

Novel immunogenomic insights of corona virus disease (COVID-19): Available potential immunotherapeutics, current challenges, immune cell recognition and ongoing managerial strategies

Kabeer Haneef^{1,*}, Muhammad Umer Asghar^{1,2,3}, Ashiq Ali⁴



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¹Institute of Microbiology (IOM), University of Agriculture Faisalabad (UAF), Pakistan

²National Institute for Biotechnology and Genetic engineering (NIBGE), Faisalabad 38000, Punjab Pakistan

³Pakistan Institute of Engineering and Applied Sciences (PIEAS), Nitor, 45650, Islamabad, Pakistan

⁴Department of Pathology, Faculty of Veterinary sciences, University of Agriculture Faisalabad-38000, Pakistan

Correspondence

Kabeer Haneef, Institute of Microbiology (IOM), University of Agriculture Faisalabad (UAF), Pakistan

Email: Kabeerhaneef16@gmail.com

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ABSTRACT

The emerging Corona virus strain (severe acute respiratory syndrome corona virus-2 (SARS-CoV-2)) harbors intricate pathogenicity in the development of corona virus infection (COVID-19)-induced pneumonia and subsequently ameliorates lung infection. Genome sequence and phylogenetic interventions reveal proximal resemblance of corona virus strain COVID-19 with severe acute respiratory syndrome (SARS), transmittable to bats, suggesting similar primary hosts in the spread of infection. However, potential rapid human-to-human transmission has caused therapeutic challenges in treating a wide range of humans suffering from corona virus all over the world. However, up to now, no direct vaccines or antiviral drugs are available to treat COVID-19. Previously designed antiviral drugs and convalescent plasma are undergoing investigations as treatment for COVID-19 infected patients. Therapeutic challenges with regards to COVID-19 have prompted scientists to develop fruitful remedies to combat the pathogen. In this review, we address the role of current ongoing therapeutic strategies, immunogenomics, and complex mechanisms of adaptive immune system (B and T cells) to respond to viruses. Furthermore, we illustrate the current challenges in the treatment of COVID-19, managerial strategies, and ongoing and future perspectives.

Key words: Covid-19, immunogenomics, treatment modalities, adaptive immunity, management strategies

INTRODUCTION

Coronaviruses, especially severe acute respiratory syndrome-2 (SARS-CoV-2), are minute single-stranded micron sized RNA particles¹, harboring intricate capability to induce lung infection and pneumonia in humans¹; they are ordered in the Coronaviridae family². Previous corona virus outbreaks in China (Guangdong) have revealed their potential capability to induce intestinal and lung infections³. However, none of the quarantine measures were adopted in the 2002 and 2003 outbreaks^{4,5}. Similarly, a decade later, Asian countries experienced another deadly outbreak of middle east respiratory syndrome (MERS) virus, belonging to MERS-CoV^{6,7}. Thus, research community was engaged and therapeutic modalities were followed to combat MERS. With the emergence of the new deadly outbreak of novel coronavirus COVID-19, there was experience and knowledge about the meticulous capability of genome mutation of the virus^{8,9}. Different inoculations revealed that mortality parameters are dependent on physical health, age,

immune mechanism, and gender discrimination-ranging from 0.3% to 15%^{10,11}.

The human body is bombarded via pathogens and responds by sophisticated mechanisms to develop immunity^{12,13}. Innate immune cells (e.g. macrophages and dendritic cells) and adaptive immune cells (e.g. B and T lymphocytes) work in close proximal association to produce potent neutralizing antibodies with stringent potential to neutralize viruses and develop immunity^{14,15}. Following invasion of pathogen-associated molecular patterns (PAMPs) and viruses, antigen-presenting cells (APCs) like macrophages and dendritic cells respond quickly, processing and presenting peptide antigens to B Lymphocytes through major histocompatibility complex (pMHC) molecules^{16,17}. However, the way the immune system discriminates between the types of pathogens remains poorly understood. Typically, major histocompatibility complex- 1 (pMHC-1) and pMHC-2 molecules provide efficient potential to discriminate through substantial mechanism of antigen presentation^{18,19}. In addition, recent evidence from COVID-19 investigations have suggested

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that mutational interventions interlinked with pMHC molecules could be crucial to devastate COVID-19 induced pathogenicity and suggest pMHC as a suitable candidate for drug discovery^{20,21}.

Considering the structural complexity features of COVID-19²², currently no promising therapeutic strategies are available. However, several antiviral drugs previously employed for MERS-CoV and SARS-CoV are ongoing as therapeutic remedies after clinically-approved applications^{23,24}. Remdesivir, alone or in adjacent combination with chloroquine and interferon-beta (IFN- β), has been proven promising against SARS-CoV-2, and thus has been suggested as an available promising therapeutic strategy²⁵⁻²⁷. However, recently, several groups have actively reported on the efficiency of plasma-derived monoclonal antibodies from blood of COVID-19 infection-recovered patients, and have suggested the use of such antibodies as passive immunization therapy^{28,29}. However, considering the aforementioned strategies, there is a dire need to develop more potent antiviral drugs to target viral proteins, nucleotides, capsids and nucleosides.

MORPHOLOGIC AND KEY GENOME PROSPECTIVE FEATURES OF COVID-19

Coronaviruses - especially SARS-COVID-19 (of the Coronaviridae family) - have a morphologic configuration which shows minute single-stranded, enveloped particles ranging in size from 150-160 μm ³⁰. Further evidence have suggested that surface-flanked S proteins as well as matrix and nucleocapsid proteins harbor stringent pathogenicity factors to devastate immune mechanisms³¹. COVID-19 virus particles additionally encodes for hemagglutinin (HA) proteins, revealing key genome differences with other strains^{10,24}. Considering sequence interventions and key genome identity features, COVID-19 has been revealed to show proximal resemblance with SARS-CoV, in contrast to MERS-COVID¹⁰. In addition, surface-anchored glycoproteins and S proteins grant discriminating potential, thereby suggesting them as suitable therapeutic candidates to target surface-flanked S components. In addition, amino acid sequence interventions have revealed that S protein is divided into two parts: S1 (which facilitates COVID-19 entry into the human body), and S2 (which interferes with the host immune system)²⁴. Similarly, additional evidence have suggested that COVID-19 shows resemblance to SARS-COVID in terms of S1,

i.e. with respect to amino acid sequence interventions³². However, considering the key genome identity features, it is interesting and noteworthy that both strains gain access to invade the hosts³³. Structural and conformational analyses have already revealed that human angiotensin-2 (hACE-2) receptor provides an intricate attachment site to trigger COVID-19 while facilitating SARS-COVID entry into the host (Figure 1)³⁴.

MECHANISMS OF THE IMMUNE SYSTEM IN RESPONSE TO VIRUS PARTICLES INVADING THE BODY AND THE ASSOCIATED IMMUNOPATHOLOGY

The human immune system, *i.e.* innate and adaptive immunity, works in close proximal coordination to produce potent neutralizing antibodies to combat virus particles invading the body³⁵. Aberrant host immune mechanisms could initiate the onset of immunopathology with subsequent potential to devastate immune mechanism³⁶. However, evidence have suggested that COVID-19, through human angiotensin converting enzyme 2 (hACE2) receptor, transduces genomic material into the host and mediates pattern recognition receptors (PRRs), especially toll-like receptor (TLR)-3, TLR-7 and TLR-8, which potentially detect persistence of viral particles in the cytoplasm³⁷, thus mediating a series of immune mechanisms. Likewise, several PRRs like melanoma differentiation gene-5 (MADG-5) and retinoic acid inducible gene 1 (RIG-1) have been identified for their ability to detect cytosolic viral pathogen interlinked molecular patterns (PAMPs), triggering a proximal series of events^{38,39}. However, some prescribed activities initiate signaling cascade events through proximal recruitment of signaling and adaptor proteins, including mitochondria conceived antiviral protein (MAVS), stimulant of interferon gene (STING), and IFN- β , to trigger downstream series of proximal events²⁴. However, these activities together can further lead to the recruitment of adaptor protein MyD88, which has stringent potential to regulate transcription factors, and subsequently recruits interferon-1(IFN- α/β) molecules, and pro-inflammatory cytokine candidates as key players to combat infection⁴⁰.

CYTOKINE BOMBARDMENT AGAINST COVID-19

Following viral infection, the coordinated immune system shows an intricate capability to produce pro-inflammatory cytokines⁴¹ and induce a specific lineage

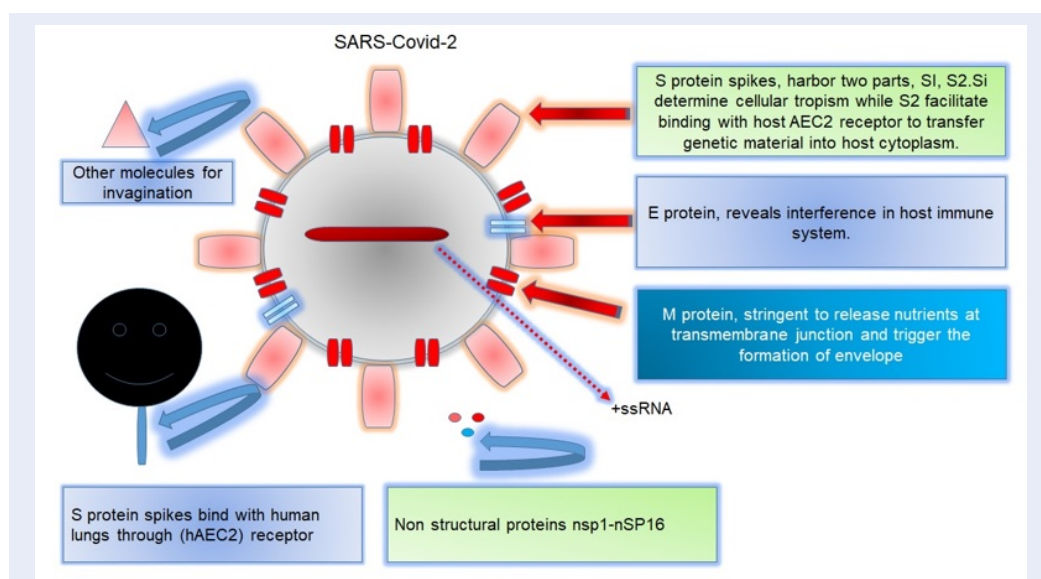


Figure 1: Morphological features of SARS-CoV-2. Structural features revealed that SARS-CoV-2 uses S protein spikes to adhere to host angiotensin converting enzyme (hACE2) and induces lung infection and pneumonia. E structural protein reveals interference with host immune system. M protein triggers the release of nutrients at the junctional interface. Small dots revealed 16 nonstructural proteins ranging from Nsp1-Nsp16.

of T cells, including CD8⁺ and CD4⁺ T cells, as well as induction of other danger-alarming signals to potentially fight the virus⁴². Following infection, and injury mechanism, the pro-inflammatory cytokine milieu recruits innate immune cells, especially macrophages and granulocytes, at virus accumulated localized periphery to combat infection⁴³. However, collectively, these efforts recruit macrophages, thus resulting in macrophage-collecting syndrome (MCS) to devastate infected tissues⁴⁴. Similar incursions have already revealed that cytokine release syndrome (CRS) is associated with the onset of morbidity leading to devastation and severity of disease⁴⁵. Interestingly, interleukin (IL)-6 has been reported as a hallmark of MERS-COV infection⁴⁶. Recent investigations have suggested that elevated serum concentrations of IL-6 and other pro-inflammatory cytokines result in the onset of respiratory distress and failure. Likewise, a decrease of blood cells (lymphopenia) cannot be considered as a biomarker for COVID-19 diagnosis because of its correlation with H1N1 influenza outbreak in 2009⁴⁶. Thus, the elevated serum interleukin level resulting in the onset of other reactive proteins is fundamental to better deciphering proximal association in terms of disease progression. Similar interventions have suggested that C reactive protein (CRP) may serve as a prognostic factor which has a contributing pivotal role in corona virus related pathologies. In addition, cytokines induced during

CRS could be targeted with high-affinity antibodies to treat COVID-19 patients, and have been suggested as suitable clinical drug targets⁴⁶.

OVERVIEW OF ONGOING THERAPEUTIC STRATEGIES AGAINST SARS-COV-2

In spite of progressive cutting-edge technologies and substantial efforts, there is currently no direct evidence of intricate therapeutic strategies to treat corona virus (COVID-19) patients³⁷. Following infection, several healthcare organizations initially used adjacent combination of antiviral and antibacterial drugs (interferon alpha- nebulization) to reduce viral load²⁷. Antiviral drugs (Remdesivir), alone or in adjacent combination with antibacterial (Arbidol chloroquine salts) and antimalarial drugs, have undergone ongoing tests but have been unable to achieve complete therapeutic efficacy^{25,26}. In addition, Remdesivir- together with interferon- β - have been clinically proven to be effective at stopping SARS-CoV-2 replication^{47,48}. In contrast, in spite of recovery of Covid-19 patients, higher incidences of side effects (including mental stress, and epigastric stress together with cardiac and renal complications) have been observed in elderly patients⁴⁹. Similarly, in China, several Chinese traditional medicines have been administered with antiviral and antibacterial drugs to treat SARS-CoV-2 infected patients⁴⁸.

Plasma-isolated antibodies from blood of convalescent patients have been proven effective to neutralize COVID-19 virus, suggesting that the plasma represents an efficient and available therapeutic strategy⁴⁹. Several experimental inoculations revealed the therapeutic efficacy of monoclonal antibody CR-3022 to bind with the spike glycoprotein of SARS-CoV-2, suggesting it can be an efficient therapeutic strategy in the future, possibly in combination with antibodies⁵⁰. In spite of the dilemma of therapeutics, vaccines are still considered the most efficient formulation to immunize people for prevention and to treat corona virus patients⁵¹. However, in spite of progressive efforts, there are still no vaccine candidates which have been clinically approved yet to generate immune efficacy⁵¹. Following a substantial increase in SARS-CoV-2 -induced mortality, several notable pharmaceutical companies and research centers around the globe have been trying to configure a vaccine; more time is required to achieve this goal which can lead to therapeutic efficacy⁵². In addition, recently, PicoVac vaccine has been formulated in China and has shown some effectiveness against 10 strains of SARS-Covid-2²⁴.

POTENT ANTIVIRAL STRATEGIES

From phylogenetic interventions and key genome resemblance features of SARS-CoV-2 with SARS-COVID and MERS, previously designed antiviral drug Remdesivir and ribavirin have been under ongoing investigations for their potential therapeutic efficacy⁵³. Following COVID-19 infection, some health organizations have worked together with research centers and declared adjacent treatment with chloroquine and antiviral drug Remdesivir. Interestingly, so far, Remdesivir has been a broad spectrum antiviral drug and currently tested in major countries including America, Europe and UK; it has been declared as a promising therapeutic strategy to treat SARS-CoV-2 infected patients (**Table 1**)²⁶. Likewise, several broad spectrum antiviral drugs, including Ribavirin, Lopinavir, Ritonavir, Favipiravir and Umifenovir, and anti-malarial drugs (such as chloroquine and hydroxychloroquine) are being investigated in the treatment of SARS-CoV-2 infected patients^{34,54-57}.

In addition, major investigations are ongoing to release large-scale slots for the betterment of humanity⁵³. Specified targeted therapeutic interventions did not reveal obvious side effects, suggesting a comprehensive treatment modality. Thus, based on genome identity features, comprehensive drug modalities could be designed for proximal candidates of COVID-19, SARS-CoV-2, and MERS-COVID⁶⁵.

Furthermore, suitable drug candidates could be designed to target viral nucleotides, nucleosides and nucleic acids^{53,54}. Moreover, structural investigations of surface glycoproteins (S) could offer deeper understanding for the development of potent antiviral drugs against COVID-19. More importantly, with respect to COVID-19, viral entry requires intricate cleavage at S1/S2 junction; thus, potent monoclonal antibodies could be targeted to stop S1 cleavage with subsequent application of inhibitors to stop S2 phase of infection^{24,27,28}. Indeed, following SARS-COVID-19 infection in China, clinicians employed other antiviral drugs including Lopinavir/Ritonavir (LPV/RTV), which showed mild improvement only in patients harboring initial stage of symptoms within 12 days (**Table 1**)⁵³.

PHYLOGENETIC GENOME INTERVENTIONS AND KEY VARIATIONS IN SARS-COV-2

Previously reported coronaviruses (*e.g.* SARS, MERS, etc.) show 80% genome identity features with SARS-CoV-2²⁴. Surface-flanked proteins are potentially encoded by four genes (M, N, S, and E), each with stringent capability to encode respective proteins including membrane proteins, nucleocapsids, surface proteins and envelope proteins, respectively, to mediate specified events²⁴. Sixteen nonstructural proteins and pp1ab are encoded by large gene segment Off1 ab of SARS-CoV-2⁶⁶. According to sequence interventions, the phylogenetic tree genome of SARS-CoV-2 seems close to that of SARS coronaviruses²⁴. In addition, genomic sequence interventions to decipher the variations in genome features have been fundamental to better decipher strategies to generate more effective drug candidates. Genome variation analysis revealed that SARS-CoV-2 shows an absence of gene segments 8a and 8b, in contrast to SARS-CoV genome (**Figure 2**)⁶⁶. In addition, surface glycoprotein intervention reveals that SARS-CoV-2 surface proteins are a mixture of bat and other coronaviruses' proteins⁶⁷. Additionally, fluorescent studies conducted by some groups have reported that both SARS-coronaviruses and SARS-CoV-2 use the same proximity of ACE2 enzyme for attachment to lung³⁸. Genome mutation interventions have demonstrated that N501Y mutations in spike S proteins trigger their intricate binding with host receptors (**Figure 2**)⁶⁸.

Table 1: Overview of available potential antiviral strategies to treat nSARS-CoV-2

Antiviral drug	Mode of activities and mechanism
Remdesivir	GS5734 (inhibitor of nucleoside), attained worldwide attention and frequently in use to treat COVID-19 infected patients. Remdesivir also have been employed to induce premature termination of Ebola viruses. In vivo studies revealed its potential to mitigate viral load in lungs pneumonia (Y. Cao et al., 2020 ²⁵ ; Y. Wang et al., 2020 ⁴).
Umifenovir	Non-nucleoside immune potentiating antiviral drug, employed by Russia and China for the treatment of many corona virus pathologies and influenza prophylaxis. During current epidemic Chinese government recommend 200 mg dose thrice a day to treat COVID-19 patients (Costanzo et al., 2020 ⁵⁴ ; Lian et al., 2020 ⁵⁸).
Favipiravir	Favipiravir currently recommended in china against COVID-19 infection. Its clinical efficacy proved effective than ritonavir/ritonavir. In addition, Bangkok government declared its massive applications against COVID-19 in march. In vivo investigations declared its efficacy against SARS-CoV-2 and MERS on Vero cell lines (Cai et al., 2020 ⁵⁹ ; C. Chen et al., 2020 ⁵⁷).
Ritonavir/Liponavir	Alone or in adjacent combination with interferons have been recommended at 200mg/50mg dose rate twice a day. Lponavir and ritonavir have been previously used for the treatment of retroviruses, are recommended efficient against COVID-19 (B. Cao et al., 2020 ⁶⁰).
Hydroxychloroquine	Potential inhibitor of heme polymerase with potent antiviral strategies against SARS-CoV-2, infected patients have been approved clinically to achieve therapeutic efficacy. Triggered endosomal pH to block SARS-CoV-2 fusion events. In addition, chloroquine and hydroxychloroquine are used for the treatment of lupus nephritis and rheumatoid arthritis (RA). Likewise, in vivo investigations have declared its antiviral and immune modulation activities (Colson et al., 2020 ⁵⁶ ; Ferner & Aronson, 2020 ⁶¹ ; Gautret et al., 2020 ⁶²).
Ribavirin	Broad spectrum antiviral drug ribavirin Inhibit mRNA capping and synthesis of viral RNA. In addition, Investigations have proven effective against MERS, SARS, and SARS-CoV. However, proper dose evaluations require further research to maintain clinical efficacy (Elfiky, 2020 ⁶³ ; Taber et al., 1983) ⁶⁴ .

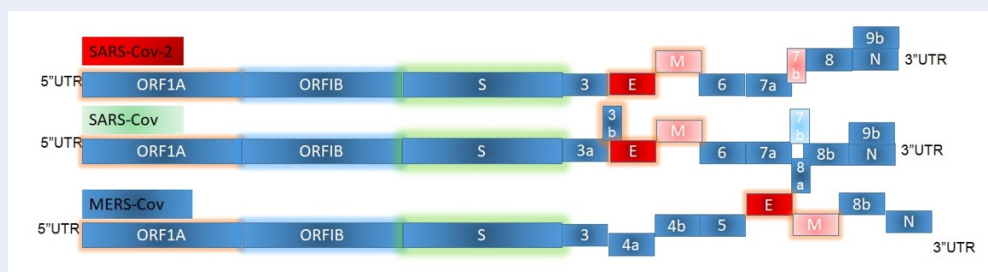


Figure 2: Novel genome variation features of SARS-CoV-2 from SARS-CoV and MERS. Coronaviruses (SARS-CoV-2, SARS-CoV, and MERS) are potent at inducing disease in humans (beta coronaviruses) and harbor an untranslated region (5' UTR) and open reading frame (ORF1A, ORF1B) (blue box). These regions encode non structural proteins; S box in blue encodes surface glycoproteins; E box in red encodes envelope; M box encodes membrane proteins; nucleocapsid proteins are encoded through N box flanked at the end. Similarly, box 3 and 8 (in SARS-CoV-2), and 8a (in SARS-CoV) represent genome variations.

CONVALESCENT PLASMA AS A PROMISING OPTION FOR THE TREATMENT OF COVID-19 INFECTION

Considering the outbreak of SARS-CoV-2 virus worldwide which potently induced COVID-19 infections, many research institutions and medical professionals around the world are still trying to seek suitable treatment options⁶⁹. Infected elderly patients are receiving oxygenation, while severely infected people are receiving extracorporeal oxygenation to treat the corona virus induced disease^{24,70}. Moreover, convalescent plasma isolated from people who have recovered from COVID-19 infection has been proven as a promising therapeutic option⁷⁰. Similar investigations have suggested that following infection with COVID-19, the patient's body develops immunity at around 10-14 day after infection. Thus, administration of convalescent plasma should be considered effective^{28,69}. In addition, to reduce viremia, it is promising to administer convalescent plasma at early stage of disease²⁸. Subsequent investigations are now focused on whether concurrent administration of convalescent plasma with other antiviral drugs may increase therapeutic efficacy. Similar inculcations have already revealed that co-administration of steroids, convalescent plasma, and oxygen therapy may reduce the production of antiviral antibodies²⁸. Studies have demonstrated that frequent use of anti-steroids should be prohibited, while convalescent plasma should be tested to determine if efficacy is improved⁶⁹⁻⁷¹.

RECENT CHALLENGES IN THE TREATMENT AGAINST SARS-COV-2

In spite of substantial progress in the treatment modalities against SARS-CoV-2, there are still many countries that are experiencing challenges and concerns about therapies⁵³. Some experimental inculcations have revealed the persistence of SARS-CoV-2 in stool samples of infected patients. Detailed investigations are needed to better decipher if fecal/oral route could trigger dissemination of SARS-CoV-2 as this remains unclear⁷². Likewise, experimental investigations during previous SARS-CoV and MERS-CoV outbreaks have shown that the virus can survive over inanimate objects and environments for a long period; further detailed investigations into SARS-CoV-2 persistence in the environment is greatly warranted⁷². Moreover, it remains unclear how efficient disinfectants are at reducing the risk of being infected with SARS-CoV-2; this area of study still requires attention

and investigation⁷³. Likewise, some experimental interventions have revealed the efficacy of Remdesivir alone to treat corona viruses; however, some cases have reported that co-administration of Remdesivir with chloroquine is effective^{27,54}. Thus, detailed experimental investigations are required to solve this ambiguity. Most importantly, several studies revealed that 43% of patients suffered from fever and 15.7% suffered from pneumonia; detailed clarification and epidemiological investigations are needed to address asymptomatic carriers⁷⁴. Likewise, subsequent studies are needed to decipher the timely updates in therapeutic interventions, particularly in the context of cytokine milieu, which is lacking and requires collective attention⁴⁶.

ONGOING STRATEGIES USED IN THE COVID-19 EPIDEMIC ESPECIALLY IN PAKISTAN

Since there is no vaccine available against COVID-19, the prevention against the disease will remain the focus of strategy⁷⁵. The primary goal should be to slow down the transmission of the virus in order to reduce the associated illnesses and deaths⁵⁵. Likewise, potential ways that government and health authorities should be working in close and coordinated proximity to control the SARS-CoV-2 pandemic is a matter of utmost concern and still requires strict implementation of laws. To mitigate the mortality ratio, people in developing countries, especially, could avoid negligence and irresponsiveness when following strict strategies implemented by healthcare authorities. Thus, this prevents the chance for rapid human-human transmission and spread in communities. Therefore, each government must work together with the relevant health authorities to implement strict measures, including strict adherence to SOPs and core public health strategies, in order to control person-to-person transmission. Such strategies include identification, quarantine measures, strict individual testing, and clinical care for all cases⁷⁶.

Furthermore, tracing and quarantine of all contacts should be a part of all national COVID-19 responses⁷⁷. Such strategy has been successfully demonstrated in places like Wuhan, China, and has been practiced in Pakistan, as well as recognized and implemented by other countries like Germany, Vietnam and India. The actions taken by the respective governments include a range of measures in the field of public health as well as social measures to contain the spread of virus. The measures include limiting person-to-person interaction, enforcing physical and

social distancing, and restricting movement. Since the emergence of the first case, governments have been effectively containing the virus. The containment measures include engaging communities both at individual and societal levels, providing information on how to protect oneself and others, interpreting scientific information into simplified messages, and encouraging the sharing of information at individual levels; all of these are fundamental to stop the risk of spreading.

CONCLUSION

In this review, we summarized the ongoing therapeutic interventions to treat SARS-CoV-2, key morphological features, genome variations, immunogenomics, and current challenges in treatment. Furthermore, we illustrated the current ongoing managerial strategies to manage the SARS-CoV-2 pandemic, especially in Pakistan. These revelations could lend future support for the discovering of more effective therapeutic modalities for COVID-19.

ABBREVIATIONS

APCs: antigen presenting cells

LPV, RTV: Liponavir / Ritonavir

MADG-5: melanoma differentiation gene-5

MAVS: mitochondria conceived antiviral protein

MCS: macrophage collecting syndrome

MERS: middle east respiratory syndrome

PAMPs: pathogen associated molecular patterns.

RIG-1: retinoic acid inducible gene 1

SARS-CoV: Severe acute respiratory syndrome

SARS-CoV-2: severe acute respiratory syndrome corona virus-2

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Kabeer Haneef (K.H), Muhammad Umer Asghar (M.U.A) and Ashiq Ali (A.A) are the leading authors. All these authors made substantial contributions to conception, design, acquisition of data, analysis and interpretation of data; actively contribute in drafting the article and critically provide final approval of the version to be published; and agree to be accountable for all aspects of the work.

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CONSENT FOR PUBLICATION

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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