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Role of HPV Vaccination in the Prevention of Cervical Cancer Distributed Throughout Bosnia and Herzegovina

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Abstract

Human papilloma virus (HPV) is an envelopeless, epitheliotropic virus that carries double-stranded, circular DNA that belongs to the Papillomaviridae virus family. It represents one of the most commonly sexually transmitted diseases (STD) in the world with higher prevalence in low developed socio-economic countries. Infection occurs as a result of sexual intercourse and epithelial micro-trauma of the vagina and cervix, where HPV reaches the epithelial basal membrane and starts its replication process. HPV is often divided into high-risk and low-risk HPV type groups based on differences in their viral genome structure. High-risk HPV types such as HPV-16 and HPV-18 are responsible for almost 70% of cases involving cervical carcinoma. Currently, the licensed HPV vaccines are developed based on virus-like particles (VLP) of the major papillomavirus capsid protein L1. VLP-containing vaccines

do not consist protein base and do not contain viral genome therefore this vaccine form is non-infectious and non-oncogenic. This form makes them safer rather than attenuated vaccines. Gardasil 9 vaccine, licensed by the FDA in 2014, offers protection against HPV6, 11, 16, 18, 31, 33, 45, 53, and 58 therefore increasing the protection rate of cervical carcinoma to 90%. Currently available Gardasil 9 HPV vaccine in Bosnia and Herzegovina represents the most modern vaccine in combat with HPV infection and HPV-related complications. The total number of doses given from the beginning of the HPV immunization program sponsored by the Institute for Public Health of FBiH started in 2023 extending into late 2025 shows tendency of a double positive response of the target age and sex groups to the immunization program.

Keywords: Human Papilloma Virus (HPV), Sexually Transmitted Diseases (STD), Cervical Carcinoma, Immunization, Gardasil 9

1. Introduction

Human papilloma virus (HPV) is an envelopeless, epitheliotropic virus that carries double-stranded, circular DNA that belongs to the Papillomaviridae family. It represents one of the most commonly sexually transmitted diseases (STD) in the world. More than 40 HPV subtypes have been identified that could lead to potential infections of genital areas in both genders. HPV subtypes are categorized into low and high-risk groups. Among all the HPV subtypes, only 15 human papilloma virus subtypes are related to the development of cervical cancer. The classification of PVs is based on the analysis of differences and similarities in the viral DNA sequence ^[1, 2]. The high-risk HPV genotypes 16 and 18 are responsible for approximately 70 percent of all cervical cancers worldwide whereas types 31, 33, 45, 52, and 58 account for the additional 20 percent. Non-vaccinated patients infected with high-risk types 35, 39, 51, 56, 59, and 68 cause almost all of the remaining 10 percent. HPV types 16 and 18 also cause nearly 90 percent of anal cancers and a significant proportion of oropharyngeal, vulvar, vaginal cancer, and penile cancer. It is estimated that more than 80% of women will have been infected with HPV at least once by the age of 50, with the highest incidence rates being observed in young sexually-active women under 25 years of age ^[3]. HPVs

are resistant to many disinfectants and relatively unsusceptible to external conditions. There is still no drug available to inhibit viral replication, and treatment is based on removing lesions or stimulating the host immune system [1].

2. Aim

Reviewing the viral genome and the process of HPV infection is the first step to understanding then stopping its replication with the goal of preventing PV related diseases or carcinomas. The aim of this article is to display and dissect appropriate HPV vaccination that can result in lowering and even eradication of HPV related diseases in the future.

3. Materials and Methods

A systematic literature review was conducted to collect and analyze scientific evidence on the efficacy and safety of HPV vaccination in the prevention of cervical carcinoma. Relevant peer-reviewed publications were identified through searches of internationally recognized biomedical database. Inclusion criteria focused on studies evaluating HPV vaccine immunogenicity, effectiveness, safety profiles, and public health outcomes. All included sources were critically assessed to extract and synthesize the most relevant data regarding the role of HPV immunization and the characteristics of currently available vaccine formulations.

4. HPVs Structure

HPV has an icosahedral capsid consisting of 72 capsomers. A single HPV virus capsomer consists of five L1 proteins and a minor capsid protein L2 that are incorporated within the viral particle (4.-11.). The HPV genome can be divided into three regions: E (early), L (late), and LCR (long control region). The E region encodes early proteins responsible for replication, transcription, viral release and creation of an environment favorable to virus replication including evasion of the host immune system and maintenance of epithelial cell proliferation [12]. The L region encodes the L1 and L2 capsid proteins, while the non-coding LCR (long control region) contains cis regulatory elements and is involved in the regulation of viral replication and viral gene expression [13].

5. HPV Infection

HPV infects basal epithelial cells where micro-trauma exposes the base of the membrane. Initially, HPV replicates along the hosts basal cells [14]. Viral particles do not enter the blood and the replication cycle does not involve cytolysis, which reduces contact with the hosts immune system and therefore the immune response to infection [15]. HPV can only infect dividing keratinocytes of the basal layer, e.g., in the healing process of an injury leading to clathrin-independent endocytosis of HPV into the cell [16]. At further stages, viral DNA is released from the capsid with the participation of cyclophilins, although the disassembly of the capsid is probably not complete. The L1–L2–viral DNA complex binds to cytoplasmic trafficking factors and is transported through the structures of the Golgi apparatus toward the cell nucleus, into which it enters using the moment of nuclear membrane disintegration at the beginning of mitosis. Vesicles containing viral DNA, L2, and probably L1 are then transported along microtubules, connect to mitotic chromatin, and at the end of mitosis

become part of newly formed promyelocytic leukemia nuclear bodies (PML NBs) which protect the viral DNA from destruction by host restriction enzymes. The initiation of viral gene transcription is likely to be influenced by interactions with some PML NB-forming proteins, including Sp100. The first to be expressed are the HPV *E1* and *E2* genes which, among other things, leads to the activation of viral DNA replication [17]. Expression in and above the basal layer of *E5*, *E6*, and *E7* creates the right conditions for HPV replication by, among other things, stimulating cell proliferation, inhibiting cell apoptosis, and evading the host immune response. Unfortunately, similar conditions can also promote the development of precancerous conditions and cancer [16, 18, 19]. The L1 and L2 genes are expressed in terminally differentiated cells in the upper layers of the epithelium [4]. It has been shown that the production of specific antibodies is of primary importance in the prevention of HPV infection, whereas cell-mediated immunity plays a greater role in the eradication of an existing infection or the resolution of lesions. In the course of a natural infection, antibodies are produced in 50–80% of women and 2–51% of men, usually after 6–12 months of infection. The concentration of antibodies is usually low, and they do not play a major role in the immune response against HPV infection.

6. HPV Vaccines

In contrast, prophylactic HPV vaccines induce a much higher concentration of antibodies and thus effectively prevent infection [20]. Quadrivalent HPV vaccine [21], Gardasil (Merck & Co., Kenilworth, NJ, USA), is the first commercially available HPV vaccine licensed by the United States Food and Drug Administration (FDA), in 2006. The bivalent HPV vaccine, Cervarix (GSK, Brentford, UK) was approved by the European Medicines Agency (EMA) in 2007 and by the FDA in 2009 [22]. Cervarix protects against the most common oncogenic genotypes of HPV (types 16 and 18), which cause around 70% of cervical cancers [23]. In 2014, a nine-valent vaccine, Gardasil 9 (Merck & Co., Kenilworth, NJ, USA), was licensed by the FDA, which offers protection against HPV6, 11, 16, 18, 31, 33, 45, 53, and 58. The five additional types covered by Gardasil 9 could cover HPV types related to another 20% of cervical cancer cases; thus, Gardasil 9 has the potential to protect against approximately 90% of cervical cancers [24]. Currently, the licensed HPV vaccines are developed based on a virus-like particle (VLP) of the major papillomavirus capsid protein L1 [25]. Cervarix induces high anti-HPV16 and 18 antibody titers and can prevent the incidence of infection for at least 10 years [27]. In addition, Cervarix invokes a significantly high and long-term cross-reactive immunogenicity against HPV31 and 45. [28]. In addition, Cervarix efficiently protects against HPV related abnormalities and precancerous lesions, including cervical intraepithelial neoplasia 2 (CIN2), CIN3 and adenocarcinoma in situ (AIS) [29, 30]. Notably, Cervarix also showed strong protection against oral HPV16 and 18 infections. Gardasil 9 can efficiently prevent infections and cervical cancer precursor lesions (injection prior to HPV exposure) of any grade related to HPV types covered in the vaccine [31–33]. Gardasil 9 also showed around 90% and 80–85% inhibition in the incidence of vulvar and vaginal diseases, respectively [32, 34, 35]. A recent study reported that antibodies induced by Gardasil 9 could transfer across the

placenta, which potentially protects the infant from HPV6 and 11 infections [36]. For HPV types not covered by the vaccine, Gardasil 9 has low cross-protective efficacy and has little effect on infections and diseases related to HPV types besides the nine vaccine types [33, 37]. There are many potential effects that influence vaccine coverage and efficacy, such as vaccine age, geographical regions, and education. The ideal time for the best protection against HPV-related diseases is prior to HPV exposure [38]. Studies demonstrated that vaccination before first sexual contact could protect more than 90% of targeted HPV-related infections, abnormalities, and precancerous lesions, while vaccination after HPV exposure only protects about 50–60% infections [29, 39]. SAGE suggests changing HPV dosage schedules as follows: One or two doses for the primary target of girls aged 9-14; one or two doses for young women aged 15-20; two doses separated by six months for women over the age of 21. If possible, immunocompromised people, including those with HIV, should receive three doses; if not, they should receive at least two doses. The first dose must be given between 9 and 12 years of age and should be completed before 26 years of age [2, 40].

7. Research Results

Multiple studies have demonstrated that all three vaccines exhibit excellent safety and tolerance in different age groups [41-44]. A 10-year-follow-up study showed that Gardasil is immunogenic, clinically effective, and generally well-tolerated in preadolescents and adolescents [45]. Furthermore, Cervarix and Gardasil 9 demonstrate great tolerance and antibody sustenance after vaccination for up to 9.4 years and 6 years, respectively [46]. In phase I-III clinical trials before marketing, all three vaccines showed excellent protection against vaccine-targeted HPV-related infection and pre-lesions of cervical cancer [33, 47, 48]. Gardasil and Gardasil 9 were efficacious against vaginal, vulvar, and anal dysplasia [33, 49-52].

A large phase III trial study on Cervarix, called PATRICIA, demonstrated 100% protection against HPV 16 and 92.3% protection against HPV18. Furthermore, other studies on Cervarix have shown a high cross-protection against HPV31 and HPV45, with around 78% and 81% efficacy for protection against persistent HPV31 and HPV45 infection, respectively, and a 100% vaccine efficacy against CIN2+ or adenocarcinoma in situ caused by these two HPV types [53, 54]. Gardasil clinical trials, called FUTURE I and FUTURE II, prevented 98% of HPV 16 and HPV18 related high-grade cervical lesions, if participants had not been previously exposed to either HPV 16 or HPV 18. Especially for HPV18, this vaccine demonstrated a 100% vaccine efficacy against CIN2+ [48, 50]. The Gardasil 9 vaccine study (NCT00543543) showed 96% efficacy in preventing persistent infection and high-grade cervical, vulvar, and vaginal diseases related to HPV31, 33, 45, 52, and 58. Furthermore, it displayed equal efficacy as Gardasil to prevent diseases caused by HPV types 6, 11, 16, and 18 [33]. HPV vaccines also showed strong efficacy against oral HPV infections in a few studies, but whether HPV vaccination can inhibit the progress of HPV related oropharyngeal cancers has not yet been evaluated [30, 55, 56]. The question arises whether currently approved prophylactic vaccines can be used as therapeutic vaccines. A study performed in a group of women after cervical conization for HSIL-type

lesions showed that 4.3% of those who received bivalent or quadrivalent vaccine and 9.8% of unvaccinated women had recurrent lesions. The difference was statistically significant. A further study showed 58.7% efficacy of quadrivalent HPV vaccine in women with CIN 1-3. In another study, women with CIN 1-3 were vaccinated with a bivalent vaccine showed a vaccine efficacy 60 days after treatment of 88.2% for CIN 2-3 and 42.6% for CIN 1. There are also studies that have found a reduced risk of recurrence of anal intraepithelial neoplasia (AIN) in MSM and recurrence of vulvar lesions. None of the studies reported serious adverse reactions to the vaccines. All these results encourage the use of the vaccines in patients after the removal of lesions caused by HPV. Also there is no clear evidence of HPV elimination or cessation of HPV-induced lesions by prophylactic vaccines [57-60]. Therapeutic vaccines most often contain E6 and/or E7, and possibly E5 or E2 in the form of proteins or DNA or RNA encoding them. The problem is the low immunogenicity of these proteins and their ability to inhibit the host immune response. HPV genes/proteins contained in therapeutic vaccines are usually modified to increase immunogenicity and to eliminate oncogenic and immunosuppressive properties and that is why wider introduction is currently practically impossible due to the need to produce the vaccine individually for each patient, which significantly increases the price and makes it difficult to control vaccine quality [61-63].

In 2023, the procurement and distribution of vaccines from the Mandatory Immunization Program according to epidemiological indications proceeded in accordance with the planned dynamics. The HPV vaccine, Gardasil, was procured in a number of 4696 doses, manufactured by Merck Sharp & Dohme BV, the Netherlands. At the end of 2023, a total of 1678 children in the target age group were vaccinated. The total number of vaccinated other age groups in the Federation of Bosnia and Herzegovina (FBiH) in 2023 was 367 children (this ratio of vaccinated in the target and other age groups is probably different, because in the Sarajevo Canton (KS) records are not kept by age groups). Table 1. shows a higher number of vaccinated with the second dose compared to the first dose of the HPV vaccine in the target age group, because vaccination with the HPV vaccine began at the end of 2022. The Canton of Sarajevo independently procured HPV vaccines [64].

Table 1: Presents comparison between the total number of HPV 1 and HPV 2 (age-specific targeted groups) dosages administered in each of the 10 cantons on the territory of FBiH during 2023 [64]

Canton	Targeted age group (up to 15 years old)		Other age groups	
	HPV 1	HPV 2	HPV 1	HPV 2
Una-Sana Canton	72	0	6	0
Posavina Canton	0	0	0	0
Tuzla Canton	245	32	126	117
Zenica-Doboj Canton	115	93	55	55
Bosnian-Podrinje Canton	35	0	9	0
Central Bosnia Canton	37	0	0	0
Herzegovina-Neretva Canton	55	0	93	0
West Herzegovina-Neretva Canton	1	0	0	0
Sarajevo Canton	497	723	0	0
Canton 10	0	0	0	0
Total number of dosages administered in FBiH	1905		461	

Table 2: Presents comparison between the total number of HPV 1 and HPV 2 (age-specific targeted groups) dosages administered in each of the 10 cantons on the territory of FBiH during 2024 ^[64]

Canton	Targeted age group (up to 15 years old)		Other age groups	
	HPV 1	HPV 2	HPV 1	HPV 2
Una-Sana Canton	139	152	16	5
Posavina Canton	70	56	24	1
Tuzla Canton	521	399	98	57
Zenica-Doboj Canton	513	208	146	57
Bosnian-Podrinje Canton	36	53	0	0
Central Bosnia Canton	174	149	3	0
Herzegovina-Neretva Canton	165	94	31	18
West Herzegovina-Neretva Canton	3	2	0	0
Sarajevo Canton	778	324	355	243
Canton 10	24	12	0	0
Total number of dosages administered in FBiH	3872		1054	

Table 3: Presents comparison between the total number of HPV 1 and HPV 2 (age-specific targeted groups) dosages administered in each of the 10 cantons on the territory of FBiH during august,2025 and number of total dosages during the period from 1st of January until 31st of August 2025 ^[65]

Canton	Targeted age group (up to 15 years old)		Other age groups	
	HPV 1	HPV 2	HPV 1	HPV 2
Una-Sana Canton	5	27	0	0
Posavina Canton	1	1	0	0
Tuzla Canton	21	140	5	15
Zenica-Doboj Canton	68	96	5	7
Bosnian-Podrinje Canton	3	4	0	0
Central Bosnia Canton	7	5	0	0
Herzegovina-Neretva Canton	3	2	0	0
West Herzegovina-Neretva Canton	0	0	0	0
Sarajevo Canton	0	94	0	1
Canton 10	1	1	0	0
Total number of dosages administered in FBiH 08/25	109	370	10	23
Total number of dosages administered in FBiH 01.01.-31.08.	1572	1441	362	207

The HPV vaccine Gardasil 9 was purchased in a quantity of 2700 doses, manufactured by Merck Sharp & Dohme BV, the Netherlands. In 2024, a total of 2,423 persons in the target age group were vaccinated with the first dose of HPV vaccine. The total number of vaccinated persons in other age groups in the Federation of BiH in 2024 was 1,054, with the first and second dose of HPV vaccine (Table 2). A total of 4,926 doses of HPV vaccine were administered in 2024 ^[64].

Table 3 displays tabular representation and comparison of the immunization program for the during the month of august and from January 1st until 31st of august (the immunization program and data for the rest of the 2025 is ongoing and in processing) shows a sustained response of the target population in comparison to the immunization program conducted during 2024 Institute for Public Health of the FBiH (ZZJZ) ^[65].

Table 4: Presents comparison between the total number of HPV 1 and HPV 2 (age-specific targeted groups and other age groups) dosages administered in each of the 9 municipalities on the territory of Canton of Sarajevo (KS) and cumulative coverage on the territory of KS since the start of the year until august,2025 ^[66]

Age specific targeted group											
Municipality											%
Stari grad	Centar	Novo Sarajevo	Novi Grad	Ilidža	Hadžići	Vogošća	Ilijaš	KS 08/25	KS, planned Nr	Nr of vaccinations in 2025	
Number of vaccinated											
HPV (9) I	0	0	0	0	0	0	0	0	1835	490	26,7
HPV (9)II	0	9	27	52	3	0	1	2	94	329	15,6

Other age groups											
Municipality											%
Stari grad	Centar	Novo Sarajevo	Novi Grad	Ilidža	Hadžići	Vogošća	Ilijaš	KS 08/25	KS, planned Nr	Nr of vaccinations in 2025	
Number of vaccinated											
HPV (4) I	0	0	0	0	0	0	0	0	-	-	
HPV (4)II	0	0	0	0	0	0	0	0	-	-	
HPV (9) I	0	0	0	0	0	0	0	0	-	-	
HPV (9)II	0	0	0	0	0	0	0	0	-	-	

Table 4. could serve as a demonstrator of each municipality's affection to the immunization program and their socio-economic statuses.

Table 5: Display of HPV vaccinations between the administration departments within BiH (2023-2024) [64, 67, 68]

Entity	Coverage	Database
Federation of Bosnia and Herzegovina (FBiH)	12 %	Institute for public health FBiH,2024
Republic of Srpska (RS)	38%	Institute for public health RS,2024
District of Brčko	<5%	World Health Organization BiH, 2024

Table 5 shows percentage of HPV vaccine coverage between each of the three administrative units in Bosnia and Herzegovina (BiH), where entity RS holds an impressive response rate to the immunization program implemented by the Institute for Public Health of RS.

Table 6: Display of most common reasons for HPV vaccine refusal [64, 67, 68]

Reason	Frequency (%)
Limited or lack of information about vaccination	39%
Fear of adverse effects	24%
Religion/social beliefs	16%
Limited vaccine availability	11%
Other	10%

Table 6 shows most common reasons of rejection to the vaccination program, where limitation and lack in information or knowledge are on the forefront of reasons not to get vaccinated.

8. Discussion

Information provided in section Research results could serve as potential indicator for socio-economic and education status of each Canton on the territory of FBiH and in between each municipality on the territory of the Sarajevo Canton. Statistical tabular presentation and comparison of the immunization program for the past two years on the territory of FBiH (the immunization program and data for 2025 are ongoing and in processing) show a positive response with a potential growth trend and response of the target population to the immunization program conducted by the Institute for Public Health of the FBiH. Bosnia and Herzegovina shows a promising exponential potential yet is still undeveloped regarding most common refusal reasons that have nothing to do with virusology and immunization as a matter of fact the most common problem is lack of education and propaganda. Results from studies all around the world show a nearly 100% prevention of HPV infection and HPV related diseases are facts that need to be looked up on in the future as the main goal and argument for target population.

9. Conclusion

HPV vaccines significantly reduce HPV infection and related diseases. Increasing vaccine coverage, including pan-gender vaccination programs, is expected to further decrease HPV-related cancers. Education, vaccine accessibility, and public health campaigns are essential for the success of immunization programs, especially in low-

and middle-income countries. Reducing side effects and developing high-valent vaccines with broader protection will improve vaccine acceptance at a young age. Although current vaccines do not cover all HPV types, next-generation vaccines and the development of therapeutic vaccines offer a promising perspective for the prevention and treatment of HPV-related diseases.

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