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Short Communication

Adaptation of a Russian population to SARS-CoV-2: Asymptomatic course, comorbidities, mortality, and other respiratory viruses – A reply to Fear versus Data

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ABSTRACT

This study was conducted to assess the spread of SARS-CoV-2 in Russia and the adaptation of the population to the virus in March to June 2020. Two groups were investigated: 1) 12 082 individuals already proven positive for SARS-CoV-2 (clinical information was studied); 2) 7864+4458 individuals with suspected respiratory infections (polymerase chain reaction [PCR] tests and clinical information were studied). In the latter, SARS-CoV-2-positive individuals comprised 5.37% in March and 11.42% in June 2020. Several viral co-infections were observed for SARS-CoV-2. Rhinoviruses accounted for the largest proportion of co-infections (7.91% of samples were SARS-CoV-2-positive); followed by respiratory syncytial virus (7.03%); adenoviruses (4.84%); metapneumoviruses (3.29%); parainfluenza viruses (2.42%); enterovirus D68 (1.10%) and other viruses (entero-, echo-, parecho-) (<1%). Average SARS-CoV-2 case fatality rate in the group of 12 537 individuals was determined to be 0.6% (in contrast to official Russian government statistics of 1.5% mortality). This rate is within the range of mortality caused by other common seasonal respiratory viruses (0.01-2.21% in Russia in 2012 to 2020). Most fatalities occurred in individuals with comorbidities, as for other respiratory viruses. The proportion of SARS-CoV-2 asymptomatic carriers was 56.68% in March and 70.67% in June 2020. This new pathogen presents a substantial risk to human beings as it was not contained at the start of its outbreak in Wuhan and spread worldwide. However, surveillance, prevention and treatment must be strictly evidence-based and not dictated by fear.

1. Introduction

1.1. Background

In their paper "SARS-CoV-2: fear versus data", Roussel et al. [1] noted that "systematic studies of other coronaviruses (but not yet for SARS-CoV-2) have found that the percentage of asymptomatic carriers is equal to or even higher than the percentage of symptomatic patients. The same data for SARS-CoV-2 may soon be available, which will further reduce the relative risk associated with this specific pathology." SARS-CoV-2 asymptomatic carriers constitute a considerable proportion of the population, particularly children and adolescents, as is seen for other coronaviruses and many other acute respiratory infection (ARI) viruses [2-7]. Such a substantial proportion of asymptomatic carriers may indicate not only an increased risk of hidden contagiousness [8] but, more importantly, a lower hazard of SARS-CoV-2 to the population than was thought by the world community at the beginning of the outbreak [9-10]. The real risk of SARS-CoV-2 to the population, as specified by Jean-Marc Rolain and Po-Ren Hsueh and their research teams, may be assessed by studying: 1) the proportion of asymptomatic patients; 2) COVID-19 clinical manifestation for different groups of the population; and 3) mortality; and comparing these indicators with other, mostly seasonal, ARI viruses in the population [11].

When the first fears created by the new pathogen SARS-CoV-2 have subsided, scientific groups and the medical care sector must evaluate the real level of threat associated with COVID-19, not the imaginary horrors boosted by media [1,12-14] because "fear could have a larger impact than the virus itself" [1]. In the official SARS-CoV-2 population screening programme in Russia, 584 680 respiratory samples from around 17 million tests (11.64% of the Russian population have already been tested) were found to be positive at

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the national level as of 20 June 2020. The current study may extend the conclusions of Jean-Marc Rolain, Didier Raoult and the research team from Assistance Publique-Hôpitaux de Marseille and may be of interest for different European countries.

1.2. Aim

The current Short Communication provides up-to-date (as of 20 June 2020) information about the number of asymptomatic patients, comorbidities, mortality rates associated with SARS-CoV-2, patients with different coronaviruses and ARI viruses, shifts in ARI panel composition from March to June, age breakdown of COVID-19 clinical course, and viral co-infections in COVID-19 patients/carriers in Russia.

2. Materials and Methods

2.1. Methods

Samples and clinical information were investigated from individuals with suspected respiratory infections from 12 Russian hospitals transformed to COVID-19 infirmaries, 22 outpatient clinics and ambulance centres, and 8 non-commercial test laboratories and medical centres (Moscow, Moscow region, St Petersburg, Nizhny Novgorod, Murmansk, Syktyvkar, Krasnoyarsk, and Vladivostok). *Sampling set 1.* 7864 samples from individuals with suspected respiratory infections were analysed by molecular biology for different ARI viral aetiological agents in time interval 1 and 4458 additional samples in time interval 2 (see section 2.3. for description of time intervals). Clinical data were analysed along with molecular biological testing. *Sampling set 2.* 12 082 clinical cases were investigated of patients already tested positive for SARS-CoV-2 by various laboratories, and were treated both at home and in hospital. Only clinical information was studied for this set. Age, sex, results of clinical blood/urine tests, symptomatic picture and outcome were known.

2.2. Time intervals

The work was carried out in two time intervals: 1) 2 March to 30 April 2020; and 2) 5 May to 20 June 2020. The COVID-19 epidemic is a rapidly changing situation with important alterations occurring almost on a weekly, sometimes daily, basis. A need for the most relevant and urgent information led us to revise the paper after time interval 1 to include the latest data collected. The data obtained during time interval 2 enabled us to consider and report new dimensions of SARS-CoV-2 spread in the Russian population, namely viral co-infections with SARS-CoV-2, age breakdown of the clinical picture of COVID-19 patients, and change in the proportion of SARS-CoV-2 in the ARI virus panel with transition from seasonal ARI surge (spring) to ARI decline (summer).

2.3. Software

OriginLab Origin 8.1 was used for statistical calculations and visualisation.

2.4. Ethical guidelines

Reporting of the study conforms to broad EQUATOR [15] and STROBE-NI cohort studies [16] guidelines. All clinical information studied in the current work was completely anonymised. Written informed consent was taken from every patient in the study, including clear permission to use their data for scientific research and publications. All written informed consents duly signed were kept in the hospitals, clinics, and ambulance and medical centres. The Ethical Committee of Koltzov Institute of Developmental Biology of Russian Academy of Sciences regarded the current study as ethically appropriate and exempt from human subjects review because no clinical trials were performed. The authors were not personally involved in collecting the clinical data in medical institutions and hence do not possess any information that might identify the patients.

3. Results and Discussion

3.1. Different ARI viruses

As the research teams from Assistance Publique-Hôpitaux de Marseille mentioned, there are four coronaviruses in circulation with fatality rates comparable to SARS-CoV-2 [1,17]. As of 19 February 2020, these teams tested 4084+5080 samples and revealed the presence of two *alpha*- and two *beta*- common seasonal human coronaviruses in the samples, and there were no samples with SARS-CoV-2 [17].

In a composite sampling comprising 7864 samples from individuals with suspected respiratory infections from eight Russian cities/regions, tested in time interval 1 (sampling set 1), we revealed the presence of several human coronaviruses and other ARI viruses (Figure 1, panel A). Different viral aetiological agents were detected in 5436 samples. In 4602 cases, they were identified with known serotypes and strains. Only 5.37% were SARS-CoV-2-positive individuals, with 56.68% of them asymptomatic. The proportion of asymptomatic carriers for all ARI viruses identified is presented in Figure 1, panel B. SARS-CoV-2 does not stand apart from the ARI group. The results of additional testing of 4458 respiratory samples taken in time interval 2 are presented in Figure 1, panel C; and the proportion of asymptomatic carriers in Figure 1, panel D. In 2533 cases for time interval 2, viral aetiological agents were detected; in 1822 cases they were identified with known serotypes and strains. Time interval 1 coincided with seasonal ARI surge (spring 2020), while during time interval 2, there was seasonal ARI fade (summer 2020). This was elucidated from drastic contraction of infection cases for influenzas, parainfluenza viruses, respiratory syncytial virus and metapneumoviruses that usually constitute the bulk of ARI in Russia every year. Infection cases caused by different seasonal coronaviruses (229E, NL63, HKU1) diminished on transition from time interval 1 to time interval 2, but not so sharply. The number of OC43 cases increased, even in absolute values. SARS-CoV-2 accounted for 11.42% of all identified aetiological agents for time interval 2.

The change of proportion of different viruses in the ARI group studied, with transition from time interval 1 to time interval 2, is provided in Figure 1, panel E. This factor was calculated as follows:

$$\text{Change} = \frac{\text{proportion of a virus in time int.2} - \text{proportion of a virus in time int.1}}{\text{proportion of a virus in time int.1}} \times 100\%.$$

There is a noticeable, but not dramatic, rise in proportion of SARS-CoV-2 in the ARI viral panel. The proportion of OC43 increased much more (probably due to a local surge in Far East Russian regions). SARS-CoV-2 increase is comparable with increase of enteroviruses, echoviruses and parechoviruses in the ARI viral panel, and these viruses are far from causing any epidemic in Russia nowadays. This finding may indicate that SARS-CoV-2 contagiousness is not very high (its basic reproduction number is not very large for any environment); therefore, the virus spread is limited. The observation that the proportion of SARS-CoV-2 asymptomatic carriers increased from time interval 1 to time interval 2 (from 56.68% to 70.67%) (Figure 1, panels B and D) may be an evi-

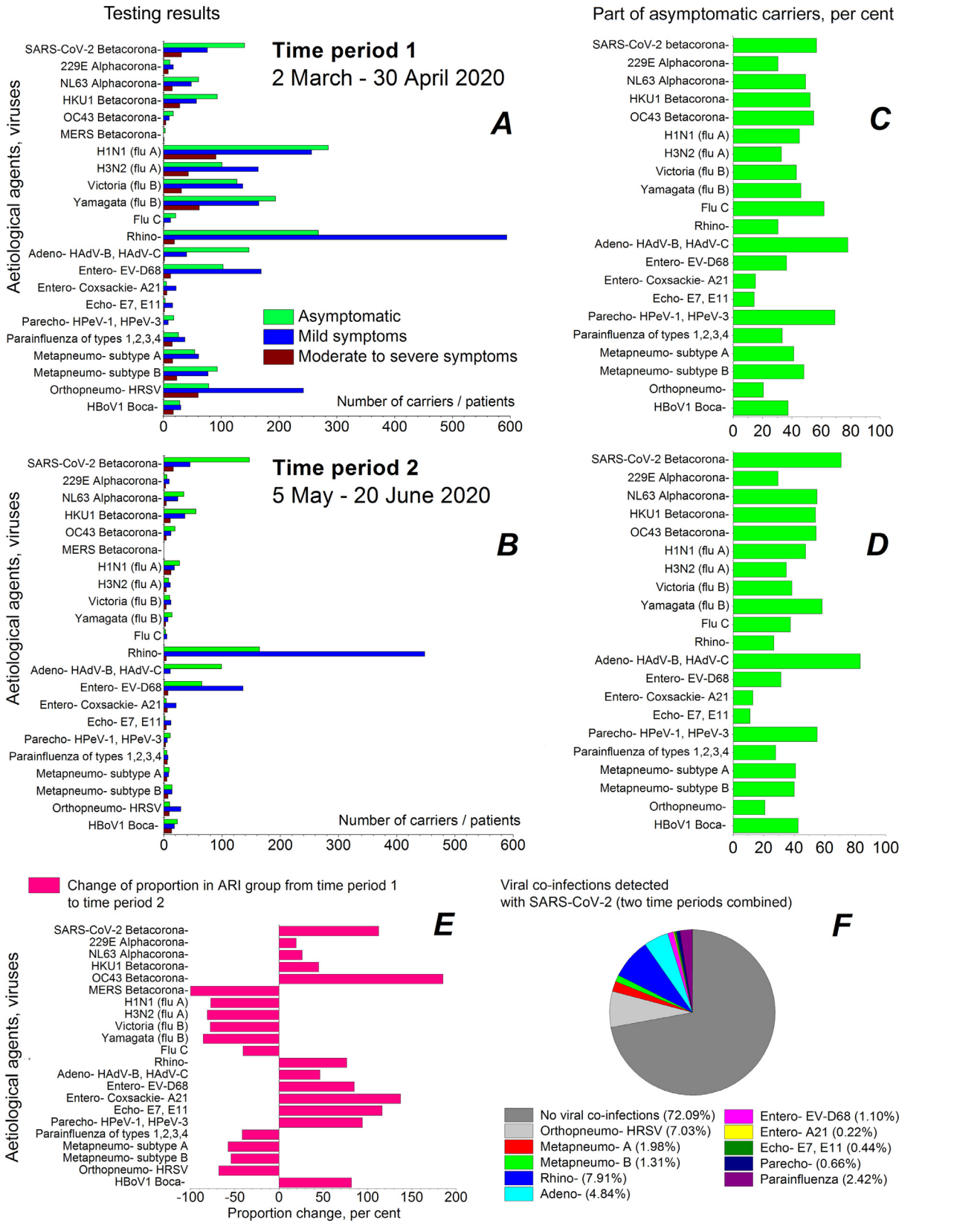

Figure 1. Results of testing the respiratory samples for acute respiratory infection (ARI) panel. The samples have been taken in eight Russian cities/regions. ***A***: 7864 individuals aged up to 78 years. ***B***: Percentage of samples with different ARI viruses corresponding to asymptomatic carriers for time interval 1. ***C***: 4458 individuals aged up to 96 years. ***D***: Percentage of samples with different ARI viruses corresponding to asymptomatic carriers for time interval 2. ***E***: Change of proportion in ARI panel for different viral aetiological agents with transition from time interval 1 to time interval 2. ***F***: Viral co-infections detected for 455 samples positive for SARS-CoV-2 (time intervals 1 and 2 combined).

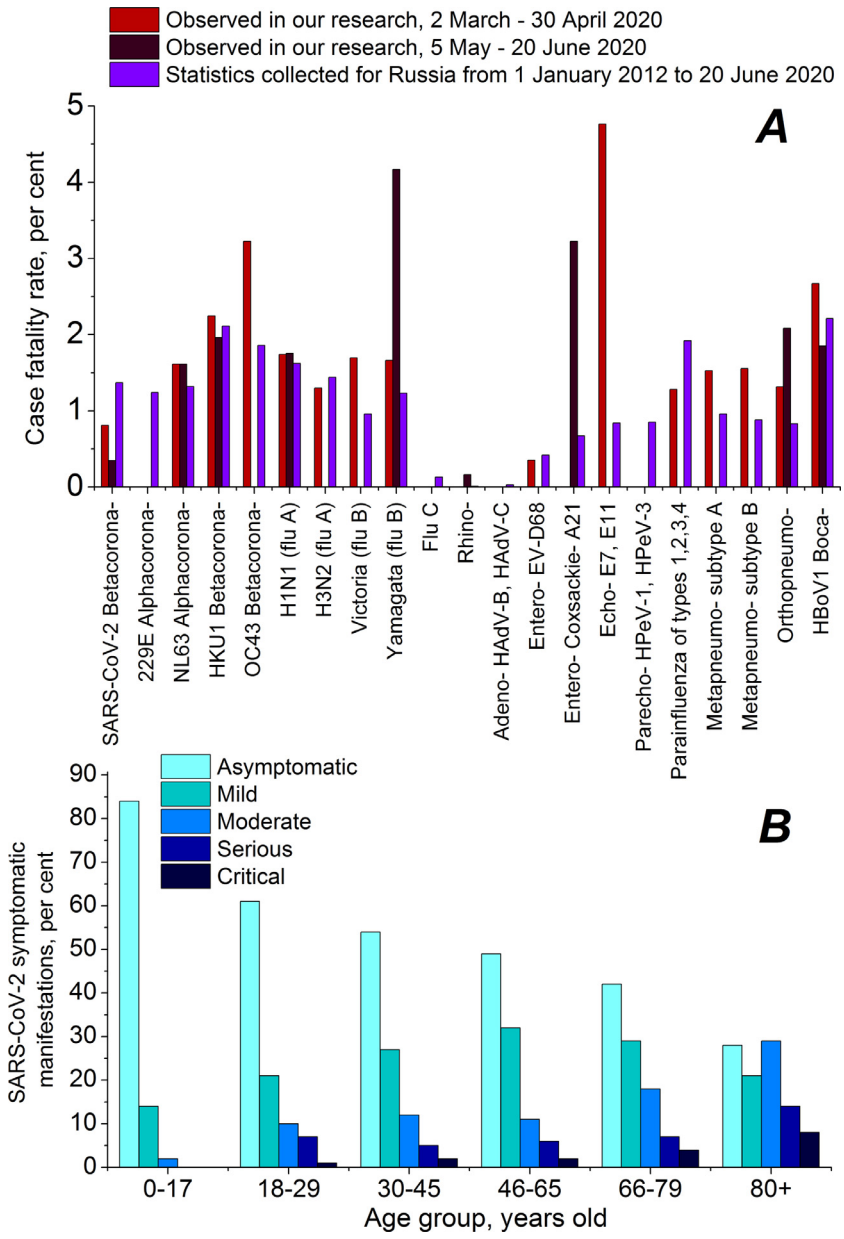

Figure 2. Mortality and clinical course for COVID-19 patients. ***A***: Mortality observed for patients with different ARI viruses (time interval 1: sampling sets 1 and 2 combined; time interval 2: only sampling set 1). ***B***: Age breakdown of symptomatic course of SARS-CoV-2 patients/carriers (time intervals 1 and 2 combined; sampling sets 1 and 2 combined).

dence that the population is already gradually adapting to the new pathogen.

3.2. Viral co-infections

SARS-CoV-2 viral co-infections with different ARI viruses were assessed. Around one quarter of all 455 SARS-CoV-2-positive samples from sampling set 1 contained other viral RNAs or DNAs (Figure 1, panel F). Rhinoviruses accounted for the largest proportion of co-infection (7.91% of samples tested positive for SARS-CoV-2); respiratory syncytial virus (7.03%); adenoviruses (4.84%); metapneumoviruses (3.29%); parainfluenza viruses (2.42%); enterovirus D68 (1.10%) and other viruses (entero-, echo-, parecho-) <1%. Respiratory viral co-infections are not extraordinary or novel. Many human respiratory viruses are known to be present as co-infections [18]. Viral co-infections with SARS-CoV-2 have been reported recently [19,20]. The current research showed that viral co-infection cases with SARS-CoV-2 were predominantly related to young patients/carriers (≤17 years old) and adult patients aged up to 45 years, with decay after this age. This may indicate a possible connection with the most active period of life. Cases of respiratory viral co-infections with SARS-CoV-2 were not proven to be related to immune system dysfunction.

It is interesting that there were no detected SARS-CoV-2 co-infections with other coronaviruses or influenza viruses. This may be because of their similar stereometric configuration (size, conformation of envelope proteins) and/or molecular mechanisms of attachment to cellular surfaces in humans, which may result in their competitive exclusion. The presence of angiotensin-converting enzyme 2 (ACE2) receptor may also play a role here [13].

In any case, currently viral co-infections with SARS-CoV-2 are not very common. This may indicate that in winter-spring 2020-2021 the seasonal ARI rise will hardly lead to a dramatic increase of SARS-CoV-2 cases that a lot of media prophesy as a "COVID-

19 second wave." A second wave of the pandemic, if present, will be scarcely associated with viral co-infections. Of 455 SARS-CoV-2-positive samples, no triple viral co-infections were revealed.

3.3. Mortality

Mortality registered for sampling sets 1 and 2 combined is presented in Figure 2, panel A, separately for time intervals 1 and 2. A comparison with statistics collected for Russia in 2012 to 2020 indicates that SARS-CoV-2 is not as exceptionally "deadly" as, say, Ebola haemorrhagic fever or H5N1 highly pathogenic "bird" flu, i.e. its case fatality rate is not high despite initial opinions in January to February 2020. As shown in Figure 2, panel A, many ARI viruses are associated with similar or higher fatality rates. Most of them have case fatality rates very close to 1% or between 1-2%. The main danger associated with SARS-CoV-2 is its free spread around the world without mental, religious, racial, ethnic, national, cultural or any other borders, and in a world with enormous tourist and supply chain torrents [21]. It is this persistent worldwide spread of the virus that causes many fatalities, not its putative "deadliness."

The current official COVID-19 case fatality rate for Russia is 1.4-1.5% [22]. Fatality age breakdown (official data for the end of April 2020) is as follows: 0.6% (18-29 years); 14.2% (30-49); 19.6% (50-64); and 65.6% (65+) [22]. In sampling sets 1 and 2 combined, median case fatality rate was 0.6%. Careful analysis of clinical information shows that the overwhelming majority of deaths were cases with comorbidities. Of 477 deaths (sampling set 1) available for the current analysis, 442 (92.6%) were in patients with at least one comorbidity. The most common comorbidities were: metabolism disorders, including diabetes, obesity, gout and hormonal impairments (84%); cardiovascular diseases, including hypertension, ischaemic heart disease, cardiac decompensation, stenocardia and coronary artery disease (82%); social habits, including chronic alcoholism, constant smoking and narcotic addiction (21%); internal organ diseases, including functional impairments, such as chronic obstructive pulmonary disease (COPD), asthma, kidney and liver diseases (18%); neurological diseases (15%), cancer (10%); and immune system disorders (3%).

3.4. Clinical manifestations in sampling set 2

An average of 54.5% of COVID-19 patients from sampling set 2 who were treated at home and in hospital exhibited no symptoms (time interval 1). A total of 28.6% showed mild symptoms (slight cough, mild pyrexia up to 37.5°C, fatigue, mild upper respiratory tract disease, moderate myalgia, pharyngitis, stuffy nose and catarrhal inflammation). More serious and pronounced symptoms (bronchitis, obliterative bronchiolitis, wheezing, shortness of breath, rapid breathing with cracklings, moderate to strong dry/humid cough and pyrexia up to 38.3°C) were reported in 11.0% of patients, and 5.9% of patients exhibited severe symptoms (viral or bacterial pneumonia of different severity, pyrexia up to 40.1°C with median 38.7°C). Critical patients with acute respiratory distress syndrome and respiratory failure who required intensive care made up no more than 1.4% of all individuals in the set. The numbers of severe patients and hospital critical patients who required oxygenating ICU treatment were considerably lower than those predicted by the World Health Organization (WHO).

Age breakdown of symptomatic clinical course is given in Figure 2, panel B, for sampling sets 1 and 2 combined (12 537 individuals). The number of asymptomatic patients decreases with age, whereas the number of cases with serious manifestations increases with age. These statistics for asymptomatic and symptomatic COVID-19 patients in Russia agree with predictions from the research groups of Jean-Marc Rolain and Didier Raoult [1].

4. Conclusions

In Russia in January to June 2020, there were an estimated 16 000 deaths from pneumonia (Rosstat data). The current number of deaths associated with a COVID-19 diagnosis is half that number. It is still a considerable amount but proper steps in surveillance, prevention, diagnosis and treatment may effectively curb disease-related mortality. In January to June 2019, there were 15 206 pneumonia-related deaths, and in 2012 to 2016 approximately 16 000 to 28 000. Therefore, in Russia the current risk of contagiousness and fatality associated with SARS-CoV-2 (as of 21 June 2020) is statistically comparable with the risk from other human coronaviruses and many other ARI viral pathogens that have already became seasonal, and less than that of pneumonia of different aetiology. This does not mean that we can relax, however, just because this emerging pathogen may turn out to be less dangerous than we deemed several months ago. A search for new therapeutics must continue along with development of vaccines. Nonetheless, panicking or regarding SARS-CoV-2 as a once-in-an-age threat and "plague of the twenty-first century" is not productive and sometimes even counterproductive. The measures for containing COVID-19 must be determined by research, statistics and thorough calculations, not by apprehension or fear.

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Declarations

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