reach these decisions.

In this setting, our work could give a support to evaluate HPV vaccine efficacy. We have to point out that we chose the persistent infection as outcome to evaluate vaccine efficacy, even if it is not the principal end-point for vaccine efficacy; indeed, it is adopted by the WHO to use CIN2/3 as surrogate endpoints for cervical cancer in RCTs assessing vaccine efficacy. This choice was due to two different arguments: first of all persistent infection represents the indispensable condition for cancer development; moreover, since clinical trials on vaccine efficacy in preventing CIN or cervical carcinoma have, by now, short follow up time, it is plausible that they currently do not fully estimate vaccine efficacy in preventing cancer. This is high-lightened by our meta-regression results too: the analysis showed an inverse relation between relative risk to become infected for vaccinated women decrease.

relative risk thus meaning that by increasing of follow up time the relative risk to became infected for vaccinated women decrease.
vaccine efficacy. Moreover, time elapsed from HPV cervical persistent infection and development of CIN is not yet well known and it is surely above 18 months since persistent infection could clear by 18–24 months. Therefore, we carried out this first evaluation looking forward results on long-term vaccine efficacy and the possibility to make a pooled analysis on vaccine efficacy in preventing cervical cancer. Our evaluation pointed out that tetravalent and bivalent vaccines pooled efficacy is 87% (95% CI: 80–91%) and 78% (95% CI: 62–87%) in preventing cervical persistent infections from HPV 16 and HPV 18, respectively. Finally, considering the intention-to-treat population analysis, similar results were obtained.

Our meta-analysis has some strength and limitations. First of all, we must emphasize that all studies included in the pooled analysis are clinical trials with common study outcomes. Selection bias and confounding were therefore minimised. Since the same technique of HPV DNA identification was used by the authors of the different trials, even the potential for misclassification bias was reduced.

Concerning the weaknesses, firstly one could argue that the systematic review has been conducted using five RCTs only, but a review is an ongoing process that can be updated in any moment a further RCT has come to an end. Anyway, considering the few studies occurred, the results are to be seen as preliminary.

On the other hand, selected studies investigated different treatments (HPV vaccines) and had different sample size and time of follow up. Moreover as we selected only five studies for our first meta-analysis and restricted to three of them the last ones, our estimate is far from being absolutely accurate. Publication bias is unbelievable as shown by the funnel plots.

Notwithstanding our systematic review and meta-analysis showed that even if there are a lot of studies on HPV vaccine efficacy, most of them have a short follow up phase and this was the reason why we decided to evaluate vaccine efficacy in preventing persistent infection and not CIN, AIS or invasive carcinoma.

A few number of clinical trial evaluate efficacy of vaccination in adolescent: Reisinger et al. [32] and Pedersen et al. [33] investigated vaccine immunogenicity in adolescent. Studies on health impact of male vaccination still miss. Finally, it must be considered that the selected studies represent sponsored trials by the two HPV vaccine manufacturers, but the funnel plots did not give evidence of any publication bias.

The short follow up period of the selected studies is also responsible for other potential weaknesses of the data. Among the others, one can point out the need of pharmacovigilance data, of research on vaccine protection against other oncogenic HPV types, and on persistence on neutralizing HPV antibodies against vaccine HPV types. Moreover, male studies are lacking, as well as research on catch-up vaccination of older women, some of whom may already have been exposed to one or more vaccine HPV types.

The lack of studies with a long follow up period makes it impossible to define the long-term vaccine efficacy and the extent of immunization status thus the need of screening persists.

Vaccination in fact does not eliminate the need to screen women, since 30% of cervical cancers are related to HPV types not covered by the vaccines and since the vaccine effect would be valuable in two to three decades. The American Cancer Society guidelines recommend that women should continue to be screened regardless of whether or not they have been vaccinated [34]. In fact, screening is necessary because most women will not be compulsory vaccinated, as it is not foreseeable the percentage of parents who will approve their daughters’ vaccination and since there is not enough scientific evidence in relation to the duration of immunization and long-term vaccine efficacy. Our work group has proposed a new approach to the assessment of all aspects concerning a new vaccine introduction, following the Health Technology Assessment (HTA) approach [35]. According to this we consider different concerns about a new vaccine such as epidemiology, burden of disease and population health needs of related infections/diseases, evaluation of alternative strategies for preventing infection/disease, economic evaluation of vaccine, organizational, legal and ethic involvements of vaccine introduction. Following this approach, a HTA on HPV vaccine could represent a new important tool to support the choice of decision makers in order to better inform the allocation of economic resources and maximize healthcare services [35].

References


