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# Comprehensive spotlight on SARS-CoV-2: a disease with global reach

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## ABSTRACT

The abrupt outbreak of 2019 novel coronavirus (2019-nCoV, Known as SARS-CoV-2) in Wuhan, China, which soon expanded into a global pandemic. The coronavirus has made its way into human society, harming not just the healthcare system but also the global economy. It is the one of the biggest disaster mankind has ever faced in recent times, bringing disruption to the human life worldwide. COVID-19 is caused by the severe acute respiratory syndrome coronavirus (SARS-CoV)-2, which shares many similarities with its closest homologs Middle East respiratory syndrome (MERS) and SARS-CoV. Nowadays SARS-CoV-2 genome-based specific vaccines and therapeutic antibodies are currently being tested. On the other hand, therapeutic agents previously designed for other virus infections which are existing and have already been tested for their safety is the only practical approach as a rapid response measure to the emergent pandemic. This evidence will provide a comprehensive understanding of the COVID-19, determine the origin, symptoms and modes of transmission of COVID and may help to guide subsequent measures for future development.

## KEYWORDS

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Coronavirus, epidemic, pathophysiology, clinical manifestation, mutation etc.

## INTRODUCTION

Coronavirus (CoV) is clustered under the viral family group that causes disease in mammals and birds. A pandemic novel coronavirus was named as ''Corona Virus Disease 2019'' (2019-nCoV) by World Health Organization (WHO) in Geneva, Switzerland.[1,2] Conversely, the society has first time observed epidemic of three previously unidentified coronaviruses namely severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, and SARS-CoV-2 in December 2019; all of them belonging to Coronaviridae family.[3] SARS-CoV and MERS-CoV have caused more than 10,000 cumulative infections with high mortality rates of almost 10% and 34% respectively whereas, the very recent pandemic of SARS-CoV-2 has had an unprecedented impact, resulted in critical public health emergency. This infectious disease was declared as Public Health Emergency of International Concern (PHEIC) by the World Health Organization on 30 January 2020 and labeled it as novel coronavirus disease 2019 (COVID-19).[4] The *Coronavirinae* comprise one of two subfamilies in the *Coronaviridae* family, with the other being the *Torovirinae*.[5]

SARS-CoV-2 has been given this name because it is 85% similar to the SARS-CoV virus genome.[6] The coronavirus invades two types of cells in the lungs. They are the mucus producing goblet cells that keep the lungs from drying, as well as protecting them from pathogens, and the ciliated cells that are responsible for clearing debris from the lungs by beating the mucus to the body's exterior. The cilia cells are the preferred viral host.[7] The spike protein, based on the virion surface, are responsible for binding with the host cell receptors, called ACE2 that are found in human cells in the lungs, heart, kidneys and intestines. The S-protein has two receptor binding domains (RBD's), called the S1 and S2. These domains are used to bind with the ACE2 receptors, allowing the virion to penetrate eventually into the human cells by a process known as endocytosis.[8]

Human to human transmissibility of SARS-CoV-2 is much higher than that of either MERS-CoV or SARS-CoV and occurs mainly via respiratory droplets and direct contact.[9] The ability of COVID-19-infected individual to carry and spread the virus while being in asymptomatic or in pre-symptomatic phase are some probable reasons for high infection rate, making its control extremely challenging.[10] There is an imperative and urgent need to further control the COVID-19 infection and develop therapeutic strategies to reduce the mortality rate and to make the recovery better. So, in the present work an attempt was made to compile the information regarding COVID-19 pandemic.

## EPIDEMIOLOGY

The first reported confirmed COVID-19 case was presented as atypical pneumonia on December 8, 2019 in Wuhan, China.[11] The patient was among a cluster of 41 cases reported to WHO on January 11, 2020.[12] Thereafter, coronavirus has affected more than 200 countries and territories around the world.[13] As on 18$^{th}$ Feb, 2021, total 10,95, 94,835 coronavirus confirmed cases and 24,24,060 deaths are reported globally. The total number of active cases with currently infected patients are 22,596,462 out of which almost 99.6% patients i.e. 22,502,801 are having mild symptoms and approximately 95,482 (0.4%) patients are seriously ill or at critical condition.[14] 85,824,282 cases are recovered from coronavirus infection. The information about total number of reported cases, active cases, death and recovered cases is depicted in figure 1 from the countries/regions which are most affected due to COVID-19 pandemic. The reported death numbers were high in patient with age of 80 years and above having pre-existing health conditions such as cardiovascular diseases and diabetes.

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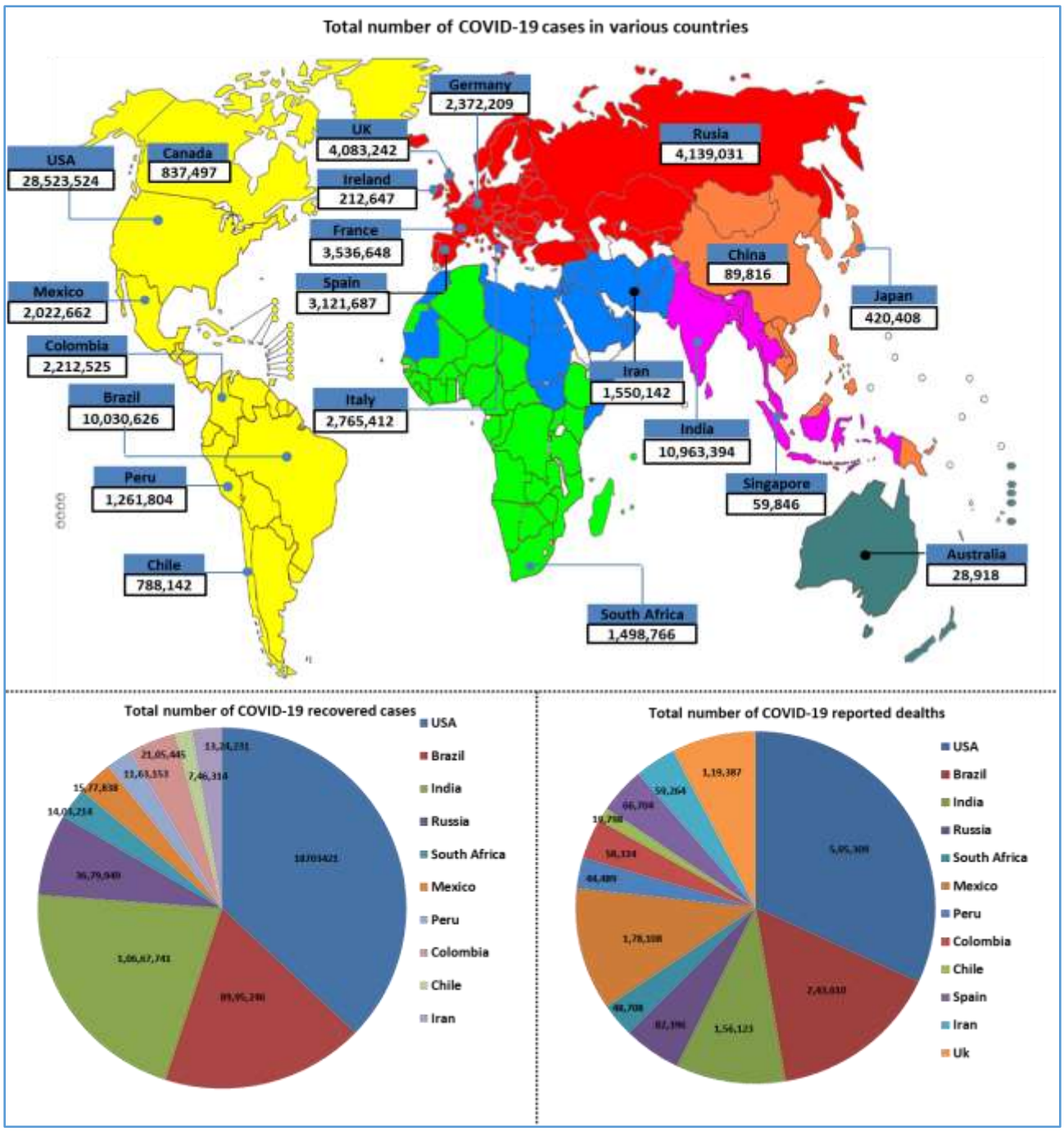


**Figure No. 1: Current global epidemiology of COVID-19 disease**

Relatively fewer cases were reported in younger children. The prevalence data shows that the risk of COVID-19 infection is almost 66% in population older than 70 years of age and 5% in those younger than 20 years. It estimated that 6% (3–12) of males to be at high risk compared with 3% (2–7) of females.[15,16]

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## SPREAD OF THE INFECTION AND PRIMARY PREVENTION MEASURES

People can catch COVID-19 from others who have the virus. People with the virus in their noses and throats may leave infected droplets on objects and surfaces (called fomites) when they sneeze, cough on, or touch surfaces, such as tables, doorknobs and handrails. Other people then catch infection by touching these objects or surfaces, then touching their eyes, nose or mouth. People can also catch COVID-19 if they breathe in droplets from a person with COVID-19 who coughs out or exhales droplets. This series of steps is the chain of infection. It is important to understand and follows the protection measures to break this chain and stop the spread of virus. There is limited evidence which suggest the spread of virus through air. Table 1 shows important measures to protect ourselves and others in this COVID-19 pandemic situation.

**Table 1: Protection measures to protect ourselves and others during COVID-19 pandemic**

| S.N. | Protection measures | |
|---|---|---|
| 1. | Stay home and self-isolate if you feel unwell, even with mild symptoms | |
| 2. | Clean hands frequently with soap & water for 40 seconds or with alcohol-based hand rub for 20 seconds after going to the bathroom; before eating; and after coughing, sneezing, or blowing nose | |
| 3. | Cover your nose and mouth with a disposable tissue or flexed elbow when cough or sneeze | |
| 4. | Avoid touching your eyes, nose and mouth | |
| 5. | Maintain a minimum physical distance of at least 1 metre from others | |
| 6. | Stay away from crowds and stay away from poorly ventilated indoor spaces | |
| 7. | Use a fabric /N-95 mask where physical distancing of at least 1 metre is not possible | |
| 8. | Use a medical / surgical mask if you may be at higher risk (age, medical conditions) | |
| 9. | Regularly clean frequently-touched surfaces with 1% sodium hypochlorite or phenolic disinfectants. | |
| 10. | Wear Personal protective equipment (PPE) by health care workers and others working in points of entries (POEs), quarantine centers, hospital, laboratory and primary health care / community settings. | |
| | ***PPE Kit specification:*** | |
| | Gloves: | Nitrile, non-sterile, powder free, EU standard directive 93/42/EEC Class I, EN455, EU standard directive 89/686/EEC Category Ill, EN 374, ANSI/SEA 105-2011, ASTM D6319-10 |
| | Coverall: | Impermeable to blood and body fluids, single use, meets ISO 16603 class 3 exposure pressure, or equivalent |
| | Goggles: | With transparent glasses, zero power, well fitting, covered from all sides, fog & scratch resistant, indirect venting to reduce the fogging, meets EU standard directive 86/686/EEC, EN 166/2002, ANSI/SEA Z87.1-2010 |
| | N-95 masks: | Shape that will not collapse easily, high filtration efficiency, good breathability, with expiratory valve, fluid resistance, meets NIOSH N95, EN 149FFP2, or equivalent standard |
| | Shoe cover: | Made up of the same fabric as of coverall, should cover the entire shoe and reach above ankles |
| | Face shield: | made of clear plastic, good visibility, preferably fog resistant, quality |

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| | | |
|---|---|---|
| | | compliant with the EU standard directive 86/686/EEC, EN 166/2002, ANSI/SEA Z87.1-2010 |

There has been a great surge in demand for hand sanitization products leading to shortages in their supply. A recent study reveals that both commercial alcohols and the WHO-recommended alcohol-based hand rubs (ABHR) [ABHR containing 60-90% v/v ethanol and/or 2-propanol, hydrogen peroxide (3%), glycerol (98%), distilled water and other excipients depending on the type of the formulation] can effectively inactivate SARS-CoV-2.[17] However, a consequent increase of substandard products in the market has raised safety concerns. Hence regulatory bodies should revisit current regulations on hand sanitisers to better safeguard consumers. Similarly, WHO stress that medical masks and respirators be prioritized for health care workers. In case of non-medical masks, the numbers of layers of fabric/tissue, breathability of material used, water repellence/hydrophobic qualities, shape of mask, fit of mask should be taken into consideration.[18] All PPE kit items to be supplied need to be accompanied with certificate of analysis from national/ international organizations/labs indicating conformity to standards and expiry upto 5 years.[19]

## CLINICAL FEATURE OF COVID-19 DISEASE

Corona viruses have either DNA or RNA genetic materials. SARS-CoV-2 belongs to a large family of RNA viruses and has a single stand RNA structured genome with 32 kilobases length.[20] The usual symptoms of COVID-19 include fever (83–98%), cough (59–82%), shortness of breath (19–55%), and muscle ache (11–44%), which are similar to those of SARS and MERS. Some patients may have sore throat, rhinorrhea, headache and confusion a few days before the onset of fever, indicating that fever is a critical symptom, but not the only initial manifestation of infection.[12] The pattern of fever has not yet been fully understood. A small proportion of patients had hemoptysis[21] and a number of cases were found relatively asymptomatic.[22] However, the clinical course of COVID-19 pneumonia exhibits a broad spectrum of severity and progression patterns. In some patients, dyspnea develops within a median of 8 days after the onset of illness (range of 5–13 days), while in others, respiratory distress may be absent. Around 3–29% patients may need the admission to the intensive care unit. Severely ill patients may have poor disease course of rapid progression to multiple organ dysfunction and even death.[23]

Individuals of any age can acquire SARS-CoV-2 infection, although adults of middle age and older are most commonly affected, and older adults are more likely to have severe disease. The MIS-C is a new pediatric disease associated with SARS-CoV-2 that is dangerous and potentially lethal. The presentation of this includes the hyperinflammatory shock manifested with high fever, rash, conjunctivitis, peripheral edema, and gastrointestinal symptoms. Prompt recognition and medical attention will help for children survival but the long-term outcomes from this condition are unknown.[24] Pregnancy and childbirth generally do not increase the risk for acquiring SARS-CoV-2 infection. However, maternal symptoms and epidemiologic exposure, results of maternal testing, clinical status of the neonate at birth, and results of neonatal testing should be considered to rule out the risk of infection.[25] Figure 2 highlights the clinical manifestation of COVID-19 symptoms.

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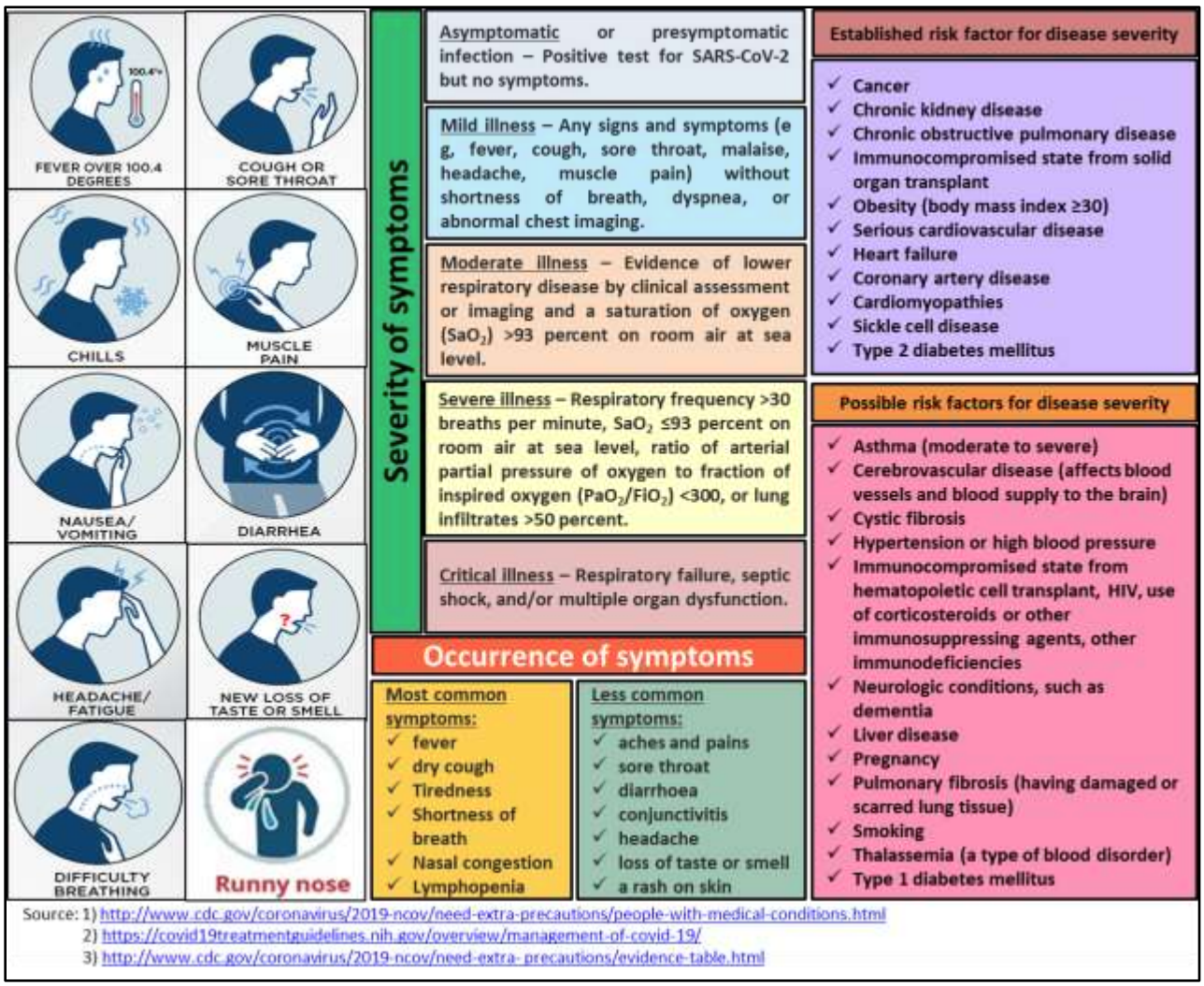


**Figure 2 Clinical manifestation of COVID-19 symptoms**

## MICROBIOLOGY OF COVID-19 PATHOGEN

A transmission electron microscope identified corona structure containing virus particles of about 60 to 140 nm in size. The same research team identified that this ~30 Kb virus was a single-stranded RNA virus belonging to the Betacoronavirus genus in Coronaviridae family.[6] Their genomes are typically composed of a 50-methylguanosine cap at the beginning, a 30-poly-A tail at the end, and a total of 6-10 genes in between.[26] These viruses are encircled with an envelope containing viral nucleocapsid.[5] SARS-CoV-2 has four main structural proteins including spike (S) glycoprotein, small envelope (E) glycoprotein, membrane (M) glycoprotein, and nucleocapsid (N) protein.[27] Besides the important structural proteins, the SARS-CoV-2 genome also contains 15 non-structural proteins (nsps), nsp1 to nsp10 and nsp12 to nsp16, and 8 accessory proteins (3a, 3b, p6, 7a, 7b, 8b, 9b, and ORF14).[28] A single Coronavirus holds more than 10 separate ORFs enabling the virus to grow and spread at an uncontrollable rate.[29] The spike or S glycoprotein is a most important therapeutic target. The spike proteins, based on the virion surface, are responsible for binding with the host cell receptors. It forms homotrimers protruding in the viral surface and facilitates binding and entry of envelope viruses to host

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cells.[8] The M protein is the most abundant viral protein present in the virion particle, giving a definite shape to the viral envelope.[30] The E protein plays a multifunctional role in the pathogenesis, assembly, and release of the virus.[31] The N protein is involved in processes related to the viral genome, the viral replication cycle, and the cellular response of host cells to viral infections.[32] The structure & genome characteristic of SARS-CoV-2 virus is highlighted in figure 3.

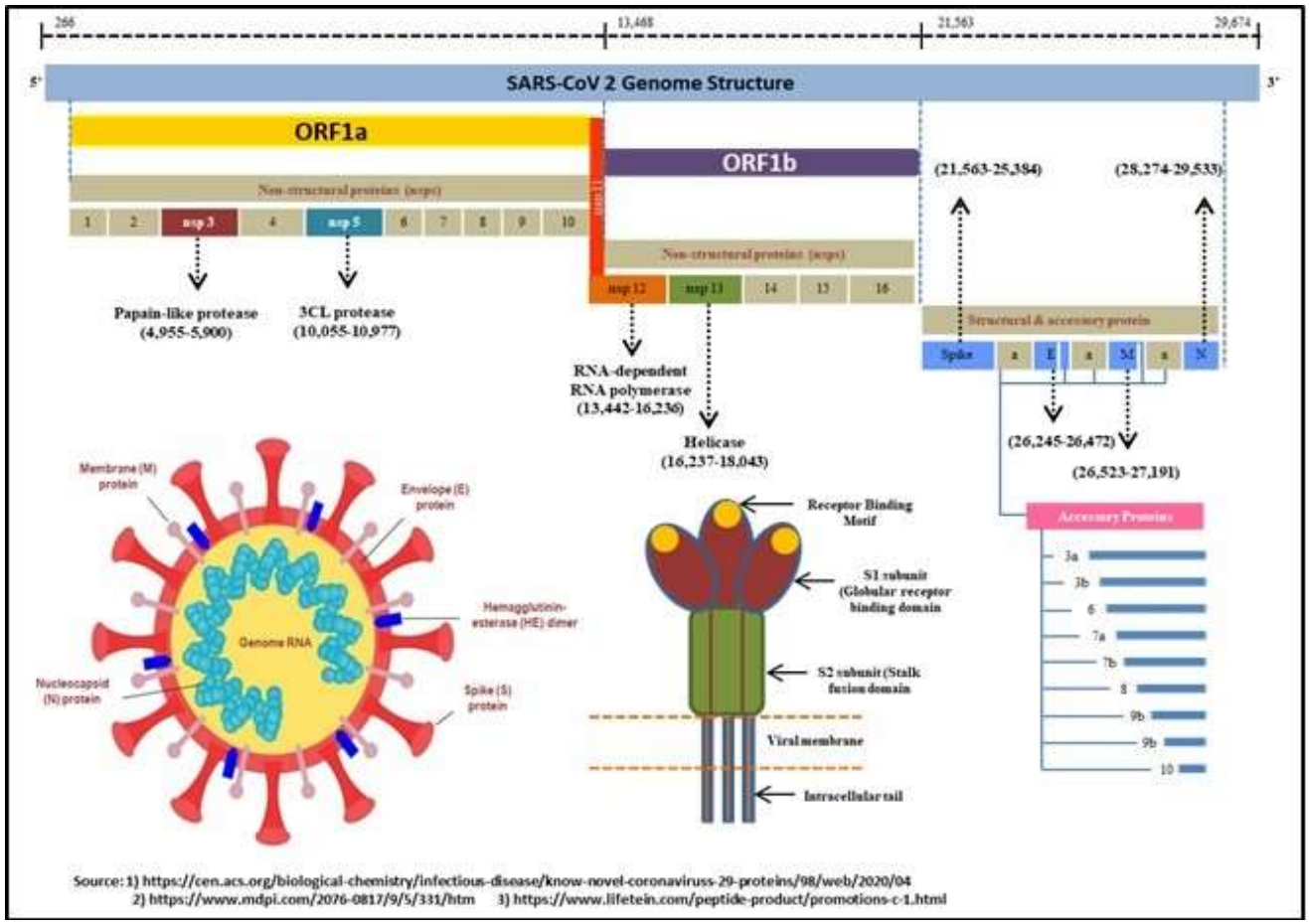


**Figure 3 The structure & characteristic of SARS-CoV-2 virus**

## IMMUNOLOGICAL EXPRESSION

The spike proteins (S glycoprotein) are spike-like protrusions present on the coronavirus's transmembrane, which helps the virus enter host cells.[33] The entry of virus inside the host cells stimulates the host's immune response. The body's immune response to viral infection by SARS-CoV-2 is similar to that of SARS-CoV and it is mediated by innate, adaptive immunity including cellular & humoral immune response.

### *Innate immunity by host cell*

The spike proteins of the SARS-CoV-2 behave like RBDs, specifically targeting the host cell receptor ACE2 of the human cells and forming the initial viral attachment step between the virus and the cell receptor. Studies conducted on the crystal structures of SARS-CoV-2 RBD, complexed with ACE2, revealed that the RBDs contain a core structure and a receptor-binding motif. It binds itself to the claw-like structure of the ACE2 host cell receptor.[34, 35] This ACE2 is highly expressed on the epithelial cells

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in the alveolar spaces in the lungs, and on the ciliated and goblet cells in the airways.[36] These cells provide the entry of virus in humans. Hence, epithelial cells, alveolar macrophages and dendritic cells (DCs) are three main frontline antigens presenting cells (APC) for immunity. This APC contains Toll-like receptors (TLR-)3 and 7 and/or cytoplasmic RNA sensors, namely retinoic acid-inducible gene I (RIG-I), melanoma differentiation-associated protein 5 (MDA5), NOD-like receptors (NLRs) and other small free molecules located in various places in the cells. These pattern recognition receptors (PRRs) sense viral infection through identification of virus derived pattern associated molecular patterns (PAMPs), such as viral RNA, nucleic acids, carbohydrate moieties, glycoproteins, lipoproteins and other small molecules and results in cascade signaling and further immune activation.[37, 38]

***Adaptive immunity by host cell***

Antigen-specific T cells are able to eradicate cancer cells as well as viral infections; generating large amounts of T cells with viral antigen specificity in a timely manner may well help us withstand the invasion of SARS-CoV-2. Efficient methods to produce massive amounts of T cells include appropriate antigen-presenting cells that can activate effector T cells, and the differentiation and proliferation of corresponding effector, cytotoxic T cells.[39] As far as concerns the adaptive immunity, understanding the key features and evolution of B-cell and T-cell mediated immunity to SARS-CoV-2 is essential. The APC present COVID antigen to the CD4+ T cell via MHC-II, this will lead to the release of IL-12. This will further activate the T helper effector cells Th1, Th2 & Th17. The Th1 activation and MHC expression is required for resistance of viral replication. It also produces pro-inflammatory cytokines like IL-4, IL-17, IL-22 & IFN-γ via the NF-κB signaling pathway. These cytokines further recruit neutrophils and monocytes to the site of infection and activate several other pro-inflammatory cytokines and chemokines including IL-1, IL-6, IL-8, IL-21, TNF-β.[38,40] CD4+ T cells also activate T-dependent-B cells to promote the production of virus-specific antibodies through humoral immune response. The antibodies production is also supported by plasmablast expansion. The antibodies produce in response to COVID-19 infection are serum IgM, IgG & to some extend IgA with unique presence pattern.[41] The IgM & IgA antibodies usually last for 7-8 weeks whereas IgG remains for longer period. [42]

***Cytokine and/chemokines storm and hyperinflammation***

Excessive inflammatory innate response and dysregulated adaptive host immune defense may cause harmful tissue damage both at the site of virus entry and at systemic level. Multiple changes in serum level of various cytokines, chemokines and its excessive release play pivotal role in pathogenesis of COVID-19 infection.[43]

***Survival mechanism by virus against host immune response***

The SARS-CoV-2 virus tried to evade immune system recognition through suppression of various mechanisms both at the time of its presentation to the cell and when it enters the host cell. The virus forms the double vesicles on outer side of cell during recognition process. The formation of this vesicle protects the dsRNA, an important product for virus replication.[41] The virus nsp 14 initiates cap formation and nsp 16 modify the cap so that RNA viral looks similar to that of host cell RNA and avoid its destruction by host immune cells.[44]

Similarly, nsp 3 having two encoded functional proteins macrodomains and PLpro help coronavirus evade attack from a host's immune response by antagonizing the IFN response.[45] The gene segment located on ORF3b of this virus has the ability to antagonize the INF signaling pathway and cause inhibition of the effector cell activation cascade for eradication and inhibition of viral replication.[46] Equally of concern, the protein encoded in ORF6 could inhibit JAK-STAT signaling pathway by binding to karyopherin-α2, and tethers karyopherin-β1 on internal membranes to lead to blocking nuclear translocation of the transcription factor STAT1.[47] Taken together, novel coronavirus has number of avoidance ways against host immune response and survive better.

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### *Herd immunity in context of COVID-19*

Herd immunity is the indirect protection of individuals from an infectious disease when a high proportion of a population is immune (usually through vaccination). Persons who haven't been infected, or who haven't had a good immune response, are protected because there are enough immune people around them to slow or stop person-to-person transmission. As vaccination of global population will be a long process hence, worldwide most people are remained susceptible to COVID-19 infection with chances of getting reinfection.

## POSSIBLE THERAPUTIC MANAGEMENT OF COVID-19

Remdesivir (GS-5734) is by far the most promising drug that exhibits broad-spectrum antiviral activities against RNA viruses. It is a prodrug, whose structure resembles adenosine.[48] In the case report of the first COVID-19 patient in the USA, remdesivir was used on the 7th day of hospitalization without any noticeable adverse effect, and the patient's condition improved on the 8th day.[49] Similar to remdesivir, favipiravir, developed by Toyama Chemical (division of Fujifilm, Japan), functions as an inhibitor of the RNA-dependent RNA polymerase by structurally resembling the endogenous guanine.[50] Dong et al. addressed the possible effects of drugs such as Favipiravir, Chloroquine, Remdesivir, and Arbidol against SARS-CoV-2 and successful results were obtained.[51] An in vivo study has proven Ivermectin's capability to reduce viral RNA up to 5,000-fold after 48 h of infection with SARS-CoV-2.[52] Lopinavir/ritonavir combination was engaged in a clinical trial against COVID-19 in patients with mild and moderate COVID-19 (NCT04252885), however, it showed little benefit for improving the clinical outcome.[53] In another trial performed on patients with severe COVID-19 (ChiCTR2000029308), no benefits of lopinavir/ritonavir beyond standard care were observed.[51] Recently, in vitro testing revealed its ability to effectively reduce the viral copy number of SARS-CoV-2.[54] Therefore, a number of clinical trials have been quickly conducted in China, which demonstrated that hydroxychloroquine was to various degree effective in treatment of COVID-19-associated pneumonia. Similarly, in a small open-label non-randomized clinical trial from France, hydroxychloroquine demonstrated positive effect in combination with azithromycin.[55] Yuli et al. highlighted the clinical research performed by Dr. Sulianti Saroso, Infectious Disease Hospital, utilizing biochemical assays. The biological samples were obtained from 13 patients with MERS-CoV infection. Viral RNA was insulated and transformed to C-DNA, and used as the guide to identify 12 viral panels based on traditional PCR and sequencing. Viral etiological agents found in patients were Human Metapneumovirus, Enterovirus D68, Rhinovirus C, HCoV 229E, Herpes Simplex Virus Type 1, H1N1, H3N2, Dengue Virus and Rhinovirus A60. The genomes of nine viral agents within various taxa were identified in the MERS-CoV patients, including human metapneumovirus, influenza virus, coronavirus, herpesvirus enterovirus, and paramyxovirus. This study highlights the need for a detailed examination to encounter other secondary viruses that cause more damage than COVID-19. By this method, the mortality rate of COVID19 can be controlled by treating the secondary catalyst viruses responsible for demises.[56] Nanoparticle-based platforms represent an alternative strategy to incorporate antigens. Through encapsulation or covalent functionalization, nanoparticles can be conjugated with antigenic epitopes, mimic viruses and provoke antigen-specific lymphocyte proliferation as well as cytokine production. In addition, mucosal vaccination through intranasal or oral spray can not only stimulate immune reactions at the mucosal surface, but also provoke systemic responses.[57] The development of vaccine represents a more long-term strategy to prevent COVID-19 outbreaks in the future. With the sequencing of SARS-CoV-2 genome, multiple nucleic acid-based vaccine candidates have been proposed, mostly based on the S protein-coding sequence.

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## MUTATIONS OF SARS-COV-2

SARS-COV-2 virus can replicate multiple times, after expressing in human cells. The figure 4 demonstrate, how the virus replicates and multiply after entering in human body. During expression and replication all viruses often show mutation which increase their chances of survival. The coronavirus has also been undergoing multiple mutations. Its rapidly spreading variants from UK and South Africa are of significance. These mutations are located in spike proteins with N501Y substitution.[58,59] This S-glycoprotein is a receptor binding site of virus for cell entry and key targets of virus neutralizing antibodies. It is highly glycosylated and increases the binding affinity of virus to ACE-2 receptor. These strains circling around the UK and South Africa are thought to be more transmissible than the original strain, thrust the United Kingdom into a lockdown. By posing a significant challenge toward the public health system and the existing antiviral strategies, SARS-CoV-2 has undoubtedly grabbed the globe's attention in the beginning of 2020.

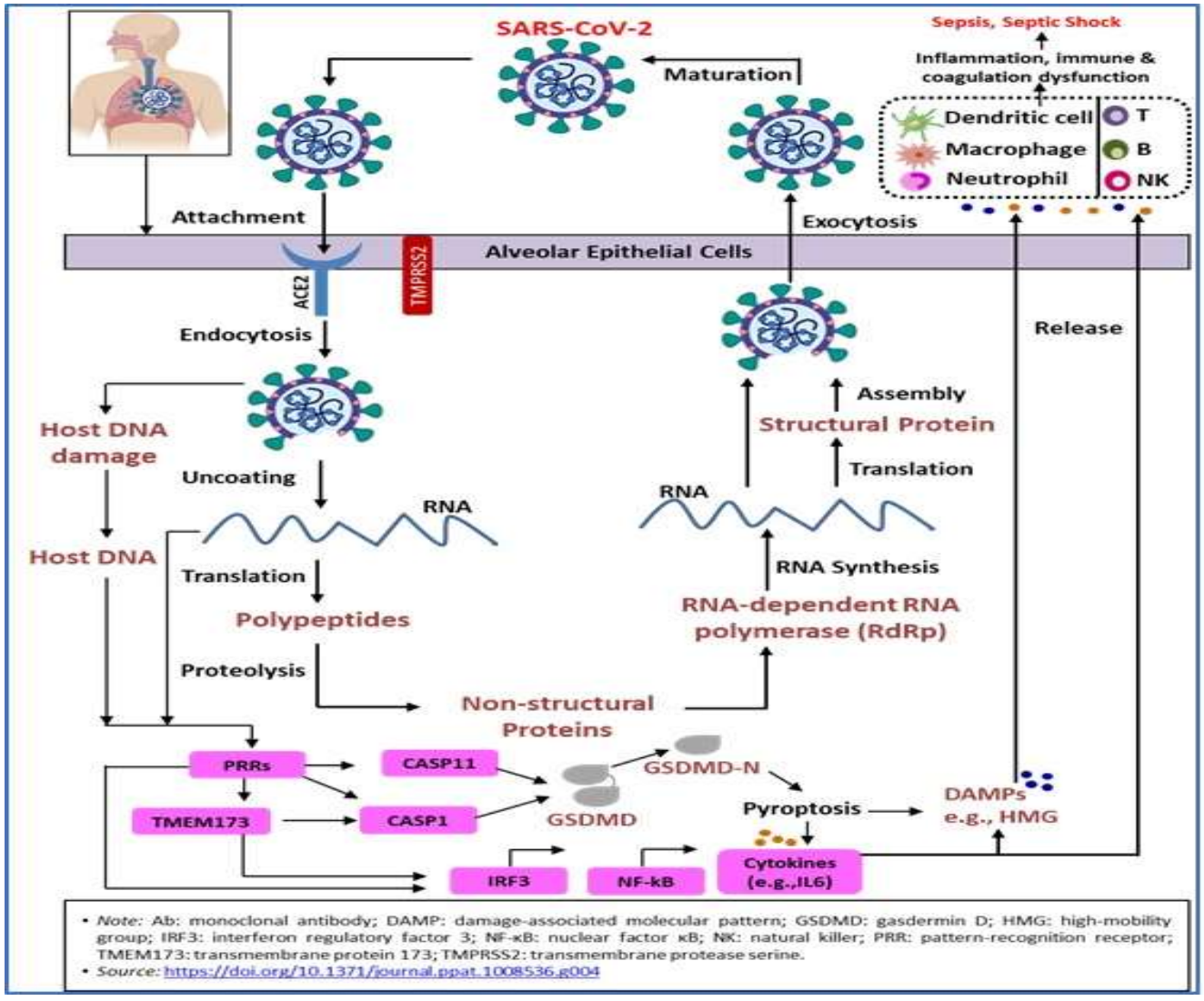


**Figure 4 The SARS-CoV-2 virus life cycle**

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## CONCLUSION & FUTURE LANDSCAPE

The COVID-19 pandemic is still ongoing, and a long time may pass before we can fully grasp the complete picture of the pathogen's characteristics; including its vulnerabilities, which can be used to inform development of effective and efficient treatments Since the first attack of corona-virus in Wuhan, the disease is spreading worldwide and represents one of the greatest global public health emergencies. The common symptoms include shortness of breath, fever, sputum production, dry cough, sore throat, fatigue, nausea/vomiting, muscle or joint pain, nasal congestion, headache, chills, and diarrhea. The new mutations of virus specifically in glycoproteins, might be so caution and complete preparation by scientist and health authorities is required. Researchers have gathered information on COVID-19 clinical spectrum, underlying immune signaling pathways, systemic effects, and long-term pathological signatures, up to certain extend which has given hope for faster identification of future virus expressions. These agents can be divided into two broad categories, those that can directly target the virus replication cycle, and those based on immunotherapy approaches either aimed to boost innate antiviral immune responses or alleviate damage induced by deregulated inflammatory responses. However, the treatment and containment of this pandemic over the next 5–10 years will largely depend upon clearing all uncertainties regarding the virus–host cell interaction and life cycle mechanism of the virus.

**Disclaimer:**

All opinions expressed herewith are those of the authors and do not reflect the views of their organization.

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## REFERENCES

1. Harapan H, Itoh N, Yufika A, Winardi W, Keam S, Te H. et.al. Coronavirus disease 2019 (COVID-19): A literature review. J Infect Public Health. 2020;13(5):667-673. doi: 10.1016/j.jiph.2020.03.019
2. Zhang C, Zheng W, Huang X, Bell EW, Zhou X, Zhang Y. Protein Structure and Sequence Reanalysis of 2019-nCoV Genome Refutes Snakes as Its Intermediate Host and the Unique Similarity between Its Spike Protein Insertions and HIV-1. J Proteome Res. 2020;19(4):1351-1360. doi: 10.1021/acs.jproteome.0c00129.
3. Tu YF, Chien CS, Yarmishyn AA, Lin YY, Luo YH, Lin YT. et.al. A Review of SARS-CoV-2 and the Ongoing Clinical Trials. Int J Mol Sci. 2020 Apr 10;21(7):2657. doi: 10.3390/ijms21072657.
4. Rolling updates on coronavirus disease (COVID-19) by WHO. Available online from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen (Accessed on 11th September 2020)
5. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol. 2015;1282:1-23. doi: 10.1007/978-1-4939-2438-7_1.
6. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J. et.al. China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020 Feb 20;382(8):727-733. doi: 10.1056/NEJMoa2001017.
7. Fahy JV, Dickey BF. Airway mucus function and dysfunction. N Engl J Med. 2010 Dec 2;363(23):2233-47. doi: 10.1056/NEJMra0910061.
8. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ. et.al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res. 2020 Mar 13;7(1):11. doi: 10.1186/s40779-020-00240-0.
9. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) 16-24 Feb 2020. Available online from: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf?sfvrsn=fce87f4e_2 (Accessed on 18th November 2020)
10. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z. et.al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. N Engl J Med. 2020 Mar 19;382(12):1177-1179. doi: 10.1056/NEJMc2001737.
11. World Health Organization. Novel Coronavirus- China. 12 January 2020. Available online from: http://www.who.int/csr/don/12-january2020-novel-coronavirus-china/en. (Accessed on 21st April 2020)
12. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y. et.al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5.
13. Johns Hopkins University SoM. Coronavirus resource Center. Available online from https://coronavirus.jhu.edu/ (Accessed on 21st January 2021)
14. World Health Organization Coronavirus disease dashboard. Available online from: https://covid19.who.int/ (Accessed on 19th February 2021)
15. Worldometer. Available online from: https://www.worldometers.info/coronavirus/ (Accessed on 10th October 2020)
16. Clark A, Jit M, Warren-Gash C, Guthrie B, Wang HHX, Mercer SW. et.al. Global, regional, and national estimates of the population at increased risk of severe COVID-19 due to underlying health

conditions in 2020: a modelling study. Lancet Glob Health. 2020 Aug;8(8):e1003-e1017. doi: 10.1016/S2214-109X(20)30264-3.
17. Berardi A, Perinelli DR, Merchant HA, Bisharat L, Basheti IA, Bonacucina G. et.al. Hand sanitisers amid CoViD-19: A critical review of alcohol-based products on the market and formulation approaches to respond to increasing demand. Int J Pharm. 2020 Jun 30;584:119431. doi: 10.1016/j.ijpharm.2020.119431.
18. Advice on the use of masks in the context of COVID-19. WHO. 5th June 2020: Available online from: https://apps.who.int/iris/bitstream/handle/10665/332293/WHO-2019-nCov-IPC_Masks-2020.4-eng.pdf?sequence=1&isAllowed=y (Accessed on 21st September 2020)
19. Guidelines on rational use of Personal Protective Equipment. Ministry of Health and Family Welfare. Government of India. Available online from: https://www.mohfw.gov.in/pdf/GuidelinesonrationaluseofPersonalProtectiveEquipment.pdf (Accessed on 21st September 2020)
20. Song Z, Xu Y, Bao L, Zhang L, Yu P, Qu Y. et.al. From SARS to MERS, Thrusting Coronaviruses into the Spotlight. Viruses. 2019 Jan 14;11(1):59. doi: 10.3390/v11010059.
21. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J. et.al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA. 2020;323(11):1061–1069. doi:10.1001/jama.2020.1585
22. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX. et.al. Clinical Characteristics of Coronavirus Disease 2019 in China. New Engl J Med. 2020; 382(18):1708-1720. doi: 10.1056/NEJMoa2002032
23. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J. et.al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: A study of a family cluster. Lancet 2020; 395: 514-523. doi: https://doi.org/10.1016/S0140-6736(20)30154-9
24. Ahmed M, Advani S, Moreira A, Zoretic S, Martinez J, Chorath K. et.al. Multisystem inflammatory syndrome in children: A systematic review. EClinicalMedicine. 2020 Sep;26:100527. doi: 10.1016/j.eclinm.2020.100527.
25. Shah PS, Diambomba Y, Acharya G, Morris SK, Bitnun A. Classification system and case definition for SARS-CoV-2 infection in pregnant women, fetuses, and neonates. Acta Obstet Gynecol Scand. 2020 May;99(5):565-568. doi: 10.1111/aogs.13870.
26. de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol. 2016 Aug;14(8):523-34. doi: 10.1038/nrmicro.2016.81.
27. Jiang S, Hillyer C, Du L. Neutralizing Antibodies against SARS-CoV-2 and Other Human Coronaviruses. Trends Immunol. 2020 May;41(5):355-359. doi: 10.1016/j.it.2020.03.007.
28. Wu A, Peng Y, Huang B, Ding X, Wang X, Niu P. et.al. Genome Composition and Divergence of the Novel Coronavirus (2019-nCoV) Originating in China. Cell Host Microbe. 2020 Mar 11;27(3):325-328. doi: 10.1016/j.chom.2020.02.001.
29. Sexton NR, Smith EC, Blanc H, Vignuzzi M, Peersen OB, Denison MR. Homology-based identification of a mutation in the coronavirus RNA-dependent RNA polymerase that confers resistance to multiple mutagens. Journal of Virology. 2016 Aug;90(16):7415-7428. doi: 10.1128/jvi.00080-16.
30. Neuman BW, Kiss G, Kunding AH, Bhella D, Baksh MF, Connelly S. et.al. A structural analysis of M protein in coronavirus assembly and morphology. J Struct Biol. 2011 Apr;174(1):11-22. doi: 10.1016/j.jsb.2010.11.021.
31. Nieto-Torres JL, DeDiego ML, Verdiá-Báguena C, Jimenez-Guardeño JM, Regla-Nava JA, Fernandez-Delgado R. et.al. Severe acute respiratory syndrome coronavirus envelope protein ion

channel activity promotes virus fitness and pathogenesis. PloS Pathog. 2014;10(5):e1004077. doi: https://doi.org/10.1371/journal.ppat.1004077
32. Tai W, He L, Zhang X, Pu J, Voronin D, Jiang S. Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine. Cell Mol Immunol. 2020:1–8
33. Tortorici MA, Veesler D. Structural insights into coronavirus entry. Adv Virus Res. 2019;105:93-116. doi: 10.1016/bs.aivir.2019.08.002.
34. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA. et.al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003 Nov 27;426(6965):450-4. doi: 10.1038/nature02145.
35. Li F. Receptor recognition mechanisms of coronaviruses: a decade of structural studies. J Virol. 2015 Feb;89(4):1954-64. doi: 10.1128/JVI.02615-14.
36. Sungnak W, Huang N, Bécavin C, Berg M, Queen R, Litvinukova M. et.al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nat Med. 2020 May;26(5):681-687. doi: 10.1038/s41591-020-0868-6.
37. Yi Y, Lagniton PNP, Ye S, Li E, Xu RH. COVID-19: what has been learned and to be learned about the novel coronavirus disease. Int J Biol Sci. 2020 Mar 15;16(10):1753-1766. doi: 10.7150/ijbs.45134.
38. Li G, Fan Y, Lai Y, Han T, Li Z, Zhou P. et.al. Coronavirus infections and immune responses. J Med Virol. 2020 Apr;92(4):424-432. doi: 10.1002/jmv.25685.
39. Lan L, Xu D, Ye G, Xia C, Wang S, Li Y. et.al. Positive RT-PCR Test Results in Patients Recovered From COVID-19. JAMA. 2020 Apr 21;323(15):1502-1503. doi: 10.1001/jama.2020.2783.
40. Rabi FA, Al Zoubi MS, Kasasbeh GA, Salameh DM, Al-Nasser AD. SARS-CoV-2 and Coronavirus Disease 2019: What We Know So Far. Pathogens. 2020 Mar 20;9(3):231. doi: 10.3390/pathogens9030231.
41. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal. 2020 Apr;10(2):102-108. doi: 10.1016/j.jpha.2020.03.001.
42. Stephens DS, McElrath MJ. COVID-19 and the Path to Immunity. JAMA. 2020;324(13):1279–1281. doi:10.1001/jama.2020.16656
43. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. et.al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020 Mar 28;395(10229):1033-1034. doi: 10.1016/S0140-6736(20)30628-0.
44. Chen Y, Cai H, Xiang N, Tien P, Ahola T, Guo D. Functional screen reveals SARS coronavirus nonstructural protein nsp 14 as a novel cap N7 methyltransferase. Proc Natl Acad Sci Unit States Am. 2009;106:3484–3489. doi: 10.1073/pnas.0808790106
45. Nelemans T, Kikkert M. Viral Innate Immune Evasion and the Pathogenesis of Emerging RNA Virus Infections. Viruses. 2019 Oct 18;11(10):961. doi: 10.3390/v11100961.
46. Freundt EC, Yu L, Park E, Lenardo MJ, Xu XN. Molecular determinants for subcellular localization of the severe acute respiratory syndrome coronavirus open reading frame 3b protein. J Virol. 2009;83:6631–6640. doi: 10.1128/jvi.00367-09
47. Totura AL, Baric RS. SARS coronavirus pathogenesis: host innate immune responses and viral antagonism of interferon. Curr Opin Virol. 2012 Jun;2(3):264-75. doi: 10.1016/j.coviro.2012.04.004.
48. Siegel D, Hui HC, Doerffler E, Clarke MO, Chun K, Zhang L.et.al. Discovery and Synthesis of a Phosphoramidate Prodrug of a Pyrrolo[2,1-f][triazin-4-amino] Adenine C-Nucleoside (GS-5734)

for the Treatment of Ebola and Emerging Viruses. J Med Chem. 2017 Mar 9;60(5):1648-1661. doi: 10.1021/acs.jmedchem.6b01594.
49. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H. et.al. First Case of 2019 Novel Coronavirus in the United States. N Engl J Med. 2020 Mar 5;382(10):929-936. doi: 10.1056/NEJMoa2001191.
50. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proc Jpn Acad Ser B Phys Biol Sci. 2017;93(7):449-463. doi: 10.2183/pjab.93.027.
51. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther. 2020;14(1):58-60. doi: 10.5582/ddt.2020.01012.
52. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 2020 Jun;178:104787. doi: 10.1016/j.antiviral.2020.104787.
53. Agostini ML, Andres EL, Sims AC, Graham RL, Sheahan TP, Lu X. et.al. Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. mBio. 2018 Mar 6;9(2):e00221-18. doi: 10.1128/mBio.00221-18.
54. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G. et.al. Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020 May 7;382(19):1787-1799. doi: 10.1056/NEJMoa2001282.
55. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M. et.al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020 Jul;56(1):105949. doi: 10.1016/j.ijantimicag.2020.105949.
56. Setianingsih TY, Wiyatno A, Hartono TS, Hindawati E, Rosamarlina, Dewantari AK. et.al. Detection of multiple viral sequences in the respiratory tract samples of suspected Middle East respiratory syndrome coronavirus patients in Jakarta, Indonesia 2015–2016. Int J Infect Dis. 2019(86):102-107. doi: 10.1016/j.ijid.2019.06.022.
57. Al-Halifa S, Gauthier L, Arpin D, Bourgault S, Archambault D. Nanoparticle-Based Vaccines against Respiratory Viruses. Front Immunol. 2019 Jan 24;10:22. doi: 10.3389/fimmu.2019.00022.
58. Volz E, Mishra S, Chand M, Barrett JC, Johnson R, Geidelberg L. et al. Report 42 - Transmission of SARS-CoV-2 Lineage B.1.1.7 in England: Insights from linking epidemiological and genetic data. Available online from: https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-42-sars-cov-2-variant/. (Accessed on 12th January 2021)
59. Tegally H, Wilkinson E, Giovanetti M, Iranzadeh A, Fonseca V, Giandhari J. et.al. Emergence and rapid spread of a new severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) lineage with multiple spike mutations in South Africa. (Pre-print). 2020. medRxiv. doi: https://doi.org/10.1101/2020.12.21.20248640