ORIGINAL RESEARCHES

Patterns of the SARS-CoV-2 epidemic spread in a megacity

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The purpose of the study is to analyze patterns demonstrated by the COVID-19 epidemic process in a megacity during the increase, stabilization and reduction in the incidence, and to evaluate the effectiveness of the epidemic prevention measures.
Materials and methods. The comprehensive study incorporating epidemiological, molecular genetic and statistical research methods was conducted to analyze the spread of SARS-CoV-2 in Moscow during the COVID-19 pandemic.
Results and discussion. It was found that the exponential growth in COVID-19 cases was prevented due to the most stringent control and restrictive measures deployed in Moscow to break the chains of SARS-CoV-2 transmission and due to people who were very disciplined in complying with the self-isolation rules. The analysis of the dynamics in detection of new COVID-19 cases showed that in a megacity, the impact of social distancing and self-isolation would become apparent only after 3.5 incubation periods, where the maximum length of the period is 14 days. It was discovered that the detection frequency of SARS-CoV-2 RNA in relatively healthy population and its dynamics are important monitoring parameters, especially during the increase and stabilization in the COVID-19 incidence, and are instrumental in predicting the development of the epidemic situation within a range of 1–2 incubation periods (14–28 days). In Moscow, the case fatality rate was 1.73% over the observation period (6/3/2020–23/6/2020).
Conclusion. The epidemiological analysis of the COVID-19 situation in Moscow showed certain patterns of the SARS-CoV-2 spread and helped evaluate the effectiveness of the epidemic prevention measures aimed at breaking the routes of transmission of the pathogen.

***Keywords**: SARS-CoV-2 RNA; COVID-19; epidemic process; incidence; relatively healthy residents.*

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Закономерности эпидемического распространения SARS-CoV-2 в условиях мегаполиса

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Цель исследования – изучить закономерности, свойственные эпидемическому процессу COVID-19 в условиях мегаполиса, в фазах подъёма, стабилизации и снижения заболеваемости, а также оценить эффективность противоэпидемических мероприятий.
Материал и методы. Проведено комплексное исследование по изучению распространения SARS-CoV-2 в Москве в период пандемии COVID-19 с использованием эпидемиологического, молекулярно-генетического и статистического методов.
Результаты и обсуждение. Показано, что применение максимально жёстких организационно-ограничительных мер в масштабах Москвы, обеспечивающих разрыв механизма передачи SARS-CoV-2, и высокая дисциплина населения по соблюдению режима самоизоляции позволили не допустить экспоненциального роста заболеваемости COVID-19. Анализ динамики выявления новых случаев COVID-19 показал, что эффект от применения мер по разобщению и режима самоизоляции в условиях мегаполиса наступает через временной промежуток, равный 3,5 инкубационного периода, при его максимальной длительности 14 дней. Установлено, что показатель частоты определения РНК SARS-CoV-2 среди условно здорового населения и его динамика – важные параметры мониторинга, особенно в фазах роста и стабилизации заболеваемости COVID-19, позволяющие в перспективе 1–2 инкубационных периодов (14–28 дней) прогнозировать развитие эпидемической ситуации. Общий коэффициент летальности, рассчитанный за период наблюдения (06.03.2020–23.06.2020) в Москве, составил 1,73%.
Заключение. В результате проведённого эпидемиологического анализа ситуации с COVID-19 в Москве определены некоторые закономерности распространения SARS-CoV-2 и оценена эффективность противоэпидемических мероприятий, направленных на разрыв механизма передачи возбудителя.

***Ключевые слова**: РНК SARS-CoV-2; COVID-19; эпидемический процесс; заболеваемость; условно здоровое население.*

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The COVID-19 pandemic has posed a significant challenge for the healthcare sector in most countries. The pandemic was caused by the virus belonging to the family *Coronaviridae*, the genus *Betacoronavirus*, which was called SARS-CoV-2 [1]. The studies have shown that it is a new virus, which originated through natural processes in the People's Republic of China (PRC) in October–November 2019; it gained an entry to the human population

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through the ability to bind to the human ACE2 receptor.

The first recorded case of the infection associated with the novel coronavirus was a 55-year-old male, in Wuhan, China, November 17, 2019. By the end of 2019, China reported 266 cases with respiratory conditions, which, supposedly, were related to the new variant of the coronavirus. On the final day of December 2019, the World Health Organization (WHO) was informed about the outbreak of pneumonia of unknown etiology. At the beginning of 2020, cases of the new disease, later named COVID-19, were recorded in many countries, mostly in Europe and the United States [2–5]. Numerous deaths, damage caused by COVID-19 to people's health, and the rapid worldwide spread of the virus urged WHO to declare a coronavirus pandemic on March 11, 2020 [6]. By that date, the global community had reported 123,079 COVID-19 cases and 4,450 deaths. In Russia, the COVID-19 epidemic started much later than in Europe; there were only 18 confirmed cases when the pandemic was declared.

The purpose of the study is to analyze patterns demonstrated by the COVID-19 epidemic process in a megacity during the increase, stabilization and reduction in the incidence, and to evaluate the effectiveness of the epidemic prevention measures.

Materials and methods

The study was performed at the Central Research Institute of Epidemiology of the Russian Federal Service for Surveillance of Consumer Rights Protection and Human Wellbeing (Rospotrebnadzor). The comprehensive study was conducted in Moscow from 6/3/2020 to 23/6/2020 and incorporated epidemiological, molecular genetic and statistical research methods.

The dynamics of detection of new COVID-19 cases in Moscow was analyzed by using the officially recorded data available at the stopcoronavirus.rf website.

SARS-CoV-2 RNA detection tests were performed with the AmpliSens® Cov-Bat-FL (Registration Certificate RZN 2014/1987, 25/3/2020) designed and manufactured by the Central Research Institute of Epidemiology. From April 6 to June 23, 2020, a total of 89,097 samples from relatively healthy residents of Moscow were examined. The molecular genetic testing was conducted in compliance with the Provisional Regulations on Information Recording to Prevent the Spread of the Novel Coronavirus Infection (COVID-19), which were adopted by Decree No. 373 of the RF Government on 31/3/2020; Guidelines MR 3.1.0169-20, Laboratory Diagnostics of COVID-19, approved by the Chief State Sanitary Doctor of the Russian Federation on 30/3/2020; the Provisional Guidelines, Prevention, Diagnostics and Treatment of the Novel Coronavirus Infection (COVID-19), approved by the Health Ministry of the Russian Federation on 8/4/2020.

Binomial confidence intervals (CI) for average frequencies of detection of SARS-CoV-2 RNA were calculated with the exact Clopper-Pearson method. CIs for average numbers of new COVID-19 cases were calculated with the Microsoft Excel software program. The dynamics of the analyzed parameters was estimated by calculating the trend values, which, in their turn, were calculated by the method of least squares. The strength of the trends (upward/downward) was defined by using the criteria offered by V.D. Belyakov et al. [7].

Results

During the observation period (6/3/2020–23/6/2020) in Moscow, a total of 216,095 COVID-19 cases (1,727.9 per 100 thousand residents) and 3,643 deaths (29.1 per 100 thousand residents) were recorded.

It should be noted that public authorities at all levels realized the seriousness of the threat; therefore, the first decisions on prevention of the SARS-CoV-2 spread in Moscow and in the entire country had been adopted before the first case of COVID-19 was detected in Russia. The National Plan for Prevention of Importation and Spread of the Novel Coronavirus Infection in Russia was approved by the Chairman of the RF Government. It was followed by other important documents issued by the RF Chief State Sanitary Doctor: Decree No. 2 On Measures Aimed at Prevention of the Spread of the Novel Coronavirus Infection Caused by 2019-nCoV, adopted on 24/1/2020; Decree No. 3 On Additional Sanitary and Anti-Epidemic (Preventive) Measures Aimed at Prevention of Importation and Spread of the Novel Coronavirus Infection Caused by 2019-nCoV, adopted on 31/1/2020; Decree No. 5 On Additional Measures Aimed at Decreasing Risks of Importation and Spread of COVID-2019, adopted on 2/3/2020; Decree No. 6 On Additional Measures Aimed at Decreasing Risks of COVID-2019 Spread, adopted on 13/3/2020; and Decree No. 7 On Imposing the Lockdown to Prevent the COVID-2019 Spread, adopted on 18/3/2020.

The Moscow government also adopted a number of decisions on prevention of the COVID-19 spread. At first (on March 2, 2020), the Moscow City Mayor issued the directive ordering all the people who came from the countries affected by the COVID-19 outbreak to stay at home and follow self-isolation precautions for 14 days. Later (on March 5, 2020), all public events were called off, schools were shut down, and adults aged 65 years and older were to comply with the self-isolation regime that was imposed from March 26 through April 14 and then extended to June 14, 2020. In Moscow, the megacity most involved in the epidemic process, the self-isolation regime was introduced from March 30 for all residents, regardless of age. The self-isolation was discontinued on June 9, 2020, when the epidemic situation improved.

The first case of COVID-19 in Russia (in Moscow) was detected on March 2; it was a tourist who came back from Italy. Afterwards, the number of new COVID-19 cases was increasing steadily. The largest number of newly identified cases was recorded in the first half of May 2020; the peak values were 6,703 (7/5/2020) and 6,169 (11/5/2020). From the second half of May, the number of daily detected new cases of COVID-19 started gradually decreasing. On 23/6/2020, in Moscow, the total number of COVID-19 cases was 216,095 at the incidence rate of 1,727.9 cases per 100 thousand residents. A total of 3,643 deaths (29.1 deaths per 100 thousand residents) were recorded.

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The analysis of the dynamics in the detection of COVID-19 cases led to the conclusion that there were several periods of time, each of them having its distinctive characteristics attributable to the patterns of the COVID-19 epidemic process and affected by the adopted epidemic prevention measures **(Table 1**).

When the COVID-19 epidemic started developing in Moscow (from March 6 to March 24, 2020), the disease was generally diagnosed in people who had traveled to other countries. During the first days, there were only few cases – from 3 to 9 patients; no new cases were detected on March 7, 8 and 15. Later, COVID-19 cases were recorded every day, and the number of new cases reached 54 (March 22) and 71 (March 23). It should be noted that at this stage of epidemic development, SARS-CoV-2 just started its spread, and the intensity of the epidemic process was low. At the same time, the dynamics in detection of new COVID-19 cases demonstrated a clear upward trend (+16.4% a day); the average new COVID-19 case counts and incidence rates were 15.3 cases a day and 0.1 cases per 100 thousand residents, respectively.

During the 25/3/2020–1/4/2020 period, the epidemic process started growing in intensity. The daily detected cases ranged from 114 (March 28) to 387 (March 31) cases; the average daily case count for new COVID-19 cases was 171.9 cases a day, demonstrating a 13-fold increase as compared to the initial epidemic period. The average incidence rate rose to 1.6 per 100 thousand residents. Note that the records included only the cases with clinically apparent symptoms. During the same period, the first cases of infection among healthcare workers were reported. It can be assumed that this stage of epidemics gave birth to the cohort of potentially infected people (asymptomatic COVID-19 cases, who were not recorded and, consequently, were not quarantined) who contributed to the rapid spread of SARS-CoV-2 among the residents. During this period, the SARS-CoV-2 infection rate showed a clear upward trend (+12.9% a day).

During the next week (2/4/2020–8/4/2020), the daily case count for new COVID-19 cases increased dramatically, ranging from 434 (April 4) to 697 (April 7). The average case count was 565.9 patients a day, thus 2.8 times exceeding the average case count recorded during the previous 8 days. It should be pointed out that this period is characterized by a significant increase in the number of new cases, though at slightly lower intensity (+5.4% a day). The average incidence rate increased 3 times and reached 4.5% per 100 thousand residents. On 6/4/2020, Moscow medical professionals started tests aimed at detection of SARS-CoV-2 RNA among relatively healthy people (**see Figure**). During 3 days, a total of 180 people were examined; 7 of them had SARS-CoV-2 RNA (3.9%; 95% CI 1.6–7.9), thus setting a precedence proving the existence of asymptomatic COVID-19 forms (**Table 2**).

The detection of infected people without COVID-19 symptoms is critically important from the epidemiological perspective, as it serves for revealing hidden and active sources of infection contributing to high activity of the epidemic process.

During the next 8 days (April 9–16), the number of daily recorded new COVID-19 cases increased significantly, first of all, due to actively detected asymptomatic patients. The lowest/highest numbers are recorded on April 9 and April 15, 857 and 1,774 cases, respectively. The average case count reached 1,288.1 people a day, and the growth rate was +6.4% a day. During that period, in Moscow, the tests were performed in 6,624 people (relatively healthy residents); 510 (7.7%) of them were tested positive for SARS-CoV-2 RNA. At the end of the period (April 16), the highest SARS-CoV-2 RNA detection frequency was recorded, reaching 11.9%. The above parameter demonstrated a moderate growth rate (+2.4% a day), thus giving grounds for expecting further intensification of the COVID-19 epidemic process (see Figure).

During the 17/4/2020–1/5/2020 period, the epidemic situation changed for the worse, which was quite predictable, considering the dynamics of the analyzed parameters for the previous period. The average daily case count for new COVID-19 cases was 2,743.6 people a day, thus exceeding 2.2 times the case count in the previous period; the average detection frequency for SARS-CoV-2 RNA among relatively healthy residents reached its maximum level of 9.1%. Note that during this period, the all-time highest detection frequencies for SARS-CoV-2 RNA were recorded among the relatively healthy residents of Moscow: 10.3% (April 19), 11.0% (April 17) and 11.9% (April 21). The main increase in the number of COVID-19 cases was re-

Table 1. Dynamics of average frequencies of confirmed COVID-19 cases and incidence rates in Moscow during different time intervals, from March 6 to June 23, 2020

Time interval	Incidence rate per 100 thousand population	Average number of daily detected COVID-19 cases (95% confidence interval)	Upward/downward trend of daily cases, %
March 6–24	0.1	15.3 (13.0–17.5)	+16.4
March 25 – April 1	1.6	171.9 (168.7–175.0)	+12.9
April 2–8	4.5	565.9 (562.8–569.0)	+5.4
April 9–16	10.1	1,288.1 (1,282.6–1,293.6)	+6.4
April 17 – May 1	22.0	2,743.6 (2,738.5–2,748.7)	+0.9
May 2–15	44.8	5,583.1 (5,579.1–5,587.2)	-1.3
May 16–23	26.1	3,241.6 (3,237.0–3,246.2)	-2.8
May 24 – June 4	18.6	2,318.1 (2,314.8–2,321.4)	-1.7
June 5–15	13.2	1,640.9 (1,636.8–1,645.0)	-3.7
June 16–23	8.9	1,103.9 (1,101.1–1,106.7)	-2.3

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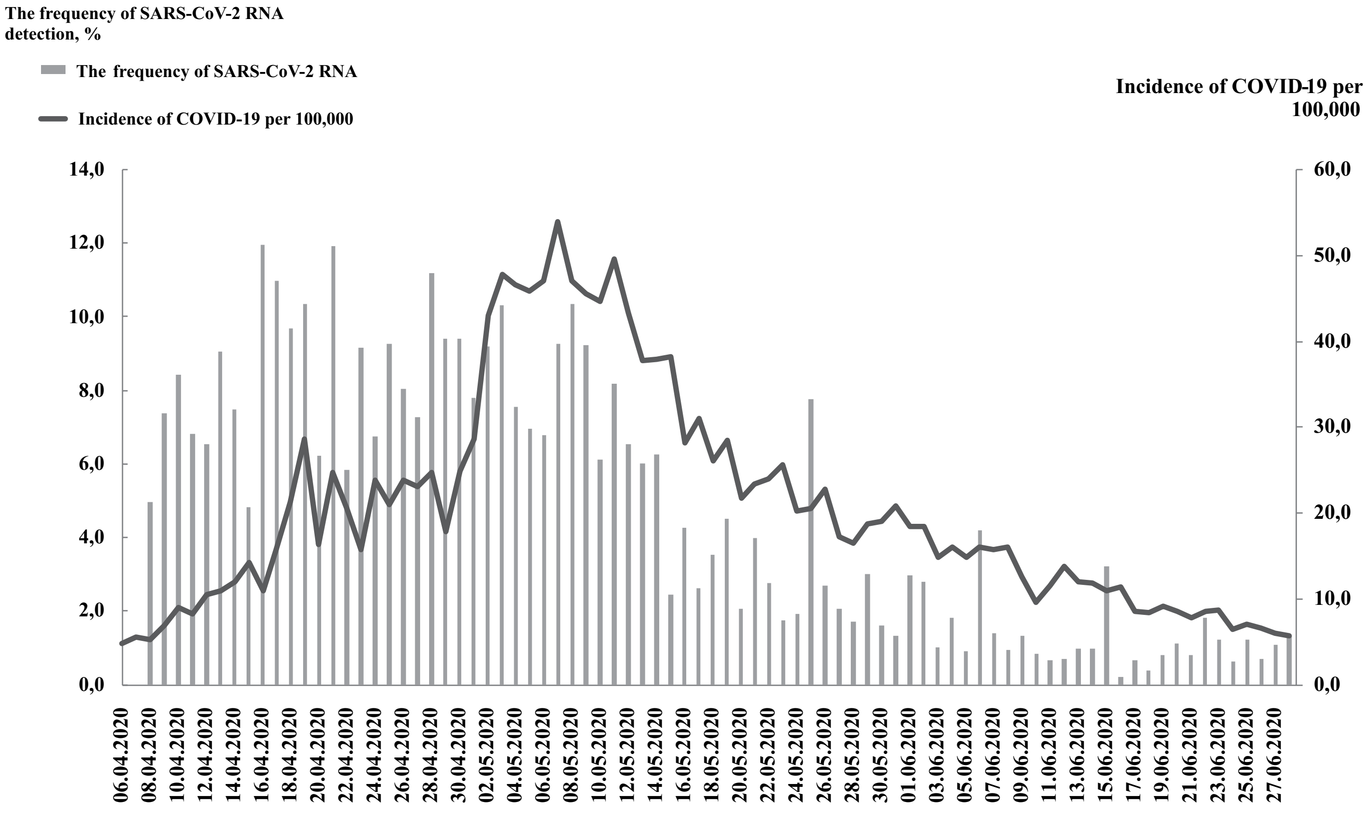
Table 2. Dynamics of SARS-CoV-2 RNA detection frequency among relatively healthy residents of Moscow during different time intervals from April 2 to June 23, 2020

Time interval	*n*	Average SARS-CoV-2 RNA detection rate, % (95% confidence interval)	Upward/downward trend of daily cases, %
April 2–8	180	3.9* (1.6–7.9)	–**
April 9–16	6,624	7.7 (7.1–8.4)	+2.4
April 17– May 1	12,607	9.1 (8.6–9.6)	-0.7
May 2–15	13,469	7.2 (6.8–7.7)	-4.0
May 16–23	9,841	3.1 (2.8–3.5)	-5.8
May 24 – June 4	18,283	2.4 (2.2–2.7)	-1.9
June 5–15	16,702	1.2 (1.0–1.4)	-2.3
June 16–23	9,127	0.8 (0.6–1.0)	+16.4

Note. * Tests for SARS-CoV-2 RNA were performed on 6/4/2020–8/4/2020; ** The dynamics of detection frequency for SARS-CoV-2 RNA was not estimated.



The SARS-CoV-2 RNA detection frequency among relatively healthy residents and COVID-19 incidence in Moscow from 6/4/2020 to 28/6/2020.

corded during the first days of this period (April 17–19), when there were 1,959, 2,649 and 3,570 cases detected. During the next days, the number of new COVID-19 cases ranged from 1,959 (April 23) to 3,561 (May 1). During this period, the upward trend was recorded for the first time, demonstrating a significant and steady increase in new COVID-19 cases (+0.9% a day). The last days of this period fell on the so-called picnic weekend entailing multiple contacts among people and being a probable cause of the escalation in the number of new COVID-19 cases.

From May 2 to May 15, 2020, the average daily COVID-19 case count increased to 5,583.1 patients a day, demonstrating a double increase as compared to the previous period. The increase was recorded from May 1 to May 2 (3,561 and 5,358 patients, respectively); apparently, it can be explained by the large-scale violation of the self-isolation regime during the last days of April. On May 7 and May 11, the record number of daily detected COVID-19 cases was recorded – 6,703 and 6,169, respectively. Concurrently, for the first time, the reduction in the number of COVID-19 cases was recorded (-1.3% a day), thus representing a moderate rate. The average detection frequency for SARS-CoV-2 RNA among relatively healthy residents decreased to 7.2%, showing a trend of moderate reduction at 4.0% a day.

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From May 16 to May 23, 2020, for the first time, there was a decrease (a significant one equal to 41.8%) in the average number of detected cases (3,241.6 cases a day), which retained a moderate trend of reduction in daily detected cases (-2.8% a day). It can be said that due to the compliance with the self-isolation regime, the development of the COVID-19 epidemic in Moscow showed a steady regressive pattern. The average SARS-CoV-2 RNA detection frequency also decreased significantly to 3.1% and continued decreasing rapidly at 5.8% a day (a significant decrease).

From May 24 to June 4, 2020, the number of detected COVID-19 cases kept decreasing at moderate intensity (-1.7% a day); the average count was 2,318.1 cases a day, or by 28.5% less than during the previous period. The average SARS-CoV-2 RNA detection frequency also decreased (2.4%).

The period from June 5 to June 15 was also characterized by a reduction in the average number of detected COVID-19 cases and average SARS-CoV-2 RNA detection frequency, which amounted to 1,640.9 cases a day and 1.2%, respectively. For both parameters, the reduction was moderate and was equal to 3.7% and 2.3% a day, respectively.

The final time interval of the analyzed period (16/6/2020–23/6/2020) is also characterized by a decrease in average counts. The average new COVID-19 cases amounted to 1,103.9 cases a day; the SARS-CoV-2 RNA was detected in 0.8% cases among relatively healthy population. The dynamics of new COVID-19 cases showed a moderate downward trend (-2.3% a day); however, the SARS-CoV-2 RNA detection frequency demonstrated the opposite trend, having increased significantly (+16.4% a day). At the same time, such increase may not be a significant indicator, when accompanied by steady reduction in the number of new COVID-19 cases and in the proportion of individuals with SARS-CoV-2 RNA among relatively healthy population, where the average proportion is low (0.8%). It should be noted that the incidence rate was 8.9 per 100 thousand residents, which can be assessed as a relatively high level, considering slow reduction.

Discussion

The COVID-19 epidemic, which is going on in the Russian Federation at the moment, became the biggest challenge in 2020. Enormous damage was caused to the health of the country's population; the size of economic losses and decline in the quality of life are still unknown.

In Moscow, the escalation in COVID-19 is characterized, on the one hand, by relatively slow rates (no exponential growth was observed) and, on the other hand, by several spikes resulting in a sharp increase in new cases. The major spikes were recorded on April 16–17 (from 1,370 to 1,959 new cases of COVID-19) and on May 1–2, 2020 (from 3,561 to 5,358 cases). Note that at that time, relatively healthy residents went through testing and a significant number of detected cases did not present any COVID-19 symptoms (up to 40% on some days). The experience of active detection of asymptomatic COVID-19 cases with tests for SARS-CoV-2 RNA and the subsequent administration of self-isolation regime showed that the detection was a highly efficient tool to limit the virus spread. In our previous article, we stated that the daily monitoring of the proportion of individuals with SARS-CoV-2 RNA among relatively healthy population can be a critical element of epidemiological surveillance of COVID-19 [8].

It should be noted that even during the self-isolation regime, there are a lot of people in Moscow who have to go to work to maintain the required level of city life, who use public transport, go to stores and pharmacies where they are exposed to sources of infection. The high frequency of the infected (every 13th) in the relatively healthy population should result in higher intensity of the epidemic process and cause a further increase in new cases. There are reasons to assume that asymptomatic COVID-19 cases, which could not be detected, involuntarily became the driving force for further spread of SARS-CoV-2. In the meantime, the large-scale tests for SARS-CoV-2 RNA, which were performed in Moscow, helped decrease significantly the level of virus circulation and contributed to the total reduction in new COVID-19 cases. Such studies produce a positive effect, which becomes apparent only some time later and depends both on the coverage and incubation period of COVID-19. Based on today's assumptions and underlying calculations, the length of the incubation period for COVID-19 ranges from 0 to 14 days, while a number of authors think that it can last longer [9, 10].

There is every reason to believe that the COVID-19 epidemic in Moscow was reversed mainly through timely adopted epidemic prevention measures, especially through social distancing and self-isolation. As a result, Moscow was able to escape the explosive growth of the incidence and, getting advantage in time, to prepare the medical infrastructure for providing of professional and effective assistance to patients. With the self-isolation still in place, the tide of the COVID-19 epidemic in Moscow, in our opinion, was turned on May 16, 2020, when the first significant decrease in the new cases was recorded; the number of cases dropped from 4,748 to 3,505 and remained stable at the reached level to start a downward trend. We can state that reduction in COVID-19 cases, which was driven by the implemented epidemic prevention measures, started after the time interval equal to 3.5 incubation periods, each of them lasting 14 days [9].

In our opinion, the SARS-CoV-2 RNA detection frequency among relatively healthy people during the ongoing COVID-19 epidemic is a highly informative parameter for monitoring of the epidemic situation. This parameter provides important information about the proportion of asymptomatic cases, which are seen as hidden sources of infection. Its changes give a clear picture of the intensity of the epidemic process, help understand the course of its development within a range of 1–2 incubation periods and the effectiveness of the epidemic prevention measures.

At present, the epidemiological analysis of the COVID-19-related situation has to allow some assumptions due to the lack of accurate quantitative characteristics of the epidemic process. For example, the assumed maximum length of the incubation period is 14 days, while there is evidence that it can be much longer [9]. Besides, there are only provisional estimates of the basic reproduction number (R0) representing the maximum epidemic potential of the source of infection. Based on the data from different researchers, COVID-19 R0 ranges from 2.2 to 4.7 [11–15].

The case fatality rate (CFR) is an important indicator to measure the severity of COVID-19 outcomes. It estimates the proportion of people who died from a specific disease among all individuals diagnosed with this disease over a certain period of time. CFR estimated for Moscow was 1.73%. Today, in the COVID-19 pandemic, there are broad variations in estimations of CFR in different countries, depending on the way cases and deaths are reported and classified [16]. In China, CFR was 1.38% [17, 18]. In their review, E. Puca et al. [19] show different CFRs estimated for 11 European countries; the highest rates were 4.6–4.8% (Albania, Bulgaria, Greece), while the lowest rates were 1.4–1.5% (Montenegro, Croatia). In Canada and the United States, the adjusted CFRs amounted to 1.6 and 1.78%, respectively [20].

Today, it can be said that the COVID-19 pandemic has caused enormous damage to the health of people in many countries of the world, including Russia. It is impossible to predict when the pandemic will be over. At the end of June 2020, a surge in new cases of COVID-19 was reported by several countries (Germany, South Korea, Spain), which seemingly have solved the problem. Furthermore, many experts admit the probability of a second wave of the COVID-19 epidemic [21–24].

The self-isolation regime was discontinued due to the significantly improved epidemic situation in Moscow; the residents were asked to practice social distancing in public transport, stores and other public spaces, and to use face masks and gloves. The imposition of stringent measures of social isolation caused medical and social problems, the severity of which is still unknown. Topping the list of epidemic-related challenges is the stress experienced by obedient citizens during the lockdown. For many of them, this stress turned into flare-ups of chronic conditions, weakened natural resistance of the body, depression development. At the moment, the size of the problem is difficult to estimate, as the epidemic continues in Russia, including Moscow, though it is past its peaks.

Conclusion

Based on the dynamics of the frequency of new recorded cases of COVID-19 and results of the SARS-CoV-2 RNA detection among relatively healthy residents, we can make several conclusions.

1. The timely adopted stringent control and restrictive measures aimed at breaking the routes of SARS-CoV-2 transmission, along with the high personal responsibility of residents during the self-isolation regime in Moscow, were instrumental in prevention of the exponential growth in the number of COVID-19 cases, which was observed in many countries [24–27].

2. In a megacity, the impact of social distancing and self-isolation becomes apparent after 3.5 incubation periods, where the maximum length of the period is 14 days.

3. Studies on detection of SARS-CoV-2 RNA among relatively healthy people during the increase and stabilization (the plateau) in the COVID-19 incidence are an important anti-epidemic measure critical in detection of asymptomatic cases and their further self-isolation aimed to decrease significantly the number of hidden sources of infection.

4. The detection frequency for SARS-CoV-2 RNA among relatively healthy people and its dynamics are important parameters for monitoring, especially during an increase and stabilization in the COVID-19 incidence, serving as predictors of development of the epidemic situation.

5. The assessment of the dynamics of the increase in new COVID-19 cases in Moscow suggests that the length of the incubation period in some patients with COVID-19 exceeds 14 days.

6. The case fatality rate estimated during the period from the epidemic onset to 23/6/2020 when the number of new COVID-19 cases in Moscow was gradually decreasing was 1.73%.

The fact that within a short period of time (from 2002 to 2019) the global community faced three times severe epidemic situations caused by recombinant coronaviruses emerging not only in China, but also in Saudi Arabia (MERS) raises serious concerns that such situations can reoccur in future. The acquired experience can be useful for curbing future outbreaks; the essential measures have been tried and tested, so they will be easier to implement. Yet, to prevent pandemic-like situations we need a systemic approach based on results of fundamental studies on virus evolution within viral families and genera [28].

REFERENCES

1. Lu R., Zhao X., Li J., Niu P., Yang B., Wu H., et al. Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020; 395(10224): 565-74. DOI: http://doi.org/10.1016/S0140-6736(20)30251-8
2. Romagnani P., Gnone G., Guzzi F., Negrini S., Guastalla A., Annunziato F., et al. The COVID-19 infection: lessons from the Italian experience. *J. Public Health Policy.* 2020; 41(3): 238-44. DOI: http://doi.org/10.1057/s41271-020-00229-y
3. Sebastiani G., Massa M., Riboli E. Covid-19 epidemic in Italy: evolution, projections and impact of government measures. *Eur. J. Epidemiol.* 2020; 35(4): 341-5. DOI: http://doi.org/10.1007/s10654-020-00631-6
4. Rothe C., Schunk M., Sothmann P., Bretzel G., Froeschl G., Wallrauch C., et al. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. *N. Engl. J. Med.* 2020; 382(10): 970-1. DOI: http://doi.org/10.1056/NEJMc200146
5. Holshue M.L., DeBolt C., Lindquist S., Lofy K.H., Wiesman J., Bruce H., et al. First case of 2019 novel coronavirus in the United States. *N. Engl. J. Med.* 2020; 382(10): 929-36. DOI: http://doi.org/10.1056/NEJMoa2001191
6. WHO. Coronavirus disease 2019 (COVID-19) Situation Report – 51. Available at: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf
7. Belyakov V.D., Degtyarev A.A., Ivannikov Yu.G. *The Quality and Effectiveness of Anti-Epidemic Measures [Kachestvo i effektivnost' protivoepidemicheskikh meropriyatiy]*. Leningrad: Meditsina; 1981. (in Russian)
8. Akimkin V.G., Kuzin S.N., Shipulina O.Yu., Yatsyshina S.B., Tivanova E.V., Kalenskaya A.V., et al. Epidemiological significance of

detection of SARS-CoV-2 RNA among different groups of population of Moscow and Moscow Region during the COVID-19 outbreak. *Zhurnal mikrobiologii, epidemiologii i immunobiologii.* 2020; 97(3): 197-201.
DOI: http://doi.org/10.36233/0372-9311-2020-97-3-197-201 (in Russian).

9. Lauer S.A., Grantz K.H., Bi Q., Jones F.K., Zheng Q., Meredith H.R., et al. The incubation period of coronavirus disease 2019 (Covid-19) from publicly reported confirmed cases: estimation and application. *Ann. Intern. Med.* 2020; 172(9): 577-82. DOI: http://doi.org/10.7326/M20-0504
10. Backer J.A., Klinkenberg D., Wallinga J. Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travelers from Wuhan, China, 20–28 January 2020. *Euro Surveill.* 2020; 25(5) : 2000062. DOI: http://doi.org/10.2807/1560-7917.ES.2020.25.5.2000062
11. Liu T., Hu J., Kang M., Lin L., Zhong H., Xiao J., et al. Transmission dynamics of 2019 novel coronavirus (2019-nCoV). *J. Med. Virol.* 2020; 92(5): 501-11. DOI: http://doi.org/10.1101/2020.01.25.919787
12. Read J.M., Bridgen J.R.E., Cummings D.A.T., Ho A., Jewell C.P. Novel coronavirus 2019-nCoV: early estimation of epidemiological parameters and epidemic predictions. *medRxiv.* 2020. DOI: http://doi.org/10.1101/2020.01.23.20018549
13. Riou J., Althaus C.L. Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV), December 2019 to January 2020. *Euro Surveill.* 2020; 25(4): 2000058. DOI: http://doi.org/10.2807/1560-7917.ES.2020.25.4.2000058.
14. Shen M., Peng Z., Xiao Y., Zhang L. Modelling the epidemic trend of the 2019 novel coronavirus outbreak in China. *bioRxiv.* 2020. DOI: http://doi.org/10.1101/2020.01.23.916726
15. Wu J.T., Leung K., Leung G.M. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. *Lancet.* 2020; 395(10225): 689-97. DOI: http://doi.org/10.1016/S0140-6736(20)30260-9
16. Randolph H.E., Barreiro L.B. Herd Immunity: Understanding COVID-19. *Immunity.* 2020; 52(5): 737-41. DOI: http://doi.org/10.1016/j.immuni.2020.04.012
17. Verity R., Okell L.C., Dorigatti I., Winskill P., Whittaker C., Imai N., et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. *Lancet Infect. Dis.* 2020; 20(6): 669-77. DOI: http://doi.org/10.1016/S1473
18. Wu J.T., Leung K., Bushman M., Kishore N., Niehus R., de Salazar P.M., et al. Estimating clinical severity of COVID-19 from the transmission dynamics in Wuhan, China. *Nat. Med.* 2020; 26(4): 506-10. DOI: http://doi.org/10.1038/s41591-020-0822-7-3099(20)30243-7
19. Puca E., Čivljak R., Arapović J., Popescu C., Christova I., Raka L., et al. Short epidemiological overview of the current situation on Covid-19 pandemic in Southeast European (SEE) countries. *J. Infect. Dev. Ctries.* 2020; 14(5): 433-7. DOI: http://doi.org/10.3855/jidc.12814
20. Abdollahi E., Champredon D., Langley J.M., Galvani A.P., Moghadas S.M. Temporal estimates of case-fatality rate for COVID-19 outbreaks in Canada and the United States. *CMAJ.* 2020; 192(25): E666-70. DOI: http://doi.org/10.1503/cmaj.200711
21. Xu S., Li Y. Beware of the second wave of COVID-19. *Lancet.* 2020; 395(10233): 1321-2. DOI: http://doi.org/10.1016/S0140-6736(20)30845-X
22. de Brouwer R., van Veldhuisen D.J., de Boer R.A. Surviving the first COVID-19 wave and learning lessons for the second. *Eur. J. Heart Fail.* 2020; 22(6): 975-7. DOI: http://doi.org/10.1002/ejhf.1938
23. Vogel L. Is Canada ready for the second wave of COVID-19? *CMAJ.* 2020; 192(24): E664-5. DOI: http://doi.org/10.1503/cmaj.1095875
24. Ceylan Z. Estimation of COVID-19 prevalence in Italy, Spain, and France. *Sci. Total Environ.* 2020; 729: 138817. DOI: http://doi.org/10.1016/j.scitotenv.2020.138817
25. Li Q., Guan X., Wu P., Wang X., Zhou L., Tong Y., et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N. Engl. J. Med.* 2020; 382(13): 1199-207. DOI: http://doi.org/10.1056/NEJMoa2001316
26. Chatterjee A., Gerdes M.W., Martinez S.G. Statistical explorations and univariate timeseries analysis on COVID-19 datasets to understand the trend of disease spreading and death. *Sensors (Basel).* 2020; 20(11): 3089. DOI: http://doi.org/10.3390/s20113089
27. Abdollahi E., Champredon D., Langley J.M., Galvani A.P., Moghadas S.M. Temporal estimates of case-fatality rate for COVID-19 outbreaks in Canada and the United States. *CMAJ.* 2020; 192(25): E666-70. DOI: http://doi.org/10.1503/cmaj.200711
28. L'vov D.K., Al'khovskiy S.V. Source of the COVID-19 pandemic: ecology and genetics of coronaviruses (Betacoronavirus: Coronaviridae) SARS-CoV, SARS-CoV-2 (subgenus Sarbecovirus), and MERS-CoV (subgenus Merbecovirus). *Voprosy virusologii.* 2020; 65(2): 62-70. DOI: http://doi.org/10.36233/0507-4088-2020-65-2-62-70 (in Russian)

ЛИТЕРАТУРА

1. Lu R., Zhao X., Li J., Niu P., Yang B., Wu H., et al. Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020; 395(10224): 565-74. DOI: http://doi.org/10.1016/S0140-6736(20)30251-8
2. Romagnani P., Gnone G., Guzzi F., Negrini S., Guastalla A., Annunziato F., et al. The COVID-19 infection: lessons from the Italian experience. *J. Public Health Policy.* 2020; 41(3): 238-44. DOI: http://doi.org/10.1057/s41271-020-00229-y
3. Sebastiani G., Massa M., Riboli E. Covid-19 epidemic in Italy: evolution, projections and impact of government measures. *Eur. J. Epidemiol.* 2020; 35(4): 341-5. DOI: http://doi.org/10.1007/s10654-020-00631-6
4. Rothe C., Schunk M., Sothmann P., Bretzel G., Froeschl G., Wallrauch C., et al. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. *N. Engl. J. Med.* 2020; 382(10): 970-1. DOI: http://doi.org/10.1056/NEJMc200146
5. Holshue M.L., DeBolt C., Lindquist S., Lofy K.H., Wiesman J., Bruce H., et al. First case of 2019 novel coronavirus in the United States. *N. Engl. J. Med.* 2020; 382(10): 929-36. DOI: http://doi.org/10.1056/NEJMoa2001191
6. WHO. Coronavirus disease 2019 (COVID-19) Situation Report – 51. Available at: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf
7. Беляков В.Д., Дегтярев А.А., Иванников Ю.Г. *Качество и эффективность противоэпидемических мероприятий.* Л.: Медицина; 1981.
8. Акимкин В.Г., Кузин С.Н., Шипулина О.Ю., Яцышина С.Б., Тиванова Е.В., Каленская А.В. и др. Эпидемиологическое значение определения РНК SARS-CoV-2 среди различных групп населения Москвы и Московской области в период эпидемии COVID-19. *Журнал микробиологии, эпидемиологии и иммунобиологии.* 2020; 97(3): 197-201. DOI: http://doi.org/10.36233/0372-9311-2020-97-3-197-201
9. Lauer S.A., Grantz K.H., Bi Q., Jones F.K., Zheng Q., Meredith H.R., et al. The incubation period of coronavirus disease 2019 (Covid-19) from publicly reported confirmed cases: estimation and application. *Ann. Intern. Med.* 2020; 172(9): 577-82. DOI: http://doi.org/10.7326/M20-0504
10. Backer J.A., Klinkenberg D., Wallinga J. Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travelers from Wuhan, China, 20–28 January 2020. *Euro Surveill.* 2020; 25(5) : 2000062. DOI: http://doi.org/10.2807/1560-7917.ES.2020.25.5.2000062
11. Liu T., Hu J., Kang M., Lin L., Zhong H., Xiao J., et al. Transmission dynamics of 2019 novel coronavirus (2019-nCoV). *J. Med. Virol.* 2020; 92(5): 501-11. DOI: http://doi.org/10.1101/2020.01.25.919787
12. Read J.M., Bridgen J.R.E., Cummings D.A.T., Ho A., Jewell C.P. Novel coronavirus 2019-nCoV: early estimation of epidemiological parameters and epidemic predictions. *medRxiv.* 2020. DOI: http://doi.org/10.1101/2020.01.23.20018549
13. Riou J., Althaus C.L. Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV), December 2019 to January 2020. *Euro Surveill.* 2020; 25(4): 2000058. DOI: http://doi.org/10.2807/1560-7917.ES.2020.25.4.2000058.
14. Shen M., Peng Z., Xiao Y., Zhang L. Modelling the epidemic trend of the 2019 novel coronavirus outbreak in China. *bioRxiv.* 2020. DOI: http://doi.org/10.1101/2020.01.23.916726

15. Wu J.T., Leung K., Leung G.M. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. *Lancet.* 2020; 395(10225): 689-97. DOI: http://doi.org/10.1016/S0140-6736(20)30260-9
16. Randolph H.E., Barreiro L.B. Herd Immunity: Understanding COVID-19. *Immunity.* 2020; 52(5): 737-41. DOI: http://doi.org/10.1016/j.immuni.2020.04.012
17. Verity R., Okell L.C., Dorigatti I., Winskill P., Whittaker C., Imai N., et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. *Lancet Infect. Dis.* 2020; 20(6): 669-77. DOI: http://doi.org/10.1016/S1473
18. Wu J.T., Leung K., Bushman M., Kishore N., Niehus R., de Salazar P.M., et al. Estimating clinical severity of COVID-19 from the transmission dynamics in Wuhan, China. *Nat. Med.* 2020; 26(4): 506-10. DOI: http://doi.org/10.1038/s41591-020-0822-7-3099(20)30243-7
19. Puca E., Čivljak R., Arapović J., Popescu C., Christova I., Raka L., et al. Short epidemiological overview of the current situation on Covid-19 pandemic in Southeast European (SEE) countries. *J. Infect. Dev. Ctries.* 2020; 14(5): 433-7. DOI: http://doi.org/10.3855/jidc.12814
20. Abdollahi E., Champredon D., Langley J.M., Galvani A.P., Moghadas S.M. Temporal estimates of case-fatality rate for COVID-19 outbreaks in Canada and the United States. *CMAJ.* 2020; 192(25): E666-70. DOI: http://doi.org/10.1503/cmaj.200711
21. Xu S., Li Y. Beware of the second wave of COVID-19. *Lancet.* 2020; 395(10233): 1321-2. DOI: http://doi.org/10.1016/S0140-6736(20)30845-X
22. de Brouwer R., van Veldhuisen D.J., de Boer R.A. Surviving the first COVID-19 wave and learning lessons for the second. *Eur. J. Heart Fail.* 2020; 22(6): 975-7. DOI: http://doi.org/10.1002/ejhf.1938
23. Vogel L. Is Canada ready for the second wave of COVID-19? *CMAJ.* 2020; 192(24): E664-5. DOI: http://doi.org/10.1503/cmaj.1095875
24. Ceylan Z. Estimation of COVID-19 prevalence in Italy, Spain, and France. *Sci. Total Environ.* 2020; 729: 138817. DOI: http://doi.org/10.1016/j.scitotenv.2020.138817
25. Li Q., Guan X., Wu P., Wang X., Zhou L., Tong Y., et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N. Engl. J. Med.* 2020; 382(13): 1199-207. DOI: http://doi.org/10.1056/NEJMoa2001316
26. Chatterjee A., Gerdes M.W., Martinez S.G. Statistical explorations and univariate timeseries analysis on COVID-19 datasets to understand the trend of disease spreading and death. *Sensors (Basel).* 2020; 20(11): 3089. DOI: http://doi.org/10.3390/s20113089
27. Abdollahi E., Champredon D., Langley J.M., Galvani A.P., Moghadas S.M. Temporal estimates of case-fatality rate for COVID-19 outbreaks in Canada and the United States. *CMAJ.* 2020; 192(25): E666-70. DOI: http://doi.org/10.1503/cmaj.200711
28. Львов Д.К., Альховский С.В. Истоки пандемии COVID-19: экология и генетика коронавирусов (Betacoronavirus: Coronaviridae) SARS-CoV, SARS-CoV-2 (подрод Sarbecovirus), MERS-CoV (подрод Merbecovirus). *Вопросы вирусологии.* 2020; 65(2): 62-70. DOI: http://doi.org/10.36233/0507-4088-2020-65-2-62-70