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Review article

HPV Vaccination: Prevention of Cervical Cancer in Serbia and in Europe

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SUMMARY

The identification of the high-risk human papilloma viruses (HPVs) as a cause of cervical cancer offered the possibility for the development of a HPV vaccine. Twenty years after this identification of the HPV types, the first HPV vaccine came to the market. There are three HPV vaccines today on the market, all containing the virus-like particles (VLPs) of the HPV types 16 and 18, which are considered to cause 77 % of all cancers caused by HPVs. In addition, two of the vaccines contain two low-risk HPV types (6 and 11)-quadrivalent or the same as low-risk types and additional high-risk HPV types (31, 32, 45, 52, 58)-nonavalent vaccines. The cervical cancer protection efficacy of the vaccines is very high, around 100%. The VLPs of the 6- and 11-type offer efficient protection against genital warts. Unfortunately, the implementation of the vaccination is actually not so high despite all scientific and medical facts, but their rates in Europe are steadily increasing reaching about 90% in one country after another. In Serbia, all of the three vaccines are on the market but are highly underused. Actually, there is no national program and the Serbian vaccination rates are very low. High vaccination rates in Serbia need to be achieved as a goal of prevention of cervical cancer.

Key words: **human papilloma virus (HPV), cervical cancer, virus-like particles (VLPs), HPV vaccine, vaccination rates, national program strategies**

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INTRODUCTION

At this time, a large number of bacteria and viruses have been identified either to contribute or cause human cancers. It is considered that nowadays 20% of the cancers is linked to infectious events, but the expectation is that this number is going to rise. Among others, those include high risk and low risk human papilloma viruses (HPV) as the most important cause of cervical cancer (1). The HPV is not only responsible for the mentioned cervical cancer, but also is an important cause of anal, vulvar, penile and oropharyngeal cancers (2). Globally, the cervical cancer is the forth most common cancer in women with worldwide 528,000 new cases in 2012 and the second largest cause of mortality in women due to cancer in developing world (3). Cervical cancer is the fourth leading cause of female cancer in Serbia, and the second most common female cancer in women aged 15 to 44 years. It is also the fifth leading cause of death of female cancer deaths, and the second cause of death in women aged 15-44 years (4). In 1977, Harald zur Hausen, a German virologist, was the first one successfully found the HPV infection to be the major causative agent of cervical cancer. Historically, this is based on the research of the Italian doctor D. A. Rigoni-Stern (1842) who noted high frequency of cervical cancer in married women, widows and prostitutes, but a rare incidence in nuns and virgins (5). Experiments to address this point started in 70s and resulted in a hypothesis that cervical cancer may arise from infections with the virus found in condylomata acuminata (6, 7). In the 80s, with the discovery of related HPV types and the development of nucleic-acid application procedures (8), it was possible to isolate the first HPV types from cancer biopsies of the cervix (HPV 16 (9) and HPV18 (10)). HPV DNA is integrated into the host cell genome (10) (Figure 1).

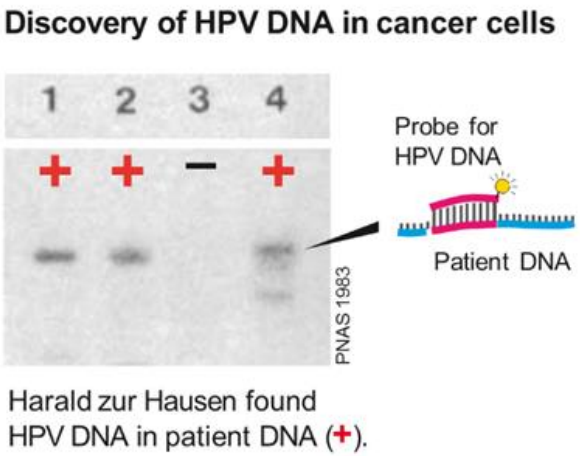

Figure 1. Detection of HPV DNA in cancer cells (copyright: © The Nobel Committee for Physiology or Medicine. Illustrator: Mattias Karlén)

HPV and its types

HPVs are small viruses containing double-stranded DNA genome protected by a capsid of two late proteins, L1 and L2. The major capsid protein L1 is composed of 72 capsomers, each of them is a pentamer of 55kDa units. Minor capsid protein L2 has approximately 75kDa. The complete structure has 72 copies of L1 and a variable number of L2 copies. It forms a struc ture with icosahedra symmetry (50-60 nm in size) (11) (Figure 2).

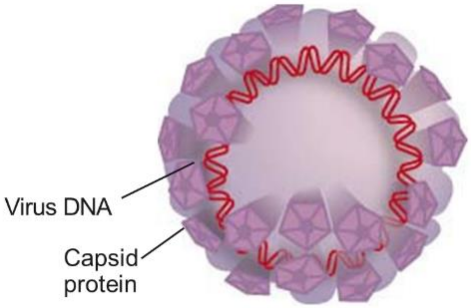

Figure 2. Viral DNA and capsid protein from HPV(copyright: © The Nobel Committee for Physiology or Medicine. Illustrator: Mattias Karlén)

More than 150 HPV subtypes can be separated based on their oncogenic potential from high to low risk HPV oncogenic types (Figure 3) (12). Low risk HPV types, such as HPV 6 and HPV 11, may cause genital warts, while HPV 16 and 18 infections are associated with malignant lesions (11). Genital HPV types are classified as Alpha papillomavirus genera. Despite different genomic sequences, the species are related concerning phylogenesis and show similar properties. The two high risk oncogenic types belong to the species 9 (HPV 16) and species 7 (HPV 19) (13).

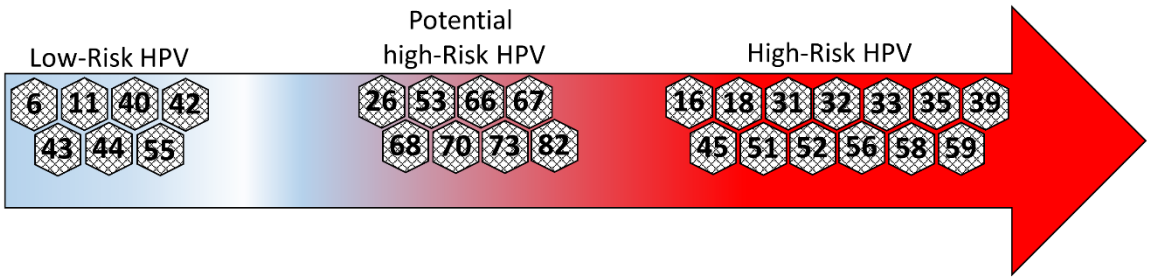

Figure 3. HPV types and their classification

Viral part of the HPV genome consists of between 6800 - 8000 base pairs organized in eight open reading frames: E6, E7, E1, E2, E4, E5, and L2 and L1-coding for ”early” or ”late” functions. One strand of the DNA is used as the template for the viral gene expression, most often opened within L2 reading frame (8). The E6 and E7 genes are responsible for the viral genome, where as E1, E2, E4 E5 and E8 are involved in DNA replication. L1 and L2 are responsible for the assembly of viral particles (8, 12).

HPV pathogenesis

Most probably HPV accesses basal cells, which rest on basal membrane, supported by the dermis, through micro-abrasions in cervical epithelium (14). Within weeks after the infection, the early genes E1, E2, E4, E5, E6, and E7 are expressed and the virus replicates. The replication continues in the upper parts of epithelium, and the late genes L1, L2, and E4 are expressed. The shed virus can cause new infections, whereas 90% of infected tissues cure within two years.

After 10-30 years, persistent infections as well as untreated lesions are associated with the integration of the HPV genome into the host DNA, upon disruption of E2 and up - regulation of E6 and E7 oncogene expression (Figure 4) (13, 14).

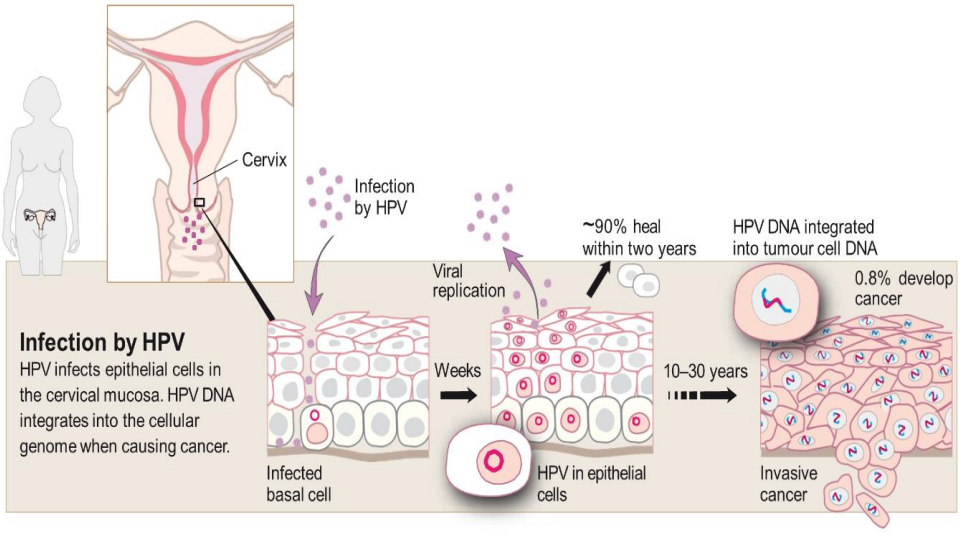

Figure 4. Pathogenesis of HPV in cervical cancer (copyright: © The Nobel Committee for Physiology or Medicine. Illustrator: Mattias Karlén)

Epithelial cervix abnormalities are observed shortly after the first detection of the HPV. The most common clinical sign of a persistent HPV infection is cervical intraepithelial neoplasia (CIN). Different levels of CIN are recognized: CIN grade 1, CIN grade 2 and CIN grade 3, and all of them, even CIN 3, can be healed up spontaneously. Diagnostically, it is shown that CIN grade 3 characterization is much more reproducible and with higher significance as that for CIN grade 1 and CIN grade 2 characterizations (16).

CIN 1 is considered as low-grade lesion. It refers to mild atypical cellular changes in the lower third (basal 1/3) of the epithelium. This corresponds to infection with HPV, and normally is cleared by the immune response within a year or so, although sometimes it can take several years to clear. CIN 2 is considered a high-grade lesion. It refers to moderate atypical cellular changes confined to basal two-thirds of the epithelium with preservation of epithelial maturation. CIN 3 is also considered a high grade lesion. It refers to apparent atypical cellular changes encompassing greater than two-thirds of the epithelial thickness, and includes full-thickness lesions (formerly called carcinoma in situ). In the past, the HPV DNA integration was considered as a late event in the development of the cervical cancer, but more recent studies show high frequency of the integrated forms of HPV 16 in women with CIN 3 and similar in those with cervical cancer. In low-grade CIN lesions this integration seems not to be completed. All of the CIN 1, CIN 2 and CIN 3 represent premalignant phases in cervix cancer development and prevention of the CIN 3 is considered a necessary step in the prevention of cervical cancer (17).

HPV vaccination

Vaccines that prevent viral diseases are widely recognized by the medical community as one of the most effective public health method. Ironically, the hesitant attitudes to the vaccination are prevalent and may be increasing since the influenza pandemic in 2009. The reasons are probably diverse, but the most important are two reasons. On the one hand, a lot of online and social media sources are available delivering fake news or unproven relationships, which are not controlled or checked by health professionals; on the other hand, it is nowadays much more challenging to form a trustworthy relationship with patients (18). As it is a scientifically proven fact that cervical cancer is caused by this virus, the search for an effective and safe HPV vaccine was open. Since the HPV family has over 150 known subtypes (12), the most critical decision was on which subtype one should focus at first. Approximately 50-60% of cervical cancers contain HPV 16 and another 10-20% contain HPV 18 (19). The HPV vaccine development was principally focused on the prevention of cervical cancer, even though those two types are found in other cancers

(vulvar, anal etc.), but with lower incidence (20). The major milestone in the development of the HPV vaccine was made after the L1 major capsid protein of bovine papillomavirus type 1 and HPV 16 in insect cells via a baculo virus vector were expressed. Not only that L1 proteins were expressed, but those also resembled papillomavirus virons and were good candidates for serological tests (21). Those virus-like-particles (VLPs) were detected in vivo, in the HPV 16 containing cell line W12, derived from cervical tissue (22). The VLPs dependent on L1 protein were able to induce high titres of antibodies and successful immunization (Figure 5) (23). The self-assembling into the VLPs was possible for each HPV type (21, 24). Its hould be emphasized that the VLPs themselves have no oncogenic potential as they do not contain genome or genetic material of the virus itself.

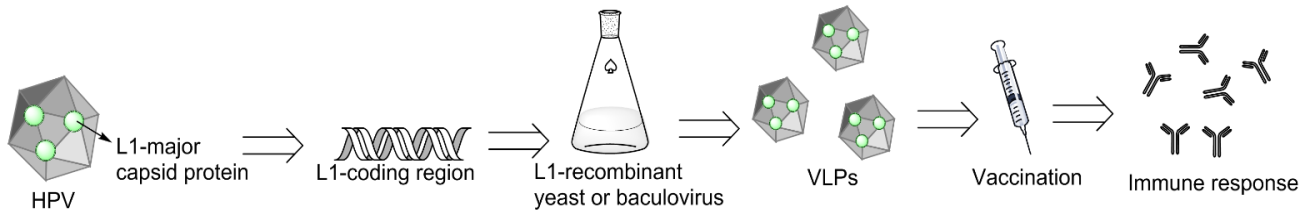

Figure 5. Schematic HPV vaccine production (adopted from (20))

Several companies and academic research institutions were engaged in preclinical and clinical trials of vaccines, based on the VLPs of high-risk HPV types. Already the first completed phase I trial showed that HPV 16 L1 VLP vaccine was well tolerated and highly immunogenic. The antibody titres were 10-fold higher than those by natural infections (8).

Actually, three different HPV vaccines are on the market: bivalent HPV vaccine (Galaxo Smith Kline plc.), quadrivalent HPV and nonavalent HPV vaccine by Merck (Table 1) (25).

Table 1. Overview on available HPV vaccines

HPV Vaccine	HPV VLPs	Adjuvant
Bivalent (Cervarix®)	16, 18	AS04 (monophosphoryl lipid A and an aluminum phosphate)
Quadrivalent (Gardasil®)	6, 11, 16, 18	Aluminumhydroxyphosphatesulfate
Nonavalent (Gardasil 9®)	6, 11, 16, 18, 31, 33, 45, 52, 58	Aluminumhydroxyphosphatesulfate

Prophylactic efficacy

Before and after 2008, when the first HPV vaccine came into the market, a number of clinical trials were performed (HPV-023, PATRICIA, FUTURE 1, FUTURE 2, NCT00543543 etc.). The vaccines were administered as three separate injections, with the second administration after one month for bivalent or after two months for nona and quadrivalent vaccines, and the third administration took place six months after the initial one.

All trials were randomized with at least three years of follow-up (so far the longest follow up is 9.4 years), evaluating the antibody status in all vaccinated women (15-26 years) and in HPV naïve women, as well as their CIN levels. Overall results have shown that high vaccine efficacy against CIN 2 or greater (CIN2+) lesions

in HPV naïve population was approximately 99%. The efficacy against CIN 3 was 100% in HPV naïve women and 46% in all women. In the HPV-023 study, with 9.4 years of follow-up, vaccination efficacy was 96% against incident infection, 100% against 6- and 12-month persistent infections, CIN 1+, CIN 2+ infections associated with HPV 16 and 18.The studies that contain HPV vaccine with VLP type 6 and 11 (quadrivalent and nonavalent) were additionally evaluated in efficacy for the prevention of genital warts. Their efficacy was around 99% in both men and women in preventing genital warts (Figure 6) (25).

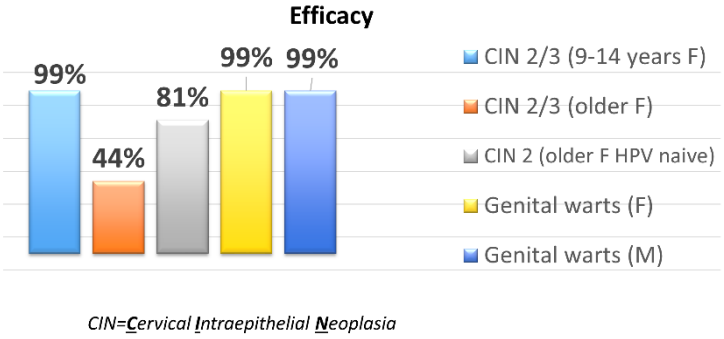

Figure 6. HPV vaccination efficacies

The vaccines may also be considered to offer a cross-protection against HPV genotypes, which are not included in the vaccines. The cross-protection is not considered trivial as the remaining 30% of cervical cancers are associated with numerous other types of HPV (26). None of the studies performed was designed to study cross-protection, but the obtained re-evaluated data suggest that cross-protection against species 7 and species 9 related HPV types. The overall efficacy against CIN2+, associated with any of the ten most common oncogenic non-vaccine types, was 30-70% (27). The efficacy data consider women up to 25 years of age, but the data available suggest that also women over 25, if not already infected with the oncogenic types, may also benefit from vaccination (28).

Safety of HPV vaccine

The safety data concerning HPV vaccination are regularly reviewed and reports on adverse events are studied. Injection site reactions including pain, redness and swelling are reported. From the systemic reactions pyrexia, headache, dizziness and myalgia are seen. In a safety trial pre-licence and post-licence, no trends for other systemic reactions were found (26). In the systematic evaluation, from time to time, a few other systemic reactions as complex regional pain syndrome, postural orthostatic tachycardia syndrome and chronic fatigue syndrome appear in connection with HPV vaccines. The cluster analysis of reports in VigiBase®, the WHO Program for International Drug Monitoring (cf. www.vigiaccess.org), summarized those events reported up to 2017. However, the connection in-between those events and the HPV vaccination remains uncertain. In addition, the data coming from different country clusters are largely heterogeneous, making it difficult to draw any general conclusion (29).

Public and economic benefits and concerns

Meanwhile, fifty-seven countries have introduced HPV vaccination in their national immunization programs. Promising results of the HPV vaccination were corroborated until September 2014. It is fundamental and essential to work on disease prevention, as general health costs for cancer treatment (chemotherapy etc.) are by far much higher that the costs related to screening and vaccination (25). It is expected that the costs of the vaccination can be reduced if it is shown that two or even one dose of the HPV vaccine have similar efficacy as the actually recommended application of three doses. Recent efficacy data have shown that a two-dose sche-

dule can have a similar protection with the three-dosage schedule (30). In addition to clear benefits, there are still some potential concerns. It is clear that the HPV vaccination prevents precancerous lesions, but the goal to prevent a cervical cancer is still followed, as the 10-year follow-up for this endpoint is not fully sufficient. Here, one must stress that most of the cancerous lesions do not progress to cancer and there are still 30% of cervical cancers that are not related to HPV 16 and 18 infections. Therefore, the vaccination does not provide complete protection against cervical cancer (25). The duration of the protection is still an open question, where with certainty it can be answered that the bivalent vaccines offer protection for 9.4 years and the quadrivalent for five years due to the experience obtained so far (25).

All of the three vaccines available on the market are used with a prophylactic and not therapeutic purpose. The development of the therapeutic vaccine is also a current medical need with a lot of research effort in this field (31). Another concern is that even HPVs are considered as stable viruses and therefore, there is still a possibility that the new mutations may lead to new oncogenic viruses and a careful follow-up has to be done (32).

Another important point is a gender-neutral vaccination that is controversially discussed. If the main goal is to reduce the cervical cancer, it is commonly argumented that a male vaccination leads to a small benefit connected to high costs. However, males develop other cancers caused by HPV infections (genital warts, anus, penile etc.) and they are the carriers of the HPV infections. From a scientific point of view, there is no doubt whether boys should be included in the vaccination programs, but the cost effectiveness of such activities is still under evaluation. Universal vaccination and its economic impact was a centre of several studies. The results confirm that this gender-neutral vaccination is cost-effective and that several models for achieving this goal can be applied (26). Not only that the vaccination of men makes more rapid and effective protection of women through herd immunity but also prevents HPV-related cancer at non-cervical sites (33). Since the pharmaceutical companies marketing the vaccines pay these studies, one can always argue against some biased protocols.

The age of vaccination is another important question for all of the studies and national programs were concerned about that. It is essential that vaccination be done before the initiation of sexual activities. A study in 9-15-year-old female adolescents in comparison with 16-26-year-old women also showed higher immune responses (33). Early vaccination can bring advantages, for example, in the abuse cases but one has to stress that at this moment there is no certainty about duration of the protection (25).

Country-specific vaccination examples

Until 2012, at least 40 countries had implemented HPV vaccination in their immunization programs (34). Among the first countries, which introduced HPV vaccination shortly after licensing, were United Kingdom and Australia. Public-funded programs started in 2007 and 2008 with school-based vaccinations for girls 12-13 years of age and catch-up programs for girls up to 17 years of age. The school-based program in Australia resulted in the three-dose coverage greater than 70%, exceeded 90% in Scotland and 80% in England. Vaccination through primary care providers in USA started for girls in 2006 and for boys in 2011 (11-12 years). The three-dose coverage among the girls was around 38% in 2013 (one-dose 57%) and around 14% among boys (35). In Germany, vaccination for girls in-between 12-17 years has been recommended since 2007. The immunisation includes the girls from 9-15 years of age with two doses of the vaccine (36). Complete protection in 17-year-old girls in 2013 has reached 41% (37). Similarly to the USA, in Germany, the protection is offered by primary care settings. In Denmark, through a publicly financed vaccination program, the vaccination rate of 79% could be reached (36). In the national programs of Austria, Italy (some parts), Sweden and United Kingdom (only males who have sex with males) men are also vaccinated (26). Twenty-nine European countries have a national program concerning HPV vaccination; unsatisfyingly, Serbia is not among them. The vaccination rates in European countries with the latest available results vary between 17 and 88% (either from 2012 or 2015)(Figure 7) (38). Most of the countries achieved high vaccination rates through school-based publicly funded programs (Figure 7).

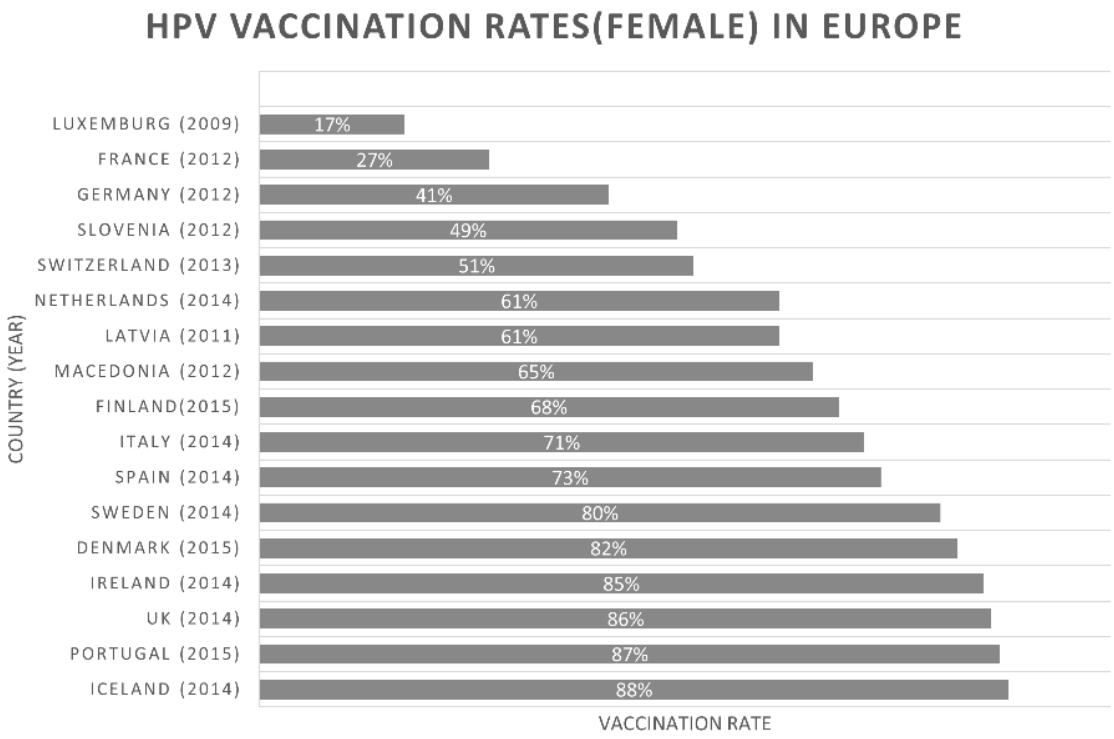

Figure 7. Vaccination rates in Europe (available data (38))

Sometimes, mandatory vaccinations are considered to improve compliance to vaccination programs, but in Europe, most of the programs are effective also with recommendations. All European countries have such a recommendation for the HPV vaccine (39). In Serbia, the first HPV vaccine was registered in 2008. The expert group prepared an official recommendation, but unfortunately, this recommendation was not announced. Up to date, there is no national program in Serbia (4). The institute of public health "Dr Milan Jovanović Batut" (Belgrade) started the campaign of the HPV immunisation in 2016, but the effects are still very hard to predict. The immunisation is recommended for boys and girls from 11 years of age and is cost-free (40). In Serbia, from 2011, approximately only 600 doses of the HPV vaccines seem to be on the market, and even from such a low number, 340 doses expired unused, indicating that less than 300 doses were applied for protection. This makes clear that the vaccination rate is very low, even though exact numbers are not known. In the surrounding countries, the highest vaccination rates has Macedonia (the former Yugoslav Republic of Macedonia) which with school-based program achieved 65% protection among 12-year-old females until 2012 (38).

CONCLUSION

HPV vaccines represent a milestone in the prevention of cervical cancer with the very high efficacy against pre-cancer lesions aiming round 100%. The real efficacy, those against cervical cancer should be confirmed after at least 20 (better 30-40 years) years of follow-up (25). The HPV vaccine is in general underused, with some positive examples (United Kingdom, Denmark) and unfortunately some countries with very low vaccination rates as Serbia. The goal of the prevention should be to increase the vaccination rates either thorough education of pediatricians, public funded educating programs of the community (Denmark) or/and school-based free of charge vaccinations. For the successful prevention, HPV vaccination accompanied with screening is considered a good pathway in prevention of cervical cancer. The aim of the most national programs are the protection of adolescent girls, but in order to achieve full protection, the adolescent boys also need to be included (33). One of the important issues in the public vaccination program is lowering the price of the vaccine and there is constant research work done in order to achieve that goal. Negative public perception on

vaccination is one of the most important issues health professionals need to work on and educate patients in order to increase prevention from the second common cause of death of women worldwide. For the high community protection, vaccination rates around 90% are considered to be an advisable prevention. The cross-protection against HPV types is one of the prophylactic properties of the HPV vaccine constantly under investigation. A study comparing efficacy and safety of the three vaccines is not available. The best protection against HPV-related diseases can be obtained by vaccination and it should be done.

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Vakcinacija protiv humanog papiloma virusa: prevencija kancera cerviksa u Srbiji i Evropi

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SAŽETAK

Identifikacija visokorizičnih humanih papiloma virusa (HPVs) kao uzročnika kancera cerviksa omogućila je za razvoj vakcine protiv humanog papiloma virusa. Na tržištu se pojavila prva vakcina protiv ovog virusa dvadeset godina nakon identifikacije HPV tipova. Danas su na tržištu prisutne tri vakcine protiv humanog papiloma virusa i sve sadrže virusu slične partikule (VLPs-eng.) HPV tipova 16 i 18, za koje se smatra da uzrokuju 77% svih kancera uzrokovanih HPV virusima. U prilog tome, dve vakcine sadrže dva tipa HPV niskog rizika (6 i 11)-kvadrivalentna ili iste tipove niskog rizika i dodatno HPV tip visokog rizika (31, 32, 45, 52, 58)-devetovalentne vakcine. Efikasnost zaštite ovom vakcinom od kancera cerviksa je veoma visoka, oko 100%. Virusu slične partikule HPV tipova 6 i 11 pružaju efikasnu zaštitu od genitalnih bradavica. Nažalost, primena ovih vakcina još uvek nije visoka, uprkos svim naučnim i medicinskim činjenicama. Međutim, u evropskim zemljama stopa primene dostiže 90%. U Srbiji su na tržištu prisutne sve tri vakcine, ali se nedovoljno primenjuju. U Srbiji ne postoji nacionalni program i stopa vakcinacije je veoma niska. Trebalo bi postići visoke stope vakcinacije u Srbiji kako bi se postigla prevencija kanera cerviksa.

Ključne reči: **humani papiloma virus (HPV), kancer cerviksa, virusu slične partikule (VLPs), vakcine protiv humanog papiloma virusa, stopa vakcinacije, strategije nacionalnog programa**