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## SADRŽAJ

### ORIGINALNI RAD

*Milan Bjekić*

KARAKTERISTIKE OBOLELIH OD GONOREJE I SIFILISA LEČENIH U GRADSKOM ZAVODU  
ZA KOŽNE I VENERIČNE BOLESTI U BEOGRADU 2016. I 2024. GODINE.....8 - 21

### PREGLEDNI RAD

*Nela Puškaš*

MIKROFOTOGRAFSKI ATLAS NORMALNE HISTOLOGIJE (1925) —  
PIONIRSKI DOPRINOS ALEKSANDRA Đ. KOSTIĆA MEDICINSKOM OBRAZOVANJU.....22 - 31

*Ivana Ilić Savić, Mirjana Petrović-Lazić*

STARENJE KAO INDIKATOR PROMENE KVALITETA GLASA I GOVORA.....32 - 43

*Sara Simanić, Sandra Šipetić Grujičić*

EFIKASNOST HPV VAKCINE U PREVENCIJI RAKA GRLIĆA MATERICE I DRUGIH  
MALIGNOMA.....44 - 57

*Kristina Stamenković*

UTICAJ BIHEVIORALNIH FAKTORA RIZIKA NA NEPLODNOST.....58 - 73

*Katarina Pavić, Nikola Savić, Dušica Perović, Goran Malenković*

STAVOVI I ZNANJA RODITELJA ŠKOLSKE DECE O HPV INFEKCIJI I VAKCINACIJI  
U ZEMLJAMA BIVŠE JUGOSLAVIJE: PREGLEDNI RAD.....74 - 83

### SERIAJ SLUČAJEVA

*Mihajlo Ćurčić, Dražen Radanović, Andrija Savić, Sonja Giljača, Milutin Mrvaljević, Vanja Misić  
Mandić, Marija Rudić, Lukas Rasulić*

TUMORI OVOJNICA PERIFERNIH NERAVA: KLINIČKE I EPIDEMIOLOŠKE KARAKTERISTIKE –  
RETROSPEKTIVNA ANALIZA 46 PACIJENATA.....84 - 93

---

## CONTENTS

### ORIGINAL ARTICLE

*Milan Bjekić*

CHARACTERISTICS OF PATIENTS WITH GONORRHEA AND SYPHILIS TREATED AT THE CITY INSTITUTE FOR SKIN AND VENEREAL DISEASES IN BELGRADE IN 2016 AND 2024 .....8 - 21

### REVIEW ARTICLE

*Nela Puškaš*

MICROPHOTOGRAPHIC ATLAS OF NORMAL HISTOLOGY (1925) —  
PIONEERING CONTRIBUTION OF ALEXANDER Đ. KOSTIĆ TO MEDICAL EDUCATION.....22 - 31

*Ivana Ilić Savić, Mirjana Petrović-Lazić*

AGING AS AN INDICATOR OF CHANGES IN VOICE AND SPEECH QUALITY.....32 - 43

*Sara Simanić, Sandra Šipetić Grujičić*

EFFICACY OF HPV VACCINES IN THE PREVENTION OF CERVICAL CANCER  
AND OTHER MALIGNANCIE.....44 - 57

*Kristina Stamenković*

THE IMPACT OF BEHAVIORAL RISK FACTORS ON INFERTILITY.....58 - 73

*Katarina Pavić, Nikola Savić, Dušica Perović, Goran Malenković*

ATTITUDES AND KNOWLEDGE OF PARENTS OF SCHOOL CHILDREN ABOUT HPV INFECTION  
AND VACCINATION IN THE COUNTRIES OF THE FORMER YUGOSLAVIA: REVIEW.....72 - 81

### CASE SERIES

*Mihajlo Ćurčić, Dražen Radanović, Andrija Savić, Sonja Giljača, Milutin Mrvaljević, Vanja Misić  
Mandić, Marija Rudić, Lukas Rasulić*

PERIPHERAL NERVE SHEATH TUMORS: CLINICAL AND EPIDEMIOLOGICAL CHARACTERISTICS –  
A RETROSPECTIVE ANALYSIS OF 46 PATIENTS.....84 - 93

---

## KARAKTERISTIKE OBOLELIH OD GONOREJE I SIFILISA LEČENIH U GRADSKOM ZAVODU ZA KOŽNE I VENERIČNE BOLESTI U BEOGRADU 2016. I 2024. GODINE

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### SAŽETAK

**Uvod/Cilj:** Gonoreja i sifilis su česte bakterijske polno prenosive infekcije čiji se kontinuirani porast beleži širom sveta, a objašnjava se porastom rizičnog seksualnog ponašanja, upoznavanjem seksualnih partnera preko mobilnih aplikacija, praktikovanjem hemseksa ali i češćim testiranjem na ove polne bolesti među vulnerabilnim grupama. Cilj ovog rada je bio da utvrdi da li postoje razlike u karakteristikama obolelih od gonoreje i sifilisa lečenih u Gradskom zavodu za kožne i venerične bolesti u Beogradu tokom 2016. i 2024. godine i da se identifikuju faktori koji utiču na trenutnu epidemiološku situaciju vezanu za gonoreju i sifilis.

**Metode:** Podaci o osnovnim demografskim karakteristikama, seksualnoj orijentaciji, HIV statusu i prethodnom obolevanju od polnih bolesti obolelih od gonoreje i sifilisa prikupljeni su iz elektronskih kartona i obrazaca za notifikaciju partnera obolelih od ovih infekcija. U statističkoj analizi podataka korišćeni su  $\chi^2$  test i studentov t-test.

**Rezultati:** Oboleli od gonoreje u 2024. godini, u poređenju sa obolelim osobama iz 2016. godine, su značajno češće muškarci ( $p < 0,001$ ), neoženjeni ( $p < 0,001$ ), sa višim stepenom obrazovanja ( $p < 0,001$ ), zaposleni ( $p < 0,001$ ), strani državljani ( $p < 0,001$ ), homoseksualne orijentacije ( $p < 0,001$ ), imali podatak o preležanoj i gonoreji i sifilisu u ličnoj anamnezi ( $p < 0,001$ ) i dijagnozu gonoreje postavljenu uzorkovanjem sa ekstragenitalnih mesta ( $p < 0,001$ ). Oboleli od sifilisa u 2024. godini, u poređenju sa obolelim osobama iz 2016. godine, su značajno češće neoženjeni/neudati ( $p < 0,001$ ), sa višim stepenom obrazovanja ( $p = 0,022$ ), zaposleni ( $p < 0,001$ ), strani državljani ( $p = 0,011$ ), homoseksualne orijentacije ( $p = 0,001$ ) i imali su podatak o preležanoj i gonoreji i sifilisu u ličnoj anamnezi ( $p = 0,014$ ).

**Zaključak:** Češća testiranja na gonoreju i sifilis kod muškaraca koji imaju seksualne odnose sa muškarcima u nevladinim organizacijama i u sklopu propisivanja pre ekspanzije profilakse za HIV, savremeno dijagnostikovanje gonoreje uzorkovanjem materijala iz rektuma i farinksa, praktikovanje rizičnih seksualnih odnosa uz upotrebu hemseksa, kao i migracije izazvane ratom u Ukrajini su uticali na pojavu razlika u karakteristikama obolelih od gonoreje i sifilisa registrovanih u Beogradu u posmatranim godinama.

**Ključne reči:** gonoreja, sifilis, demografske karakteristike, dijagnoza, lečenje, seksualna orijentacija

### Uvod

Prema procenama Svetske zdravstvene organizacije (engl. *World Health Organization* – WHO) iz 2020. godine, u svetu godišnje od gonoreje oboli 82 miliona, a od sifilisa 7,1 miliona osoba starosne dobi od 15 do 49 godina, što predstavlja porast u odnosu na procene iz 2012. godine i to za 5% za gonoreju i 26% za sifilis (1). I u Beogradu se poslednjih godina registruje porast broja novoobolelih od ove dve bakterijske polno prenosive infekci-

je. Podaci iz Beograda pokazuju da je u periodu od 2016. do 2024. godine došlo do porasta incidencije gonoreje za 229,8% (sa 4,16 na 100.000 stanovnika u 2016. godini na 9,56 na 100.000 stanovnika u 2024. godini), a incidencije sifilisa za 165,8% (sa 5,12 na 100.000 stanovnika u 2016. godini na 8,49 na 100.000 stanovnika u 2024. godini) (2, 3).

Podaci iz literature ukazuju da je veći broj faktora uticao na porast obolevanja od sifilisa i gonore-

## CHARACTERISTICS OF PATIENTS WITH GONORRHEA AND SYPHILIS TREATED AT THE CITY INSTITUTE FOR SKIN AND VENEREAL DISEASES IN BELGRADE IN 2016 AND 2024

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### SUMMARY

**Background/Aim:** Gonorrhoea and syphilis are common bacterial sexually transmitted infections, with a continuous increase being recorded worldwide. This rise is explained by the increase in risky sexual behaviors, meeting sexual partners through mobile applications, engaging in chemsex, as well as more frequent testing for these sexually transmitted infections among vulnerable groups. The aim of this study was to determine whether there are differences in the characteristics of patients with gonorrhoea and syphilis treated at the City Institute for Skin and Venereal Diseases in Belgrade during 2016 and 2024, and to identify factors that influence the current epidemiological situation related to gonorrhoea and syphilis.

**Methods:** Data on basic demographic characteristics, sexual orientation, HIV status, and history of previous sexually transmitted infections among patients with gonorrhoea and syphilis were collected from electronic medical records and partner notification forms of individuals diagnosed with these infections. The statistical analysis of the data was performed using the  $\chi^2$  test and Student's t-test.

**Results:** Patients diagnosed with gonorrhoea in 2024, compared to those diagnosed in 2016, were significantly more often male ( $p<0.001$ ), unmarried ( $p<0.001$ ), had a higher level of education ( $p<0.001$ ), were employed ( $p<0.001$ ), foreign citizens ( $p<0.001$ ), with a homosexual orientation ( $p<0.001$ ), had a history of both gonorrhoea and syphilis in their personal medical records ( $p<0.001$ ), and were more often diagnosed with gonorrhoea through sampling from extra genital sites ( $p<0.001$ ). Patients diagnosed with syphilis in 2024, compared to those from 2016, were significantly more often unmarried ( $p<0.001$ ), had a higher level of education ( $p=0.022$ ), were employed ( $p<0.001$ ), foreign citizens ( $p=0.011$ ), with a homosexual orientation ( $p=0.001$ ), and had a history of both gonorrhoea and syphilis in their personal medical records ( $p=0.014$ ).

**Conclusion:** More frequent testing for gonorrhoea and syphilis among men who have sex with men, conducted by non-governmental organizations and as part of HIV pre-exposure prophylaxis programs, modern diagnostic methods for gonorrhoea using samples from the rectum and pharynx, engagement in risky sexual behavior involving chemsex, as well as migration driven by the war in Ukraine, have all contributed to the observed differences in the characteristics of individuals diagnosed with gonorrhoea and syphilis in Belgrade during the years under study.

**Keywords:** gonorrhoea, syphilis, demographic characteristics, diagnosis, treatment, sexual orientation

### Introduction

According to the estimates of the World Health Organization (WHO) from 2020, each year globally there are 82 million new cases of gonorrhoea and 7.1 million new cases of syphilis among adults aged 15 to 49 years, which is an increase by 5% for gonorrhoea and 26% for syphilis compared to the estimates from 2012 (1). An increase in the number of persons newly infected with these two bacterial sexually transmitted infections has also

been registered in Belgrade. Data from Belgrade show that from 2016 to 2024, the incidence of gonorrhoea increased by 229.8% (from 4.16 per 100,000 inhabitants in 2016 to 9.56 per 100,000 inhabitants in 2024), while the incidence of syphilis increased by 165.8% (from 5.12 per 100,000 inhabitants in 2016 to 8.49 per 100,000 inhabitants in 2024) (2,3).

je u svetu u poslednjoj deceniji: lakše upoznavanje seksualnih partnera putem društvenih mreža i mobilnih aplikacija (4, 5); primena preekspozicione profilakse (PrEP) za HIV, naročito u populaciji muškaraca koji imaju seksualne odnose sa muškarcima (MSM), koja štiti od dobijanja HIV infekcije, ali ne i od ostalih polno prenosivih infekcija (6, 7); upotreba droga koje utiču na seksualno ponašanje (hemseks) tako što povećavaju intenzitet seksualnog zadovoljstva kod korisnika, ali sa druge strane potenciraju nebezbedno seksualno ponašanje – seks bez kondoma i praktikovanje grupnog seksa (8), kao i veći obuhvat testiranja na sifilis i gonoreju, naročito među vulnerabilnim grupama za polno prenosive infekcije, i primenu novog protokola za dijagnostiku gonoreje polimeraznom lančanom reakcijom – PCR metodom (engl. *Polymerase chain reaction*) koji podrazumeva uzimanje i testiranje uzoraka i sa ekstragenitalnih regija – farinksa i rektuma (9).

Cilj rada je bio da utvrdimo da li postoje razlike u karakteristikama obolelih od gonoreje i sifilisa lečenih u Gradskom zavodu za kožne i venerične bolesti u Beogradu tokom 2016. i 2024. godine i da identifikujemo faktore koji utiču na trenutnu epidemiološku situaciju vezanu za gonoreju i sifilis.

## Metode

U okviru studije preseka, sprovedene prvi put 2016. i drugi put 2024. godine, analizirani su oboleli od gonoreje i sifilisa koji su tokom navedenih godina lečeni od gonoreje i sifilisa u Gradskom zavodu za kožne i venerične bolesti u Beogradu. Podaci o osnovnim demografskim karakteristikama obolelih od gonoreje i sifilisa u Gradskom zavodu za kožne i venerične bolesti u Beogradu tokom 2024. godine (pol, državljanstvo, uzrast, obrazovanje, zaposlenost i bračni status) i podaci o seksualnoj orijentaciji, HIV statusu i prethodnom obolevanju od polnih bolesti prikupljeni su iz elektronskih kartona, kao i iz obrazaca za notifikaciju partnera obolelih od sifilisa i gonoreje. Podatke o obolelima od gonoreje i sifilisa lečenih u Gradskom zavodu za kožne i venerične bolesti u Beogradu tokom 2016. godine preuzeli smo iz ranije publikovane epidemiološke studije preseka koja je proučavala razlike u seksualnom ponašanju između obolelih od gonoreje i sifilisa tokom 2016. godine (10).

Dijagnoza gonoreje postavljena je na osnovu kliničkog pregleda obolelih i laboratorijske pot-

vrde oboljenja izolovanjem Gram-negativnih intracelularnih diplokokka iz uretre muškaraca ili endocerviksa žena i pozitivnim PCR testom na *Neisseria gonorrhoeae* sa ekstragenitalnih mesta (rektuma i/ili farinksa). Dijagnoza sifilisa postavljena je kliničkim pregledom i pozitivnim netreponemskim (*Venereal Disease Research Laboratory* - VDRL; laboratorijski test za istraživanje veneričnih bolesti) i treponemskim (*Treponema Pallidum Haemagglutination Assay* - TPHA; *Treponema Pallidum* hemaglutinacioni test) serološkim testovima za sifilis U statističkoj analizi podataka korišćeni su  $\chi^2$  test i studentov t-test.

## Rezultati

U tabeli 1 prikazane su karakteristike obolelih od gonoreje u 2016. godini (140 pacijenata) i u 2024. godini (153 pacijenta), a koji su lečeni u Gradskom zavodu za kožne i venerične bolesti u Beogradu. Oboleli od gonoreje u 2024. godini, u poređenju sa obolelim osobama iz 2016. godine, su značajno češće bili muškarci ( $p < 0,001$ ), pripadali su neoženjenim osobama ( $p < 0,001$ ), imali su viši stepen obrazovanja ( $p < 0,001$ ), bili su zaposlena lica ( $p < 0,001$ ), među njima je bilo više stranih državljana ( $p < 0,001$ ), bili su homoseksualne orijentacije ( $p < 0,001$ ), češće su imali podatak o preležanim i gonoreji i sifilisu u ličnoj anamnezi ( $p < 0,001$ ) i češće im je dijagnoza gonoreje postavljena pozitivnim PCR testom uzorkovanim sa ekstragenitalnih mesta ( $p < 0,001$ ). U odnosu na uzrast, podatke o polno prenosivim infekcijama u ličnoj anamnezi i HIV pozitivni status nisu uočene značajne razlike između obolelih u ove dve posmatrane godine.

Karakteristike obolelih od sifilisa lečenih u Gradskom zavodu za kožne i venerične bolesti tokom 2016. godine (138 pacijenata) i u toku 2024. godine (154 pacijenta) prikazane su u Tabeli 2. Oboleli od sifilisa u 2024. godini, u poređenju sa obolelima iz 2016. godine, su značajno češće pripadali neoženjenim/neudatim licima ( $p < 0,001$ ), imali su viši stepen obrazovanja ( $p < 0,05$ ), bili su zaposleni ( $p < 0,001$ ), među njima je bilo više stranih državljana ( $p = 0,011$ ), bili su homoseksualne orijentacije ( $p = 0,001$ ) i češće su imali podatak o preležanoj i gonoreji i sifilisu u ličnoj anamnezi ( $p = 0,014$ ). U odnosu na uzrast, pol, podatke o polno prenosivim infekcijama u ličnoj anamnezi i HIV pozitivnom statusu nisu postojale značajne razlike među obolelima u posmatranim godinama.

Data from the literature indicate that a greater number of factors have influenced the increase in the incidence of syphilis and gonorrhea in the world in the last decade: easier meeting of sexual partners through social networks and mobile applications (4,5); the implementation of pre-exposure prophylaxis (PrEP) for HIV, especially in the population of men who have sex with men (MSM), which protects from getting HIV, but not from other sexually transmitted infections (6,7); the use of drugs that affect sexual behavior (chemsex) by increasing the intensity of sexual pleasure of the user, but on the other hand encouraging unsafe sexual behavior – sex without condoms and practicing group sex (8), as well as greater share of testing for syphilis and gonorrhea, especially among vulnerable groups for sexually transmitted infections and the application of the new protocol for the diagnosis of gonorrhea using the polymerase chain reaction (PCR) method, which involves taking and testing samples from extragenital sites – the pharynx and rectum (9).

The aim of this study was to determine whether there are differences in the characteristics of patients with gonorrhea and syphilis treated at the City Institute for Skin and Venereal Diseases in Belgrade in 2016 and 2024, and to identify factors that affect the current epidemiological situation related to gonorrhea and syphilis.

## Methods

As part of the cross sectional study, which was conducted for the first time in 2016 and the second in 2024, patients with syphilis and gonorrhea, who were treated at the City Institute for Skin and Venereal Diseases in Belgrade during the mentioned years, were analyzed. Data on basic demographic characteristics of patients with gonorrhea and syphilis treated at the City Institute for Skin and Venereal Diseases in Belgrade during 2024 (sex, citizenship, age, education, marital status) and data on sexual orientation, HIV status and previous sexually transmitted diseases were collected from electronic medical records and partner notification forms of individuals diagnosed with gonorrhea and syphilis. Data on patients affected by gonorrhea and syphilis, who were treated at the City Institute for Skin and Venereal Diseases in Belgrade in 2016, were taken from the previously published epidemiological

cross-sectional study which analyzed differences in sexual behavior among patients with gonorrhea and syphilis during 2016 (10).

The diagnosis of gonorrhea was established based on the clinical examination of patients and the laboratory confirmation of disease with the isolation of Gram-negative intracellular diplococci from the urethra in men or the endocervix in women and with the PCR test for *Neisseria gonorrhoeae* from extragenital sites (rectum and/or pharynx). The diagnosis of syphilis was established using the clinical examination and positive nontreponemal (Venereal disease Research Laboratory – VDRL; laboratory test for the examination of venereal diseases) and treponemal (Treponema Pallidum Haemagglutination Assay – TPHA) serological tests for syphilis. The  $\chi^2$  test and Student's t-test were used in the statistical analysis of data.

## Results

The characteristics of patients with gonorrhea in 2016 (140 patients) and in 2024 (153 patients), treated at the City Institute for Skin and Venereal Diseases in Belgrade were shown in Table 1. The patients diagnosed with gonorrhea in 2024 compared to patients in 2016 were significantly more often men ( $p < 0.001$ ), unmarried ( $p < 0.001$ ), had a higher degree of education ( $p < 0.001$ ), were employed ( $p < 0.001$ ), were more often foreign citizens ( $p < 0.001$ ), were persons with a homosexual orientation ( $p < 0.001$ ), more often had a history of both gonorrhea and syphilis in their personal medical records ( $p < 0.001$ ) and the diagnosis of gonorrhea was more often established using the positive PCR test sampled from extragenital sites ( $p < 0.001$ ). In relation to age, data on sexually transmitted infections in personal medical history and HIV status, there were no significant differences between these two observed years.

The characteristics of patients with syphilis treated at the City Institute for Skin and Venereal Diseases during 2016 (138 patients) and during 2024 (154 patients) were shown in Table 2. Patients diagnosed with syphilis in 2024, compared to patients in 2016 were more often unmarried persons ( $p < 0.05$ ), had a higher degree of education ( $p < 0.001$ ), were more often foreign citizens ( $p = 0.011$ ), were persons with a homosexual orientation ( $p = 0.001$ ) and more often had a history of both gonorrhea and syphilis in their personal

**Tabela 1.** Izabrane karakteristike pacijenata obolelih od gonoreje u Gradskom zavodu za kožne i venerične bolesti Beograd u 2016. i 2024. godini

Karakteristike	Oboleli od gonoreje 2016. godina N=140	Oboleli od gonoreje 2024. godina N=153	p vrednost za $\chi^2$ test
<b>Uzrast (AS<math>\pm</math>SD)</b>	31,04 $\pm$ 9,77	32,79 $\pm$ 8,61	0,105*
<b>Pol</b>			
Muški	125 (89,3)	151 (98,7)	<0,001
Ženski	15 (10,7)	2 (1,3)	
<b>Bračni status</b>			
Neoženjen/neudate	114 (81,4)	148 (96,7)	<0,001
Oženjen/udate	14 (10,0)	4 (2,6)	
Razvedeni	12 (8,5)	1 (0,7)	
Udovci/Udovice	0 (0,0)	0 (0,0)	
<b>Obrazovanje (godine školovanja)</b>			<0,001
≤12	92 (65,7)	60 (39,2)	
>12	48 (54,3)	93 (60,8)	
<b>Zanimanje</b>			
Zaposlena lica	74 (52,6)	124 (81,0)	<0,001
Nezaposlena lica	42 (30,0)	6 (3,9)	
Izdržavana lica	21 (15,0)	21 (13,7)	
Penzioneri	3 (2,4)	2 (1,4)	
<b>Državljanstvo</b>			
Republika Srbija	140 (100,0)	134 (87,6)	<0,001
Strano	0 (0,0)	19 (12,4)	
<b>Seksualna orijentacija</b>			<0,001
Heteroseksualna	85 (60,7)	22 (14,4)	
Homoseksualna	47 (33,6)	131 (85,6)	
Biseksualna	8 (5,7)	0 (0)	
<b>Polno prenosive infekcije u ličnoj anamnezi</b>			
Gonoreja	60 (42,9)	80 (52,3)	0,106
Sifilis	31 (22,1)	39 (22,5)	0,502
Gonoreja i sifilis	6 (4,3)	14 (9,2)	0,099
HIV pozitivan status	3 (2,1)	27 (17,6)	<0,001
PCR pozitivan test na <i>Neisseria gonorrhoeae</i> sa ekstragenitalnog mesta	8 (5,7)	17 (11,1)	0,098
	0 (0,0)	47 (30,7)	<0,001

AS- aritmetička sredina; SD-standardna devijacija; \*p vrednost za Studentov t-test; PCR- polimerazna lančana reakcija (engl. *Polymerase chain reaction*)

## Diskusija

Gradski zavod za kožne i venerične bolesti predstavlja referentnu ustanovu za lečenje polno prenosivih infekcija u Beogradu u kojoj se registruje preko 95% novoobolelih od sifilisa i gonoreje (2,3). Porast incidencije gonoreje i sifilisa u Beogradu u periodu od 2016. do 2024. godine je u skladu sa porastom incidencije ovih oboljenja i u zemljama Evropske unije (EU). U periodu 2014-2023. godina u zemljama EU došlo je do porasta incidencije gonoreje za 321%, a sifilisa za 100% (11, 12). Najviša zabeležena stopa incidencije gonoreje

bila je u 2023. godini i iznosila je 24,8 na 100.000 stanovnika, dok je najviša stopa incidencije sifilisa takođe zabeležena u 2023. godini i iznosila je 9,9 na 100.000 stanovnika.

Prema rezultatima našeg istraživanja prema uzrastu nisu postojale značajne razlike kod obolelih od gonoreje i sifilisa u posmatranim godinama (2016. vs. 2024), a oboljenja su najčešće registrovana kod osoba uzrasta 20 do 39 godina, što je u skladu sa izveštajima o obolelima od gonoreje i sifilisa u Republici Srbiji i u zemljama EU. Prema podacima Instituta za javno zdravlje Re-

**Table 1.** Selected characteristics of patients with gonorrhoea at City Institute for Skin and Venereal Diseases in Belgrade in 2016 and 2024.

Characteristics	Gonorrhoea cases 2016 N=140	Gonorrhoea cases 2024 N=153	p value for $\chi^2$ test
<b>Age (AM<math>\pm</math>SD)</b>	31.04 $\pm$ 9.77	32.79 $\pm$ 8.61	0.105*
<b>Gender</b>			
Male	125 (89.3)	151 (98.7)	<0.001
Female	15 (10.7)	2 (1.3)	
<b>Marital status</b>			
Never married	114 (81.4)	148 (96.7)	<0.001
Married	14 (10.0)	4 (2.6)	
Divorced	12 (8.5)	1 (0.7)	
Widowed	0 (0.0)	0 (0.0)	
<b>Education (years spent in school)</b>			<0.001
$\leq$ 12	92 (65.7)	60 (39.2)	<0.001
>12	48 (54.3)	93 (60.8)	
<b>Occupation</b>			
Employed	74 (52.6)	124 (81.0)	<0.001
Unemployed	42 (30.0)	6 (3.9)	
Supported persons	21 (15.0)	21 (13.7)	
Retired	3 (2.4)	2 (1.4)	
<b>Citizenship</b>			
Republic of Serbia	140 (100.0)	134 (87.6)	<0.001
Foreign	0 (0.0)	19 (12.4)	
<b>Sexual orientation</b>			<0.001
Heterosexual	85 (60.7)	22 (14.4)	<0.001
Homosexual	47 (33.6)	131 (85.6)	
Bisexual	8 (5.7)	0 (0)	
<b>Sexually transmitted infections in personal history</b>			
<b>Gonorrhoea</b>	60 (42.9)	80 (52.3)	0.106
<b>Syphilis</b>	31 (22.1)	39 (22.5)	0.502
<b>Both gonorrhoea and syphili</b>	6 (4.3)	14 (9.2)	0.099
<b>HIV positive</b>	3 (2.1)	27 (17.6)	<0.001
<b>PCR positive test for <i>Neisseria gonorrhoeae</i> from an extragenital site</b>	8 (5.7)	17 (11.1)	0.098
	0 (0.0)	47 (30.7)	<0.001

AM- arithmetic mean; SD-standard deviation; \*p value for Student t-test; PCR- Polymerase chain reaction

medical records ( $p=0.014$ ). In relation to age, sex, data on sexually transmitted infections in their personal medical history and HIV positive status, there were no significant differences between patients in the observed years.

## Discussion

The City Institute for Skin and Venereal Diseases is the reference institution for the treatment of sexually transmitted infections in Belgrade, where more than 95% of new cases of syphilis and gonorrhoea are registered (2,3). The increase in the incidence of gonorrhoea and syphilis

in Belgrade from 2016 to 2024 is in accordance with the increase in incidence of these diseases in the countries of the European Union (EU). In the period 2014-2023, in the EU countries, the incidence of gonorrhoea increased by 321%, and the incidence of syphilis by 100% (11,12). The highest recorded incidence rate of gonorrhoea was in 2023 and it amounted to 24.8 per 100,000, while the highest incidence rate of syphilis was also recorded in 2023 and it amounted to 9.9 per 100,000.

According to the results of our research, there was no significant difference in relation to

**Tabela 2.** Izabrane karakteristike pacijenata obolelih od sifilisa u Gradskom zavodu za kožne i venerične bolesti Beograd u 2016. i 2024. godini

Karakteristike	Oboleli od gonoreje 2016. godina N=138	Oboleli od gonoreje 2024. godina N=154	p vrednost za $\chi^2$ test
<b>Uzrast (AS<math>\pm</math>SD)</b>	34,03 $\pm$ 10,21	36,31 $\pm$ 11,34	0,073*
<b>Pol</b>			
Muški	132 (95,7)	148 (96,1)	0,845
Ženski	6 (4,3)	6 (3,9)	
<b>Bračni status</b>			<0,001
Neoženjen/neudate	114 (82,6)	150 (97,4)	
Oženjen/udate	14 (10,1)	4 (2,6)	
Razvedeni/	9 (6,5)	0 (0,0)	
Udovci/Udovice	1 (0,7)	0 (0,0)	
<b>Obrazovanje (godine školovanja)</b>			0,022
≤12	75 (54,3)	63 (40,9)	
>12	63 (45,7)	91 (59,1)	
<b>Zanimanje</b>			<0,001
Zaposlena lica	84 (60,9)	137 (89,0)	
Nezaposlena lica	42 (30,4)	3 (1,9)	
Izdržavana lica	8 (5,8)	10 (6,5)	
Penzioneri	4 (2,9)	4 (2,6)	
<b>Državljanstvo</b>			0,011
Republika Srbija	138 (100,0)	147 (95,5)	
Strano	0 (0,0)	7 (4,5)	
<b>Seksualna orijentacija</b>			0,001
Heteroseksualna	31 (22,5)	19 (12,3)	
Homoseksualna	95 (68,8)	132 (85,7)	
Biseksualna	12 (8,7)	3 (2,0)	
<b>Polno prenosive infekcije u ličnoj anamnezi</b>		65 (42,2)	0,277
<b>Gonoreja</b>	18 (13,0)	16 (10,4)	0,480
<b>Sifilis</b>	24 (17,4)	28 (18,2)	0,860
<b>Gonoreja i sifilis</b>	4 (2,9)	18 (11,7)	0,014
<b>HIV pozitivan status</b>	31 (22,5)	28 (18,2)	0,363

AS- aritmetička sredina; SD-standardna devijacija; \*p vrednost za Studentov t-test;

publike Srbije u 2023. godini (13) najveće uzrasno specifične stope za gonoreju su bile u grupi od 20 do 29 godina (6,6 na 100.000) i od 30 do 39 godina (5,01 na 100.000), dok su za sifilis bile najveće od 20 do 29 godina (14,2 na 100.000) i od 30 do 39 godina (14,1 na 100.000). Podaci iz zemalja EU za 2023. godinu (11, 12) pokazuju da su najveće uzrasno specifične stope za gonoreju kod muškaraca bile u grupi 25 do 34 godina (131,1 na 100.000) i od 20 do 24 godine (126,8 na 100.000) a kod žena od 20 do 24 godina (71,7 na 100.000) i od 15 do 19 godina (33,1 na 100.000), dok su za sifilis najveće stope kod muškaraca bile u uzrasnoj grupi od 25 do 34 godina (43,1 na 100.000) i od 35 do 44 godine (35,5 na 100.000) a kod žena od 20 do 24

godine (7,5 na 100.000) i od 25 do 34 godine (6,2 na 100.000).

Oboleli od gonoreje u 2024. godini, u poređenju sa obolelim osobama iz 2016. godine, su značajno češće bili neoženjeni zaposleni muškarci sa višim stepenom obrazovanja homoseksualne orijentacije, pripadali su stranim državljanima i u ličnoj anamnezi su imali podatak o preležanoj gonoreji i sifilisu, a gonoreja im je češće dijagnostikovana PCR testom uzorkovanim sa ekstragenitalnih mesta. Prema našim rezultatima u 2024. godini MSM osobe su činile čak 86% obolelih od gonoreje, dok je njihov udeo u obolelima od gonoreje u zemlji EU u toku 2023. godine bio 58% (11). Češće obolevanje od gonoreje među MSM populacijom

**Table 2.** Selected characteristics of patients with syphilis at City Institute for Skin and Venereal Diseases in Belgrade in 2016 and 2024

Characteristics	Syphilis cases 2016 N=140	Syphilis cases 2024 N=153	p value for $\chi^2$ test
<b>Age (AM<math>\pm</math>SD)</b>	34.03 $\pm$ 10.21	36.31 $\pm$ 11.34	0.073*
<b>Gender</b>			
Male	132 (95.7)	148 (96.1)	0.845
Female	6 (4.3)	6 (3.9)	
<b>Marital status</b>			<0.001
Never married	114 (82.6)	150 (97.4)	
Married	14 (10.1)	4 (2.6)	
Divorced	9 (6.5)	0 (0.0)	
Widowed	1 (0.7)	0 (0.0)	
<b>Education (years spent in school)</b>			0.022
$\leq$ 12	75 (54.3)	63 (40.9)	
>12	63 (45.7)	91 (59.1)	
<b>Occupation</b>			<0.001
Employed	84 (60.9)	137 (89.0)	
Unemployed	42 (30.4)	3 (1.9)	
Supported persons	8 (5.8)	10 (6.5)	
Retired	4 (2.9)	4 (2.6)	
<b>Citizenship</b>			0.011
Republic of Serbia	138 (100.0)	147 (95.5)	
Foreign	0 (0.0)	7 (4.5)	
<b>Sexual orientation</b>			0.001
Heterosexual	31 (22.5)	19 (12.3)	
Homosexual	95 (68.8)	132 (85.7)	
Bisexual	12 (8.7)	3 (2.0)	
<b>Sexually transmitted infections in personal history</b>		65 (42.2)	0.277
<b>Gonorrhoea</b>	18 (13.0)	16 (10.4)	0.480
<b>Syphilis</b>	24 (17.4)	28 (18.2)	0.860
<b>Both gonorrhoea and syphili</b>	4 (2.9)	18 (11.7)	0.014
<b>HIV positive</b>	31 (22.5)	28 (18.2)	0.363

AS- aritmetička sredina; SD-standardna devijacija; \*p vrednost za Studentov t-test;

age between patients affected by gonorrhoea and syphilis in the observed years (2016 vs. 2024), while these diseases were most often registered in persons aged 20 to 39, which is in accordance with reports on patients diagnosed with gonorrhoea and syphilis in the Republic of Serbia and EU countries. According to the data of the Institute of Public Health of the Republic of Serbia in 2023 (13), the highest age-specific rates for gonorrhoea were in the age group 20 to 29 years (6.6 per 100,000) and in the group 30 to 39 years (5.01 per 100,000), while the highest rates for syphilis were in the age group 20 to 29 (14.2 per 100,000) and in the group 30 to 39 (14.1 per 100,000). Data from the EU countries for the year 2023 (11,12) show that the

highest age-specific rates for gonorrhoea in men were in the age group 25 to 34 years (131.1 per 100,000) and in the group 20 to 24 years (126.8 per 100,000), and in women in the age group 20 to 24 years (71.7 per 100,000) and in the group 15 to 19 years (33.1 per 100,000), while for syphilis the highest rates were in men in the age group 25 to 34 years (43.1 per 100,000) and in the group 35 to 44 years (35.5 per 100,000) and in women in the age group 20 to 24 years (7.5 per 100,000) and in the group 25 to 34 years (6.2 per 100,000).

Patients diagnosed with gonorrhoea in 2024, compared to patients in 2016 were significantly more often single employed men with a higher level of education, persons with a homosexual

moglo bi se objasniti visoko rizičnim seksualnim ponašanjem, seksom sa nepoznatim osobama upoznatim preko mobilnih aplikacija, upotrebom hemseksa, ali i ekspanzijom testiranja na gonoreju zbog propisivanja PrEP-a za HIV, kao i uzorkovanjem materijala sa ekstragenitalnih mesta, jer su infekcije farinksa i rektuma obično asimptomatske (11). Tokom 2016. godine u Beogradu se nisu vršila testiranja na gonoreju iz farinksa i rektuma, tako da se dijagnoza gonoreje postavljala direktnom mikroskopijom (10), a tokom 2024. godine kod skoro  $\frac{1}{3}$  novoobolelih dijagnoza je postavljena pozitivnim PCR testom na *Neisseria gonorrhoeae* iz rektuma i/ili farinksa. Ova testiranja se sprovode u privatnim laboratorijama i ne praktikuju se u državnim ustanovama, tako da su dostupnija zaposlenim osobama višeg stepena obrazovanja i boljeg materijalnog statusa. Nevladine organizacije koje rade sa MSM populacijom u Beogradu, svoje korisnike, a naše pacijente, upućuju na ova testiranja u okviru savetovanja za PrEP za HIV (14), a oni sa pozitivnim nalazom dolaze u Gradski zavod za kožne i venerične bolesti radi ordiniranja terapije.

Oboleli od sifilisa u 2024. godini u poređenju sa obolelim osobama iz 2016. godine su značajno češće pripadali zaposlenim neoženjenim/neudatim licima sa višim stepenom obrazovanja, a među njima je bilo i više stranih državljana, bili su homoseksualne orijentacije i češće su imali podatak o preležanoj i gonoreji i sifilisu u ličnoj anamnezi. Prema našim rezultatima u 2024. godini MSM osobe su činile čak 86% obolelih od sifilisa, dok je njihov udeo u obolelima od sifilisa u zemljama EU u toku 2023. godine bio 72% (12). Faktori koji utiču da se sifilis najčešće registruje u ovoj populaciji su visoko rizična seksualna ponašanja (veći broj partnera, analni seksualni odnosi bez upotrebe kondoma, upotreba hemseksa), HIV pozitivan status, upotreba PrEP-a i regularna testiranja na sifilis pre uvođenja PrEP-a za HIV prema vodiču Međunarodne unije za borbu protiv seksualno prenosivih infekcija (engl. *International union against sexually transmitted infections* – IUSTI) u Evropi (15). Prema podacima istraživanja sprovedenog u Beogradu koje je obuhvatilo 469 MSM osoba u toku 2023. godine 26,2% ispitanika je praktikovalo hemseks koji je bio povezan i sa visokorizičnim seksualnim ponašanjem i podatkom o ponavljanom obolevanju od sifilisa i gonoreje u ličnoj anamnezi (16). Rezultati ovog istraživanja takođe potvrđuju da su

oboleli od sifilisa u 2024. godini u anamnezi imali podatak o češćem obolevanju od sifilisa i gonoreje. Studija među pacijentima sa ponovnim obolevanjem od polno prenosivih infekcija rađena u Beogradu je pokazala da pored specifičnih dimenzija ličnosti ovi pacijenti praktikuju visoko rizična seksualna ponašanja (17). Praksa čestog testiranja na sifilis i HIV među MSM populacijom sprovodi se brzim testovima kod korisnika usluga nevladinih organizacija koje rade sa ovom osetljivom grupom na polno prenosive infekcije i u našoj sredini (18). U istraživanju razloga dolaska MSM osoba u jednu nevladinu organizaciju u Beogradu, čak 95% korisnika je došlo radi testiranja na sifilis i HIV, a 12,1% njih je došlo radi uvođenja PrEP-a za HIV (14). U toku 2016. godine u Beogradu nije postojala mogućnost testiranja na sifilis u nevladinim organizacijama, niti su bili dostupni lekovi za PrEP čija je upotreba podrazumevala i prethodno testiranje na sifilis.

Oboleli od sifilisa i gonoreje u 2024. godini u poređenju sa obolelima iz 2016. godine su značajno češće bili strani državljanima, naime tokom 2016. godine u našoj ustanovi nisu ni registrovani strani državljanima oboleli od sifilisa i/ili gonoreje. Broj stranaca koji su imigrirali u toku 2023. godine u Republiku Srbiju je bio 9,5 puta veći u odnosu na 2012. godinu, a  $\frac{2}{3}$  njih su činili muškarci. Najveći broj imigranata u toku 2023. godine je došao u Beograd (44%), a čak 83,5% njih je došlo iz Ruske Federacije, Narodne Republike Kine, Turske i Indije (19). U našem istraživanju preko 90% obolelih stranaca od sifilisa i gonoreje bili su Ruski državljanima. Broj Ruskih državljana koji su imigrirali u Republiku Srbiju u 2023. godini bio je 47 puta veći u odnosu na 2012. godinu i 54,4% osoba su bili muškarci prosečne starosti od 30 godina (19). Studija koja se bavila istraživanjem polno prenosivih infekcija među populacijom migranata, imigranata i raseljenih lica je utvrdila da su incidencija i prevalencija HIV infekcije, hepatitisa B, hepatitisa C i sifilisa u pomenutoj populaciji bile veće u odnosu na domaće stanovništvo (20). Stigmatizacija, kulturološke i jezičke barijere, kao i teža dostupnost zdravstvenih usluga ovu populaciju čine vulnerabilnom za polno prenosive infekcije.

## Zaključak

Oboleli od gonoreje i sifilisa u 2024. godini su u poređenju sa obolelima iz 2016. godine bili obrazovaniji, češće neoženjeni, zaposleni muškar-

orientation, foreign citizens and had a history of gonorrhea and syphilis, while gonorrhea was more often diagnosed using the PCR test sampled from extragenital sites. According to our results in 2024, MSM accounted for 86% of patients with gonorrhea, while their share in patients affected by gonorrhea in the EU countries in 2023 was 58% (11). The more frequent incidence of gonorrhea among the MSM population could be explained by high-risk sexual behavior, including sex with unknown persons met through mobile applications, the use of chemsex, as well as by the expansion of testing for gonorrhea due to the prescription of PrEP for HIV, and sampling the material from extragenital sites, because infections of the pharynx and rectum are usually asymptomatic (11). During 2016, tests for gonorrhea sampled from the pharynx and rectum were not performed in Belgrade, so the diagnosis of gonorrhea was established using direct microscopy (10), and in 2024, in almost 1/3 of new cases the diagnosis was established using the positive PCR test for *Neisseria gonorrhoea* from the pharynx and/or rectum. These tests are conducted in private laboratories and they are not practiced in state institutions, and therefore, they are more accessible to employed persons with a higher degree of education and better financial status. Non-governmental organizations that work with the MSM population in Belgrade refer their users to these tests as part of counseling for PrEP for HIV (14), and those with a positive result come to the City Institute for Skin and Venereal Diseases in order to get the therapy.

Patients diagnosed with syphilis in 2024 compared to patients in 2016 were significantly more often employed unmarried persons with a higher degree of education, and there were more foreign citizens among them, they were persons with a homosexual orientation, and more often they had data on both gonorrhea and syphilis in their personal medical records. According to our results in 2024, MSM accounted for even 86% of patients affected by syphilis, while their share in syphilis cases in the EU countries in 2023 was 72% (12). The factors that affect the fact that syphilis is most frequently registered in this population are high-risk sexual behaviors (greater number of partners, anal sexual relations without the use of condoms, use of chemsex), HIV positive status, use of PrEP and regular testing for syphilis before the introduction of PrEP for HIV according

to the Guidelines of the International Union Against Sexually Transmitted Infections (IUSTI) in Europe (15). According to the data of the study conducted in Belgrade, which included 469 MSM persons in 2023, 26.2% of respondents practiced chemsex, which was also related to high-risk sexual behavior and information about repeated cases of syphilis and gonorrhea in the personal medical records (16). The results of this study also confirm that patients with syphilis in 2024 had a history of more frequent syphilis and gonorrhea in their personal medical records. A study which was conducted among patients with recurrent sexually transmitted infections in Belgrade showed that in addition to specific dimensions of personality, these patients practiced high-risk sexual behaviors (17). The practice of frequent testing for syphilis and HIV among the MSM population is conducted using rapid tests in users of the services of non-governmental organizations that work with this group which is vulnerable to sexually transmitted diseases in our environment (18). In a study that analyzes the reasons why MSM persons visit a non-governmental organization in Belgrade, as many as 95% of users came in order to be tested for HIV and syphilis, while 12.1% of them came in order to get PrEP for HIV (14). During 2016, there was no possibility of testing for syphilis in non-governmental organizations in Belgrade, and PrEP drugs were not available, the use of which also required previous testing for syphilis.

Patients with syphilis and gonorrhea in 2024 compared to patients in 2016 were significantly more often foreign citizens, namely, during 2016, no foreign citizens diagnosed with gonorrhea and syphilis were registered in our institution. The number of foreigners who immigrated to the Republic of Serbia in 2023 was 9.5 times higher than in 2012, and 2/3 of them were men. The largest number of immigrants came to Belgrade in 2023 (44%), and as many as 83.5% of them came from the Russian Federation, the People's Republic of China, Turkey and India (19). In our study, more than 90% of foreigners diagnosed with gonorrhea and syphilis were Russian citizens. The number of Russian citizens who immigrated to the Republic of Serbia in 2023 was 46 times higher than in 2012, and 54.4% of them were men with an average age of 30 (19). A study that dealt with the investigation of sexually transmitted infections in the population of migrants, immigrants and displaced persons

ci, lica homoseksualne orijentacije sa podatkom o prethodnom obolevanju od gonoreje i sifilisa i među njima je bilo više stranih državljana naročito iz Ruske Federacije i sa dijagnozom gonoreje postavljenom PCR testom sa ekstragenitalnih lokacija. Češća testiranja na gonoreju i sifilis kod MSM osoba u nevladinim organizacijama i u sklopu propisivanja PrEP-a, savremeno dijagnostikovanje gonoreje uzorkovanjem materijala iz rektuma i farinksa, praktikovanje rizičnih seksualnih odnosa uz upotrebu hemseksa, kao i migracije izazvane ratom u Ukrajini, su uticali na pojavu razlika u karakteristikama obolelih od gonoreje i sifilisa registrovanih u Beogradu u posmatranim godinama.

## Konflikt interesa

Autor je izjavio da nema konflikta interesa.

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found that the incidence and prevalence of HIV infection, hepatitis B, hepatitis C and syphilis in the above mentioned population were higher than in the local population (20). Stigmatization, cultural and language barriers, as well as limited availability of health services make this population vulnerable to sexually transmitted infections.

## Conclusion

Patients with gonorrhea and syphilis in 2024 compared to patients in 2016 were more educated, more often unmarried, employed men, persons with a homosexual orientation, with information on previous gonorrhea and syphilis and there were more foreign citizens among them, especially from the Russian Federation, with a diagnosis of gonorrhea which was established using the PCR test sampled from extragenital sites. More frequent testing for gonorrhea and syphilis among MSM in non-governmental organizations and as part of prescribing PrEP, modern diagnostic methods for gonorrhea using samples from the rectum and pharynx, engagement in risky sexual behavior involving chemsex, as well as migrations caused by the war in Ukraine have contributed to the appearance of differences in the characteristics of individuals diagnosed with gonorrhea and syphilis in Belgrade in the observed years.

## Competing interests

The author declared no competing interests.

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## MIKROFOTOGRAFSKI ATLAS NORMALNE HISTOLOGIJE (1925) — PIONIRSKI DOPRINOS ALEKSANDRA Đ. KOSTIĆA MEDICINSKOM OBRAZOVANJU

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### SAŽETAK

Tokom prvih godina rada Medicinski fakultet se suočavao sa brojnim izazovima, među kojima se posebno isticao nedostatak stručne literature, naročito one na srpskom jeziku. U oblasti histologije, dodatni izazov je bio prikazivanje mikroskopskih preparata i njihovo prepoznavanje u okviru praktične nastave, jer se oslanjalo isključivo na crteže. Inovaciju u nastavi doneo je 1925. godine *Mikrofotografski atlas normalne histologije*, autora Aleksandra Kostića. Bio je to prvi histološki atlas namenjen studentima Medicinskog fakulteta u Beogradu i jedan od prvih u svetu koji je u potpunosti sadržao mikrofotografije. Kostić je set mikrofotografija za atlas izradio u Fotografskom odeljenju, osnovanom pri Institutu 1924. godine.

Objavljivanjem ovog atlasa, Aleksandar Kostić je utemeljio svoju naučno-fotografsku misiju, čime je postao pionir medicinske fotografije, kako u Srbiji, tako i u tadašnjoj Kraljevini Srba, Hrvata i Slovenaca.

**Ključne reči:** Aleksandar Đ. Kostić, mikrofotografija, histološki atlas

Profesor Aleksandar Đ. Kostić bio je prvi profesor histologije i embriologije na Medicinskom fakultetu u Beogradu i osnivač Histološkog instituta (danas Institut za histologiju i embriologiju), koji od 1983. godine nosi njegovo ime.

Diplomirao je 1921. godine na Medicinskom fakultetu u Strazburu, a već u januaru naredne godine vratio se u Beograd. Uslovi za rad koje je zatekao na Fakultetu bili su izuzetno skromni i ograničeni, kako u pogledu nastave, tako i naučnoistraživačkog rada, jer se zemlja još uvek oporavljala od posledica Velikog rata. Poseban izazov predstavljao je nedostatak stručne literature, naročito one na srpskom jeziku. Prve generacije studenata učile su iz skripti napisanih na osnovu stenografskih beležaka sa predavanja, koja je objavljivalo Udruženje jugoslovenskih medicinara. Prvi originalni udžbenik histologije Kostić je objavio 1927. godine. Pre njega, jedino je profesor anatomije Ilija Šapšal izdao udžbenik iz anatomije (1923), međutim, bio je to prevod sa ruskog jezika (1).

Predavanja i vežbe iz histologije i embriologije održavani su svim radnim danima, u trajanju od jednog, odnosno dva sata<sup>1</sup>. Na vežbama se radilo u grupama od po tridesetak studenata. Mikroskopi su bili pozajmljeni sa Instituta za fiziologiju i Instituta za patologiju, koji su ranije osnovani. Stolovi i klupe su pozajmljeni od Dunavske bolničarske čete. Nije se oskudevalo jedino u histološkim preparatima, jer je komplet od oko 2.000 preseka Kostić izradio još tokom boravka u Strazburu, u laboratoriji profesora Pola Buena (fr. *Pol Bouin*) (2, 3).

### Istorijski kontekst i značaj mikrofotografije u histologiji

Do ranih 1920-ih, većina histoloških atlasa sadržala je ručno izrađene crteže, koji su, iako često umetnički kvalitetni, bili podložni subjektivnim interpretacijama autora i nisu uvek verno odražavali mikroskopske detalje. I sam Kostić u predgovoru

<sup>1</sup> Podatak dobijen uvidom u Univerzitetske kalendare, objavljivane za svaku školsku godinu tokom međuratnog perioda

## MICROPHOTOGRAPHIC ATLAS OF NORMAL HISTOLOGY (1925) — PIONEERING CONTRIBUTION OF ALEXANDER Đ. KOSTIĆ TO MEDICAL EDUCATION

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### SUMMARY

During its early years, the Faculty of Medicine faced numerous challenges, one of which was the lack of medical literature, especially in the Serbian language, which was particularly pronounced. In histology, an additional challenge was the presentation and identification of microscopic specimens during practical classes because it relied solely on drawings. An innovation in teaching was introduced in 1925 with the Microphotographic Atlas of Normal Histology, authored by Aleksandar Kostić. It was the first histological atlas intended for students of the Medical Faculty in Belgrade and one of the first in the world to contain complete microphotographs. Kostić prepared the set of microphotographs for the atlas in the Photography Department, established at the Institute in 1924.

By publishing this atlas, Aleksandar Kostić established his scientific-photographic mission, making him a pioneer in medical photography both in Serbia and in the then Kingdom of Serbs, Croats, and Slovenes.

**Keywords:** Aleksandar Đ. Kostić, microphotography, histology atlas

Professor Aleksandar Đ. Kostić was the first professor of Histology and Embryology at the Faculty of Medicine in Belgrade and the founder of the Institute of Histology (now the Institute of Histology and Embryology), which has been named after him since 1983.

He graduated from the Faculty of Medicine in Strasbourg in 1921, and already in January of the following year he returned to Belgrade. The working conditions, which he found at the Faculty, were extremely modest and limited, both in terms of teaching and scientific research, because the country was still recovering from the consequences of the Great War. A special challenge referred to the lack of literature, especially in the Serbian language. The first generations of students learned from scripts written on the basis of shorthand notes from lectures, which were published by the Association of Yugoslav Medics. Kostić published the first original Histology textbook in 1927. Before him, only Anatomy Professor Ilija Šapšal published

a textbook on Anatomy (1923), however, it was a translation from the Russian language (1).

Histology and Embryology lectures and laboratory exercises were held on all weekdays and lasted one or two hours<sup>1</sup>. Exercises were done in groups of about thirty students. Microscopes were borrowed from the Institute of Physiology and the Institute of Pathology, which had been established before. Desks and chairs were borrowed from the Danube Army Hospital Unit. However, the only thing they did not lack were histological slides, because Professor Kostić made a set of about 2,000 sections during his stay in Strasbourg in the laboratory of Professor Pol Bouin (2,3).

### Historical context and importance of microphotography in histology

Until the early 1920s, most histological atlases contained drawings, which although, often of

<sup>1</sup> Data obtained from University calendars, published for each school year during the interwar period

svog Atlasa kaže da „prilikom reprodukcije rukom postoji nesvesna sklonost ka uproščavanju slike, ako ne i ka jačem i vidnijem isticanju detalja koji se s toliko jasnoće stvarno ne zapažaju. Otud se crtež gotovo uvek manje ili više udaljuje od originala.” (4).

Upravo je razvoj mikroskopije i fotografije omogućio stvaranje autentičnih snimaka tkiva i organa, čime je znatno unapređena objektivnost i tačnost prikaza. Mikrofotografija se kao metoda u histologiji razvijala od kraja 19. veka, ali je njen značajan prodor usledio tek početkom 20. veka, zahvaljujući tehničkim unapređenjima fotografskih sistema i mikroskopa. To je omogućilo izradu atlasa koji su, pored brojnih crteža, bili ilustrovani i mikrofotografijama, u početku malobrojnim (5, 6). Razlog tome leži u činjenici da je mikrofotografska tehnika ipak bila slabije dostupna i vrlo skupa, a zahtevala je dobro poznavanje i histologije i same fotografske tehnike. Prof. Emil Holmgren sa Karolinska instituta u Švedskoj u predgovoru svog, inače, prvog udžbenika iz histologije na švedskom jeziku (1920), takođe se osvrće na te probleme. Njegov udžbenik je sadržao veliki broj mikrofotografija, i objavljen je uz finansijsku pomoć donatora (7).

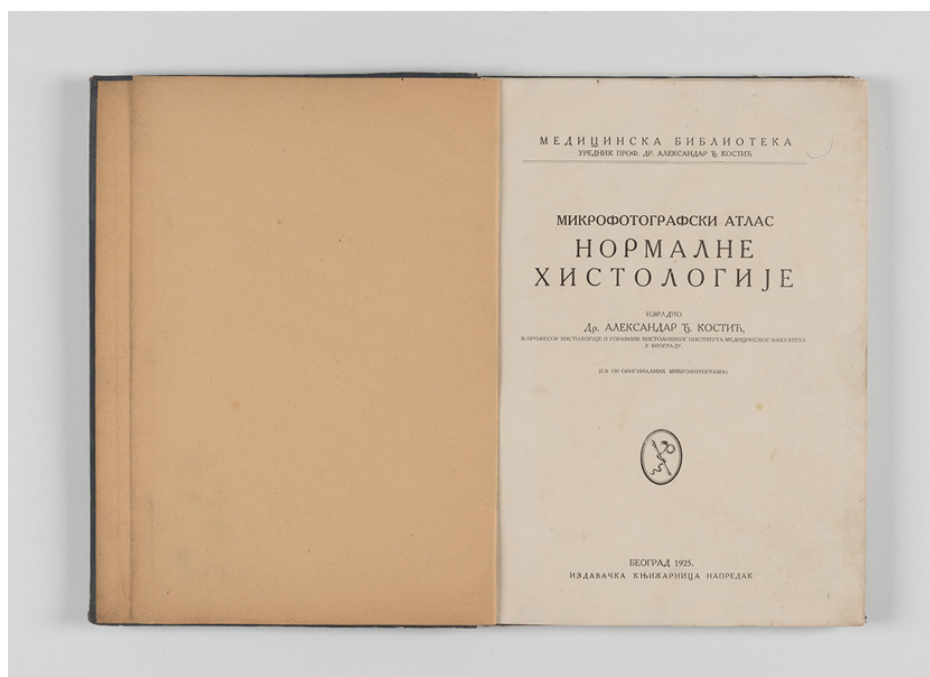
### Mikrofotografski atlas normalne histologije

*Mikrofotografski atlas normalne histologije* je nastao za nepunih godinu dana rada Fotografskog odeljenja, koje je 1924. godine osnovano pri His-

tološkom institutu. Kako je naglasio sam Kostić, bio je i „prva tekovina” Odeljenja (slika 1) (3). U pitanju je histološki atlas kompletno opremljen autentičnim mikrofotografijama. Gotovo sve histološke preparate je izradio sam profesor Aleksandar Kostić, dok su svega dva izradili njegovi saradnici Svetislav Popović (kora malog mozga) i Aleksandar Telebaković (nervna vlakna).

Na stranicama Atlasa, 143 mikrofotografije su raspoređene u 70 „tablica” (duplih strana). Najpre su predstavljeni različiti oblici ćelija (jedna tablica), zatim faze ćelijskog ciklusa (pet tablica) (slika 2), vrste tkiva (16 tablica) i najzad preparati različitih organa. Na najvećem broju tablica se prikazane strukture vide na malom, a zatim i na velikom uveličanju, kako bi se bolje sagledali pojedini specifični detalji (slika 3). Na tablicama su najpre navedeni naziv preparata, poreklo uzorka, korišćeno uveličanje, vrsta fiksativa i tehnika bojenja, uglavnom i legenda za označene strukture, a zatim slede detaljna, često i vrlo živopisna i detaljna objašnjenja. Takvim metodološkim postupkom Kostić je studentima obezbedio izvanredno učilo, koje im je nesumnjivo olakšavalo razumevanje i usvajanje gradiva, a moglo je da im bude korisno i kasnije, pri izučavanju patohistologije.

Pored značaja koji je imao u svoje vreme, Atlas je iz današnje perspektive, vrlo interesantan za dodatnu analizu iz nekoliko aspekata. Naime, poznato je da se Kostić bavio medicinskom terminologijom



**Slika 1.** Mikrofotografski atlas normalne histologije (digitalizovano u Audiovizualnom arhivu i centru za digitalizaciju SANU)

artistic quality, were subject to authors' subjective interpretations and did not always faithfully reflect microscopic details. Kostić himself says in the preface of his Atlas that "when reproducing by hand, there is an unconscious tendency towards simplifying the image, and even towards a stronger and more visible highlighting of details that are not really noticed with such clarity. Therefore, the drawing deviates from the original more or less." (4).

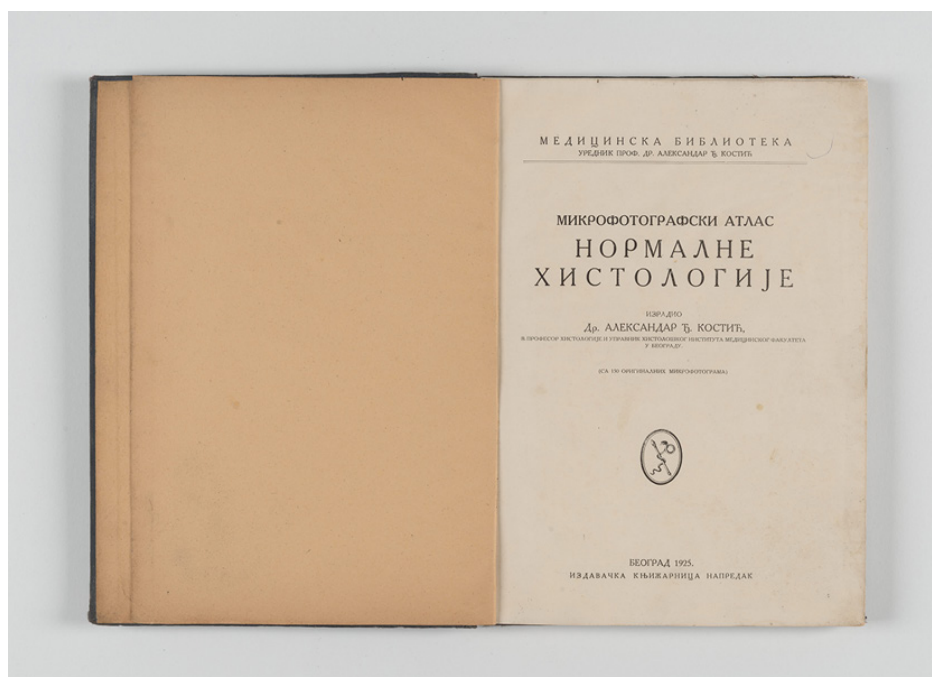
It was precisely the development of microscopy and photography that made it possible to create authentic images of tissues and organs, which significantly improved the objectivity and accuracy of the presentation. Microphotography as a method in histology has developed since the end of the 19th century, but its significant breakthrough came at the beginning of the 20th century, thanks to the technical improvements of photographic systems and microscopes. This enabled the creation of atlases, which, in addition to numerous drawings, were also illustrated with microphotographs that were not numerous in the beginning (5,6). The reason for this lies in the fact that the microphotographic technique was still less available and very expensive, and it required knowing both histology and the photographic technique well. Prof Emil Holmgren from the Karolinska Institute in Sweden, in the preface of his textbook on histology, which is the first textbook

on histology in the Swedish language (1920), also referred to these problems. His textbook contained a lot of microphotographs, and it was published with the financial help of donors (7).

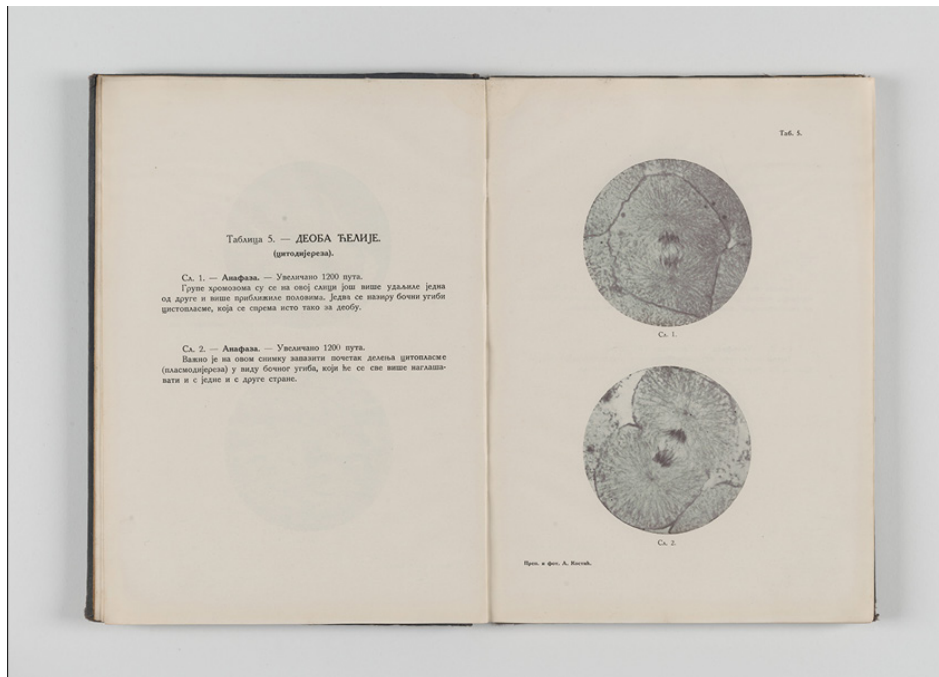
## Microphotographic Atlas of Normal Histology

*The Microphotographic Atlas of Normal Histology* was created in less than a year by the Department of Photography, which was established at the Institute of Histology in 1924. As Professor Kostić emphasized, it was "the first achievement" of the Department (Picture 1) (3). It is a histological atlas completely equipped with authentic microphotographs. Almost all histological slices were made by Professor Aleksandar Kostić himself, while only two were made by his associates Svetislav Popović (the cerebellar cortex) and Aleksandar Telemeković (nerve fibers).

On the pages of the Atlas, 143 microphotographs were arranged in 70 "panels" (double pages). First, different shapes of cells were presented (one panel), then phases of the cell cycle (five panels) (Picture 2), types of tissue (16 panels) and, finally, histological slides of different organs. In the majority of panels, the structures are shown at low and then at high magnification, to provide a clearer view of specific details (Picture 3). The name of the slide, the origin of the sample,



**Picture 1.** Microphotographic Atlas of Normal Histology (digitized in SASA Audiovisual Archive and Center for Digitalization)

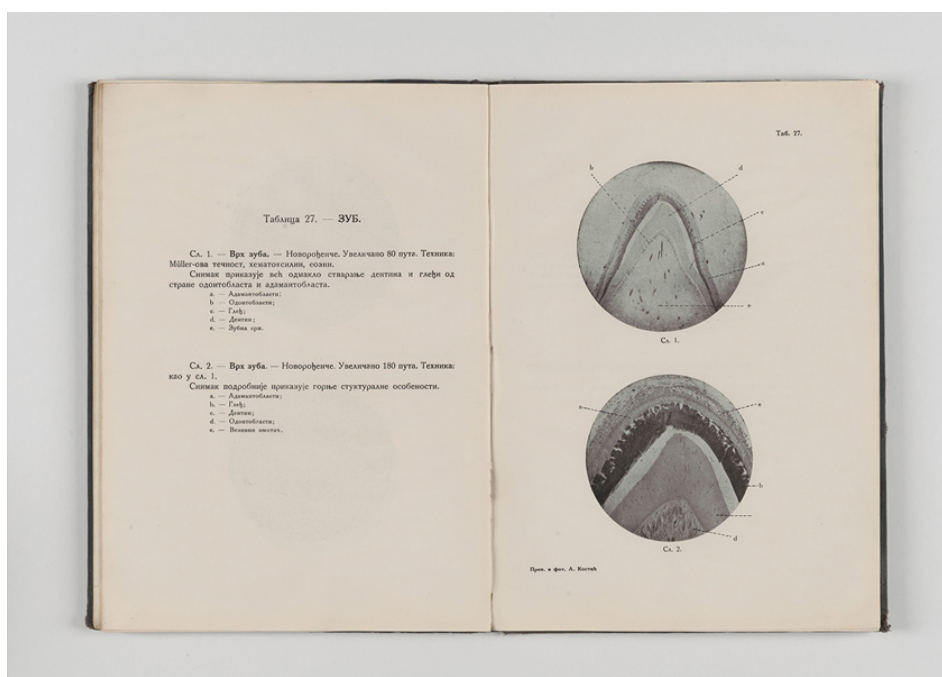


Slika 2. Tablica 5 – „Deoba ćelije” (digitalizovano u AVA SANU)

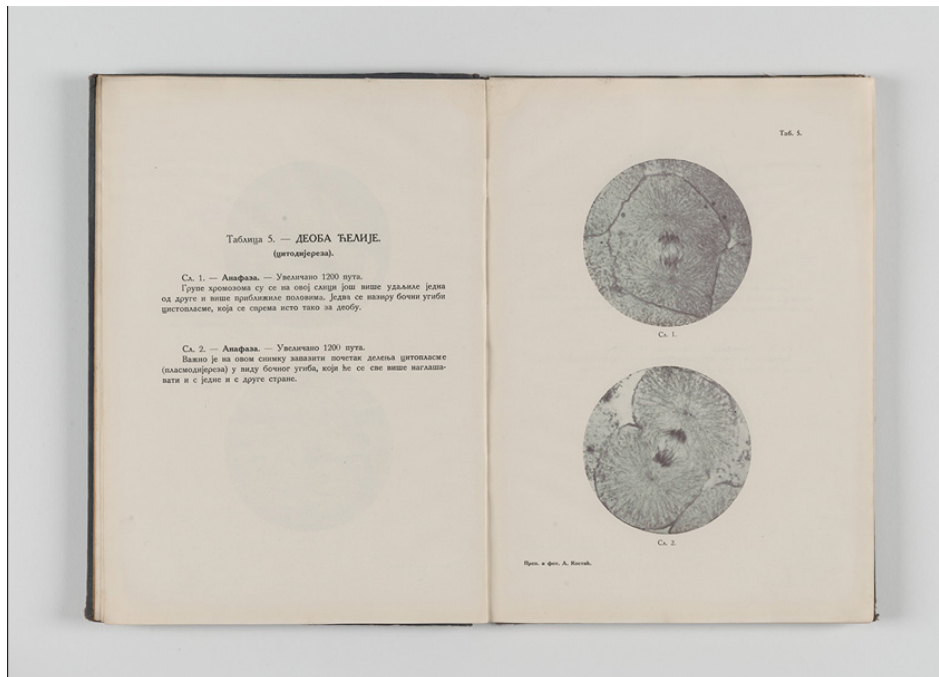
i da je bio autor višezjezičnog Medicinskog rečnika. Pojedini termini korišćeni u Atlasu, koji danas više nisu u upotrebi, kao na primer: citodijereza (deoba ćelije), polutarski venac (ekvatorijalna ravan), zona ušorene rskavice (zona proliferacije), podgrlačna žlezda (štitasta žlezda), vezivne obge (vezivne lamele) i brojni drugi, predstavljaju interesantan materijal za proučavanje razvoja srpske medicinske tj. histološke terminologije. Kostićevi opisi snimaka preparata su vrlo živopisni, sa mnogo prideva, i veoma se razlikuju od današnjih, koji su

kratki, jasni i vrlo precizni. Zanimljiv primer je opis pasemnika (epididimisa): „Ovaj snimak izvanredno jasno prikazuje izgled epididimnog kanala, kada se njegove ćelije nalaze u punom jeku lučenja sekretornih zrna” (4).

Za razliku od savremene prakse u medicinskoj histologiji, koja se bazira na korišćenju humanog materijala i uzoraka dobijenih od ograničenog broja životinjskih vrsta, Kostić je pored humanih, koristio i uzorke vrlo različitog porekla: od riba, žaba, zmija, ježeva, ptica, ovaca, pasa, zečeva, i



Slika 3. Tablica 27 – „Zub” (digitalizovano u AVA SANU)

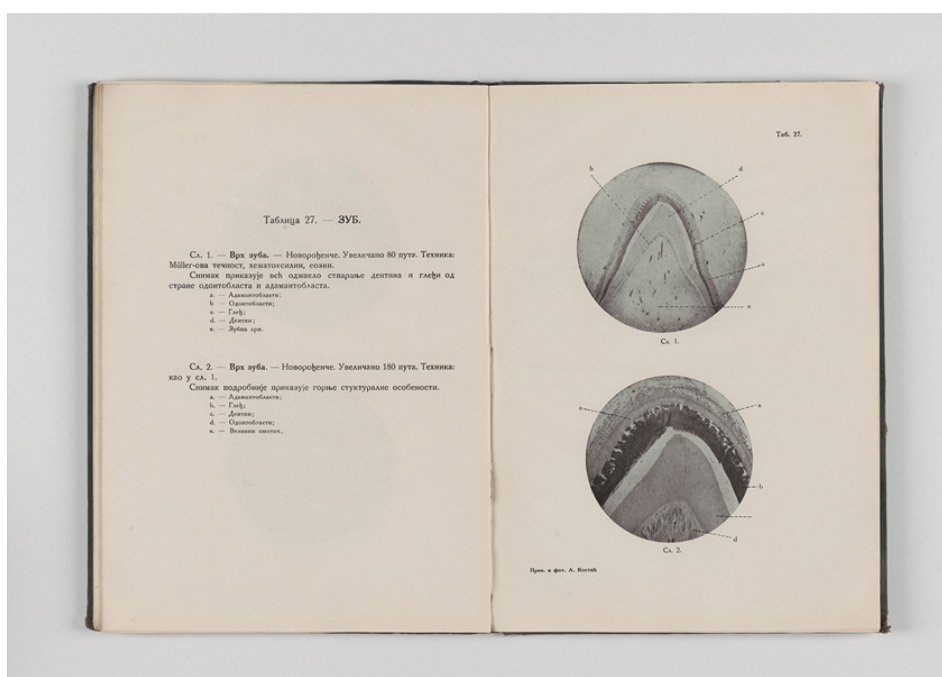


Picture 2. Panel 5 – “Cell Division” (digitized in SASA AVA)

the used magnification, the type of fixative, the staining technique and usually the legend for the labeled structures were listed on the panels first, followed by detailed and often very comprehensive explanations. With this methodological approach, Kostić provided students with an excellent learning tool that not only facilitated their understanding and acquisition of the material, but could also serve them later during their study of pathohistology.

In addition to its significance at that time, the Atlas is, from today’s perspective, very

interesting for additional analysis from several aspects. Namely, it is known that Kostić dealt with medical terminology and that he was the author of the multilingual Medical dictionary. Certain terms used in the Atlas, which are no longer used today, such as: cytodieresis (cell division), semilunate wreath (equatorial plane), zone of linearly arranged cartilage (proliferative zone in cartilage), subthroat gland (thyroid gland), membranous sheets of connective tissue (connective lamellae), and numerous other terms



Picture 3. Panel 27 – “Tooth” (digitized in SASA AVA)

drugih životinja, sve do krupnih sisara poput konja i bikova. Kao primer specifične strukturne organizacije mehanoreceptora prikazao je i Herbstov i Grandrijev korpuskul u koži i kljunu patke. Herbstov korpuskul u koži ptica, inače, ima strukturu sličnu Vater-Pačinijevom korpuskulu kod ljudi.

Iz opisa preparata se može videti da je za fiksiranje uzoraka tkiva uglavnom koristio Buenovu tečnost, fiksativ koji je u praksu uveo njegov nekadašnji mentor, profesor Pol Buen. Danas se uglavnom koristi formalin, jer je praktičniji za rukovanje, jeftiniji, bezbedniji, a često i efikasniji (8,9). Najveći broj preparata prikazanih u Atlasu je obojen gvožđevitim hemateinom po Hajdenhajnu (*Heidenhain*), koji boji jedra crno, a citoplazmu sivkasto. Prema Kostićevim rečima, upravo su to bili tonovi, koje je bilo moguće savršeno reprodukovati na crno-belim mikrofotografijama (4). Međutim, za pojedine strukturne detalje, koji se nisu mogli jasno uočiti na tako obojenim preparatima, upotrebljena su druga histohemijska bojenja, od kojih se pojedina danas retko koriste, poput bojenja osmijumovom kiselinom (danas se koristi prevashodno u elektronskoj mikroskopiji) ili bojenje zlatnim hloridom sa mravljom kiselinom. Razlog njihovoj ređoj upotrebi u savremenoj histologiji leži najpre u činjenici da su tehnički zahtevnija, a sa druge strane zdravstveno nebezbedna. Pojedine histohemijske metode su zamenjene uvođenjem gotovih histohemijskih kitova, a sedamdesetih godina prošlog veka započeo je intenzivan razvoj imunohistohemije. Međutim, preparati obojeni imunohistohemijskim metodama još uvek nisu uključeni u studentske vežbe, zbog visoke cene antitela i vizualizacionih kitova, ali su zato fotografije dostupne online, na brojnim veb-stranicama.

Na kraju, možemo primetiti i da su pojedine mikrofotografije slabijeg kvaliteta, što i sam Kostić komentariše: „Nedostatak dovoljne jasnosti i oštine dolaze od izvanredne teškoće da se ganglion snimi” (4). Može se pretpostaviti da su neki isečci tkiva bili neujednačene ili prevelike debljine, što je otežavalo izoštravanje slike na mikroskopu i posledično davalo lošiji kvalitet fotografija. Ovaj tehnički nedostatak na pojedinim mikrofotografijama ni u kom slučaju ne umanjuje kvalitet i značaj Atlasa u celini.

Mikrofotografski atlas normalne histologije je publikovan kao osma knjiga *Medicinske biblioteke*,

koju je izdavala knjižara Napredak Armina Švarca, a uređivao profesor Kostić (4). Bio je to zaista izdavački i tehnički (štamparski) poduhvat za to vreme u koji su, pored izdavača, bila uključena još dva preduzeća – Grafički zavod Tipografija iz Zagreba (izrada klišea za štampu) i Štamparija „Markarije” iz Zemuna. Kostić se u predgovoru posebno zahvalio Švarcu zbog „materijalnih žrtava” kojima se „podvrgao” i izrazio zadovoljstvo zbog dobro obavljenog posla „udruženim snagama”. Sagledavajući unapred dimenzije i značaj celog poduhvata, u predgovoru je izrazio nadu i da će aktuelni napredak u štamparstvu omogućiti dobru tehničku opremu „naših medicinskih izdanja tako potrebnih fakultetima u zemlji.” (4). Sam Kostićev atlas je u metodološkom pogledu bio uzor za izradu još jednog važnog atlasa u međuratnom periodu – Atlasa patološke histologije, autora prof. Ksenofona Šahovića i doc. Dimitrija Tihomirova (1932) (10).

U posleratnom periodu nije bilo novih izdanja Mikrofotografskog atlasa normalne histologije, ali je Kostić objavio više dopunjenih izdanja udžbenika iz histologije i embriologije. Svi oni su bili bogato ilustrovani mikrofotografijama prvobitno objavljenim u Atlasu. Kostićevi udžbenici su bili u upotrebi decenijama. Naime, tek je 1977. godine objavljen udžbenik iz embriologije, autora profesora Steve Popovića (11), dok je 1981. izašao iz štampe udžbenik iz histologije grupe nastavnika sa Katedre (12). Pošto je „novi” udžbenik bio uglavnom opremljen crtežima, ponovo se pojavila potreba za histološkim atlasom, koji je zatim i publikovan 1988. godine (13) i do danas imao osam izdanja. Međutim, značaj tog atlasa poslednjih godina je umanjen velikom dostupnošću digitalnih fotografija, kako na zvaničnoj stranici Instituta, tako i na drugim veb-stranicama.

## Zaključak

*Mikrofotografski atlas normalne histologije* Aleksandra Đ. Kostića iz 1925. godine predstavlja važan iskorak u istoriji medicinskog obrazovanja u Srbiji, a takođe je i reprezent tehničkog i pedagoškog napretka u prvim decenijama 20. veka. Povodom stogodišnjice od njegovog objavljivanja, u maju ove godine u Galeriji nauke i tehnike SANU organizovana je izložba *Pogled kroz okular*, na kojoj su predstavljeni Atlas i naučna zaostavština profesora Aleksandra Kostića.

constitute a valuable resource for examining the evolution of Serbian medical — and especially histological — terminology. Kostić's descriptions of the slide images are very vivid, rich in adjectives and markedly different from today's descriptions, which are brief, clear, and highly precise. An interesting example is the description of the epididymis: "This image shows the appearance of the epididymal canal remarkably clearly, when its cells are in full swing of secreting secretory granules" (4).

In contrast to modern practice in medical histology, which is based on the use of human material and samples obtained from the limited number of animal species, Kostić, in addition to human samples, also used samples of very different origins: from fish, frogs, snakes, hedgehogs, birds, sheep, dogs, rabbits and other animals, to large mammals, such as horses and bulls. As an example of the specific structural organization of mechanoreceptors, he presented Herbst and Grandry corpuscles in the skin and beak of a duck. Herbst corpuscle in the skin of birds has a structure similar to the Vater-Pacini corpuscle in humans.

From the description of the preparation, it can be seen that he mainly used Bouin's solution for fixing tissue samples, a fixative introduced into practice by his former mentor, Professor Paul Bouin. Formalin is mainly used today, because it is more convenient to handle, it is cheaper, safer and often more effective (8,9). The majority of specimens presented in the Atlas were stained with Heidenhain's iron hematoxylin, which stains the nuclei black and the cytoplasm grey. According to Kostić, these were the tones that could be perfectly reproduced on black-and-white microphotographs (4). However, for certain structural details, which could not be clearly seen on specimens stained in that way, other histochemical staining methods were used, some of which are rarely used today, such as staining with osmic acid (today it is primarily used in electron microscopy) or gold chloride staining with formic acid. The reason for their less frequent use in modern histology primarily lies in the fact that they are technically more demanding, and, on the other hand, pose health hazards. Certain histochemical methods were replaced by ready-to-use histochemical kits, and also, the intensive development of immunohistochemistry began in the 1970s of the last century. However, histological specimens

stained by immunohistochemical methods have not been included in student exercises yet due to the high cost of antibodies and visualization kits; nevertheless, photographs are available online on numerous websites.

Finally, we can also notice that certain microphotographs are of lower quality, which Kostić himself comments: "The lack of sufficient clarity and sharpness comes from the extraordinary difficulty to take a picture of ganglion" (4). It can be assumed that some tissue sections were uneven or too thick, which made it difficult to focus the image on the microscope and consequently gave a lower quality of photographs. This technical defect in individual microphotographs did not diminish the quality and importance of the Atlas as a whole.

The Microphotographic Atlas of Normal Histology was published as the eighth book of *Medical Library*, which was published by the Armin Švarc's bookstore Napredak and edited by Professor Kostić (4). It was truly a publishing and technical (printing) undertaking for that time, in which, in addition to the publisher, two other companies were involved – Graphic Institute Tipografija from Zagreb (production of clichés for printing) and Printing House "Makarije" from Zemun. In the preface, Kostić especially thanked Švarc for the "material sacrifices" he made and expressed his satisfaction with the job that was done well by the "joined forces". By realizing the dimensions and significance of this undertaking in advance, he expressed his hope in the preface that the current progress in printing will enable good technical equipment "of our medical editions so needed by the faculties in our country." (4). Kostić's atlas itself was in the methodological sense a model for the creation of another important atlas in the interwar period – the Atlas of Pathological Histology, authored by Professor Ksenofon Šahović and Associate Professor Dimitrije Tihomirov (1932) (10).

In the post-war period, there were no new editions of the Microphotographic Atlas of Normal Histology, however, Kostić published several updated editions of Histology and Embryology textbooks. All of them were richly illustrated with microphotographs originally published in the Atlas. Kostić's textbooks were in use for decades. Namely, not earlier than 1977 a textbook on Embryology was published and it was authored by Professor Steva Popović (11) while in 1981, a textbook on

## Konflikt interesa

Autor je izjavio da nema konflikta interesa.

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Histology was published by a group of authors from the Institute (12). Since the “new” textbook was primarily illustrated with drawings, the need for a histological atlas emerged again. As a result, one was published in 1988 (13) and has had eight editions to date. However, the importance of that atlas has been diminished in recent years because of the wide availability of digital photos, both on the official website of the Institute and on other websites.

## Conclusion

*The Microphotographic Atlas of Normal Histology* by Aleksandar Đ. Kostić from 1925 represents an important step forward in the history of medical education in Serbia and is also representative of technical and pedagogical progress in the first decades of the 20th century. On the occasion of the centenary of its publication, the exhibition *A View Through the Eyepiece* was held in May this year at the Gallery of Science and Technology of the Serbian Academy of Sciences and Arts, showcasing the Atlas and the scientific legacy of Professor Aleksandar Kostić.

## Competing interests

The author declared no competing interests.

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## STARENJE KAO INDIKATOR PROMENE KVALITETA GLASA I GOVORA

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### SAŽETAK

Tokom procesa starenja dolazi do određenih promena u glasu i govoru. Glas osobe se tokom starenja menja, postaje nestabilniji, manje fleksibilan i javlja se promuklost. Ova studija ima za cilj da analizira efekte starenja na frekvenciju glasa, intenzitet glasa i ritam i tempo govora. Literatura je proučavana korišćenjem elektronskih baza podataka, posebno Google Scholar Advanced Search i Konzorcijuma biblioteka Srbije za objedinjenu nabavku - KoBSON. Rezultati pokazuju da postoji pogoršanje akustičkih parametara glasa (frekvence i intenziteta glasa) sa godinama. Takođe je primećeno da je proces starenja u glasu izraženiji kod žena nego kod muškaraca. To se može objasniti hormonskim promenama koje su posebno izražene kod žena u periodu menopauze. Posle šezdesete godine intenzitet glasa postaje niži nezavisno od pola osobe. U zavisnosti od starosti osobe, menja se i ritam i tempo kojim govori. Utvrđeno je da starijim ispitanicima treba više vremena da izgovore određene glasove, što je povezano sa odlaganjem početka fonacije pri izgovoru alveolarnih i bilabijalnih glasova, a što se najčešće pripisuje degradaciji vilice. Studije pokazuju da starenje glasa i govora protiče postepeno i očekivano, sa jasno izraženim posledicama po svakodnevni život, što treba imati u vidu u kliničkoj praksi radi unapređenja kvaliteta života starijih osoba.

**Ključne reči:** starenje, frekvencija glasa, intenzitet glasa, ritam i tempo govora

### Uvod

Starenje je prirodan i univerzalan biološki proces u životnom ciklusu svakog ljudskog bića. Kada govorimo o starenju, to je nepovratan fiziološki proces, koji utiče na smanjenje fizičkih i mentalnih sposobnosti osobe, a takođe utiče i na kvalitet samog glasa, u zavisnosti od starosne dobi te osobe (1). Veoma je važno razlikovati hronološko od biološkog starenja, zato što neki stariji ljudi mogu da budu funkcionalno sposobni (1,2,3).

Tokom procesa starenja dolazi do određenih promena u glasu i govoru. Glas osobe se menja tokom starenja, postaje nestabilniji, manje fleksibilan i javlja se promuklost. Kada dođe do promena glasa zbog starenja, taj proces se naziva prezbi-fonija. Primećeno je takođe da je proces starenja glasa izraženiji kod muškaraca nego kod žena (4).

Promene tokom proizvodnje glasa dešavaju se tokom celog života, i povezuju se sa brojnim činje-

nicama koje postoje u ljudskom životu, kao što su kognitivno, socijalno, biološko i emocionalno sazrevanje čoveka (1).

Od samog početka ljudskog života, fiziološke potrebe se izražavaju kroz fonaciju različitih glasova. Na primer, beba izražava i pokazuje glad, zadovoljstvo, sreću i tugu plakanjem ili kasnije gukanjem. U kasnijim fazama, postepeno se razvija govor, i na te načine dete počinje da izražava svoje misli, osećanja, zadovoljstvo i nezadovoljstvo. Nakon toga, od osamnaeste godine, glas postaje zreliji i pojedinac je u stanju da kontroliše svoj glas, kao i da menja frekvencije. Međutim, odrasle osobe često podižu tonalitet govora, i u tim situacijama dolazi do oštećenja glasa (5).

Veličina farinksa i usta varira čak i kod vrlo mlade dece. Međutim, kada je u pitanju larinks, on se ne razlikuje kod dečaka i devojčica sve do

## AGING AS AN INDICATOR OF CHANGES IN VOICE AND SPEECH QUALITY

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### SUMMARY

During the aging process, certain changes occur in the voice and speech. A person's voice changes during aging, becoming more unstable, less flexible, and hoarseness occurs. This study aims to analyze the effects of aging on voice frequency, voice intensity, and the rhythm and tempo of speech. The literature was studied using electronic databases, in particular Google Scholar Advanced Search and the Serbian Library Consortium for Coordinated Acquisition - KoBSON. The results show that there is a deterioration in the acoustic parameters of the voice (voice frequency and intensity) with age. It has also been observed that the aging process in the voice is more pronounced in women than in men. This can be explained by hormonal changes that are especially pronounced in women during menopause. After the age of sixty, the intensity of the voice becomes lower regardless of the person's gender. Depending on the person's age, the rhythm and tempo of speech also change. It was found that older subjects take longer to pronounce certain sounds, which is associated with a delay in the onset of phonation when pronouncing alveolar and bilabial sounds, which is most often attributed to jaw degradation. Studies show that voice and speech aging occurs gradually and as expected, with clearly expressed consequences for everyday life, which should be taken into account in clinical practice in order to improve the quality of life of older people.

**Key words:** aging, voice frequency, voice intensity, rhythm and pace of speech

### Introduction

Aging is a natural and universal biological process in the life cycle of every human being. When we talk about aging, it is an irreversible physiological process, which affects the reduction of a person's physical and mental abilities, and also leads to an impact on the quality of the voice itself, depending on the person's age (1). It is very important to distinguish chronological aging from biological aging, because some people who are older may be more functionally capable (1,2,3).

During the aging process, there are certain changes in the voice and speech. A person's voice changes during aging, becoming more unstable, less flexible and hoarseness occurs. When voice changes occur due to aging, the process is called presbyphonia. It has also been observed that the aging process in the voice is more pronounced in women than in men (4).

Changes during voice production occur throughout life, and are related to numerous facts that exist in human life, such as the cognitive, social, biological and emotional maturation of a human being (1).

From the very beginning of human life, physiological needs have been expressed through the phonation of various voices. For example, a baby expresses and shows its hunger, contentment, happiness and sadness by crying and later cooing. In the later stages, speech gradually develops, and in these ways the child begins to express his thoughts, feelings, satisfaction and dissatisfaction. After that, from the age of eighteen, the voice becomes more mature, and the individual is able to control his voice, as well as change frequencies. However, adults often raise the tonality of their speech, and in those situations lead to voice damage (5).

puberteta. Mutacija glasa kod dečaka obično traje od 11. do 14. godine, a zatim dolazi do rasta larinksa. Kada su u pitanju devojčice, primećene su određene promene tokom puberteta, međutim, farinks i larinks rastu proporcijalno sa ostalim delovima tela. Značajnija razlika između dečaka i devojčica i promene koje nastaju ogledaju se u promenama na membrani glasnih žica, koje se dešavaju različitom brzinom kod dečaka i devojčica što dovodi do brojnih razlika koje se ogledaju u karakteristikama glasa (6).

Larinks, odnosno njegova struktura i funkcija opadaju kako osoba sazreva i stari. U starosti dolazi do narušavanja strukturnog, ćelijskog i neuromuskularnog integriteta. Promene koje nastaju u larinksu, a nastaju zbog starenja dovode do uništavanja površine zgloba, hrskavice, potpornih struktura, ligamenata i glasnih žica. Kada su u pitanju osobe starosti do 80 godina, iako u nekim slučajevima to može biti ranije, javlja se takozvani „senilni glas“, kada dolazi do promene rezonancije i visine tona glasa. Do ovoga dolazi zbog gubitka fleksibilnosti hrskavice. Zglobne hrskavice postaju nepravilne, što dovodi do promena u vokalnim ligamentima, koje uzrokuju pojavu  $F_0$  varijabilnosti (vibracije glasnih žica, koje dovode do promuklosti tokom govora) (7).

Promene starosne dobi takođe dovode do promena visine glasa, tako da sa većom starosnom dobi kod muškaraca raste i visina glasa, dok kod žena postaje niža. Praćenjem i slušanjem moguće je zaključiti kog je uzrasta određena osoba (8,9,10,11).

Takođe, atrofija određenih vokalnih mišića dovodi do toga da glasne žice postanu tanje, a kod muškaraca to dovodi do povećanja treperenja, titranja i  $F_0$  vrednosti. Kod ljudi starijih od 60 godina ima manje vlakana u larinksu (12).

Cilj ovog rada je da se pregledom relevantne literature analiziraju promene frekvencije glasa, intenziteta glasa, ritma i tempa govora koje su izazvane starenjem.

## Metod

Literatura je proučavana uz pomoć elektronskih baza podataka, posebno *Google Scholar Advanced Search* i Konzorcijuma biblioteka Srbije za objedinjenu nabavku – KoBSON u periodu od 1990. do 2025. godine. Prikupljeni podaci analizirani su kombinovanjem sistematskog i narativnog pristu-

pa. U početnoj fazi istraživanja, pregledan je veliki broj radova na osnovu odabranih ključnih reči (starenje, glas, govor, kvalitet glasa, promene u govoru, prezbifonija, komunikacija, stariji/gerijatrija). Međutim, za potrebe ove analize, detaljno su razmatrana 24 pregledna i istraživačka rada, kao i 2 monografije. Analiza je uključila studije napisane na srpskom i engleskom jeziku.

## Promene frekvencije glasa izazvane starenjem

Osnovna frekvencija je frekvencija osnovnog tona larinksa. Njena oznaka je  $F_0$ , a vrednost je označena sa Hz. Osnovna frekvencija se menja tokom života. Tokom puberteta, frekvencija se menja zbog rasta glasnih žica. Kada odrastu, frekvencija glasa devojčica može pasti na 220 Hz, dok je kod dečaka do 18 godina frekvencija oko 130 Hz. Promene postoje u vidu zadebljanja glasnih žica, glasne žice menjaju oblik, a takođe raste i deo tiroaritenoidnog mišića, što dovodi do promene frekvencije (13).

Pored toga, činjenica da se larinks spušta veoma je važna za govor i frekvenciju. Kada se dete rodi, larinks se nalazi visoko u vratu. Resice dodiruju meko nepce, a larinks se nalazi u nivou trećeg vratnog pršljena. Činjenica da se larinks nalazi visoko omogućava da dete diše tokom dojenja, i takođe doprinosi da se dete ne guši tokom dojenja. Nakon određenog vremena, grkljan se spušta, a do pete godine grkljan se nalazi u nivou šestog vratnog pršljena. Čak i nakon toga se larinks spušta, tako da se između petnaeste i dvadesete godine nalazi u nivou sedmog vratnog pršljena (14).

Kada su u pitanju glasne žice, bez obzira na pol, glasne žice su duge 3 mm, međutim, njihov rast se razlikuje kod žena i muškaraca, i glasne žice muškaraca rastu za 0,7 mm, a žena za 0,4 mm. Do dvanaeste godine, nema razlika između muškaraca i žena. Međutim, nakon ulaska u pubertet dolazi do promena i rast glasnih žica kod muškaraca se ubrzava, tako da brzo rastu do 10 mm, a pored toga se i zadebljaju, što rezultira smanjenjem frekvencije glasa kod muškaraca. Kada su u pitanju žene, glasne žice rastu sporijim tempom nego kod muškaraca i iznose do 4 mm. Glasne žice žena se histološki ne zadebljavaju, ali dolazi do smanjenja frekvencije glasa kod žena za samo tri tona. Nakon puberteta, glasne žice kod žena su 12,5 do 17 mm duge, a kod muškaraca do 20 mm (6).

The size of the pharynx and mouth varies even in very young children. However, when it comes to the larynx, it does not differ in girls and boys until puberty. The mutation of a boy's voice usually lasts from 11 to 14 years of age, and then the growth of the larynx occurs. When it comes to girls during puberty, certain changes have been noticed, however, the pharynx and larynx grow in proportion to other parts of the body. A more significant difference between boys and girls and the changes that occur are reflected in the changes in the vocal cord membrane, which is of different speed in girls and boys and which lead to numerous differences that are reflected in the characteristics of the voice (6).

The larynx, (i.e. its structure and function), deteriorates as an individual matures and ages. Destruction of structural, cellular, as well as neuromuscular integrity occurs in old age. The changes that occur in the larynx, which occur due to aging, lead to the destruction of the joint surface, cartilage, supporting structures, ligaments, and the vocal cords. When it comes to individuals up to the age of 80, although in some cases it can be earlier, the so-called "senile voice" appears, in which there are changes in the resonance and pitch of the voice. This occurs due to the fact that there is a loss of cartilage flexibility. The articular cartilages become irregular, which lead to changes in the vocal ligaments, which lead to the occurrence of  $F_0$  variability (vibrations of the vocal cords, which lead to hoarseness during speech) (7).

Changes in age also lead to changes in the pitch of the voice, so with age in men the pitch of the voice rises, while in women it becomes lower. By following and listening, it is possible to conclude in which age a certain individual is (8, 9, 10, 11).

Also, atrophy of the vocal muscles causes the vocal cords to thin, and in men this leads to an increase in jitter, shimmer, and  $F_0$  value. There are fewer fibers in the larynx in people over 60 years old (12).

The aim of this paper is to analyze changes in voice frequency, voice intensity, rhythm and pace of speech caused by aging by reviewing the relevant literature.

## Method

The literature was studied using electronic databases, specifically Google Scholar Advanced

Search and the Serbian Library Consortium for Coordinated Acquisition –KoBSON, in the period from 1990 to 2025. The collected findings were processed by combining a systematic and narrative approach. In the initial phase of the research, a large number of papers were reviewed based on selected keywords (aging, voice, speech, voice quality, changes in speech, presbyphonia, communication, elderly/geriatrics). However, for the purposes of this analysis, 24 review and research papers, as well as 2 monographs, were considered in detail. The analysis included studies written in Serbian and English.

## Changes in voice frequency caused by aging

The fundamental frequency is the frequency of the basic tone of the larynx. Its marking sign is  $F_0$ , and the value is marked with Hz. The fundamental frequency changes during life. During puberty, due to the growth of the vocal cords, the frequency changes. When they grow up, the frequency of a girl's voice can drop to 220 Hz, while when it comes to boys up to the age of eighteen, the frequency is around 130 Hz. Changes exist in the form of thickening of the vocal cords, the vocal cords change their shape, and also part of the thyroarytenoid muscle grows, and this leads to changes in frequency (13).

In addition, the fact that the larynx moves down is very important for speech and frequency. When a child is born, the larynx is located high in the neck. The soft palate is touched by villi, and the larynx is located at the third cervical vertebra. The fact that the larynx is located high allows the child to breathe during breastfeeding, and also contributes to the fact that the child does not suffocate during breastfeeding. After a certain time, the larynx descends, and by the age of five the larynx is located at the sixth cervical vertebra. Even after that, the larynx descends, so between the ages of fifteen and twenty, the larynx is located at the seventh cervical vertebra (14).

When it comes to the vocal cords, regardless of gender, the vocal cords are 3 mm long, however, their growth differs between men and women, and men's vocal cords grow by 0.7 mm and women's by 0.4 mm. Until the age of twelve, there are no differences between men and women. However, upon entering puberty, changes occur, and the growth of the vocal cords in men accelerates,

Tokom života, frekvencija glasa se menja kod oba pola. Muškarac dostiže svoju najvišu vrednost frekvencije do 85. godine. Frekvencija kod žena ostaje skoro identična od 20. do 50. godine starosti. Čak i nakon 50. godine nema promene frekvencije kod žena. Karakteristično je za žene da ulazak u menopauzu zbog hormonskih poremećaja izaziva promene frekvencije (15).

Frekvencija muškog glasa je mnogo niža nego frekvencija ženskog glasa, a to rezultira time da je muški glas mnogo dublji od ženskog glasa (16).

### Promene intenziteta glasa usled starenja

Intenzitet glasa se označava kao jačina glasa, odnosno, glasnoća. Sam intenzitet zavisi od subglotičke visine vazduha i amplitude vibracija glasnih žica. Što je veća amplituda vibracija glasa, to je veći intenzitet glasa. Intenzitet glasa se označava u decibelima (dB). Promene intenziteta glasa se javljaju tokom starenja. Na promene intenziteta takođe utiče pol osobe. Intenzitet kod muškaraca se povećava do šezdesete godine, kada može da dostigne svoj maksimum, dok kod žena to nije slučaj. Međutim, isto je kod muškaraca i žena da se intenzitet glasa smanjuje nakon 60. godine (17).

### Promene ritma i tempa govora koje nastaju tokom starenja

U zavisnosti od starosti osobe, menja se i brzina kojom govori. Upoređivanjem govora mlađih i starijih ljudi, može se videti jasna razlika brzine kojom izgovaraju reči. Brzina govora neke osobe može se proceniti čitanjem reči, rečenica i dužih pasusa. Takođe, kao jedna od metoda za merenje tempa govora može se koristiti vremenski raspon potreban za početak fonacije nakon pauze u govoru. Vremenski raspon za početak fonacije nakon pauze u govoru varira u zavisnosti od starosti osobe (18,19,20).

U jednom istraživanju u kojem su učestvovali ispitanici starosti od 70 do 80 godina i mlađi ispitanici starosti od 20 do 30 godina, zaključeno je da ne postoje značajne razlike kada se izgovaraju zvučni i bezzvučni glasovi među ispitivanim starosnim grupama (21). Kada je sprovedena studija, u kojoj su učestvovali samo žene, utvrđene su određene razlike. Naime, kod starijih žena je primećeno kraće vreme za početak fonacije samoglasnika i suglasnika. Imajući u vidu da je istraživanje uključilo izgovaranje različitih glasova

od strane muškaraca i žena, zaključeno je da se brzina govora u odnosu na starosnu dob razlikuje u zavisnosti od glasova koji se izgovaraju (21).

Isto istraživanje je ponovljeno kod ispitanika starosti od 70 do 90 godina i mlađih ispitanika starosti od 21 do 32 godine (22). Tokom istraživanja, utvrđeno je da se odlaže početak fonacije kada se izgovaraju alveolarni i bilabijalni glasovi kod starijih ispitanika u poređenju sa mlađim ispitanicima. Takođe je utvrđeno da starijim ispitanicima treba više vremena da izgovore određene glasove. U daljem istraživanju, uključeni su ispitanici starosti od 5 do 17 godina. Zaključeno je da se brzina izgovora samoglasnika i suglasnika smanjuje u zavisnosti od uzrasta ispitanika (22).

Veoma je važno utvrditi tempo govora. Da bi se utvrdilo da li ima određenih promena tempa govora u zavisnosti od starosne dobi osobe, ispitano je 16 starijih muškaraca koji su imali 82 godine i 14 mlađih muškaraca koji su imali približno 24 godine (23). Dobijeni rezultati su ukazali da je tempo govora kod starijih ispitanika bio sporiji u poređenju sa mlađim ispitanicima, dok je frekvencija govora kod starijih ispitanika bila viša u poređenju sa mlađim ispitanicima (23).

Kao rezultat fizičkih promena koje se javljaju sa starenjem respiratornog sistema, smanjuje se kapacitet pluća. Zbog histoloških promena na glasnim žicama, starijim ljudima takođe treba više vazduha tokom fonacije nego mlađim ljudima. Tokom procesa fonacije, glotis se ne zatvara adekvatno, i zbog toga dolazi do povećanog protoka vazduha kroz larinks, što dovodi do znatno veće potrošnje vazduha (24,25,26).

U tabeli su prikazane tipične akustičke promene u glasu kod muškaraca i žena u odnosu na deceniju života. Kako godine rastu, primećuje se opadanje frekvencije i intenziteta glasa, kao i ograničenje vokalnog raspona. Kod muškaraca se glas obično snižava i postaje promukao sa godinama, dok kod žena dolazi do blagog smanjenja frekvencije i snižavanja tonaliteta.

Promene se povezuju sa fiziološkim starenjem glasnih žica, smanjenjem elastičnosti i tonusa laringealnih mišića, kao i degenerativnim promenama drugih anatomskih i fizioloških struktura uključenih u fonaciju. Ove karakteristike glasa su ključni indikatori prezbifonije i mogu imati značajan uticaj na komunikaciju i kvalitet života starijih osoba.

which grow rapidly, up to 10 mm, and in addition, they also thicken, which results in a decrease in the frequency of the voice in men. When it comes to women, the vocal cords grow at a slower pace than men's vocal cords and they amount to 4 mm. The vocal cords of women do not thicken histologically, but there is a decrease in the frequency of the voice in women by only three tones. After puberty, female vocal cords are up to 12.5 to 17 mm long, and male vocal cords are up to 20 mm long (6).

During life, the voice frequency changes in both sexes. A man reaches his highest frequency value by the age of 85. The frequency remains almost identical in women from 20 to 50 years of age. Even after the age of 50, there is no change in frequency in women. It is characteristic for women that entering menopause due to hormonal disorders causes frequency changes (15).

The male voice frequency is much lower than the female voice frequency, and this results in the male voice being much deeper than the female voice (16).

### Changes in voice intensity due to aging

The intensity of the voice is denoted as the volume of the voice, that is, loudness. The intensity itself depends on the subglottic height of the air and the amplitude of the vibrations of the vocal cords. The greater the amplitude of the voice vibration, the greater the intensity of the voice. Voice intensity is indicated in dB (decibels). Changes in voice intensity occur during aging. Changes in intensity are also influenced by a person's gender. The intensity in men increases until the age of 60, when it can reach its maximum, while in women this is not the case. However, it is the same for men and women that after the age of 60 the volume of the voice decreases (17).

### Changes in the rhythm and tempo of speech occurring with aging

Depending on a person's age, the speed at which they speak also changes. Comparing the speech of younger and older people, a clear difference can be seen based on the speed with which they pronounce words. A person's speaking speed can be assessed by reading words, sentences and longer paragraphs. Also, as one of the methods for measuring the tempo of speech, the range in time required for the beginning of phonation after

a pause in speech can be used. The time span for the onset of phonation after a pause in speech varies with the age of the individual (18, 19, 20).

In one research in which people from 70 to 80 years of age and younger respondents from 20 to 30 years of age participated, it was concluded that there are no significant differences when pronouncing voiced and voiceless sounds among the examined age group (21). When a study was conducted in which only women participated, certain differences were found. Namely, in older women, a shorter time was observed for the beginning of phonation of vowels and consonants. Bearing in mind that the research involved the pronunciation of different voices by men and women, it was concluded that the speed of speech related to age differs depending on the voices that are spoken (21).

The same research was repeated with respondents from 70 to 90 years of age and younger respondents from 21 to 32 years of age (22). During the research, it was determined that the onset of phonation when pronouncing alveolar and bilabial sounds in older subjects was delayed compared to younger subjects. It was also found that older subjects took longer to pronounce certain sounds. Through further investigation, respondents aged 5 to 17 were also included in the research. It was concluded that the speed of pronouncing vowels and consonants decreased depending on the age of the subjects (22).

It is very important to determine the pace of speech. In order to determine whether the pace of speech has certain changes depending on the age of the person, 16 older men who were 82 years old and 14 younger men who were approximately 24 years old were examined (23). The obtained results indicated that the pace of speech in older respondents was slower compared to younger respondents, while the frequency of speech in older respondents was higher compared to younger respondents (23).

As a result of physical changes that occur with aging in the respiratory system, lung capacity decreases. Due to histological changes in the vocal cords, older people also need more air during phonation than younger people. During the phonation process, the glottis does not close adequately, as a result of which there is an increased flow of air through the larynx, which leads to significantly more air consumption (24, 25, 26).

**Tabela 1.** Akustičke promene koje se javljaju sa starenjem u odnosu na pol

Starosna grupa	Pol	Frekvencija glasa (Hz)	Intenzitet (dB)	Raspon glasa	Ton/Kvalitet	Zapažanja
20–29	M	110–130	70–75	Normalan	Jasan, fleksibilan	Referentna grupa mladih
	Ž	200–220	70–75	Normalan	Jasan, fleksibilan	—
30–39	M	108–128	68–73	Blago smanjen	Neznatno dublji	Rane promene elastičnosti glasnih žica
	Ž	195–215	68–73	Blago smanjen	Neznatno dublji	—
40–49	M	105–125	65–70	Smanjen	Dublji, blago promukao	Početak prezbifonije
	Ž	190–210	65–70	Smanjen	Niži, blago promukao	—
50–59	M	100–120	63–68	Značajno smanjen	Promukao, manje fleksibilan	Degeneracija mišića glasnih žica
	Ž	185–205	63–68	Značajno smanjen	Promukao, niža visina tona	—
60–69	M	95–115	60–65	Ograničen	Veoma promukao, slab intenzitet	Otežana fonacija i artikulacija
	Ž	180–200	60–65	Ograničen	Promukao, slabiji ton	—
70+	M	90–110	55–60	Veoma ograničen	Grub, slab	Tipični znaci prezbifonije
	Ž	175–195	55–60	Veoma ograničen	Grub, slab	—

Predstavljanje ovih karakteristika u odnosu na deceniju života i pol omogućava bolje razumevanje normalnog procesa starenja glasa i može pomoći u planiranju logopedске terapije i gerijatrijskih intervencija.

### Zaključak

Ova studija ispituje kako se glas menja sa starenjem ljudi, odnosno analizira promene frekvencije glasa, jačine (intenziteta), kao i promene ritma i tempa govora. Sve ove promene mogu značajno da utiču na svakodnevni život osobe, i stoga je važno uzeti ih u obzir ne samo u naučnim istraživanjima, već i u praktičnom, kliničkom radu. Zbog toga je neophodno uraditi detaljne testove glasa i sveobuhvatan lekarski pregled da bi se tačno utvrdilo da li postoje problemi sa glasom i šta ih uzrokuje.

S obzirom da se broj starijih osoba u svetu brzo povećava, ova vrsta istraživanja postaje sve više važna za istraživače, edukatore i praktičare. Njihov cilj je da bolje razumeju kako starenje utiče na sve aspekte govora i jezika kod ljudi. Glas igra ključnu ulogu u komunikaciji, a sa godinama dolazi do promena u glasu, što takođe menja način na koji ljudi komuniciraju. Ako se ovom problemu pristupi na vreme, to bi moglo da otvori prostor za dodatna istraživanja u oblasti logopedске terapije, kako bi se pronašao najefikasniji logopedski tretman za ovu starosnu grupu.

Preporuke za kliničku praksu:

- Uvođenje redovnog fonijatrijskog skrininga za osobe starije od 65 godina kako bi se rano otkrile promene glasa i potencijalna patološka stanja.

**Table 1.** Acoustic changes that occur with aging in relation to gender

Age Group	Gender	Voice Frequency (Hz)	Intensity (dB)	Vocal Range	Tone/Quality	Notes
20–29	M	110–130	70–75	Normal	Clear, flexible	Reference young adult group
	F	200–220	70–75	Normal	Clear, flexible	—
30–39	M	108–128	68–73	Slightly reduced	Slightly deeper	Early changes in vocal fold elasticity
	F	195–215	68–73	Slightly reduced	Slightly deeper	—
40–49	M	105–125	65–70	Reduced	Deeper, slightly hoarse	Beginning of presbyphonia
	F	190–210	65–70	Reduced	Darker, slightly hoarse	—
50–59	M	100–120	63–68	Significantly reduced	Hoarse, less flexible	Vocal fold muscle degeneration
	F	185–205	63–68	Significantly reduced	Hoarse, lower pitch	—
60–69	M	95–115	60–65	Limited	Very hoarse, weak intensity	Difficult phonation and articulation
	F	180–200	60–65	Limited	Hoarse, weaker tone	—
70+	M	90–110	55–60	Greatly limited	Rough, weak	Typical signs of presbyphonia
	F	175–195	55–60	Greatly limited	Rough, weak	—

The table shows typical acoustic changes in the voice in men and women by decade. As age progresses, a gradual decrease in the frequency and intensity of the voice, as well as a limitation of the vocal range, is observed. In men, the voice usually drops and becomes hoarse with age, while in women there is a slight decrease in frequency and darkening of the tonality.

The changes are associated with physiological aging of the vocal cords, a decrease in the elasticity and tone of the laryngeal muscles, as well as degenerative changes in other anatomical and physiological structures involved in phonation. These acoustic characteristics are key indicators of presbyphonia and can have a significant impact on the communication and quality of life of older people.

The presentation of these changes by decade and gender allows a better understanding of the normal process of voice aging and can help in planning speech therapy and geriatric interventions.

## Conclusion

This study examines how the voice changes as people age - more specifically, it looks at changes in voice frequency, volume (intensity), as well as speech rhythm and tempo. All these changes can significantly affect a person's daily life, and therefore it is important to take them into account not only in scientific research but also in practical, clinical work. That is why it is necessary to do detailed voice tests and a comprehensive medical

- Primena standardizovanih testova glasa i akustičke analize kako bi se pratili parametri glasa (frekvencija, intenzitet, raspon, tonalitet).

- Saradnja logopeda, fonijatara i gerijatrijskih timova u planiranju individualnog tretmana, uključujući vežbe disanja, artikulacije i higijenu glasa.

- Praćenje i edukacija pacijenata i njihovih porodica o prirodnim promenama glasa i tehnikama koje mogu očuvati kvalitet govora.

- Korišćenje preventivnih programa i glasovnih vežbi kako bi se odložile ili ublažile posledice prezbifonije.

Ove preporuke omogućavaju blagovremenu intervenciju, poboljšavaju komunikaciju i kvalitet života kod starijih ljudi, i pružaju osnovu za dalja istraživanja u oblasti logopedije i gerijatrije.

## Zahvalnica

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## Konflikt interesa

Autori su izjavili da nema konflikta interesa.

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examination, in order to determine exactly if there are voice problems and what causes them.

As the number of older people in the world increases rapidly, this type of research becomes increasingly important for researchers, educators and practitioners. Their goal is to better understand how aging affects all aspects of speech and language in humans. The voice plays a key role in communication, and with age there are changes in the voice, which also changes the way people communicate. If this problem is approached in time, it could open up space for additional research in the field of speech therapy, in order to find the most effective speech therapy treatment for this age group.

Recommendations for clinical practice:

- Introduction of regular phoniatic screening for people over 65 years of age for early detection of voice changes and potential pathological conditions.

- Application of standardized vocal tests and acoustic analysis to monitor voice parameters (frequency, intensity, range, tonality).

- Collaboration of speech therapists, phoniaticians and geriatric teams in individual treatment planning, including breathing exercises, articulation and voice hygiene.

- Monitoring and education of patients and their families about natural voice changes and techniques that can preserve speech quality.

- Use of preventive programs and voice exercises to delay or mitigate the consequences of presbyphonia.

These recommendations enable timely intervention, improve communication and quality of life in older people, and provide a foundation for further research in speech therapy and geriatrics.

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## Competing interests

The authors declared no competing interests.

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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-

## 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). Uzrokuje 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 igranke), 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. godini, 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 karcinoma 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
<b>Ukupno za sve lokalizacije povezane sa HPV infekcijom</b>	<b>920.000</b>	<b>780.000</b>	<b>84,7</b>

\*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*<sup>®</sup> kreće se od 93% do 100%, devetovalentne *Gardasil9*<sup>®</sup> od 97% do 100%, a bivalentne *Cervarix*<sup>®</sup> 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*<sup>®</sup> (četvorovalentna vakcina) i *Gardasil 9*<sup>®</sup> (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	Grlič 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
Oropharynx (C01, C09-10)	106,000	32,000	30.8
<b>Total HPV-related sites</b>	<b>920,000</b>	<b>780,000</b>	<b>84.7</b>

\*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
<b>Naziv</b>	<b>Cervarix®*</b>	<b>Gardasil®*</b>	<b>Gardasil 9®*</b>	<b>Cecolin®*</b>	<b>Walrinwax®*</b>	<b>Cervavac®***</b>
<b>Proizvođač</b>	GlaxoSmith Kline, UK	Merck & Co., SAD	Merck & Co., SAD	Xiamen Innovax, Kina	Walvax, Kina	Institut za serume Indija
<b>Ekspresioni sistem</b>	<i>Baculovirus</i>	<i>Saccharomyces cerevisiae</i>	<i>Saccharomyces cerevisiae</i>	<i>Escherichia coli</i>	<i>Pichia pastoris</i>	<i>Hansenula polymorpha</i>
<b>Godina odobranja</b>	2007.	2006.	2014.	2019.	2022.	2022.
<b>HPV tipovi koji se preveniraju</b>	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
<b>Uzrast za vakcinaciju</b>	9-45	9-45	9-45	9-45	9-30	9-45
<b>Plan vakcinacije</b>	0 M, 1M, 6M **	0M, 2M, 6M **	0M, 2M, 6M **	0M, 1M, 6M **	0M, 1M, 6M	0M, 6M
<b>Mesto vakcinacije</b>	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 terapijske 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, terapijske 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
<b>Name</b>	Cervarix®*	Gardasil®*	Gardasil 9®*	Cecolin®*	Walrinwax®*	Cervavac®***
<b>Manufacturer</b>	GlaxoSmith Kline, UK	Merck & Co., USA	Merck & Co., USA	Xiamen Innovax, China	Walvax, China	Serum Institute of India
<b>Expression system</b>	<i>Baculovirus</i>	<i>Saccharomyces cerevisiae</i>	<i>Saccharomyces cerevisiae</i>	<i>Escherichia coli</i>	<i>Pichia pastoris</i>	<i>Hansenula polymorpha</i>
<b>Time of approval</b>	2007.	2006.	2014.	2019.	2022.	2022.
<b>HPV types prevented</b>	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
<b>Age for vaccination</b>	9-45y	9-45y	9-45y	9-45y	9-30y	9-45y
<b>Vaccination schedule</b>	0 M, 1M, 6M **	0M, 2M, 6M **	0M, 2M, 6M **	0M, 1M, 6M **	0M, 1M, 6M	0M, 6M
<b>Site of inoculation</b>	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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## UTICAJ BIHEVIORALNIH FAKTORA RIZIKA NA NEPLODNOST

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### SAŽETAK

Bihevioralni faktori predstavljaju promenljive faktore rizika koji mogu uticati na pojavu brojnih stanja i bolesti, a podaci iz literature ukazuju da mogu imati negativan uticaj i na mogućnost začeća. Cilj ovog preglednog rada je bio da se kroz analizu naučnih radova prikaže doprinos bihevioralnih faktora za razvoj neplodnosti kod oba pola i predlože preventivne mere. U istraživanju su pretražene sledeće baze podataka: *MEDLINE*, *PubMed* i *KoBSON*. Potom je urađena analiza prikupljenih podataka kliničkih i drugih epidemioloških studija objavljenih u poslednjih 30 godina. Istraživanja pokazuju da ishrana bogata dijetnim vlaknima, omega-3 masnim kiselinama, biljnim proteinima, vitaminima i mineralima, pozitivno utiče na plodnost žena i muškaraca. S druge strane, ishrana bogata industrijski prerađenim namirnicama, trans-mastima i rafiniranim ugljenim hidratima može negativno uticati na plodnost. Umerena fizička aktivnost pomaže u održavanju optimalnog indeksa telesne mase i poboljšanju fiziološke funkcije jajnika. Intenzivni sportovi, zbog uticaja na hipotalamo-hipofiznu osovину, mogu dovesti do hipotalamske amenoreje i posledične neplodnosti. Pušenje, zloupotreba alkohola i psihoaktivnih supstanci negativno utiču na plodnost i žena i muškaraca, kao i na razvoj ploda. Uravnotežena i zdrava ishrana, umerena fizička aktivnost, prevencija polno prenosivih bolesti, kao i dizajniranje i implementacija strategija za prevenciju neplodnosti, mogu doprineti boljem ishodu plodnosti i sigurnom materinstvu.

**Ključne reči:** plodnost, faktori rizika, ishrana, fizička aktivnost

### Uvod

Neplodnost se definiše kao neuspeh da se postigne klinička trudnoća nakon dvanaest ili više meseci od redovnog nezaštićenog seksualnog odnosa (1). U savremenom svetu neplodnost predstavlja zdravstveni, psihološki i sociološki problem koji utiče na kompletan aspekt ličnosti, njen integritet i identitet i može ozbiljno psihofizički uticati na ceo organizam čoveka (2). Posledice su jače izražene kod žena, kod kojih se često javlja emocionalni stres, depresija, anksioznost i pad samopouzdanja. Infertilitet dovodi do suočavanja partnera sa društvenom stigmom i čest je uzrok razvoda (1). Za mnoge pojedince i parove, nemogućnost da ostvare željenu trudnoću može dovesti do socijalne izolacije, kliničke depresije, smanjenog radnog učinka i kvaliteta života (3).

U svetu, stopa ukupnog fertiliteta u 2024. godini je bila 2,2 (prosečan broj dece koju u reproduktivnom dobu rodi jedna žena) i kontinuirano je opadala od 1970. godine, kada je iznosila 4,8 (4). Prema podacima Svetske zdravstvene organizacije (SZO), neplodnost pogađa 80 miliona žena širom sveta, a dostupni podaci sugerišu da se jedna od šest osoba u određenom momentu svog života suoči sa ovim problemom (1,5). Incidencija neplodnosti nije ista u svim krajevima sveta i poslednjih godina raste u ekonomski razvijenim zemljama. U Sjedinjenim Američkim Državama (SAD) incidencija neplodnosti u poslednjoj deceniji iznosila je 14%, što znači da 2,5 miliona američkih bračnih parova je imalo poteškoće da dobije potomstvo (6).

## THE IMPACT OF BEHAVIORAL RISK FACTORS ON INFERTILITY

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### SUMMARY

Behavioral factors are modifiable risk factors that can significantly influence the development of various health conditions and diseases. Literature suggests that these factors may also have a detrimental effect on fertility. The aim of this review paper was to present the contribution of behavioral factors to the development of infertility in both sexes through the analysis of scientific literature, and to propose preventive measures. The following databases were searched: MEDLINE, PubMed, and KOBSON. Subsequently, an analysis was conducted on the collected data from clinical and other epidemiological studies published over the past 30 years. Research findings indicate that diets rich in dietary fiber, omega-3 fatty acids, plant-based proteins, vitamins, and minerals positively influence fertility in both men and women. Conversely, diets high in processed foods, trans fats, and refined carbohydrates have been shown to have a negative impact on fertility. Moderate physical activity plays a critical role in maintaining an optimal body mass index and improving ovarian function. However, intensive physical activity, due to its effect on the hypothalamic-pituitary axis, can lead to hypothalamic amenorrhea and subsequent infertility. Smoking, alcohol abuse, and the use of psychoactive substances adversely affect fertility in both sexes, as well as fetal development.

A balanced and healthy diet, moderate physical activity, prevention of sexually transmitted infections, and the design and implementation of targeted infertility prevention strategies can significantly improve fertility outcomes and contribute to safe motherhood.

**Keywords:** fertility, risk factors, diet, physical activity

### Introduction

Infertility is defined as the failure to achieve clinical pregnancy after twelve months or more of regular, unprotected sexual intercourse (1). In the modern world, infertility is a health, psychological and social problem that affects the individual's entire personality, integrity and identity and it can have a serious psycho-physical impact on the entire human organism (2). The repercussions are more pronounced in women, who often experience emotional stress, depression, anxiety and lack of self-esteem. Infertility causes partners to face social stigma and it is a frequent cause of divorce (1). For many individuals and couples, the inability to achieve the desired pregnancy can lead to social isolation, clinical depression, reduced work performance and quality of life (3).

The global fertility rate was 2.2 in 2024 (the average number of children per woman) and it has continuously declined since 1970, when it amounted to 4.8 (4). According to the data of the World Health Organization (WHO), infertility affects 80 million women worldwide, while the available data suggest that one in six people experience infertility at some point in their lifetime (1,5). The incidence of infertility is not the same in all parts of the world and it has increased recently in economically developed countries. In the United States of America, the incidence of infertility amounted to 14% in the last decade, which means that 2.5 million American married couples had difficulty conceiving (6).

Stopa fertiliteta kod svih evropskih zemalja je bila ispod globalnog proseka. Prema podacima za 2022. godinu, među državama članicama EU, Francuska je imala najvišu stopu fertiliteta sa 1,8 živorođene dece po ženi. Nasuprot tome, najniže stope fertiliteta su bile zabeležene na Malti (1,1), u Španiji i Italiji (1,2) (7).

U našoj zemlji problem neplodnosti pogađa oko 16–18% ukupne populacije, dok kod žena starijih od 35 godina, učestalost neplodnosti prelazi 25% (2). Imajući u vidu da se naša sredina suočava sa negativnim prirodnim priraštajem, i da po najnovijim statističkim podacima stopa ukupnog fertiliteta iznosi 1,6, bračna neplodnost nije samo medicinski već i društveni problem. U Republici Srbiji, u 2023. godini, najveći broj porođaja u odnosu na starost majke je bio u dobnoj grupi od 30 do 39 godina, što ukazuje na trend odlaganja roditeljstva (8). Podaci iz literature govore da neplodnost žena čini 35% od ukupnog broja slučajeva neplodnosti, 20% slučajeva se odnosi na žene i muškarce kombinovano, 30% uključuje probleme samo kod muškaraca, dok kod 15% slučajeva uzrok neplodnosti ostaje nepoznat (1). Primarna i sekundarna neplodnost s kojom se parovi u Srbiji suočavaju može se javiti kao posledica uticaja bihejvioralnih faktora rizika na reproduktivno zdravlje (9). Osim bolesti urogenitalnog sistema i sistemskih bolesti koje direktno utiču na plodnost žena i muškaraca, narušavanju reproduktivne sposobnosti kod oba pola u velikoj meri doprinose način života i socijalni uslovi. Visoka prevalencija neplodnosti u kombinaciji sa visokim finansijskim troškovima i ograničenim pristupom lečenju inicira potrebu da se identifikuju promenljivi faktori koji utiču na mogućnost začeća. U bihejvioralne promenjive faktore koji nepovoljno utiču na plodnost spadaju nezdrava i neuravnotežena ishrana, intenzivna fizička aktivnost, kao i sedentarni način života, pušenje, konzumiranje alkohola, zloupotreba psihoaktivnih supstanci i rizično seksualno ponašanje. Savremena medicina i profesionalci koji se bave ovim problemom, posmatraju neplodnost kao problem u kome podjednako učestvuju oba partnera. Zato se u rešavanje neplodnosti uključuje veći broj stručnjaka, jer se tako ostvaruje timski rad koji omogućava da se sa različitih aspekata sačuva fizičko i mentalno zdravlje i radna efikasnost partnera, a istovremeno dođe do krajnjeg rešenja problema, odnosno ostvarivanja potomstva (1,10).

Cilj ovog preglednog rada je bio da se kroz analizu naučnih radova prikaže doprinos bihejvioralnih faktora za razvoj neplodnosti kod oba pola i predlože preventivne mere.

## Metode

U okviru ovog rada prikupljeni su i analizirani podaci iz prethodno objavljenih kliničkih i drugih epidemioloških studija koji su se odnosili na uticaj bihejvioralnih faktora na reproduktivni sistem i plodnost. U istraživanju su korišćene baze podataka: *MEDLINE*, *PubMed* i *KoBSON*. Ključne reči koje su korišćene prilikom pregleda literature su: „fertility“, „female reproductive system“, „male reproductive system“, „nutrition“, „diet“, „age“, „physical activity“, „smoking“, „alcohol“, „drugs“, „sexual and reproductive health“. Literatura je pretražena za vremenski period 1994-2025. godine. Od svih publikacija koje su dobijene pretraživanjem uključene su samo one koje su se odnosile na analizu uticaja koji bihejvioralni faktori imaju na muški i ženski reproduktivni sistem i plodnost. Svi uključeni radovi su bili na srpskom i engleskom jeziku.

## Promenjivi faktori rizika za nastanak neplodnosti

Podaci koji se odnose na države iz različitih delova sveta ukazuju na smanjenu stopu fertiliteta u poslednjih šest decenija, a naročito u razvijenim zemljama. Istraživači smatraju da ovaj pad stope fertiliteta može biti posledica uticaja koji promenljivi faktori rizika imaju na reproduktivno zdravlje i opšte zdravlje populacije (11). Bihejvioralni faktori mogu uticati na reproduktivno zdravlje pozitivno ili negativno, a pojedinac može da ih kontroliše i menja u cilju poboljšanja zdravlja. Smatra se da određeni bihejvioralni faktori mogu imati kumulativni efekat na plodnost (12).

## Ishrana

Pod pravilnom ishranom podrazumeva se svakodnevni unos raznovrsnih namirnica raspoređen u više obroka tokom dana (doručak, ručak, večera i dve užine). Potrebno je da energetski unos bude usklađen sa ukupnom potrošnjom energije. U okviru Istraživanja zdravlja stanovništva Republike Srbije iz 2019. godine, analizirane su navike u ishrani, uključujući svakodnevni unos određenih namirnica. Voće (sveže, smrznuto, konzervirano, sušeno, izuzimajući sveže ceđene sokove) svakod-

The fertility rate in all European countries was below the global average. According to the data for 2022, among EU member states, France had the highest fertility rate with 1.8 live births per woman. In contrast, the lowest fertility rates were recorded in Malta (1.1), Spain and Italy (1.2) (7).

In our country, the problem of infertility affects about 16-18% of the total population, while in women older than 35, the incidence of infertility exceeds 25% (2). Bearing in mind that our country is facing the negative natural increase, and that according to the latest statistical data, the total fertility rate is 1.6, marital infertility is not only a medical, but also a social problem. In 2023, in the Republic of Serbia, the largest number of births in relation to the age of the mother was in the age group 30 to 39 years, which indicates a trend of delaying parenthood (8). Literature data show that female infertility accounts for 35% of the total number of infertility cases, 20% of cases refer to both women and men, 30% involve problems only in men, while in 15% of cases the cause of infertility remains unknown (1). Primary and secondary infertility experienced by the couples in Serbia can occur as the result of impact of behavioral risk factors on reproductive health (9).

Apart from diseases of the urogenital system and systemic diseases that directly affect the fertility of men and women, lifestyle and social conditions greatly contribute to the impairment of the reproductive capacity in both sexes. The high prevalence of infertility combined with high financial costs and limited access to treatment initiates the need to identify modifiable factors that affect the possibility of conception. Behavioral modifiable factors that adversely affect fertility include unhealthy and unbalanced diet, intense physical activity, as well as sedentary lifestyle, smoking, alcohol abuse, abuse of psychoactive substances and risky sexual behavior. Modern medicine and professionals that deal with this problem see infertility as a problem in which both partners participate equally. Therefore, greater number of experts is involved in the treatment because the team work enables the preservation of physical and mental health from different aspects, and at the same time the ultimate solution of the problem, that is, the realization of offspring (1,10). The aim of this review article was to show the contribution of behavioral factors

to the development of infertility in both sexes through the analysis of scientific papers, and to propose preventive measures.

## Methods

Within this review article, data from previously published clinical and other epidemiological studies related to the influence of behavioral factors on the reproductive system and fertility were collected and analyzed. The following databases were used in the research: MEDLINE, PubMed and KoBSON. The key words that were used during literature search were: "fertility", "female reproductive system", "male reproductive system", "nutrition", "diet", "age", "physical activity", "smoking", "alcohol", "drugs", "sexual and reproductive health". The literature was searched for the time period 1994-2025. Of all publications, which were obtained by the search, only those which related to the analysis of the impact of behavioral factors on male and female reproductive system and fertility were included. All included papers were in Serbian and English.

## Modifiable risk factors for the development of infertility

Data related to different parts of the world indicate a reduced fertility rate in the last six decades, especially in developed countries. Researchers believe that this decline in the fertility rate may be the consequence of the impact that modifiable risk factors have on the reproductive health and general health of the population (11). Behavioral factors can affect reproductive health positively and negatively, and the individual can control and change them in order to improve health. It is believed that certain behavioral factors can have a cumulative effect on fertility (12).

## Diet

Proper diet implies the daily intake of a variety of foods in several meals during the day (breakfast, lunch, dinner and two snacks). The energy intake should be in balance with the total energy expenditure. As part of the 2019 Serbian National Health Survey, dietary habits were analyzed, including the daily intake of certain foods. Fruit (fresh, frozen, canned, dried, not including freshly squeezed juices) was consumed by 39.4% of

neveno je konzumiralo 39,4% stanovnika, a povrće ili salatu (u svim oblicima, izuzimajući sokove od povrća i supe) 50,2% stanovnika (13).

Ishrana, odnosno specifični nutritivni faktori prednjače po svom uticaju na plodnost čoveka među bihevioralnim faktorima (14). Elementi ishrane koji mogu imati uticaj na fertilitet žena i muškaraca su ukupna energetska vrednost unete hrane i unos pojedinih hranljivih materija, posebno proteina. Zdrav način ishrane i za muškarce i za žene u reproduktivnom dobu podrazumeva upotrebu namirnica koje sadrže specifične hranljive materije potrebne za hormonalnu funkciju i ravnotežu, zdravlje jajnih ćelija i spermatozoida i razvoj fetusa. U poslednjih nekoliko decenija, glavni prehrambeni obrazac postao je takozvana „Zapadnjačka ishrana“, koja može negativno uticati na plodnost. Ovu ishranu karakteriše visok unos industrijski obrađene hrane, bogate životinjskim proteinima, jednostavnim ugljenim hidratima, trans i zasićenim mastima i prerađenim mesom (kobasice, salame itd.), a siromašnu dijetalnim vlaknima i esencijalnim nezasićenim masnim kiselinama (5). Iako definicija nezdravog načina ishrane u određenoj meri varira u različitim studijama, postoje značajna preklapanja rezultata o ishrani bogatoj kalorijama, trans-masnim kiselinama (engl. *Trans Fatty Acids* - TFA), zasićenim mastima i holesterolom koji su bili povezani sa poremećajima proizvodnje hormona i spermatogeneze, menstrualnim poremećajima, anovulacijom, neplodnošću, pobačajem i komplikacijama u trudnoći (15). TFA su zastupljene u hidrogenizovanim biljnim uljima koja se koriste u industriji brze hrane, pržene hrane i gotovih jela, te ove proizvode treba izbegavati (16). Podaci pokazuju da ishrana zasnovana na mediteranskim obrascima ishrane, odnosno ishrana bogata dijetnim vlaknima, omega-3 ( $\omega$ -3) masnim kiselinama, biljnim proteinima i vitaminima i mineralima, pozitivno utiče na plodnost žena i muškaraca. Istraživanja su pokazala da mediteranska ishrana u periodu pre koncepcije može poboljšati šanse za začeće i do 40% (17).

Gojaznost je, prema podacima za 2019. godinu, česta kod muškaraca i žena, pri čemu je, prema poslednjim podacima 19% žena starijih od 18 godina u Srbiji klasifikovano kao gojazno, a 26% muškaraca (18). Žene i muškarci sa gojaznošću (*Body Mass Index* – BMI  $\geq$  30 kg/m<sup>2</sup>) imaju veći rizik od neplodnosti. Ovaj rizik se odnosi i na žene koje su pothranjene (BMI < 20 kg/m<sup>2</sup>). Nedovoljna tele-

sna masa, odnosno masa koja je 10-15% manja od idealne telesne mase može dovesti do poremećaja menstrualnog ciklusa, dok blago povećanje telesne mase kod žena sa izuzetno niskim procentom telesne masti može poboljšati plodnost (19). Žene sa BMI preko 30 imaju lošu endometrijalnu receptivnost, a samim tim niže stope trudnoće i značajno veći procenat spontanih pobačaja u poređenju sa fiziološkim BMI (20). Kod muškaraca, povećanje BMI od samo 3 jedinice značajno smanjuje parametre kvaliteta sperme i povećava broj mutacija DNK spermatozoida (21). Pothranjenost, baš kao i prekomerna akumulacija masti u predelu stomaka, povezana je sa smanjenom sintezom testosterona i posledično lošim kvalitetom sperme (22).

Proteini su makronutrijenti koji su neophodni za začeće i trudnoću. Rezultati istraživanja sugerišu da zamena životinjskih izvora proteina, posebno piletine i crvenog mesa, biljnim izvorima proteina može smanjiti rizik od anovulacije i posledične neplodnosti (23). Ishrana siromašna proteinima može biti potencijalni faktor rizika za neplodnost kod muškaraca, jer dovodi do značajnog smanjenja volumena testisa, epididimisa i seminalnih vezikula, kao i smanjenja nivoa testosterona u serumu (24). Preporuke su da u ishrani treba da preovladavaju biljni izvori proteina (23).

Količina i vrsta ugljenih hidrata u ishrani je od suštinskog značaja za žene koje planiraju da zatrudne. Studije su pokazale da je veća potrošnja ugljenih hidrata i proizvoda sa visokim glikemijskim indeksom, odnosno visoka potrošnja jednostavnih šećera, u poređenju sa unosom vlakana, povezana sa manjim šansama za trudnoću usled poremećaja ovulacije. Ishrana sa niskim glikemijskim opterećenjem, bogata vlaknima i sa puno integralnih žitarica, može poboljšati plodnost žena pozitivnim uticajem na nivo estrogena (16). Prema sistematskom pregledu literature kojim je obuhvaćen vremenski period od dve decenije, unos ugljenih hidrata i glikemijsko opterećenje u ishrani negativno utiču na viskozitet sperme dovodeći do smanjenog kvaliteta sperme, nevezano za godine starosti muškarca (14).

Trans masne kiseline štetno deluju na reproduktivne funkcije i kod muškaraca i kod žena. Za povećanje plodnosti kod žena se sugeriše veći unos polinezasićenih masnih kiselina (engl. *Polyunsaturated Fatty Acid* - PUFA), posebno dugolančanih omega-3 masnih kiselina, i manji unos trans masnih kiselina. U studiji u kojoj su bili obuhvaćeni

inhabitants every day, and vegetables and salads (in all forms, not including vegetable juices and soups) by 50.2% of inhabitants (13).

Diet, that is, specific nutritional factors are predominant factors among behavioral factors regarding their impact on fertility (14). The elements of diet that can have an impact on the fertility of men and women include the total energy value of taken food and the intake of certain nutrients, especially proteins. A healthy diet for both men and women in the reproductive age implies the use of foods that contain specific nutrients needed for hormonal function and balance, the health of ovarian cells and spermatozooids and fetal development. In recent decades, the main dietary pattern has been the so called "Western diet", which can have a negative impact on fertility. This diet is characterized by the high intake of industrially processed food, rich in animal proteins, simple carbohydrates, trans and saturated fats and processed meat (sausages, salami, etc.), and poor in dietary fibers, and essential unsaturated fatty acids (5). Although the definition of unhealthy diet varies to a certain extent in different studies, there is a significant overlap of results about diet rich in calories, trans fatty acids (TFA), saturated fat and cholesterol, which are associated with disorders relating to the production of hormones and spermatogenesis, menstrual disorders, anovulation, infertility, miscarriages and complications in pregnancy (15). TFAs are present in hydrogenated vegetable oils that are used in fast food, fried food and ready meals industries, and these products should be avoided (16). Data show that diet based on Mediterranean dietary patterns, that is, diet rich in dietary fibers, omega-3 fatty acids, vegetable proteins and vitamins and minerals, has a positive impact on fertility of men and women. Research has shown that the Mediterranean diet used in the period before conception can improve chances of conception by up to 40% (17).

According to data for 2019, obesity was common in both men and women, while according to the latest data in Serbia, 19% of women older than 18 were classified as obese, and 26% of men (18). Women and men with obesity (Body Mass Index - BMI  $\geq 30$  kg/m<sup>2</sup>) have a higher risk of infertility. This risk also applies to women who are underweight (BMI < 20 kg/m<sup>2</sup>). Insufficient body mass, specifically 10-15% below the ideal

body mass can lead to menstrual cycle disorders, while the slight increase in body weight in women with an extremely low percentage of body fat can improve fertility (19). Women with a BMI higher than 30 have poor endometrial receptivity, and therefore, lower pregnancy rates and a significantly higher percentage of miscarriages compared to the physiological BMI (20). In men, an increase in BMI of only 3 units significantly reduces sperm quality parameters and increases the number of sperm DNA mutations (21). Being underweight, as well as the excessive accumulation of fats in the abdominal area, is associated with reduced testosterone synthesis and consequently poor sperm quality (22).

Proteins are macronutrients that are necessary for conception and pregnancy. Research results suggest that the replacement of animal sources of proteins, especially chicken and red meat with the vegetable sources of proteins can reduce the risk of anovulation and subsequent infertility (23). Diet poor in proteins may be a potential risk factor for infertility in men because it leads to a significant reduction in the volume of the testicles, epididymis and seminal vesicles, as well as a decrease in serum testosterone levels (24). It is recommended that vegetable sources of proteins should be predominant in the diet (23).

The amount and type of carbohydrates in the diet is essential for women planning pregnancy. Studies have shown that higher consumption of carbohydrates and products with a high glycemic index, that is, high consumption of simple sugars, compared to the intake of fibers, is associated with lower chances of pregnancy due to ovulation disorders. A diet with a low glycemic load, rich in fibers and full of whole grains can improve female fertility with the positive impact on estrogen levels (16). According to a systematic review of literature covering the period of two decades, the intake of carbohydrates and the glycemic load have a negative impact on the sperm viscosity, leading to reduced sperm quality, regardless of men's age (14).

Trans fatty acids have a harmful effect on reproductive functions in both men and women. To increase fertility, a higher intake of polyunsaturated fatty acids (PUFA), especially long-chain omega-3 fatty acids and a lower intake of trans fatty acids are recommended. In a study, which included men who had practiced the "Western diet" before the

muškarci koji su pre ispitivanja imali „zapadnjački način ishrane”, primenom omega-3 masnih kiselina u koncentraciji od 75 g dnevno, u vremenskom periodu tokom 12 nedelja, došlo je do značajnog poboljšanja parametara sperme u odnosu na kontrolnu grupu ispitanika, koja nije koristila omega-3 masne kiseline (25).

Ishrana punomasnim mlečnim proizvodima je bila povezana sa manjim rizikom od ovulatorne neplodnosti, dok je upotreba mlečnih proizvoda sa niskim sadržajem masti bila povezana sa većim rizikom od ovulatorne neplodnosti (26).

Reproduktivno zdravlje se može poboljšati modifikacijom ishrane, odnosno povećanjem unosa voća i povrća, mahunarki i ribe, a manjeg unosa crvenog mesa (13).

### Fizička aktivnost

Umerena fizička aktivnost pomaže u održavanju optimalnog indeksa telesne mase, pozitivno utiče na mentalno zdravlje, kao i poboljšanje fiziološke funkcije jajnika kod žena (27). Prema rezultatima istraživanja zdravlja, koje je omogućilo procenu nivoa fizičke aktivnosti stanovništva Srbije, u 2019. godini, 11,0% građana Srbije u starosnoj grupi od 18 do 64 godine, bavilo se aerobnim aktivnostima (kao što su fitness, sport, rekreacija ili vožnja bicikla) najmanje 150 minuta nedeljno (13). Fizička aktivnost pokazala je zaštitni efekat na plodnost kada je kombinovana sa gubitkom težine kod gojaznih žena (28). Intenzivni sportovi, zbog uticaja na hipotalamo-hipofiznu osovinu, s druge strane mogu dovesti do hipotalamusne amenoreje i posledične neplodnosti (27). Način vežbanja koji je naročito karakterističan za sportistkinje, a koji podrazumeva povećanu učestalost, intenzitet i trajanje fizičke aktivnosti, može izazvati smanjenu plodnost kod žena. Intenzivni biciklizam tokom 16 nedelja pokazao je negativne efekte na zapreminu sperme, koncentraciju, pokretljivost i broj spermatozoida, koji su bili značajno niži od početne vrednosti merene pre početka treniranja (29). Prema preporukama SZO, neophodno je da su sve odrasle osobe fizički aktivne, a fizička aktivnost treba da je većim delom aerobna i da uključi kombinaciju vežbi umerenog (najmanje sto pedeset minuta nedeljno) i visokog intenziteta (najmanje sedamdeset pet minuta nedeljno) kako bi se postigli značajni zdravstveni benefiti (30).

### Pušenje

Prema Istraživanju iz 2019. godine, u Srbiji ukupno 31,9% populacije uzrasta 15 godina i starijih svakodnevno ili povremeno koristi duvanske proizvode. Posmatrano po polu, 33,9% muškaraca i 30,1% žena su pušači (13). Studijom preseka koja je obuhvatila 3.910 ispitanika uzrasta 18 godina i starijih anketiranih u periodu od 20. maja do 30. avgusta 2023. godine utvrđeno je da je prevalencija svakodnevnog pušenja duvana u Autonomnoj Pokrajini Vojvodini (APV) bila 28,8%, a povremenog 7,2% (ukupno 36,0%), što je prevazilazilo tadašnji nacionalni nivo u Srbiji i bilo među najvišim u Evropi (31). Većina studija potvrđuje da je prevalencija neplodnosti veća, a vreme potrebno da do začeca dođe duže kod pušača u poređenju sa nepušačima. Smatra se da je ukupno 13% slučajeva neplodnosti izazvano pušenjem cigareta (32,33). Istraživanje sprovedeno u Velikoj Britaniji obuhvatilo je 15.000 trudnica kako bi se utvrdila povezanost aktivnog i pasivnog izlaganja duvanskom dimu sa vremenom koje je potrebno da do začeca dođe. Pored pušenja cigareta, u analizi su uzeti u obzir i faktori kao što su starosna dob, obrazovanje, zaposlenost, tip stanovanja, indeks telesne mase pre trudnoće i konzumacija alkohola, kako bi se eliminisao njihov potencijalni uticaj na plodnost. Posmatrano u odnosu na žene nepušače, žene koje su pušile imale su za 54% veći procenat odloženog začeca (vreme potrebno za začecanje je bilo duže od 12 meseci). Dokazano je da aktivno pušenje bilo kog partnera ima negativne efekte na plodnost, a pasivno izlaganje dimu cigareta može imati negativne posledice na plodnost u istoj meri kao i aktivno pušenje jednog od partnera. Pušačima je potrebno dvostruko više pokušaja tokom procesa vantelesne oplodnje da bi postigli začecanje u poređenju sa nepušačima (33,34). Povezanost između pušenja i zapremine sperme, ukupnog broja spermatozoida i procenta pokretnih spermatozoida je doznno zavisna. Konzumiranje više od 10 cigareta dnevno smanjuje koncentraciju sperme za 13% do 17% (35). Koncentracija sperme merena kod teških pušača bila je za 19% niža nego kod nepušača (36). Toksične materije nastale pušenjem cigareta mogu se akumulirati u folikularnoj tečnosti te ispoljiti produženo negativno dejstvo na funkciju jajnika koje je takođe doznno zavisno. Pušenje može dovesti do kraćeg menstrualnog ciklusa, iscrpljivanja folikula i ranije pojave menopauze (34).

research, the use of omega-3 fatty acids in the concentration of 75 g a day in the period of 12 weeks led to a significant improvement of sperm parameters in comparison to the control group of respondents, who did not use omega-3 fatty acids (25).

A diet rich in full-fat dairy products was associated with the lower risk of ovulatory infertility, while the use of low-fat dairy products was associated with an increased risk of ovulatory infertility (26).

The reproductive health can be improved by modifying the diet, including the increase in the intake of fruits and vegetables, legumes and fish, and reduction in the intake of red meat (13).

### Physical activity

Moderate physical activity helps to maintain an optimal BMI, has a positive effect on mental health, as well as on the improvement of the physiological function of ovaries in women (27). According to the results of a health survey, which enabled the assessment of the level of physical activity of the population of Serbia in 2019, 11.0% of citizens of Serbia in the age group 18 to 64 years were engaged in aerobic activities (such as fitness, sport, recreation or cycling) at least 150 minutes a week. Physical activity has shown a protective effect on fertility when it is combined with the loss of weight in obese women (28). Intense sports, due to the impact on the hypothalamic-pituitary axis, on the other hand can lead to hypothalamic amenorrhea and consequent infertility (27). The way of exercising, which is particularly characteristic of female athletes, and which implies increased frequency, intensity and duration of physical activity can cause reduced fertility in women. Intense cycling during 16 weeks showed negative effects on sperm volume, concentration, motility and sperm count, which were significantly lower compared to the initial values measured before the beginning of training (29). According to the WHO, all adults should be physically active, and physical activity should be mostly aerobic and include the combination of moderate-intensity training (at least one hundred and fifty minutes a week) and high-intensity training (at least seventy-five minutes a week) in order to achieve significant health benefits (30).

### Smoking

According to the study, which was conducted in Serbia in 2019, 31.9% of citizens aged 15 and older used tobacco products daily or occasionally. Smoking rate trends by sex show that 33.9% of men and 30.1% of women were smokers (13). In a cross-sectional study, which included 3,910 subjects aged 18 and older, who were interviewed in the period from May 20th, 2023 to August 30th, 2023, it was found that the prevalence of daily tobacco smoking in the Autonomous Province of Vojvodina (APV) was 28.8%, and occasional 7.2% (the total of 36.0%), which exceeded the national level in Serbia at that time and was among the highest in Europe (31). The majority of studies confirm that the prevalence of infertility is higher and the time needed to conceive longer in smokers in comparison to non-smokers. It is believed that a total of 13% of infertility cases are caused by cigarette smoking (32,33). A study conducted in Great Britain included 15,000 pregnant women in order to determine the association of active and passive exposure to tobacco smoke with the time it takes to conceive. In addition to cigarette smoking, in this analysis, factors such as age, education, type of residence, body mass index before pregnancy and alcohol consumption were also considered in order to eliminate their potential impact on fertility. In comparison to women who did not smoke, women who smoked had a 54% higher percentage of delayed conception (the time required for conception was longer than 12 months). It was proved that active smoking of any partner had a negative impact on fertility, while passive exposure to tobacco smoke can have negative effects on fertility to the same extent as when one of the partners is an active smoker. Smokers need twice as many attempts during the IVF process to achieve conception compared to non-smokers (33,34). The association between smoking and sperm volume, the total number of spermatozooids and the percentage of motile spermatozooids is dose-dependent. Smoking more than 10 cigarettes a day reduces the concentration of sperm by 13% to 17% (35). The concentration of sperm measured in heavy smokers was 19% lower than in non-smokers (36). Toxic substances from cigarette smoking can accumulate in the follicular fluid and therefore, have a negative impact on the ovarian function, which is also dose-dependent.

## Zloupotreba alkohola

Poznato je da je hronična zloupotreba alkohola povezana sa smanjenom plodnošću i većim rizikom od razvoja menstrualnih poremećaja, ali mehanizam kojim prekomerno konzumiranje alkohola negativno utiče na plodnost nije utvrđen (37). Kod muškaraca, konzumiranje alkohola je povezano sa brojnim negativnim posledicama, kao što su atrofija testisa, smanjen libido i smanjen broj spermatozoida. Meta-analiza koja je obuhvatila 57 studija i 29.914 ispitanika je pronašla značajnu povezanost između konzumiranja alkohola i zapremine semene tečnosti, morfologije i pokretljivosti spermatozoida (38). Prema rezultatima istraživanja u Indiji, nalaz spermograma u okviru referentnih vrednosti ima samo 12% muškaraca koji hronično konzumiraju alkohol (39). Još uvek nije precizno utvrđeno koja količina alkohola negativno utiče na reproduktivnu funkciju žena, jer ne postoji univerzalna definicija mere „jedne čaše“. Tako količine alkohola koje variraju od jedne čaše nedeljno do 5 jedinica dnevno mogu imati različite efekte, uključujući povećanje vremena potrebnog da do trudnoće dođe, smanjenje verovatnoće za začeće za više od 50% i smanjenje stope implantacije, povećanje rizika od spontanog pobačaja i fetalne smrti, kao i anovulacije, disfunkcije lutealne faze i abnormalnog razvoja blastociste (29). U Istraživanju iz 2019. godine, primenjen je kriterijum za rizičnu upotrebu alkohola, unos više od 20 grama etanola dnevno za žene i više od 40 grama etanola dnevno za muškarce, pri čemu je količina etanola u standardnom piću uzeta kao 13 grama. Prema rezultatima istraživanja iz 2019. godine, ovu količinu alkohola svakodnevno je konzumiralo 1,1% stanovništva Srbije starosti 15 i više godina (13). Iako je mehanizam kojim alkohol dovodi do smanjene plodnosti još uvek nepoznat, smatra se da njegova konzumacija dovodi do hormonskih promena kod žena, uključujući povećanje nivoa estrogena, što smanjuje FSH (folikulostimulišući hormon) i potiskuje folikulogenezu i ovulaciju (29).

## Zloupotreba psihoaktivnih supstanci

Zloupotreba svih psihoaktivnih supstanci negativno utiče na plodnost i žena i muškaraca, kao i na razvoj ploda, a može dovesti i do trajne neplodnosti. Kanabis, kokain i heroin, metilendioksimetamfetamin („ekstazi“), te ostale droge smanjuju nivo testosterona kod muškaraca (28,40). Prema rezultatima Istraživanja iz 2019. godine, 4,2% sta-

novništva Srbije je tokom svog života koristilo neku od ilegalnih droga obuhvaćenih istraživanjem (13). Marihuana je jedna od najčešće korišćenih droga u Srbiji i u svetu. Sadrži kanabinoide koji se vezuju za receptore na reproduktivnim organima ili strukturama kao što su materica ili ductus deferens (29). Kod muškaraca, kanabinoidi smanjuju nivo testosterona, smanjuju spermatogenezu i pokretljivost spermatozoida (40). Danska kohortna studija koja je obuhvatila 1.215 učesnika, dokazala je da je povezanost između upotrebe marihuane i koncentracije spermatozoida obrnuto proporcionalna (41). Redovno pušenje marihuane više od jednom nedeljno bilo je povezano sa 28% nižom koncentracijom spermatozoida, dok je kombinovana upotreba marihuane više od jednom nedeljno i drugih droga smanjila koncentraciju spermatozoida za 52% (42). Žene koje koriste marihuanu imaju povećan rizik od primarne neplodnosti u poređenju sa ženama koje je ne koriste (29). Kod žena, zloupotreba kanabisa može dovesti do disbalansa hormona koji utiču na ovulaciju i tako umanjiti šanse za trudnoću (40). Korišćenje kokaina negativno utiče na spermatogenezu i dovodi do smanjenja ukupnog i slobodnog testosterona u serumu, a efekti kokaina kod muškaraca zavise od doze, dužine korišćenja i interakcije sa drugim drogama. Parametri spermatozoida takođe opadaju upotrebom heroina i metadona, a negativan uticaj se u najvećoj meri odražava na pokretljivost spermatozoida (29). Kod žena, upotreba kokaina i heroina može dovesti do odlublivanja posteljice (29,40).

## Seksualno ponašanje

U cilju obezbeđivanja dobrog reproduktivnog zdravlja žena neophodno je raditi na smanjivanju rizika od polno prenosivih infekcija primenom kondoma, edukacijom i preduzimanjem drugih mera prevencije (43). Među odraslima starijim od 20 godina u R. Srbiji, 50,5% osoba je imalo povremene partnere sa kojima su koristile kondom prilikom poslednjeg seksualnog odnosa, pri čemu ovaj postotak opada sa godinama i znatno je ređi među osobama sa nižim obrazovnim nivoom i manjim prihodima domaćinstva (13). Istraživanjem sprovedenim u APV ispitana je povezanost između neželjenog seksualnog odnosa i sociodemografskih faktora, kao i evaluacija efikasnosti vanškolske edukacije o reproduktivnom zdravlju u podizanju svesti srednjoškolaca. Uključeno je 5.026 učenika drugog razreda iz 72 srednje škole u APV. Jedan od

Smoking can lead to a shorter menstrual cycle, follicle depletion and earlier occurrence of menopause (34).

### Alcohol abuse

It is known that chronic alcohol abuse is associated with reduced fertility and increased risk of menstrual disorders, but the mechanism by which excessive alcohol consumption negatively affects fertility has not been established (37). In men, alcohol consumption is associated with numerous negative consequences, such as testicular atrophy, reduced libido and reduced sperm count. A meta-analysis, which included 57 studies and 29,914 respondents, found a significant association between alcohol consumption and volume of seminal fluid, sperm morphology and motility (38). According to the research results in India, only 12% of men who chronically consumed alcohol had a spermogram within reference values (39). It has not been determined precisely what amount of alcohol has a negative impact on the reproductive function of women, because there is no universal definition of the measure of "one glass". Thus, quantities that vary from one glass of alcohol per week to 5 units a day can have a variety of effects, including the increase in time necessary to get pregnant, the reduction of the probability of conception by more than 50% and decrease in the implantation rate, the increase in the risk of miscarriage and fetal death, as well as anovulation, luteal phase dysfunction and abnormal blastocyst development (29). In a study conducted in 2019, the criterion for risky alcohol use was the intake of more than 20 grams of ethanol a day for women and more than 40 grams of ethanol a day for men, while the amount of ethanol in a standard drink was deemed to be 13 grams. According to research results from 2019, this amount of alcohol was consumed daily by 1.1% of Serbia's citizens aged 15 and older (13). Although the mechanism by which alcohol leads to reduced fertility is still unknown, its consumption is thought to lead to hormonal changes in women, including an increase in estrogen levels, which reduces FSH (follicle-stimulating hormone) and suppresses folliculogenesis and ovulation (29).

### Abuse of psychoactive substances

The abuse of psychoactive substances negatively affects the fertility of both women and men, as

well as the development of the fetus and can lead to permanent infertility. Cannabis, cocaine, heroin, methylenedioxymethamphetamine ("ecstasy"), and other drugs reduce the levels of testosterone in men (28,40). According to the research results from 2019, 4.2% of citizens in Serbia used one of the illegal drugs included in the research (13). Marijuana is one of the most commonly used drugs in Serbia and in the world. It contains cannabinoids that bind to receptors on reproductive organs or structures such as the uterus or ductus deferens (29). In men, cannabinoids reduce testosterone levels, reduce spermatogenesis and sperm motility (40). A Danish cohort study, which included 1,215 participants, proved that the relationship between marijuana use and sperm concentration was inversely proportional (41). Regular marijuana use more than once a week was associated with a 28% lower sperm concentration, while the combined use of marijuana and other drugs more than once a week reduced sperm concentration by 52% (42). Women who used marijuana had an increased risk of primary infertility compared to women who did not use it (29). In women, the abuse of cannabis can lead to the imbalance of hormones that affect ovulation and thus reduce the chances of pregnancy (40). The use of cocaine negatively affects spermatogenesis and leads to a decrease in total and free testosterone in the serum, and the effects of cocaine in men depend on the dose, length of use, and interaction with other drugs. Sperm parameters also decline with the use of heroin and methadone, and the negative impact is mostly reflected in sperm motility (29). In women, the use of cocaine and heroin can lead to placental abruption (29,40).

### Sexual behavior

In order to ensure good reproductive health of women, it is necessary to work on reducing the risk of sexually transmitted infections by using condoms, education and other preventive measures (43). Among adults older than 20 in the Republic of Serbia, 50.5% of persons had occasional partners who used a condom during their last sexual intercourse, while the percentage decreases with age and it is significantly less frequent in persons with a lower level of education and lower household income (13). In a study, which was conducted in the APV, the association between the unwanted sexual intercourse and

četiri ispitanika je imao neželjen seksualni odnos, a nakon sprovedenog programa edukacije, utvrđeno je da je edukacija imala pozitivan uticaj na psihosocijalne kompetencije koje doprinose odgovornom seksualnom ponašanju (44). Pod rizičnim seksualnim ponašanjem podrazumeva se rano stupanje u seksualne odnose, česta promena seksualnih partnera i istovremeno postojanje više seksualnih partnera, nekorišćenje kondoma pri svakom seksualnom odnosu, na pravilan način, do odluke o potomstvu, neautonomnosti u donošenju odluka u vezi sa seksualnošću, neadekvatna higijena genitalnih organa (45). Zdravlje pre koncepcije je važan faktor koji utiče na ishod trudnoće i zdravlje novorođenčeta (46). Većina slučajeva neplodnosti je uzrokovana zapaljenskim oboljenjima genitalnih organa, što je posledica nelečenih polno prenosivih infekcija koje imaju tendenciju da se šire uzlazno duž reproduktivnog trakta (47). Podaci iz literature ukazuju da mikroorganizmi kao što su *Chlamydia trachomatis*, *Mycoplasma spp.*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, *Ureaplasma urealyticum* itd., mogu dovesti do neplodnosti. Humani papiloma virusi i *Herpes simplex* virus mogu smanjiti pokretljivost i koncentraciju spermatozoida (48,49). Ispravna upotreba postojećih i razvoj novih metoda zaštite od polno prenosivih infekcija, upotreba masovnih medija u cilju promocije zdravlja, kao i besplatne usluge planiranja porodice (primena kontraceptiva i redukcija neplaniranih ranih trudnoća) u dobro organizovanim jedinicama zdravstvene zaštite mogu doprineti boljem ishodu plodnosti i sigurnom materinstvu (46).

## Zaključak

Neplodnost je globalni javnozdravstveni problem. Iako se ne može uticati na sve faktore rizika neplodnosti, neki važni faktori rizika se mogu redukovati ili eliminisati. Uočeno je da postoji značajna veza između određenih bihevioralnih faktora i neplodnosti. Uravnotežena i zdrava ishrana svakog pojedinca pre i tokom pokušaja začeća može biti od vitalnog značaja za poboljšanje plodnosti. Savetuje se umerena fizička aktivnost, prestanak konzumiranja cigareta, alkohola i psihoaktivnih supstanci, kao i odgovorno (bezbedno) seksualno ponašanje, rano otkrivanje i lečenje polno prenosivih infekcija. Da bi se efikasno rešio problem neplodnosti, zdravstvene politike moraju prepoznati da se ne-

plodnost često može sprečiti, čime se smanjuje potreba za skupim tretmanima. Jasno razumevanje mogućih faktora rizika za neplodnost ključno je za dizajniranje i sprovođenje efikasnih strategija za zaštitu plodnosti oba partnera. Neophodna su dalja istraživanja u ovoj oblasti radi donošenja adekvatnih preventivnih programa.

## Konflikt interesa

Autor je izjavio da nema konflikta interesa.

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sociodemographic factors was examined, as well as the evaluation of the effectiveness of extracurricular education on reproductive health in raising the awareness of high school students. 5,026 second-grade students from 72 secondary schools in the APV were included. One out of four participants had an unwanted sexual intercourse, and after the education program was implemented, it was observed that the education had a positive impact on psychosocial competences that contribute to responsible sexual behavior (44). Risky sexual behavior means early sexual intercourse, frequent change of sexual partners and having multiple sexual partners simultaneously, failure to use a condom correctly during every sexual intercourse until the decision about offspring is made, lack of autonomy in making decisions about sexuality, inadequate hygiene of genital organs (45). Preconception health is an important factor that affects the outcome of pregnancy and the health of the newborn (46). Most cases of infertility are caused by inflammatory diseases of the genital organs, which is a consequence of untreated sexually transmitted infections that tend to spread upward along the reproductive tract (47). Literature data indicate that microorganisms such as *Chlamydia trachomatis*, *Mycoplasma spp.*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, *Ureaplasma urealyticum* ect. can lead to infertility. Human papillomaviruses and Herpes simplex virus can reduce sperm motility and concentration (48,49). The correct use of existing and development of new methods of protection in order to ensure protection against sexually transmitted diseases, as well as the use of mass media aimed at promoting health, and the free services of family planning (use of contraceptives and reduction of unplanned early pregnancies) in well-organized health care units can contribute to better fertility outcomes and safe motherhood (46).

## Conclusion

Infertility is a global public health problem. Although we cannot influence all risk factors related to infertility, some important risk factors can be reduced or eliminated. It has been noticed that there is a significant relationship between certain behavioral factors and fertility. A balanced and healthy diet of each individual before and

during trying to conceive can be of vital importance for improving fertility. Moderate physical activity, the cessation of cigarette smoking, alcohol and psychoactive substances abuse are advised, as well as responsible (safe) sexual behavior, early detection and treatment of sexually transmitted diseases. In order to solve the problem of infertility effectively, health policies must recognize that infertility can often be prevented, thus reducing the need for expensive treatments. A clear understanding of possible risk factors for infertility is essential for designing and implementing effective strategies to protect the fertility of both partners. Further research in this field is needed in order to adopt adequate preventive programs.

## Competing interests

The author declared no competing interests.

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## STAVOVI I ZNANJA RODITELJA ŠKOLSKE DECE O HPV INFEKCIJI I VAKCINACIJI U ZEMLJAMA BIVŠE JUGOSLAVIJE: PREGLEDNI RAD

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### SAŽETAK

U svetu, 2022. godine, rak grlića materice je bio četvrti najčešći rak kod žena sa preko 660.000 novoobolelih slučajeva godišnje. Uzrokuje ga perzistentna infekcija humanim papiloma virusom (HPV). Ključne mere prevencije raka grlića materice su skrining (Pap test) i HPV vakcina. U svetu, od 2023. godine, postoji 6 vrsta vakcina protiv HPV. Prema strategiji Svetske zdravstvene organizacije, kada bi pokrivenost vakcinacijom devojčica do 15 godina dostigla 90% bolest bi bila eliminisana. Zemlje članice SZO još uvek ne prelaze procenat obuhvata od 55%, dok zemlje bivše Jugoslavije imaju znatno niže procenat. Cilj ovog preglednog rada je da se analiziraju stavovi i znanja roditelja o HPV vakcinaciji njihove dece u državama bivše Jugoslavije. Pretražene su elektronske baze podataka (*PubMed*, *Scopus* i *Google Scholar*) pomoću sledećih ključnih reči na engleskom jeziku: stavovi roditelja, prihvatanje vakcinacije, neodlučnost prema vakcinaciji i HPV vakcina. Identifikovana su četiri članka koja su ispunjavala kriterijume za uključivanje. Analizirani radovi pokazali su da na prihvatanje vakcinacije protiv HPV infekcije od strane roditelja najveći uticaj ima preporuka pedijatra. U studijama sprovedenim u Srbiji pronađeno je da se češće vakcinišu devojčice nego dečaci. Roditelji su se izjasnili da se vakcinacija protiv HPV nedovoljno promovise, te bi bilo značajno da se tome posveti više pažnje u budućnosti. Uočeno je da su roditelji ciljna populacija u kojoj treba sprovesti edukativne intervencije o HPV infekciji i vakcinaciji, kako bi se postigla veća pokrivenost ovom vakcinom.

**Ključne reči:** HPV infekcija, HPV vakcina, stavovi roditelji, rak grlića materice

### Uvod

U svetu, rak grlića materice je četvrti najčešći rak kod žena sa preko 660.000 novoobolelih slučajeva godišnje i oko 350.000 smrtnih slučajeva u 2022. godini (1). U zemljama Evrope, u 2022. godini, bilo je prijavljeno 58.219 novih slučajeva raka grlića materice, a 27.000 smrtnih slučajeva (2). Uprkos efikasnim i dostupnim merama prevencije, vakcinaciji i skriningu, i dalje postoji visoka stopa smrtnosti od ove bolesti. Rak grlića materice uzrokuje perzistentna infekcija humanim papiloma virusom (HPV). Identifikovano je preko 200 serotipova HPV-a, a kao visokorizični za nastanak malignih lezija označeni su podtipovi 16, 18, 31, 35, 39, 45, 51, 52 i 56 (3).

Vakcina protiv HPV-a odobrena je od strane FDA (eng. *Food and Drug Administration*) 2006. godine kao dvovalentna, a od 2014. godine dostupna je devetovalentna vakcina Gardasil 9. Od 2023. godine, u svetu postoji 6 vrsta vakcina protiv HPV-a i sve štite od seroloških tipova 16 i 18 koji su najčešći uzročnici karcinoma grlića materice (1,4). Prioritet je da se vakcina primeni pre kontakta sa virusom, odnosno pre stupanja u seksualne odnose, te su preporuke da je najbolje sprovesti vakcinaciju dece oba pola 9-14 godina sa dve doze vakcine u razmaku od 6 meseci (1). Svetska zdravstvena organizacija ulaže velike napore da se poveća obuhvat HPV vakcinom širom sveta.

## ATTITUDES AND KNOWLEDGE OF PARENTS OF SCHOOL CHILDREN ABOUT HPV INFECTION AND VACCINATION IN THE COUNTRIES OF THE FORMER YUGOSLAVIA: REVIEW

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### SUMMARY

In 2022, cervical cancer was the fourth most common cancer among women worldwide, with over 660,000 new cases annually. It is caused by persistent infection with the human papillomavirus (HPV). The key measures for cervical cancer prevention are screening (Pap test) and the HPV vaccine. As of 2023, six types of HPV vaccines are available worldwide. According to the World Health Organization (WHO) strategy, if vaccination coverage of girls up to the age of 15 were to reach 90%, the disease could be eliminated. However, WHO member states have not yet exceeded a coverage rate of 55%, while the countries of the former Yugoslavia show significantly lower rates. The aim of this review paper is to analyze parents' attitudes and knowledge regarding HPV vaccination of their children in the countries of the former Yugoslavia. Electronic databases (PubMed, Scopus, and Google Scholar) were searched using the following keywords in English: parental attitudes, vaccine acceptance, vaccine hesitancy, and HPV vaccine. Four articles meeting the inclusion criteria were identified. The analyzed studies showed that pediatricians' recommendations have the greatest influence on parents' acceptance of HPV vaccination. Studies conducted in Serbia found that girls are vaccinated more often than boys. Parents stated that HPV vaccination is insufficiently promoted, and that more attention should be dedicated to this issue in the future. It has been observed that parents are the target population for implementing educational interventions on HPV infection and vaccination in order to achieve higher coverage with this vaccine.

**Keywords:** HPV infection, HPV vaccine, parental attitudes, cervical cancer

### Introduction

In the world, cervical cancer is the fourth most common cancer in women with more than 660,000 new cases per year and about 350,000 deaths registered in 2022 (1). In 2022, 58,219 new cases of cervical cancer and 27,000 deaths were reported in European countries (2). Despite the efficient and available preventive measures, vaccination and screening, there is still a high rate of mortality caused by this disease. Cervical cancer is caused by the persistent human papillomaviruses (HPV). More than 200 serotypes of HPV have been identified,

while the subtypes 16, 28, 31, 35, 39, 45, 51, 52 and 56 have been designated as high-risk for the development of malignant lesions (3).

The HPV vaccine was approved by the Food and Drug Administration (FDA) in 2006 as bivalent, while since 2014, the nine-valent HPV vaccine known as Gardasil 9, has been available. Since 2023, six types of HPV vaccines have been licensed worldwide, and all of them protect against the serological types 16 and 18, which are the most common causes of cervical cancer (1,4). The priority is to administer

Strategija doneta 2020. godine podrazumeva da je potrebno vakcinisati 90% devojčica do 15 godina (5), ali i posle 18 godina od uvođenja ove vakcine i dalje samo 55% država članica SZO primenjuje HPV vakcinu kao primarnu profikasu (6).

U zemljama Evrope procenat pokrivenosti sa dve doze HPV vakcine dečaka i devojčica do 15 godina je oko 30%, a razvijene zemlje kao što su Belgija, Kanada, Danska, Kipar, Island, Letonija, Portugal, Španija, Norveška i Švedska dostigle su obuhvat preko 80% dece do 15 godina oba pola (7).

Cilj ovog preglednog rada bio je da se analiziraju stavovi i znanja roditelja o HPV vakcinaciji njihove dece u državama bivše Jugoslavije.

## Metod

Izvršena je pretraga literature i analiza radova drugih istraživača. Pretražene su elektronske baze podataka: *PubMed*, *Google Scholar*, *Web of Science* i *Embase* od januara do februara 2025. godine. Pretraživanje je sprovedeno za poslednjih deset godina korišćenjem sledećih ključnih reči: stavovi roditelja, prihvatanje vakcinacije, neodlučnost prema vakcinaciji i HPV vakcina. Napredna pretraga uključivala je kombinaciju relevantnih ključnih reči i veznika „i“: HPV vakcina, roditelji, stav, uverenje, prihvatanje, odbijanje, znanja i imena država. Obuhvaćeni su samo radovi koju su se bavili prihvatanjem HPV vakcinacije od strane roditelja u zemljama bivše Jugoslavije.

Kriterijumi za uključivanje bili su: originalno istraživanje objavljeno u poslednjih 10 godina sprovedeno u zemljama bivše Jugoslavije; članci koji su istraživali stavove i percepciju roditelja o HPV vakcinaciji; članci objavljeni na engleskom jeziku; i članci dostupni u punom tekstu. Iz pretrage su

isključeni članci koji su izveštavali samo o statusu vakcinacije ili nekim drugim aspektima HPV vakcinacije, zatim članci sa konferencija, sistematski pregledi i meta-analize.

## Procenat obuhvata HPV vakcinom u zemljama bivše Jugoslavije

Države bivše Jugoslavije imaju izuzetno nizak procenat obuhvata HPV vakcinom, a tačni podaci iz baze SZO prikazani su u tabeli 1.

Iz navedene tabele vidimo da Republika Srbija i Bosna i Hercegovina imaju značajno niže procenat pokrivenosti HPV vakcinacijom u odnosu na ostale države bivše Jugoslavije, iako je i kod njih pokrivenost daleko ispod poželjnih 80%. Iako direktni podaci o incidenciji HPV infekcija kod školske dece u Srbiji nisu dostupni, postoje indikacije da je prisutnost HPV-a među mladima značajna. Nizak obuhvat vakcinacijom ukazuje na potrebu za dodatnim naporima u informisanju i motivaciji roditelja i dece za vakcinaciju.

Nacionalni programi vakcinacije protiv HPV-a podrazumevaju davanje saglasnosti roditelja dece do 15 godina za vakcinaciju. Svetska zdravstvena organizacija definisala je neodlučnost o vakcinaciji kao kasno prihvatanje ili odbijanje vakcinacije od strane roditelja (8).

## Stavovi roditelja o prihvatanju vakcinacije njihove dece HPV vakcinom u zemljama bivše Jugoslavije i poređenje sa drugim zemljama sveta

Studije koje su se bavile ispitivanjem stavova roditelja o prihvatanju vakcinacije njihove dece HPV vakcinom prikazane su na tabeli 2.

**Tabela 1.** Procenat obuhvata sa dve doze HPV vakcine za decu do 15 godina oba pola u državama bivše Jugoslavije u 2023. godini (7)

Država	Procenat obuhvata HPV vakcinom sa dve doze devojčice do 15 godina (%)	Procenat obuhvata HPV vakcinom sa dve doze dečake do 15 godina (%)
Srbija	5	5
Crna Gora	20	/
Severna Makedonija	29	/
Hrvatska	55	36
Bosna i Hercegovina	5	/
Slovenija	52	/

\*/ - nema podataka

the vaccine before any exposure to the virus, that is, before a person becomes sexually active, and therefore, the two-dose schedule with a 6-month interval between doses is recommended for children of both sexes aged 9 to 14 years (1). The World Health Organization is making great efforts to increase HPV vaccination coverage globally. The strategy adopted in 2020 implies that it is necessary to achieve 90% HPV vaccination coverage in girls by the age of 15 (5), but even after 18 years since the introduction of this vaccine, only 55% of WHO member states administer the HPV vaccine as the primary prophylaxis (6).

In European countries, the percentage of HPV vaccination coverage with two doses in boys and girls by the age of 15 is around 30%, while developed countries such as Belgium, Canada, Denmark, Cyprus, Iceland, Latvia, Portugal, Spain, Norway and Sweden have reached the vaccination coverage rates of over 80% in children of both sexes by the age of 15 (7).

The aim of this review article was to analyze the attitudes and knowledge of parents about the HPV vaccination of their children in the countries of the former Yugoslavia.

## Methods

A literature search was done and the articles of other researchers were analyzed. The electronic databases PubMed, Google Scholar, Web of Science and Embase were searched from January to February 2025. The search was conducted for the last ten years using the following key words: parents' attitudes, acceptance of vaccination, vaccine hesitancy and HPV vaccine. The advanced search included the combination of relevant keywords

and the conjunction "and": HPV vaccine, parents, attitude, belief, acceptance, refusal, knowledge and names of countries. Only articles that dealt with the parental acceptance of HPV vaccination in the countries of the former Yugoslavia were included.

The inclusion criteria were the following: original research published in the last 10 years and conducted in the countries of the former Yugoslavia; articles that investigated parents' attitudes and perceptions about HPV vaccination; articles published in the English language; and articles available in full text. Articles that reported only on vaccination status or some other aspects of HPV vaccination, then conference articles, systematic reviews and meta-analyses were excluded from the search.

## The percentage of HPV vaccination coverage in the countries of the former Yugoslavia

The countries of the former Yugoslavia have an extremely low percentage of HPV vaccination coverage, and the exact data from the WHO database are shown in Table 1.

From the above table, we can see that the Republic of Serbia and Bosnia and Herzegovina have significantly lower percentages of HPV vaccination in comparison to the other countries of the former Yugoslavia, even though the coverage in these countries is also far below the desirable 80%. Although direct data on the incidence of HPV infections in school children are not available, there are indications that the presence of HPV among young people is significant. Low vaccination coverage points to the need that additional efforts should be made to inform and motivate parents and children to agree to vaccination.

**Table 1.** Percentage of coverage for the full two-dose HPV vaccination in children of both sexes by the age of 15 in the countries of the former Yugoslavia in 2023 (7)

State	Percentage of HPV vaccination coverage in girls by age 15, two doses (%)	Percentage of HPV vaccination coverage in boys by age 15, two doses (%)
Serbia	5	5
Montenegro	20	/
North Macedonia	29	/
Croatia	55	36
Bosnia and Herzegovina	5	/
Slovenia	52	/

\* / - there are no data

**Tabela 2.** Specifičnosti studija koje su se bavile ispitivanjem stavova roditelja o prihvatanju vakcinacije njihove dece HPV vakcinom

Studija	Država	Ispitivana populacija	Veličina uzorka	Uzrast dece	Vreme prikupljanja podataka	Broj vakcinisane dece	Broj nevakcinisane dece
Štrbac M et al. (2023) [9]	Srbija	Roditelji	436	12-18 godina	Januar – Decembar 2021.godine	676	/
Rančić N et al (2022) [10]	Srbija	Roditelji	615	9-19 godina	Jun - Oktobar 2022. godine	499 prvom dozom; 116 drugom dozom	/
Belavic A, Simetic Pavic I. (2020) [11]	Hrvatska	Roditelji	3350	14 godina	Maj 2016. godine	2077	1273
Marić G et al. (2018) [12]	Srbija	Roditelji	282	9-18 godina	Decembar 2015.- Maj 2016. godine		

Studija Štrbac i saradnika (9) sprovedena je u Novom Sadu na pedijatrijskom odeljenju Doma zdravlja Novi Sad putem strukturiranog upitnika konstruisanog za potrebe istraživanja sa 17 motiva/stavova o prihvatanju HPV vakcinacije od strane roditelja. Najsnažniji motiv za prihvatanje vakcinacije koji je izabrala većina roditelja (33%) bio je „preporuka pedijatra“. Slične rezultate pokazuje i istraživanje sprovedeno među roditeljima adolescenata u Španiji, gde se navodi da su pedijatri najrelevantniji izvor informacija o HPV vakcinaciji (13). Veliki broj novosadskih roditelja (15,4%) naveo je da bi vakcinisao svoje dete zbog svesti da HPV vakcina štiti od raka na različitim lokalizacijama, dok je nešto manji broj roditelja (13,3%) iskazao slaganje sa tvrdnjom da je „bolje vakcinisati dete nego ga izložiti riziku od HPV infekcija“ (9). U ovoj studiji otkriveno je i da je u ispitivanom uzorku devet puta više vakcinisanih devojčica od dečaka. To nije neuobičajeno, postoje zemlje u kojima se još uvek ne sprovodi vakcinacija dečaka ili se ona započinje kasnije, pa je obuhvat manji (14). Edukacija roditelja o HPV infekciji, raku grlića materice, informisanje o bezbednosti i efikasnosti HPV vakcine značajni su za prihvatanje vakcinacije. Ovi rezultati koreliraju sa rezultatima istraživanja sprovedenih i u drugim zemljama (9,15,16).

Istraživanje Rančića i sar. (10) je sprovedeno u Nišu i ispitivali su stavove roditelja o HPV vakcinaciji u jugoistočnoj Srbiji putem upitnika koji se sastojao iz dva dela: sociodemografski podaci i 15 stavki o HPV infekciji, znanjima i svesti o HPV vakcinaciji. Deca svih 615 roditelja uključenih u istraživanje bila su vakcinisana sa bar jednom dozom vakcine, a 3,9 puta više je bilo vakcinisanih devojčica nego

dečaka (398 devojčica, 101 dečak). Znatno više su vakcinisana deca iz gradskih sredina (90,2%), a roditelji koji su imali medicinsko obrazovanje su pokazali viši stepen znanja o HPV infekciji i vakcinaciji. Veliki procenat roditelja (78%) naveo je sve načine prenošenja HPV-a, a 82% roditelja znalo je načine prevencije infekcije. Preporuka pedijatra za vakcinaciju je značajno uticala na prihvatanje HPV vakcine, kao i u istraživanju Štrbac i sar. (9).

U studiji sprovedenoj u Hrvatskoj 2016. godine (11), pre primene upitnika o znanjima i stavovima o HPV infekciji i prihvatanju vakcinacije protiv HPV-a sprovedena je edukacija roditelja od strane školskih lekara i epidemiologa. Nakon toga roditelji su popunjavali evaluacioni upitnik koji se sastojao od sociodemografskih podataka i 10 tvrdnji o HPV infekciji i vakcinaciji. Roditelji su bili podeljeni u dve grupe: oni koji su zdravstveni profesionalci i oni koji nisu, a potom su odgovori ove dve grupe poređeni. Nisu pronađene značajne razlike u znanjima i stavovima o HPV infekciji i vakcinaciji između ove dve grupe roditelja što je u suprotnosti sa rezultatima drugih istraživanja gde su zdravstveni radnici pozitivno uticali na stavove roditelja i adolescenata o HPV vakcinaciji (17,18).

Istraživanje Marić i sar. (12) sprovedeno je u Beogradu u periodu 2015-2016. godine u dva doma zdravlja. Primenjen je upitnik kreiran za ovo istraživanje sa 43 stavke (sociodemografski podaci, znanja o HPV infekciji i stavovi o HPV vakcinaciji). Većina roditelja (71%) je znala da vakcina protiv HPV-a postoji, a jedna četvrtina njih je imala pozitivan stav prema vakcinaciji. Većina roditelja se složila sa tvrdnjom da se vakcinacija protiv HPV-a nedovoljno promoviše u Republici Srbiji. Pozi-

**Table 2.** Specificities of studies that investigated parents' attitudes about the acceptance of vaccination of their children with the HPV vaccine

Study	Country	Study population	Sample size	Children's age	Time of data collection	Number of vaccinated children	Number of unvaccinated children
Štrbac M et al. (2023) [9]	Serbia	Parents	436	12-18 years	January – December 2021	676	/
Rančić N et al (2022) [10]	Serbia	Parents	615	9-19 years	June 2022-October 2022	499 first dose; 116 second dose	/
Belavic A, Simetic Pavic I. (2020) [11]	Croatia	Parents	3350	14 years	May 2016	2077	1273
Marić G et al. (2018) [12]	Serbia	Parents	282	9-18 years	December 2015-May 2016		

National HPV programs require the consent of parents of children up to 15 years of age for vaccination. The World Health Organization defined vaccine hesitancy as the delay in acceptance or refusal of vaccination by parents (8).

### Parents' attitudes about the acceptance of vaccination of their children with the HPV vaccine in the countries of the former Yugoslavia and comparison with other countries of the world

Studies that examined parents' attitudes about the acceptance of HPV vaccination of their children are shown in Table 2.

A study by Štrbac et al. (9) was conducted in Novi Sad at the pediatric department of the Health Center Novi Sad using the structured questionnaire that was developed for research purposes with 17 motives/attitudes about the parental acceptance of HPV vaccination. The strongest motive for accepting vaccination chosen by the majority of parents (33%) was "pediatrician's recommendation". A study conducted among parents of adolescents in Spain shows similar results, where it is stated that pediatricians are the most relevant source of information about HPV vaccination (13). A large number of parents in Novi Sad (15.4%) stated that they would vaccinate their children because of the awareness that the HPV vaccine protects against cancer in different locations, while a slightly smaller number of parents (13.3%) expressed agreement with the statement that "it is better to vaccinate a child than to expose him to the risk of HPV infection" (9). In this study, it was also found out that there

were nine times more vaccinated girls than boys in the examined sample. This is not unusual, there are countries where vaccination of boys has not been conducted yet or it is started later, so the coverage is lower (14). Educating parents about the HPV infection, cervical cancer, informing them about the safety and effectiveness of the HPV vaccine are important for vaccination acceptance. These results correlate with the results of studies conducted in other countries (9,15,16).

A study by Rančić et al. (10) was conducted in Niš and examined the parents' attitudes about HPV vaccination in Southeastern Serbia using the questionnaire that consisted of two parts: sociodemographic data and 15 items about HPV infection, knowledge and awareness about HPV vaccination. The children of all 615 parents included in the study were vaccinated with at least one dose of the vaccine, and there were 3.9 times more vaccinated girls than boys (398 girls and 101 boys). Children from urban areas were vaccinated significantly more often (90.2%), and parents who had medical education showed a higher level of knowledge about HPV infection and vaccination. A large percentage of parents (78%) mentioned all ways of transmitting HPV, while 82% of parents knew ways to prevent this infection. The pediatrician's recommendation for vaccination significantly influenced the acceptance of the HPV vaccine, as in the study by Štrbac et al. (9).

In a study conducted in Croatia in 2016 (11), before the questionnaire about knowledge and attitudes about the HPV infection and the acceptance of HPV vaccination was applied, parents were educated by school doctors and

tivnije stavove prema vakcinaciji imali su roditelji ženske dece do 9 godina, roditelji sa više znanja o HPV infekciji, i oni koji su dobili preporuku pedijatra za vakcinaciju.

Iako direktni podaci o incidenciji HPV infekcija kod školske dece u Srbiji nisu dostupni, postoje indikacije da je prisutnost HPV-a među mladima značajna. Nizak obuhvat vakcinacijom ukazuje na potrebu za dodatnim naporima u informisanju i motivaciji roditelja i dece za vakcinaciju.

Podaci pokazuju da su zemlje sa najvećim obuhvatom HPV vakcinacijom Sjedinjene Američke Države i Australija. Izveštaj CDC za 2023. godinu pokazuje da je u Sjedinjenim Američkim Državama procenat vakcinisanih adolescenata do 17 godina sa obe doze HPV vakcine 61,4% (19). Australija je dostigla poželjnih 80% pokrivenosti HPV vakcinacijom. Podaci za 2023. godinu pokazuju da je 84,2% devojčica i 81,8% dečaka dobilo dve doze vakcine (20).

## Zaključak

U bivšim zemljama Jugoslavije na prihvatanje vakcinacije protiv HPV-a od strane roditelja najveći uticaj su imale preporuke pedijataru. U većini studija češće se vakcinišu devojčice nego dečaci, a roditelji navode nedovoljno promovisanje HPV vakcine. Neophodna je edukacija roditelja o HPV infekciji i značaju HPV vakcine, uvođenje HPV vakcine u kalendar obavezne imunizacije i obezbeđivanje besplatne vakcine, što će doprineti većem obuhvatu mladih HPV vakcinom. Potrebna su dalja istraživanja faktora koji doprinose odbijanju roditelja da vakcinišu svoju decu HPV vakcinom.

## Konflikt interesa

Autori su izjavili da nema konflikta interesa.

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epidemiologists. After that, the parents filled out the evaluation questionnaire that consisted of sociodemographic data and ten statements about the HPV infection and vaccination. The parents were divided into two groups: those who are health professionals and those who are not, and then the answers of these two groups were compared. There were no significant differences in knowledge and attitudes about the HPV infection and vaccination between these two groups of parents, which is in contrast to the results of other studies, where health professionals positively influenced the attitudes of parents and adolescents about HPV vaccination (17,18).

A study by Marić et al. (12) was conducted in Belgrade in two Health Centers in the period 2015-2016. The questionnaire which was created for this study was applied and it contained 43 items (sociodemographic data, knowledge about HPV infection and attitudes about HPV vaccination). The majority of parents (71%) knew that the HPV vaccine existed, and a quarter of them had a positive attitude towards vaccination. The majority of parents agreed with the statement that HPV vaccination was insufficiently promoted in the Republic of Serbia. The parents of female children aged up to 9 years old had more positive attitudes towards vaccination, as well as those who had more knowledge about HPV infection and those who got pediatrician's recommendation for vaccination.

Although direct data on the incidence of HPV infections among school children in Serbia are not available, there are indications that the presence of HPV among young people is significant. Low vaccination coverage indicates that additional efforts should be made to inform and motivate children and parents to agree to vaccination.

Data show that the countries with the highest HPV vaccination coverage are the United States of America and Australia. The CDC Report for the year 2023 shows that in the United States, the percentage of adolescents by the age of 17 vaccinated with both doses of the HPV vaccine was 61.4% (19). Australia reached the desirable 80% HPV vaccination coverage, and data for 2023 show that 84.2% of girls and 81.8% of boys received two doses of the vaccine (20).

## Conclusion

In the former Yugoslav countries, pediatricians' recommendations had the greatest influence on parents' acceptance of HPV vaccination. In most studies, girls are vaccinated more often than boys, and parents report the insufficient promotion of the HPV vaccine. It is necessary to educate parents about the HPV infection and significance of the HPV vaccine, to introduce the HPV vaccine into the calendar of mandatory immunization, and provide the free vaccine, which will contribute to the greater coverage of young people with the HPV vaccine. Further research of factors that contribute to parents' refusal to vaccinate their children with the HPV vaccine is necessary.

## Competing interests

The authors declared no competing interests.

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## PERIPHERAL NERVE SHEATH TUMORS: CLINICAL AND EPIDEMIOLOGICAL CHARACTERISTICS – A RETROSPECTIVE ANALYSIS OF 46 PATIENTS

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### SAŽETAK

**Uvod/Cilj:** Tumori omotača perifernih nerava (PNST) predstavljaju raznoliku grupu neoplazmi koje nastaju iz Švanovih ćelija i fibroblasta perifernih nerava. Njihova heterogena priroda i varijabilna povezanost sa sindromima neurofibromatoze (NF) zahtevaju sveobuhvatno razumevanje njihovih epidemioloških i kliničkih karakteristika. Cilj ove studije je bio da se analiziraju kliničke i epidemiološke karakteristike osoba sa tumorom omotača perifernih nerava (PNST) kod kojih je dijagnoza postavljena tokom poslednjih pet godina.

**Metode:** U ovoj studiji, sprovedena je retrospektivna analiza 46 pacijenata sa histološki potvrđenim tumorima omotača perifernih nerava. Svi ispitanici uključeni su u studiju u vremenskom periodu od 1. januara 2020. do 1. januara 2025. Iz istorija bolesti ovih pacijenata prikupljeni su svi neophodni podaci. Procenjeni su demografski podaci, tip tumora, anatomsko lokalizacija, prisustvo neurofibromatoze, vreme od pojave simptoma do operacije i kliničke manifestacije.

**Rezultati:** Švanomi su bili najčešći tip tumora (73,9%), a zatim maligni tumori omotača perifernih nerava (MPNST) (15,2%) i neurofibromi (10,9%). Najčešća lokalizacija tumora bili su gornji ekstremiteti. Neurofibromatoza tip 1 (NF1) je bila prisutna kod 19,6% pacijenata.

**Zaključak:** Tumori omotača perifernih nerava su pretežno benigni i najčešće se nalaze na gornjim ekstremitetima. Neurofibromatoza ostaje važan faktor rizika, posebno kod pacijenata sa višestrukim lezijama.

**Ključne reči:** Tumori omotača perifernih nerava, Švanom, Neurofibromatoza tip 1, MPNST

### Uvod

Tumori perifernih nervnih omotača (PNN) predstavljaju heterogenu grupu lezija koje uključuju benigne oblike - najčešće švanome i neurofibrome - i maligne oblike poznate kao maligni tumori perifernih nervnih omotača (MPNN). Iako retki, ovi tumori zahtevaju značajnu kliničku pažnju zbog svog potencijalnog maligniteta, lokalne agresivnosti i povezanosti sa genetskim sindromima kao što je neurofibromatoza tipa 1 (NF1) (1–3).

Epidemiološke studije su pokazale da se PNN

najčešće javljaju na gornjim ekstremitetima, posebno pogađajući živce kao što su srednji, ulnarni i radijalni živac (4). Iako ređi, MPNN predstavljaju najveću kliničku pretnju i često su povezani sa NF1 (5,6).

### Metod

Ova serija slučajeva je obuhvatila 46 pacijenata sa histološki potvrđenim tumorima perifernih nervnih omotača (PNNN), identifikovanim iz baze podataka patologije jednog tercijarnog centra

## PERIPHERAL NERVE SHEATH TUMORS: CLINICAL AND EPIDEMIOLOGICAL CHARACTERISTICS – A RETROSPECTIVE CASE SERIES OF 46 PATIENTS

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### SUMMARY

**Introduction/Aim:** Peripheral nerve sheath tumors (PNSTs) represent a diverse group of neoplasms arising from Schwann cells and fibroblasts of peripheral nerves. Their heterogeneous nature and variable association with neurofibromatosis (NF) syndromes necessitate a comprehensive understanding of their epidemiological and clinical profiles. The aim of this study was to analyze the clinical and epidemiological characteristics of persons with peripheral nerve sheath tumors (PNSTs) diagnosed during the last five years.

**Methods:** In this study, the retrospective analysis of 46 patients with histologically confirmed peripheral nerve sheath tumors was conducted. All subjects were included in the study in the period from January 1st, 2020 to January 1st, 2025. All necessary data were collected from the medical records of these patients. Demographic data, tumor type, anatomical location, presence of neurofibromatosis, time from symptom onset to surgery, and clinical manifestations were evaluated.

**Results:** Schwannomas were the most common tumor type (73.9%), followed by malignant peripheral nerve sheath tumors (MPNSTs) (15.2%) and neurofibromas (10.9%). The most frequent tumor localization was the upper extremities. Neurofibromatosis type 1 (NF1) was present in 19.6% of patients.

**Conclusion:** Peripheral nerve sheath tumors are predominantly benign and most commonly located in the upper extremities. Neurofibromatosis remains an important risk factor, particularly in patients with multiple lesions.

**Keywords:** peripheral nerve sheath tumors, Schwannoma, Neurofibromatosis type 1, MPNST

### Introduction

Hearing is the sense that allows us to perceive soPeripheral Nerve Sheath Tumors (PNSTs) represent a heterogeneous group of lesions that include benign forms - most commonly schwannomas and neurofibromas - and malignant forms known as malignant peripheral nerve sheath tumors (MPNSTs). Although rare, these tumors warrant significant clinical attention due to their potential malignancy, local aggressiveness, and association

with genetic syndromes such as neurofibromatosis type 1 (NF1) (1–3).

Epidemiological studies have shown that PNSTs most frequently occur in the upper extremities, particularly affecting nerves such as the median, ulnar, and radial nerves (4). Although less common, MPNSTs pose the greatest clinical threat and are frequently associated with NF1 (5,6).

za negu, Neurohirurške klinike Univerzitetskog Kliničkog Centra Srbije. Analizirana je baza podataka Neurohirurške klinike za poslednjih pet godina (2020-2024. godine). Za svakog pacijenta prikupljeni su podaci o polu, starosti, tipu tumora, anatomskoj lokaciji, simptomima koji se javljaju, prisustvu NF1/NF2 i vremenskom intervalu od pojave simptoma do hirurške intervencije.

U statističkoj analizi podataka izračunata je srednja vrednost i standardna devijacija (SD) za numeričke varijable, a za kategorijalne varijable frekvencije i procenti.

## Rezultati

Ova serija slučajeva je obuhvatila 46 ispitanika sa tumorima omotača perifernih nerava. Od toga, 22 (47,8%) ispitanika su bile žene, a 24 (52,1%) muškarci. Što se tiče anatomske distribucije (slika 1), većina pacijenata je imala tumor lociran na gornjim ekstremitetima (58,7%), a zatim na donjim (34,78%). Tumori u predelu glave i vrata primećeni su kod 6,5% ispitanika, dok kod ispitanika nije pronađen tumor u predelu trupa.

Što se tiče tipova tumora (slika 2), švanomi su bili najčešće primećeni i to kod 34 od 46 ispitanika (73,9%). Neurofibromi su identifikovani kod 5 pacijenata (10,9%), a maligni tumori perifernih nervnih omotača kod 7 pacijenata (15,2%).

Najčešća klinička manifestacija tumora omotača perifernih nerava (slika 3) je bilo prisustvo opipljive mase, prijavljene kod 71,7% pacijenata. Bol je bio prisutan u 52,2% slučajeva, zatim senzorni deficiti u 28,3% i motorna slabost kod 10,9% pacijenata.

Što se tiče neurofibromatoze, kod 9 pacijenata (19,6%) je dijagnostikovana neurofibromatoza tipa 1 (NF1), a kod jednog pacijenta (2,2%) neurofibromatoza tipa 2 (NF2).

Prosečno vreme od pojave simptoma do hirurške intervencije za ovih 46 pacijenata je bilo  $3,10 \pm 3,64$  godine.

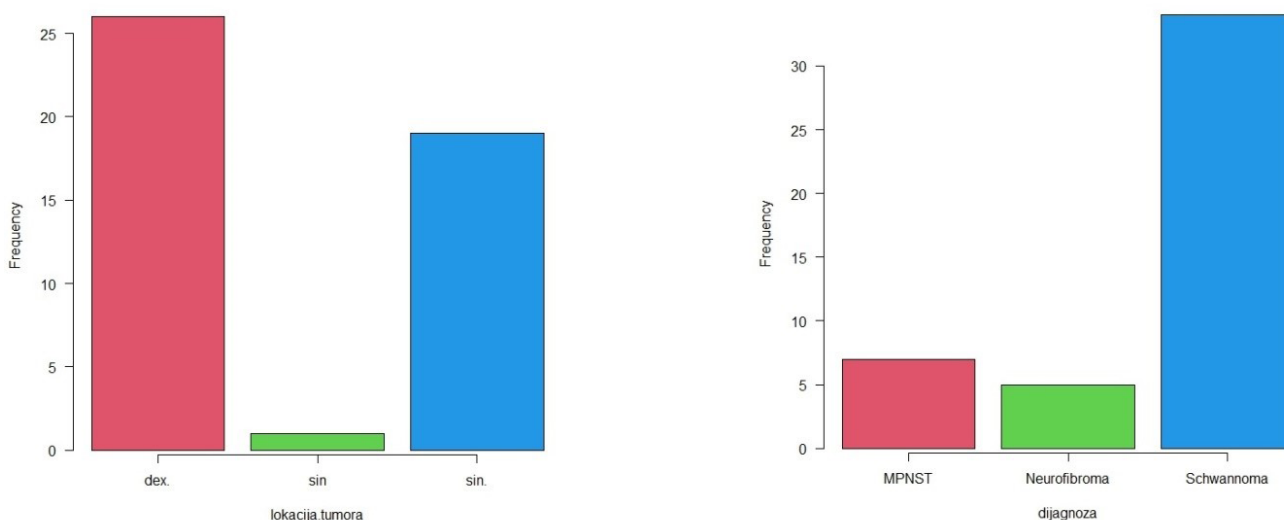
## Diskusija

Ova studija predstavlja jednu od retkih domaćih retrospektivnih analiza tumora perifernih nervnih omotača, pružajući vredne uvide u njihovu distribuciju, kliničku prezentaciju i povezanost sa neurofibromatozom. Naši rezultati su u skladu sa većinom prethodnih istraživanja sprovedenih u Evropi i Severnoj Americi.

## Prevalencija i distribucija tumora

Najčešći tip tumora kod naših ispitanika je bio švanom (73,9%), što je u skladu sa podacima koje su objavili *Sandberg* i dr., koji su identifikovali švanome kao dominantne benigne tumore perifernih nerava tokom perioda od 22 godine u Švedskoj (1). Pored toga, naša studija je pokazala da se ovi tumori češće nalaze na gornjim ekstremitetima (58,7%), što se i očekuje s obzirom na veću gustinu perifernih nerava i veću dostupnost za otkrivanje i dijagnozu u ovom regionu (2).

S druge strane, MPNST su činili 15,2% svih slučajeva – što predstavlja veći udeo u poređenju sa većim epidemiološkim istraživanjima kao što je SEER (*Surveillance Epidemiology and Results*), gde je učestalost incidencija ovih maligniteta bila



Slika 1. Tumori prema anatomskoj lokalizaciji i dijagnozi

## Methods

The case series included 46 patients with histologically confirmed peripheral nerve sheath tumors (PNSTs), identified from the pathology database of a tertiary care center, the Clinic of Neurosurgery of the Univeristy Clinical Center of Serbia. The electronic database of the Clinic of Neurosurgery was analyzed for the last five years (2020-2024). For each patient, data were collected on sex, age, tumor type, anatomical location, presenting symptoms, presence of NF1/NF2, and the time interval from the symptom onset to surgical intervention.

In the statistical analysis of data, the mean value and standard deviation (SD) were calculated for numerical variables, and frequencies and percentages for categorical variables.

## Results

This case series included 46 subjects with peripheral nerve sheath tumors. Of these, 22 (47.8%) were women and 24 (52.1%) were men. According to anatomical distribution (Figure 1), the majority of patients had a tumor located in the upper extremities (58.7%), followed by the lower extremities (34.8%). Tumors in the head and neck region were observed in 6.5% of subjects, while no tumors were found in the trunk region.

As far as tumor types are concerned (Figure 2), schwannomas were the most common tumors and they were observed in 34, out of 46 patients (73.9%). Neurofibromas were identified in 5 patients (10.9%), and malignant peripheral nerve

sheath tumors (MPNST) in 7 patients (15.2%).

The most common clinical manifestation of peripheral nerve sheath tumors (Figure 3) was the presence of a palpable mass, reported in 71.7% of patients. Pain was present in 52.2% of cases, followed by sensory deficits in 28.3% and motor weakness in 10.9% of patients.

As far as neurofibromatosis is concerned, 9 patients (19.6%) were diagnosed with neurofibromatosis type 1 (NF1), and one patient (2.2%) with neurofibromatosis type 2 (NF2).

The average time from the onset of symptoms to the surgical intervention for these 46 patients was  $3.10 \pm 3.64$  years.

## Discussion

This study represents one of the few domestic retrospective analyses of peripheral nerve sheath tumors (PNSTs), offering valuable insights into their distribution, clinical presentation, and association with neurofibromatosis. Our results are consistent with the majority of previous studies conducted in Europe and North America.

### Prevalence and Tumor Distribution

The most prevalent tumor type in our subjects was schwannoma (73.9%), which is in line with data reported by Sandberg et al, who identified schwannomas as the dominant benign peripheral nerve tumors over a 22-year period in Sweden (1). Additionally, our study shows that these tumors are more commonly located in the upper extremities (58.7%), which is expected given the

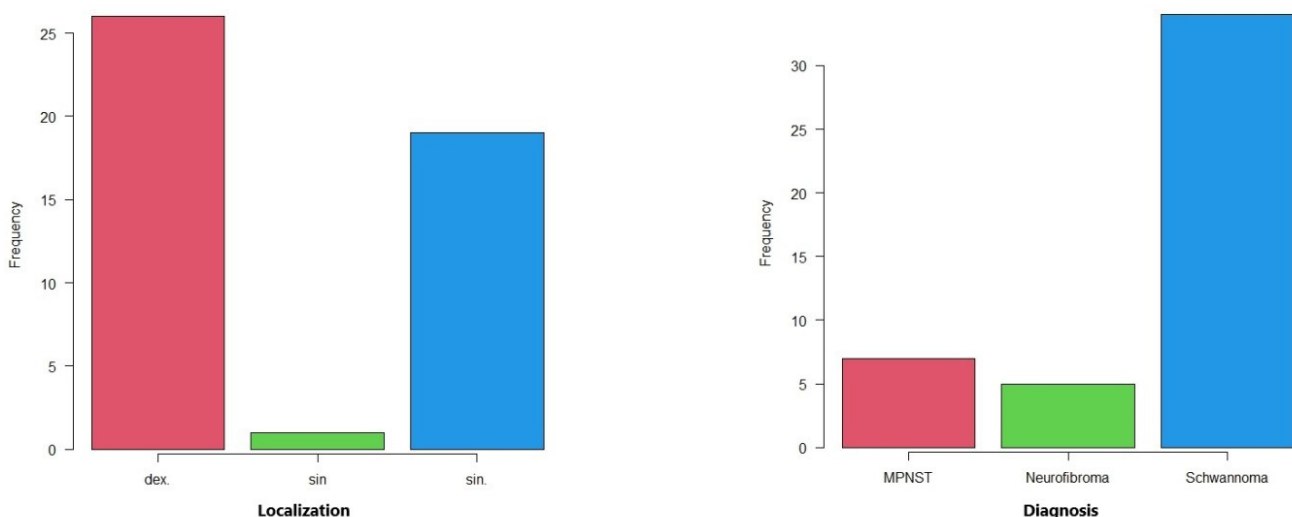
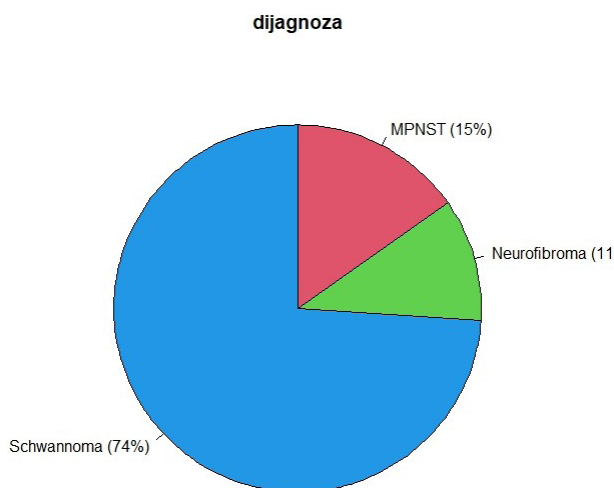


Figure 1. Tumors by anatomical region and diagnosis



**Slika 2.** Distribucija pacijenata sa kliničkim manifestacijama tumora omotača perifernih nerava prema tipu tumora

znatno niža (manje od 0,1% svih sarkoma mekih tkiva) (3,4). Ova neslaganja mogu biti rezultat pristranosti u izboru ispitanika za uključivanje u istraživanje svojstvenu tercijarnom centru za negu ili ograničen vremenski obim studije.

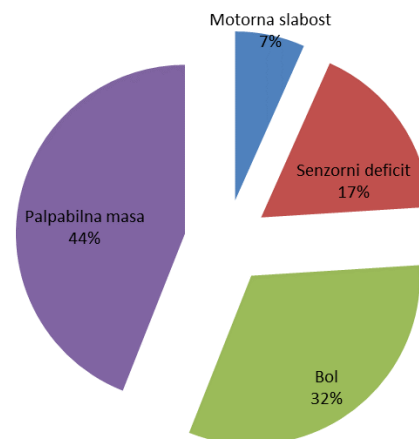
### Klinička prezentacija i dijagnostički izazovi

Najčešće kliničke manifestacije naših ispitanika u našoj kohorti bile su palpabilna masa i bol, što se poklapa sa nalazima drugih studija (2,5). Međutim, senzorni i motorni deficiti su bili ređi, što ukazuje na to da su mnogi benigni tumori dijagnostikovani u kasnijoj fazi, često nakon što dostignu značajnu veličinu.

Primetno je da je prosečno vreme od pojave simptoma do hirurške intervencije bilo približno 3 godine, što ističe podmuklu prirodu kliničke progresije i verovatna kašnjenja u postavljanju dijagnoze. Ovo zapažanje je u skladu sa nalazima *Amirijana* i sar., koji su takođe istakli da MPNST često ostaju nedijagnostikovani dok ne postanu značajni ili ne proizvedu neurološke deficite (3).

### Neurofibromatoza kao faktor rizika

Približno 20% pacijenata u našoj kohorti imalo je potvrđenu neurofibromatozu tipa 1 (NF1), što je u skladu sa prethodnim kliničkim serijama koje su izveštavale o učestalosti NF1 kod 15–25% pacijenata sa tumorima perifernih nerava (6). Važno je naglasiti da su pacijenti sa NF1 pokazali povećan rizik od višestrukih tumora, što je u našoj studiji



**Slika 3.** Distribucija pacijenata sa kliničkim manifestacijama tumora omotača perifernih nerava prema kliničkoj manifestaciji

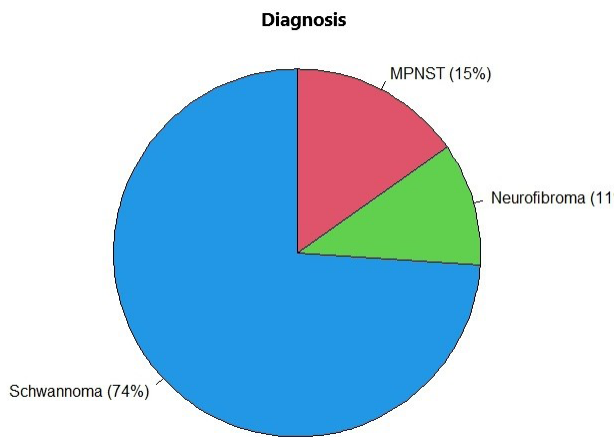
dokazano slučajevima koji uključuju višestruke švanome ili kombinacije švanoma i neurofibroma.

Iznenadujuće, u našem istraživanju nijedan slučaj MPNST u našem uzorku nije bio povezan ni sa NF1 ni sa NF2, što je u suprotnosti sa nalazima iz većih serija slučajeva (npr. SEER i brazilske studije), gde je NF1 identifikovan kao glavni faktor rizika za malignu transformaciju benignih lezija (3,7). Ovaj nalaz se može pripisati malom broju ispitanika uključenih u našu studiju, ali takođe pokreće mogućnost nepoznatih patogenih mehanizama koji leže u osnovi sporadičnih MPNST.

### Uporedni podaci i kontekst zdravstvene zaštite

Studije iz Brazila koje analiziraju lečenje u okviru javnog zdravstvenog sektora ukazuju na to da je hirurško lečenje tumora perifernih nerava finansijski zahtevno i da postoje značajne razlike u pristupu dijagnostičkim i terapijskim resursima (7,8). Iako nije direktno procenjeno u našoj studiji, produženo vreme do operacije ukazuje na potencijalne sistemske prepreke ranoj dijagnozi – kritično područje za poboljšanje sistema zdravstvene zaštite.

Štaviše, istraživanja koja se bave socioekonomskim i rasnim razlikama u preživljavanju MPNST ističu značajnu heterogenost u pristupu lečenju i ishodima, čak i unutar zemalja sa visokim prihodi- ma (9). Ovi uvidi su ključni za oblikovanje strategija javnog zdravlja i planiranje specijalizovanih centara za tumore nerva.



**Figure 2.** Distribution of patients with clinical manifestations of peripheral nerve tumors by type of tumor

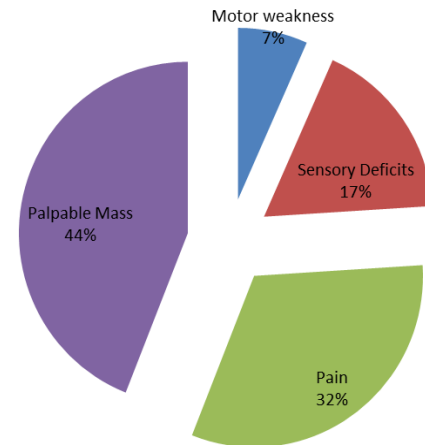
higher density of peripheral nerves and the greater accessibility for detection and diagnosis in this region (2).

On the other hand, MPNSTs accounted for 15.2% of all cases - representing a higher proportion compared to larger epidemiological datasets such as SEER (Surveillance Epidemiology and Results), where the incidence of these malignancies is considerably lower (less than 0.1% of all soft tissue sarcomas) (3,4). This discrepancy may reflect sample selection bias inherent to a tertiary care center or the limited temporal scope of the study.

### Clinical Presentation and Diagnostic Challenges

The most frequent clinical manifestations in our cohort were palpable mass and pain, which is consistent with the findings from other studies (2,5). However, sensory and motor deficits were less common, suggesting that many benign tumors were diagnosed at a later stage, often after reaching significant size.

It was observed that the mean duration from symptom onset to surgical intervention was approximately 3 years, highlighting the insidious nature of clinical progression and likely delays in diagnostic evaluation. This observation is consistent with the findings of Amirian et al, who also reported that MPNSTs often remain undiagnosed until they become sizable or produce neurological deficits (3).



**Figure 3.** Distribution of patients with clinical manifestations of peripheral nerve tumor by clinical manifestation

### Neurofibromatosis as a Risk Factor

Approximately 20% of patients in our cohort had confirmed neurofibromatosis type 1 (NF1), which is consistent with prior clinical series reporting NF1 prevalence in 15–25% of patients with peripheral nerve tumors (6). It is important to emphasize that patients with NF1 exhibited an increased risk for multiple tumors, as evidenced in our study by cases involving multiple schwannomas or combinations of schwannomas and neurofibromas.

Surprisingly, in our study, no MPNST cases in our sample were associated with either NF1 or NF2, which contrasts with findings from larger series (e.g. SEER and Brazilian studies), where NF1 is identified as a major risk factor for malignant transformation of benign lesions (3,7). This finding may be attributed to the small number of subjects included in our study, but also raises the possibility of unknown pathogenic mechanisms underlying sporadic MPNSTs.

### Comparative Data and Healthcare Context

Studies from Brazil analyzing treatment within the public healthcare sector indicate that surgical management of peripheral nerve tumors is financially demanding and that significant disparities exist in access to diagnostic and therapeutic resources (7,8). Although not directly assessed in our study, the prolonged time to surgery suggests potential systemic barriers to early diagnosis—a

### Ograničenja studije

Glavno ograničenje studije je retrospektivni dizajn i mali broj ispitanika, što ograničava generalizaciju rezultata. Nedostatak multivarijantne analize i molekularnih podataka dodatno smanjuje dublje razumevanje patogeneze tumora.

### Preporuke za buduća istraživanja

Buduća istraživanja treba da obuhvate veće, multicentrične prospektivne studije koje uključuju molekularne biomarkere, praćenje recidiva, poređenje sporadičnih i sindromskih oblika tumora, kao i analizu troškova i dostupnosti lečenja.

### Zaključak

Tumori perifernog nervnog omotača su retki, ali klinički značajni entiteti. Švanomi su najčešći i pretežno su benigni, dok MPNST predstavljaju maligni oblik sa potencijalno lošom prognozom. Povezanost sa NF1 ostaje klinički važna, posebno zbog povećanog rizika od višestrukih lezija. Neophodna su dalja detaljnija istraživanja u ovoj oblasti.

### Konflikt interesa

Autori su izjavili da nema konflikta interesa.

### Etičko odobrenje

Studija je odobrena od strane Etičkog odbora naše katedre i sprovedena je u skladu sa Helsinškom deklaracijom i njenim amandmanima. Porodica je dala informisani pristanak.

### Etička izjava

Retrospektivna studija, koja analizira podatke u periodu koji prethodi početku istraživanja, a u skladu sa odredbama Zakona o zaštiti podataka o ličnosti Republike Srbije, sa uvidom u dokumentaciju tokom istraživanja, u skladu sa članom 3 ovog Zakona nameće potrebu da se precizno definiše mogućnost korišćenja ovih medicinskih podataka iz dokumentacije. U skladu sa Pravilnikom Univerzitetskog Kliničkog Centra Srbije, pacijent daje saglasnost za učešće u retrospektivnim studijama potpisivanjem saglasnosti za hospitalizaciju i prateće lečenje. Svi pacijenti su potpisali saglasnost za medicinsko lečenje i učešće u bilo kojoj vrsti studija.

### Finansiranje

Autori nisu dobili posebno finansiranje za ovaj rad. Rad je urađen pro bono.

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critical area for healthcare system improvement.

Furthermore, research addressing socioeconomic and racial disparities in MPNST survival highlights significant heterogeneity in treatment access and outcomes, even within high-income countries (9). These insights are crucial for shaping public health strategies and planning for specialized nerve tumor centers.

### Study Limitations

The main limitation of this study is its retrospective design and the small number of subjects, which may limit the generalizability of findings. The lack of multivariate analysis and molecular data additionally reduces a deeper understanding of tumor pathogenesis.

### Recommendations for Future Research

Future research should include larger, multi-center prospective studies that include molecular biomarkers, tracking of recurrence rates, comparative analysis of sporadic and syndromic tumor forms, as well as the analysis of costs and availability of treatment.

### Conclusion

Peripheral nerve sheath tumors are rare but clinically significant entities. Schwannomas are the most common and are predominantly benign, whereas MPNSTs represent the malignant form with potentially poor prognosis. The association with NF1 remains clinically important, particularly due to the increased risk of multiple lesions. More detailed research is needed in this field.

### Competing interests

The authors declared no competing interests.

### Ethical Approval

The study was approved by the local Ethics Committee of our University Department and was performed in accordance with the Helsinki declaration and its amendments. Informed consent was obtained from the family.

### Ethical statement

Retrospective study, which analyzes data in the period preceding the beginning of the research, and in accordance with the provisions of the Law on the Protection of Personal Data in the Repub-

lic of Serbia, with the insight into the documentation provided for in this research, and according to Article 3 of this Law, imposes the need to precisely define the possibility of using this medical data from the documentation. In accordance with the Regulations of the University Clinical Center of Serbia, the patient gives his consent to participate in retrospective studies by signing his consent to hospitalization and accompanying treatment. All patients have signed their consent for medical treatment and participation in any type of studies.

### Competing interests

Authors declare no conflicts of interest.

### Funding

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8. Cao Y, Wang YB, Bai Y, Tan X, Ma C. Epidemiology of primary intradural MPNST in the spinal canal: a systematic review. *Front Oncol*. 2022.



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The introduction should be clear and directly related to the subject of the research. It should provide the most important information about the problem that is being dealt with, as well as what has been investigated so far about the problem, what is known and what is unknown, or little known, or if there is controversial information. After the introductory notes, the aim of the paper should be stated.

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In this section, the authors describe how the study was conducted, explain the choice of methods and design of the research. The sub-sections of the methods may be: study design (eg quantitative or qualitative research, descriptive or analytical or experimental study, etc.), choice of respondents (inclusion and exclusion criteria from the study), ethical aspects (the number under which the study was approved by the ethics committee), research instruments (method of data collection, specificity of instruments used), and statistical analysis of the data (types of tests). It is important to provide literature data for known methods, including statistical methods.

### **The results**

Describe the results of the research presented in a logical order through tables, charts and illustrations (appendices are cited after the Literature).

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### **Acknowledgment**

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### **Appendices**

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