The Brazilian Journal of
INFECTIOUS DISEASES

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Review article

# Safety, tolerability and side effects of human papillomavirus vaccines: a systematic quantitative review

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ARTICLE INFO

*Article history:*
Received 25 October 2013
Accepted 28 February 2014
Available online 27 April 2014

*Keywords:*
HPV
Vaccines
Adverse effects

ABSTRACT

Recently, many studies have evaluated HPV vaccine safety and adverse effects. Two vaccines have been recently evaluated in randomized controlled trials: the bivalent vaccine for HPV 16 and 18 (Cervarix, GlaxoSmithKline Biologicals, Rixensart, Belgium) and the quadrivalent vaccine for HPV 6, 11, 16, and 18 (Gardasil, Merck and Co., Inc., Whitehouse Station, NJ). We have performed a systematic review of all randomized controlled trials in which HPV vaccines were compared with placebo regarding safety, tolerability and adverse effects. Studies were searched up to March 2013 in the databases: Pubmed, Embase, Scielo and Cancerlit. Odds Ratios (OR) of most incident adverse effects were obtained. Twelve reports, involving 29,540 subjects, were included. In the HPV 16/18 group, the most frequently reported events related to the vaccine were pain (OR 3.29; 95% CI: 3.00–3.60), swelling (OR 3.14; 95% CI: 2.79–3.53) and redness (OR 2.41; 95% CI: 2.17–2.68). For the HPV 6/11/16/18 group the events were pain (OR 2.88; 95% CI: 2.42–3.43) and swelling (OR 2.65; 95% CI: 2.0–3.44). Concerning the HPV 16/18 vaccine, pain was the most common outcome detected. These effects can be due to a possible VLP-related inflammation process. Fatigue was the most relevant general effect observed followed by fever, gastrointestinal symptoms, and headache. In the HPV 6/11/16/18 group, only general symptoms, pain and swelling were observed. Pain and swelling were the most frequent. Comparing HPV 16/18 to HPV 6/11/16/18 vaccines, the former presented more adverse effects, perhaps because there are many more trials evaluating the bivalent vaccine. Other studies are needed to clarify this issue.



## Introduction

Cervical cancer is the third most common cancer in women and the fourth most common cause of death worldwide.[1] Infection with certain types of human papillomavirus (HPV) is necessary to develop cervical cancer.[2–4] This has led to an increase in effectiveness of screening for cervical cancer using Pap smears and the development of primary prevention through the use of prophylactic vaccines against HPV.[5–11]

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http://dx.doi.org/10.1016/j.bjid.2014.02.005

The prophylactic vaccine stimulates the development of the humoral immune response, which occurs after contact with the "virus-like particles" (VLPs), which are non-infectious structures and simulate a natural HPV infection. The two oncogenic types included in both vaccines are HPV 16 and 18, responsible for at least 70% of the cases of cervical cancer worldwide. In the case of the quadrivalent vaccine, it also included two non-oncogenic types of HPV, 6 and 11, responsible for approximately 90% of cases of anogenital condylomata acuminata.[12]

Safety and tolerability of both vaccines have been evaluated extensively with similar profiles in the vaccinated and control groups, irrespective of age or ethnicity.[1] Studies about safety assessment indicated that local and systemic injection-related symptoms were generally mild. Serious adverse effects (AE) that are considered to be vaccine related are rare and similar to other vaccine types.[13,14]

Studies indicate that the most common AE is injection-related local reaction, such as pain, swelling and erythema with a rate of 95% of light to moderate intensity.[15,16] Regarding systemic symptoms, fever, nausea, vomiting, dizziness, myalgia and diarrhea were reported.[15,17,18] Severe AE, such as severe headache with hypertension, gastroenteritis and bronchospasm, were described in 0.5%.[15] There are more data available of AE associated with the quadrivalent vaccine than the bivalent vaccine; however, the major AE for the latter vaccine is also in the injection-related local pain (78%).[15]

Both HPV vaccines are classified as Pregnancy Category B by the FDA. Therefore, the vaccine is not recommended for pregnant women, because there are not enough data to ensure safety to the fetus.[19,20]

Studies have also demonstrated efficacy and safety of the vaccine in heterosexual and homosexual men.[21] This is important as HPV also causes disease in men.

The safety profiles of HPV vaccines have been confirmed by their huge use worldwide, and they has been included in immunization schedules of 28 countries. So far, there has not been any absolute contraindication for the use of these vaccines.[15] The vaccines are well tolerated and the number of systemic AE, serious AE, and discontinuations due to a serious event are similar between the two vaccines and control groups.[19]

The purpose of this study was to evaluate safety and AE of HPV vaccines.

## Materials and methods

This study adhered to PRISMA guidelines.[22] As a secondary study, no Institutional Review Board approval was required.

### *Inclusion criteria*

Studies meeting the following criteria were included: (1) double-blind randomized clinical trials evaluating safety and adverse effects of human papillomavirus (HPV) vaccines (against 16/18 and/or 6/11/16/18 serotypes); (2) studied subjects were older than nine years old; (3) exclusion of study participants with high risk of contracting, such as female sex workers and women who were sexual partners of HIV-infected men, and (4) exclusion of pregnant women.

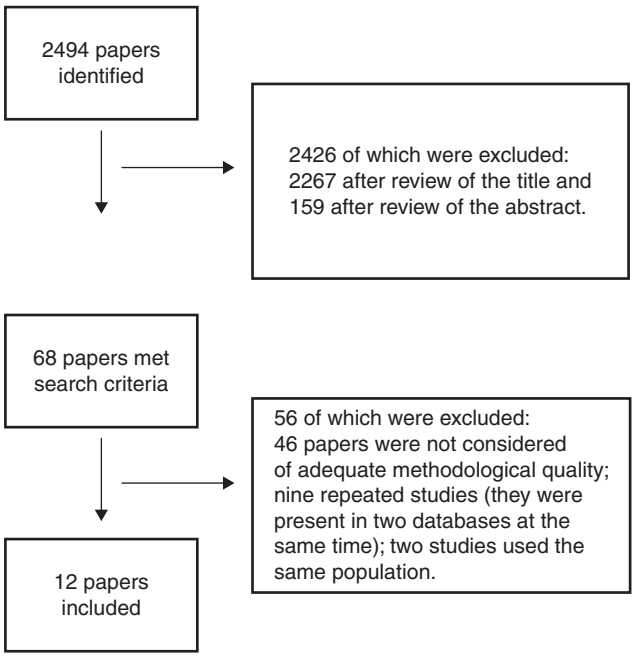


**Fig. 1 – Inclusion and exclusion of trials in study selection. RCTs, randomized controlled trials.**

### *Search and selection of literature*

The studies were identified by a wide literature search of databases (PubMed, Embase, Scielo and Cancerlit) following medical subject heading terms and/or text words: (vaccines OR vaccination) AND (randomized controlled trial) OR (controlled clinical trial) OR (randomized controlled trials) OR (random location) OR (double blind method) OR (single blind method) OR (clinical trial) AND (Human papillomavirus) OR (HPV) OR (papilloma virus) OR (papillomavir*). Reference lists of the identified publications for additional pertinent studies were reviewed. No language restrictions were imposed. Three researchers (AGM, HMR and RNC) searched for articles published up to March 2013.

Study identification and selection is illustrated in the flow diagram in Fig. 1. After searching the databases, 2494 potentially relevant papers were identified, of which 2426 were excluded: 2267 after reviewing the title, and 159 after reviewing the abstract. Reviews were done by AGM, HMR, and RNC; disagreements were solved by a fourth reviewer (AKG). Thus, 68 papers met the criteria and were reviewed in full. There were no articles in languages other than English, which, based on the abstract review, met the inclusion criteria. After full review, 46 papers were not considered to have adequate methodological quality according to the Jadad Scale.[23] Finally, nine repeated studies were found (they were present in two databases at the same time), and two studies that used the same group, showing the same results (in this case, only the first publication was included). Finally, 12 papers were approved for data extraction (Fig. 1).