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EVOLUTION OF CLINICAL MANIFESTATIONS OF WHOOPING COUGH IN CHILDREN IN THE POST-COVID-19 PANDEMIC PERIOD

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In recent years, an increase in the number of cases of pertussis has been recorded in Europe and Ukraine. The purpose of the study was to find out the features of pertussis in children in the first three years of life after the COVID-19 pandemic and compare them with clinical and laboratory data of similar patients who had pertussis before the pandemic COVID-19. A retrospective analysis of 97 patient charts of inpatients aged 0-36 months diagnosed with pertussis who were treated in the Lviv Regional Clinical Infectious Diseases Hospital in 2017–2019 and 2023–2024 was conducted. It was found that the course of the disease in the post-epidemic cohort was milder, with a higher incidence of respiratory complications; a number of differences in clinical manifestations, complete blood counts in children of different age groups, and in the period before and after the SARS-CoV-2 pandemic were identified. After the end of the COVID-19 pandemic, the weakening of population immunity, genetic mutations of Bordetella pertussis and the possible impact of SARS-CoV-2 infection on the immune response contributed to an increase in children's susceptibility to pertussis and changes in clinical manifestations of the disease.

Key words: pertussis, children, COVID-19, course of disease, immune response.

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ЕВОЛЮЦІЯ КЛІНІЧНИХ ПРОЯВІВ КАШЛЮКУ У ДІТЕЙ У ПЕРІОД ПІСЛЯ ПАНДЕМІЇ COVID-19

В Європі й Україні у останні роки реєструють зростання захворюваності на кашлюк. Метою дослідження було з'ясувати особливості перебігу кашлюку у дітей перших трьох років життя у період після пандемії COVID-19 та порівняти їх з клінічними та лабораторними даними аналогічних пацієнтів які хворіли на кашлюк до початку пандемії. Проведено ретроспективний аналіз 97 карт стаціонарного хворого віком 0-36 міс з діагнозом кашлюк, які перебували на стаціонарному лікуванні у Львівській обласній клінічній інфекційній лікарні в періоди 2017–2019 рр. і 2023–2024 рр. Встановлено, що перебіг захворювання у когорті дітей у період після епідемії був легшим, водночас з вищою частотою респіраторних ускладнень; виявлено низку відмінностей в клінічних проявах, показниках загального аналізу крові у дітей різних вікових груп, та у період до та після виникнення пандемії SARS-CoV-2. Після завершення пандемії COVID-19 ослаблення популяційного імунітету, генетичні мутації Bordetella pertussis та можливий вплив перенесеної SARS-CoV-2-інфекції на імунну відповідь сприяли зростанню сприйнятливості дітей до кашлюку та зміні клінічних проявів захворювання.

Ключові слова: кашлюк, діти, COVID-19, перебіг хвороби, імунна відповідь.

The work is a fragment of the research project "Clinical features of infectious diseases in children and current diagnostic and treatment methods during different stages of the SARS-CoV-2 epidemic", state registration No. 0124U000805.

In European countries, over the past decade, there has been a cyclical increase in cases of whooping cough in children every 3-4 years, with annual peaks in regions with a temperate climate occurring between July and September. However, since April 2020, the number of pertussis cases has fallen sharply, reaching its lowest level since the beginning of the century. In the UK, for example, the incidence of pertussis in infants in 2020 was 0.50 per 100.000 population, which is significantly lower than in 2014 (24.6 per 100.000) [10]. However, in the post-epidemic period, the incidence of this disease began to rise rapidly and in a number of countries significantly exceeded the figures before the start of the COVID-19 epidemic [1]. In Ukraine, according to the Public Health Center, there has also been a significant increase in the incidence of whooping cough. In the first half of 2024 y. almost 4.900 cases of the disease were registered. Despite the availability of effective vaccines, whooping cough remains a pressing problem. This is due to a number of factors, such as reduced immunity, the emergence of new strains of Bordetella pertussis bacteria, insufficient vaccination, and underestimation of the danger of the disease.

The purpose of the study was to determine the characteristics of pertussis in children under three years of age in the period after the COVID-19 pandemic and to compare them with the clinical and laboratory data of similar patients who had pertussis before the pandemic.

Materials and methods. We conducted a retrospective analysis of 97 medical records of hospitalized children aged 0-36 months who were treated at the Lviv Regional Clinical Infectious Diseases Hospital during two periods: in 2017–2019 and 2023–2024. Only cases with a laboratory-confirmed diagnosis of whooping cough, established by PCR-RT and/or detection of IgM antibodies in the blood, were included in the study. The patients were divided into two age groups: Group 1 comprised 56 children aged 0–12 months, and Group 2 included 41 children aged 12–36 months. Each group was further subdivided into pre-pandemic and post-pandemic subgroups, based on whether the pertussis infection occurred before or after the onset of the COVID-19 pandemic. A total of 39 parameters were analyzed, encompassing clinical data, disease severity, and results from laboratory and instrumental investigations. Disease severity was assessed using the 20-point scale developed by M.-P. Preziosi and E. Halloran. Data analysis was performed using Microsoft Excel and Statistica 8.0.

Results of the study and their discussion. The average age of patients in Group 2 during the post-COVID-19 epidemic period was 26.08±2.18 months, which was statistically significantly higher than the average age of patients hospitalized before the epidemic (22.40±4.99 months). In contrast, the age of patients in Group 1 did not differ significantly between the pre- and post-epidemic periods. Most children in the study were hospitalized at the onset of the spasmodic cough phase. According to medical histories, parents of patients in both groups reported a gradual progression of the disease, initially noting the appearance of a dry cough, predominantly nocturnal, while the child's general condition remained satisfactory. The average duration of the prodromal period (from the onset of dry cough to the onset of spasmodic cough) was 7.61±1.56 days in Group 1 and 10.38±2.79 days in Group 2. The primary reasons for clinic visits and hospitalization were respiratory symptoms. A paroxysmal or spasmodic cough characteristic of Bordetella pertussis, usually culminating in a prolonged, high-pitched inhalation, was observed in all children 5-10 days prior to hospital admission. Paroxysmal cough was not the only respiratory symptom; 35 % of patients in group 1 and 22 % of children in group 2 had mild respiratory distress.

Among hospitalized children, the vaccination coverage rate was low, not exceeding 21 %; in most patients, routine vaccination was incomplete or performed late. The exception was a subgroup of children in their first year of life, 50 % of whom received preventive vaccinations in the post-epidemic period.

The course of pertussis was considered severe in 9 (45.0 %) children under 1 year of age in the pre-pandemic period, and the average score on the M-P-Preziosi disease severity scale was 8.53±2.54 points in the post-COVID-19 period, the severity of whooping cough in infants in this group was determined to be 7.88±3.26 points ($p<0.05$). An even more pronounced difference in the severity of whooping cough was observed in children in group 2, as on the 5th day of inpatient treatment, the severity of the disease was assessed at 10.17±4.13 points in the period before COVID-19 and at 6.13±2.13 points ($p<0.05$) in patients hospitalized after the end of the pandemic (Table 1).

Table 1

Whooping cough symptoms in children, frequency, and time of onset in the periods before and after COVID-19

Indicator	Group 1 (age 0–12 months) n = 56		Group 2 (age 12–36 months) n = 41	
	Before COVID-19 (n = 20)	After COVID-19 (n = 36)	Before COVID-19 (n = 22)	After COVID-19 (n = 19)
Day of onset of spasmodic coughing (days)	9.65±7.32	10.56±7.32	11.54±4.57	16.31±13.42 *
Day of onset of reprise (days)	11.00±6.06	12.22±7.12	12.07±5.37	17.67±8.65 *
Frequency of reprises (%)	31.5	55.6	59.0	50.0
Frequency of apnea (%)	15.0	25.0	9.0	0
Severity on the 5th day of inpatient treatment (points)	8.53±2.54	7.88±3.26 *	10.17±4.13	6.13±2.13 *
Frequency of complications (%)	25.0	27.8	31.8	36.8
Fever >37.5°C (%)	15.0	8.3	45.5	31.6
Duration of inpatient treatment (days)	9.60±5.77	9.00±3.21*	10.72±5.57	9.89±7.36

* $p<0.05$ comparing the results of subgroups before and after the COVID-19 pandemic.

Spasmodic coughing attacks occurred in children in group 1 were on average 10 days after the onset of the first symptoms of the disease, and the occurrence of this symptom in children at different

periods of the epidemic process was approximately the same. In children in group 2, in the period before the coronavirus epidemic, spasmodic coughing occurred on 11.54±4.57 days after the onset of the disease, and in the period after the pandemic, only on 16.31±13.42 days ($p<0.05$). In children in group 1, hospitalized after the pandemic, episodes of apnea were more frequently detected: in 9 (25.0 %), compared with patients in this group before COVID-19 (3 infants, 15.0 %). Spasmodic coughing was often accompanied by a high-pitched "whoop" sound or reprises (convulsive inhalations with a “whistling” or “cockcrow” sound), which occurred due to laryngeal spasm after a series of coughing fits. Reprises were common in children in both groups, but were more frequently described in children in group 2 (in 59 % of patients before COVID-19 and 50 % of children in the post-epidemic period). In patients in this group, they occurred on 17.67±8.65 days from the onset of the disease (or approximately one day after the onset of spasmodic coughing), statistically significantly later than in patients hospitalized in the pre-epidemic period. In infants in group 1, relapses occurred on average two days after the onset of spasmodic coughing.

All patients were hospitalized in the paroxysmal stage of whooping cough. For this stage hyperthermia is not classically considered a typical symptom of the disease, but may be both a marker of secondary bacterial infection. Hyperthermia caused by B. pertussis of the ciliated epithelium of the respiratory tract or (and) increased production of pro-inflammatory cytokines (IL-1, TNF-α) by immune cells. Elevated body temperature above 37.5°C was more common in patients in both subgroups in the pre-pandemic period—in 15 % of children in group 1 and 45.5 % of patients in group 2. In children hospitalized after the COVID-19 epidemic, it was 8.3 % and 31.6 %, respectively.

According to the results of a complete blood count (Table 2) an elevated leukocyte count at hospitalization was detected in 43 (76.8%) children in group 1 and in 31 (64.6%) children in group 2. In patients in group 1, the total number of leukocytes was higher before the epidemic with an average of $22.78±9.73×10^9$/L, compared to patients of the same age hospitalized after the end of the epidemic, where this indicator averaged $14.83±6.40×10^9$/L ($p<0.05$). Similar patterns were found for the absolute number of lymphocytes, which was higher in children in group 1 ($14.14±6.14×10^9$/L) compared to children in the same group who fell ill after the epidemic ($8.9±1.87×10^9$/L, $p<0.05$).

Table 2

Complete blood count in patients with whooping cough

Indicator	Group 1 (age 0–12 months) n = 56		Group 2 (age 12–36 months) n = 41	
	Before COVID-19 (n = 20)	After COVID-19 (n = 36)	Before COVID-19 (n = 22)	After COVID-19 (n = 19)
Total white blood cell count ($×10^9$/L)	22.78±9.73	14.83±6.40 *	13.89±5.71	13.32±6.17
Absolute lymphocyte count ($×10^9$/L)	14.14±6.14	9.6±4.67 *	6.37±4.11	6.67±4.43
Absolute neutrophil count ($×10^9$/L)	14.40±11.73	8.40±8.26 *	4.69±3.00	5.18±3.03
Anemia (frequency. %)	25.0 %	22.2 %	27.27 %	10.52 %
ESR (mm/h)	4.65±2.25	7.34±5.34 *	8.81±7.38	13.05±8.96

* $p<0.05$ comparing the results of subgroups before and after the COVID-19 pandemic.

In patients in group 2, the total number of leukocytes and the absolute number of lymphocytes did not differ in patients hospitalized at different periods of the COVID-19 epidemic. Anemia in children in groups 1 and 2 was detected in approximately one in five patients; the frequency of anemia was slightly lower in children hospitalized after COVID-19, but these differences were not statistically significant. ESR indicators in children in both groups did not differ significantly and did not exceed the acceptable norm for children of the corresponding age.

We consider bronchitis, pneumonia, and bronchial obstructive syndrome as complications of whooping cough. The highest frequency of complications was observed in children from both age groups who contracted whooping cough during the post-COVID-19 epidemic period - 27.8 % in children under 1 year and 36.8 % in those aged 12-36 months. Although complications occurred slightly more often than in comparable groups from the 2017-2019 yy. period, these differences were not statistically significant.

According to the literature, the incidence of whooping cough during the COVID-19 pandemic and for several months afterward was significantly lower than in the pre-epidemic period. This decline is primarily attributed to the implementation of non-pharmaceutical interventions, including social distancing, restrictions on population mobility, quarantine measures in educational institutions (schools and preschools), and mask-wearing. These anti-epidemic measures reduced the transmission of Bordetella pertussis within the population. However, the absence of B. pertussis circulation during the early years of the COVID-19 pandemic led to a decline in population immunity. Combined with waning vaccine-induced immunity during adolescence, this increased children’s susceptibility to infection, especially amid the

emergence of new, more contagious B. pertussis strains. Genetic mutations in the pathogen have enhanced its virulence, resulting in strains that evade post-vaccination immune responses. Notably, some outbreak-associated strains lack pertactin (PRN), a key antigen, which may reduce their recognition by the immune system.

Whooping cough is a highly contagious respiratory disease caused by the gram-negative bacterium Bordetella pertussis, which infects humans exclusively. The disease occurs worldwide in both endemic and epidemic forms, affecting individuals of all ages. The highest incidence is observed among unvaccinated or incompletely vaccinated infants and young children, who often experience severe illness and a high rate of complications. Infants under six months of age, particularly those born prematurely or with low birth weight, are at greatest risk for severe disease, complications, prolonged hospitalization, and mortality. Currently, no vaccines against pertussis are licensed or recommended for newborns. The most effective preventive strategies include maternal vaccination during pregnancy, the cocoon strategy (vaccinating close contacts), vaccination of all individuals in contact with the infant, and timely administration of routine childhood vaccinations.

In the typical course of pertussis infection, the bacterium enters the respiratory tract through airborne droplets, spreads through the respiratory tract, attaches to the ciliated epithelial cells of the trachea and nasopharynx, and begins to multiply and colonize neighboring areas. The toxins secreted by the microorganism damage the epithelium and affect the ciliated cells. The cessation of cilia function, disruption of the G-protein signaling system in cells, and suppression of immune cell function by increasing cAMP levels are all examples of the effects of various toxins produced by B. pertussis [2]. They allow the bacteria to evade the host's immune response (primarily by reducing phagocyte activity, suppressing the production of inflammatory cytokines, and reducing T-lymphocyte activation) and promote the survival of B. pertussis in the body.

To meet our objectives we formed patient cohorts based on clearly defined criteria. Group 1 included children aged 29 days to 1 year and those aged 1 to 3 years who were hospitalized with a diagnosis of whooping cough before the onset of the COVID-19 pandemic. A similar age distribution was applied to Group 2, which comprised children hospitalized after the pandemic period (2022-2024 yy.). Our working hypothesis was that a certain proportion of patients aged 1 to 3 years in Group 2 may have had prior COVID-19 infection, as 86% of these patients had a history of at least one episode of acute respiratory viral infection during the pandemic, while only 13.3 % of cases were documented as COVID-19. Previous SARS-CoV-2 infection, even in the absence of pronounced clinical symptoms, could have influenced the course of bacterial respiratory tract infections, particularly whooping cough, or reduced the effectiveness of immunity induced by pertussis vaccination, despite adherence to the vaccination schedule.

The inflammatory response of a child to SARS-CoV-2 infection closely correlates with the severity and duration of the disease. Pro-inflammatory mediators, such as interleukins (IL-6, IL-10, TNF-α, IL-2) and chemokines (CCL2/MCP-1, CCL7, CXCL8/IL-8, CXCL10/IP-10, CXCL11) play a central role in the cascade of inflammatory reactions accompanying the course of COVID-19 [4]. Patients infected with SARS-CoV-2 show elevated levels of IL-1β, IFN-γ, CXCL10/IP-10, and CCL2/MCP-1, which activates the cellular response of type 1 T helper cells (Th1). At the same time, there is an increase in the secretion of type 2 T helper (Th2) cytokines, in particular IL-4 and IL-10, which have anti-inflammatory effects and can modulate the immune response [6]. This imbalance between Th1 and Th2 responses potentially contributes to a prolonged decrease in the effectiveness of post-vaccination immunity against Bordetella pertussis.

Since effective protection against B. pertussis largely depends on the activation of innate immunity, in particular through Toll-like receptors (TLR4 and TLR2), and SARS-CoV-2 can suppress the immune response mediated by TLR4, while activating TLR2, this may lead to a more severe or atypical course of pertussis [11]. Other ways in which SARS-CoV-2 affects the functioning of the immune system include suppression of macrophage and dendritic cell activity in the respiratory tract. In addition, SARS-CoV-2 causes damage to the respiratory epithelium, changes in mucus production, and a decrease in the synthesis of secretory immunoglobulin A (sIgA) [9]. Such effects can modify the course of pertussis, since B. pertussis toxins, in particular pertussis toxin and adenylate cyclase, also suppress local immunity and potentiate inflammatory processes in the respiratory tract.

SARS-CoV-2 infection can affect the composition of the respiratory microbiome, creating conditions more favorable for B. pertussis colonization. The use of antibiotics during COVID-19 treatment may have an additional impact on the microbiome, potentially leading to an altered immune response to subsequent infections, including pertussis. At the same time, SARS-CoV-2 can activate antiviral interferons that suppress other pathogens.

Some infections, including coronaviruses, “train” the innate immune system (after infection or vaccination, innate immune cells - monocytes, macrophages, NK cells - can change their functional activity) and the immune response becomes faster and more effective when in contact with subsequent pathogens [3]. After a viral infection, epigenetic changes occur in the cells of the innate immune system (for example, post-translational modifications of histones affect the activity of genes associated with the immune response, in particular those that regulate inflammation). This resembles “immune memory,” but is not as specific as acquired immunity (involving T and B lymphocytes). Immune cells become more reactive: they detect pathogens faster and activate inflammatory signals (e.g., interferons), which can reduce the severity of new infections [7].

Children who have had COVID-19 or received a coronavirus vaccine may have a “prepared” immune system. Even when infected with whooping cough, their macrophages or neutrophils identify the bacteria faster, limit its reproduction, reduce the severity of symptoms, and change (prolong) the time of their onset.

Conclusion

Analyzing the course of whooping cough in children before and after the COVID-19 pandemic, we found that disease severity, assessed comprehensively on the fifth day of inpatient treatment, was statistically significantly lower in children from both groups who contracted the illness after the pandemic.

In patients aged 12–36 months who were hospitalized significantly later after the pandemic (approximately 1.5 times longer), spasmodic coughing and reprises were observed more frequently, whereas hyperthermic syndrome was less common. However, the incidence of respiratory complications was higher in both groups during the post-pandemic period.

Among children from Group 1 a significant differences were noted in complete blood count: total leukocyte count, as well as absolute and relative numbers of neutrophils and lymphocytes, were significantly lower in those hospitalized after the COVID-19 pandemic. The differences in hematological indicators in children aged 1-12 months (Group 1) may be explained by enhanced post-vaccination immunity, as the cohort born after the pandemic had better vaccination coverage (50 % vaccinated infants compared to 20 % before the pandemic). Conversely, the severity and timing of symptom onset in children aged 12-36 months (Group 2) cannot be attributed to vaccination status, as vaccination rates were similar across periods (21-22 %). It is likely that some patients had prior COVID-19 infection (confirmed in only 13.3 %), which could have affected their immune response to Bordetella pertussis infection.

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