When Will the COVID-19 Pandemic End?

Kaushik Bharati*

Abstract

The COVID-19 pandemic, which originated in Wuhan, China, has spread across the world and has wreaked havoc the globe. It has been ongoing for over two years and has killed over 6 million people! Several interventions are available for tackling the virus. These include drugs such as dexamethasone for treating severe and critical patients, as well as public health measures such as wearing masks, handwashing with soap and water, using alcohol-based hand sanitizers, physical distancing, and avoiding crowds, among others. The recent development and deployment of safe and effective COVID-19 vaccines have been a game-changer in tackling the disease on a war footing. However, despite these life-saving interventions, hurdles still remain. These include the emergence of variants and inequitable distribution of vaccines, significantly prolonging the pandemic and unnecessarily taking away countless lives. The present review article will try to answer the million-dollar question of when the pandemic will eventually end and what strategies will be required to achieve this goal.

Keywords: COVID-19, Pandemic, Vaccine

Indian Journal of Physiology and Allied Sciences (2022); **ISSN:** 0367-8350 (Print)

Introduction

Coronaviruses are so-called because they resemble a crown (Latin: *"corona"* = *"crown"*) due to the projection of the spike proteins from their surface. Coronaviruses originated long ago and can be traced back to pre-biblical times. The first coronaviruses could have originated as far back as 8000 BC. It is believed that these primitive coronaviruses co-evolved with bats, their natural host. There are four types of coronaviruses – alpha, beta, gamma, and delta. The beta coronaviruses are considered the oldest, having originated way back in 3,300 BC.[1]

In the modern era, coronaviruses were first detected in animals and birds in the US during the 1920s.[2] These viruses have been reported in multiple animal species, including cats, dogs, pigs, rats, rabbits, calves, and mice.

In 1965, Dr. David Tyrrell and Dr. Malcolm Bynoe discovered the first human coronavirus that resembled the common cold virus, which they designated as B8140.[3] Since then, several new human coronaviruses have been discovered, including the severe acute respiratory syndrome coronavirus (SARS-CoV), which was responsible for the SARS outbreak. The World Health Organization (WHO) renamed SARS-CoV SARS-CoV-1 when SARS-CoV-2 emerged, which is responsible for the current coronavirus disease 2019 (COVID-19). SARS-CoV-1 was first detected in Yunnan Province of China in 2003.[4,5] Interestingly, this was the first time where a virus *"jumped"* from its animal host (bats) to humans through an intermediate host (civets). The 2003 SARS epidemic was the largest to be reported then and was considered a *"wake-up call"* to prepare for larger ones in the future. Other coronaviruses that were discovered during the past decade are presented in Table 1.

Table 1: Recently Discovered Human Coronaviruses

Virus	*Year of Discovery*	*Place of Discovery*
SARS-CoV-1	2003	Yunnan, China
NL63 / NL	2004	Amsterdam, Netherlands
HCoV-NH	2005	New Haven, Connecticut, USA
HKU-1	2005	Hong Kong
MERS-CoV	2012	Saudi Arabia
SARS-CoV-2	2019	Wuhan, China

Origin and Progression of the COVID-19 Pandemic

The COVID-19 pandemic originated in the city of Wuhan in the Hubei Province of China, where a cluster of atypical pneumonia cases was reported on 31 December 2019. The Chinese Government initially dismissed these as normal pneumonia cases and paid little attention. As a result, the number of cases started to mount from January onwards and spiraled out of control, eventually spreading across the globe to hitherto unaffected areas. Consequently, the WHO Director-General, Dr. Tedros Adhanom Ghebreyesus, declared it as a Public Health Emergency of International Concern (PHEIC) on 30 January 2020.[6] Subsequently, on 11 March 2020, WHO dubbed COVID-19 the first coronavirus pandemic in recorded history.[7] As of 9 March 2022, COVID-19 had spread to 224 countries and territories, resulting in more than 449 million cases and over 6 million deaths.[8]

This COVID-19 pandemic is the fifth and arguably the largest in magnitude since the Spanish Flu of 1918, which killed at least 50 million people across the globe. Other pandemics were the Asian Flu (1957), Hong Kong Flu (1968),

Health Policy Consultant – UNESCO, New Delhi, India

*Corresponding author: Kaushik Bharati, Health Policy Consultant – UNESCO, New Delhi, India, Email: dr.kaushik.bharati@gmail.com

How to cite this article: Bharati K. When Will the COVID-19 Pandemic End?. Indian Journal of Physiology and Allied Sciences. 2022;74(2):19-24.

Conflict of interest: None

Submitted: 17/11/2021 **Accepted:** 14/03/2022 **Published:** 15/06/2022

and Pandemic Flu (2009), which killed 1.5 million, 1 million, and 300,000 people, respectively. In comparison, COVID-19 killed over 6 million people on 9 March 2022.[8] Undoubtedly, it's the deadliest pandemic since the Spanish flu.

WHO's Initial Response to the COVID-19 Pandemic

The WHO quickly responded to the pandemic and didn't sit idle. It promptly activated its emergency response team that set the ball rolling and which has been sustained till date. The timeline of WHO's initial response is provided in Table 2.

SARS-CoV-2: The Virus that Causes COVID-19

SARS-CoV-2 is the virus that causes COVID-19, which is currently wreaking havoc across the globe. Previously, it was called the 2019 novel coronavirus (2019-nCoV). Taxonomically, this virus is classified as a severe acute respiratory syndrome-related coronavirus (SARSr-CoV), belonging to the Family *Coronaviridae* and Sub-family *Betacoronavirus*. SARS-CoV-2 is the 7th coronavirus capable of causing human infections. Other human viruses are infecting include SARS-CoV-1, MERS-CoV, HKU1, NL63, OC43, and 229E. SARS-CoV-1, SARS-CoV-2, and MERS-CoV cause severe disease, while the other four causes mild disease. Mild disease is characterized symptomatically by fever, headache, dry cough, and fatigue. Severe symptoms include shortness of breath, painful congestion in the chest, difficulty speaking, and restricted movement. The most severe symptom, which often results in death, is acute respiratory distress syndrome (ARDS).

SARS-CoV-2 is a very contagious virus having a basic reproduction number (Ro) between 1.5 and 7 and a doubling time of 2-3 days. It exhibits a mortality rate of 1%, which is 10-times higher than influenza viruses. Hence, it's transmitted at lightning speed, and it's a killer! SARS-CoV-2 is believed to have originated in the "wet market" in Wuhan, selling meat from exotic animals for consumption. Here, it "jumped" from bats to humans via pangolins, which are presumed to act as intermediate hosts. It then underwent a genetic mutation that allowed it to spread to humans.[9] The virus again mutated, thereby giving it the ability to cause human-to-human transmission.

SARS-CoV-2 is spread through droplets or aerosols by coughing or sneezing. It can also be spread by touching infected surfaces. On average, the incubation period of this virus is 5-6 days. This is why the quarantine period is generally kept at 14 days, allowing ample time to reduce infectivity should the virus be present in the body of the quarantined individual. Studies have shown that a single infection with SARS-CoV-2 can lead to 2 to 4 infections in the absence of COVID-appropriate behavior or diminished immunity.

SARS-CoV-2 has a single-stranded, positive sense RNA genome of approximately 30 kb in length and a diameter of 50-200 nanometres. SARS-CoV-2, like other coronaviruses, is made up of four structural proteins, with three on the surface, i.e., spike (S), envelope (E), and membrane (M). In contrast, the nucleocapsid (N) protein remains bound to the genomic RNA and protects it from degradation, stabilizing it (Figure 1). Of these, the S protein is vital for attachment and virus entry into a cell, thereby causing infection. The cellular receptor to which the virus attaches is the angiotensin-converting enzyme 2 (ACE2) receptor.

Vaccines: Key to Ending the COVID-19 Pandemic

The current COVID-19 pandemic, which started more than two years ago, is still not showing any signs of slowing down. This type of unprecedented health calamity comes only once in a century.

Since the pandemic began, scientists have agreed unequivocally that a vaccine was the answer to ending it. However, developing a vaccine hasn't been easy, particularly

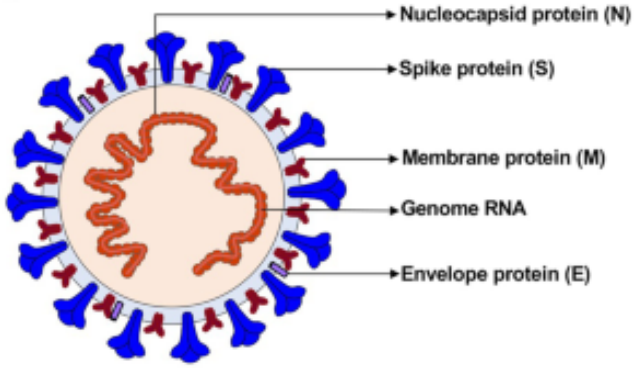

Figure 1: SARS-CoV-2 structure

Table 2: Timeline of WHO's Initial Response to the COVID-19 Pandemic

Date	*Response*
31 December 2019	The cluster of atypical pneumonia cases of unknown etiology reported from Wuhan, China
1 January 2020	WHO activated its Incident Management Support Team
2 January 2020	The Global Outbreak Alert and Response Network (GOARN) was informed about the developments by WHO
5 January 2020	WHO warned that human-to-human transmission could occur
11 January 2020	• Chinese scientists shared first genomic sequence of SARS-CoV-2 isolated in Wuhan (Wuhan strain) • First death from COVID-19 reported in China
13 January 2020	First COVID-19 case reported outside China, in Thailand
22 January 2020	Human-to-human transmission in Wuhan confirmed by WHO
30 January 2020	WHO declared COVID-19 as a Public Health Emergency of International Concern (PHEIC)
11 March 2020	WHO dubbed COVID-19 as a "pandemic."

since the pathogen is absolutely new and completely unknown. Generating the correct type of immune response is critical for neutralizing the virus, which was difficult to achieve with the limited knowledge available at the beginning of the pandemic. However, the knowledge gleaned from the previous two epidemics of SARS (2003) and MERS (2012) was instrumental in designing the vaccines for generating optimal immunogenicity. Since vaccines are vital for ending the pandemic, scientists around the globe have made concerted efforts to develop these life-saving tools.

Immune Responses Generated by Vaccines

The immune system acts like a shield against various pathogens and other toxic insults, just like an umbrella provides a shield against the rain. The immune system is bombarded by pathogens incessantly 24x7. The lymphocytes, which are a subset of the WBCs, circulate through the lymphatic and blood vascular system. These lymphocytes either mature in the thymus gland or in the bone marrow. Accordingly, they are termed T-cells or B-cells, respectively. While the T-cells generate cell-mediated immunity, B-cells generate humoral immunity. These two types of immune responses collectively act in a concerted manner to provide protection against disease-causing microbes. These two pathways are depicted in Figure 2 in the context of SARS-CoV-2.

Factors Impacting the Immune Responses Generated by Vaccines

Many factors can influence the immune responses generated by vaccines, the major factor being the vaccine itself. This can include the vaccine type, the type of pathogen used in the formulation, the nature of the adjuvant, the dose and schedule of the vaccine, as well as the route of administration during vaccination. Several host factors also influence vaccine immunogenicity, including age, gender, presence of comorbidities, as well as whether the vaccinee is immunocompromised or on immunosuppressant medication. Besides these, several behavioral factors, especially smoking and alcohol consumption, also significantly influence the magnitude and intensity of the immune response.

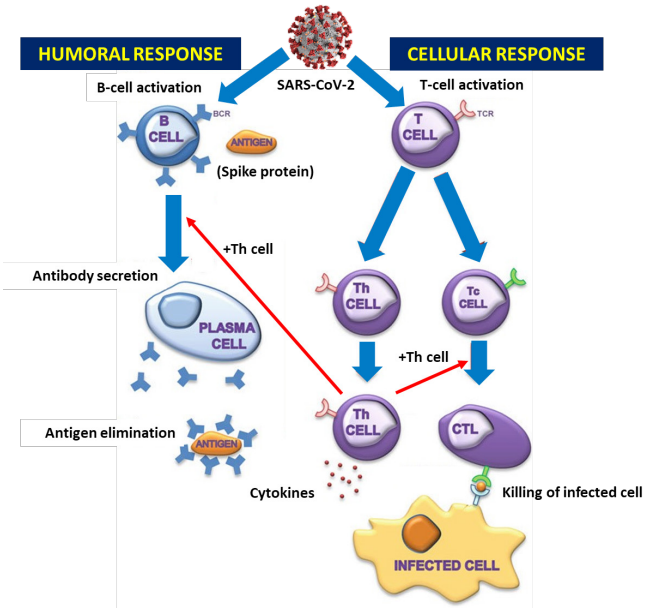

Figure 2: Humoral and cellular immune responses against SARS-CoV-2

SARS-CoV-2 Spike Protein: The Antigen Used for Vaccine Development

The SARS-CoV-2 S protein is of vital importance in eliciting the immune response. The ACE2 receptor on the cell surface is the structure to which the S protein binds, resulting in the fusion of the virus followed by its entry into the cell. The S protein has two subunits – S1 and S2 that mediate receptor binding and fusion, respectively. The receptor-binding domain (RBD) is present in the S1 subunit and is responsible for binding to the ACE2 receptor.10 Therefore, while designing the vaccines, the main focus has been on the RBD so that the antibodies generated would specifically bind to this domain of the S1 subunit, thereby preventing infection much more effectively (Figure 3).

Optimization of Vaccine Design: Importance of Immunodominant Epitopes

SARS-CoV-2 has specific surface projections known as immunodominant epitopes that allow the virus to stimulate the immune system more effectively than other surface structures. Hence, while designing the vaccine constructs, the idea is to incorporate as many of the immunodominant epitopes as possible so that they generate a highly specific and robust immune response. Moreover, harmful adverse effects can be avoided by excluding non-immunogenic and redundant surface proteins from the vaccine constructs. Hence, during the initial stages of vaccine development, efforts were directed at identifying useful immunodominant B- and T-cell epitopes. The efforts paid off as more than 50 such immunodominant epitopes were discovered. Importantly, these epitopes were safe, non-allergenic, non-toxic, and didn't cause autoimmunity either. Therefore, these epitopes were selected as possible candidates for designing vaccines.[11]

COVID-19 Vaccine Platforms

As of 1 March 2022, there were 342 candidate vaccines under development, including 147 in clinical trials and 195 in pre-clinical development. There are various types of vaccine platforms, including traditional ones such as killed/inactivated and live-attenuated virus; recombinant protein

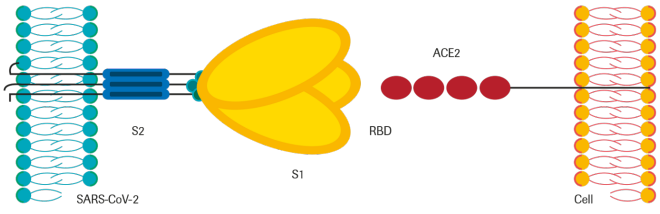

Figure 3: Structure of the SARS-CoV-2 spike protein

platforms such as protein subunit and virus-like particle (VLP) candidates; replicating/non-replicating viral vector platforms, as well as newer ones, the so-called nucleic acid or genetic vaccine platforms such as DNA and RNA, to name a few (Figure 4).[12] Notably, several of these vaccines are already approved internationally and currently being used globally for mass vaccination. Some of these vaccines have also received WHO's Emergency Use Listing (EUL), which is a stamp of quality that ensures that the vaccines are absolutely safe and efficacious.[13]

The COVID-19 vaccines have been developed at lightning speed – the fastest in medical history! Much of the groundwork for the speedy development of these vaccines was laid by the Coalition for Epidemic Preparedness Innovations (CEPI), a global collaboration launched in 2017 with the goal of developing vaccine platforms for emergency use if a deadly pathogen happened to emerge unexpectedly. This unparalleled global effort had paid off, as the vaccine platforms were ready and waiting when SARS-CoV-2 suddenly emerged. The magnitude and intensity of these collaborations between scientists across the globe have never been witnessed before in the history of medical research.

COVID-19 Vaccines: Current Status

There are currently 342 candidate vaccines under different stages of development, of which 147 are undergoing clinical trials. Of the various types of candidate vaccines, the protein subunit vaccines are the front-runners, with a total of 48 candidates in clinical trials. Others include RNA (25 candidates), non-replicating viral vector (21 candidates), inactivated virus (21 candidates), and DNA (16 candidates), among several others. The top eight front-runners are presented in Figure 5.

Vaccines: Not "Silver Bullets"

Although vaccines are the best tools to end the pandemic, it must be stressed that they are not "silver bullets". Vaccines are not a panacea for all our COVID-related woes. They are a part of the solution but not the entire solution. This stems from the fact that vaccinated individuals can still acquire infection and pass it on to others. It should be kept in mind that the antibodies generated by all the currently available vaccines are either IgM or IgG, both of which are present only in the blood. This indicates that these antibodies can neutralize the virus only after it enters the blood circulation. Since the primary portal of entry is through the nose, the antibodies are not available to neutralize the virus at this location. Therefore, to prevent transmission of the virus, COVID-appropriate behavior must be followed, and public health measures must adhere. These include masking, physical distancing, handwashing with soap and water, and using alcohol-based hand sanitizers (Figure 6). Only when mucosal immunity-generating intranasal vaccines become available will it be possible to block transmission through IgA antibodies, which will be capable of neutralizing the virus in the nasal mucosa. However, for the present, all the public health measures highlighted in Figure 6 will still need to be stringently followed.

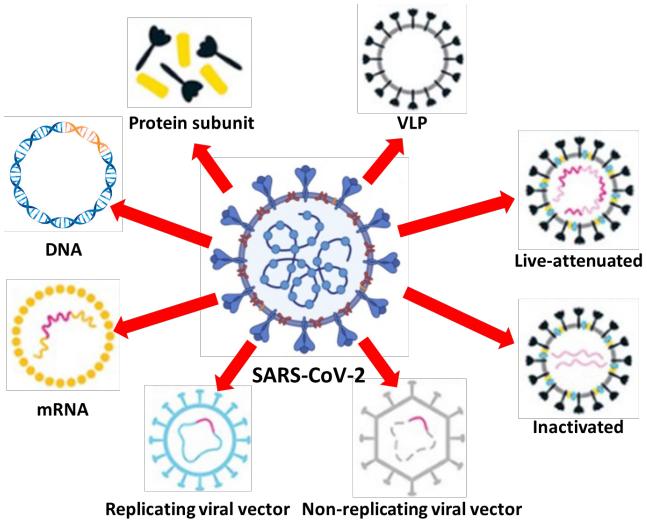

Figure 4: Major types of COVID-19 vaccine platforms

Reasons for Prolongation of the COVID-19 Pandemic

There are primarily two significant reasons why the pandemic is being prolonged unnecessarily. These are (i) the emergence of variants and (ii) vaccine inequity.

- *The emergence of Variants:* Various variants of concern (VOC) are repeatedly emerging around the world. Until

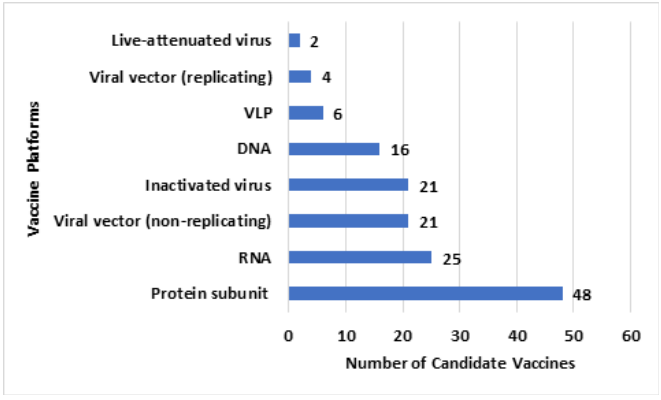

Figure 5: COVID-19 vaccines in clinical trials
(Source of data: WHO, 2021)

Figure 6: Public health measures

November 2021, there were four VOCs globally, namely, the Alpha variant (B.1.1.7), which originated in the UK in September 2020. This was followed by the Beta variant (B.1.351) that originated from South Africa in October 2020. After this, the Gamma variant (P.1) emerged, which was first reported from Japan in December 2020 but caused the most damage in Brazil. This was followed by the devastating Delta variant (B.1.617) that wreaked havoc in India. These four variants emerged quickly, and the Delta variant became the most dominant and spread across the globe at lightning speed. Then there was a long gap, and the Delta variant remained dominant until the dreaded Omicron variant emerged on 24 November 2021, spreading like wildfire across the globe. The reason for its high level of transmission is because it (i) adheres to cells much more easily than previous variants, (ii) exhibits an immune escape phenomenon that allows it to evade the immune response, and (iii) replicates in the upper respiratory tract as opposed to the lower respiratory tract and lungs, as was seen for the other four variants. The third characteristic allows the virus to replicate and rapidly colonize the trachea and nasopharynx, thereby making it easy to transmit by coughing or sneezing by an infected person. This rapid transmission is exemplified by the fact that the doubling time of Omicron is just 2-3 days and has so far been responsible for 130 million cases and 0.5 million (5 lakh) deaths. In the present scenario, 100 cases are reported every 3 seconds, and one person is dying every 12 seconds, making it the fastest spreading variant.

- Moreover, the ability of recombination provides the opportunity to give rise to even deadlier variants. An example is Deltacron, which developed as a result of recombination between the Delta and Omicron variants. Deltacron was first reported from Cyprus and has recently also been reported from France, Netherlands, and Denmark. Even reports of recombination between two different viruses have also been reported. Flurona virus is a glaring example, which arose due to recombination between the flu (influenza) virus and a coronavirus (SARS-CoV-2). This novel virus was first reported in Israel and has not been reported from any other country.

Sadly, Omicron won't, in all likelihood, be the last variant. More will follow because the more the virus circulates in the human population, the more opportunity it will have to mutate and produce new variants. Hence, there is an urgent need to increase vaccine coverage as much as possible.

- *Vaccine Inequity:* The issue of vaccine inequity is currently very depressing. Even though over four billion people out of the seven billion global population have been vaccinated, the majority are from high-income countries. In these well-off countries, 70-80% vaccine coverage is seen, whereas in low-income countries in Africa, there is only 5-10% vaccine coverage. Hence, there is a huge disparity in vaccination coverage, the gap between the "haves" and "have-nots" is widening day by day, and the pandemic is increasingly becoming a two-track pandemic. Moreover, three billion people are yet to receive their primary course, i.e., 1st and 2nd doses. Most importantly, leaving large unvaccinated populations will jeopardize the entire global vaccine efforts, as these people will be most vulnerable to infection and act as factories to produce more new and deadlier variants. Hence, there is an urgent need to tackle the issue of vaccine inequity on a war footing and close the gap between the rich and poor countries as quickly as possible.

When is the COVID-19 Pandemic Likely to End?

History tells us that all pandemics in the past have ended within two years, with the Spanish flu lasting the longest (Table 3). From this aspect, it appears that the COVID-19 pandemic has proven history wrong. This pandemic has already entered its 3rd year. Hence, how long it will last is the million-dollar question. Having said this, experts predict that the acute phase of the pandemic will, in all probability, end by the end of 2022 or early 2023. However, the virus is likely to persist at low levels in the population for years to come, with small flare-ups and sporadic cases from time to time, but which will be easily manageable with the public health tools at hand.

The Way Forward

Given the current state of affairs, there is only one way out of this pandemic to decrease virus transmission and simultaneously increase vaccination coverage as fast as possible but equitably. So, the onus is on us to end this pandemic. Public health measures must be stringently followed if we choose to end the pandemic soon, especially wearing masks. This should go hand-in-hand with increasing

Table 3: Major Pandemics Caused by Respiratory Viruses and their Duration

Name of Pandemic	*Deaths*	*Duration*	*Time to end*
Russian flu	1 million	1889-1890	1 year
Spanish flu	20-100 million	1918-1920	2 years
Asian flu	1-1.5 million	1957-1958	1 year
Hong Kong flu	0.75-1 million	1968-1969	1 year
Swine flu	284,000	2009-2010	1 year
COVID-19	6.03 million (As of 09.03.2022)	2019-ongoing (3rd year running)	?

vaccination coverage across the globe uniformly so that "vaccine inequity" is changed to "vaccine equity." Everyone everywhere should get the vaccine. No one should be left behind. We must remember that no one is safe until everyone is safe. Therefore, if we act collectively, responsibly, and in a concerted and coordinated manner, we will definitely emerge victorious and defeat the pandemic together – sooner than later!

References

1. Wertheim JO, Chu DKW, Peiris JSM, Pond SLK and Poon LLM (2013): A case for the ancient origin of coronaviruses. J Virol. 87(12), 7039-45.
2. Wertheim JO, Chu DKW, Peiris JSM, Pond SLK and Poon LLM (2013): A case for the ancient origin of coronaviruses. J Virol. 87(12), 7039-45.
3. Tyrrell DA and Bynoe ML (1965): Cultivation of a novel type of common-cold virus in organ cultures. Br Med J. 1(5448), 1467-70.
4. Drosten C, Gunther S, Preiser W, van der Werf S, Brodt H-R, Becker S, et al., (2003): Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med. 348(20), 1967-76.
5. Ksiazek TG, Erdman D, Goldsmith CS, Zaki SR, Peret T, Emery S, et al., (2003): A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med. 348(20), 1953-66.
6. WHO (2020a): Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV). Available at: https://www.who.int/news/item/30-01-2020-statement-on-the-second-meeting-of-the-internationalhealth-regulations-(2005)-emergency-committee-regardingthe-outbreak-of-novel-coronavirus-(2019-ncov); Accessed on 09.03.2022.
7. WHO (2020b): WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. Available at: https://www.who.int/director-general/speeches/detail/ who-director-general-s-opening-remarks-at-the-mediabriefing-on-covid-19---11-march-2020; Accessed on 09.03. 2022.
8. Worldometer (2022): COVID-19 coronavirus pandemic – weekly trends. Available at: https://www.worldometers.info/coronavirus/; Accessed on 09.03.2022.
9. Andersen KG, Rambaut A, Lipkin WI, Holmes EC and Garry RF (2020): The proximal origin of SARS-CoV-2. Nat Med. 26, 450-2.
10. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al., (2020): SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 181(2), 271-80.e8.
11. Mukherjee S, Tworowski D, Detroja R, Mukherjee SB and FrenkelMorgenstern M (2020): Immunoinformatics and structural analysis for identification of immunodominant epitopes in SARS-CoV-2 as potential vaccine targets. Vaccines (Basel). 8(2), 290.
12. WHO (2022): COVID-19 – Landscape of novel coronavirus candidate vaccine development worldwide. Available at: https://www.who.int/publications/m/item/draft-landscape-ofcovid-19-candidate-vaccines, Accessed on 09.03.2022. 13.
13. Q evaluation process. Available at: https://extranet.who.int/pqweb/sites/default/files/documents/Status_COVID_VAX_29Sept2021_0.pdf; Accessed on 09.03.2022.