COVID-19

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THE PHASE DYNAMICS OF THE COVID-19 PANDEMIC: A SYSTEMATIC ANALYSIS OF 213 COUNTRIES AND TERRITORIES

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The study was carried out to evaluate the dynamics of monthly numbers of cases, deaths, tests and case fatality ratio worldwide during three phases of the COVID-19 pandemic.
Material and methods: Twenty-three sets of databases, dated the 22nd of each month from January 2020 to November 2021, for 213 countries were collected from the Worldometer website. The number of cases, deaths, tests, case fatality ratio, infection fatality ratio, etc. were counted for various periods of time for each of the 213 countries, then the results related to different periods of time were compared.
The analysis of main epidemiological parameters resulted in division of three phases of the global pandemic evolution. The first phase (23.01.20–22.07.20), the second phase (23.07.20–22.01.21) and the third phase (23.01.21–22.07.21) were different in terms of the number of tests performed, new cases and mortality due to COVID-19. By the end of second phase, the worldwide statistics indicated imminent end of the pandemic, but the third phase was characterized by sudden rise in the number of new cases and deaths that could not be explained rationally. The most dramatic evolution of epidemic curve occurred in the countries where physicians had successfully confronted COVID-19 during the first two phases of the pandemic.
Despite the decrease in the overall numbers deaths during the latest months analyzed, additional study is necessary to identify the cause of increasing in the number of new cases and deaths during the third phase of the pandemic.
Presumably, there are several causes of negative evolution of the current pandemic, including over-reliance on polymerase chain reaction tests, application of non-specialized premises for quarantine and treatment, non-professional management, following therapeutic protocols applied in countries with high number of deaths, ignoring preventive treatment, and decreasing in mass and individual immunity.
It can be suggested that the use of drugs modulating T-cell immunity is necessary, and preventive and therapeutic protocols should be changed from the 'standard' to 'personalized' types.

Ключевые слова: COVID-19; phases of the pandemic; mortality rate; case fatality ratio; infection fatality ratio; polymerase chain reaction

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1. Introduction

Since the previous study dealing with the case fatality ratio and infection fatality ratio caused by COVID-19 [1], the author has received many comments that prompted the question: «Why did an optimistic prognosis fail?» To answer this question, a more detailed and expanded analysis was carried out in a new study.

1.1. Initial and current state of the COVID-19 pandemic narrative

On December 31, 2019, the WHO's China Country Office was alerted to cases of pneumonia of unknown cause detected in Wuhan City, Hubei Province of China. On January 3, 2020, the first complete genome of the novel coronavirus (2019-nCoVs) was identified. On February 11, 2020, a new disease was named «the coronavirus disease 2019» or CoViD-19 [2]. Further studies revealed that SARS-CoV-2 was circulating in various countries, including Spain, Italy, France, Brazil, USA, etc. before the outbreak of the epidemic in China [3].

During the initial stage of the COVID-19 pandemic two well-known discoveries, namely: "Unique inserts in the 2019-nCoV spike protein" [4] and "Reduction and functional exhaustion of T-cells in patients with coronavirus disease 2019 (COVID-19)" [5], were published. These discoveries demonstrated structural and functional similarities between two viruses and prompted a common sense question about the origin of SARS-CoV-2. Questions about the origins of the virus resurfaced in December 2020 when production of an Australian vaccine was discontinued as healthy vaccinated people became tested positive for HIV [6].

Other curious issues of the pandemic related to the anomalous epidemic curve:

(1) *New patterns*: In April 2020, an expert in epidemiology, Prof. Vladimir Nikiforov mentioned: «if the virus followed the 'classical pattern', the epidemic would

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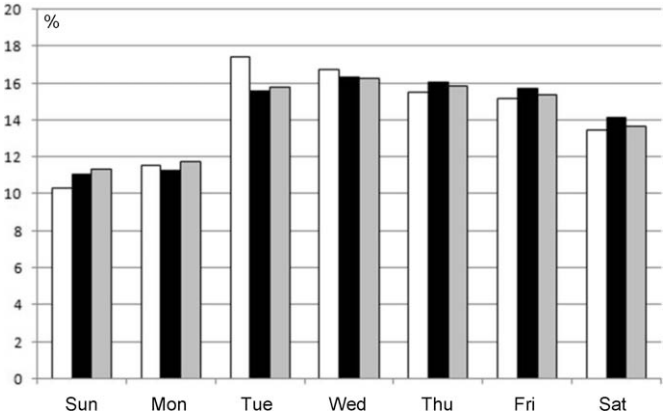

Fig. 1. Daily mortality due to COVID-19 on various days of the week.

have ended within three months, but now we are faced with something new» [7].

(2) *Data adjustments*: During the first year of the pandemic there were many cases of local number adjustments that affected the worldwide statistics related to COVID-19. For example, on May 25, 2020, a report of Spain was reduced by 1915 deaths; on June 3, 2020, a report of France was reduced by 37,895 cases; on August 13, 2020, a report of the United Kingdom was reduced by 29,726 cases and by 5,319 deaths; on August 14, 2020, a report of Peru increased by 3,935 new deaths, and so on [8].

(3) *A synchronization-like phenomena*: The first example of synchronization was a weekly mortality cycle which became noticeable in Brazil, Chili, in the United Kingdom, and the United States of America since April 2020. Later this anomalous cycle of daily death spread to many other countries. A comparison of the percentage of fatal cases on different days of the week for a period of 100 weeks (26.01.20–25.12.21) revealed almost identical distribution as described in a previous study [9] (Fig. 1).

There is another example of synchronization related to the daily new cases of COVID-19. During 1.5 years of the pandemic the highest number of daily new cases in the United States and the United Kingdom were recorded on the same day, on January 8, 2021; together they accounted for 44% of the total number of new cases worldwide [8].

White columns — period of 4 weeks (05.04.20–02.05.20) in the USA; black columns — period of 40 weeks (01.03.20-05.12.20) worldwide; grey columns — period of 100 weeks (26.01.20–25.12.21) worldwide. The vertical axis shows percentages; the horizontal axis shows days of the week.

(4) *A Strange evolution of the pandemic*: In mid-December 2021, a well-known expert in infectious diseases, Dr. Anthony Fauci, said: "it's 'unprecedented' how long the COVID-19 pandemic has lasted globally, with many countries enduring multiple major waves of infections since it was declared in March 2020" [10]. So, a pertinent question that pops up is: why, despite unprecedented control measures to prevent the spread of a new virus, including worldwide quarantines, isolation, movement control order, curfew, social distancing, wearing of masks and mass vaccinations, the epidemic curve still has a 'wave-like' or 'propagated' shape instead of going down? Were preventive measures effective, or simply useless or harmful?

1.2. Infectious disease — a battle between the human body's defense and viruses or bacteria

History of the battle against viruses and bacteria dates back at least several thousand years. Ancient physicians already knew about external pathogens which could cause acute febrile diseases. They also knew that an evolution of any clinical case depended on the health status of the patient before the onset of the disease, so they talked about «body defense». At the beginning of modern microbiology, the importance of body resistance was confirmed by a Prof. Max von Pettenkofer, who swallowed the entire contents of a tube filled with germs of cholera, but nothing happened to him. So, he claimed: «The important thing is the disposition of the individual!» [11].

Despite a variety of external pathogens, the human body has a limited number of defense mechanisms, which is accompanied by a few clinical syndromes, consisting of common symptoms, such as fatigue, chills or hot feeling, headache, cough, shortness of breath, nausea, vomiting, diarrhea, skin rashes or discoloration of the skin, etc.

In ancient times the mechanism of the onset of fever was differentiated into two main groups based on the presence of thirst, sweating, chills, or feelings of heat; and the choice of individual treatment was determined by the type of fever. According to the modern view on fever, which commonly accompanies infectious diseases, one can define only two mechanisms leading to an increase in temperature: one is an increase in heat production and the other, a decrease in heat transfer, or their combination [12]. Thus ancient and modern explanations of fever are quite similar, and two types of antipyretic medicines are necessary and sufficient to manage any case of excessive fever. Similarly, 2–3 mechanisms can be identified that underlie each of the remaining symptoms of any acute viral disease, so, a small group of commonly used drugs would be sufficient to manage any infectious diseases, including *old* and *new* ones.

After the discovery of bacteria and viruses as a cause of infectious diseases, the main emphasis was changed from supporting the body resistance to the fighting against pathogens. It was successful in the majority of bacterial infection cases, but it was almost useless when disease was caused by a virus.

Therefore, if there is no etiotropic treatment, then there is no need to identify a new viral disease. All pharmaceutical and non-pharmaceutical therapeutic modalities would be addressed to the well-known protective mechanisms of the human body, and treatment should be based on the leading syndromes and symptoms, using the principle called *off-label* therapy.

1.3. The classical foundation of medicine is wisdom, which is evergreen

Multiplication tables, the Pythogorean theorem, Archimedes' law, ideas of inertia and atomic structure of matter appeared several thousand years ago. In the course of history, ancient knowledge developed and improved until it turned into higher Mathematics and quantum Physics. However, the multiplication table, Archimedes' law and other basic knowledge have not lost their value in our time.

Similarly, ancient medicine also had its own canon, preserved within the framework of traditional Chinese medicine. The most important law of that canon was postulate: to strengthen or reinforce that which is deficient, and drain or sedate that which is excessive [13]. Over the centuries, it has taken on new forms, and was introduced in the theory of *Sthenic* and *Asthenic* diseases by Dr. John Brown [14]. At the beginning of the 20th century, two physiologists presented this postulate in the form of theories of *Dominant* and *Parabiosis* [15]. In the 1930s, Hans Selye discovered a dynamic interaction between excess and deficiency, and described General Adaptation Syndrome theory, which distinguished the *Alarm Phase* (= excess, sthenic disease, dominant) and *Exhaustion Phase* (= deficiency, asthenic disease, parabiosis) [16].

At the beginning of organotherapy doctors used extracts of animal organs to treat various age-related problems, also commonly known as frailty nowadays [17]. Later a modern branch of organotherapy, taking the form of hormonotherapy, became a powerful tool to treat various diseases caused by hormonal insufficiency. They followed the first part of the ancient postulate: *to strengthen or reinforce that which is deficient*. When antibiotics were discovered, physicians got a tool to inhibit bacterial growth. Application of antibiotics was an example of following the second ancient postulate: *drain or sedate that which is excessive*.

Further development of medicine did not follow the basic canon, and treatment was not addressed to a primary cause of disease. Nowadays despite the fact that deficiency patterns are the causes of the majority of chronic diseases, especially among elderly people, antagonists, blockers, or inhibitors, such as α-blockers, β-blockers, calcium channel blockers, ACE inhibitors, PDF-5 inhibitors, and H2 antagonists are used for therapy. Before prescribing sedative therapy, patients are not tested whether the corresponding target is in an excited state or not. So, a rational medical sense is ignored, and patients have to take medication for all their life.

The same problem has arisen with the treatment of COVID-19. The main pathologic target was T-cell immune-deficiency [5], nevertheless a lot of attention was paid to the cytokine storm, which was a consequence, but not a primary cause. According to basic medical law, treatment should be focused more at restoring T-cell immunity [18], and less against increased activity of certain components of the immune system.

1.4. Treatment of patients suffering from acute infectious diseases

About 1800 years ago, Dr. Zhang Zhongjing summarized the results of research from previous generations and developed a theory of acute infectious diseases, which explained therapy based on leading clinical symptoms and syndromes [19]. According to this theory, there could be only 6 phases, and certain phases could have 2–3 variants. Thus, the whole variety of clinical syndromes related to infectious diseases was limited to 10–12 variants, each having specific treatment and prevention.

There are some examples of treatment of the initial phases of infectious diseases: in the case of initial fever with general cold feelings without sweating — *Herba Ephedrae* was recommended; if there is initial fever with general hot feelings — *Folium Mori Albae* or *Herba Menthae Haplocalycis* should be used; if there is initial fever with intensive sweating or tension in the muscles — *Ramulus Cinnamomi Cassiae* was recommended; in the case of fever with alternating cold and hot feelings — *Radix Bupleuri*, was used, etc. A change in symptoms pointed to a change in the phase of the disease and required an adjustment of therapy. If a patient has a severe fever with hemorrhagic symptoms, skin rashes, kidney and liver impairment, delirium, etc. — *Radix of Isatis tinctoria* should be applied [20].

It would be useful for modern pathophysiology to distinguish between various types of fever and choose antipyretic medicines (*paracetamol*, *ibuprofen*, etc) based on the pharmacodynamic of these popular drugs, but not empirically, as they are usually used.

During later centuries, protocols of infectious disease treatment were updated according to the new scientific discoveries of that time. Excepting deadly epidemic diseases (plague, smallpox, or cholera), therapy of other infectious diseases was effective and successful. Theoretically, modern medicine having a long history in the past and advanced pharmaceutical science nowadays must be able to treat any problem more effectively than our predecessors, but the helplessness of the modern medical system during the current pandemic was beyond common sense [21], and raised questions about the quality of medical education of the distinguished leaders and their followers. Surprising but true, a great deal of medical recommendations were developed and introduced by people who had no medical education, or lacked adequate knowledge in epidemiology, and no experience in battling infectious diseases.

1.5. Treatment of COVID-19 at initial phase of pandemic

At the beginning of the pandemic, WHO encouraged doctors to use well-known medicines as *off-label* treatment of a new disease since there were no approved drugs yet for the treatment of COVID-19 [22]. The majority of knowledgeable and experienced doctors who received high quality medical education treated patients suffering from COVID-19 with great success. They recommended using antiviral and anti-inflammatory drugs, including *ivermectin*, *colchicine*, *methylene blue*,

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chloroquine and *hydroxychloroquine*; anticoagulants, such as *dipyridamole* or *heparine*; immune modulators, such as *thymic extracts*, *thymic peptides*, solution of *formaldehyde*, *melatonin* and common adjuvants. A group of physicians, who had identified the similarity between COVID-19 and toxic damage to red blood cells, recommended using therapeutic protocols which were effective in cases of acute intoxication. Other experts recommended an inhalation with ethanol vapor and helium-oxygen mixture since those methods had already been applied to similar cases before. Plant derived medicines, including extracts of *Artemisia*, *Isatis* or *Colchicum* as well as green and black tea, and various complex prescriptions were also used either for prophylaxis or for combined therapy.

During the early days of the COVID-19 epidemic, doctors in Russia used their own treatment protocols, that resulted in very low mortality, and even raised questions and skepticism from the international medical community [23]. For example, in April–June 2020, in a hospital attached to the Moscow State University, 420 out of 424 indoor patients suffering from COVID-19 were successfully treated with routine medication. Effectiveness of the therapy was around 100%.

As basic medicines these doctors used *Colchicine*, *Dipyridamole*, *Bromhexine*, and *Spironolactone*; additional application of certain anticoagulants and corticosteroids depended on a particular case [24]. Thus, common medical knowledge and experience were enough to treat the infectious disease caused by the *new virus*.

Every doctor knows that effective therapy of any patient requires individual approach due to the natural difference between even two similar cases, especially if a patient suffers from COVID-19. Following standard protocols without dose adjustment and individual correction of used medicines in certain clinical trials resulted in decreasing or even losing effectiveness of the drugs that had been used by other doctors earlier on [25]. Nevertheless, knowledgeable doctors continued their successful and effective treatments [26–28]. The therapeutic effects of the medicines mentioned above have been proven in further clinical trials and the results were published in various peer-reviewed journals.

After recent discussions on therapeutic protocols taking place between various experts, Dr. Peter A. McCullough recommended to his colleagues to treat COVID-19 patients according to their own knowledge and experience. One can only deduce there is no common sense for doctors to follow the protocol of an expert or a country where mortality was high, otherwise they would witness the same high mortality among their patients.

1.6. Clinical trials

Early in the 18th century, homeopathic doctors, who studied pathogenesis of new remedies, introduced extensive and multi-centered clinical trials to the medical public. They needed to differentiate the primary and secondary symptoms, and to separate important symptoms from non-important ones, and so on. According to the demand of homeopathic pharmacy, there was a rationale for using large groups of people. Nevertheless, extensive trials were criticized by Dr. Rudolf Virchow, the father of modern Pathology. He insisted that despite certain similarities in pathology discovered in different patients with a similar disease, each patient has his/her individual disease, so instead of using statistics collected from large groups of patients, doctors should pay more attention to detailed analysis of every case [29].

As far as acute infectious diseases are concerned, their pathological condition is not stable, but has several phases. Each of the phases requires the use of different medicines and patient care. It would be illogical to look for the treatment of COVID-19 in general, when each phase of the disease requires an appropriate group of medicines. Then a doctor should choose one or two medicines, taking into account the main symptoms of a certain patient. Multiple attempts to find a unique medicine against 'COVID-19' have failed. That suggests that treatment of COVID-19 or any further new acute viral infectious diseases should be managed by means of routine drugs applied as *off-label* therapy.

When COVID-19 was announced as a new disease, healthcare worldwide was challenged to conduct new clinical trials to find medicines that were safe and effective in treating COVID-19 and comorbidities. After Dr. T. A. Ghebreyesus expressed an opinion about the pandemic [21], all patients suspected of being infected with SARS-CoV-2 were automatically made participants of clinical trials which were the most extensive in the history of mankind.

Since all the pathogenic mechanisms encountered in COVID-19 were already well-known before May, 2020, the further treatment of COVID-19 should not have been difficult.

Moreover, since some routine medicines had already been used successfully, the main goal of further clinical trials should have been to design the most effective and adjustable protocols, but not to reject the effects of the used medicines. Unfortunately, many ongoing clinical trials have ended up demonstrating insufficient knowledge and experience of the physicians conducting the research.

For experienced physicians with a solid background, clinical trials were not necessary. Since they knew the pathogenesis of COVID-19 and pharmacodynamic of the medicines used, in their clinics efficacy, of therapy must be around 100% [26–28]. But results of clinical trials were very important and useful for beginners, since standard protocols help them to reduce the number of adverse reactions of their treatment.

1.7. Case fatality ratio and infection fatality ratio

There are two most important characteristics of infectious diseases: the first is a case fatality ratio (CFR) and the second, an infection fatality ratio (IFR). Case fatality ratio is the proportion between the number of patients who died from COVID-19 and the number of confirmed cases of COVID-19, while infection fatality ratio is the proportion between the number of patients who died from COVID-19 and the number of estimated cases infected with SARS-CoV-19.

To identify the total number of infection prevalence, tests were carried out for the presence of the viral genome — Polymerase chain reaction (PCR), or for specific antibodies against SARS-CoV-2 virus (IgM and IgG). Since PCR provided positive results for a limited time after infection, and specific antibodies were produced and circulated in the blood of an infected person from several months up to a year, the percentage of seroprevalence would always be lower than the real one, and, therefore, IFR from COVID-19 would be always overestimated.

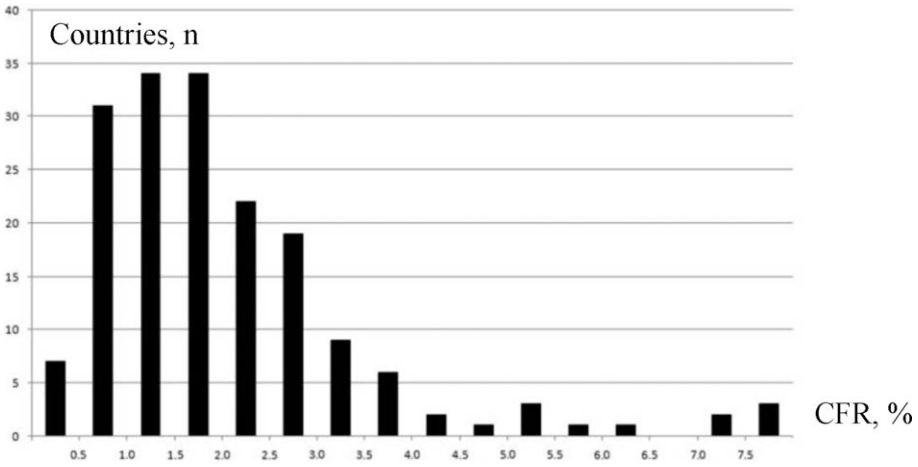

Fig. 2. Distribution of 175 countries into 16 groups according to a CFR value. 16 groups are: 1) CFR < 0.5%, n=7; 2) 0.5-1.0%, n=31; 3) 1.0-1.5%, n=34; 4) 1.5-2.0%, n=34; 5) 2.0-2.5%, n=22; 6) 2.5-3.0%, n=19; 7) 3.0-3.5%, n=9; 8) 3.5-4.0%, n=6; 9) 4.0-4.5%, n=2; 10) 4.5-5.0%, n=1; 11) 5.0-5.5%, n=3; 12) 5.5-6.0%, n=1; 13) 6.0-6.5%, n=1; 14) 6.5-7.0%, n=0; 15) 7.0-7.5%, n=2; 16) CFR>7.5%, n=3.

In a study published by J. Ioannidis (2020), at the end of October 2020, the number of infected people worldwide reached 10% [30]. Similar proportion of infected people in October 2020 was calculated for Belgium, Brazil, and the United States [31]. On January 29, 2021, the Mayor of Moscow, Sergei Sobyanin announced that «half of Moscow's 12 million residents have had Covid-19» and recovered. That estimation was based on a trial where antibodies to the SARS-CoV-2 virus were found in more than half of the blood samples taken randomly from a thousand healthy residents of Moscow [32]. One may suppose that since the beginning of the pandemic, major populations of large cities have already been infected with SARS-CoV-2 and have some circulated antibodies or have memory about this virus stored in the T-cells.

1.8. Databases were collected from Worldometer website

Information on cumulative numbers of the total cases and deaths due to COVID-19 is available at the Worldometer website from January 21, 2020 [8]. On January 23, 2020, a controversial article on RT-PCR tests was published [33], and a historical session of the World Economic Forum devoted to Wuhan Coronavirus took place in Davos [34]. Despite the fact that there was no cause for alarm yet, January 23, 2020 was chosen as the first day of the current study.

To provide an overall and detailed analysis of the COVID-19 pandemic, one year and a half was divided into three phases: (23.01.20–22.07.20), (23.07.20–22.01.21) and (23.01.21–22.07.21). Twenty-three sets of databases, dated the 22nd of each month from January 2020 to November 2021, were collected. Raw data included more than 20,000 figures in total. Only simple calculations using MS Excel easily understandable by any doctor have been used.

The databases related to each month for every country were calculated by subtracting the previous month's data from the analyzed month's data. For example, in China on 22.02.20 there were 76,923 cases, and 2,441 deaths, and on 22.01.20 there were 571 cases and 17 deaths. Subtracting the second from the first, one concludes that from 23.01.20 to 22.02.20 there were 76,352 cases and 2,424 deaths, and so on. The same method was used to count the database related to each phase for every country. Since only 213 countries[1] were affected by COVID-19 during the first phase, these 213 countries were analyzed during the current study.

2. One and a half years of the pandemic: Case fatality ratio and infection fatality ratio

Objective: To evaluate CFR and IFR in 213 countries during one and a half years of COVID-19 pandemic.

2.1. Calculation of CFR among COVID-19 patients in 213 countries

Material and Methods: To calculate the CFR and IFR worldwide, the databases of 213 countries dated July 22, 2021, 23:49 GMT, were collected at the Worldometer website. A case fatality ratio was calculated by dividing the number of deaths by the number of confirmed cases.

Results: The overall case fatality ratio for 213 countries, counted by dividing the number of deaths (n=4,150,526) by the number of confirmed cases (n=193,348,564), was 2.147 %.

2.2. Calculation of CFR among COVID-19 patients in 175 countries

Material and Methods. To increase the homogeneity of the main group of study, 38 countries with death numbers fewer than 50 were excluded from further analysis. Thus, the main group of study was reduced to 175 countries, with a total population of 7,734,426,580 people. These countries had 193,207,132 confirmed cases and 4,149,944 fatal cases. For each country, the CFR was calculated by dividing the number of deaths by the number of confirmed cases.

Results. The overall case fatality ratio for 175 countries was 2.148 %. In this group the CFR ranged from 0.267 % in Qatar to 19.597 % in Yemen, and the average value of CFR was 2.146±1.965%. Based on the calculat-

[1] Here and below "Countries" means "Countries and Territories".

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ed CFR values, all countries were divided into 16 groups as shown in Fig. 2.

The first group (n=7) where CFR was less than 0.500 %, included Qatar (0.267%), Maldives (0.285%), UAE (0.286%), Cyprus (0.418%), Seychelles (0.490%), Mongolia (0.495%), and Vietnam (0.498%).

The groups # 9–16, where CFR exceeded 4.00 %, included 13 countries: Bulgaria (4.296%), Afghanistan (4.432%), Bosnia and Herzegovina (4.710%), China (5.017%), Taiwan (5.042%), Somalia (5.151%), Egypt (5.801%), Ecuador (6.415%), Syria (7.370%), Sudan (7.475%), Mexico (8.807%), Peru (9.316%), and Yemen (19.597%)

Conclusion. The calculations done in this section showed that in 38 out of 175 countries, CFR was less than 1.00%, in 68 countries CFR varied between 1.00% and 2.00%, and in 69 countries CFR was more than 2.00%. In 7 out of 175 countries, CFR was less than 0.50%.

2.3. Calculation of CFR among patients in 38 countries excluded from the main study

Material and Methods. The group of countries excluded from the main study consisted of 8 countries without fatal cases related to COVID-19, and 30 countries where the number of fatal cases was from 1 to 49. In 30 countries with a total population of 102,945,260, there were 140,853 cases of COVID-19 and 582 deaths caused by COVID-19. For each country, a CFR was calculated.

Results. In 18 out of 30 countries CFR was less than 1.00% (including 10 with CFR < 0.50%), in 8 countries CFR was between 1.00% and 2.00%, and in the remaining 4 countries, CFR was more than 2.00%. Since there were no fatal cases due to COVID-19 in 8 countries, the CFR was «0».

Conclusion. If the previous calculations done in section 2.2. were to be considered, then in 64 out of 213 countries, CFR was less than 1.00%; in 76 countries CFR varied between 1.00 and 2.00%; and in 73 countries, CFR was more than 2.00%. In 25 out of 213 countries, CFR was less than 0.50%.

2.4. Calculation of IFR among COVID-19 patients of 136 countries

Background. Before estimation of an infection fatality ratio, it was assumed that each person was tested only once, and the distribution of infected people among the entire population was equal. Therefore, the number of infected people was expected to increase in direct proportion to the increase in the number of new tests performed. The total number of infected people (IP) was derived from the number of total confirmed cases (C) divided by the total number of tests performed (T) and multiplied by the total population (P). Then, IFR was calculated by dividing the number of deaths due to COVID-19 (D) by the estimated number of people infected with the SARS-CoV-2 virus.

In the previous study[1] to estimate the number of infected people, a formula {IP=C · P/T} was used, but it was assumed that results of IFR {IFR=D/IP} would be overestimated. Further comparison of the results calculated using this formula, with the results estimated in other studies [30,31] revealed the consistency of the results with a difference of around 1.8 fold; so, a corrected formula was {IP = (C · P/T) · 1.8}. The final adjusted formula used in the current study was IFR = [(D · T)/(C · P)]/1.8.

Material and Methods. After collecting the databases, countries with fewer than 50 reported cases of deaths, countries without information on the number of tests on SARS-CoV-2, and countries where the number of tests performed exceeded the total population, were excluded from the IFR study group.

The main group consisted of 136 countries with a total population of 6,864,034,602 people, 121,373,035 confirmed COVID-19 cases, 2,768,774 fatal cases related to COVID-19 and 1,370,764,127 COVID-19 tests. To calculate the number of infected people, a formula {IP=(C · P/T) · 1.8} was used. To calculate infectious fatality ratio for each country a formula {IFR = [(D · T)/(C · P)]/1.8} was used.

Results. Since 121,373,035 COVID-19 cases were detected after 1,370,764,127 tests, it can be expected that if the number of tests would reach the total population (6,864,034,602), the number of infected people would increase up to 1,093,985,210. Thus, the overall IFR for 136 countries would be [(2,768,774 · 1,370,764,127)/(121,373,035 · 6,864,034,602)]/1.8 = 0.253%.

Among 136 countries analyzed, the IFR ranged from 0.003% in the Democratic Republic of Congo (the minimal value) to 2.340% in Peru (the maximal value).

Based on the estimated IFR values, all the countries analyzed were divided into 16 groups, as illustrated in Fig. 3.

The first and largest group with the lowest value of IFR (< 0.10%) included 52 countries. Some of the countries had quite large populations, for example, Pakistan (P=225,392,516; IFR=0.088%), Nigeria (211,492,907; 0.008%), Bangladesh (166,414,749; 0.040%), Ethiopia (117,947,327; 0.022%), Egypt (104,359,775; 0.095%); Vietnam (98,259,748; 0.033%), etc. But other countries in this group had small populations, for example, Seychelles (P=98,988; IFR=0.059%), French Polynesia (282,617; 0.039%), Réunion (902,035; 0.049%), Equatorial Guinea (1,451,181; 0.090%), etc.

The groups # 11-16 with high values of IFR (>1.00%) included 8 countries: Slovakia (1.001%), Canada (1.030%), Germany (1.065%), Chile (1.134%), Bulgaria (1.207%), Hungary (1.343%), Australia (1.425%), and Peru (2.340%).

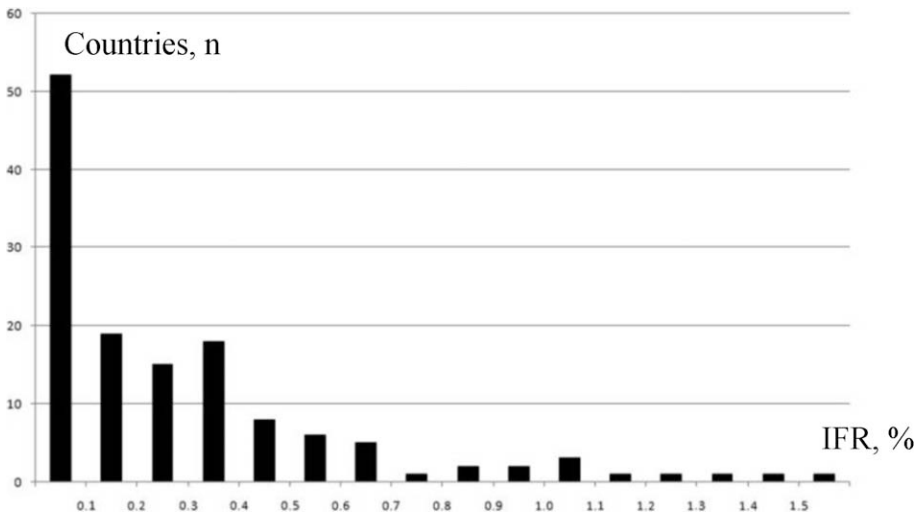
Conclusion. The calculations done in this section showed that in 128 out of 136 countries, the IFR was below 1.00 %, in 7 countries IFR was between 1.00 and 2.00 %, and only in 1 country IFR was above 2.00 %. In 112 out of 136 countries IFR was less than 0.50 %.

2.5. Estimation of IFR in the 77 countries excluded from the main study

Material and Methods. To estimate IFR for 52 countries, including 5 countries without information on the number of tests, and 47 countries where the number of

tests performed exceeded the total population, a ratio between average CFR and average IFR in the main group of countries was calculated.

The main group (n=136) was divided into 4 subgroups: (1st) CFR was less than 1.00%, N=24; (2nd) CFR was between 1.00 and 2.00%, N=50; (3rd) CFR was between 2.00 and 3.00%, N=35; and (4th) CFR was higher than 3.00%, N=27. For each of these subgroups a ratio or a coefficient between average CFR and average IFR was counted: (1st) CFR/IFR=4.369; (2nd) CFR/IFR=5.991; (3rd) CFR/IFR=7.565; (4th) CFR/IFR=11.586. These four coefficients were used to calculate IFR in the group of 52 countries mentioned above.



Fig, 3. Distribution of 136 countries into 16 groups according to a IFR value. 16 groups are: 1) IFR < 0.1%, n=52; 2) 0.1-0.2%, n=19; 3) 0.2-0.3%, n=15; 4) 0.3-0.4%, n=18; 5) 0.4-0.5%, n=8; 6) 0.5-0.6%, n=6; 7) 0.6-0.7%, n=5; 8) 0.7-0.8%, n=1; 9) 0.8-0.9%, n=2; 10) 0.9-1.0%, n=2; 11) 1.0-1.1%, n=3; 12) 1.1-1.2%, n=1; 13) 1.2-1.3%, n=1; 14) 1.3-1.4%, n=1; 15) 1.4-1.5%, n=1; 16) IFR > 1.5%, n=1.

In the group of countries (n=17) where the number of tests performed was higher than «0» but less than the population, and the number of deaths was less than 50, IFR was counted using the formula IFR = [(D · T)/(C · P)]/1.8, which was used in section 2.4.

Results. In 47 countries without information on the number of tests performed and 5 countries where the number of tests performed exceeded the total population (52 countries in total), the estimated IFR was less than 1.00%, including 51 countries, where IFR was less than 0.50%. In all countries where the number of deaths was less than 50 (n=17), IFR was less than 1.00 %; and in 14 out of 17 countries, IFR was less than 0.50%. In 8 countries without deaths, IFR was «0».

Conclusion. The calculations done in the section 2.4 and 2.5 revealed that in 205 out of 213 countries, IFR was less than 1.00 %; in 7 countries IFR was between 1.00% and 2.00 %; and only in 1 country IFR was more than 2.00 %. In 185 out of 213 countries IFR was less than 0.50 %. Taking into account the results of a study conducted in January 2021, when 50 % of Moscow's city population had already developed antibodies against SARS-CoV-2 [32], one may assume that in July, 2021, the percentage of seroprevalence could be even higher and IFR could be lower than estimated in the current study.

2.6. Dynamics of the main cumulative data during 22 months of the COVID-19 pandemic

Background. The current pandemic curve has a wave-like form with a gradual increase and decrease of

Table 1

Dynamics of the main cumulative data during 22 months of COVID-19 pandemic

#	Date	Cases	Deaths	Tests	Population	CFR	IFR	C/M	D/M
0	22.01.20	579	17	—	—	2.936	—	—	—
1	22.02.20	78,001	2,457	—	—	3.150	—	—	—
2	22.03.20	334,886	14,603	—	—	4.361	—	—	—
3	22.04.20	2,632,559	183,879	23,282,447	—	6.985	—	—	—
4	22.05.20	5,296,813	339,374	67,673,680	7,749,928,184	6.407	0.031	683	44
5	22.06.20	9,176,001	473,406	130,810,378	7,756,390,179	5.159	0.048	1,183	61
6	**22.07.20**	**15,362,745**	**625,395**	**302,374,544**	7,762,530,924	4.071	0.088	1,979	81
7	22.08.20	23,358,160	807,665	409,774,283	7,768,876,378	3.458	0.101	3,007	104
8	22.09.20	31,750,352	974,050	609,767,516	7,775,221,824	3.068	0.134	4,084	125
9	22.10.20	41,959,098	1,142,057	759,449,532	7,781,362,578	2.722	0.148	5,392	147
10	22.11.20	58,947,048	1,392,963	955,296,514	7,787,708,023	2.363	0.161	7,569	179
11	22.12.20	78,280,842	1,721,802	1,164,332,290	7,793,848,775	2.200	0.183	10,044	221
12	**22.01.21**	**98,669,593**	**2,113,750**	**1,375,887,509**	7,800,194,225	2.142	0.210	12,650	271
13	22.02.21	112,239,378	2,484,426	1,589,416,906	7,806,539,667	2.214	0.250	14,378	318
14	22.03.21	124,265,956	2,734,688	1,805,314,644	7,812,271,038	2.201	0.283	15,907	350
15	22.04.21	145,297,992	3,083,902	2,087,974,472	7,818,616,492	2.122	0.315	18,584	394
16	22.05.21	167,027,095	3,467,994	2,378,274,484	7,825,090,334	2.076	0.350	21,345	443
17	22.06.21	179,871,406	3,896,149	2,660,800,034	7,831,231,088	2.166	0.409	22,968	498
18	**22.07.21**	**193,348,564**	**4,150,533**	**2,926,443,254**	7,837,371,840	2.147	0.445	24,670	530
19	22.08.21	212,552,947	4,443,846	3,218,070,808	7,843,921,989	2.010	0.477	27,098	567
20	22.09.21	230,824,305	4,731,461	3,598,394,533	7,850,062,735	2.050	0.522	29,404	603
21	22.10.21	243,676,239	4,952,263	3,889,118,661	7,856,203,486	2.032	0.559	31,017	630
22	22.11.21	258,262,254	5,172,861	4,212,580,383	7,862,548,934	2.003	0.596	32,847	658

daily, weekly, and monthly numbers related to cases and deaths.

*Material and Method*s. Twenty-three sets of databases, which were dated the 22nd of each month from January 2020 to November 2021, were collected. The number of total COVID-19 cases, deaths due to COVID-19, tests performed, and population were presented in Table 1. CFR, IFR as well as number of cases per 1 million (C/M) and death per 1 million (D/M) were counted for each date (Table 1).

Results. During 22 months of the pandemic there was an increase in the total number of cases, deaths, and tests on COVID-19 as well as population worldwide. Comparisons between numbers related to the pandemic collected on January 22, 2021 (12 months, or 1 year) and July 22, 2021 (18 months, or 1.5 years), revealed that during the six months, parameters of the pandemic were almost doubled compared to the similar cumulative parameters during the previous one year. The number of COVID-19 cases and deaths increased by 1.96 fold, and the number of tests increased by 2.13 fold. The cumulative CFR was highest in April and May 2020, followed by a decreasing trend, but the estimated cumulative IFR increased gradually.

Conclusion. During the last 6 months of the analyzed 1.5 years of the pandemic, the number of COVID-19 cases, deaths and tests was dramatically increasing. To provide a more detailed analysis of this negative trend, 1.5 years was divided into 3 phases: the 1st phase (23.01.20–22.07.20), the 2nd phase (23.07.20–22.01.21), and the 3rd phase (23.01.21–22.07.21), which are analyzed in the next section.

Foot Note: An expanded version of this study with 10 tables, 96 illustrations, and 349 references has been published as a preprint: Teppone, M. COVID-19: Three Phases of the Pandemic. *Preprints* 2021, 2021070185 (doi: 10.20944/preprints202107.0185.v4).

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