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EFIKASNOST HPV VAKCINE U PREVENCIJI RAKA GRLIĆA MATERICE I DRUGIH MALIGNOMA

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SAŽETAK

Infekcija humanim papiloma virusom (HPV) je jedna od najrasprostranjenijih polno prenosivih infekcija širom sveta, odgovorna za značajan broj obolelih i umrlih godišnje. Predstavlja jedan od faktora rizika za nastanak raka grlića materice, raka usne duplje i ždrela, raka vagine, raka vulve, raka penisa i raka anusa, a uzrokuje i nastanak genitalnih bradavica. Uvođenjem licenciranih globalno priznatih profilaktičkih HPV vakcina (npr. *Cervarix, Gardasil, Gardasil 9, Cecolin, Walrinvax* i *Cervavac*), baziranih na česticama sličnim virusu (engl. *Virus-Like Particles*), napravljenih od proteinskih komponenti virusa, ali bez genetskog materijala virusa, je doprinelo značajnom smanjivanju broja obolelih od raka grlića materice posebno u visoko razvijenim zemljama, gde se koristi i skrining test (Pap test). Uprkos uvođenju i implementaciji ovih vakcina, maligniteti povezani sa HPV-om i dalje predstavljaju globalni problem. Cilj ovog preglednog rada je da analizira efikasnost HPV vakcine u prevenciji raka grlića materice i drugih malignih tumora.

Ključne reči: humani papiloma virus (HPV), vakcina, incidencija, rak grlića materice, efikasnost, obuhvat vakcinacijom.

Uvod

Priča o razvoju vakcine protiv Humanog papiloma virusa (HPV) počinje otkrićem HeLa ćelija, ćelija raka grlića materice koje su se pokazale besmrtnim i sposobnim za kloniranje u *in vitro* uslovima, a porekla adenokarcinoma grlića materice od kojeg je preminula pacijentkinja po imenu *Henrietta Lacks* 1951. godine u bolnici *Johns Hopkins* u Baltimoru u Sjedinjenim Američkim Državama (SAD). Ove ćelije postale su najstarija kontinuirana ljudska ćelijska linija i od tada su nezaobilazne u naučnim istraživanjima (1).

HeLa ćelije su bile ključne za mnoga revolucionarna otkrića. Jedan od naučnika koji je iskoristio njihov potencijal bio je *dr Harald zur Hausen,* nemački virolog. Njegovo izuzetno znanje i fundamentalni doprinosi doveli su do objašnjenja HPV karcinogeneze, za šta je 2008. godine nagrađen Nobelovom nagradom. Njegovo istraživanje je otvorilo put ka otkriću HPV vakcina (2).

Glavni cilj nakon ovih otkrića bio je razvoj vakcine koja bi obezbedila dugotrajan imunitet. Prekretnicu su postigla dva istraživača iz Brizbejna, Australija, *dr I. Fraser* i *dr J. Zhou*, koji su 1991. godine, uspešno koristeći tehnike genetskog inženjeringa, proizveli specifične virusne proteine L1 i L2. To je dovelo do stvaranja čestica sličnih virusu (VLP). Ove VLP čestice su se pokazale sposobnim da indukuju humoralni imunitet i proizvodnju antitela protiv različitih virusnih genotipova (3). Bilo je odmah jasno da ove vakcine ne mogu izlečiti već postojeće infekcije, ali pružaju efikasnu zaštitu od budućih HPV infekcija. Štaviše, primena ovih vakcina bila je bez rizika od razvoja potencijalne HPV infekcije.

Trenutno na tržištu dostupno je više licenciranih profilaktičkih vakcina baziranih na VLP tehnologiji. Među njima su bivalentne, četvorovalentne i devetovalentne varijante, koje su us-

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EFFICACY OF HPV VACCINE IN PREVENTING CERVICAL CANCER AND OTHER MALIGNANCIES

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SUMMARY

Human papillomavirus (HPV) infection is one of the most widespread sexually transmitted infections globally, responsible for a significant number of cases and deaths annually. It is one of the risk factors for cervical cancer, oral and pharyngeal cancer, vaginal cancer, vulvar cancer, penile cancer, and anal cancer, and it also causes genital warts. The introduction of licensed, globally recognized prophylactic HPV vaccines (e.g., Cervarix, Gardasil, Gardasil 9, Cecolin, Walrinvax, and Cervavac), based on virus-like particles (VLPs) made from viral protein components but without the virus's genetic material, has significantly contributed to reducing the number of cervical cancer cases, especially in highly developed countries where screening tests (Pap tests) are also used. Despite the introduction and implementation of these vaccines, HPV-related malignancies continue to be a global problem. The aim of this review is to analyze the effectiveness of the HPV vaccine in preventing cervical cancer and other malignant tumors.

Keywords: human papillomavirus (HPV), vaccine, incidence, cervical cancer, efficacy, vaccination coverage.

Introduction

The story of the development of the Human Papillomavirus (HPV) vaccine begins with the discovery of HeLa cells, cervical cancer cells that proved to be immortal and capable of cloning in in vitro conditions, originating from the cervical adenocarcinoma from which a patient named Henrietta Lacks died in 1951 in the Johns Hopkins Hospital in Baltimore, United States. These cells became the oldest continuous human cell line and have been indispensable in scientific research ever since (1).

HeLa cells were crucial for many groundbreaking discoveries. One of the scientists who harnessed their potential was Dr. Harald zur Hausen, a German virologist. His exceptional knowledge and fundamental contributions led to the explanation of HPV carcinogenesis, for which he was awarded the Nobel Prize in 2008. His research paved the way for the discovery of HPV vaccines (2).

The main goal after these discoveries was to develop a vaccine that would provide long-lasting immunity. The breakthrough was achieved by two researchers from Brisbane, Australia, Dr. I. Fraser and Dr. J. Zhou, who in 1991 successfully used genetic engineering techniques to produce specific viral proteins, L1 and L2. Their work led to the creation of virus-like particles (VLPs). These VLP particles have been shown to be capable of inducing humoral immunity and antibody production against different viral genotypes (3). It was immediately clear that these vaccines could not cure existing infections, but they do provide effective protection against future HPV infections. Furthermore, the application of these vaccines posed no risk of developing a potential HPV infection.

Currently, several licensed prophylactic vaccines based on VLP technology are available on the market. Among them are bivalent, quadrivalent,

merene prema različitim sojevima HPV-a, a čiji su detalji navedeni u tabeli 3 (4).

Cilj ovog preglednog rada je da analizira efikasnost HPV vakcine u prevenciji raka grlića materice i drugih malignih tumora.

Metode

U okviru ovog preglednog rada, korišćenjem *Pub Med* baze podataka prikupljeni su radovi koji su se bavili ispitivanjem efikasnosti HPV vakcine tokom poslednjih 30 godina. Pretraživanje baze podataka sprovedeno je korišćenjem sledećih ključnih reči: humani papiloma virus (HPV), HPV vakcina, incidencija, rak grlića materice, efikasnost i obuhvat vakcinacijom. U ovaj pregledni rad uključeni su samo oni radovi koji su bili na engleskom jeziku.

Specifičnosti HPV infekcije

Infekcija HPV virusom je jedna od najčešćih polno prenosivih bolesti na globalnom nivou među seksualno aktivnim osobama, pri čemu se većina pojedinaca zarazi u nekoj fazi života (8). Uzročnik je nano-dvostruki lančani DNK virus iz porodice *Papillomaviridae* koji ima afinitet prema koži i sluzokožnom epitelu, što opisuje primarna mesta zahvaćenih tkiva, uzrokujući infekcije grlića materice, anogenitalne infekcije i infekcije orofaringealnog regiona. Trenutno je identifikovano preko 200 sojeva HPV-a, kategorisanih u pet podtipova, pri čemu je alfa podtip uključen u onkogenezu maligniteta povezanih sa HPV-om. Na osnovu alfa podtipova, kategorizacija se vrši prema onkogenom potencijalu, pri čemu se alfa HPV virusi dele na grupe niskog onkogenog rizika (HPV 6, 11, 42, 43, 44) i visokog onkogenog rizika (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68). Infekcija se može preneti direktnim kontaktom kože na kožu ili sluzokože, kao i putem predmeta (npr. seksualne igračke), budući da je virus veoma otporan na faktore spoljašnje sredine (8,9). HPV DNK je identifikovan u reproduktivnom traktu i ćelijama i muškaraca i žena, kao i u placenti i horionu, što ukazuje da infekcija može biti prisutna tokom oplodnje i embriogeneze, objašnjavajući intrauterini i hematogeni prenos (10).

Početna HPV infekcija razvija se u bazalnom epitelu nakon mikrolezija, budući da bazalne ćelije održavaju kontinuirani replikativni ciklus koji omogućava inkorporaciju HPV-a u replikativni sistem domaćina. Virusne čestice se zatim proizvode nakon diferencijacije bazalnih ćelija, kulminirajući proizvodnjom HPV viriona u površinskim slojevima epitela, koji se oslobađaju putem deskvamacije (11). Slab imuni odgovor nastaje zbog odsustva virusne citolize i mehanizama koji olakšavaju nisku ekspresiju proteina, što rezultira time da je indukovani humoralni imunitet inferioran u odnosu na imunitet i antitela generisana preventivnom HPV vakcinacijom. S druge strane, T-ćelijski posredovani imunitet je odgovoran za ograničavanje infekcije na subkliničko stanje sa jedva detektabilnom HPV DNK; međutim, ostaje neizvesno da li se ova nedetektabilnost javlja zbog uspešnog eliminisanja infekcije (12). Pored uloge sistemskog imuniteta, ključno je prepoznati da različiti faktori doprinose hroničnoj infekciji i riziku od razvoja prekanceroznih lezija i raka, uključujući lokalni imunitet i dodatne infekcije koje menjaju lokalni mikrobiom, pušenje, upotrebu oralne kontraceptivne terapije i naslednu predispoziciju za određene vrste karcinoma (13).

Maligniteti povezani sa HPV-om

Prema podacima *Globocan*-a za 2022. godinu, HPV infekcija je povezana sa razvojem mnogih maligniteta, pri čemu je rak grlića materice najčešći, odgovoran za oko 662.301 novoobolelih i 348.874 smrtnih slučajeva godišnje (14). Posmatrajući po regionima, najviša standardizovana stopa incidencije raka grlića materice, u 2022. goodini, je u Africi (26,4 na 100.000), a najniža u Severnoj Americi (6,4 na 100.000) i Okeaniji (9,6 na 100.000). Poslednjih godina zabeležen je porast učestalosti javljanja orofaringealnog karcinoma skvamoznih ćelija, tako da je 2022. godine bilo registrovano oko 106.000 novoobolelih i oko 52.000 umrlih. Međutim, HPV virusi visokog rizika (prvenstveno HPV-16 i HPV-18) takođe su povezani sa karcinomima vulve, vagine, penisa, anusa, jednjaka i kože skvamoznih ćelija, kao i sa rakom pluća i mozga (15).

Međunarodna agencija za istraživanje raka izveštava o učestalosti javljanja karcinoma povezanih sa HPV infekcijom u okviru *Globocan*-a, a podaci se odnose na 2022. godinu (tabela 1)(14). Precizna uloga i doprinos HPV infekcije u javljanju maligniteta, dobijena je iz brojnih studija, jer registri raka ne prikupljaju podatke o malignim tkivima zaraženim HPV-om. Podaci ukazuju da je HPV odgovoran za skoro 100% karcinoma grlića materice, 88,0% analnih karcinoma, 24,9% karcinoma vulve, 78,0% vaginalnih karcinoma, 50,0% karcinoma penisa i 30,8% orofaringealnih karcino-

and nonavalent variants, which target different HPV strains, and whose details are listed in Table 3 (4).

The aim of this review is to analyze the effectiveness of the HPV vaccine in preventing cervical cancer and other malignant tumors.

Method

Within the scope of this review, studies examining the efficacy of the HPV vaccine over the past 30 years were collected using the PubMed database. The database search was conducted using the following keywords: human papilloma virus (HPV), HPV vaccine, incidence, cervical cancer, efficacy, and vaccination coverage. Only papers written in English were included in this review.

Specifics of HPV infection

HPV infection is one of the most common sexually transmitted diseases globally among sexually active individuals, with most individuals becoming infected at some point in their lives (8). It is caused by a nano-double-stranded DNA virus from the Papillomaviridae family, which has an affinity for skin and mucosal epithelium, describing the primary sites of affected tissues, causing cervical infections, anogenital infections, and oropharyngeal region infections. Currently, over 200 HPV strains have been identified, categorized into five subtypes, with the alpha subtype being involved in the oncogenesis of HPV-related malignancies. Based on alpha subtypes, categorization is done according to oncogenic potential, with alpha HPV viruses divided into groups of low oncogenic risk (HPV 6, 11, 42, 43, 44) and high oncogenic risk (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68). The infection can be transmitted through direct skin-to-skin or mucous membrane contact, as well as through objects (e.g., sex toys), since the virus is very resistant to environmental factors (8, 9). HPV DNA has been identified in the reproductive tracts and cells of both men and women, as well as in the placenta and chorion, indicating that infection can be present during fertilization and embryogenesis, explaining intrauterine and hematogenous transmission (10).

Initial HPV infection develops in the basal epithelium after microlesions, as basal cells maintain a continuous replicative cycle that allows HPV to be incorporated into the host's replicative system. Viral particles are then produced after differentiation of basal cells, culminating in the production of HPV virions in the superficial layers of the epithelium, which are released through desquamation (11). A weak immune response occurs due to the absence of viral cytolysis and mechanisms that facilitate low protein expression, resulting in induced humoral immunity being inferior to the immunity and antibodies generated by preventive HPV vaccination. On the other hand, T-cell-mediated immunity is responsible for limiting the infection to a subclinical state with barely detectable HPV DNA; however, it remains uncertain whether this undetectability occurs due to successful elimination of the infection (12). In addition to the role of systemic immunity, it is crucial to recognize that various factors contribute to chronic infection and the risk of developing precancerous lesions and cancer, including local immunity and additional infections that alter the local microbiome, smoking, the use of oral contraceptive therapy, and a hereditary predisposition to certain types of cancer (13).

HPV-related malignancies

According to Globocan data for 2022, HPV infection is associated with the development of many malignancies, with cervical cancer being the most common, responsible for approximately 662,301 new cases and 348,874 deaths annually (14). Looking at regions, the highest standardized incidence rate of cervical cancer in 2022 was in Africa (26.4 per 100,000), and the lowest was in North America (6.4 per 100,000) and Oceania (9.6 per 100,000). In recent years, there has been an increase in the incidence of oropharyngeal squamous cell carcinoma, so that in 2022, approximately 106,000 new cases and around 52,000 deaths were registered. However, high-risk HPV viruses (primarily HPV-16 and HPV-18) are also associated with cancers of the vulva, vagina, penis, anus, esophagus, and squamous cell skin, as well as lung and brain cancer (15).

The International Agency for Research on Cancer reports the incidence of HPV-related cancers within Globocan, with data referring to the year 2022 (Table 1) (14). The precise role and contribution of HPV infection to the occurrence of malignancies have been obtained from numerous studies, as cancer registries do not collect data on

Tabela 1. Maligni tumori koji se dovode u vezu sa HPV infekcijom, svet, 2022. godina (14,16)

Karcinom povezan sa HPV infekcijom (ICD -10 kod)	Broj incidentnih slučajeva *	Broj incidentnih slučajeva koji se mogu pripisati HPV infekciji**	Odgovarajuća atributivna frakcija -AF (%)***
Cerviksa uterusa (C53)	660.000	660.000	100,0
Anusa (C21)	54.000	47.000	88,0
Vulve (C51)	47.000	11.000	24,9
Vagine (C52)	18.000	14.000	78,0
Penisa (C60)	37.000	18.000	50,0
Orofarinksa (C01, C09-10)	106.000	32.000	30,8
Ukupno za sve lokalizacije povezane sa HPV infekcijom	920.000	780.000	84,7

*Izvor: Globocan 2022. (14).
Napomena: brojevi su zaokruženi na dve decimalne jedinice.
** Približan broj se izračunava množenjem broja incidentnih slučajeva sa odgovarajućom atributivnom frakcijom (AF) i zatim deli sa 100. Brojevi su zaokruženi na dve decimalne jedinice.
*** Preuzeto iz reference 16.

ma (tabela 1) (16). Tako da se, na globalnom nivou, procenjuje da je broj incidentnih slučajeva koji se mogu pripisati HPV infekciji negde oko 780.000.

Rak grlića materice i efikasnost HPV vakcine

U svetu, prema podacima Međunarodne agencije za istraživanje raka, *Globocan*-a za 2022 godinu, rak grlića materice je, prema standardizovanim stopama incidencije, peti vodeći uzrok obolevanja (iza raka prostate, dojke i kolorektuma) i, prema standardizovanim stopama mortaliteta, šesti uzrok umiranja (iza raka pluća, dojke, kororektuma, jetre i prostate) (tabela 2) (14). Prisutnost maligniteta povezanih sa HPV-om opada u zemljama sa visokim prihodima, dok opterećenje i dalje postoji u zemljama u razvoju zbog odsustva nacionalnih programa skrininga, budžetskih ograničenja i neadekvatnog obuhvata HPV vakcinom i skriningom. Cilj Svetske zdravstvene organizacije (SZO) nalaže da 90% devojčica do 15. godine mora biti vakcinisano protiv HPV-a u periodu 2020-2030. godine (17). Organizovani nacionalni programi skrininga i uvođenje HPV vakcine u kalendar obavezne imunizacije, mogu smanjiti incidenciju raka grlića materice za čak 70-100% kada se primene kod devojčica u dobi između 11-13 godine života, pre početka seksualne aktivnosti, jer je efikasnost vakcine najbolja pre samog nastanka infekcije (18).

Nakon uvođenja licenciranih preventivnih vakcina baziranih na VLP-u (detaljno prikazanih u tabeli 3), procenjena je njihova efikasnost, koja dostiže do 100%, zavisno od broja ciljanih HPV serotipova. Efikasnost četvorovalentne vakcine *Gardasil®* kreće se od 93% do 100%, devetovalentne *Gardasil9®* od 97% do 100%, a bivalentne *Cervarix®* 93%. Sve ove vakcine ne samo da sprečavaju prekancerozne lezije grlića materice, već i vulve, anusa, penisa i usne duplje, pri čemu su npr. *Gardasil®* (četvorovalentna vakcina) i *Gardasil 9®* (devetovalentna vakcina) takođe efikasne u prevenciji

Tabela 2. Vodeći maligni tumori širom sveta, prema standardizovanim stopama incidencije i mortaliteta, oba pola zajedno, 2022. godina (14)

Karcinom	Standardizovana stopa incidencije*/100.000	Karcinom	Standardizovana stopa mortaliteta*/100.000
Dojka	46,8	**Pluća**	16,8
Prostata	29,4	**Dojka**	12,7
Pluća	23,6	**Kolorektum**	8,1
Kolorektum	18,4	**Jetra**	7,4
Grčić materice	*14,1*	***Prostata***	7,3
Želudac	*9,2*	***Grlić materice***	7,1

*standardizovana prema populaciji sveta

Table 1. Malignant tumors associated with HPV infection, world, 2022 (14, 16)

HPV related cancer site (ICD -10 code)	Number of incident cases *	Number of incident cases attributable to HPV **	Corresponding attributable fraction AF (%) ***
Cervix uteri (C53)	660,000	660,000	100.0
Anus (C21)	54,000	47,000	88.0
Vulva (C51)	47,000	11,000	24.9
Vagina (C52)	18,000	14,000	78.0
Penis (C60)	37,000	18,000	50.0
Orophyrynx (C01, C09-10)	106,000	32,000	30.8
Total HPV-related sites	920,000	780,000	84.7

*Source: Globocan 2022. (14).
Note: numbers are rounded to two decimal places.
**The approximate number is calculated by multiplying the number of incidents by the corresponding attribute fraction (AF) and then dividing by 100. Numbers are rounded to two decimal places.
***The information is derived from reference 16.

malignant tissues infected with HPV. Data indicate that HPV is responsible for nearly 100% of cervical cancers, 88.0% of anal cancers, 24.9% of vulvar cancers, 78.0% of vaginal cancers, 50.0% of penile cancers, and 30.8% of oropharyngeal cancers (Table 1) (16). Thereby, globally, the estimated number of incident cases attributable to HPV infection is around 780,000.

Cervical cancer and the effectiveness of the HPV vaccine

Globocan 2022 data from the International Agency for Research on Cancer shows that cervical cancer is the fifth leading cause of morbidity (behind breast, prostate, lung and colorectal cancer) based on standardized incidence rates and the sixth leading cause of death (behind lung, breast, colorectal, liver and prostate cancer) based on standardized mortality rates (Table 2) (14). The prevalence of HPV-related malignancies is decreasing in high-income countries, while the burden persists in developing countries due to the absence of national screening programs, budget constraints, and inadequate HPV vaccination and screening coverage. The World Health Organization's (WHO) goal mandates that 90% of girls by the age of 15 must be vaccinated against HPV between the years 2020 and 2030 (17). Organized national screening programs and the introduction of the HPV vaccine into the mandatory immunization schedule can reduce the incidence of cervical cancer by as much as 70-100% when administered in girls aged 11-13, before the onset of sexual activity, as the vaccine's efficacy is best before the infection itself occurs (18).

After the introduction of licensed VLP-based preventive vaccines (detailed in Table 3), their efficacy was assessed, reaching up to 100% depending on the number of targeted HPV serotypes. The efficacy of the quadrivalent

Table 2. Leading malignant tumors worldwide, according to standardized incidence and mortality rates, both sexes combined, 2022 year (14)

Cancer	Standardized incidence rate*/100,000	Cancer	Standardized mortality rate*/100,000
Breast	46.8	**Lung**	16.8
Prostate	29.4	**Breast**	12.7
Lung	23.6	**Colorectum**	8.1
Colorectum	18.4	**Liver**	7.4
Cervix uteri	*14.1*	***Prostate***	7.3
Stomach	*9.2*	***Cervix uteri***	7.1

*standardized according to the world population

Tabela 3. Specifičnosti najčešće korišćenih HPV vakcina širom sveta (6,7)

Vakcine	bv-HPV vakcina	qv-HPV vakcina	9v-HPV vakcina	bv-HPV vakcina	bv-HPV vakcina	qv-HPV vakcina
Naziv	**Cervarix®***	**Gardasil®***	**Gardasil 9®***	**Cecolin®***	**Walrinwax®***	**Cervavac ®*****
Proizvođač	GlaxoSmith Kline, UK	Merck & Co., SAD	Merck &Co., SAD	Xiamen Innovax, Kina	Walvax, Kina	Institut za serume Indija
Ekspresioni sistem	*Baculovirus*	*Saccharomyces cerevisae*	*Saccharomyces cerevisae*	*Escherichia coli*	*Pichia pastoris*	*Hansenula polymorpha*
Godina odobravanja	2007.	2006.	2014.	2019.	2022.	2022.
HPV tipovi koji se preveniraju	HPV 16/18	HPV 6/11/16/18	HPV 6/11/16/18/ 31/33/45/52/58	HPV 16/18	HPV 16/18	HPV 6/11/16/18
Uzrast za vakcinaciju	9-45	9-45	9-45	9-45	9-30	9-45
Plan vakcinacije	0 M, 1M, 6M **	0M, 2M, 6M **	0M, 2M, 6M **	0M, 1M, 6M **	0M, 1M, 6M	0M, 6M
Mesto vakcinacije	Intramuskularna injekcija, deltoidna regija nadlaktice ili gornja strana anterolateralne površine butine u količini od 0,5 ml.					

M- mesec

* Vakcine koje su dobile komercijalnu autorizaciju i SZO prekvalifikaciju (5).

** Vakcine koje je odobrila SZO za jednokratnu dozu umesto dvojne doze za devojčice uzrasta 9-14 godina; od 15. godine života preporučuju se tri doze (6).

*** Ne nalazi se na globalnom tržištu, međutim, ima značaj za Indiju i druge zemlje sa niskim i srednjim prihodima zbog svoje tržišne cene (7).

genitalnih bradavica uzrokovanih HPV-om (19,20). Sve tri ove vakcine su pokazale značajne rezultate u kliničkim ispitivanjima, ali u budućnosti će biti potreban dodatni fokus na procenu uticaja HPV vakcine na druge malignitete povezane sa HPV infekcijom (20).

Brojne terapeutske vakcine su razvijene do danas sa mnogim kliničkim ispitivanjima koja su još uvek u toku. One uključuju vakcine na bazi proteina (poput vakcine *Accum™-E7* razvijene od strane *Vancouver, BC, Canada*), DNK i adenovirusne vektorske vakcine, terapeutske oralne vakcine (poput vakcine *Lactobacillus-expressing HPV 16 E7*) i mRNA vakcine, od kojih nijedna još uvek nije licencirana (19).

Krajnji budući cilj je razvoj i licenciranje vakcina koje ciljaju sojeve HPV-a koji nisu pokriveni postojećim profilaktičkim vakcinama. Proširenje je postignuto razvojem jedanaesto i petnaesto valentnih HPV vakcina, dok je petnaesto valentna vakcina još uvek u razvoju, pokazujući obećavajuću zaštitu protiv 15 najčešćih HPV serotipova (21).

Svetski programi vakcinacije protiv HPV-a

Kada je reč o primeni HPV vakcinacije u svetu, 149 od 194 zemlje je, prema podacima o imunizaciji SZO iz 2025. godine, uvelo HPV vakcinu u svoje nacionalne programe imunizacije, pri čemu je Srbija uvela HPV vakcinu 2022. godine, kao preporučenu aktivnu imunizaciju lica određenog uzrasta (od navršenih devet do navršenih 19 godina, a sprovodi se devetovalentnom HPV vakcinom, dve doze vakcine u razmaku od 6 meseci za uzrast 9-14 godina, a tri doze za uzrast 15 i više godina, po šemi 0,2,6 meseci). Vakcina se daje dečacima i devojčicama, besplatna je i aplikuje se intramuskularno (22) (23).

U Evropskoj uniji, obavezna HPV imunizacija je prisutna samo u Letoniji, dok druge članice EU imaju opšte preporuke za vakcinu, nudeći HPV vakcinu kroz nacionalne programe imunizacije. Neke zemlje nude rodno neutralnu vakcinaciju i gotovo sve (sa izuzetkom Rumunije) su finansirane od strane nacionalnog zdravstvenog sistema (24). Najviša stopa obuhvata HPV vakcinom u Evropi trenutno postoji u Danskoj, Norveškoj, Švedskoj i Portugalu, približno 90%, dok je najniža u zemljama u jugoistočnoj Evropi (22).

Četiri od pedeset država u Sjedinjenim Američkim Državama zahtevaju obaveznu HPV imunizaciju za ostvarivanje upisa u škole: Vašington D.C., Virdžinija, Roud Ajland i Havaji, dok ostale države snažno podstiču vakcinaciju kroz edukativne kampanje i preporučene kalendare vakcinacije (25).

Table 3. Specifications of the most commonly used HPV vaccines worldwide (6,7)

Vaccine	bv-HPV vaccine	qv-HPV vaccine	9v-HPV vaccine	bv-HPV vaccine	bv-HPV vaccine	qv-HPV vaccine
Name	**Cervarix®***	**Gardasil®***	**Gardasil 9®***	**Cecolin®***	**Walrinwax®***	**Cervavac ®*****
Manufacturer	GlaxoSmith Kline, UK	Merck & Co., USA	Merck &Co., USA	Xiamen Innovax, China	Walvax, China	Serum Institute of India
Expression system	*Baculovirus*	*Saccharomyces cerevisae*	*Saccharomyces cerevisae*	*Escherichia coli*	*Pichia pastoris*	*Hansenula polymorpha*
Time of approval	2007.	2006.	2014.	2019.	2022.	2022.
HPV types prevented	HPV 16/18	HPV 6/11/16/18	HPV 6/11/16/18/ 31/33/45/52/58	HPV 16/18	HPV 16/18	HPV 6/11/16/18
Age for vaccination	9-45y	9-45y	9-45y	9-45y	9-30y	9-45y
Vaccination schedule	0 M, 1M, 6M **	0M, 2M, 6M **	0M, 2M, 6M **	0M, 1M, 6M **	0M, 1M, 6M	0M, 6M
Site of inoculation	Intramuscular injection, deltoid region of the upper arm or the upper side of the anterolateral surface of the thigh, in a volume of 0.5 ml.					

M - month

* Vaccines that have received commercial authorization and WHO prequalification (5).

** WHO-approved single-dose vaccines instead of dual-dose for girls aged 9-14; from the age of 15, three doses are recommended (6).

***It is not found in the global market; however, it is significant for India and other low- and middle-income countries due to its market price (7).

vaccine Gardasil® ranges from 93% to 100%, the nonavalent Gardasil 9® from 97% to 100%, and the bivalent Cervarix® is 93%. All these vaccines not only prevent precancerous lesions of the cervix but also of the vulva, anus, penis, and oral cavity, with, for example, Gardasil® (quadrivalent vaccine) and Gardasil 9® (nonavalent vaccine) also being effective in preventing genital warts caused by HPV (19, 20). All three of these vaccines have shown significant results in clinical trials, but in the future, additional focus will be needed on assessing the impact of the HPV vaccine on other malignancies associated with HPV infection (20).

Numerous therapeutic vaccines have been developed to date, with many clinical trials still ongoing. These include protein-based vaccines (such as the Accum™-E7 vaccine developed by Vancouver, BC, Canada), DNA and adenovirus vector vaccines, therapeutic oral vaccines (such as the Lactobacillus-expressing HPV 16 E7 vaccine), and mRNA vaccines, none of which are yet licensed (19).

The ultimate future goal is the development and licensing of vaccines that target HPV strains not covered by existing prophylactic vaccines. Expansion has been achieved through the development of eleven- and fifteen-valent HPV vaccines. While the fifteen-valent vaccine is still under development, it is showing promising protection against the 15 most common HPV serotypes (21).

Global HPV vaccination programs

When it comes to world HPV vaccination implementation, 149 out of 194 countries have implemented the HPV vaccine, according to the immunization data of the World Health Organization in 2025, into their state immunization programs, with Serbia introducing the HPV vaccine into the national schedule in 2022 (as recommended active immunization for individuals of a certain age (from nine to 19 years old), administered with the nine-valent HPV vaccine, two doses of the vaccine six months apart for ages 9-14, and three doses for ages 15 and older, according to the 0, 2, 6-month schedule). The vaccine is given to boys and girls, it is free, and it is administered intramuscularly (22) (23).

In the European Union, mandatory HPV vaccination is only present in Latvia, while other EU members have general recommendations for the vaccine, offering the vaccination through

Do maja 2025. godine, 29 od 47 afričkih država članica SZO prihvatilo je program vakcinacije. Cilj (koji je dala Afrička regionalna tehnička savetodavna grupa za imunizaciju Regionalnom uredu Svetske zdravstvene organizacije za Afriku - WHO/AFRO) je uspostavljanje režima jednodozne vakcinacije, implementacija rodno neutralne vakcinacije, proširenje starosnog raspona za vakcine, prevazilaženje loših zdravstvenih usluga i ograničenih resursa zdravstvene zaštite u svim državama članicama (22, 26).

U azijsko-pacifičkom regionu, prema trenutnim preporukama (Međunarodne federacije za akušerstvo i ginekologiju za Aziju i Okeaniju, 2024. godine), HPV vakcina nije obavezna; međutim, mora se smatrati obaveznom za osobe sa HIV-om i druge visokorizične grupe. Najveća prevalencija raka grlića materice širom sveta je u Aziji, uglavnom zbog odsustva uvođenja HPV vakcinacije u nacionalne programe imunizacije (zemlje kao što su Kina, Indija, Pakistan i Vijetnam). U zemljama u kojima se primenjuje HPV vakcina, stope obuhvata se razlikuju, pri čemu Turkmenistan postiže najvišu stopu od 99%, a slede ga Uzbekistan, Kambodža, Republika Koreja, Indonezija, Australija i Novi Zeland (22, 27).

HPV vakcina u Republici Srbiji

Srbija je, prema podacima iz 2020. godine, jedna od vodećih zemalja u Evropi po godišnjoj incidenciji raka grlića materice, sa približno 1.200 novih slučajeva i 700 smrtnih ishoda svake godine. Pored toga, učestalost javljanja HPV infekcije kod mladih žena i muškaraca u Srbiji dostižu i do 50%, što predstavlja značajno opterećenje za zdravstveni sistem i javno zdravlje u celini (28).

Pored postojanja organizovanih programa skrininga za rak grlića materice (gde dominira konvencionalni Papanikolau test – PAPA test umesto savremenije opcije PAPA testa na tečnoj podlozi, odnosno *Liquid-Based Cytology - LBC* zbog veće pouzdanosti I HPV testiranja iz istog uzorka) za žene od 25 do 64 godina starosti, od 2012. godine, devetovalentna HPV vakcina *Gardasil 9* je besplatna (putem Republičkog fonda za zdravstveno osiguranje u Srbiji) za decu uzrasta 9–19 godina od 2022. godine. Preporučuje se da se vakcina daje u sedmom razredu osnovne škole, zajedno sa vakcinacijom protiv difterije i tetanusa (23).

Uprkos značaju uvođenja i primene HPV vakcine, odsustvo mandatorne vakcinacije rezultira time da je približno samo 5% populacije u Srbiji vakcinisano protiv HPV infekcije (29). Ovaj ishod je uzrokovan neadekvatnim zdravstvenim kampanjama i opštom svesti javnosti, dezinformacijama i nedostatkom informacija, nedovoljnim obrazovnim inicijativama, nedostatkom promocije i angažovanja zdravstvenih radnika, socioekonomskim izazovima i odsustvom zakonske regulative koja bi obavezala mandatornu HPV vakcinaciju, što čini rak grlića materice četvrtim najčešćim karcinomom kod žena u Srbiji (30).

Zaključak

Primarni metod za smanjenje obolelih i smanjenje maligniteta uzrokovanih HPV infekcijom je da se nacionalni programi vakcinacije protiv HPV-a učine obaveznim i da se implementiraju nove vakcine za serotipove HPV-a koji nisu uključeni u trenutne profilaktičke vakcine. Globalno, unapređenje znanja, prihvatanje programa vakcinacije i zdravstvene kampanje za podsticanje HPV vakcinacije su imperativ širom sveta.

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Konflikt interesa

Autori su izjavili da nema konflikta interesa.

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national immunization programs, with some countries offering gender-neutral vaccination and nearly all of them (with the exception of Romania) being funded by the national health system. (24). The highest vaccination coverage rate in Europe currently exists in Denmark, Norway, Sweden, and Portugal, approximately 90%, while the lowest is found in Southeast Europe. (22)

Four states out of fifty in the United States of America require mandatory HPV vaccination for school entries: Washington, D.C., Virginia, Rhode Island, and Hawaii, while others strongly encourage it through educational campaigns and recommended vaccination schedules. (25)

By May 2025, 29 of the 47 WHO African member states have accepted the vaccination program. The objective (given by the African Regional Immunisation Technical Advisory Group to the World Health Organization (WHO) Regional Office for Africa (WHO/AFRO)) is to establish a single-dose vaccine regimen, implement gender-neutral vaccination, broaden the age range for vaccines, and overcome the burden of poor health services, insufficient public awareness, and limited healthcare resources in all of the member states. (22, 26)

In the Asia-Pacific region, according to the current recommendations (provided by the Asia and Oceania Federation of Obstetrics and Gynecology in 2024), the HPV vaccine is not mandatory; however, it needs to be regarded as mandatory for HIV patients and other high-risk groups. The largest prevalence of cervical cancer worldwide is in Asia, mostly due to the absence of HPV vaccination introductions into national immunization programs (countries such as China, India, Pakistan, and Vietnam). In countries where the vaccination has been implemented, coverage rates differ, with Turkmenistan achieving the highest rate at 99 percent, followed by Uzbekistan, Cambodia, the Republic of Korea, Indonesia, Australia, and New Zealand. (22, 27).

HPV vaccine in the Republic of Serbia

According to the data for 2020, Serbia is one of the foremost countries in Europe regarding annual cervical cancer incidence, reporting approximately 1,200 new cases and 700 deaths each year. Furthermore, HPV infection rates among young females and males in Serbia reach up to 50%, posing a significant burden on the Serbian healthcare system and public health overall (28).

In addition to organized cervical cancer screening programs (where the conventional Papanicolaou test — PAPA test —is dominant instead of the more modern option of the liquid-based PAPA test, i.e., Liquid-Based Cytology—LBC, due to higher reliability and HPV testing from the same sample) for women aged 25 to 64, which have been present since 2012, the nine-valent HPV vaccine Gardasil 9 is free (through the Republic Fund for Health Insurance in Serbia) for children aged 9–19 since 2022. It is recommended that the vaccine should be given in the seventh grade of elementary school, along with diphtheria and tetanus vaccinations (23).

Despite the importance of introducing and implementing the HPV vaccine, the absence of mandatory vaccination results in approximately only 5% of the population in Serbia being vaccinated against HPV infection (29). This outcome is caused by inadequate health campaigns and general public awareness, misinformation and lack of information, insufficient educational initiatives, lack of promotion and engagement of healthcare workers, socioeconomic challenges, and the absence of legal regulations mandating HPV vaccination, making cervical cancer the fourth most common cancer in women in Serbia (30).

Conclusion

The primary method to reduce HPV-contributable diseases and malignancies is to make HPV vaccination programs mandatory and to create new vaccines for HPV types not included in the current prophylactic vaccines. Global public knowledge, acceptability, and health campaigns to advocate for HPV vaccination are imperative worldwide.

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Competing interests

The authors declared no competing interests.

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