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REVIEW ARTICLE

Safety of human papillomavirus 6, 11, 16 and 18 (recombinant): systematic review and meta-analysis

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KEYWORDS
Papillomavirus vaccines;
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Abstract
Objective: To identify and quantify the adverse effects associated with the recombinant human papillomavirus (types 6, 11, 16 and 18) vaccine in adolescents.
Data source: Systematic review of randomized clinical trials from PubMed, SciELO and Lilacs databases. Articles investigating the safety of the vaccine in subjects under 18 years and comparing the recombinant human papillomavirus types 6, 11, 16 and 18 vaccine with a control group were included. Meta-analyses were performed for the outcomes of pain, erythema, swelling and fever, using clinical trials with maximum Jadad score.
Data synthesis: Fourteen studies were included. The most common adverse effects related to the human papillomavirus vaccine were effects with no severity (pain, erythema, edema, and fever). Five studies were used for the meta-analyses: pain–risk difference (RD)=11% (p<0.001); edema–RD=8% (p<0.001); erythema–RD=5% (p<0.001); fever–RD=2% (p<0.003).
Conclusions: The recombinant human papillomavirus types 6, 11, 16 and 18 vaccine was safe and well tolerated. The main adverse effects related to vaccination were pain, erythema, edema and fever. The low frequency of severe adverse effects encourages the administration of the vaccine in the population at risk.

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PALAVRAS-CHAVE
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Efeitos adversos;
Adolescente;
Metanálise;
Segurança

Segurança da vacina papillomavirus humano 6, 11, 16 e 18 (recombinante): revisão sistemática e metanálise

Resumo

Objetivo: Identificar e quantificar os efeitos adversos associados à vacina papillomavirus humano 6, 11, 16 e 18 (recombinante) em adolescentes.

Fontes de dados: Revisão sistemática de ensaios clínicos randomizados nas bases de dados do PubMed, SciELO e Lilacs. Foram incluídos artigos que abordavam a segurança da vacina em menores de 18 anos e que comparavam a vacina papillomavirus humano 6, 11, 16 e 18 (recombinante) com grupo controle. Foram feitas metanálises para os desfechos de dor, eritema, edema e febre com o uso de ensaios clínicos com escore de Jadad máximo.

Síntese dos dados: Foram incluídos 14 estudos. Os efeitos adversos mais comuns relacionados à vacina foram intercorrências sem gravidade (dor, eritema, edema e febre). Cinco estudos foram usados para as metanálises, incluindo os desfechos: Dor – Diferença de Risco (DR)=11% (p<0,001); Edema – DR=8% (p<0,001); Eritema – DR=5% (p<0,001); Febre – DR=2% (p<0,003).

Conclusões: A vacina papillomavirus humano 6, 11, 16 e 18 (recombinante) mostrou-se segura e bem tolerada. Os principais efeitos adversos relacionados à vacinação foram dor, eritema, edema e febre. A baixa frequência de efeitos adversos graves encoraja a aplicação da vacina na população de risco.

Introduction

Cervical cancer is the second most common type of cancer that affects women worldwide, with an incidence of approximately 500,000 cases and 270,000 deaths each year.[1,2] The disease is often detected at advanced stages due to the lower efficiency of screening strategies in the initial stage and treatment options that are not always effective.[3–6] At least 80% of deaths from cervical cancer occur in developing countries, most of them in the poorest regions of the world, such as Southern Asia, Sub-Saharan Africa and parts of Latin America. In those areas, which receive only 5% of the resources for cancer in the world, cervical involvement is responsible for 15% of all cancer deaths.[7]

Infection by human papillomavirus (HPV) is a common occurrence, and the probability of acquiring it throughout an individual's lifetime is higher than 50%.[8] Approximately 35–40 types of HPV can infect the genital epithelium. The infection may be transient and not clinically detectable, but can also cause genital warts and a variety of pre-malignant and malignant anogenital lesions in both genders.[9–14] Studies show that the peak incidence of HPV infection occurs 5–10 years after the first sexual intercourse (between 15 and 25 years old),[15–19] and infection persistence by an oncogenic HPV type is crucial in the pathogenesis of cervical cancer.[2,20–22] Thus, it becomes possible to prevent the disease onset through vaccination before the start of sexual activity.[19,23–26]

The currently available vaccines against HPV differ in the number of genotypes, in the way they are manufactured and the adjuvant they contain. Both vaccines currently available for use, bivalent and quadrivalent, are highly immunogenic and prevent the primary infection against HPV genotypes and CIN 2/3 adenocarcinoma (CIN – cervical intraepithelial neoplasia, which refers to squamous epithelial lesions in the lower genital tract, which are precursors of invasive cancer, presenting as tissue impairment, from cytoplasmic alterations to severe dysplasia). Studies indicate a very similar safety profile for severe and mild adverse effects for each one of the vaccines.[27,28]

The introduction of new vaccines requires safety studies. Concerns about the adverse effects is considered a barrier to vaccination and one of the reasons for low adherence to the recommendations for human papillomavirus quadrivalent (types 6, 11, 16, 18) recombinant vaccine administration.[29,30] The opinion of health professionals regarding its safety is yet to be unanimous. Several debates have been carried out with persistent controversies about the advantages and disadvantages of its use. Therefore, the knowledge of the possible local and systemic adverse effects can subsidize adherence strategies and guide health care actions for the population at risk.

Therefore, the objective of this study is to identify and quantify the adverse effects associated with the administration of the human papillomavirus quadrivalent (types 6, 11, 16, 18) recombinant vaccine, as a tool to determine the safety of its use in adolescents.

Method

A search for publications was carried out in April 2014, in the National Center for Biotechnology Information Advances Science and Health – US National Library of Medicine – National Institutes of Health – PubMed electronic databases, with no restrictions regarding date and language of publication. Additionally, a search was performed in the LILACS and SciELO databases using the descriptor ''Papillomavirus Vaccines'', followed by a manual search for randomized controlled trials (RCTs). In