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COVID-19 AND SARS-COV-2: WHAT WE KNOW SO FAR

Beenish Khurshid[1*], Saira Farman[1], Zahida Parveen[1], Mohammad Assad[1], Umia Shams[1], Nosheen Faiz[2]

[1*]Department of Biochemistry, Abdul Wali Khan University Mardan, 23200, Pakistan.
[2] Department of Statistics, Abdul Wali Khan University Mardan, 23200, Pakistan.

***Corresponding Author:** Dr. Beenish Khurshid
*Department of Biochemistry, Abdul Wali Khan University Mardan, 23200, Pakistan,
Email: beenish_khurshid@awkum.edu.pk

Abstract
Currently, more than 500 million individuals have been infected with SARS-CoV-2 and more than 6 million have died from this deadly virus in 222 countries. This mini-review sheds light on some of the important aspects of COVID-19 disease and the information that the researchers have gathered so far regarding epidemiology, virology, pathogenesis, diagnosis, treatment, variants of concerns, and vaccine development. We also summarize the timeline for the development of the disease and milestones achieved so far so that the readers can grasp the timing of some of these critical events. Notables are the rapid development and regulatory approval of diagnostics, antiviral medicines, and vaccines within a year of the virus's discovery. Because the development of understanding the mechanism of this viral infection and drug design occurred concurrently, we provide a chronology to help readers understand the progression of research findings as well as their interpretation. Scientists from across the globe are collaborating to combat this pandemic. This analysis also identifies future directions for research and development in these areas.

Keywords: COVID-19; SARS-CoV-2; Pandemic; Vaccines; Virus

1 Introduction

1.1 1st disease outbreak

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or 2019 novel coronavirus (2019-nCoV) was first identified in December 2019 in Wuhan, Hubei Province, China, as a pneumonia of unidentified origin. In the next few weeks, this strange virus progressively spread across the globe. The virus originated in bats and was transferred to humans by an unknown intermediate carrier, which was largely believed to be of zoonotic origin. On 7 January 2020, a Chinese scientific research institute declared that the viral pneumonia was caused by a novel coronavirus (SARS-COV-2), later designated COVID-19 by the World Health Organization [1]. Although COVID-19 has a lower death rate (2.3%) than other coronaviruses such as SARS (9.5%) and MERS (34.4%), it is highly transmissible and spreads rapidly due to its ability to spread through respiratory droplets and contact[2].

Current status 2023

As of May 3, 2023, WHO reported 765,222,932 confirmed cases of COVID-19, with 6,921,614 deaths globally. From January 2020 to April 2022, the United Kingdom reported 24,581,706 confirmed cases of COVID-19, with 224,106 deaths to the WHO. The United States has reported 103,266,404

confirmed cases with 1,124,063 deaths to WHO [3]. Figure 1 shows the number of deaths in the 20 most affected countries by COVID-19. As of today, Pakistan has reported 1,580,631 confirmed cases and 30,656 deaths. [4] Luckily, most of the children with COVID-19 cases are mild and very few need hospitalization [5]. These numbers may not be the true depiction of the severity of the disease due to the lack of testing and surveillance, especially in the developing countries. Furthermore, with the rapidly mutating virus, its future path is unpredictable. This review presents an overview of the current status of COVID-19 disease. With the rapidly evolving research on this virus, readers are encouraged to update their knowledge on it on a regular basis.

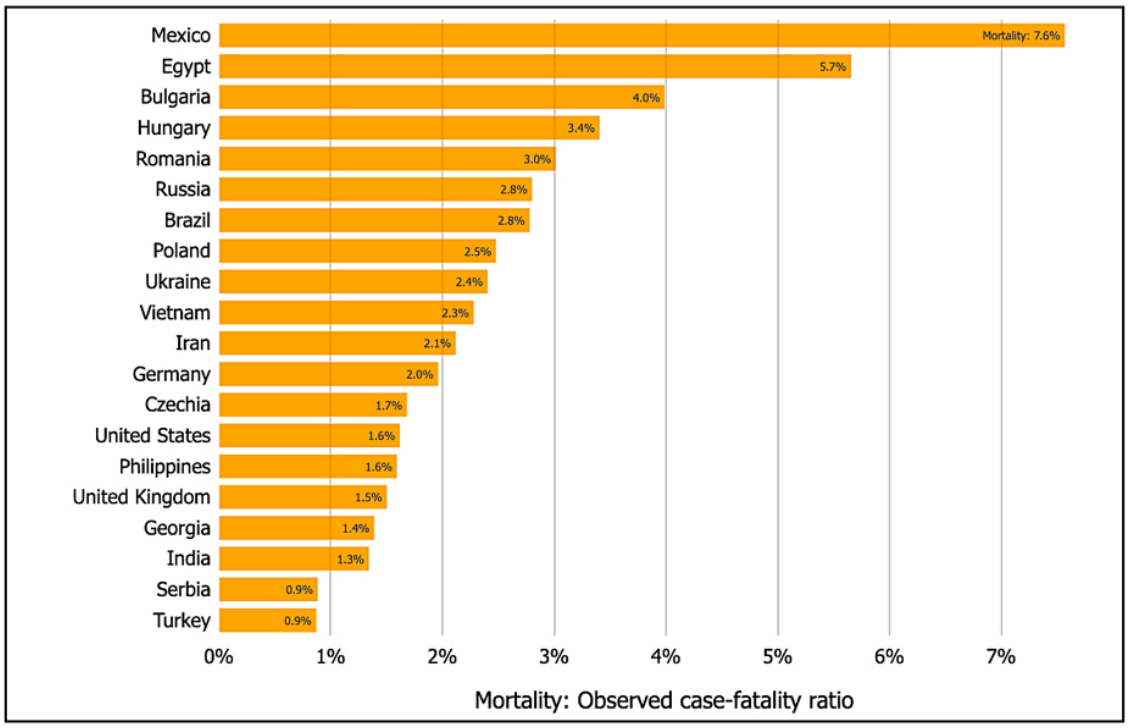

Figure 1. This chart shows top 20 COVID effected countries based on fatality ratios (the number of deaths divided by the number of confirmed cases)[6].

1.2 Structure of Corona virus (SARS CoV-2)

Coronaviruses are single-stranded, positive-sense RNA (+ssRNA) viruses that infect both animals and humans, making them a public health issue as well as a veterinary and economic burden. Coronaviruses belong to the Coronaviridae family and subfamily Orthocoronavirinae. Alphacoronavirus (alphaCoV), betacoronavirus (betaCoV), gammacoronavirus (gammaCoV), and deltacoronavirus (deltaCoV) are the four main genera of coronaviruses [7]. SARS-CoV-2 is a round or elliptic, often pleomorphic, enveloped virus with diameters ranging from 50 to 200 nm [8]. The single-strand RNA of Corona virus consists of 29,891 nucleotides encoding 9860 amino acids. Single-stranded RNA hijacks host cells' molecular machinery of host cells to produce virus proteins. These proteins facilitate the virus to maintain its structure and replicate. The viral envelope, which is made up of lipids and encapsulates the RNA genome, protects the virus when it is outside a host cell. This waxy covering serves as an anchor for the various structural proteins required by the virus to infect cells. Once a virus has infected a cell, envelope proteins embedded in this layer aid in the assembly of new viral particles. The viral envelope has three main structural proteins: The membrane protein (M), the envelope protein (E) and the spike protein (S) as shown in Figure 2. The M and E proteins aid in virus assembly, while the S protein facilitates virus entry into host cells. Furthermore, several coronaviruses encode an envelope-associated hemagglutinin-esterase protein (HE), which promotes the escape of the virus from infected cells. [9]

Spike proteins are globular projections on the outside of the coronavirus that give it a crown-like appearance, hence the name coronavirus. The spike proteins (1273 residues) use their two subunits S1 and S2 to mediate virus entry into the host cell. The S1 subunit (14–685 residues) contains a signal peptide, an N-terminal domain (NTD; 14–305 residues), and a receptor-binding domain (RBD; 319–541 residues), and it functions as a hook for the virus to connect to the surface of the host cell. The S2 subunit (686–1273 residues) is in charge of the fusion of the virus-host membrane and virus entrance into the host cell. It has a fusion peptide (FP; 788–806 residues), a heptapeptide repeat sequence (HR 1; 912–984 residues and HR 2; 1163–1213 residues), a transmembrane domain (TM; 213–1237 residues), and a cytoplasmic domain (CP; 1237–1273 residues) [10]. Coronaviruses, like all viruses, are unable to thrive and proliferate in the absence of a living host.

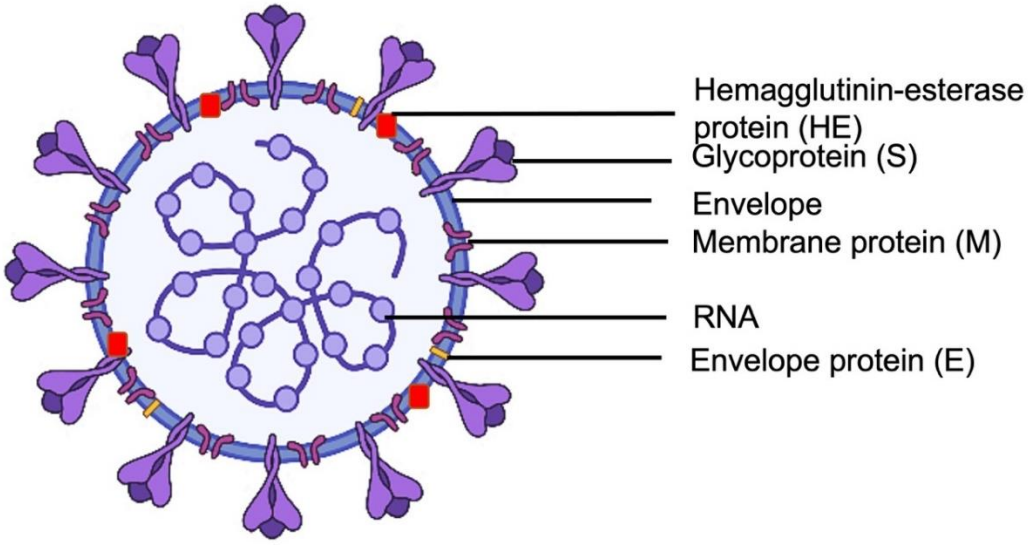

Figure 2. The structure of coronavirus. Adapted from "SARS-CoV (SARS virus)", by BioRender.com (2021). Retrieved from [11]

1.3 Symptoms

According to the WHO, fever, breathlessness, and invasive lesions in both lungs were among the initial clinical signs and symptoms of COVID-19 [15]. Fever and a dry cough are common early symptoms of pneumonia, according to studies, but in around 10% of cases, patients experience Acute Respiratory Stress Syndrome (ARDS) and septic shock, leading to multiple organ failure and death[14]. The development of ARDS and substantial lung impairment strengthen the evidence that ACE2 could be the point of entry for covid virus, due to its abundance in type II alveolar epithelial cells.

The incubation time for COVID-19 disease is generally 14 days but can persist up to 24 days. Most patients with COVID-19 have minor symptoms, but they can quickly worsen, particularly in the elderly or those with other chronic illnesses.

The SARS CoV-2 infection spreads predominantly by large airborne droplets produced by coughing and sneezing from symptomatic patients, as well as asymptomatic people, before they acquire symptoms if they are in close contact. [16]. According to studies, the nasal cavity has a higher viral loads than the throat, with symptomatic and asymptomatic people having equal viral burdens [17]. Patients can be infectious for as long as they have symptoms and even after they have recovered clinically. Infected droplets can travel up to 12 metres before settling on the surface. These droplets can last in the air for up to 3 hours, 24 hours on cardboard, and 2-3 days on plastic and stainless steel. This could possibly explain the stability of SARS-CoV-2 and the fast person to person transmission [18]. Infection spreads by inhaling these droplets or contacting infected surfaces and then touching the nose, mouth, and eyes. There are reported cases of perinatal transmission from mother to baby, but it is not clear if the route is transplacental or the transcervical or exposure to the environment [19].

Several viruses, such as influenza A or B, can produce symptoms that are comparable to COVID-19, making it hard to differentiate, especially during the flu season. [20]. Because of difficult diagnosis and nonavailability of specific drugs, it's critical to learn more about the virus so that rapid and accurate diagnostic methods, as well as potentially effective drugs, can be developed.

1.4 Mechanism of SARS-CoV-2 entry into host cell

The surface is extensively glycosylated, with 21 to 35 N-glycosylation sites. The spike proteins are arranged in a trimeric pattern on the virus's surface, giving it a crown-like appearance. The spike protein's receptor-binding portion S1 binds to the host cell receptor, causing it to shed and the fusion fragment S2 subunit to adopt a very stable post-fusion conformation. One of the three RBDs on the spike protein protrudes upwards, allowing it to bind to the host receptor readily. SARS-CoV-2 uses angiotensin converting enzyme 2 (ACE2), and the cellular transmembrane protease serine 2 (TMPRSS2) to enter target cells (see Figure 3) [21]. ACE2 is a dimer that may take on either an "open" or "closed" conformation, according to cryo-electron microscopy [22].

The SARS-CoV-2 and SARS-CoV spike proteins (isolated from people, civet cats, or bats) have nearly identical sequences i-e ~ 76-78% , and the RBD sequence similarity is ~ 73-76%, which implies that SARS-CoV-2 and SARS-CoV can use the same receptor structurally [23,24]. Researchers used HeLa cells from humans, Chinese horseshoe bats, civets, pigs, and mice that expressed or did not express the ACE2 protein to study virus infectivity in detail. Except for mouse ACE2, SARS-CoV-2 was able to bind to ACE2 in all animals with ACE2-expressing cells, while it was unable to enter cells without ACE2. This shows that ACE2 is the SARS-CoV-2 entrance receptor and that animals with ACE2 are prospective SARS-CoV-2 hosts [25]. According to kinetic studies, SARS-CoV-2 has a substantially higher affinity for ACE2 than SARS-CoV, which could be the underlying explanation for the high infectivity [26]. In addition to ACE2, transmembrane serine protein 2 (TMPRSS2) which is also an endothelial call surface protein, is shown to promote viral entry into host cells and spread of SARS-CoV-2 infection [27]. Studies involving a TMPRSS2-positive cell line showed that if TMRPSS2 expression in target cells is blocked, the entrance of SARS-CoV-2 is reduced, suggesting that SARS-CoV-2-S may employ TMPRSS2 for the initiation. Thus, targeting proteins involved in the entrance of SARS-CoV-2 could be a promising treatment method.

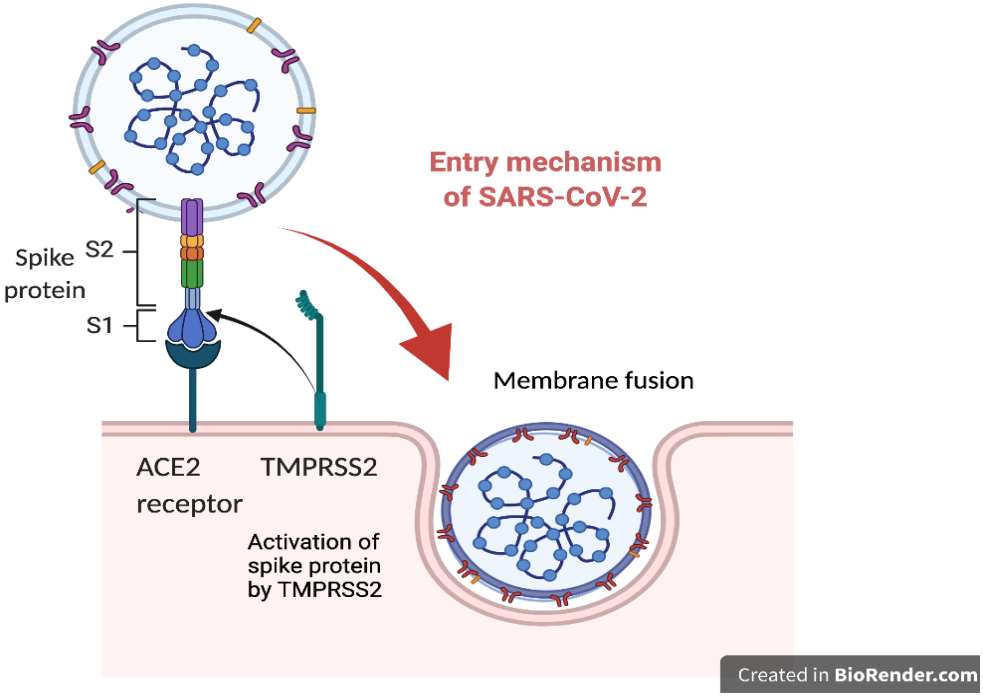

Figure 3. This figure shows how SARS-CoV-2 enters the host cell via the ACE2 receptor and the serine protease TMPRSS2. Figure adapted from [28] and recreated using biorender 2021 [11]

1.5 The variants

The word "mutation" has emerged on an ominous notation among SARS-Co-2 pandemic. Viruses are technically not alive, but they still evolve and reproduce just like living cells. Virus mutates regularly and frequently; some mutations have clear advantages, such as better evasion of the host's immune system, but others are harmful to the virus, limiting its spread throughout the population.

Genetic variations cause diversity in the virus. Every time there is a mutation, there is a greater chance that it will survive and circulate widely. Some mutations are harmless, but others can increase the infection and transmission rate of the virus, that is, when a particular mutant becomes a variant of concern (VOC).

One of the fundamental questions that arises with the evolution of corona virus during this pandemic is; why this mutation is occurring at such a fast pace? SARS-CoV-2, being an RNA virus, is more susceptible to mutation than DNA viruses due to differences in genome replication mechanisms. Coronaviruses, ironically, have lower mutation rates than many other RNA viruses, owing to a minor genetic proofreading ability. But this is not good enough to prevent coronaviruses from mutating and, as a result, this virus hops around the world from one continent to the other giving rise to a range of variants.

A single amino acid substitution in any of the SARS-CoV-2 proteins can substantially alter the characteristics of the virus. Most alarming mutations occur in the spike protein, and hence it is being considered as the major drug target. Out of these mutations, the ones occurring in the RBD are more worrisome, as this is the part that is involved in the attachment of the spike protein to receptors on human cells. A team of scientists at Duke University combined biochemical assays, cryo-electron microscopy, and modeling to explore how mutations affect the interaction of spike protein with the ACE2 receptor. They found that mutations can increase the binding affinity of the spike protein to the receptor protein in several ways [1].

VOC	1st detected	Total mutations	In spike protein	RBD	Furin cleavage site	Infectivity compared to the original virus
Alpha	United Kingdom	15	9	**N501Y**		50–70%
Beta	South Africa	12	9	**N501Y**, **K417N**, **E484K**		50%
Epsilon	US (California)	6	4	**L452R**		20%
Gamma	Brazil	17	11	**N501Y, E484K** and **K417T**		2.5%
Delta	India	15		L452R	a swap of a proline to an arginine (P681R) in the furin cleavage site	
Delta plus		Same as Delta		a swap of a leucine to an arginine (L452R) like delta but an additional swap of a lysine to an asparagine (K417N)	Same as Delta	
Omicron	South Africa		30	G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H	H655Y, N679K	

1.6 Clinical Features

SARS-CoV-19 presented a variety of clinical features. Fever [29], shortness of breath and dry cough that leads to more severe cough over time are some of the common symptoms of COVID-19. Headaches, dizziness, shivering, abdominal discomfort, nausea, pink eyes, rash, darkened fingers, and a loss of taste and smell are some of the less common symptoms [30]. Among these, anosmia (loss of

smell) and ageusia (loss of taste) are emerging as distinguishing symptoms of covid infection [31,32]. Although a study shows that at least one third of all covid patients are asymptomatic [33]. One of the most difficult aspects of the rapid diagnosis of covid infection is the detection and quantification of the virus because most of the symptoms overlap with other viral symptoms. Although fever and cough are important indicators, yet these may not be present in asymptomatic patients.

1.7 Comorbidities

According to WHO and CDC, sickle cell disease, chronic obstructive pulmonary disease (COPD), diabetes, hypertension, high BMI (>30), high D-dimer, chronic kidney disease (CKD) and cardiovascular disease (CVD) are all major risk factors for covid mortality. In patients with COPD, where there is already an airflow blockage resulting in breathing problems, the infection led to a higher rate of hospitalization and death [34]. Diabetic individuals may develop a respiratory distress condition known as acute respiratory distress syndrome (ARDS), which results in more severe covid infection and high mortality [35]. Increased D-dimer levels indicate the presence of a blood clot in the body. High levels of D- dimer are also observed in covid patients and are directly correlated with the severity of the disease. This has significantly increased the odds of severe disease and mortality compared to the patients who have normal D-dimer levels [36]. A recent study explored the combined effect of COVID-19 and cancer and observed that it significantly increased the risk of death in cancer patients who are male, Asian and have other underlying haematological and pulmonary malignancies[37].

1.8 Biomarkers of COVID-19 disease progression

1.8.1 Demographic distribution

The higher likelihood of severe COVID-19 has been associated with certain demographic characteristics documented in the literature. Older age is an important factor in clinical severity risk ratings because it is a strong predictor of mortality [38,39]. According to the demographic data available from the CDC, between January 2020 and November 17, 2021, of the 0.7 million deaths caused by COVID-19 in the US, more than 2 million occurred among patients 85 years and older [40]. A meta-analysis of around 3 million reported cases around the world suggested that men were three times more likely to be admitted to an intensive care unit and had a higher risk of death than female patients, which implies that men's sex is another independent predictor of the severity of COVID-19 [41].

1.8.2 COVID and children

Fortunately, compared to adults, children and adolescents have milder covid disease but its still much worse than influenza. A recent study compared around 2 Million children diagnosed or hospitalized with covid and found that despite negligible mortality, symptoms such as anosmia, ageusia, bronchiolitis, and gastrointestinal such as diarrhea or vomiting were more common in children affected by covid compared to influenza [42]. Underlying conditions such as chronic bronchitis and asthma, cardiovascular disease, cancer, thrombocytopenia, anemia, epileptic encephalopathy, autism, and an age of less than 1 year are associated with more severe condition in children aged 0 to 17 years [43,44]. Because ACE2 serves as the first interaction site for the RBD of the spike protein, it is the primary factor that facilitates the internalisation of the covid virus. The lower incidence of COVID-19 in children may be attributed to the lower expression of ACE2 in the nasal epithelia of the children compared to adults [45]. However, what is still not confirmed is that the lower nice in children is due to lower levels of ACE2 or lack of research in this area.

1.8.3 SARS-CoV-2 infection in Pregnant women

Latest studies show that pregnant women seem to less likely manifest severe symptoms, i.e. less fever or muscle discomfort, but more likely to be admitted to intensive care and need invasive ventilation once infected than nonpregnant women. These women with preexisting comorbidities such as diabetes, obesity, hypertension, high child-bearing age, and nonwhite ethnicity are more susceptible to the infection. If they are infected, they have a higher risk of developing more severe disease than

nonpregnant women of a similar age. COVID-19 infection during pregnancy has also been associated with a higher risk of premature birth [46] and one in four babies went to the neonatal care at birth, according to one study [47]. Pregnant women, as well as those in close contact, must take precautionary measures to protect themselves against COVID-19. If you feel ill (fever, cough, or difficulty breathing, for example), they should seek medical help as soon as possible. Recent studies also show that pregnant women can spread the virus to their fetus in third trimester through transplacental transmission. And the neonate thus born might present neurological manifestations due to cerebral vasculitis [19].

1.9 Antiviral Strategies Against SARS-CoV-2

COVID-19 is one of the deadliest challenges modern societies has ever faced. Scientists and researchers around the world are in a frenzy to find any drug or vaccine that can help the infected people or might prophylactically prevent new infections from happening for uninfected people.

There are two categories of antiviral drugs, i.e., direct acting antivirals (DAA) and indirect acting antivirals (IAA). DAA specifically targets viral components, for example, viral polymerase, or a specific stage in the viral life cycle without compromising other cellular processes in the host. IAAs, on the other hand, are not focused on any one site of the virus life cycle; rather, they interfere with the host proviral components and their cellular activity thus indirectly decreasing viral replication and infection. Studies show that DAA's can cure a high percentage of patients by achieving a sustained virological response with better tolerance and less side effects, resulting in substantial reduction in the number of interventional surgeries [48]. IAAs are generally immune to viral mutations, which makes them better than DAAs in this respect, but their potential to disrupt the host cellular system makes them less viable. Due to the limited number of available vaccines against SARS-CoV-2, DAAs with their improved safety features can target viral entry, proteases, and replication of the virus and can be potent antivirals. These therapeutic agents can exert their synergistic effects when used in combination with vaccines and not only treat patients with active infection but also prevent the occurrence of new infections. In this regard, the FDA in 2020 has approved the emergency use of several treatments including remdesivir, casirivimab/imdevimab, baricitinib/remdesivir, bamlanivimab and convalescent plasma [49].

1.10Vaccines against Covid-19

Vaccines generally require 5-10 years of research and trials before becoming commercially available, but during this pandemic, experts from all fields share in the quest to develop safe and efficient coronavirus vaccines in fairly short order of time. The New York Times reports that 119 vaccines are now being tested in human clinical trials, of which 50 are near completion. More than 75 are being tested on animals in preclinical trials. In this section, we will discuss some of the most effective vaccines that are approved by the FDA for use in public till October 2021; see

Table **1**. As of now, over 11 billion doses have been administered in 184 countries, which equates to more than 17 million doses per day. In the US alone, 568 million doses have been administered so far, with an average of 1.15 million doses per day [50]. As of April, 2022, 243 million doses have been administered in Pakistan with an average of 0.27 million doses per day [50]. Seven vaccines have been approved for use in Pakistan including two RNA-based vaccines Moderna mRNA-1273 and Pfizer/BioNTech BNT162b2, three viral vector-based vaccines; CanSino Ad5-nCoV, Gamaleya, Sputnik V, and Oxford/AstraZeneca AZD1222, and two inactivated virus vaccines; Sinopharm (Beijing) BBIBP-CorV (Vero Cells) and Sinovac CoronaVac. While two protein subunit-based vaccines Anhui Zhifei Longcom ZF2001 and Livzon Mabpharm Inc V-01 and a viral vector-based vaccine CanSino Ad5-nCoV are in clinical trials [51].

Table 1. Covid-19 vaccines in development worldwide [52]

Phase	Pre-clinical	Phase-1	Phase-2	Phase-3	In-use	Phase-4
Number of vaccines	194	42	44	40	23	10
	In-vitro and In-vivo experiments	Being tested in healthy individuals	Broad spectrum testing	International trials	Currently in-use for general masses	Being monitored for efficacy after approval

Table 2. The table enlists top 10 approved vaccines and their types across the globe

No.	Candidate	Characteristic	Principal developer	Origin
1.	Comirnaty[53](BNT162b2)	mRNA-based	Pfizer, BioNTech; Fosun Pharma	Multinational
2.	Moderna[54] (mRNA-1273); Spikevax	mRNA-based	Moderna, BARDA, NIAID	US
3.	AstraZeneca[55] (AZD1222); Vaxzevria / Covishield	Adenovirus-based	BARDA, OWS	UK
4.	Sputnik V[56]	Recombinant adenovirus vaccine (rAd26 and rAd5)	Gamaleya Research Institute	Russia
5.	Sputnik Light[57]	Recombinant adenovirus vaccine (rAd26)	Gamaleya Research Institute.	Russia
6.	Janssen[58] (JNJ-78436735; Ad26.COV2.S)	Non-replicating viral vector	Janssen Vaccines	The Netherlands, US
7.	CoronaVac[59]	Inactivated vaccine	Sinovac	China
8.	BBIBP-CorV[59]	Inactivated vaccine	Beijing Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	China
9.	EpiVacCorona[60]	Peptide vaccine	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology	Russia
10.	Convidicea[61] (PakVac, Ad5-nCoV)	Recombinant vaccine	CanSino Biologics	China

The first human vaccine that was developed against smallpox used cowpox; a virus that was structurally similar to smallpox but was weaker enough to not cause a disease rather generate immunity. Since then, weaker or attenuated viruses have been used to form vaccines. Vaccines are created using different methodologies, for example, using genetically modified viruses, attenuated or weakened viruses, inactivated viruses and/or merely fragments of the viral proteins.

1.10.1 Genetic Vaccines

These are vaccines where instead of full virus active/inactive, a gene or genes that encode the virus protein are transported to the cells to stimulate and trigger the immune response. This immune response is what keeps us safe if the real virus gets into the system. In these types of vaccines, generally an engineered mRNA is delivered to the system where it dictates the system to make antibodies, after which the mRNA breaks down.

This vaccine employs genetically modified mRNA to guide cells on how to produce the surface of the S protein located on the COVID-19 virus. Immune cells begin to produce S protein fragments and expressing them on cell surfaces after vaccination. As a result, antibodies are produced by the body. Pfizer and Moderna are both mRNA-based genetic vaccines against SARS CoV-2.

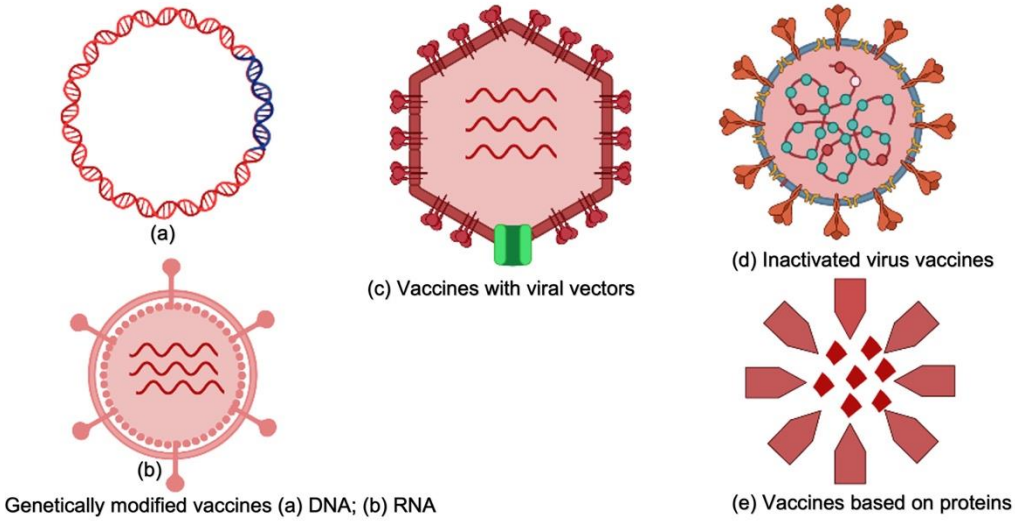

Figure 4. Types of leading vaccines developed against SARS CoV-2

a) Pfizer's Comirnaty (also known as tozinameran or BNT162b2) is a vaccine stored at –25°C to –15°C with 91% efficacy and is administered through a muscle injection in two dosages three weeks apart. Pfizer and BioNTech researchers, on Nov. 9, 2020, announced that Comirnaty had an efficacy rate of over 90% [62]. BioNTech teamed up with Pfizer to launch a clinical trial in May 2021. Comirnaty was shown to be less effective against some variants in research published in May 2021, although it still gave good protection. On Aug. 23, 2021, the FDA approved the Comirnaty for adults aged 16 and older.[63]. Pfizer declared that a low-dose use of this vaccine safe and effective in children 5 to 11 years of age [64]. Comirnaty had an 88% efficiency against Delta infection and 96% effective in preventing Delta hospitalization [65].
b) Moderna also known as Spikevax or mRNA-1273 is another covid vaccine given as muscle injection in 2 doses that are 4 weeks apart. This vaccine can be refrigerated for around 30 days, or frozen for 6 months at –20°C). FDA granted emergency use authorization for Moderna, on December 18, 2020 [54]. Moderna, like Pfizer, uses mRNA to create the vaccine. The vaccination had a 98.2% efficacy in preventing serious illness [66]. Moderna, later in May announced that Spikevax could also be used effectively and safely in older children i.e., 12 years [67]. The effectiveness of the vaccine is now being tested in younger children. The vaccination of Pfizer and Moderna administered to pregnant women resulted in significant levels of antibodies in their babies [68]. Moderna vaccination tests show that it offers good protection against dominant variants such as Beta and Delta [69].

1.10.2 Vaccines with Viral Vectors

The genetic material from SARS-CoV-2 is engineered into a new modified virus called the vector virus. When this viral vector enters a cell, it delivers genetic material there and directs the cell to create spike proteins. When these spike proteins begin to emerge on the cell surface, the system responds by generating antibodies. These antibodies protect the person if infected by the virus later in the future.

The following is a brief overview of the vector vaccines effective against covid.

a) Sputnik V (Gam-Covid-Vac) has ~ 92 % success rate.[56]. It is administered as a muscle injection in 2 doses, 3 weeks apart. The Gamaleya Research Institute of the Russian Ministry of Health developed Sputnik V vaccine in fall 2020, which is now extensively utilised throughout the world [56]. In December 2020, the Gamaleya Institute and AstraZeneca combined their vaccines to create a "vaccine cocktail" to check if the mixture improves the effectiveness of the AstraZeneca vaccine. The results showed that the cocktail vaccine did not generate any adverse effects or new instances of Covid-19, after vaccination [71]. Russian officials reported on Aug. 4, 2021 that mixing Sputnik Light with AstraZeneca, Sinopharm, and Moderna vaccines was also found to be safe [57]. Gamaleya

Institute announced that Sputnik light antibodies can neutralize the Delta variant with 70% efficiency, although this study is still to be published [72].

b) Vaxzevria (AZD1222, or Covishield) is 74% effective against symptomatic Covid19 and 100% effective against critical Covid-19. It is given in 2 doses as a muscle injection. This vaccine designed by the University of Oxford and produced by AstraZeneca has holds a significant place in the drive to meet the global demand for Covid-19 vaccinations. Vaxzevria is being produced in large quantities at a low price. It simply needs to be refrigerated rather than frozen, which makes it easy to use as compared to the other mRNA vaccines. Oxford stated in July 2021 that a billion doses of Vaxzevria have already been released worldwide [73].

On Feb. 14, 2021, AstraZeneca stated that they would start testing on children as young as 6 years old[74]. The researchers at Oxford presented preliminary results demonstrating that a combination of AstraZeneca vaccination followed by Comirnaty produced substantial levels of antibodies. AstraZeneca also conducted a comparable trial with Russia's Sputnik V vaccine. The results of the trial suggest that the combination provided at least a four-fold increase in antibodies in 85% of subjects [75]. But in March 2021, European medical regulators became concerned about a tiny number of blood clots in younger patients who used Vaxzevria. The European Medicines Agency stated that vaccination caused a very unusual side effect in which people had blood clots in major veins paired with low platelets. The regulators stressed that the vaccination is effective and that the benefits it provided outweighed the modest risk of its negative effects. In response, some governments sought to limit the danger by restricting the immunisation to older adults [74].

c) Convidecia (Ad5-nCoV), a single-dose vaccine, is developed by the Chinese company CanSino Biologics in conjunction with the Institute of Biology at the country's Academy of Military Medical Sciences. CanSino started Phase 3 trials in several countries, including Pakistan, Russia, Mexico and Chile and announced the interim results in February 2021 stating that after 28 days of administration, this vaccine had a success rate of ~65% against symptomatic covid infection [76].

d) The Johnson & Johnson's (Ad26.COV2.S) vaccine is based on a special type of low prevalence human adenovirus that is genetically modified and is known to cause common cold and flu like symptoms. On February 27, 2021, FDA granted it emergency use authorization as a single shot vaccine for those aged 18 and up. This vaccine has a72% efficacy in the US, 68% in Brazil, and 64% in South Africa. Johnson & Johnson found that its vaccine was only 52 % efficient in South Africa against the dominant Beta variant. This vaccine was also approved by FDA as a heterologous booster dose to follow the completion of primary vaccination, such as Pfizer-BioNTech and Moderna vaccines for people 18 years and older. Although this vaccine has a reasonable efficacy profile, it had its own setbacks. CDC announced on May 12, 2021, that it has found 28 occurrences of blood clotting among over 9M people who got their vaccination 3-15 days earlier. It was more significant (12.4 cases per million doses) in younger women i.e. 30 to 39. But there were also a few cases in older women i-e 40 to 49 (9.4 cases per million doses), above 50 years of age (less than 3 cases per million doses). As a result, the US government added a warning to this vaccination that younger women might be at risk of experiencing thrombosis with thrombocytopenia syndrome (TTS) [58].

1.10.3 3Vaccines bBased on Proteins

These vaccines that include a protein subunit of the coronavirus but not the virus's own genetic material. This protein can stimulate the immune system, as it contains harmless spike proteins. Once the body recognizes the virus protein as a foreign entity, it starts producing antibodies against it. And when the person gets covid infection in future, these antibodies fight against them.

EpiVacCorona (Aurora-CoV) and Novavax, (Covovax) vaccines belong to this category. Russia launched a broad immunisation campaign containing EpiVacCorona in January 2021, despite the lack of results from the trial. Novavax, on the other hand, has an efficacy of 96% against the original

corona virus and 86% against the Alpha variant as announced by Novaax in March 2021 [77]. Despite its high efficacy rate, this vaccine is also struggling with manufacturing and quality issues.

1.10.4 Inactivated virus vaccines

Vaccines made from coronaviruses that have been chemically destroyed or weakened.

a) BBIBP-CorV, a vaccine developed by the Beijing Institute of Biological Products and Sinopharm, is administered in two doses three weeks apart as muscle injection and has an efficacy of 78%, making it one of China's leading vaccines. The vaccine is based on inactivated coronaviruses that cannot infect cells but can trigger immunity. The vaccine demonstrated promising results in monkeys, with no serious side effects [78]. WHO approved the vaccine for emergency authorization on May 7, 2021, citing a 78.1% efficacy estimate [59].

2 Conclusion:

Two years ago, terms like lockdown, quarantine, social distancing, and mask mandates were unknown to most of us. But today, these have become an integral part of our everyday language. Human history has seen a crisis like no other. Covid-19 generated a health crisis that triggered/led to an economic crisis, pushing the world into the worst global recession since World War II. The World Bank Group analysis shows that 18M people have crossed the poverty line only in one year, i.e. 2020, and in a worst-case scenario, this figure could rise upto 115M in the coming time. And the largest population getting effected by this economic crisis will be in South Asia, with Sub-Saharan Africa close behind[79].

With the tests and experimentation of vaccines against Covid-19 still going-on, most of the governments across the globe have employed non-pharmaceutical interventions (NPIs) to regulate the transmission of the virus. After reviewing epidemiological data to estimate the possible spread of covid infections domestically or internationally, these NPIs have been rigorously observed. Diverse hypotheses have been tested and validated because of effective communication and collaboration across various countries. Quarantine, lock downs, social distancing, and the general usage of facemasks are all recommended control strategies to reduce or restrict virus transmission. These measures, in principle, could reduce per capita contact rate and as a result the viral transmission and infectivity. These NPIs together with vaccination are the only way forward to fight against this deadliest infection.

Covid-19 is without a doubt one of the biggest health care concerns that human history has ever faced, creating a social and economic crisis across the globe. The scientific community embraced this challenge and has unravelled the SARS-CoV-2 disease mechanism and developed vaccines in a timeline that is unprecedented. This brief overview tried to cover all the important aspects of the disease, including epidemiology, diagnosis, clinical management, and vaccine development. But we still believe that there is a great knowledge gap between science and the real world. For example, how long will the implementation of NPIs be needed? Covid-19 is here to stay, but how are we going to live with it? With the virus mutating so fast, will vaccines be that effective against new strains? If so, how long does immunity last after vaccination? Will booster doses be required after main vaccination? How about the recovered patients; How long their immunity will keep them safe from the virus? Do children get less infected with covid due to fewer ACE2 receptor cells in their noses[80] or is it due to low testing rates among children. We still do not know how and whether covid infection transmits from the mother to the infant.

Although there have been more deaths from Covid-19 all around the globe than many of the other past pandemics, it is also true that due to rapidly mutating virus, it becomes even difficult to keep track but as Desiderius Erasmus Once "Prevention is better than cure". It is not impossible to fight with this virus by practicing social distancing and wearing a mask. In addition, with recent advances in science and technology, the use of authentic vaccines has significantly reduced the covid mortality rate. There is still much more to know about COVID-19 infection, transmission, treatment, and

pandemic potential. Nonetheless, the lessons learnt from the SARS and MERS epidemics in the past are the most effective cultural weapons against this new global menace.

Conflict of Interest

The authors declare no competing financial interest.

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