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# The immunity and sanitary conditions among people regarding the Covid-19 infection in the post-pandemic period

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**Abstract**

Background and Aim. A year after the official declaration of the end of the pandemic, this study aimed to assess the epidemic situation by testing a small group of individuals for the presence of the SARS-CoV-2 virus and neutralizing antibodies.

Materials and Methods. Nasopharyngeal swabs were collected to isolate SARS-CoV-2 virus in cell culture, while venous blood samples were tested for neutralizing antibodies using a quantitative neutralization reaction. The study included 20 participants (approximately 10% of the team), of whom 16 had been vaccinated against COVID-19, and 4 remained unvaccinated. Vaccinated individuals included 4 who received Sputnik V (over 30 months prior) and 12 who received QazCOVID-in.

Results. All 20 participants demonstrated neutralizing antibodies against the Wuhan variant of the virus. For the Delta and Omicron variants, 19 participants showed neutralizing antibodies. Average antibody titers were 6.4 ± 1.39 $\log_2$ for the Wuhan variant, 6.2 ± 1.89 $\log_2$ for the Delta variant, and 4.75 ± 1.84 $\log_2$ for the Omicron variant.

Conclusion. The study highlights the persistence of antibodies against SARS-CoV-2 among both vaccinated and unvaccinated participants, though variation in neutralization efficacy was observed among different virus variants. These findings emphasize the importance of monitoring immune responses to track population-level immunity and guide future vaccination strategies.

**Keywords:** Antibodies; immune status; post-pandemic period; SARS-CoV-2 virus; titer; virus-neutralizing.

## Introduction

After the end of the pandemic, there was a relative lull in the number of cases of coronavirus infection COVID-19 among the population. Large-scale immunization campaigns with vaccine preparations ceased and only in rare cases, except for the risk group, people voluntarily underwent vaccination and were subjected to diagnostic studies using laboratory tests. However, cases of respiratory diseases with a benign course were recorded. The etiology of these cases was not confirmed by medical studies. Therefore, in most cases, except in cases of laboratory testing, the presence and intensity of circulation of the SARS-CoV-2 virus in the community remained unknown [1]. The epidemic situation regarding coronavirus infection was assessed based on cases of official visits of sick people to medical institutions and diagnosis through laboratory tests. The decrease in cases of clinical disease and the absence of

mass laboratory tests indicated a real decrease in the intensity of the epidemic situation. However, cases of clinical coronavirus infection among the population continued to be identified, and the mutating causative agent of the disease spread on an interstate and intercontinental scale [2]. According to WHO and national health data, information regarding the number of people who fell ill, died, and recovered, as well as those vaccinated against the pandemic disease, was available [3, 4]. But there was no information about the population's immunity. This situation did not make it possible to predict the dynamics of the epidemic situation and evaluate the effectiveness of immunoprophylactic measures and immunization agents. In this connection, the purpose of the studies presented in this work was to establish the epidemic state among the population. This was done through indicator testing of a group of people for immune and sanitary status in relation to the coronavirus infection COVID-19 in the postpandemic period.

**Materials and Methods**

Virus

To set up the neutralization reaction, the SARS-CoV-2 viruses of the "Wuhan", "Delta", and "Omicron" variants were used, adapted in Vero cell culture with a biological activity of 6.00 lg $TCD_{50/cm3.}$

Cell culture

To isolate, titrate, and perform a neutralization reaction, we used the Vero (WHO certified) cell culture line grown in a monolayer in plastic mattresses and tablets.

Cells were grown in DMEM nutrient medium containing 5-10% fetal bovine serum (FBS). To maintain cell viability, the same nutrient medium was used, but containing 1-2% FBS.

Volunteers

20 employees of a research institute located remotely from large cities in the Zhambyl region acted as volunteers for the research. The volunteers included 11 men aged 22 to 52 years and 9 women aged 22 to 49 years. Volunteer serum samples collected on October 17, 2023 were used as research objects.

According to the anamnesis, volunteers constantly live in the locality where the research enterprise is located, and from time to time on weekends and days of labor leave they travel to different cities and towns of the Republic of Kazakhstan, as well as foreign countries.

Assessment of the immune state of volunteers

The immune status of volunteers was assessed based on the level of specific seropositivity and antibody titers to the SARS-CoV-2 virus detected in human blood serum. Specific antibodies were detected and their titer was determined using a quantitative neutralization reaction.

Setting up the neutralization reaction

The neutralization reaction was performed on a monolayer of Vero cell culture prepared in 96-well plastic plates. As a reaction mixture, we used two-fold dilutions (1:2, 1:4, etc.) of the tested blood serum of volunteers in a maintenance medium and a cultural suspension of the SARSCoV-2 virus of the "Wuhan", "Delta" and "Omicron" variant with a titer of 100 TCD50, taken in equal volumetric ratios. The resulting mixture was kept at a temperature of 37 °C for 60 minutes and added in equal doses to at least 4 wells of a 96-well plate with a test cell culture. As a dose control, the virus suspension of each variant was titrated on the same cell culture using its tenfold (10-1, 10-2, 10-3, 10-4) dilutions in a maintenance medium. To control the quality of the cell culture, at least 4 wells were left without adding the reaction mixture and virus, but replaced with a supporting medium. The cell culture in plates with a neutralization reaction was kept at a temperature of 37 °C for 5 days, after which the results of the virus CPE (cytopathic effect) were recorded. The absence of CPE in the cell culture, if it was present in the control wells with a dose of the virus and absent in the wells with the quality control of the cell culture, was considered to be neutralization of the virus or the presence of antibodies, and the presence of CPE, under the specified conditions in the listed controls, was considered to be the absence of neutralization and specific antibodies. The antibody titer was taken to be the highest dilution of blood serum that neutralized virus reproduction in at least 50% of cases. Antibody titers were given in logarithms of twofold dilutions of the blood serum. The virus and antibody titers in the blood serum were calculated according to Reed and Muench [5]. The reliability of the difference in antibody titers between groups (model animals) was determined using Student's t-test [6].

Assessment of the sanitary status of volunteers

The sanitary status of study participants was determined based on information provided by the volunteers themselves, external clinical signs and the results of virological testing for the presence of the virus by isolation in cell culture.

Virus isolation in vitro

Human infection with the SARSCoV-2 virus was determined by isolating the virus in cell culture from nasopharyngeal swab samples. The swabs were collected using sterile cotton swabs on a plastic stick, which were placed in a transport liquid and stored at minus 40 °C until the study. To isolate the virus, swab samples were thawed at room temperature, the cotton swabs were wrung out and removed, and the remaining liquid was centrifuged at 3000 g for 20 minutes, the sediment was transferred to a sterile tube, mixed with antibiotics and used to infect a Vero cell culture prepared in a monolayer in mattresses, seed area 25 $cm^2$. Before adding clinical samples, the cell monolayer was freed from the growth medium and washed twice with the DMEM nutrient medium without blood serum. The clinical sample under study, diluted with a nutrient medium without serum in a dilution of 1:2-1:4, was added to a monolayer of cells and kept at a temperature of 37 °C for 60 minutes. The inoculum was removed, the cell monolayer was cleared from the clinical sample by rinsing 3-4 times with the nutrient medium. Then, a monolayer of cells infected with a clinical sample was cultured at a temperature of 37 °C for up to 5 days. The presence of the virus was determined by the CPE, manifested in a monolayer of infected cells. In case of development of CPP, its etiology was identified using a neutralization reaction. In the absence of CPE, at least two blind passages in cell culture were performed. The isolated virus was identified using PCR and neutralization reaction.

Immunogenicity study design

Those wishing to undergo the study were selected from 10 divisions of the enterprise, 2 people from each on a voluntary basis. Before collecting blood samples, their medical history was recorded, including vaccination history against COVID-19, pandemic disease, and clinical condition at the time of blood donation. Each volunteer provided blood samples from a vein and nasopharyngeal swabs, collected using cotton swabs.

Serum was isolated from the blood, which was aliquoted in 1.0 ml portions and frozen at minus 40 °C until the study. Oropharyngeal swabs along with cotton swabs in a transport medium were also frozen at the same temperature and stored until the study. Before testing in the pH, blood serum samples were subjected to heat treatment at a temperature of 56 °C for 30 minutes.

Before performing the neutralization reaction, virus samples were titrated in a Vero cell culture prepared in 96-well plates. In the neutralization reaction, a cultural suspension with a virus titer of at least 106.0 TCD50/ml was used.

Each blood serum sample was tested in a neutralization reaction in parallel with three variants of the SARS-CoV-2 virus.

Statistical processing

The statistical data processing was carried out using the GraphPad Prism program, Version 8.

**Results and Discussion**

Anamnestic data and laboratory results for the detection of virus-neutralizing antibodies in serum samples and virus isolation from clinical samples collected from volunteers are shown in Table 1.

Table 1 – Immuno-sanitary status of people for coronavirus infection COVID-19

| No | Subjects of the study | Vaccination period and vaccine against COVID-19 | Anamnesis | Virus-neutralizing antibody titers for SARS-CoV-2 virus variant | | | Results of isolation of the SARS-CoV-2 virus |
|---|---|---|---|---|---|---|---|
| | | | | Wuhan | Delta | Omicron | |
| 1 | EG no.1 | QazVac, 27.05.21 (29 month) | Clinically healthy | 7 | 7 | 5 | - |

Continuation of table 1

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 2 | EG no.1 | QazVac, 10.06.21 (28 month) | Clinically healthy | 5 | 5 | 3 | - |
| 3 | EG no.1 | QazVac, 14.06.21 (28 month) | Clinically healthy | 6 | 6 | 5 | - |
| 4 | EG no.1 | QazVac, 31.01.22 (21 month) | Clinically healthy | 6 | 5 | 5 | - |
| 5 | EG no.1 | QazVac, 17.01.22 (21 month) | Malaise | 6 | 8 | 5 | ++ (1-passage) |
| 6 | EG no.1 | QazVac, 07.06.21 (28 month) | Clinically healthy | 5 | 5 | 4 | - |
| 7 | EG no.1 | QazVac, 11.06.21 (28 month) | Clinically healthy | 8 | 7 | 6 | - |
| 8 | EG no.1 | QazVac, 22.04.22 (18 month) | Clinically healthy | 5 | 4 | 3 | - |
| 9 | EG no.1 | QazVac, 01.02.22 (20 month) | Clinically healthy | 7 | 6 | 5 | - |
| 10 | EG no.1 | QazVac, 01.02.22 (20 month) | Clinically healthy | 8 | 8 | 6 | - |
| 11 | EG no.1 | QazVac, 04.08.21 (26 month) | Clinically healthy | 7 | 8 | 5 | - |
| 12 | EG no.1 | QazVac, 14.03.22 (19 month) | Clinically healthy | 5 | 7 | 5 | - |
| | **Average data** | **18-29** month | **1/12 (8.33 %)** | **6.25+1.09** | **6.33+1.52** | **4.75+2.96** | **1/12 (8.33%)** |
| 13 | EG no.2 | Sputnik-V, 04.21 (30 month) | Clinically healthy | 8 | 8 | 7 | - |
| 14 | EG no.2 | Sputnik-V, 04.21 (30 month) | Clinically healthy | 8 | 8 | 6 | - |
| 15 | EG no.2 | Sputnik-V, 04.21 (30 month) | Clinically healthy | 7 | 6 | 5 | - |
| 16 | EG no.2 | Sputnik-V, 04.21 (30 month) | Clinically healthy | 8 | 7 | 5 | - |

Continuation of table 1

| | **Average data** | **30** month | **0/4 (0%)** | **7.75+0.43** | **7.25+0.83** | **5.75+0.83** | **0/4 (0 %)** |
|---|---|---|---|---|---|---|---|
| 17 | CG | Not vaccinated | Clinically healthy | 5 | 6 | 4 | - |
| 18 | CG | Not vaccinated | Got sick in 2 weeks | 8 | 8 | 6 | - |
| 19 | CG | Not vaccinated | Loss of taste, smell | 6 | 5 | 5 | ++ (1-passage) |
| 20 | CG | Not vaccinated | Clinically healthy | 3 | 0 | 0 | - |
| | **Average data** | | **2/4 (50%)** | **5.5+1.80** | **4.75+2.95** | **3.75+2.28** | **1/4 (25%)** |
| | **According to virus variants** | | | **6.4+1.39** | **6.2+1.89** | **4.75+1.84** | |

Note: In the numerator, the number of positive results; in the denominator – the total number of samples tested; "++" - positive result; "-" - negative result; antibody titer is given in log2 dilutions of serum; in parentheses, the percentage of positive results; CG - Control group; EG no.1 - Experimental group number 1; EG no.2 - Experimental group number 2

As can be seen from the data in Table 1, out of 20 volunteers studied, according to the anamnesis, 12 people were vaccinated with the inactivated vaccine “QazCOVID-in” (KZ) over 18-29 months, 4 people over 30 months were vaccinated with the vector vaccine “Sputnik-V” (RU), and the remaining 4 people did not take the vaccine against coronavirus infection COVID-19 during the pandemic and post-pandemic period.

The survey and clinical examination showed that at the time of collecting blood serum samples, among those vaccinated with the QazCOVID-in vaccine, one person felt unwell without an increase in body temperature. Other members of the group vaccinated with this vaccine did not experience illness resembling coronavirus infection during the post-vaccination period. Among the group of people vaccinated with the Sputnik-V vaccine, no illness resembling the COVID-19 coronavirus infection was observed during the post-vaccination period. Among the third group of people, at the time of the study, there was one case of clinical illness with symptoms of loss of taste and smell, and the second suffered a clinical illness of no more than moderate severity 2 weeks before the study.

During virological testing using Vero cell culture, the SARS-CoV-2 virus was isolated from clinical samples of one volunteer from the first group, consisting of those vaccinated with the QazCOVID-in vaccine, and one volunteer from the group without vaccination.

The results of the neutralization reaction showed that in both groups of people vaccinated against COVID-19 coronavirus infection, there are virus-neutralizing antibodies in 100% of cases. The identified antibodies in both groups of people vaccinated against COVID-19 coronavirus infection had the ability to neutralize all three variants of the SARS-CoV-2 virus used. The average antibody titer in the QazCOVID-in vaccine group was 6.25+1.09 $\log_2$ against the Wuhan variant, 6.25+1.09 $\log_2$ against the Delta variant and 4.75+2.96 $\log_2$ against the variant "Omicron" of the SARS-CoV-2 virus. In the group of people vaccinated with the Sputnik-V vaccine, antibody titers against the Wuhan, Omicron and Delta variants were 7.75+0.43 $\log_2$, 7.25+0.83 $\log_2$ and 5.75+ 0.83 $\log_2$, respectively. Antibodies specific to the SARS-CoV-2 virus were also present in people from the group who did not receive the COVID-19 vaccine. In three out of four people, antibodies were detected for all three variants of the Wuhan, Omicron and Delta virus in titers of 6.33 + 1.25 $\log_2$, 6.33 + 1.25 $\log_2$ and 5.0 + 0.81 $\log_2$ respectively. The fourth representative of this group had trace titers (3 log2) of antibodies to the Wuhan variant, but no antibodies to the other two variants of the pathogen.

With the official end of the pandemic in the fall of 2022 in all countries of the world, including the Republic of Kazakhstan [7], the number of anti-epidemic vaccinations against the coronavirus infection COVID-19 has sharply decreased. The regime of mandatory respiratory tract protection with masks in public places, work, educational and other groups and areas was canceled [8] For more than a year of the post-pandemic period, the intensity of the epidemic situation was low and stable. However, isolated cases of clinical manifestations of the disease with varying degrees of severity were recorded [9]. According to the Ministry of Health, by the end of 2022 and during 2023, mixed and superinfections of seasonal influenza (A and B) and coronavirus infection COVID-19 were observed among the population [10, 11, 12].

In national health care, the question of the advisability of routine vaccination in the vaccination calendar has arisen. The current and forecast state of immunity against COVID-19 in the future, in the absence of vaccine prevention and the development of an epidemic situation after the end of post-vaccination immunity, remains unknown. Since, as is known, the duration of post-vaccination and post-infectious immunity according to the dynamics of specific antibodies lasts from 6 to 9 months [13, 14, 15].

In connection with this situation, the need arose for preliminary monitoring of the immune state of people against coronavirus infection in the post-pandemic period after the completion of post-vaccination and post-infectious immunity. For such studies, a group of 20 people from one work team consisting of more than 200 employees was selected.

The studies consisted of collecting and analyzing anamnesis, consisting of information about vaccination and the timing of its receipt, the type of vaccine, coronavirus infection COVID-19, identifying and assessing the level of virus-neutralizing antibodies and their ability to neutralize different variants of the SARS-CoV-2 virus that have circulated and are circulating among the population of the Republic of Kazakhstan. According to data from the Committee for Sanitary and Epidemiological Control of Domestic Health Care, different genetic lines of the Omicron variant of the pandemic virus circulated in the country in 2022-2023 [16, 17]. The data obtained, according to the collected anamnesis, showed that the target group included subjects who received the Sputnik V vaccine (20%), RU, for 30 months, and QazCOVID-in (60%), KZ, for 18-29 months, as well as those who did not receive immunoprophylaxis (20%) with any vaccine. At the time of the study, from among those vaccinated with QazCOVID-in, one subject felt unwell, from the group of unvaccinated subjects, one subject was in a state of loss of taste and smell, and the second suffered from the disease for two weeks. There were no clinically ill participants among the participants who received the Sputnik V vaccine.

Serological testing showed that 95% of participants had virus-neutralizing antibodies to the Wuhan, Omicron and Delta variants of the SARS-CoV-2 virus. Seropositivity was observed in all participants receiving both Sputnik V (100%) and QazCOVID-in (100%) vaccines. Seronegativity was observed in one (25%) of four subjects in the nonvaccination group. Antibody titers to the SARS-CoV-2 virus in the group previously vaccinated with the Sputnik V vaccine were significantly higher against all three variants of the pandemic virus. They averaged 6.91 + 0.85 $\log_2$, 7.75 + 0.43 $\log_2$, 7.25 +0.83 $\log_2$, and 5.75+0.83 log2 against the Wuhan, Omicron and Delta variants, respectively). Antibody titers to the SARS-CoV-2 virus in the group previously vaccinated with the Sputnik V vaccine were significantly higher against all three variants of the pandemic virus. They averaged 6.91 + 0.85 $\log_2$ against the Wuhan variant, 7.75 + 0.43 $\log_2$ against the Omicron variant, and 7.25 + 0.83 $\log_2$ against the Delta variant.

In the group of subjects previously vaccinated with the QazCOVID-in vaccine, the average titer of antibodies against different variants of the virus was 5.75 + 0.71 $\log_2$, 6.25 + 1.09 $\log_2$, 6.25 + 1.09 $\log_2$, and 4.75 +2.96 $\log_2$ vs. Wuhan, Omicron, and Delta variants, respectively). In the group of subjects who had not previously received the vaccine, seropositivity was observed in 75%, in whom the average antibody titer was at the level of the antibody titer detected in people previously vaccinated with the QazCOVID-in vaccine, and averaged 5.89 + 0.62 $\log_2$, 6.33+1.25 $\log_2$, 6.33+1.25 $\log_2$, 5.0+0.81 $\log_2$ vs. Wuhan, Omicron and Delta variants, respectively).

Analysis of the level of antibody titers against each variant of the virus indicates that in all three groups the level of antibodies to the Wuhan and Delta virus variants was the highest and averaged 6.4 + 1.39 $\log_2$ and 6.2 + 1.89 $\log_2$, respectively, while for the Omicron variant the antibody titers were comparatively lower and averaged 4.75+1.84 $\log_2$. A high level of seropositivity with maximum antibody titers among the studied population long after the cessation of vaccination indicates the presence of a constantly operating immunizing factor that supports herd immunity. It must be assumed that such

a factor is the causative agent of a pandemic coronavirus infection, which is widespread among the population and, transmitted from person to person, regardless of his immunity [18, 19, 20], multiplies in the body and stimulates the formation of antibodies. However, in most cases, due to the presence of residual immunity or immune memory formed from vaccination with a vaccine or a previous infection, the virus causes a subclinical infection without clinical signs. The disease manifests itself clinically in varying degrees of severity in the absence or weakness of specific and general immunity, as well as the development of mixed and superinfections [21, 22, 23]. Based on a comparison of antibody titers, it can be assumed that previous vaccination and the type of vaccine used have a positive effect on protection from the development of clinical disease and the formation of humoral immunity factors. This is indicated by 100% seropositivity and a high level of antibodies with no and low levels of clinical disease (8.3%) in the anamnesis in subjects previously vaccinated with the Sputnik V vector vaccine and the inactivated QazCOVID-in vaccine, while in those not previously vaccinated, seropositivity was 75% with a no less low titer of antibodies, but with the development of clinical disease in 50%.

Using in parallel a neutralization reaction with three variants of the virus that circulated among the population of the republic, the protective effectiveness of existing factors of humoral immunity of subjects against these pathogens was assessed in a comparative aspect. The data obtained show that the studied blood serum samples in all three groups neutralize the variants of the pathogen "Wuhan" and "Delta" with a relatively greater activity, and the variant "Omicron" to a slightly lesser extent, indicating a probable antigenic difference between the first two variants of the pathogen and the third. The reliability of such a judgment requires confirmation by additional detailed studies. It is possible that such a difference in antibody titers is associated with the dominant spread of the "Delta" variant, which in terms of its appearance is closer to the original variant of the pathogen, before the appearance of the "Omicron" variant.

Thus, the data obtained indicate that in the studied cohort of people, regardless of previous immunoprophylaxis, there was 95% seroconversion to the SARS-CoV-2 virus with high antibody titers, reminiscent of post-infectious or post-vaccination immunity. Failure to take the vaccine for at least the last 18 months indicates a post-infectious etiology of humoral immunity factors. Additional confirmation of this are clinical cases of the disease with the isolation of the virus among the studied volunteers, previously vaccinated and not vaccinated with the vaccine. Based on this statement, it follows that the SARS-CoV-2 virus continuously circulates with widespread prevalence among people with and without the development of clinical disease.

**Conclusion**

1. Of the people studied, 95% were seropositive for antibodies that neutralize the SARS-CoV-2 virus of the Wuhan, Delta and Omicron variants related to coronavirus infection COVID-19. Among the volunteers, 20% were vaccinated with the Sputnik V vaccine within 30 months, 60% with the QazCOVID-in vaccine within 18-29 months, and the remaining 20% did not receive immunoprophylaxis with any vaccine.

2. Average antibody titers in people previously vaccinated with the Sputnik V vaccine were 7.75+0.43 $\log_2$ against the Wuhan variant, 7.25+0.83 log2 against the Delta variant and 5.75+0.83 $\log_2$ against the Omicron variant. Similar antibody titers in volunteers vaccinated with the QazCOVID-in vaccine were 6.25 + 1.09 $\log_2$ against the Wuhan variant, 6.25 + 1.09 $\log_2$ against the Delta variant and 4.75 + 2.96 $\log_2$ versus the Omicron option. Virus-neutralizing antibodies were also detected in three out of four unvaccinated individuals. Their average antibody titers to the Wuhan, Omicron and Delta variants were 6.33 + 1.25 $\log_2$, 6.33 + 1.25 $\log_2$ and 5.0 + 0.81 $\log_2$, respectively.

3. The presence of antibodies to the SARS-CoV-2 virus in the studied subjects in the long term after the use of vaccines, as well as seropositivity for this pathogen in people who did not take an immunoprophylactic drug, indicates that the causative agent of coronavirus infection COVID-19 is circulating among the population in the post-pandemic period without massive stimulation of clinical disease development. This circulating virus causes a sub infection, during which ongoing immunity is formed.

4. The neutralizing activity of antibodies to the three variants of the SARS-CoV-2 virus used indicates that there is a close relationship between the antigens of the virus variants and the immunity factors formed against one of them have protective effectiveness against the other two variants of the pathogen. A significant difference in antibody titers to different variants indicates a possible antigenic drift in the Omicron variant from the antigenic specificity of the previous two variants.

5. It is likely that post-vaccination immunity, depending on the type of vaccine used, has a different positive stimulus on the level of post-infectious immunity formed during subinfection, since in those vaccinated with the Sputnik V vector vaccine, antibody titers exceeded those in persons vaccinated with the inactivated QazCOVID-in vaccine by 1.0-1.5 $\log_2$, and by 0.75-1.39 $\log_2$ in unvaccinated subjects. The level of antibody immunity formed during subinfection is equivalent among those vaccinated with the whole-virion inactivated vaccine and unvaccinated individuals.

**Authors' Contributions**

Conceptualization, LK. Data curation, BM and LK. Formal analysis, LK. Methodology, LK, BM, MR, KZh. Investigation, GZ, TT, AT, KB. Writing original draft, LK. Writing-review and editing, BM and LK. All authors have read and agreed to the published version of the manuscript.

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