Eksplorium *p*-ISSN 0854-1418
Volume 46 No. 1, 2025: 1467–1474 *e*-ISSN 2503-426X

Immune Response in Repeated Covid-19 Infections Differences by Age Group

[1]Patimat Daudovna Kurkieva, [2]Arina Vladimirovna Gut, [3]Ibragim Kuraevich Zakhaev, [4]Zaira Shoipovna Osmaeva, [5]Mikhail Mikhailovich Losev, [6]Ekaterina Alexandrovna Kleymenova, Svetlana Alexandrovna [7]Kosobutskaya

[1]Russian University of Medicine, 127473, 20 Delegatskaya Street, Moscow, patimat.osmanova02@mail.ru 0009-0001-3392-3376

[2]Institute of Clinical Medicine, Samara State Medical University, 443099, 89 Chapayevskaya Street, Samara Sunny-2012-01@list.ru
0009-0006-0097-2012

[3]Astrakhan State Medical University, 121 Bakinskaya Street, 414000, Ibragimzahaev.123@mail.ru
0009-0008-1800-6597

[4]Astrakhan State Medical University, 121 Bakinskaya Street, 414000, 0000-0003-0508-7654
Zajka.osmaeva@mail.ru

[5]Astrakhan State Medical University, 121 Bakinskaya Street, 414000, m.loseff2002@yandex.ru
0009-0004-0678-3381

[6]Pirogov Russian National Research Medical University (RNRMU) Ostrovityanova str., Moscow, 117997, Russia, kleymenova2002@yandex.ru
0009-0000-1743-3214

[7]Federal State Autonomous Educational Institution of Higher Education I.

M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), 8 Trubetskaya str., building 2, Moscow, 119048, Russia,fotinia78@mail.ru, 0000-0002-5484-9574

Article Received: 25 Feb 2025, Revised: 20 April 2025, Accepted: 03 May 2025

Annotation. Repeated infection with SARS-CoV-2 allows us to evaluate the body's immune memory response and its effectiveness in defense against infection. Age is an important factor affecting the intensity of the immune response in COVID-19. The aim of the present study was to compare the immune response to a recurrent episode of COVID-19 in patients of different age groups. Unvaccinated patients (n=140) with confirmed first and second episodes of SARS-CoV-2 infection, divided into four age categories (<18, 18-49, 50-64 and ≥65 years) were included in the study; indices of humoral immunity (titres of specific IgG antibodies) and cellular immunity (number of virus-specific T-lymphocytes) were studied several weeks after each episode of disease.In young individuals, re-infection was found to result in a significant increase in antibody levels (~2-fold increase in titre on average) and an enhanced T-cell response, whereas in elderly patients the increase in immune response was significantly less pronounced. The young groups had higher mean antibody titres and higher numbers of specific T cells after both the first and second infection compared to the elderly (differences statistically significant, $p<0.05$). Thus, the immune response to recurrent COVID-19 varies considerably according to age: the young have a stronger and more effective immune response that provides better protection against reinfection, whereas the elderly have a weakened immune response that may increase the risk of recurrent severe disease.

Keywords: COVID-19; re-infection; immune response; humoral immunity; cellular immunity; age-related differences; immune memory.

INTRODUCTION.

A new coronavirus infection (COVID-19) caused by the SARS-CoV-2 virus has become a global pandemic affecting all age groups in 2020. The severity of COVID-19 has been found to be significantly associated with the age of the patient: the elderly are significantly more likely to have severe infection, while children and young adults are predominantly mild or asymptomatic.

According to epidemiological observations, people over 65 years of age account for a disproportionately large proportion of hospital admissions and deaths in COVID-19, while in children there are only a few cases of critical course. Such differences may be due to the age-related characteristics of the immune system[5]. The elderly develop the phenomenon of immune aging - a decrease in the functional activity of both innate and adaptive immunity, depletion of the pool of naive lymphocytes and impaired coordination of the immune response. In addition, older age groups are characterised by chronically elevated levels of pro-inflammatory cytokines (‘inflammaging’), which contributes to the development of a hyper inflammatory response to infection (cytokine storm). In contrast, in children and young adults, the immune system has greater functional reserve and flexibility.

It is assumed that they have a more effective early innate antiviral response, in particular the production of type I interferons at the initial stages of infection, which limits the initial viral load. Adaptive immunity in the young also rapidly mounts a full defense, including active production of neutralizing antibodies and virus-specific T-lymphocytes.

Together, these factors may explain the milder course of COVID-19 in younger patients. Even after surviving COVID-19, the risk of re-infection with SARS-CoV-2 remains. Reinfection has been observed over time, facilitated by the emergence of new virus variants with mutations in antigenic determinants (e.g. Delta, Omicron strains), as well as a gradual decline in the level of neutralizing antibodies and memory immune cells [6].

It has been suggested that age-related immune memory may influence the likelihood and outcome of recurrent infections.

In older individuals, naturally acquired immunity has been reported to be less robust: the effectiveness of protection after COVID-19 in patients over 65 years of age is significantly lower than in young adults[8]. For example, one large study noted that protection against re-infection is reduced to ~50% in individuals over 65 years of age, whereas protection against re-infection exceeds 80% in those under 50 years of age. In addition, elderly patients, even when re-infected, often have severe or complicated disease, whereas younger patients tend to have milder episodes of re-infection. All these indicate significant differences in immune response to reinfection between age groups [2].

Therefore, the aim of the present study was to investigate how age affects the immune response in recurrent COVID-19 cases.

In particular, it was of interest to compare humoral immunity (specific antibody levels) and cellular immunity (T-lymphocyte response) after SARS-CoV-2 reinfection in patients of different age categories (from children to the elderly).

The results of the study were expected to provide a better understanding of age-related differences in immunological defense in COVID-19 and may contribute to the development of optimal protection strategies for the most vulnerable populations.

MATERIALS AND METHODS OF THE STUDY.

The study was conducted as a retrospective cohort study. Patients who had undergone COVID-19 twice between 2020 and 2022 were selected based on the records of the electronic medical database.

Inclusion criteria were: PCR-positive first episode of SARS-CoV-2 infection, subsequent repeat PCR-confirmed infection at least 3 months later (to exclude long-term viral carriage), no vaccination against COVID-19 before the second episode, and age between 5 and 80 years. Persons with severe chronic diseases or immunosuppression that could affect immune response parameters were not included.

A total of 140 patients divided into four age groups were included in the analysis: <18 years (children and adolescents, n=30), 18-49 years (young adults, n=50), 50-64 years (middle-aged, n=40), and ≥65 years (elderly, n=20). The median interval between the first and second episode of COVID-19 was 10 months (range 6 to 18 months).

For each patient, data on the clinical course of each episode (presence and severity of symptoms, need for hospitalization) were collected according to a standard severity classification (mild, moderate, severe).

Blood samples were taken from all patients during the period of recongestion (~4 weeks after the disappearance of symptoms) for immunological examination. Humoral immunity was assessed by the level of specific IgG-antibodies to SARS-CoV-2. IgG concentration was determined by enzyme-linked immunosorbent assay (ELISA) using a standardized reagent kit; the results were expressed as a quantitative titer (BAU/ml) according to the international standard.

For assessment of the neutralizing activity of the antibodies, a virus-neutralization assay was additionally performed on cell culture (the result was expressed as the maximum serum dilution at which 50% of the cytopathic action of the virus was inhibited). In the present study, the geometric mean titre (GMT) of neutralizing antibodies in each age category after first and re-infection was used to compare groups. Cellular immunity was assessed ~6 weeks after each episode of infection.

ELISpot quantitative interferon-γ test was used: peripheral blood mononuclear cells were stimulated with peptides of viral antigens (S-protein, etc.), after which the number of IFN-γ-producing cells was measured (the result was expressed as the number of spot-forming cells (SFC) per 10⁶ lymphocytes). In some cases, an additional flow cytometry analysis was performed to count antigen-specific CD4^+ and CD8^+ memory T cells.

In the present study, an integral indicator of T-cell response, the total number of IFN-γ-producing SARS-CoV-2-specific memory T lymphocytes (per 10⁶ blood cells), was used to compare groups. In addition to humoral and cellular indices, markers of the inflammatory response during the acute phase of the disease were recorded. In particular, the maximum level of C-reactive protein (CRP) and interleukin-6 (IL-6) in the blood during each COVID-19 episode were determined as indicators of systemic inflammation.

Data on the clinical course (duration of fever, presence of pneumonia, need for oxygen support) were also analyzed for comparison with immunological parameters. Statistical processing of data was performed using a package of standard programmes (R, SPSS, etc.).

Comparison of quantitative indices between groups was performed by analysis of variance (ANOVA) followed by post hoc test (Tukey) for pair wise comparisons. The χ^2 test was used to compare the proportions. Differences were considered statistically significant at the $p<0.05$ level. Normally distributed quantitative indices are presented as mean ± standard deviation (M±SD) unless otherwise stated.

RESULTS OF THE STUDY AND THEIR RATIONALE.

All study participants had specific IgG antibodies after their first COVID-19 episode, but the magnitude of this humoral response varied significantly by age. As shown in Table 1, the mean antibody level after the first episode was the higher the younger the age group. In those aged ≥65 years, the IgG antibody count was only about 100, which was 1.5-2 times lower than in younger groups.

Re-infection resulted in increased antibody titres in each category, but the extent of the increase varied. Younger adults (children and adults <50 years of age) showed an approximately twofold increase in GMT, whereas older adults showed only about 60% of the increase. As a result, the gap between groups persisted after recurrent disease: for example, ≥65 years old had a mean titre of ~160, whereas <18 years old had a mean titre of about 300. Notably, the paediatric group (<18 years) had comparable, and in absolute value even slightly higher antibody titres than the 18-49 years group, despite the milder course of infection in children.

Statistical analysis confirmed the significant influence of age: the differences in antibody levels between the groups younger than 50 years and the group ≥65 years were significant ($p<0.01$). Thus, the humoral immune response during reinfection is significantly stronger in young patients compared to elderly patients.

Table 1 shows the mean neutralizing antibody titres in patients of different age groups after first and re-infection with COVID-19.

Table 1. Geometric mean neutralizing antibody titres after first and re-infection with COVID-19 in different age groups.

Age group	N	IgG titre (after 1st)	IgG titre (after 2nd)
<18 years old	30	150 ± 60	300 ± 100
18-49 years old	50	140 ± 50	280 ± 90

50-64 years old	40	120 ± 40	210 ± 70
≥65 years old	20	100 ± 35	160 ± 50

Figure 1 graphically shows the comparison of mean antibody levels after first and re-infection between age groups.

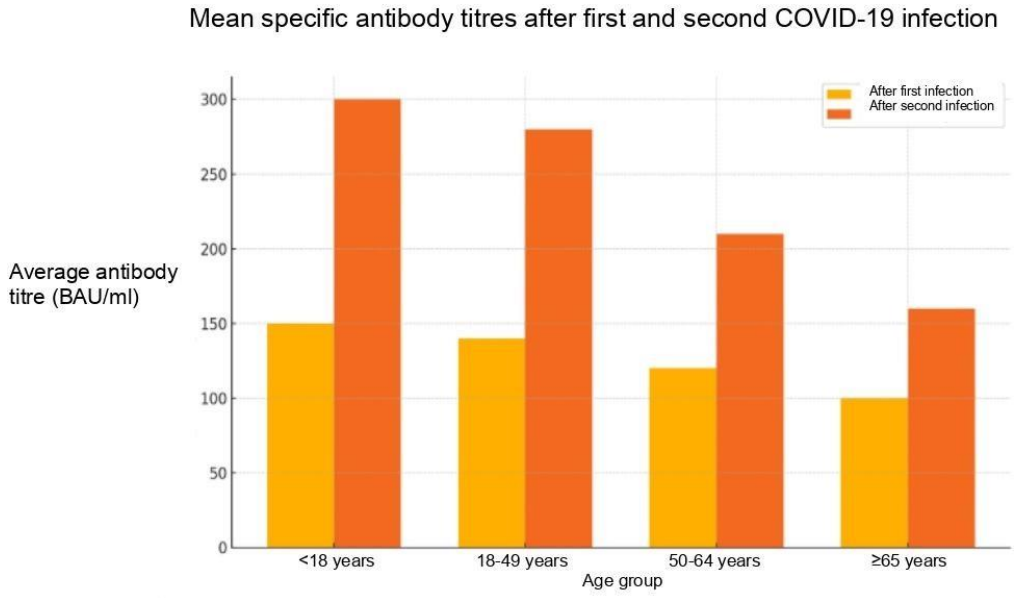

Figure 1 - Mean titres of specific neutralizing antibodies (IgG) after first and re-infection with COVID-19 in different age groups (humoral immune response).

The cellular (T-lymphocyte) immune response also showed significant age-related differences. After primary COVID-19, a defined pool of memory T cells was formed in all patients, but its size was significantly higher in younger age groups. In elderly patients, the number of SARS-CoV-2-specific T lymphocytes in the blood after the first episode was about 2-3 times lower than in young adults.

Re-infection caused additional activation of cellular immunity: all groups showed an increase in the number of specific T-lymphocytes compared with the values after the first episode. However, in the elderly, the absolute number of memory T cells and the magnitude of their increase remained significantly lower than in younger patients. For example, the mean number of IFN-γ-producing T lymphocytes after reinfection was about 150 per 10⁶ cells in the ≥65-year-old group, compared with about 300 in 18-49-year-olds and up to 350 per 10⁶ cells in <18-year-olds. Table 2 summarizes the quantitative T-cell response by age group.

Table 2. Average number of SARS-CoV-2-specific memory T-lymphocytes (producing IFN-γ) per 10⁶ blood cells after the first and repeated infection with COVID-19 by age group.

Age group	N	N T-lymphocytes (after 1st)	T-lymphocytes (after 2nd)
<18 years old	30	200 ± 60	350 ± 80
18-49 years old	50	150 ± 50	300 ± 70
50-64 years old	40	100 ± 30	220 ± 60
≥65 years old	20	70 ± 25	150 ± 40

As shown in Table 2, the younger groups (<50 years) had stronger T-cell immunity: they had a significantly higher number of specific memory T-lymphocytes both after the first and after re-infection compared to the elderly ($p<0.05$). The difference after re-infection was particularly marked, with the elderly having on average a 2-fold lower number of T cells.

These data confirm that the ability to form and maintain effective cellular immunity against SARS-CoV-2 declines with age.

Figure 2 provides a graphical illustration of the dynamics of T-cell response to reinfection in different age groups.

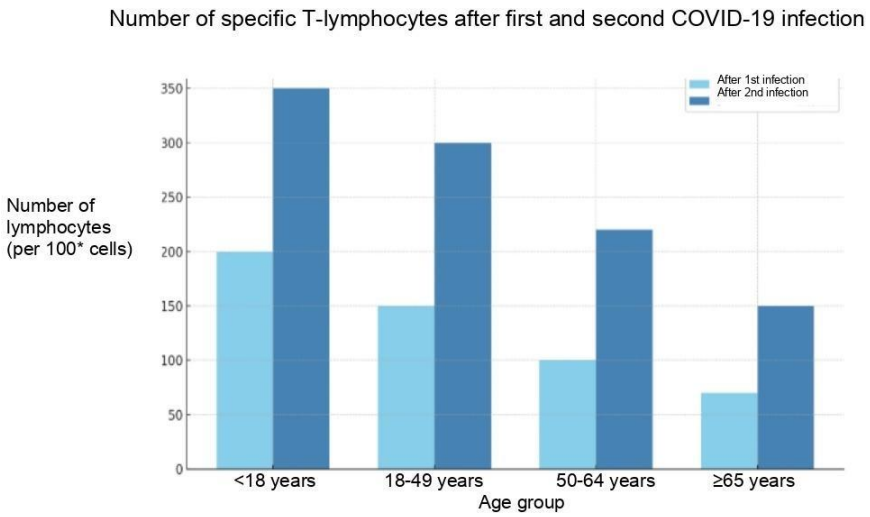

Figure 2 - Mean number of SARS-CoV-2-specific T lymphocytes (producing IFN-γ) per 10⁶ cells after first and second COVID-19 infection (cellular immune response) in different age groups.

The observed differences in immune response were consistent with the observed clinical outcomes of recurrent infections. Only in the older group were cases of severe course of recurrent COVID-19 reported: 20% of patients ≥65 years of age required hospitalization with pneumonia at the second episode, whereas no severe complications of recurrent infection were observed in any of the younger groups.

In our study, we found a trend that a weaker T-cell response was associated with a more severe course: patients with specific T-lymphocyte counts below the median value were more likely to have a complicated course. In addition, an inadequate immune response in the elderly was associated with greater systemic inflammation during reinfection.

The mean peak CRP level during the second episode was ~90±20 mg/L in the ≥65-year-old group versus ~30±10 mg/L in those younger than 50 years; similarly, IL-6 concentrations were significantly higher in the elderly (up to ~80±25 pg/mL) compared with the young (≈20±10 pg/mL). This suggests that poor adaptive immunity in the elderly results in inadequate control of viral replication, prolonged inflammation, and more severe tissue damage.

Notably, children and adolescents (<18 years of age) demonstrated immune responses comparable or even superior to those of young adults. For example, in the paediatric group, mean antibody titres and memory T-cell counts were at levels equal to or slightly higher than in the 18-49 year old group (see Tables 1 and 2). This shows that the immune system of children is able to form a highly effective immune memory for SARS-CoV-2 even when the primary infection is relatively mild. A possible explanation could be the cross-reactivity of immunity in children due to frequent contacts with other seasonal corona viruses, as well as the high functional activity of their naive lymphocytes [3].

In contrast, the weakened immune response in the elderly is consistent with the phenomena of immune ageing. The number of naive B- and T-cells capable of recognising new antigens decreases with age, and the capacity for clonal lymphocyte expansion and high-affinity antibody formation decreases. Also, the elderly have a background chronic inflammatory status, which may reduce the effectiveness of adaptive immunity and paradoxically exacerbate tissue damage during infection. Our results support these notions: poor antibody and memory T-cell formation in individuals ≥65 years of age indicates a reduced functional reserve capacity of their immune system[6].

Age is a key determinant of the strength of the immune response in repeated COVID-19 infections. The presented data emphasise the need to take into account age specificity when planning anti-epidemic measures. Older adults, even those who have had COVID-19, remain at increased risk due to a less effective immune response, and vaccination and revaccination to maintain protective immunity is particularly indicated [10].

Young people generally develop more robust natural immunity, but even in their case, the emergence of new virus variants can lead to reinfection, so maintaining immune memory (naturally or with vaccines) remains important.

CONCLUSIONS.

Young patients (children, adolescents and adults under 50 years of age) have a significantly stronger humoral and cellular immune response to SARS-CoV-2 reinfection than older patients. They have high titres of neutralizing antibodies and an active T-cell response, which provides more effective protection during reinfection.

In contrast, the immune response in the elderly (≥65 years of age) is weaker: less robust immunity is produced after the first episode, and upon reinfection, antibody and T-cell gains are insufficient to completely neutralize the virus. This results in the elderly remaining susceptible to recurrent COVID-19 and having a higher risk of severe disease course upon reinfection.

Thus, age-related differences in the immune response to COVID-19 are significant. The young immune system has a high potential for immunological memory, whereas the elderly have a relative immunological failure during reinfection.

These findings should be taken into account when designing preventive measures: older patients who have been re-infected need particularly careful protection (e.g. timely revaccination), given the relative weakness of their natural immune response.

LIST OF REFERENCES

[1] Alpidovskaya O. V. A rare case of complications due to SARS-CoV-2 and Acinetobacter Baumannii after re-infection with SARS-CoV-2 //Russian Journal of Preventive Medicine. - 2024. - T. 27. - №. 5.

[2] Andreev I. V. et al. Postvaccinal and postinfection humoral immune response to SARS-CoV-2 infection //Immunology. - 2022. - T. 43. - №. 1. - C. 18-32.

[3] Glazanova T. V. et al. Changes in some immunological parameters after COVID-19 infection: general trends and individual characteristics //Medicine of extreme situations. - 2024. - T. 26. - №. 2. - C. 125-132.

[4] Glazanova T. V., Shilova E. R., Pavlova I. E. Risk factors for the development of COVID-19: immunological aspects // RMZh. Medical Review. - 2023. - T. 7. - №. 11. - C. 752-759.

[5] Ivanov A. V., Uvarova M. A., Semenova E. V. Features of adaptive immunity after COVID-19. - 2022. - 48 c.

[6] Olenkova O. M. et al. Dynamics of changes in immunological parameters in adults with COVID-19 // Journal of Infectology. - 2023. - T. 15. - №. 1. - C. 78-85.

[7] Perevariukha A. Yu. Modelling of two regional epidemic situations and analysis of factors of repeated waves COVID-19 // TRUDY. - 2023. - T. 73. - №. 3. - C. 114-126.

[8] Platonova T. A. et al. Characteristics of specific t-cell immune response in COVID-19-infected employees of medical organisations //Problems of medical mycology Founders: North-West State Medical University named after I.I. Mechnikov. AI Mechnikov. - 2022. - T. 24. - №. 2. - C. 118.

[9] Semenova E. V. et al. Features of humoral immunity after COVID-19 //Medical Immunology. - 2022. - T. 24. - №. 2. - C. 337-350.

[10] Scherbak S. G. et al. Cellular immunity in COVID-19 patients: molecular biology, pathophysiology and clinical significance //Clinical Practice. - 2022. - T. 13. - №. 2. - C. 66-87.