REVIEW 10.1111/j.1469-0691.2012.03946.x

Prophylactic human papillomavirus vaccination and primary prevention of cervical cancer: issues and challenges

M. Poljak

Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

Abstract

Two prophylactic human papillomavirus (HPV) vaccines have been recently approved: one quadrivalent and the other a bivalent vaccine. When administered in a three-dose course to HPV-naive individuals, both vaccines exhibited excellent safety profiles and were highly efficacious against targeted clinical endpoints in large-scale international phase III clinical trials. Where coverage has been high for the appropriate target population, a reduction of HPV-related diseases with the shortest incubation periods has already been seen. By March 2012, universal HPV vaccination had been introduced into national vaccination programmes in more than 40 countries, but only in a few low-income and middle-income countries. With the growing market for HPV vaccines and competition between manufacturers, negotiated prices are already beginning to decline although they still remain out of reach of many countries. The great majority of countries are struggling to reach a level of coverage that will have the most impact on cervical cancer rates. Increasing coverage and improving completion of the HPV vaccine schedule, particularly of sexually naive females, is now the most important public-health issue in HPV vaccine efforts. A clear strategy for integrating primary (HPV vaccination) and secondary (screening) cervical cancer prevention must be agreed as soon as possible. Several second-generation prophylactic vaccines are being developed with the aim of resolving some of the limitations of the two current HPV prophylactic vaccines.

Keywords: Cervical cancer, human papillomaviruses, vaccination
Original Submission: 25 March 2012; **Accepted:** 9 May 2012
Editor: M. Paul
Clin Microbiol Infect 2012; **18** (Suppl. 5): 64–69

Corresponding author: M. Poljak, Institute of Microbiology and Immunology, Medical Faculty, Zaloška 4, 1105 Ljubljana, Slovenia
E-mail: mario.poljak@mf.uni-lj.si

Human papillomaviruses

Human papillomaviruses (HPV) are aetiologically linked to various benign and malignant neoplastic lesions of mucosal and skin epithelia. At present, 148 distinct HPV types are officially recognized, ranging from HPV-1 to HPV-152 (HPV-46, HPV-55, HPV-64 and HPV-79, which have not met the criteria as unique HPVs, are now classified as subtypes) [1]. All known HPV types are classified on the basis of the similarity of their genome into five genera (α, β, γ, μ, ν) and 33 species. Approximately 40 HPV types from the α genus infect the mucosal epithelium, with a subset of 12 types that are associated with lesions that can progress to cancer [2]. These cancer-associated or high-risk HPVs are the aetiological agents of virtually all cervical carcinomas and their immediate precursors—high-grade cervical intraepithelial neoplasias. The two most important high-risk types are HPV-16 and HPV-18, which are found in 70% of cases of cervical cancer. In addition to cervical carcinoma, high-risk HPVs also play the leading aetiological role in the development of anal and vaginal cancers and a substantial proportion of penile, vulvar and oropharyngeal (tonsillar) cancers. Low-risk HPV genotypes (the most important are HPV-6 and HPV-11) are causally involved in the development of virtually all genital warts and laryngeal squamous cell papillomas of both genders.

The burden of HPV-associated vaccine-preventable tumours

Cervical cancer is the third most common cancer in women, causing an estimated 530 232 cases and 275 008 deaths in 2008 [3]. Cytological screening has dramatically reduced the burden of cervical cancer in countries that have implemented wide-scale screening programmes. The major burden of cervical cancer (over 85%) today therefore occurs in developing countries with little or no access to screening programmes [4]. Although other HPV-associated cancers are significantly rarer than cervical cancer, a recent analysis of US cancer

registry data estimated that the total HPV-related cancer burden for non-cervical cancers in the USA is of the same magnitude as their cervical cancer burden [5]. A recent study showed a remarkable increase in the population-level incidence of HPV-positive oropharyngeal cancers from 1988 to 2004 in the USA and predicted that by 2020, the annual number of HPV-positive oropharyngeal cancers will surpass that of cervical cancers [6]. Genital warts are common and frequently self-limiting benign tumours but they pose a considerable burden because of the embarrassment, shame, pain and financial costs of treatment [4]. Laryngeal squamous cell papillomas are a rare disease (incidence 1–4 per 100 000) associated with high morbidity and with potentially devastating consequences for the patient.

Current HPV prophylactic vaccines

Two prophylactic HPV vaccines have so far been approved by the European Medicines Agency and the US Food and Drug Administration: a quadrivalent vaccine targeting HPV-6, HPV-11, HPV-16 and HPV-18 (Gardasil or Silgard; Merck and Co., Whitehouse Station, NJ, USA) and a bivalent vaccine targeting HPV-16 and HPV-18 (Cervarix; GlaxoSmithKline, London, UK). Current European Medicines Agency and US Food and Drug Administration indications for both vaccines are presented in Table 1. Both vaccines contain L1 virus-like particles of the respective HPV types, which contain no HPV DNA and are neither infectious nor oncogenic. The quadrivalent vaccine uses an aluminium salts adjuvant and the bivalent vaccine uses an AS04 adjuvant system. When administered in a three-dose course to HPV-naive individuals, both vaccines exhibited excellent safety profiles and were highly efficacious against targeted clinical endpoints in large-scale international phase III clinical trials [7–14]. In addition, the first evidence of the impact of HPV vaccination in the general population recently came from Australia, one of the first countries to introduce free universal HPV vaccination, with a three-dose coverage of 70% in women aged 12–26 years [15]. Studies from Australian sexual health clinics have shown a remarkable decline in the incidence of genital warts [16,17] and from the Victorian Cervical Cytology Registry a modest but significant decline in histologically confirmed high-grade cervical lesions since the implementation of HPV vaccination with the quadrivalent HPV vaccine in 2007 [18]. There was also a 39% decline in the incidence of genital warts among heterosexual men of the same age (non-vaccinated population), but not among older women or men who have sex with men, which provides the first evidence of a possible herd immunity effect of HPV vaccine [16].

Several in-depth reviews of the safety and efficacy of current prophylactic HPV vaccines are available in the literature [11,19–23]. The purpose of this review is to provide a brief summary of the most important current issues and challenges.

Current status of HPV vaccine implementation

Since 2006, the quadrivalent and bivalent vaccines have each been licensed in more than 110 countries. Over 120 million doses of the vaccines have already been distributed. By March 2012, universal HPV vaccination had been introduced into national vaccination programmes in more than 40 countries across all continents. The USA, Australia and Canada were among the first countries to introduce HPV vaccine into their national immunization programmes, followed by several European countries (currently 23 European countries).

TABLE 1. US Food and Drug Administration (FDA) and European Medicines Agency (EMA) indications for quadrivalent vaccine (Gardasil) and a bivalent vaccine (Cervarix), as of March 2012

	FDA	EMA
Gardasil®	Gardasil is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of the following diseases caused by human papillomavirus (HPV) types included in the vaccine: cervical, vulvar, vaginal and anal cancer caused by HPV types 16 and 18 and genital warts (condyloma acuminata) caused by HPV types 6 and 11 and the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16 and 18: cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma *in situ* (AIS), cervical intraepithelial neoplasia (CIN) grade 1, vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3, vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3 and anal intraepithelial neoplasia (AIN) grades 1, 2 and 3 Gardasil is indicated in boys and men 9 through 26 years of age for the prevention of the following diseases caused by HPV types included in the vaccine: anal cancer caused by HPV types 16 and 18 and genital warts (condyloma acuminata) caused by HPV types 6 and 11 and the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16 and 18: anal intraepithelial neoplasia (AIN) grades 1, 2 and 3	Gardasil is a vaccine for use from the age of 9 years for the prevention of: premalignant genital lesions (cervical, vulvar and vaginal) and cervical cancer causally related to certain oncogenic human papillomavirus (HPV) types and genital warts (condyloma acuminata) causally related to specific HPV types
Cervarix®	Cervarix is a vaccine indicated for the prevention of the following diseases caused by oncogenic human papillomavirus (HPV) types 16 and 18: cervical cancer, cervical intraepithelial neoplasia (CIN) grade 2 or worse and adenocarcinoma *in situ*, and cervical intraepithelial neoplasia (CIN) grade 1. Cervarix is approved for use in females 9 through 25 years of age	Cervarix is a vaccine for use from the age of 9 years for the prevention of premalignant cervical lesions and cervical cancer causally related to certain oncogenic human papillomavirus (HPV) types