

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Seasonal distribution of pertussis

Mioljub Ristić^{1,2}, Biljana Radosavljević¹¹Institute of Public Health of Vojvodina, Novi Sad, Serbia;²University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia**SUMMARY****Introduction/Objective** The seasonality of pertussis is not exactly determined.

The aim of this study was to describe the seasonal distribution of pertussis in the South Bačka District of Vojvodina, Serbia, during four consecutive years.

Methods Data for this observational study were obtained from outpatient and inpatient health care facilities in the South Bačka District from January 1, 2013 to December 31, 2016. We evaluated the seasonal distribution of pertussis among the patients who fulfilled one or more criteria of clinical case definitions of pertussis proposed by the Global Pertussis Initiative. Laboratory confirmations of pertussis were obtained using real-time polymerase chain reaction or ELISA serology tests.**Results** A total of 1,043 participants were included, of which 28.8% were laboratory-confirmed pertussis, with the highest prevalence of laboratory confirmation (66%) in June 2016.Observed by seasons (spring, summer, fall, and winter), there was no significant difference in the average number of testing patients or laboratory-confirmed pertussis during the study period. The average number of laboratory-confirmed cases was significantly higher in patients 0–6 years of age ($p = 0.020$), and with a borderline of significance in the 7–10 years age group ($p = 0.049$) in summer, compared to other three seasons during four consecutive years.**Conclusions** With the increased physician awareness after implementation of the new clinical case definitions, pertussis was recognized throughout all four consecutive years without a clear seasonal pattern of occurrence in our area. Paralleling increase of laboratory-confirmed pertussis during summer months in comparison with other seasons in younger and older age groups suggests a possible transmission within families.**Keywords:** pertussis; seasonality; surveillance**INTRODUCTION**

Many infectious diseases show clear seasonal patterns in both temperate and tropical climates, and seasonality has been well-documented, particularly for viral respiratory infections. However, the seasonality of pertussis is not exactly determined. Therefore, there are some suggestions that pertussis does not have a clear seasonality [1]. Before introducing immunization, pertussis peaked in spring as well as summer months with epidemics of pertussis at intervals of two to three years [1, 2, 3]. Even in countries with high vaccination coverage, pertussis shows epidemic peaks every three to four years, but the seasonality of pertussis is still not time and place consistent [3, 4, 5].

Because pertussis has a substantial increase globally, understanding the seasonal pattern of pertussis within a high vaccine coverage population can help perform the plan of effective public health programs, determine special strategies, and improve the available resources thus making them more effective [6].

To improve pertussis diagnosis, the Global Pertussis Initiative (GPI) proposed an algorithm of the signs/symptoms of pertussis for three age groups: 0–3 months old, four months to nine years old, and the group of 10 year olds and older. According to their recommendations,

the real-time polymerase chain reaction is the diagnostic method of choice in patients of all ages with cough illness of ≤ 3 weeks duration, and a serologic diagnosis should be the method of choice in patients coughing for more than three weeks. Furthermore, real-time polymerase chain reaction is the diagnostic method of choice in the infants (0–3 months of age), regardless of the cough duration [7].

The main goal of this study was to describe the seasonal distribution of pertussis in the South Bačka District after implementation of the new clinical case definitions of pertussis, during four consecutive years (2013–2016).

METHODS

Pertussis is a mandatory notifiable disease in Serbia. Data for this observational study were obtained from outpatient and inpatient health care facilities in the South Bačka District from January 1, 2013 to December 31, 2016. The South Bačka District is one of seven administrative districts of Vojvodina, Serbia. According to the 2011 census results, the South Bačka District has a population of 615,371 inhabitants, which covers 32% of the total Vojvodina population. As previously described in detail, the surveillance of pertussis was conducted in

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accordance with the recommendations given from the GPI [7, 8]. In brief, there only patients that were included, who fulfilled one or more criteria of the GPI clinical case definitions of pertussis for three age groups (0–3 months old, 4 months–9 years old, and ≥ 10 years old). We included all clinically suspected pertussis cases and laboratory confirmed cases. Information on sociodemographic characteristics of participants, the case reporting date and age at the time of the report were collected from physicians at both (inpatient and outpatient facilities) health care levels as a part of the daily routine. In accordance with the GPI proposition, the type of laboratory method (real-time polymerase chain reaction or ELISA antibody tests) depended on the duration of coughing as well as on the age of the suspected case. Nasopharyngeal swabs and single-serum from patients were analysed at the Centre for Microbiology of the Institute of Public Health of Vojvodina, Novi Sad.

Verbal informed consent was obtained from patients at the moment of swab taking in accordance with national regulations. The names of all participants were deleted from the dataset. In accordance with applicable laws and regulations, no clearance by an Ethics Committee is required in Serbia for the retrospective analysis of anonymised data collected within routine pertussis surveillance systems.

The educations about pertussis disease, the specificities of the new case definitions of pertussis proposed by GPI, as well as the adequate sampling and the samples handling procedures of all included physicians were conducted before starting the research.

Statistical analysis

Differences by months and age groups between the laboratory-confirmed pertussis and among those without laboratory confirmation of pertussis were compared by odds ratio with 95% confidence intervals (univariate analysis). To measure the cumulative occurrence of monthly cases, daily number of cases in each month was summed. Seasonal patterns of the clinically suspected and laboratory-confirmed pertussis cases during four seasons into five age groups (0–6, 7–10, 11–14, 15–19, and ≥ 20 -year-olds) were compared. Seasons were defined as spring (April–June), summer (July–September), fall (October–December), and winter (January–March). Differences between the suspected or laboratory-confirmed cases observed by seasons, as well as by age groups were calculated using the analysis of variance (ANOVA).

Two tailed *p*-values less than 0.05 were considered statistically significant.

RESULTS

During the period between 2013 and 2016, a total of 1,043 suspected pertussis cases were reported. Of these, 300 (28.8%) were laboratory-confirmed pertussis.

Observed during four consecutive years, the minimum and maximum number of clinically suspected pertussis

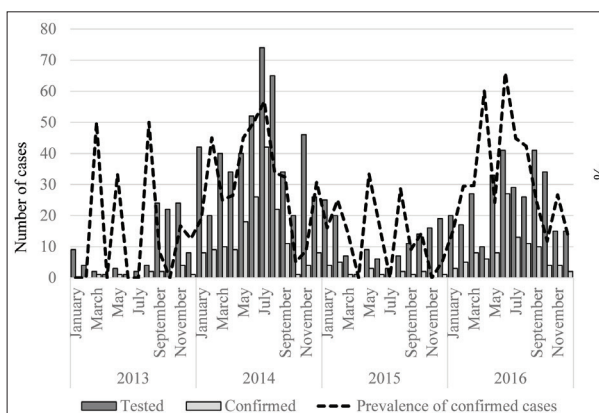


Figure 1. Number and prevalence of pertussis cases by months in the South Bačka District, Vojvodina, 2013–2016

cases was registered in April and September (46 and 110 cases, respectively). Among laboratory-confirmed pertussis, the minimum number of cases during four years was registered in October (seven cases), while the maximum number of confirmed cases was registered in July (55 cases). The highest prevalence of the laboratory-confirmed pertussis was recorded in August, and ranged between 29% (2015) and 50% (2013).

Observed by certain years, the majority of clinically suspected pertussis cases were registered in July 2014 (7.1%, 74/1,043), while the highest prevalence of the laboratory-confirmed cases was registered in June 2016 (65.9%, 27/41) (Figure 1).

In comparison with January, there was an increased probability of laboratory evidence of pertussis in February ($p = 0.024$), and during the period between April and August ($p = 0.023$, $p = 0.003$, $p < 0.0001$, $p < 0.0001$, and $p = 0.001$, respectively). Furthermore, patients who were laboratory tested for pertussis in June and July were six times more likely to have laboratory-confirmed pertussis than those tested in January (OR 6.34, 95% CI 3.22–12.47 and OR 5.60, 95% CI 2.87–10.93, respectively). Regarding the age distribution, the laboratory-confirmed pertussis was more frequently registered in patients of three age groups (7–10, 11–14, and 15–19-year-olds) than among the youngest one (0–6-year-olds) ($p < 0.0001$, $p < 0.0001$, and $p = 0.007$, respectively) (Table 1).

Observed by seasons (spring, summer, fall, and winter) during four consecutive years, no significant differences in the average number of tested or laboratory-confirmed cases of pertussis were determined ($p = 0.696$ and $p = 0.123$, respectively) (Figure 2a, b).

The seasonal differences regarding tested and laboratory-confirmed pertussis cases taken together by the age group in the South Bačka District are presented in Table 2. With the exception of patients in the age groups 11–14 and 15–19 years old, with whom the highest average of laboratory-confirmed cases was detected during spring, and patients aged ≥ 20 years old with the highest average of tested patients registered in fall, in all other age groups, the highest average of tested or laboratory-confirmed pertussis cases was observed during summer months. Requests for pertussis laboratory confirmation in the three age groups

Table 1. Distribution of pertussis cases reported by month and age in the South Bačka District, Vojvodina, 2013–2016

Variable	All participants (n = 1,043) n (%)	Pertussis-positive (n = 300) n (%)	Pertussis-negative (n = 743) n (%)	OR (95% CI)	p
Months					
January	96 (9.2)	15 (5.0)	81 (10.9)	Reference	
February	61 (5.8)	19 (6.3)	42 (5.6)	2.44 (1.13–5.30)	0.024
March	76 (7.3)	20 (6.7)	56 (7.5)	1.93 (0.91–4.09)	0.087
April	46 (4.4)	15 (5.0)	31 (4.2)	2.61 (1.14–5.98)	0.023
May	85 (8.2)	30 (10.0)	55 (7.4)	2.95 (1.45–5.98)	0.003
June	100 (9.6)	54 (18.0)	46 (6.2)	6.34 (3.22–12.47)	< 0.0001
July	108 (10.4)	55 (18.3)	53 (7.1)	5.60 (2.87–10.93)	< 0.0001
August	102 (9.8)	37 (12.3)	65 (8.7)	3.07 (1.55–6.09)	0.001
September	110 (10.5)	24 (8.0)	86 (11.6)	1.51 (0.74–3.07)	0.260
October	90 (8.6)	7 (2.3)	83 (11.2)	0.46 (0.18–1.18)	0.104
November	101 (9.7)	12 (4.0)	89 (12.1)	0.73 (0.32–1.65)	0.446
December	68 (6.5)	12 (4.0)	56 (7.5)	1.16 (0.50–2.66)	0.731
Age (years)					
0–6	265 (25.4)	50 (16.7)	215 (28.9)	Reference	
7–10	186 (17.8)	94 (31.3)	92 (12.4)	4.39 (2.88–6.69)	< 0.0001
11–14	161 (15.4)	64 (21.3)	97 (13.1)	2.84 (1.83–4.41)	< 0.0001
15–19	110 (10.6)	35 (11.7)	75 (10.1)	2.01 (1.21–3.33)	0.007
≥ 20	321 (30.8)	57 (19.0)	264 (35.5)	0.93 (0.61–1.41)	0.729

Statistically significant differences (p < 0.05) are marked in bold

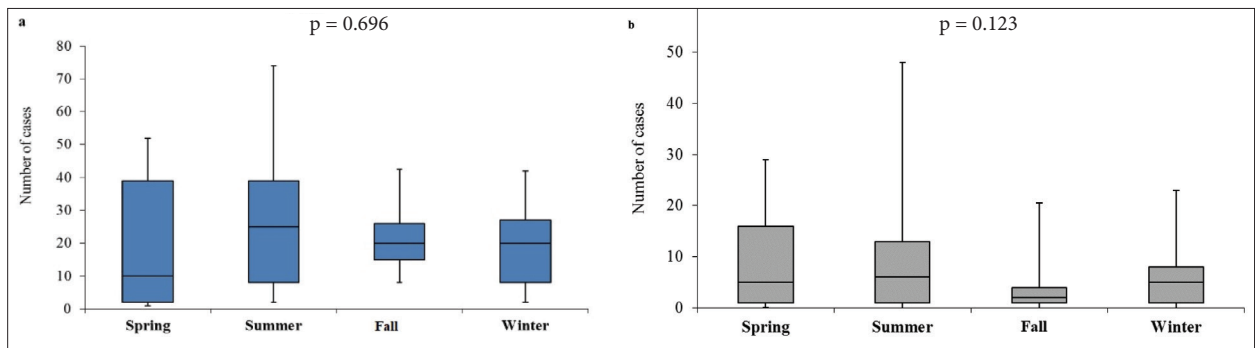


Figure 2. Seasonal pattern of pertussis in the South Bačka District, Vojvodina, 2013–2016: (a) all tested participants; (b) laboratory-confirmed cases; Box plot: The length of the box represents the interquartile range (the distance between the 25th and the 75th percentile); the horizontal line in the box represents the median; the whiskers extend to the group minimum and maximum value

Table 2. Seasonal differences in pertussis cases by age group in the South Bačka District, Vojvodina, 2013–2016

Variable	Age group (years)	Spring			Summer			Fall			Winter			p ^a
		Total	Mean	SD	Total	Mean	SD	Total	Mean	SD	Total	Mean	SD	
All tested participants	0–6	48	12.0	6.8	84	21.0	19.6	71	17.8	2.7	60	15.0	9.9	0.001
	7–10	58	14.5	14.7	61	15.3	16.7	35	8.8	2.9	30	7.5	4.9	0.010
	11–14	42	10.5	11.0	47	11.8	8.8	31	7.8	3.3	43	10.8	7.3	0.223
	15–19	26	6.5	7.1	42	10.5	7.7	27	6.8	1.8	21	5.3	4.1	0.004
	≥ 20	54	13.5	10.7	87	21.8	11.7	92	23.0	9.5	84	21.0	7.6	< 0.0001
Laboratory-confirmed cases	0–6	8	2.0	1.6	29	7.3	7.4	6	1.5	0.5	7	1.8	1.5	0.020
	7–10	30	7.5	7.5	37	9.3	10.8	11	2.8	1.5	16	4.0	2.5	0.049
	11–14	27	6.8	7.2	16	4.0	3.5	9	2.3	1.8	12	3.0	3.1	0.063
	15–19	13	3.3	3.4	10	2.5	1.8	2	0.5	0.5	11	2.8	3.7	0.676
	≥ 20	21	5.3	4.1	24	6.0	6.4	3	0.8	0.8	8	2.0	1.9	0.126

SD – standard deviation;

^aANOVA – analysis of variance;

Statistically significant differences (p < 0.05) are marked in bold

(0–6, 7–10, and 15–19 years old) were more common during summer months ($p = 0.001$, $p = 0.010$, and $p = 0.004$, respectively), while patients over 20 were significantly less tested during spring in comparison with other three seasons ($p < 0.001$). The average number of laboratory-confirmed cases was significantly higher in patients aged 0–6 years ($p = 0.020$), and with a borderline of significance among those aged 7–10 years ($p = 0.049$) during summer months than in other seasons.

DISCUSSION

Although this study refers to only a part of Serbia's territory, seasonal patterns of pertussis showed some specificities. We revealed a high prevalence of laboratory-confirmed pertussis (about 30%) with the highest number of confirmed cases during summer months and the highest prevalence of the laboratory-confirmed cases in August. Multiple studies have reported similar results [4, 9, 10].

Because of the absence of an adequate laboratory support for definitive laboratory confirmation, pertussis is under-reported in children as well as in adolescents and adults. Recognition of the disease by physicians is hampered by the nonspecific pertussis symptoms in adolescents and adults. Furthermore, only patients presented with classic pertussis symptoms were registered and only a small number of cases was reported [11]. Our results clearly demonstrated an increasing risk of laboratory-confirmed pertussis in February, and during next five consecutive months (April, May, June, July, and August). Except for patients under 20, participants of all other age groups had a higher probability to have positive laboratory pertussis tests in comparison with those aged 0–6 years. We believe that an explanation for this lies in the fact that the new case definitions of pertussis along with an adequate laboratory support was implemented. To support this, our study findings suggest that the probability of laboratory confirmation of pertussis significantly increased throughout the year and in virtually all age groups.

Regarding the seasonal trend of pertussis, several studies showed a pattern corresponding to summer and spring months in the Southern Hemisphere, and winter and autumn months in the Northern Hemisphere [1, 4, 6, 12–15]. Previously published studies found a seasonal predominance in the period July–September during epidemic years which changed to periods October–December and January–March in the post-epidemic period [10, 16]. The results of a Korean study which was conducted among participants aged 11 and older with cough duration of less than 30 days, showed a peak incidence of pertussis in February and August. However, there were no laboratory-confirmed pertussis cases between March and June. A probable explanation for the absence of pertussis cases during one part of the year may lie in the fact that this study lasted only one year [17]. On the other hand, results of other authors show no seasonal occurrence of pertussis [18]. The presentation of seasonal distribution of pertussis in all of the aforementioned studies was mainly

based on the results obtained after implementation of the clinical case definitions of pertussis recommended by the World Health Organization (WHO), the US Centers for Disease Control Prevention (CDC) or the European Centre for Disease Prevention and Control (ECDC) which are not universally applicable and are mostly used for vaccine efficacy testing [7]. Due to the implementation of the new GPI case definitions of pertussis, we found that pertussis was recognized almost equally throughout all four seasons (spring, summer, fall, and winter), without significant differences in the occurrence among suspected or laboratory-confirmed cases. Among participants who met one or more clinical criteria of pertussis and therefore requested pertussis tests, we found that patients aged 20 years and older were rarely tested during spring in comparison with summer, fall or winter months. The reasons for the mentioned differences are not completely clear, and they should be addressed in the future research.

In terms of the seasonal patterns of pertussis, in a study by Ghorbani et al. [6], 6.6% out of 3,629 of suspected pertussis cases was laboratory-confirmed. They used microbial culture or real-time polymerase chain reaction, and revealed that the majority of laboratory-confirmed pertussis were patients aged 0–6 years and school children who were reported mostly during summer months (July–September), which is in line with the findings of our study.

In addition, because the most pertussis cases among preschool and school aged children were registered during summer months, results of several published studies indicated no evidence of association between the increased incidence and the reopening of kindergartens and schools [1, 6, 9, 19]. On the other hand, results of other studies have suggested an association between opening of schools and an annual increase in pertussis incidence [15, 20, 21]. Interestingly, results of a study conducted in the Netherlands showed that peak incidence of pertussis was reported in August into all age groups, except in patients aged 13–18 years, who mostly were registered in November [4]. A possible explanation for the obvious absence of connection between the seasonal peak of pertussis and reopening of collectives is found in high pertussis vaccine coverage in the population of the aforementioned studies [1, 4, 6, 9, 19]. With the exception of patients aged 11–19 years, we found that the number of laboratory-confirmed pertussis was the highest during summer months in all other age groups. The observed variation by age of participants can indicate the transmissions within family members during summer holidays and among schoolmates during spring months.

In support of the results of other authors, our study has not shown a connection between opening of schools after summer holidays and an increased number of pertussis cases [1, 4, 6, 9, 19]. Taking into account the waning of vaccine induced immunity as well as the lack of typical symptoms or subclinical pertussis infections, we believe that many of suspected cases, especially in school collectives, have been unrecognized.

The study in adolescent and adult population in which the majority of laboratory-confirmed pertussis was registered

between May and August, highlighted that clinical characteristics of the disease were similar in comparison with those who had *M. pneumoniae*, *C. pneumoniae*, and mixed – infection of pertussis with other pathogens [14].

Respiratory tract infections are the most common cause of acute cough among children, while recurrent infections are the most frequent cause of prolonged (subacute or chronic) cough [22, 23]. Furthermore, other medical conditions such as asthma, viral and bacterial respiratory infection, as well as exposures to allergens (allergic constitution) are important causes of prolonged cough illness in children and older age groups [14, 24, 25]. In accordance with this, we found that the number of tested and laboratory-confirmed cases was slightly higher during summer months. We think that the reasons for this occurrence lie in the fact that pertussis-like medical conditions that may mask clinical presentation of pertussis, are less common during summer which consequently led to increase of awareness for recognition of pertussis.

The risk of severe pertussis and death is highest among infants. Early diagnosis and management of cases allow targeted antibiotic therapy, which may reduce the severity of the disease and play an important role in minimizing pertussis transmission [26]. Unfortunately, we revealed that the time from the first day of illness to a laboratory test depends on the age of participants, with the highest values among elderly patients who can be potential reservoirs for pertussis transmission to susceptible children (data not shown).

The main limitation of this study includes the lack of detection of other pathogens or pertussis-like illnesses. Thus, further studies are required to take this aspect into account. Furthermore, because of high vaccination coverage against pertussis in our area, and due to the fact that the typical signs and symptoms of pertussis are often absent in adolescents and adults as well as previously vaccinated persons, we believe that our data have not included

all pertussis cases in our region [27]. However, we suppose that these limitations did not discriminate the main findings of this study.

CONCLUSION

With increased physician awareness after implementation of the new clinical case definitions, pertussis was recognized throughout all four consecutive years without a clear seasonal pattern of occurrence in our region. Therefore, our results indicate that active surveillance of pertussis throughout the year is necessary. Paralleling increase of laboratory-confirmed pertussis during summer months in younger and older age groups suggests a possible transmission within families. Based on the criteria of the GPI clinical case definitions of pertussis, future studies are needed in Serbia as well as in other regions where seasonality of pertussis is unspecified.

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NOTE

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The authors declare that there is no conflict of interest.

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Сезонска дистрибуција великог кашља

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САЖЕТАК

Увод/Циљ Сезонски карактер великог кашља (*pertussis*) (ВК) није прецизно утврђен. Циљ овог рада је био да се опише сезонско јављање великог кашља у Јужнобачком округу Војводине, Србија, током четири узастопне године.

Метод Подаци за ову опсервациону студију добијени су из ванболничких и болничких установа Јужнобачког округа, у периоду од 1. јануара 2013. до 31. децембра 2016. године. Сезонска дистрибуција ВК је процењивана међу болесницима који су испуњавали један или више критеријума клиничких дефиниција случаја ВК предложених од Глобалне пертусисне иницијативе. Лабораторијска потврда ВК добијена је употребом *PCR* метода или серолошким (*ELISA*) тестовима.

Резултати Од укупно 1 043 испитаника, код 28,8% је добијена лабораторијска потврда ВК са највећом преваленцијом (66%) у јуну 2016. године. Посматрано по годишњим доби-

ма (пролеће, лето, јесен и зима), није утврђено постојање значајне разлике у просечном броју свих лабораторијских тестираних болесника или у броју лабораторијских потврђених случајева ВК. Просечан број лабораторијски потврђених случајева ВК код болесника узраста до шест година и код болесника узраста од седам до 10 година био је значајно већи лети у поређењу са остала три годишња доба током четири узастопне године посматрања ($p = 0,020$ и $p = 0,049$).

Закључак После увођења нових дефиниција, повећањем свести међу лекарима о присуству ВК нису утврђене јасне сезонске разлике у његовој појави на испитиваној територији. Упоредни пораст учешћа лабораторијски потврђених случајева ВК током лета међу млађом и одраслом популацијом указује на могућност да се он преноси унутар породица.

Кључне речи: велики кашаљ; сезонска дистрибуција; надзор