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Coronavirus Pandemic

Caring for patients with rare diseases during the COVID-19 pandemic

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Abstract

Rare diseases frequently attack and weaken the immune system, increasing the patient's vulnerability to develop severe conditions after viral infections, such as COVID-19. Many patients with rare diseases also suffer from mental retardation and disability. These rare disease phenotypes do not emerge in older people who are susceptible to COVID-19 infection, but present at a very young age or at birth. These factors must be taken in consideration when caring for this vulnerable patient population during a pandemic, such as COVID-19. Patients with a rare disease have to take their regular medication continuously to control their condition and frequently, the medications, directly or indirectly, affect their immune system. It is important for this patient population, if infected with COVID-19 or another severe form of infection, to adjust the treatment protocol by specialists, in consultation with their own medical team. Special awareness and educational programs, understandable for mentally retarded patients, must be developed to educate them about social distancing, curfew, sanitization, and sensitization to the disease and quarantine. The COVID-19 pandemic highlighted the importance to reconsider the care required by patients with a rare disease during a pandemic or disaster, a program that should be adopted by the World Health Organization and governmental institutions for consideration.

Key words: rare diseases; pandemic; COVID-19; MERS-COV; vaccines; anti-viral therapy.

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COVID-19 is one of the most severe pandemics in human history

In human history, at least 20 devastating epidemics and pandemics have been witnessed globally. Not only did these diseases devastate human health, but they simultaneously threatened the existence of humanity, and changed the course of history. None, however, have completely shut down the planet as COVID-19 did since its emergence in Wuhan, China in December 2019 [1].

The first recorded epidemic dates back to almost 5000 years ago when a prehistoric village in China was wiped out by what is currently known as the "Circa 3000 B.C." prehistoric epidemic. Right at the beginning of the Peloponnesian War (431-404 BC) between Athens and Sparta, an aggressive epidemic hit the people of Athens. Within five years, the "Plague of Athens" killed about 100,000 people. Based on the recorded symptoms and epidemiological information, this plague was probably caused by typhoid fever or Ebola. The military campaign of the Roman Empire coming back from the Near East started the "Antonine Plague" (165-180 A.D.). It is believed that the Antonine Plague was caused by smallpox or measles. The Antonine Plague killed over 5 million inhabitants of the Roman Empire. In the Middle Age, the "Black Death" plague caused millions of deaths throughout Asia and Europe (1346-1353). Epidemics continued to largely affect growing human populations during modern ages. During the 16th century, a series of Eurasian diseases including measles and smallpox conveyed to the Americas by European expeditions lead to the spread of several "American Plagues" which collectively caused the collapse of many indigenous civilizations.

The development of new methods of transportation in the late 19th century expedited the spread of disease outbreaks between human populations. During the 1889-1890 flu pandemic, the mortality peak was reached within five weeks with a death toll of 1 million people. By the End of World War I (1918-1920), the Spanish Flu spread through the area extending from the South Seas to the North Pole, killing an estimated 50 million people. In 1957-1958, rooted in China and caused by a blend of avian flu viruses, the Asian flu claimed the lives of more than 1 million people globally. Towards the end of 20th century, a new

pandemic emerged. Caused by HIV, AIDS claimed an estimated 35 million lives since it was first identified in 1981. HIV most probably developed from a chimpanzee virus and then transferred to humans in West Africa, sometime during the 1920s.

During the last 15 years several pandemics spread globally. In 2009, a new strain of H1N1 caused the swine flu pandemic. The disease originated in Mexico in the spring of 2009 and spread to the rest of the world. Within one year, swine flu infected as many as 1.4 billion people globally and killed between 151,700 and 575,400 people. In 2014-2016 Ebola ravaged West Africa with 28,600 reported cases and 11,325 deaths. The Zika virus followed in 2015 and continues to spread up to the present time. Zika is usually spread through mosquitoes of the Aedes genus, however, its impact on human health is not yet known (1). In the 21st century, the two coronavirus infections affecting global public health, were caused by SARS-CoV and MERS-CoV (de Wit *et al*., 2016). Both viruses had a zoonotic origin with human-to-human transmission after their initial outbreak [2].

COVID-19 infects the respiratory tract causing severe pneumonia leading to acute respiratory distress syndrome (ARDS). The disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first detected in Wuhan, China. People infected by the SARS-CoV-2 virus can remain asymptomatic for up to 14 days. They may develop a mild-to-moderate disease, characterized by upper respiratory tract symptoms. Approximately 20% of patients progress to develop severe pneumonia with ARDS, unable to breath and ultimately many die, particularly older patients. As of today, SARS-CoV-2 has infected 33.1 million and caused 998,000 deaths. The pandemic has caused a global economic shutdown, which is forecasted to result in a depression more serious than the great depression of the 1930s [3]. Mortality due to SARS-CoV-2 were only reported for the critical cases (49%), mainly for patients with pre-existing comorbidities such as cardiovascular disease, diabetes, chronic respiratory disease, hypertension, or cancer [4]. Although COVID-19 has a milder clinical impairment compared to SARS and MERS for the vast majority of patients, SARS-CoV-2 infection has a dramatically increased human-to-human transmission rate, with the total number of deaths significantly exceeding those of SARS and MERS patients within the first three months of the COVID-19 outbreak.

Corona viruses belong to the subfamily Coronavirinae in the family of Coronaviridae of the order Nidovirales, and this subfamily includes four genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus. Coronaviruses are minute (65-125nm in diameter) encapsulated viruses with a crown-like appearance under an electron microscope, due to the presence of spike glycoproteins on the envelope. Coronaviruses have large (26-32 kb) single-stranded, positive-sense RNA genomes. The viral particles contain four main structural proteins. These are the spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins [5].

The SARS-CoV and SARS-CoV-2 virus bind to the host cells via the receptor binding domain (RBD) of the S protein that interact with the Angiotensin-converting enzyme 2 (ACE2) [6,7]. ACE2 is highly expressed on the surface of lung alveolar epithelial cells and enterocytes of the small intestine and are also present in arterial and venous endothelial cells, and arterial smooth muscle cells of multiple organs [8]. Once the virus bind to ACE2, it accesses the host cell's cytosol for proteolytic cleavage of the S protein, followed by the fusion of the viral and cellular membranes involving the protease TMPRSS2 [9]. Fusion ultimately results in the release of the viral RNA genome into the cell cytoplasm. The next steps, resulting in viral replication, would involve viral RNA translation, assembly of viral replicase transcription complexes, viral RNA synthesis, assembly of virions within the endoplasmic reticulum–Golgi intermediate compartment, and transport of these to the cell surface inside the vesicles. The newly formed infectious virions are then released from the host cell by exocytosis [8].

Patients with a rare disease are prone to deteriorate after COVID-19 infection

Based on the literature search, no special caring program was created for patients with a rare disease during the pandemics. Rare Diseases (RDs) are generally considered to be any disease that affects fewer people ~ 1 in 200,000 people and they are a complex mix of heterogeneous diseases, currently numbering 5,000 to 7,000 in total. The Saudi population is known to have a high rate of rare diseases due to consanguinity, specifically a very high prevalence of inborn errors of metabolism compared to global statistics, and affecting 1 in 1000 newborns [10,11]. Examples of these rare diseases are sickle-cell anemia, thalassemia, intellectual disability, congenital glaucoma, Bardet-Biedl syndrome, Meckel-Gruber syndrome, organic acidaemia, lysosomal storage disorders, retinal dystrophies, hearing loss, primary microcephaly, cystic fibrosis, muscular dystrophies and Huntington disease [12]. For many rare diseases, the exact cause remains

unknown, but the problem can be traced to changes, or mutations, in a single gene and / or chromosomal anomalies resulting from deletions, duplications, triplications and uniparental disomy. Many of these genetic mutations and translocation can be passed on from one generation to the next, explaining why certain rare diseases run in families.

The severity of COVID-19 disease appears to be linked to a genetic predisposition. Patients who have cancer, asthma, immunological linked diseases, obesity, diabetes, and hypertension are more likely to develop the serious condition. It is important to highlight and discuss the patient population with rare diseases in the context of COVID-19 infection. Even without COVID-19 infections, these patients have medical complications and when infected with COVID-19, they are more prone to develop serious disease. They need special treatment and attention, especially patients diagnosed with rare diseases with immune deficiencies such as cryopyrin associated periodic syndrome (CAPS) and TNF receptor-associated periodic syndrome (TRAPS), as well as patients with cardiovascular disorders, such as Brugada syndrome and Kawasaki disease. The effects of COVID-19 could worsen the rare disease related conditions due to several factors, including:

Cytokine storm

A cytokine storm is characterized by inducing special immune signatures and pathways that poses a threat to patients. SARS-CoV-2 symptoms range from inducing high fever, sore throat, cough, pain, and general malaise in most cases [13]. A small proportion, 5-10% of COVID-19 cases develop ARDS and acute lung injury, caused by damaging the alveolar lumen that induces inflammation and pneumonia leading to morbidity and mortality [14,15]. After the viral infection, the body's response is initiated at the cell level once the virus is replicating [16]. The host cell detects the virus particles through one of their cytoplasmic pattern recognition receptors (PRRs) [17]. The PRRs are the cellular sensors for a variety of microbes by recognizing common pathogen structures such as SARS-CoV-2. In the case of a virus infection, the cellular detection of the replication is largely mediated by a family of intracellular PRRs sensing aberrant RNA structures that are frequently formed during virus replication [17]. The virus entry and initiation of its replication result in the oligomerization of the PRRs and as a consequence, pathways such as the Interferon regulator factors (IRFs) and nuclear factor kB (NF-kB) are activated to induce general antiviral programs [18]. This leads to the activation of the antiviral defenses mediated by the type I (IFN-I) and III interferons (IFN-III) that upregulate IFN-stimulated genes (ISGs) [19]. The interferon pathways and cytokine secretion is supported by the second arm of the anti-viral physiological defense mechanism by involving the recruitment and coordination of specific subsets of leukocytes [20,21]. In most cases, these cellular antiviral activities lead to a limitation of virus replication and its elimination from the body. However, aggressive forms of infection, such as COVID-19, escape these pathways and cause severe damage in the body. There are studies that followed the COVID-19 infection and cellular response using different cellular and animal models, as well as human patient samples. Blanco-Melo *et al*., 2020 [22], characterized the transcriptional response to COVID-19 and compared it with common respiratory viruses, including influenza A virus (IAV). The COVID-19 and IAV process a variety of different antagonists to the IFN-I and -III response [23]. For the SARS-CoV-2, the gene ORF3B,ORF6, and the nucleocapsid (N) genes products play a role as IFN antagonists [24]. The SARS-CoV nsp1 gene that encodes for a nuclease has been implicated in cleaving host mRNA. It prevents ribosomal loading from turning off the host antiviral machinery [25]. The influenza A virus (IAV) virus express nonstructural protein 1 (NS1) that play a role in IFN-I and -III antagonism. It blocks the initial detection by the PRR through binding and masking aberrant RNA produced during infection [23]. Blanco-Melo *et al*., 2020 indicated that the overall transcriptional footprint of SARS-CoV-2 infection was distinct in comparison with other highly pathogenic coronaviruses and common respiratory viruses such as IAV, HPIV3, and RSV. The virus does not induce the IFN-I and -III system at low MOIs, indicating that the virus is not strong, which agrees with the its course of infection [17]. Cytokine induction starts as early as 3 days after COVID-19 infection and continues beyond clearance of the virus. The large induction of CCL2 and CCL8, monocyte-associated chemokines, and the induction of the engagement of macrophages predominated in the lungs of severe cases [26]. There is also an induction of CXCL2 and CXCL8, an indication of the elevated circulating neutrophil levels in COVID-19 patients [13], which may have a prognostic value for identifying individuals at risk for developing severe disease. The two cytokines that are uniquely elevated in COVID-19 infected patients are IL-6 and IL1RA, an early sign of cytokine release syndrome (CRS). The CRS is a complication frequently seen after CAR T-cell treatment [27]. In this regard, the treatment for COVID-

19 have less to do with the IFN response and more with controlling inflammation. As a waning immune response would enable sustained viral replication, it explains why serious cases of COVID-19 are more frequently observed in individuals with comorbidities.

Cardiovascular damage and failure

Infection with COVID-19 affects the lungs first and can lead to interstitial pneumonitis and ARDS. The virus also attaches to other organs, including the cardiovascular system, and patients with an advanced age are more likely to experience severe infection and death. Cardiovascular damage is characterized by arrhythmia, cardiac injury, heart failure and disseminated intravascular coagulation (DIC) [28]. The mortality rate increases in patients who suffer from cardiovascular disease, hypertension, diabetes, chronic pulmonary disease, and cancer.

The association between cardiovascular complications and COVID-19 infection is due to the fact that the virus enters the cells through the transmembrane ACE2. After the proteases cleave the virus S protein, it binds to ACE2 to enter type 2 endothelial cells, pneumocytes, macrophages, perivascular pericytes, and cardiomyocytes. As the angiotensin system is required for proper cardiovascular function, the viral usage of ACE2 leads to myocardial dysfunction and damage, endothelial dysfunction, microvascular dysfunction, plaque instability, and myocardial infarction (MI). In clinics, it is a normal practice to evaluate early and continued monitoring of cardiac damage (cTnI and NT-proBNP) and coagulation (D-dimer). It is essential to identify patients with cardiac injury to predict COVID-19 complications [28].

Myocardial injury that happens due to elevated troponin levels could be linked to myocardial ischemia or nonischemic myocardial progressions including myocarditis. With severe respiratory infection and ARDS due to COVID-19, it is expected that some patients would suffer from such injury. It was noted that the troponin serum levels were elevated significantly in patients who died as a result of COVID-19 compared to the survived ones [28,29].

Apart from hypertension, Type 2 diabetes mellitus (T2DM) is another risk factor for COVID-19 infection mortality, similar to SARS-CoV and MERS-CoV infection. Both hyperglycemia and T2DM are considered as independent predictors of mortality and morbidity in patients with SARS [29]. These patients are more prone to a cytokine storm, as they already are in a state of metabolic inflammation, resulting in multi-organ failure in patients with severe disease [30]. The disease inflammation caused by T2DM also weakens the immune system and reduces the ability of the body to combat the infection. It also impairs the healing process subsequently prolonging recovery [31]. COVID-19 enter the cell through the binding of S protein to ACE2 with the assistance of the cellular serine protease TMPRSS2 [9]. The ACE2 acts as key regulator of the angiotensin system and degrades the angiotensin II into angiotensin-(1–7) [32].

ACE1 and ACE2 function in a highly coordinated manner and their levels are closely regulated. The inhibition of ACE2 expression and the increase in ACE1 activity, results in the ability of angiotensin II to activate the angiotensin 1 receptor (AT1R) or AT2R to increase pro-inflammatory responses and stimulate aldosterone secretion. This activation leads to an increased blood pressure and can potentially cause hypokalemia, and local vascular permeability, which increases the risk of respiratory distress syndrome. On the other hand, the angiotensin 1–7 acts on the Mas receptor pathway. It causes the activation of the anti-inflammatory and anti-fibrotic pathways that is required for the recovery of COVID-19 patients [32]. The imbalance and disturbance of these pathways causes the severity in the patients infected by SARS-CoV-2. There is also a report that the SARS-CoV-2 infection can lead to the destruction of B cells in the pancreas which causes further complications [33].

Neurological affects

COVID-19 infection does not generally cause neurological disease, but the virus is known to infect the central nervous system (CNS), as well as presumed para-infectious disorders [34]. CT and MRI scans indicated symptoms of necrotizing hemorrhagic encephalopathy (ANE) in COVID-19 patients [35]. ANE is a rare disorder caused by a virus infection and can cause full brain dysfunction, including seizures, liver problems, and mental disorientation. The disease is manifested by multifocal symmetric lesions in the brain, which affects the brain stem, thalami, cerebellum, and cerebral white matter. ANE also causes neuroinflammation due to the increased expression of cytokines such as IL6 , IL2, IL7 and granulocyte–macrophage colony-stimulating factor (GM-CSF) caused by the activation of helper T cells [30], monocyte chemoattractant protein and other cytokines. This systemic inflammation causes severe encephalopathy in the patient, which may even result in stroke. MRI images of patients with COVID-19, who developed ANE, displayed clear evidence of

hemorrhage through hypointense signal intensity in the susceptibility-weighted images and increase in the rim on the postcontrast images [35].

The neuroinvasive nature of COVID-19 could increase the risk of neurodegenerative diseases with the involvement in the pathogenesis of neurological disorders such as Parkinson's disease or multiple sclerosis [36]. These conditions are more likely to deteriorate in patients with COVID-19 with pre-existing neurological disorders.

Caring for patients with a rare disease infected with COVID-19

The immunological, cardiovascular, and neurological effects of COVID-19 target the most frequently affected organs and body mechanisms that are principally malfunctioning in patients with rare diseases. Many of these patients are immuno-compromised, comorbid with conditions such as obesity, diabetes, and heart conditions, for example Chediak-Higashi syndrome and chronic granulomatous disease (CGD). In addition, some are mentally retarded due to several inborn errors of metabolism, such as propionic acidemia and methylmalonic acidemia, increasing the challenges to manage their condition should they become COVID-19 infected. Treating patients with rare diseases who are infected with COVID-19 require extra care. Several cases of Chediak-Higashi syndrome [37,38], CGD [39], propionic acidemia and methylmalonic academia [40,41] have been reported. In the absence of specific therapy and vaccination against the COVID-19 infection, the current treatment regime is to use a combination of protocols.

The COVID-19 treatment is given in conjunction with the treatment for the rare disease and a well-studied protocol should be considered as guidance for the combined treatment. The patients are managed in the daycare center at hospitals where they receive their chronic enzyme replacement therapies (ERT) weekly, for example for lysosomal storage disorders and intravenous immunoglobulins (IVIG) for severe combined immune deficiency (SCID).

As recommended by the WHO and CDC, there is a Clinical Guidance for the Management of Patients with Confirmed Coronavirus Disease (COVID-19). In addition, there is a recommendation for clinicians regarding the testing of investigational Therapeutics for Patients with COVID-19 [42]. However, none of these protocols recommends guidelines to manage patients with rare diseases, who are COVID-19 positive. In terms of the rare diseases, diagnostic tests are available and some advanced treatments exist. Inborn errors of metabolism disorders are usually treated with enzyme replacement and/or dietary therapy and if it is successfully managed, it results in significant improvement in the quality-of-life. For instance, hypophosphatasia is treated by asfotase alfa, a chimeric recombinant protein with an alkaline phosphatase ectodomain. For organic acidemia, a protein restricted diet and special synthetic formula is the mainstay of therapy.

Various sources have cautioned of an increase in the number of children presenting with a toxic shock-like syndrome, similar to Kawasaki disease's clinical features, in children with and without confirmed COVID-19 disease [43,44]. Kawasaki disease is a multisystem vasculitis that could be triggered by various infections, including common coronaviruses [45,46]. Although the disease is rare and the majority of the children recover, awareness of its possibility and clinical presentation by first-line physicians and pediatricians is essential. Early diagnosis and prompt treatment is critical to avoid complications, particularly those affecting the coronary arteries (eg. aneurysms) [47]. There appears to be a link between COVID-19 and a rare but serious health condition, affecting children after infection by SARS-CoV-2, called Multi-System Inflammatory Syndrome in Children (MIS-C) [48]. In MIS-C, the heart, lungs, kidneys, brain, skin, eyes, or gastrointestinal organs become infected, which may be serious and deadly. This is further supported by the strong association reported between the SARS-CoV-2 epidemic and Kawasaki disease development by the Italian Center for the COVID-19 epidemic. This association suggests a possible triggering effect of SARS-CoV-2 infection for the development of Kawasaki disease [49]. However, it is argued that individuals with rare diseases, such as hyperglycinuria and iminoglycinuria, caused by an inborn mutation of the *SLC6A20* gene encoding proline transporter SIT, a protein that interacts with ACE2, could be more susceptible to SARS-CoV-2 infection [50].

There are more than 100 vaccines in development and a number of investigational therapies. As summarized in Tables 1 to 5, various types of vaccines are being developed, including virus-based vaccines, nucleic acid-based vaccines, viral vector-based vaccines and protein-based vaccines. The investigational agents are either re-purposed or adjunctive therapy agents. During the development of these vaccines and therapies, it is vital to consider patients with rare diseases to optimize the doses.

Table 1. Virus based vaccines.

Inactivated virus vaccines				
Vaccine type	**Adjuvant**	**Phase of evaluation**	**Developing organization(s)**	**Country**
Inactivated SARS-CoV-S2	Inactivated Vero cell	Phase 3	Wuhan Institute of Biological Products and Sinopharm	China
Inactivated SARS-CoV-S2	Inactivated Vero cell	Phase 3	Beijing Institute of Biological Products and Sinopharm	China
Inactivated SARS-CoV-S2	Inactivated vaccine	Phase 3	Sinovac	China
Inactivated SARS-CoV-S2	Inactivated whole-viron	Phase 3	Bharat Biotech International	India
Inactivated SARS-CoV-S2	Inactivated Vero cell	Phase 1/2	Institute of Medical Biology and Chinese Academy of Medical Sciences	China
Inactivated SARS-CoV-S2	Inactivated vaccine	Phase 1/2	Research Institute for Biological Safety Problems	Kazakhstan
Inactivated SARS-CoV-S2	Inactivated virus	Phase 1/2	Valneva and National Institute for Health Research	France/UK
Inactivated SARS-CoV-S2	Inactivated virus	Pre-clinical	Osaka University, BIKEN and NIBIOHN	Japan
Inactivated SARS-CoV-S2	Inactivated virus plus CpG 1018	Pre-clinical	Sinovac and Dynavax	China/USA
Inactivated SARS-CoV-S2	Inactivated virus plus CpG 1018	Pre-clinical	Valneva and Dynavax	France/USA
Inactivated SARS-CoV-S2	Inactivated chimeric Newcastle disease virus-expressing trimeric SARS-CoV-2 S protein + CpG 1018	Pre-clinical	Institute of Vaccines and Medical Biologicals (IVAC), Dynavax and PATH	Vietnam/USA
Inactivated SARS-CoV-S2	Inactivated chimeric Newcastle Disease virus expressing trimeric SARS-CoV-2 S protein + CpG 1018	Pre-clinical	Government Pharmaceutical Organization (GPO), Dynavax and PATH	Thailand/USA
Inactivated SARS-CoV-S2	Inactivated chimeric Newcastle Disease virus expressing trimeric SARS-CoV-2 S protein + CpG 1018	Pre-clinical	Institute Butantan, Dynavax and PATH	Brazil/USA
Inactivated SARS-CoV-S2	Inactivated virus plus alum	Pre-clinical	KM Biologics	Japan
Inactivated SARS-CoV-S2	Inactivated virus	Pre-clinical	Selcuk University	Turkey
Inactivated SARS-CoV-S2	Inactivated virus	Pre-clinical	Erciyes University	Turkey
Inactivated SARS-CoV-S2	Inactivated virus	Pre-clinical	National Research Centre,	Egypt
Inactivated SARS-CoV-S2	Inactivated virus	Pre-clinical	Kocak Farma Ilac ve Kimya San. A.S.	Turkey
Live attenuated virus vaccines				
Vaccine type	**Adjuvant**	**Phase of Evaluation**	**Developing Organization(s)**	**Country**
Live attenuated SARS-CoV-S2	Codon de-optimized live attenuated virus	Phase 1	Codagenix and Serum Institute of India	USA/India

The information is retrieved from "The COVID-19 candidate vaccine landscape" at WHO.int as of January 6th, 2021.

Table 2. Nucleic acid based vaccines.

DNA-based vaccines					
DNA Type	**DNA delivery method**	**SARS-CoV-2 encoded protein in DNA sequence**	**Phase of evaluation**	**Developing organization(s)**	**Country**
DNA plasmid	Electroporation		Phase 2/3	Inovio Pharmaceuticals	USA
DNA			Phase 1	Entos Pharmaceuticals	Canada
DNA			Phase 1	Providence Health and Services	USA
bacTRL-Spike		Spike protein	Phase 1	Symvivo	Canada
DNA plasmid			Phase 1/2	Osaka University, AnGes, and Takara Bio	Japan
DNA plasmid			Phase 1/2	Cadila Healthcare	India
DNA			Phase 1/2	Genexine Consortium	South Korea
DNA			Phase 1/2	GeneOne Life Science	South Korea
DNA	Electroporation		Pre-clinical	Karolinska Institute and Cobra Biologics	Sweden
DNA			Pre-clinical	Takis Biotech, Evvivax, and Applied DNA Sciences	Italy/USA
DNA plasmid	Needle-Free Delivery		Pre-clinical	Immunomic Therapeutics, EpiVax, and PharmaJet	USA
DNA			Pre-clinical	BioNet Asia	Thailand
DNA			Pre-clinical	University of Waterloo	Canada
DNA	Multiple delivery systems		Pre-clinical	DIOSynVax and University of Cambridge	UK
DNA			Pre-clinical	Ege University	Turkey
DNA plasmid			Pre-clinical	Scancell, University of Nottingham, and Nottingham Trent University	UK
DNA	Electroporation		Pre-clinical	Chula Vaccine Research Center	Thailand
DNA			Pre-clinical	National Research Centre	Egypt
DNA plasmid		Spike protein	Pre-clinical	Biosun Pharmed	Iran
DNA plasmid			Pre-clinical	Globe Biotech	Bangladesh
DNA plasmid		RBD	Pre-clinical	National institute of Chemistry	Slovenia
DNA plasmid		RBD	Pre-clinical	Vaccibody and Oslo Research Park	Norway
DNA		Immunostimulatory sequences	Pre-clinical	Inserm	France
RNA-based vaccines					
RNA Type	**Encapsulation type**	**SARS-CoV-2 encoded protein in RNA sequence**	**Phase of evaluation**	**Developing organization(s)**	**Country**
mRNA	Lipid nanoparticles (LNP)		Phase 3	Moderna and NIAID	USA
Several mRNAs	3 Lipid nanoparticles (LNP)		Phase 2/3	BioNTech, Fosun Pharma, and Pfizer	Germany/China/USA
mRNA			Phase 2/3	Curevac	Germany
mRNA			Phase 1/2	Arcturus therapeutics and Duke-NUS	USA/Singapore
saRNA			Phase 1	Imperial College London	UK

mRNA			Phase 1	Shulan (Hangzhou) Hospital and Center for Disease Control and Prevention of Guangxi Zhuang Autonomous Region	China
mRNA			Phase 1	Chulalongkorn University	Thailand
mRNA	LNP		Pre-clinical	Translate Bio and Sanofi Pasteur	USA/France
mRNA cocktail	LNP	VLP	Pre-clinical	Fudan University, Shanghai JiaoTong University and RNACure Biopharma	China
mRNA	LNP	RBD	Pre-clinical	Fudan University, Shanghai JiaoTong University and RNACure Biopharma	China
Several replicating defective SARS-CoV2 derived RNAs			Pre-clinical	Centro Nacional Biotecnología	Spain
mRNA	LNP-encapsulated		Pre-clinical	University of Tokyo and Daiichi-Sankyo	Japan
mRNA	Liposome encapsulated		Pre-clinical	BIOCAD	Russia
Several mRNAs			Pre-clinical	RNAimmune	USA
mRNA			Pre-clinical	FBRI SRC VB VECTOR	Russia
mRNA			Pre-clinical	China CDC, Tongji University, and Stermina therapeutics	China
mRNA	Intranasal delivery system		Pre-clinical	eTheRNA	Belgium
mRNA			Pre-clinical	Greenlight Biosciences	USA
saRNA	Formulated in a NLC		Pre-clinical	Infectious Disease Research Institute (IDRI) and Amyris	USA
mRNA	LNP-encapsulated	Spike protein	Pre-clinical	Max-Planck-Institute of Colloids and Interfaces	Germany
Self-amplifying RNA			Pre-clinical	Gennova	India
mRNA			Pre-clinical	Selcuk University	Turkey
mRNA			Pre-clinical	IDIBAPS-Hospital Clinic	Spain
mRNA			Pre-clinical	Providence Therapeutics	Canada
mRNA			Pre-clinical	Cell Tech Pharmed	Iran
mRNA			Pre-clinical	ReNAP	Guatemala
mRNA	LNP-encapsulated		Pre-clinical	Globe Biotech	Bangladesh
mRNA	Encapsulated		Pre-clinical	CEA	

The information is retrieved from "The COVID-19 candidate vaccine landscape" at WHO.int as of January 6th, 2021.

Table 3. Viral vector based vaccines.

Non-replicating vectors				
Vector type	**SARS-CoV-2 protein expressed in vector**	**Phase of evaluation**	**Developing organization(s)**	**Country**
Adenovirus type 5 vector		Phase 3	CanSino Biological and Beijing Institute of Biotechnology	China
Adenovirus type ChAdOx1 vector	Covishield	Phase 3	AstraZeneca and University of Oxford	UK
Adeno-based (rAd26-S+rAd5-S)		Phase 3	Gamaleya Research Institute and Health Ministry of the Russian Federation	Russia
Adenovirus serotype 26		Phase 3	Janssen Pharmaceutical	Belgium
LV-SMENP-DC	Covid-19 minigene SMENP and immune modulatory genes	Phase 1/2	Shenzhen Geno-Immune Medical Institute	China
Replication defective Simian adenovirus	S protein	Phase 1	ReiThera, Leukocare, and Univercells	Italy Germany Belgium
Oral virus		Phase 1	Vaxart	USA
MVA-SARS-2-S	Spike protein	Phase 1	University of Munich	Germany
hAd5-S-Fusion and N-ETSD vaccine		Phase 1	ImmunityBio	USA
COH04S1 (MVA-SARS-2-S)	Spike protein	Phase 1	City of Hope Medical Center and National Cancer Institute	USA
Modified Vaccinia Ankara (MVA)	VLP	Pre-clinical	GeoVax and BravoVax	USA/China
MVA-S	Surface protein	Pre-clinical	DZIF – German Center for Infection Research and IDT Biologika GmbH	Germany
Adenovirus type NasoVAX	Spike protein	Pre-clinical	Altimmune	USA
Ad5 S		Pre-clinical	Greffex	USA
Oral Ad5 S		Pre-clinical	Stabilitech Biopharma	UK
adenovirus-based and HLA-matched peptides		Pre-clinical	Valo Therapeutics	Finland/UK
MVA	Structural proteins	Pre-clinical	Centro Nacional Biotecnología	Spain
parainfluenza virus 5 (PIV5)	Spike protein	Pre-clinical	University of Georgia and University of Iowa	USA
Recombinant deactivated rabies virus	Spike S1 protein	Pre-clinical	Bharat Biotech and Thomas Jefferson University	India/USA
Sendai virus vector		Pre-clinical	ID Pharma	Spain
Adenovirus-based		Pre-clinical	Ankara University	Turkey
Adeno-associated virus vector (AAVCOVID)		Pre-clinical	Massachusetts Eye and Ear, Massachusetts General Hospital, and AveXis	USA
Influenza A H1N1 vector		Pre-clinical	National Research Centre	Egypt
Newcastle disease virus	Spike protein	Pre-clinical	Icahn School of Medicine at Mount Sinai	USA
Lentiviral Vector		Pre-clinical	Theravectys – Institut Pasteur	France
Lentiviral Vector		Pre-clinical	AIOVA	USA

Lentiviral Vector Retro-VLP Particles		Pre-clinical	Sorbonne University	France
Ad 5 vector for intranasal administration		Pre-clinical	University of Helsinki and University of Eastern Finland	Finland
Non replicating vector		Pre-clinical	Vaxart	USA
Replicating vectors				
Vector	**SARS-CoV-2 protein expressed in vector**	**Phase of evaluation**	**Developing organization(s)**	**Country**
Flu-based	RBD	Phase 2	Jiangsu Provincial Center for Disease Prevention and Control	China
Measles	NA	Phase 1/2	Merck and Co., Themis, Sharp and Dohme, Institute Pasteur, and Univeristy of Pittsburgh	France/Austria/USA
Dendritic cell vaccine AV-COVID-19	Autologous dendritic cells loaded with antigens from SARS-CoV-2, with or without GM-CSF	Phase 1/2	Aivita Biomedical	USA
Modified lentivirus	Immune modulatory genes and the viral minigenes	Phase 1	Shenzhen Geno-Immune Medical Institute	China
rVSV-SARS-CoV-2-S Vaccine		Phase 1	Israel Institute for Biological Research	USA
AdCLD-CoV19			Cellid Co.	South Korea
YF17D		Pre-clinical	KU Leuven	Belgium
Measles		Pre-clinical	Cadila Healthcare	India
Measles		Pre-clinical	FBRI SRC VB VECTOR	Russia
Measles	Spike and nucleoside proteins	Pre-clinical	DZIF – German Center for Infection Research and CanVirex AG	Germany
Horsepox	Spike protein	Pre-clinical	Tonix Pharma and Southern Research	USA
Attenuated influenza virus		Pre-clinical	BiOCAD and IEM	Russia
Influenza A virus□		Pre-clinical	FBRI SRC VB VECTOR	Russia
Influenza vector	Spike protein	Pre-clinical	Fundação Oswaldo Cruz and Instituto Buntantan	Brazil
Influenza vector	RBD	Pre-clinical	University of Hong Kong	Hong Kong
Replication-competent VSV chimeric virus	Spike protein	Pre-clinical	IAVI and Merck	USA
Replicating VSV vector-based DC-targeting		Pre-clinical	University of Manitoba	Canada
VSV-S		Pre-clinical	University of Western Ontario	Canada
VSV-S		Pre-clinical	Aurobindo	USA
VSV		Pre-clinical	FBRI SRC VB VECTOR	Russia
M2-deficient single replication (M2SR) influenza vector		Pre-clinical	UW–Madison, FluGen, and Bharat Biotech	USA/India
Newcastle disease virus vector (NDVSARS-CoV-2/Spike)	Spike protein	Pre-clinical	Intravacc, Wageningen Bioveterinary Research, and Utrecht Univ	Netherlands
Avian paramyxovirus vector (APMV)		Pre-clinical	The Lancaster University	UK
Intranasal Newcastle disease virus vector	RBD	Pre-clinical	Farmacológicos Veterinarios SAC and Universidad Peruana Cayetano Heredia	Peru

The information is retrieved from "The COVID-19 candidate vaccine landscape" at WHO.int as of January 6th, 2021.

Table 4. Protein based vaccines.

Protein subunit				
Antigen Protein	**Protein expression system**	**Phase of evaluation**	**Developing organization(s)**	**Country**
SARS-CoV-2 rS/Matrix M1-Adjuvant		Phase 3	Novavax	USA
Recombinant SARS-CoV-2 vaccine (CHO Cell)		Phase 3	Anhui Zhifei Longcom Biopharmaceutical, Institute of Microbiology, and Chinese Academy of Sciences	China
RBD (baculovirus production expressed in Sf9 cells) Recombinant SARS-CoV-2 vaccine (Sf9 Cell		Phase 2	West China Hospital and Sichuan University	China
KBP-COVID-19 (RBD-based)		Phase 1/2	Kentucky Bioprocessing	USA
SARS-CoV-2 vaccine formulation 1 with adjuvant 1 (S protein)	Baculovirus production	Phase 1/2	Sanofi Pasteur and GSK	France/UK
FINLAY-FR anti-SARS-CoV-2 Vaccine (RBD + adjuvant)		Phase 1/2	Instituto Finlay de Vacunas	Cuba
EpiVacCorona (EpiVacCorona vaccine based on peptide antigens for the prevention of COVID-19)		Phase 1/2	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology "Vector"	Russia
BECOV2		Phase 1/2	Biological E	India
Recombinant Sars-CoV-2 Spike protein plus Aluminum adjuvanted		Phase 1/2	Nanogen Pharmaceutical Biotechnology	USA
Recombinant protein vaccine S-268019	Baculovirus expression vector	Phase 1/2	Shionogi	Japan
CIGB-669 (RBD and AgnHB)		Phase 1/2	Center for Genetic Engineering and Biotechnology	Italy
CIGB-66 (RBD and aluminium hydroxide)		Phase 1/2	Center for Genetic Engineering and Biotechnology	Italy
VLA2001		Phase 1/2	Valneva and National Institute for Health Research	UK
IMP CoVac-1 (SARS-CoV-2 HLA-DR peptides)		Phase 1	University Hospital Tuebingen	Germany
UB-612 (Multitope peptide based S1-RBD-protein based vaccine)		Phase 1	COVAXX and United Biomedical	USA
AdimrSC-2f (recombinant RBD with and without Aluminium)		Phase 1	Adimmune Corporation	Taiwan
SCB-2019 + AS03 or CpG 1018 adjuvant plus Alum adjuvant (Native		Phase 1	Clover Biopharmaceuticals, GSK and Dynavax	China/UK/USA

like Trimeric subunit Spike Protein vaccine)				
COVID19 vaccine		Phase 1	Vaxine Pty and Medytox	Australia
MVC-COV1901 (S-2P protein + CpG 1018)		Phase 1	Medigen Vaccine Biologics, Dynavax, and NIAID	Taiwan/USA
RBD protein		Pre-clinical	Ohio State University and Kazakh National Agrarian University	Kazakhstan/USA
Recombinant spike protein		Pre-clinical	Kazakh National Agrarian University	Kazakhstan
Peptides		Pre-clinical	Neo7Logic	USA
Recombinant spike protein		Pre-clinical	Kazakh National Agrarian University and National Scientific Center for Especially Dangerous Infections	Kazakhstan
Recombinant S protein		Pre-clinical	Max-Planck-Institute of Colloids and Interfaces	Germany
RBD protein and FAR-Squalene adjuvant	Baculovirus		Farmacológicos Veterinarios SAC and Universidad Peruana Cayetano Heredia	Peru
Protein Subunit		Pre-clinical	Research Institute for Biological Safety Problems	Kazakhstan
RBD-protein		Pre-clinical	Mynvax	India
Recombinant S protein		Pre-clinical	Izmir Biomedicine and Genome Center	Turkey
Peptide and novel adjuvant		Pre-clinical	Bogazici University	Turkey
S subunit		Pre-clinical	University of Virginia	USA
S-Protein and adjuvant	E coli based Expression	Pre-clinical	Helix Biogen Consult, Ogbomoso and Trinity Immonoefficient Laboratory, Ogbomoso, and Oyo State	Nigeria
Protein subunits: S,N,M andS1		Pre-clinical	National Research Centre	Egypt
Protein Subunit		Pre-clinical	University of San Martin and CONICET	Argentina
RBD protein fused with Fc of IgG and adjuvant		Pre-clinical	Chulalongkorn University and GPO	Thailand
Capsid-like Particle		Pre-clinical	AdaptVac (PREVENT-nCoV consortium)	Germany
Protein S2	Drosophila insect cell expression system VLPs	Pre-clinical	ExpreS2ion	Denmark
Peptide antigens formulated in LNP		Pre-clinical	IMV	Canada
S protein		Pre-clinical	WRAIR and USAMRIID	
S protein and adjuvant		Pre-clinical	National Institute of Infectious Disease, Shionogi and UMN Pharma	Japan
VLP-recombinant protein and adjuvant		Pre-clinical	Osaka University, BIKEN, and National Institutes of Biomedical Innovation	Japan
microneedle arrays S1 subunit		Pre-clinical	University of Pittsburgh	USA
Peptide		Pre-clinical	Vaxil Bio	Canada
Adjuvanted protein subunit (RBD)		Pre-clinical	Biological E	India
Peptide		Pre-clinical	Flow Pharma	USA
S protein		Pre-clinical	AJ Vaccines	Denmark
Ii-Key peptide		Pre-clinical	Generex and EpiVax	Canada\USA
S protein		Pre-clinical	EpiVax and University of Georgia	USA
Protein Subunit EPV-CoV-19		Pre-clinical	EpiVax	USA
gp-96 backbone		Pre-clinical	Heat Biologics and University Of Miami	USA
Subunit vaccine		Pre-clinical	FBRI SRC VB VECTOR, Rospotrebnadzor, and Koltsovo	Russia
S1 or RBD protein		Pre-clinical	Baylor College of Medicine	USA
Subunit protein	Plant produced	Pre-clinical	iBio and CC-Pharming	USA\China
Recombinant protein, nanoparticles (based on S-protein and other epitopes)		Pre-clinical	Saint-Petersburg scientific research institute of vaccines and serums	USA
COVID-19 XWG-03 truncated S (spike) proteins		Pre-clinical	Innovax, Xiamen University and GSK	China\UK
Adjuvanted microsphere peptide		Pre-clinical	VIDO-InterVac and University of Saskatchewan	Canada
Synthetic Long Peptide Vaccine candidate for S and M proteins		Pre-clinical	OncoGen	Romania
Oral E. coli-based protein expression system of S and N proteins	E. coli	Pre-clinical	MIGAL Galilee Research Institute	
Nanoparticle vaccine		Pre-clinical	LakePharma	USA
Plant-based subunit (RBD-Fc and adjuvant)		Pre-clinical	Baiya Phytopharm and Chula Vaccine Research Center	
OMV-based vaccine		Pre-clinical	Quadram Institute Biosciences	UK
OMV-based vaccine		Pre-clinical	BiOMViS Srl and University of Trento	Italy
structurally modified spherical particles of the tobacco mosaic virus (TMV)		Pre-clinical	Lomonosov Moscow State University	
Spike-based		Pre-clinical	University of Alberta	Canada
Recombinant S1-Fc fusion protein		Pre-clinical	AnyGo Technology	China
Recombinant protein		Pre-clinical	Yisheng Biopharma	China
Recombinant S protein in IC-BEVS	Baculovirus expression system in insect cell line	Pre-clinical	Vabiotech, Vietnam and University of Bristol,	Vietnam/UK
Orally delivered, heat stable subunit		Pre-clinical	Applied Biotechnology Institute	USA
Peptides derived from Spike protein		Pre-clinical	Axon Neuroscience SE	Slovakia
Protein Subunit		Pre-clinical	MOGAM Institute for Biomedical Research, and GC Pharma	South Korea
RBD-based		Pre-clinical	Neovii and Tel Aviv University	
Outer Membrane Vesicle (OMV)-subunit		Pre-clinical	Intravacc and Epivax	USA
Spike-based (epitope screening)		Pre-clinical	ImmunoPrecise and LiteVax BV	Canada
Spiked-based		Pre-clinical	Nanografi Nano Technology, Middle East Technical University, Ankara University,	Turkey
Recombinant spike with adjuvant		Pre-clinical	Iran	Iran

Recombinant S protein produced in BEVS		Pre-clinical	Tampere University	Finland
Protein Subunit Nanoformulated		Pre-clinical	Vaxinano, CEA and INRAE	France
Protein Subunit Adenoviral Carrier		Pre-clinical	CEA and CNRS	France
Protein DC-targeted epitopes		Pre-clinical	LinkinVax and VRI	France
Virus-Like Particle (VLP)				
VLP type	**Particle synthesis system**	**Phase of evaluation**	**Developing organization(s)**	**Country**
Virus-like particle		Phase 2/3	Medicago Inc.	Virus-like particle
RBD SARS-CoV-2 HBsAg VLP vaccine		Phase 1/2	Serum Institute of India and Accelagen Pty	India
VLP		Pre-clinical	Max Planck Institute for Dynamics of Complex Technical Systems	Germany
Virus-like particle-based Dendritic Cell(DC)		Pre-clinical	University of Manitoba	Canada
VLP		Pre-clinical	Bezmialem Vakif University	Turkey
VLP		Pre-clinical	Middle East Technical University	Turkey
Enveloped Virus-Like Particle		Pre-clinical	VBI Vaccines	USA
S protein integrated in HIV VLPs		Pre-clinical	IrsiCaixa AIDS Research, IRTA-CReSA, Barcelona Supercomputing Centre, and Grifols	Portugal
VLP and adjuvant		Pre-clinical	Mahidol University, The Government Pharmaceutical Organization (GPO), and Siriraj Hospital	Thailand
Virus-like particles	Lentivirus and baculovirus vehicles	Pre-clinical	Navarrabiomed, Oncoimmunology group	Spain
Virus-like particle, based on RBD displayed on virus-like particles		Pre-clinical	Saiba GmbH	Switzerland
ADDomerTM multiepitope display		Pre-clinical	Imophoron, Bristol University and Max Planck Centre	UK/Germany
Unknown		Pre-clinical	Doherty Institute	Australia
VLP		Pre-clinical	OSIVAX	France
eVLP		Pre-clinical	ARTES Biotechnology	Germany
VLPs peptides/whole virus		Pre-clinical	University of Sao Paulo	Brazil
VLPs	BEVS	Pre-clinical	Tampere University	Finland
Plant derived VLP	Plant	Pre-clinical	Shiraz University	Iran

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Table 5. Antiviral agents.

Investigational agents		
Agent	**Target**	**Phase of evaluation**
Remdesivir	RNA polymerase inhibitor	Phase 3
Favipiravir	RNA polymerase inhibitor	Phase 3
Re-purposed agents		
Agent	**Target**	**Phase of evaluation**
Chloroquine phosphate	Inhibits viral entry and activates immune-modulatory effects in host cells	Phase 3
Hydroxychloroquine sulfate	Similar mechanism to chloroquine phosphate	Phase 3
Lopinavir/ritonavir	3CL protease inhibitor	Phase 3
Umifenovir (Arbidol)	Inhibits viral S protein association with host ACE2	Phase 3
Tocilizumab (Actemra)	IL-6 inhibitor	Phase 3
Darunavir	3CL protease inhibitor	Phase 3
Dexamethasone	Immune system suppression	Phase 3
Interferon beta-1b	NA	Phase 2

The information is retrieved from ClinicalTrials.gov as of January 6th, 2021.

Most of the patients with rare diseases have deficiencies in their immune system, an important consideration in terms of the vaccination these patient populations. Some rare diseases develop after a flu vaccination, such as the Guillain-Barre syndrome (GBS) [51,52]. GBS is a rare disorder where the body's immune system damages the nerve cells, causing muscle weakness and sometimes paralysis. While its cause is not yet fully understood, the syndrome often develops after an infection with a virus or bacteria. All can develop GBS, but people older than 50 years are at the greatest risk. Approximately two-thirds of people who develop GBS, do so several days or weeks after they have had diarrhea or a lung or sinus illness. On very rare occasions, people develop GBS in the days or weeks after being vaccinated. In 1976, there was a small increased risk of GBS after the swine flu vaccination, a special flu vaccine for a potential pandemic strain of flu virus [53,54].

Conclusions

Rare diseases represent a very serious group of life-threatening and debilitating disorders. Globally, 8000 rare diseases have been identified to date, affecting approximately 350 million. The pathology and mechanisms causing these diseases are complex and only a small number are correctly diagnosed and treated. In addition, the patients require life-long treatment, which is typically very expensive, raising the concerns of national governments [55].

A number of these governments, as in Saudi Arabia, follow a strict program of genetic counseling, perinatal

pre-marriage testing, and the peri-implantation genetic diagnosis to limit the prevalence of rare diseases [56,57]. The Saudi population is known to have a high rate of rare diseases due to consanguinity. It has a very high number of inborn errors of metabolism compared to global statistics, affecting 1 in 1000 newborns [10,11]. Considering the vulnerability of patients with rare diseases to infections and the high cost of their treatment, special measures should be taken to care for this patient population during a pandemic such as COVID-19. These measures should be activated three strategies:

(1) Clinical care for infected patients with rare diseases who are COVID-19 positive. Ongoing care for the rare disease must be adapted to the current treatment protocol to include COVID-19 therapy, which is already very intensive. As a general rule, 10-15% of patients are admitted to an ICU for mechanical ventilation, the same scenario would be true for patients with rare diseases.
(2) An educational program to raise the awareness of patients with rare diseases patients in terms of a pandemic. As many of these patients also suffer from mental retardation and are under continuous treatment, a special program should be developed to teach them about social distancing, quarantine, curfew and other aspects of COVID-19 management.
(3) Psychological support to care for the family members and patients with a rare disease and infected by a COVID-19 type of disease. These patients and families are already under pressure and emotional support is essential to reduce their suffering.
(4) Avoid the discontinuation of their chronic medication such as ERT, by facilitating the management at the day care centers during quarantine or established home care visits to receive the ERT and other treatment at home, which will reduce morbidity and mortality.

Patients with rare diseases are an example of a patient community that may suffer at a higher rate in a global pandemic, who may become a neglected population due to the severity of the pandemic. However, global organizations such as the WHO and governmental health ministers must prepare programs providing guidelines for the care for these patients in this situation.

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