ORIGINAL RESEARCHES

Preliminary Clinical and Epidemiological Analysis of the First 1,000 Pediatric COVID-19 Cases in Moscow Region

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Rationale. The novel coronavirus infection caused by SARS-CoV-2 (COVID-19) continues to spread worldwide, though the epidemiological situation varies across countries. It is of interest to estimate the pediatric incidence in a separate constituent entity of the Russian Federation, Moscow Region (MR) closely connected with Moscow (accounting for the highest number of COVID-19 cases in Russia). Assessment of the epidemiological data is interesting due to the late onset of the epidemic outbreak, the preventive lockdown imposed during the early stages, and extensive testing of all the identified contacts.
Purpose of the study: Assessment of the pediatric incidence of COVID-19, including identification of its main clinical and epidemiological characteristics, based on the monitoring data for the current situation in MR.
Materials and methods. A retrospective analysis of all pediatric cases of laboratory-confirmed COVID-19 in MR (1,047 children of all ages) was performed. The time span covered the data of the daily monitoring of the epidemiological situation from the beginning of reporting (53 days in total). The information was obtained from the database of the Rospotrebnadzor Territorial Administration of MR and collected in compliance with the regulations on Daily Monitoring of Children with Coronavirus Infection, Management Section, State Information System, MR.
Results. The pediatric cases of COVID-19 accounted for 6.3% (95% CI[1] 5.9–6.7) of all the cases reported by 6/5/2020 (16,590); the total infection rate of the pediatric population in the region was 0.07% (0.06–0.09). The basic reproduction number ranged from 4.8 (during the two-week exponential growth phase) to 2.7 (during the later period characterized by a slowdown in the incidence rate) and averaged 3.8 (3.0–4.57). The clustering rate of COVID-19 among children was high, reaching 82.8% (79.7–85.6) with a small average number of cases detected in the cluster — 1.21 (1.16–1.26). Asymptomatic COVID-19 cases prevailed significantly, amounting to 62.2% (59.2–65.1), including 73.1% in newborns; severe cases accounted for 0.38% (0.35–0.41) and hospitalized cases totaled 12.0 (10.1–14.2). No death cases were reported. The mean age of the diseased and infected was 8 [4; 13] years old. Boys prevailed insignificantly (53.2%).
Conclusion. There is a distinct stage-by-stage development of the epidemic situation among children in MR. In the pediatric population, COVID-19 was generally acquired from a secondary household transmission within family clusters. Early preventive measures and extensive testing helped to reduce the period of exponential growth and, therefore, to avoid large clusters of infection. In addition, 17.2% of the COVID-19 clusters were identified as those where the child was the first to become sick. In the future, it is necessary to practice distancing and provide effective isolation of diseased children and adults, since the high rate of incidence in children can lag behind the incidence rate in adults.

Keywords: *children; coronavirus infection; SARS-CoV-2; COVID-19 epidemiology; epidemiological analysis.*

Acknowledgments. The study had no sponsorship.

Conflict of interest. The author declares no apparent or potential conflicts of interest related to the publication of this article.

For citation: Meskina E.R. Preliminary clinical and epidemiological analysis of the first 1,000 pediatric COVID-19 cases in Moscow Region. *Journal of microbiology, epidemiology and immunobiology = Zhurnal mikrobiologii, èpidemiologii i immunobiologii.* 2020; 97(3): 202–215.
DOI: https://doi.org/10.36233/0372-9311-2020-97-3-2

Received 20 May 2020
Accepted 25 May 2020

Предварительный клинико-эпидемиологический анализ первых 1000 случаев COVID-19 у детей в Московской области

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[1] Hereinafter parentheses contain a 95% confidence interval.

Актуальность. Новая коронавирусная инфекция, вызванная SARS-CoV-2 (COVID-19), продолжает распространяться по миру, однако эпидемиологическая ситуация отличается в разных странах. Представляет интерес оценить педиатрическую заболеваемость в отдельном субъекте России — Московской области (МО), тесно взаимосвязанной с Москвой (где зарегистрировано максимальное количество случаев COVID-19 в России). Оценка эпидемиологических данных интересна в связи с поздним началом эпидемического подъема, внедрением на ранних этапах превентивного локдауна, широким тестированием всех выявленных контактных лиц.

Цель работы — оценить педиатрическую заболеваемость COVID-19 с определением ее ведущих клинико-эпидемиологических характеристик на материалах официального мониторинга за текущей ситуацией в МО.

Материалы и методы. Проведен ретроспективный анализ всех педиатрических случаев лабораторно подтвержденной COVID-19 в МО (1047 детей всех возрастов) с момента начала регистрации в порядке ежедневного мониторинга за эпидемиологической ситуацией (суммарно в течение 53 дней). Информация извлечена из базы данных Территориального управления Роспотребнадзора МО и собрана в рамках свода по форме «Ежедневный мониторинг детей с коронавирусной инфекцией», приложение ГАС «Управление» МО.

Результаты. Доля педиатрических случаев COVID-19 среди всех зарегистрированных на 06.05.2020 (16 590) составила 6,3% (95% ДИ 5,9–6,7), общая инфицированность педиатрической популяции субъекта — 0,07% (0,06–0,09). Средний индекс репродукции колебался в пределах от 4,8 (на этапе двухнедельного экспоненциального роста) до 2,7 (в последующем периоде более медленного прироста заболеваемости) и составил в среднем 3,8 (3,0–4,57). Коэффициент очаговости COVID-19 среди детей был высоким — 82,8% (79,7–85,6) с небольшим средним числом выявленных случаев в очаге — 1,21 (1,16–1,26). Значительно преобладали бессимптомные формы COVID-19 — 62,2% (59,2–65,1), в том числе у новорожденных — 73,1%, с низкой частотой тяжелых форм — 0,38% (0,35–0,41) и низким индексом госпитализации — 12,0 (10,1–14,2). Летальность отсутствовала. Средний возраст заболевших и инфицированных — 8 [4; 13] лет. Мальчики преобладали незначительно (53,2%).

Выводы. Прослеживается отчетливая этапность развития эпидемической ситуации среди детей в МО. Передача COVID-19 в детской популяции осуществлялась главным образом в семейных очагах с вторичным распространением. Благодаря ранним превентивным мерам и широкому тестированию период экспоненциального роста был коротким, удалось избежать крупных очагов инфекции, дополнительно выявлено 17,2% очагов COVID-19, в которых первым заболевшим был ребенок. Необходимо в дальнейшем соблюдать дистанцирование и обеспечивать эффективную изоляцию заболевших детей и взрослых, поскольку вероятность высокой педиатрической заболеваемости может запаздывать по сравнению со взрослыми.

Ключевые слова: *дети; коронавирусная инфекция; SARS-CoV-2; эпидемиология COVID-19; эпидемиологический анализ.*

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Для цитирования: Мескина Е.Р. Предварительный клинико-эпидемиологический анализ первых 1000 случаев COVID-19 у детей в Московской области. *Журнал микробиологии, эпидемиологии и иммунобиологии*. 2020; 97(3): 202–215.
DOI: https://doi.org/10.36233/0372-9311-2020-97-3-2

Поступила 20.05.2020
Принята в печать 25.05.2020

Rationale

The pandemic caused by a novel coronavirus associated with severe acute respiratory syndrome (SARS-CoV-2) is rapidly spreading, with many countries reporting exponential growth. Over a little more than four months, the pandemic overwhelmed the most resilient health systems; it is exacting a huge toll on individuals, communities and societies across the world by bringing social and economic life to a near stop[2]. At the same time, it triggered an unprecedented increase in the number of scientific studies addressing various aspects of the problem, from studies on the SARS-CoV-2 genome, epidemiological and clinical characteristics of the disease (COVID-19) to development of effective therapeutics and vaccines. New scientific information becomes accessible extremely rapidly, thus dynamically changing the response to the epidemiological situation and contributing to upgrading measures aimed at suppression of the SARS-CoV-2 spread.

The epidemiological curves demonstrating the COVID-19 dynamics in different countries can capture geographical differences[3] caused by a number of factors (external and internal transport communication, the size of a country and the density of population, geographical locations, the type and the swiftness of adopting critical

[2] WHO. COVID-19 Strategy Update. 14/4/2020. URL: https://www.who.int/ru/emergencies/diseases/novel-coronavirus-2019/strategies-plans-and-operations (reference date 20/5/2020).

[3] Geographic distribution of COVID-19. European Centre for Disease Prevention and Control. URL: https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases (reference date 20/5/2020).

DOI: https://doi.org/10.36233/0372-9311-2020-97-3-2

restrictive measures, use of personal protective equipment and the level of social responsibility of population). Furthermore, the reported number of COVID-19 cases directly depends on the testing criteria specified by the national pandemic response programs. In Russia, testing is extensive and is performed not only on individuals who came recently from other countries and on patients displaying symptoms that may be associated with COVID-19, but also on exposed individuals in disease clusters, healthcare workers, people older than 65 years old, children and adults from boarding facilities, if any respiratory symptoms are present[4]. This approach enhances the accuracy of the assessment of the epidemiological situation, which can be different from those reported by other countries due to a wide-scale registration of mild and asymptomatic forms of infection.

At present, SARS-CoV-2 is developing outside Southeast Asia that was first to hit by the pandemic. Region-specific European, North American and Asian strains co-exist [1]. The virus is replicated inside the host and evolves in different countries during epidemic transmission; the observed mutation frequency, strain variability, and genetic selection produce a complex clinical scenario [1–3]. Some scholars believe that at the moment there are three main genomic variants that can modulate the clinical presentation and epidemiology of the disease [4]. The assessment of the epidemiological status of Russia, which was hit by the spread of SARS-CoV-2 later than Europe or the United States and which imposed a preventive lockdown at an early stage, can significantly contribute to the global profile of the pandemic.

Epidemiological studies on COVID-19 incidence in the pediatric population are of high importance, as the lower susceptibility of children as compared to adults is one of the distinctive and unclear features of the SARS-CoV-2 pandemic. The systematic reviews of J.F. Ludvigsson (45 publications) [5] and the "latest" work by I. Liguoro et al. (65 publications) [6] clearly demonstrated the lower frequency of cases, the milder form of the disease and extremely rare fatal outcomes. In this way, COVID-19 is markedly different from other respiratory infections, including infections caused by other coronaviruses. The discussion of causes of these phenomena is based on assumptions. Some of them are as follows: Children have a qualitatively different immune response to SARS-CoV-2 as compared to adults; competition with other respiratory viruses; differences in the expression of the angiotensin-converting enzyme-2 receptor required for binding SARS-Cov2 and infection; pharmaceuticals used by adults and blocking angiotensin receptors in treatment of hypertension [7, 8]. It should be noted that the observations generally cover a small number of pediatric cases. The most noteworthy work by Y. Dong et al. [9] covered more than 2,135 cases; most of them had disease symptoms, though only 728 of them had laboratory-confirmed COVID-19, while 1,407 patients were suspect cases.

Thus, results of the clinical and epidemiological analysis of large cohorts of children and extensive testing for COVID-19 will be able to give better insights into children incidence. There is another factor enhancing the significance of such analysis. Moscow Region (MR) is an individual constituent entity of the Russian Federation; it borders Moscow that reported the largest number of COVID-19 cases in Russia[5]. MR ranks second in Russia in total population, yielding only to Moscow, though having much lower density of population. Close economic, social and cultural ties as well as the integrated transportation system suggest risks of spreading the novel coronavirus infection in the region.

The above said defines the significance of the performed study.

The purpose of the study is to assess pediatric incidence of COVID-19 and identify its main clinical and epidemiological characteristics based on the data obtained from the official monitoring of the current situation in MR.

Materials and methods

A retrospective analysis was performed for all the pediatric cases of confirmed COVID-19 in MR; the analyzed data covered the time span from the beginning of the registration and captured the daily monitored (from 2/4/2020) epidemiological situation as of 6/5/2020. The information about patients (age, sex, residence, reasons for examination and its date, clinical form of the disease) was retrieved from the database of the Rospotrebnadzor Territorial Administration of MR. The data on the disease severity, duration of hospitalization or outpatient observation were collected and consolidated in compliance with the regulations on Daily Monitoring of Children with Coronavirus Infection, Management Section of the State Information System, MR. The cases were recorded on the date of their reporting (the date when the data on the positive test for COVID-19 were received).

To diagnose COVID-19 the MR accredited laboratories used different test systems registered in Russia: PCR testing with hybridization-fluorescence detection by using the Vector-PCRrv-2019-nCoV-RG test system (Vector State Research Center of Virology and Biotechnology, Novosibirsk, Koltsovo), PCR testing

[4] Methodological Guidelines MR 3.1.0170-20. Epidemiology and Prevention of COVID-19 (read with MR 3.1.0175-20, Amendment No. 1 in MR 3.1.0170-20, Epidemiology and Prevention of COVID-19, approved by Rospotrebnadzor on 30/4/2020). URL: https://www.rospotrebnadzor.ru/upload/iblock/070/metod_recomend_3.1.0170_20_v_1.pdf (reference date 20/5/2020).

[5] Official website of the Ministry of Health, COVID-19 in Russia. URL: https://covid19.rosminzdrav.ru (reference date 20.05.2020).

DOI: https://doi.org/10.36233/0372-9311-2020-97-3-2

with hybridization-fluorescence detection by using the Vector-OneStep PRC-CoV-RG» (Vector State Research Center of Virology and Biotechnology, Novosibirsk, Koltsovo), the RealBest RNA SARS-CoV-2 assay kit based on real-time RT-PCR (Vector-Best JSC), the real-time RT-PCR based SARS-CoV-2/SARS-CoV test kit (DNA-Technology LLC, Moscow), PCR testing with hybridization-fluorescence detection by using the AmpliSens® Cov-Bat-FL (Central Research Institute of Epidemiology, Moscow). During the first 3 weeks, positive and equivocal biological samples were retested at the Vector State Research Center of Virology and Biotechnology in Novosibirsk.

No ethical review was performed, as the information about the patients was provided in a standard referral for the COVID-19 test and was required for monitoring of the epidemiological situation for taking organizational measures (if applicable).

The statistical processing of the data was performed by using a Statistica 6.0 software package (Stat Soft Inc., USA). Qualitative variables are given as the mean value ± standard error (σ) or as a median value (Me) of the lower and upper quartiles. Discrete variables are given as an event rate expressed as a percentage (%) or percent mille ($^0/_{0000}$) of the total number of patients. The χ^2 criterion was used to compare two groups by their qualitative variables; several groups were compared at the same time by using the χ^2 criterion for random tables. The differences at $p < 0.05$ were deemed statistically significant. If any statistical difference was found, the further pairwise comparison of the groups was performed by using Yates' correction. To ensure high-quality estimation of the difference value, the 95% confidence interval for mean values and proportions as well as odds ratios were calculated.

The rates characterizing an epidemic process were analyzed. The reproduction rate (R, the basic reproduction number) of an infection [10] was calculated by assuming that the duration of a COVID-19 incubation and contagious period is approximately 4 days [11]. As the prerequisite, it was agreed that the infection in the population was maintained, if R > 1, otherwise the average number of secondary cases of infection, which are caused by one infected individual in the population of susceptible residents, must be more than 1. The force of infection (λ) was seen as an infection incidence for the susceptibles per unit time [12]. The infection rate for the pediatric population (%) was calculated as the number of confirmed COVID-19 cases per the total number of children under 18 in MR; the hospitalization rate was calculated as a proportion (%) of the number of hospitalized cases in the total number of the detected cases. The clustering was estimated as the ratio (%) of the number of detected cases to the number of infection clusters; the clustering rate represented a proportion (%) of clusters with secondary transmission as compared to the total number of clusters; the clustering index was calculated as the average number of cases in one cluster [13]. The clustering was estimated only among children. The entire children population was deemed susceptible, considering that the infection caused by SARS-CoV-2 is novel for the human population.

Results

By 6/5/2020, MR had reported 1,047 pediatric cases of COVID-19 varying in severity, 6.3% of the total incidence (16,590 cases[6], **Table 1**). The cumulative infection rate of the children population was rather low during that period (Table 1).

The first pediatric cases of COVID-19 were detected in the middle of March 2020 in 3 teenagers who visited Europe.

We can single out three stages in the epidemic outbreak, which are characterized by clearly defined time intervals:

- *the first stage* — from onset to 2/4/2020, when only a few cases (11 people) were reported among those who visited Europe and the United Arab Emirates (8 cases, including a 9-month-old baby) or who were in close contact with someone who came from another country (3 people);
- *the second stage* — 2 weeks of exponential growth in case incidence (R = 3.85–4.77) when the number of cases doubled on average within 2–3 days;
- *the third stage* — a longer period that did not end by the time of the study and was characterized by a slowdown in the intensity of infection; the absolute increase in the infected cases is expressed by a broken curve (R = 2.92–2.69; **Fig. 1**).

Within the review period, the infection reproduction rate ranged from 4.77 to 2.69, and the basic reproduction number was 3.8 (95% CI 3.0–4.57). Rare cases COVID-19 associated with travel exposures and close contacts with travelers were reported before 15/4/2020; however, starting from 2/4/2020 there was an increase in disease cases among children due to a secondary spread of infection in family clusters, accounting for most cases in the pediatric population of MR.

At the time-point of the conducted analysis, COVID-19 cases were reported in 55 (82.1%) urban and municipal districts of MR. However, 43.2% of the total incidence among children was contributed by 8 (11.9%) territorial units surrounding Moscow.

The average age of the infected was 8 [4; 13] years old; the age structure showed that children older than 3 years old accounted for most cases. The age composition of those included in the study was as follows: children of 1 year of age — 7.3% (76), including new-

[6] The official website of the Ministry of Health, COVID-19 in Russia. URL: https://covid19.rosminzdrav.ru (reference date 20/5/2020).

JOURNAL OF MICROBIOLOGY, EPIDEMIOLOGY AND IMMUNOBIOLOGY. 2020; 97(3)
DOI: https://doi.org/10.36233/0372-9311-2020-97-3-2

Table 1. The main epidemiological criteria for the epidemic situation of COVID-19 in the pediatric population of Moscow Region by May 6, 2020

Indicator	Indicator value	95% CI
The proportion of pediatric cases in the total number of reported cases, %	6,3	5,9–6,7
Pediatric infection, %	0,07	0,06–0,09
Incidence in children, April, 2020, $^{0}/_{0000}$	52,0	50,9–53,1
Reproduction number, *M* ± σ	3,8 ± 0,91	3,0–4,6
Clustering, %	121,2	97,7–149,2
Focal rate, %	82,8	79,7–85,6
Clustering index, *M* ± σ	1,21 ± 0,61	1,16–1,26
Mean age, Me [lower; upper quartile]	8 [4; 13]	8,13–8,77
Hospitalization rate, %	12,0	10,1–14,2
Severe forms, %	0,38	0,35–0,41
Asymptomatic forms, %	62,2	59,2–65,1
Pneumonia, %	11,7	9,8–13,8
Upper respiratory tract infection, %	26,1	23,4–28,9
Mortality	0	–

borns — 2.5% (26); infants — 10.3% (108); 3–10 year-olds — 38.0% (398), adolescents — 44.4% (465). Except for one baby who was with his parents on vacation in the UAE, new cases of COVID-19 among children under one year of age were reported by the end of the 4th week of the monitoring, while the first cases among newborns were reported even later, by the end of the 5th week (**Fig. 2**). As can be seen in Fig. 2, the incidence among infants and newborns lagged far behind the incidence among children older than 3 years old, the gap increased with the further developing of the epidemic situation, though the age structure of COVID-19 remained statistically unchanged during the monitoring (Fig. 2; **Table 2**). In the gender distribution, the per-

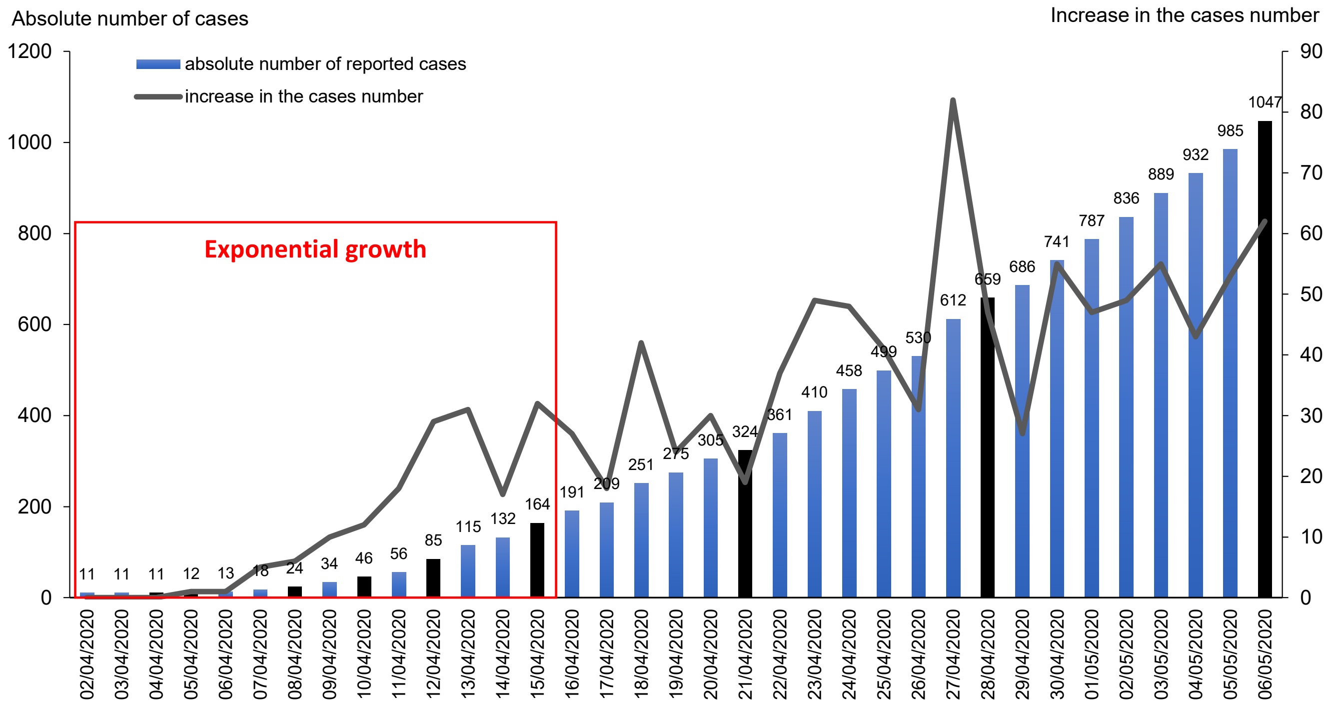

Fig. 1. The cumulative total of the absolute number and increase in COVID-19 cases in the pediatric population of Moscow Region.
Black bars indicate the doubling in the number of COVID-19 cases.

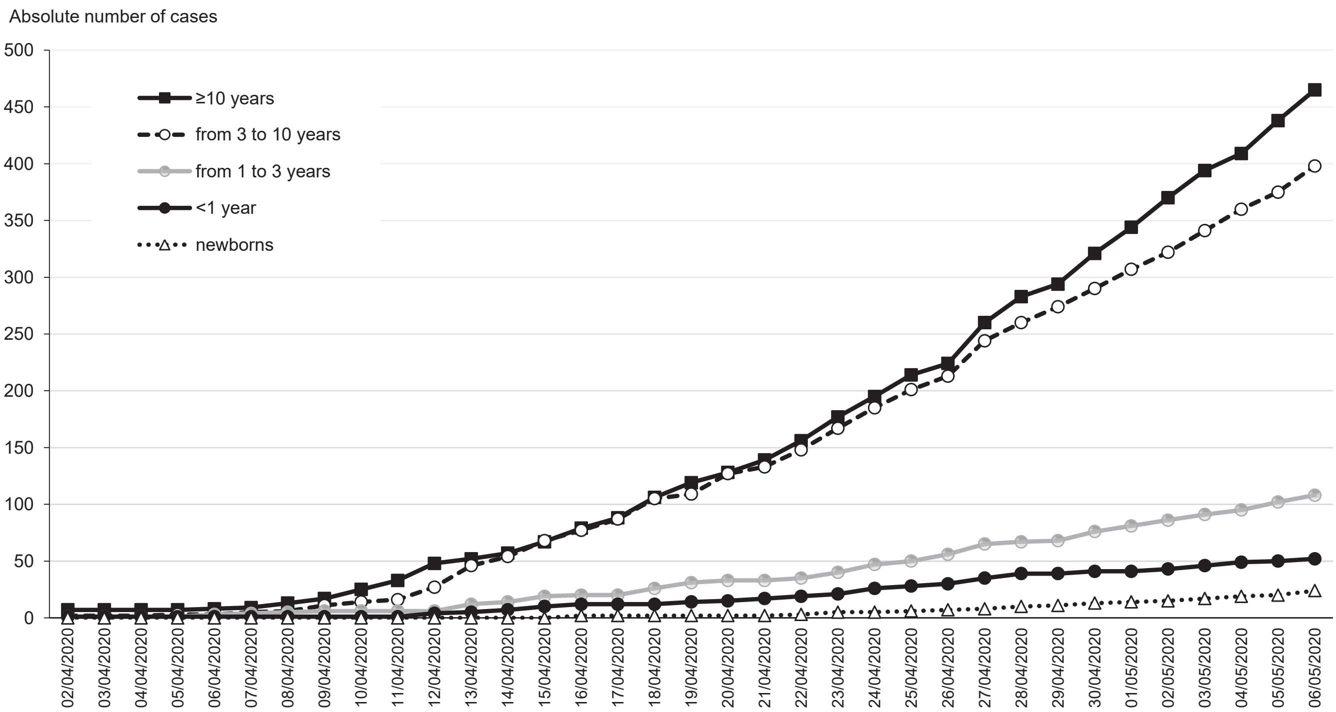

Fig. 2. Cumulative result of the absolute number of COVID-19 cases among children of different age in Moscow Region by the date of reporting.

centage of boys was insignificantly higher, amounting to 53.2% (girls accounted for 46.8%).

The epidemiological history was available for the analysis in 808 children. It shows a clear clustering nature of COVID-19 (**Table 3**). The maximum number of COVID-19 cases were detected in family clusters — 665 (82.3%). Other exposures were observed much more rarely: 12 children (1.5%) visited other countries, 3 children (0.4%) had a close contact with travelers, 4 children (0.5%) were exposed at healthcare facilities, 11 children (1.4%) had close contacts with other people. 42 children (5.2%) were examined due to the presence of symptoms of respiratory infection, and 71 children (8.8%) were examined for pneumonia.

As can be seen in Tables 1 and 3, clusters of COVID-19 transmission prevailed in MR during the development of the epidemic outbreak, though the clustering index was low. Among the detected clusters, there were those with one case of children infection, which can be explained by the cluster sizes. In multi-child families, all the children were often infected; the largest number of the diseased was 8 people. There were no large clusters with multiple secondary infections in children healthcare facilities and other organizations as well as in day-and-night care facilities. The extensive examination of children displaying symptoms of acute respiratory infection and pneumonia, which did not exclude the COVID-19 infection, made it possible to detect another 17.2% of infection clusters.

In clinical forms of COVID-19, asymptomatic cases prevailed significantly (62.2%; **Table 4**). The incidence of pneumonia was low — 11.7%. Only 4 teenagers older than 12 years old were diagnosed with a severe form of pneumonia; only 1 patient needed invasive mechanical ventilation. In 2 patients, the acute respiratory distress syndrome of Type I was accompanied

Table 2. Force (λ) and COVID-19 age structure during the four week increase in pediatric incidence in Moscow Region

Monitoring week (dates)	Force of infection (λ), $^{0}/_{0000}$	Number of cases per week	Age structure of COVID-19, abs (%)				*p* (age structure)
			<1 year	from 1 to 3 years old	from 3 to 10 years old	≥10 years old	
06.04–12.04.2020	5,71	74	4 (5,4)	4 (5,4)	25 (33,8)	41 (55,1)	>0,05 df = 9
13.04–19.04.2020	18,46	190	12 (6,3)	25 (13,2)	82 (43,2)	71 (37,4)	
20.04–26.04.2020	35,58	255	21 (8,2)	25 (9,8)	104 (40,8)	105 (41,2)	
27.04–03.05.2020	59,69	359	26 (7,2)	35 (9,7)	128 (35,7)	170 (47,4)	

DOI: https://doi.org/10.36233/0372-9311-2020-97-3-2

Table 3. COVID-19 clusters in the pediatric population of Moscow Region

COVID-19 clusters	Number of clusters		Number of children	
	abs	%	abs	%
Total clusters	657	100	796	100
Single-case clusters (the child is the only case in the cluster)	113	17,3	113	14,2
Clusters with the infection transmission, including	544	83,3	683	85,8
the only sick child in the cluster	447	68,5	447	56,2
2 or more sick children in the cluster	97	14,8	236	29,6

Note. The presented data were analyzed in children with an available epidemiological history (*n* = 808).

Table 4. Force (λ) and structure of the COVID-19 clinical forms during the four week increase in pediatric incidence in Moscow Region

Monitoring week (dates)	Force of infection (λ), $^0/_{0000}$	Number of cases per week	Clinical structure of COVID-19, abs (%)			*p* (clinical structure)
			pneumonia	upper respiratory tract infection	asymptomatic forms	
06.04–12.04.2020	5,71	74	6 (8,1)	15 (20,3)	53 (71,6)	<0,01 df = 6
13.04–19.04.2020	18,46	190	16 (8,4)	44 (23,2)	130 (68,4)	
20.04–26.04.2020	35,58	255	24 (9,4)	61 (23,9)	170 (66,7)	
27.04–03.05.2020	59,69	359	42 (11,7)	125 (34,8)	192 (53,5)	

by diffuse alveolar damage in the lungs (>75% lung involvement on CT imaging), thus being the reason for diagnosis of a severe form of the disease. Most (73.1%) of the newborns had a confirmed asymptomatic form of COVID-19; 23.1% had a mild form; 1 newborn (3.8%) was diagnosed with pneumonia.

The dynamics of the epidemic situation shows a relatively proportional increase in the number of clinical forms (**Fig. 3**), while the proportion of asymptomatic forms, after remaining stable during 3 weeks, statistically decreased during the 4th and 5th weeks of the monitoring as compared to the previous period ($p = 0.0014$; Table 4), and the proportion of mild forms increased ($p = 0,005$). The proportion of pneumonia cases remained statistically unchanged. Fatal outcomes were absent.

The age and gender structure of COVID-19 clinical forms is shown in **Table 5**. Half of the pneumonia patients were older than 5 years old ($p = 0.007$); mild and asymptomatic forms were most common in children older than 3 years old ($p = 0.004$). The rate of clinical cases in newborns and infants as well as the gender structure of COVID-19 clinical forms did not show any differences (Table 5). The risk of developing

Table 5. Age and gender structure of COVID-19 clinical forms in children in Moscow Region, abs (%)

Parameter	Pneumonia (*n* = 123)	Upper respiratory tract infection (*n* = 273)	Asymptomatic forms (*n* = 651)	*p* (clinical structure)
Age, years				<0,01 df=6
<1	11 (8,9)	23 (8,4)	42 (6,5)	
1–3	15 (12,2)	34 (12,4)	59 (9,1)	
3–10	30 (24,4)	113 (41,5)	255 (9,2)	
≥10	67 (54,5)	103 (41,5)	295 (45,3)	
Gender				
boys	62 (50,4)	153 (56,0)	342 (52,5)	>0,05 df = 2
girls	61 (49,5)	120 (44,0)	309 (47,5)	

DOI: https://doi.org/10.36233/0372-9311-2020-97-3-2

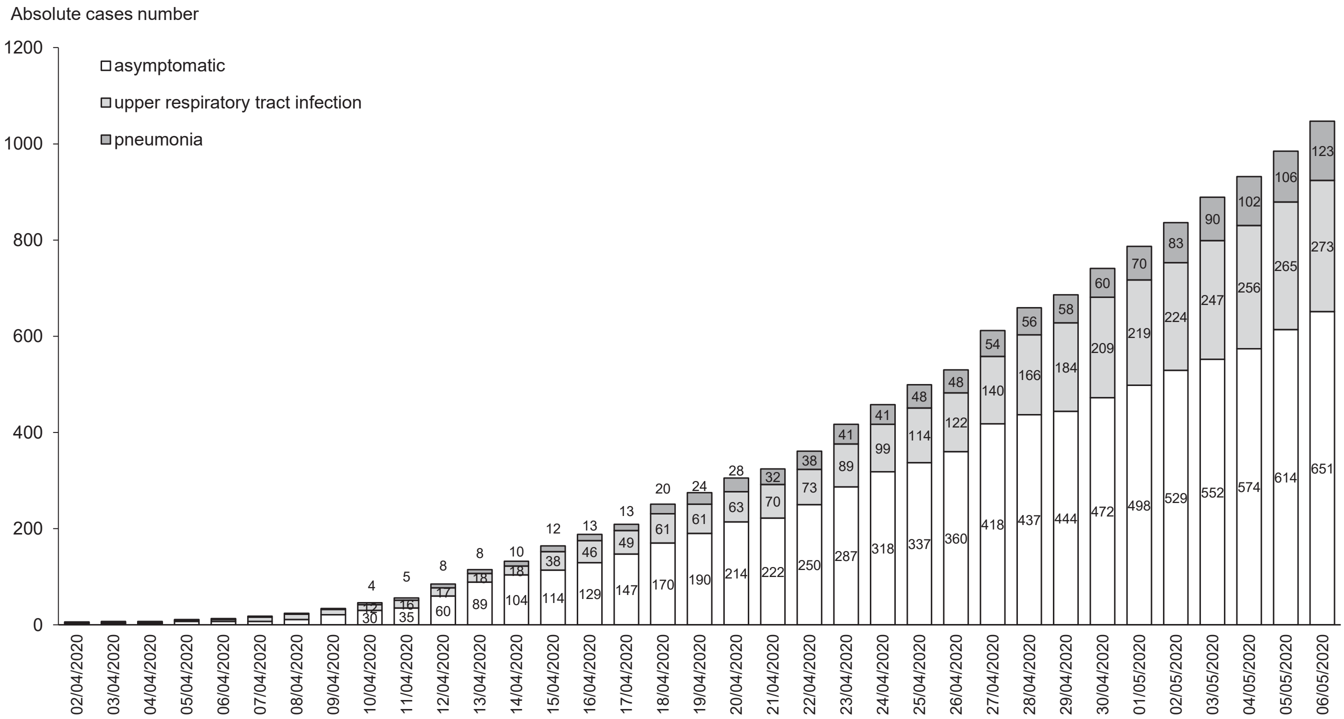

Fig. 3. The cumulative result of the absolute number of COVID-19 clinical forms in the pediatric population of Moscow Region by the date of reporting.

pneumonia in children older than 10 years old was as high as that one in children of another age (the odds ratio was 1.34; 95% CI 0.92–1.95).

Logical enough, infants accounted for most of the hospitalized patients ($p < 0.001$; Table 6), with girls prevailing ($p = 0.003$). Children with COVID-19 were hospitalized not only for clinical and epidemiological reasons, but also based on social grounds, when the whole family had to be hospitalized. The proportion of pneumonia cases among the hospitalized patients was substantial — 53 (42.1%) cases. At the same time, although outpatient children made up a considerably low proportion of pneumonia (7.9%), the absolute number of cases was also high (73 or 57.9% of the total cases).

Discussion

The emphasis should be put on the following key factors that may have affected the obtained results.

1. Moscow and MR are different entities having maximum population in Russia and closely interconnected. Many MR residents are employed in Moscow, while many Moscow citizens go regularly to MR to their country houses and allotments. The communication between these two territories is extremely close. Therefore, having started in Moscow, the COVID-19 epidemic outbreak started synchronously gathering pace. The MR territory hosts Moscow airports, which is also important, as the first COVID-19 cases were imported to MR from Europe and the Middle East.

Table 6. Age and gender structure of COVID-19 clinical forms in children in the Moscow Region, abs (%)

Parameter	Hospitalized (*n* = 126)	Outpatient (*n* = 921)	*p* (clinical structure)
Age, years			<0,001 df = 3
<1	17 (13,5)	59 (6,4)	
1–3	19 (15,1)	89 (9,7)	
3–10	32 (25,4)	366 (39,7)	
≥10	58 (46,0)	407 (44,2)	
Gender			
boys	56 (44,4)	501 (54,4)	0,036 df = 1
girls	70 (55,6)	420 (45,6)	

2. The epidemic increase in the incidence in Moscow and MR began later than in Southeast Asia, the Middle East, Europe and the United States, and, hypothetically, considering continuously evolving SARS-CoV-2, could have an impact on its scenario [1–3].

3. The Ordinance of the Chief Sanitary Inspector[7] and the Decree of the RF Government[8] were issued to organize and implement measures unprecedented in their scale and aimed at prevention of any spread of infection caused by SARS-CoV-2, including extensive examination of people who came from other countries, contact persons and other groups of population. The preventive lockdown was imposed in Moscow and MR on 28/3/2020, and the restrictive measures were uniform.

The biology of the virus, which is new for the human population, contributes significantly to the pattern of the epidemic process. The estimated median incubation period of COVID-19 is 5.4 days (4.1–7.0), the 95th percentile of distribution — 12.5 days (9.2–18.0) [14]. In children, the incubation period can last longer [15]. The mean time of infection transmission in clusters is slightly shorter — averaging 4.6 days (3.5–5.9) [11]. The peak of infection takes place before or during occurrence of symptoms in a patient; it turned out that 44–62% of the secondary COVID-19 cases were infected during the pre-symptom stage of the disease of the infection source [11, 16, 17].

Like clinically apparent cases, pauci-symptomatic and asymptomatic individuals shed a potentially infectious virus and, most likely, pose a threat generally 2.5 days before the beginning of the disease and during 5–11 days after being infected or after starting to manifest symptoms [18, 19]. Some data show that the peak viral load can be reached during the 2nd week from the onset of the disease [20]. It has been confirmed that the virus shedding can last for a long time (30 days and longer), depending on the patient's clinical condition [20]. At present, the viral RNA has been detected in children and adults, not only in nasal, deep throat swabs or sputum samples, but also in blood, urine and feces [19, 21, 22].

The above said demonstrates that the novel infection can be easily transmitted in a highly susceptible environment, including clusters with asymptomatic infection, the latter being especially important in pediatric practices, as children do not have sufficiently developed social skills. Among strong points of the conducted study is the evaluation of the results of extensive testing in clusters and demonstration of a highly realistic epidemiological situation. This study revealed a distinct stage-by-stage pattern of the epidemic process and the decrease in the incidence 2 weeks after strict restrictive measures had been adopted; the same findings were reported by China where the local outbreak spiraled into the pandemic. Note that the incidence among children continued to increase when the decrease in the total number of cases was reported [23].

For most of the respiratory infections, including influenza, the reproduction number ranges from 1 to 2 [24], thus being much lower than the number estimated for COVID-19 by using actual data and mathematical models. The initial estimates of the early dynamic of the outbreak in Wuhan (China) suggested the doubling in the time of infection during 6–7 days, with the basic reproduction number (R_0) ranging from 2.24 (1.96–2.55) to 3.58 (2.89–4.39) [14, 25, 26]. However, in real life, the time of doubling in the number of cases was 2.3–3.3 days at R_0 5.7 (3.8–8.9) [25], and the same was observed in Singapore and Korea [17, 27]. In European countries where control measures were aimed at localization of the infection spread, R_0 was much higher and reached 6.3 [28]; in contrast to the 1st and 2ns weeks, during the 3rd–5th week of the increase, the density of population played a significant role in the spread of infection [29]. The indirect evidence of the latter is the fact that 8 units of MR (11.9%) surrounding Moscow and characterized by the highest density of population accounted for 43.2% of the total incidence among children by the 8th week of the epidemic upsurge.

The estimation of the reproduction number demonstrated that COVID-19 develops in the pediatric population in conformity with the same laws. The beginning of the exponential spread (R = 3.8–4.8) coincided with the beginning of the secondary infection in family clusters; then, 2 weeks after the lockdown, the spread started slowing down (R = 2.6–2.9). Indeed, in China and Korea, a flatter curve was reached through rapid isolation of all the diseased, along with the using of advanced digital technologies to trace the maximum number of contacts at onset of the outbreak [30]. It should be noted that the performed estimation may need correction because of the significantly lower number of COVID-19 cases in the children population. Yet, the dynamics of the reported cases was very noticeable.

It can be assumed that it was the preventive lockdown that helped avoid large clusters with multiple secondary infections in children healthcare facilities and other organizations as well as in day-and-night care facilities. Mathematical modeling proves that the low level of changes in the behavior can lead to a large-scale SARS-CoV-2 transmission per capita [31, 32].

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7 The Ordinance of the Chief Sanitary Inspector, adopted on 31/1/2020, No. 3 On Additional Sanitary and Epidemiological (Preventive) Measures Aimed at Prevention of Importation and Spread of the Novel Coronavirus Infection Caused by 2019-nCoV. URL: https://www.rospotrebnadzor.ru/deyatelnost/epidemiological-surveillance/?ELEMENT_ID=13625 (reference date 21/5/2020).

8 The Decree of the RF Government, adopted on 16/3/2020, No. 635-r (revised on 15/5/2020) On Temporary Restrictions of Entry to the Russian Federation for Foreign Citizens and Stateless Persons, and Temporary Suspension of Issuing Visas and Invitations. URL: http://www.consultant.ru/document/cons_doc_LAW_347693 (reference date 21/5/2020).

DOI: https://doi.org/10.36233/0372-9311-2020-97-3-2

The analysis confirmed the distinct cluster pattern of COVID-19, which was mentioned previously [15, 33]. At the same time, the frequency of clusters with secondary transmission among children amounted to 83.3% at the low rate of infection (0.07%), which is significantly higher than the data reported earlier (11% at the much higher rate of infection among children – 7.4%) [33]. It can be explained by the active detection of cases, including all the possible contacts, as well as by testing not only the diseased, but also asymptomatic individuals. In addition, 17.2% of the clusters were detected; all of them had a child as the primary case, thus evidencing the necessity of tests if society tends to be socially irresponsible in its perception of the quarantine measures, especially taking into account that SARS-CoV-2 is a novel and highly contagious virus. The role of family clusters in the spread of infection is emphasized by the fact that nearly half of the patients were infected during the pre-symptom stage of index cases outside their household when the quarantine measure were put into effect [16].

On the whole, the analysis confirmed that children are less susceptible to COVID-19 than adults and that respiratory distress and fatal outcomes are rare for this disease [5, 6, 15]. The infection rate among the children population of MR was higher than the rate observed in Italy [34], and was approximately the same as the rate in the USA [35].

The frequency of pneumonia cases was low (11.7%), including pneumonia in newborns, thus being much lower than the levels reported by I. Liguoro et al. [6] — 29 and 48%, respectively. On the one hand, it may evidence a certain number of missed cases, as the described radiologic abnormalities were accidentally found in children with a mild form of the disease or even in asymptomatic cases [6]; on the other hand, it could result from extensive testing. The authors note that children are tested less frequently than adults. MR has the similar approach to examination of children and adults, and this approach is integral to data collection. Mild forms of COVID-19 in children can also be proved by the low rate of hospitalization and by a large proportion of mild forms in infants.

It should be pointed out that the last weeks of monitoring in MR demonstrated an increase in symptomatic forms of COVID-19. It may be assumed that at this time-point the above fact can evidence certain weakening of the control over the situation and should be taken into consideration in further practical work.

The performed analysis has some limitations due to differences in the sensitivity of several test systems used for diagnosis of COVID-19. Nevertheless, the first stages can be captured fairly accurately thanks to the repeat testing of samples at the reference center of Rospotrebnadzor of Russia. Undoubtedly, the pediatric estimates were affected by the infection and incidence rates in adults, while the general development of COVID-19 was not monitored. Nevertheless, we can assume that the trends were quite accurately identified and can represent the results of the preventive measures adopted in Russia and MR. Apparently, these measures delayed the beginning of the increase in COVID-19 incidence and slowed down its spread.

Conclusion

1. The analysis of 1,047 COVID-19 cases during the early imposed preventive lockdown and extensive testing demonstrated a distinct stage-by-stage pattern of the epidemic increase in the pediatric incidence of COVID-19. The period of exponential growth associated with secondary cases of infection in family clusters lasted 2 weeks and then slowed down, though the number of reported cases kept growing. The higher incidence rate among children was observed in the MR territorial units neighboring Moscow and characterized by a high density of population.
2. The basic reproduction number was 3.8 (3.0–4.57).
3. The clustering rate of COVID-19 among children was high and amounted to 82.8% (79.7–85.6), though the average number of the detected cases in clusters was quite low — 1.21 (1.16–1.26), being limited by the size of a family cluster.
4. The early measures aimed at prevention of the COVID-19 spread helped avoid large clusters with multiple secondary infections of children.
5. Asymptomatic forms of COVID-19 prevailed significantly, totaling 62.2% (59.2–65.1), including 73.1% in newborns; severe cases accounted only for 0.38% (0.35–0.41) and hospitalized cases accounted for 12.0 (10.1–14.2). No death cases were reported.
6. The mean age of the diseased and infected children was 8 [4; 13] years old. Boys prevailed insignificantly, accounting for 53.2%.
7. Taking into account the persistent high reproduction number and the likelihood of the increased infection rate among children amid the ongoing stabilization, it is important to maintain the measures aimed at localization of COVID-19. Extensive testing of children can increase the detectability of additional COVID-19 clusters, especially if society does not show high social responsibility in its perception of the quarantine measures.

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