Streptococcus pneumoniae serotype distribution in Vojvodina before the introduction of pneumococcal conjugate vaccines into the National Immunization Program

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SUMMARY

Introduction *Streptococcus pneumoniae* is the most common causative agent of bacterial pneumonia and meningitis. Mandatory childhood immunization against pneumococcal diseases is introduced in the new Law on Protection of Population against Communicable Diseases in Serbia.

Objective The objective of this study was to determine the prevalence of pneumococcal serotype distribution in Vojvodina region before routine use of pneumococcal conjugate vaccine in Serbia.

Methods A total of 105 isolates of *Streptococcus pneumoniae* were collected in the period from January 2009 to April 2016. Based on the results of serotyping in the National Reference Laboratory, we analyzed distribution of circulating serotypes and coverage of conjugate and 23-valent polysaccharide pneumococcal vaccines in different age groups.

Results Among 105 isolates, a total of 21 different serotypes of *Streptococcus pneumoniae* were determined. The most frequent serotypes were 3 (21.9%), 19F (20.0%), and 14 (10.5%). The serotype coverage of pneumococcal conjugate vaccines (PCV7, PCV10, and PCV13) was 48.6%, 54.3%, and 84.8%, respectively, while pneumococcal polysaccharide vaccine (PPV23) covered 89.5% of the total number of isolates in all age groups. Serotypes included in PCV7, PCV10, and PCV13 represented 72.0%, 76.0%, and 88.0% of the total number of isolates in children ≤5 years, respectively. Vaccine serotype coverage of PCV13 and PPV23 ranged from 87.1% to 90.3% in adults 50–64 years of age, and 77.8% to 85.2% in adults ≥65 years old.

Conclusion Serotype distribution of *Streptococcus pneumoniae* in the population fairly overlaps with the serotypes contained in pneumococcal vaccines, so that implementation of childhood immunization is justified. The study was done in the Province of Vojvodina but the findings may be applied to Serbia as a whole.

Keywords: *Streptococcus pneumoniae*; serotypes; vaccine serotypes

INTRODUCTION

Streptococcus pneumoniae (pneumococcus) is the most common causative agent of bacterial pneumonia and meningitis. Prior to introduction of pneumococcal conjugate vaccines, 6–11 serotypes accounted for ≥70% of all invasive pneumococcal disease (IPD) occurring in children worldwide [1]. Incidence rates, as well as case fatality rates of invasive pneumococcal diseases (IPD) are the highest in children under two years old and elderly, even in developed countries. In the European Union (EU)/ European Economic Area (EEA) countries in 2012, average case fatality rate was 11%, ranging 4–29% [2].

Development of pneumococcal vaccines and immunization enabled efficient prevention of infections. Pneumococcal polysaccharide vaccine (PPV23), which contains 23 serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F) was licensed in 1983. PPV23 is poorly immunogenic in the most vulnerable group, children younger than two years of age. Therefore, pneumococcal conjugate vaccines (PCVs) were developed, including pneumococcal polysaccharides conjugated with highly immunogenic protein carrier. First conjugate vaccine, PCV7, was licensed in Europe in 2001 and contains seven serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F). Ten-valent conjugate vaccine (PCV10) was licensed in 2009 and contains additional three serotypes (1, 5, and 7F). The last, 13-valent vaccine (PCV13), licensed in 2010, contains all previously mentioned and three more serotypes (3, 6A, and 19A). Unlike the PPV23, conjugate vaccines trigger both humoral and cellular immune response and are therefore efficient in all age groups including infants and children under two years of age [1].

Conjugate vaccines are used in 29 EU/EEA countries, while in 23 countries they are included in their respective national immuniza-

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tion programs (NIPs) [2]. In Serbia so far, pneumococcal vaccines were only used for immunization according to clinical indications [3]. Mandatory childhood immunization against *Streptococcus pneumoniae* is introduced in the new Law on Protection of Population against Communicable Diseases, (LPPCD) adopted in March 2016 [4].

World Health Organization considers that it should be a priority to all countries to include conjugate vaccine in national immunization programs for children. Countries are encouraged to conduct appropriate surveillance of IPD and to monitor the impact of vaccination, including the occurrence and magnitude of replacement disease. Surveillance should be introduced at least two years prior to and maintained at least five years after the immunization introduction [1]. It is also recommended to follow up the trends in serotype distribution in order to (i) monitor changes, (ii) guide most adequate strategy of immunization, and (iii) assess the impact of immunization on the population structure of circulating pneumococcal serotypes [1, 2, 5].

Surveillance of IPD in Serbia is based on reporting of clinically diagnosed illness with different clinical presentations (pneumonia, sepsis, bacterial meningitis) with etiological agent being identified in a small number of cases. New LPPCD introduces reporting of IPD as a separate entity that will improve surveillance [4].

OBJECTIVE

The objective of this study was to determine the prevalence of pneumococcal serotype distribution in Vojvodina region before routine use of pneumococcal conjugate vaccine in Serbia.

METHODS

A total of 105 pneumococcal isolates were collected from the same number of patients in the period from January 2009 to April 2016. The youngest patient was a newborn, five days old, while the oldest one was 82 years old. In children under five years of age, adults 50–64 years of age and older than 65, a total of 25, 31, and 27 isolates were obtained, respectively.

Analyses encompassed isolates from middle ear aspirate (14), bronchoalveolar lavage fluid (4), tissue bioptate (1), and wound swab (1). Invasive strains (83) were obtained from blood (48), cerebrospinal fluid (17), pleural fluid (17), and pericardial fluid (1) (Table 1).

A total of 52 *Streptococcus pneumoniae* strains were isolated in the clinical microbiological laboratory of the Institute of Public Health of Vojvodina from the clinical specimens of patients treated in the Clinical Centre of Vojvodina (Clinic for Otorhinolaryngology, Clinic for Internal Medicine and Clinic for Infectious diseases) as well as from the Institute for Child and Youth Health Care of Vojvodina. Forty-three isolates were collected from microbiological laboratory of the Institute for Pulmonary Diseases of Vojvodina, Institute for Cardiovascular Diseases of Vojvodina, Institute for Oncology of Vojvodina, and the remaining 10 strains were obtained from Regional Public Health Institutes in Vojvodina (Sombor, Kikinda, Subotica). All isolates were identified using standard microbiological methods – colony morphology, optochin susceptibility, and bile solubility.

Streptococcus pneumoniae isolates were transported in Amies transport media to the National Reference Laboratory for Streptococci, Institute for Microbiology and Immunology, School of Medicine, Belgrade. Capsular serotyping was done by the Quellung reaction, using the antisera from Statens Serum Institut (Copenhagen, Denmark).

We analyzed whether the isolates are covered by pneumococcal vaccines related to the target groups for the immunization by conjugate vaccines (children ≤5 years old) and PCV13 and PPV23 (adults 50–64 years of age and elderly ≥65 years).

RESULTS

Among 105 isolates, a total of 21 different serotypes of *Streptococcus pneumoniae* were determined, whereas only one isolate was non-typable. The most frequent serotypes were 3 (21.9%), 19F (20%), and 14 (10.5%) (Graph 1).

Serotypes included in seven-, 10-, and 13-valent conjugate vaccines and a 23-valent polysaccharide vaccine represented 48.6%, 54.3%, 84.8%, and 89.5% of the total number of isolates, respectively (Table 2).

Among 25 isolates from children ≤5 years of age, a total of 11 different serotypes of *Streptococcus pneumoniae* were detected, out of which three are not included in conjugate vaccines (11A, 23A and 33F). The most frequent serotypes were 19F (44%) and 14 (16%), which are incorporated in all three conjugate vaccines. The serotype coverage by PCV7, PCV10, and PCV13 in this age group were 72%, 76%, and 88%, respectively. In a subset of children ≤2 years of age, 20 strains were isolated and 19F was the most common one (10 out of 20 strains). Among children younger than two years of age, coverage with PCV7, PCV10, and PCV13 was 56%, 60%, and 72%, respectively. Three out of five strains isolated from children aged two to five years belonged to type 14, one was 19F, and the remaining 33F is present in PPV23 only.

Table 1. Type and number of examined specimens

Type of specimens	Number (%)
Blood	48 (45.7)
Cerebrospinal fluid	17 (16.2)
Blood and cerebrospinal fluid	2 (1.9)
Pleural fluid	17 (16.2)
Pericardijal punctate	1 (1.0)
Middle ear aspirate	14 (13.3)
Bronchial aspirate or bronchial lavage	4 (3.8)
Tissue bioptate	1 (1.0)
Wound swab	1 (1.0)
Total	105 (100)

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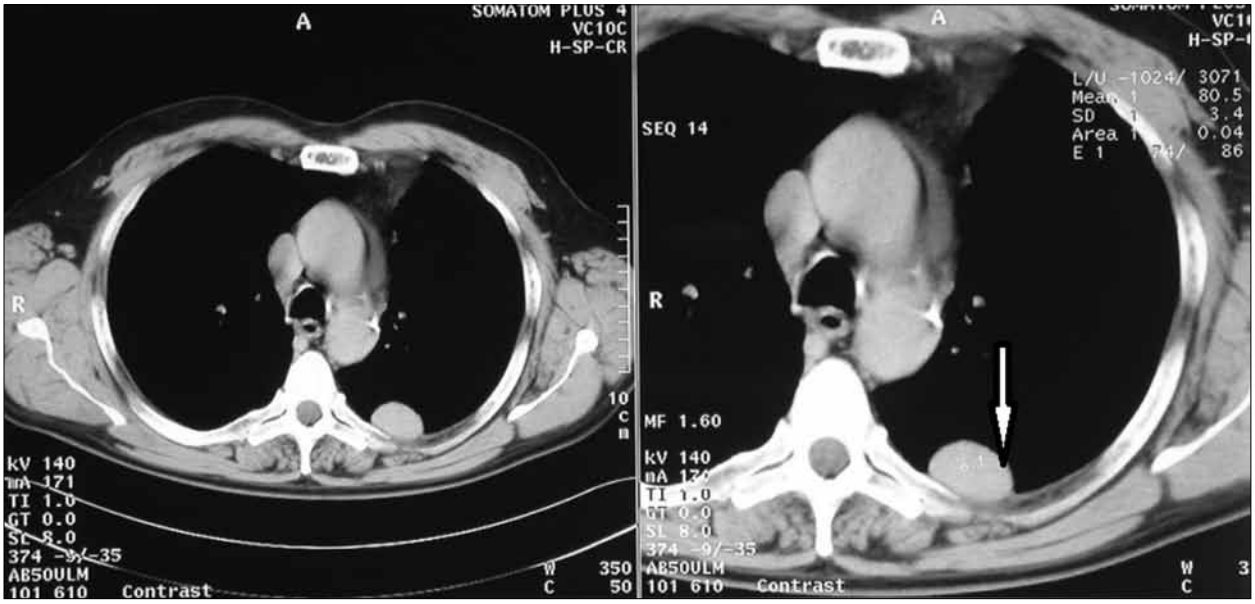

Graph 1. Circulating serotypes of Streptococcus pneumoniae in Vojvodina in the period from January 2009 to April 2016

Serotypes included in PPV23 and PCV13 represented 90.3 % and 87.1% of the total number of isolates in adults 50–64 years of age. The most frequent was serotype 3 (32.3%), which is present in both vaccines. Serotypes 8 and 9N presented only on PPV23 were detected in two isolates, which is 6.4% of the total number of isolates in this age group.

Vaccine coverage among adults aged ≥65 years were 85.2% and 77.8% for PPV23 and PCV 13, respectively. In this age group, the most frequent serotypes were 3 (25.9%), 19F (18.05%) and 6A (11.1%), incorporated in both vaccines. Serotypes present only in PPV23 (8, 9N, 11A, 17F) accounted for 18.5% of all isolates in the oldest age group.

DISCUSSION

There are over 90 serotypes of *Streptococcus pneumoniae* with only 20 of them responsible for >80% of IPD cases in all age groups, and 13 leading serotypes caused 70–75% of IPD cases in children worldwide, before the introduction of immunizations [6]. Distribution of serotypes still varies geographically, according to age, clinical form and severity of illness, and is also subject to change over time [1].

In countries that introduced conjugate vaccine in NIP for children, direct and indirect (herd) protection rapidly reduced IPD incidence across all age groups. [7]. However, PCV immunization led to changes in the circulating serotypes and serotype replacement was detected. Significant reduction of the vaccinal serotypes and an increased frequency of serotypes not included in vaccine were noticed [7]. Before the introduction of PCV7, the most frequent types were those included in the vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F). At the end of the 20th century these serotypes caused 59% of IPD cases in adults and 87% in children [7]. After the introduction of PCV7 in the United States in 2000, most European countries have gradually introduced this vaccine in their vaccination schedules between 2006 and 2009 [8]. They reported a drastic reduction of vaccine preventable serotypes in IPD cases, but the emergence of serotype 19A was noticed. After the introduction of PCV13 in the United States in 2010, the occurrence of serotype 19A decreased by 58% [9]. However, even after introduction of PCV10, a significant reduction in frequencies of both PCV10-related IPD and 6A and 19A (not included in PCV10) was observed, suggesting that PCV10 may also provide cross-protection against vaccine-related serotypes [10].

In this study we provide data on serotype distribution in Vojvodina region in Serbia in the period before the introduction of mandatory vaccination against IPD in children, which is implemented in the new National Immunization Schedule for 2016. Among 105 isolates, a total of 21 different serotypes of *Streptococcus pneumoniae* were determined and the most frequent in all age groups were serotype 3 (21.9%), which is included only in PCV13, and PPV23, followed by serotypes 19F (20.0%) and 14 (10.5%), which are included in all the vaccines. Unlike the serotype 3, which is susceptible to antibiotics, 19F and 14 are most often antibiotic-resistant types [2]. Our results indicate that one third of all pneumococcal isolates and 60% of isolates from children ≤5 years old belong to 19F and 14 serotypes, which is worrisome. Clinical impact of pneumococcal antibiotic resistance is a worldwide problem. High level of pneumococcal resistance has already been documented in our country, especially in 19F and 14 serotypes. Besides the effect on IPD, it was demonstrated that the introduction of PCV has been associated with a reduction in antimicrobial-resistant pneumococcal disease. This is particularly important in countries such as ours, with relatively high incidence rate of pneumococcal resistance to penicillin and macrolides. In the period from 2009 to 2011, 34% and 36% of pneumococcal invasive isolates in Serbia were nonsusceptible to penicillin and erythromycin,

Table 2. Circulating serotypes of *Streptococcus pneumoniae* by age groups for immunization in Vojvodina in the period from January 2009 until April 2016 and coverage by conjugate vaccines and PPV23

Vaccine	Serotype	Isolates in children 2 years of age		Isolates in children 2–5 years of age		Isolates in children ≤5 years of age		Isolates in adults 50–64 years of age		Isolates in elderly ≥65 years of age		All Isolates	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
PPV23 serotypes, PCV13 serotypes, PCV10 serotypes, PCV7 serotypes	4	0	0.0	0	0.0	0	0.0	4	12.9	1	3.7	6	5.7
	6B	2	8.0	0	0.0	2	8.0	1	3.2	0	0.0	4	3.8
	9V	0	0.0	0	0.0	0	0.0	1	3.2	1	3.7	3	2.9
	14	1	4.0	3	12.0	4	16.0	3	9.7	1	3.7	11	10.5
	18C	0	0.0	0	0.0	0	0.0	1	3.2	0	0.0	2	1.9
	19F	10	40.0	1	4.0	11	44.0	2	6.5	5	18.5	21	20.0
	23F	1	4.0	0	0.0	1	4.0	2	6.5	1	3.7	4	3.8
	Subtotal (PCV7 serotypes)	14	56.0	4	16.0	18	72.0	14	45.2	9	33.3	51	48.6
	1	1	4.0	0	0.0	1	4.0	0	0.0	0	0.0	1	1.0
	5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	7F	0	0.0	0	0.0	0	0.0	2	6.5	1	3.7	5	4.8
	Subtotal (PCV10 serotypes)	**15**	60.0	**4**	16.0	19	76.0	16	51.6	10	37.0	57	54.3
	3	1	4.0	0	0.0	1	4.0	10	32.3	7	25.9	23	21.9
	6A	1	4.0	0	0.0	1	4.0	1	3.2	3	11.1	6	5.7
	19A	1	4.0	0	0.0	1	4.0	0	0.0	1	3.7	3	2.9
	Subtotal (PCV13 serotypes)	18	72.0	4	16.0	22	88.0	27	87.1	21	77.8	89	84.8
PPV23 serotypes	2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	8	0	0.0	0	0.0	0	0.0	1	3.2	2	7.4	3	2.9
	9N	0	0.0	0	0.0	0	0.0	1	3.2	1	3.7	2	1.9
	10A	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	11A	1	4.0	0	0.0	1	4.0	0	0.0	1	3.7	2	1.9
	12F	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	15B	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	17F	0	0.0	0	0.0	0	0.0	0	0.0	1	3.7	2	1.9
	20	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	22F	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.0
	33F	0	0.0	1	4.0	1	4.0	0	0.0	0	0.0	1	1.0
Subtotal (PPV23 serotypes) (6A excluded)		18	72.0	5	20.0	23	92.0	28	90.3	23	85.2	94	89.5
Non vaccinal serotypes	23A	1	4.0	0	0.0	1	4.0	0	0.0	0	0.0	2	1.9
	15A	0	0.0	0	0.0	0	0.0	1	3.2	0	0.0	1	1.0
	15C	0	0.0	0	0.0	0	0.0	0	0.0	1	3.7	1	1.0
	Non typable	0	0.0	0	0.0	0	0.0	1	3.2	0	0.0	1	1.0
Subtotal		1	4.0	0	0.0	1	4.0	2	6.5	1	3.7	5	4.8
Total		20	80.0	5	20.0	25	100.0	31	100.0	27	100.0	105	100.0

respectively [11]. More than one third (36.4%) of pneumococcal isolates in Serbia in the 2009–2012 period expressed co-resistance to macrolides and penicillin. Multiresistant isolates were significantly more prevalent among children than adults [12].

Serotypes included in pneumococcal seven-valent, 10-valent, and 13-valent vaccines represented 48.6%, 54.3%, and 84.8% of the total number of our isolates, respectively. In children ≤5 years of age, who are the target group for the immunization with conjugate vaccines, coverage of circulating isolates was higher – 72% for PCV7, 76% for PCV10, and 88% for PCV13, because majority of serotypes in this age group belonged to serotypes 14 and 19F, which are in all vaccines. The serotypes presented only in PCV13-3 and 19A, were found in two (one from each) of 25 strains isolated in this age group. Average coverage of circulating isolates by PCV7 in European countries in the period before 2008 was 71%, and rose to 78% for PCV10 and to 87% for PCV13 [13]. In Europe and North America, the serotypes included in PCV10 and PCV13 are estimated to cover approximately 80–85% and 85–90% of IPD, respectively, in children younger than five years of age [14]. Nevertheless, the majority of isolates of children in Vojvodina were obtained from younger than two years, who are the target group for conjugate vaccines only. Vaccine-preventable serotypes covered by PCV7,

PCV10, and PCV13 were represented in somewhat lower percentages – 56.0%, 60.0%, and 72.0% of the total number of isolates in the youngest, respectively – but it is still high enough to justify implementation of immunization.

A polyvalent polysaccharide vaccine, PPV23, comprises only T-cell-independent antigens and therefore induces only B-cells that are short-lived and produce low-affinity antibodies. This vaccine is recommended for adults ≥65 years old and for those two years or older at high risk for IPD [15]. PPV23 is not effective in infants and the main advantage of this vaccine is that it protects against 23 types of pneumococci. There were only five isolates obtained from children aged two to five years in Vojvodina, and all of them are covered by PPV23. Still, four out of five strains are also covered by PCVs. PPV23, unlike conjugate vaccines, has no impact on nasopharyngeal carriage and does not alter circulating serotypes. Although the efficacy for prevention of non-bacteriaemic pneumonia is questionable, epidemiological studies showed that the immunization with PPV23 reduced the risk of IPD by 60% [16]. Additionally, recent meta-analysis provided evidence supporting the recommendation for PPV23 to prevent IPD in adults. However, the evidence from randomized clinical trials was less clear with respect to adults with chronic illness. Same meta-analyses did not provide compelling evidence to support the routine use of PPV to prevent all-cause pneumonia or mortality [17]. Out of total number of identified isolates, PPV23 covered 85.2% and 90.3% in elderly and adults 50–64 years of age, respectively. Approximately one third of the isolates in both age groups belonged to type 3 (25.9% in ≥65 and 32.3% in 50–64 age group) which is related to higher risk of death compared to other serotypes [2, 16]. Having in mind higher immunogenicity and effectiveness of PCV13 compared to PPV23, we should consider introduction of this vaccine for adults older than 50 years, especially those at high risk (immunocompromised, persons with functional or anatomic asplenia, those with chronic illness, etc.) similar to practice adopted in some European countries and the United States [18].

CONCLUSION

Although the number of isolates included in this analysis is relatively low, our results contribute to overall comprehension of circulating serotypes of *Streptococcus pneumoniae* in Vojvodina region in the pre-vaccinal period. Serotype distribution of *Streptococcus pneumoniae* in the population fairly overlaps with the serotypes contained in pneumococcal vaccines, so that implementation of childhood immunization is justified. The study was done in the Province of Vojvodina but the findings may be applied to Serbia as a whole. The introduction of PCV13 into the National Immunization Programme should be considered for adults older than 50 years, with risk factors, such as chronic illness.

Further follow-up of circulating serotypes of *Streptococcus pneumoniae* in our population will enable assessment of impact of immunization on distribution and possible changes in the circulation of serotypes.

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Дистрибуција серотипова *Streptococcus pneumoniae* у Војводини у периоду пре увођења конјуговане вакцине у Национални програм имунизације

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КРАТАК САДРЖАЈ

Увод *Streptococcus pneumoniae* је најчешћи изазивач бактеријске пнеумоније и менингитиса. Нови Закон о заштити становништва од заразних болести у Србији предвиђа увођење обавезне имунизације деце против обољења изазваних пнеумококом.

Циљ Циљ ове студије је био да се одреди заступљеност циркулишућих серотипова пнеумокока у Војводини у периоду пре увођења обавезне конјуговане пнеумококне вакцине у Србији.

Метод У периоду од јануара 2009. до априла 2016. године сакупљено је 105 изолата *Streptococcusa pneumoniae*. Анализирали смо резултате серотипизације пнеумокока, која је урађена у Националној референтној лабораторији и утврдили каква је дистрибуција циркулишућих серотипова и њихова покривеност конјугованим вакцинама и 23-валентном полисахаридном вакцином у различитим узрасним групама.

Резултати У колекцији од 105 изолата *Streptococcusa pneumoniae* нађен је 21 серотип. Најзаступљенији су били серотипови 3 (21,9%), 19*F* (20,0%) и 14 (10,5). Подударност изолата са серотиповима садржаним у вакцини била је 48,6% за *PCV*7, 54,3% за *PCV*10 и 84,8% за *PCV*13, док је пнеумококна полисахаридна вакцина (ППВ23) покривала 89,5% од укупног броја изолата. Серотипови садржани у *PCV*7, *PCV*10 и *PCV*13 били су заступљени код 72,0%, 76,0% и 88,0% изолата деце млађе од пет година. Подударност изолата са серотиповима садржаним у *PCV*13 и ППВ23 износила је 87,1% и 90,3% код одраслих старости 50–64 године и 77,8% и 85,2% код старијих од 65 година.

Закључак Заступљеност циркулишућих серотипова *S. pneumoniae* у популацији се у великој мери преклапа са серотиповима садржаним у пнеумококним вакцинама, што оправдава увођење имунизације у дечјем узрасту. Иако је истраживање спроведено у Војводини, налази се могу применити на целу Србију.

Кључне речи: *Streptococcus pneumoniae*; серотипови; вакцинални серотипови

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