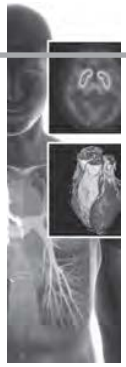

A global review of COVID - 19 pandemic

In December 2019, the WHO identified causative agent of outbreak as the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that causes to a disease the so called coronavirus disease-2019 (COVID-19) after a pneumonia cases with unspecified etiology was reported in Wuhan, Hubei province, China. According to a phylogenetic investigation, the virus is meticulously correlated to bat coronavirus RaTG13. Now, in human, asymptomatic carriers can also transmit the virus. The COVID 19 virus is affecting 213 countries and territories around the world and 2 international conveyances and on May 26, 2020 more than 5,603,558 confirmed cases and 348,194 deaths have been reported. The disease has a manifestation of fever, dry cough, and chest pain with pneumonia in severe cases. Initially, it is tried to eliminate the disease in China via isolation but are now transmitted globally. Yet, there are no vaccines and drugs to treat the virus. As it is a novel virus, there are knowledge gaps that misleads to any preventive actions. Therefore, this review provides current scientific facts about the COVID-19 pandemic.

Keywords: Covid 19 ▪ Pandemic ▪ Review

Impact statement

A novel coronavirus (COVID 19) has spread rapidly through person to person contact, likely respiratory droplets around the world since it was first identified in china as of January 2020.

Introduction

Coronaviruses are enveloped, single-strand RNA viruses that can infect a wide range of hosts including avian, wild, domestic mammalian species, and humans. Coronaviruses are well known for their ability to mutate rapidly, alter tissue tropism, cross the species barrier, and adapt to different epidemiological situations [1]. Six human coronaviruses have been reported since the 1960s; four of them (OC43, 229E, NL63, and HKU1) cause mild illness similar to the common cold and gastrointestinal tract infection. The other two, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), have raised significant public health concerns due to their zoonotic emergence and crossing of the species barrier, causing high pathogenicity and mortality in humans [2]. SARS- and MERS-CoVs were reported to be transmitted from the main host (bats) to palm civets or dromedary camels, respectively, then finally to humans [3–5]. Both SARS- and MERS-CoVs were and are highly pathogenic, resulting in 8096 and 2519 human cases, with 9.6% and 34.3% fatality rate in 2003–2004 and 2012–present, respectively [6,7].

Pneumonia cases of unknown causes were reported in Wuhan city, Hubei province, China, in December 2019. The causative agent of this pneumonia was confirmed as the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), previously named 2019 novel coronavirus (2019-nCoV), and the diseases was termed coronavirus disease-2019 (COVID-19) [8,9]. Based on phylogenetic analysis, SARS-CoV-2 forms a distinct lineage with Bat-SARS-like coronaviruses that belong to the order Nidovirales, family Coronaviridae, genus Betacoronavirus, and subgenus Sarbecovirus [9]. SARS-CoV-2 shares 96.3%, 89%, and 82% nucleotide similarity with bat CoV RaTG13, SARS-like CoV ZXC21, and SARS-CoV, respectively, which confirms its zoonotic origin [10, 11]. At the beginning of the outbreak, scientists thought that the disease was initially only transmitted from animals to humans, and then only between people who are symptomatic, until the first human-to-human transmission case from an asymptomatic carrier was documented in Germany [10, 12,13]. This is also now evidenced by cases of community spread in which no direct links between current patients and suspected COVID-19 carriers can be made. As of May 26, 2020, the virus affects 213 countries and territories around the world and 2 international conveyances and more than 5,603,558 confirmed cases and 348,194 deaths. SARS-CoV-2 is reported to be transmitted between humans through direct contact, aerosol droplets, fecal–oral

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route, and intermediate fomites from both symptomatic and asymptomatic patients during the incubation period [9, 14]. The disease is characterized by fever, dry cough, dyspnea, and diarrhea in 20–25% of patients who do not exhibit upper respiratory signs such as sneezing or sore throat [8, 13]. In severe cases, the disease is characterized by pneumonia, metabolic acidosis, septic shock, and bleeding [14, 15].

Control measures are being instituted by nations around the world to extinguish the SARS-CoV-2 pandemic, including the issuance of travel advisories or even flight bans to and from infected countries, strict quarantine measures and traveler screenings, implementation of mitigation measures by healthcare specialists, application of social distancing measures for schools and popular gatherings, strict personal hygiene such as frequent hand washing, and wearing face masks [16]. Currently, world public health authorities such as the Centers for Disease Control and Prevention (CDC), World Health Organization (WHO), and other global partner s are trying to control and prevent the spread of SARS-CoV-2. Additionally, WHO issued a guide to managing the recent pandemic including instructions for the rapid detection of the disease, emergency treatment, and application of prevention and control strategies, supportive therapy, and prevention of disease complications [15]. Due to misleading information that is circulating and knowledge gaps about the newly emerged SARS-CoV-2. This review provides insights for the control of pathogenic infections in humans with novel coronaviruses and spillovers in the future.

■ Genome of SARS-CoV-2

Since December 2019, in China, the appearance of SARS-CoV-2 in various laboratories has been working on sequencing the genome of the etiologic agent. As of 26 April 2020, there are a total of 7655 complete genomes from 67 countries in the Global Initiative on Sharing All Influenza Data (GISAID) database [17]. A reference genome is now available in the NCBI genome database (29,903 nucleotide, Reference Sequence: NC_045512.3) [18]. To date, there are a total of 875 sequences including one RefSeq sequence and 768 complete genomes at NCBI.

SARS-CoV-2 is a single-stranded and positive-sense RNA virus with a genome size of 29,903 nucleotides, making it the second-largest known RNA genome. The virus genome consists of two untranslated regions at the 5' and 3' ends and 11 open reading frames that encode 27 proteins

The first open reading frames constitutes about two-thirds of the virus genome, encoding 16 non-structural proteins, while the remaining third of the genome encodes 4 structural proteins and at least 6 accessory proteins. The structural proteins are spike glycoprotein (S), matrix protein (M), envelope protein (E), and nucleocapsid protein (NP). While, the accessory proteins are open reading frames (3a, 6, 7a, 7b, 8, and 10) [2, 13, 19, 20].

■ Mutations of SARS-CoV-2

As to the whole-genome sequence alignment, SARS-CoV-2 shares 89 % identity with bat SARS-like CoVZXC, 21,82% with SARS-CoV, and 96.3% with bat CoVRaTG13 [11,13]. Alignment of the predicted protein sequences of SARS-CoV-2 to those of SARS-CoV or SARS-like coronaviruses revealed a total of 380 amino acid substitutions between these viruses [2]. These amino acid substitutions were distributed as follows: 348 mutations in nonstructural proteins (Open region frame1ab, 3a, 3b, 7a, 7b, 9b, and 14), 27 in spike glycoprotein, and 5 in nucleocapsid protein. No amino acid substitutions were detected in envelope protein or matrix protein, signifying that envelope and matrix proteins are highly conserved among these viruses. The SARS-CoV-2 uses the same cellular receptor, hACE2, as SARS-CoV to enter the cell [9, 21, 22].

The analysis of the receptor-binding domains (RBD) of SARS-CoV and SARS-CoV-2 S protein revealed similar binding affinities [23]. A total of 27 amino acid substitutions in the S protein but not in the receptor-binding motif (RBM) that directly interacts with hACE2, which may affect host tropism. These 27 substituted residues were distributed as follows: 17 in the S1subunit [6 in the RBD and 6 in the sub domain (SD)] and 10 in the S2 subunit 58reported similarity in the spike protein RBD, including RBM, of both SARS-CoV and SARS-CoV-2, in addition to the presence of several residues in SARS-CoV-2 RBM that favor the interaction with human ACE2. These results agree with the genomic analysis of SARS-

CoV-2, according to which the S2 subunit of the spike protein shares 99% identity with those of two bat SARS-like CoVs (SL-CoVZXC21 and ZC45) and of human SARS-CoV [13].

While the SARS-CoV-2 S2 subunit was conserved, the S1 subunit shares an overall 70 % identity with those of bat and human SARS-CoV. The RBD core domain of S1 is highly conserved, with most of the amino acid differences located in the external subdomain that is responsible for the direct interaction with host receptors [13]. Differences in SARS-CoV-2 S protein and the high contagious nature of this virus suggest that SARS-CoV-2 has evolved via natural selection for binding to human ACE2 receptor [24]. Open Region Frame 3b also differs in SARS-CoV-2. Open Region Frame 3b deletion mutations in SARS-CoV do not affect viral replication in vitro [25]. Open Region Frame 3b may play a role in viral pathogenicity in addition to its inhibitory effects on interferon (IFN) expression and signaling [26, 27]. Currently, a novel short putative protein was identified in Open Region Frame 3b of SARS-CoV-2 [13]. However, the function of this novel protein is still not known. SARS-CoV-2 Open Region Frame 8 is closer to those of bat SARS CoV ZXC21 and ZC45 and distant from that of human SARS-CoV [13].

■ Genetic variety of SARS-CoV-2

About 86 Complete or semi-complete genomes of SARS-CoV-2 viruses identified revealed that three deletions in the genome of isolates from Japan, USA, and Australia. The deletion mutations were in the open region frame 1ab gene (3-nucleotideand 24-nucleotidedeletion) and at the 3' end of the genome (10-nucleotide deletion). Of the 93 substitution mutations, 42 changed the amino acid sequence of structural and non-structural proteins [28]. The 3 and 24-nucleotide deletions in open region frame 1ab are expected to reduce the protein sequence by 1 and 8 amino acid residues, respectively, without changing the reading frame, but the functional effects have yet to be investigated. The alignment of SARS-CoV-2 reference S protein against all SARS-CoV-2 sequenced genomes from China, USA, Japan, Australia, and Taiwan revealed 99.97–100% identity, with 100% query coverage. While the identity and coverage for SARS-CoV S protein gene were 74.5% and 91 %, respectively. Moreover, the S protein gene from bat SARS and SARS-like coronavirus isolates shared 76.5–83% identity with that of SARS-CoV-2. This agrees with previous conclusions regarding the evolutionary analysis of SARS-CoV-2 [11, 18]. These results strongly suggest the possibility of a recent common ancestor for all SARS-CoV-2 or the transmission of the same virus strain across countries.

■ Source of Infection of SARS-CoV-2

The source of infection for coronavirus is considered zoonotic. Bats are currently considered a reservoir for all human coronaviruses [5, 29]. Many coronaviruses are circulating in animals but have not yet infected humans. The type of animal that SARS-CoV-2 originated from is still unclear. At the beginning of the outbreak in Wuhan, China, many patients were linked to the Huanan Seafood Wholesale Market, suggesting animal-to-person spread. After retrospectively studying case reports, the number of patients that did not have exposure to animal markets has risen, indicating person-to-person spread was also occurring at that time [30]. SARS-CoV-2 is closely related to bat coronaviruses [8]. A group of researchers reported early in the outbreak that the novel SARS-CoV-2 has the highest similarity of codon usage bias with snakes [31,32]; however, this method to determine initial host origins is dubious. Interestingly, researchers also reported one amino acid difference in the receptor-binding domain of the S protein of Pangolin-CoV compared to that of SARS-CoV-2, suggesting that pangolins might play a role as an intermediate host (Xiao et al., data currently under review). Another group of researchers reported that the virus originated from bats based on the genome sequence of SARS-CoV-2, which is 96% identical to bat coronavirus RaTG13. Recently, a group of researchers found that SARS-CoV-2 replicates poorly in dogs, pigs, chickens, and ducks but efficiently in ferrets and cats [33]. Therefore, researchers are still trying to find the main source of the disease outbreak and identify the definitive intermediate hosts.

■ Mode of Transmission of SARS-CoV-2

SARS-CoV-2 infection was reported to be transmitted directly from person to person like most respiratory viruses via close contact with an

infected person or through respiratory droplets produced when an infected person cough. These droplets can be inhaled to reach the lung. The virus can be indirectly transmitted via touching a surface or an object that was previously contaminated with the virus and then touching the face, eyes, or mouth [34] and possibly via the fecal–oral route [35,36]. Asymptomatic carriers and patients after recovery from the acute form of the disease are also considered a potential source of virus transmission to healthy persons [10, 12]. Interestingly, human coronaviruses can survive on steel, metal, wood, aluminum, paper, glass, plastic, ceramic, disposable gowns, and surgical gloves for 2–9 days. High temperature (≥30◦C) can reduce the persistence period, while low temperature (4◦C) increases the persistence time up to 28 days [37]. Transmission of the virus vertically from mother to fetus or via breast milk has not been confirmed yet [38].

■ Risk Factors for SARS-CoV-2 Infection

Risk factors that affect SARS-CoV-2 transmission include: travel to or contact with individuals who have recently visited Wuhan, China, or other places experiencing an outbreak; close contact with persons who are diagnosed positive for the disease, such as healthcare workers caring for patients with SARS-CoV-2; contact with droplets and secretions from an infected person and eating or handling wild animals native to China such as bats. Additionally, the risk of infection is higher for the elderly and for patients' suffering from pre-existing illnesses such as cardiovascular disease, hypertension, diabetes, and chronic respiratory disease [30]. The reported fatality rate based on age is 14.8% for people >80 years of age, 8% for people between 70 and 79 years, 3.6% for people between 60 and 69 years, 1.3% for people between 50 and 59 years, 0.4% for people between 40 and 49 years, 0.2% for people between 10 and 39 years; no fatalities have been reported for children under 10 years of age. Notably, the fatality rate is higher in males (2.8%) than in females (1.7%) [39, 40].

■ Clinical Features of SARS-CoV-2

In humans, the estimated incubation period of the novel coronavirus infection ranges from 2 to 14 days. However, some cases had an incubation period of 21, 24, or 27 days [41]. The complete clinical representation of SARS-CoV-2 is still uncertain. The disease begins with flu-like symptoms that include fever, fatigue, dry cough, sore throat, shortness of breath, headache, chest tightness, chest pain, and muscle pain, runny nose, nausea, vomiting, and diarrhea [42]. People can be infected without showing symptoms, which allows the virus to spread more effectively from person to person. Complications can occur due to COVID-19 leading to severe infections, such as pneumonia, kidney failure, and death [8]. Based on the data analysis of 72,314 confirmed cases of SARS-CoV-2 in Wuhan City, China, by 11 February, 80.9% of the cases were mild with flu-like symptoms, and patients recovered at home, 13.8% were severe with pneumonia and shortness of breath, 4.7% were critical with respiratory failure and septic shock resulting in organs failure, and approximately 2% of the cases were fatal [43]. Another study was conducted on 99 hospitalized patients, and symptoms were classified as follow: fever (83%), cough (82%), shortness of breath (31%), muscle ache (11%), confusion (9%), headache (8%), sore throat (5%), runny nose (4%), chest pain (2%), diarrhea (2%), and nausea and vomiting (1%) [8].

■ Diagnosis of SARS-CoV-2 Infection

As the WHO published interim guidance for laboratory testing of suspected human cases, with precautions for specimen collection, packing, shipment, and amplification of nucleic acid to detect viral genes (N, E, S, and RdRp), the rapid diagnosis of SARS-CoV-2 infection is the keystone of disease control [40]. Therefore, oral swabs, broncho-alveolar lavage fluid, blood, as well as anal swabs are the best samples used for virus diagnosis [44].

Monitoring of case history in suspicious patients is considered the first step in the early diagnosis of SARS-CoV-2 infection. Clinically suspicious patients are those who suffer from fever and lower respiratory tract infection symptoms and reside within or have traveled to endemic regions or had close contact with a confirmed or suspected case. Moreover, SARS-CoV-2 can be transmitted by symptomatic and asymptomatic patients especially to the high-risk group [13].

The blood samples taken from SARS-CoV-2 infected patients showed an increased C-reactive protein and erythrocytes, increased myohemoglobin, liver enzymes, muscle enzymes, with a high level of D-dimer in

severe cases, normal or decreased white blood cell counts and lymphocytes in the early stage of the disease [13]. Furthermore, in SARS-CoV-2 infected patients admitted to intensive care unit, the levels of plasma granulocyte colony-stimulating factor, IP10, IL2, IL7, IL10, TNF-α, and MIP1a were increased [19].

The typical SARS-CoV-2 coronavirus morphology has been investigated by electron microscope examination. In addition, SARS-CoV-2 was successfully isolated from human respiratory epithelial cells samples of infected patients using Huh7 cells and Vero E6 cells. The isolated strain was confirmed by immunofluorescent antibody techniques using the cross-reactive nucleoprotein (NP) antibody. Serum neutralization tests (SNT) using Vero E6 cells were conducted to confirm the neutralization activity in IgG-positive viral samples [45].

As a serological tool, IgM and IgG ELISA detection kits using bat SARSr-CoV Rp3 NP were established with no cross-reaction against human coronaviruses [38]. By this diagnostic method, the viral antibody titers were increased in SARS-CoV-2-infected patients [19].

The main, fastest, and most sensitive test for the diagnosis of SARS-CoV-2 infection is nucleic acid detection. Currently, two nested RT-PCR and two real-time RT-PCR assays have been established with successful detection of the first 25 positive cases of infection in Japan [46]. Three real-time RT-PCR techniques have been designed based on the E, RdRp, and N genes [47]. Researchers have proven the S gene as the molecular detection tools for SARS-CoV-2 [44].

Treatment options of SARS-CoV-2 infection

To date, there are no approved specific antiviral drugs for SARS-CoV-2infection. Therefore, preventive measures and inactivation of the virus are essential to stop and control the spread of the disease. Human coronaviruses can be inactivated using 0.5% hydrogen peroxide, 62–71% ethanol, 0.1% sodium hypochlorite, 0.7–1% formaldehyde, 2% glutaraldehyde, or 0.23% povidone iodine within 1 minute. Other disinfectants such as 0.02% chlorhexidine digluconate, 0.55% orthophtalaldehyde, or 0.05–0.2% benzalkonium chloride are less effective. As of urgency in clinical demand, many drugs are approved to be used for clinical trials against SARS-CoV-2 infection, such as lopinavir/ritonavir, arbidol, interferon-alpha, favipiravir, chloroquine phosphate, darunavir/cobicistat, oseltamivir, and methylprednisolone.. Generally, coronaviruses are not sensitive to current antiviral drugs, and high concentrations of drugs effective on these viruses cannot be used in vivo. Therefore, combinations of different therapies have been used for the treatment of coronavirus infections [48]. The drug combinations that could be successful for the treatment of SARS-CoV-2 patients are lopinavir and ritonavir [49, 50], lopinavir/ritonavir plus arbidol [51], and ribavirin and interferon [52,53].

■ Preventive actions to SARS-CoV-2 infection

As there are not any treatment options for SARS-CoV-2 infection is still unclear. Hence, it is overbearing to follow preventive measures and safety precautions issued to limit exposure to the virus and to reduce further spread. General hygienic measures should be implemented, such as washing hands often with soap and water or an alcohol-based hand sanitizer, cough or sneeze etiquette, recommending covering of the mouth, avoiding touching eyes, nose, and mouth if the hands are not clean, avoiding close contact with sick persons, avoiding sharing dishes, glasses, bedding, and other household items with sick people, cleaning and disinfection of surfaces that are often touched, and staying home from work, school, and public areas when feeling sick. [13,54]. Since the SARS-CoV-2 spread is primarily driven by travel, screening of travelers who arrive at airports from pandemic areas for possible SARS-CoV-2 infection and entry-screening procedures are necessary. Strict hygienic measures should be implemented to avoid virus transmission to healthcare workers and other contacts. The control of coronaviruses is based on biosecurity regarding animals as well as on shifts in food habits, including discouraging the consumption of bush meat and of animal products without appropriate cooking [55].

■ Vaccination

Thus far, scholars are in the initial stages of trials of vaccine development research. Several vaccine candidates such as adenovirus-vectored, recombinant protein live attenuated, and nucleic

acid vaccines are in the conduit. Therefore, there is no vaccine to prevent SARS-CoV-2 infection.

Conclusion

In December 2019, the SARS-CoV-2 outbreak started in Wuhan City, China. It is now a global pandemic, with 5,603,558 confirmed cases and 348,194 deaths (as of May 26, 2020). The virus has the potential for rapid and extensive spread between people and countries. There are a lot of misleading information and knowledge gaps on the newly emerged SARS-CoV-2. Therefore, we reviewed the latest updates about COVID 19. Coronaviruses are genetically diverse and have a high tendency towards frequent genetic mutations and gene recombination, which increases the risk of interspecies transmission. Information about the incubation period can help in establishing effective quarantine for asymptomatic carriers, thus preventing the virus spread. From our perspectives and based on the currently available information about the virus and its epidemiology, the control of the SARS-CoV-2 requires an effective and global disease coordination effort through collaboration different bodies. At this stage of the disease pandemic, developing vaccines is crucial to limit the spread of the infection.

■ Declaration of interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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