ISSN print: 1224-5984
ISSN online: 2248-3942

Rom Biotechnol Lett. 2022; 27(5): 3730-3745
doi: 10.25083/rbl/27.5/3730.3745

Received for publication, March, 07, 2022
Accepted, March, 08, 2023

Review

SARS CoV-2 virus and the COVID-19 pandemic worldwide and in Romania. An updated data review

MARIAN CONSTANTIN[1,2]

[1]Institute of Biology Bucharest of Romanian Academy, 296 Splaiul Independenţei, 060031 Bucharest, Romania

[2]Fellow of the Research Institute of the University of Bucharest, ICUB, Bucharest, Romania

Abstract

SARS CoV-2 is a coronavirus first identified in November-December 2019 in Wuhan, China that causes respiratory infections of varying severity. Spreading rapidly in human populations, SARS CoV-2 has caused concern worldwide, and on 11 March 2020 the World Health Organization declared a pandemic with the virus for two months, with most countries entering a lockdown period between March and May 2020 in the hope of stopping the spread of the virus. The main symptoms of SARS CoV-2 infection include fever, cough, shortness of breath and fatigue, but less common symptoms such as loss of smell and taste and gastrointestinal disturbances including vomiting, lack of appetite, diarrhoea, etc. are also reported. From March 2020 to March 2023, there were eight waves of increasing numbers of infections, the largest being the sixth wave between January and April 2022. The total number of deaths also followed roughly the same trends with the increase in newly confirmed cases. As an RNA virus with RNA-dependent RNA polymerase, SARS CoV-2 mutates frequently, leading to the stabilisation of several variants: B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.614.2 (Delta), B.1.427 and B.1.429 (Epsilon), P.2 (Zeta), B1.525 (Eta), P.3 (Theta), B.1.617.1 (Kappa) and C.37 (Lambda). The severity of some cases and the intense spread in human populations around the world has led the scientific community to focus its efforts on developing effective vaccines against SARS CoV-2, with nine approved vaccines being developed, BNT162b/2, mRNA-1273, AZD1222 Covishield, Sputnik V rAd26 rAd5, Ad26. CoV.S JNJ-78436735, COVAXIN BBVI52, Corona Vac, NVX-CoV2373 Covavax and BBIBP-CoV vaccines, with which a large part of the global population has been immunised.

Keywords SARS CoV-2, pandemics, COVID-19, virus, viral infection

To cite this article: MARIAN CONSTANTIN. SARS CoV-2 virus and the COVID-19 pandemic worldwide and in Romania. An updated data review. *Rom Biotechnol Lett.* 2022; 27(5): 3730-3745 DOI: 10.25083/rbl/27.5/3730.3745

*Corresponding author: Marian Constantin, Institute of Biology Bucharest of Romanian Academy, 296 Splaiul Independenţei, 060031 Bucharest, Romania; Fellow of the Research Institute of the University of Bucharest, ICUB, Bucharest, Romania. E-mail: cvgmarian@gmail.com

Introduction

SARS CoV-2 viruses. SARS CoV-2 (*Severe Acute Respiratory Syndrome Coronavirus-2*) viruses are members of the family Coronaviridae, order Nidovirales, genus Coronavirus, with numerous members, which cause respiratory and gastrointestinal infections. Coronaviruses are enveloped viruses and infect a wide variety of wild and domestic animal hosts and humans [1] (*Fig. 1*). They are classified into four major genera, *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus* [2, 3], have a pleiomorphic appearance, ranging in size from 80 to 160 nm [4].The name coronavirus comes from the protein projections on the surface of the virions, which are shaped like a brood and, under the electron microscope, give them the appearance of a crown (in Latin, corona means crown) [5].

Coronavirus genome

Coronaviruses have a large, unsegmented, positive-sense, single-stranded RNA genome ranging in size from 27 to 32 kb (kilobases) [4], capped at the 5' end, with a poly-A sequence at the 3' end and 6-11 open reading frames (ORFs). Thus, ORF 1 covers approximately 67% of the viral genome and comprises two overlapping coding regions encoding 16 non-structural proteins. The remaining 33% of the genome comprises the remaining ORFs, which encode structural proteins and accessory proteins [6].

SARS Cov-2 virus genome

The SARS CoV-2 genome (*Fig. 2*) is almost 30 kb long and encodes 29 proteins, four of which are structural and 25 putative non-structural and accessory proteins. The four structural proteins are used during virion assembly and enter into the composition of mature viral particles, the non-structural proteins have an enzymatic role and are involved in viral RNA replication and immune evasion, and the accessory proteins are involved in viral infectivity, virion survival and cell propagation. At the 5' end, the SARS CoV-2 genome includes the replicase gene, with two non-overlapping ORFs, ORF1a and ORF1b, covering about two-thirds of the genome, followed by several ORFs towards the 3' end, including spicular glycoprotein (S), membrane glycoprotein (M), envelope glycoprotein or hemagglutinin esterase (E) and nucleocapsid protein (N). Of these, the S, E

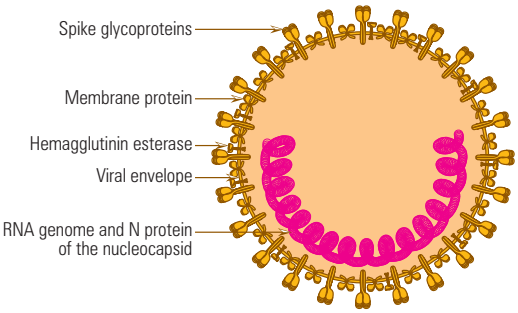

Fig. 1. The structure of the SARS CoV-2 virion

and M glycoproteins protrude into the virion membrane, the spicular glycoprotein forms those strands that give virions their crown-like appearance under the electron microscope, and the nucleocapsid protein is embedded in the envelope and packages the RNA genome. Other ORFs, 3a, 3b, 6, 7a, 7b, 9a, 9c, 10 and others up to 29 encode accessory and non-structural proteins [7]. Translation of ORF1 results in the replicase polyprotein 1a, pp1a, and the -1 shift of the ribosomal frame at the 3' end of ORF1a contributes to translation of ORF1b and synthesis of the replicase polyprotein pp1ab. Proteolytic cleavage of pp1a gives rise to 11 functional non-structural proteins, whereas pp1ab cleavage gives rise to 15 non-structural proteins. Thus, nonstructural protein 1 interacts with ribosomes in infected cells and inhibits the production of host proteins, nonstructural protein 2 can interfere with viral transcription and translation by interacting with ribosomes and replication-transcription complexes [8]. Non-structural protein 3 includes several domains, ubiquitin-like, nucleic acid-binding macrodomain (found only in SARS), transmembrane (with a role in the rearrangement of endoplasmic reticulum membranes, for the formation of the vesicle double membrane and for promoting viral replication), Y1-3 and a papain-like proteolytic sequence (PLpro) and, by cleavage into three sites, forms nonstructural proteins 1, 2 and 3, while nonstructural protein 5 or major protease (Mpro) and, by cleavage pp1a and pp1ab into 11 sites, gives rise to nonstructural proteins 4–16 [9, 10]. Nonstructural proteins 7 and 8 interact with nonstructural protein 12 and stimulate RNA polymerase activity. Non-structural proteins 7–16 contribute to SARS CoV-2 transcription and replication by forming the replication and transcription complex, nonstructural protein 9 inhibits the nucleotidyl-

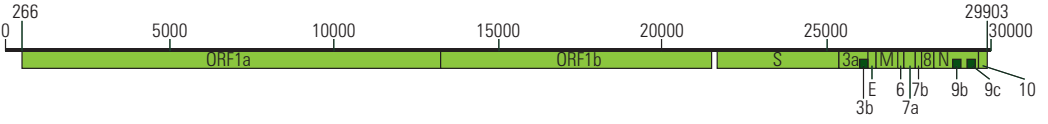

Fig. 2. The structure of the SARS CoV-2 genome

transferase activity of the nonstructural protein, nonstructural protein 10 is a cofactor for nonstructural proteins 14 and 16, non-structural protein 12 is RNA-dependent RNAse and nucleotidyltransferase, non-structural protein 13 is helicase, non-structural protein 14 is exoribonuclease and N7-guanine methyltransferase, non-structural protein 15 has uridine-specific endoribonuclease activity, and non-structural protein 16 is 2'-O-methyltransferase, which is involved in the mRNA cap process. Structural protein N serves to package the viral genome, and the structural proteins on the viral envelope have the following functions: protein S is involved in the binding of receptors such as the angiotensin-converting enzyme or angiotensin-converting enzyme II (ACE2) on host cells and in the fusion of the envelope to the cell membrane; proteins M and N promote viral assembly, and protein E forms an ion channel with a function in pathogenesis and viral assembly. The remaining ORFs have an accessory role. Thus, ORF3a forms a homodimer and forms an ion channel in the host cell membrane; ORF7a participates in the evasion of host immune effectors and is involved in inflammation; ORF7b promotes increased virulence of SARS-CoV-2; ORF8 interacts with HLA-A/CMH I molecules, degrading them; ORF9b is involved in suppressing the interferon response, and ORF3b, ORF6, ORF9c and ORF10 have unknown functions [11].

SARS CoV-2 multiplication cycle

The multiplication cycle of SARS CoV-2 (*Fig. 3*) begins with the triggering of mucopolysaccharidase activity of the viral spicules on the glycocalyx layer, which covers and protects the apical pole of the epithelial cells, exposing the cell receptors, to which it becomes bound. SARS CoV-2 spicular glycoprotein S has 71% amino acid sequence homology to SARS-CoV glycoprotein S and 97% homology to RaTG13 virus isolated from bats, explaining the cross-species spread of these viruses. After binding of the spicular protein S on the virion surface to cell receptors and fusion of the envelope to the cytoplasmic membrane, the viral nucleocapsid is endocytosed in the cytosol [1]. Under the action of proton pumps, the environment in the endocytosis vesicle (endosome) becomes acidic, favouring the cleavage of spikelets into S1/S2 and S20 sites by furin, present in the lungs, liver and small intestine, for which the virus shows tropism [12, 13].

The viral genome is associated with the replication and transcription complex and is transcribed into negative (antigenomic)mRNA in a set of seven subgenomic-length variants, each with the same 5′ leader sequence of 75-78 nucleotides derived from the 5′ end of the genomic RNA and the 3′ terminal sequence, with the 5′ leader sequence remaining

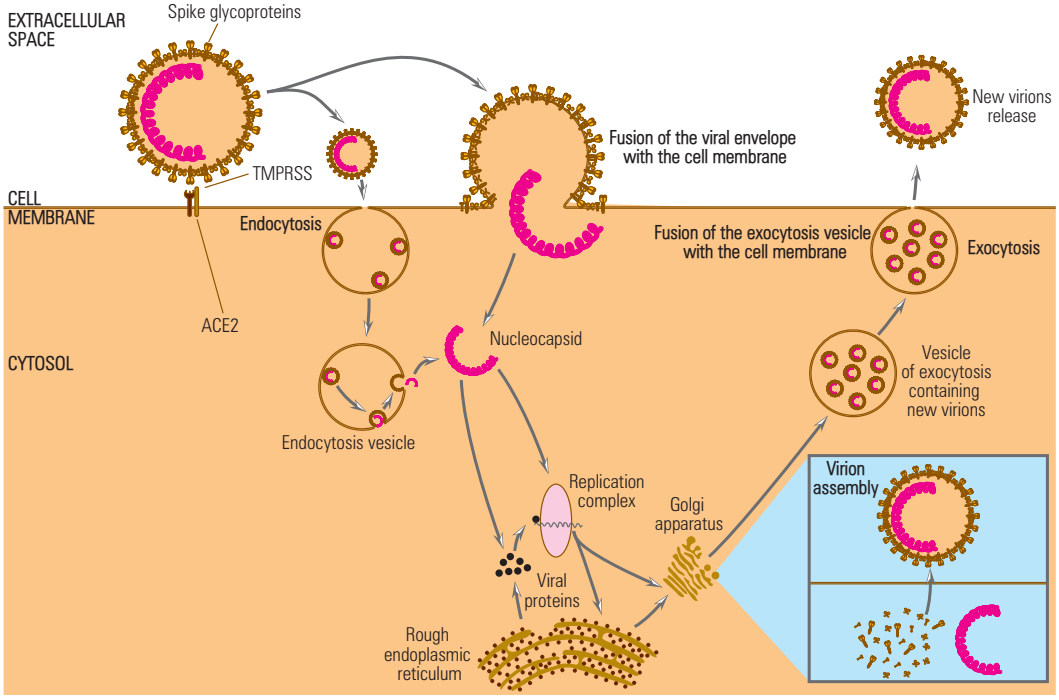

Fig. 3. Multiplication cycle of SARS CoV-2.

associated with RNA polymerase and being transcribed into all mRNA types. Structural proteins S, M and E are synthesized and inserted into endoplasmic reticulum membranes, passing to the Golgi complex, and protein N, synthesized by free polyribosomes, becomes associated with genomic RNA and forms the nucleocapsid [14].

By budding from the endoplasmic reticulum and cisternae of the Golgi apparatus, this assembly is covered with envelopes, becoming virions, in which form they are transported in exocytosis vesicles to the cell surface, where they are released [15].

SARS CoV-2 pandemic

Origin of SARS CoV-2

SARS CoV-2 is the ninth coronavirus to infect humans and the seventh identified in the last 20 years. Since all previous human coronaviruses are of zoonotic origin and the penetration of SARS CoV-2 into the human population does not appear to differ from their penetration (SARS-CoV spread in November 2002 in Foshan, Guangdong Province, China, and in 2003 in Guangzhou, Guangdong Province, China), the transmission of SARS CoV-2 to humans is regarded as a natural interspecific transmission event. The source of SARS CoV has been identified as the cages and raccoon dogs sold in live animal markets in these cities, whereas the source of SARS CoV-2 appears to be bats (based on the 97% homology of SARS CoV-2 spicular proteins with those of bat RaTG13) sold in the Wuhan market. The hypothesis of zoonotic transmission is also supported by similarities between SARS CoV-2 and four endemic human coronaviruses, human coronavirus-OC43 (HCoV-OC43), human coronavirus-HKU1 (HCoV-HKU1), human coronavirus-229E (HCoV-229E), and human coronavirus NL63 (HCoV-NL63), transmitted from animals but with no known circumstances of transmission. The hypothesis of SARS CoV-2 escape from the laboratory has been considered, but its low pathogenicity in commonly used laboratory animals and the absence of genomic markers associated with virus adaptation to them indicate that this event is unlikely [16].

SARS CoV-2 pandemic in the world

On 17 November 2019, China reported the first confirmed case of infection from an unknown virus [17, 18], with a 95% confidence interval, dropping to no earlier than 4 October [18]. Initially, this was named 2019-nCoV, and later SARS CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2). The first confirmed case was a woman who, according to the epidemiological pathway, contracted it in a market in Wuhan city (Hubei province) where live animals were sold. On the other hand, a retrospective study reports the onset of the first known case of 2019-nCoV infection on 8 December 2019 [7], with the first cases positioned in the second part of November 2019 and the first part of December 2019. By the end of 2019, the virus had already spread to some extent in the human population, and in December 2019, several health facilities in Wuhan reported the diagnosis of pneumonia of unknown etiology in several people, but which, similar to patients with SARS-CoV (*Severe Acute Respiratory Syndrome Coronavirus*) and MERS-CoV (*Middle East Respiratory Syndrome Coronavirus*), the coronaviruses that had produced small-scale outbreaks in 2002–2003 and 2012, had symptoms of viral pneumonia, including fever, coughing and chest discomfort [19], and severe cases, dyspnea and bilateral pulmonary infiltration. Although unconfirmed, 2019-nCoV has been predicted to represent the causative agent of this pneumonia [20]. Genome sequencing of the novel viral agent was performed soon after its identification, and the first sequence was published a day after confirmation, on 10 January, by Yong-Zhen Zhang [21–23] and researchers at Fudan University in Shanghai, with five more sequences published on 11 January. The publication of the sequences has enabled the beginning of the search and identification of the SARS CoV-2 genome worldwide. The first hospitalized cases of 2019-nCoV infection in China were identified in people frequenting the Huanan Seafood Wholesale Market in downtown Wuhan, where seafood, poultry and several wildlife species were sold. As of 17 January 2020, 62 cases had been confirmed in China, two cases in Thailand and one in Japan, but in reality the number of existing cases may have been higher, a situation proven by the identification on 19 January of a batch of 136 cases in Wuhan, 126 with mild symptoms, 35 in serious condition and 9 in critical condition, bringing the total number of cases in China to 198 [24], following the development of diagnostic tests for infection with the new coronavirus. Symptomatology was complemented by fever, dry cough, shortness of breath and leukopenia, and severe cases required extracorporeal membrane oxygenation. At that time, 26 deaths had been recorded, many with comorbidities and aged over 50 years. Compared to SARS-CoV, in which mortality had been 10%, and MERS-CoV, in which mortality had been 35%, 2019-nCoV appeared, at the start of the pandemic, to be less virulent, affecting mainly older people and those with pre-existing conditions [20]. Soon, several cases unrelated to Huanan Seafood Wholesale Market were identified, with some contracting the infection in health care facilities, proving human-to-human transmission [7, 23], especially favored by New Year's travel, contributing to the spread of the infection to other areas in China [23]. As new cases were continuously identified, on 30 Janu-

ary, the World Health Organization declared a global public health emergency and the new virus was recognized as having epidemic potential [25, 26], on 11 February 2020, the name of the virus was changed to SARS CoV-2, and the disease caused by it was named COVID-19 [27].

The spread of SARS CoV-2 infection has continued apace, and in mid-February it reached pandemic levels in China, with more than 3,000 cases a day, after the city of Wuhan was shut down on 23 January. In the following weeks, outdoor activities, gatherings and travel were restricted, in many localities in China, leading to a reduction in the number of cases in the country [28, 29]. However, the frequency of international travel has allowed the spread and spread of SARS CoV-2 infection to many countries around the world, prompting the World Health Organization to declare a COVID-19 pandemic. The next outbreaks where the rapid expansion of the virus occurred were in Europe, particularly Italy (as of 11 March 2020, there were 10 149 confirmed cases and 631 deaths in infected persons), Iran (as of 11 March 2020, there were 8 042 confirmed cases and 291 deaths in infected persons) and South Korea (as of 11 March 2020, there were 7 755 confirmed cases and 60 deaths in infected persons), with 696 cases of infection and 7 deaths confirmed on the International conveyance (Diamond Princess). Globally, 37 364 confirmed cases of infection and 1 130 deaths were reported, of which 4589 cases of infection and 258 deaths were reported on 11 March 2020 alone [25].

As of the second half of February 2020, the measures taken in China have been successful, with the country managing the SARS CoV-2 infection well, and in the following months, other countries have followed suit and closed down, limiting contact between residents to a minimum. Although in February-March 2020, Europe was the leader in terms of the number of confirmed cases of SARS CoV-2 infection, since April 2020, it has been overtaken by North America, with the United States of America as the main exponent, where the number of SARS CoV-2 cases has exploded, and since June 2020, also by Asia. Thus, at the end of June 2020, globally, there were a total of 10 112 754 confirmed cases of coronavirus infection (with 159 964 new cases), of which 501 562 deaths (3 043 deaths were new). Five months later, on 11 August 2020, a total of 20 274 865 COVID-19 cases and 807 530 deaths were reported globally, with 222 318 cases and 5701 new deaths recorded on 11 August 2020. The end of 2020 found humanity in the midst of the SARS CoV-2 pandemic, which had already seen three waves of increasing numbers of cases of infection in February–March, June–August and October 2020–January 2021. As of 31 December, a total of 82,626,055 cases of COVID-19 (including 681 694 new cases) and 1 804 223 deaths (including 15 283 new deaths) were reported worldwide.

The first six months of 2021 were marked by the end of the third pandemic wave, towards the end of February, which mainly affected Europe and the Americas, and the transition to the fourth wave, between April and May, with a peak of 997 105 cases on 24 April, which mainly affected Asia. In the second half of 2021, the evolution of the SARS CoV-2 pandemic crossed the fifth pandemic wave, between July and October, predominantly affecting Europe and the Americas, with a new phase of increase in the number of new confirmed cases in November. On 31 December 2021, the total number of confirmed SARS CoV-2 cases was 286 826 415, of which 1 889 175 on 31 December alone, and the number of deaths was 5 445 957, with 7 058 deaths on 31 December.

The year 2022 began with a sharp increase in the number of SARS CoV-2 infections in what was to become the sixth pandemic wave and the one with the most cases. Between January and April 2022, more than one million new confirmed cases were reported almost daily worldwide, with up to 3 652 595 new cases, including 9 063 deaths on 22 January. This surge led to an increase in statistics and by the end of June 2022, globally, a total of 551 746 601 cases were reported (865 480 cases on 30 June alone), of which 6 356 176 deaths, with 1 608 reported on 30 June, and after a reduction in the number of reported cases in May and June, from July onwards, a new small pandemic surge was recorded. Thus, the sixth pandemic wave almost doubled the number of confirmed cases of SARS CoV-2 infection worldwide, with the European population predominantly affected, followed by the Asian population and the Americas. In July and August, the number of SARS Cov-2 infections worldwide increased again, but much less than in wave 6 and compared to wave 4 from April to May 2021. This seventh wave mainly affected Asia and, less so, the Americas and Europe, and was followed by a small increase in the number of cases in October 2022 in Europe. After China dropped the zero COVID policy towards the end of 2022, a new pandemic wave affected mainly East Asia and was extended until mid-January 2023. According to the World Health Organization, the eighth wave is the most active, with more than 6 000 000 daily cases from 21–25 December globally and peaking at 7 946 896 cases on 23 December 2022 (Fig. 4–5). On the other hand, the www.worldometers.info website and Johns Hopkins University of Medicine describe it as modest, with magnitude at most at the level of the fifth pandemic wave. According to the latter, cited by the Romanian Ministry of Health, at the end of 2022, there were 664 480 798 confirmed cases of SARS CoV-2 infection worldwide (with 443 500 new cases as of

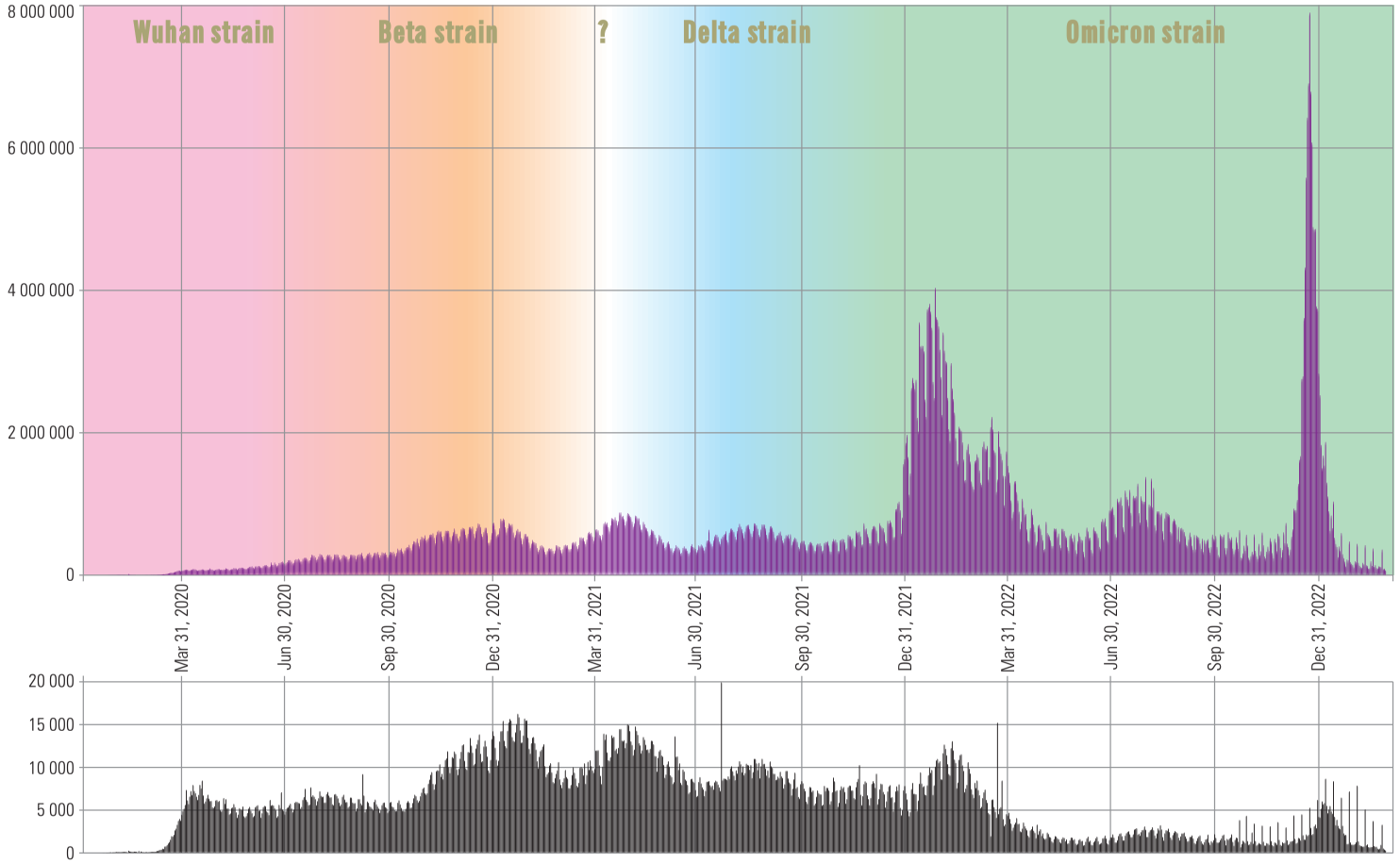

Fig. 4. SARS CoV-2 infection (puple bars, top) and the number of deaths (black bars, bottom) in people infected with SARS CoV-2, worldwide, between December, 31,2019–February, 28,2023. Source: WHO COVID-19 Dashboard. Geneva: World Health Organization, 2020. Available online: https://covid19.who.int/ (last cited: [07.03.2023]).

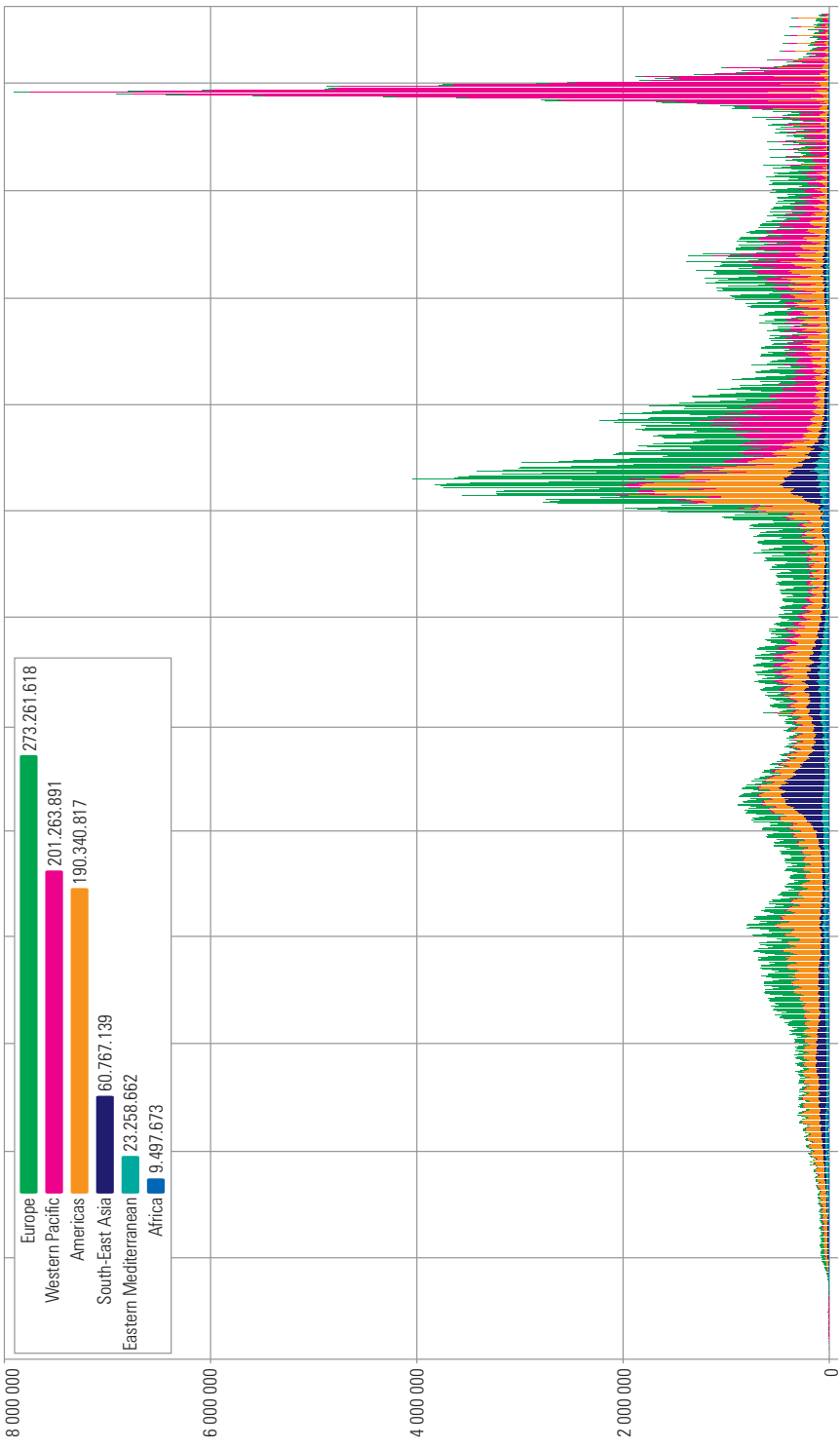

Fig. 5. Share of each WHO region in the total number of SARS CoV-2 confirmed cases, worldwide, between December, 31,2019–February, 28,2023. Source: WHO COVID-19 Dashboard. Geneva: World Health Organization, 2020. Available online: https://covid19.who.int/ (last cited: [07.03.2023]).

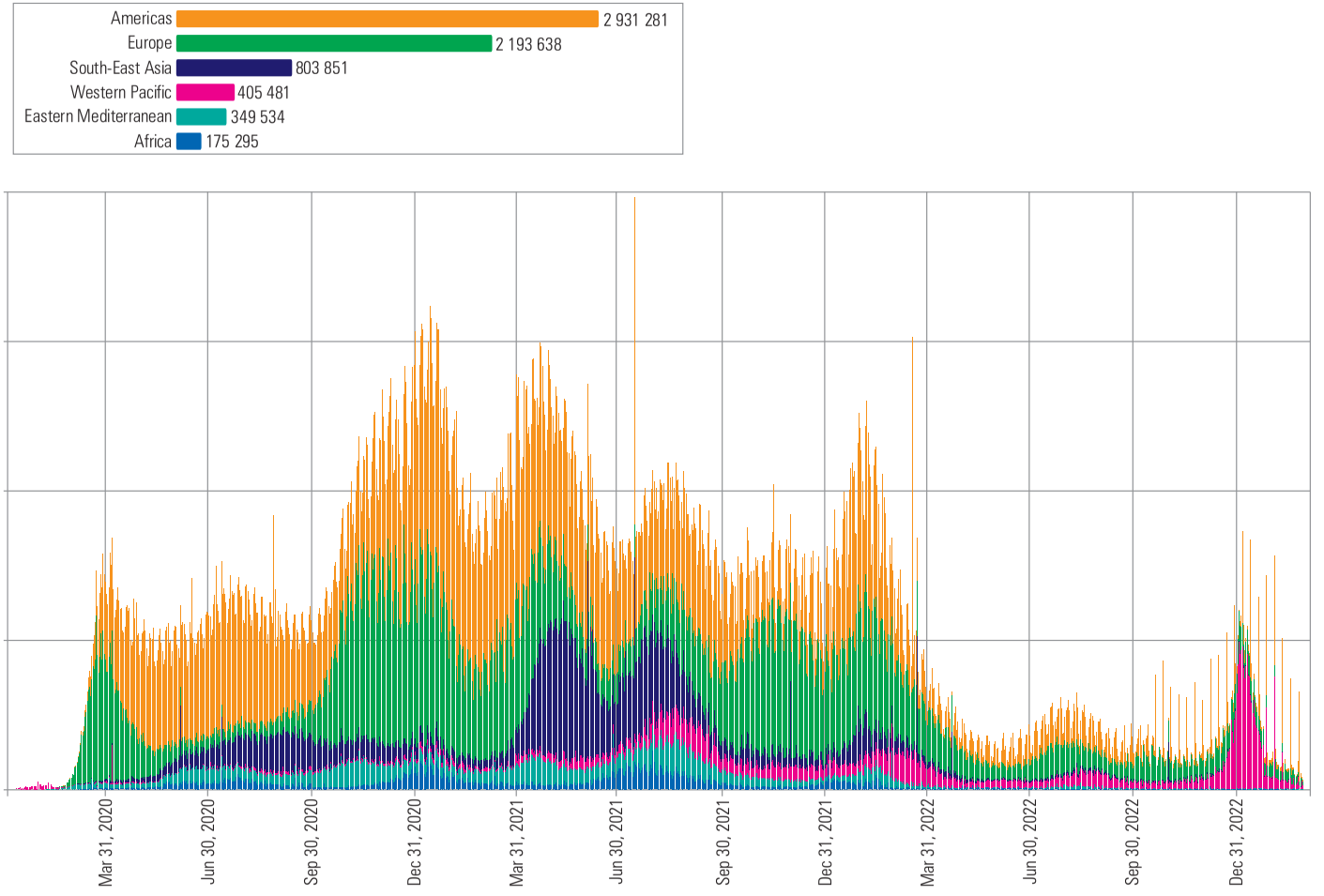

Fig. 6. Share of each WHO region in the total number of SARS CoV-2 deaths, worldwide, between December, 31,2019–February, 28,2023. Source: WHO COVID-19 Dashboard. Geneva: World Health Organization, 2020. Available online: https://covid19.who.int/ (last cited: [07.03.2023]).

31 December), including 6 696 132 deaths (with 1 399 new deaths as of 31 December).

The year 2023 marks a reduction in the number of SARS CoV-2 cases to less than 200 000 new confirmed cases every day, with the majority of cases reported in Asia. The most recent World Health Organization report on 28 February indicates 758 390 564 confirmed cases of SARS CoV-2 infection and 6 859 093 deaths, and the most recent report from Johns Hopkins University of Medicine indicates, as of 7 March 2023, a total of 676 125 671 confirmed cases worldwide, including 638 000 cases in the period 26 February to 5 March, and 6 877 999 deaths, with 4,750 deaths recorded in the period 26 February to 5 March [30–35] (Fig. 4–6).

SARS CoV-2 pandemic in Romania

In Romania, the first SARS CoV-2 infection was reported in a 25-year-old man from Gorj county on 26 February 2020, after testing all persons with whom a 71-year-old Italian man had come into contact in Romania and who had been confirmed on 25 February 2020. He had recently arrived from Italy, travelling in a coach, and had come into contact with the 25-year-old man on 19 February. The second case was that of a 38-year-old woman from Timişoara who had travelled by plane from Italy and infected a 47-year-old man from Timişoara en route. The fourth case involved a man from Maramureş. The fifth case was that of a man from Timiş, a direct contact of the 47-year-old man. The sixth confirmed case was a 16-year-old boy from Timişoara, who infected a classmate and was registered as the seventh case. Travelling in a coach with the 71-year-old Italian man, a 51-year-old man was infected by him and is the eighth case. A 49-year-old man arriving from Italy is the ninth case. He has infected a 42-year-old woman and others, both of whom have been confirmed in Bucharest and indicate the start of intra-Community transmission of SARS CoV-2 infection. On 26 February, a 60-year-old former MAI officer arrived from Israel and, on 2 March, handed out marzipan at the ADP headquarters in Bucharest's 4th sector, in a building with 120 people, the next day he showed symptoms, was admitted and, on 9 March, was confirmed with SARS CoV-2 infection. This is the 17th case and he has transmitted the virus intra-communitarily to several people. Intra-community transmission became more pronounced after a state of epidemiological emergency was instituted in Romania on 15 March 2020 at 22:00 Romania time, with the population having movement restrictions, except in special cases, aimed at exercising, going out with pets, obtaining food and medicines and travelling for work purposes, for areas with continuous professional activity. As of 0900 on 16 March 2020, 139 confirmed cases of SARS CoV2 infection had been recorded, including 16 in the last 24 hours. The first psychological threshold of 25 confirmed cases in Romania was recorded on 10 March 2020. The second psychological threshold of 50 cases was exceeded on 12 March (64 cases, with 19 new cases) and the third psychological threshold of 100 cases was exceeded on 14 March (113 cases, with 24 new cases). On 26 March 2020, the total number of 1000 newly confirmed cases was exceeded (1029, with 123 in the last 24 hours alone), and on 23 April the number exceeded 10 000 (10 096, with 386 new cases). After two months of restrictions, on 15 May 2020, Romania came out of the epidemiological emergency, with 16 437 confirmed cases of SARS CoV-2, surpassing the first wave of infection (*Fig. 4*). This peaked at 523 daily infections on 11 April 2020. On 18 May 2020, Romania entered a state of alert, which was extended until 8 March 2022. With the onset of the second wave of the pandemic at the beginning of June 2020, the number of confirmed infections started to increase again, more sharply in June, leading to a total of 26 970 cases (with 388 cases recorded in the last 24 hours) on 30 June 2020, of which 19 050 people were cured (70.634%), and 1 651 deaths (with 17 in the last 24 hours). According to official estimates, 6 269 people were still active but under observation and quarantine. In July-August 2020, the number of newly confirmed daily cases remained at a standstill, after which it began to rise more sharply, reaching a peak of 10 269 cases on 18 November, with more than 10 000 cases being recorded daily on 6, 12, 18 and 19 November. Towards the end of 2020, the number of confirmed cases per day began to fall to below 5–6 000, marking the end of the second wave. As of 31 December 2020, Romania reported a total of 632,263 confirmed cases, up from 4,322 on 31 December, and 15,767 deaths, including 171 in the last 24 hours. Of the total reported cases, 560 793 people were cured (88.696%), with 6 737 cases reported cured in the last 24 hours, 55 703 cases still active but quarantined.

The steep rise in the number of newly confirmed cases of SARS CoV-2 infection since the early days of 2022 characterised the onset of the fifth pandemic wave, which had three peaks, on 26 January with 34 255 newly confirmed cases, on 1 February with 40 018 cases, and on 8 February with 36 269 cases. The fifth wave was characterised by the greatest amplitude in the evolution of the daily number of newly-confirmed SARS CoV-2 cases, which dropped sharply in the second part of February to 7 191 cases on 26 February. The drop in the number of newly confirmed daily cases and public pressure led the Romanian authorities to completely lift the restrictions as of 8 March 2022. At that time, Romania came out of the alert status and the request for a green

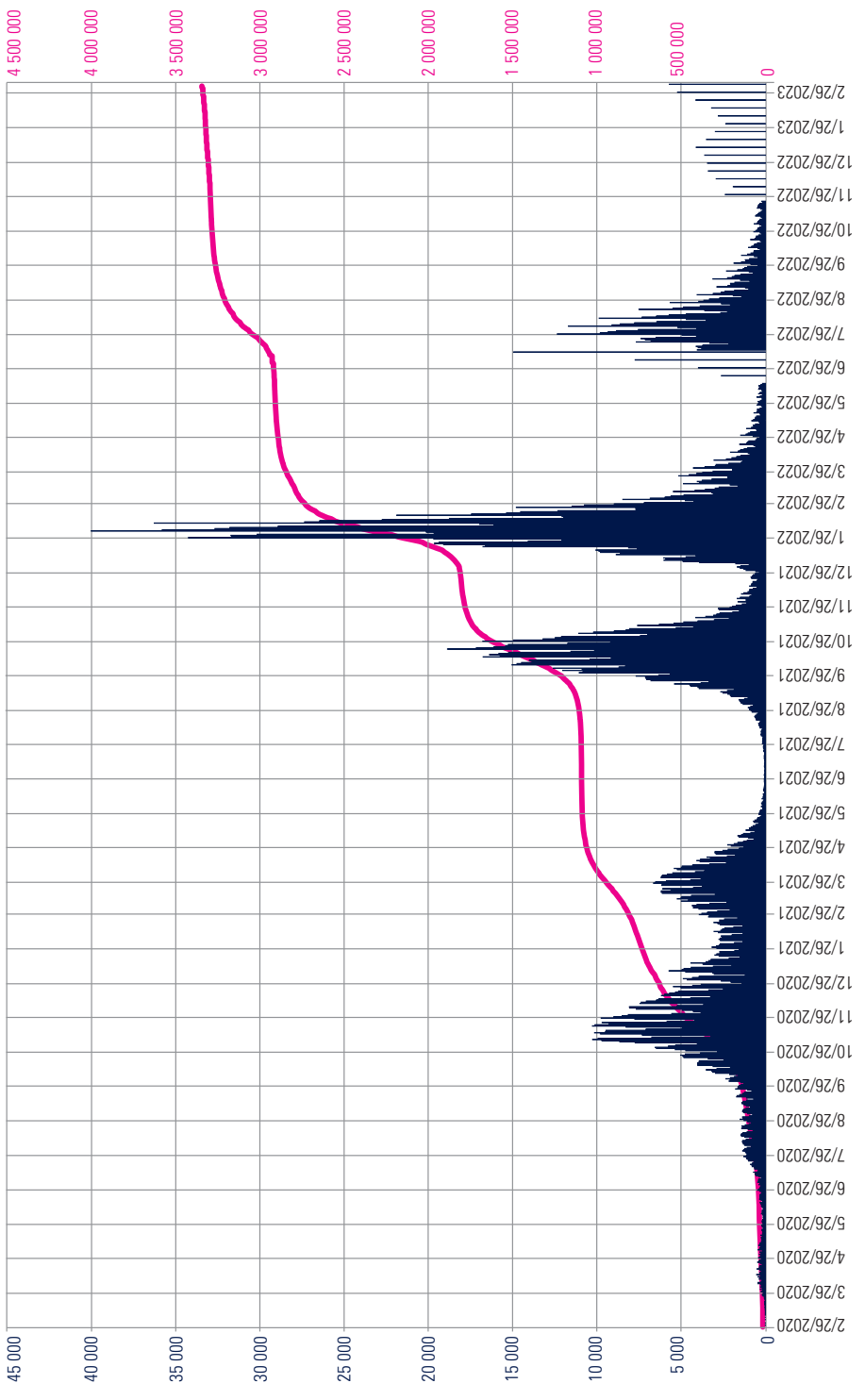

Fig. 7. Combined graph illustrating the daily/weekly number of newly confirmed SARS CoV-2 cases in Romania between 26 February 2020 and 5 March 2023 (with blue bars and baseline values on the left side of the graph) and their cumulative curve (with magenta and baseline values on the right side of the graph).
Source: https://www.ms.ro/buletine-de-presa-covid/.

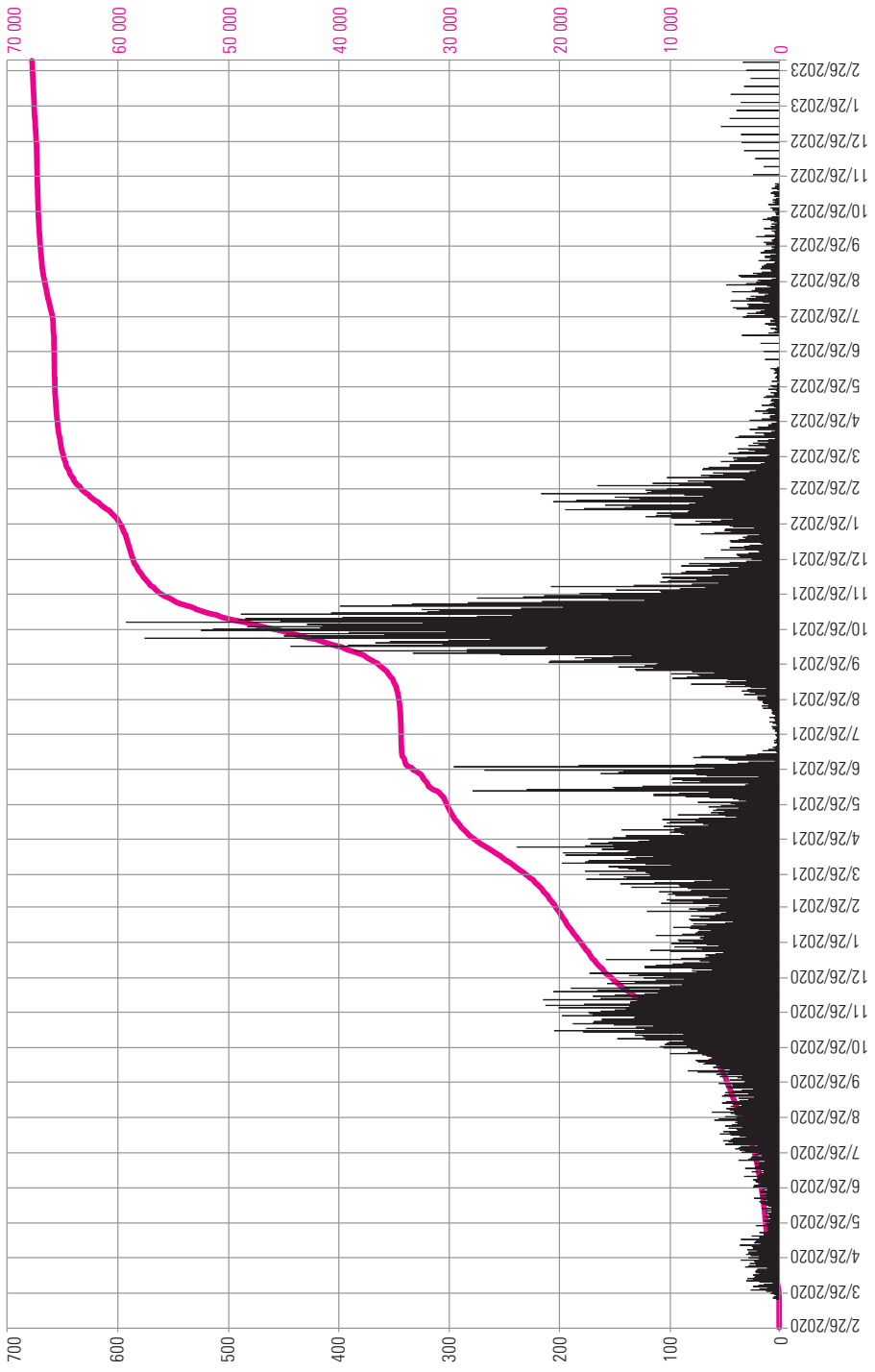

Fig. 8. Combined graph illustrating the daily/weekly number of deaths in persons confirmed with SARS CoV-2 infection in Romania between 26 February 2020 and 5 March 2023 (with black bars and baseline values on the left side of the graph) and their cumulative curve (with magenta and baseline values on the right side of the graph). Source: https://www.ms.ro/buletine-de-presa-covid/.

certificate for access to non-food and food shops or some public institutions was stopped. The low number of cases during the spring of 2022 led the Romanian authorities to stop reporting the number of cases on a daily basis, starting on 12 June, when 168 cases were recorded. For 12 June, the press release (official communiqué) of the Romanian Ministry of Health indicated a cumulative total of 2 912 705 cases of SARS CoV-2 infections at national level, and on the same day a press release (official communiqué) of the Romanian Ministry of Health was issued for 6–12 June, which reports a cumulative national total of 2 912 878 cases of SARS CoV-2 infections, resulting in a difference of 173 cases, which is maintained in subsequent releases, without resulting from daily or weekly reporting of the number of cases of SARS CoV-2 infection. On 1 October 2022, this difference increased to 174 cases and is maintained to date. It may be generated by an error in daily reporting or by an error in the accumulation of the total number of cases. All official bulletins issued by the Romanian Ministry of Health are available at: https://www.ms.ro/buletine-de-presa-covid/.

Towards the end of June and beginning of July, the number of SARS CoV-2 cases started to rise again, and from 12 July, the authorities reverted to daily reporting. As of 3 July 2022, a total of 2 927 014/2 927 187 cases of SARS CoV-2 infection had been confirmed, including 7 726 in the last 7 days, and 65 755 deaths, with 16 deaths in the last 7 days.

On 12 July, 4 044 new cases were confirmed, rising to over 5 000 cases after 17 July, reaching a peak of 12 353 cases on 26 July, the peak of the sixth wave. Less intense than the previous one, it began to decrease in intensity and by autumn 2022 the number of newly confirmed daily cases had fallen to below 500. For this reason, since 22 November, the Romanian authorities have resorted to weekly reporting of cases of SARS CoV-2 infection. On 1 January 2023, Romania totalled 3 311 911/3 312 085 cases of COVID-19, with 3 615 in the last 7 days, and 67 408 deaths, including 34 deaths recorded in the last 7 days.

The latest report, dated 6 March 2023, which totals cases from 27 February to 5 March 2023, shows 5 704 new cases and 32 deaths. In total, as of 5 March, Romania had 3 345 872/3 346 046 cases of SARS CoV-2 infection and 67 736 deaths (Fig. 7, 8).

In terms of the number of people infected with SARS CoV-2 who died (Figure 5), the first two deaths were recorded on 22 March 2020 and the first wave of deaths in spring 2020, with three peaks: 34 deaths on 25 April and 13 May, and 35 deaths on 8 May. After a relative decrease in the number of deaths in the second part of May, the second wave of deaths began in June and lasted until the end of January 2021, with the daily maximum of SARS CoV-2 deaths recorded on 8 December 2020 (213 people). February and the first part of March 2021 saw a reduction in the number of deaths, with a low of 41 people recorded on 14 February, after which the third wave of deaths began, extending into early May. During this, the daily peak of 237 deaths was recorded on 20 April. After a short period of decline, the number of cases increased again in June 2021, with daily highs of 277 deaths on 8 June, 266 deaths on 26 June and 294 deaths on 29 June 2021, with the lowest number of deaths of SARS CoV-2-infected persons recorded on 3 and 4 July, followed by steep positive and negative variations, considered the fourth wave or the end of the third wave of deaths. On 11 July, there was a low of one death, then between 12 July and 18 August, the number of deaths was reduced. From the second part of August, the fifth and largest wave of deaths associated with SARS CoV-2 infection began, with two days when more than 550 deaths were recorded, on 19 October (574 cases) and 2 November (591 cases), as many as the population of small towns in Romania. Towards the end of November, the number of deaths went into a steep downward slope, so that at the halfway point between 2021 and 2022, there would be a clear gap between the fifth and sixth waves, stretching from the end of January to the beginning of March 2022. The highest number of deaths recorded daily was on 22 February (215). Since March, the number of deaths of people infected with SARS CoV-2 has been kept low, with zero reported on 16 and 30 May 2022. On 27 July, the seventh wave of deaths associated with SARS CoV-2 infection began, peaking on 23 August (47). After the Romanian authorities stopped daily reporting of the number of cases and deaths, it is difficult to follow the evolution of these from official data [30–33] (Fig. 8).

SARS CoV-2 variants

Being propagated in a very large number of human individuals (hosts) in a relatively short and sustained time, SARS CoV2 is an RNA virus susceptible to a high mutation rate and the evolution of several variants. The main reasons for their occurrence are related to strand switching, RNA-dependent RNA polymerase activity, an enzyme lacking corrective mechanisms, and frequent recombination events of different strains of SARS CoV-2. Point mutations cause the replacement of one nitrogenous base by another and of one amino acid by another, altering cell tropism, transmissibility and pathogenicity of viruses [3]. Thus, between February and June 2020, the D614G mutation in the C-terminal region of the S1 domain of the spicular protein predominated in 74% of published sequences.

Table 1. SARS CoV-2 variants and their characteristic mutations

Pango lineage	WHO label	Isolated from	Mutations in eceptor-binding domain	Mutations in S-glycoprotein
B.1.1.7	Alpha	UK (November, 2020)	E484K, S494P, N501Y	69/70del, 144del, A570D, D614G, P681H, T716I, S982A, D1118H, K1191N
B.1.351	Beta	South Africa (October, 2020)	K417N, E484K, N501Y	D80A, D215G, 241/243del, D614G, A701V
P.1	Gamma	Japan/Brazil (December, 2020)	K417T, E484K, N501Y	L18F, T20N, P26S, D138Y, R190S, D614G, H655Y, T1027I
B.1.614.2	Delta	India (December, 2020)	L452R, T478K	T19R, G142D, D614G, P681R, R158G, 156/157del, D950N
B.1.427	Epsilon	USA (July, 2020)	L452R	D614G
B.1.429	Epsilon	USA (July, 2020)	L452R	S13I, W152C, D614G
P.2	Zeta	Brazil (April, 2020)	E484K	F565L, D614G, V1176F
B1.525	Eta	USA (December, 2020)	E484K	A67V, 69/70del, 144del, D614G, Q677H, F888L
P.3	Theta	Japan/Philippines (February, 2021)	E484K, N50	141/143del, D614G, P681H, E1092K, H1101Y, V1176F
B.1.617.1	Kappa	India (December, 2020)	E484Q, L452R	T95I, D614G, E154K, P681R, G142D, Q1071H
C.37	Lambda	Peru (November 2020)	L452Q, F490S	G75V, T76I, D614G, T859
B.1.1.529	Omicron	South Africa/Botswana (May, 2020)	?	A67V, 69–70del, 142–144del, T95I, Z145D, 211del, L212I, 214epe, G339D, R346K, S371L, S373P, S375F, K417N, N440K, G446S, L452X, S477N, T478K, E484A, F486V, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, K679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F

This mutation provides more efficient virus functionality, is associated with higher nasopharyngeal viral load and is the only mutation present in all six variants of interest (Epsilon, Eta, Iota, Kappa, Zeta and Lambda) and five variants of concern (Alpha, Beta, Gamma, Delta, and Omicron) circulating worldwide (*Table 1*) [36, 37].

Worldwide, in the first wave (February–March 2020) and the second wave (June–August 2020) the Wuhan strain (Wuhan waves) predominated, in the third wave (October 2020–January 2021) the Beta strain (Beta wave) predominated, in the fifth wave (July–October 2021) the Delta variant (Delta wave) predominated, and in the following waves (sixth, between January and April 2022, seventh, between July and August 2022, and eighth, between mid-December 2022 and mid-January 2023), the Omicron variant became dominant [36, 38, 39].

In Romania, the Wuhan strain was dominant at the end of 2020, but from the second half of February 2021 it was overtaken by the Alpha variant. In spring 2021, a few cases of Beta and Gamma variant infections were identified, but they never became dominant. From late April, the Delta variant emerged and became prevalent from July 2021. Towards the end of 2021, the Omicron variant emerged and dominated almost all of 2022, towards the end of the year sharing cases with variants other than Omicron [40] (Fig. 9).

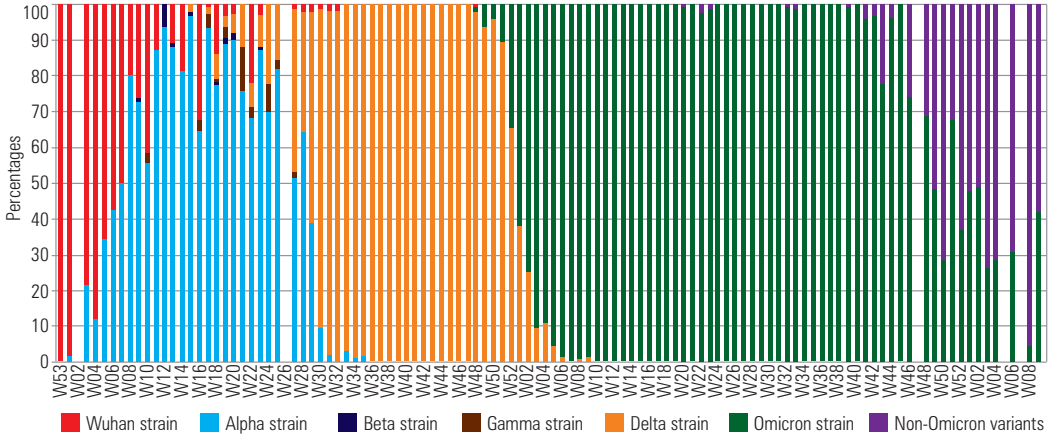

Fig.9. The proportion of variants in SARS CoV-2 samples collected from Romania and sequenced between weeks 53/2020 and 9/2023. Source: https://insp.gov.ro/centrul-national-de-supraveghere-si-control-al-bolilor-transmisibile-cnscbt/infectia-cu-noul-coronavirus-sars-cov-2/analiza-cazuri-confirmate-covid19/

Table 2. Anti-SARS CoV-2 vaccines and their main characteristics

Vaccine name	Vaccine type	Producer	Origin country	Administration	Efficiency (%)
BNT162b/2	Nucleoside-modified mRNA-based vaccine	Pfizer-BioNTech	USA	2 doses 3 weeks apart	91.3
mRNA-1273	mRNA-based vaccine encapsulated in lipid nanoparticle	Moderna	USA	2 Doses 4 weeks apart 94.5	
AZD1222 Covishield	Recombinant ChAdOx1 adenovirus vector encoding spike protein Ag of the SARS-CoV-2	AstraZeneca-Oxford	UK, USA	2 doses between 4 and 12 weeks apart	90.0
Sputnik V rAd26 rAd5	Recombinant adenovirus vector-based COVID-19 vaccine	Gamaleya Research Institute	Russia	2 different doses 3 weeks apart	92.0
Ad26.CoV.S JNJ-78436735	Recombinant, non-replicating adenovirus type 26 vectored vaccine encoding SARSCoV-2 spike protein	Johnson & Johnson, Janssen vaccines	Netherland, USA	Single dose	72.0
COVAXIN BBVI52	The whole SARSCoV-2 virus inactivated (Vero cell)	Bharat Biotech	India	2 doses 4 weeks apart	81.0
Corona Vac	Inactivated vaccine (Vero cell, formalin with alum)	Sinovac	China	2 doses	50.0–84.0
NVX-CoV2373 Covavax	Recombinant NP profusion spike protein formulated with matrix-M adjuvant	NovaVax	USA	2 doses	89.3
BBIBP-CoV vaccine	Inactivated SARSCoV-2 vaccine produced in Vero cell	Sinopharm	China	2 doses	78.0

Anti-SARS CoV-2 vaccines

During the pandemic, 9 vaccines targeted against SARS CoV-2 were developed (*Table 2*). Two of these, BNT162b/2, produced by Pfizer-BioNTech of the US, and mRNA-1273, produced by Moderna of the US, are based on mRNA platforms, AZD1222 Covishield vaccines, produced by Astra-Zeneca-Oxford, a UK-US collaboration, Sputnik V rAd26 rAd5, produced by Gamaleya Research Institute of Russia, and Ad26.CoV. S JNJ-78436735, produced by the Americans from Johnson & Johnson and the Dutch from Janssen vaccines, are based on recombinant adenoviral vectors, COVAXIN BBVI52 vaccines, produced by Bharat Biotech of India, and BBIBP-CoV vaccine, produced by the Chinese from Sinopharm, use inactivated SARSCoV-2 vaccine produced in Vero cell, Corona Vac vaccine, produced by the Chinese of Sinovac, is an inactivated vaccine, in Vero cell and formalin with alum, and NVX-CoV2373 Covavax, produced by the Americans of NovaVax, uses Recombinant NP profusion spike protein. These are capable of inducing the synthesis of specific anti-SARS CoV-2 antibodies with variable efficiency. Thus, BNT162b/2 and mRNA-1273 vaccines are more than 90% effective against Alpha variant infections, but less effective against Gamma variant. Most CoV-2 SARS vaccines are less effective against the Beta variant [Thakur, 2022].

Globally, by the end of February 2023, 13228728467 doses of SARS CoV-2 vaccine had been administered, immunising 5 512 995 309 people who had received at least one dose of vaccine, of which 5 073 870 238 people were fully immunised against SARS CoV-2 [32]. In Romania, the administration of SARS CoV-2 vaccines began on 27 December 2020, and by 5 March 2023, 16 919 549 doses of vaccine had been administered, immunising 8 141 569 people with the first dose, of whom 8 130 345 people received the full vaccination schedule and 2 666 628 people with the last booster dose [40].

Bibliografie

1. Mihaescu G, Chifiriuc MC, Iliescu C, Vrancianu CO, Ditu LM, Marutescu LG, Grigore R, Berteșteanu Ș, Constantin M, Gradisteanu Pircalabioru G. SARS-CoV-2: From Structure to Pathology, Host Immune Response and Therapeutic Management. Microorganisms. 2020 Sep 24;8(10):1468. doi: 10.3390/microorganisms8101468. PMID: 32987852; PMCID: PMC7600570
2. Pal M, Berhanu G, Desalegn C, Kandi V. Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2): An Update. Cureus. 2020 Mar 26;12(3):e7423. doi: 10.7759/cureus.7423. PMID: 32337143; PMCID: PMC7182166
3. Parczewski M, Ciechanowicz A. Molecular epidemiology of SARS-CoV-2: a review of current data on genetic variability of the virus. Pol Arch Intern Med. 2020 Jan 29;131(1):63-69. doi: 10.20452/pamw.15550. Epub 2020 Aug 11. PMID: 32785209
4. Sahin A, Erdogan A, Mutlu Agaoglu P, Dineri Y, Cakirci A, Senel M, et al. 2019 Novel Coronavirus (COVID-19) Outbreak: A Review of the Current Literature. EJMO. 2020; 4(1): 1-7
5. Ksiazek TG, Erdman D, Goldsmith CS, Zaki SR, Peret T, Emery S, Tong S, Urbani C, Comer JA, Lim W, Rollin PE, Dowell SF, Ling AE, Humphrey CD, Shieh WJ, Guarner J, Paddock CD, Rota P, Fields B, DeRisi J, Yang JY, Cox N, Hughes JM, LeDuc JW, Bellini WJ, Anderson LJ. SARS Working Group. A novel coronavirus associated with severe acute respiratory syndrome.

N Engl J Med. 2003 May 15;348(20):1953-66. doi: 10.1056/NEJMoa030781. Epub 2003 Apr 10. PMID: 12690092

6. Norouzi M, Miles MA, Norouzi S. Genetics and Biological Characteristics of SARS-CoV-2. In: Adibi S, Griffin P, Sanicas M, Rashidi M, Lanfranchi F. (eds). Frontiers of COVID-19. Springer Cham. 2022. https://doi.org/10.1007/978-3-031-08045-6_4
7. Wu CR, Yin WC, Jiang Y, Xu HE. Structure genomics of SARS-CoV-2 and its Omicron variant: drug design templates for COVID-19. Acta Pharmacol Sin. 2022 Dec;43(12):3021-3033. doi: 10.1038/s41401-021--00851-w. Epub 2022 Jan 20. PMID: 35058587; PMCID: PMC8771608
8. Gupta M, Azumaya CM, Moritz M, Pourmal S, Diallo A, Merz GE, Jang G, Bouhaddou M, Fossati A, Brilot AF, Diwanji D, Hernandez E, Herrera N, Kratochvil HT, Lam VL, Li F, Li Y, Nguyen HC, Nowotny C, Owens TW, Peters JK, Rizo AN, Schulze-Gahmen U, Smith AM, Young ID, Yu Z, Asarnow D, Billesbølle C, Campbell MG, Chen J, Chen KH, Chio US, Dickinson MS, Doan L, Jin M, Kim K, Li J, Li YL, Linossi E, Liu Y, Lo M, Lopez J, Lopez KE, Mancino A, Moss FR, Paul MD, Pawar KI, Pelin A, Pospiech TH, Puchades C, Remesh SG, Safari M, Schaefer K, Sun M, Tabios MC, Thwin AC, Titus EW, Trenker R, Tse E, Tsui TKM, Wang F, Zhang K, Zhang Y, Zhao J, Zhou F, Zhou Y, Zuliani-Alvarez L; QCRG Structural Biology Consortium; Agard DA, Cheng Y, Fraser JS, Jura N, Kortemme T, Manglik A, Southworth DR, Stroud RM, Swaney DL, Krogan NJ, Frost A, Rosenberg OS, Verba KA. CryoEM and AI reveal a structure of SARS-CoV-2 Nsp2, a multifunctional protein involved in key host processes. bioRxiv [Preprint]. 2021 May 11:2021.05.10.443524. doi: 10.1101/2021.05.10.443524. PMID: 34013269; PMCID: PMC8132225
9. Lei J, Kusov Y, Hilgenfeld R. Nsp3 of coronaviruses: Structures and functions of a large multi-domain protein. Antiviral Res. 2018 Jan;149:58-74. doi: 10.1016/j.antiviral.2017.11.001. Epub 2017 Nov 8. PMID: 29128390; PMCID: PMC7113668
10. Shin D, Mukherjee R, Grewe D, Bojkova D, Baek K, Bhattacharya A, Schulz L, Widera M, Mehdipour AR, Tascher G, Geurink PP, Wilhelm A, van der Heden van Noort GJ, Ovaa H, Müller S, Knobeloch KP, Rajalingam K, Schulman BA, Cinatl J, Hummer G, Ciesek S, Dikic I. Papain-like protease regulates SARS-CoV-2 viral spread and innate immunity. Nature. 2020 Nov;587(7835):657-662. doi: 10.1038/s41586-020-2601-5. Epub 2020 Jul 29. PMID: 32726803; PMCID: PMC7116779
11. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020 Apr 7;323(13):1239-1242. doi: 10.1001/jama.2020.2648. PMID: 32091533
12. Xia S, Lan Q, Su S, Wang X, Xu W, Liu Z, Zhu Y, Wang Q, Lu L, Jiang S. The role of furin cleavage site in SARS-CoV-2 spike protein-mediated membrane fusion in the presence or absence of trypsin. Signal Transduct Target Ther. 2020 Jun 12;5(1):92. doi: 10.1038/s41392-020-0184-0. PMID: 32532959; PMCID: PMC7289711
13. Li G, Fan Y, Lai Y, Han T, Li Z, Zhou P, Pan P, Wang W, Hu D, Liu X, Zhang Q, Wu J. Coronavirus infections and immune responses. J Med Virol. 2020 Apr;92(4):424-432. doi: 10.1002/jmv.25685. Epub 2020 Feb 7. PMID: 31981224; PMCID: PMC7166547
14. Masters PS. The molecular biology of coronaviruses. Adv Virus Res. 2006;66:193-292. doi: 10.1016/S0065-3527(06)66005-3. PMID: 16877062; PMCID: PMC7112330
15. McBride R, van Zyl M, Fielding BC. The coronavirus nucleocapsid is a multifunctional protein. Viruses. 2014 Aug 7;6(8):2991-3018. doi: 10.3390/v6082991. PMID: 25105276; PMCID: PMC4147684
16. Holmes EC, Goldstein SA, Rasmussen AL, Robertson DL, Crits-Christoph A, Wertheim JO, Anthony SJ, Barclay WS, Boni MF, Doherty PC, Farrar J, Geoghegan JL, Jiang X, Leibowitz JL, Neil SJD, Skern T, Weiss SR, Worobey M, Andersen KG, Garry RF, Rambaut A. The origins of SARS-CoV-2: A critical review. Cell. 2021 Sep 16;184(19):4848-4856. doi: 10.1016/j.cell.2021.08.017. Epub 2021 Aug 19. PMID: 34480864; PMCID: PMC8373617
17. Bryner J. 1st known case of coronavirus traced back to November in China. 2020 March 14. [cited 2023 March 06]. Available from: https://www.livescience.com/first-case-coronavirus-found.html
18. Roberts DL, Rossman JS, Jarić I. Dating first cases of COVID-19. PLoS Pathog. 2021 Jun 24;17(6):e1009620. doi: 10.1371/journal.ppat.1009620. PMID: 34166465; PMCID: PMC8224943
19. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China,

2019. N Engl J Med. 2020 Feb 20;382(8):727-733. doi: 10.1056/NEJMoa2001017. Epub 2020 Jan 24. PMID: 31978945; PMCID: PMC7092803
20. Gralinski LE, Menachery VD. Return of the Coronavirus: 2019-nCoV. Viruses. 2020 Jan 24;12(2):135. doi: 10.3390/v12020135. PMID: 31991541; PMCID: PMC7077245
21. Virological.org; 10th January 2020 [cited 2023 March 06]. Available from: https://virological.org/t/novel-2019-coronavirus-genome/319
22. Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1, complete genome; 2020 [cited 2023 March 06]. Available from: https://www.ncbi.nlm.nih.gov/nuccore/MN908947
23. Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol. 2021 Mar;19(3):141-154. doi: 10.1038/s41579-020-00459-7. Epub 2020 Oct 6. Erratum in: Nat Rev Microbiol. 2022 May;20(5):315. PMID: 33024307; PMCID: PMC7537588
24. Jiang S, Du L, Shi Z. An emerging coronavirus causing pneumonia outbreak in Wuhan, China: calling for developing therapeutic and prophylactic strategies. Emerg Microbes Infect. 2020 Jan 31;9(1):275-277. doi: 10.1080/22221751.2020.1723441. Erratum in: Emerg Microbes Infect. 2020 Dec;9(1):539. PMID: 32005086; PMCID: PMC7033706
25. World Health Organization. Coronavirus disease 2019 (COVID-19). Situation report – 51. 2020 [cited 2023 March06].Availablefrom:https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57_10
26. Eurosurveillance editorial team. Note from the editors: World Health Organization declares novel coronavirus (2019-nCoV) sixth public health emergency of international concern. Euro Surveill. 2020 Feb;25(5):200131e. doi: 10.2807/1560-7917.ES.2020.25.5.200131e. Epub 2020 Jan 31. PMID: 32019636; PMCID: PMC7014669
27. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 2020 Apr;5(4):536-544. doi: 10.1038/s41564-020-0695-z. Epub 2020 Mar 2. PMID: 32123347; PMCID: PMC7095448
28. Fisher D, Heymann D. Q&A: The novel coronavirus outbreak causing COVID-19. BMC Med. 2020 Feb 28;18(1):57. doi: 10.1186/s12916-020-01533-w. PMID: 32106852; PMCID: PMC7047369
29. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents. 2020 Mar;55(3):105924. doi: 10.1016/j.ijantimicag.2020.105924. Epub 2020 Feb 17. PMID: 32081636; PMCID: PMC7127800
30. https://www.ms.ro/buletine-de-presa-covid/
31. https://covid19.stirioficiale.ro/informatii
32. WHO COVID-19 Dashboard. Geneva: World Health Organization, 2020. Available online: https://covid19.who.int/ (last cited: [07.03.2023])
33. Situația la nivel global, actualizată zilnic. Infecția cu noul coronavirus (SARS-CoV-2). 2020 [cited 2023 March 06]. Available from: https://insp.gov.ro/centrul-national-de-supraveghere-si-control-al-bolilor-transmisibile-cnscbt/infectia-cu-noul-coronavirus-sars-cov-2/situatia-la-nivel-global-actualizata-zilnic/
34. https://www.worldometers.info/coronavirus/
35. https://coronavirus.jhu.edu/map.html
36. He X, Hong W, Pan X, Lu G, Wei X. SARS-CoV-2 Omicron variant: Characteristics and prevention. MedComm (2020). 2021 Dec 16;2(4):838-845. doi: 10.1002/mco2.110. PMID: 34957469; PMCID: PMC8693031
37. Thakur V, Bhola S, Thakur P, Patel SKS, Kulshrestha S, Ratho RK, Kumar P. Waves and variants of SARS-CoV-2: understanding the causes and effect of the COVID-19 catastrophe. Infection. 2022 Apr;50(2):309-325. doi: 10.1007/s15010-021-01734-2. Epub 2021 Dec 16. Erratum in: Infection. 2022 Jan 14;: PMID: 34914036; PMCID: PMC8675301
38. Wassenaar TM, Wanchai V, Buzard G, Ussery DW. The first three waves of the Covid-19 pandemic hint at a limited genetic repertoire for SARS-CoV-2. FEMS Microbiol Rev. 2022 May 6;46(3):fuac003. doi: 10.1093/femsre/fuac003. PMID: 35076068; PMCID: PMC9075578
39. Koné A, Diallo D, Kané F, Diarra B, Coulibaly TA, Sameroff SC, Diarra HB, Diakité MT, Camara F, Maiga O, Keita D, Dolo O, Somboro A, Coulibaly Y, Bane S, Togo ACG, Somboro AM, Togo J, Coulibaly M, Coulibaly G, Kone M, Degoga B, Dramé HB, Traoré FG, Diallo F, Sanogo F, Kone K, Diallo IB, Sanogo M, Diakité M, Mishra N, Neal A, Saliba-Shaw K, Sow Y, Hensley L, Lane HC, Briese T, Lipkin WI, Doumbia S. Dynamics of SARS-CoV-2 variants characterized during different COVID-19 waves in Mali. IJID Reg. 2023 Mar;6:24-28. doi: 10.1016/j.ijregi.2022.11.009. Epub 2022 Nov 25. PMID: 36448028; PMCID: PMC9691504
40. https://insp.gov.ro/