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Роль генетических вариантов вируса SARS-CoV-2 в формировании внутригодовых подъёмов заболеваемости COVID-19 на территории Пермского края

В.И. Сергевнин[1], И.С. Исаева[2], М.В. Рожкова[3], Н.И. Маркович[4]

[1] Пермский государственный медицинский университет имени академика Е.А. Вагнера, Пермь, Российская Федерация;
[2] Центр гигиены и эпидемиологии в Пермском крае, Пермь, Российская Федерация;
[3] Пермский краевой центр по борьбе и профилактике со СПИД и инфекционными заболеваниями, Пермь, Российская Федерация;
[4] Пермский центр иммунопрофилактики, Пермь, Российская Федерация

АННОТАЦИЯ

Обоснование. Причины внутригодовых подъёмов заболеваемости COVID-19 остаются недостаточно изученными.

Цель исследования — изучить роль генетических вариантов SARS-CoV-2 в формировании внутригодовых подъёмов заболеваемости COVID-19 на территории Пермского края.

Материалы и методы. Проведена оценка помесячной динамики заболеваемости COVID-19 и летальности населения Пермского края за период с марта 2020 года по 31 декабря 2022 года. Анализ помесячной частоты выделения от больных разных генетических вариантов SARS-CoV-2 осуществляли по результатам исследований 2592 проб материала больных Пермского края, проведенных специализированными лабораториями ряда научно-исследовательских институтов Российской Федерации, за период с марта 2021 года по декабрь 2022 года. Оценку показателя встречаемости IgG-антител к коронавирусу среди населения проводили по данным исследований сыворотки крови 14 006 человек.

Результаты. В течение 2020–2022 годов на территории Пермского края отмечено 4 подъёма заболеваемости COVID-19 на фоне появления новых генетических вариантов возбудителя, основными из которых были Alpha, Delta и Omicron. Подъёмы заболеваемости COVID-19 и смена генетической структуры возбудителя наблюдались несмотря на увеличение среди населения доли лиц с содержанием в сыворотке крови IgG к SARS-CoV-2. На фоне третьего и четвёртого подъёмов заболеваемости, когда ведущее этиологическое значение приобрёл генотип Omicron, летальность инфекции существенно снизилась.

Заключение. Внутригодовые подъёмы заболеваемости COVID-19 в значительной степени связаны с изменениями генетической структуры возбудителя и наблюдаются несмотря на увеличение среди населения количества лиц с наличием в сыворотке крови IgG к SARS-CoV-2.

Ключевые слова: COVID-19; генетические варианты SARS-CoV-2; IgG-антитела; летальность.

Как цитировать

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The role of genetic variants of the SARS-CoV-2 virus in forming of intra-annual increases in the incidence of COVID-19 in Perm Region

Victor I. Sergevnin[1], Irina S. Isaeva[2], Marina V. Rozhkova[3], Nina I. Markovich[4]

[1] Perm State Medical University named after Academician E.A. Wagner, Perm, Russian Federation;
[2] Center of Hygiene and Epidemiology in Perm Region, Perm, Russian Federation;
[3] Perm Regional Center for Control and Prevention of AIDS and Infectious Diseases, Perm, Russian Federation;
[4] Perm Center for Immunization, Russian Federation, Perm, Russian Federation

ABSTRACT

BACKGROUND: The causes of intra-annual increases in COVID-19 incidence remain insufficiently studied.

AIM: This study aimed to investigate the role of genetic variants of SARS-CoV-2 in intra-annual increases of COVID-19 incidence in the Perm region.

MATERIALS AND METHODS: The monthly dynamics of COVID-19 morbidity and mortality of the population of the Perm region from March 2020 to December 31, 2022 was assessed. The analysis of the monthly frequency of isolation of patients with different genetic variants of SARS-CoV-2 was conducted based on the study results of 2,592 samples from patients in the Perm region performed by specialized laboratories of research institutes in Russia between March 2021 and December 2022. The assessment of the incidence of IgG antibodies to coronavirus among the population was provided according to blood serum studies of 14,006 people.

RESULTS: In 2020–2022, 4 rises in the incidence of COVID-19 were detected in the Perm region against the background of the emergence of new genetic variants of the pathogen, mainly Alpha, Delta, and Omicron. Increases in COVID-19 incidence and a change in the genetic structure of the pathogen were observed despite an increase in the proportion of people with SARS-CoV-2 IgG in the blood serum. Against the background of the third and fourth increases in morbidity, when the Omicron genotype acquired the leading etiological significance, the infection fatality rate decreased significantly.

CONCLUSIONS: Intra-annual increases in COVID-19 incidence are largely associated with changes in the genetic structure of the pathogen and are observed despite an increase in the number of people among the population with IgG to SARS-CoV-2 in the blood serum.

Keywords: COVID-19; genetic variants of SARS-CoV-2; IgG antibodies; mortality.

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BACKGROUND

To date, various epidemic patterns of the coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have been established, particularly the wave-like course of the epidemic. In the intra-annual dynamics of the incidence of COVID-19 during the epidemic, increases were noted in different seasons of the year, including in months atypical for acute respiratory viral infection seasons [1, 2]. In the Russian Federation (RF), five increases in incidence were registered in 2020–2022 [3], which occurred during thespring and summer period (March 30–August 30, 2020), cold period of the year (August 31, 2020–May 9, 2021), spring and summer months (May 10–July 12, 2021), autumn–interperiod (September 13, 2021–January 9, 2022), and winter–spring months (January 10–March 27, 2022). Simultaneously, parallel to the increases in incidence, new genetic variants of the pathogen were noted, of which the most significant were the alpha, delta, and omicron [4]. In different regions, the manifestations of the COVID-19 epidemic, including the intra-annual dynamics of the incidence and genetic structure of the pathogen, are not the same, which indicates the relevance of the analysis of the regional epidemiological characteristics of the infection.

This **study aimed** to analyze the role of genetic variants of SARS-CoV-2 in the intra-annual increases in the incidence of COVID-19 in the Perm region.

MATERIALS AND METHODS

The monthly dynamics of the incidence and mortality of COVID-19 in the population of the Perm region for the period from March 2020 to December 31, 2022 were assessed. Reports from Rospotrebnadzor No. 970 "Information on cases of infectious diseases in individuals suspected of a new coronavirus infection," data from the Epidemiology Department of the Center for Hygiene and Epidemiology in the Perm region, and the information portal Stopcoronavirus.rf, were used. Annually, the average monthly incidence rate (AMI) was calculated, and increases in incidence were determined based on the AMI.

The monthly frequency of genetic variants of SARS-CoV-2 was analyzed based on the sequencing results of 2592 samples of materials from patients in the Perm region for the period from March 2021 to December 2022. In accordance with the order of A. Yu Popova "On improving the molecular genetic monitoring of strains of the causative agent of the new coronavirus infection" dated February 19, 2021, sequencing of samples from patients from the Perm region was performed by the Russian Research Anti-Plague Institute "Microbe" of Rospotrebnadzor, State Research Center for Virology and Biotechnology "Vector" of Rospotrebnadzor, A.A. Smorodintsev Research Institute of Influenza, Centre for Strategic Planning and Management of Biomedical Health Risks of the Federal Medical and Biological Agency of Russia, Research Institute of Disinfectology of Rospotrebnadzor, and Nizhny Novgorod Research Institute of Epidemiology and Microbiology. Information about the typing results was obtained from the platform for aggregating the results of the genome transcripts of pathogens of infectious and parasitic diseases (Virus Genome Aggregator of Russia, VGARus) of the Central Research Institute of Epidemiology of Rospotrebnadzor.

The incidence of IgG antibodies to the coronavirus was assessed based on the results of blood serum analyses of 14,006 apparently healthy individuals who contacted the laboratory of the Center for Hygiene and Epidemiology in the Perm region. The studies were performed by enzyme-linked immunosorbent assay (ELISA) using the SARS-CoV-2-IgG quantitative-ELISA-BEST test system manufactured by Vector-Best (Novosibirsk, Russia). The results were considered positive when the value exceeded the cutoff. The percentage of the positive results from the total number of IgG tests performed monthly was calculated.

For the statistical analysis, intensive and extensive indicators were calculated.

RESULTS

In the comparison of the monthly incidence rates of COVID-19 in the population of the Perm region with the average monthly rates for each year, four periods of intensification of the epidemic were identified (Fig. 1), which occurred from October 2020 to February 2021 (first period), June 2021 to January 2022 (second period), January 2022 to March 2022 (third period), and September 2022 (fourth period). In general, the increased in the incidence in the Perm region coincided with that in the RF (Fig. 2). The only exception was the increase in incidence in the RF at the initial stage of the epidemic in 2020, which was registered only in large cities such as Moscow and St. Petersburg. Accordingly, the first period of increase in incidence in the Perm region coincided with the second period of increase in the RF, the second period of increase coincided with the third period of increase in the RF, the first period of increase from January 2022 to March 2022 was noted somewhat later than that in the RF, and the fourth period of increase coincided with the increase in the RF.

An analysis of the genetic structure of SARS-CoV-2 from March 2021 to December 2022 showed (Table 1) that in March–April 2021, the alpha strain (B.1.1.7) was isolated in 100% of cases. In May 2021, three strains were circulating, namely, alpha (23.1%), B.1.1.523 (46.2%), and the emerging delta strain (30.7%). From June to December 2021, the delta strain was isolated in 93.9%–100% of cases. From January to July 2022, the genetic subvariants omicron BA.1 and BA.2 were the most common (up to 100%). In August 2022, the BA.1 and BA.2 variants were replaced by omicron BA.4/BA.5. In general, these results largely coincided with the data for the RF [4]. The alpha genovariant (B.1.1.7) was widespread in

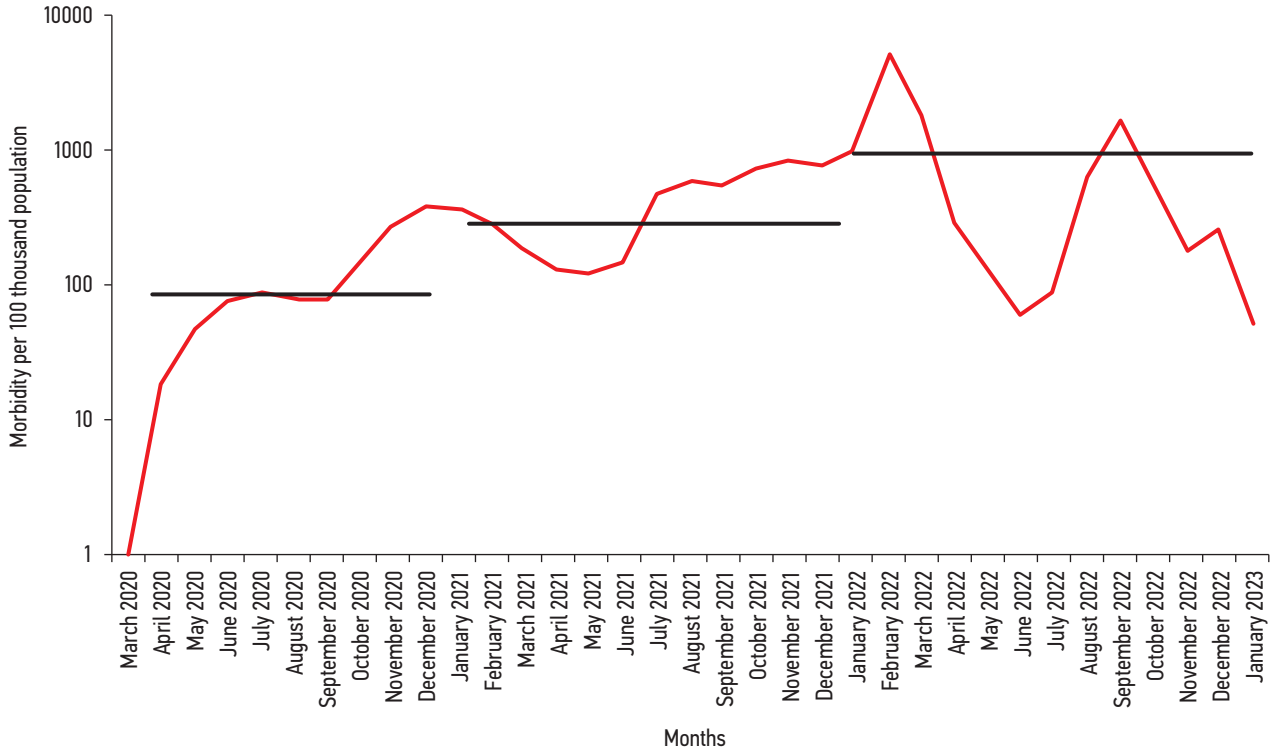

Fig. 1. Monthly incidence of COVID-19 in the Perm Region population for the period from March 2020 to December 2022.

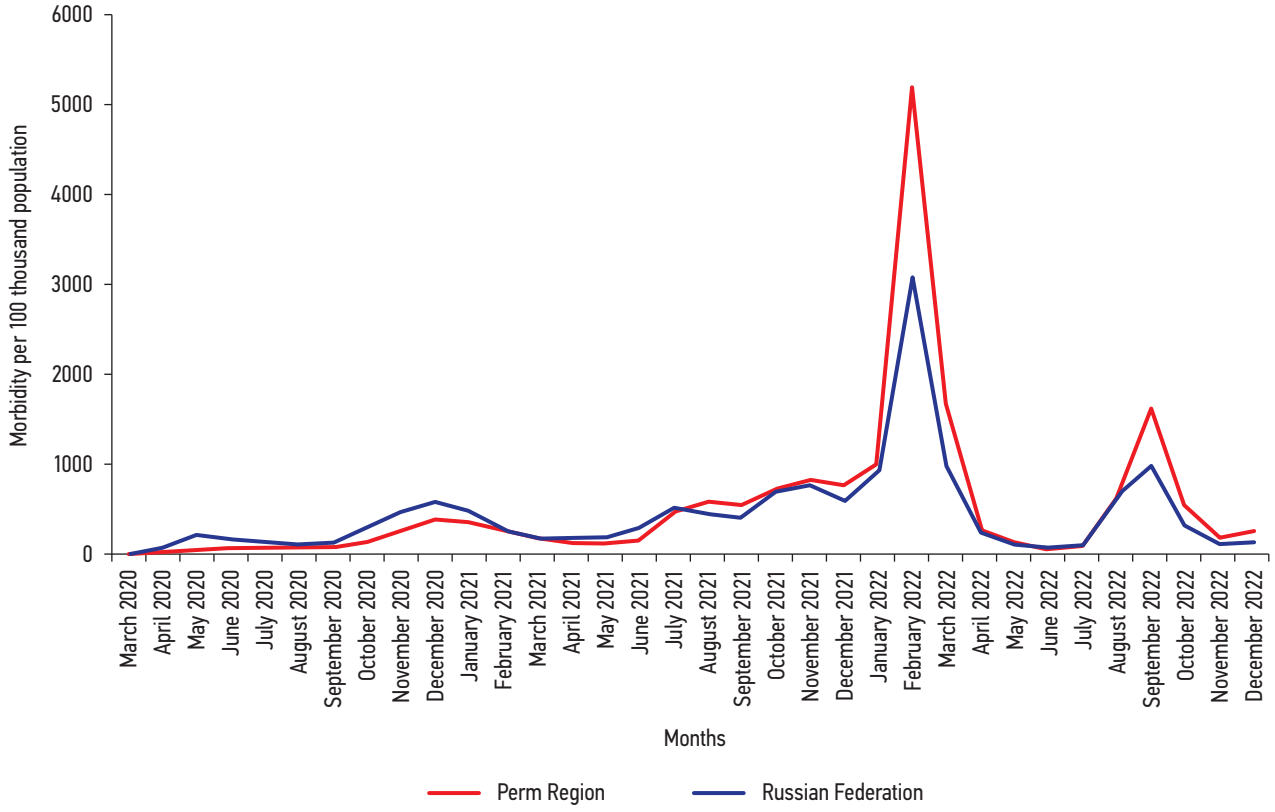

Fig. 2. Incidence of COVID-19 both in Perm Region and the Russian Federation.

Table 1. Monthly structure of SARS-CoV-2 genetic lines collected from patients with COVID-19 between March 2021 and December 2022

Month	Total samples	Proportion of genetic variants, %				
		Alpha	B.1.1.523	Delta	Omicron BA.2 or BA.1	Omicron BA.4/BA.5
2021						
March	10	100	0	0	0	0
April	18	100	0	0	0	0
May	13	23.1	46.2	30.7	0	0
June	56	1.8	1.8	96.4	0	0
July	33	0	6.1	93.9	0	0
August	29	0	0	100	0	0
September	35	0	0	100	0	0
October	28	0	0	100	0	0
November	24	0	0	100	0	0
December	48	0	0	100	0	0
2022						
January	695	0	0	21.6	78.4	0
February	332	0	0	0	100	0
March	97	0	0	0	100	0
April	82	0	0	0	100	0
May	48	0	0	0	100	0
June	35	0	0	0	100	0
July	34	0	0	0	100	0
August	44	0	0	0	47.7	52.3
September	278	0	0	0	4.0	96.0
October	238	0	0	0	7.6	92.4
November	237	0	0	0	10.1	89.9
December	103	0	0	0	34.0	66.0

Russia in the winter of 2021. The delta genovariant (B.1.617) was prevalent from May to December 2021. The omicron genovariant (B.1.1.529) was discovered in December 2021 and has been dominant in the RF since January 2022.

A comparison of the incidence and genetic structure enabled us to establish (Fig. 3) that the onset of all increases in incidence corresponds to the appearance of a new genetic variant of the pathogen. The first period of increase in the incidence from October 2020 to February 2021, considering the genotyping data of the pathogen in the RF since the beginning of the epidemic, was apparently caused by the alpha strain. Genetic research in the Perm region, which began in March 2021, confirmed the leading significance of this pathogenic strain. The second period of increase (July–December 2021) was registered with the dominance of the delta strain. The third period of increased incidence (January–March 2022) was caused by the omicron BA.1 and BA.2 subvariants. Finally, the increase in incidence starting in September 2022 corresponded with the emergence of the omicron BA.4/BA.5 strain.

Increases in the incidence of COVID-19 and changes in the genetic variants of the virus were registered in individuals with high serum IgG levels to SARS-CoV-2 (Fig. 4). The percentage of seropositive patients ranged from 7.1% to 49.2% in 2020, from 23.9% to 80.8% in 2021, and from 84.1% to 100% in 2022. On average, the proportion of seropositive patients was 18.8% in 2020, 54.8% in 2021, and 92.9% in 2023. Thus, the increase in the seropositivity rate of the population

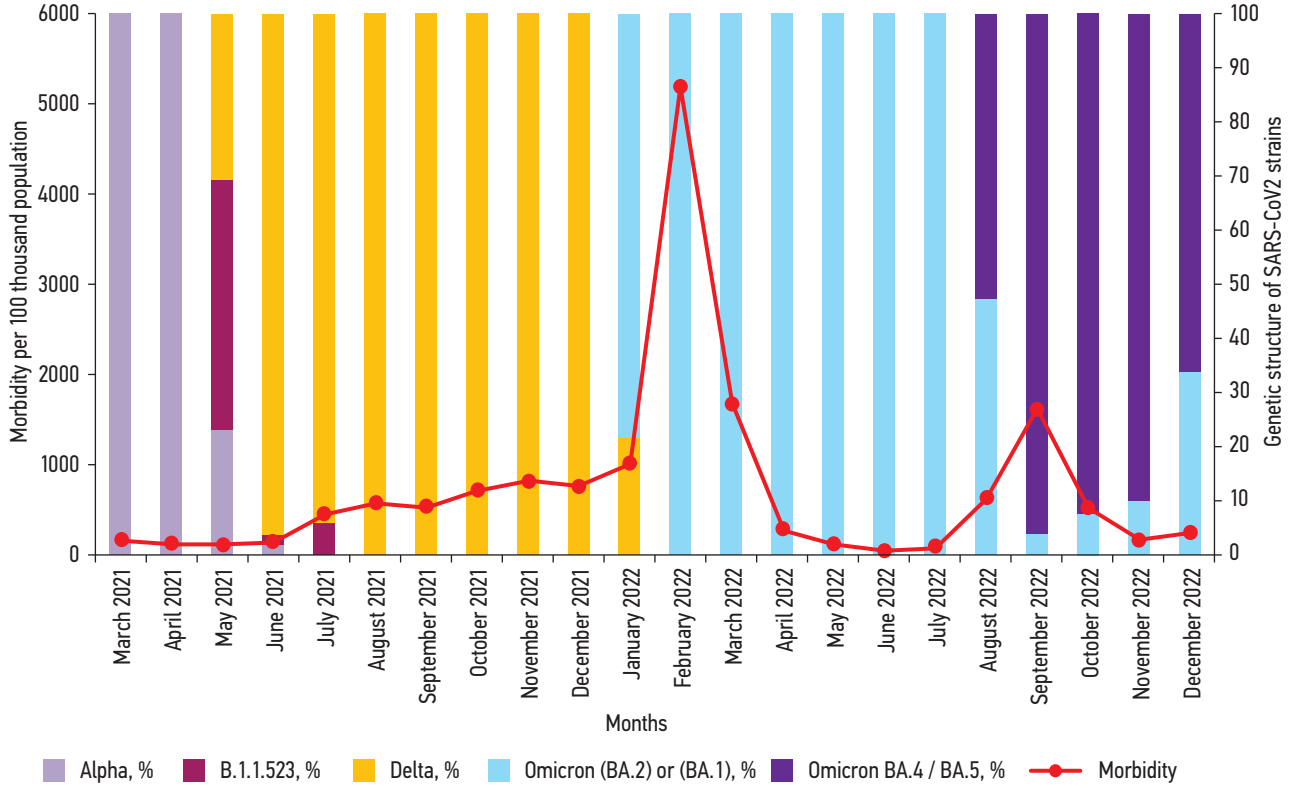

Fig. 3. Monthly genetic structure of SARS-CoV-2 strains and incidence of COVID-19 in Perm Region from March 2021 to December 2022.

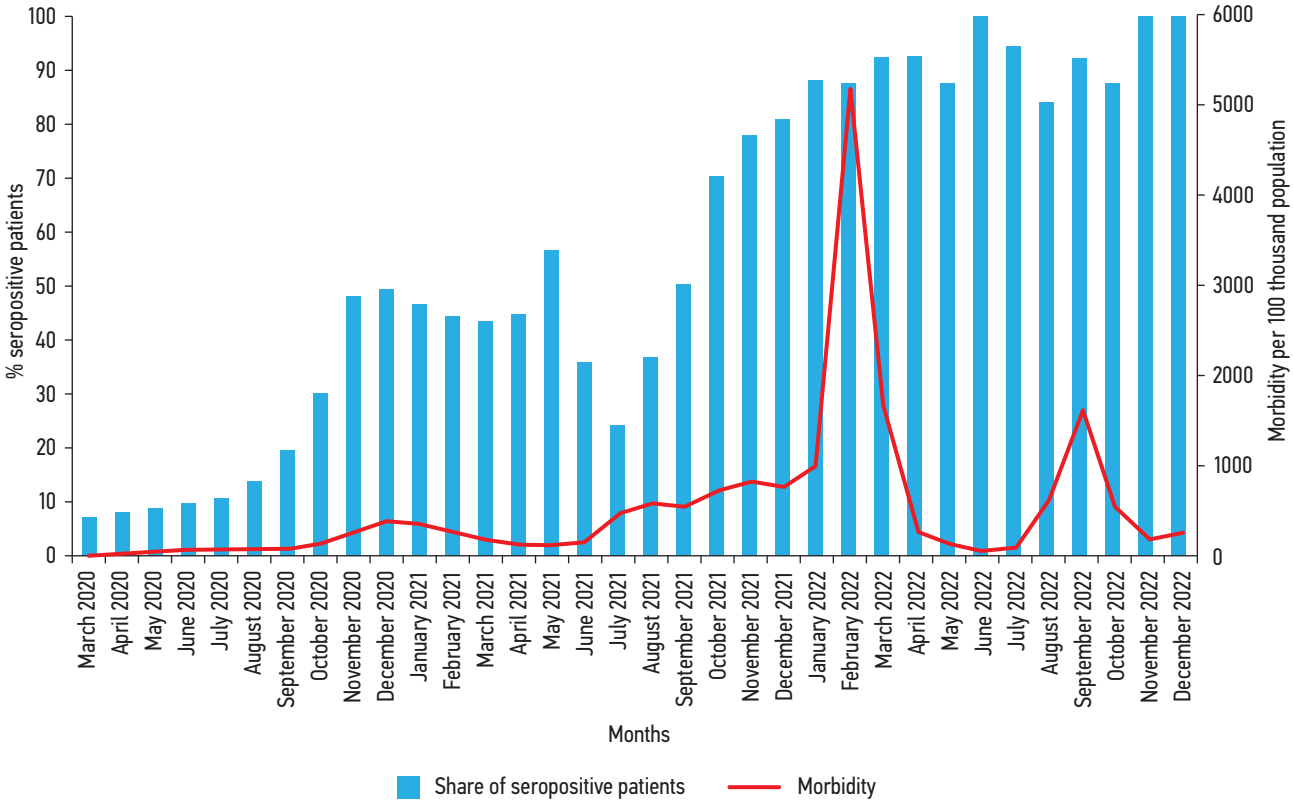

Fig. 4. Incidence of COVID-19 and frequency of occurrence of IgG antibodies to SARS-CoV-2 in the population of Perm Region.

did not prevent a continuing increase in the incidence. The last two periods of increases in incidence caused by the omicron strain were registered in >80% of the population with antibodies.

When assessing the COVID-19 mortality rate, which, as is known, largely indicates the degree of pathogen virulence, in 2020–2021 (Fig. 5), when alpha and delta strains were circulating, this parameter increased. The average mortality rate was 3.9% during the maximum dominance of the alpha strain (March–April 2021) and 4.6% during the dominance of the delta strain (June–December 2021). During the third and fourth periods of increase in incidence, when the omicron strain and its subvariants were predominant (2022), the mortality rate decreased at an average of only 2.7%.

DISCUSSION

In 2020–2022, four increases in the incidence of COVID-19 were registered in the Perm region. Intra-annual increases in the incidence coincided with the emergence of a new genetic variant of the pathogen. The first period of increase in the incidence of the population (October 2020 to February 2021) was caused by the alpha strain, and the second period (June 2021 to January 2022) was caused by the delta strain. The third period, which was most pronounced from January 2022 to March 2022 and the fourth period of increase in September 2022 were caused by the omicron variant. These results are largely consistent with the scientific literature. Since the beginning of the COVID-19 pandemic caused by SARS-CoV-2, the emergence of mutations in this coronavirus has been regularly recorded worldwide. In particular, several variants have been discovered globally since the late 2020, including alpha (B.1.1.7), beta (B.1.351), gamma (P.1), delta (B.1.617), and omicron (B.1.1.529). This coincides with an increase in the incidence [5].

Despite the obvious relationship between the increase in incidence and a change in the genetic variant of the pathogen, attention should still be paid to the finding that two of the four periods of increase in incidence occurred during the cold season; therefore, the influence of seasonal factors characteristic of aerosol anthroponoses cannot be excluded. Several studies have shown that factors such as high population density and high frequency of social contacts, which are characteristic of urban agglomerations, contribute to an increase in the intensity of the COVID-19 epidemic, regardless of the restrictive measures taken [6]. In addition, the finding of a decrease in air humidity in the winter contributes to the increased survival of the virus in the environment [3].

Increases in the incidence of COVID-19 and changes in the genetic variants of the pathogen were noted against an increase in the proportion of individuals with serum IgG levels to SARS-CoV-2. In other words, the increase in the seropositivity rate of the population did not prevent a continuing rise in

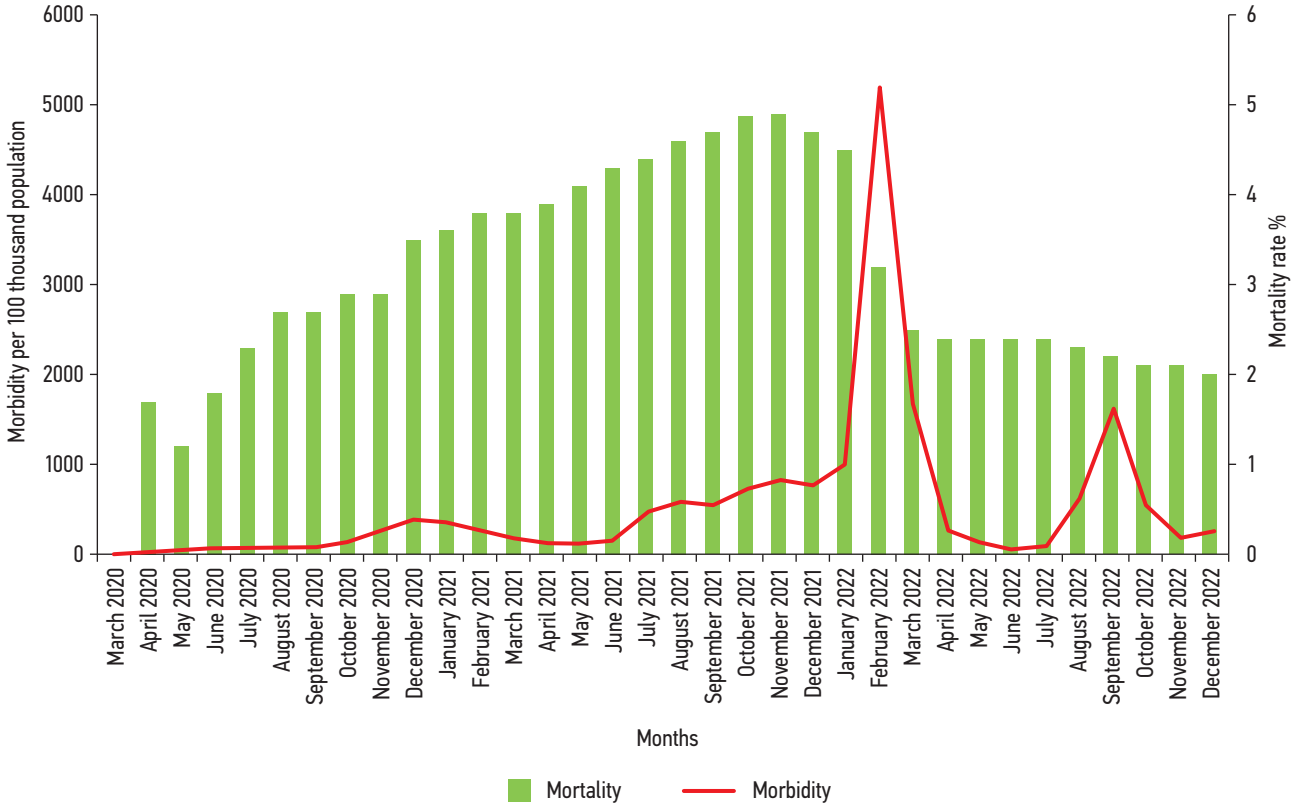

Fig. 5. Morbidity and mortality from COVID-19 in Perm Region.

the incidence. The last two increases in incidence due to the omicron strain were registered in the presence of IgG antibodies in >80% of the population. It stands to reason that the omicron variant is currently the most resistant to immunity induced by COVID-19 vaccines and past infection because it has >50 mutations, including substitutions, deletions, and insertions of 26–32 amino acids [7–10]. Because of the pathogen's immune evasion, patients infected with the omicron genetic variant are probably more infectious than those infected with other coronavirus variants [11].

During the third and fourth periods of increase in incidence, when the omicron strain was etiologically most widespread, the mortality rate decreased significantly compared with the periods with dominance of other variants. This may be due to the relatively low virulence of the omicron strain. Assessment of virulence in a laboratory animal model showed that Omicron subvariants are less virulent than other coronavirus variants [12–14].

CONCLUSION

In 2020–2022, four periods of increase in the incidence of COVID-19 were identified in the Perm region because of the emergence of new genetic variants of the pathogen, mainly the alpha, delta, and omicron variants. Increases in the incidence of COVID-19 and changes in the genetic structure of the pathogen occurred despite an increase in the proportion of individuals in the population with serum IgG levels to SARS-CoV-2. During the third and fourth periods of increase in incidence, when the omicron strain acquired leading etiological significance, the mortality rate of the infection decreased significantly.

ADDITIONAL INFORMATION

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Authors' contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work. I.V Sergevnin — concept of the study, writing the text of the article; I.S. Isaeva — collection of material; M.V. Rozhkova — design of figures and tables; N.I. Markovich — analysis of scientific literature data, statistical processing of the material.

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AUTHORS' INFO

*** Marina V. Rozhkova**, MD;
address: 21 Arkhitektor Sviyazev street, 614065 Perm, Russia;
ORCID: 0000-0002-1113-1001;
e-mail: RozhkovaMary@yandex.ru

Victor I. Sergevnin, MD, Dr. Sci. (Med.), Professor;
ORCID: 0000-0002-2729-2248;
eLibrary SPIN: 4705-0671;
e-mail: viktor-sergevnin@mail.ru

Irina S. Isaeva, MD;
ORCID: 0009-0000-2629-6995;
e-mail: isaeva27iris@gmail.com

Nina I. Markovich, MD, Dr. Sci. (Med.);
ORCID: 0000-0002-5596-4611;
eLibrary SPIN: 1313-1740;
e-mail: barhat120140@mail.ru

ОБ АВТОРАХ

*** Рожкова Марина Владимировна**;
адрес: Россия, 614065, Пермь, ул. Архитектора Свиязева, д. 21;
ORCID: 0000-0002-1113-1001;
e-mail: RozhkovaMary@yandex.ru

Сергевнин Виктор Иванович, д-р мед. наук, профессор;
ORCID: 0000-0002-2729-2248;
eLibrary SPIN: 4705-0671;
e-mail: viktor-sergevnin@mail.ru

Исаева Ирина Сергеевна;
ORCID: 0009-0000-2629-6995;
e-mail: isaeva27iris@gmail.com

Маркович Нина Ивановна, д-р мед. наук;
ORCID: 0000-0002-5596-4611;
eLibrary SPIN: 1313-1740;
e-mail: barhat120140@mail.ru

* Corresponding author / Автор, ответственный за переписку