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Review

HPV Vaccines: Effectiveness and Adverse Effects

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Abstract

Preventive vaccination against human papillomavirus is the new practice in the treatment of cervical cancer. The successful vaccination programs include the use of three vaccines, capable of causing neutralization of antibodies from the virus particles, together with their envelope: the bivalent, quadrivalent and ninevalent HPV vaccines. Following administration of the vaccines, the immune system is being stimulated, producing antibodies to the HPV particles that protect against infection and disease. The safety profile of licensed HPV vaccines based on clinical and post-marketing data is reassuring.

Keywords: Vaccination, Human Papillomavirus, safety, recommendations.

INTRODUCTION

The Human Papillomavirus (HPV) and HPV infection should by no means be considered as a problem of the last few decades. HPV is detected tens of thousands of years in the past, following the human and other mammalian species throughout their evolutionary course. Although HPV has been known since antiquity, its infectious nature was not established, until the beginning of the last century. In 1907, with the detection of transmission of the papillomas from human to human, the Italian physician Giuseppe Giuffo documented the viral etiology of the genital warts and laid the foundations for further scientific research, concerning the correlation between HPV and human carcinogenesis (Giuffo, 1907; Javier and Butel, 2008).

HPV infection is the most common sexually transmitted disease nowadays and the main cause of the development of cervical cancer (Herrero et al, 2005). Global research studies have indicated that the greatest incidence of the disease occurs in the female population, mainly among women of reproductive age, five to ten years after commencing their sexual activity (Muñoz et al, 2009). Cervical cancer is the third most common type of malignancies among women in the developed countries. It is estimated that approximately 530000 new cases are diagnosed each year and 275000 deaths are recorded, with most of them occurring in developed countries (Forman et al, 2012; Bosch et al, 2013). The prevalence of HPV subtypes varies among different geographical areas of a country, as well as among different ones (Moore and Tajima, 2004; Yabroff et al, 2005, Tornesello et al., 2007).

The evidence of a causal relationship between HPV and cervical cancer has led the scientific community to develop HPV prophylactic vaccines. Certainly, in the course of the investigations, although many problems and controversies have arisen with regard to the disposal of vaccines (manufacturing costs, cross-prophylaxis, cost-effectiveness), it is commonly accepted that with the vaccination against HPV one major health issue is now close to its effective treatment (Brookes, 2016). Vaccination changes the course of the disease at a very early stage, resulting in an impact not only on the progression of cancer, but also on the precancerous stages of the disease (Goldie et al, 2004; Taira et al., 2004).

The introduction of vaccination against human papillomavirus is one of the most important developments of modern gynecology. The HPV vaccine has been approved for use in more than 100 countries worldwide (WHO, 2014; WHO, 2014). In Europe, according to a

Table 1. Basic characteristics of the HPV prophylactic vaccines.

Characteristics	Quadrivalent HPV vaccine	Bivalent HPV vaccine	Ninevalent HPV vaccine
Manufacturing Company	Merk and Co	GlaxoSmithKline	Merk and Co
Trademark	Gardasil	Cervarix	Gardasil 9
VLPs and genotypes	6, 11, 16, 18	16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58
Substrate	Yeasts	Baculovirus	Yeasts
Volume	0.5 ml per dose	0.5 ml per dose	0.5 ml per dose
Synthesis (Antigens)	L1 HPV 6 20 μg L1 HPV 11 40 μg L1 HPV 16 40 μg L1 HPV 18 20 μg	L1 HPV 16 20 μg L1 HPV 18 20 μg	L1 HPV 6 30 μg L1 HPV 11 40 μg L1 HPV 16 60 μg L1 HPV 18 40 μg L1 HPV 31 20 μg L1 HPV 33 20 μg L1 HPV 45 20 μg L1 HPV 52 20 μg L1 HPV 58 20 μg
Adjuvant	Aluminum hydroxyphosphate sulphate (225 μg)	AS04 500 μg, Al(OH)3 50 μg	Aluminum hydroxyphosphate sulphate
Administrtation	0 – 2 – 6 months intramascular	0 – 1 – 6 months intramascular	0 – 2 – 6 months intramascular

survey by the European Center for Disease Control and Prevention, most European Union Members have adopted the vaccination against HPV (ECDC, 2014). Organized HPV vaccination programs targeting in high vaccination coverage, are estimated to be able to lead to a reduction in precancerous intraepithelial cervical lesions of up to 90% and invasive cervical cancer to a rate that appears to exceed 70% (Bonanni et al., 2011).

HPV Vaccines

The detection and typing of HPV using specific molecular methods, led to the development of HPV prophylactic vaccines as the latest scientific achievement in the history of cervical cancer prevention. Three prophylactic vaccines are now available, that are capable of neutralizing antibodies from the virus particles, together with their envelope: the bivalent, quadrivalent and ninevalent HPV vaccines.

The quadrivalent vaccine (Gardasil®)

The quadrivalent vaccine against HPV types 6, 11, 16 and 18 was the first vaccine that have been administered for cervical cancer prophylaxis. Gardasil® was manufactured in the United States of America by Merk and Co., was approved by the FDA in June 2006 and released by Sanofi Pasteur MSD in September of the same year in several European countries. In Greece, it was available in January of 2007. The mechanisms with which vaccines protect against HPV infection have not been fully elucidated. Most researchers nowadays estimate that both humoral and cellular immunity appear to be involved. However, what is certain and undeniable is that the use of L1 capsular protein causes the production of antibodies that effectively protect against HPV infection (Christensen et al, 1996; Day et al., 2007).

Gardasil® contains Virus Like Particles (VLPs) from four different types of HPV (HPV 6, 11, 16 and 18) and is produced by gene technology using yeast (Table 1). VLPs particles contain the L1 protein but are lucking viral DNA, so they are not infectious and, as they do not contain the E6 and E7 genes, they are unable to cause malformations, cervical – vulvar – vaginal malignancies, as well as genital warts. The L1 particle bears the same surface structure, shape and size as the infectious natural virus and contains its major neutralizing epitopes. After administation, the immune system is highly stimulated, producing antibodies against the HPV virus particles, protecting against infection and disease (Stanley et al, 2012).

The bivalent vaccine (Cervarix®)

The bivalent vaccine against HPV types 16 and 18 was released a year later. In 2007, Cervarix® was manufactured in the United States of America by GlaxoSmithKline, approved by the FDA and since December of the same year it has been released in Greece, among other European countries. Like Gardasil®, Cervarix® is an enhanced, non-virulent recombinant vaccine, prepared from highly purified HPV 16 and 18 particles, that can not infect, replicate, or cause disease (Table 1). The vaccine protects against cervical cancer and other forms of malignancies of the

Table 2. The estimated contribution of the quadrivalent and ninevalent HPV vaccines, in the reduction of the incidence of both cervical intraepithelial neoplasias and carcinogenesis of the female genital tract

DISEASE	HPV 6, 11, 16, 18	HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58
Cervical Cancer	70%	90%
Vulvar Cancer	75%	90%
Vaginal Cancer	65%	85%
Anal Cancer	85%	90% – 95%
LGSIL	50%	80%
HGSIL	25%	50%
Warts	90%	90%

rectum and genitalia (Stanley et al, 2012). The high titers of antibodies currently achieved with both vaccines, can provide prolonged protection even after the possible attenuation of the original antibody titer (Stanley et al, 2012).

The ninevalent vaccine (Gardasil 9®)

The ninevalent vaccine against the HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 was first introduced in America in 2014. In June 2015 the European Commission granted a marketing authorization for the vaccine to the European Union, while from March 2017 is also available in Greece. Similar to the foregoing vaccines, the ninevalent one contains non-contagious virulent particles (Table 2), consisting only of L1 protein without viral DNA and provides protection from precancerous lesions, genital warts, as well as from cervical, vulvar, vaginal and anal cancer. The Committee of Medical Products for Human Use considered that Gardasil 9® provides a wider range of protection against cervical cancer than precursor vaccines, as it can prevent the infection from five additional types of HPV virus (31, 33, 45, 52 and 58). These types, although less common than the oncogenic types 16 and 18, are considered to be of similar risk.

Regardless the selected vaccine, HPV vaccination is best to be done before the onset of sexual intercourse, particularly in ages 11 to 12, not only because the body has not yet been exposed to the virus, but because the response of the organism to the generation of antibodies against the HPV is much greater in younger ages (Markowitz et al 2007; Saslow et al., 2007).

Most researchers nowadays estimate that the early diagnosis of HPV infection in combination with the active immunization offered by the modern HPV vaccines in non exposed individuals, are the cornerstones of the contemporary primary and secondary cervical cancer prevention, promising a lot of auspices prospects for combating and possibly eradicating the disease in the future (Koshiol et al, 2008).

Effectiveness of HPV Vaccines

The efficacy of the HPV prophylactic vaccines was tested in randomized, double-blind and controlled phase III clinical trials. The post-vaccination immune response, evaluated by the measurement of antibodies in the peripheral blood, was judged to be satisfactory in all clinical trials. The methods used for the measurements were not the same for both vaccines (bivalent and quadrivalent) and therefore can not be comparable. However, irrespective of the type of the vaccine administered (Gardasil® or Cervarix®), the level of the antibodies among women aged up to 26 years who received the three – dose scheme, was significantly higher compared to antibodies observed after natural infection (Castellsagué et al, 2002; Harper et al., 2006; Villa et al., 2006).

Published studies have indicated a very strong immune response after the completion of vaccination, especially when it concerns young people before the beginning of their sexual life. Taking into account the studies published so far, it is estimated that the protection against an HPV infection, persists for up to 5 years after vaccination with the quadrivalent vaccine and for 6.4 years after the administration of the bivalent one. With regard to the current scientific data, it is estimated that long-term predictions for both the quadrivalent and the bivalent vaccines, indicate that the immune response of the individual will remain at satisfactory levels several years after the last dose, without the need for an additional one (Villa, 2007; Barr and Sings, 2008).

Furthermore, the studies revealed that both vaccines demonstrate cross-protection against HPV types that are not included in the vaccine. More specifically, they have been displayed partial protection against HPV types similar to the HPV 16 (39, 45, 59, 68) and HPV 31, while there have been studies from Finland providing significant indications of cross-protection by types , such as HPV 35, among young people (Kemp et al, 2011, Malagón et al, 2012, Hawkes et al., 2013).

Efficacy – clinical trials of Gardasil®

The efficacy in preventing neoplasia, achieved by the quadrivalent HPV vaccine, was evaluated in Phase III clinical trials with FUTURE studies (Females United to Unilaterally Reduce Endo / Ectocervical Disease). Analysis of the results of the FUTURE I study indicated that the quadrivalent HPV vaccine was 100% effective in preventing CIN II - III lesions, genital warts and rectal-intraepithelial lesions (Garland et al, 2007). Furthermore the FUTURE II study concluded that the quadrivalent vaccine proved to be 100% effective in the prevention of CIN II intraepithelial lesions and in situ adenocarcinoma, 97% effective in preventing CIN III uterine cervical lesions, 94% in preventing intraepithelial lesions of the vagina or vulva and 98.9% effective in the prevention of genital warts (FUTURE II Study Group, 2007).

According the analysis of the FUTURE studies, it was apparent that women who had not been infected by the HPV before the commencement of the study, the vaccine was effective in preventing the 95% - 96% of intraepithelial cervical lesions and the 99% of genital warts. In women who had been in contact with the virus in the past, the efficacy of the vaccine in preventing precancerous cervical lesions and genital warts was 73% and 80.3% respectively. The efficacy of the quadrivalent HPV vaccine in the reduction of persistent HPV infection, intraepithelial cervical lesions and genital warts, among women aged 25 to 45 years as assessed in the FUTURE III study, was 91% (Luna et al., 2007). In addition, other studies concerning the efficacy of the Gardasil® vaccine, indicated high and long lasting protection against genital warts (83%) and the ones associated with HPV types 6 and 11 (100%)(Muñoz et al, 2010).

Efficacy - Clinical trials of Cervarix®

The efficacy in preventing neoplasia achieved by the bivalent HPV vaccine, was evaluated in Phase III clinical trials with the ”PATRICIA” (PApilloma TRIal against Cancer in Young Adults) study and “The Costa Rika HPV Vaccine Trial”. The PATRICIA study, in which women aged 15 to 25 years, from 14 different countries around the world, who did not have more than six sexual partners until the start of the research process, were involved, was the largest trial investigating the efficacy of the bivalent HPV vaccine. The analysis of the final results of the study concluded in a high protection rate of about 93.2%, against high-grade intraepithelial cervical lesions, independent of the HPV type (Lehtinen et al, 2012).

Other research studies indicated that the effectiveness of the bivalent HPV vaccine, was 91.6% in transient infections and 100% in persistent ones, caused by HPV subtypes 16 and 18. The same authors, analyzing the results of their later study, revealed that the protection rate of the bivalent vaccine was about 96.9% in transient infections and 100% in 12-month persistent ones. During a 4.5 year follow-up, the vaccine was 100% effective in preventing intraepithelial cervical lesions associated with specific HPV subtypes 16 and 18 (Harper et al, 2004; Harper et al., 2006).

Recently, a research study of 8.4 years of follow-up concluded that the efficacy of the bivalent HPV vaccine was high enough in transient infections (95.1%). In addition, according to the results of the same study, the bivalent vaccine proved to be 100% effective against CIN II / III (Roteli - Martins et al, 2012), persisting for a tome span of six to twelve months. More recently, De Vincenzo and colleagues in the PATRICIA study demonstrated that the effectiveness of the bivalent HPV prophylactic vaccine was 100% against HPV subtypes 16 and 18 (De Vincenzo et al, 2014).

Efficacy – clinical trials of Gardasil 9®

The increased scientific interest and the systematic research in order to decrease the incidence of all types of squamous cell epithelium malignancies, up to 90% worldwide, led to the development of the ninevalent HPV prophylactic vaccine, by adding another five strains of HPV to the already existing quadrivalent one (Serrano et al , 2012; Dochez et al., 2014). The new Gardasil 9® is far more effective against HPV infection than the two existing vaccines. The new vaccine protects against nine types of the virus, seven of which are estimated to be responsible for the majority of cervical cancers and by extend, for most of the malignancies found in the genital area (Garland et al, 2009; de Sanjose et al, 2010, Guan et al, 2012, de Sanjos et al, 2013, Alemany et al, 2014, Alemany et al, 2015, Joura et al., 2014).

Many studies have commenced since 2014 in order to assess the efficacy of the ninevalent vaccine, while comparing it to the quadrivalent one (Van Damme et al, 2015; Vesikari et al., 2015; Castellsagué et al., 2015; Van Damme et al., 2016; Iversen et al., 2016). The study that investigated the efficacy of the 9-valent vaccine, was conducted in Austria by the Medical School of the University of Vienna. Following the assessment of the efficacy of the above mentioned HPV vaccine in approximately 14,000 women aged 16 to 26, Joura et al. concluded that among women who were not infected by an HPV strain, Gardasil 9® was up to 97% effective in preventing intra epithelial neoplasias and cancer from HPV types 31, 33, 45, 52 and 58, remaining though as effective as the older Gardasil® against HPV 6, 11, 16 and 18 subtypes. Moreover, the vaccine was effective in preventing cervical, vaginal and vulvar disease associated with HPV types 31, 33, 45, 52 and 58, reducing the abnormalities found in cervical cytological examinations and the need for cervical surgery (Joura et al, 2014).

Table 3. Adverse effects of the modern HPV vaccines.

Side Effect	9vHPV Vaccine	4vHPV Vaccine
Pain	89.9%	83.5%
Swelling	40%	28.8%
Redness	34%	25.6%
Itching	5.5%	4%
Headache	14.6%	13.7%
Fever	5%	4.3%
Nausea	4.4%	3.7%
Dizziness	3%	2.8%
Fatigue	2.3%	2.1%

Precautions for HPV Vaccines

The safety of HPV vaccines is a serious Public Health issue. Thus, since the release of HPV prophylactic vaccines has been approved, it has been considered necessary to record any side effects and adverse drug reactions, that they would be subsequently evaluated by a specific scientific team. Even in those cases where some side effects do not appear to be vaccine-related, but coincide with HPV vaccination, it is desirable to be reported, in order to be early identified and recorded. The World Health Advisory Committee for Vaccine Safety of the World Health Organization (WHO Global Advisory Committee for Vaccine Safety – GACVS) has ruled on the full safety of HPV prophylactic vaccines since March 2014 (WHO, 2014).

Comparative safety studies of the HPV vaccines versus placebo, demonstrated no significant differences. However, the vaccinated individuals exhibited a greater degree of skin reactions at the injection site, than the placebo recipients (Harper et al, 2004). Mild pain, redness or swelling and itching at the point of vaccination, are the most common side effects that a modern gynecologist or pediatrician has to combat with, in the daily clinical practice. Regarding the systemic complications, the most common occurrences are decadent feverish movement or fever, headache and nausea. Serious side effects such as bronchospasm, gastroenteritis, hypertension with headache, severe pain and the difficulty in joint movement nearby the injection site, are uncommon and are similar to placebo (Saslow et al, 2007; Reisinger et al, 2007; Petäjä et al, 2009; Tsakiroglou et al., 2011).

Serious cases, such as the appearance of Guilain - Barre syndrome that have been described in the literature, can not be attributed to HPV vaccination with certainty, as HPV vaccines have been administered parallel with other vaccination regimens (Villa et al, 2005). The number of deaths did not differ between the group of vaccinated women and the control group and none of the deaths were associated with the vaccines (Block et al, 2006; Garland et al., 2007, Paavonen et al, 2007). Although HPV vaccine trials precluded pregnant women, no difference was observed with respect to congenital abnormalities in women who accidentally became pregnant during the clinical trials (Block et al, 2006).

Finally, the new Gardasil 9® vaccine does not appear to have more side effects than the quadrivalent one (Table 3). With the exception of swelling and erythema at the injection site, usually occurring within five days after Gardasil 9 administration, no other local or systemic side effects were reported (Joura et al, 2014).

CONCLUSIONS

The vaccination against HPV is a common practice and directive nowadays. Vaccines stimulate human immunity and protect against infection and disease. Three prophylactic vaccines are now available, that are capable of neutralizing antibodies from the virus particles, together with their envelope: the bivalent, quadrivalent and the ninevalent HPV vaccines. The bivalent vaccine protects against infection by HPV types 16 and 18, whereas the quadrivalent one against the HPV types 6, 11, 16 and 18 and it was the first vaccine to be administered for cervical cancer prophylaxis. In recent years, the ninevalent vaccine against HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 subtypes, has been developed. The latter provides a wider range of protection against cervical cancer, in comparison to the precursor vaccines.

In studies evaluating the effectiveness of the vaccines, significant conclusions were drawn regarding the provided protection by their administration. The FUTURE I and II studies evaluating the quadrivalent vaccine, indicated that it was 97% to 100% effective in the prevention of CIN III and CIN II intraepithelial cervical lesions respectively, 100% effective in the prevention of warts associated with the included in the vaccine HPV types and 100% effective in the prevention of anal intraepithelial lesions (Garland et al, 2007). Furthermore, the possibility of developing adenocarcinoma in situ has dramatically decreased after the administration of its vaccine. In particular, the FUTURE II study indicated 94% efficacy in the prevention of vaginal and vulvar

intraepithelial lesions and 98.9% in the prevention of genital warts (FUTURE II Study Group, 2007).

The bivalent HPV vaccine proved a high efficacy against transient HPV infections (95.1%) and 100% effectiveness against persistent infections (with a duration more than six months), due to the subtypes 16 and 18 (Roteli-Martins et al, 2012; De Vincenzo et al., 2014).

The newly developed vaccine protects against nine types of the virus, seven of which are estimated to be responsible for the majority of cervical and genital cancers and is more effective than its precursors (Garland et al, 2009; de Sanjose et al, 2010, Guan et al, 2012, de Sanjos et al, 2013, Alemany et al, 2014, Alemany et al, 2015, Joura et al., 2014). Following the administration of the ninevalent vaccine to non-HPV infected women, the efficacy in preventing cancer due to the HPV 31, 33, 45, 52 and 58 subtypes was about 97%, remaining as effective as the older Gardasil® against an infection with the 6, 11, 16 and 18 strains of the virus. Moreover, the vaccine was effective in preventing cervical, vaginal and vulvar disease, decreasing the occurrence of an abnormal cervical cytological examination and the need for cervical surgical procedures in women who had been administered (Joura et al, 2014).

The safety and the recording of possible side effects, displayed an important role in the use of vaccines. The most common of those recorded, were mild pain, redness or swelling at the site of vaccination, as well as itching. Regarding the systemic complications, the most common occurrences are decadent feverish movement or fever, headache and nausea. Serious side effects such as bronchospasm, gastroenteritis, hypertension with headache, severe pain, and difficulty in the movement of joints near the injection site, are uncommon and were similar to placebo (Saslow et al, 2007; Reisinger et al, 2007; Petäjä et al, 2009; Tsakiroglou et al., 2011). Serious life-threatening complications have not been recorded in any of the three types of the vaccines (Block et al, 2006, Garland et al, 2007, Paavonen et al, 2007).

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