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Pertussis in children under the age of 10

Велики кашаљ код деце млађе од 10 година

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SUMMARY

Introduction/Objective Pertussis is a vaccine-preventable disease that causes a large number of cases and hospitalizations worldwide.

The aim of this study was to determine predictors of hospitalization in cases of pertussis among children under 10 years of age in the South Bačka District of Vojvodina (SBDV).

Methods Data for this observational study were obtained from inpatient and outpatient health care facilities in the SBDV from January 1, 2013 to December 31, 2016. We evaluated predictors of hospitalization among the patients who fulfilled the criteria of case definitions of pertussis proposed by the Global Pertussis Initiative. Pertussis was confirmed by DNA polymerase chain reaction (PCR) or ELISA serology tests.

Results Out of 122 laboratory-confirmed pertussis cases, 43 (35.2%) were hospitalized. Apnoea and pneumonia were associated with hospitalization, and all six hospitalized patients aged 0-3 months had cyanosis. Apnoea was a good predictor of hospitalization among children with any duration of cough ($p<0.05$). Among children with a cough that lasted longer than 14 days, post-tussive emesis or pneumonia or contact with a person who had a prolonged cough were associated with hospitalization ($p=0.035$, $p=0.042$, and $p=0.046$, respectively). There were fewer hospitalizations in properly vaccinated cases than in partly or non-vaccinated cases between two months and four years of age ($p<0.008$).

Conclusions Among the pertussis cases under 10 years of age, apnoea, pneumonia and cyanosis were factors associated with hospitalization. Immunization against pertussis corresponding to age reduces the disease severity and hospitalizations in children from two months to four years of age.

Keywords: pertussis; hospitalization; surveillance; epidemiology

САЖЕТАК

Увод/Циљ Велики кашаљ је вакцинама спречива заразна болест која је узрок великог броја оболелих и хоспитализованих широм света.

Циљ рада био је да се одреде предиспонирајући фактори за хоспитализацију оболелих од великог кашља у узрасту млађих од 10 година у Јужнобачком округу (Војводина).

Методе Подаци за ову обсервациону студију добијени су из болничких и ванболничких здравствених установа Јужнобачког округа, у периоду од 1. јануара 2013. до 31. децембра 2016. Предиспонирајући фактори за хоспитализацију оболелих процењивани су на основу клиничких критеријума Глобалне пертусисне иницијативе за дефиницију великог кашља. Велики кашаљ је доказиван употребом *PCR* метода или серолошким (*ELISA*) тестовима.

Резултати Од 122 потврђена случаја великог кашља, 43 (35,2%) је хоспитализовано. Апнеа и пнеумонија су корелирали са хоспитализацијом, а свих шест хоспитализованих пацијената млађих од три месеца имали су цијанозу. Апнеа је била добар прогностички знак хоспитализације за све оболеле без обзира на дужину трајања кашља ($p<0.05$). Код оболелих са кашљем дуже од 14 дана, прогностички знаци за хоспитализацију су били повраћање након кашља, пнеумонија и контакт са особом која је имала дуготрајни кашаљ ($p=0,035$; $p=0,042$ и $p=0,046$). Потпуно имунизована деца узраста од два месеца до четири године била су ређе хоспитализована у односу на непотпуно имунизовану и невакцинисану децу истог узраста ($p<0,008$).

Закључак Код деце узраста млађих од 10 година, апнеа, пнеумонија и цијаноза показали су се као добри прогностички знаци за хоспитализацију оболелих од великог кашља. Вакцинација против пертусиса у складу са узрастом доприноси појави блажих клиничких форми обољења и смањењу броја хоспитализација код деце узраста од два месеца до четири године.

Кључне речи: велики кашаљ; хоспитализација; надзор; епидемиологија

INTRODUCTION

Pertussis (whooping cough) as a vaccine-preventable disease is a prevalent cause of acute cough in both children and adults occurring in outpatient and inpatient health care facilities [1]. Despite high immunization coverage, pertussis is still present around the world [2, 3, 4, 5]. In 2016, more than 139,000 pertussis cases were reported worldwide [6]. The majority (approximately 95%) of infections occurred in developing countries, with most deaths occurring in young infants who were either unvaccinated or incompletely vaccinated [3, 4, 5]. Even in countries with high vaccination coverage, pertussis causes a high number of cases and hospitalizations [2, 5]. A dramatic resurgence

of pertussis worldwide, with large outbreaks and deaths mainly in infants, has drawn the attention of health-care providers [5].

Protection against pertussis was achieved only after completed 3-dose primary vaccination series at approximately 6 months of age [2, 3, 7]. According to the annual reports in the South Bačka District of Vojvodina (SBDV) between 2013 and 2016, the average immunization coverage of pertussis was 95% for the primary series (at 2, 4, and 6 months), and 90% for one booster dose (one year after the third dose of vaccine) [8].

The main goal of this study was to determine predictors of hospitalization in cases of pertussis among children under 10 years of age in the SBDV.

METHODS

Study design

The design and methods of improved surveillance of pertussis have been described previously [9, 10]. Surveillance of pertussis from inpatient and outpatient health care facilities in the SBDV was conducted for four consecutive years, in the period from January 1, 2013 to December 31, 2016. We included all children under 10 years of age, regardless of the duration of cough. Additionally, when children fulfilled one or more criteria of pertussis proposed by the Global Pertussis Initiative (GPI) [9], they were enrolled after admission to health care facilities during the whole week. During the study period, we included children who were hospitalized at the Department of Pulmonology of the Institute for Child and Youth Health Care of Vojvodina (an inpatient facility), and at 11 health centres (the primary health care level) of the SBDV.

Eligible children were under 10 years of age who met one or more criteria of clinical case definitions of pertussis proposed by the GPI for two age groups (0–3 months old, and four months–nine years old) (Table 1).

Table 1. Clinical Case Definitions of Pertussis and Diagnostic Tests Proposed by the Global Pertussis Initiative[a] for patients aged younger than 10 years old.

Age groups	0-3 months	4 months-9 years
Signs/symptoms/contact	Cough and coryza with no or minimal fever plus: -whoop or apnoea or -post-tussive emesis or -cyanosis or one of the following: seizure, pneumonia, close exposure to an adolescent or adult (usually a family member) with a prolonged afebrile cough illness	Paroxysmal cough with no or minimal fever plus: -whoop or apnoea or one of the following: -post-tussive emesis, seizure, worsening of symptoms at night, pneumonia, close exposure to an adolescent or adult (usually a family member) with a prolonged afebrile cough illness
Diagnostic method-cough illness in a person with no or minimal fever plus cough duration[b]	PCR for all children aged 0-3 months	PCR or Serology (IgG-PT), if ≥ 1 year post-pertussis vaccination

[a]Adapted from the Global Pertussis Initiative;
[b]For patients aged 4months-9 years old: PCR if cough duration less than 3 weeks, and serology if cough duration longer than 3 weeks;
PCR-polymerase chain reaction; IgG-immunoglobin G; PT-pertussis toxin

We excluded children who did not fulfil the GPI clinical case definitions of pertussis proposed for the two age groups (0–3 months old, and four months–nine years old).

This research was conducted as a part of the daily clinical routine practice. The training of all included physicians and nurses was conducted before starting our research. Verbal informed consent was obtained from parents or guardians of children at the moment of swab taking in accordance with national regulations. All data about the children were anonymised and de-identified.

Participants

We obtained children's demographic and clinical data as well as the data about vaccination against pertussis in a structured questionnaire of parents or guardians. At the primary health care level, vaccination status was obtained from vaccination records of participants. Vaccination status at inpatient facilities was determined from a parental report of the child's vaccination record, and therefore it was checked from vaccination records at primary health care level. The choice of clinical management, including hospitalization and laboratory procedures, was determined by the child's physician. Depending on the clinical course of the disease, all clinical and laboratory data were obtained at inpatient or outpatient health care facilities.

Posterior nasopharyngeal swabs and whole blood samples (single-serum) from patients were collected by trained physicians and nurses at inpatient and outpatient medical care facilities as well as at the Institute of Public Health of Vojvodina, Novi Sad (IPHV). All samples were analysed at the Centre for Microbiology of IPHV. According to the GPI case definitions of pertussis [9], the type of laboratory method (real-time polymerase chain reaction (PCR) or serology tests) depends on the duration of cough and on the age of the suspected case (Table 1).

As we previously described in detail [10], nasopharyngeal specimens were defined as positive if *Bordetella pertussis* was detected by the PCR. Additionally, ELISA antibody test from whole blood samples was considered as positive if cut-off values were above 100 IU/mL. Because of potentially false positive results, we excluded all participants four months-nine years of age who were vaccinated within one year before the collection of whole blood samples [9].

Statistical analysis

We examined an association between potential predictors of hospitalization regarding certain signs/symptoms, gender, the duration of cough, residence, asthma, prescribed antibiotics, diagnostic methods, and vaccination status. In accordance with the vaccination status, we divided two groups of participants: 1. properly vaccinated (children who received the number of vaccine doses corresponding to their age), and 2. partly or non-vaccinated participants (partly vaccinated children were the ones who received some but not all vaccines, while the non-vaccinated patients were those who did not receive any dose of pertussis vaccine). Patients under two months of age were excluded from the study because they were below vaccination age.

The two-tailed Fisher's exact test or chi-square were used for associations between categorical variables, with the Yate's correction for continuity used for the analysis of dichotomous variables, and the Mann-Whitney U test for continuous variables. We calculated the difference between the laboratory-confirmed pertussis in inpatient and outpatient health care facilities using univariate and multivariate logistic-regression models by the odds ratio (OR) with 95% confidence interval (95% CI) regarding certain signs/symptoms.

The results were considered statistically significant when the p-value of all applied models was <0.05. The data were analysed using the SPSS version 22 software and MedCalc for Windows, version 12.3.0 (MedCalc Software, Mariakerke, Belgium).

RESULTS

General characteristics of children with the laboratory-confirmed pertussis

During 2013-2016, a total of 122 laboratory-confirmed pertussis cases under 10 years of age were reported. Of these, 43 (35.2%) were inpatients and 79 (64.7%) were outpatients. Patients aged 0-3 months and four-12 months had higher risk of hospitalization in comparison with other two age groups ($p<0.001$). Among all laboratory-confirmed cases, inpatients were significantly more partly or non-vaccinated against pertussis, and had antibiotic treatment prior to inclusion in the study in comparison with outpatients ($p=0.015$ and $p=0.028$, respectively) (Table 2).

Risk factors for hospitalization

To assess the effects of certain signs/symptoms of clinical case definitions of pertussis for the two age groups and the vaccination status of participants, we compared the results of pertussis-positive children who were hospitalized with those who were not (Table 3, 4 and 5).

Taking into account the required signs/symptoms (RSS) in children aged 0-3 months and four months – 9 years (Table 1), the Table 3 shows the signs/symptoms in hospitalized and outpatient cases. The most frequent clinical sign/symptom among inpatients and outpatients was whoop (58.1% and 48.1, respectively). In patients four months – 9 years of age, the prevalence of worsening of symptoms at night was 72.7 in outpatients and 67.6% among inpatients. All six hospitalized patients aged 0-3 months with the laboratory-confirmed pertussis had cyanosis. According to univariate and multivariate logistic regression analysis, we revealed that RSS in combination with apnoea or pneumonia was associated with hospitalization ($p<0.05$). Although the combinations of RSS and whoop or post-tussive emesis were not significantly associated with hospitalization, the association of these variables increased after adjustment for the confounding effect of vaccination status.

The RSS along with apnoea was a good predictor of hospitalization among children with any duration of cough ($p<0.05$). In children who had a cough for more than 14 days, the RSS combined with post-tussive emesis or pneumonia or with information of close exposure to a person with a

prolonged cough were associated with hospitalization (p=0.035, p=0.042, and p=0.046, respectively) (Table 4).

Table 2. Characteristics of laboratory-confirmed pertussis cases under 10 years old in the South Bačka District, 2013–2016.

Variable	Total cases No./total No. (%)	Hospitalized No./total No. (%)	Outpatients No./total No. (%)	p value[a]
Gender				
Female	59/122 (48.4)	23/43 (53.5)	36/79 (45.6)	0.518
Male	63/122 (51.6)	20/43 (46.5)	43/79 (54.4)	
Age				
0–3 months	8/122 (6.6)	6/43 (14.0)	2/79 (2.5)	**<0.001[b]**
4–12 months	11/122 (9.0)	9/43 (20.9)	2/79 (2.5)	
2–5 years	22/122 (18.0)	7/43 (16.3)	15/79 (19.0)	
6–9 years	81/122 (66.4)	21/43 (48.8)	60/79 (76.0)	
Duration of cough in days (Mean ± SD)	25.5±17.3	26.5±19.3	25.0±16.1	0.920[c]
Residence				
Urban area	87/122 (71.3)	29/43 (67.4)	58/79 (73.4)	0.626
Rural area	35/122 (28.7)	14/43 (32.6)	21/79 (26.6)	
Asthma or bronchitis or laryngitis				
Yes	34/122 (27.9)	15/43 (34.9)	19/79 (24.1)	0.288
No	88/122 (72.1)	28/43 (65.1)	60/79 (75.9)	
Diagnostic method				
PCR positive	37/122 (30.3)	17/43 (39.5)	20/79 (25.3)	0.154
Serology (IgG-PT) positive	85/122 (69.7)	26/43 (60.5)	59/79 (74.7)	
Vaccination status[d]				
Properly vaccinated according to age	100/116 (86.2)	28/38 (73.7)	72/78 (92.3)	**0.015**
Partly vaccinated or non-vaccinated	16/116 (13.8)	10/38 (26.3)	6/78 (7.7)	
Antibiotic treatment before sampling				
Yes	25/122 (20.5)	14/43 (32.6)	11/79 (13.9)	**0.028**
No	97/122 (79.5)	29/43 (67.4)	68/79 (86.1)	

[a]Chi-square test;
[b]Two-tailed Fisher's exact test;
[c]Mann-Whitney test;
[d]Only for patients aged 2 months-9 years old;
SD-standard deviation; PCR-polymerase chain reaction; IgG-immunoglobin G; PT-pertussis toxin;
Values that differ significantly (p<0.05) between hospitalized and outpatients laboratory-confirmed cases are marked in bold.

We analysed the association between hospitalization and vaccination in properly vaccinated cases and among those who were partly or non-vaccinated against pertussis. There were 116 pertussis

cases two months - 9 years of age. Of these, 38 (32.8%) were hospitalized. There were fewer hospitalizations in properly vaccinated cases than in partly or non-vaccinated ones between two months and 4 years of age (p<0.008). However, there was no significant difference between hospitalization in properly and partly or non-vaccinated children against pertussis in patients from 5 to 9 years of age (p=0.570) (Table 5).

Table 3. Predictive signs/symptoms and contact in hospitalized and outpatients under 10 years old in the South Bačka District, 2013–2016.

Signs/symptoms/ contact	Hospitalized No./total No. (%)	Outpatients No./total No. (%)	Crude OR (95%CI)	p value	Adjusted OR[a] (95%CI)	p value
Whoop	25/43 (58.1)	38/79 (48.1)	1.50 (0.71-3.17)	0.290	1.63 (0.69-3.89)	0.268
Apnoea	18/43 (41.9)	11/79 (13.9)	4.45 (1.85-10.72)	**0.001**	3.05 (1.11-8.39)	**0.031**
Post-tussive emesis	24/43 (55.8)	31/79 (39.2)	1.96 (0.92-4.15)	0.081	2.26 (0.94-5.44)	0.068
Cyanosis[b]	6/6 (100)	1/2 (50.0)	NA	ND	-	-
Seizure	5/43 (11.6)	0 (-)	NA	ND	-	-
Worsening of symptoms at night[c]	25/37 (67.6)	56/77 (72.7)	0.78 (0.33-1.83)	0.570	0.91 (0.28-2.03)	0.585
Pneumonia	9/43 (20.9)	1/79 (1.3)	20.65 (2.52-169.43)	**0.005**	15.21 (1.60-144.71)	**0.018**
Contact[d]	16/43 (37.2)	21/79 (26.6)	1.64 (0.74-3.62)	0.224	1.14 (0.43-2.99)	0.794

[a]Adjusted for the following variables: Symptoms, gender, duration of cough, residence, asthma, antibiotic prescribed, diagnostic method, and vaccination status;
[b]Only for patients aged 0-3 months;
[c]Only for patients aged ≥4 months;
[d]Close exposure to an adolescent or adult (usually a family member) with a prolonged afebrile cough illness;
CI-confidence interval; NA-not applicable; ND-not determined;
Values that differ significantly (p<0.05) between hospitalized and outpatients laboratory-confirmed cases are marked in bold.

Table 4. Predictive signs/symptoms and contact in hospitalized and outpatients under 10 years old in accordance with the cough duration before sampling in the South Bačka District, 2013–2016.

Signs/symptoms/contact	Cough duration of ≤ 14 days (n=39)			Cough duration of > 14 days (n=83)		
	Hospitalized No./total No. (%)	Outpatients No./total No. (%)	p value[a]	Hospitalized No./total No. (%)	Outpatients No./total No. (%)	p value[a]
Whoop	8/15 (53.3%)	14/24 (58.3%)	NS	17/28 (60.7%)	22/55 (40.0%)	NS
Apnoea	6/15 (40.0%)	1/24 (4.2%)	0.008	12/28 (42.9%)	8/55 (14.5%)	0.007
Post-tussive emesis	7/15 (46.7%)	10/24 (41.7%)	NS	17/28 (60.7%)	19/55 (34.5%)	0.035
Worsening of symptoms at night[b]	10/12 (83.3%)	18/23 (78.3%)	NS	15/25 (60.0%)	31/54 (57.4%)	NS
Pneumonia	5/15 (33.3%)	0 (-)	NA	4/28 (14.3%)	1/55 (1.8%)	0.042
Contact[c]	6/15 (40.0%)	9/24 (37.5%)	NS	10/28 (35.7%)	8/55 (14.5%)	0.046

[a]Two-tailed Fisher's exact test;
[b]Only for patients aged ≥4 months;
[c]Close exposure to an adolescent or adult (usually a family member) with a prolonged afebrile cough illness;
NS-not significant; NA-not applicable.

Table 5. Association between vaccination and hospitalization for pertussis among children aged 2 months-9 years old in the South Bačka District, 2013-2016.

Age group	Vaccination status	Hospitalized No./total No. (%)	Outpatients No./total No. (%)	p value[a]
2months–4 years n=26	Properly vaccinated	4/14 (28.6)	10/12 (83.3)	0.008
	Partly vaccinated or non-vaccinated	10/14 (71.4)	2/12 (16.7)	
5–9 years n=90	Properly vaccinated	24/24 (100.0)	62/66 (93.9)	0.570
	Partly vaccinated or non-vaccinated	0 (-)	4/66 (6.1)	

[a]Two-tailed Fisher's exact test

DISCUSSION

This is the first study to evaluate predictors of hospitalization among laboratory- confirmed pertussis cases in our country. Our findings provide a comprehensive view of the pertussis burden among children during the first 9 years of life.

We revealed that 35.2% of laboratory-confirmed cases under 10 years of age were hospitalized because of pertussis. Furthermore, out of total pertussis cases younger than 12 months of age, about 80% were hospitalized. The study conducted by Crespo at al. [7] found that above 90% hospitalized patients with pertussis were younger than 12 months of age. A probable explanation for the obvious high prevalence of hospitalized cases lies in the fact that the authors of the mentioned study included not only the primary cases, but also all secondary cases of pertussis (contacts with primary cases).

Our results show that RSS in combination with apnoea increased the probability of hospitalization by about four times and the combination of RSS accompanied with pneumonia by more than 15 times. In addition, among patients aged 0-3 months, a cough and coryza with no or minimal fever, as the required sign/symptom, combined with cyanosis was a good predictor of hospitalization. Considering a lot of research conducted with heterogeneous inclusion/exclusion criteria in varying clinical settings, with different types of diagnostic pertussis tests, as well as various immunization schedules, multiple studies reported different results regarding predictors of pertussis hospitalizations. The results of the study stated above [7] highlighted that whoop, apnoea and cyanosis were more frequent in hospitalized than in outpatient cases, and pneumonia was not associated with an increasing risk of hospitalization. Limitation of mentioned study was the duration of the study period (for only two years).

The results of another study, which was conducted among children with pertussis in hospital settings, showed that children who were readmitted had more cyanotic episodes per day and with the larger number of hospital days [11]. Furthermore, the results of the recently published meta-analysis indicated that apnoea and cyanosis are helpful for detection of pertussis in infants younger than 12 months of age [1].

Many of the implemented case definitions of pertussis predicted the cough duration of ≥ 2 weeks for patients of all ages. Due to the implementation of the new GPI case definitions of pertussis, which predicted inclusion of patients under 10 years of age, regardless of the cough duration [9], we found that as many as 32% (39/122) of total cases had a cough duration less than 14 days. Our results are very important if we know that early diagnosis of pertussis in infants allows targeted antibiotic therapy, which could reduce the severity of the disease, the duration of cough and could play an important role in reducing of pertussis transmission to close contacts. It is noteworthy that both vaccination and early treatment strategies are equally important for improving outcomes [12, 13, 14, 15, 16].

Observing the vaccination status among children from two months to four years of age, we clearly demonstrated an increasing risk of hospitalization among partly or non-vaccinated children in comparison with those who were fully immunized against pertussis. Multiple studies have reported similar results [7, 15, 16, 17, 18, 19]. Similar to the results of our research, a study conducted among infants (aged <12 months) found that properly vaccinated children were protected against hospitalization [20]. In addition, probably because only participants aged <12 months were included, the authors of the stated study [20] revealed that protection against hospitalization was the same after immunization with whole-cell or acellular pertussis vaccines.

Our study findings suggest that the risk of hospitalization was the same regardless of vaccine doses among children aged 5-9 years. We believe that the reasons for this lie in the fact that vaccine-induced immunity waned over time, which consequently led to a decrease of the protective role of vaccination regarding the hospitalization. According to the recently published review data, the estimated duration of protection obtained from the whole-cell pertussis vaccine is from 5 to 14 years, and the one from the acellular vaccine is from 4 to 7 years [21, 22]. One of the recently mentioned explanations for the resurgence of pertussis worldwide, both in school children and adolescents is connected with changes in the antigens in circulating *Bordetella pertussis* in comparison with the vaccine strains [23].

In regard to the signs/symptoms, the results of the study among fully immunized children with the median age of 9 years and the median cough duration of 14 days, showed that only 21% of the patients had paroxysmal cough, 13% had post-tussive emesis, 7% apnoea and 6% had classic whoop [24]. Results of another study which was conducted on hospitalized children from one month to 15 years of age with prolonged cough (duration ≥ 14 days) who were previously vaccinated with four doses of vaccine against pertussis, demonstrated that the prevalence of paroxysmal cough was 84.4%, but post-tussive emesis and whoop were rare (31.3% and 28.2%, respectively) [25]. The mentioned differences can be interpreted as the result of various inclusion criteria of the study population. In our research, there were 74% of properly immunized hospitalized children from two months to 9 years of age. Probably because of the implementation of active surveillance together with training of all staff

included in our research and low vaccination coverage among hospitalized children, there were 58.1% patients with whoop, 55.8% with post-tussive emesis and as many as 41.9% children with apnoea.

Due to the quality and comparability of the results of our study, we are convinced that this research has the potential to be a standard model in the preparation of more comprehensive hospital surveillance among children with the pertussis infection throughout the Republic of Serbia.

CONCLUSION

We revealed that apnoea, pneumonia and cyanosis were good predictors of hospitalization in pertussis cases. In addition, apnoea was a good predictor for hospitalization among children, regardless of the duration of cough. On the other hand, post-tussive emesis, pneumonia and contact with a person with the prolonged afebrile cough illness were associated with hospitalization among children with the cough duration of >14 days. Immunization against pertussis corresponding to age reduces the disease severity and hospitalizations in children from 2 months to 4 years of age.

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