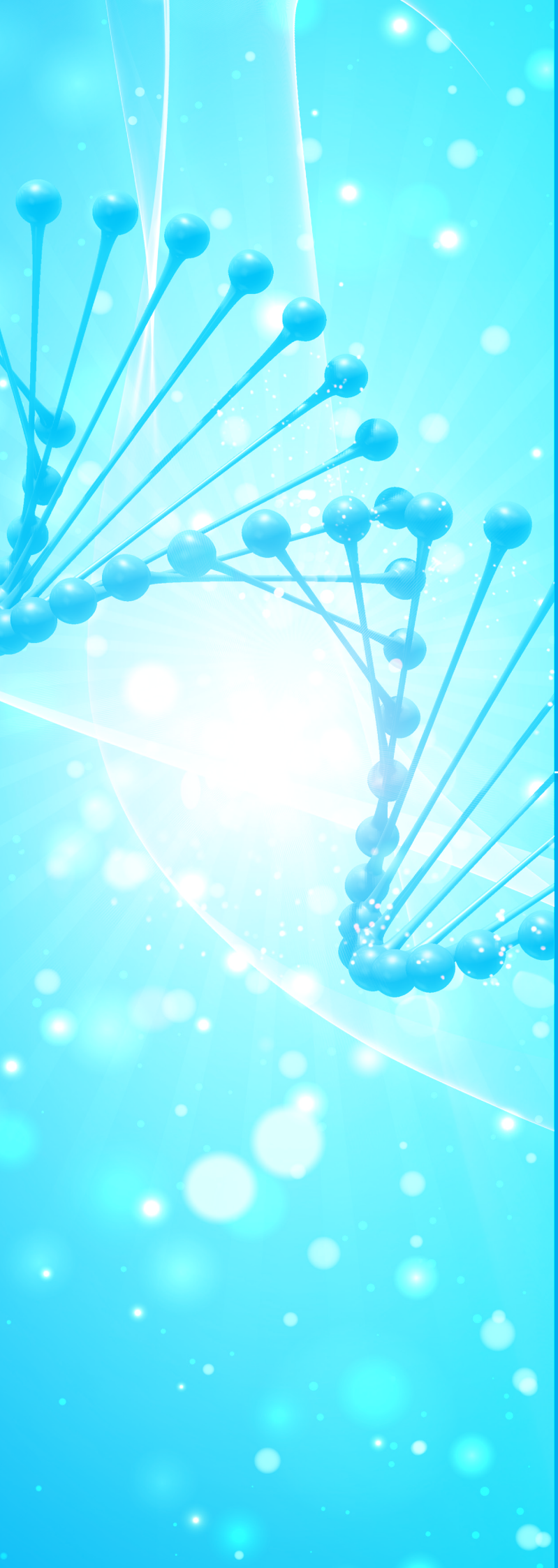

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SADRŽAJ

ORIGINALNI RAD

PRIKAZ SLUČAJA

AKTUELNA TEMA

CONTENTS

ORIGINAL ARTICLE

CASE REPORT

ACTUAL TOPIC

ORIGINALNI RAD

UDK BROJEVI: 331.316.2(497.11)
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SUBJEKTIVNA PROCENA ZDRAVSTVENOG STATUSA I BROJ DANA NA BOLOVANJU KOD LJUDI KOJI BOLUJU OD ASTME I HRONIČNE OPSTRUKTIVNE BOLESTI PLUĆA

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SAŽETAK

Uvod/Cilj: Nema dovoljno studija koje se bave poređenjem kvaliteta života u vezi sa zdravljem (engl. *Health-Related Quality of Life* – HRQoL) kod osoba koje boluju od astme i osoba koje boluju od hronične opstruktivne bolesti pluća (HOBP). Cilj ovog istraživanja je bio da se ispita i uporedi zdravstveni status koji su prijavljivale osobe obolele od astme i HOBP.
Metode: Podaci su prikupljani od odraslih ispitanika, koji su dolazili u ustanove primarne zdravstvene zaštite uz pomoć opšteg upitnika za ispitivanje zdravstvenog statusa i srpske verzije HRQoL-14. Metod mečovanja tzv. „*propensity score*“ korišćen je da se uporede ispitanici oboleli od astme i HOBP u odnosu na pol, godine, nivo obrazovanja i pridržavanje terapije.
Rezultati: Ukupno je 1954 pacijenata (47% muškaraca i 53% žena) učestvovalo u studiji. Prosečna starosna dob pacijenata obolelih od astme bila je 49,4±15,5, dok su pacijenti oboleli od HOBP bili stariji – 59,5±12,4. U obe grupe, 60% pacijenata je prijavilo loš zdravstveni status. Nije bilo razlike između pacijenata koji boluju od astme i pacijenata koji boluju od HOBP po pitanju subjektivne procene zdravstvenog statusa i broja dana na bolovanju. Pacijenti oboleli od astme i HOBP prijavili su najveći broj dana sa poremećajima sna, zatim dana sa simptomima anksioznosti i depresivnih simptoma, a najmanji broj dana kada su bili prisutni bolovi.
Zaključak: Ovi podaci ukazuju na potrebu da se poboljša ciklus sna kod pacijenata sa astmom i HOBP. Oni bi mogli da se koriste u cilju ispitivanja specifičnih karakteristika sna kod osoba sa astmom i HOBP.

Ključne reči: astma, HOBP, primarna zdravstvena zaštita, pacijenti, subjektivni zdravstveni status

Uvod

Napredak u lečenju hroničnih bolesti doveo je do povećanja očekivanog životnog veka osoba koje žive sa hroničnim stanjima. Međutim, očekivani životni vek i nije toliko relevantan ako osobe koje boluju od hroničnih bolesti nemaju zadovoljavajući kvalitet života (1,2). Tokom prethodnih decenija, dobar kvalitet života povezan sa zdravljem (engl. *Health Related Quality of Life* - HRQoL) kod osoba koje boluju od hroničnih oboljenja dospeo je u fokus pacijenata, njihovih negovatelja, zdravstvenih radnika i drugih zainteresovanih lica (2). Merenje kvaliteta života koji se povezuje sa zdravljem kod osoba sa hroničnim bolestima uključuje individualno viđenje bolesti i omogućava detaljan uvid u ograničenja i aktivnosti u svakodnevnom životu, kao i efikasnost terapije (2,3).

Astma i hronična opstruktivna bolest pluća (HOPB) su česte hronične bolesti respiratornog trakta. Svetska prevalencija astme varira od manje od 10% u Aziji do otprilike 20% u Ujedinjenom Kraljevstvu, drugim zapadnoevropskim zemljama i Australiji, dok prevalencija HOBP varira od 11,6% u

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SELF-PERCEIVED HEALTH STATUS AND NUMBER OF SICK DAYS IN PEOPLE WITH ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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SUMMARY

Introduction/Aim: There is a lack of studies focusing on the comparison of health-related quality of life (HRQOL) between people with asthma and people with chronic obstructive pulmonary disease (COPD). The purpose of this study was to examine and compare self-reported health status in people who have asthma and people who have COPD.

Methods: Data were collected from adult participants who came to primary health care institutions using a general questionnaire to examine their health status and the Serbian version of the HRQOL-14. The propensity score method was used to match people with asthma and COPD on age, gender, education level and adherence to therapy.

Results: A total of 1,954 patients (47% men, 53% women) were included in the study. The average age of patients with asthma was 49.4±15.5, whereas the patients with COPD were older - 59.5±12.4. In both groups, 60% of the participants reported their health status as poor. No difference was found between patients with asthma and patients with COPD in terms of self-perceived general health status and the number of sick days. Patients with asthma and COPD reported the greatest number of days with sleep disorders, followed by days with symptoms of anxiety and depressive symptoms and the least number of days with having pain.

Conclusion: These data indicate the need to improve sleep patterns in people with asthma and COPD. These data could be used to further examine specific features of sleep among people with asthma and COPD.

Keywords: asthma, COPD, primary health care, patients, self-reported health status

Introduction

Advances in the treatment of chronic diseases have led to the increase in life expectancy of people who live with chronic conditions. However, life expectancy may not be as relevant unless people with chronic diseases have satisfactory quality of life (1,2). Over the last decades good health-related quality of life (HRQOL) in people with chronic diseases have become the focus of patients, their caregivers, health care workers and other stakeholders (2). The measurement of HRQOL among people with chronic diseases includes an individual perception of the disease and allows for a more detailed insight into the limitations and activities of daily living as well as the effectiveness of therapy (2,3).

Asthma and chronic obstructive pulmonary disease (COPD) are common chronic diseases of the respiratory tract. The worldwide prevalence of asthma ranges from to less than 10% in Asia to around 20 % in the United Kingdom, other Western European countries and Australia, rope, while the COPD prevalence ranges from 11.6% in Oceania to 13.9% in Africa (4, 5). The prevalence of asthma and COPD in the Republic of Serbia accounts for less than 5% (4.1% for asthma and 4.5% for COPD) (6). Because of the global aging of the population, we may anticipate that the prevalence of asthma and COPD will be rising. It is not surprising that previous studies found that people with asthma and COPD have lower HRQOL compared to their

Okeaniji do 13,9% u Africi (4,5). Prevalencija astme i HOBP u Republici Srbiji iznosi manje od 5% (4,1% za astmu i 4,5% za HOBP) (6). Zbog činjenice da je stanovništvo na globalnom nivou sve starije, može se predvideti da će prevalencija astme i HOBP rasti. Ne iznenađuje što je u prethodnim studijama pokazano da osobe koje boluju od astme i HOBP imaju niži HRQoL u poređenju sa zdravim pojedincima (7,10). U stvari, postoji jedan broj faktora koji utiču na pad HRQoL kod osoba koje boluju od astme i HOBP, poput starije dobi, ženskog pola, nižeg socijalnog statusa, dužeg trajanja bolesti, postojanja komorbiditeta, loše kontrole bolesti, pridržavanja terapije, prihvatanja bolesti itd. (8,11). Ovi podaci ukazuju da su neki faktori nereverzibilni i ne mogu se modifikovati. Ovi faktori treba da budu cilj u naporima da se poboljša HRQoL kod osoba obolelih od astme i HOBP.

Dok su prethodne studije istraživale HRQoL kod osoba sa astmom i HOBP odvojeno, nedostaju studije koje se fokusiraju na poređenje HRQoL među osobama koje boluju od astme i osobama koje boluju od HOBP. S obzirom da se ove hronične bolesti uglavnom leče na nivou primarne zdravstvene zaštite, od ključne važnosti je da lekari opšte prakse dovoljno razumeju izazove sa kojima se sreću ovi pacijenti u svakodnevnom životu. Cilj ove studije je bio da ispita i uporedi zdravstveni status koji su prijavljivale osobe obolele od astme i osobe obolele od HOBP.

Metode

Ispitanici

Ovo istraživanje predstavlja deo veće studije, koja je sprovedena od januara do decembra 2011, a fokus ove studije bio je na kvalitetu života u vezi sa zdravljem kod osoba sa hroničnim bolestima u Republici Srbiji (12). Studija preseka je sprovedena u više institucija primarne zdravstvene zaštite. Ukupno 36 od 157 ustanova primarne zdravstvene zaštite je nasumično izabrano iz ruralnih i urbanih područja zemlje. Odabrane su ustanove primarne zdravstvene zaštite koje se nalaze u Vojvodini, Šumadiji i zapadnoj Srbiji, južnoj i istočnoj Srbiji, na severu Kosova i u Beogradu. Kriterijumi za uključivanje bili su starosna dob od 18 do 90 godina, mentalna sposobnost da se popuni upitnik i pristanak da se učestvuje u studiji. Ispitanike su činili pacijenti sa astmom i HOBP koje su dijagnostifikovali lekar opšte prakse i pulmolog. Astma je dijagnostifikovana na osnovu preporuke Globalne inicijative za astmu (engl. *Global Initiative for Asthma* - GINA) (13), dok je dijagnoza HOBP postavljena na osnovu preporuke Globalne inicijative za hroničnu opstruktivnu bolest pluća (engl. *Global Initiative for Chronic Obstructive Lung Disease* - GOLD) (14). Klasifikacija astme i HOBP sprovedena je na osnovu 10. verzije Internacionalne klasifikacije bolesti (ICD-10).

Studiju je etički odobrila svaka ustanova primarne zdravstvene zaštite gde je studija sprovedena.

Instrument

Korišćen je upitnik za prikupljanje podataka. Prvi deo upitnika je popunjavao lekar koji je unosio podatke o bolesti, trajanje u mesecima i pridržavanje terapije.

Drugi deo upitnika su popunjavali ispitanici. Sastojao se od pitanja koja su ispitivala socijalne i demografske karakteristike i pitanja koja su se ticala HRQoL.

Da bismo ispitali HRQoL, koristili smo srpsku verziju HRQoL-14, generički upitnik koji je izdao Centar za kontrolu i prevenciju bolesti (CDC), a koji je ispitivao četiri domena HRQoL: opšte zdravlje, fizičko zdravlje, mentalno zdravlje i ograničenu aktivnost (15). Pokazalo se da je upitnik HRQoL-14 validan i pouzdan u populacijonim studijama (2). Upitnik je preveden na srpski jezik uz pomoć standardne metodologije za kulturnu adaptaciju upitnika na novom jeziku. Dvoje ljudi kčiji je maternji jezik srpski jezik i koji su odlični poznavaoci engleskog jezika preveli su upitnik svako za sebe. Stručnjaci su razmatrali prevode i generisana je jedna finalna verzija upitnika HRQoL-14. Ova verzija je prevedena na engleski jezik radi poređenja. Nisu primećene velike razlike. Pilot-testiranje upitnika na srpskom jeziku je sprovedeno na 10 osoba koje boluju od astme i HOBP da bi se proverilo razumevanje i opšte shvatanje stavki u upitniku. Nisu zabeleženi posebni komentari. Psihometrijsko testiranje srpske verzije HRQoL-14 pokazalo je Kronbahov alfa koeficijent od 0,78, što se smatralo odgovarajućim.

Za procenu opšteg zdravlja, ispitanici su ocenjivali trenutni zdravstveni status zaokruživanjem jednog od sledećih odgovora: „Odličan“, „Vrlo dobar“, „Dobar“, „Prosečan“ i „Loš“. Odgovori su

healthy counterparts (7-10). In fact, there is a number of factors affecting the decline of HRQOL in persons with asthma and COPD, such as being older, female gender, lower social status, longer disease duration, having comorbidities, poor disease control, compliance with therapy, disease acceptance etc. (8, 11). These findings suggest that some factors are irreversible and cannot be modified (age, gender, disease duration), however, some factors may be modifiable. These factors should be targeted in efforts to improve the HRQOL in people with asthma and COPD.

While previous studies explored HRQOL among people with asthma and COPD separately, there is a lack of studies focusing on the comparison of HRQOL between people with asthma and people with COPD. As these chronic diseases are typically managed at the primary health care level, it is essential that general practitioners sufficiently understand the challenges that these patients encounter in everyday life. The purpose of this study was to examine and compare self-reported health status in people who have asthma and people who have COPD.

Methods

Participants

This research is a part of a larger study, conducted between January and December 2011, focusing on HRQOL of people with chronic diseases in the Republic of Serbia (12). A cross-section study was conducted in multiple primary health care institutions. A total of 36 out of 157 primary health centers (PHC) were randomly chosen from both rural and urban areas of the country. The selection of PHC included the ones located in Vojvodina, Šumadija and Western Serbia, Southern and Eastern Serbia, Northern Kosovo and Belgrade. The inclusion criteria were age range from 18 to 90 years, being mentally able to participate in this study by filling in the questionnaire and providing a signed consent for participation. The participants comprised patients with asthma and COPD diagnosed by a general practitioner and a pulmonologist. Asthma was diagnosed based on the recommendation of the Global Initiative for Asthma (GINA) (13), while COPD was diagnosed according to the recommendation of Global Initiative for Chronic Obstructive Lung Disease (GOLD) (14). The classification of asthma and COPD was performed according to the 10th version of the International Classification of Diseases (ICD-10).

The study was ethically approved by each primary health care institution where the study was conducted.

Instrument

A questionnaire was used to collect data. The first part of the questionnaire was filled in by a treating physician who entered the information about the disease, its duration in months and adherence to treatment.

The second part of the questionnaire was filled in by the participants. It consisted of questions examining social and demographic characteristics and questions concerning HRQOL.

To examine HRQOL, we used the Serbian version of HRQOL-14, a generic questionnaire issued by the Center for Disease Control and Prevention (CDC) questionnaire, which explored four domains of HRQOL: general health, physical health, mental health and restricted activity (15). The HRQOL-14 questionnaire was shown to be valid and reliable in population-based studies (2). The questionnaire was translated to Serbian using the standard methodology for cultural adaptation of questionnaires in a new language. Two people who were native Serbian speakers and who were proficient in English language translated the questionnaire separately. The translations were discussed among the experts and one final version of Serbian HRQOL-14 was generated. This version was translated back to English for comparison. No major differences were observed. The questionnaire in Serbian was pilot tested on 10 people with asthma and COPD to check understanding and overall comprehension of items. No particular comments were recorded. The psychometric testing of the Serbian version of HRQOl-14 suggested a Cronbach's alpha coefficient of 0.78, which was deemed appropriate.

To assess general health, participants were asked to rate their current health status by circling one of the following answers: 'Excellent', 'Very good', 'Good', 'Average' and 'Poor'. Answers were subsequently divided into two groups: 'Excellent/very good/good' vs. 'average/poor'. The estimation of asthma and COPD impact on the domains of physical and mental health and everyday activity

potom podeljeni u dve grupe: „Odličan/vrlo dobar/dobar“ naspram „prosečan/loš“. Procena uticaja astme i HOBP na domene fizičkog i mentalnog zdravlja i ograničenja svakodnevnih aktivnosti sprovedena je korišćenjem stavki u kojima su učesnici sami ocenjivali sopstveni zdravstveni status i prisustvo simptoma (bol, depresija, anksioznost i poremećaji sna) u proteklih 30 dana. Odgovori su bili dihotomni: „retko“, ako su simptomi trajali manje od 14 dana i „često“ bolovanje ukoliko su simptomi bili prisutni više od 14 dana tokom proteklih 30 dana. Ovaj pristup je pomogao da se utvrdi kod kojih osoba je hronična bolest imala ozbiljan uticaj na svakodnevno funkcionisanje.

Statistička analiza

Deskriptivna statistika, uključujući prosečnu i standardnu devijaciju kontinualnih varijabli ili brojeva i procenti kategoričkih varijabli, korišćeni su za karakterizaciju uzorka studije. Korišćen je metod mečovanja tzv. „*propensity score*“, odnosno verovatnoća da osobe imaju određeni set varijabli. Mečovanje je izvedeno prema polu, starosti, nivou obrazovanju i primenjene terapije. Ova procedura je izvršena u statističkom programu za obradu podataka R uz korišćenje paketa *MatchIt* (16). Ovaj pristup je korišćen da bi se smanjio potencijalni efekat zabune koji nastaje zbog socio-demografskih i kliničkih razlika.

Pirsonov hi-kvadrat test je korišćen za poređenje kategoričkih varijabli između ljudi sa astmom i HOBP. Man-Vitnijev test je primenjen da bi se testirale razlike u kontinualnim varijablama između dva poduzorka.

Nivo značajnosti testa je bio p=0,05. Statistička analiza je sprovedena uz pomoć SPSS, verzije 20.

Rezultati

Nakon sprovođenja procedure mečovanja, 1.954 ispitanika je uključeno u ovu studiju (47% muškaraca i 53% žena). Ispitanici su podeljeni u dve grupe. Prvu grupu su činili ispitanici sa potvrđenom dijagnozom astme (977, 46,3% muškaraca i 53,7% žena), dok su drugu grupu činili ispitanici sa potvrđenom dijagnozom HOBP (takođe 977, 47,7% muškaraca, 52,3% žena). Prosečna starosna dob ispitanika bila je 54,7±14,8 godine – kod ispitanika obolelih od astme prosečna starost bila je 49,4±15,5, dok su ispitanici oboleli od HOBP bili stariji – 59,5±12,4. U obe grupe većina ispitanika (47,8% sa astmom i

Tabela 1. Demografske karakteristike i pridržavanje terapije uzorka studije prema dijagnozi i ispitivanje adherentnosti u ispitivanom uzorku u odnosu na dijagnozu

Varijabla	Astma (n=977)	HOBP (n=977)	p vrednost
Pol, n (%)			0.526
Muški	452 (46,3)	466 (47,7)	
Ženski	525 (53,7)	511 (52,3)	
Starost, n (%)			1,000
<20	1 (0,1)	1 (0,1)	
20-29	20 (2)	20 (2)	
30-39	79 (8,1)	79 (8,1)	
40-49	197 (20,2)	197 (20,2)	
50-59	263 (26,9)	264 (27)	
60-69	284 (29,1)	284 (29,1)	
70+	133 (13,6)	132 (13,5)	
Nivo obrazovanja, n (%)			0,768
Osnovna škola	235 (24,1)	235 (24,1)	
Srednja škola/gimnazija	467 (47,8)	466 (47,7)	
Visoko obrazovanje	275 (28,1)	276 (28,2)	
Pridržavanje terapije, n (%)			1,000
Ne	6 (0,6)	6 (0,6)	
Da, na osnovu samoinicijative	30 (3,1)	30 (3,1)	
Da, po preporuci lekara	941 (96,3)	941 (96,3)	

HOBP – hronična opstruktivna bolest pluća

restriction was carried out using items where the participants themselves assessed their own health status and presence of the symptoms (pain, depression, anxiety and sleep problems) in the past 30 days. The answers were dichotomized as "rare", if the symptoms appeared at a frequency of less than 14 days and "frequent" sick days, if the symptoms were present over more than 14 days in the past 30 days. This approach helped to distinguish people whose chronic disease who had a more severe impact on their daily functioning.

Statistical analysis

The descriptive statistics, including mean and standard deviation of continuous variables or numbers and percentages of categorical variables, were used to characterize the study sample. We used the propensity score method to match people with asthma and COPD on age, gender, education level and adherence to therapy. The R package MatchIt was used to match the subsamples of participants based on the propensity score with one-to-one nearest-neighbor matching on the following covariates: age, gender, education and therapy administration (16). This approach was undertaken to reduce potential confounding effect arising from socio-demographic and clinical differences.

The Pearson's chi-square test was used to compare categorical variables between people with asthma and COPD. The Mann-Whitney test was applied to test the differences in the continuous variables between the two subsamples.

The significance level was considered at p=0.05. The statistical analysis was conducted using the SPSS, version 20.

Results

After performing the matching procedure, 1,954 participants were included in this study (47% men, 53% women). The participants were divided into two groups. The first group included participants with verified asthma (977, 46.3% men, 53.7% women), while the second group consisted of participants with verified COPD (also 977, 47.7% men, 52.3 women). The average age of

Table 1. Demographic characteristics and adherence to treatment of the study sample according to the diagnosis

Variable	Asthma (n=977)	COBP (n=977)	p value
Gender, n (%)			0.526
Male	452 (46.3)	466 (47.7)	
Female	525 (53.7)	511 (52.3)	
Age, n (%)			1.000
<20	1 (0.1)	1 (0.1)	
20-29	20 (2)	20 (2)	
30-39	79 (8.1)	79 (8.1)	
40-49	197 (20.2)	197 (20.2)	
50-59	263 (26.9)	264 (27)	
60-69	284 (29.1)	284 (29.1)	
70+	133 (13.6)	132 (13.5)	
Education level, n (%)			0.768
Primary school	235 (24.1)	235 (24.1)	
Secondary/high school	467 (47.8)	466 (47.7)	
Higher	275 (28.1)	276 (28.2)	
Adherence to the treatment, n (%)			1.000
No	6 (0.6)	6 (0.6)	
Yes, due to self-initiative	30 (3.1)	30 (3.1)	
Yes, due to physician's recommendation	941 (96.3)	941 (96.3)	

COPD- chronic obstructive pulmonary disease

Tabela 2. Subjektivna procena zdravstvenog statusa i broj dana bolovanja u toku proteklog meseca kod pacijenata koji boluju od astme i hronične opstruktivne bolesti pluća

Varijabla		Astma N (%)	HOBP N (%)	p vrednost
Subjektivna procena zdravstvenog statusa	Odličan, vrlo dobar, dobar	388 (40,3)	385 (39,7)	0,788
	Prosečan, loš	575 (59,7)	585 (60,3)	
Broj dana bolovanja ($\bar{x}$ ± SD)	Zdravstveni problemi	14,2 ± 10,9	14,3 ± 10,8	0,867
	Loše fizičko zdravlje	9,3 ± 8,4	9,5 ± 8,4	0,690
	Loše mentalno zdravlje	7,2 ± 8,4	7,3 ± 8,2	0,896
	Ograničene aktivnosti	6,7 ± 7,9	7,3 ± 8,2	0,169
Pacijenti sa ≥14 dana bolovanja	Zdravstveni problemi	324 (33,2)	343 (35,1)	0,365
	Loše fizičko zdravlje	206 (21,1)	230 (23,5)	0,192
	Loše mentalno zdravlje	140 (14,3)	159 (16,3)	0,233
	Ograničene aktivnosti	148 (15,1)	163 (16,7)	0,354

HOBP – hronična opstruktivna bolest pluća; $\bar{x}$ - srednja vrednost; SD-standardna devijacija

47,1% sa HOBP) je prijavila srednji nivo obrazovanja. Više od 95% ispitanika u obe grupe izjasnilo se da koriste terapiju redovno kao što im je prepisao njihov lekar. Nije bilo razlike između ove dve grupe ispitanika u odnosu na pol, starost, nivo obrazovanja i pridržavanje terapije (Tabela 1).

U obe grupe, 60% ispitanika označilo je zdravstveni status kao loš. Nije bilo razlike između ispitanika koji boluju od astme i ispitanika koji boluju od HOBP u smislu subjektivne percepcije opšteg zdravstvenog stanja. Takođe, kada je u pitanju broj dana na bolovanju, nije bilo razlike između ispitanika sa astmom (14,2 ± 10,9) i ispitanika sa HOBP (14,3 ± 10,8). Od ispitanika koji su oboleli od astme, 21,1% je prijavilo da su 14 i više dana bili lošeg zdravstvenog stanja, dok je 14,3% prijavilo loše mentalno zdravlje. Od ispitanika koji boluju od HOBP, 32,5% se osećalo fizički loše 14 i više dana tokom proteklog meseca, dok je 16,3% imalo problema sa mentalnim zdravljem (Tabela 2).

Tabela 3 pokazuje prisustvo bola, simptoma depresije, simptoma anksioznosti i poremećaja sna tokom prethodnog meseca, kod ispitanika sa astmom i HOBP. Ispitanici oboleli od astme su prijavljivali najveći broj dana u kojima su bili prisutni poremećaji sna 9,8 ± 8,1, zatim sa simptomima anksioznosti 8,4±8,0 i simptomima depresije 7,2±7,7. Najmanji broj dana 4,5 ± 6,7 je bio bez bola. Slični rezultati su bili kod ispitanika obolelih od HOBP (10,3 ± 8,4; 8,8 ± 8,1; 7,5 ± 8,0; 4,8 ± 7,1). Nije primećena razlika u učestalosti dana bolovanja između dve grupe ispitanika.

Tabela 3. Prisustvo bola, simptoma depresije, simptoma anksioznosti i poremećaja sna tokom proteklog meseca kod pacijenata sa astmom i hroničnom opstruktivnom bolešću pluća

Varijabla		Astma (n=977) $\bar{x}$ ± SD	HOBP (n=977) $\bar{x}$ ± SD	p vrednost
Trajanje simptoma	Prisustvo bola	4,5 ± 6,7	4,8 ± 7,1	0,504
	Prisustvo simptoma depresije	7,2 ± 7,7	7,5 ± 8,0	0,507
	Prisustvo simptoma anksioznosti	8,4 ± 8,0	8,8 ± 8,1	0,405
	Prisustvo poremećaja sna	9,8 ± 8,1	10,3 ± 8,4	0,239
Dobro zdravlje		8,7 ± 9	7,9 ± 9	0,131
Pacijenti sa ≥14 dana bolovanja, n (%)	Prisustvo bola	75 (7,7)	88 (9)	0,288
	Prisustvo simptoma depresije	125 (12,8)	143 (14,6)	0,237
	Prisustvo simptoma anksioznosti	159 (16,3)	176 (18)	0,308
	Prisustvo poremećaja sna	189 (19,3)	220 (22,5)	0,085
Dobro zdravlje ≥14, n (%)		179 (18,3)	170 (17,4)	0,595

HOBP- hronična opstruktivna bolest pluća; $\bar{x}$ - srednja vrednost; SD-standardna devijacija; trajanje simptoma i dobrog zdravlja su takođe uračunati u dane proteklog meseca

Tabela 2. Subjective assessment of health status and number of sick days during the past month in patients with asthma and chronic obstructive pulmonary disease

Variable		Ashtma N (%)	COBP N (%)	p value
Self-perceived health status	Excellent, very good, good	388 (40.3)	385 (39.7)	0.788
	Average, poor	575 (59.7)	585 (60.3)	
Number of sick days (x̄ ± SD)	Having health problems	14.2 ± 10.9	14.3 ± 10.8	0.867
	Having poor phyical health	9.3 ± 8.4	9.5 ± 8.4	0.690
	Having poor mental health	7.2 ± 8.4	7.3 ± 8.2	0.896
	Having restricted activities	6.7 ± 7.9	7.3 ± 8.2	0.169
People with ≥14 sick days	Having health problems	324 (33.2)	343 (35.1)	0.365
	Having poor physical health	206 (21.1)	230 (23.5)	0.192
	Having poor mental health	140 (14.3)	159 (16.3)	0.233
	Having restricted activities	148 (15.1)	163 (16.7)	0.354

COPD- chronic obstructive pulmonary disease; x̄ - mean; SD-standard deviation

participants was 54.7±14.8 years – in participants with asthma the average age was 49.4±15.5, whereas the participants with COPD were older - 59.5±12.4. In both groups most participants (47.8% with asthma, 47.1% with COPD) reported secondary education level. Over 95% of people in both groups reported using their therapy regularly as prescribed by the treating physician. There was no difference between these two groups regarding gender, age, education level and adherence to the treatment (Table 1).

In both groups, 60% of the participants reported their health status as poor. No difference was found between people with asthma and participants with COPD in terms of self-perceived general health status. Also, with regards to the number of sick days, no difference was found between persons with asthma (14.2 ± 10.9) and persons with COPD (14.3 ± 10.8). Of people with asthma, 21.1% reported having spent 14 and more days in poor physical health, and 14.3% reported poor mental health. Of people with COPD, the proportion of participants feeling physically unwell for 14 or more days in the past month accounted for 32.5%, while 16.3% had problems with their mental health (Table 2).

Table 3 shows the presence of pain, depressive symptoms, anxiety symptoms and sleep disorders in the past month, in people with asthma and COPD. People with asthma reported the greatest

Table 3. Presence of pain, depressive symptoms, anxiety symptoms and sleep disorders over the last month in people with asthma and chronic obstructive pulmonary disease

Variable		Asthma x̄ ± SD	COBP x̄ ± SD	p value
Symptom duration	Having pain	4.5 ± 6.7	4.8 ± 7.1	0.504
	Having symptoms of depression	7.2 ± 7.7	7.5 ± 8.0	0.507
	Having symptoms of anxiety	8.4 ± 8,0	8.8 ± 8.1	0.405
	Having sleep disorders	9.8 ± 8.1	10.3 ± 8.4	0.239
Being in good health		8.7 ± 9	7.9 ± 9	0.131
Patients with ≥14 sick, n (%)	Having pain	75 (7.7)	88 (9)	0.288
	Having symptoms of depression	125 (12.8)	143 (14.6)	0.237
	Having symptoms of anxiety	159 (16.3)	176 (18)	0.308
	Having sleep disorders	189 (19.3)	220 (22.5)	0.085
Being in good health ≥14, n (%)		179 (18.3)	170 (17.4)	0.595

COPD- chronic obstructive pulmonary disease; x̄ - mean; SD-standard deviation; symptom duration and being in good health were also calculated in days in the past month

Diskusija

Rezultati ove studije su pokazali da su ispitanici koji boluju od astme i HOBP bili više dana na bolovanju tokom proteklog meseca. Međutim, nije bilo razlike između ove dve grupe ispitanika sa hroničnim pulmološkim oboljenjima po pitanju zdravstvenog stanja koje su sami prijavljijvali i broja dana bolovanja tokom proteklog meseca. Od svih teškoća koje su ispitanici oboleli od astme i HOBP iskusili, najveći uticaj na njihovo zdravlje imao je loš san.

Više od jedne polovine ispitanika u obe grupe ocenili su svoj zdravstveni status kao prosečan ili loš, a jedna trećina je prijavila često bolovanje, koji su ometali njihove svakodnevne aktivnosti. Ovi rezultati su u skladu sa rezultatima prethodnih studija iz literature (3,17,18). Uticaj pola, starosti, nivoa obrazovanja i pridržavanja terapije na zdravstveni status koji su osobe sa astmom i HOBP prijavljivale nije prethodno testiran uz pomoć metode mečovanja tzv. „*propensity score*“. Prethodni empirijski dokazi ukazuju da su ženski pol i starija životna dob u negativnoj korelaciji sa prijavljenim zdravstvenim statusom osoba obolelih od astme i HOBP (17,19). Kod muškaraca obolelih od HOBP, pokazano je da je fizičko zdravlje više narušeno zbog bolesti, dok su žene imale više problema sa mentalnim zdravljem i prihvatanjem bolesti (17). Ovi rezultati naglašavaju razliku u percepciji bolesti među polovima. Takođe, nizak nivo obrazovanja i slabo pridržavanje terapije bili su u korelaciji sa nižim HRQoL među osobama sa astmom i HOBP (19). Jedna studija iz Turske je pokazala da se samo 60% osoba sa astmom i 50% osoba sa HOBP pridržavalo terapije u velikoj meri (20). Stoga, da bi pomogao pacijentima koji boluju od astme i HOBP, lekar opšte prakse bi trebalo da ispita koliko se pacijenti pridržavaju terapije i obezbedi uslove kako da se pacijenti sa astmom i HOBP bolje pridržavali terapije.

Nakon uparivanja pola, starosti, novoa obrazovanja i pridržavanja terapije, nije primećena razlika između ispitanika koji boluju od astme i HOBP u zdravstvenom stanju koje su prijavili. Ranije studije su pokazale da simptomi respiratornog trakta i njihov intenzitet najčešće utiču na kvalitet života pacijenata, bez obzira na bolest (21,22). Kliničke manifestacije ova dva stanja se u velikoj meri preklapaju, i stoga je, diferencijacija između astme i HOBP često problematična i pogrešne dijagnoze se dešavaju (23). Sa druge strane, postoje studije koje pokazuju da osobe obolele od HOBP imaju lošiji HRQoL u poređenju sa osobama koje boluju od astme, ali bolji HRQoL u poređenju sa osobama kod kojih se preklapa sindrom astma-HOBP (engl. ACOS) (24,25). Nasuprot tome, u našoj studiji je korišćen metod mečovanja tzv. „*propensity score*“ gde je izvršeno mečovanje ispitanika po polu, starosti, nivou obrazovanja i pridržavanju terapije, i studija je uključila samo pacijente iz primarne zdravstvene zaštite. Ovi pacijenti mogu imati bolju kontrolu bolesti sa manje prisutnim ozbiljnim simptomima bolesti. Takođe, kada su korišćeni drugi generički HRQoL upitnici poput SF-36, da se izmeri HRQoL, pokazano je da se promene u jedinicama (3-5) smatraju klinički značajnim poboljšanjem. Ovaj prag je bio sličan kod ispitanika koji boluju od astme i HOBP (26).

U našoj studiji korišćen je generički upitnik za procenu zdravstvenog statusa osoba obolelih od astme i HOBP, što je omogućilo poređenje pacijenata sa različitim hroničnim stanjima u okviru iste opšte populacije (2,7). Prethodne studije, koje su koristile SF-36 za merenje HRQoL, pronašle su da je HRQoL pacijenata koji boluju od astme i HOBP bio 20 jedinica niži u poređenju sa opštom populacijom (9,10). To znači da HRQoL osoba obolelih od astme i HOBP treba da bude praćen tokom vremena da bi se otkrile određene specifičnosti po pitanju izazova i teškoća sa kojima se oboleli sreću na dnevnoj bazi.

U skladu sa rezultatima iz literature, ispitanici u ovoj studiji, u obe grupe, potvrdili su da je njihovo fizičko zdravlje bilo lošije u poređenju sa drugim aspektima zdravlja (7,21). Prethodne studije su ukazale da su problemi sa kretanjem, ograničena aktivnost i bol/nelagodnost najveći problemi pacijenata koji boluju od astme i HOBP (9,10). Ove rezultate bi trebalo imati u vidu pri definisanju najčešćih prisutnih teškoća za osobe obolele od astme i HOBP.

Ispitanici oboleli od astme i HOBP u našoj studiji prijavili su da im je prisustvo bolesti uglavnom uticalo na san, dok su osećanja anksioznosti i depresije bila na drugom mestu. Prisustvo bola je najređe prijavljivano. Prethodne studije su ukazale da je oko 90% osoba koje boluju od astme i 60% osoba koje boluju od HOBP imalo probleme sa snom i posledično sa osećajem umora i pospanosti tokom dana, što je uticalo na svakodnevno funkcionisanje (27,28). Loš san kod osoba

number of days with sleep disorders 9.8 ± 8.1, followed by days with symptoms of anxiety 8.4 ± 8.0 and depressive symptoms 7.2 ± 7.7. The least number of days 4.5 ± 6.7 accounted for having pain. Similar results were found in people with COPD (10.3 ± 8.4; 8.8 ± 8.1; 7.5 ± 8.0; 4.8 ± 7.1, respectively). No difference was observed in the frequency of sick days between the two groups. results were found in people with COPD (10.3 ± 8.4; 8.8 ± 8.1; 7.5 ± 8.0; 4.8 ± 7.1, respectively). No difference was observed in the frequency of sick days between the two groups.

Discussion

The results of this study showed that people with asthma and COPD experienced multiple sick days in the past month. However, no difference in self-reported health and number of sick days in the past month were found between these two groups of people with chronic pulmonary diseases. Of all difficulties that people with asthma and COPD experienced, the one that has the strongest impact on their health was poor sleep.

More than one half of people in both groups assessed their health status as average or poor and one third reported frequent sick days, that interfered with their everyday activities. These results are in line with the findings that were previously observed in literature (3,17,18). The impact of gender, age, education level and adherence to the treatment on self-reported health of people with asthma and COPD were not tested previously using the propensity score matching. Previous empirical evidence suggests that female sex and older age were negatively correlated with self-reported health of people suffering from asthma and COPD (17, 19). In men with COPD, it was previously shown that physical health is more strongly impaired due to the illness, whereas women had more problems with mental health and dealing with illness (17). These results highlight the difference in perception of illness between genders. Also, low education level and poor compliance with the treatment were correlated with lower HRQOL among people with asthma and COPD (19). A study conducted in Turkey showed that only about 60% of people with asthma and 50% of those with COPD had high compliance with the treatment. (20) Therefore, to help people with asthma and COPD optimize their health, primary care physician should examine the adherence to therapy and provide clues as to how people with asthma and COPD can better adhere to treatment.

After matching on gender, age, education level and adherence to treatment, no difference in self-reported health was observed between people with asthma and COPD. Previous studies have shown that respiratory tract symptoms and their intensity most commonly affect patients' quality of life, regardless of the disease (21,22). Clinical manifestation of these two conditions largely overlap, therefore, differentiation between asthma and COPD is often problematic and misdiagnoses does occur (23). On the other hand, there are studies showing that people with COPD have worse HRQOL in comparison with those with asthma, but better in comparison with those with asthma-COPD overlap syndrome (ACOS) (24,25). In contrast, our study used the propensity score matching on gender, age, education level and adherence to the treatment, and the study included only patients from primary health care setting. These patients may have better disease control and there are fewer people with severe symptoms. Also, other generic HRQOL questionnaires such as the SF-36 were used to measure HRQOL and found that the change in 3-5 units was the threshold seen as a clinically significant improvement. This threshold was quite similar in both people with asthma and COPD (26).

We used a generic questionnaire to assess self-reported health of people with asthma and COPD, which enabled a comparison of patients with different chronic conditions within the same general population (2,7). Previous studies, using SF-36 to measure HRQOL, found that HRQOL of patients with asthma and COPD was 20 units lower compared with the general population (9, 10). This means that HRQOL of people with asthma and COPD should be monitored over time in order to detect certain specificities regarding the challenges and difficulties that are enountered on a daily basis.

In accordance with the results from literature, people in this study, in both groups, confirmed that their physical health was worse compared to other aspects of health (7, 21). Previous studies suggested that mobility disorder, restricted

obolelih od HOBP je u korelaciji sa pogoršanjem bolesti i češćom hospitalizacijom (29). *Brandl et al*. (30) su dokumentovali da otprilike jedna trećina pacijenata koji boluju od HOBP prijavljuje prisustvo simptoma depresiije, dok 25% ima simptome anksioznosti. Takođe, *Leander et al*. (31). su u svojoj studiji pronašli jaku korelaciju između težih respiratornih simptoma i lošijeg psihološkog statusa osoba obolelih od astme i HOBP. Sa druge strane, pokazano je da je depresija najjača determinanta u specifičnom i opštem HRQoL kod osoba koje boluju od astme i HOBP i kao takva je važan medijator veze između HOBP i HRQoL (30-34). Korelacija između depresije i anksioznosti sa komponentom mentalnog zdravlja HRQoL bila je izuzetno istaknuta (33).

Snaga naše studije je prilično veliki uzorak korisnika usluga primarne zdravstvene zaštite koji su upareni na osnovu metoda mečovanja „*propensity score*“ i koji su imali potvrđenu dijagnozu astme i HOBP širom Republike Srbije. To nam omogućava da generalizujemo naše rezultate za celu populaciju pacijenata sa ovim stanjima u primarnoj zdravstvenoj zaštiti. S obzirom da astma i HOBP utiču na HRQoL pojedinaca (35), naši rezultati čine bazu za razumevanje problema osoba koje boluju od astme i HOBP, kao i aspekata bolesti koji treba da budu poboljšani.

Naša studija je imala nekoliko ograničenja. Ispitanici su popunjavali upitnike sami, što je podložno informacionoj pristrasnosti. Ispitanici su izabrani iz centara primarne zdravstvene zaštite, što znači da osobe sa ozbiljnijim formama nisu učestvovale u studiji. Ispitanici koji su izabrani iz centara primarne zdravstvene zaštite su pacijenti kod kojih je bolest uglavnom pod kontrolom, tako da nije bilo moguće proceniti uticaj ozbiljnih i nekontrolisanih formi ovih stanja na zdravstveni status koji su prijavljivali (39). Još jedno ograničenje se odnosi na dnevnu preopterećenost doktora medicine tako da nisu mogli da koriste prošireni upitnik koji bi obezbedio sveobuhvatne podatke o socijalnim i demografskim karakteristikama ispitanika, njihovim životnim navikama i karakteristikama bolesti koji bi doprineli subjektivnoj proceni zdravlja. Takođe, uticaj pojedinačnih simptoma nije uključen.

Zaključak

Nakon mečovanja po polu, starosnoj dobi, nivou obrazovanja i pridržavanju terapije, zdravstveni status koji su prijavljivali ispitanici oboleli od astme i HOBP bio je sličan. I u slučaju astme i HOBP san je najčešće bio narušen. Ovi podaci bi se mogli koristiti za dalje ispitivanje specifične osobine sna u cilju poboljšanja ciklusa spavanja kod osoba obolelih od astme i HOBP. Buduće studije bi mogle da koriste ove rezultate kao osnovu da se dalje ispitaju razlike u zdravstvenom statusu koje prijavljuju osobe sa ozbiljnom i nekontrolisanom astmom i HOBP.

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Konflikt interesa

Autori su izjavili da nema konflikta interesa.

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activity and pain/discomforts represent the largest problems in patients with asthma and COPD (9, 10). These results should be kept in mind when defining the most common difficulties for people with asthma and COPD.

People with asthma and COPD in our study reported that presence of the disease mostly affected their sleep, while feelings of anxiety and depression were ranked second; the presence of pain was least frequently reported. Previous studies suggested that about 90% of people with asthma and 60% of people with COPD have problems with sleep and consequently with feeling tired and sleepy during day which, in turn, interferes with their daily functioning (27, 28). Poor sleep in people with COPD is correlated with the disease deterioration and more frequent hospitalization (29). Brandl et al. (30) documented that around one third of COPD patients report presence of depression symptoms, and 25% have symptoms of anxiety. Also, a study by Leander et al. (31) found a strong correlation between worse respiratory symptoms and poorer psychological status of people with asthma and COPD. On the other hand, depression was found as the strongest determinant disease-specific and general HRQOL in people with asthma and COPD and as such it is a very important mediator of the association between COPD and HRQOL (30-34). The correlation between depression and anxiety with mental health component of HRQOL was especially prominent (33).

The strength of our study is the fairly large sample of propensity score matched users of primary health care services with verified asthma and COPD throughout Serbia. This allows us to generalize our results to the entire population of primary health care patients with these conditions. As asthma and COPD affects HRQOL of individuals (35), our results provide the basis for understanding the problems of people with asthma and COPD as well as what aspects of the disease need to be improved and treated.

Our study had several limitations. Participants were filling in the questionnaires on their own, which is open to information bias. The selection of the participants was carried out from the primary health centers, which means that persons with more severe forms of the disease were omitted. The participants selected from the primary health care institutions are the patients in which the disease is mostly under control, so it was not possible to estimate the impact of severe and uncontrolled forms of the condition on self-reported health (39). Another limitation is related to doctors' daily workload and thus, we were unable to use a more extensive questionnaire which could provide a comprehensive data on social and demographic characteristics of the participants, their life habits and disease characteristics which could contribute to self-rated health. Particularly, the impact of separate symptoms was not included.

Conclusions

After controlling for gender, age, education level and adherence to treatment self-reported health of people with asthma and people with COPD was similar. In both asthma and COPD sleeping was the most frequently impaired. These data could be used to further examine specific features of sleep in efforts to improve sleeping patterns among people with asthma and COPD. Future studies could use these results as the baseline to further explore the differences in self-reported health between people with severe and uncontrolled asthma and COPD.

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Competing interests

The authors declare no competing interests.

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KRETANJE OBOLEVANJA I UMIRANJA OD RAKA PANKREASA U CENTRALNOJ SRBIJI, U PERIODU OD 1999. DO 2019. GODINE

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SAŽETAK

Uvod/Cilj: Rak pankreasa je četrnaesti vodeći uzrok obolevanja i sedmi vodeći uzrok umiranja među svim malignim bolestima. Cilj istraživanja je bio da se analizira kretanje obolevanja i umiranja od raka pankreasa u centralnoj Srbiji za period 1999-2019. godine.
Metode: Podaci o obolelima i umrlima od malignih tumora, kao i o broju stanovnika, po polu i uzrastu, za period od 1999. do 2015. godine, preuzeti su iz registara za rak u Centralnoj Srbiji, a podaci za 2016.,2017., 2018. i 2019. dobijeni su od Instituta za javno zdravlje Srbije. Na osnovu dobijenih podataka izračunate su sirove, specifične i standardizovane stope incidencije i mortaliteta za rak pankrasa. Kretanje obolevanja i umiranja za šesnaestogodišnji period analiziran je korišćenjem *joinpoint* regresione analize.
Rezultati: U periodu 1999-2019. godine u centralnoj Srbiji prosečan godišnji broj obolelih je bio 378 muškaraca i 305 žena, a umrlih 406 muškaraca i 336 žena. Prosečna godišnja standardizovana stopa incidencije (na 100.000) je iznosila 7,7 za muškarce i 5,0 za žene, a standardizovana stopa mortaliteta (na 100.000) 7,9 za muškarce i 5,1 za žene. Kod muškaraca, najviša prosečna godišnja uzrasno specifična stopa incidencije zabeležena je u uzrastu 60-69 godina (39,7 na 100.000), a stopa mortaliteta u uzrastu 70 i više godina (42,4 na 100.000). Kod žena, najviše stope incidencije i mortaliteta su bile u najstarijem uzrastu (70 i više) i iznosile su 25,7 i 34,8 na 100.000. Tokom posmatranog perioda zabeležen je značajan porast standardizovanih stopa incidencije kod muškaraca od 2,9% i kod žena od 3,7% godišnje. Takođe, uočen je trend porasta standardizovanih stopa mortaliteta kod muškaraca (od 1,2%) i žena (od 0,6%), ali je značajnost postignuta samo kod muškaraca.
Zaključak: U periodu 1999-2019. godine u centralnoj Srbiji stope incidencije i mortaliteta su u porastu. Neophodna su istraživanja o faktorima rizika za nastanak ove bolesti u cilju preduzimanja preventivnih mera. Takođe, rano otkrivanje i pravovremena terapija treba da doprinesu redukciji umiranja od ovog malignoma.

Ključne reči: rak pankreasa, incidencija, mortalitet, trend, *joinpoint* regresiona analiza

Uvod

Rak pankreasa je četrnaesti vodeći uzrok obolevanja i sedmi vodeći uzrok umiranja među svim malignim bolestima (1). U 2020. godini u svetu je dijagnostikovano 495.773 slučajeva raka pankreasa, a kao posledica istog zabeleženo je 466.003 slučajeva smrti (1). Drugim rečima, rak pankreasa je, zbog svoje loše prognoze, odgovoran za sličan broj obolelih i smrtnih slučajeva. Na globalnom nivou u 2020. godini zabeležena je i značajna razlika u obolevanju među polovima. Kod muškaraca je veća stopa incidencije (5,7 na 100.000) nego kod žena (4,1 na 100.000) (1). Slično je i sa stopama mortaliteta koje su veće kod muškaraca (5,3 na 100.000) nego kod žena (3,8 na 100.000). Starenjem se incidencija ove bolesti povećava kod oba pola. Skoro da ove bolesti i nema pre 55. godine života, a posle 70. godine zapaža se najveća incidencija (2). Takođe, mortalitet raste sa uzrastom, skoro 90% smrtnih slučajeva je kod osoba starosti 55 i više godina.

Kao faktori rizika za nastanak raka pankreasa navode se pozitivna porodična anamneza, pušenje cigareta, unošenje veće količine alkohola, ishrana, fizička neaktivnost i prisustvo dijabetes melitu-

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TRENDS IN INCIDENCE AND MORTALITY FROM PANCREATIC CANCER IN CENTRAL SERBIA, IN THE PERIOD FROM 1999 TO 2019

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SUMMARY

Introduction: Pancreatic cancer is the fourteenth leading cause of disease and the seventh leading cause of death among all malignant diseases. The aim of the research was to analyze the trends in the incidence and death of pancreatic cancer in central Serbia for the period 1999-2019. years.
Methods: The data about diseased and dead, as well as population by sex and age, in the period 1999-2015 were taken over from the Cancer registry of Central Serbia, and the data for 2016, 2017, 2018 and 2019 were obtained from the Institute of Public Health of Serbia. Based on obtained data, we counted crude, specific and standardized rates of incidence and mortality for pancreatic cancers, for all ages. Trends rate in incidence and mortality were counted using joinpoint regression analysis.
Results: In the period 1999-2019. In central Serbia, the average annual number of patients was 378 men and 305 women, and the average number of deaths was 406 men and 336 women. The average annual standardized incidence rate (per 100,000) was 7.7 for men and 5.0 for women, and the standardized mortality rate (per 100,000) was 7.9 for men and 5.1 for women. In men, the highest average annual age-specific incidence rate was recorded at the age of 60-69 (39.7 per 100,000), and the mortality rate at the age of 70 and over (42.4 per 100,000). Among women, the highest incidence and mortality rates were in the oldest age (70 and over) and were 25.7 and 34.8 per 100,000. During the observed period, there was a significant increase in standardized incidence rates for men of 2.9% and for women of 3.7% per year. Also, a trend of increasing standardized mortality rates was observed in men (of 1.2%) and women (of 0.6%), but significance was achieved only in men.
Conclusion: In the period 1999-2019. in central Serbia, incidence and mortality rates are on the rise. Research on risk factors for the development of this disease is necessary in order to take preventive measures. Also, early detection and timely therapy should contribute to the reduction of death from this malignancy.

Keywords: pancreatic cancer, incidence, mortality, trend, joinpoint regression analysis

Introduction

Pancreatic cancer is the fourteenth leading cause of disease and the seventh leading cause of death among all malignant diseases (1). In 2020, 495,773 cases of pancreatic cancer were diagnosed worldwide, while 466,003 cases of death were reported due to pancreatic cancer (1). In other words, pancreatic cancer is, due to its poor prognosis, responsible for the similar number of new cases and deaths. Globally, a significant difference between sexes was noted in 2020. In men, the incidence rate was higher (5.7 per 100,000) than in women (4.1 per 100,000) (1). Similarly, mortality rates were higher in men (5.3 per 100.000) than in women (3.8 per 100,000). The incidence of this disease increases with age in both sexes. Pancreatic cancer is seldom diagnosed before 55 years of age, while the highest incidence is reported in people over 70 years (2). Also, mortality increases with age, and almost 90% of deaths were reported in people over 55 years of age.

Risk factors for the occurrence of pancreatic cancer are the following: positive family history, smoking, alcohol consumption, diet, physical inactivity, and diabetes mellitus (3-8). Pancreatic

sa (3–8). Rak pankreasa je jedan od najmalignijih tumora, i njegova prognoza je vrlo loša. Podaci pokazuju da je petogodišnje preživljavanje manje od 10%, a razlike u preživljavanju malo variraju između razvijenih i zemalja u razvoju (7,9). U prilog ovako visokom mortalitetu ide i podatak da se ovaj tumor otkriva u uznapredovalom stadijumu, zato što je u ranom stadijumu bez simptoma, a i kada ima simptome, oni su nespecifični. Kada se otkrije u uznapredovalom stadijumu, kod 80-90% pacijenata ga je nemoguće operisati (2).

Bolji uvid u epidemiološke trendove raka pankreasa doprineo bi i boljem razumevanju njegove etiologije i imao bi implkacije na preventivne mere i kliničku negu. Cilj istraživanja je bio da se analizira kretanje obolevanja i umiranja od raka pankreasa u centralnoj Srbiji, u periodu od 1999. do 2019. godine.

Metod

Podaci o obolelima i umrlima od raka pankreasa, kao i o broju stanovnika, po polu i uzrastu, za period od 1999. do 2015. godine, preuzeti su iz registara za rak u centralnoj Srbiji Instituta za javno zdravlje Srbije „Dr Milan Jovanović Batut". Podaci za 2016., 2017., 2018. i 2019. dobijeni su na zahtev od Instituta za javno zdravlje Srbije „Dr Milan Jovanović Batut", jer nisu publikovani u registrima. Na osnovu dobijenih podataka izračunate su sirove, specifične i standardizovane stope incidencije i mortaliteta za rak pankreasa, za sve uzraste. Direktnom metodom standardizacije izračunate su standardizovane stope incidencije i mortaliteta i to tako što je za standardnu populaciju korišćena standardna populacija sveta prema Segi-ju (1960) (10). Trendovi standardizovanih stopa incidencije i mortaliteta su izračunati korišćenjem *joinpoint* regresione analize (*Joinpoint Regression Program, Version 4.9.0.1. February, 2022; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute*), prema metodu *Kim et al*. (11). *Joinpoint* regresionom analizom određena je procentualna godišnja promena (engl. *Annual percent change*-APC), kao i tačke u kojima dolazi do značajnih promena u trendovima. Određena je i prosečna procentualna godišnja promena (engl. *Average annual percent change* – AAPC) za celokupan posmatrani period. Kao nezavisna varijabla postavljene su godine, dok je zavisna varijabla bila odgovarajuća uzrasno-specifična ili standardizovana stopa. Minimalan broj podataka od početka serije bio je podešen na 2, dok je najmanji broj podataka između dva *joinpoint*-a bio 2. Maksimalan broj joinpointa bio je podešen na 3. Korišćen je *Grid Search* metod (12). *Permutation Test* je korišćen za selekciju najboljeg modela joinpoint-a sa uopštenim nivoom značajnosti od 0,05 i 4499 slučajno permutovanih setova. Pored toga, 95% intervali poverenja računati su za svaku procenu APC kako bi se utvrdilo da li je APC za svaki segmet različit od 0. Korišćen je test uporedivosti (engl. *comparability test*) kako bi se uporedile dve segmentirane linije regresije, odnosno trendovi szandardizovanih stopa po polu. Cilj je bio da se uporedi da li su trendovi bili paralelni.

Rezultati

U periodu od 1999-2019. godine u centralnoj Srbiji je prosečno godišnje od raka pankreasa obolevalo 378 muškaraca (tabela 1). Prosečna stopa incidencije za muškarce iznosila je 14,7 na 100.000, a standardizovana 7,7 na 100.000. U istom periodu prosečno je godišnje od raka pankreasa obolevalo 305 žena. Prosečna sirova stopa incidencije kod žena iznosila je 11,2 na 100.000, a standardizovana 5 na 100.000. Najviše obolelih registrovano je 2017. godine, i to 572 muškarca i 461 žena.

U periodu od 1999-2019. godine u centralnoj Srbiji je prosečno godišnje od raka pankreasa umiralo 406 muškaraca (tabela 2). Prosečna stopa mortalitata za muškarce iznosila je 15,7 na 100.000, a standardizovana 7,9 na 100.000. U istom periodu prosečno je godišnje od raka pankreasa umiralo 336 žena. Prosečna sirova stopa incidencije kod žena iznosila je 12,3 na 100.000, a standardizovana 5,1 na 100.000. Najviše umrlih muškaraca registrovano je 2017. godine, i to 487, a 2016. najviše umrlih žena 414.

Najviše uzrasno-specifične stope incidencije za rak pankreasa kod muškaraca beleže se za uzrast 60-69 godina (39,7 na 100.000) (tabela 3). Značajan prosečan procentualni godišnji porast obolevanja bio je u uzrastima 50-59, 60-69 i 70+, a najveći značajan porast od 5,6% u uzrastu 70+. Kod žena je najviša uzrasno-specifična stopa incidencije zabeležena u uzrastu 70+ (25,7 na 100.000). Značajan godišnji porast zabeležen je u uzrasnim grupama 40-49, 50-59 i 60-69, a najviši u uzrastu 50-59 od 5,7% godišnje. Beleži se i značajan go-

cancer is one of the most malignant tumors, and its prognosis is very poor. Data show that five-year survival is less than 10%, and there is a slight difference between developed and developing countries (7,9). High mortality rates may be attributed to the fact that this tumor is diagnosed in an advanced stage, because at its early stages it has no symptoms, and when symptoms appear, they are non-specific. When it is detected at an advanced stage, in 80-90% of patients, it can no longer be operated.

A better insight into the epidemiological trends of pancreatic cancer would contribute to better understanding of its etiology and would have implications for preventive measures and clinical care. The aim of the research was to analyze the trends in pancreatic cancer incidence and mortality in central Serbia in the period 1999-2019.

Methods

The data about new cases and deaths caused by pancreatic cancer, as well as about population by sex and age for the period 1999-2015, were taken from the Cancer Registry of Central Serbia of the Institute of Public Health of Serbia "Dr Milan Jovanovic Batut". The data for 2016, 2017, 2018 and 2019 were requested and obtained from the Institute of Public Health "Dr Milan Jovanovic Batut" because they were not published in registries. The obtained data were used to calculate crude, specific and standardized incidence and mortality rates for all age groups. Standardized incidence and mortality rates were calculated using the method of direct standardization, where the population of the world by Segi was used as the standard population (1960) (10). The trends in standardized incidence and mortality rates were calculated with the help of joinpoint regression analysis (Joinpoint Regression Program, Version 4.9.0.1. February, 2022; Statistical Methodology and Applications Branch, Surveillance Research program, National Cancer Institute), according to the method by Kim et al. (11). Using the joinpoint regression analysis, the annual percentage change (APC) was estimated, as well as the time intervals of important trend changes. The average annual percentage change (AAPC) for the entire observed period was also determined. Age was set as an independent variable, while corresponding age-specific or standardized rate was a dependent variable. Grid Search method was used (12). The minimum number of data from the beginning of the series was set to 2, while the minimum number of data between the two joinpoints was 2. The maximum number of joinpoints was set to 3. Permutation Test was used for the selection of the best model of joinpoint with the general significance level from 0.05 to 4499 of accidentally permuted sets. In addition, 95% confidence intervals were calculated for each APC and AAPC estimate to determine if the APC/AAPC for each segment was different from 0. Comparability test was used to compare two segmented line regression functions, that is, trends by gender. The aim was to compare whether the trends were parallel.

Results

In the period 1999-2019, in central Serbia the average annual number of cases was 378 men (Table 1). The average incidence rate for men was 14.7 per 100,000, while the standardized rate was 7.7 per 100,000. During the same period, the average annual number of cases was 305 women. The average crude incidence rate in women was 11.2 per 100,000, while the standardized rate was 5 per 100,000. The greatest number of new cases was registered in 2017, that is, 572 men and 461 women.

In the period 1999-2019 in central Serbia, the average annual number of deaths caused by pancreatic cancer was 406 men (Table 2). The average mortality rate for men was 15.7 per 100,000, while the standardized rate was 7.9 per 100,000. In the same period, the average annual number of deaths was 336 women. The average crude mortality rate was 12.3 per 100,000, while the standardized rate was 5.1 per 100,000. The highest number of deaths among men was registered in 2017, that is, 486 men, while the highest number of deaths among women was registered in 2016, that is, 414 women.

The highest age-specific incidence rates for pancreatic cancer were registered in the age group 60-69 years (39.7 per 100,000) (Table 3). A significant average incidence increase was in the age groups 50-59, 60-69 and 70+, while the highest significant increase of 5.6% was in the age group 70+. In women, the highest age-specific incidence rate was found in the group of people

dišnji porast standardizovanih stopa incidencije i kod muškaraca (2,9%) i kod žena (3,7%).

Najviše uzrasno-specifične stope mortaliteta od raka pankreasa bile su kod muškaraca u uzrastu 70+ (42,4 na 100.000) i 60-69 godina (41,4 na 100.000) (tabela 4). Značajan porast stopa mortaliteta kod muškaraca zabeležen je za uzraste 60-69 (od 1,7% godišnje) i 70+ (4,6% godišnje). Kod žena su najviše vrednosti stopa mortaliteta zabeležene za uzrast 70+ (34,8 na 100.000). Značajan je porast stopa mortalita u uzrastima 50-59, 60-69 i 70+, s najvišim porastom u uzrastu 70+ od 3,9% godišnje. Standardizovane stope mortaliteta rastu kod muškaraca (od 1,2%) i kod žena (0,6%) godišnje, ali značajnost je postignuta samo kod muškaraca.

Test paralelizma trendova stopa incidencije kod muškaraca i žena, kao i stopa mortaliteta kod muškaraca i žena pokazao je da su trendovi po polu bili paralelni $p > 0,05$ (grafikon 1).

Diskusija

U centalnoj Srbiji u periodu 1999-2019. godine prosečna standardizovana stopa incidencije (na 100.000) od raka pankreasa kod muškaraca bila je 7,7, a kod žena 5 (odnos stopa 1,5). U razvijenim i visoko razvijenim zemljama standardizovana stopa incidencije (na 100.000) za rak pankreasa kod muškaraca iznosila je 7,2, a u srednje i slabije razvijenim 1,6 (1). Kod žena u razvijenim zemljama stope incidencije (na 100.000) iznosile su 5,0, a u slabije razvijenim zemljama 1,0. Odnosno, stope su 4 do 5 puta više u razvijenim zemljama. Najviše stope incidencije (na 100.000) beleže se u Australiji (15,3 za muškarce i 10 za žene), Severnoj Americi (14,2 za muškarce i 10,0 za žene) i Evropi. Nisu u potpunosti jasne razlike u stopama incidencije između zemalja, ali je moguće da su posledica različitih sredinskih faktora, kao i izloženosti faktorima rizika, kao što su pušenje, faktori ishrane

Tabela 1. Broj obolelih, sirove i standarizovane* stope incidencije (na 100.000), centralna Srbija, 1999-2019. godine

Godine	Muškarci			Žene		
	Broj obolelih	Sirova stopa	Standardizovana stopa	Broj obolelih	Sirova stopa	Standardizovana stopa
1999	245	9,1	5,3	205	7,3	4,3
2000	245	9,2	5,4	187	6,6	3,2
2001	314	11,8	6,9	206	7,3	3,6
2002	332	12,5	7,2	238	8,5	4,2
2003	302	11,4	6,4	240	8,6	4,0
2004	342	12,9	7,3	251	9,0	4,3
2005	325	12,3	7,0	309	11,1	5,0
2006	266	10,1	5,7	208	7,5	3,6
2007	356	13,6	7,6	265	9,6	4,3
2008	356	13,6	7,3	234	8,5	3,7
2009	312	12,0	6,6	258	9,4	4,5
2010	312	12,0	6,6	270	9,9	4,4
2011	420	16,3	8,7	317	11,6	5,1
2012	322	12,5	6,4	272	10,0	4,4
2013	455	17,8	8,6	362	13,4	5,3
2014	473	18,6	8,9	365	13,6	5,4
2015	472	18,6	9,2	403	15,1	6,5
2016	463	18,4	8,5	451	17,0	6,6
2017	572	22,8	10,8	461	17,5	6,7
2018	525	21,1	10,2	456	17,4	7,6
2019	528	21,2	10,4	454	17,3	7,6
Prosek	378	14,7	7,7	305	11,2	5,0

*Standardizovane stope prema populaciji sveta

aged 70 and older (25.7 per 100,000). A significant annual increase was registered in the age groups 40-49, 50-59 and 60-69, while the highest increase of 5.7% annually was in the age group 50-59. A significant annual increase of standardized incidence rates was registered in men (2.9%) and women (3.7%).

The highest age-specific mortality rates of pancreatic cancer were in men aged 70+ (42.4 per 100,000) and 60-69 (41.4 per 100,000) (Table 4). A significant increase of mortality rates in men was registered in the age groups 60-69 (of .7% annually) and 70+ (4.6% annually). In women, the highest mortality rates were registered in the age group 70+ (34.8 per 100,000). A significant increase of mortality rates was found in the age groups 50-59, 60-69 and 70+, with the highest annual increase of 3.9% in the age group 70+. Standardized mortality rates increased in men (1.2%) and in women (0.6%) annually, but the significance was found only in men.

Comparability test of trends in incidence rates in men and women, as well as in mortality rates in men and women showed that trends regarding gender were parallel p>0.05 (Figure 1).

Discussion

In central Serbia in the period 1999-2019, the average standardized incidence rate (per 100,000) of pancreatic cancer was 7.7 in men and 5 in women (rates ratio 1.5). In developed and highly developed countries, standardized incidence rate (per 100,000) for pancreatic cancer in men was 7.2, while in middle-income countries and less developed countries it was 1.6 (1). In developed countries, incidence rates (per 100,000) amounted to 5.0 in women, while in less developed countries, they amounted to 1.0. These rates were 4 to 5 times higher in developed countries. The highest incidence rates (per 100,000) were found in Australia (14.3 for men and 10 for women), North America (14.2 for men and 10.0 for women) and in

Table 1. The number of cases, crude and standardized* incidence rates (per 100,000), central Serbia, 1999-2019.

Year	Men			Women		
	Number of cases	Crude rate	Standardized rate	Number of cases	Crude rate	Standardized rate
1999	245	9.1	5.3	205	7.3	4.3
2000	245	9.2	5.4	187	6.6	3.2
2001	314	11.8	6.9	206	7.3	3.6
2002	332	12.5	7.2	238	8.5	4.2
2003	302	11.4	6.4	240	8.6	4.0
2004	342	12.9	7.3	251	9.0	4.3
2005	325	12.3	7.0	309	11.1	5.0
2006	266	10.1	5.7	208	7.5	3.6
2007	356	13.6	7.6	265	9.6	4.3
2008	356	13.6	7.3	234	8.5	3.7
2009	312	12.0	6.6	258	9.4	4.5
2010	312	12.0	6.6	270	9.9	4.4
2011	420	16.3	8.7	317	11.6	5.1
2012	322	12.5	6.4	272	10.0	4.4
2013	455	17.8	8.6	362	13.4	5.3
2014	473	18.6	8.9	365	13.6	5.4
2015	472	18.6	9.2	403	15.1	6.5
2016	463	18.4	8.5	451	17.0	6.6
2017	572	22.8	10.8	461	17.5	6.7
2018	525	21.1	10.2	456	17.4	7.6
2019	528	21.2	10.4	454	17.3	7.6
Average	378	14.7	7.7	305	11.2	5.0

*Standardized rates according to the world population

Tabela 2. Broj obolelih, sirove i standarizovane* stope mortaliteta (na 100.000), centralna Srbija, 1999-2019. godine

Godine	Muškarci			Žene		
	Broj obolelih	Sirova stopa	Standardizovana stopa	Broj obolelih	Sirova stopa	Standardizovana stopa
1999	338	12,6	7,3	248	9,2	5,2
2000	299	11,2	6,5	246	8,7	4,1
2001	326	12,2	6,8	240	8,5	3,6
2002	342	12,9	7,1	270	9,6	4,4
2003	355	13,4	7,4	277	9,9	4,4
2004	358	13,5	7,3	261	9,3	4,0
2005	389	14,7	8,1	348	12,5	5,2
2006	377	14,3	7,8	296	10,7	4,7
2007	365	13,9	7,3	355	12,8	5,3
2008	426	16,3	8,3	354	12,8	5,1
2009	402	15,4	8,1	358	13,0	5,2
2010	423	16,3	8,5	379	13,8	5,7
2011	449	17,4	8,9	349	12,8	5,4
2012	441	17,2	8,1	386	14,3	5,4
2013	462	18,1	8,7	359	13,3	5,1
2014	432	17	7,9	352	13,1	5,1
2015	474	18,7	8,7	392	14,7	5,8
2016	441	17,5	8,0	414	15,6	5,7
2017	487	19,4	8,8	387	14,6	5,4
2018	473	19,0	8,6	395	15,0	5,6
2019	473	19,0	8,6	400	15,2	5,7
Prosek	406	15,7	7,9	336	12,3	5,1

*Standardizovane stope prema populaciji sveta

Tabela 3. Prosečne uzrasno-specifične i standardizovane stope incidencije (na 100.000) za rak pankreasa, joinpoint analiza kretanja stopa, centralna Srbija, 1999-2019. godine

Uzrasne grupe	Muškarci			Žene		
	Stope incidencije	Period	APC/AAPC (95% IP)	Stope incidencije	Period	APC/AAPC (95% IP)
0-29	0	-	-	0	-	-
30-39	1,2	1999-2019	-2,7 (-6,1 – 0,9)	0,8	1999-2019	0,1 (-3,9 – 4,3)
40-49	5,9	1999-2019	0,9 (-1,1 – 3,0)	3,7	1999-2019	3,3* (0,6 – 6,0)
50-59	19,8	1999-2002 2002-2014 2014-2019 1999-2019	13,0 (-3,6 – 32,5) -0,9 (-3,0 – 1,3) 10.1* (2,5 – 18,2) 3,8* (0,8 – 6,9)	24,9	1999-2008 2008-2019 1999-2019	0,1 (-3,3 – 3,7) 6,4* (3,7 – 9,2) 3,5* (1,5 – 5,6)
60-69	39,7	1999-2019	3,2* (2,0 – 4,5)	24,9	1999-2017 2017-2019 1999-2019	6,8* (5,0 – 8,7) -22,5 (-54,8 – 32,7) 3,5 (-1,8 – 8,9)
70+	33,3	1999-2019	5,6* (4,0 -7,2)	25,7	1999-2017 2017-2019 1999-2019	6,8* (5,0 – 8,7) -22,5 (-54,8 – 32,7) 3,5 (-1,8 – 8,9)
Standardizovana stopa	7,7	1999-2019	2,9* (2,0 – 3,8)	5,0	1999-2010 2010-2019 1999-2019	1,2 (-0,9 – 3,4) 6,8* (3,7 – 9,9) 3,7* (2,0 – 5,4)

Standardizovane stope prema populaciji sveta; APC – *Anual Percent Change*; AAPC *Annual Percent Change* – prosečna procentualna godišnja promena; 95%IP - 95% interval poverenja; *APC/AAPC je značajno različit od 0 za alfa=0,05; joinpoint rezultati nisu prikazani za uzrast 0-29 jer je bilo manje od 5 slučajeva godišnje.

Table 2. The number of deaths, crude and standardized* mortality rates (per 100,000), central Serbia, 1999-2019.

Year	Men			Women		
	Number of deaths	Crude rate	Standardized rate	Number of deaths	Crude rate	Standardized rate
1999	338	12.6	7.3	248	9.2	5.2
2000	299	11.2	6.5	246	8.7	4.1
2001	326	12.2	6.8	240	8.5	3.6
2002	342	12.9	7.1	270	9.6	4.4
2003	355	13.4	7.4	277	9.9	4.4
2004	358	13.5	7.3	261	9.3	4.0
2005	389	14.7	8.1	348	12.5	5.2
2006	377	14.3	7.8	296	10.7	4.7
2007	365	13.9	7.3	355	12.8	5.3
2008	426	16.3	8.3	354	12.8	5.1
2009	402	15.4	8.1	358	13.0	5.2
2010	423	16.3	8.5	379	13.8	5.7
2011	449	17.4	8.9	349	12.8	5.4
2012	441	17.2	8.1	386	14.3	5.4
2013	462	18.1	8.7	359	13.3	5.1
2014	432	17.0	7.9	352	13.1	5.1
2015	474	18.7	8.7	392	14.7	5.8
2016	441	17.5	8.0	414	15.6	5.7
2017	487	19.4	8.8	387	14.6	5.4
2018	473	19.0	8.6	395	15.0	5.6
2019	473	19.0	8.6	400	15.2	5.7
Average	406	15.7	7.9	336	12.3	5.1

*Standardized rates according to the world population

Table 3. Average age-specific and standardized incidence rates (per 100,000) for pancreatic cancer, joinpoint analysis of trends, central Serbia, 1999-2019.

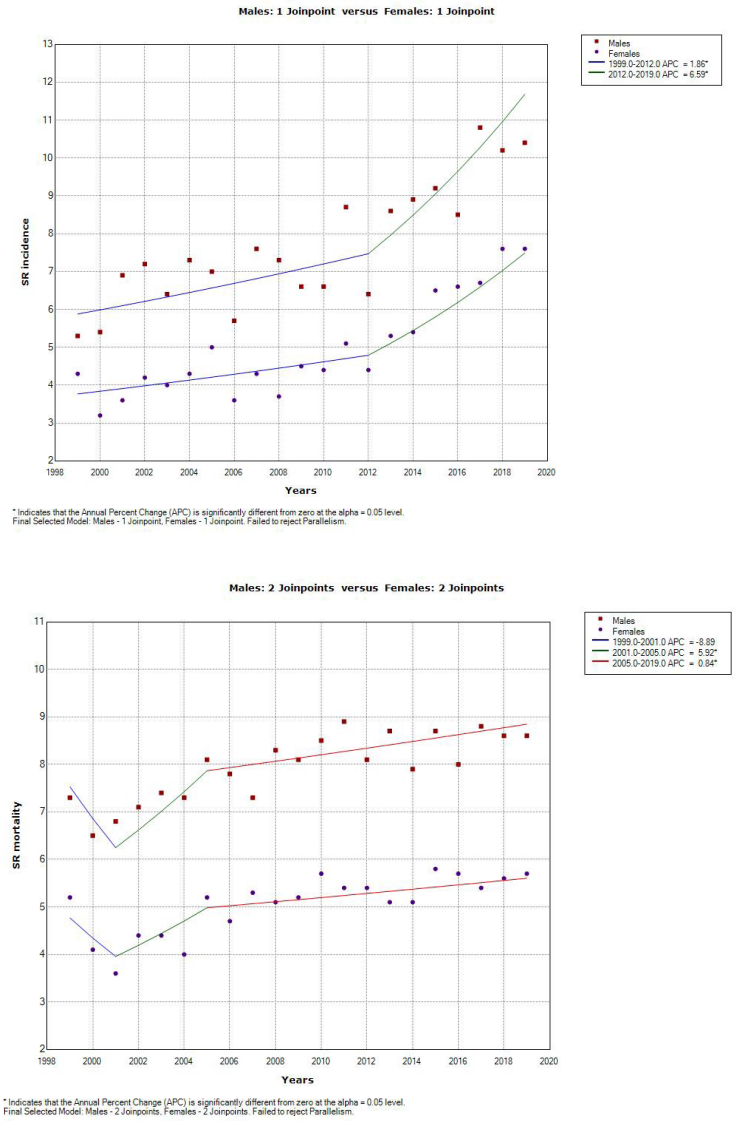
Age groups	Men			Women		
	Incidence rates	Period	APC/AAPC (95% CI)	Incidence rates	Period	APC/AAPC (95% CI)
0-29	0	-	-	0	-	-
30-39	1.2	1999-2019	-2.7 (-6.1 – 0.9)	0.8	1999-2019	0.1 (-3.9 – 4.3)
40-49	5.9	1999-2019	0.9 (-1.1 – 3.0)	3.7	1999-2019	3.3* (0.6 – 6.0)
50-59	19.8	1999-2002 2002-2014 2014-2019 1999-2019	13.0 (-3.6 – 32.5) -0.9 (-3.0 – 1.3) 10.1* (2.5 – 18.2) 3.8* (0.8 – 6.9)	24.9	1999-2008 2008-2019 1999-2019	0.1 (-3.3 – 3.7) 6.4* (3.7 – 9.2) 3.5* (1.5 – 5.6)
60-69	39.7	1999-2019	3.2* (2.0 – 4.5)	24.9	1999-2017 2017-2019 1999-2019	6.8* (5.0 – 8.7) -22.5 (-54.8 – 32.7) 3.5 (-1.8 – 8.9)
70+	33.3	1999-2019	5.6* (4.0 -7.2)	25.7	1999-2017 2017-2019 1999-2019	6.8* (5.0 – 8.7) -22.5 (-54.8 – 32.7) 3.5 (-1.8 – 8.9)
Standardized rate	7.7	1999-2019	2.9* (2.0 – 3.8)	5.0	1999-2010 2010-2019 1999-2019	1.2 (-0.9 – 3.4) 6.8* (3.7 – 9.9) 3.7* (2.0 – 5.4)

Standardized rates according to the world population; APC – Annual Percent Change; AAPC – Average Annual Percent Change; 95% CI-95% confidence interval; *AAPC is significantly different from 0 at the alpha=0.05 level; joinpoint results were not presented for age group 0-29 because there were less than 5 cases per year.

Tabela 4. Prosečne uzrasno-specifične i standardizovane stope mortaliteta (na 100.000) za rak pankreasa, joinpoint analiza kretanja stopa, centralna Srbija, 1999-2019. godine

	Muškarci			Žene		
Uzrasne grupe	**Stope mortaliteta**	**Period**	**APC/AAPC (95% IP)**	**Stope mortaliteta**	**Period**	**APC/AAPC (95% IP)**
0-29	0	-	-	0	-	-
30-39	0,8	1999-2019	-5,0 (-12,0 – 2,5)	0,5	1999-2019	-10,1 (-20,2 – 1,3)
40-49	4,5	1999-2019	-1,0 (-2,6 – 0,6)	2,6	1999-2019	1,2 (-1,5 – 4,0)
50-59	18,8	1999-2019	-0,1 (-1,0 -0,8)	10,33	1999-2019	2,3* (1,3 – 3,2)
60-69	41,4	1999-2019	1,7* (0,7 – 2,7)	25,0	1999-2019	1,4* (0,5 – 2,2)
70+	42,4	1999-2019	4,6* (3,4 – 5,9)	34,8	1999-2008 2008-2019 1999-2019	8,2* (5,2 – 11,3) 0,8 (-1,3 – 2,9) 3,9* (2,8 – 5,1)
Standardizovana stopa	7,9	1999-2019	1,2* (0,8 – 1,6)	5,0	1999-2001 2001-2007 2007-2019 1999-2019	-13,3 (-28,8 – 4,3) 5,5* (1,2 – 10,0) 0,6 (-0,5 – 1,7) 0,6 (-1,5 – 2,7)

Standardizovane stope prema populaciji sveta; APC – *Anual Percent Change*; AAPC – *Average Annual Percent Change* – prosečna procentualna godišnja promena; 95%IP - 95% interval poverenja; *APC/AAPC je značajno različit od 0 za alfa=0,05; joinpoint rezultati nisu prikazani za uzrast 0-29 jer je bilo manje od 5 slučajeva godišnje.



Grafikon 1. Joinpoint analiza (test paralelizma) kretanja stopa a) incidencije i b) mortaliteta od raka pankreasa, centralna Srbija, 1999-2019. godine

Tabela 4. Prosečne uzrasno-specifične i standardizovane stope mortaliteta (na 100.000) za rak pankreasa, joinpoint analiza kretanja stopa, centralna Srbija, 1999-2019. godine

	Men			Women		
Age groups	**Mortality rates**	**Period**	**APC/AAPC (95% CI)**	**Mortality rates**	**Period**	**APC/AAPC (95% CI)**
0-29	0	-	-	0	-	-
30-39	0.8	1999-2019	-5.0 (-12.0 – 2.5)	0.5	1999-2019	-10.1 (-20.2 – 1.3)
40-49	4.5	1999-2019	-1.0 (-2.6 – 0.6)	2.6	1999-2019	1.2 (-1.5 – 4.0)
50-59	18.8	1999-2019	-0.1 (-1.0 -0.8)	10.33	1999-2019	2.3* (1.3 – 3.2)
60-69	41.4	1999-2019	1.7* (0.7 – 2.7)	25.0	1999-2019	1.4* (0.5 – 2.2)
70+	42.4	1999-2019	4.6* (3.4 – 5.9)	34.8	1999-2008 2008-2019 1999-2019	8.2* (5.2 – 11.3) 0.8 (-1.3 – 2.9) 3.9* (2.8 – 5.1)
Standardized rate	7.9	1999-2019	1.2* (0.8 – 1.6)	5.0	1999-2001 2001-2007 2007-2019 1999-2019	-13.3 (-28.8 – 4.3) 5.5* (1.2 – 10.0) 0.6 (-0.5 – 1.7) 0.6 (-1.5 – 2.7)

Standardized rates according to the world population; APC – Annual Percent Change; AAPC – Average Annual Percent Change; 95% CI-95% confidence interval; *AAPC is significantly different from 0 at the alpha=0.05 level; joinpoint results were not presented for age group 0-29 because there were less than 5 cases per year.

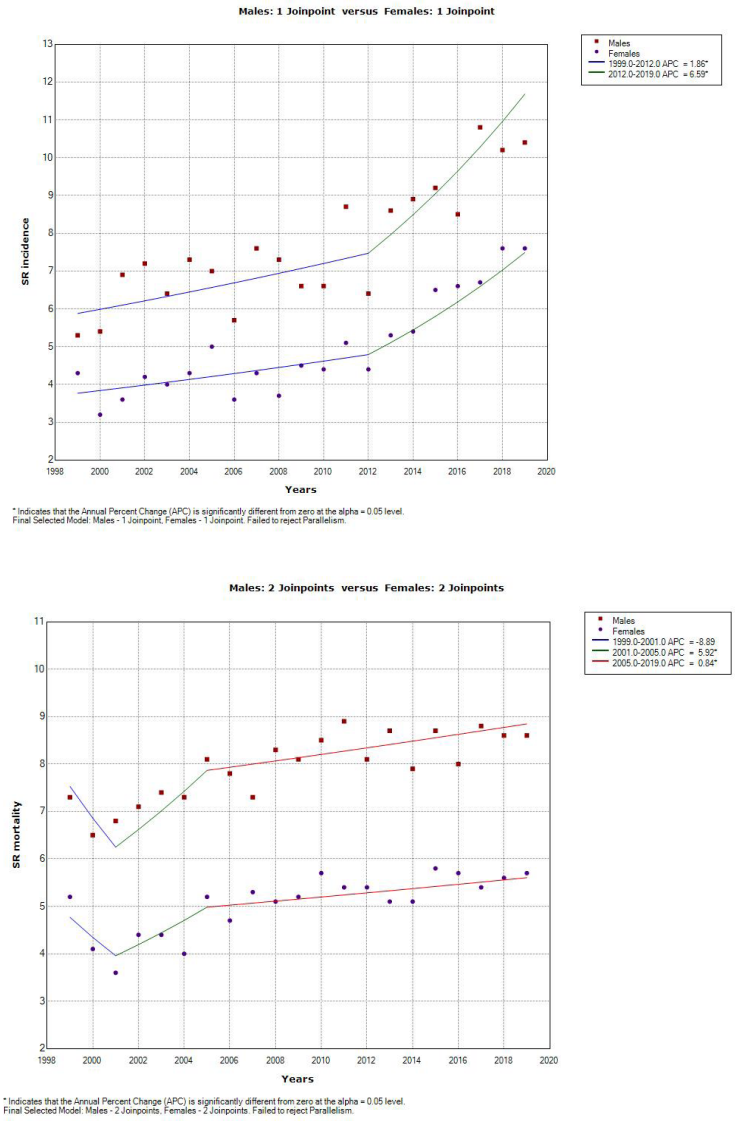


Figure 1. Joinpoint analysis (parallelism test) of trends a) incidence i b) mortality of pancreatic cancer, central Serbia, 1999-2019.

i gojaznost (2,4,13,14). Zemlje sa višim stopama incidencije i mortaliteta su češće imale veću prevalenciju pušenja, konzumiranja alkohola, fizičke neaktivnosti, gojaznosti, hipertenzije i visok holesterol (8). Ono što treba uzeti u obzir jeste i različita dostupnost dijagnostičkih procedura između razvijenih i nerazvijenih zemalja, kao i razlike u kvalitetu registara za rak. U razvijenijim zemljama veća incidencija može biti posledica veće dostupnosti zdravstvene zaštite i zdravstvene svesti. Osim toga, moguće je da su incidencija raka pankreasa i srodni faktori rizika potcenjeni u regionima sa nižim stepenom razvoja zbog manjeg prijavljivanja. Niže stope incidencije kod žena mogu se pripisati manjoj sklonosti ovom oboljenju ili izloženosti faktorima sredine, odnosno faktorima rizika, u manjoj meri.

Stope incidencije raka pankreasa rastu sa uzrastom. Posle 70+ se beleži najveća incidencija kod oba pola (2). Međutim, kod nas se u datom periodu beleži najveća stopa incidencije u uzrastu od 60-69 godina kod muškaraca (39,7 na 100.000), dok je kod žena stopa incidencije najveća u grupi starih 70 i više godina (25,7 na 100.000). U Kanadi je 99% obolelih bilo uzrasta 50 i više godina (15). Kina beleži najveću stopu incidencije u grupi starijih od 85 godina, kod oba pola (muškarci 59,8 na 100.000, žene 47,5 na 100.000) (16).

U periodu 1999-2019. godine u centralnoj Srbiji kod muškaraca se beleži značajan prosečan procentualni godišnji porast obolevanja od +2,9%, a kod žena +3,7%. Sličan trend porasta stopa incidencije beleži se i u drugim zemljama. *Huang et al*. (8) su, pored faktora povezanih sa nastankom raka pankreasa, analizirali i kretanje stopa incidencije i mortaliteta od raka pankreasa u 48 zemalja, u periodu od 2008. do 2017. godine. U Evropi 9 zemalja beleži porast stopa incidencije kod muškaraca, a najviše povećanje stopa beleži se na Islandu (AAPC, +8,8%), Kipru (+5,5%), i Francuskoj (+4,3%). Od ostalih regiona, najveći porast beleže Tajland (+4,5%) i Japan (+1,5%). Kod žena se porast beleži u 12 Evropskih zemalja, a najveće povećanje je na Malti (+6,0%), u Slovačkoj (+4,4%) i Francuskoj (+4,2%). Od ostalih zemalja uključenih u analizu najveći porast je na Novom Zelandu (+2,6%), u Japanu (+1,5%) i Južnoj Koreji (+1,7%). Jedino je Danska pokazala opadajući trend (-2,4%). U istoj studiji, u 18 zemalja opažen je porast stopa incidencije kod osoba od 50 i više godina, i to najviše na Islandu, Malti i Francuskoj. Kod mlađih od 50 godina došlo je do porasta stopa incidencije u 8 zemalja (Nemačka, Švedska, Holandija, Ujedinjeno Kraljevstvo, Kanada, Češka, Turska i Australija). Porast stopa incidencije kod mlađih od 40 godina zabeležen je u četiri zemlje (Holandija, Kanada, Framžncuska i Ujedinjeno Kraljevstvo).

U periodu od 1999-2019. godine u centralnoj Srbiji je prosečna standardizovana stopa mortaliteta (na 100.000) za muškarce iznosila je 7,9, a za žene 5,0. Vrednosti stopa mortaliteta od raka pankreasa u svetu značajno variraju. Najviše stope mortaliteta beleže Zapadna Evropa (8,6 na 100.000 kod muškaraca, i 7,8 kod žena), Severna Amerika (8,0 muškarci i 6,5 žene), Centralna, Istočna i Severna Evropa, Australija i Novi Zeland (17). Više od 50% smrtnih ishoda od raka pankreasa registrovano je u visoko razvijenim zemljama (53,9%, 251.333 smrtna ishoda). Mortalitet od raka pankreasa raste sa uzrastom, skoro 90% smrtnih ishoda je nakon 55 godina starosti. U našoj studiji, najveće vrednosti stopa mortaliteta, kod oba pola, zabeležene se u uzrastu od 70 i više godina. Slične vrednosti stopa incidencije i mortaliteta od raka pankreasa pokazatelji su upravo fatalne prirode ove bolesti (2,18). Procenjuje se da 80-90% pacijenata ima neresektabilni tumor, jer se bolest otkrije tek u uznapredovalom stadijumu. Zbog svoje asimptomatske prirode, rak pankreasa se često otkrije tek tokom obdukcije. Osim toga, trenutni hemioterapijski režimi su često neefikasni za tumore koji se otkriju u uznapredovalom stadijumu (18). Još uvek nema markera za ranu detekciju, pa samim tim ni efikasnih skrining programa, koji bi zasigurno doprineli smanjenju stopa mortaliteta.

U centralnoj Srbiji u periodu 1999-2019. godine se beleži značajan porast standardizovanih stopa mortaliteta od +1,2% godišnje kod muškaraca, dok se kod žena beleži porast od 0,6% godišnje, ali on nije bio značajan. U istraživanju Huang i saradnika (8) u periodu 2008-2017. godine do porasta stopa mortaliteta od raka pankreasa kod muškaraca došlo je u tri evropske zemlje: Rusiji (+0,7%), Španiji (+0,6%), i Nemačkoj (+0,6%). Porast beleže Filipini (+4,2%), Tajland (+4,1%) i Čile (+1,8%). Kad se posmatraju stope mortaliteta kod žena, 14 zemalja je zabeležilo uzlazni trend. Od Evropskih zemalja Malta, Slovačka, i Litvanija imale su najveće vrednosti porasta.

Europe. This difference in incidence rates between different countries is not completely clear, but it may be the consequence of different environmental factors, as well as the exposure to risk factors, such as smoking, dietary factors and obesity (2,4,13,14). Countries with higher incidence and mortality rates had more frequently higher prevalence of smoking, alcohol consumption, physical inactivity, obesity, hypertension and high cholesterol (8). One should also take into consideration the availability of different diagnostic procedures between developed and undeveloped countries, as well as differences regarding the quality of cancer registries. In developed countries, higher incidence may be the result of greater availability of health care and health awareness. Beside, the incidence of pancreatic cancer and related risk factors may be underestimated in regions with lower level of development because the disease is reported less. Lower incidence rates in women may be attributed to the fact that women are less prone to this disease, or are less exposed to environmental factors, or risk factors.

Incidence rates of pancreatic cancer increase with age. The highest incidence in reported in both sexes after the age of 70 (2). However, in the given time period of our study, the highest incidence rate was registered in the age group 60-69 years in men (39.7 per 100,000), while in women the incidence rate was the highest in the group of patients aged 70 and older (25.7 per 100,000). In Canada, 99% of patients were aged 50 and older (15). In China, the highest incidence rate was registered in the group of patients older than 85 in both sexes (men 59.8 per 100,000 and women 47.5 per 100,000) (16).

In the period 1999-2019 in central Serbia, the significant average annual increase of 2.9% was registered in men, and in women it was +3.7%. A similar trend of increase in incidence rates was reported in other countries. Huang et al. (8) analyzed, beside factors related to the occurrence of pancreatic cancer, trends in incidence and mortality rates in 48 countries, in the period 2008-2017. In Europe, nine countries reported the increase of incidence rates in men, and the highest increase was reported in Iceland (AAPC, +8.8%), Cyprus (+5.5%), and France (+4.3%). As far as other regions are concerned, the highest increase is reported by Thailand (+4.5%) and Japan (+1.5%). In women, the increase is reported in 12 European countries, while the highest increase is in Malta (+6.0%), Slovakia (+4.4%) and France (4.2%). Of other countries included in the analysis, the highest increase is in New Zealand (+2.6%), Japan (+1.5%), and South Korea (+1.7%). Only Denmark reported a trend of decrease (-2.4%). In the same study, in the group of people aged 50 and older, the increase in incidence rates was noted in 18 countries, and the highest increase was in Iceland, Malta and France. In people younger than 50, there came to the increase of incidence rates in 8 countries (Germany, Sweden, Holland, United Kingdom, Canada, Czechia, Turkey and Australia). The increase in incidence rates in people younger than 40 was noted in four countries (Holland, Canada, France and United Kingdom).

In the period 1999-2019, in central Serbia, the average standardized mortality rate (per 100,000) was 7.9 for men, and 5.0 for women. The values of mortality rates of pancreatic cancer vary significantly in the world. The highest mortality rates are registered in Western Europe (8.6 per 100,000 in men and 7.8 in women), North America (8.0 men and 6.5 women), Central, Eastern and Northern Europe, Australia and New Zealand (17). More than 50% of deathly outcomes caused by pancreatic cancer were registered in highly developed countries (53.9%, 251,333 deaths). Mortality of pancreatic cancer increases with age, and almost 90% of deaths was after 55 years of age. In our study, the highest mortality rates in both sexes were noted in the age group 70 years and older. Similar values of incidence and mortality rates of pancreatic cancer show the fatal nature of this disease (2,18). It has been estimated that 80-90% of patients have unresectable tumors due to the advanced stage of diagnosis. Due to its asymptomatic nature, pancreatic cancer is often detected only after autopsy. Additionally, the current chemotherapeutic regimen is often ineffective for tumors that are detected at advanced stages (18). There are no markers for early detection, and therefore, no efficient screening programs which would certainly contribute to the decrease in mortality rates.

In central Serbia in the period 1999-2019, a significant annual increase of +1.2% in standardized mortality rates was reported in men, and in women the increase of 0.6% was registered annually, but it was not significant. In the study of Huang and associates (8) in the period 2008-2017, there came to the increase of mortality rates of pancreatic

Najvažniji sredinski faktor rizika za rak pankreasa je pušenje. Pušači imaju skoro dva puta veći rizik da obole od raka pankreasa (3,13,19). Rizik za obolevanje raste sa dužinom pušenja i brojem dnevno popušenih cigareta (19). Prema rezultatima meta-analize relativni rizik za rak pankreasa za sadašnje pušače bio je 1,7, a za bivše 1,2, i ostaje povišen bar 10 godina od prestanka pušenja (20). Da je pušenje značajan faktor u nastanku raka pankreasa pokazuje i studija u Kanadi, gde se sa opadanjem broja pušača beleži značajan pad stope incidencije od -10% godišnje kod muškaraca (15). Kao i kod drugih malignih tumora povezanih sa pušenjem, međunarodne razlike u trendovima mortaliteta odražavaju različitu prevalenciju pušenja. Dok prevalencija pušenja u mnogima razvijenim zemljama opada, s druge strane ostaje visoka ili raste među ženama i u zemljama u razvoju. Prema podacima Nacionalnog istraživanja o zdravlju stanovništva u Republici Srbiji u 2019. godini, izloženost duvanskom dimu u Srbiji je visoka. Prevalencija navike pušenja duvanskih proizvoda (svakodnevno ili povremeno), u populaciji uzrasta 15 i više godina, iznosila je 31,9% (21). Nešto veći procenat pušača zabeležen je kod muškaraca (33,9%) nego kod žena (30,1%).

Osim pušenja, u populaciji Srbije rasprostanjeni su i drugi značajni faktori rizika za rak pankreasa. Konzumiranje alkohola je značajan faktor rizika za rak pankreasa (2,3). Alkohol konzumira 49,3% stanovnika Srbije, više muškaraca (65,0%), nego žena (35,2%) (21). Konzumiranje hrane bogate mastima povećava rizik od raka pankreasa, kao i prekomerna telesna težina i gojaznost (2). U Srbiji je 2019. godine, na osnovu ideksa telesne mase više od polovine (57,1%) stanovništva uzrasta 15 i više godina bilo prekomerno uhranjeno, odnosno predgojazno (36,3%) i gojazno (20,8%) (21). Prevalencija gojaznosti u Srbiji se neznatno razlikovala u odnosu na 2013. godinu (21,2%), ali je značajno veća u odnosu na 2006. godinu (17,3%). Osim toga, svakodnevno je povrće konzumiralo 50,2% stanovnika, a voće 39,4%. Skoro dve trećine stanovništva (64,6%) starosti od 18 do 64 godine ispunjavalo je preporuke Svetske zdravstvene organizacije za izvođenje fizičke aktivnosti koja utiče na poboljšanje zdravlja. Prema istom istraživanju 7,8% ispitanika navelo je da ima dijabetes, koji takođe predstavlja rizik za nastanak raka pankreasa (21).

Prema našim rezultatima uočava se da su stope incidencije niže u odnosu na stope mortaliteta. Slično je zabeleženo i u istraživanju koje je obuhvatilo period 1960-2003. godine u Švedskoj (22). To se može pripisati niskoj specifičnosti prijavljenih umrlih. Moguće je i da je izvestan broj smrtnih slučajeva pogrešno klasifikovan kao primarni rak pankreasa. Pretpostavlja se da je to zato što oboljenje nije dijagnostikovano za vreme života pacijenta, ali se prepoznalo kao uzrok smrti na obdukciji, ili bolest nije prijavljena Registru za rak. Međutim, poslednjih godina kod nas se primećuje da je broj obolelih veći od broja umrlih, što možda govori u prilog tome da se ovo oboljenje ranije dijagnostikuje i uspešnije leči nego na početku ispitivanog perioda.

Jedan od nedostataka studije mogao bi da bude i sam kvalitet podataka u registrima za rak, pre svega zbog težine postavljanja dijagnoze ovog oboljenja. Podaci o stadijumu tumora, kao i o njegovoj veličini u trenutku dijagnoze nisu dostupni. Porast stopa incidencije mogao bi da bude posledica i boljih mogućnosti za dijagnostiku koje su se vremenom razvijale. Dodatne epidemiološke studije, koje bi uključile i identifikaciju faktora rizika, kao što su pušenje, konzumiranje alkohola, fizička aktivnost i gojaznost u budućnosti bile bi značajne.

Zaključak

U centralnoj Srbiji u periodu 1999-2019. godine stope incidencije i mortaliteta su u porastu kod oba pola. U cilju redukcije umiranja akcenat treba staviti na ranom otkrivanju poremećaja zdravlja (skriningu), kao i blagovremenom lečenju primenom savremenih terapija. Neophodna su dalja istraživanja za identifikaciju potencijalnih faktora rizika za nastanak ove bolesti. U cilju prevencije nastanka ove bolesti neophodna je edukacija stanovništva o zdravim stilovima života. U budućnosti bi trebalo raditi na edukaciji lekara i starijeg stanovništva o prevenciji, simptomima i poboljšanju primarne zdravstvene zaštite u gerijatrijskom dobu.

Konflikt interesa

Autori su izjavili da nema konflikta interesa.

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cancer in men in three European countries: Russia (+0.7%), Spain (+0.6%) and Germany (+0.6%). The increase was reported in the Philippines (+4.2%), Thailand (+4.1%) and Chile (+1.8%). As for the mortality rates in women, 14 countries registered increasing mortality trends. Of the European countries, Malta, Slovakia, and Lithuania had the highest values of increase.

Smoking is the most important environmental risk for pancreatic cancer. The risk of getting pancreatic cancer is about twice as high among people who smoke (3,13,19). The risk of getting the disease increases with smoking duration and the number of cigarettes smoked per day (19). According to the results of meta-analysis, the relative risk of getting pancreatic cancer for current smokers was 1.7, and 1.2 for ex-smokers, and it stayed elevated at least 10 years after they quit smoking (20). A study in Canada showed that smoking was a significant factor for pancreatic cancer, where the decrease in the number of smokers was correlated with the decrease in incidence rates of -10% annually in men (15). As in other malignant tumors associated with smoking, international differences in mortality trends reflect different prevalence of smoking. While the prevalence of smoking decreases in many developed countries, it remains high or increases among women or in developing countries. According to the data of the National research on the population health in the Republic of Serbia in 2019, the exposure to tobacco smoking (every day or occasionally), in the population aged 15 years and older, amounted to 31.9% (21). Higher percentage of smokers was registered in men (33.9%) in comparison to women (30.1%).

In addition to smoking, in the population of Serbia, there are other significant risk factors for pancreatic cancer. Alcohol consumption is a significant risk factor for pancreatic cancer (2,3). Alcohol is consumed by 49.3% of population in Serbia, more by men (65.0%) than by women (35.2%) (21). Consuming food rich in fats increases the risk of pancreatic cancer, as well as overweight and obesity (2). In 2019, in Serbia, according to the body mass index, more than half of the people aged 15 and more were overweight (57.1%), pre-obese (36.3%) and obese (20.8%) (21). The prevalence of obesity in Serbia was slightly different in comparison to 2013 (21.2%), but it was significantly higher in comparison to 2006 (17.3%). Additionally, 50.2% of residents consumed vegetables every day, and 39.4% consumed fruit. Almost two thirds of the population (64.6%) aged 18 to 64 years satisfied the recommendations of the World Health Organization for doing physical activity which improves health. According to the same study, 7.8% of participants reported to have diabetes, which is also a risk factor for pancreatic cancer (21).

According to our results, incidence rates were lower than mortality rates. Similar findings were noted in the study which included the period 1960-2003 in Sweden (22). This may be attributed to the low specificity of reported deaths. It is possible that a certain number of deaths were wrongly classified as a primary pancreatic cancer. It is assumed that this happens because the disease was not diagnosed during patient's lifetime, but was recognized as a cause of disease during autopsy, or the disease was not reported to the Cancer Registry. However, in recent years it has been noted that the number of new cases is higher than the number of deaths, which possibly speaks in favor of the fact that this disease is diagnosed earlier and treated more successfully than at the beginning of the examined period.

One of the weaknesses of this study may be the quality of data in Cancer Registries, first of all, because the disease is hard to be diagnosed. The data about tumor stages, as well as about its size at the moment of diagnosis are not available. The increase in incidence rates may be the consequence of better diagnostic possibilities that have developed over time. Additional epidemiological studies, which would include the identification of risk factors, such as smoking, alcohol consumption, physical inactivity and obesity, would be significant in the future.

Conclusion

In the period 1999-2019 in central Serbia, incidence and mortality rates increased in both genders. The accent should be put on the early detection of disorders (screening), and on timely treatment using modern therapies, which is aimed at the reduction of dying. Further research is necessary for the identification of risk factors for the occurrence of this disease. The education of population about healthy lifestyles is necessary in order to prevent this disease. In the future,

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education of physicians and older residents about prevention, symptoms and the improvement of primary health care of the elderly should be encouraged.

Competing interests

The authors declare no competing interests.

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EPIDEMIOLOŠKE KARAKTERISTIKE SALMONELOZA U POPULACIJI BEOGRADA ZA PERIOD 1994-2013. GODINE

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SAŽETAK

Uvod/Cilj: Procenjuje se da prijavljeni slučajevi salmoneloze širom sveta predstavljaju samo 1-10% realne učestalosti ove bolesti. Cilj istraživanja je bio da se analiziraju epidemiološke karakteristike salmoneloza u populaciji Beograda za period od 1994. do 2013. godine.
Metode: Podaci o broju obolelih od salmoneloza po polu, uzrastu i opštinama, za navedeni period su preuzeti iz Gradskog zavoda za javno zdravlje Beograd i računate su opšte, uzrasno-specifične i standardizovane stope incidencije. Za procenu trenda incidencije korišćena je *joinpoint* regresiona analiza.
Rezultati: U posmatranom dvadesetogodišnjem periodu registrovana su 12.452 obolela od salmoneloza, a ženski pol je bio više zastupljen (53,5%) u odnosu na muški (46,5%). Kod oba pola najviše prosečne uzrasno-specifične stope incidencije za posmatrani period su bile u uzrasnoj grupi 0-4 godine, a najniže kod osoba starih 70 i više godina. Prema rezultatima joinpoint regresione analize kod muškaraca postoji značajan pad incidencije od uzrasne grupe 15-19 godina pa na dalje, a kod žena od uzrasne grupe 10-14 godina. U periodu od 1994. do 2013. godine, prosečna standardizovana stopa incidencije za salmoneloze (na 100.000) u populaciji Beograda bila je 61,6 (61,7 za muškarce i 61,4 za žene). Najčešći serotipovi salmonela izolovanih iz humanog materijala bili su *S. enteritidis* (81,6%), *S. typhimurium* (7,7%) i *S. infantis* (2,6%).
Zaključak: Trend opadanja salmoneloza, zapažen u našoj studiji, govori o boljoj kontroli uzgoja na farmama, proizvodnje i prometa mesa i primeni higijensko-sanitarnih mera u ovim procesima i sve zastupljenijoj primeni HACCP standarda za zdravstvenu bezbednost hrane u Beogradu.

Ključne reči: salmoneloze, incidencija, trend, joinpoint regresija, serotipovi salmonela

Uvod

Salmonella je vodeći uzročnik akutnog bakterijskog gastroenteritisa širom sveta. Procenjuje se da oko 55% slučajeva ima veze sa trovanjem hranom, 14% sa putovanjem, 13% sa životnom sredinom, 9% sa direktnim ljudskim kontaktom i 9% sa direktnim kontaktom sa životinjom (1,2).

Procenjuje se da u Sjedinjenim Američkim Državama ima oko milion slučajeva salmoneloza godišnje, što dovodi do otprilike 19.000 hospitalizacija i 370 smrtnih ishoda (3). U Evropskoj uniji, 6,2 miliona ljudi oboli svake godine (4), u Africi taj broj iznosi 2,5 miliona sa 4.100 smrtnih ishoda (5). Smatra se da je stvaran broj slučajeva salmoneloza veći, s obzirom da se mnogi slučajevi sa blagom atipičnom formom bolesti ne registruju. Procenjuje se da prijavljeni slučajevi čine 1-10% stvarne učestalosti ove bolesti (6). Iako velike epidemije salmoneloze obično privlače pažnju medija, 60-80% svih slučajeva salmoneloza se klasifikuju kao pojedinačni slučajevi (7).

Rezultati praćenja laboratorijski potvrđenih infekcija 2010. godine, koje su činile 15% stanovništva Sjedinjenih Američkih Država, pokazali su da su ove infekcije najčešće prijavljivane, sa incidencijom od 17,6 na 100.000 stanovnika. Incidencija je bila najveća kod dece mlađe od 5 godina (69,5 na

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EPIDEMIOLOGICAL CHARACTERISTICS OF SALMONELLOSIS IN THE POPULATION OF BELGRADE FOR THE PERIOD 1994-2013

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SUMMARY

Background/Aim: The registered salmonella cases are estimated to constitute 1-10% of the real frequency of this disease. The aim of the research was to analyze epidemiological salmonella characteristics in Belgrade population for the period 1994-2013.
Methods: The data on the number of salmonella cases regarding gender, age and municipalities for the given period were taken from the City Institute of Public Health in Belgrade and used to calculate crude, age-specific and standardized incidence rates were used. For estimating the incidence trend joinpoint regression analysis was used.
Results: In the given 20-year period there were 12,452 salmonellosis cases, and female infected persons were more present (53.5%) than males (46.5%). In both sexes, the highest average age-specific rates were found in age group 0-4, and the lowest for people age 70 and older. According to joinpoint regression analysis there is a significant incidence decline in men from the age group 15-19 and further on, while in women that decline starts with the age group 10-14. The average standardized salmonellosis incidence rate (per 100,000) was 61.6 (61.7 for men and 61.4 for women). The most frequent *Salmonella* serotypes isolated from human material were *S. enteritidis* (81.6%), *S. typhimurium* (7.7%) and *S. infantis* (2.6%).
Conclusion: The decline in salmonellosis noticed in our study suggests better farming control, better control of meat production and turnover and application of hygienic and sanitary measures in these processes as well as the greater presence of the HACCP standard for the health safety of food in Belgrade.

Keywords: salmonellosis, incidence, trend, joinpoint regression, *salmonella* serotypes

Introduction

Salmonella is the leading cause of acute bacterial gastroenteritis across the world. It is estimated that about 55% of the cases has to do with food poisoning, 14% with travelling, 13% with environmental sources, 9% with direct human contact and 9% with direct contact with an animal (1,2).

It is estimated that in the USA there are about one million *Salmonella* cases per year, leading to around 19,000 hospitalizations and 370 fatalities (3). Within the European Union, there are 6.2 million of people every year (4), in Africa the number is 2.5 million with 4,100 fatalities (5). The real number of salmonella cases is considered to be larger, as many mild cases are not registered. The registered cases are estimated to constitute 1-10% of the real frequency of this disease (6). Very large salmonella epidemics tend to draw media attention, 60-80% of cases are considered to be isolated (7).

The results of the laboratory confirmed infections monitoring in 2010 comprising 15% of the US population, showed that these infections were the most frequently reported ones, with the incidence of 17.6 per 100,000 persons. The incidence was the largest in children under 5 (69.5 per 100,000 children), and only 5% of the reported cases were associated with epidemic outbreaks. The incidence was significantly higher in 2010 (10%) than in the period 2006-2008. The same

100.000 dece), a samo 5% prijavljenih slučajeva je bilo povezano za epidemijom. Incidencija je bila značajno viša 2010. godine (10%) nego u periodu 2006-2008. Iste godine, serotipovi *Salmonella enteritidis* (22%), *Salmonella Newport* (14%) i *Salmonella typhimurium* (13%) izolovani su kao najčešći (8). U periodu 1998-2008. godine u Sjedinjenim Američkim Državama registrovana je 1.491 epidemija salmoneloze.

Najčešći uzročnici ovih epidemija bila su 4 serotipa salmonela: *Salmonella enteritidis*, *Salmonella typhimurium*, *Salmonella Newport* i *Salmonella Heidelberg* (9). U periodu od 2008. do 2012. godine, u okviru Evropske unije, registrovan je značajan pad incidencije salmoneloza (32%) (10).

U skladu sa navedenim trendovima, cilj ovog istraživanja je bio da se analiziraju epidemiološke karakteristike salmoneloza u populaciji Beograda za period od 1994. do 2013. godine.

Metode

U istraživanju je korišćena deskriptivna epidemiološka studija. Podaci o broju obolelih od salmoneoza po polu, uzrastu i opštinama za navedeni vremenski period preuzeti su iz Gradskog zavoda za javno zdravlje Beograd. Individualno prijavljivanje zarazne bolesti korišćeno je kao izvor podataka o broju obolelih od salmoneloza. Svi oboleli su bili laboratorijski potvrđeni slučajevi. Podaci o serotipu salmoneloza iz humanog materijala na teritoriji Beograda preuzeti su iz Nacionalne referentne laboratorije za salmonelu (Institut za javno zdravlje Srbije „Dr Milan Jovanović Batut“). Podaci o serotipovima salmonela iz namirnica i iz biološkog materijala kliconoša dobijeni su iz mikrobiološke laboratorije Gradskog zavoda za javno zdravlje. Podaci o smrtnim ishodima od salmoneloza za period od 1994. do 2013. godine preuzeti su iz Gradskog zavoda za javno zdravlje.

Tabela 1. Uzrasno-specifične stope incidencije (na 100.000) za salmonelozu, muškarci, Beograd, 1994-2013.

	Uzrasne grupe									
Godina	**0-4**	**5-9**	**10-14**	**15-19**	**20-29**	**30-39**	**40-49**	**50-59**	**60-69**	**≥70**
1994.	292,1	118,4	66,5	67,8	35,5	19,2	19,2	21,9	25,4	10,0
1995.	247,4	132,3	73,9	73,6	43,6	27,5	22,1	23,8	11,5	4,3
1996.	247,4	108,6	73,9	36,8	37,5	18,4	13,5	10,5	19,1	2,9
1997.	216,8	45,4	35,1	23,2	23,3	17,5	18,3	12,4	12,7	2,9
1998.	268,6	73,0	25,9	42,6	35,5	25,9	29,8	13,3	17,8	11,4
1999.	216,8	79,0	40,7	32,9	39,5	25,9	27,9	5,7	16,5	5,7
2000.	296,9	167,8	42,5	42,6	37,5	27,5	32,7	17,1	25,4	15,7
2001.	209,7	55,3	12,9	27,1	28,4	8,4	17,3	22,8	17,8	5,7
2002.	307,7	101,6	53,4	38,6	29,8	10,0	16,4	20,0	5,8	9,1
2003.	584,1	304,9	62,7	46,4	59,6	36,1	51,8	35,0	22,1	12,1
2004.	496,6	149,9	62,7	44,4	31,6	25,1	12,1	24,0	5,8	16,6
2005.	319,1	142,3	39,5	9,7	19,9	16,1	12,1	10,0	10,5	15,1
2006.	216,5	55,9	30,2	17,4	26,2	16,1	10,4	12,0	9,3	1,5
2007.	247,9	96,6	25,5	25,1	23,5	19,1	4,3	24,0	17,4	0
2008.	205,1	48,3	11,6	13,5	11,7	3,0	7,8	11,0	4,6	1,5
2009.	267,8	129,6	25,5	15,5	22,6	13,1	6,0	11,0	4,6	7,6
2010.	242,2	73,7	7,0	9,7	8,1	9,0	3,5	5,0	5,8	1,5
2011.	254,0	130,6	5,3	64,6	30,9	16,7	14,3	9,6	6,9	3,7
2012.	223,2	77,9	16,0	20,8	20,9	18,3	5,7	7,0	11,5	9,9
2013.	194,7	120,6	31,9	18,4	16,4	7,2	3,8	6,1	3,5	3,7
Prosek za 1994-2013.	268,3	112,8	40,1	36,8	27,4	17,4	16,6	15,0	11,9	6,9

year, serotypes *S. enteritidis* (22%), *S. Newport* (14%) and *S. typhimurium* (13%) were isolated as the most frequent ones (8). In the period 1998-2008 in the USA 1491 salmonella epidemics were registered.

The most frequent causes of these epidemics were 4 serotypes of salmonella: *S. enteritidis*, *S. typhimurium*, *S. Newport* and *S. Heidelberg* (9). In the period 2008 -2012, within the EU, a significant decline in *Salmonella* incidence (32%) was registered (10).

According to the mentioned trends, the aim of the research was to analyze epidemiological *salmonella* characteristics in Belgrade population for the period 1994-2013.

Methods

The research used descriptive epidemiological study. The data on the number of salmonella cases regarding gender, age and municipalities for the given period were taken from the City Institute of Public Health in Belgrade. Individual registrations of the contagious disease were used as a data source on the number of the cases of salmonellosis. All the infected were laboratory confirmed cases. The data on salmonella serotypes from human material on the territory of Belgrade were taken from the National reference salmonella laboratory (the Institute of Public Health of Serbia „Dr Milan Jovanović Batut“). The data on salmonella from food and bio material of the carriers were provided by microbiological laboratory of the City Institute of Public Health. The data on salmonellosis fatalities in the period 1994-2013 were taken from the City Institute of Public Health.

In the analysis, crude, age-specific and standardized incidence rates were used. As the nominator for counting incidence rates, the census data for 1991 (for the period 1994-2001), 2002 (for the period 2002-2010) and 2011 (for the period 2011-2013) were used. Standardized incidence rates were calculated using the method

Table 1. Age-specific incidence rates (per 100,000) for salmonellosis, men, Belgrade, 1994-2013

	Age groups									
Year	**0-4**	**5-9**	**10-14**	**15-19**	**20-29**	**30-39**	**40-49**	**50-59**	**60-69**	**≥70**
1994	292.1	118.4	66.5	67.8	35.5	19.2	19.2	21.9	25.4	10.0
1995	247.4	132.3	73.9	73.6	43.6	27.5	22.1	23.8	11.5	4.3
1996	247.4	108.6	73.9	36.8	37.5	18.4	13.5	10.5	19.1	2.9
1997	216.8	45.4	35.1	23.2	23.3	17.5	18.3	12.4	12.7	2.9
1998	268.6	73.0	25.9	42.6	35.5	25.9	29.8	13.3	17.8	11.4
1999	216.8	79.0	40.7	32.9	39.5	25.9	27.9	5.7	16.5	5.7
2000	296.9	167.8	42.5	42.6	37.5	27.5	32.7	17.1	25.4	15.7
2001	209.7	55.3	12.9	27.1	28.4	8.4	17.3	22.8	17.8	5.7
2002	307.7	101.6	53.4	38.6	29.8	10.0	16.4	20.0	5.8	9.1
2003	584.1	304.9	62.7	46.4	59.6	36.1	51.8	35.0	22.1	12.1
2004	496.6	149.9	62.7	44.4	31.6	25.1	12.1	24.0	5.8	16.6
2005	319.1	142.3	39.5	9.7	19.9	16.1	12.1	10.0	10.5	15.1
2006	216.5	55.9	30.2	17.4	26.2	16.1	10.4	12.0	9.3	1.5
2007	247.9	96.6	25.5	25.1	23.5	19.1	4.3	24.0	17.4	0
2008	205.1	48.3	11.6	13.5	11.7	3.0	7.8	11.0	4.6	1.5
2009	267.8	129.6	25.5	15.5	22.6	13.1	6.0	11.0	4.6	7.6
2010	242.2	73.7	7.0	9.7	8.1	9.0	3.5	5.0	5.8	1.5
2011	254.0	130.6	5.3	64.6	30.9	16.7	14.3	9.6	6.9	3.7
2012	223.2	77.9	16.0	20.8	20.9	18.3	5.7	7.0	11.5	9.9
2013	194.7	120.6	31.9	18.4	16.4	7.2	3.8	6.1	3.5	3.7
Average for 1994-2013	268.3	112.8	40.1	36.8	27.4	17.4	16.6	15.0	11.9	6.9

Tabela 2. Uzrasno-specifične stope incidencije (na 100.000) za salmonelozu, žene, Beograd, 1994-2013.

	Uzrasne grupe									
Godina	**0-4**	**5-9**	**10-14**	**15-19**	**20-29**	**30-39**	**40-49**	**50-59**	**60-69**	**≥70**
1994.	281,6	96,5	68,8	63,8	43,0	36,7	37,5	19,8	25,1	12,0
1995.	239,6	94,4	60,9	51,8	88,9	54,3	62,8	26,2	26,2	9,6
1996.	234,6	98,6	76,6	53,8	48,8	34,4	30,5	19,8	13,6	12,0
1997.	180,3	41,9	31,4	33,9	28,3	34,4	35,8	18,9	18,8	4,8
1998.	219,8	81,8	31,4	39,9	35,2	27,6	37,5	24,4	29,3	14,4
1999.	187,7	41,9	29,5	35,9	51,8	42,1	54,9	26,2	25,1	18,0
2000.	298,9	136,3	49,1	71,8	68,4	54,3	77,6	35,2	20,9	8,4
2001.	209,9	71,3	19,7	31,9	35,2	25,3	38,4	28,9	20,9	15,6
2002.	351,1	67,1	22,1	36,3	42,1	28,8	26,7	28,4	13,8	9,3
2003.	564,2	284,6	36,8	54,4	64,9	69,6	70,1	56,8	28,6	18,7
2004.	435,1	142,3	73,5	46,3	38,6	30,6	32,0	39,6	11,8	10,4
2005.	300,1	80,6	34,3	38,3	28,9	15,8	25,2	20,7	10,8	14,5
2006.	156,1	51,0	12,3	2,0	10,5	23,2	25,2	26,7	6,9	5,2
2007.	273,1	77,9	17,2	24,2	23,7	23,2	11,4	22,4	27,6	0
2008.	207,1	34,9	9,8	14,1	14,9	23,2	13,7	15,5	6,9	3,1
2009.	243,1	96,7	22,1	14,1	22,8	12,1	10,7	15,5	9,9	4,1
2010.	240,1	77,9	22,1	8,1	12,3	12,1	8,4	15,5	5,9	4,1
2011.	235,3	74,3	5,6	43,7	31,8	24,3	27,3	15,7	11,0	13,5
2012.	177,7	74,3	14,1	14,6	22,1	19,0	22,9	16,4	7,4	7,6
2013.	145,2	124,8	25,3	4,9	14,5	9,9	15,0	14,2	3,7	3,4
Prosek za 1994-2013.	250,5	93,0	35,4	36,2	35,5	30,0	33,4	23,3	15,7	9,1

U analizi su korišćene opšte, uzrasno-specifične i standardizovane stope incidencije. Za imenilac prilikom računanja stopa incidencije korišćeni su podaci iz popisa stanovništva za 1991. godinu (za period 1994-2001.), za 2002. (za period 2002-2010.) i za 2011. (za period 2011-2013.). Standardizovane stope incidencije su računate uz pomoć metoda direktne standardizacije, gde je populacija sveta po Segiju korišćena kao standardna populacija (11). Za procenu trenda incidencije korišćena je joinpoint regresiona analiza (*Joinpoint Regression Program, Version 4.0.4. May 2013; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute*), prema metodi Kima i saradnika (12). Uz pomoć ove analize, procenjena je prosečna procentualna godišnja promena trenda i identifikovani su periodi u vremenu kada su se značajne promene desile. Za svaku procentualnu godišnju promenu, izračunati su 95% intervali poverenja, i pomoću njih je utvrđeno da li je promena u svakom segmentu značajno različita od nule (nula označava da nije bilo promena u trendu).

Rezultati

U Beogradu u periodu od 1994. do 2013. godine, prosečni udeo obolelih od salmoneloza bio je 18,7% od svih obolelih od gastrointestinalnih zaraznih bolesti. U datom dvadesetogodišnjem periodu registrovana su 12.452 obolela od salmoneloza, a ženski pol je bio više zastupljen (53,5%) u odnosu na muški (46,5%).

Uzrasno-specifične stope incidencije (na 100.000) za salmonelozu u Beogradu, za period 1994-2013. godine prikazane su u tabeli 1 za muškarce i tabeli 2 za žene. Kod oba pola, najviše prosečne uzrasno-specifične stope incidencije bile su u uzrasnoj grupi 0-4 godine, a najniže kod osoba starih 70 i više godina.

Prema rezultatima *joinpoint* regresione analize, kod muškaraca postoji značajan pad incidencije kod uzrasne grupe 15-19 godina pa na dalje, a

Table 2. Age-specific incidence rates (per 100,000) for salmonellosis, women, Belgrade, 1994-2013

	Age groups									
Year	**0-4**	**5-9**	**10-14**	**15-19**	**20-29**	**30-39**	**40-49**	**50-59**	**60-69**	**≥70**
1994	281.6	96.5	68.8	63.8	43.0	36.7	37.5	19.8	25.1	12.0
1995	239.6	94.4	60.9	51.8	88.9	54.3	62.8	26.2	26.2	9.6
1996	234.6	98.6	76.6	53.8	48.8	34.4	30.5	19.8	13.6	12.0
1997	180.3	41.9	31.4	33.9	28.3	34.4	35.8	18.9	18.8	4.8
1998	219.8	81.8	31.4	39.9	35.2	27.6	37.5	24.4	29.3	14.4
1999	187.7	41.9	29.5	35.9	51.8	42.1	54.9	26.2	25.1	18.0
2000	298.9	136.3	49.1	71.8	68.4	54.3	77.6	35.2	20.9	8.4
2001	209.9	71.3	19.7	31.9	35.2	25.3	38.4	28.9	20.9	15.6
2002	351.1	67.1	22.1	36.3	42.1	28.8	26.7	28.4	13.8	9.3
2003	564.2	284.6	36.8	54.4	64.9	69.6	70.1	56.8	28.6	18.7
2004	435.1	142.3	73.5	46.3	38.6	30.6	32.0	39.6	11.8	10.4
2005	300.1	80.6	34.3	38.3	28.9	15.8	25.2	20.7	10.8	14.5
2006	156.1	51.0	12.3	2.0	10.5	23.2	25.2	26.7	6.9	5.2
2007	273.1	77.9	17.2	24.2	23.7	23.2	11.4	22.4	27.6	0
2008	207.1	34.9	9.8	14.1	14.9	23.2	13.7	15.5	6.9	3.1
2009	243.1	96.7	22.1	14.1	22.8	12.1	10.7	15.5	9.9	4.1
2010	240.1	77.9	22.1	8.1	12.3	12.1	8.4	15.5	5.9	4.1
2011	235.3	74.3	5.6	43.7	31.8	24.3	27.3	15.7	11.0	13.5
2012	177.7	74.3	14.1	14.6	22.1	19.0	22.9	16.4	7.4	7.6
2013	145.2	124.8	25.3	4.9	14.5	9.9	15.0	14.2	3.7	3.4
Average for 1994-2013	250.5	93.0	35.4	36.2	35.5	30.0	33.4	23.3	15.7	9.1

of direct standardization, where the population of the world by Segi was used as the standard population (11). For estimating the incidence trend joinpoint regression analysis was used (Joinpoint Regression Program, Version 4.0.4. May 2013; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute), according to the method by Kim et al. (12). Using this analysis, the average annual percentage trend change was estimated and the time intervals of important changes were identified. For every percentage of annual change, the 95% trust intervals were calculated, and using them it was established whether the change in every segment is significantly different from zero (zero means no change in trend).

Results

In Belgrade in the period 1994-2013 the average part that salmonellosis cases formed in all intestinal contagious disease cases was 18.7%. In the given 20-year period there were 12,452 salmonellosis cases, and female infected persons were more present (53.5%) than male (46.5%).

Age-specific incidence rates (per 100,000) for salmonellosis in Belgrade, for the period 1994-2013 are given in Table 1 for men and in Table 2 for women. In both sexes, the highest average age-specific rates were found in age group 0-4, and the lowest for people age 70 and older.

According to joinpoint regression analysis there is a significant incidence decline in men from the age group 15-19 and further on, while in women that decline starts with the age group 10-14 (Table 3). In men, a significant incidence decline was registered in the age group 10-14, but only in the period 1994-2001 and 2004-2011, and in women in the age group 0-4 only in the period 2003-2013.

In the period 1994-2013 the average standardized salmonellosis incidence rate in Belgrade (per 100,000) was 61.6 (61.7 for men and 61.4 for women) (Table 4).

In the period 1994-2013 there has been a decline in standardized salmonellosis incidence rates in total

Tabela 3. Trendovi uzrasno-specifičnih stopa incidencije za salmonelozu prema *joinpoint* regresionoj analizi, muškarci i žene, Beograd, 1994-2013.

Muškarci					Žene				
Uzrasne grupe	Period	APC	Niži od 95% IP	Viši od 95% IP	Uzrasne grupe	Period	APC	Niži od 95% IP	Viši od 95% IP
0-4	1994-2000.	-3,6	-9,2	-9,2	**0-4**	1994-2003.	6,1	-0,9	13,5
	2000-2003.	33,5	-6,5	-6,5		2003-2013.	-6,9*	-12,1	-1,3
	2003-2006.	-22,1	-45,4	-45,4	**5-9**	1994-2013.	-0,1	-4,0	4,0
	2006-2013.	-1,5	-6,1	-6,1	**10-14**	1994-2013.	-7,9*	-11,6	-4,0
5-9	1994-2013.	-0,1	-0,1	-4,0	**15-19**	1994-2013.	-9,6*	-14,8	-4,0
10-14	1994-2001.	-15,0*	-15,0*	-27,7	**20-29**	1994-2013.	-6,7*	-9,9	-3,4
	2001-2004.	41,7	41,7	-57,6	**30-39**	1994-2013.	-6,2*	-8,9	-3,4
	2004-2011.	-29,3*	-29,3*	-42,3	**40-49**	1994-2013.	-7,1*	-10,6	-3,5
	2011-2013.	135.5	135.5	-29,6	**50-59**	1994-2003.	7,1*	1,9	12,5
15-19	1994-2013.	-5,7*	-5,7*	-9,6		2003-2013.	-10,2*	-13,9	-6,4
20-29	1994-2013.	-4,8*	-4,8*	-7,6	**60-69**	1994-2013.	-7,6*	-10,7	-4,4
30-39	1994-2013.	-4,5*	-4,5*	-8,5	**≥70**	1994-2013.	-6,8	-14,7	1,9
40-49	1994-2013.	-8,8*	-8,8*	-12,7					
50-59	1994-2013.	-4,2*	-4,2*	-8,1					
60-69	1994-2013.	-6,9*	-6,9*	-10,4					
≥70	1994-2013.	-4,8	-4,8	-13,6					

APC - *Annual percent change*; 95% IP - 95% interval poverenja

kod žena taj pad počinje od uzrasne grupe 10-14 godina (tabela 3). Kod muškaraca, značajan pad incidencije registrovan je u uzrasnoj grupi 10-14 godina, ali samo u periodu 1994-2001. i 2004-2011. godine, dok je kod žena taj pad registrovan u uzrasnoj grupi 0-4 samo u periodu 2003-2013. godine.

U periodu od 1994. do 2013. godine, prosečna standardizovana stopa incidencije salmoneloza u Beogradu (na 100.000) bila je 61,6 (61,7 za muškarce i 61,4 za žene) (tabela 4).

U periodu od 1994. do 2013. godine došlo je do pada standardizovanih stopa incidencije salmoneloza u opštoj populaciji i prema polu, ali je značajan pad registrovan samo kod žena (slika 1).

U periodu od 1994. do 2013. godine u Beogradu, pet najčešćih serotipova salmonela izolovanih iz humanog materijala bili su *S. enteritidis* (81,6%), *S. typhimurium* (7,7%), *S. infantis* (2,6%), *S. hadar* (1,8%) i *S. agona* (0,6%). Ovih pet serotipova salmonela činili su 94,3% svih salmoneloza izolovanih iz humanog materijala.

U periodu od 1994. do 2013. godine u laboratoriji za sanitarnu mikrobiologiju Gradskog zavoda za javno zdravlje, u okviru redovnog nadzora, mikrobiološka analiza je uključila 151.129 prehrambenih namirnica na teritoriji Beograda, a salmonella je izolovana u 295 (0,2%).

Najćešće izolovan serotip bila je *S. enteritidis* sa 146 izolata (49,8%), *S. infantis* sa 34 izolata (11,6%) bila je na drugom mestu, zatim slede *S. typhimurium* sa 28 izolata (9,6%), *S.hadar* sa 11 izolata (3,8%) i *S. agona* sa 8 izolata (2,7%).

Salmonella (laboratorija za sanitarnu mikrobiologiju Gradskog zavoda za javno zdravlje) je najčešće bila prisutna u pilećem mesu (49,2%), zatim u tortama i kolačima (8,8%), svinjskom mesu (5,1%), sladoledu (3,1%), ruskoj salati i svinjetini (2,7%).

Prosečna opšta stopa mortaliteta za salmonelozu u Beogradu za period od 1994. godine do 2013. godine bila je 0,06 na 100.000 stanovnika.

Diskusija

Prema našim rezultatima, slučajevi salmoneloza činili su 18,7% svih slučajeva intestinalnih zaraznih bolesti u Beogradu u periodu od 1994. do 2013. godine, dok su u Kantonu Sarajevo ovi slučajevi imali mnogo manji udeo, 11,2% u periodu od 2005. do 2009. godine (13), a u Durham regiji u Kanadi ovi slučajevi imali su veći udeo, jednu čet-

Table 3. Trends of age-specific incidence rates for salmonellosis according to the joinpoint regression analysis, men and women, Belgrade, 1994-2013

Muškarci					Žene				
Age	Period	APC	Lower 95% IP	Higher 95% IP	Age	Period	APC	Lower 95% IP	Higher 95% IP
0-4	1994-2000	-3.6	-9.2	-9.2	**0-4**	1994-2003	6.1	-0.9	13.5
	2000-2003	33.5	-6.5	-6.5		2003-2013	-6.9*	-12.1	-1.3
	2003-2006	-22.1	-45.4	-45.4	**5-9**	1994-2013	-0.1	-4.0	4.0
	2006-2013	-1.5	-6.1	-6.1	**10-14**	1994-2013	-7.9*	-11.6	-4.0
5-9	1994-2013	-0.1	-0.1	-4.0	**15-19**	1994-2013	-9.6*	-14.8	-4.0
10-14	1994-2001	-15.0*	-15.0*	-27.7	**20-29**	1994-2013	-6.7*	-9.9	-3.4
	2001-2004	41.7	41.7	-57.6	**30-39**	1994-2013	-6.2*	-8.9	-3.4
	2004-2011	-29.3*	-29.3*	-42.3	**40-49**	1994-2013	-7.1*	-10.6	-3.5
	2011-2013	135.5	135.5	-29.6	**50-59**	1994-2003	7.1*	1.9	12.5
15-19	1994-2013	-5.7*	-5.7*	-9.6		2003-2013	-10.2*	-13.9	-6.4
20-29	1994-2013	-4.8*	-4.8*	-7.6	**60-69**	1994-2013	-7.6*	-10.7	-4.4
30-39	1994-2013	-4.5*	-4.5*	-8.5	**≥70**	1994-2013	-6.8	-14.7	1.9
40-49	1994-2013	-8.8*	-8.8*	-12.7					
50-59	1994-2013	-4.2*	-4.2*	-8.1					
60-69	1994-2013	-6.9*	-6.9*	-10.4					
≥70	1994-2013	-4.8	-4.8	-13.6					

APC - Annual percent change; 95% CI - 95% confidence interval

population and regarding genders, but a significant decline was registered only in women (Figure 1).

In the period 1994-2013 in Belgrade five most frequent salmonella serotypes isolated from human material were *S. enteritidis* (81.6%), *S. typhimurium* (7.7%), *S. infantis* (2.6%), *S. hadar* (1.8%) and *S. agona* (0.6%). These five *Salmonella* serotypes formed 94.28% of all *Salmonella* isolates from human material.

In the period 1994-2013 in the laboratory for sanitary microbiology of the City Institute of Public Health, within the regular monitoring, microbiological analysis included 151,129 groceries on the territory of Belgrade, and in 295 *Salmonella* was isolated (0.2%).

The most frequently isolated serotype was *S. enteritidis* with 146 izolates (49.8%), *S. infantis* with 34 isolates (11.6%) was on the second place, then *S. typhimurium* with 28 isolates (9.6%), *S. hadar* with 11 isolates (3.8%) and *S. agona* with 8 isolates (2.7%).

Salmonella (laboratory for sanitary microbiology of the City Institute of Public Health in Belgrade) was most frequently present in chicken meat (49.2%), then in cakes and cookies (8.8%), pork (5.1%), ice cream (3.1%), Russian salad and pork (2.7%).

The average crude mortality rate for salmonellosis in Belgrade for the period 1994-2013 was 0.06 per 100,0000 people.

Discussion

According to our results, salmonella cases formed 18.7 % of all cases of intestinal contagious diseases in Belgrade in the period 1994-2013, while in Sarajevo Canton these cases formed much smaller part, 11.2%, in the period 2005-2009 (13), and in Durham region in Canada these cases formed a larger part, a quarter (25.1%) of all intestinal contagious diseases in the monitored period (14).

In the Belgrade region, in the period 1994-2013 a decline in salmonellosis was noticed (15-19). Similar trend was observed within the EU (20), as well as in London where a salmonellosis decline of 50% was observed in the period 2007-2011 (21). The salmonellosis decline within the EU in the last five years can be ascribed to the implementation of salmonella control programs in poultry industry starting with 2007 (20).

In the monitored 20-year-period in Belgrade, the highest age-specific incidence rate was registered in the age group 0-4 (259.6 per 100,000),

Tabela 4. Standardizovane stope salmoneloze, kod muškaraca i žena, Beograd, 1994-2013.

	Standardizovana*/100.000		
Godina	**Oba pola**	**Muškarci**	**Žene**
1994.	72,3	72,8	72,6
1995.	76,9	73,3	79,4
1996.	65,4	62,9	67,2
1997.	45,1	44,2	45,5
1998.	58,1	59,0	56,7
1999.	55,0	54,7	54,7
2000.	83,8	77,2	89,4
2001.	48,8	43,4	56,2
2002.	66,7	65,0	67,5
2003.	135,8	135,5	135,6
2004.	93,7	95,4	91,6
2005.	62,8	65,0	60,5
2006.	39,0	44,1	33,7
2007.	53,5	53,5	53,4
2008.	36,0	34,9	36,9
2009.	52,6	56,3	48,7
2010.	42,0	40,5	43,3
2011.	58,1	62,3	53,8
2012.	44,3	47,0	41,7
2013.	43,0	46,3	39,4
1994-2013.	61,6	61,7	61,4

Prema svetskoj populaciji po Segiju

vrtinu (25,1%) svih intestinalnih bolesti u posmatranom periodu (14).

Na području Beograda, u periodu od 1994. do 2013. godine primećen je pad salmoneloza (15-19). Sličan trend je primećen i u zemljama Evropske unije (20), kao i u Londonu gde je pad salmoneloza od 50% primećen u periodu od 2007. do 2011. godine (21). Pad salmoneloza u okviru Evropske unije tokom prethodnih pet godina može se pripisati primeni programa kontrole salmoneloza u živinarskoj industriji koji je započet 2007. godine (20).

U posmatranom dvadesetogodišnjem periodu u Beogradu, najviša uzrasno-specifična stopa incidencije registrovana je u uzrasnoj grupi 0-4 godine (259,6 na 100.000), i ova stopa je takođe bila najviša u ovoj najmlađoj grupi u Evropskoj uniji (94,8 na 100.000), a 2011. godine ova stopa bila je tri puta viša u odnosu na stariju decu i pet puta viša u poređenju sa drugim uzrasnim grupama (20). Najviša stopa incidencije salmoneloza registrovana je u uzrasnoj grupi mlađih od jedne godine (880 na 100.000) u Novom Zagrebu u periodu od 1990. do 2009. godine (22). Rezultati drugih studija su takođe pokazali da je najviša učestalost salmoneloza registrovana u najmlađoj grupi osoba, ispod 4 godine starosti, tako je u Londonu u periodu od 2007. do 2011. godine ova najmlađa grupa činila 27,6% svih registrovanih slučajeva salmoneloza, što je malo manje u odnosu na našu studiju (32,4%) (21). U jednoj studiji koja je sprovedena u Kantonu Sarajevo u periodu od 2005. do 2009. godine uzrasna grupa od 0 do 6 godina bila je na drugom mestu po učestalosti obolevanja od salmoneloza (31,1%), odmah iza grupe 25-49 godina (43,6%) (21). Prema našim podacima prosečna uzrasno-specifična stopa za uzrasnu grupu od 0-4 godine za muški pol iznosila je 268,25 na 100.000 stanovnika, a za ženski pol 250,52 na 100.000 stanovnika, što su oko deset puta više uzrasno-specifične stope u istoj uzrasnoj grupi nego što su zabeležene u 2012. godini u Irskoj i iznose 26,4 na 100.000 stanovnika za muški pol i 23,5 na

Table 4. Standardized salmonellosis rates, in men and women, Belgrade, 1994-2013

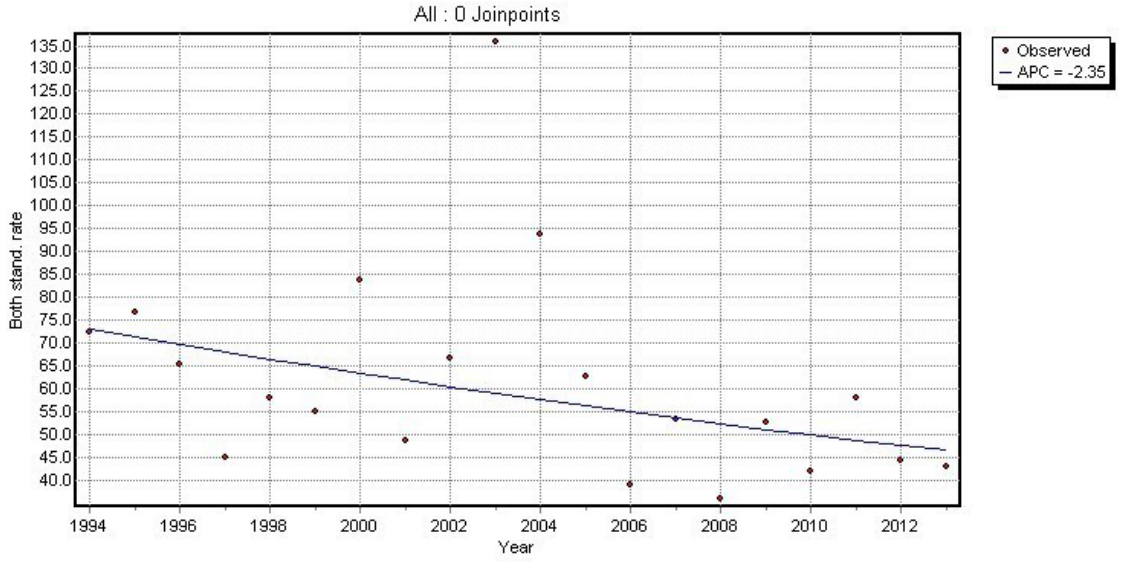
	Standardized*/100,000		
Year	**Both sexes**	**Men**	**Women**
1994	72.3	72.8	72.6
1995	76.9	73.3	79.4
1996	65.4	62.9	67.2
1997	45.1	44.2	45.5
1998	58.1	59.0	56.7
1999	55.0	54.7	54.7
2000	83.8	77.2	89.4
2001	48.8	43.4	56.2
2002	66.7	65.0	67.5
2003	135.8	135.5	135.6
2004	93.7	95.4	91.6
2005	62.8	65.0	60.5
2006	39.0	44.1	33.7
2007	53.5	53.5	53.4
2008	36.0	34.9	36.9
2009	52.6	56.3	48.7
2010	42.0	40.5	43.3
2011	58.1	62.3	53.8
2012	44.3	47.0	41.7
2013	43.0	46.3	39.4
1994-2013	61.6	61.7	61.4

According to the population of the world by Segi

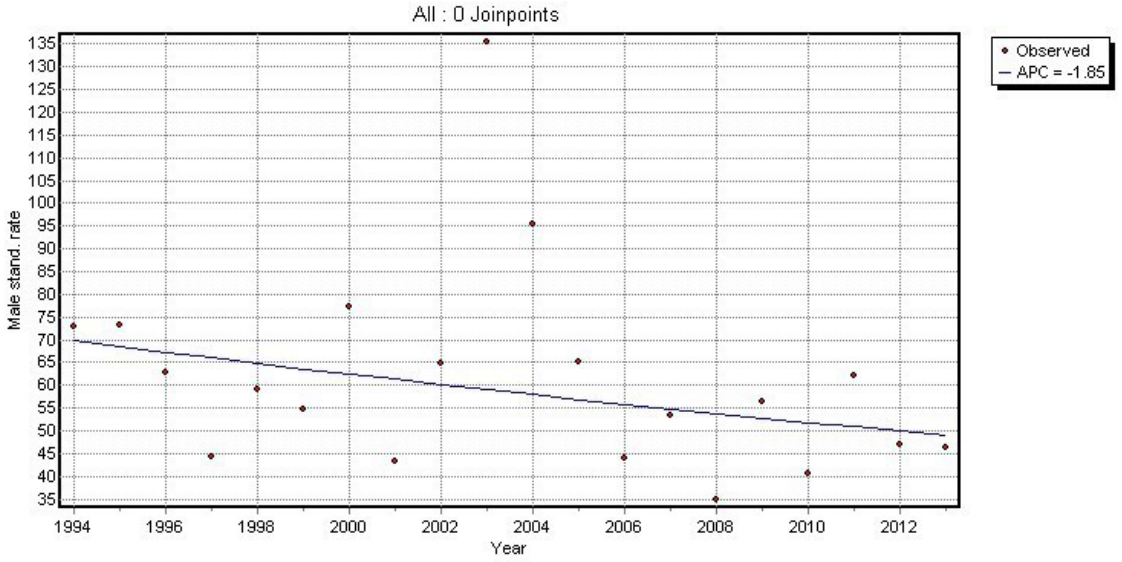
and this rate was also the highest in this youngest group in the EU (94.8 per 100,000 people) and in 2011 it was three times higher than in older children and five times compared to other age groups (20). The highest salmonellosis incidence rate was registered in the age group of under-one-year old (880 per 100,000) in Novi Zagreb in the period 1990-2009 (22). Other studies' results also showed that the highest frequency of salmonellosis is registered in the youngest group of persons, under the age of 4, so in London in the period 2007-2011 this youngest age group made 27.6% of all registered salmonellosis cases, which is slightly smaller presence compared to our study (32.4%) (21). In a study conducted in Sarajevo Canton in the period 2005-2009 age group of 0-6 was second in frequency of contracting salmonellosis (31.1%), right behind the group 25-49 (43.6%) (13). According to our data, the average age-specific rates for the age group of 0-4 for male children were 268.2 per 100,000 people, and for female 250.5 per 100,000 people, which are ten times higher age-specific rates in the same age group than in Ireland in 2012, with 26.4 per 100,000 people for male and 23.5 per 100,000 people for female children (23). The reasons for the highest salmonellosis incidence rate in the youngest group are that the infective dose in children is small, it is possible that symptomatic infections are more frequent, samples of biological material for laboratory analysis are taken more often, clinical presentation can be more serious, so the hospitalizations are more frequent, which makes the infection registration better.

In our study average age-specific salmonellosis incidence rates in the period 1994-2013 are higher for male persons in the age group under 14, and for women in age group older than 20. Women tend to contract the disease more frequently than men. In our study the ratio of infected women and men was 1.15:1, which is slightly smaller than that registered in Novi Zagreb in the period 1990-2009

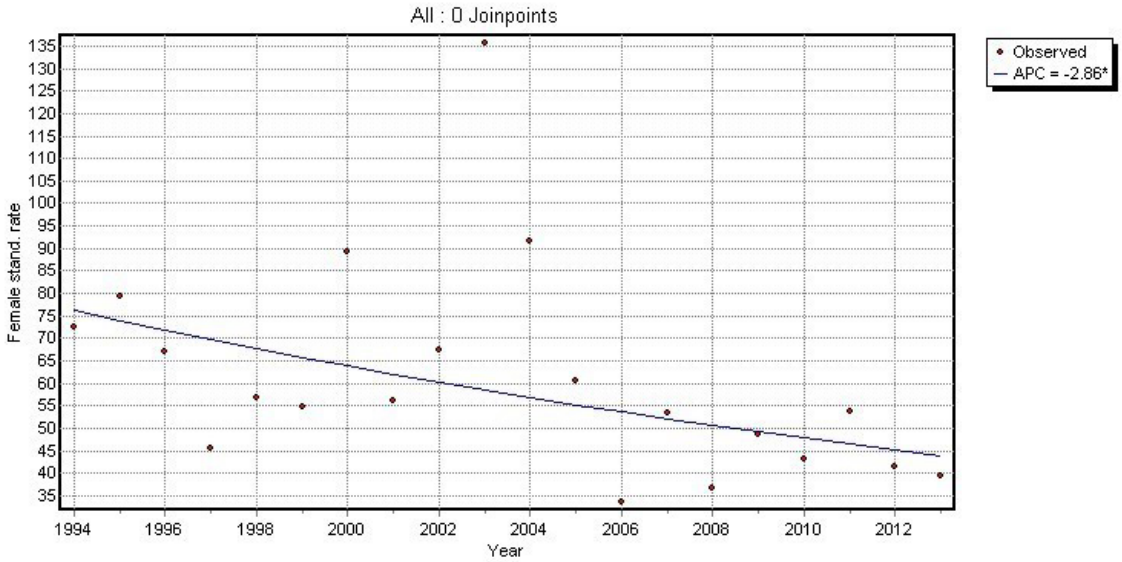
a)



b)

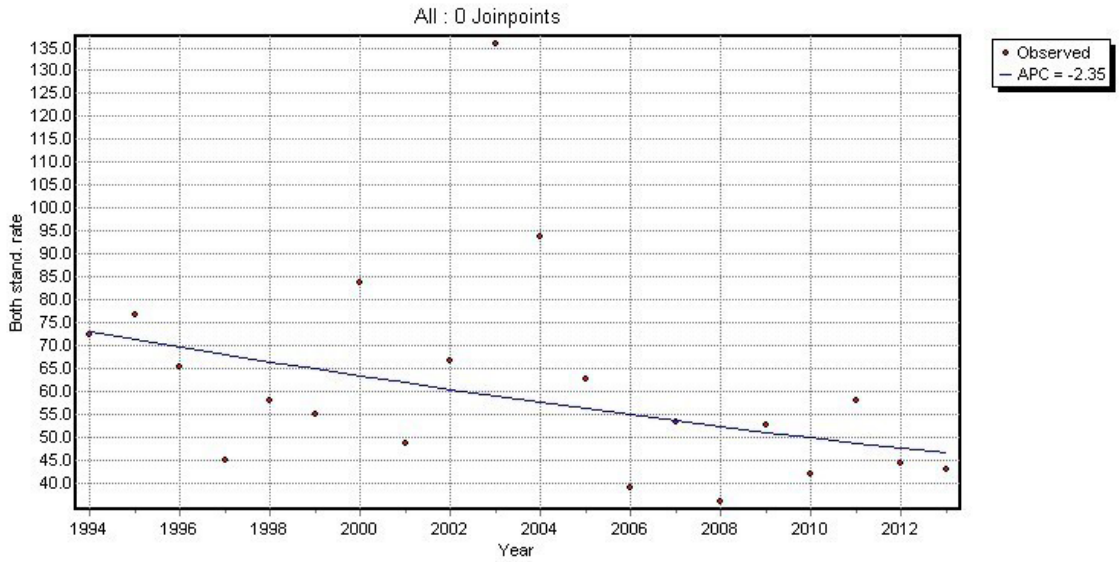


c)

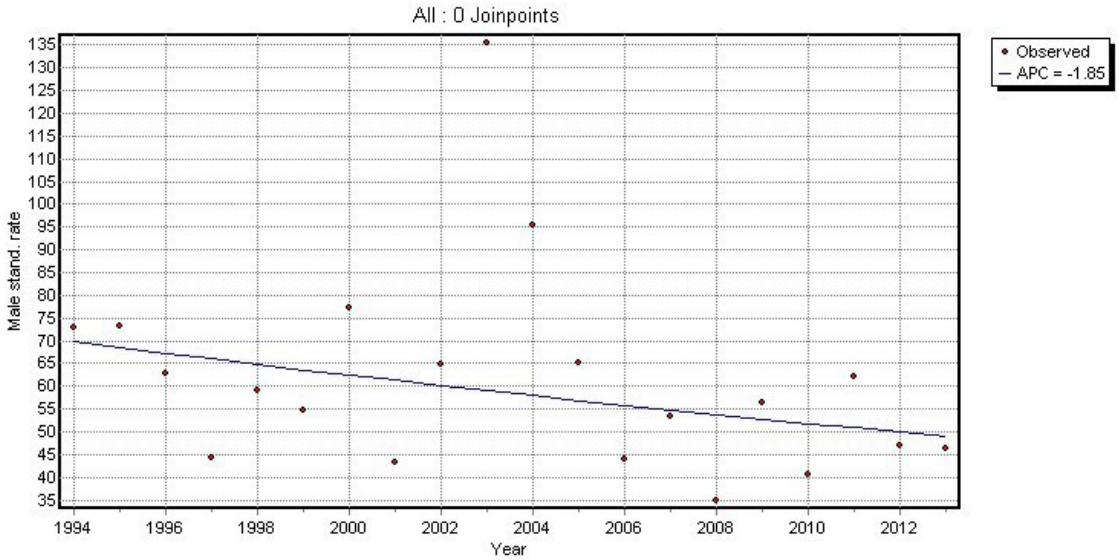


Slika 1. Praćeni i procenjeni terndovi standardizovanih stopa incidencije salmoneloze za a) oba pola, b)muškarci i c) žene, Beograd, 1994-2013.

a)



b)



c)

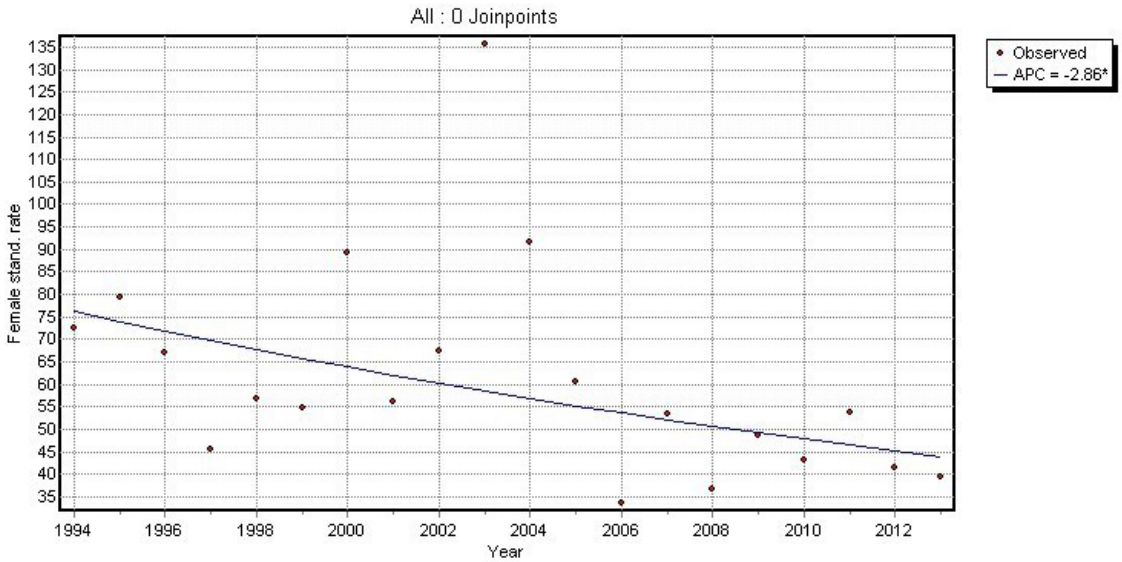


Figure 1. Observed and estimated trends of the standardized salmonellosis incidence rates for both gender, men and women, Belgrade, 1994-2013

100.000 stanovnika za ženski pol (23). Razlozi za najvišu stopu incidencije salmoneloza u najmlađoj uzrasnoj grupi su što je infektivna doza kod dece mala, moguće je da su češće simptomatske infekcije, uzorci biološkog materijala za laboratorijsku analizu se češće uzimaju, klinička slika može biti teža, tako da su učestalije hospitalizacije, a samim tim i bolja prijava infekcija.

U našoj studiji, prosečne uzrasno-specifične stope incidencije salmoneloza u periodu od 1994. do 2013. godine bile su više kod muškaraca u uzrasnoj grupi ispod 14 godina, a kod žena u uzrasnoj grupi starijih od 20 godina. Žene češće obolevaju od muškaraca. U našoj studiji odnos obolelih od salmoneloza žena i muškaraca je bio 1,15:1, što je nešto manji odnos od onog zabeleženog u Novom Zagrebu u periodu 1990-2009. godine (1,2:1) (22) i Hong Kongu u periodu od 2003. do juna 2011. godine (1,24:1) (24). U drugim studijama je takođe bilo više žena među obolelima od salmoneloza. Odnos obolelih žena i muškaraca u Sjedinjenim Američkim Državama 2011. godine bio je 1,09:1 (24). Razlog za nešto veći broj obolelih među osobama ženskog pola može biti što žene češće učestvuju u pripremi hrane, češće dolaze u kontakt sa sirovim mesom ili jajima, koji mogu biti kontaminirani salmonelama. U jednoj studiji koja je sprovedena u Londonu u periodu od 2007. do 2011. godine, nije bilo značajne razlike između polova po pitanju obolevanja (21), a u Irskoj 2012. godine odnos inficiranih žena i muškaraca bio je 0,90:1,11 (23).

Prema našim podacima najzastupljeniji serotipovi salmonela izolovani iz humanog materijala bili su *S. enteritidis* i *S. typhimurium*. Ovi serotipovi su takođe bili najčešći u humanom materijalu u periodu od 2001. do 2007. godine širom sveta, osim u Okeaniji i Severnoj Americi. U Severnoj Americi i Okeaniji (Australija i Novi Zeland), najčešći serotip u datom periodu bio je *S. typhimurium*, a *S. enteritidis* je bio drugi najčešći serotip. U nekim regionima, učestalost ova dva serotipa je mnogo niža. Rezultati studije koja je sprovedena 2008. godine u gradu Damaru, u Jemenu, pokazali su da je kod pregledanih pacijenata jedne bolnice učestalost *S. enteritidis* bila 24,4%, a *S. typhimurium* 13,3% (25). U datom periodu (2001-2007), procentualno učešće *S. enteritidis* i S. *typhimurium* širom sveta u odnosu na 15 najčešćih serotipova iznosili su 43,5% i 17,1% (26), a u zemljama članicama Evropske unije učešće ova dva serotipa u 2012. godini iznosi 41,3% i 22,1% (10), što se razlikuje od učestalosti ova dva serotipa salmonele u našoj studiji gde *S. enteritidis* iznosi 81,6%, a *S. typhimurium* 7,7%. Rezultati studije sprovedene u Novom Zagrebu u periodu od 1990. do 2009. godine pokazuju približno istu zastupljenost dva najčešća serotipa salmonele kao i u našoj studiji i iznose – *S. enteritidis* – 84% i *S. typhimurium* - 7% (22). Ostali serotipovi salmonela se češće registruju na određenim kontinentima i regionima: *S. Newport* (3,5%) je najčešći serotip u Latinskoj i Severnoj Americi, kao i u Evropi. *S. infantis* (1,8%) je dominantan serotip koji se registruje u svim regionima. *S. Virchow* (1,5%) se najviše registruje u Aziji, Evropi i Okeaniji. *S. Hadar* (1,5%) je naročito prisutan u Evropi, dok je *S. agona* (0,8%) veoma čest u Latinskoj i Severnoj Americi i Evropi (26). Prema našim rezultatima, nakon *S. enteritidis* i *S. typhimurium*, najčešći serotipovi salmonela, slično situaciji u svetu, su *S. infantis* (2,6%), *S. hadar* (1,8%), *S. agona* (0,6%). Postoje velike razlike u najčešće izolovanim serotipovima između regiona, ali su te razlike manje između zemalja u okviru istog regiona (26).

U studiji sprovedenoj u gradu Sana u Jemenu od 2009. do 2010. godine, najveći procenat salmonela u hrani registrovan je u crvenom mesu (14,7%), piletini (12,1%), kuvanim jelima (9,5%), mleku i mlečnim proizvodima (5%), sokovima (4,8%), povrću (4,4%), sandvičima (3%) i tortama (2,6%) (27). U studiji koja je sprovedena u Novom Zagrebu u periodu 1990-2009. godine, učešće namirnica u kojima je dokazano prisustvo salmonela iznosi 32% za jaja, 10% za torte i piletinu, 5% za mleveno meso, 2% za sladoled, 1,5% za sir i 1% za francusku salatu i svinjetinu (22). Rezultati pomenute dve studije se znatno razlikuju od rezultata dobijenih u našoj studiji gde je procentualno najzastupljenija namirnica u kojoj je potvrđeno prisustvo salmonele bila piletina, koja čini skoro polovinu svih namirnica sa izolatima salmonela (49,15%), a zatim slede torte i kolači.

Mortalitet od salmoneloza je nizak. Prosečna sirova stopa mortaliteta u našoj studiji je iznosila 0,06 na 100.000 stanovnika. Godišnja stopa mortaliteta u Nemačkoj, u periodu 2004-2008. godine je iznosila 0,055 na 100.000 stanovnika (28). Stopa mortaliteta u Sjedinjenim Američkim Državama, u periodu 1996-2005. godine, bila je 0,07 na 100.000 (29). U drugoj studiji, koja je obuhvatila stanovništvo Sjedinjenih Američkih Država u periodu 1990-2006, godišnja stopa mortaliteta bila je 0,03 na 100.000 stanovnika (30).

(1.2:1) (22) and in Hong Kong in the period 2003-June 2011 (1.24:1) (24). In other studies women were also more present among salmonellosis cases. The ratio of infected women and men in the USA in 2011 was 1.09:1 (24). The reason for the greater number of women among the infected could be the fact that women are more involved in food preparation, they are more likely to handle raw meat and eggs, which can be contaminated with salmonella. In a study conducted in London in the period 2007-2011 there was no significant difference regarding contracting salmonella between the genders (21), and in Ireland in 2012 the ratio of infected women and men was 0.90:1.11 (23).

As our data suggest, *S. enteritidis* and *S. typhimurium* were the most present in human material. These were also the most present serotypes in human material in the period 2001-2007 worldwide, except for Oceania and North America. In North America and Oceania (Australia and New Zealand) the most present serotype in the given period was *S. typhimurium*, and *S. enteritidis* was the second most frequent. In some regions, the frequency of these two serotypes is much lower. The results of a study conducted in 2008 in the city Thamar, Yemen, showed that in examined patients of one hospital the frequency of *S. enteritidis* was 24.4%, and *S. typhimurium* 13.3% (25). In the given period (2001-2007) the percentages of *S. enteritidis* and *S. typhimurium* worldwide among the 15 most common serotypes were 43.5% and 17.1% (26), and within the EU the percentages for these two serotypes in 2012 were 41.3% and 22.1% (10), which is different than in our study, where the percentage for *S. enteritidis* was 8.6%, and for S. typhimurium 7.7%. The results of a study conducted in Novi Zagreb in the period 1990-2009 showed similar percentages for the two most frequent salmonella serotypes as in our study - *S. enteritidis* – 84% and *S. typhimurium* – 7% (22). Other serotypes are more likely to be registered in other continents and regions: *S. Newport* (3.5%) is mostly present in Latin and North America, as well as in Europe. S. infantis (1.8%) is a dominant serotype registered in all regions. *S. Virchow* (1.5%) is mostly registered in Asia, Europe and Oceania. *S. hadar* (1.5%) is especially present in Europe, while *S. agona* (0.8%) is very frequent in Latin and North America and Europe (26). According to our results, after *S. enteritidis* and *S. typhimurium* the most frequent salmonella serotypes are, similar to the situation in world, *S. infantis* (2.6%), *S. hadar* (1.8%) and *S. agona* (0.6%). There are major differences in the most frequently isolated serotypes between regions, but these differences are less prominent between the countries of the same region (26).

In a study conducted in the city of Sana'a in Yemen in the period 2009-2010.the largest percentage of *salmonella* in food was registered in red meat (14.7%), chicken (12.1%), cooked dishes (9.5%), milk and dairy products (5.0%), juice (4.8%), vegetables (4.4%), sandwiches (3.0%) and cakes (2.6%) (27). In the study conducted in Novi Zagreb in the period 1990-2009 the percentage of food with registered *salmonella* was 32% for eggs, 10% for cakes and chicken, 5% for minced meat, 2% for ice cream, 1.5% for cheese and 1% for French salad and pork (22). The results of the two mentioned studies are significantly different than those of our study, where the most frequent food with *salmonella* was chicken, which formed a half of all food with *salmonella* isolates (49.2%), followed by cakes and cookies.

Salmonellosis mortality is low. The average raw mortality rate in our study was 0.06 per 100,000 people. The annual mortality rate in Germany, in the period 2004-2008 was 0.055 per 100,000 people (28). The mortality rate in the USA, in the period 1996-2005 was 0.07 per 100,000 people (29). In another study including the population of the USA in the period 1990-2006, the annual mortality rate was 0.03 per 100,000 people (30).

The decline in salmonellosis noticed in our study, on one hand suggests better farming control, better control of meat production and turnover and application of hygienic and sanitary measures in these processes as well as the greater presence of the HACCP standard for health safety of food in Belgrade. This makes it less likely for the contaminated food to reach the consumers. On the other hand, it is important, but not sufficient for the Belgrade population to be informed about the risks of using groceries without thermal treatment (eggs), as well as about the importance of hygienic and epidemiological habits and conditions among them. The reason for this decline might be the greater number of infected with an atypical form of the disease, which makes such patients unrecognized and unregistered.

Trend opadanja salmoneloza, zapažen u našoj studiji, sa jedne strane govori o boljoj kontroli uzgoja na farmama, proizvodnje i prometa mesa i primeni higijensko-sanitarnih mera u ovim procesima, kao i sve zastupljenijoj primeni HACCP standarda za zdravstvenu bezbednost hrane u Beogradu. Stoga je manja verovatnoća da će kontaminirana hrana dospeti do potrošača. S druge strane, značajna je, ali ne i dovoljna, prosvećenost stanovništva o rizicima korišćenja termnički neobrađenih namirnica (jaja), kao i o važnosti higijensko-epidemioloških navika i uslova među stanovništvom Beograda. Razlog za uočeni trend opadanja obolevanja od salmoneloza može biti i veći broj obolelih sa atipičnom formom bolesti, što dovodi do toga da ovi pacijenti ostaju neprepoznati, a samim tim i neprijavljeni.

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Konflikt interesa

Autori su izjavili da nema konflikta interesa.

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Competing interests

The authors declare no competing interests.

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EPIDEMIJE ŠARLAHA U VRTIĆIMA U BEOGRADU

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SAŽETAK

Uvod/Cilj: Šarlah je uglavnom dečija bolest i u oko 90% slučajeva se javlja kod dece mlađe od 10 godina. Epidemije šarlaha uvek se javljaju u dečijim kolektivima (vrtićima, školama i ustanovama za decu). Cilj ovoga rada je da se analiziraju epidemiološke karakteristike epidemija šarlaha u vrtićima u Beogradu tokom petogodišnjeg perioda (2016-2020. godine).
Metode: Podaci o obolevanju od šarlaha prikupljeni su, za posmatrani period, iz Gradskog zavoda za javno zdravlje Beograd. Korišćeni izvori podataka su: epidemiološki upitnik, medicinska dokumentacija i laboratorijski rezultati. Prisustvo β-hemolitičkog streptokoka grupe A kod obolele dece dokazano je bakteriološkim pregledom briseva grla i nosa. U analizi podataka korišćene su opšte i specifične stope incidencije.
Rezultati: Tokom petogidišnjeg perioda registrovano je 30 epidemija šarlaha u kojima je ukupno obolelo 114 dece iz 23 beogradska vrtića. U 2017. godini bilo je 12 epidemija sa ukupno 49 obolelih, što predstavlja najveći ukupan broj obolelih u jednoj godini. U periodu 2016-2020. godine, najveći broj obolelih među svim obolelima od šarlaha je bio među decom uzrasta 4 godine (33,3%), a najmanji među decom uzrasta od 2 godine (1,7%). Nešto je više bilo novoobolelih dečaka (57,9%) nego devojčica (42,1%). Najveće prosečne petogodišnje stope incidencije za šarlah zabeležene su u uzrastu 1-4 godine (383,7 na 100.000) i u uzrastu 5-9 godina (262,8 na 100.000), a najniže su bile kod osoba starosti 15 i više godina. Oko ⅓ obolele dece registrovan je u opštini Novi Beograd, a oko ⅓ obolelih registrovan je u perodu ranog proleća (mart-april).
Zaključak: Poštovanje i blagovremena primena protivepidemijskih mera doprinose uspešnom zaustavljanju daljeg širenja infekcije (prijava oboljenja, izolacija, lečenje obolele dece, kao i pooštrene mere higijene i tekuća dezinfekcija).

Ključne reči: šarlah, β-hemolitički streptokok grupe A, epidemija, vrtić

Uvod

Šarlah (lat. *Scarlatina*) je oblik streptokokne bolesti karakterističan po ospi, koja nastaje kada soj streptokoka koji je izazvao infekciju produkuje pirogeni egzotoksin. Uzročnik šarlaha je β-hemolitički streptokok grupe A (1). Klinička slika oboljenja se manifestuje iznenadnom febrilnošću, bolovima u grlu, eksudativnim tonzilitisom ili faringitisom, malinastim jezikom i specifičnom ospom u vidu tačkastog egzantema (kao šmirgl papir). Ospa se najčešće javlja po vratu, grudima, u predelu potpazušnih jama, laktovima i preponama, kao i na unutrašnjim stranama butina. Karakteristično je da šarlahna ospa ne zahvata lice, ali su na licu karakteristični zajapurenost obraza i bledilo koje okružuje usne (1).

Rezervoar infekcije je čovek. Najčešće se prenosi kapljičnim putem ili direktnim kontaktom sa obolelima ili kliconošama, ređe indirektnim kontaktom preko predmeta (1). Period inkubacije najčešće iznosi 2-5 dana (minimalna jedan dan, a maksimalna 7 dana). Dijagnoza šarlaha najčešće se postavlja na osnovu kliničke slike, a potvrđu-

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OUTBREAKS OF SCARLET FEVER IN KINDERGARTENS IN BELGRADE

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SUMMARY

Introduction/Aim: Scarlet fever is mostly a childhood disease and in about 90% of cases it occurs in children younger than 10 years. Outbreaks of scarlet fever always occur in children's collectives (kindergartens, schools and institutions for children). The aim of this paper is to analyze the epidemiological characteristics of scarlet fever epidemics in kindergartens in Belgrade during the five-year period (2016-2020).
Methods: Data about new cases of scarlet fever were collected for the observed period from the City Institute for Public Health Belgrade. The data sources used are: epidemiological questionnaire, medical documentation and laboratory results. The presence of β-hemolytic streptococcus group A in diseased children was proven by bacteriological analysis of throat and nose swabs. General and specific incidence rates were used in the data analysis.
Results: During the observed five-year period, 30 epidemics of scarlet fever were registered, in which a total of 114 children from 23 Belgrade kindergartens became ill. In 2017, there were 12 epidemics with a total of 49 cases, which represents the largest total number of cases in one year. In the period from 2016 to 2020, the highest number of patients among all patients with scarlet fever was among children aged 4 years (33.3%), and the lowest among children aged 2 years (1.7%). There were slightly more sick boys (57.9%) than girls (42.1%). The highest average five-year incidence rates for scarlet fever were recorded at the age 1-4 (383.7 per 100,000) and 5-9 years (262.8 per 100,000), and the lowest were in persons aged 15 and over. About ⅓ of sick children were registered in the municipality of New Belgrade, and about ⅓ of sick children were registered in the period of early spring (March-April).
Conclusion: Respect and timely application of anti-epidemic measures contribute to the successful cessation of further spread of infection (disease reporting, isolation, treatment of sick children, as well as stricter hygiene measures and ongoing disinfection).

Key words: scarlet fever, β-hemolytic streptococcus group A, epidemic, kindergarten

Introduction

Scarlet fever (Latin: *Scarlatina*) is a streptococcal illness characterized by a rash, which appears when a streptococcal strain that caused the infection produces pyrogenic exotoxins. Group A ß-hemolytic streptococcus is the causative agent of scarlet fever (1). Clinical manifestations of this disease are sudden fever, sore throat, exudative tonsillitis or pharyngitis, "the strawberry tongue," and a distinctive rash that appears as papular exanthema (as sandpaper). The rash usually appears on the neck, chest, underarms, elbows, and groin, as well as on the inner thighs. It is characteristic that scarlet rash does not spread to the face, but the cheeks become flushed, and the area around the mouth stays pale (1).

Humans are the primary reservoir of infection. It is typically transmitted through respiratory droplets or direct contact with infected persons or reservoirs, and more rarely, indirectly by contact with objects used by infected persons (1). The incubation period is most frequently 2 to 5 days (minimum 1 day, maximum 7 days). Scarlet fever

je izolacijom β-hemolitičkog streptokoka grupe A brisa grla (2).

Terapija je antibiotska, a lekovi izbora su penicilin ili amoksicilin (3). Ukoliko se šarlah ne leči osoba može biti zarazna 2 do 3 nedelje nakon pojave simptoma. Uz adekvatnu terapiju pencilinom zaraznost prestaje u roku od 24 sata (1).

Šarlah je uglavnom dečija bolest i u oko 90% slučajeva se javlja kod dece mlađe od 10 godina. Najveća učestalost ovog oboljenja je među decom uzrasta od 4 godine, a često se javlja u uzrastu od 2 do 8 godine (2). Streptokokna angina-faringitis i šarlah su uobičajni u zoni sa umerenom klimom, ređi u suptropskim predelima i još ređi u tropskim predelima. Oboljenje se javlja u toku cele godine, ali je vrh obolevanja krajem zime i u rano proleće (1). Epidemije šarlaha uvek se javljaju u dečijim kolektivima (vrtićima, školama i ustanovama za decu) (4). Tokom 17. i 18. veka epidemije šarlaha prijavljene su širom Evrope i Severne Amerike (5). Od početka 20. veka ova bolest nije među vodećim ozbiljnim bolestima dece zbog povećanja broja antibiotika kojim se leči i poboljšanja životnog standarda (6).

Poštovanje i blagovremena primena protivepidemijskih mera doprinose uspešnom zaustavljanju daljeg širenja infekcije (rano otkrivanje izvora, rezervoara i puteva prenošenja zaraznih bolesti, epidemiološko ispitivanje i istraživanje, postavljanje dijagnoze, prijavljivanje obolelih, izolacija, lečenje obolele dece, lična zaštita od infekcije, tekuća dezinfekcija, zdravstveno vaspitanje i edukacija zdravstvenih radnika) (1,4).

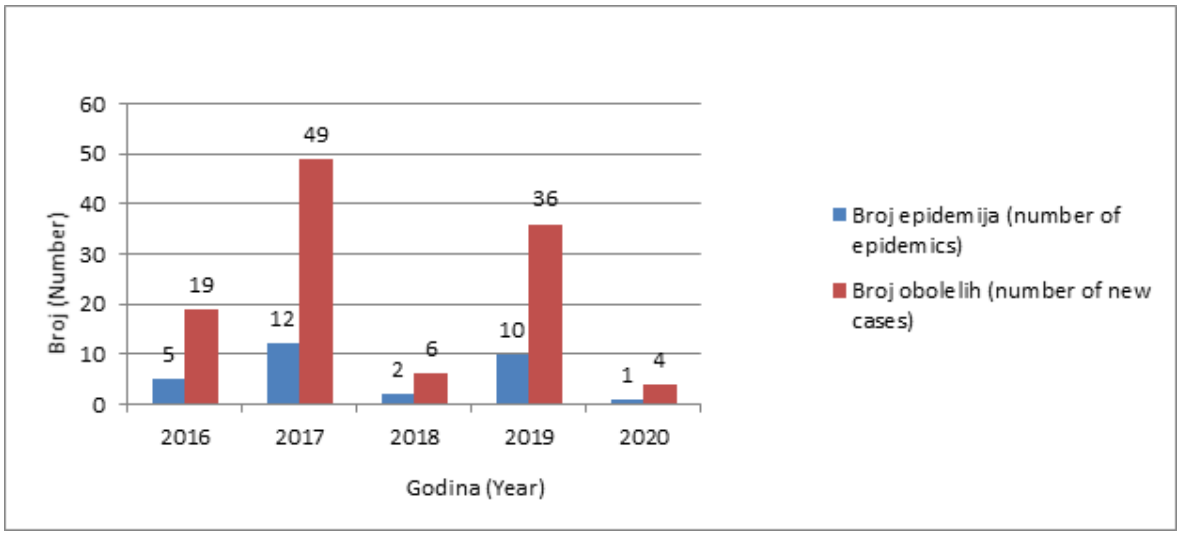
Cilj ovoga rada je da se analiziraju epidemiološke karakteristike epidemija šarlaha koje su se javile u vrtićima u Beogradu tokom perioda od 2016. do 2020. godine.

Metode

U cilju analize epidemioloških karakteristika epidemija šarlaha u vrtićima Beograda prikupljeni su podaci iz Gradskog zavoda za javno zdravlje Beograd za petogodišnji period (2016-2020. godine). Korišćeni izvori podataka su: epidemiološki upitnici, medicinska dokumentacija i rezultati bakterioloških analiza obavljeni u laboratoriji Gradskog zavoda za javno zdravlje Beograd. Prisustvo β-hemolitičkog streptokoka grupe A kod obolele dece dokazano je bakteriološkim pregledom briseva grla i nosa. Statistička obrada podataka urađena je primenom SPSS programa (IBM SPSS Statistics 22). U analizi podataka korišćen je apsolutan broj obolelih, kao i opšte i specifične stope incidencije. Specifične stope incidencije računate su kao količnik broja novoobolelih od šarlaha za određen uzrast i broja stanovnika za dati uzrast. Sve stope su iskazane na 100.000. Podaci o broju stanovnika preuzeti su iz popisa stanovništva za 2011. godinu.

Rezultati

U periodu od 2016. do 2020. godine registrovano je 30 epidemija šarlaha u kojima je ukupno obolelo 114 dece iz 23 beogradska vrtića. Godišnji broj epidemija kretao se od jedne do 12, a broj obolelih od 4 do 49 (grafikon 1). U 2017. godini bilo je 12 epidemija sa ukupno 49 obolelih, što



Grafikon 1. Broj epidemija i novoobolelih od šarlaha, Beograd, 2016 – 2020. godine

diagnosis is usually made according to the clinical presentation, and it is confirmed by the isolation of Group A ß-hemolytic streptococcus in throat swabs (2).

The treatment includes antibiotics, and the drug of choice is penicillin or amoxicillin (3). If scarlet fever is not treated, it can be infectious 2 to 3 weeks after the symptoms appear. When penicillin is used in the treatment, contagiousness stops within 24 hours (1).

Scarlet fever is mainly a childhood disease, and in 90% of cases, it affects children younger than 10 years. The highest incidence of this disease is among children aged 4, and it is often seen between the ages 2 to 8 years (9). Streptococcal tonsilitis-pharyngitis and scarlet fever are common in moderate climates, while they are rarely seen in subtropical and very rarely in tropical climates. The disease appears at any time of year, but it peaks in late winter and early spring (1). Scarlet fever outbreaks always appear in children's collective institutions (kindergartens, schools, and institutions for children) (4). During the 17th and 18th centuries, epidemics of scarlet fever were reported throughout Europe and North America. Since the beginning of the 20th century, this disease has not been among the leading serious children's diseases due to the increase in the number of antibiotics used for the treatment and due to the improvement of standards of living (6).

Respect and timely application of anti-epidemic measures contribute to the successful cessation of further spread of infection (early detection of cause, reservoirs, and ways of transmission of contagious disease, epidemiological investigation and examination, early diagnosis, disease reporting, isolation, treatment of ill children, personal protection from infection, ongoing disinfection, health education and education of health care workers) (1,4).

The aim of this paper is to analyze the epidemiological characteristics of scarlet fever epidemics in kindergartens in Belgrade in the period 2016 to 2020.

Methods

In order to analyze the epidemiological characteristics of scarlet fever epidemics in kindergartens in Belgrade, data were collected from the City Institute of Public Health Belgrade for the five-year period (2016-2020). The data sources used are: epidemiological questionnaires, medical documentation, and the results of bacteriological analyzes performed in the laboratory of the City Institute of Public Health in Belgrade. The presence of Group A ß-hemolytic streptococcus in ill children was proved by bacteriological examination of nose and throat swabs. The statistical analysis of data was done with the help of the SPSS program (IBM SPSS Statistics 22). The total number of cases was used for the analysis of data, as well as crude and specific incidence rates. Specific incidence rates were calculated as the total number of new cases of scarlet fever for the specific age group divided by the total population in that age group. All rates were calculated per 100,000. Population data were taken from the 2011 census.

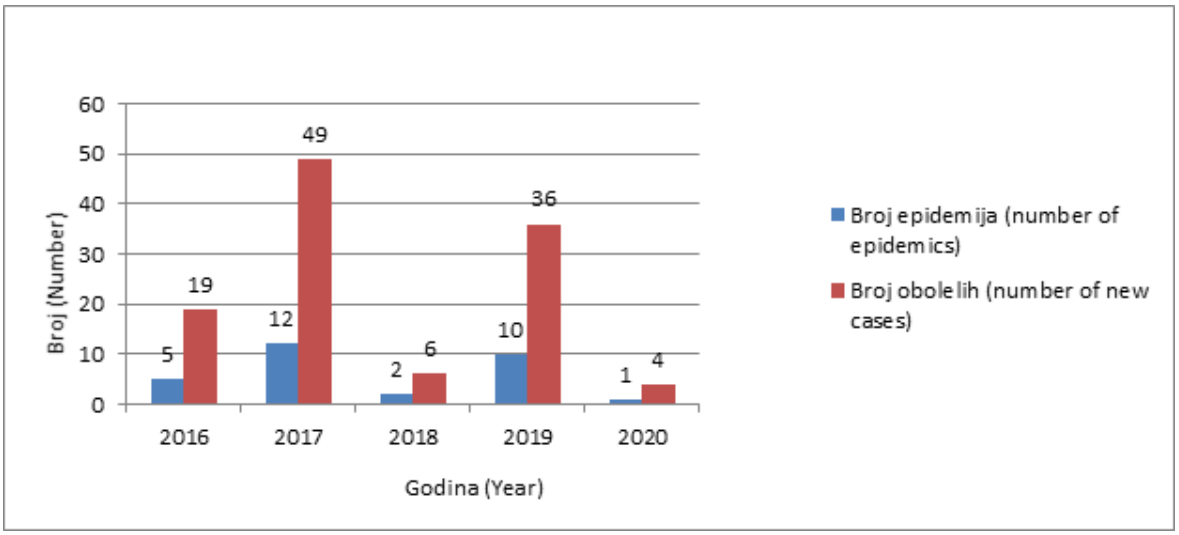


Figure 1. Number of epidemics and new cases of scarlatina fever, Belgrade, 2016 - 2020

Tabela 1. Distribucija novoobolelih od šarlaha i uzrasno specifične stope incidencije (na 100.000) prema polu i uzrastu, Beograd, 2016 – 2020. godine

Uzrast (godine)	Dečaci Broj (%) n=66	Dečaci (Stopa*)	Devojčice Broj (%) n=48	Devojčice (Stopa*)	Ukupno Broj (%) n=114	Ukupno (Stopa*)
1	0	0	0	0	0	0
2	1 (1,5)	11,7	1 (2,0)	12,5	2 (1,7)	12,3
3	17 (25,7)	207,3	18 (37,5)	232,5	35 (30,7)	219,6
4	17 (25,7)	214,4	21 (43,7)	276,2	38 (33,3)	244,6
5	13 (19,6)	163,7	4 (8,3)	53,0	17 (14,9)	109,7
6	12 (18,1)	152,2	2 (4,1)	26,2	14 (12,2)	90,4
7-9	6 (9,0)	25,0	2 (4,1)	8,8	8 (7,0)	17,2

predstavlja najveći ukupan broj obolelih u jednoj godini. Najmanji broj epidemija (i to samo jedna), kao i najmanji broj obolelih u epidemijama (samo četvoro obolelih), registrovani su 2020. godine. U ovom petogodišnjem periodu, prosečan broj prijavljenih epidemija je iznosio 6, a prosečan broj obolelih u epidemijama 22.

Tokom posmatranog petogodišnjeg perioda, najveći broj obolelih među svim obolelima od šarlaha je bio među decom uzrasta 4 godine (33,3%), a najmanji među decom uzrasta od dve godine (1,7%) (tabela 1). Nešto je veći broj obolelih dečaka (57,9%) nego devojčice (42,1%). Najviša uzrasno specifična stopa kod dečaka bila je u uzrastu od četiri godine (214,4/100.000), a najmanja u uzrastu od dve godine (11,7/100.000). Dok kod devojčica najviša uzrasno specifična stopa takođe bila u uzrastu od 4 godine (276,2/100.000), a najmanja u uzrasnoj grupi od 7-9 godina (8,8/100.000) (tabela 1).

U svakoj posmatranoj godini najviša uzrasna specifična stopa incidencije je bila u uzrastu 1-4 godine, a zatim u uzrastu 5-9 godina, a najmanje kod osoba starijih od 15 godina (tabela 2). Prosečna petogodišnja stopa incidencije je iznosila 383,7 na 100.000 za uzrast 1-4 godine, a 262,8 na 100.000 za uzrast 5-9 godina (tabela 2).

Najveći broj novoobolele dece registrovan je u gradskim opštinama Novi Beograd – 38 (33,3%), Palilula-24 (21,1%), Čukarica – 22 (19,3%), Vračar-12 (10,5%) i Zvezdara-11 (9,64%),a najmanji u prigradskoj opštini Obrenovac – 7 (6,14%). U ostalim opštinama Beograda nije registrovano obolevanje.

Sezonska distribucija ukazuje da je najveći broj novoobolelih registrovan u rano proleće (mart-april) – 35 (30,7%) i na kraju zime (januar-februar) – 28 (24,6%), što odgovara sezonskoj distribuciji ovoga oboljenja (grafikon 2).

Kod svih obolelih klinička slika se manifestovala povišenom telesnom temperaturom, bolom u grlu, hiperemijom ždrela i ospom po koži. Od 114 obolele dece od šarlaha tokom posmatranog peri-

Tabela 2. Broj novoobolelih i uzrasno specifične stope incidencije (na 100.000) za šarlah, Beograd, 2016 – 2020. godine

Uzrasne grupe Godine	< 1 Broj (Stopa*)	1-4 Broj (Stopa*)	5-9 Broj (Stopa*)	10-14 Broj (Stopa*)	15-19 Broj (Stopa*)	20-29 Broj (Stopa*)	60+ Broj (Stopa*)	Ukupno Broj (Stopa*)
2016	5 (29,4)	304 (466,9)	290 (374,3)	32 (43,7)	3 (3,5)	6 (2,6)	0	640 (38,35)
2017	2 (11,7)	464 (712,7)	347 (447,8)	37 (50,5)	4 (4,7)	9 (4,0)	1 (0,2)	864 (52,07)
2018	0	182 (279,5)	173 (265,7)	23 (31,4)	1 (1,1)	7 (3,1)	2 (0,5)	388 (23,38)
2019	3 (17,6)	229 (351,7)	176 (227,1)	15 (20,4)	0	6 (2,6)	0	429 (25,85)
2020	0	70 (107,5)	32 (41,3)	10 (13,6)	1 (1,1)	8 (3,5)	0	121 (7,14)
2016-2020	10 (11,7)	1249 (383,7)	1018 (262,8)	117 (31,9)	9 (2,1)	36 (3,22)	3 (0,1)	2442 (29,4)

*U svakoj posmatranoj godini najviša uzrasna specifična stopa incidencije je bila u uzrastu 1-4 godine, a zatim u uzrastu 5-9 godina, a najmanje kod osoba starijih od 15 godina (tabela 2). Prosečna petogodišnja stopa incidencije je iznosila 383,7 na 100.000 za uzrast 1-4 godine, a 262,8 na 100.000 za uzrast 5-9 godina.

Table 1. Distribution of new cases of scarlet fever and age-specific incidence rates (per 100,000) by gender and age, Belgrade, 2016 - 2020

Age (years)	Boys Number (%) n=66	Boys (Rate*)	Girls Number (%) n=48	Girls (Rate*)	Total Number (%) n=114	Total (Rate*)
1	0	0	0	0	0	0
2	1 (1.5)	11.7	1 (2.0)	12.5	2 (1.7)	12.3
3	17 (25.7)	207.3	18 (37.5)	232.5	35 (30.7)	219.6
4	17 (25.7)	214.4	21 (43.7)	276.2	38 (33.3)	244.6
5	13 (19.6)	163.7	4 (8.3)	53.0	17 (14.9)	109.7
6	12 (18.1)	152.2	2 (4.1)	26.2	14 (12.2)	90.4
7-9	6 (9.0)	25.0	2 (4.1)	8.8	8 (7.0)	17.2

Results

In the period from 2016 to 2020, 30 scarlet fever epidemics were registered, with a total of 114 ill children from 23 Belgrade kindergartens. The annual number of epidemics ranged from 1 to 12, while the number of new cases ranged from 4 to 49 (Graph 1). In 2017, there were 12 epidemics with 49 affected persons, which is the largest total number of new cases in one year. The smallest number of epidemics (only one) and the smallest number of new cases in epidemics (only 4 new cases) were registered in 2020. In this five-year period, the average number of reported epidemics was 6, while the average number of new cases was 22.

During the observed five-year period, the highest number of patients among all patients with scarlet fever was among children aged 4 years (33.3%), while the lowest number was among children aged 2 years (1.7%) (Table 1). There were slightly more sick boys (57.9%) than girls (42.1%). The highest age-specific rate in boys was in the age group 4 years (214.4/100,000), while the lowest was in the age group 2 years (11.7/100,000). In girls, the highest age-specific rate was also in the age group 4 years (276.2/100,000), while the lowest was in the age group 7-9 years (8.8/100,0000 (Table 1).

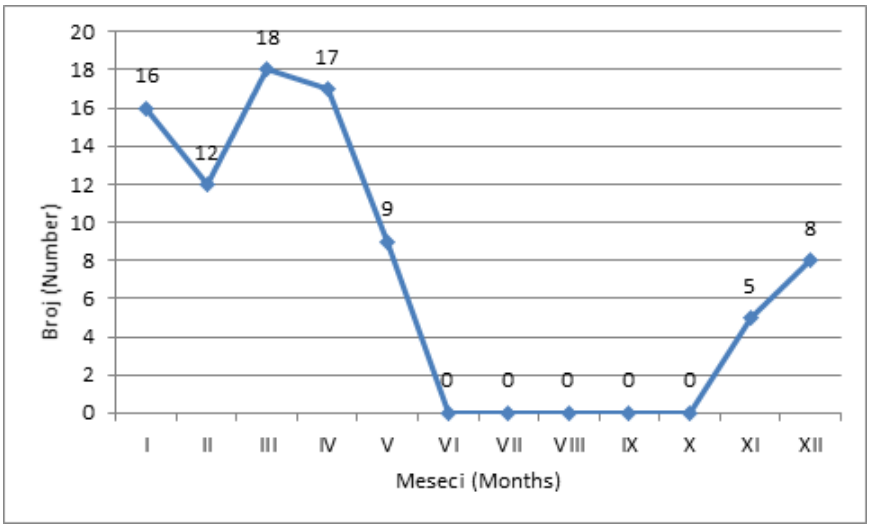
In each observed year, the highest age-specific incidence rate was in the age group 1-4 years, then in the age group 5-9 years, whereas the lowest rate was in persons older than 15 years (Table 2). The average five-year incidence rate was 383.7 per 100,000 in the age group 1-4 years and 262.8 per 100,000 in the age group 5-9 years (Table 2).

The largest number of ill children was registered in the following municipalities: Novi Beograd – 38 (33.3%), Palilula – 24 (21.1%), Cukarica – 22 (19.3%), Vracar – 12 (10.5%), and Zvezdara - 11 (9.64%), while the smallest number was in the suburban municipality Obrenovac – 7 (6.14%). The

Table 2. Number of new cases and age-specific incidence rates (per 100,000) for scarlatina, Belgrade, 2016-2020

Age groups Years	< 1 Number (Rate*)	1-4 Number (Stopa*)	5-9 Broj (Rate*)	10-14 Number (Rate*)	15-19 Number (Rate*)	20-29 Number (Rate*)	60+ Number (Rate*)	Total Number (Rate*)
2016	5 (29.4)	304 (466.9)	290 (374.3)	32 (43.7)	3 (3.5)	6 (2.6)	0	640 (38.35)
2017	2 (11.7)	464 (712.7)	347 (447.8)	37 (50.5)	4 (4.7)	9 (4.0)	1 (0.2)	864 (52.07)
2018	0	182 (279.5)	173 (265.7)	23 (31.4)	1 (1.1)	7 (3.1)	2 (0.5)	388 (23.38)
2019	3 (17.6)	229 (351.7)	176 (227.1)	15 (20.4)	0	6 (2.6)	0	429 (25.85)
2020	0	70 (107.5)	32 (41.3)	10 (13.6)	1 (1.1)	8 (3.5)	0	121 (7.14)
2016-2020	10 (11.7)	1249 (383.7)	1018 (262.8)	117 (31.9)	9 (2.1)	36 (3.22)	3 (0.1)	2442 (29.4)

*In each observed year, the highest age-specific incidence rate was at the age of 1-4 years, followed by 5-9 years, and the lowest in persons older than 15 years (Table 2). The average five-year incidence rate was 383.7 per 100,000 for ages 1-4, and 262.8 per 100,000 for ages 5-9.



Grafikon 2. Distribucija novoobolelih od šarlaha po mesecima, Beograd, 2016 – 2020. godine

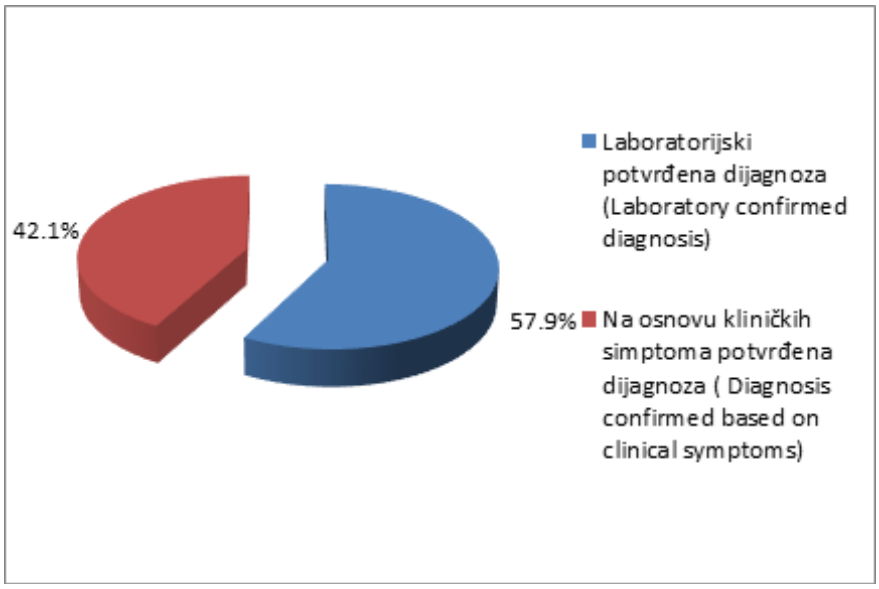
oda, kod 66 (57,9%) obolele dece dijagnoza šarlaha je postavljena na osnovu laboratorijske potvrde prisustva β-hemolitičkog streptokoka grupe A u brisu grla i/ili nosa, a kod 48 (42,1%) prema kliničkoj slici (grafikon 3).

U cilju utvrđivanja prisustva beta hemolitičkog streptokoka grupe "A" kod dece i zaposlenih u vrtićima, u okviru epidemioloških istraživanja u posmatranom petogodišnjem periodu uzorkovana su ukupno 1.393 brisa grla i nosa i to od dece – 151 i zaposlenih – 243. Bakteriološkim pregledom briseva grla i nosa od dece i zaposlenih iz kontakta sa obolelom decom, kod 349 (30,3%) dece i 13 (5,3%) zaposlenih dokazano je prisustvo beta hemolitičkog streptokoka grupe "A".

Najveći broj novoobolele dece od šarlaha je bio prvog dana – 45 (39,4%), a nešto manje drugog – 18 (15,7%) i trećeg dana – 14 (12,2%) od pojave prvog slučaja ovog oboljenja u kolektivu (tabela 3).

Diskusija

U našoj studiji, u periodu od 2016. do 2020. godine, registrovano je 30 epidemija šarlaha i 114 novoobolele dece iz 23 beogradska vrtića. U Srbiji, u periodu od 2015. do 2019. godine registrovano je 45 epidemija šarlaha u kojima je obolelo 286 dece (7). U Nemačkoj, u okrugu Rojtligen samo u 2017. godini registrovano je 57 epidemija šarlaha,



Grafikon 3. Distribucija obolele dece od šarlaha na osnovu načina postavljene dijagnoze, Beograd, 2016 – 2020. godine

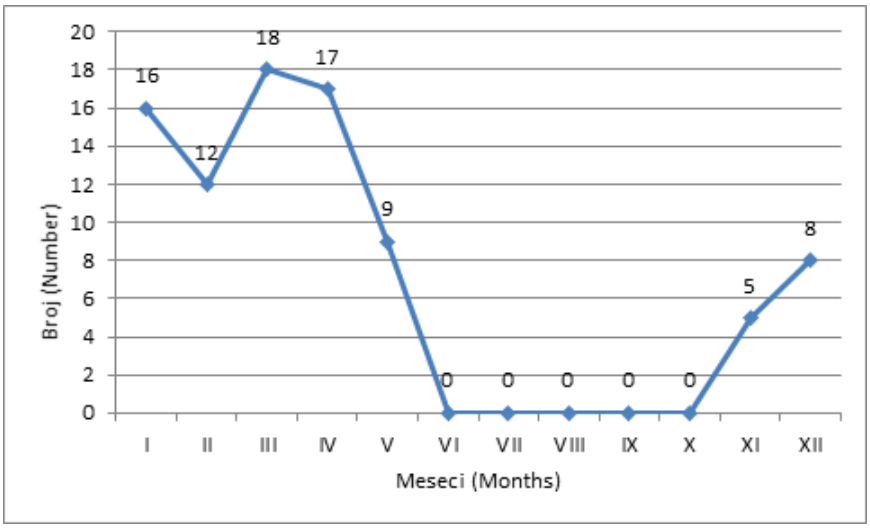


Figure 2. Distribution of new cases of scarlet fever by months, Belgrade, 2016 – 2020.

disease was not registered in other municipalities of the city of Belgrade.

Seasonal distribution pointed to the fact that the largest number of new cases was registered in early spring (March-April) – 35 (30.7%) and in late winter (January-February) – 28 (24.6%), which corresponds to the seasonal distribution of this disease (Graph 2).

In all patients, the disease was clinically manifested as fever, sore throat, throat hyperemia, and skin rash. Of 114 children affected by scarlet fever during the observed period, in 66 (57.9%) ill children, the diagnosis was made according to the laboratory confirmation of group A ß-hemolytic streptococcus in the throat and/or nose swabs, while in 48 children (42.1%) the diagnosis was made according to the clinical presentation (Graph 3).

In order to determine the presence of Group A ß-hemolytic streptococci in children and employees in kindergartens, within the scope of epidemiological investigations, in the observed time period, the total of 1393 throat and nose swabs were sampled, that is, from children – 151 and employees – 243. Bacteriological examination of the nose and throat swabs taken from children and employees who had contact with ill children, in 349 children (30.3%) and 13 employees (5.34%), the presence of Group A ß-hemolytic streptococci was confirmed.

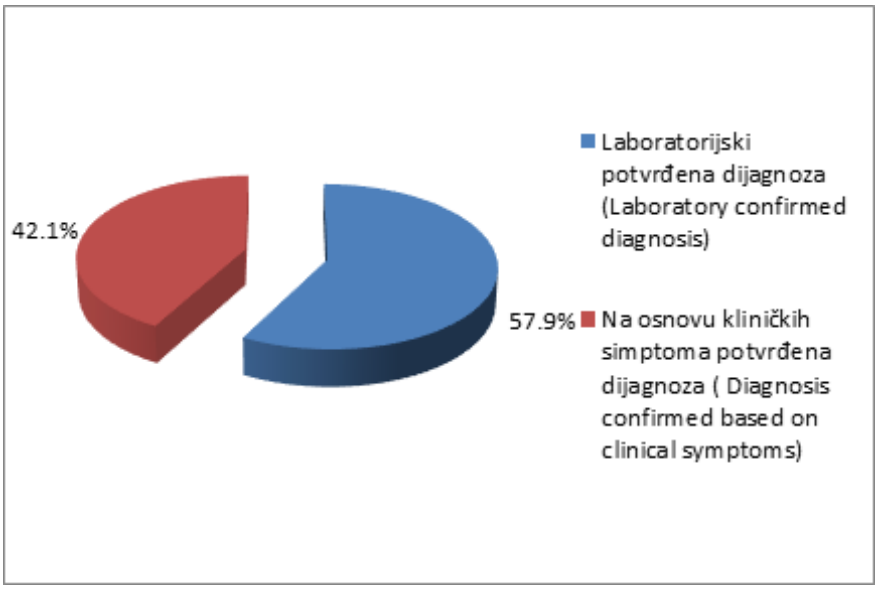


Figure 3. Distribution of children with scarlet fever based on the method of diagnosis, Belgrade, 2016 – 2020.

Tabela 3. Distribucija obolevanja od šarlaha po danima u odnosu na pojavu prvog slučaja ovog oboljenja u vrtiću, Beograd, 2016 – 2020. godine

Dan od pojave prvog slučaja obolelog od šarlaha u kolektivu	Dečaci Broj (%) n=66	Devojčice Broj (%) n=48	Ukupno Broj (%) n=114
1	28 (42,4)	17 (35,4)	45 (39,4)
2	10 (15,1)	8 (16,6)	18 (15,7)
3	8 (12,1)	6 (12,5)	14 (12,2)
4	3 (4,5)	4 (8,3)	7 (6,1)
5	3 (4,5)	6 (12,5)	9 (7,8)
6	5 (7,5)	4 (8,3)	9 (7,8)
7	1 (1,5)	1 (2,0)	2 (1,7)
8	5 (7,5)	0	5 (4,3)
9	3 (4,5)	2 (4,1)	5 (4,3)

što je činilo 55% svih prijavljenih slučajeva obolelih od šarlaha u okrugu (8).

Šarlah uzrokovan streptokokom grupe A (Streptococcus pyogenes), bio je uobičajna zarazna bolest kod dece pre početka 20. veka i glavni uzrok smrti, sa rizikom od smrtnog ishoda > 30%. Različiti faktori, uključujući poboljšanje higijene i uvođenje efikasnih antibiotika, doveli su do nestanka šarlaha kao glavnog uzrokasmrtnosti kod dece do sredine 20. veka. Međutim, tokom protekle decenije velike epidemije su prijavljene u Vijetnamu (< 23.000 slučajeva u 2009), Kini (>100.000 slučajeva koje je prijavilo Ministarstvo zdravlja) i Hong Kongu (> 1.000 slučajeva, dok su pre 2011. godine prijavljeni samo sporadični slučajevi). Manje epidemije prijavljene su u Kanadi (>100 slučajeva, 2012), Kanzasu, SAD 2012, Meksiku 2000. i Valensiji, Španiji (40 slučajeva 2011.). Razlog ove nove epidemije šarlaha u svetu ostaje nejasan. Pretpostavlja se da je ovaj fenomen posledica mikrobnih determinanti (novi sojevi sa većim kapacitetom virulencije). Verovatno je da su uključeni i faktori životne sredine i domaćina, kao i višestruki kombinovani faktori kao što su meterološke promene (9).

Prema rezultatima naše studije, tokom posmatranog petogodišnjeg perioda u Beogradu su registrovane ukupno 2442 obolele osobe od šarlaha. Najviša uzrasno specifična stopa incidencije zabeležena je u uzrasnoj grupi od 1 do 4 godine (383,7/100.000), a najniža u najstarijem uzrastu (60 i više godina) (0,1/100.000). Tokom posmatranog petogodišnjeg perioda, najčešće su obolevala deca uzrasta 4 godine (244,6/100.000), a najređe uzrasta od 2 godine (12,3/100.000). Epidemiološka istraživanja sprovedena u Hong Kongu u periodu 2012-2015. godine, ukazuju da je najveća incidencija obolevanja bila registrovana kod dece mlađe od pet godina (18,1/100.000) (10). Takođe, prema podacima epidemiološkog nadzora sprovedenog u Poljskoj 2013. godine, najviša incidencija obolelih od šarlaha registrovana je među decom uzrasta pet godina (949/100.000) I četri godina (916.6/100.000), što je slično rezultatima naše studije (11).Rezultati studije sprovedene u provinciji Dždžu u Koreji (2002-2016), ukazuju da je najviše obolelih od šarlaha bilo u starosnoj grupi 0-2 godine, što je suprotno našim rezultatima (12).

U našoj studiji dečaci su nešto više obolevali od šarlaha nego devojčice. Proporcija obolelih dečaka prema devojčicama iznosi 1,37:1. Slično našim rezultatima, studija sprovedena u provinciji Dždžijang u Kini, u period 2004-2018 godine, pokazuje da proporcija obolelih osoba muškog pola je nešto veća nego kod žena (1,62:1) (13). Tokom perioda 01.07.2016. – 30.06.2018. godine sprovedena je studija u sedam pedijatrijskih centara u Australiji, koja je pratila decu obolelu od oboljenja izazvanih težom formom beta hemolitičkog streptokoka grupe “A”. Kod svih obolelih (181) laboratorijski je potvrđen izolat streptokoka. Češće su obolevali dečaci (107; 59,1%). Većina pacijenata je bilo mlađe od 5 godina (115; 63,5%), uključujući 32 (17,7%) osobe mlađe od godinu dana. Ozbiljnu formu oboljenja je imalo 74 (40,9%) pacijenta, a 26 (14,4%) je imalo sindrom toksičnog šoka. Iako se većina pacijenata oporavila (122, 67,4%), kod 5 (2,8%) je došlo do smrtnog ishoda (14). U poređenju sa navedenom epidemijom, naše epidemije su

Tabela 3. Distribution of disease by days in relation to the occurrence of the first case of the disease in kindergartens, Belgrade, 2016 - 2020

The day since the appeaeance of the first case of a scarlet fever in the time	Boys No (%) n=66	Boys No (%) n=48	Boys No (%) n=114
1	28 (42.4)	17 (35.4)	45 (39.4)
2	10 (15.1)	8 (16.6)	18 (15.7)
3	8 (12.1)	6 (12.5)	14 (12.2)
4	3 (4.5)	4 (8.3)	7 (6.1)
5	3 (4.5)	6 (12.5)	9 (7.8)
6	5 (7.5)	4 (8.3)	9 (7.8)
7	1 (1.5)	1 (2.0)	2 (1.7)
8	5 (7.5)	0	5 (4.3)
9	3 (4.5)	2 (4.1)	5 (4.3)

The largest number of newly diagnosed children with scarlet fever was on the first day – 45 (39.4%), and slightly less on the second – 18 (15.7%) and the third day – 14 (12.2%) since the first case of this disease in the collective (Table 3).

Discussion

In our study, in the period from 2016 to 2020, 30 scarlet fever epidemics and 114 newly diseased children from 23 Belgrade kindergartens were registered. In Serbia, in the period from 2015 to 2019, 46 scarlet fever epidemics were registered, with 286 affected children (7). In Germany, in Reutlingen, 57 scarlet fever epidemics were registered in 2017, which made up 55% of all reported cases of scarlet fever in that region (8).

Scarlet fever caused by Group A streptococcus (*Streptococcus pyogenes*) was a common contagious disease in children before the 20th century and the main cause of death, with a risk of deathly outcome > 30%. Different factors, including better hygiene and the introduction of efficient antibiotics, led to the reduction in mortality caused by scarlet fever by the 1950s. However, during the last decade, great epidemics were reported in Vietnam (<23,000 cases in 2009), in China (>100,000 cases were reported by the Ministry of Health), and in Hong Kong (>1,000 cases, while before 2011, only sporadic cases were reported). Smaller epidemics were reported in Canada (>100 cases, 2012), Kansas, USA 2012, Mexico 2000, and in Valencia, Spain (40 cases, 2011). The reason for this new scarlet fever epidemic in the world remains unclear. It is assumed that this phenomenon is the consequence of microbial determinants (new strains with greater virulence capacity). It is possible that environmental factors are included, as well as factors relating to the host and multiple combined factors such as meteorological changes (9).

According to our results, during the observed five-year period, a total of 2442 persons affected by scarlet fever was registered in Belgrade. The highest age-specific incidence rate was registered in the age group 1 to 4 years (383.7/100,000), while the lowest rate was in the oldest age group (60 years and older) (0.1/100,000). During the observed five-year period, children aged 4 became ill most frequently (244.6/100,000), while children aged 2 became ill most rarely 12.3/100,000). Epidemiological investigations conducted in Hong Kong in the period 2012-2015 indicated that the highest incidence was registered in children younger than 5 years (18.1/100,000) (10). Also, according to the data of one epidemiological investigation conducted in Poland in 2013, the highest incidence of new cases of scarlet fever was registered in children aged 5 (949/100,000) and 4 years (916.6/100,000), which is similar to the results of our study (11). The results of one study conducted in the province Jeju in Korea (2002-2016) indicated that the highest number of new cases of scarlet fever was in the age group 0-2 years, which is contrary to our results (12).

In our study, boys became ill slightly more frequently than girls. The ratio of boys to girls is 1.37:1. Similar to our results, a study which was conducted in Zhejiang in China, in the period 2004-2018, showed that the proportion of new cases in men was slightly higher than in women (1.62:1) (13). From the 1st of July 2016 to the 30th of June

prošle bez komlikacija, sa brzim i potpunim oporavkom dece u kratkom vremenskom periodu.

Najveći broj novoobolele dece od šarlaha je bilo u gradskoj opštini Novi Beograd 38 (33,3%), a najmanji u prigradskoj opštini Obrenovac 7 (6,14%). Prema podacima epidemiološke studije sprovedene u gradu Hefei u Kini, u periodu 2004-2008. godine, broj obolelih od šarlaha u urbanim sredinama bio je veći nego u ruralnim, što odgovara našim rezultatima (15). Mogući razlog većeg broja obolelih od šarlaha u navedenom gradu u Kini može biti i mogućnost dostupnosti većem broju laboratorija u gradskim opštinama u odnosu na ruralna područja. Takođe, razlog većeg broja obolelih u gradskim opštinama može biti dostupnost većeg broja zdravstvenih ustanova i samim time veća mogućnost pružanja zdravstvenih usluga stanovnicima ovih opština.

U našoj studiji, šarlah je zadržalo sezonski karakter, sa najvećim brojem obolelih u martu i aprilu (30,7%) i zimskim mesecima januaru i februaru (24,6%), a najmanjim u novembru mesecu (4,3%). Suprotno našoj studiji, epidemiološko ispitivanje sprovedeno u mestu Šenjug u Kini 2018. godine, pokazuje da je najveći broj obolelih bio tokom leta u junu mesecu i u zimskom periodu u decembru (16).

Kod svih novoobolelih od šarlaha u našoj studiji klinička slika se manifestovala povišenom telesnom temperaturom, bolom u grlu, hiperemijom ždrela i ospom po koži. Od 114 obolele dece od šarlaha tokom posmatranog petogodišnjeg perioda, kod 57,9% dijagnoza šarlaha je postavljena na osnovu brisa grla i nosa, a kod 42,1% prema kliničkoj slici. U epidemiološkoj studiji sprovedenoj 2017. godine u jednoj osnovnoj i srednjoj školi Berlina, od 16 obolele dece od šarlaha kod većeg broja dece 7 (44%) dijagnoza šarlaha je postavljena prema kliničkoj slici, a kod 5 (31%) na osnovu brisa grla i nosa, suprotno rezultatima naše studije (17).

Rezultati našeg istraživanja pokazuju da su se u beogradskim vrtićima svi oboleli od šarlaha javili do devetog dana od pojave prvog slučaja bolesti u kolektivu, što ukazuje na uspešno sprovedene protivepidemijske mere. Suprotno našim rezultatima, studija sprovedena 2017. godine u vrtiću provincije Gjongi, mestu Suvon u Koreji, ukazuje da je epidemija šarlaha u tom kolektivu u odnosu na prvi slučaj oboljenja 28.03.2017. godine trajala čak 16 dana (18). Sve ovo govori o važnosti pravovremene primene protiepidemijskih mera.

Ograničenja ove studije odnose se na analizu podataka samo za jedan kratak vremenski period od pet godina, nedovoljno informacija o svakoj epidemiji posebno, kao i ne postojanju informacija o izolovanim sojeva *Streptococus pyogenes* potvrđenih kod novoobolelih slučajeva.

Zaključak

Poštovanje i blagovremena primena protivepidemijskih mera doprinose uspešnom zaustavljanju daljeg širenja infekcije (prijava oboljenja, izolacija, lečenje obolele dece, kao i pooštrene mere higijene i tekuća dezinfekcija). Neophodna su dalja istraživanja u ovoj oblasti u cilju identifikacije modela koji bi pratili i razumeli vremenske karakteristike zaraznih bolesti, odnosno kojima je bi bilo moguće predvidjanje pojave epidemije.

Konflikt interesa

Autori su izjavili da nema konflikta interesa.

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2018, a study was conducted in seven pediatric centers in Australia, and the children with the disease caused by the severe form of Group A beta-hemolytic streptococcus were monitored in this study. The isolate of streptococcus was confirmed by laboratory analyses for all new cases (181). Boys were more frequently ill (107; 59.1%). The majority of patients were younger than 5 years (115; 63.5%), including 32 (17.7%) persons younger than 1 year. Seventy-four patients (40.9%) had a severe form of the disease, while 26 (14.4%) had toxic shock syndrome. Although the majority of patients recovered (122, 67.4%), there came to the deathly outcome in 5 of them (2.8%) (14). In comparison to the mentioned epidemics, our epidemics passed without complications, with rapid and complete recovery for a short period of time.

The largest number of newly diseased children from Scarlet fever was in the city municipality of Novi Beograd 38 (33.3%), while the smallest number was in the suburban municipality Obrenovac – 7 (6.14%). According to the data of the epidemiological study conducted in the city of Hefei in China, in the period 2004-2008, the number of cases of scarlet fever was higher in urban than in rural areas, which corresponds to our results (15). A possible reason for a higher number of cases in the mentioned city in China may be the availability of a greater number of laboratories in city municipalities in comparison to rural regions. Also, a reason for the greater number of cases in city municipalities may be the availability of a greater number of health care institutions and, therefore, greater possibility of providing health care to the residents of these municipalities.

In our study, scarlet fever had seasonal character, with the largest number of cases in March and April (30.7%) and winter months January and February (24.6%), while the smallest number of cases was registered in November (4.3%). Contrary to the results of our study, one epidemiological investigation conducted in Shenyang in China in 2018 showed that the largest number of cases was in June and winter, in December (16).

In all new cases of scarlet fever in our study, the disease was manifested as fever, sore throat, hyperemia of the pharynx, and rash. Of 114 children affected by scarlet fever during the observed five-year period, in 57.9%, the diagnosis was made according to the nose and throat swabs, and 42.1% according to the clinical manifestation. In an epidemiological study conducted in 2017, in one primary and middle school in Berlin, of 16 children affected by scarlet fever, the diagnosis was made according to the clinical manifestation in 7 of them (44%), while in 5 (31%) of them, the disease was diagnosed according to the nose and throat swabs, contrary to the results of our study (17).

The results of our study indicate that in Belgrade kindergartens, all new cases of scarlet fever appeared till the ninth day of the appearance of the first case in the group, which points to the successful implementation of prevention measures. Contrary to our results, a study conducted in one kindergarten in the province of Gyeonggi in Suwon, Korea, in 2017 showed that the epidemics of scarlet fever in that collective institution lasted 16 days, in relation to the first case, which was registered on the 28th of March, 2017 (18). All this speaks in favor of the significance of timely implementation of prevention measures.

The limitations of this study refer to the analysis of data relating to the short period of time, that is, a five-year period, the insufficient information about each separate outbreak, as well as the lack of information regarding the isolation of strains streptococcus pyogenes confirmed in new cases.

Conclusion

Respect and timely application of anti-epidemic measures contribute to the successful cessation of further spread of disease (disease reporting, isolation, treatment of sick children, as well as stricter hygiene measures and ongoing disinfection). Further research is necessary in this field to identify models with which it would be possible to monitor and understand the time characteristics of contagious diseases, which would enable us to predict possible outbreaks.

Competing interests

The authors declare no competing interests.

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PRIKAZ SLUČAJA

KLINIČKE KARAKTERISTIKE I LABORATORIJSKI REZULTATI TRUDNICE SA SARS-CoV-2 INFEKCIJOM

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SAŽETAK

Uvod/Cilj: : Najčešći klinički simptomi i laboratorijski znaci SARS-CoV-2 infekcije u trudnoći su povišena temperatura, kašalj, dispneja, dijareja, limfocitopenija, leukocitoza i porast vrednosti C reaktivnog proteina. Međutim, trudnice sa komorbiditetima imaju veći rizik od teže forme kovida-19. Mnoge studije upućuju na to da trudnice sa potvrđenom SARS-CoV-2 infekcijom imaju više od dva puta povišen rizik od prevremnog porođaja, da su pod većim rizikom za razvoj preeklampsije i potrebom za hitnim carskim rezom. Cilj ovog rada je da se analizira tok i ishod SARS-CoV-2 infekcije potvrđene kod mlade žene u 39 nedelji trudnoće.
Prikaz bolesnika: Trudnica sa dokazanom SARS-CoV-2 infekcijom u 39. nedelji trudnoće porađaja se šesti dan od pojave simptoma i znakova bolesti. Na početku infekcije pacijentkinja navodi temperaturu i opšte loše stanje, a potom kašalj i na kraju bol u grudnom košu. Infekciju prate povišene vrednosti C reaktivnog proteina, D-dimera i limfocitopenija. Trudnica je mlađa osoba, osoba bez komorbiditeta, ali se kod nje šestog dana od pojave simptoma i znakova bolesti dijagnostikuje pneumonija sa tendencijom progresije, zbog čega je njena hospitalizacija nakon porođaja produžena. Nalaz kompjuterizovane tomografije odgovara bilateralnoj intersticijalnoj kovid-19 pneumoniji. Pacijentkinja je bila, sve vreme tokom hospitalizacije, hemodinamski stabilna bez potrebe za kiseoničnom potpornom terapijom. Dete je rođeno vaginalnim putem i na rođenju je bilo dobrog zdravstvenog stanja (Apgar skor 9/10, telesna težina). SARS-CoV-2 infekcija nije dokazana brzim antigenskim testom kod novorođenog deteta.
Zaključak: Neophodna su dalja istraživanja u ovoj oblasti, pogotovo o toku i ishodu infekcije kod trudnica tokom prvog i drugog trimestra trudnoće, kao i kako smanjiti neželjene neonatalne ishode kod trudnica sa SARS-CoV-2 infekcijom.

Ključne reči: COVID-19, trudnoća, prikaz slučaja

Uvod

COVID-19 je visoko kontagiozno infektivno oboljenje prouzrokovano SARS-CoV-2 virusom koje predstavlja veliki javnozdravstveni problem i vodeći je uzrok umiranja na globalnom svetskom nivou (1). Procenjuje se, prema podacima Svetske zdravstvene organizacije, da je u svetu do 14. marta 2022. godine potvrđeno oko 457 miliona slučajeva COVID-19 i oko 6 miliona smrtnih slučajeva (1). Ova infekcija uticala je na sve ginekologe i akušere (kao i na njihova udruženja) da pokušaju da daju odgovore na brojna pitanja vezana za uticaj ove infekcije, kako na tok i ishod trudnoće, tako i kakav efekat ova infekcija ima na fetus (2).

SARS-CoV-2 infekcija predominantno doprinosi nastanku pneumonije, ali ova sistemska virusna infekcija može dovesti do disfunkcije mnogobrojnih organa i sistema (kardiovaskularnog, hematološkog, gastrointestinalnog, endokrinog, urogenitalnog) (2). Infekcija COVID-19 može da bude od asimptomatske do klinički manifestne (od blage, srednje teške, teške, do fatalne). Teže kliničke forme ove infekcije dovode se u vezu sa prisustvom jednog ili više komboditeta (stariji uzrast, hipertenzija, dijabetes, astma, HIV infekcija, hronična bolest srca, hronična bolest jetre, hronična bolest pluća, hronična bolest bubrega, transplantacija solidnih organa, maligni tumori, imunodeficitna stanja) (3-5).

Neka istraživanja ukazuju da trudnice nisu u većem riziku od COVID-19 infekcije ili teške forme

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CASE REPORT

CLINICAL CHARACTERISTICS AND LABORATORY RESULTS OF A PREGNANT WOMAN WITH SARS-COV-2 INFECTION

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SUMMARY

Introduction/Aim: The most common symptoms and laboratory signs of SARS-CoV-2 infection in pregnancy are the following: fever, cough, dyspnea, diarrhea, lymphocytopenia, leukocytosis and a high level of CRP. However, pregnant women with comorbidities are at an increased risk of severe forms of COVID-19. Numerous studies point to the fact that pregnant women with the confirmed SARS-CoV-2 infection have more than two times higher risk of preterm labor, and that they are at an increased risk of preeclampsia and emergency Cesarean section. The aim of this paper is to analyze the course and outcome of SARS-CoV-2 confirmed in a young woman in the 39th week of pregnancy.

Case report: A pregnant woman with the confirmed SARS-CoV-2 infection in the 39th week of pregnancy delivered a baby on the sixth day from the appearance of symptoms and signs of disease. At the beginning of infection, the patient reported fever, poor general health status, and then cough and chest pain. The infection was accompanied by increased levels of C reactive protein, D-dimer and lymphocytopenia. The patient is a young woman without comorbidities, but pneumonia with a tendency toward progression was diagnosed six days after symptoms and signs appeared, due to which her hospitalization after delivery was prolonged. The findings of computerized tomography showed bilateral interstitial COVID-19 pneumonia. The patient was hemodinamically stable all the time during hospitalization and did not need oxygen support. The baby was delivered vaginally with good general health status (Apgar score 9/10, body weight). SARS-CoV-2 infection was not confirmed with the rapid antigen test in the newborn.

Conclusion: Further research is needed in this field, especially research on the course and outcome of infection in pregnant women during the first and second trimester of pregnancy, as well as on the ways how to reduce unwanted neonatal outcomes in pregnant women with SARS-CoV-2 infection.

Keywords: COVID-19, pregnancy, case report

Introduction

COVID-19 is a highly contagious disease caused by SARS-CoV-2 virus, which presents a great public health problem and it is the leading cause of deaths globally (1). It is estimated, according to the data of the World Health Organization, that 457 million cases of COVID-19 and about 6 million deaths were confirmed in the world by 14th March 2022 (1). This infection influenced all gynecologists and obstetricians (as well as their associations) to try to give response to numerous questions regarding the impact of this infection on the course and outcome of pregnancy, as well as the effect which this infection has on the fetus (2).

SARS-CoV-2 infection predominantly contributes to the occurrence of pneumonia, but this systemic viral infection may lead to the dysfunction of numerous organs and systems (cardiovascular, hematological, gastrointestinal, endocrine, urogenital) (2). The COVID-19 infection may be asymptomatic or it can have different clinical manifestations (from mild, moderate, severe to fatal). Severe clinical forms of this infection are associated with the presence of one or more comorbidities (older age, hypertension, diabetes, asthma, HIV infection, chronic heart disease, chronic liver disease, chronic pulmonary disease, chronic kidney disease, solid organ transplants, malign tumors, immunodefficient conditions) (3-5).

Some studies point to the fact that pregnant women are not at an increased risk of COVID-19

bolesti ili češćeg boravka u jedinicama intezivne nege ili smrtnog ishoda u odnosu na žene koje nisu trudne (6). Međutim, neke studije ukazuju da trudnice sa komorbiditetima imaju veći rizik od teže forme COVID-19 (7).

Najčešći klinički simptomi i laboratorijski znaci SARS-CoV-2 infekcije u trudnoći su povišena temperatura, kašalj, dispneja, dijareja, limfocitopenija, leukocitoza i porast nivoa C reaktivnog proteina (8).

Mnogi radovi upućuju na to da trudnice sa potvrđenom SARS-CoV-2 infekcijom imaju više od dva puta povišen rizik od prevremnog porođaja, perinatalnog mortaliteta (kod trudnica sa težim oblikom bolesti), da su pod većim rizikom za razvoj preeklampsije i potrebom za hitnim carskim rezom (9-11). Oboje, i majka i novorođenče, su pod većim rizikom da imaju produženu hospitalizaciju nakon porođaja, a i češća je poteba za ponovnom hospitalizacijom porodilja nakon porođaja (9,12).

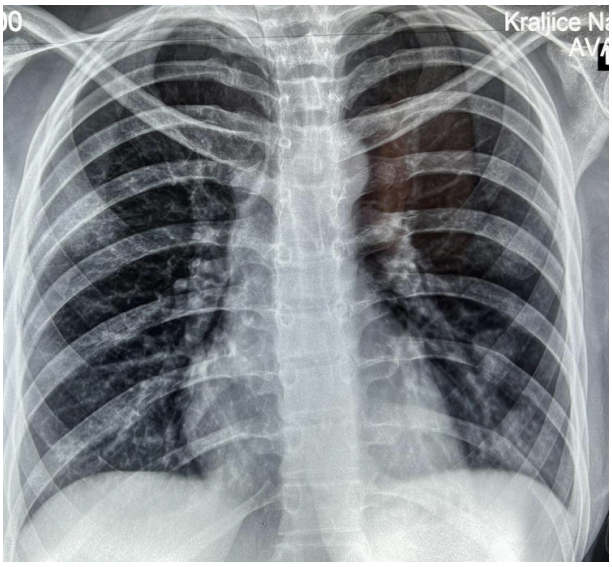
Cilj ovog rada je da se analizira tok i ishod SARS-CoV-2 infekcije potvrđene kod mlade žene u 39. nedelji trudnoće.

Prikaz pacijenta

Trudnica stara dvadeset i šest godina sa urednim tokom trudnoće, u anamnezi sa jednim porođajem i trudnoćom bez komplikacija, bez pobačaja, kao i bez hroničnih oboljenja, redovno je kontrolisala tok trudnoće ambulantno u Domu zdravlja Voždovac, Beograd. Na svim rutinskim pregledima koji su obuhvatali i laboratorijske analize krvi, uključujući i test opterećenja glukozom (OGTT), rezultati su bili u fiziološkim granicama. Trudnica je bila normotenzivna, dobro se osećala, a indeks telesne mase na početku trudnoće je bio 22,5 kg/m^2. Do kraja trudnoće telesna težina je uvećana za još 15 kg. Svi ultrazvučni nalazi ukazivali su na eutrofičan rast morfološki urednog ploda, a akušerski pregledi su bili uredni. Pacijentkinja nije bila vakcinisana protiv SARS-CoV-2.

U trideset devetoj nedelji trudnoće javlja se u COVID ambulantu pri Domu zdravlja zbog povišene telesne temperature (37,8^{o}C), navodi bol u gornjem delu leđa i zapušenost nosa. Fizički status na plućima je uredan. Brzim antigenskim testom se dokazuje prisustvo SARS-CoV-2 infekcije, a laboratorijske analize su ukazale samo na povišene vrednosti laboratorijskog parametra inflamacije – C reaktivnog proteina (CRP), koji je bio 11,3 mg/l (granična vrednost 0-3 mg/l). Ordinirana je antibiotska, antipiretična i vitaminska terapija uz izolaciju i mirovanje.

Na kontroli nakon tri dana od pojave simptoma, trudnica navodi da nema tegobe, da je bez temperature i da se oseća bolje. Nalaz na plućima je bio uredan, a CRP je iznosio 28,5 mg/l. Nakon šest dana od pojave simptoma, trudnica dobija trudove i javlja se u porodilište radi porođaja. Po prijemu je kompletno laboratorijski i klinički ispitana. Laboratorijske analize na prijemu ukazuju na povišene vrednosti CRP-a od 32,4 mg/l i D dimera od 2110 ng/l (referentne vrednosti za treći trimestar trudnoće kreću se 300-1700 ng/l). Trudnica se dobro osećala, negirala je respiratorne tegobe i bila je afebrilna sa urednim internistčkim nalazom. Na rentgenskom (Rtg) snimku pluća opisuje se sa



Slika 1. Prvi rendgenski snimak pluća

infection, severe forms of disease, more frequent stay at intensive care units, or deathly outcomes in comparison to non-pregnant women (6). However, some studies indicate that pregnant women with comorbidities are at an increased risk of severe forms of COVID-19 (7).

The most common clinical symptoms and laboratory signs of SARS-CoV-2 infection in pregnancy are fever, cough, dyspnea, diarrhea, lymphocytopenia, leukocytosis and increased levels of C reactive protein (8).

Numerous studies indicate that the risk of preterm birth is more than twice as high in pregnant women with the confirmed SARS-CoV-2 infection, as well as the risk of perinatal mortality (in pregnant women with severe forms of disease), of preeclampsia and emergency Cesarean section (9-11). Both the mother and the child are at an increased risk of prolonged hospitalization after delivery, and the need for repeated hospitalization of pregnant women after delivery is more frequent (9,12).

The aim of this paper is to analyze the course and outcome of SARS-CoV-2 infection, which was confirmed in a young woman in the 39th week of pregnancy.

Case report

A twenty-six-year old pregnant woman with normal pregnancy course had one delivery and pregnancy without complications in her anamnesis, with no miscarriages, and chronic diseases. She regularly controlled the course of pregnancy at the Health Center Vozdovac, Belgrade. The results of all routine check-ups, which included the laboratory analyses of blood including the oral glucose tolerance test (OGTT), were within reference values. The pregnant woman was normotensive, she felt well, while the body mass index at the beginning of pregnancy was 22.5 kg/m^2. Her body weight increased for 15 kg till the end of pregnancy. All ultrasound findings indicated the eutrophic growth of fetus with normal morphology, and the obstetric examination was normal. The patient was not vaccinated against SARS-CoV-2.

In the thirty-ninth week of pregnancy, the patient came to an outpatient COVID clinic at the Health Center due to fever (37.8^{0}C), upper back pain and congested nose. Physical lung status was normal. A rapid antigen test proved the presence of SARS-CoV-2 infection, while laboratory results indicated only the increased levels of the laboratory inflammation parameter – C reactive protein (CRP), which was 11.3 mg/l (reference values 0-3 mg/l). Antibiotic, antipyretic and vitamin therapy was administered together with isolation and bed rest.

During the control check-up, three days after the symptoms appeared, the pregnant woman stated that she did not have symptoms, that she had no fever and that she felt better. Findings on the lungs were normal, and CRP was 28.5 mg/l. Six days after the symptoms appeared, the pregnant woman experienced labor contractions and went to the maternity hospital. After she was admitted, complete clinical and laboratory examination was

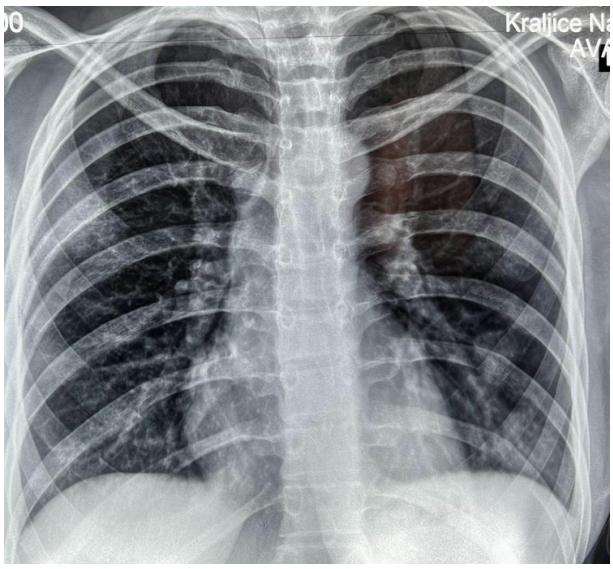
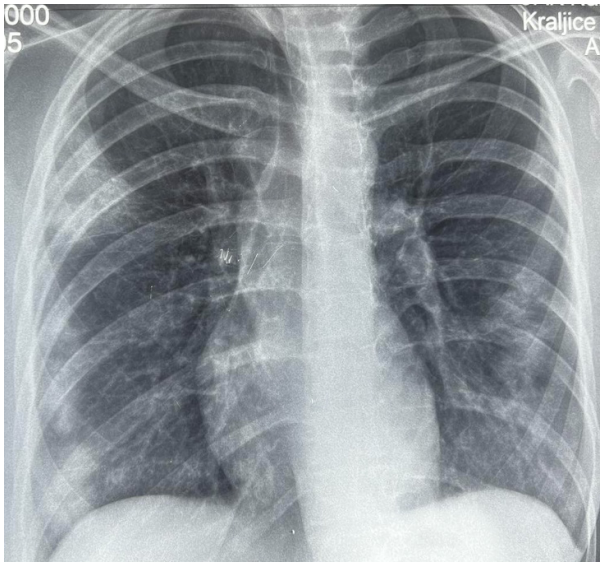


Figure 1. The first X-ray of the lungs



Slika 2. Drugi rendgenski snimak pluća

leve strane parakardijalno manja zona konsolidacije parenhima po tipu inflamacije (slika 1). Trudnica se istog dana spontano vaginalno porađa i rađa dete telesne mase 3920 grama sa Apgar ocenom 9/10. Dete je nakon rođenja testirano brzim antigenskim testom. Test je bio negativan. Porođaj i postporođajni tok protekli su uredno. Pacijentkinja je tokom hospitalizacije bila pod konstatnim intezivnim nadzorom, uz svakodnevno merenje telesne temperature, saturacije kiseonikom (nivoa zasićenja hemoglobina crvenih krvnih zrnaca kiseonikom - SpO_2) i ostalih vitalnih parametara, koji su bili uredni.

Četvrtog dana od porođaja, odnosno devetog dana od pojave simptoma, urađen je kontrolni Rtg snimak pluća i konstatovano je difuzno prisustvo zona konsolidacje u plućnom parenhimu po tipu inflamacije, dominantnije sa desne strane (slika 2). Zbog radiografskog pogoršanja u smislu bilateralne pneumonije u progresiji u odnosu na ranije načinjen snimak, a uz uredan ginekološki nalaz, porodilja se prevodi u Kovid bolnicu u Batajnicu. Na dan otpusta ona navodi tegobe u vidu suvog kašlja, afebrilna je, normotenzivna, eupnoična, puls 91/min, SpO_2 98% (normalne vrednosti su preko 95%), bez kiseonične potpore, laboratorijske analize u granicama referetnih vrednosti sem CRP -a koji je iznosio 22,3 mg/l.

Pacijentkinja se prima na odeljenje poluintezivne nege Kovid bolnice, a laboratorijska analiza na dan prijema ukazuje na povišene vrednosti CRP (40,6 mg/l) i limfocitopeniju (0,83 x 10^9/l; referentne vrednosti se kreću 1,19-3,35x10^9/l). Svi drugi parametri su bili uredni, a njeno opšte stanje je bilo dobro. Drugog dana od prijema u Kovid bolnicu urađen je Rtg snimak pluća i srca na kome je opisana naglašena bronhovaskularna šara obostrano. Tokom hospitalizacije u Kovid bolnici pacijentkinja je lečena prema aktuelnom Nacionalnom protokolu za lečenje COVID-19 uz primenu sistemske kortikosteroidne, parenteralne antibiotske, antikoagulantne i gastroprotektivne terapije uz nadoknadu tečnosti i elektrolita. Petog dana od prijema u Kovid bolnicu urađena je kompjuterizovana tomografija (CT) grudnog koša gde se navodi da se u svim lobusima pluća vide fokalne kružne promene povišenog denziteta parenhima pluća po tipu mlečnog stakla, lokalizovane dominantno periferno. Nalaz odgovara bilateralnoj intersticijalnoj COVID-19 pneumoniji. CT skor pluća (engl. *severity score*) je 6/25. Posle primenjene terapije dolazi do subjektivnog i kliničkog poboljšanja uz pad CRP-a koji je 2,8 mg/l, ali i povišenih vrednosti D dimera (do 910 ng/ml). Pacijentkinja je sve vreme hospitalizacije hemodinamski stabilna bez potrebe za kiseoničnom potpornom terapijom, te se otpušta nakon trinaest dana od pojave simptoma sa odeljenja uz nastavak terapije (*per os*) još narednih sedam dana i izolaciju od dve nedelje.

Nakon 10 dana od otpusta iz Kovid bolnice pacijentkinja se javlja u Dom zdravlja na kontrolni pregled, a od tegoba navodi jedino osećaj pritiska u grudima. Rtg snimak pluća i srca je ukazao na obostrane difuzne trakaste senke zadebljalog intersticijuma u sklopu organizacije COVID infekcije. CRP je iznosio 5,1 mg/l, a SpO_2 je bila 98%.

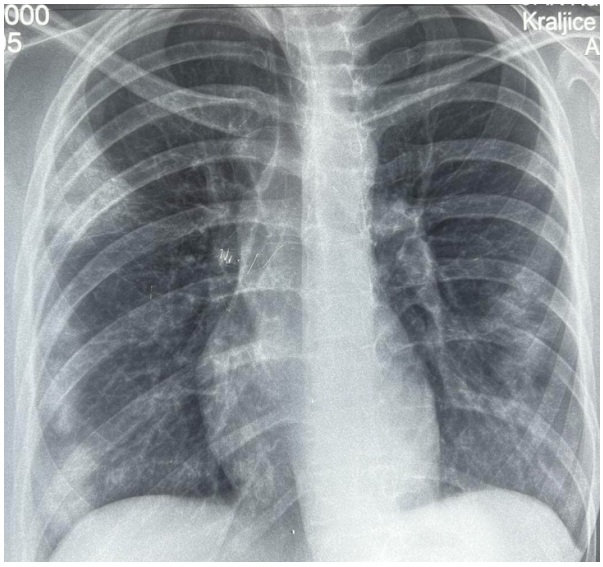


Figure 2. The second X-ray of the lungs

done. Laboratory analyses on admission indicated increased values of CRP of 32.4 mg/l and D-dimer of 2110 ng/l(reference values for the third trimester range between 300-1700 ng/l). The pregnant woman felt well, she negated the respiratory problems and was not febrile with normal clinical findings. On chest radiography, a smaller zone of parenchymal consolidation, whose type of change was inflammatory, was described on the left side pericardially (Figure 1). The pregnant woman delivered a baby spontaneously and vaginally on that day, and she gave birth to a baby with Apgar score 9/10 and body weight 3920 grams. The baby was tested with the rapid antigen test. The test was negative. Delivery and postpartum course were normal. During hospitalization, the patient was under constant supervision, and body temperature was measured every day, as well as oxygen saturation (the fraction of oxygen-saturated hemoglobin relative to total hemoglobin in blood) and other vital parameters, which were within normal ranges.

Four days after delivery, that is, nine days after the appearance of symptoms, control chest X-ray was done and it showed diffuse presence of consolidation in lung parenchyma, reflecting inflammation, which was more dominant on the right side (Figure 2). Due to the radiographic worsening, that is, bilateral pneumonia which progressed in comparison to the previous image, and with normal gynecological findings, the patient who had given birth was transported to the COVID Hospital "Batajnica". On the day of discharge from the hospital, she reported cough, she was not febrile, she was normotensive, eupneic, her heart rate was 91/min, SpO^2 98% (normal values are over 95%), without oxygen support, and laboratory analyses were within reference values, except CRP which amounted to 22.3 mg/l.

The patient was admitted to high dependency unit of COVID Hospital, and laboratory results showed elevated values of CRP (40.6, mg/l) and lymphocytopenia ($0.83x10^9$/l; reference values range from $1.19\text{-}3.35x10^9$/l). All the other parameters were normal, and her general health status was good. Two days after admission to the hospital, a chest X-ray was done and prominent bronchovascular marking was described bilaterally. During the hospitalization in the COVID Hospital, the patient was treated according to the National Protocol for the treatment of COVID-19, with the application of corticosteroids, parenteral antibiotics, anticoagulant and gastroprotective therapy with the replenishment of fluids and electrolytes. Five days after admission to the hospital, computerized chest tomography was done and focal ground-glass changes of increased parenchymal density were seen in all pulmonary lobules, and the localization was dominantly peripheral. The findings corresponded to the bilateral interstitial COVID-19 pneumonia. The CT score was 6/25. After the administered therapy, there came to the clinical and subjective improvement with a decline in CRP, which was 2.8 mg/l, but also the increase in D-dimer values (to 910 ng/ml). The patient was hemodinamically

Pacijentkinja se upučuje na pregled u pulmološku ambulatnu Kliničko bolničkog centra Zemun, gde je D dimer 865 ng/ml, EKG urednog zapisa, a srčana frekvencija 90/min. Na osnovu urađene CT pulmoangiografije utvrđeno je da je glavno stablo bez defekata u punjenju. Pacijentkinja se otpušta uz nastavak sistemske antikoagulantne terapije još dve nedelje. Poslednji pregled je obavljen u Domu zdravlja nakon 62 dana od početka simtoma i nakon završene terapije, kada se pacijentkinja osećala dobro, urednog fizičkog nalaza i uz uredne laboratorijske analize.

Diskusija

U našem radu prikazan je tok i ishod SARS-CoV-2 infekcije kod trudnice kod koje je dokazana infekcija u 39 nedelji trudnoće i koja se porađa šesti dan od pojave simptoma i znakova bolesti (u 40 nedelji trudnoće). Trudnica je mlađa osoba, bez komorbiditeta, ali kod nje se šestog dana od pojave simptoma i znakova bolesti dijagnostikuje bilateralna intersticijalna pneumonija uzrokovana SARS-CoV-2 infekcijom, zbog čega je njena hospitalizacija nakon porođaja bila produžena. Osim toga, nije došlo do infekcije novorođenog deteta i ono je na rođenju bilo dobrog zdravstvenog stanja (ocena prema Apgar skoru 9/10).

Dosadašnja istraživanja ukazuju da trudnice imaju isti rizik od zaražavanja SARS-CoV-2 infekcijom kao i ostale zdrave osobe (13). Većina trudnica, tj. oko dve trećine onih koje su inficirane SARS-CoV-2 virusom su bez simptoma ili sa blagim oblikom bolesti, a jedna trećina sa srednje teškim /teškim oblikom COVID-19. One trudnice koje su imale težu formu bolesti imale su veći rizik za pojavu komplikacija, kao što su preterminski porođaj i mala telesna težina ploda na porođaju, neonatalna infekcija, kao i potreba za intezivnom negom novorođenčeta (13). Neke studije ukazuju na značajnu povezanost između težeg oblika COVID-19 kod trudnica i preterminskog porođaja jatrogeno izazvanog, naročito u trećem trimestru (13). Ovi nepovoljni ishodi u trudnoći naročito su povezani sa pneumonijom, koja je glavni faktor komplikacija kod trudnice sa COVID-19. Takođe je uočena i češća hospitalizacija kod trudnica koje se nalaze u kasnijem periodu trudnoće (14). Moguća je i vertikalna transmisija virusa sa majke na dete, ali ona nije česta (15,16). Novorođenčad SARS-CoV-2 pozitivnih trudnica češće imaju potrebu za intezivnom negom nakon rođenja, a neke sudije ukazuju da kod inficirnih trudnica možemo da očekujemo češći preterminski porođaj i fetalnu smrt (7,15,16).

Neophodna su dalja istraživanja u ovoj oblasti, pogotovo tok i ishod infekcije kod trudnica tokom prvog i drugog trimestral trudnoće, kao i kako smanjiti neželjene neonatalne ishode kod trudnica sa SARS-CoV-2 infekcijom.

Zaključak

Dosadasnja znanja o SARS-CoV-2 infekciji su nepotpuna. Kod prikazane pacijentkinje nije se očekivao ozbiljniji razvoj toka bolesti s obzirom da nije postojao ni jedan faktor rizika udružen sa COVID-19, jer se radilo o mladoj osobi bez komorbiditeta. Međutim, zbog specificnosti stanja organizma u trudnoći, trudnice sa laboratorijski pozitivnim testom na infekciju SARS-CoV-2, spadaju u deo populacije na koju treba obratiti posebnu pažnju zbog mogućih komplikacija, kao i zbog mogućnosti prenošenja infekcije sa majke na plod.

Konflikt interesa

Autori su izjavili da nema konflikta interesa.

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stable all the time during hospitalization with no need for oxygen support, and therefore, she was discharged thirteen days after the appearance of symptoms with the continuation of therapy (per os) during the following seven days and isolation of two weeks.

Ten days after she had been discharged from the COVID hospital, the patient came to the Health Center for the control examination, and she reported only the feeling of chest pressure. Rtg image of lungs and heart showed bilateral diffuse patchy shadows with interstitial thickening caused by COVID-19 infection. CRP was 5.1 mg/l, while SpO2 was 98%. The patient was directed to the outpatient respiratory clinic within the Clinical Center "Zemun", where D-dimer was 865 ng/ml, ECG was normal, and heart rate was 90/min. According to the CT pulmonary angiography, the main pulmonary trunk was without filling defects. The patient was discharged with the continuation of systemic anticoagulant therapy lasting two weeks. The last examination was done in Health Center, 62 days from the appearance of symptoms and after therapy, when the patient felt good, with normal physical examination and normal laboratory analyses.

Discussion

The course and outcome of SARS-CoV-2 infection in the pregnant woman, whose infection was confirmed in the 39th week of pregnancy and who delivered a baby six days after the appearance of symptoms and signs (in the 40th week of pregnancy), was presented in our paper. The pregnant woman is a younger person, without comorbidities, however, bilateral interstitial pneumonia caused by SARS-CoV-2 infection was diagnosed on the sixth day after the appearance of symptoms, due to which her hospitalization after delivery was prolonged. In addition, the newborn baby was not infected, and it had a good health status at birth (Apgar score 9/10).

Previous studies indicate that pregnant women are at the same risk of SARS-CoV-2 infection as other healthy persons (13). The majority of pregnant women, that is, about two thirds of them, who are infected with SARS-CoV-2 virus have no symptoms/or mild form of disease, while one third of them have moderately severe/severe forms of COVID-19. Those pregnant women, who had a severe form of disease, were at an increased risk of complications, such as preterm birth and small body weight of fetus at the time of birth, neonatal infection, as well as the need for the intensive care of the newborn (13). Some studies point to the significant correlation between severe forms of COVID-19 in pregnant women and iatrogenic preterm birth, especially in the third trimester (13). These unfavorable outcomes in pregnancy are associated with pneumonia, which is the main factor of complications in a pregnant woman with COVID-19. More frequent hospitalization was noticed in pregnant women, who were in late periods of pregnancy (14). Vertical mother-to-child transmission is possible, but it is not frequent (15,16). Newborns of SARS-CoV-2 positive pregnant women need intensive care after birth more frequently, and some studies indicate that in infected pregnant women, preterm birth and fetal death can be expected (7,15,16).

Further research is needed in this field, especially research on the course and outcome of infection in pregnant women during the first and second trimester of pregnancy, as well as on the ways how to reduce unwanted neonatal outcomes in pregnant women with SARS-CoV-2 infection.

Conclusion

Previous knowledge of SARS-CoV-2 infection is not complete. In the presented patient, severe development of the course of disease was not expected because there were no risk factors linked to COVID-19 because the patient was a young person without comorbidities. However, due to the specific state of organism in pregnancy, pregnant women with the laboratory confirmed positive test for SARS-CoV-2 infection belong to the population group, which requires special attention due to possible complications and mother-to child transmission.

Competing interests

The authors declare no competing interests.

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AKTUELNA TEMA

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JAVNOZDRAVSTVENI NADZOR NAD LEGIONARSKOM BOLEŠĆU POVEZANOM SA PUTOVANJIMA U EVROPI I CRNOJ GORI

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SAŽETAK

Cilj ovog rada je da prikaže način sprovođenja javnozdravstvenog nadzora nad legionarskom bolešću povezano sa putovanjima kako u Evropi, tako i u Crnoj Gori. Procene Evropskog centra za kontrolu i prevenciju bolesti (engl. European Centre for Disease Prevention and Control - ECDC) ukazuju da se oko hiljadu turista iz Evrope godišnje inficira legionelama prilikom odmora i boravka u hotelima širom kontinenta. Evropske mreže za nadzor nad legionarskom bolešću (engl. E*uropean Legionnaires' Disease Surveillance Network* - ELDSNet) je osnovana sa ciljem otkrivanja, suzbijanja i prevencije slučajeva obolevanja, formiranja klastera i izvora epidemija legionarske bolesti koja je najčešće povezana sa putovanjima, a koji su prijavljeni na području Evropske unije (engl. *European Union - EU*) i Evropske ekonomske zone (engl. *European Economic Area* - EEA), kao i pružanja pomoći pri otkrivanju i odgovoru na epidemije izvan EU/EEA. Razmena informacija dovodi do konkretnih i pravovremenih akcija članica ELDSNet-a, kako bi se zaštitili stanovnici EU/EEA koji putuju i van Evrope. ECDC preporučuje set mera koje treba da sprovedu javnozdravstvene vlasti i turistički sektor zemlje koju je posetio oboleli putnik. Ukoliko se te mere sprovode, informacije se objavljuju *online* i veliki evropski turoperatori mogu da ih koriste pri odabiru rezervacije aranžmana u inostranstvu. Operativne procedure obezbeđuju set zajedničkih mera koje treba da budu praćene od strane svih EU/EEA zemalja koje su uključene u zaštitu svojih građana od legionarske bolesti. Svaki slučaj obolevanja od legionarske bolesti kod turista u evropskom regionu, koji je u naveo boravak u Crnoj Gori, se takođe, epidemiološki obrađuje i to po propisanim procedurama ELDSNet mreže.

Ključne reči: legionarska bolest, evropska mreža za nadzor legionarske bolesti, putovanja

Uvod

Legionarska bolest (LB) je prvi put identifikovana 1976. godine u Filadelfiji, registrovanjem teške upale pluća među učesnicima Američke legije i prvi put je opisana od strane *Fraser*-a i sar. 1977. godine (1,2).

Legionella je bakterija široko rasprostranjena u prirodi. U manjem broju se može naći u okruženju vodenih izvora (reka , jezera, rezervoara). Iz prirodnih izvora, prelazi na mesta koja sadrže veštačke rezervoare (vodovodni sistemi u naseljima, vodovodni sistemi u individualnim zgradama, itd.) (3). *Legionella* se ne razmnožava na temperaturi ispod 20°C (posebno soj *Legionella pneumophila*) i ne može preživeti u vodi koja se održava iznad 60°C (3). Može, međutim, da ostane u stanju mirovanja u hladnoj vodi i da se razmnožava kada je temperatura između 20°C i 45°C. Prisustvo sedimenata, mulja, kamenca, rđe i ostalih materijala u okviru vodenog sistema, zajedno sa biofilmovima, igraju značajnu ulogu u zadržavanju i pružanju povoljnih uslova u kojima *Legionella* može da raste (3).

U svetu je do sada opisana 61 vrsta legionele, a 28 vrsta izaziva oboljenja kod ljudi (4,5). *L. pneumophila* serogrpa-1 je u gotovo 80% prouzrokovač legionarske bolesti, dok ostali deo čine manje rasprostranjeni ili retki uzročnici iz ostalih serogrupa.

Legionarska bolest se javlja sporadično, u vidu registrovanja klastera i u epidemijskoj formi, kao i više slučajeva povezanih sa zajedničkom vremenskom i prostornom izloženošću (3).

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ACTUAL TOPIC

PUBLIC HEALTH SURVEILLANCE OF TRAVEL-ASSOCIATED LEGIONNAIRES' DISEASE IN EUROPE AND MONTENEGRO

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SUMMARY

The aim of this study is to show how public health surveillance of travel-associated Legionnaires' disease was conducted in Europe, as well as in Montenegro. The estimations of the European Centre for Disease Prevention and Control (ECDC) indicate that every year about one thousand tourists from Europe get infected by legionellae during their holiday and stay at hotels across the continent. The European Legionnaires' Disease Surveillance Network (ELDSNet) was established with the aim to detect, control and prevent cases, clusters and sources of outbreaks of travel-associated Legionnaires' disease within the European Union (EU) and European Economic Area (EEA), and to assist with detection and response to outbreaks outside the EU/EEA. Sharing information leads to concrete and timely actions of member states of ELDSNet, so that residents of the EU/EEA who travel abroad are protected. ECDC recommends a set of measures that should be followed by public health authorities and tourist sector of the country which was visited by the traveler who caught this disease. If the measures are not carried out, information is published online and European tour operators can use the information when booking holiday packages abroad. Operating procedures provide a set of common measures which should be followed by all EU/EEA member states involved in the protection of their residents against Legionnaires' disease. Each case of Legionnaires' disease which is reported in tourists, who stayed in Montenegro, is epidemiologically analyzed according to the operating procedures of ELDS Network.

Key words: Legionnaires' disease, European Legionnaires' Disease surveillance Network, travels

Introduction

Legionnaires' disease was first identified in 1976 in Philadelphia, when severe pneumonia was registered among the participants of the American Legion and it was first described by Fraser and associates in 1977 (1,2).

Legionella is a bacterium which is widespread in nature. It can be found in low numbers in environmental water sources (rivers, lakes and reservoirs). From natural sources, it passes into sites that constitute an artificial reservoir (channeled water systems in towns and water systems in individual buildings, etc.) (3). *Legionella* does not multiply below 20oC (particularly *Legionella pneumophila* strains) and cannot survive in water maintained above 60°C (3). However, it may remain dormant in cool water and multiply when water temperature is between 20°C and 45°C. The presence of sediment, sludge, scale, rust and other material within the water system together with biofilms play an important role in harboring and providing favorable conditions in which Legionella may grow (3).

In the world, 61 different species of *Legionella* have been described so far, while 28 species cause human disease (4,5). *L. pneumophila* serogroup-1 causes almost 80% of cases of Legionnaires' disease, while less widespread or rare species from other serogroups make the remaining part.

Legionnaires' disease appears sporadically, in the form of clusters and outbreaks, as well as several cases connected with the mutual temporal and spatial exposure (3). It affects more frequently people older than 40 years, men, smokers, people who drink alcohol, as well as people, who

Češće se javlja kod osoba starijih od 40 godina, muškaraca, pušača, korisnika alkohola, kao i kod osoba koji u ličnoj anamnezi navode transplantaciju organa, postojanje hroničnih bolesti i imunodeficijenciju (6).

Učestalost i rasprostranjenost legionarske bolesti u EU/EEU i Crnoj Gori

U Evropskom regionu u 2019. godini, 28 zemalja je prijavilo 11.298 slučajeva obolevanja od legionarske bolesti, od kojih su 10.636 (94%) klasifikovani kao potvrđeni slučajevi. Broj novoobolelih od legionarske bolesti je iznosio 2,2 na 100.000 stanovnika, što je najveća do sada zabeležena stopa incidencije u EU/EEA (7). U posljednjih pet godina stope incidencije gotovo su se udvostručile u zemljama EU/EEA, i to sa 1,4/100.000 stanovnika u 2015. godini na 2,2/100.000 stanovnika u 2019. godini (tabela 1). U četiri zemlje EU (Francuskoj, Nemačkoj, Italiji i Španiji) broj prijavljenih slučajeva legionarske bolesti iznosio je čak 71% ukupnog broja prijavljenih slučajeva u EU/EEA, iako populacija ovih zemalja predstavlja oko 50% stanovništva EU/EEA (7).

Prema podacima Centra za suzbijanje i prevenciju bolesti iz Atlante (engl. *Centers for Disease Control and Prevention* – CDC), u Sjedinjenim Američkim Državama u 2018. godini prijavljeno je oko 10.000 slučajeva ove bolesti, što se može smatrati potcenjenim brojem slučajeva, zbog nedovoljnog sprovođenja dijagnostike legionarske bolesti (8). Nedavno sprovedena studija procenila je da stvarni broj obolelih od legionarske bolesti može biti 1,8-2,7 puta veći od onog što je prijavljeno (8).

Na osnovu podataka dobijenih iz registra za zarazne bolesti, Instituta za javno zdravlje, u periodu od 01.01.2011. do 31.12.2020. godine u Crnoj Gori, ukupno su registrovana 4 novoobolele osobe od legionarske bolesti i to 2013. godine dva slučaja (stopa incidencije 0,32/100.000 stanovnika) i 2019. godine dva slučaja (stopa incidencije 0,32/100.000 stanovnika) (9,10). Svi oboleli bili su muškarci, uzrasta od 30 do 60 godina. Svi oboleli nisu putovali i nisu bili epidemiološki povezani.

Kliničke karakteristike legionarske bolesti i dijagnostika

Legionarska bolest se klinički manifestuje pneumonijom, a letalitet se kreće 10 –15% (3). Ova teška sistemska bakterijska infekcija, izazvana gram negativnom bakterijom, često se manifestuje kao atipična upala pluća sa subakutnom temperaturom, kašljem i kratkim dahom (11).

Nije moguće klinički razlikovati pacijente s legionarskom bolešću od pacijenata s drugim vrstama upale pluća izazvanim nekim drugim uzročnikom. Međutim, na rendgenskom snimku prisutni alveolarni infiltrati su češći kod legionarske bolesti u odnosu na upale pluća uzrokovane drugim patogenima. Klinički simptomi koji opisuju legionarsku bolest su groznica, neproduktivni kašalj, glavobolja, bolovi u mišićima, ukočenost, otežano disanje, proliv, mentalna konfuzija i delirijum (12). Približno 25-50% ljudi inficirano legionelama može imati proliv, dok se kod oko 50% mogu pojaviti znaci mentalne konfuzije (6).

Period inkubacije se obično kreće od 2 do 10 dana, a u retkim slučajevima može biti od 16 do 20 dana nakon izlaganja agensu. Ukoliko se oboleli ne leče, simptomi se u normalnim okolnostima brzo pogoršavaju i mogu da dovedu do respiratorne insuficijencije, šoka, višestruke organske insuficijencije i smrti (3).

Pontijačna groznica je blaža forma bolesti izazvana ovom bakterijom, koja je slična gripu. Inkubacioni period je kraći, najčešće od 12 do 48 sati i javlja se kao bolest slična gripu koja traje nekoliko dana. Stopa javljanja je viša nego kod legionarske bolesti (do 95% od onih koji su izloženi). Slučajevi su uglavnom detektovani prilikom pojave epidemije pontijačne groznice, na primer izlaganje povezano sa upotrebom zajedničkog banjskog bazena u rekreativnom centru ili hotelu (3).

Za laboratorijsku dijagnostiku ove bolesti koristi se detekcija antigena u uzorku urina tokom akutne faze bolesti, uzimanje respiratornog uzorka za kulturu ćelija, serološka ispitivanja i PCR dijagnostika (12-14).

Izvori i putevi prenošenja

Legionarska bolest pripada grupi zaraznih bolesti koje se prenose indirektnim putem, tj. prilikom udisanja vazduha koji sadrži legionele u aerosolu (16). Aerosol se formira iz sitnih kapljica koje mogu da se stvaraju pomoću rasprskavanja vode ili pomoću uduvavanja vazduha u vodu ili stajanjem izlivene vode na čvrstim površinama. Što su manje kapljice, veća je verovatnoća da će one izazvati infekciju (3).

report organ transplants, chronic diseases and immunodeficiency in their personal anamnesis (6).

The incidence and prevalence of Legionnaires' disease in the EU/EEA and Montenegro

In 2019, 28 countries from the European region reported 11.298 cases of Legionnaires' disease, while 10.636 (94%) cases were classified as confirmed cases. The number of new cases accounted for 2.2 per 100.000 population, which is the highest incidence rate reported so far in the EU/EEA (7). During the last five years, incidence rates in the EU/EEA countries grew by nearly two times, from 1.4/100.000 in 2015 to 2.2/100.000 in 2019 (Table 1). In four European countries (France, Germany, Italy and Spain), the number of registered cases of Legionnaires' disease accounted for 71% of all notified cases in the EU/EEA, although the population of these countries makes 50% of the EU/EEA population (7).

According to the data of the Center for Disease Control and Prevention from Atlanta in the United States of America in 2018, around 10.000 cases of this disease were reported, which may be an underestimated number of cases due to the insufficient diagnostics of Legionnaires' disease (8). A recent study estimated that the real number of cases of Legionnaires' disease might be 1.8-2.7 times higher than the notified number (8).

According to the data obtained from the infectious diseases register of the Institute of Public Health of Montenegro, there were 4 new cases of Legionnaires' disease that were registered from 1st January 2011 to 31st December 2020, that is, two cases in 2013 (incidence rate 0.32/100.000) and two cases in 2019 (incidence rate 0.32/100.000) (9,10). All affected people were men, aged 30 to 60 years. The affected people did not travel and they were not epidemiologically connected.

Clinical characteristics of Legionnaires' disease and diagnosis

Legionnaires' disease is clinically manifested as pneumonia, while case-fatality rate ranges from 10-15% (3). This severe systemic bacterial infection, which is caused by gram-negative bacteria, is often manifested as atypical pneumonia with subacute temperature, cough and short breath (11).

It is not clinically possible to make difference between patients with Legionnaires' disease and patients with other types of pneumonia caused by other agents. However, alveolar infiltrates are more often present on chest X-rays in case of Legionnaires' disease in comparison to pneumonias caused by other agents. Clinical symptoms that describe Legionnaires' disease are the following: fever, non-productive cough, headache, muscle pains, arthralgia, difficulty in breathing, diarrhea, mental confusion and delirium (12). Approximately 25-50% of people infected with Legionella may experience diarrhea, while signs of mental confusion may appear in 50% of people (6).

The incubation period usually ranges from 2 to 10 days, and rarely up to 16-20 days after exposure. If not treated, the symptoms normally worsen rapidly and may result in respiratory failure, shock, multi-organ failure and death (3).

Pontiac fever is a mild form of disease, which is caused by *Legionella* bacteria, and which is similar to influenza. The incubation period is shorter, most frequently 12 to 48 hours and it presents an influenza-like illness lasting a few days. The attack rate is much higher than for Legionnaires' disease (up to 95% of those who are exposed). Cases are mainly detected when outbreaks of Pontiac fever occur, for example when exposure is linked to the use of communal spa pool in a leisure center or hotel (3).

The following laboratory procedures are used to obtain diagnosis: the detection of antigen in a urine specimen during the acute phase of the illness, obtaining a respiratory specimen for culture of cells, serological tests and PCR diagnostics (12-14).

Sources and routes of transmission

Legionnaires' disease belongs to the group of contagious diseases which are transmitted indirectly, by breathing in air that contains Legionella bacteria in an aerosol (16). An aerosol is formed from tiny droplets that can be generated by spraying the water or by bubbling air into it, or by water impacting on solid surfaces. The smaller the droplets, the more likely they are to cause infection (3).

The most common sources of Legionnaires' disease are the following: hot and cold water systems, cooling towers and evaporative

Tabela 1. Distribucija prijavljenih novoobolelih slučajeva legionarske bolesti i stope incidencije na 100.000 stanovnika za zemlje EU/EEA za period 2015-2019. godine (Izvor: Godišnji izveštaj o kretanju LB u Evropi objavljen od strane ECDC; link: https://www.ecdc.europa.eu/sites/default/files/documents/AER-legionnaires-2019.pdf)

Zemlja	2015		2016		2017		2018		2019		
	broj obolelih	stopa inci-dencije	broj obolelih	stopa inci-dencije	broj obolelih	stopa inci-dencije	broj obolelih	stopa inci-dencije	broj obolelih	stopa inci-dencije	uzrasno standard-izovana stopa
Austrija	160	1,9	161	1,9	219	2,5	237	2,7	255	2,9	2,6
Belgija	118	1,1	157	1,4	235	2,1	270	2,4	224	2	1,8
Bugarska	1	0,0	0	0,0	2	0,0	11	0,2	5	0,1	0,1
Češka	120	1,1	147	1,4	217	2,1	231	2,2	277	2,6	2,3
Danska	185	3,3	170	3,0	278	4,8	264	4,6	270	4,7	4,2
Estonija	6	0,5	14	1,1	16	1,2	18	1,4	12	0,9	0,8
Finska	17	0,3	15	0,3	27	0,5	24	0,4	44	0,8	0,7
Francuska	1389	2,1	1218	1,8	1630	2,4	2133	3,2	1816	2,7	2,7
Grčka	29	0,3	31	0,3	43	0,4	65	0,6	45	0,4	0,4
Hrvatska	48	1,1	31	0,7	33	0,8	43	1,0	-	-	-
Holandija	419	2,5	454	2,7	561	3,3	584	3,4	566	3,3	3,0
Irska	11	0,2	10	0,2	25	0,5	25	0,5	21	0,4	0,5
Island	1	0,3	3	0,9	3	0,9	5	1,4	-	-	-
Italija	1572	2,6	1733	2,9	2037	3,4	3018	5,0	3143	5,2	4,2
Kipar	2	0,2	3	0,4	1	0,1	5	0,6	4	0,5	0,5
Latvija	22	1,1	24	1,2	31	1,6	37	1,9	42	2,2	2,1
Lihtenštajn	-	-	-	-	-	-	-	-	-	-	-
Litvanija	7	0,2	11	0,4	14	0,5	21	0,7	17	0,6	0,6
Luksemburg	5	0,9	3	0,5	9	1,5	10	1,7	14	2,3	2,3
Mađarska	58	0,6	66	0,7	62	0,6	74	0,8	113	1,2	1,1
Malta	6	1,4	8	1,8	11	2,4	13	2,7	5	1	0,8
Norveška	60	1,2	43	0,8	52	1,0	69	1,3	65	1,2	1,2
Njemačka	842	1	974	1,2	1278	1,5	1446	1,7	1545	1,9	1,6
Poljska	23	0,1	24	0,1	38	0,1	70	0,2	74	0,2	0,2
Portugal	145	1,4	197	1,9	232	2,3	211	2,1	201	2,0	1,7
Rumunija	3	0,0	2	0,0	19	0,1	62	0,3	19	0,1	0,1
Slovačka	14	0,3	14	0,3	14	0,3	54	1,0	85	1,6	1,6
Slovenija	106	5,1	93	4,5	117	5,7	160	7,7	195	9,4	8,3
Španija	1024	2,2	951	2,0	1363	2,9	1513	3,2	1542	3,3	2,9
Švedska	142	1,5	145	1,5	189	1,9	198	2,0	182	1,8	1,6
Ujedinjeno Kraljevstvo	412	0,6	383	0,6	504	0,8	532	0,8	517	0,8	0,7
EU/EEA	6947	1,4	7085	1,4	9260	1,8	11403	2,2	11298	2,2	1,9

Izvor: Izveštaji zemalja; . nema dostavljenih podataka; - nije izračunata stopa incidencije

Table 1. Distribution of reported cases of Legionnaires' disease and incidence rates per 100.000 population for the EU/EEA states for the period 2015-2019 (Source: Annual report on LD in Europe published by ECDC; link: https://www.ecdc.europa.eu/sites/default/files/documents/AER-legionnaires-2019.pdf)

Country	2015		2016		2017		2018		2019		
	Number of cases	Incidence rate	Number of cases	Incidence rate	Number of cases	Incidence rate	Number of cases	Incidence rate	Number of cases	Incidence rate	Age-standardized rate
Austria	160	1.9	161	1.9	219	2.5	237	2.7	255	2.9	2.6
Belgium	118	1.1	157	1.4	235	2.1	270	2.4	224	2	1.8
Bulgaria	1	0.0	0	0.0	2	0.0	11	0.2	5	0.1	0.1
Czechia	120	1.1	147	1.4	217	2.1	231	2.2	277	2.6	2.3
Denmark	185	3.3	170	3.0	278	4.8	264	4.6	270	4.7	4.2
Estonia	6	0.5	14	1.1	16	1.2	18	1.4	12	0.9	0.8
Finland	17	0.3	15	0.3	27	0.5	24	0.4	44	0.8	0.7
France	1389	2.1	1218	1.8	1630	2.4	2133	3.2	1816	2.7	2.7
Greece	29	0.3	31	0.3	43	0.4	65	0.6	45	0.4	0.4
Croatia	48	1.1	31	0.7	33	0.8	43	1.0	-	-	-
Netherlands	419	2.5	454	2.7	561	3.3	584	3.4	566	3.3	3.0
Ireland	11	0.2	10	0.2	25	0.5	25	0.5	21	0.4	0.5
Island	1	0.3	3	0.9	3	0.9	5	1.4	-	-	-
Italy	1572	2.6	1733	2.9	2037	3.4	3018	5.0	3143	5.2	4.2
Cyprus	2	0.2	3	0.4	1	0.1	5	0.6	4	0.5	0.5
Latvia	22	1.1	24	1.2	31	1.6	37	1.9	42	2.2	2.1
Liechtenstein	-	-	-	-	-	-	-	-	-	-	-
Lithuania	7	0.2	11	0.4	14	0.5	21	0.7	17	0.6	0.6
Luxembourg	5	0.9	3	0.5	9	1.5	10	1.7	14	2.3	2.3
Hungary	58	0.6	66	0.7	62	0.6	74	0.8	113	1.2	1.1
Malta	6	1.4	8	1.8	11	2.4	13	2.7	5	1	0.8
Norway	60	1.2	43	0.8	52	1.0	69	1.3	65	1.2	1.2
Germany	842	1	974	1.2	1278	1.5	1446	1.7	1545	1.9	1.6
Poland	23	0.1	24	0.1	38	0.1	70	0.2	74	0.2	0.2
Portugal	145	1.4	197	1.9	232	2.3	211	2.1	201	2.0	1.7
Romania	3	0.0	2	0.0	19	0.1	62	0.3	19	0.1	0.1
Slovakia	14	0.3	14	0.3	14	0.3	54	1.0	85	1.6	1.6
Slovenia	106	5.1	93	4.5	117	5.7	160	7.7	195	9.4	8.3
Spain	1024	2.2	951	2.0	1363	2.9	1513	3.2	1542	3.3	2.9
Sweden	142	1.5	145	1.5	189	1.9	198	2.0	182	1.8	1.6
United Kingdom	412	0.6	383	0.6	504	0.8	532	0.8	517	0.8	0.7
EU/EEA	6947	1.4	7085	1.4	9260	1.8	11403	2.2	11298	2.2	1.9

Source: Country Reports; . no data provided; - incidence rate not calculated

Najčešći izvori legionarske bolesti su hladni i topli vodeni sistemi, rashladni tornjevi i kondenzatori za isparavanje, banjski bazeni/prirodni bazeni/termalni izvori, fontane/prskalice, ovlaživači vitrine za hranu, oprema za respiratornu terapiju, baštenska zemlja/kompost, uređaji za pranje, mašinski alati za vodeno hlađenje itd. (15).

Javnozdravstveni nadzor nad zaraznim bolestima u Crnoj Gori

Zakonskim aktima u Crnoj Gori definisane su bolesti koje se obavezno prijavljuju, način njihovog prijavljivanja, javnozdravstveni nadzor i mere sprečavanja i suzbijanja zaraznih bolesti (16). Međunarodne obaveze u vezi sa sprečavanjem, suzbijanjem, odstranjivanjem i iskorenjivanjem zaraznih bolesti utvrđenih Listom zaraznih bolesti, kao i ozbiljne prekogranične pretnje zdravlju, izvršavaju se u skladu sa međunarodnim zdravstvenim propisima, programima Svetske zdravstvene organizacije (SZO) i drugim međunarodnim aktima (17-19).

U Crnoj Gori, u nadzoru nad zaraznim bolestima učestvuje Institut za javno zdravlje kao krovna institucija i 11 lokalnih epidemioloških službi koje pokrivaju teritorije za koje su zadužene. Sve primorske opštine imaju razvijene epidemiološke službe, kako bi pravovremeno i potpuno odgovorile na javnozdravstvene rizike zbog velikog priliva turista tokom letnje turističke sezone. U ostalim delovima zemlje pojedine epidemiološke službe pokrivaju više opština.

Prema zakonskoj regulativi legioneloza (prema MKB 10 šifra je A48.1.) se obavezno prijavljuje Institutu za javno zdravlje Crne Gore, u kome se nalazi registar za zarazne bolesti (17,18). Svi domovi zdravlja i opšte bolnice, elektronski prijavljuju zarazne bolesti, dok se iz Kliničkog Centra Crne Gore, specijalnih bolnica i privatnih zdravstvenih ustanova, prijavljivanje zaraznih bolesti vrši u papirnoj formi, tj. preko zakonom definisanih prijavnih kartica za zarazne bolesti, koje se naknadno ukucavaju u bazu podataka za zarazne bolesti.

Evropska mreža za nadzor nad legionarskom bolešću

Međunarodna saradnja po pitanju praćenja obolevanja od legionarske bolesti koja je povezana sa putovanjima na Evropskom nivou je počela 1986. godine, kada je je formirana Evropska radna grupa za infekcije izazvane legionelom (engl. *European Working Group for Legionella Infections* - EWGLI), dok je nadzor nad legionarskom bolešću koja je povezana sa putovanjima počeo da se sprovodi od 1987. godine. Od aprila 2010. godine za rad mreže je odgovoran ECDC i njeno prvobitno ime je promenjeno u Evropsku mrežu za nadzor legionarske bolesti (engl. *European Legionnaires' disease Surveillance Network* - ELDSNet). Mreža pokriva sve države članice EU/EEA, kao i zemlje koje su na putu pristupa EU, a koordiniše ga ECDC (20).

Glavni cilj postojanja ELDSNet-a jeste detekcija, suzbijanje i prevencija slučajeva obolevanja, formiranja klastera i izvora epidemija legionarske bolesti povezane sa putovanjima, a koje su prijavljene u područjima EU/EEA, kao i pružanje pomoći pri otkrivanju i odgovoru na epidemije izvan EU/EEA. Operativne procedure obezbeđuju set zajedničkih mera koje treba da budu praćene od strane svih EU/EEA zemalja koje su uključene u zaštitu svojih građana od legionarske bolesti. Cilj ovih procedura je napraviti standardizovan pristup registrovanju slučajeva koji su prijavljeni od strane zemalja članica EU i drugih zemalja koje su uključene u sistem nadzora, kako bi se detektovali klasteri i kako bi se odgovorilo na pojavu klastera obolevanja od legionarske bolesti udružene sa putovanjima (engl. *Travel-associated Legionnaires' disease* - TALD) (3). Klasteri predstavljaju registrovanje više slučajeva obolelih od neke bolesti koji se mogu povezati sa istom vremenskom ili prostornom izloženošću određenom agensu. Članovi ELDSNet-a su zvanično imenovani od strane nacionalnih vlasti za javno zdravlje i deluju kao nacionalna kontakt osoba za nadzor nad legionarskom bolešću, i to jedna nacionalna kontakt osoba za epidemiološki nadzor i jedna nacinalna kontakt osoba za mikrobiološki nadzor. Oni poseduju naučna znanja u pogledu legionarske bolesti i odgovorni su za epidemološki i mikrobiološki nadzor nad ovom bolešću u svojoj zemlji. Od 2014. godine Crna Gora ima imenovane kontakt osobe za epidemiološki i mikrobiološki nadzor.

U aktivnosti ELDSNet nadzora i odgovora uključeno je 50 zemalja sveta. Preostale zemlje obaveštavaju se putem saradnje sa SZO preko kontakt osobe za Međunarodni zdravstveni pravilnik (engl. *International Health Regulation* – IHR) (20).

Ciljevi mreže nadzora nad legionarskom bolešću u evropskom regionu podrazumevaju brzo otkrivanje slučajeva i klastera legionarske bolesti udružene sa putovanjima, koji su prijavljeni u zem-

condensers, spa pools/natural pools/thermal springs, fountains/sprinklers, humidifiers for food display cabinets, equipment for respiratory therapy, potting soil/compost, vehicle washes, water-cooled machine tools etc. (15).

Public health surveillance of infectious diseases in Montenegro

Laws and regulations in Montenegro define diseases that are mandatory to be reported, ways of reporting, epidemiological surveillance and measures of control and prevention of infectious diseases (16). International obligations relating to preventing, controlling, eliminating and eradicating infectious diseases, as well as to cross-border threats to health, are carried out according to the International Health Regulations, programs of the World Health Organization and other international legal acts (17-19).

In Montenegro, the surveillance of infectious diseases is conducted by the Institute of Public Health as the main institution, as well as by 11 local epidemiological services which are in charge of some territories. All coastal municipalities have developed epidemiological services that enable timely and complete response to public health risks due to a large number of tourists during the tourist season. In other parts of the country, some epidemiological services cover several municipalities.

According to health regulations, Legionellosis (according to the ICD-10, disease code is A48.1) must be reported to the Institute of Public Health of Montenegro, which coordinates the infectious diseases register (17,18). All health care centers and general hospitals report infectious diseases electronically, while the Clinical Center of Montenegro, special hospitals and private health care institutions report infectious diseases with the help of paper report cards for infectious diseases, which are regulated by the law, and which are later entered into the data base for infectious diseases.

The European Network for the surveillance of Legionnaires' disease

The international collaboration across Europe with regards to travel-associated Legionnaires' disease started in 1986, when the European Working Group for Legionella Infections (EWGLI) was set up, while they started to carry out the surveillance of travel-associated Legionnaires' disease in 1987. Since April 2010, the Network has been coordinated by ECDC and its name changed to the European Legionnaires' disease Surveillance Network – ELDSNet. The Network includes all member states of the EU/EEA, as well as countries who have applied to join the EU, while it is coordinated by ECDC (20).

The main objective of ELDSNet is to detect, control and prevent new cases, clusters and sources of outbreaks of travel-associated Legionnaires' disease that were reported in the EU/EEA area, as well as to assist with the detection and response to outbreaks outside the EU/EEA. Operating procedures provide a set of common measures which should be followed by all member states of the EU/EEA that are involved in the protection of all residents against Legionnaires' disease. The aim of these procedures is to create a standardized approach to registering cases that were reported by the EU member states and other countries that are involved in the surveillance system, in order to detect clusters and to respond to the occurrence of clusters of travel-associated Legionnaires' disease (3). Clusters present several registered cases of disease which can be associated with the same temporal or spatial exposure to some agent. Members of the ELDSNet were officially nominated by the national authorities for public health and they are national points for the surveillance of Legionnaires' disease, that is, one national contact person for the epidemiological surveillance and one national contact person for the microbiological surveillance. They have scientific knowledge about Legionnaires' disease and they are responsible for the epidemiological and microbiological surveillance of this disease in their country. Since 2014, Montenegro has nominated contact persons for the epidemiological and microbiological surveillance.

Fifty member countries are included in the activities of ELDSNet surveillance and response. Other countries are informed through collaboration with the WHO and contact points for the International Health Regulation (IHR) (20).

The objectives of the European surveillance network are to detect rapidly cases and clusters of travel-associated Legionnaires' disease reported in the EU and EEA area and affecting European residents, as well as to disseminate information on these cases and respond in a coordinated

ljama EU/EEA, a koji utiču na zdravlje evropskog stanovništva, kao i distribuciju informacija o slučajevima ove bolesti i koordinisan odgovor država. Preventivnim standardizovanim aktivnostima vrši se i povećanje svesti o legionarskoj bolesti koja je najčešće povezana sa putovanjima, kao i smanjenje učestalosti ove bolesti, kroz podršku i podizanje svesti o aktivnom suzbijanju i prevenciji u smeštajnim objektima.

Pregled metoda nadzora

Po definiciji javnozdravstveni nadzor predstavlja stalno, sistematsko prikupljanje, analizu i tumačenje podataka o zdravlju, bitnih za planiranje, primenu i evaluaciju prakse javnog zdravlja, kao i pravovremeno slanje podataka svima koji treba da ih znaju (22). Nadzor nad legionarskom bolešću povezanom sa putovanjima u Crnoj Gori se sprovodi od 2010. godine i u nadzoru nad ovom bolešću primjenjuju se definicije legionarske bolesti povezane sa putovanjima prema preporukama ECDC (20).

Prema navedenim definicijama pojedinačni slučaj legionarske bolesti povezan sa putovanjem je slučaj koji je boravio ili posetio komercijalni smeštajni objekat 2 do 10 dana pre pojave bolesti, pri čemu se smeštajni objekat u poslednje dve godine ne dovodi u vezu sa pojavom legionarske bolesti. Klaster legionarske bolesti povezan sa putovanjem predstavlja dva ili više slučajeva bolesti koji su odseli ili posetili isti komercijalni smeštajni objekat 2 do 10 dana pre pojave bolesti, pri čemu je do obolevanja došlo u istom dvogodišnjem periodu. Klaster može biti okarakterisan kao brzo progredirajući, što podrazumeva pojavu tri ili više slučajeva obolevanja sa početkom bolesti u periodu od tri meseca, tokom šest meseci nakon otkrivanja klastera. Kompleksni klaster opisuje kombinaciju klasterskih lokaliteta sa jednim ili više zajedničkih slučajeva. Klaster može biti i aktivni klaster, u kojem se registruje bar jedan novi slučaj bolesti u dvogodišnjem periodu od pojave poslednjeg slučaja i može biti završen klaster, kada se ne registruju novi slučajevi obolevanja povezani sa smeštajnim objektom tokom dvogodišnjeg perioda od početka bolesti poslednjeg slučaja. Ukoliko se nakon isteka perioda od dve godine registruje slučaj obolevanja povezan sa istim smeštajnim objektom, prijaviće se kao novi pojedinačni slučaj.

Prijava slučajeva legionarske bolesti povezane sa putovanjima

Na nivou jedne zemlje, kliničari i mikrobiolozi prijavljuju pojedinačne slučajeve legioneloze povezane sa putovanjima u svoju nacionalnu mrežu nadzora nad legionarskom bolešću. Nacionalna kontakt tačka (odgovorna osoba za nadzor) preko ELDSNet-a slučajevima ECDC koristeći definiciju slučaja prema EU. Sa kompletnim i brzim izveštavanjem, ELDSNet može otkriti klastere slučajeva koji imaju zajedničku istoriju putovanja i smeštaja. Razmena informacija dovodi do konkretnih i pravovremenih akcija članica ELDSNet-a, kako bi se zaštitili stanovnici EU/EEA koji putuju u i van Evrope. Slučajevi se obično prijavljuju ECDC-u od strane člana ELDSNet preko IT platforme. Informacije moraju da sadrže istoriju putovanja, datum boravka i svaku adresu smeštaja gde je putnik boravio. Poželjno je upisati i dodatne informacije kao što su telefonski broj, lokacija i internet strana smeštaja (3,20).

Treba naglasiti da pojedinačni slučajevi i klasteri povezani sa specifičnim smeštajem mogu nastati slučajno, dok izvor infekcije može biti na drugom mestu. U ELDSNet-u se podrazumeva da obaveštenje koje se odnosi na obolevanje od legionarske bolesti povezane sa putovanjima, slučaj ili klaster, ne mora nužno da implicira da je navedeni objekat pravi izvor infekcije, ali se očekuje da se preduzmu sve standardizovane procedure i aktivnosti u cilju provere da li taj smeštajni objekat može biti povezan sa obolevanjem (3,20).

Jednom kada se slučaj unese u bazu podataka ECDC-a, ECDC proverava podatke o slučaju i podatke o smeštaju. Pretraživanje se vrši u bazi podataka kako bi se identifikovali prethodno prijavljeni slučajevi povezani sa ovom smeštajnom lokacijom, utvrdjuje se da li su ovi slučajevi imali početak bolesti u roku od dve godine pre ovog prijavljenog slučaja. Ako takvi slučajevi nisu identifikovani u bazi podataka, ECDC obaveštava zemlju u kojoj se nalazi smeštajno mesto za tzv. „notifikaciju jednog slučaja“. Zemlje van EU/EEA se obaveštavaju o pojedinačnim slučajevima preko kontakt tačke ELDSNet-a ili alternativno putem SZO, preko IHR i kontakt tačke za IHR za zemlju. Obaveštenje se, takođe, elektronski šalje u zemlju koja je prijavila slučaj (3,20).

Primer notifikacije jednog slučaja legionarske bolesti, koji je poslat od strane ECDC-a nacionalnoj

way. Preventive standardized activities increase awareness of travel-associated Legionnaires' disease and reduce the incidence of this disease through the support of active control and prevention in accommodation sites.

A review of epidemiological methods

Epidemiological surveillance is defined as the ongoing systematic collection, analysis and interpretation of health data that are essential to the planning, implementation and evaluation of public health practice and timely dissemination of health data (22). Epidemiological surveillance of travel-associated Legionnaires' disease has been carried out in Montenegro since 2010 and definitions of travel-associated Legionnaires' disease according to the ECDC recommendations have been applied for this surveillance.

According to the mentioned definitions, single cases of travel-associated Legionnaires' disease are cases who in the two to ten days before the onset of illness stayed at or visited a commercial accommodation site that has not been associated with other cases of Legionnaires' disease in the two years prior to the date of onset of disease. A cluster of travel-associated Legionnaires' disease represents two or more cases who stayed at or visited the same accommodation site two to ten days before the onset of illness, and whose onset is within the same two-year period. A cluster can be classified as rapidly evolving when three or more cases appear and the onset of illness is within a three-month period occurring in the six months preceding the cluster notification. A complex cluster is described as a combination of cluster sites having one or more cases in common. A cluster can be active when at least one new case is registered within two years from the most recent case and it can be expired when no new cases associated with the accommodation site are reported within two years of the most recent case disease onset. If a new case associated with the same accommodation site is reported after two years, it will be reported as a new single case.

Reporting cases of travel-associated Legionnaires' disease

At the national level, clinicians and microbiologists report single cases of travel-associated Legionellosis to their national networks of surveillance of Legionnaires' disease. These cases are reported to ECDC through ELDSNet by the national contact point (person responsible for the surveillance), using the case definition of the EU. Complete and timely reporting enables ECDC to detect clusters of cases that have common history related to travels and accommodation. Sharing information leads to concrete and timely actions of ELDSNet member states, so that the EU/EEA residents who travel within the EU or abroad are protected. Cases are usually reported to ECDC by an ELDSNet member via an IT platform. The information must contain the travel history, dates of stay and each accommodation site's address. Some additional information such as the telephone number, location and the accommodation's web page should be provided (3,20).

It should be emphasized that single cases and clusters associated with the specific accommodation site can occur accidentally, while the source of infection can be somewhere else. In ELDSNet, the notification of a single case or cluster of travel-associated Legionnaires' disease does not imply that the accommodation site is the real source of infection, but it is expected that all standardized procedures and activities should be carried out in order to check whether that accommodation site may be associated with the infection (3,20).

Once a case is entered into the ECDC database, ECDC checks the data about the case and the accommodation. A search is performed in the database in order to identify previously reported cases associated with this accommodation site and to determine if these cases had the onset of illness within the two years prior to this reported case. If such cases were not identified in the database, ECDC notifies the country where the accommodation site is located of a "single-case notification". Countries outside the EU/EEA are issued a single-case notification through the ELDSNet contact point or alternatively through WHO, through IHR or contact points of IHR for the country. The notification is also electronically sent to the country that reported the case (3,20).

One example of notification of one case of Legionnaires' disease, which was sent by ECDC to the national contact person for the epidemiological surveillance in Montenegro, is presented in picture 1. When the ELDSNet sends notification that a tourist, who reported to have stayed in

kontakt osobi za epidemiološki nadzor u Crnoj Gori prikazan je na slici 1. Kada se dobije obaveštenje od ELDSNet-a, o obolevanju turiste od legionarske bolesti, a koji je naveo da je boravio u Crnoj Gori, nacionalna kontakt osoba za epidemiološki nadzor u Crnoj Gori, obaveštava nadležnu higijensko-epidemiološku službu (HES), čiji predstavnici, epidemiolog i tehničar, zajedno sa sanitarnom inspekcijom obavljaju epidemiološko istraživanje (obilaze smeštajnu jedinicu, prikupljaju podatke, uzorke, predlažu preventivne i korektivne mere, itd). Nakon epidemiološkog istraživanja nadležni epidemiolog u pisanoj formi izveštava nacionalnu kontakt osobu o zatečenom stanju u smeštajnom objektu, a ona je u obavezi da, na propisanom obrascu (A i B), o istom povratno izvesti ELDSNet mrežu ECDC-a. Pojava grupisanja obolelih (klastera) zahteva neodložno reagovanje i ECDC-a i javnozdravstvenih ustanova u zemlji gde se nalazi smeštajni objekat povezan sa obolevanjem, tj. neodložno reagovanje Instituta za javno zdravlje, higijensko-epidemioloških službi i Sanitarne inspekcije u Crnoj Gori.

U ELDSNet mreži se formira identifikacioni kôd klastera i izdaje se obaveštenje sa datumima putovanja i datumima pojave bolesti za svaki pojedinačni slučaj u okviru klastera. Svi članovi ELDSNet mreže bivaju odmah informisani o pojavi klastera. Takođe, ukoliko je u prethodnih pet godina registrovana pojava pojedinačnih slučajeva ili klastera obolevanja od legionarske bolesti koji su povezani sa istim smeštajnim objektom, članovi ELDSNet-a se i o tome obaveštavaju. Primer obaveštenja nacionalne kontakt tačke za epidemiološki nadzor nad legionarskom bolešću u Crnoj Gori, od strane ELDSNet mreže za klaster obolevanja od legionarske bolesti koja je povezana sa putovanjem prikazan je na slici 2.

Nakon obaveštavanja o pojavi klastera, član ELDSNet mreže u državi u kojoj se nalazi smeštajni objekat koji može biti povezan sa obolevanjem, dalje preuzima komunikaciju sa relevantnim javnozdravstvenim autoritetima u svojoj državi, koja rezultira započinjanjem ispitivanja i sprovođenjem mera suzbijanja.

Kontakt osoba za nadzor u Crnoj Gori obaveštava nadležnu HES. Vrši se obilazak smeštajnog objekta od strane nadležne HES i zdravstveno-sanitarne inspekcije. Istraživanje i procena rizika se vrši u skladu sa nacionalnim i evropskim vodičima. Istraživanje uključuje i uzorkovanje iz sredine, npr. prikupljanje uzoraka vode iz vodovodnog sistema. U istraživanju se implementiraju mere suzbijanja i daju preporuke za smanjenje rizika od pojave obolevanja od legionarske bolesti u narednom periodu.

U periodu od 2014. do 2019. godine, na osnovu baze podataka nacionalne kontakt osobe u Crnoj Gori, svake godine u letnjem periodu su higijensko-epidemiološke službe u Crnoj Gori vršile od 1 do 5 istraživanja na osnovu notifikacija dobijenih od ECDC-a, bilo za pojedinačan slučaj ili za klaster obolevanja kod turista koji su naveli putovanje u Crnu Goru. Rezultati procene rizika i preduzete mere se prijavljuju ECDC na standardizovanim obrascima. Država član ELDSNet-a može kontaktirati ECDC i zahtevati savet ili tehničku ekspertizu sa ciljem podrške u istraživanju.

Kontakt tačka za epidemiološki nadzor u državi obaveštava ECDC popunjavanjem i slanjem formulara A u roku od dve nedelje od registrovanja klastera; opisuje se terensko epidemiološko istraživanje i procena rizika, opisuju se mere suzbijanja koje su preduzete, a i daju se informacije o tome da li je smeštajni objekat povezan sa obolevanjem otvoren za boravak. ECDC ažurira tabelu na svojoj ELDSNet internet platformi sa ograničenim pristupom, i na taj način se informišu i ostali članovi ELDSNet mreže.

Ukoliko ECDC u roku od dve nedelje od pojave klastera ne primi formular A ili je u izveštaju navedeno da nikakve mere suzbijanja nisu preduzete, ECDC kontaktira člana ELDSNet mreže u državi u kojoj se smeštajni objekat povezan sa obolevanjem nalazi. Zajedno sa njim ELDSNet, na osnovu formulara i statusa ispitivanja, donosi odluku da li će u sledećih 48h naziv smeštajnog objekta koji je povezan sa pojavom klastera, biti naveden u listi objekata na sajtu ECDC-a, kao objekat u kom postoji povećan rizik za pojavu legionarske bolesti. Ukoliko se naziv smeštajnog objekta ne objavi online, razlog zbog kojeg to nije urađeno (npr. zato što je zatvoren) mora biti obrazložen članovima mreže ELDSNet (3,20).

Članu ELDSNet države u kojoj se nalazi smeštajni objekat povezan sa obolevanjem se prosleđuje podsetnik 2-3 dana nakon isteka roka od dve nedelje ukoliko formular A nije primljen.

Konačne informacije o sprovedenim merama suzbijanja i laboratorijskim rezultatima uzoraka vode šalju se ECDC-ju u roku od šest nedelja nakon otkrivanja klastera. Izveštavanje se vrši na formu-

Montenegro, got Legionnaires' disease, the national contact person for the epidemiological surveillance in Montenegro notifies the sanitary-epidemiological service, whose representatives, an epidemiologist and a technician, together with sanitary inspection, conduct epidemiological investigation (they go to that accommodation unit, collect data, samples, suggest preventive and corrective measures, etc.). After epidemiological investigation, public health authority notifies the national contact person in the written form about the notified accommodation site, and this person should necessarily respond to ELDSNet of ECDC using forms A and B. Identification of a cluster warrants an immediate action by ECDC and the public health authorities in the country where the associated accommodation site is located, that is, the immediate action of Public Health Institute, sanitary-epidemiological services and sanitary inspection in Montenegro.

In ELDS network, a cluster identification code is created and a notification is issued with travel dates and dates of disease onset for all cases within the cluster. All ELDSNet members are immediately informed about the cluster. Also, ELDSNet members are informed of any single cases or clusters associated with the same accommodation site in the last five years. One example of notification, when the national contact point for the epidemiological surveillance of Legionnaires' disease in Montenegro was notified by ELDSNet for the cluster of travel-associated Legionnaires' disease, is presented in picture 2.

After the notification of a cluster, the ELDSNet member for the country where the accommodation site, which may be associated with the infection, is located initiates communication with the relevant public health authorities from their country, which results in starting investigations and implementing control measures.

The contact person for the surveillance in Montenegro notifies the authorized sanitary-epidemiological service. The accommodation site is inspected by the authorized sanitary-epidemiological service and sanitary inspection. Investigations and risk assessment are carried out according to the national and European guidelines. Investigations include environmental sampling, e.g. sampling of the building's water systems. In the investigations, authorities implement control measures and draw up recommendations in order to reduce risks of Legionnaires' disease in the following period.

From 2014-2019, according to the database, contact points in Montenegro during the summer period were sanitary-epidemiological services in Montenegro and they conducted 1 to 5 investigations according to notifications sent by ECDC for single cases or clusters in tourists, who reported to have stayed in Montenegro. The results of risk assessment and taken measures are reported to ECDC in a standardized form. ELDSNet member state may contact ECDC and request advice or technical expertise in support of site investigations.

A contact point for the epidemiological surveillance in a country notifies ECDC by completing and sending Form A within two weeks of the cluster registration; field epidemiological investigations and risk assessment are described, taken control measures are described, and information whether the accommodation site remains open is provided. ECDC updates the table on the restricted ELDSNet platform, and other ELDSNet members are informed in that way.

If ECDC does not receive Form A within two weeks from the cluster notification or the form reports that no preventive control measures were taken, ECDC contacts the ELDSNet member of the accommodation site country. Together with the ELDSNet member it is agreed, based on the form and the status of the investigations, whether the accommodation site name will be listed on the accommodation site list of the ECDC website within the next 48 hours as the accommodation site which is at the increased risk of Legionella infection. If the accommodation site's name is not published online, the reasons for not doing that should be communicated to the ELDSNet network (3,20).

ELDSNet members from the country, where the accommodation site related to infection is located, will be sent a reminder 2-3 days in advance of the due date if Form A was not received. Final information about taken control measures and laboratory results of water samples should be sent to ECDC within six weeks after the cluster notification. Reporting is done with the help of Form B. ECDC informs other members of the ELDS network when Form B is received.

If a completed Form B is not received within the specified time period or if control measures

European Legionnaires' Disease Surveillance Network (ELDSNet)

European Centre for Disease Prevention and Control (ECDC)
Gustav III:s Boulevard 40
16973 Solna, Sweden

Telephone: +46 (0)8 5860 1000
Email: eldsnet@ecdc.europa.eu

Date: 13/08/2018
To: ELDSNet Montenegro - (ME)
CC: ELDSNet Poland - (PL)

CONFIDENTIAL

Notification of a Single Case of Legionnaires' Disease

ELDSNet has been informed of a confirmed case (PLLegio182200035) of Legionnaires' disease in a 52 year old male resident of Poland, whose illness may be associated with travel to: [redacted] Ulcinj, Ulcinj, Montenegro.

The reported date of onset was 25/07/2018 and the patient's outcome is unknown. Legionella infection was diagnosed by urinary antigen test.

She/he reported a history of travel to:

Accommodation/ Place of Stay	Town/ Region	Dates of Stay
[redacted]	Ulcinj/ Ulcinj	21/07/2018 - 31/07/2018

We are not aware of any cases in the past two years at the above named accommodation.

Site address: [redacted] Ulcinj.

More information may be available from the reporter: [redacted]
Narodowy Instytut Zdrowia Publicznego - Państwowy Zakład Higieny
Poland

This notification does not imply that the accommodation named is the source of the infection.

[redacted]
Acting Head of Unit
Surveillance and Response Support
ECDC

Slika 1. Primer notifikacije pojedinačnog slučaja legionarske bolesti poslate od strane ELDSNet mreže ECDC-a kontakt osobi za epidemiološki nadzor nad legionarskom bolešću u Crnoj Gori

European Legionnaires' Disease Surveillance Network (ELDSNet)

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SE 171 83 Stockholm, Sweden

Telephone: +46 (0)8 5860 1000
Fax: +46 (0)8 5860 1001
Email: eldsnet@ecdc.europa.eu

Date: 30/06/2017
To: ELDSNet Montenegro - (ME)
CC: ELDSNet Austria - (AT); ELDSNet Belgium - (BE); ELDSNet Bulgaria - (BG); ELDSNet Croatia - (HR); ELDSNet Cyprus - (CY); ELDSNet Czech Republic - (CZ); ELDSNet Denmark - (DK); ELDSNet Estonia - (EE); ELDSNet Finland - (FI); ELDSNet France - (FR); ELDSNet Germany - (DE); ELDSNet Greece - (GR); ELDSNet Hungary - (HU); ELDSNet Iceland - (IS); ELDSNet Ireland - (IE); ELDSNet Italy - (IT); ELDSNet Latvia - (LV); ELDSNet Liechtenstein - (LI); ELDSNet Lithuania - (LT); ELDSNet Luxembourg - (LU); ELDSNet Malta - (MT); ELDSNet Netherlands - (NL); ELDSNet Norway - (NO); ELDSNet Poland - (PL); ELDSNet Portugal - (PT); ELDSNet Romania - (RO); ELDSNet Slovakia - (SK); ELDSNet Slovenia - (SI); ELDSNet Spain - (ES); ELDSNet Sweden - (SE); ELDSNet United Kingdom - (GB); ELDSNet WHO Europe

CONFIDENTIAL

Cluster Update of Travel Associated Cases of Legionnaires' Disease

3 cases of Legionnaires' disease have been reported to ELDSNet whose illness may be associated with a visit to the: [redacted] Herceg Novi, Montenegro.

Cluster C17/19556

Case ID	Diagnostic Status	Date Of Onset	Dates Of Travel	Outcome	Reporter
NL1261702	Probable	16/05/2017	04/05/2017-13/05/2017	Unknown	Netherlands
NL1264804	Probable	13/06/2017	30/05/2017-08/06/2017	Unknown	Netherlands
SE274	Confirmed	16/06/2017	06/06/2017-13/06/2017	Alive	Sweden

The most recently reported case is a confirmed case in a 70 year old male diagnosed by urinary antigen test.

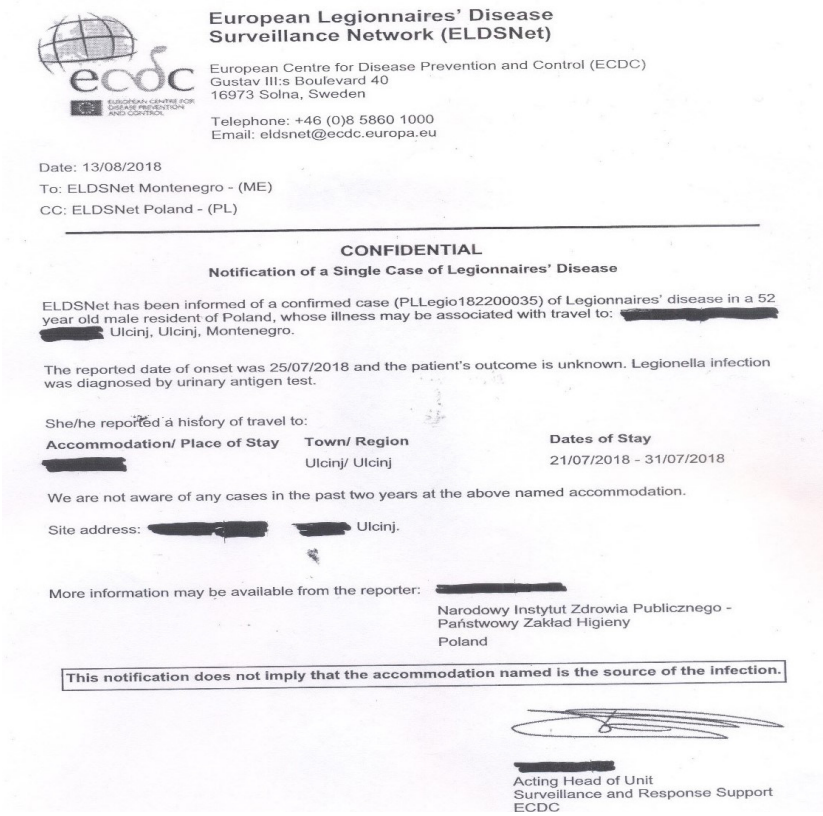
More information may be available from the reporter: [redacted]
Folkhälsomyndigheten
Sweden

This notification does not imply that the accommodation named is the source of the infection.

Authorisation

[redacted] Head of Unit, Surveillance and Response Support

Slika 2. Obaveštenje o klaster obolevanju putnika koji su u anamnezi naveli putovanje u Crnu Goru



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Poland

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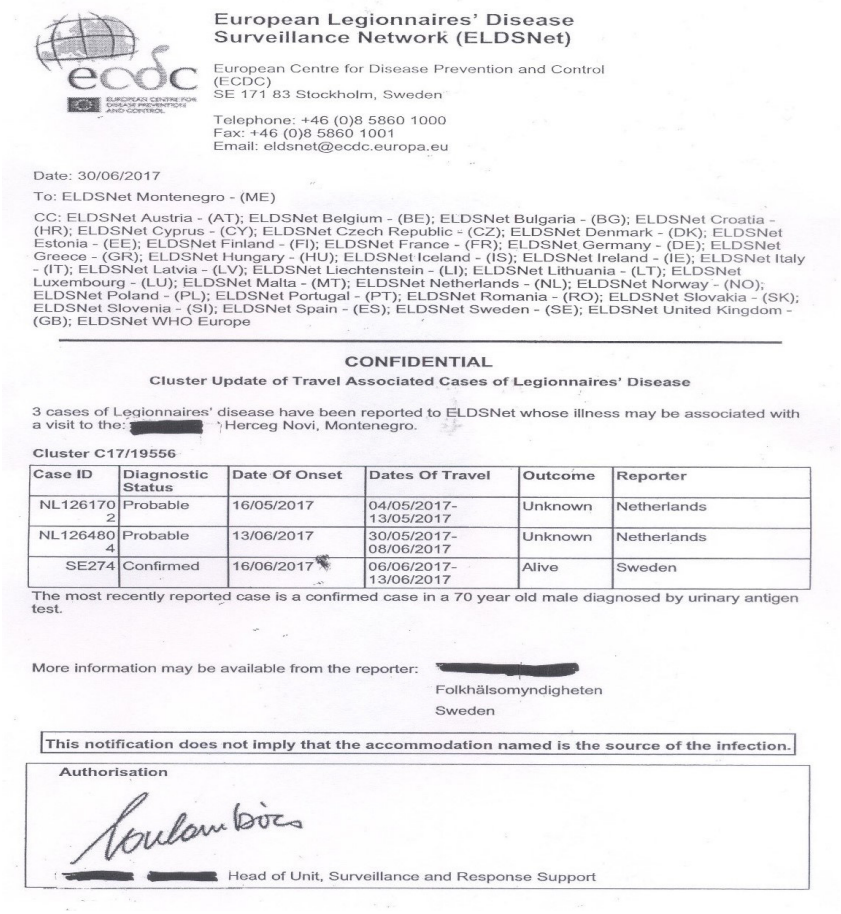
[redacted]
Acting Head of Unit
Surveillance and Response Support
ECDC

Figure 1. An example of notification of a single case of Legionnaires' disease sent by ELDSNet network to ECDC contact point for the epidemiological surveillance of Legionnaires' disease in Montenegro



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SE274	Confirmed	16/06/2017	06/06/2017-13/06/2017	Alive	Sweden

The most recently reported case is a confirmed case in a 70 year old male diagnosed by urinary antigen test.

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Folkhälsomyndigheten
Sweden

This notification does not imply that the accommodation named is the source of the infection.

Authorisation

[redacted] Head of Unit, Surveillance and Response Support

Figure 2. Notification of a cluster of tourists who stated that they traveled to Montenegro in their personal anamnesis

laru B. ECDC obaveštava ostale članove ELDSNet mreže nakon dobijanja formulara B.

Ukoliko popunjen formular B ne bude dostavljen u predviđenom roku od šest nedelja ili ukoliko su preduzete mere nezadovoljavajuće, ECDC kontaktira člana ELDSNet mreže u državi u kojoj se nalazi smeštajni objekat povezan sa obolevanjem i dalje se razmatra tok istraživanja. Na osnovu formulara B i tekućeg istraživanja, odlučuje se da li će naziv smeštajnog objekta biti javno objavljen na sajtu ECDC u roku od 48h. Ukoliko se naziv smeštajnog objekta ne nađe na listi smeštajnih objekata na sajtu ECDC, o tome se obavještavaju članovi ELDSNet mreže. Članu ELDSNet države u kojoj se nalazi smeštajni objekat povezan sa obolevanjem se prosleđuje podsetnik 2-3 dana nakon isteka roka od šest nedelja ukoliko formular B nije primljen.

Ukoliko je smeštajni objekat povezan sa pojavom klastera sezonski zatvara u periodu od šest nedelja od otkrivanja klastera, formular B se može popuniti u cilju obaveštenja o zatvaranju. Pre nego se smeštajni objekat opet otvori, ažuriran formular B sa rezultatima istraživanja treba da bude dostavljen ECDC-u. U listi objekata objavljenoj na sajtu ECDC navode se smeštajni objekti u kojima su trenutno identifikovani klasteri obolevanja od legionarske bolesti, a o kojima ELDSNet nema podatke o proceni rizika i sprovedenom istraživanju i za koji se smatra da u njima postoji povećan rizik za pojavu legionarske bolesti. Naziv smeštajnog objekta se objavljuje jer formulari A i B nisu prosleđeni ECDC u predviđenom vremenskom roku i rizik nije moguće proceniti, ili je formular B prosleđen, ali mere suzbijanja u smeštajnom objektu nisu sprovedene ili su nedovoljne.

Objavljivanje naziva smeštajnog objekta se obično vrši u roku od 48h od donošenja odluke o objavljivanju. Kao dodatno obaveštenje, naziv smeštajnog objekta se šalje članovima ELDSNet-a 48h pre objavljivanja na sajtu. Ime smeštajnog objekta se uklanja sa liste ukoliko se primi zadovoljavajući formular B ili se prijavi da su sprovedene adekvatne mere suzbijanja. Naziv smeštajnog objekta se uklanja sa liste ukoliko se ne identifikuju dodatni slučajevi legionarske bolesti tokom naredne dve godine od poslednjeg potvrđenog slučaja. Obaveštavanje nadležnih u smeštajnom objektu koji je povezan sa obolevanjem o tome da će naziv njihovog objekta biti objavljen na sajtu ECDC-a, se vrši od strane nacionalnih zdravstvenih autoriteta. Cilj objavljivanja naziva smeštajnog objekta u listi na sajtu ECDC-a, je da omogući turističkim operaterima i javnosti da odluče da li da prilikom ponuda za putovanja uzmu u obzir i navedeni smeštajni objekat (3).

Pojava novih slučajeva obolevanja u klasteru, tokom dve godine od pojave poslednjeg slučaja bolesti u klasteru, zahteva ažuriranje u prijavljivanju. Za ovakve slučajeve potrebno je proslediti nove formulare A i B (iako je prethodno prosleđen adekvatan formulara B). Potrebno je sprovesti i novo istraživanje. U slučaju pojave brzoprogredirajućih klastera u zemljama EU/EEA, o tome da li i kada je potrebno informisati goste smeštajnog objekta povezanog sa obolevanjem, obično odlučuju nacionalne i/ili lokalne zdravstvene službe. U ovim slučajevima potrebno je proslediti i dodatni formular (formular C). Svrha dodatnog prijavljivanja je dobijanje detaljnih informacija o tome koje su informacije dostupne gostima smeštajnog objekta povezanog sa obolevanjem. Formular C se dostavlja ECDC ELDSNet mreži u roku od jedne nedelje od kada je klaster označen kao brzoprogredirajući. Informacije o istraživanju, proceni rizika i sprovedenim merama se prijavljuju ECDC ELDSNet koordinacionom centru na isti način na koji se vrši i prijavljivanje kod standardnih klastera u državama EU/EEA (popunjavanjem formulara A i B u roku od dve, odnosno šest nedjelja od pojave klastera). Turoperatori imaju odgovornost za zdravlje i bezbednost svojih klijenata. Turoperatori mogu i da nemaju informacije o mestima gde su se pojavili klasteri. ELDSNet im nudi zbirni izveštaj o određenim prijavljenim klasterima legionarske bolesti povezane sa putovanjem. Turoperatori se mogu elektronski pretplatiti na ovu uslugu i tada se rutinski obaveštavaju o klasterima koji se nalaze van zemalja EU/EEA.

Klasteri koji se brzo razvijaju unutar zemalja EU/ EEA i globalno obuhvaćeni su sumarnim izveštajem. Zbirni izveštaji se izdaju pretplaćenim turoperatorima 24 sata nakon obaveštavanja preko mreže ELDSNet-a. Ova vremenska razlika postoji da bi se nacionalnim javnozdravstvenim institucijama omogućilo da o slučajevima obaveste lokalne javnozdravstvene službe. Međutim, u slučaju brzog razvoja klastera koji se prijavljuje mreži, ažuriranje ovog zbirnog izveštaja može se izdati u roku kraćem od 24 sata. Informacije navedene u izveštajima sadrže ime i adresu smeštajnog objekta i datum putovanja za svaki prijavljeni slučaj koji je povezan sa klasterom.

are unsatisfactory, the network members of the accommodation site country will be contacted by ECDC and investigation status is further discussed. Based on Form B and the ongoing investigation, it will be decided whether the name of the accommodation site should be made public on the ECDC website within the next 48 hours. If the accommodation site's name is not included in the accommodation site list on the ECDC website, the ELDSNet network is informed. ELDSNet member state of the accommodation site associated with the infection will be sent a reminder 2-3 days in advance of the due date of six weeks if Form B is not received.

If an accommodation site that is associated with the cluster notification is closed down for the season within the next six weeks, Form B may be completed to inform of the closure. Before the accommodation site reopens, an updated Form B with investigation results should be submitted to ECDC. The list of accommodation sites on the ECDC website shows current accommodation sites where clusters of Legionnaires' disease were identified, but where ELDSNet was not informed about any assessment of the risk and conducted investigation, or where ELDSNet believes that there may be an increased risk of Legionnaires' disease. The accommodation site's name is made public because Forms A and B were not submitted to ECDC by the specified due date and therefore, the risk could not be assessed, or Form B was received but control measures were not taken at the accommodation site or they were not satisfactory.

Publication of accommodation site's name usually occurs within 48 hours once the decision to publicize is made. An additional notice of the name of the accommodation site is sent to the ELDSNet network members 48 hours before publication. The name of the accommodation site will be removed from the website if a satisfactory Form B is received or if satisfactory control measures are reported as implemented. The name of the accommodation site will also be removed if no further cases of Legionnaires' disease were associated with the site in the two years after the last confirmed case. Public health authorities inform the accommodation site that its name will be published on the ECDC website. The objective of publishing the accommodation site's name on the ECDC website is to allow members of the public and tour operators to decide whether to consider the accommodation site in question.

The occurrence of new cases in a cluster within two years after the date of onset of the most recent case in a cluster demands a cluster notification update. For such cases, new forms A and B should be submitted (although an adequate Form B was previously submitted). Also, new investigations should be conducted. For rapidly evolving clusters in the EU/EEA, the national and/or local health authorities decide whether and when to inform guests of the accommodation site associated with the infection. An additional form (Form C) will be requested for such cases. The purpose of this additional form is to get more detailed information about what information was available to the guest of that accommodation site. Form C is submitted to ECDC ELDSNet one week after the cluster was notified as rapidly evolving. The information on site investigations, risk assessment and taken measures are reported to the ECDC ELDSNet coordinating center in the same manner as for standard clusters in the EU/EEA countries (by completing Forms A and B within two weeks, that is, six weeks after the cluster notification). Tour operators are responsible for the health and safety of their clients. Also, they may not have information on the sites where clusters appeared. ELDSNet offers summary reports on certain notified clusters of travel-associated Legionnaires' disease. Tour operators can electronically subscribe to this service and then they are routinely informed about clusters located in countries outside the EU/EEA.

Rapidly evolving clusters inside the EU/EEA are globally covered by the summary report. Summary reports are issued to subscribed tour operators 24 hours after the notification through the ELDSNet network. This time delay is to allow for national authorities to inform local public health authorities of this notification. However, in the event of a rapidly evolving cluster which is reported to the network, updates of the summary report may be issued within less than 24 hours. The information provided in the report contains the name and address of the accommodation site and the dates of travel for each reported case that is associated with the cluster.

Tour operators on the subscriber list will also be informed 48 hours in advance if the accommodation site's name and address in the EU/EEA member states is about to be published

Turoperatori na listi pretplatnika, takođe, će biti obavešteni 48 sati unapred, ukoliko će naziv i adresa smeštajnog objekta u zemljama EU/EEA biti objavljeni na internet stranici ECDC-a. Ukoliko se naziv i adresa smeštajnog objekta uklone sa internet stranice ECDC-a, turoperatori će biti obavešteni istog dana. Vrlo retko, turoperatori dobijaju obaveštenja o slučajevima sumnje ili potvrde TALD-a direktno od klijenta – ugostiteljskih objekata. U takvim situacijama turoperatori posavetuju klijente koji su im dostavili informacije da se prvo obrate nadležnom lekaru i zatraže od lekara da prijavi slučaj/eve odgovarajućoj nacionalnoj javnozdravstvenoj službi. Ovo pomaže ELDSNet-u da primi relevantne informacije i identifikuje relevantne klastere. To kasnije dovodi do javnozdravstvenog istraživanja u zemlji gde se nalazi smeštajni objekat (3).

Institut za javno zdravlje Crne Gore prati preporuke javnozdravstvenih autoriteta SZO, ECDC, CDC, priprema smernice namenjene turističkom sektoru, organizuje obuke za udruženja ugostitelja u cilju jačanja svesti i adekvatnog sprovođenja preventivnih mera kako bi se rizik od obolevanja od legioneloze u ugostiteljskim objektima sveo na minimum. S obzirom da je turizam jedna od vodećih privrednih grana u Crnoj Gori, Privredna komora Crne Gore, udruženja ugostitelja i turistički radnici, shvataju značaj sprovođenja preporuka za sprečavanje i suzbijanje legionarske bolesti povezane sa putovanjima (22).

Zaključak

Svaki slučaj obolevanja od legionarske bolesti kod turista u evropskom regionu, koji je naveo boravak u Crnoj Gori, se epidemiološki obrađuje po propisanim procedurama ELDSNet mreže. Operativne procedure obezbeđuju set zajedničkih mera koje treba da budu praćene od strane svih EU/EEA zemalja koje su uključene u zaštitu svojih građana od legionarske bolesti.

Institut za javno zdravlje Crne Gore svake godine šalje ažurirane preporuke za prevenciju obolevanja od legionarske bolesti Ministarstvu turizma i Nacionalnoj turističkoj organizaciji radi distribuiranja istih hotelijerima i ugostiteljskim radnicima, a u cilju jačanja svesti o postojanju legioneloze i neophodnosti preduzimanja svih mera za prevenciju ove bolesti.

Konflikt interesa

Autori su izjavili da nema konflikta interesa.

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on the ECDC's website. If the accommodation is removed from the ECDC website, tour operators will be informed on the same day. Very occasionally, tour operators receive notifications of cases of suspected or confirmed TALD directly from a client – accommodation sites. In such situations, tour operators may wish to advise clients who submitted information to contact a medical doctor and request the doctor to report the case to the appropriate national public health service. This helps ELDSNet receive relevant information and identify relevant clusters. This could then lead to public health investigations in the country of accommodation site (3).

The Institute of Public Health of Montenegro follows the recommendations of the public health authorities of the WHO, ECDC and CDC and prepares guidelines intended for the tourist sector; organizes hospitality industry training sites aimed at raising awareness and adequate implementing of preventive measures in order to minimize the risk of Legionellosis in accommodation sites. Having in mind the fact that tourism is one of the leading economic sectors in Montenegro, the Chamber of Economy of Montenegro, hospitality industry associations and tourist workers realize the significance of implementation of recommendations for the prevention and control of travel-associated Legionnaires' disease.

Conclusion

Each case of Legionnaires' disease in tourists in the European area, who reported to have stayed in Montenegro, is epidemiologically analyzed according to the regulated procedures of ELDSNet network. Operating procedures provide a set of common measures that should be followed by all EU/EEA member states that are involved in the protection of their residents against Legionnaires' disease.

Every year the Institute of Public Health of Montenegro sends the updated recommendations for the prevention of Legionnaires' disease to the Ministry of Tourism and the National Tourist Organization, so that they could be further distributed to hospitality industry workers, with the aim of raising awareness of Legionellosis and the necessity of taking all measures for the prevention of this disease.

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PREVENCIJA ATEROSKLEROZE S OSVRTOM NA GOJAZNOST I NEADEKVATNU ISHRANU KAO FAKTORE RIZIKA ZA NASTANAK KARDIOVASKULARNIH BOLESTI

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SAŽETAK

U ovom radu biće predstavljene informacije iz relevantnih izvora podataka u vezi sa prevencijom ateroskleroze s osvrtom na gojaznost i neadekvatnu ishranu kao faktore rizika za nastanak kardiovaskularnih bolesti (KVB). Svetska zdravstvena organizacija procenjuje da svake godine od KVB umre 17,9 miliona ljudi, što je trećina ukupnog broja umrlih u svetu. KVB su ne samo vodeći uzrok umiranja, nego i obolevanja i nesposobnosti, što ukazuje na njihov veliki javnozdravstveni značaj. Smatra se da je endotelna disfunkcija rana faza ateroskleroze. Ateroskleroza se javlja i kod dece mlađe od 10 godina, dok rizik od ateroskleroze raste sa godinama starosti. Postoji preko 300 faktora povezanih sa aterosklerozom i njenim ključnim komplikacijama, koronarnim oboljenjem srca i moždanim udarom. Najvažniji od njih su gojaznost, fizička neaktivnost, hipertenzija, pušenje, neadekvatna ishrana, abnormalne vrednosti lipida, nasleđe, metabolički sindrom, dijabetes i psihosocijalni faktori. Redukcijom ili eliminacijom svih navedenih faktora rizika može se doprineti smanjivanju rizika od KVB. Neophodna su dalja istraživanja u ovoj oblasti sa ciljem boljeg definisanja nezavisnih faktora rizika za nastanak ateroskleroze i posledičnih KVB.

Ključne reči: kardiovaskularne bolesti, ateroskleroza, gojaznost, ishrana, faktori rizika, prevencija

Uvod

Svetska zdravstvena organizacija (SZO) procenjuje da svake godine od kardiovaskularnih bolesti (KVB) umre 17,9 miliona ljudi, što čini oko 32% ukupnog broja umrlih (1). Broj umrlih od KVB je manji u razvijenim zemljama koje imaju program mera prevencije, dok više od ¾ umrlih od KVB je u srednje i slabo razvijenim zemljama (1-4).

KVB su ne samo vodeći uzrok umiranja, nego i obolevanja i nesposobnosti, što ukazuje na njihov veliki javnozdravstveni značaj. KVB obuhvataju: ishemijske bolesti srca (IBS), cerebrovaskularne bolesti (CVB) i periferne arterijske bolesti (5). Podaci govore da je od 1950. godine do danas došlo do pada umiranja od KVB u većini razvijenih zemalja sveta.

Framingamska studija je bila prva studija u kojoj je uočena veza između životnih navika i KVB (2). Danas se navodi da postoji preko 300 faktora povezanih sa aterosklerozom i njenim ključnim komplikacijama, IBS i moždanim udarom (6). Najvažniji od njih su gojaznost, fizička neaktivnost, hipertenzija, pušenje, neadekvatna ishrana, abnormalne vrednosti lipida, nasleđe, metabolički sindrom, dijabetes i psihosocijalni faktori (7,8).

U ovom radu biće predstavljene informacije iz relevantnih izvora podataka u vezi sa prevencijom ateroskleroze s osvrtom na gojaznost i neadekvatnu ishranu kao faktore rizika za nastanak KVB.

Ateroskleroza

Ateroskleroza je vodeći uzrok nastanka KVB. To je hronično inflamatorno oboljenje koje karakteriše prisustvo imunokompetentnih ćelija koje proizvode proinflamatorne citokine u lezijama. Takođe, tu su u obilju mrtve ćelije, kao i oksidisani oblici lipoproteina male gustine (LDL holesterol) (7).

Ateroskleroza može da se javi u ranim godinama života (9) i dovodi se u vezu sa brojnim faktorima, a manifestuje se različitim patoanatomskim

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ACTUAL TOPIC

PREVENTION OF ATHEROSCLEROSIS WITH REFERENCE TO OBESITY AND INADEQUATE NUTRITION AS RISK FACTORS FOR CARDIOVASCULAR DISEASES

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SUMMARY

This paper will present information from relevant data sources regarding the prevention of atherosclerosis, focusing on obesity and inadequate nutrition as risk factors for cardiovascular diseases (CVDs). The World Health Organization estimates that 17.9 million people die from CVDs each year, equaling a third of the world's death toll. CVDs are not only the leading cause of death but also of illness and disability, which indicates their great public health importance. Endothelial dysfunction is thought to be an early stage of atherosclerosis. Atherosclerosis also occurs in children under the age of 10, while the risk of atherosclerosis increases with age. There are over 300 factors associated with atherosclerosis and key complications, coronary heart disease, and stroke. The most important of these are obesity, physical inactivity, hypertension, smoking, inadequate diet, abnormal lipid values, heredity, metabolic syndrome, diabetes, and psychosocial factors. Reducing or eliminating all of these risk factors can help reduce the risk of CVDs. Further research in this area is needed to better define the independent risk factors for atherosclerosis and consequent CVD.

Keywords: atherosclerosis, cardiovascular diseases, obesity, diet, risk factors, prevention

Introduction

The World Health Organization (WHO) estimates that 17.9 million people die each year from cardiovascular diseases (CVDs), accounting for about 32% of all deaths (1). According to the data of the World Health Organization (WHO), every year, 17.9 million people die from cardiovascular diseases (CVDs), representing 32% of all global deaths (1). The number of deaths caused by CVDs is smaller in developed countries, which have prevention measure programs, while more than three-quarters of CVD deaths take place in low and middle-income countries (1-4).

CVDs are not only the leading cause of death but also illness and disability, which indicates their great public health importance. CVDs include coronary heart disease (CHDs), cerebrovascular diseases (CVDs), and peripheral arterial diseases (5). The data show that from 1950 until today, there has been a drop in CVD deaths in most developed countries of the world.

The Framingham study was the first study that observed a link between life habits and CVD (2). Today, it is stated that there are over 300 factors associated with atherosclerosis and its key complications, CHD and stroke (6). The most important of these are obesity, physical inactivity, hypertension, smoking, inadequate nutrition, abnormal lipid values, heredity, metabolic syndrome, diabetes, and psychosocial factors (7,8).

This paper will present information from relevant data sources related to the prevention of atherosclerosis with reference to obesity and inadequate nutrition as risk factors for CVD.

Atherosclerosis

Atherosclerosis is the main cause of CVD. It is a chronic, inflammatory disease characterized by the presence of immunocompetent cells that produce proinflammatory cytokines in lesions. Also, there

promenama, počevši od masnih pruga do kompleksnih ulcerisanih plakova. Kada se desi erozija, ruptura i nagli rast plaka, dešava se tromboza u krvnom sudu što dovodi na nivou koronarnih krvnih sudova do akutnog koronarnog sindroma.

Za nastanak ateroskleroze najznačajniji faktori rizika su dislipoproteinemija, odnosno poremećaji u metabolizmu lipida (10). U brojnim studijama visoke vrednosti lipoprotein (a) (Lp(a)) u serumu dovode se u vezu sa KVB, tako da predstavlja nezavisan faktor rizika za nastanak KVB (11).

U literaturi se navodi da se aterosklerotske promene mogu javiti i kod dece mlađe od 10 godina (10). Starost je nezavisan faktor rizika za nastanak ateroskleroze. Starenjem, usled loših sredinskih (neadekvatna ishrani, gojaznost, fizička neaktivnost, pušenje, prekomerna upotreba alkohola) i genetskih faktora, ateroskleroza se sve više razvija (10).

Gojaznost

Gojaznost je hronična bolest koja je veoma rasprostranjena, a prevalencija ove bolesti veoma varira u svetu i kreće se u opsegu 20-45%. Definiše se kao indeks telesne težine koji je jednak ili veći od 30 kg/m^2 (12). Gojaznost je rezultat prekomernog nakupljanja masti u organizmu i povećanja težine (3). Ona je faktor rizika za širok spektar bolesti, a pogotovo za aterosklerozu i KVB.

Mnoge velike studije kardiometaboličkog rizika potvrdile su da je višak visceralne gojaznosti snažno povezan s metaboličkim abnormalnostima za koje se u početku smatralo da su povezane s viškom debljine same po sebi (13). Merenjem obima struka procenjuje se veličina intraabdominalnog masnog tkiva. Osobe sa obimom struka koji je preko 94 cm (za muškarce) i preko 80 cm (za žene) imaju povećan rizik, a sa obimom struka preko 102 cm (za muškarce) i preko 88 cm (za žene) imaju jako povećan rizik za nastanak komorbiditeta, pre svega KVB.

Gojazne osobe imaju dva puta veću prevalenciju hipertrigliceridemije nego osobe koje nisu gojazne (14). Takođe, kod gojaznih osoba, kao i kod osoba sa prekomernom telesnom težinom, češća je pojava hipertrigliceridemija sa visokim vrednostima LDL holesterola i niskim vrednostima lipoproteina velike gustine (HDL holesterol) (15,16).

Najznačajnije je kod pregleda gojaznog bolesnika uzeti detaljnu anamnezu, kao i uraditi fizički pregled i laboratorijske analize (17). Fizički pregled podrazumeva merenje težine, visine, obima struka i krvnog pritiska, određivanje indeksa telesne mase i utvrđivanje postojanja komorbiditeta. Takođe je neophodno uraditi elektrokardiogram. Minimum laboratorijskih analiza koje je neophodno uraditi obuhvata fizičko-hemijski pregled urina, glikemiju našte i 2 sata posle jela, aspartat aminotransferazu, alalnin aminotransferazu, gama glutamil transferazu, lipidski status i tiroidni stimulirajući hormone (TSH).

Cilj lečenja gojaznosti je redukcija prekomerne težine, smanjivanje uticaja ili eliminacija drugih faktora rizika i postojećih komorbiditeta. Lekari primarne zdravstvene zaštite, tj. izabrani lekari imaju značajnu ulogu u tome. Lečenje gojaznih osoba bi trebalo da obuhvata odgovarajuću hipokalorijsku ishranu i povećanu fizičku aktivnost, tj. promenu stila života (18,19). Preporuka je da dnevni kalorijski unos treba da bude smanjen za 500-1000 kCal u odnosu na stvarne potrebe. Gubitak telesne mase treba da bude od 5 do 15% od inicijalne težine da bi postojao povoljan efekat na komorbiditete. Kod nekih osoba dobre rezultate može da da jedino primena farmakoterapije ili hirurško lečenje. Za smanjenje telesne mase motivacija osobe je jako važna, te je neophodno pre tretmana utvrditi njenu spremnost i motivisanost i po potrebi uključiti multidisciplinarni tim na čelu sa psihologom (17).

Ishrana

Ishrana koja je bogata zasićenim mastima značajno doprinosi nastanku IBS usled povećanja LDL-holesterola u serumu. Korekcija ovakve „aterogene“ ishrane i promena stila života su ključni u borbi protiv IBS. Preporuke za pravilnu i uravnoteženu ishranu odnose se na konzumiranje povrća i voća, žitarica od celog zrna, orašastih plodova i dosta vlakana, mršavog mesa, ribe i devičanskog maslinovog ulja što je najsličnije mediteranskoj ishrani (20,21).

U cilju prevencije ateroskleroze, pa samim tim i nastanka KVB, predlaže se niska potrošnja soli i hrane životinjskog porekla, kao i povećan unos biljne hrane – voća, povrća, integralnih žitarica, mahunarki i orašastih plodova – povezanih sa manjim kalorijskim unosom (22). Poseban akcenat se stavlja na redukciji unosa maslaca, masti i drugih zasićenih masti, kao i na njihovoj zameni

are a lot of necrotic cells, as well as oxidized forms of low-density lipoproteins (7).

Atherosclerosis can occur in the early years of life (9), and it is associated with a number of factors, while it is manifested in various pathoanatomical changes, ranging from fatty streaks to complex plaque ulcers. When erosion, rupture, and sudden growth of plaque occur, thrombosis occurs in the blood vessel, which leads to acute coronary syndrome at the level of coronary blood vessels.

The most important risk factors for atherosclerosis are dyslipoproteinemia, that is, disorders in lipid metabolism (10). In a number of studies, high levels of serum lipoprotein (a) (Lp (a)) have been linked to CVD, and it is an independent risk factor for CVD (11).

It is stated in the literature that atherosclerotic changes may appear in children younger than 10 years (10). Age is an independent risk factor for atherosclerosis. As we age, due to bad habits (inadequate diet, obesity, physical inactivity, smoking, excessive alcohol use) and genetic factors, atherosclerosis develops more and more (10).

Obesity

Obesity is a chronic disease that is very widespread, and the prevalence of this disease varies greatly and ranges from between 20-45% in the world. It is defined as the body mass index equal to or higher than 30 kg/m^2 (12). It is the result of excessive accumulation of fat in the body and weight gain (3). Obesity is a risk factor for a wide range of diseases, especially atherosclerosis and CVD.

Many large studies of cardiometabolic risk have confirmed that an excess of visceral obesity is strongly associated with metabolic abnormalities, which were deemed to be linked to excess body weight at the beginning (13). The size of intra-abdominal adipose tissue is estimated by measuring the waist circumference. People with a waist circumference that is over 94 cm (for men) and over 80 cm (for women) have an increased risk, and people with a waist circumference more than 102 cm (for men) and more than 88 cm (for women) have a very increased risk of developing comorbidly, primarily CVDs.

Obese persons have two times higher prevalence of hypertriglyceridemia in comparison to persons who are not obese (14). Also, in obese persons, as in overweight persons, hypertriglyceridemia with high levels of low-density lipoproteins (LDL cholesterol) and low levels of high-density lipoproteins (HDL cholesterol) is more frequent (15,16).

When examining obese patients, it is most important to take detailed anamnesis, as well as to do a physical examination and laboratory analyses (17). Physical examination involves measuring weight, height, waist circumference, and blood pressure, calculating body mass index, and determining the existence of comorbidities. It is also necessary to do an electrocardiogram. The minimum laboratory tests that need to be done include physical and chemical examination of urine, glycemia on an empty stomach, and two hours after eating, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, lipid status, and thyroid-stimulating hormone.

The goal of treating obesity is to reduce body weight, reduce the impact or eliminate other risk factors and existing comorbidities. Physicians from primary health care, that is, family doctors, have a significant role in that. The treatment of obese persons should include an appropriate low-calorie diet and increased physical activity, that is, the change of lifestyle (18,19). It is recommended that the daily caloric intake should be 500-1000 kCal lesser than the actual need. Weight loss should be 5 to 15% of the initial body weight to give a beneficial effect on comorbidities. In some persons, only pharmacotherapy or surgical treatment can give good results. The person's motivation is very important for reducing body mass, so it is necessary to determine their readiness and motivation before the treatment and, if necessary, involve a multidisciplinary team with a psychologist as a team leader (17).

Diet

A diet rich in saturated fats significantly contributes to the development of IHD due to an increase in serum LDL-cholesterol. The correction of such "atherogenic" diet and lifestyle changes are key in the fight against IHD. The recommendations for a proper and balanced diet refer to the consumption of vegetables and fruits, whole grains, nuts and a lot of fiber, lean meat, fish, and virgin olive oil, which is most similar to

nezasićenim mastima (posebno maslinovim uljem). Većem riziku od KVB doprinosi konzumiranje crvenog mesa i mesnih prerađevina, a manje konzumacija ribe. Namirnice sa visokim glikemijskim indeksom treba zameniti namirnicama sa niskim glikemijskim indeksom kao što su žitarice od celog zrna. Manji rizik od KVB imaju osobe koje konzumiraju niske količine alkohola, kafe i čaja, a veći oni koji unose bezalkoholna pića zbog sadržaja šećera u njima.

Nekonzistentni rezultati postoje po pitanju značaja uzimanja beta-karotena ili drugih antioksidanasa u cilju redukcije rizika od IBS, što zahteva dalja istraživanja u ovoj oblasti (23). Studija *Yang* i saradnika, ukazuje da namirnice koje su bogate antioksidansima poput ishrane koja se koristi u Kineskoj alternativnoj medicini ima jedinstvene prednosti u prevenciji IBS (24).

Nizak kalorijski unos može povećati rizik od nedovoljnog unosa polinezasićenih masnih kiselina (engl. *polyunsaturated fatty acids* – PUFA), može narušiti apsorpciju vitamina rastvorljivih u masti i biti povezan sa insuficijencijom drugih esencijalnih hranjivih sastojaka (25). Hrana bogata zasićenim mastima i holesterolom, dovodi do povećanog sistolnog pritiska, hiperglikemije i hiperholesterolemije, nezavisno od drugih faktora rizika (gojaznosti, starosti ili korišćenja alkohola i nikotina) (26). Upotreba mononezasićenih kiselina (u uljima, kao što je maslinovo i suncokretovo), kao i polinezasićenih, doprinosi redukciji vrednosti kako ukupnog holesterola tako i LDL holesterola (25). Veća potrošnja maslinovog ulja dovodi se u vezu sa nižim umiranjem od KVB u mediteranskim zemljama (26).

Studije koje ispituju faktore rizika za nastanak KVB kod dece ukazuju da je sa prevencijom KVB neophodno započeti još u dečijem dobu. Istraživanja ukazuju da je prevalencija hipertenzije kod Turske dece/adolescenata veća nego kod dece/adolesenata srednjeevropskog porekla ali samo kada su pitanju deca/adolescent koji su gojazni ili sa prekomernom telesnom težinom (25). Visok mortalitet i morbiditet od KVB kod dece, ukazuju na potrebu preduzimanja preventivnih mera već u ranom detinjstvu, uz paralelno sprovođenje populacione strategije i strategije visokog rizika (25). Mediteranska ishrana je najpoželjnija za prevenciju KVB i predstavlja idealni nutritivni model za dobro zdravlje (26).

U terapiji gojaznosti prvo mesto zauzima dijatetski režim i fizička aktivnost, ukoliko nema rezultata pristupa se medikamentoznoj terapiji sa orlistatom ili bariatrična hirurgija kada je indeks telesne mase veći od 40 kg/m² (27-29).

Zaključak

Ateroskleroza dovodi do razvoja KVB, što doprinosi pogoršanju kvaliteta života ljudi i većem riziku od smrti. U cilju prevencije ateroskleroze, a samim tim i KVB, neophodno je edukovati stanovništvo o štetnim faktorima rizika i raditi na njihovoj redukciji i eliminaciji. Poseban akcenat stavlja se na značaj fizičke aktivnosti, smanjenja telesne težine i adekvatnoj ishrani. Mediteranska dijeta se navodi kao ključna u prevenciji KVB.

Konflikt interesa

Autori su izjavili da nema konflikta interesa.

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the Mediterranean diet (20,21).

In order to prevent atherosclerosis, and thus the development of CVD, low consumption of salt and food of animal origin is proposed, as well as increased intake of plant foods - fruits, vegetables, whole grains, legumes, and nuts - associated with lower calorie intake (22). Special emphasis is placed on reducing the intake of butter, fats, and other saturated fats, as well as on their replacement with unsaturated fats (especially olive oil). Consumption of red meat and meat products contributes to a higher risk of CVD, while fish consumption contributes to a lower risk. Foods with a high glycemic index should be replaced by foods with a low glycemic index, such as whole grains. People who consume low amounts of alcohol, coffee, and tea have a lower risk of CVDs, and those who consume non-alcoholic drinks are at an increased risk due to their sugar content.

Inconsistent results exist regarding the importance of taking beta-carotene or other antioxidants in order to reduce the risk of IHDs, which requires further research in this area (23). A study by Yang and associated indicates that foods rich in antioxidants, such as the diet used in Chinese traditional medicine, have unique benefits in preventing IHD (24).

Low-calorie intake may increase the risk of insufficient intake of polyunsaturated fatty acids (PUFA), may impair the absorption of fat-soluble vitamins, and may be related to the insufficiency of other nutritive elements (25).

Foods rich in saturated fats and cholesterol lead to increased systolic blood pressure, hyperglycemia, and hypercholesterolemia, independently of other risk factors (obesity, age, or alcohol and nicotine use) (26). The use of monounsaturated acids (in oils such as olive and sunflower), as well as polyunsaturated, contributes to the reduction of both total cholesterol and LDL cholesterol (25). Higher consumption of olive oil is associated with lower deaths from CVD in Mediterranean countries (26).

Studies examining the risk factors for CVDs in children indicate that it is necessary to start preventing CVDs in childhood. Research indicates that the prevalence of hypertension in children/adolescents in Turkey is higher than in children/adolescents of Central European descent, but only in children/adolescents who are obese or overweight (25). High mortality and morbidity from CVD in children indicate the need to take preventive measures in early childhood, with the parallel implementation of population strategy and high-risk strategy (25). The Mediterranean diet is the most desirable for the prevention of CVD and is an ideal nutritional model for good health (26).

In the treatment of obesity, the dietary regimes and physical activity take the first place, if there are no results, drug therapy with orlistat or bariatric surgery is approached when the body mass index is higher than 40 kg/m² (27-29).

Conclusion

Atherosclerosis leads to the development of CVD, which contributes to the deterioration of people's quality of life and a higher risk of death. In order to prevent atherosclerosis, and thus CVD, it is necessary to educate the population about harmful risk factors and work on their reduction and elimination. Special emphasis is placed on the importance of physical activity, weight reduction, and adequate nutrition. The Mediterranean diet is cited as key in the prevention of CVDs

Competing interests

The authors declare no competing interests.

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