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COVID-19: Review on Its Etiology, Pathogenesis, and Existence in Humans

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Abstract: The world is facing a new healthcare crisis with the rise and spread of novel coronavirus since December 2019. Also known as Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2), the disease associated with SARS-CoV-2 is even called COVID-19. COVID-19 is having a pulverizing impact on the scientific community. As of August 13, 2020, the number of confirmed cases had reached up to 20,439,814 and the death toll to 744,385, affecting more than 188 territories across the globe. In these difficult times, the world is looking towards research and clinical work from different scientific communities to lead the way to a solution to the issue. In this review, we are focusing on COVID-19 emergence, pathogenicity, and existence in humans, as well as the SARS-CoV-2 infection mechanism and its similarities to previous coronavirus strains.

Introduction

The first case of mysterious pneumonia emerged in December 2019 in Wuhan, Hubei region of China (Wang *et al.*, 2020a). A new coronavirus was identified by Wu *et al.* (2020) from the samples taken from the Wuhan seafood market, and later it was named Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2) by the international committee on taxonomy of viruses (ICTV) (Yang and Wang, 2020a). As of June 12, 2020, the number of confirmed cases had reached up to 20,439,814 and the death toll to 744,385, affecting approximately 188 territories across the globe (https://www.who.int/docs/default-source/coronaviruse/situationreports/20200512-covid-19-sitrep115.pdf?sfvrsn=feac3b6d_2). The number of COVID-19 cases are increasing rapidly, and the situation is getting worsen day by day. Fig. 1 shows the global increase in COVID-19 confirmed cases and the number of deaths with time. Tab. 1 shows the total number of COVID-19 cases and confirmed death in six regions, and Tab. 2 shows a comparative analysis between some countries that are now (on August 13, 2020) the epicenter of COVID-19 outbreak (https://www.who.int/docs/default-source/coronaviruse/situationreports).

Coronaviruses are single-stranded, positive-sense, enveloped RNA viruses having genome size ranges from 27 to 34 kb (Sexton *et al.*, 2016).

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Coronaviruses have an outer spike-like projection that gives them a crown-like appearance, henceforth the name coronavirus (Wormser and Aitken, 2010). Before SARS-CoV-2, humans had two previous encounters with coronaviruses: Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) (Drosten *et al.*, 2003; Ksiazek *et al.*, 2003) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (Zaki *et al.*, 2012). In 2002, the SARS-CoV outbreak was reported in the Guangdong region of China and spread to five mainlands, infecting 8,098 individuals and causing 774 deaths (mortality rate approximately 9.6%) (http://www.who.int/csr/sars/country/table2004_04_21/en/index.html). A decade later, in 2012, another coronavirus MERS-CoV emerged in Arabian Peninsula, where it stays a significant well-being concern and later spread to 27 countries infecting 2,494 people and claiming 858 lives (fatality rate 34%) (Walls *et al.*, 2020). Both SARS-CoV and MERS-CoV originated from bats and then crossed the species barrier to humans trough intermediate host civet (Wang *et al.*, 2005) and camels, respectively (Briese *et al.*, 2014; Hemida *et al.*, 2013).

Morphology and structure of SARS-CoV-2

Coronaviruses belong to the *Coronaviridae* family. Members of this family are enveloped, single-stranded, and positive sensed RNA viruses. SARS-CoV-2 has a similar genome structure as like other coronaviruses having at least ten open reading frames (ORFs) (Chan *et al.*, 2020). They contain

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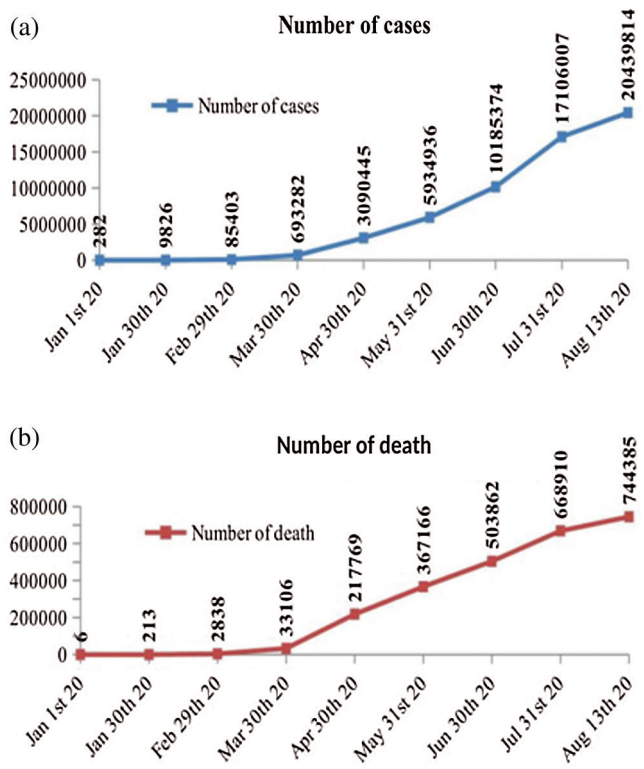

FIGURE 1. Graph shows No. of cases globally (a) and No. of deaths globally (b). Exact numbers are indicated vertically. It is clear from the graph that till 10th march no. of cases and death were linear, after that there is sudden increase. This increment in cases and death indicates the severity of COVID-19 disease. Data shown here are according to WHO daily situation report 206 (https://www.who.int/docs/default-source/coronaviruse/situation- reports/20200512-covid-19-sitrep-206.pdf?sfvrsn=feac3b6d_2).

TABLE 1

Total number of cases and death due to COVID-19 outbreak in different regions

S. No.	Region	Total Cases	Death	Fatality Rate
1	Africa	916644	17557	1.9
2	Americas	10950220	398229	3.6
3	Eastern Mediterranean	1683511	44661	2.6
4	Europe	3668652	218255	5.9
5	South-East Asia	2830404	56636	2.0
6	Western Pacific	389642	9034	2.3
7	Globally	20439814	744385	3.6

*Source: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200512-covid-19-sitrep-206.pdf?sfvrsn=feac3b6d_2.

5'-terminal non-coding region, an open reading box 1a/b region coding a non-structural polyprotein that is further cleaved by viral proteinase 3C-like serine protease (3CLpro) and papain-like cysteine protease (PLpro) to form RNA-dependent RNA polymerase and helicase (Zumla *et al.*, 2016). At 3' end, genes encoding structural proteins, i.e., Spike (S), Membrane (M), Envelop (E), and Nucleocapsid (N) are present. E and M protein together form a viral envelope. N protein, along with the 3' terminal non-coding region, is responsible for the assembly of virus (Jiang *et al.*, 2020), and S protein forms a spike-like glycoprotein that helps in the process of virus attachment with the host surface. Fig. 2a shows the genetic organization of SARS-CoV-2 (Jiang *et al.*, 2020). On the basis of genomic structure and phylogenetic examinations, coronaviruses can be divided into four genera α, β, γ, and δ, where α and β genera infect humans and mammals, whereas the other two genera infect the birds. SARS-CoV-2 belongs to the β family, having a round or oval shape with a diameter of 60–140 nm (Zhu *et al.*, 2020).

Coronaviruses are very sensitive to hot and humid conditions. They can be inactivated at 56°C for 30 min (Rabenau *et al.*, 2005). Furthermore, 75% ethanol, peracetic acid, and chlorine-containing disinfectant can successfully inactivate SARS-CoV-2 (Zhou *et al.*, 2020).

Origin and host range of SARS-CoV-2

After the novel coronavirus is discovered, it is important to understand where it originates from. It helps to decide what a suitable approach needs to be taken to control its transmission. It also helps to develop the therapeutics and vaccine against the virus (https://apps.who.int/iris/handle/10665/332197). Initially, the novel coronavirus outbreak has been referred to as 2019-nCov but, in February 2020, theinternational committee on taxonomy of viruses (ICTV) announced that it should be referred to as SARS-CoV-2 and the disease associated with it referred to as COVID-19 (Gorbalenya *et al.*, 2020). Coronavirus study group (CSG), a working group of ICTV, taxonomically proved that SARS-CoV-2 had more than 70% nucleotide identity with SARS-CoV and 90% nucleotide identity with SARSr-CoV RaTG13 (Gorbalenya *et al.*, 2020; Lu *et al.*, 2020).

In recent years, bats have been an essential reservoir for different types of coronaviruses (Cui *et al.*, 2019). In February 2017, during an outbreak of severe watery diarrhea of piglets in Guangdong Province of China, two novel swine enteric alpha coronaviruses (SeACoV) were detected by two different groups, which were very similar to bat coronaviruses (Gong *et al.*, 2017; Pan *et al.*, 2017). The confinement of these two SeACoV from sick piglets extends our insight into the host range of coronaviruses.

SARS-CoV and MERS-CoV infections started from bats, both viruses bouncing species to infect humans through a different intermediate host (Gong *et al.*, 2017). Civet sold in the live animal market was the intermediate host of SARS-CoV, and the dromedary camel was the intermediate host of MERS-CoV. Fig. 3 explains the possible interspecies transmission routes of coronaviruses (Gong *et al.*, 2017; Su *et al.*, 2016). Hence, it is clear that the previous two coronaviruses required an intermediate host before passing on to humans (Cui *et al.*, 2019), and this fact indicates that SARS-CoV-2 may have passed to humans through an intermediate host. SARS-CoV-2 shares 96% whole-genome identity with BAT CoVRaTG (Zhou *et al.*, 2020).

Although there is no recognizable proof available for an intermediate host of novel coronaviruses, early investigation suggests that it may have jumped from bat to humans (Wu

TABLE 2

Comparative analysis between some countries that are now the epicenter of COVID-19 outbreak

S. No.	Country	1st case reported	Total no. of cases	Death	Fatality rate	Test Positive rate
1	United States of America	20th Jan 2020	5094500	163340	3.2	8.0[#A]
2	Brazil	25th Feb 2020	3109639	103026	3.3	83.5[#B]
3	India	30th Jan 2020	2396637	47033	1.9	8.9[#C]
4	Russia	31st Jan 2020	907758	15384	1.6	2.8[#D]
5	South Africa	1st Mar 2020	568919	11010	1.9	17.1[#E]
6	Mexico	28th Feb 2020	492522	53929	10.9	45.0[#F]
7	Peru	6th Mar 2020	489680	21501	4.3	10.6[#G]
8	Columbia	6th Mar 2020	410453	13475	3.2	20.0[#H]
9	Chile	3rd Mar 2020	378168	10205	2.6	19.8[#I]
10	Spain	31st Jan 2020	329784	28579	8.6	6.2[#J]

*Source: WHO Situation Report 206 (https://www.who.int/docs/default-source/coronaviruse/situation- reports/20200512-covid-19-sitrep-206.pdf?sfvrsn=feac3b6d_2).
[#]Tast Positive rate=total number of test×100/number of positive sample (TPR is based upon latest data provided from different countries, links are given below:
[A]https://www.santepubliquefrance.fr/content/download/250807/2596023.
[B]https://ourworldindata.org/coronavirus/country/brazil?country=~BRA.
[C]https://main.icmr.nic.in/sites/default/files/whats_new/ICMR_testing_update 11 Aug20_9AM_IST.pdf.
[D]https://rospotrebnadzor.ru/about/info/news/news_details.php?ELEMENT_ID=15149.
[E]https://github.com/dsfsi/covid19za.
[F]https://datos.gob.mx/busca/dataset/informacion-referente-a-casos-covid-19-en-mexico.
[G]https://www.gob.pe/institucion/minsa/noticias/218573-minsa-casos-confirmados-por-coronavirus-covid-19-ascienden-a-407-492-en-el-peru-comunicado-n-191.
[H]hhttps://www.ins.gov.co/Noticias/Paginas/Coronavirus.aspx#muestras.
[I]https://github.com/jorgeperezrojas/covid19-data.
[J]https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos/COVID-19_pruebas_diagnosticas_06_08_2020.pdf.

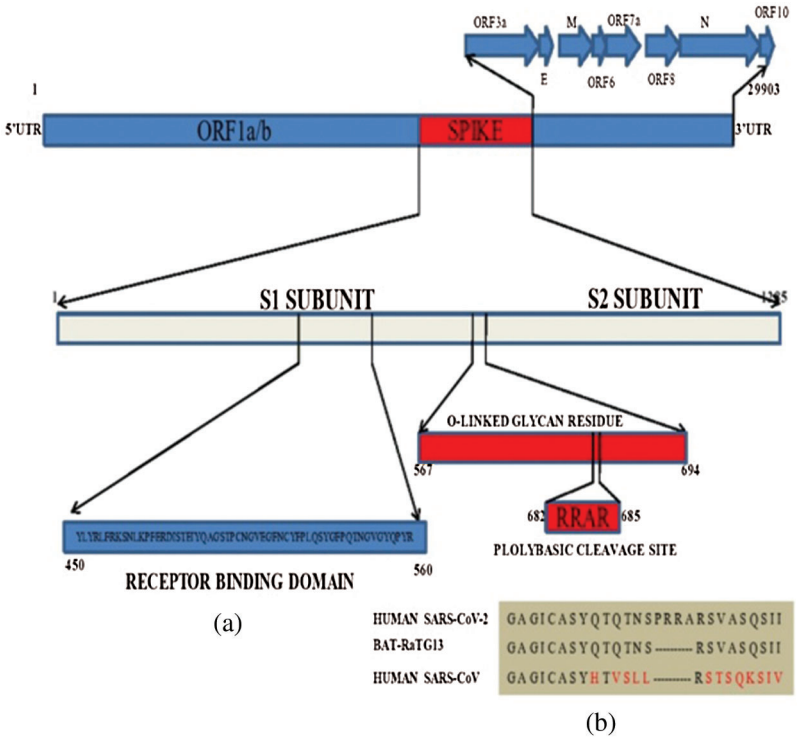

FIGURE 2. (a) Genomic organization of SARS-CoV-2 .S1 and S2 subunits of Spike protein are responsible for attachment and fusion to the host cell respectively. (b) Comparison of polybasic cleavage site of SARS-CoV-2 .BAT CoV and SARS-CoV(sequence shown here, are from NCBI gene bank accession codes MN908947, MN996532 and KY417146). Sequence comparison clearly shows the presence of an extra polybasic cleavage site in SARS-CoV-2.

et al., 2020; Zhou *et al.*, 2020). A study published by Zhang *et al.* (2020) suggests that Pangolin-CoV is 91% identical to SARS-CoV-2, and it may have been the closest relative to SARS-CoV-2 after CoVRaT. However, the probability of pangolins being the intermediate host for SARS-CoV-2 is still under discussion. Recently, a study published by Forster *et al.* (2020) revealed that three different types: A, B, and C of the virus have been circling all around the world.

Pathogenesis

Although the pathogenesis of SARS-CoV-2 is poorly understood, the clinical symptoms are similar to that of

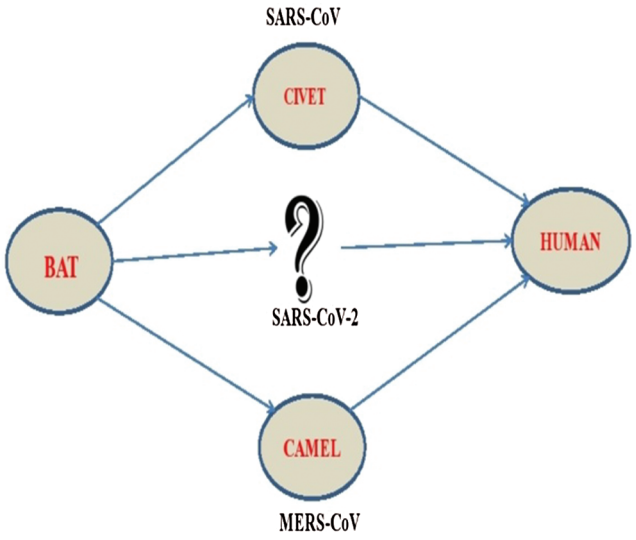

FIGURE 3. Possible route of interspecies transmission of coronaviruses (SARS-CoV and MERS-CoV both originated from Bat and cross the species barrier through CIVET and Camel respectively as intermediated host. The question mark indicates that intermediate host of SARS-CoV-2 is not yet identified.

SARS-CoV and MERS-CoV like fever, headache, sore throat, nonproductive cough, respiratory distress, myalgia pneumonia. The incubation period of disease ranges from 4 to 15 days, with an initial fatality rate of around 1.4% (Huang *et al.*, 2020; Peiris *et al.*, 2004), but as of 13th August 2020, the fatality rate has increased up to 3.6% (Tab. 1) (https://www.who.int/docs/default-source/coronaviruse/situationreports/20200512-covid-19-sitrep115.pdf?sfvrsn=feac3b6d_2). SARS-CoV-2 infects both the upper as well as the lower respiratory tract. Studies have shown that the higher viral load is detected in the nasal cavity than the throat (Zou *et al.*, 2020). All the age groups among humans are susceptible, but the infection and fatality rate are higher in people above 60 years of age. Many people having COVID-19 disease show mild symptoms, while some may be asymptomatic. But people with compromised immunity and other co-morbidities may progress to acute respiratory distress syndrome and multi-organ dysfunction (Huang *et al.*, 2020).

Similarities between SARS-CoV-2 and other CoVs

Recent studies conducted by Lu *et al.* Lu *et al.* (2020) suggest that SARS-CoV-2 is more related to bat coronaviruses than the SARS-CoV. SARS-CoV-2 and SARS-CoV share around 79% of genetic similarities. They also have shown structural similarities between the receptor-binding domain (RBD) of SARS-CoV-2 and SARS-CoV. Both viruses utilize similar host cell receptors and viral proteins for entry into the host cell (Tai *et al.*, 2020). Furthermore, on comparing the specific domain of the viral proteins that bind to the cell surface receptor, it was found that SARS-CoV-2 binds more efficiently to the host cell than the SARS-CoV (Walls *et al.*, 2020).

Entry of SARS-CoV-2

Viral infection begins with the binding of viral particles to the host cell surface receptors; hence it becomes very essential to identify the cell receptors involved in this process. Except for HCoV-OC43 and HKU1, the other four coronaviruses (HCoV-229E, SARS-CoV, HCoV-NL63, MERS-CoV) recognize proteinaceous peptidase as a receptor (Li *et al.*, 2019; Lu *et al.*, 2013; Raj *et al.*, 2013). The former two viruses are shown to engage with sugar receptors for the cell attachment (Li *et al.*, 2005). After the recent episode of COVID-19, Chinese scientists quickly verified that SARS-CoV-2 likewise uses human angiotensin-converting enzyme-2 (hACE-2) for attachment to the cell (Fig. 4) (Zhou *et al.*, 2020).

Novel coronaviruses use its spike-like glycoprotein S for fusion and entry into the cell (Lu *et al.*, 2015). Further, S protein is cleaved into S1 and S2 subunit by the host cell protease, Furin. These two subunits are responsible for receptor recognition and fusion, respectively (Dijkman and Van Der Hoek, 2009). SARS-CoV and MERS-CoV utilize the C-terminal domain (CTD) of the S1 subunit for receptor recognition called the receptor-binding domain (Li *et al.*, 2005; Lu *et al.*, 2020). S1 CTD is the critical region in SARS-CoV-2 that interacts with the human ACE2 (Walls *et al.*, 2020). Ou *et al.* (2020) showed that human lung cancer cell, Calu 3, is highly susceptible to the SARS-CoV-2v (Ou *et al.*, 2020). The binding of S protein to hACE2 requires conformational changes and protease activation. A furin site is present between S1 and S2 (AA 682-685 RRAR) in SARS-CoV-2 S protein (Fig. 2b) (Jiang *et al.*, 2020). Regardless of whether the proximity of this furin site has any impact on the viral pathogenesis and spreading among people, it stays to be resolved.

Immune system activation and invasion

Whenever our body is under attack by a viral pathogen, our immune system gets activated and antigens are presented to antigen-presenting cells (APC) by major histocompatibility complex (MHC) or human leukocyte antigen (HLA) where it is recognized by the cytotoxic T lymphocyte (CTL). Till now, there are no reports available regarding the mechanism of SARS-CoV-2 infection, but we can get some ideas from the previous research studies available on SARS-CoV and MERS-CoV. MHC-1 molecules are mainly responsible for the antigen presentation in SARS-CoV (Liu *et al.*, 2010). Previous studies have confirmed that polymorphism in the HLA gene is associated with the susceptibility to SARS-CoV and MERS-CoV (Keicho *et al.*, 2009; Chen *et al.*, 2006; Tu *et al.*, 2015).

Some initial reports during the early stage of infection have shown that out of 41 patients, six died due to the Acute Respiratory Distress Syndrome (ARDS) (Huang *et al.*, 2020). ARDS is considered as a main pathological event in SARS-CoV and MERS-CoV (Xu *et al.*, 2020). ARDS mainly occurs due to the cytokine storm, in which a large amount of pro-inflammatory cytokines is released due to uncontrolled inflammatory responses. In severe SARS-CoV-2 infections, a large amount of pro-inflammatory cytokines (IL1B, IFNγ, IL15, and IL17) are released (Huang *et al.*, 2020). This cytokine storm results in an attack on the body by the immune system causing ARDS, multiple organ failure, and finally death in severe cases, just like in SARS-CoV and MERS-CoV (Huang *et al.*, 2020).

Immune invasion of SARS-CoV-2 is not yet fully understood; however, its previous versions, SARS-CoV and

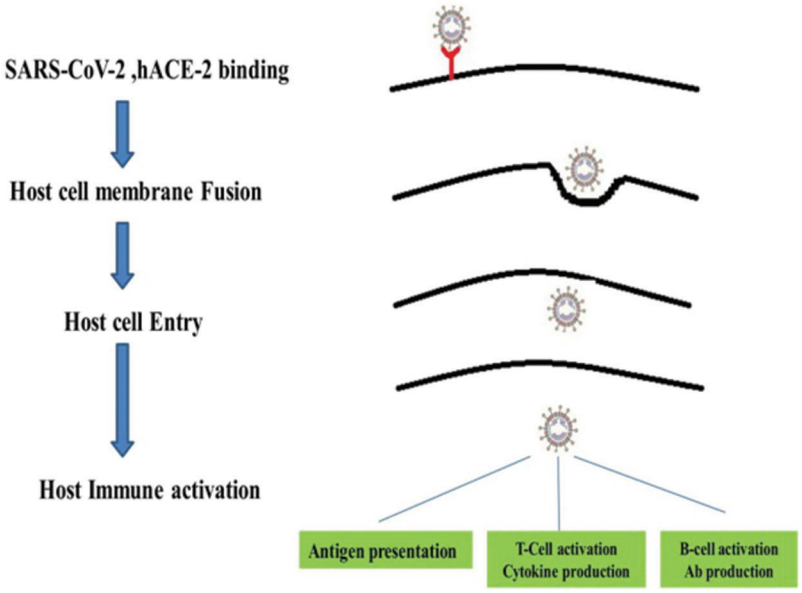

FIGURE 4. SARS-CoV-2 entry into host cell and immune system activation. SARS-CoV-2 attaches to cell through hACE-2 receptor (indicated in red) and then fusion to the cell membrane occurs. After entry into the host cell it activates host immune system such as T-cell, B-cell activation and pro-inflammatory cytokine production in uncontrolled way that may result in Acute Respiratory Distress Syndrome (ARDS).

MERS-CoV2, were able to evade the immune system. They can incite the creation of double-layered vesicles lacking the Pattern Recognition Receptor, and then they avoid the host detection system of their RNA by rapidly dividing in these vesicles (Snijder *et al.*, 2006). In mice infected with SARS-CoV and MERS-CoV, the IFN1 pathway was found to be inhibited, which has a proactive effect on these viruses (Niemeyer *et al.*, 2013).

Detection and diagnosis of COVID-19

According to the National Health Commission, detection of genetic material, neutralizing antibody, culture, and isolation of viral particles are the key laboratory diagnosis that can be performed for the rapid detection of SARS-CoV-2. The reverse transcriptase-polymerase chain reaction is also used to detect SARS-CoV-2 nucleic acid. Nasal swab, throat swab, and blood samples are used as a diagnostic standard for detecting the SARS-CoV-2 infection (http://en.nhc.gov.cn/index.html). US Centre for Disease Control (CDC) developed the specific primers and probes for the universal detection of SARS-CoV-2 by real-time RT-PCR. Recently, a novel method is developed by (Wang *et al.*, 2020b) for the rapid detection of COVID-19, known as CRISPR/Cas 12a based assay with a naked eye readout, CRISPR/Cas12a-NER. This assay is very sensitive and can detect as few as 10 copies of the viral gene within 45 min.

Prevention and control of COVID-19

Since, as of now, there are no affirmed medicines and treatments for the SARS-CoV-2 infection, avoidance is the best remedy. The best ways to control the infection are to take out the source of infection, cutting off the route of transmission, and isolation of the infected or suspected individuals. People can contract SARS-CoV-2 infections from other people already having the virus. This disease spreads principally from individual to individual through the small droplets from the nose or mouth, which are expelled when the individual with SARS-CoV-2 virus coughs, sneezes, or speaks. Since these droplets are relatively heavy, they cannot travel too far. That is why it is essential to maintain a distance of at least one meter from an infected person (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/q-a-coronaviruses). No vaccine is available for the prevention of SARS-CoV-2; although, many research institutes and private companies are trying to develop the vaccine. For instance, Moderna, a biotech organization based in Cambridge, Massachusetts, is working with the National Institutes of Health on a potential mRNA vaccine candidate against SARS-CoV-2. AbMax Biotechnology Co., Ltd., reported that it had effectively developed a SARS-CoV-2's N protein-specific monoclonal antibody (Yang and Wang, 2020b).

Conclusion

The COVID-19 outbreak was declared a pandemic on 11th March 2020 by the World Health Organization. After this, SARS-CoV-2 infection has tested the financial, clinical, and general well-being framework of the whole world. Until now, very little understanding is available regarding how SARS-CoV-2 crossed the species barrier to humans. More scientific data is required for understanding the mechanism of SARS-CoV-2 survival in humans and how it becomes so contagious (more than SARS-CoV and MERS-CoV). It is also essential to pay attention to COVID-19 vaccine development. Today, all the efforts are being made towards controlling this flare-up, but endeavors ought to be made to devise accurate measures to forestall future episodes of a zoonotic outbreak.

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