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ASSESSMENT OF THE INTENSITY OF POST-VACCINATION IMMUNITY AGAINST MEASLES IN CHILDREN WHO HAVE HAD COVID-19

R. Z. Pulatova
Department of Internal Medicine, Faculty of "Tibbiyot", NOU University "ALFRAGANUS", Tashkent, Uzbekistan

D.T. Kenjayeva
Tashkent State Medical University, Department of propaedeutics of children's diseases, Termez branch, Uzbekistan

Abstract
The state of post-vaccination immunity to measles was studied in 178 previously vaccinated children with post-COVID syndrome aged 6 months to 12 years, as well as in 30 healthy children of the same age. The high frequency of seronegative cases of measles antibodies is associated with previously suffered COVID-19. The manifestation of the underlying disease over a long period of time, expressed in post-COVID syndrome, negatively affects the production of protective antibodies to measles in comparison with healthy children.

Keywords: COVID-19, post-covid syndrome, children, post-vaccination immunity to measles, multisystem inflammatory syndrome

Аннотация
Состояние поствакцинального иммунитета к кори было изучено у 178 ранее вакцинированных детей с постковидным синдромом в возрасте от 6 месяцев до 12 лет, а также у 30 здоровых детей того же возраста. Высокая частота серонегативных случаев к коревым антителам связана с перенесенным ранее COVID-19. Проявление основного заболевания в течение длительного периода времени, выражающееся в постковидном синдроме, негативно влияет на выработку защитных антител к кори по сравнению со здоровыми детьми.

Annotatsiya
Go'shtga qarshi emlashdan keyingi immunitet holati 6 oylikdan 12 yoshgacha bo'lgan, ilgari emlangan 178 nafar post-COVID sindromi bilan kasallangan bolalarda, shuningdek, xuddi shu yoshdagi 30 nafar sog'lom bolalarda o'rganildi. Qizamiq antikorlarining seronegativ holatlarining yuqori chastotasi ilgari COVID-19 bilan bog'liq. Asosiy kasallikning uzoq vaqt davomida namoyon bo'lishi, post-COVID sindromida namoyon bo'lishi, sog'lom bolalar bilan solishtirganda go'sht uchun himoya antikorlarini ishlab chiqarishga salbiy ta'sir qiladi.

Introduction

The COVID-19 pandemic represents a global challenge both in managing patients

with acute disease progression and in addressing post-COVID complications. Systemic inflammation often develops against the background of COVID-19, accompanied by a "cytokine storm," hemostasis disorders, and severe vasculitis. New data indicate that dysfunction of various body systems may contribute to the development of post-COVID syndrome and the formation of multi-organ or poly-organ failure. It is known that viral infections have the ability to reduce immunological memory to various regulated infections [6-11]. Moreover, it is not always possible to clearly predict the immunization schedule, as the number of children and adolescents with post-COVID long syndrome has increased in recent years. These patients are often and chronically ill, with allergic, chronic, or latent infectious diseases that serve as reasons for vaccination deferral [1-4].

The lack of a well-founded, standardized approach to immunization with live vaccines in children with post-COVID long syndrome determines the goals and objectives of the present study.

Thus, studies dedicated to investigating the role of post-COVID syndrome formation and progression in children, as well as the influence of various pathogens on the body, are practically absent in the literature, which underscores the need for further research.

The aim of the study.

To examine the state of post-vaccination immunity to measles in previously vaccinated children with post-COVID syndrome, depending on age and disease duration.

Materials and methods

Under our observation were 178 children who had previously had COVID-19, as well as 30 healthy children of similar age and gender. The children's ages ranged from 6 months to 12 years (Table 1).

Таблица1

The distribution of patients with post-COVID syndrome by age.

	Age n=178	n,%
1.	6 months to 1 year	28(15,7%)
2.	From 1 year to 12 years old	150 (84,3%)

All children had previously been vaccinated with the measles vaccine (MEASLES ATTENUATED VACCINE, Serum Institute of INDIA PVT. LTD., 212/2 Hadapsar, Pune 411 028, INDIA (01)08901213041928) and the MMR vaccine (MEASLES MUMPS RUBELLA VACCINE, Serum Institute of INDIA, 0164w001 PVT. LTD., 212/2). All children were diagnosed with post-COVID syndrome, which was included in the International Classification of Diseases (ICD-10), category code U09.9 "Post COVID-19 condition, unspecified," also encompassing post-COVID state. Based on the duration of the illness, the disease was classified into "Long COVID" — clinical manifestations lasting more than 4 but less than 12 weeks from the onset of the disease — and chronic COVID or "post-COVID syndrome" — clinical manifestations extending beyond 12 weeks from the onset of the disease (Table 2).

Таблица 2.
Clinical manifestations of post-COVID syndrome in children.

	Postcovoid syndrome n=178	n,%
1.	"Long covid" (4 weeks -12 weeks)	98(55%)
2.	Chronic postcovoid syndrome (12 weeks or more)	80 (45%)

Clinical and laboratory studies, diagnosis, and treatment of patients were conducted in accordance with the current clinical protocol for diagnosis and treatment of the Ministry of Health of the Republic of Uzbekistan [7].

A previous COVID-19 infection was confirmed by detecting antibodies to S-RBD SARS-CoV-2 IgG using the ELISA-BEST (Novosibirsk) test for COVID-19 (neutralizing

S antibodies). Antibody titers to COVID-19 above 1 IU/ml were considered positive. Measles antibody titers were determined using the VectorMeasles-ELISA IgG (Novosibirsk) test for quantitative determination in blood serum. The results were interpreted as follows: up to 0.12 IU/ml – negative or seronegative; from 0.13 to 0.17 IU/ml – weakly positive; values above 0.18 IU/ml were considered positive, indicating high measles antibody titers.

All children were divided into the following groups: Group 1 (main) – 98 patients with Long-COVID (post-COVID syndrome); Group 2 – 80 patients with chronic post-COVID syndrome. Post-COVID syndrome manifested differently in children. It included frequent inflammatory diseases of the upper and lower respiratory tract (sinusitis, maxillary sinusitis, otitis, bronchitis, bronchiolitis, bronchopneumonia, etc.), systemic connective tissue diseases (arthritis, polyarthritis, etc.), nervous system involvement (polyradiculoneuritis, encephalopathies, brain cysts, etc.), as well as various vasculitis, involvement of the urinary system, kidneys, and gastrointestinal tract.

Mathematical processing of the obtained data was carried out using the method of variation statistics with the calculation of arithmetic mean values (M), their standard errors (m), confidence intervals of the arithmetic means (σ), and confidence differences according to Student's t-test.

The results of the study showed that the average IgG SARS-CoV-2 antibody titers for COVID-19 were significantly higher in chronic COVID compared to Long-COVID: 10.8±0.5 IU/ml versus 8.52±0.9 IU/ml; P <0.05; Table 3. With the progression and manifestation of clinical symptoms and the duration of post-COVID syndrome, IgG measles antibodies significantly decreased. This decrease was not statistically significant (0.34±0.01 versus 0.87±0.9; P >0.05).

Results

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Table 3

Content of IgG SARS-CoV-2 antibodies and measles antibody titers in children who had COVID-19, depending on the duration of the disease in post-COVID syndrome.

	IU/ml indicators	Chronic covid IU/ml n=34	Long-covid n=49 IU/ml	P
1	IgG SARS-CoV-2 COVID-19	10,8±0,5*	8,52±0,9	<0,05
	The limit of fluctuations	от 10,7до 16,0	От 0,56 до 16,0	
2	Antibodies to measles IgG	0,34±0,01	0,87±0,9	>0,05
	The limit of fluctuations	От 0,43 до 2,01	От 0,21до 2,18	

Note: *- the reliability between antibody titer values in chronic COVID and long COVID

An analysis of the vaccination schedule for each patient with post-COVID syndrome was conducted (Table 4). The studies showed that among children aged 6 months to 1 year, full coverage with two doses of the measles vaccine was achieved in only 8 (50%) children. When analyzing the children's developmental histories, we noted that incomplete vaccination (only one dose) was received by 22 (78.5%)

children under the age of one. A total of 14 (50%) children received the first dose (V1), while 8 (28.8%) received the second dose (V2) without the first dose. This is due to the fact that children were unable to receive their vaccinations on time because of quarantine during the pandemic. Those who were vaccinated later received an unscheduled vaccine (at 6 months and at 1 year) and were included in the group of 14 (50%) children.

Table 4

Measles vaccination indicators among children with post-COVID syndrome depending on scheduled vaccinations received.

Age	V1 (n,%)	V2(n,%)	V1+V2(n,%)
From 6 months to 1 year (n=28)	14/50	8/28,8*	8/50
From 1 year to 12 years (n=150)	30/20*	22/14,6*	98/65,3
Total vaccination coverage is complete (n=178)	-	-	106/70,6

Note: * - reliability between completed vaccination V1+V2 and incomplete V1 and V2

A similar pattern was observed in children aged one to twelve years. The first measles vaccination (V1) was received by only 30 children with post-COVID syndrome, accounting for 20%. The second vaccination (V2) without the first (V1) was received by only 22 patients, making up 14.6%. An incomplete or unfinished measles vaccination schedule was noted in 52 (53%) children in this category. In total, 178 patients with post-COVID syndrome were examined, and 106 of them received full measles vaccination, making up 70.6%.

When analyzing the developmental history of children with disrupted vaccination schedules, frequent medical exemptions from vaccinations were noted after quarantine. These were directly related to post-COVID syndrome and the involvement of other vital dysfunctions and disorders in children's bodies. Comorbid diseases also play an important role in the body, such as TORCH infections (CMV, HSV, mycoplasma, ureaplasma) and the frequently encountered Epstein-Barr virus. On the one hand, the reason for the disrupted preventive vaccination schedules was the pandemic associated with the coronavirus infection and quarantine. On the other hand, the COVID-19 virus itself negatively impacts post-vaccination immunity against measles.

The state of post-vaccination immunity to measles in children with post-COVID syndrome was studied depending on the duration of the disease (Table 5). The table shows that the frequency of seronegative patients for measles in post-COVID syndrome is 6.6 times higher than the negative antibody titers in healthy individuals ($P<0.05$). The level of measles antibody titers was considered weakly positive and varied from 0.13 to 0.17 IU/ml. In long-COVID cases, it was found in 2 (2%) patients, whereas in chronic COVID cases, the frequency was twice as high, reaching 4 (5.5%). However, this difference was not statistically significant ($P>0.05$). No patients with this antibody titer were observed among healthy individuals.

Table 2

State of post-vaccination immunity to measles in children with post-COVID syndrome depending on disease duration.

№	Titers of antibodies	"Long-covid" (4	Chronic post-covoid	Healthy

	(AT) to measles	weeks -12 weeks) n=104	syn-drome (12 weeks or more) n=74	childr en
	(IU/ml)	n/%	n /%	n/%
1	Up to 0.12-negative (seronegative)	20/19, 2*	14/19*	2/6,6
2	From 0.13 to 0.17 – weakly positive	2/2	4/5,5	-
3	Above 0.18 IU/ml is a highly positive or protective antibody (AT) level	82/78, 8*	50/67, 5*	28/93, 4
	Total n=178			

Note: * - reliability compared to the group of healthy children

A protective level of antibodies in children was considered to be above 0.18 IU/ml, which was regarded as a seropositive variant. Among children with long COVID, the frequency of seropositive antibodies was observed in 82 children (78.8%), while in the group with chronic post-COVID syndrome, antibody titers were positive in 50 children (67.5%). A comparative analysis with healthy children showed that antibody titers were high in 28 children (93.4%), which was significantly higher than in patients with post-COVID syndrome, constituting 82 (78.8%) and 50 (67.5%) respectively compared to 28 (93.4%); $p<0.01$.

The coverage of immunization against measles was lower in patients with post-COVID syndrome, and high measles antibody levels were registered in 132 patients, accounting for 74.2% of the total number. These values were significantly lower than those of healthy children (28/93.4%) ($p<0.001$).

The acute phase of COVID-19, as practice shows, was relatively mild in most children, often presenting in an asymptomatic or even subclinical form. However, 4–6 weeks later, some "convalescents" developed symptoms observed in the advanced phase of severe forms of the new coronavirus infection in adults [1, 3]. This involves a rapidly developing inflammatory reaction with active involvement of internal organs. The difficulty in diagnosing such processes is associated, firstly, with a lack of experience in dealing with such patients and, secondly, with the wide variety of clinical manifestations, up to the development of toxic shock syndrome [2].

In recent years, there have been few publications on the impact of the new coronavirus infection on post-vaccination immunity. It is known that immunization is a process through which a person acquires immunity or becomes resistant to an infectious disease, usually through the administration of a vaccine.

Conclusion

The high frequency of seronegative measles antibody cases is associated with a previous COVID-19 infection and the prolonged manifestation of the primary disease, expressed as post-COVID syndrome, which negatively affects the production of protective measles antibodies (in 34 patients (19.1%) compared to healthy children 2 (6.6%), $p<0.001$).

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