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# The role of human papillomavirus vaccines in cervical cancer: Prevention and treatment

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ABSTRACT

Human papillomavirus (HPV) is the most common sexually transmitted disease, worldwide. Primary prevention thorough vaccination si able to reduce the burden of HPV-related lesions. Ten years ago the Food and drug Administration (FDA) approved the first vaccine against HPV. In the last decades, growing data on safety and effectiveness have been collected. In the present review we report the current knowledge on vaccine against HPV, highlighting the current value and prospective regarding the widespread diffusion of HPV vaccines. The role of emerging therapeutic vaccines is reviewed.

## 1. Introduction

Human papillomavirus (HPV) is the most common sexually transmitted disease, worldwide (Harper and DeMars, 2017). It is estimated that over 14,000,000 individuals are infected by HPV annually and the lifetime risk to be infected from HPV is higher than 80% (Harper and DeMars, 2017). HPV is a DNA virus from the papillomavirus family, of which over 100 types are known. HPV is a small double-stranded circular DNA virus with a genome of approximately 8000 base pairs. HPV infection is limited to the basal cells of stratified epithelium, the only tissue in which HPV replicates (Schiller et al., 2010). HPV lesions are thought to arise from the proliferation of infected cells.

In the majority of cases, HPV infections do not cause symptoms and resolve spontaneously; while in some individuals a persistent HPV infection might cause warts, precancerous and cancerous lesions (Bogani et al., 2017a). Precancerous and cancerous lesions included disease of the male and female genital districts and of head and neck area (Harper and DeMars, 2017). Approximately, 27,000 cases of HPV-related cancers occur each year, in the United States. According to the World Health Organization (WHO) report, it is estimated that 84% of all HPV-related cancer lesions are represented by cervical cancer (World Health Organization, 2017). More than 500,00 new cases of cervical cancer are diagnosed, every year and cervical cancer still represents a major health issue (Siegel and Naishadham, 2013). In fact, in spite of the large implementation of massive screening programs in occidental countries, cervical cancer is the third most common cancer diagnosed in women aged less than 40 years, and the second most common cause of cancer-related death among females aged between 20 and 39 years (Siegel and Naishadham, 2013).

Screening is effective in detecting precancerous and cancer lesions of the uterine cervix thus allowing reducing the incidence of cervical cancer and cancer-related death (Harper and DeMars, 2017). Recently, Castle et al., reviewed clinical histories to assign “causes” of cervical cancer A, suggesting that the currently state-of-the-art intensive screening program results in very few cervical cancers being effective in reducing incidence of cervical cancer (Castle et al., 2017).

Primary prevention through vaccination has the ambitious objective to reduce much more the incidence HPV-related disease (Harper and DeMars, 2017). In the present paper, we aimed to review current evidence on the implementation of HPV vaccinations evaluating the currently available HPV vaccines. Then, we examine the safety as well as the direct and indirect effectiveness of prophylactic HPV vaccines. Moreover, we sought to explore the landscape of therapeutic vaccines.

## 2. HPV vaccines

HPV vaccines stimulate the body to produce antibodies that, in future encounters with HPV, bind to the virus and prevent it from infecting cells. The HPV vaccines are based on hollow virus-like particles (VLPs) assembled from recombinant HPV coat proteins. VLPs are not infectious, since they lack the virus’s DNA.

The vaccine was first developed by the University of Queensland in Australia. In 2006, the Food and Drug Administration (FDA) licensed the first prophylactic vaccine against HPV (Gardasil ®). Actually, three

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HPV vaccines are available: Cervarix ®, Gardasil ® and Gardasil 9 ®

Gardasil® (manufacturer: Merck & CO., Inc.) is a HPV quadrivalent (Types 6, 11, 16, 18) vaccine, recombinant. Indications included the prevention of precancerous and cancerous conditions of the lower genital tract (vulva, vagina and uterine cervix), anal area and of the head and neck, caused by HPV6, 11, 16 and 18, in females and males aged 9–25 years. Additionally, it protect against genital warts (condyloma acuminata) caused by HPV types 6 and 11 (FDA, 2017). Cervarix ® (manufacturer: GlaxoSmithKline Biologicals) is a HPV bivalent (types 16 and 18) vaccine, recombinant. Cervarix® is licensed in the early 2007. It is approved for the prevention of cervical cancer, cervical intraepithelial neoplasia (CIN) and adenocarcinoma in situ (AIS), caused by HPV16 and 18, in females aged 9–25 years (Castle et al., 2017).

In 2014, the FDA approved the nonavalent vaccines against HPV (Gardasil 9; manufacturer: Merck & CO., Inc.). The nonavalent vaccine is indicated in women and men aged 9 through 26 years for the prevention of the following diseases: precancerous and cancerous condition of the uterine cervix, vulva, vagina, and anal canal caused by HPV types 16, 18, 31, 33, 45, 52, and 58 (FDA, 2017). Additionally, it protect against genital warts caused by HPV types 6 and 11 (FDA, 2017). Recently, Joura et al., investigated the efficacy and immunogenicity of the nonavalent vaccine in women 16–26 years of age (Joura et al., 2015). They performed a randomized, international, double-blind, phase 2b-3 study comparing Gardasil ® and Gardasil 9 ® in over 14,000 women (Joura et al., 2015). The authors observed that Gardasil 9® generated an antibody response to HPV-6, 11, 16, and 18 that was noninferior to that generated by Gardasil®. Moreover, the nonvalent vaccine prevented infection and disease related to HPV-31, 33, 45, 52, and 58 (Joura et al., 2015).

## 3. Adjuvant composition of HPV vaccines

An adjuvant is a substance that is added to a vaccine to create a stronger immune response to the vaccine (CDC, 2017a). Actually, two adjuvants are associated with the currently available vaccines against HPV. The amorphous aluminium hydroxyphosphate sulfate (AAHS) in the quadrivalent and nonavalent vaccines (Gardasil® and Gardasil 9®) and Adjuvant System 04 (AS04) in the bivalent vaccine (Cervarix®). AS04 combines the TLR4 agonist MPL (3-*O*-desacyl-4′-monophosphoryl lipid A) with an aluminium salt.

Aluminum salts have been used safely in vaccines for more than 80 years. Aluminum salts were initially used in the 1930s, 1940s, and 1950s with diphtheria and tetanus vaccines after it was found that this addition strengthened the immune response to the vaccines. AS04 includes MPL. In particular, lipid A, is the primarily responsible for the endotoxicity of lipopolysaccharides, which constitute the major components on the cell surface of Gram-negative bacteri. Lipid A binds to Toll-like receptor 4 (TLR4) to activate a cascade of immunological responses, including the production of a number of cytokines and chemokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, and interferon-β (IFN-β). Lipid A might induce an antigen-specific primary immune response by provoking the migration and maturation of dendritic cells that are the physiological adjuvant of the immune system (Venezia et al., 2017). MPL guarantees a long term efficacy of the bivalent vaccine (Harper and DeMars, 2017).

## 4. Safety of vaccines against HPV

To date, over 200,000,000 doses of vaccines against HPV were administered, worldwide. Growing evidence support the safety of various HPV vaccines (Bogani et al., 2017b; European Medicines Agency, 2017; CDC, 2017b; Arbyn et al., 2016).

The Centre of Disease Control and Prevention (CDC) and the Advisory Committee on Immunization Practices (ACIP) supported the safety of vaccines against HPV (CDC, 2017b). The use of HPV vaccines is commonly related to local injection-site adverse events (including pain, swelling and erythema) (CDC, 2017b). Other adverse events might include: fever, headache or asthenia, nausea and muscle or joint pain. Injection-site pain was reported in about 84% of women having quadrivalent vaccination vs. 75% of women having inoculation of AAHS and vs. 49% of women having inoculation of saline solution (CDC, 2017b) Similarly, patients having bivalent vaccination experienced pain in 92% of cases vs. 87% among the SA04 control group (CDC, 2017b).

However, the proportion of patients experiencing severe adverse events and the incidence of potential new autoimmune disorders were similar comparing women having HPV vaccination with controls. Across, various studies evaluating the safety of quadrivalent vaccination (including more than 23,000 individuals), 21 (0.1%) and 19 (0.1%) death occurred in the vaccine and placebo group, respectively. No case of vaccine related death occurred (CDC, 2017b).

CDC monitors the safety of HPV vaccines after they are licensed. The Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD) and the Clinical Immunization Safety Assessment (CISA) Project provide an ongoing monitoring (CDC, 2017b).

In 2011, the Institute of Medicine (IOM) reviewed data from published and unpublished investigations of various vaccines (including vaccines against HPV) concluding that: (i) syncope or fainting might be cause by vaccine administration; (ii) some individuals are allergic to vaccines and vaccine's adjuvant. Although it is very rare, anaphylaxis might occur among people with severe allergies: they should not receive the vaccine. In 2014, the CDC published a report evaluating adverse events reported to VAERS in individuals undergoing quadrivalent vaccination against HPV, observing that more than 90% of the events were classified as non-serious (CDC, 2017b).

More recently, the European Medicines Agency (EMA) completed its review on the linkage between HPV vaccines administration in young women and the occurrence of two conditions (i.e., complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS)) (European Medicines Agency, 2017). The EMA supported that there is not a linkage between HPV vaccination and an increased risk of developing CRPS or POTS (European Medicines Agency, 2017).

## 5. Effectiveness of vaccines against HPV

The introduction of HPV vaccines has shown important results in term of HPV reduction rates in countries when vaccine coverage is high (Harper and DeMars, 2017). Real world data from Australia, suggested that the implementation of a HPV vaccination program reduces HPV-related disease dramatically (Garland et al., 2011). In Australia the government funded an intensive program of vaccination, starting in 2007 with the introduction of a school-based program with three doses of the quadrivalent vaccine, targeting female at age 12–13 years, with a catch-up for those aged 12–26 years until December 2009. Acceptance of the vaccine is high with coverage of 3 doses of the HPV quadrivalent vaccine in the school age cohort (about 70%), and just over 30% in the older age cohort. A reduction in new cases of genital warts of more than 70% among vaccine eligible age females has been evidenced. But more interestingly, is the reduction of 44% in term of genital warts in males (not a part of the vaccination program) that was observed during the study period, suggesting significant herd immunity.

Growing evidence support that the introduction of HPV vaccines reduces HPV prevalence and HPV related disease, including genital warts, cervical dysplasia and cervical cancer (Garland et al., 2016a,b; Bosch et al., 2016). Bruni et al., estimated cervical cancer projections based on the diffusion immunization programs worldwide (Bruni et al., 2016). The authors estimated that about 118 million women had been targeted by vaccine against HPV, worldwide. The implementation of HPV vaccination program will be result in a dramatically decrease of cervical cancer rate. However, owing to the low coverage (1%) in low incoming countries, in which the incidence of cervical cancer is high,