

A Generalized Overview of SARS-CoV-2: Where Does the Current Knowledge Stand?

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Citation: Islam H, Rahman A, Masud J, Shweta DS, Araf Y, Ullah MA, Sium SMA, Sarkar B. A Generalized Overview of SARS-CoV-2: Where Does the Current Knowledge Stand?. Electron J Gen Med. 2020;17(6):em251. <https://doi.org/10.29333/ejgm/8258>

ARTICLE INFO

Received: 4 May. 2020

Accepted: 6 May. 2020

ABSTRACT

The novel coronavirus known to have brought the world to a standstill is responsible for many deaths throughout the globe as of now. The causative agent (SARS-CoV-2) for coronavirus disease 2019 (COVID-19) has been recognized as a zoonotic transfer. Although, the medium of animal-human transmission is still unknown, bats maybe a potential reservoir of this novel strain. Due to its high rate of transmission the most favorable way of limiting the outbreak's extent is by early diagnosis followed by isolation of the infected individuals. So far, the most widely used diagnosis methods are RT-qPCR which detects specific sequences of the viral RNA. Some other methods include serological tests and the recently introduced CRISPR-CAS-12 based assays.

As of now, no specific therapeutic treatments are known for COVID-19 however the use of some broad-spectrum antiviral drugs and convalescent plasma therapy have demonstrated positive outcomes. Apart from these treatments, vaccine development for SARS-CoV-2 is also in progress by 17 known companies. This article provides a comprehensive insight on the recently emerged Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) including its origin, transmission mechanism, pathophysiology and updated treatment methods.

Keywords: COVID-19, SARS-CoV-2, origin, pathogenesis, diagnosis, treatment

INTRODUCTION

Being encountered by the coronavirus in its novel form yet again for the third time in the 21st century brings it under the limelight once more. The coronaviruses belong to the order *Nidovirales* and the subfamily *Orthocoronavirinae* within the family *Coronaviridae*, the subfamilies can be further subdivided among 4 genera α , β , γ and δ (1,2). The α and β are known to infect only mammals, while δ and γ usually infect birds and fishes with a few exceptions of mammal hosts (2,3). Their infecting capacity of the hepatic, gastrointestinal, respiratory and central nervous system of a wide range of animal hosts (human, livestock, bat, birds, mouse and other wild animals) makes them a significant pathogen of interest (4,5).

Coronaviruses are enveloped single stranded, positive-sense RNA viruses with the largest known genome for RNA viruses, being around 26-32 kilobases in size with a 5'-cap structure and 3'-poly A tail (1,6). The name 'Corona' has been derived from its morphological appearance, that includes spiked protrusions from its lipid membrane, giving it a structure similar to that of crown when viewed under electron microscope (*corona* in Latin) (7).

Human Coronaviruses (HCoVs) first described in 1965 in the name B814, when it was extracted from a patient's nasal release who was suffering from common cold (8). They are known to be associated with the infections of the respiratory and the gastrointestinal tract. To this date, seven strains of these HCoVs are known: 229E, OC43, NL63, HKU1 usually cause mild upper respiratory disorders in immunocompromised individuals with a few special cases of severe infections among newborns and elderly people; while SARS-CoV (Severe Acute Respiratory Syndrome related Coronavirus), MERS-CoV (Middle East Respiratory Syndrome related Coronavirus) and the 2019 novel Coronavirus(nCoV)/ Sars-Cov-2 are responsible for more critical lower respiratory tract conditions and SARS in humans (9-11). HCoVs are the causative agents for a broad range of pulmonary conditions ranging from mild, "self-limiting" diseases like the common cold to acute conditions like pneumonia and bronchitis, depending on the individual's immunity (10,12).

Until the emergence of SARS-CoV and MERS-CoV human coronaviruses were not considered pathogenic and were known to circulate within humans without causing any major fatal diseases. With the onset of the SARS epidemic, coronaviruses started being evaluated as the "emerging pathogens".

Initially observed in the Guangdong province of China, in February 2003, the initial cases of an unfamiliar respiratory illness were reported which was later found to have emerged in late 2002 (13,14). It was known to be a result of recombination of bat SARS-CoVs possibly through masked palm civets (*Paguma larvata*) as the intermediate hosts prior to infecting humans, causing around 8000 cases of infections and more than 800 deaths worldwide with a 10% mortality rate (15-18).

Ten years after SARS-CoV (2012) another endemic broke out in Middle East, via a zoonotic transfer from dromedary camels as the intermediate host. MERS-CoV has a history of 2494 cases of infections and 858 fatalities worldwide including 38 deaths in South Korea followed by a single transmission case, with a comparatively greater fatality rate than SARS-CoV, being 37% (19-21).

Both SARS-CoV and MERS-CoV has a history of initial zoonotic transfer followed by human-human transmission.

The most recent exposure of the human respiratory coronavirus, SARS-CoV-2 first identified in late December, 2019 in Wuhan China is the zoonotic causative agent for COVID-19, a respiratory condition resulting in severe pneumonia followed by ARDS (Acute Respiratory Distress syndrome) in more severe patients (1,22). COVID-19 may demonstrate itself as an asymptomatic carrier state, acute respiratory state and severe pneumonia and eventually cause death in immunocompromised patients. The rapid human-human transmission of the disease has been confirmed by the proof of clusters of infected family and medical personnel through nosocomial infection (23).

ORIGIN, CHARACTERISTICS AND GENETICS OF SARS-CoV-2

The recently discovered novel strain of the Human Coronavirus named SARS-CoV-2 is the causative agent for the respiratory illness COVID-19 (termed by WHO on Feb 11, 2020) that has been declared as the sixth “Public Health Emergency of International Concern” since the onset of H1N1 (2009), Polio (2014), Ebola in West Africa (2014), Zika (2016), Ebola in Democratic Republic of Congo (2019) (24).

SARS-CoV-2 (belonging to the genus of betacoronavirus and subgenus sarbecoronavirus) has a typical genomic structure like most coronaviruses in that 2/3rd of their genomic matter code for 16 non-structural proteins (nsps) associated with genome transcription and replication (with the exception being Gammacoronavirus which does not have the 1st nsp) while the remaining 1/3rd region in proximity to the 3' terminal region codes for 4 essential structural proteins: Spike (S), Envelope (E), Nucleocapsid (N) and Membrane (M) proteins, along with some other special structural and accessory proteins. The structural proteins responsible for the infectivity and “assembly” of the viruses among the different CoVs are known to vary among themselves with 43% sequence identity, in contrary to the non-structural proteins that are more similar with 58% sequence identity (7). The functions of the 4 essential structural proteins are briefly described as follows (**Figure 1**):

- Spike (S) protein are associated with the virion attachment to the host cell receptors by initiating the fusion of the cell membrane and viral envelope, the configuration of S glycoprotein determines the host range. It is also targeted site for antibodies (25,26).

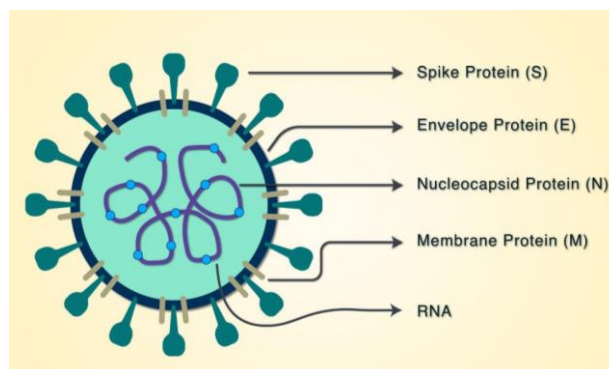


Figure 1. Typical Structure of SARS-CoV-2. The coronavirus spike (S) protein mediates membrane fusion by binding to cellular receptors. The figure was created using “BioRender.com” template and exported under the terms of premium subscription.

- Membrane protein (M) maintains the virions shape and structure it also attaches itself to the nucleocapsid (27,28).
- Envelope (E) is essentially associated with the release of the replicated virus and its assembly within the host cells (29,30).

Initially few patients were hospitalized with then unclassified pneumonic conditions in late December 2019, all with a history of exposure to a seafood and wet animal wholesale market in Wuhan province, China (31). Within the period between December 18 to December 29, five more patients were diagnosed with Acute Respiratory Distress Syndrome (ARDS) leading to the death of one (32). It was later discovered by CDC (Center for Disease Control) after subsequent analysis of the infected individual’s respiratory samples that these conditions were due to a novel coronavirus strain which was temporarily named 2019 nCoV by WHO on 12th Jan 2020 and later changed to SARS-CoV-2 based on its phylogenetic and taxonomic grounds, by the International Committee on Taxonomy of virus (33). Next generation sequence results from cultured virus samples obtained from 9 (8 of them had direct exposure to the wet market while 1 did not) patients affected during the early phase of the outbreak lead to detailed knowledge about the 2019 nCoV genomic characteristics including its similarities and differences to the other known coronaviruses (32). The complete viral genome was obtained from a patient on January 5, 2020 by next generation meta-transcriptomic sequencing (34).

Comparative genomic analysis via Blastn lead to the findings that the virus is closely to the novel strain were bat-SL-CoVZXC45, with a sequence identity of 87.99% and bat-SL-CoVZXX21 with a sequence identity of 87.23%, this leaves possibilities of SARS-CoV-2 having originated from bats within the market region (32). SARS-CoV-2 is 79% similar to SARS-CoV on the nucleotide level, while being 72% similar in their spike protein sequences. The Receptor Binding Domains of SARS-CoV-2 are ideally structured for binding to the human Angiotensin Converting Enzyme 2 (ACE2) receptor which is the same receptor recognized by SARS-CoV, however 5 out of 6 of these residues in the RBD seem to differ between them, the high affinity towards the ACE2 receptor may been acquired as a result of natural selection within a human or a human like ACE2 that allows binding (35). The most closely related virus to SARS-CoV-2 is RaTG13 derived from *Rhinolophus affinis* bat

showing 96% identical overall to SARS-CoV2, however the spikes differ in the receptor binding domains being only 85% similar where only one of the six amino acid residues match (34). Malayan Pangolins (*Manis Javanica*) too show similarity with SARS-CoV-2 (91.02% identity at the whole genome level), demonstrating strong uniformity in the RBD region including all six of the RBD residues, suggesting them to be the potential intermediate host, however there may be multiple intermediate hosts (36). Thus, incapability to identify the intermediate host is curtailing the chances of gaining deeper insights about the spillover of the virus into the human population, which in turn is also limiting the determination of the containment of the virus.

Although bats are thought to be the potential reservoirs hosts of this novel coronavirus since they have been playing pivotal roles in transmitting other viruses like Ebola and Nipah, however this hypothesis must be backed by further confirmations (34).

SARS-CoV-2 has been proved to be more infectious than both SARS-CoV and MERS-CoV and as of 16th April, 2020, there are 1,995,983 confirmed global cases with 131,037 deaths across 213 countries and territories and 2 international conveyances (37).

Much of the existing treatment methods have resulted out from understanding of the previous 2 outbreaks, particularly the SARS-CoV outbreak which shares similarities with the novel strain of the Coronavirus. However, in order to generate treatments with high efficacy, the unique features of SARS-CoV-2 must be understood to a greater extent, specially its spike protein. Beside these, different serotypes are being identified in different countries with slight variation which may responsible to different host response, pathogenesis, symptoms in different regions.

TRANSMISSION

By the end of 2019, Wuhan, the capital of China's Hubei province encountered an outbreak of a novel coronavirus, which has taken the lives of more than eighteen hundred people in the first seven weeks. The phenomenon was first informed to the World Health Organisation (WHO) by the Chinese government when they observed several cases of unusual pneumonia (38,39).

The disease was initially thought to be generated from the Huanan seafood market of Wuhan and spread rapidly from there (39). However, several researches have suggested that bats which are not available in the Huanan seafood market might be the potential reservoir of SARS-CoV-2. That only leads to two possible explanations: 1) the disease did not generate from the Huanan seafood market, or 2) an intermediate host was involved in spreading the disease from the Huanan seafood market. If we consider that bats are indeed the reason behind the origin of this disease and it was indeed initiated from the Huanan seafood market, then that only leaves us with the possibility of an intermediate host. Through phylogenetic analysis and protein sequence alignment, researchers have shown that the involvement of an intermediate host, such as turtles, pangolin etc. is more than possible (39-41).

Study shows that COVID-19 primarily spreads through the respiratory tract, droplets, respiratory secretions, and direct contact (42). The virus uses nose and mouth as the entryway

and then searches for a 'host cell' in the respiratory system. Nearby cells are infected when the host cell bursts (43). There is a possibility that a person may get infected by "touching a surface or object that has the virus on it", and then touching their nose, mouth or eyes. As a result, the CDC recommends keeping the hands clean by washing with soap or using alcohol-based hand rub (44). Several researches also explore the possibility of vertical transmission where women infected with coronavirus during pregnancy can transfer the disease to infants. A study was conducted of 33 women who were infected by the virus during their pregnancy in China. They gave birth to babies and three of the infants were infected among them. Two of the babies were delivered at full term and they experienced fever and excessive vomiting upon their birth. They also showed signs of pneumonia, and tested positive for the COVID-19. One of the babies was delivered nine weeks early due to the mother facing several complications including pneumonia. The health problems of that baby might be caused by premature birth rather than COVID-19 (45). However, a study of 31 pregnant women infected with coronavirus shows that vertical transmission is not evident. While two mothers died due to respiratory complications caused by COVID-19, the infants remained healthy (46). Recently, it has been reported that a tiger in the Bronx zoo was tested positive for coronavirus. The 4-year-old tiger named Nadia was experiencing dry cough, and it was tested for the virus on April 2 when its twin sister, Azul, two Amur tigers, and three African lions developed a dry cough as well. Zoo officials believed that Nadia was infected by a zookeeper; however, ongoing researches are exploring new possibilities (47,48).

Upon its generation, the virus has since infected 2,261,397 individuals across 210 countries and territories till the date of this writing. Amongst them, 154,726 have died and 579,187 have recovered (49). The rate of transmission of SARS-CoV-2 is far greater than that of SARS-CoV, an epidemic that affected 26 countries and resulted in more than 8000 cases in 2003. The reason behind the higher transmission rate of SARS-CoV-2 includes the genetic recombination event at spike protein in the RBD (Receptor Binding Domain) region of SARS-CoV-2 (50,51).

On January 20, the US saw its first case when the virus was found in a 35-year-old man who had just returned from Wuhan 5 days earlier (52).

Within the last week of January, Europe also saw its first case when an infected patient was confirmed in Bordeaux on January 24 (53). Australia first encountered the virus on January 25 when a returning man from Wuhan tested positive for coronavirus (54).

WHO officially declared the COVID-19 phenomenon a Public Health Emergency of International Concern (PHEIC) on January 12 and a pandemic on 11 March after the widespread of the virus throughout the world (37).

The high contagious nature of the virus makes it difficult to prevent the rapid transmission and the limited understanding about its host again imposes additional challenges which subject more research to be carried out and more about the mode of transmission is yet to be discovered.

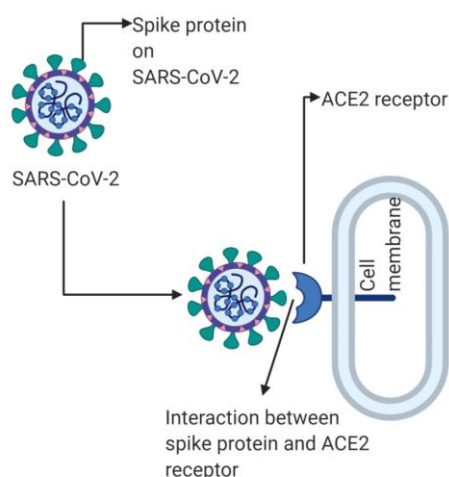


Figure 2. Interaction of spike protein of SARS-CoV-2 with ACE2 receptor during entry inside cell. The picture was created from BioRender and downloaded with the premium subscription

PATHOGENESIS OF SARS-CoV-2 INFECTION

In order to infect a host cell, gaining entry into individual human cell is a must. The virus then utilizes these cells' machinery to produce copies of themselves which then

ultimately spreads out to new cells (55). A research study mentioned about a molecular key on the novel coronavirus which provides the virus with an entryway to the cell. The molecular key is termed as Spike protein or S-protein (56). A research team in China led by Qiang Zhou in China revealed that the spike protein interacts with a “receptor on respiratory cells called angiotensin-converting enzyme 2” (**Figure 2**) (57). The spike protein has a furin cleavage site. Furin is present in the lungs, liver, and small intestines of human which basically indicate that the virus may infect several body organs (58). Some other groups also regarded the “activation site” as an efficient way of spreading between human, which however was disapproved by some researchers (59).

The interaction between spike protein and ACE2 receptors enables the entry of the virus in the human cell. Once inside, the virus infects healthy cells (60,61).

In brief, the replication begins through the binding and entry of coronavirus into the host cell with the help of endocytosis process or membrane fusion. Following its entry into the host cell, the coronavirus releases its viral genome which then undergoes a process of translation. After the viral polymerase protein is translated, RNA replication occurs. Then it is followed up with sub genomic transcription. Structural proteins of the virus are then translated. The structural proteins undergo combination with nucleocapsid. Finally, mature virion is formed and released through exocytosis mechanism. (**Figure 3**) (62).

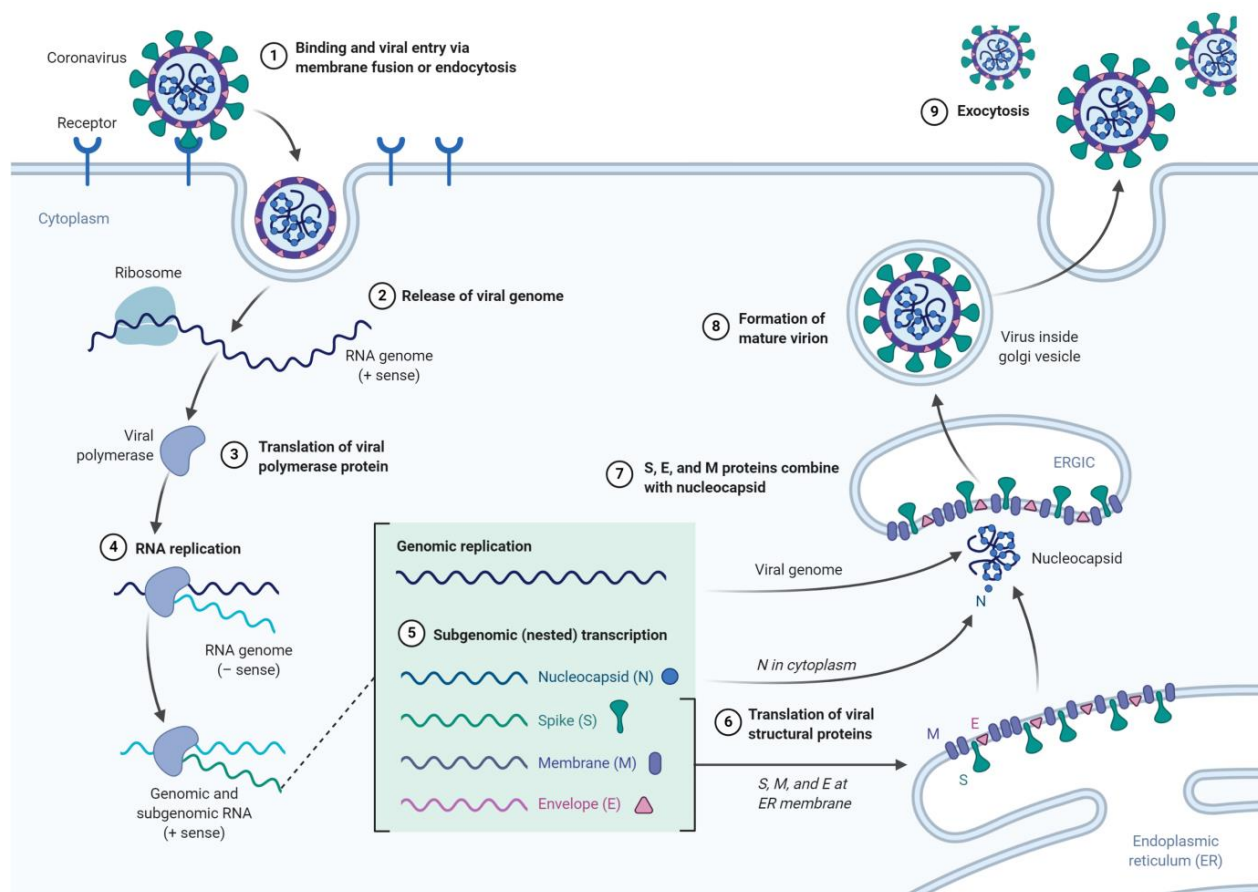


Figure 3. The SARS-CoV-2 replication cycle in mediating the viral pathogenesis. Virus enters the cell after binding to the cell surface receptor of host cell and then replicates and transcribes viral genome and proteins, respectively. After virus assembly, they lyse the cells and get outside of the infected cell and continue infection of new healthy cell. The picture was created from BioRender and downloaded with the premium subscription.

Table 1. Symptoms associated with SARS-CoV-2 infection

Symptoms	Percentage	References
Fever	83-99%	(22,65-71)
Cough	59-82%	
Fatigue	44-70%	
Anorexia	40-84%	
Shortness of breath	31-40%	
Sputum production	28-33%	
Myalgia	11-35%	

When the virus invades the respiratory tract, the lungs become inflamed. As a result, a person may experience some breathing difficulty. This may also result in pneumonia which could be fatal. In severe cases, this may lead to Acute Respiratory Distress Syndrome (ARDS) which may enhance the breathing difficulty, or result in rapid heart rate, sweating and dizziness. The patient's alveolar blood vessels and tissues might also get damaged making it even harder to breathe. Through the collection of fluids in the lungs, oxygen will be carried less to the blood. As a result, enough oxygen will not be supplied to other body organs leading slowly to organ failure (61,63).

SYMPTOMS AND CLINICAL PRESENTATION

As mentioned earlier, COVID-19 can be spread through respiratory tract, droplets, respiratory secretions and direct contact. Upon its exposure, the person infected with the novel virus may show some symptoms within 2-14 days (incubation period). Centers for Disease Control and Prevention (CDC) mentions some of the signs and symptoms that may appear in an infected patient which include fever, cough and shortness of breath. CDC also points out a few emergency warning signs which will help to determine when to see a doctor. The signs include breathing difficulty, persistent pressure on the chest, inability to be aroused etc. (44,64).

There has been a little dispute regarding the incubation period of COVID-19. According to the CDC, the incubation period may "extend to 14 days, with a median time of 4-5 days from exposure to symptoms onset". The source also mentioned that 97.5% of the people may develop the symptoms within 11.5 days. While the signs and symptoms may vary from person-to-person, CDC has altogether shown a variety of symptoms that might be observed in an infected patient over the course of the disease (Table 1). However, the incubation period is between 2 to 10 days according to WHO (72). China's National Health Commission (NHC) reported an incubation period for 10 to 14 days (73).

Prognosis: A Day-to-day Breakdown of Coronavirus Infection and COVID-19 Development

Following is a day-to-day breakdown of the novel COVID-19 symptoms and a brief view of how the disease progresses:

Day 1-3: The patient may experience fever (temperature >100°F) at the initial stage. Prolonged fatigue and dry cough might be evident. Mild muscle pain and breathing difficulty might also be an issue. The patient may also face sore throat, blocked nose, or runny nose although these are less common (43,74).

Day 4-7: This is the stage where the symptoms generally escalate and breathing difficulty becomes a major issue, especially for elderly people. Patients with a preexisting health

Table 2. Clinical courses of COVID-19

Time Interval	Clinical Course	References
Day 1-3	- Fever (temperature > 100°) - Prolonged fatigue - Dry cough - Mild muscle pain - Breathing difficulty - Sore throat - Blocked nose	(43,74)
Day 4-7	- Excessive difficulty in breathing - ARDS	(43,75)
Day 8-12	- Abdominal pain - Appetite loss	(43,74,75)

condition are also at high risk. This is the point when the patient must be admitted to a hospital (43,75).

Day 8-12: At this stage, the patients generally tend to develop symptoms of ARDS, a hazardous condition when the vital organs of the body cannot receive sufficient amount of oxygen. ARDS is often very fatal, and the patients are shifted to the ICU at this point. Abdominal pain and appetite loss can also be seen in the patients at this stage (Table 2) (43,74,75).

Although a number of common symptoms is considered to be associated to the preliminary phases of the infection but ranges of different symptoms are being recorded frequently in different region which might be due to the mutation of the viral strain.

PREVENTIVE MEASURES

The SARS-CoV-2 can be transmitted via contact, droplets and fomites. In order to avoid spreading by droplets or contact, US Centers for Disease Control and Prevention (CDC) recommends good hand hygiene by washing hands with soap or alcohol-based sanitizers and social distancing by maintaining at least 1 meter gap. And as the virus can persist on objects, mindful cleaning with soap and water of frequently touched surfaces such as door knobs, tables or light switches, is another vital practice to avoid getting infected. WHO advises symptomatic people to be isolated in one room with a separate bathroom and avoid sharing items with others (76,77). The interim guidance on infection prevention and control (IPC) by WHO has clearly set instructions for healthcare workers (HCWs) or managers to ensure clinical triage, early identification and control of source, proper use and adequate supply of Personal Protective Equipment (PPE), thorough cleaning of the environment and effective training of the HCWs. Collection of specimen for laboratory investigation must be done by personnel who are trained in safe handling of the samples; and in laboratories, biosafety practices are to be maintained. The components of PPE are face masks, face shields, gloves, eye-protective goggles and polyethylene coated gowns. The IPC guidelines also expect all the health facilities to educate caregivers and patients' families on recognizing early symptoms and basic precautions according their schemes and methods. Airborne precautions must be taken into account which holds the possibility of contamination via suspended infectious agents in the air; such as use of N95 masks in perioperative environment, education on seal checks of respirators and directing a patient's tube to appropriate Breathing System Filters (BSF) after endotracheal intubation (78,79). Safe management of corpses of people who have died of suspected or confirmed COVID-19 is important; because the

virus can live inside the lungs or other organs of the body although there is no evidence of getting infected from the dead body yet. The burial team dealing with the body must use appropriate PPE, wash hands before and after handling the body and make sure to disinfect the surfaces where the body was kept and any autopsy items: with 0.1% Sodium hypochlorite or 70% ethanol. Family members are not allowed to touch or kiss the body; they may only see the body after it has been prepared for burial with certain standard precautions. Overcrowding should be avoided by restricting the number of participants and people with respiratory difficulties are encouraged to attend only by wearing masks (80).

In a time like this when the pandemic is spreading like fire and the cure is yet to be confirmed and produced, prevention is the only retaliation in hand. But these standards mentioned above are not expected to be maintained in all countries. There are certain aspects which play a role; such as the socioeconomic condition of country, we must wonder how many countries can actually afford lockdown in order to maintain social distancing. Secondly, scientific knowledge about the infection and thus awareness regarding controlling the pandemic is not uniform among the regions that are suffering which will hamper the implementation of the preventive measures included. Therefore, all the affected countries' progress in minimizing the spread of the disease is not similar.

INCUBATION PERIOD

The incubation period is the first stage in the progression of a disease; defined as the time between the initial exposure to a microorganism and the development of the symptoms. In this stage, the replication of the pathogen begins so its duration may depend on the type of pathogen, its virulence, host's defense and site of infection. This particular period of any disease is crucial as the person does not realize being infected due to the lack of symptoms but still can spread the pathogen to others which is known as pre-symptomatic transmission (81). Total 88 COVID-19 cases confirmed from 20 to 28 January were gathered from premises outside Wuhan; and were used in an investigation to confirm the incubation period to be 6.4 days. But only few number of cases used in this study which was not enough to find out if the incubation period differs with age and sex. Also, the cases reported were from regions with proper health management and awareness so it has been suggested in the paper that more research is required regarding cases with mild symptoms, morbidity factors and older age group (82). In order to determine the geographic spread of the virus, a study was conducted using cases from both outside Wuhan and residents of Wuhan. The results showed the incubation period to be 5.0 days for 52 cases from residents outside Wuhan and 5.6 days for 158 cases who lived in Wuhan (83). Another study on 181(60% male, median age: 44.5 years) confirmed cases of the time period from 4-24 February outside of Hubei province in China, among which 161 cases had residence or had a travel history to Wuhan; the rest of them however were investigated to be in contact with the infected ones. Statistical analysis of these data was done using log-normal model which shows estimated median incubation period to be 5.1 days and estimated mean to be 5.5 days. In addition to that, less than 2.5% of infected people will show symptoms within 2.2 days of exposure and symptoms onset for

97.5% will be within 11.5 days (84). Both large health organizations CDC and WHO have also advised an active monitoring period to be 14 days; which can be supported by the findings of these researchers (85,86). The value of the mean incubation period differs from one study to another mainly because of the different cities in China used for collecting the cases. Cases in the studies mentioned were taken from Wuhan or other cities outside of Wuhan; so the testing records, healthcare management and awareness regarding the disease may vary from city to city. Moreover, cases with mild symptoms were not included in any of the studies so the finding values of the mean incubation period may fluctuate with further research.

REPRODUCTION NUMBER

The virulence of a disease depends on the reproduction number of the virus. Effective reproductive number (R) is termed as the average number of secondary cases infected from a single infective in a population that consists of both immunized (vaccinated or primarily infected) and susceptible hosts. This value is used to deduce the preventive measures taken in order to limit the spread as its magnitude depends on those measures. The value of R less than 1 is an indication that prevention steps taken to control the outbreak are being effective and there is a decrease in the number of cases. When the value of R reaches 1 it refers to an epidemic and $R > 1$ means that the number of cases is amplifying (87-89). Basic reproduction number (R_0) is also referred to the number of new cases of infection generated from one case but in a population that includes susceptible hosts only. It depends on the duration of infectious or latent period, contacts per unit of time and chances of transmitting the disease per contact (88,90). It is crucial to maintain $R_0 < 1$ so that the threshold for herd immunity is overcome and the infection is successfully eliminated by mass immunization (88,91). A number of SARS-CoV-2 cases from January 10 to 24 January, 2020 mainland China was collected for a study to initially estimate the R_0 of the novel corona virus and the results was in a range of 2.24-3.58. But the serial interval (SI) of novel corona virus was not known yet and the analysis was done based on the SI of SARS and MERS. Serial Interval is the duration recorded from the appearance of symptoms of the first case to the symptom onset of a second case infected by the first case; calculated by collecting vast amount of data on the succession of the spread of infection and thus determines the result of R_0 (92,93). Another study was carried out using data of cases from Dec 13, 2019 to Jan 28, 2020 which concludes R_0 to be approximately 2.68 and epidemic doubling time to be 6.4 days. The researchers used the estimated SI of SARS and Markov Chain Monte Carlo methods to estimate the R_0 . They also inferred their findings as an indication that there is exponential growth of the outbreak in many cities of China (94). Another experiment included results of an analysis done on time-series data of novel coronavirus-infected pneumonia-coronavirus (NCIP-CoV) till January 22 and the basic reproductive number was calculated to be 2.2. The SI was analyzed to be 7.5 days which was considered in this statistical analysis. The findings of the study helped the investigators to confirm human-to-human transmission and estimate the severity of the infection but it is also mentioned that the study did not include cases with "mild infections" which has fluctuated the results (95,96). A recent study on April showed the median basic reproduction number

Table 3. Comparison of SARS-CoV-2 with MERS-CoV, SARS-CoV and Ebola regarding incubation period and basic reproductive number

Viruses	Year and place of Identification	Mean Incubation Period	Active Monitoring Period by WHO	Basic Reproductive Number (R_0) in early stage	Number of countries and territories infected	Reference
MERS-CoV	2012 in Saudi Arabia	5-7 days	14 days	0.45–0.98 in Saudi Arabia 2.5–8.09 in South Korea	27	(102-112)
SARS-CoV	2002 in Southern China	4 days	10 days	2.9	26	(113-116)
SARS-CoV-2	2019 in Wuhan	5.5 days	14 days	2-2.5\ 5.8	210	(49,84,85, 97,100,117)
Ebola	1976 in Sudan and Democratic Republic of Congo	2-21 days	21 days	1.51 in Guinea 2.53 in Sierra Leone 1.59 in Liberia	10	[118]-[120]

to be 5.8; considering SI equals to 7-8 days (97). The data of serial interval used was collected from past analysis, i.e. 7.5 days (95). However, the value of R_0 will be lesser if the value of SI is shorter; but SI value to be less than 6 days is implausible because immediate hospitalization of patients is not always feasible (97). There is a correlation between the serial interval and the time taken for an infective to be isolated after showing symptoms; thus more the delay to be hospitalized, greater the SI value is (98). A group of analyzers has gathered all the values of the basic reproduction number from various studies and calculated the mean R_0 to be 3.28 and median to be 2.79 (99). Lastly, according to a report published by WHO, the estimation of R_0 was calculated to be 2-2.5 (100).

Table 3 compares SARS-CoV-2 with other highly infectious viruses: MERS-CoV, SARS-CoV and Ebola in terms of their mean incubation period and reproduction number. It can be deduced that the mean R_0 for COVID-19 falls in the range of estimated R_0 value of SARS. This was bound to happen as both viruses are similar and was identified within the same country. But it can be taken under consideration that COVID-19 is more contagious because it has spread to more countries in a short time compared to SARS and MERS (101,102). Ebola seems to be less transmissible but has the highest mean for incubation period (**Table 3**).

DIAGNOSIS

Efficient diagnostic testing for COVID-19 has a vital role to play in minimizing the spread of outbreak as verified drug therapy or vaccination is yet to be discovered (121). Early testing will make sure of fast hospitalization or isolation of the identified cases; preventing further spread of the infection resulting in lowering the probability of community transmission (122). A study on the effects of identification of cases and isolation shows that the percentage of contact tracing is directly proportional to the basic reproduction number (R_0). For example, R_0 value of 1.5 requires tracing of 50% of cases to control the transmission where as 70% of contact tracing is essential in case of R_0 of 2.5 or more (123). People should only get tested if they show characteristic symptoms of COVID-19 or have been in contact with an infected person. There are different diagnosis techniques available which vary on the basis of diagnosis, types of sample used, specificity and sensitivity of the diagnosis methods etc.

Real-time Quantitative Polymerase Chain Reaction (RT-qPCR)

This is commonly used to detect viruses from respiratory secretions in acute respiratory infection. The sample for testing

is collected by swabbing the nasopharyngeal with a cotton swab or the sputum is obtained by coughing. Viral transport media is added and then RNA is extracted using extraction kits (124,125). Amplification of specific gene sequence is carried out by putting the mixture of the extracted RNA, reaction buffer, reverse transcriptase enzyme, Taq Polymerase, primers and probe; in a thermal cycler. In thermal cycling, different temperature and time period are maintained for the activity of reverse transcriptase enzyme (55 °C for 10 min), denaturation, annealing and extension (126). To detect different gene sequences of the virus, specific primers and probes are used that are complementary to the sequence. Thus, different kits are used to target different sequence such as QuantiNova SYBR Green RT-PCR Kit (Qiagen) for S gene, TaqMan-based fluorescence signal to identify the genes ORF1B and N separately. However, this technique has drawbacks like takes more time to give results, chances of infection from the samples collected, high rate of false positive results and at times clumsy procedures of mixing solutions (124,127). A study was conducted in order to compare the positive ratio of other types of sample such as blood, urine and stool with oropharyngeal swab. Even though negative results were found using urine and blood samples; surprisingly, 8 out of 9 stool samples of confirmed infected cases gave positive results despite of no symptoms for diarrhea. This indicates possibilities of another mode of transmission of the disease which is through feces (128). Another process to detect the viral RNA is high-throughput sequencing (HTS) of the whole genome. But as it is expensive and requires sophisticated equipments, RT-qPCR is a better option when it comes to availability and frequent testing. RT-qPCR also has high sensitivity (50%-70%) for the infection although it is affected by the protocol used and the specimen collected (129).

Serological Tests

The main principle of serologic tests is the identification of virus specific antibody complex formed as a result of the infected person's immune response. Types of serologic tests include: Rapid Diagnostic Test (RDT), Enzyme-linked immunosorbent assay (ELISA) and Neutralization assay (**Table 4**) (130).

An investigation using combined IgM-IgG antibody ELISA kits based on both nucleocapsid protein (rN) and spike protein (rS) was conducted on 214 patients. The results showed 80.4% positive rate for rN protein and 82.2% for rS protein for either or both of the antibodies. It was concluded with ELISA technique to be highly sensitive for diagnosis of COVID-19 by using serum samples from patients 10 days after post-disease onset (131). The sensitivity and specificity of the antibody-antigen test was analyzed using blood samples from 525 cases

Table 4. Differences between the three types of serologic tests regarding their type, type of sample required, amount of time needed and what it detected for results

Name of the test	Type of test	Test Samples	Time	Results	Reference
Rapid Diagnostic Test (RDT)	Qualitative only	Blood, saliva and nasal swab	10-30 minutes	Presence of antibodies	(130)
ELISA	Qualitative and Quantitative	Whole blood, plasma and serum	1-5 hours	Presence of antibodies	
Neutralization Assay	Qualitative and Quantitative	Blood, serum and plasma	3-5 days	Presence of active antibodies and memory cells	

and the results showed to be 88.66% and 90.63% for sensitivity and specificity respectively. The study also used various type of blood sample: vein blood, plasma and fingerstick blood (132). Serology based tests can be used in large-scale, easy sample collection as antibodies are abundant in the blood serum, easy storage of sample as antibodies are more stable than RNA and antibodies are available for longer period in the blood unlike virus in sputum sample. But one limitation is that detection of antibodies may not be possible after at least 3 days of symptom development due to the slow immune response to the virus (133).

Computed Tomography Scan (CT scan)

There are high chances of infected persons missing out if CT scan is not done along with nucleic acid detection, according to this study. There are high chances of High-resolution CT scan of chest not only helps with early diagnosis but also gives an idea about the severity of the infection. HRCT has benefits like high sensitivity and easy to use. The features of the images mostly of the patients are diversified and thus radiologists must be well-informed about the characteristic changes due to the virus (128,134). Based on several studies, chest imaging features have been found to be similar to SARS-CoV and MERS-CoV. Some of these features analyzed in the studies were mostly the “presence of ground-glass opacities”, “presence of pleural effusion”, “presence of consolidation” etc. (135-137). Common characteristic of the CT scan image of COVID-19 infected patient are bilateral pulmonary parenchymal ground-glass and consolidative pulmonary opacities; but there was an absence of other abnormal features like lung cavitation, discrete pulmonary nodules, pleural effusions, and lymphadenopathy (138). CT-Scan uses X-ray beams that bombards with the organs and bones inside the body to give images from various angles ultimately combined together to demonstrate a cross-sectional structure of the body part (139,140). Drawbacks of this method are other viral pneumonia may show similar abnormalities and any malfunction of the machine may compromise the results.

CRISPR-CAS12-based Assay

Considering the lengthiness of the RT-qPCR method and dependency on the generation of antibodies in case of serologic tests, more rapid and accurate diagnostic method has been developed which is the CRISPR-CAS12-based assay (141). CRISPR technology is an effective tool to operate genomic modifications for correcting defective genes and putting a stop to the spread of a disease. “CRISPR” stands for clustered regularly interspaced short palindromic repeats; combined with CRISPR-associated (Cas) proteins; it is a defense system used by bacteria and archaea to destroy foreign nucleic acid during a viral invasion (142,143). CRISPR-Cas12a enzymes are RNA-mediated cutting enzymes that cleave double-stranded DNA and can also make targeted nonspecific single-stranded cuts. CRISPR based DETECTR (DNA

endonuclease-targeted CRISPR trans reporter) assay is a method which uses this ssDNAase activity of Cas12a combined with isothermal amplification using loop-mediated amplification for the extraction of RNA from samples (144,145). It takes about 30 minutes to give results using DETECTR platform using a lateral flow strip format and specific sets of gRNA (guide RNA) are used to whether identify SARS-CoV-2 or any strain of coronavirus such as SARS-CoV or bat. The detection of the targeted sequence depends on the design of the primers, CDC and WHO guidelines suggest it to be specific to E (Envelop) and N (Nucleocapsid) genes (141,146,147). The optimized conditions for this assay is 62 °C for 20–30 min during isothermal amplification (RT-LAMP) and 37 °C for 10 min for Cas12 detection. According to the guidelines of current US FDA EUA, the test is assumed to be positive if anyone of the E or N genes is detected and is definitely positive in case both genes are detected. Results displayed on the lateral flow strips are brought by the use of a FAM-biotin reporter molecule; cleaving of the molecule by Cas 12 creates a signal on the second detection line (test line) and negative results will be interpreted by a signal on the first detection line (control line) generated by uncleaved reporter molecules (141-149). Another protocol has been shared by a group of researchers which includes the CRISPR-based SHERLOCK (Specific High Sensitivity Enzymatic Reporter UnLocking) technique to detect the viral genome. This process requires a total of an hour for the isothermal amplification of the extracted RNA from samples, Cas13 activity for the detection of viral RNA sequence and visualization of detection using a paper dipstick. However, the study was not done using patient’s samples so it is not well-established yet (150).

All these methods have their characteristic benefits and drawbacks. But their usage may vary from country to country although most countries are using the RT-PCR method. The preference may depend on the country’s budget, methods like high throughput sequencing and CRISPR-CAS may be too expensive in a time when frequent testing is required. But then again, cheaper methods like RT-PCR have more chances of false positives and are not fast enough despite of having high sensitivity. Thus, a CT scan along with the testing can help to overcome the suspected false positive results. Tests based on antibodies on the other hand are super fast, but as antibody generation requires time (minimum 3 days); there are high chances of false negative results which will only create more hindrance during preventing the spread of the disease. Lastly, operating these methods require proper technical skills and training in order to achieve systemic testing; which may not be effective in every region.

NON-SPECIFIC THERAPEUTIC OPTIONS

Currently, there are no approved vaccines available for use nor is there any specific treatment (151-153). Patients are

treated symptomatically and observed under intensive care if needed, to provide organ support to severely ill patients (152,154,155,157). It is recommended that patients be provided with supportive care such as hydration, oxygen therapy, pain and bacterial co-infection management etc. (156,157). According to WHO, a vaccine is to emerge in the markets within the next 18 months, given funding and continued public interest in the event the threat diminishes (152). Thus, this necessitates the discovery of new antiviral drug treatments necessary to manage the crisis (152).

Drug Treatment

IFN α (5 million U bid inh) and lopinavir/ritonavir (400 mg/100 mg bid po) are currently recommended as antiviral therapy by the guidelines (155). Oral oseltamivir has also been implemented in treatment by Chinese hospitals but there is no evidence leading to its effectiveness (158). Favipiravir is yet another broad-spectrum antiviral compound that has been endorsed by Shenzhen Health Commission to treat individuals infected with SARS-CoV-2 (159).

The drugs to be explored all come from those used to treat SARS, MERS or any influenza recently encountered (155). In order to carry this out, there are 3 approaches (155). First, to test available broad-spectrum antiviral drugs (that have been previously used to treat other viral infections) via standard assays (160). Second, to screen chemical libraries (of compound or databases) and retrieve knowledge on transcription process in a variety of cell lines (161). Lastly, to redevelop new drugs basing it on the genomic and biophysical virtues of coronavirus. Antiviral drugs follow either one of the following mechanisms of action i.e., viral replication inhibition, ion channel inhibition, serine protease inhibition (154,162) and some of the most promising are listed below:

Remdesivir

Remdesivir has recently been in news highlights and may be the best potential candidate to be trialed and developed into a future drug (158). The antiviral agent was initially developed to combat Ebola in phase 2 trial and shows broad-spectrum antiviral activity (153,163,164). It is not clear how it acts as an adenosine nucleotide analog, however, it is most likely to terminate RNA synthesis leading to mutagenesis (165). It might also compete with RNA dependent RNA polymerase (RdRp) (166). It is said to cause "premature termination by entering the nascent viral RNA (167). As a matter of fact, nucleoside analogs have a number of mechanisms for action which include specific/non-specific chain termination, inhibition of nucleotide biosynthesis and lethal mutagenesis (168). The compound has been effective against viruses related to SARS-CoV-2 and MERS-CoV (169-172). Moreover, in support, another recent study has shown that GS-5734, otherwise known as remdesivir, can work against a wide range of RNA viruses, which include SARS/MERS-CoV, in infected mice and cultured cells as well as non-human primate (NHP) model (167). Another study reported that a patient infected with SARS-CoV-2 had shown positive results upon treatment (52). Two more studies found that the compound could effectively control the infection in vitro (172,173). While a study in 2020 showed that remdesivir received a score of 0.77 μM at half proximal concentration against the virus block the infection (172). When used in combination with an inflammatory drug, baricitinib, the efficacy of remdesivir increases (174).

At the moment, remdesivir is undergoing a large number of clinical trials in hospitals but the ultimate competence of the drug is unconfirmed (153,157,175).

Ribavirin

Ribavirin is a guanosine analog with antiviral activity that is used to treat hepatitis C, respiratory syncytial and some haemorrhagic viral fever (162,176). It is commonly used along with interferon α (IFN- α) (162). In a study that used rhesus macaque model, the antiviral drug favourably treated MERS-CoV infection (177). Additionally, this compound targets the RNA dependent RNA polymerase (RdRp) in SARS-CoV-2 as shown in a model that based on sequence analysis, modelling and docking (178). In a study conducted at 2020, ribavirin achieved 109.5 μM of half maximal concentration against SARS-CoV-2 which serves to strengthen its potential as an effective drug (178).

Lopinavir and Ritonavir

Lopinavir, a kind of protease inhibitor used to treat HIV and often used along ritonavir as a booster (158,162). With or without ritonavir, both usages have shown antiviral activity against SARS-CoV-2 in vitro (176,179). Hong Kong scholars found that SARS cases treated with lopinavir/ritonavir and ribavirin had a relatively lower risk of acute respiratory distress syndrome (ARDS) and death, compared to cases treated by ribavirin alone (180). The inhibitor has had success in treating SARS and MERS infections and thus, can potentially fight the SAR-CoV-2 (181). In conjunction with oseltamivir, complete recovery was observed in a patient with SARS-CoV-2 related pneumonia symptoms (182).

Note on Angiotensin-converting Enzyme (ACE) and Angiotensin Receptor Blockers (ARB)

These two drugs are used to treat hypertension by causing an increased expression of ACE2 (153). It is to be noted that, when treated with ACE and ARB, overexpression of ACE2 has been seen in patients with type 1 and type 2 diabetes (35). This is where the SARS-CoV-2 binds in host cells (153). As no strong evidence indicating a higher susceptibility in this group of people has been found, the International Pharmaceutical Federation (FIP) has advised to continue this treatment in patients unless complications arise (153). Theoretically, an ACE2-based peptide, 3CLpro-inhibitor (3CLpro-1) and a vinylsulfone protease inhibitor have been reported to show some antiviral function against SARS-CoV-2 (183).

Chloroquine and Hydroxychloroquine

Chloroquine and hydroxychloroquine are widely used as an antimalarial and autoimmune disease drug, chloroquine is known for its broad-spectrum antiviral activity (162,184-186). Both chloroquine and hydroxychloroquine are known to be immunomodulatory and suppress the immune system (187,188). Use of chloroquine phosphate has led to some success in treating SAR-CoV-2 associated pneumonia (156,189). Chloroquine works by interference with glycosylation of cellular receptors of the virus itself such as inhibition or alteration during post-translational modifications of proteins synthesized by virus or by increasing endosomal pH for cell fusion (186,190). One model, physiologically-based pharmacokinetic (PBPK) showed better effectiveness using hydroxychloroquine in SAR-CoV-2 infected Vero cells rather than chloroquine (191).

In fact, chloroquine has been prescribed for use in the treatment of SARS-CoV-2 related pneumonia (189,192). At half maximal concentration of 1.13 μ M, the drug has blocked viral infection by enhancing the endosomal pH needed for viral fusion (172,190). However, the optimal dosage still needs to be determined via clinical trials. It is to be noted that the clinical safety and protocols for use for chloroquine (and remdesivir) are yet to be established via phase 3 trials; thus, the pros and cons (toxicity, side-effects or any other complication) must be evaluated carefully before use (153). If these trials are affirmative, both chloroquine and hydroxychloroquine can be applied in prophylaxis and curative treatments in infected patients (193).

Convalescent Plasma Therapy

As vaccines and drugs are yet to be developed, convalescent plasma therapy could be an effective approach in thwarting the progress of SARS-CoV-2 infection in severe patients (194). A laboratory test succeeded in neutralizing the virus extracted from bronchoalveolar lavage fluid (of a critical case) with sera from a number of patients (40).

Patients who have recovered from SARS-CoV-2 infection produce antibodies against the virus and their serum could be collected and used to prevent reinfection (157). This plasma should be collected within 2 weeks of recovery when the antibody titer is high and can be used to prepare globulin specific to SARS-CoV-2 (157,176). The plasma must be administered within the first week of infection when viremia is very high, in major cases (195). A 2009 prospective cohort study proved that for those infected with H1N1 influenza, the relative risk of death was considerably lower in patients treated with convalescent plasma (196). These antibodies restrict viral reproduction during the acute phase of infection and help terminate thriving viruses (197). A retrospective analysis produced that convalescent therapy was more effective in treating severe SARS patients rather than severe doses of hormonal shock in terms of mortality rate and duration of hospital stays (198). The clinical application is hindered by the difficulty posed during obtaining this very plasma (176). Nonetheless, the safety, risks and efficacy associated with these plasma-derivative products need to be assessed further with well-designed clinical trials (157,176).

Given these findings, many drugs have shown satisfactory result in different clinical and laboratory experiments. Although different drugs are in different phases of clinical trials but the differences in drug response from one ethnicity to another is another concern. Variation in different trials with same drug has already been reported but it is expected that a common therapeutic measure will be developed soon.

PROGRESSES IN SARS-CoV-2 VACCINE DEVELOPMENT

At the moment, there is no vaccine for the human coronavirus, SARS-CoV-2 (152,176,194). The surface glycoprotein or spike (S) protein that is involved in cell receptor interaction is being targeted for vaccine development in a majority of trials (158,199,200). There are challenges to be overcome and for an effective vaccine to be readied, quite a time needs to elapse for it to pass regulatory tests that judge its safety (200). Take the case of Ebola pandemic in 2013, when the vaccine Ebola rVSV took 3 years to reach phase I clinical trials

in Africa and Europe (201). As per WHO, a suitable vaccine would be available within a time frame of 18 months given there is sufficient funding and public interest even when the threat wanes (202). As of now, 18 biotechnology companies and universities from China are working to bring a vaccine (Table 5). Compared to Ebola, vaccines for SARS-CoV-2 have seen a faster pace due to collaborative efforts by scientists from all over the globe (176).

There is a possibility of re-infection as the humoral immunity weakens over time and the vaccines need to address this issue as well as the problem when the virus becomes endemic and appears recurrently. Individuals over 50 make up most of the severe cases but why this occurs is yet to be cleared; thus, the vaccines should also protect this vulnerable portion of the community (203). However, older individuals generally respond less well to these vaccines because of immune senescence (204).

The first human trial in Europe has begun at Oxford University and plans to study 800 participants half of which will only be injected with the vaccine developed under 3 months. The rest is to be injected with a vaccine that protects against meningitis. The vaccine is said to be very optimistic among the researchers working on it and is based on a weakened version of adenovirus or the common cold virus that affects chimpanzees; this will prevent it from growing in humans. The same team has developed a vaccine against MERS using the same technique and have had promising clinical trials (213). Soon, a larger trial consisting of 5,000 volunteers is to take place and will be specified to no age limit. (214).

Nonetheless, the safety and efficacy of the vaccine are the prime targets set in mind as well as equipment for mass production. Apart from this, the cost of each unit of vaccine must also be considered. The vaccine has to be made available globally and must be affordable by all which is another concern.

SUMMARY

Coronaviruses have been around for centuries now, within animal and human populations. Although the previously known human coronaviruses until the SARS epidemic did not attract much attention since they were usually not highly pathogenic as compared to SARS-CoV, MERS-CoV and SARS-CoV-2, most of them were associated with only mild respiratory conditions.

However, the onset of the SARS and MERS outbreak in the years 2002/2003 and 2012 respectively have exposed the more pathogenic natures of these viruses, resulting in high fatality cases.

The Novel strain of the human Coronavirus named SARS-CoV-2 mainly shares the same typical protein and genomic structure as that of all the other coronaviruses however the accessory genes and proteins are known to vary, and also responsible for their dynamic virulence upon mutation (215). Their zoonotic origin and human-human transmission have been confirmed by now. Bats are suspected to be their natural host reservoir due to the high genomic similarities of the SARS-CoV-2 with other bat like SARS-CoVs but the intermediate host resulting in the transmission from the animal to human population is still unknown. A statistical report from July 2019 (prior to the COVID-19 outbreak) to determine the serological

Table 5. Various undergoing SARS-CoV-2 vaccine development projects in 2020

Type of vaccine	Companies working	Other details
1. Live-attenuated vaccine	Codagenix, Inc. in collaboration with Serum Institute of India, Ltd. are working to develop a live-attenuated vaccine (200).	This type of vaccine presents multiple antigens in the host to induce a range of immunogenic effectors against the pathogen (205).
2. mRNA vaccine	A vaccine, mRNA-1273 by Moderna is to go on trials by the end of April, 2020 (200). More companies include Baylor College of Medicine, BDGENE, CanSino Biologics Inc., CureVac AG, Guanhai Biotech, ZY Therapeutics Inc., Stermima Therapeutics, University of Texas and Tongji University are working each on their versions. (200). Fudan University with Shanghai Jiaotong University and Bluebird Pharmaceutical Company have 2 strategies planned to produce an mRNA vaccine (200).	The project by Fudan University aims to use mRNA that would express the S protein and RBD domain and is being tested on mice (200). The other is based on mRNA producing virus-like particles in vivo. Moderna plans to express S proteins as well and will test it on 20-25 healthy volunteers soon (200). It is known to possess LNP-encapsulated mRNA vaccine encoding S protein and is currently at phase I (206). Ad5-nCoV by CanSino Biologics Inc. uses type 5 adenovirus vector to express S protein and is also at phase 1 (206). mRNA vaccines are opted by so many companies owing to low-cost, safe administration, high potency and quick production cycles compare to traditional vaccines (207). However, so far there has been no mRNA vaccine in the market thus, it is likely to take more time to pass safety evaluation and other quality standard testing (200).
3. Live vector vaccine	Johnson & Johnson has validated an adenoviral vector, AdVac® (208), Tonix Pharmaceuticals is researching on horsepox virus (TNX-1800) and Greffex Inc. has announced to have completed an adenovirus vaccine in association with Greffex Vector Platform (200).	Live vector vaccines are said to be made of live viruses that express heterologous antigens (200). Such vaccines are said to have the strong immunogenicity of live-attenuated vaccines and the safety of subunit vaccines (200).
4. DNA vaccine	Two DNA vaccines are under development. One of them being INO-4800 by Inovio Pharmaceuticals. LineaRx, Applied DNA Sciences Subsidiary and Takis Biotech are working on a linear DNA vaccine candidate (200).	Inovio intends to deliver a plasmid coding for S protein by electroporation and has entered its phase 1 trials (206).
5. Epitope vaccine	Generex Biotechnology is working together with third-party groups to create a vaccine that uses synthetic peptide to copy key viral regions that is linked to an amino acid residue (200). A team from Hong Kong University of Science and Technology found epitopes highly conserved in SARS-CoV-2 which has the potential to contribute to a vaccine (210).	This type of vaccines is easy to produce and pass the quality control (200). But cons include, low immunogenicity due to low molecular weight and complex structure and call for the need to change in formulation by introducing structural changes, adjuvants and such (209). Generex is working on a patented technology called the NuGenerex Immuno-Oncology li-Key technology (200).
6. Subunit vaccine	Chongqing Zhifei Biological Products Co., Ltd, Johnson & Johnson and Pasteur Institute are all working on their own subunit types (200). Clover Biopharmaceuticals Inc. has made it public that they are currently working on a vaccine that would use “trimer-tag” technology (211) whereas University of Queensland is progressing via “molecular clamp technology” (212). Lastly, Novavax Inc. has a one of a kind candidates in line, nanoparticle vaccines based on the S protein (200).	There are 15 candidates to this type (206). Most of these are using S proteins as antigens (200). These vaccines are much safer and easier to produce with the added benefit of efficient stimulation of host immune system (200). Very often, they require adjuvants for a strong response (200).

evidence of the spillover of viruses from bats to humans in more rural settings Southern China did not show any direct relationship between bat contact and the infections of coronavirus within the sample population however most infections seemed to have a correlation with domestic animal exposure thus indicating the presence of an intermediate host (216). With different mode of transmission and host being reported, ranges about it is yet to be unveiled.

There is no approved specific drug available to cure COVID-19 and so preventive measures are now the general solutions. Chloroquine and hydroxychloroquine have shown inhibition of virus in vitro although the dose required for humans is estimated to be high to cause severe toxicity. Both of the compounds have been issued by the FDA as an emergency despite no conclusive evidence of their efficacy.

Hydroxychloroquine can cause several side-effects like, cardiomyopathy, however rarely, and this can only be treated by immediate discontinuation in some cases (217,218).

Tocilizumab is a humanized monoclonal antibody of IgG1 sub-class known to inhibit cytokine, interleukine-6 (IL-6) receptor bringing about immunosuppression. Recent findings from China has suggested that the mortality may be a cause of viral hyperinflammation. This drug is also being tested in patients especially vulnerable to cytokine release syndrome that is triggered by the infection (220). We know that immunosuppression is not advised to treat viral infections and may intensify the symptoms of COVID-19, however, this may prove to be beneficial in case of cytokine storm. In China, its use has been approved for patients suffering from pneumonia and elevated levels of IL-6. Hence, it is recommended that the

severe cases of hyperinflammation be highlighted and treated using this approach to see if it works (217,219-222). With different antiviral and other drugs being under clinical trial, an efficient therapeutic option is expected to be discovered soon.

While many vaccine projects are currently being worked at, one concern is the potential of the already approved BCG vaccine. Modeling this vaccine to combat COVID-19 means that the efficacy needs to be determined via phase 3 trials only saving at least a year of time. Abundance Foundation is one such example being funded for trials.

Zinc sulfate has been used successfully to treat a number of medical problems such as, herpes simplex infection, viral warts, acute cutaneous leishmaniasis and in therapy of autoimmune diseases like, Behcet's disease, alopecia areata. Hence, it is suggested that the use of oral zinc in BCG vaccines could prove positively against COVID-19 (223-229).

CONCLUDING REMARKS

As an emerging virus, most about SARS-CoV-2 is still to be unveiled and again the contagious nature of the virus makes it impervious to fight against the pandemic. Appropriate preventive measures, early diagnosis and non-specific treatments in critical cases are the general options today to combat the outbreak. Better understanding of the virus structure, genetics and the concurrent scientific effort to develop counter measure against the virus are the present global needs. All in all, the prime concern worldwide is to develop an effective vaccination and responsive drugs before it is too late. Normalcy as we know it cannot return until there is a safe vaccine ready. So far, the structure for SAR-CoV-2 has been revealed. The underlying problem is progress of trials of prospective anti-viral drugs. While hundreds of projects are ongoing, scientists all over the globe need to collaborate their findings to bring out a formula that would sell without profits. Having said that, a test kit that would detect the virus within minutes whilst being affordable is also a genuine concern. Current methods take too long and have trouble with accuracy given the huge load of samples that demand to be processed every day. However, more effective and sensitive diagnosis methods might be in the development.

ACKNOWLEDGEMENT

Authors acknowledge the members of Swift Integrity Computational Lab, Dhaka, Bangladesh, a virtual platform of young researchers for their support during the preparation of the manuscript.

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