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Focused REVIEW

SARS-CoV-2 and COVID-19: A Threat to Global Health

Otun Saha[1], Nadira Naznin Rakhi[2], Afroza Sultana[3], Md. Mahbubur Rahman[4], Md. Mizanur Rahaman[1,]*

[1]Department of Microbiology, University of Dhaka, Dhaka 1000, Bangladesh
[2]Department of Biotechnology and Genetic Engineering, Bangabandhu Sheikh Mujibur Rahman Science and Technology University, Gopalganj 8100, Bangladesh
[3]Department of Microbiology, Noakhali Science and Technology University, Noakhali 3814, Bangladesh
[4]Department of Microbiology, Stamford University of Bangladesh, Dhaka, Bangladesh

* *Corresponding authors*: Md. Mizanur Rahaman, Associate Professor, Department of Microbiology, University of Dhaka, Dhaka 1000; Email: razu002@du.ac.bd; Phone: +8801796585290.

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ABSTRACT

Since the outbreak of Coronavirus Disease 2019 (COVID-19) in China, in December 2019, scientists across the globe have been working relentlessly on the causative agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Unfortunately, despite the ongoing research at the genomic level, as well as the immunological and the pathological aspects of SARS-CoV-2, our knowledge about SARS-CoV-2 is still in the primary stage, even after one year from the beginning of the outbreak. As a result, the world is adopting a public awareness-based prevention and control strategy, together with significant efforts in developing and distributing several vaccines. Thus, this review summarizes the understandings of this pandemic, which will in turn be helpful in dealing with SARS-CoV-2 and provide a reference for future studies.

Abbreviations

Coronavirus disease 19 (COVID-19); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); World Health Organization (WHO); open reading frames (ORFs); spike surface glycoprotein (S), nucleocapsid protein (N), envelope protein (E), matrix protein (M); partial pressure of arterial oxygen (PaO2), percentage of inspired oxygen (FiO2); RNA dependent DNA polymerase (RdRp); Chinese medication (CM).

Keywords: COVID-19, Pandemic, SARS-CoV-2, 2019-nCoV, Epidemiology.

1. Introduction

After the first incidence of COVID-19 reported in China[1,2], severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was previously named 2019 novel coronavirus (2019-nCoV), rapidly spread to other countries and subsequently became a public health emergency of international concern[2] as decided by World Health Organization (WHO) on 30th of January, 2020. This was ultimately declared as a pandemic by WHO on 11th of March, 2020. After almost one year since the first outbreak, there have been a total of 58,621,594 confirmed cases, including 1,388,837 deaths from about 218 countries, areas and territories as of 22th of November, 2020. Considering the unprecedented global effect of the pandemic, extensive investigation on COVID-19 has been performed, which resulted in a total of more than 300,000 scientific articles according to WHO database covering the risk factors, pathogenesis, pandemic, clinical laboratory practices, public health aspect, vaccine and therapeutic initiatives, drug repurposing etc. regarding COVID-19. This prodigious effort of researchers has diverted the course of COVID-19 catastrophe from the worst-possible consequences observed in Italy, France, USA through drug repurposing and non-therapeutic intervention dependent containment strategies, even if the crisis is not completely resolved. However, the gradual

tendency of public negligence to follow the restrictions and containment strategies is threatening the world for consecutive waves of COVID-19 outbreaks[3]. On the other hand, while the medical advancement has caused better management of COVID-19 cases compared to the initial management, post COVID-19 symptoms among the patients of acute COVID-19 cases have arisen another issue to consider[4]. Thus, this focused review accumulates the knowledge gathered from the analysis of the first wave of COVID-19 from diverse aspects to better combat this current pandemic and to develop a research module for future emerging diseases.

2. Epidemiology of SARS-CoV-2

SARS-CoV-2 epidemiology showed an extremely interesting and aggressive pattern[5,6,7] compared to other reported viruses. The identified patient zero in China's Wuhan city was a 55 years old female shrimp seller and considered as one of the first COVID-19 victims. Along with her, 27 patients were tested positive for COVID-19, including 24 cases directly related to a common public toilet at the Huanan Seafood Market[8]. Later, on 9th of January, 2020, the first death due to COVID-19 was reported from Wuhan, China[8] and Philippines reported the first death outside China province on 1st of February, 2020[9], while outside Asia, the first death was reported from France on 14th of February, 2020[9]. However, dozens of deaths were reported from Iran, South Korea, and Italy by 28th of February, 2020. Ultimately, by 13th of March, 2020, deaths were reported from around 40 countries from all continents[8]. On the other hand, all of the reported 1st cases around the world have the traveling link to Wuhan, China or other affected countries[1,10], followed by the rapid spreading of COVID-19 around the world, primarily through air travel. No data on secondary cases infected from co-airline passengers is available[11].

However, from the beginning of the outbreak until 22th of November, 2020, WHO reported the daily new cases of ~200,000, and daily new deaths of more than 7,000. The actual number of cases is likely to be higher than the reported cases, primarily due to insufficient testing facilities and resources along with the existence asymptomatic patients[12]. The number of deaths is also believed to be higher than the reported number, taken into consideration that many individuals who died were not tested for COVID-19[12]. However, the ratio of reported deaths versus reported cases in the affected countries varied between 18.8% to 1.0 %[7,12]. This difference varies in different countries depending on various factors, including gender, age, health conditions along with the status of healthcare system such as the testing facilities and resources, development of diagnostic system etc[1,13].

High transmissibility of SARS-CoV-2 caused the outbreak to turn into pandemic. In the initial phase in China, a disproportionately higher number of healthcare workers became infected, fact also observed in other parts of the world[14,15,16], with the household secondary illness strikingly lower (19.3% to 13.8%) than the medical facility in a Guangzhou study[17]. Contrarily, the household-contact rate was higher than the nonmodel-based estimates of 14.9% for the Shenzhen and 10.2% for Guangzhou in other two studies[18]. Outside China, the secondary attack rate of SARS-CoV-2 was reported to range from ~4% to 10% (4.6% in Beijing, 8% in Hong Kong, 6.2% in Singapore, 10.2% in Toronto)[19]. However, the household-contact rates for SARS-CoV-2 are still significantly lower than other respiratory infections, such as pertussis and measles[17], although the comparison could not be done with MERS-CoV, due to the ambiguity of the data[19]. The other instances of super spreading involved casual contact with infected personnel or non-living objects along with hospital personnel who offered care after being exposed to the primary cases without proper preventive measure (Figure 1)[14,15,16].

3. Characterization of SARS-CoV-2

After the emergence of the novel coronavirus, SARS-CoV-2 causing the outbreak in Wuhan City, Hubei Province, China[1, 2], the virus strain Wuhan-Hu-1 was isolated from patients with COVID-19 and identified using a combination of classical and cutting-edge molecular techniques followed by sequencing (GenBank accession number MN908947.1)[20]. Diverse specimens, including upper respiratory tract (URT) swabs from nasal/ throat as well as sputum specimen from infected individuals, were used to confirm the presence of viral particle by real time reverse transcription polymerase chain reaction (RT-PCR), followed by next-generation sequencing[14,15], along with scanning electron microscopy (SEM)[15].

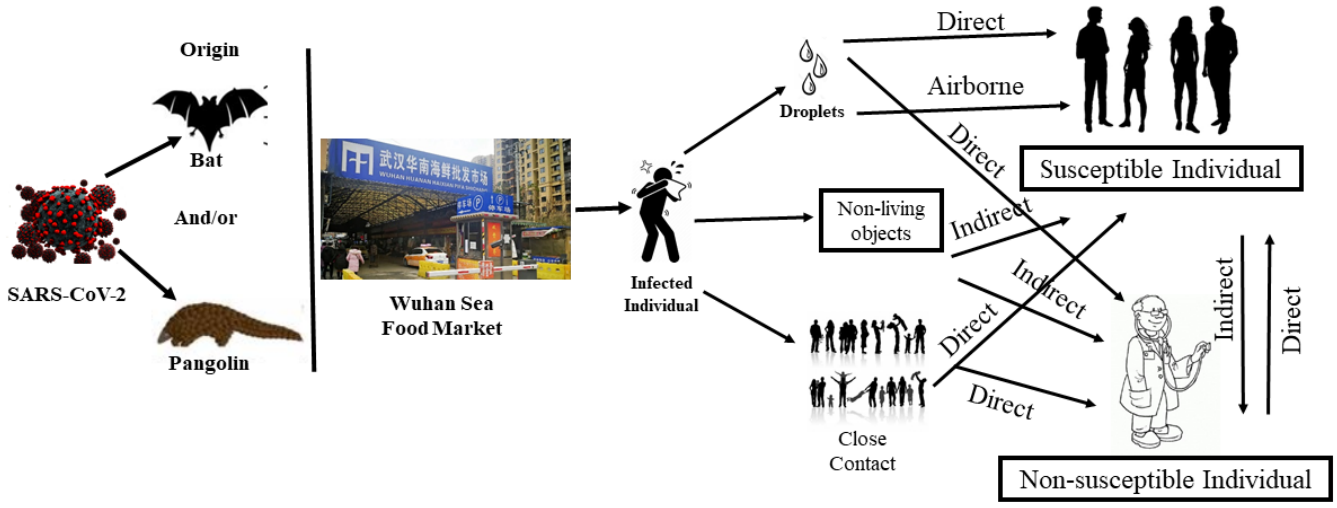

Figure 1. Possible transmission routes of pandemic SARS-CoV-2 in environments (modified from[14,15,16]).

Sequencing of this novel virus showed similarity with SARS-CoV (80%) and MERS-CoV (50%)[14,15,21], which was also evident from the in vitro culture using the vero kidney-derived cell line[14,15], although the pathogenicity is significantly lower than either of the closely related coronaviruses, SARS-CoV (10%) and MERS-CoV (40%)[21]. Within the shortest possible time, the genome was sequenced and analyzed in several laboratories across the world. As a result, over 200,000 complete genomes were deposited in the Global Initiative on Sharing Avian Influenza Data (GISAID) (https://www.gisaid.org).

The genome of SARS-CoV-2 is of 29 kilobases in length, containing 14 open reading frames (ORFs)[22] encoding 27 proteins[23] including accessory proteins (3a, 3b, p6, 7a, 7b, 8b, 9b, orf14), major structural proteins (spike surface glycoprotein (S), nucleocapsid protein (N), small envelope protein (E), matrix protein (M))[23]. The S protein is divided into the S1 domain (responsible for receptor binding) and S2 domain (responsible for cell membrane fusion), contributing in host tropism selection and transmission capacity[5]. While being an RNA virus, mutations in the SARS-CoV-2 genome spontaneously and rapidly arise due to the error-prone nature of RNA polymerases and their short replicative life cycles[5, 6, 14, 15]. So, although the initial isolates showed complete Orf8, a deletion of 382 nucleotides was observed in this ORF with the progression of the pandemic[24]. Besides, signature sequences of the spike protein were determined, which contributes in the attachment of SARS-CoV-2 to the lung epithelial cells by binding with the angiotensin-converting enzyme 2 (ACE2) receptor[10,23,24,25]. According to Khailany et al., (2020)[26], among the 116 mutations determined from the studied 95 SARS-CoV-2 genomes, the most common mutations were 8782C>T in ORF1ab gene, 29095C>T in the N gene and 28144T>C in ORF8 gene. In another phylogenetic networks analysis by Forster et al. (2020)[6] distinguished 3 major circulating variants (A, B, C) based on amino acid variation in the genome sequences of SARS-CoV-2, in which A being the ancestral type according to the bat outgroup coronavirus. Interestingly, spatial analysis of mutational profile revealed G29553A to be unique to all US isolates and absent in the genome of the isolates deposited from Italy and Spain in GenBank and GISAID[6,26], which intrigues the differential effect of this mutation in disease severity and clinical manifestation of COVID-19 in aforementioned countries. On the other hand, observation of 80% non-synonymous recurrent mutations at protein level indicats the possible adaptation of the virus[13].

4. Origin of SARS-CoV-2

The genome analysis of the SARS-CoV-2 isolated in humans revealed significance similarity with the SARS-CoV-2 genome isolated from animals such as

Rhinolophus affinis (Bat), *Rhinolophus malayanus* (Bat), *Manis javanica* (Pangolin), each of which were available in the live animal market in Wuhan, China[10], while the first COVID-19 case reported was from a patient linked to the seafood market of Wuhan[1-7]. Genome analysis of SARS-CoV-2 isolated from swabs collected from *Rhinolophus affinis* and *Manis javanica* (Pangolin)[10] showed 96% and 91.02% homology respectively to the human SARS-CoV-2, and formed a distinct phylogenetic group with the human isolates, suggesting possible animal to human transmission[10,20]. Besides, the comprehensive sequence analysis on the SARS-CoV-2 RNA genome revealed that the virus is a recombinant virus of the bat coronavirus and another origin-unknown coronavirus. The recombination occurred within the gene of viral spike glycoprotein, which is responsible for binding with the cell surface receptor[27] , while the coronavirus isolated from Malayan Pangolins (*Manis javanica*) showed very high amino acid identity with SARS-CoV-2 at E (100%), M (98.2%), N (96.7%) and S genes (90.4%)[1,7,29,29,30]. In addition, the receptor binding domain (RBD) of S protein in CoV isolated from Pangolin was almost identical, having only one amino acid difference to that of SARS-CoV-2[28,29]. Thus, it might be possible that the recombination took place between Pangolin-CoV-like viruses with that of Bat-CoV suggesting pangolins as the potential intermediate host of COVID-19. However, the environmental samples taken from the Wuhan marketplace, the origin of the outbreak resulted into positive for the novel coronavirus, but no specific animal association has yet been identified.

5. Clinical spectrum of COVID-19

Clinical manifestation of disease varies depending on individual health and immunity, as well as the geographical location[11, 23,31]. The incubation period of SARS-CoV-2 is 2–14 d, with a median incubation of 5.2 days[32] (Figure 2). Based on a few early descriptive studies of patients admitted to a Wuhan regional referral hospital with confirmed COVID-19 pneumonia, fever was the most frequent symptom among the patients (83%–98%) followed by cough (66%–82%) and roughly one-third of the patients had shortness of breath[16]. Less common symptoms include myalgia (11%), rhinorrhea (10%), headache (8%), gastrointestinal symptoms (3%) and chest pain (2%)[14,15,18,21]. Most of the patients were reported to show multiple symptoms rather than one specific symptom[16,18,21]. In some other studies, the clinical presentation of COVID-19 resembles SARS-CoV, characterized with fever, dry cough, and shortness of breath in most of the cases[6,16, 32]. Cases with critical illness showed respiratory failure, septic shock, and organs failure, which require intensive care support[7,16,23]. Increased oxygen support is required for approximately 23%–32% of the patients, who

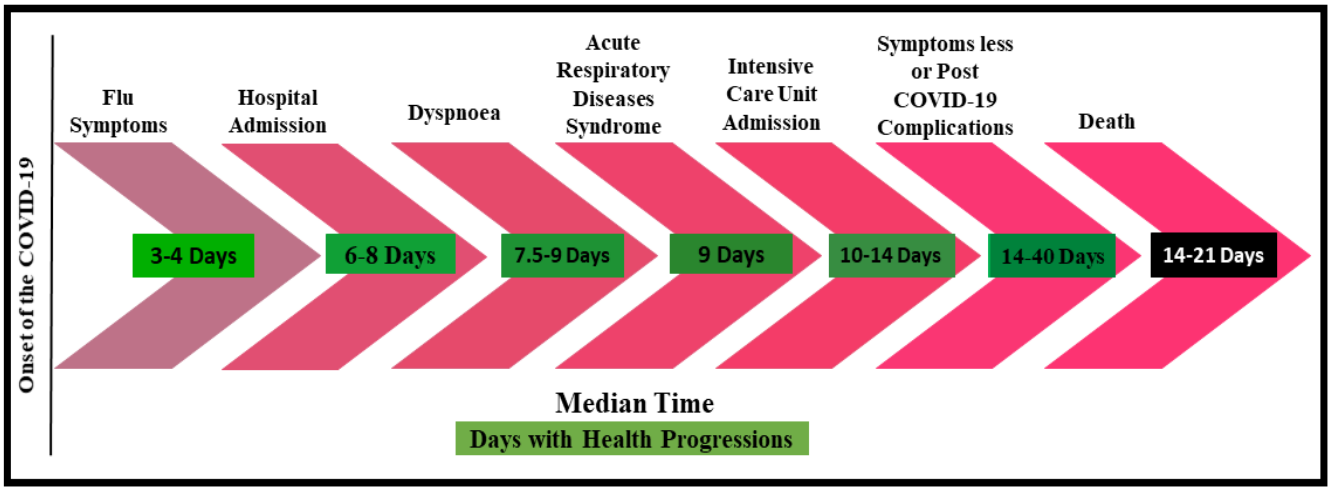

Figure 2. Timeline of SARS-CoV-2 cases after onset of illness
(modified from reference[7]).

need to get admitted to the ICU[7,16], although complications such as acute respiratory distress syndrome, acute renal injury, septic shock, ventilator-associated pneumonia were reported in the case of one-third of the patients[7,16,18]. Patients meeting any one of the three criteria: (1) dyspnea, respiratory rate >30 times/min, (2) oxygen saturation, PaO_2 (partial pressure of arterial oxygen)/FiO_2 (percentage of inspired oxygen) ratio <300 mmHg will be considered severe patient, while patients with respiratory failure, septic shock or multiple organ failure will be treated as critical patients[6,13,16,21,32,33]. Most recently, some other unusual symptoms are also reported, such as stroke, blood clots, COVID toes, silent hypoxia, gastrointestinal issues, delirium, skin rashes, multi organ failure, blood clots, neurologic damage[34].

Patients with more severe disease followed by prolonged decline in viral titers have higher level of inflammatory cytokines (IL-2, IL-6, IL-7, IL-10, GCSF, IP-10, MCP-1, MIP-1A, and TNF-α) than patients with mild disease[7,33]. Moreover, critically ill people have low number of T-cells, helper T-cells, and memory helper T-cells but contain higher naïve helper T-cells compared to mild group[35]. Increase in IgG and IgM against SARS-CoV-2 antigens was seen around day 7–10 of symptoms, followed by gradual decrease in viral load[36]. In addition, in one meta-analysis study by Huang et al. (2020)[33], the authors reported an adverse outcome (84%) and deaths (87%) in adult patients having lower lymphocyte count with a mean difference of 361.06 µL [− 439.18, − 282.95], which may rise to 376.53-377.56 µL in the case of acute respiratory distress syndrom (ARDS) and ICU patients. Although thrombocytopenia (20.0%) was also frequently reported, most of the patients had a normal complete blood count (normal hemoglobin, white blood cells and platelet count) and lactate dehydrogenase (LDH)[11,16, 32,33].

6. Effects of COVID-19 in children and pregnant women

While COVID-19 showed an age-stratified clinical manifestation and outcome, children showed a mild form of disease[16]. Early closing of educational institutes and day-care centers may explain the less infection rate in children due to less frequent exposure[12,16,37].

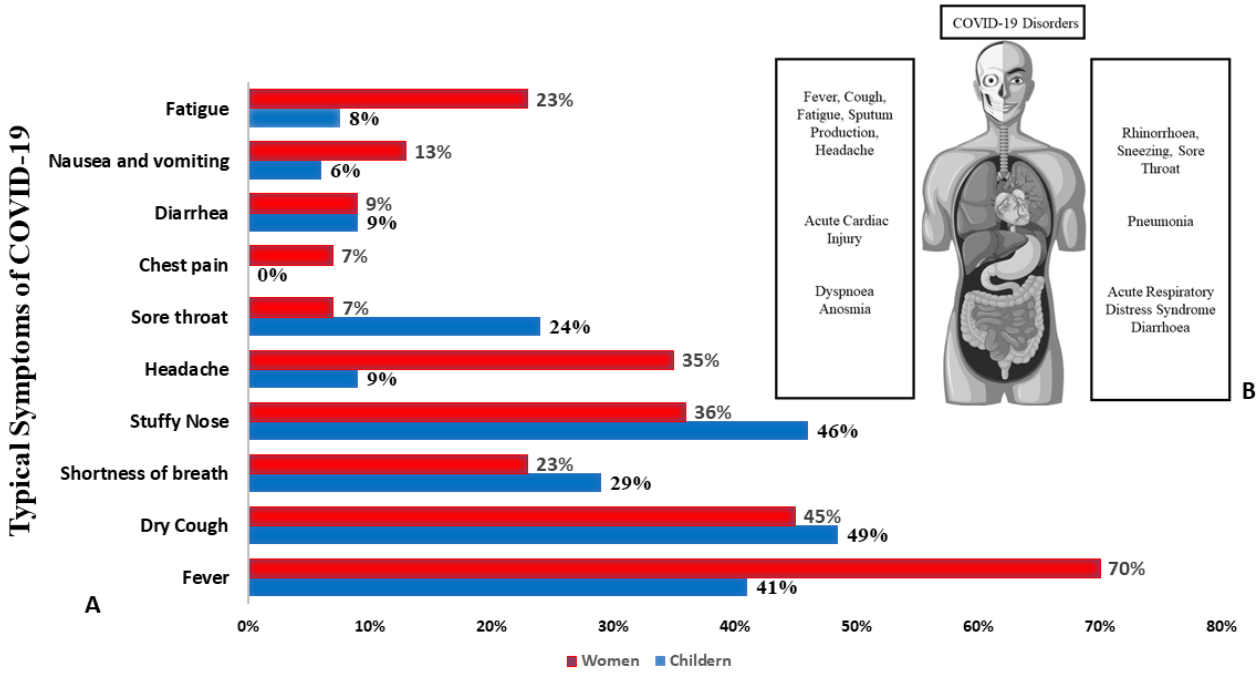

Figure 3. Representative typical symptoms of COVID-19 with tentative percentages.
A. Percent of all reported symptoms for SARS-CoV-2 affected patients; **B.** The disorders caused by SARS-CoV-2 with an approximate 5.2 days incubation period. There are general similarities of the symptoms between SARS-CoV-2 and previous life-threatening beta-coronavirus SARS and MERS. However, SARS-CoV-2 infection showed several more unique clinical features, such as rhinorrhea, sneezing, and sore throat.

The infection rate in children is reported to be less than that of adults and less severe than in adults[32], while adolescents have illness similar to adults, however, the case fatality rate in adolescents is significantly lower. Infection rate tends to be higher among males (71%) compared to females. The median age of infected individuals observed so far was 40 years[16], although age stratified death rate showed approximately 80% of COVID-19 deaths in the patients over 60 years old[16]. Besides, death was associated with co-morbid medical conditions such as hypertension, diabetes, or cardiovascular disease in over 75% of the cases[13,16]. The median time from onset of symptoms to the first day of hospital admission, and eventually to ICU admission was 7.5 days (4.0–8.0) and 11 days (8.0–17.0) respectively[32], although the prevalence of asymptomatic patients can also not be ignored[32].

Details of clinical illness in children have been reported from studies in China, Italy, USA, UK, Bangladesh, India, Singapore, and Canada[38]. A study on 171 pediatric patients in China reported an incubation period of 2–14 days in children, with the following symptoms: cough (48.5%), stuffy nose (46.2%), fever (41.5%), fast breathing (28.7%), sore throat (24%), headache (9%), diarrhea (8.8%), fatigue (7.6%), and vomiting (6.4%)[39] (Figure 3), while fever, cough were most common in children < 10 years old and headache, myalgia, chills, sore throat, and/or breathing difficulty were most common among older children (≥10 years old)[39]. Severe symptoms such as hilar adenopathy, extensive pleural effusions, lung abscess, pneumatocele, or pneumothorax were primarily absent among children with COVID-19[13, 17, 32, 39, 43]. Besides, median duration of fever was significantly shorter in children compared to adult patients (3 days vs. 10 days). On the other hand, in two studies on 230 pregnant women, the most common symptoms were fever (70%), cough (45%), stuffy nose (36%), headache (35%), shortness of breath (23.3%), fatigue (22.5%), vomiting ,(13%), diarrhea (8.8%), dyspnea (11.3%), sore throat (7.5%), myalgia (16.3%), chest pain (7%) as common symptoms (Figure 3)[37,40].

However, contrary to pediatric COVID-19 patients, adults with COVID-19 usually showed a significant or progressive decrease in the absolute number of peripheral blood lymphocytes at the early stage of disease[13,22,23], followed by adverse outcome. There are no studies of viral loads, and cytokine levels in children with COVID-19.

7. COVID-19 diagnosis and detection

The initial diagnosis of SARS-CoV-2 was symptoms-based, depending on clinical and epidemiological data. Laboratory confirmation of a SARS-CoV-2 infection can be determined by the isolation of the virus from a clinical specimen with the detection of SARS-CoV RNA by a reverse transcription PCR assay, the demonstration of serum antibody by ELISA (which suggest a previous or current infection), CT scan[1,2], next-generation sequencing[32], scanning electron microscopy (SEM)[5] and cell culture[11,13]. While chest CT reported higher sensitivity of 97% compared to RT-PCR (71%), chest CT cannot detect the asymptomatic cases. However, other studies reported that the combination of both yields higher sensitivity than either of them alone[41]. On the other hand, RT-PCR sensitivity varies with the specimen used showing the highest sensitivity for lung wash (93%) and the lowest for blood (1%)[5]. This variation probably arises from the differential viral load in different specimens, observed with the progression of disease course[1,11,41]. However, fecal specimen[1] can be recommended for testing, especially before discharging the patient, due to the presence of viral load in feces for a longer period compared to respiratory specimens.

8. Clinical Management of COVID-19

The US Food and Drug Administration (FDA) has launched a Coronavirus Treatment Acceleration Program to accelerate the development of therapeutic options against COVID-19. In addition, FDA has approved the use of remdesivir for treating COVID-19 along with five other drugs in case of emergency, while WHO has also initially recommended remdesivir for COVID-19[11,13,14,19,20,32]. Moreover, two vaccines based on mRNA received emergency approved by the US FDA and are in the process of being distributed worldwide. Despite this progress, different strategies can be used depending on the severity of the patient and local epidemiology. Home management is appropriate for asymptomatic or paucisymptomatic patients. The optimal duration of home isolation is uncertain, but

in consideration of incubation time around 14 days without symptoms are considered sufficient to end home isolation. Some patients with suspected or documented COVID-19 have severe disease that warrants hospital care. Oxygen therapy appears to be the major treatment intervention for those patients[42]. Mechanical ventilation may be an alternative in cases of respiratory failure refractory to oxygen therapy, while hemodynamic support is essential for managing septic shock[13,14,17,42]. Besides, the empirical treatment using convalescent plasma collected from patients who have recovered from COVID-19 has recently yielded satisfactory results, considering both mortality and morbidity[42]. However, drug repurposing has been promising so far in the clinical management of COVID-19 in the absence of definite therapeutics and vaccines. Since the emergence, both antiviral (ribavirin) and anti-inflammatory treatment followed by flu related medicine, combination of broad-spectrum antibiotics, corticosteroids and convalescent plasma have been applied on a trial and error basis. The US FDA developed the Coronavirus Treatment Acceleration Program to accelerate the development and to track the progress of different programs aiming COVID-19 prevention and treatment[43]. FDA is tracking over 550 individual drug programs[44] at different stages, ranging from planning to trial phase, including chloroquine, hydroxychloroquine, remdesivir, favipiravir, lopinavir, ritonavir, nafamostat, camostat, famotidine, ivermectin, methylprednisolone, bevacizumab etc., along with other supporting agents, such as IL-6 antagonists, corticosteroids, nitric oxide, ascorbic acid etc.. However, neither of them has been proved completely effective in treating COVID-19 patients[45,46].

On the other hand, among the vaccine endeavors against SARS-CoV-2, as of now, two m-RNA based vaccines received emergency approval by the US FDA, with more than ten vaccines, including one developed by the University of Oxford, being in advanced phases of clinical evaluation. Care should be used in testing and evaluating the vaccines for their short- or long-term side effects [47,48]. Besides, being an RNA virus, the vaccine might now be effective against the future strains of SARS-CoV-2 with pandemic potential. In addition, more than 110 vaccines (mRNA-1273, Ad5-nCoV, AZD1222, PittCoVacc, PiCoVacc etc.) are now going through pre-clinical evaluation. The initial success has made the scientists more optimistic about effectiveness of the vaccines in humans.

9. Containment strategy

Considering the advances in medical science and research regarding COVID-19 and SARS-CoV-2, preventing infections using a sound public health policy and the use of standard infection control procedures based on the existing knowledge of the disease and the causative virus is rational and recommended. While this pandemic has showed the vulnerability of the global health sector and its limitations, unfortunately, we may have to live with COVID-19 for the next few years. Thus, a strategy needs to be planned and devised in order to reduce the impact of COVID-19, considering the lack of effective treatments and to combat the future pandemics of infectious diseases. The main components of this strategy should include using facemasks, coughing/sneezing etiquette, washing hands frequently, maintaining the proper rules, using hand-sanitizers of recommended compositions such as at least 60% alcohol etc., avoiding contact with infected individuals, maintaining social distancing and personal hygiene including avoiding touching eyes, nose, and mouth with unwashed hands etc.[22, 26].

10. Possibility of COVID-19 eradication

To evaluate the possibility of COVID-19 eradication, the incidence of reactivation/reinfection and the feasibility of herd immunity need to be evaluated, taking into consideration the relapse capacity of the COVID-19 outbreak. Because countries such as China and South Korea reported that at least 5 and 116 patients[49] respectively re-tested positive after they were considered to be cleared of COVID-19, this raises the question about the possibility of SARS-CoV-2 reactivation or re-infection[50]. While it is not impossible for SARS-CoV-2 to possess the reactivation capacity, such as Epstein-Barr virus, Ebola virus and Varicella-zoster virus[50], it is plausible that false negative results in RT-PCR were seen as viral clearance[51].

However, unlike most of the spillover self-limiting zoonoses, COVID-19 showed an adaptation capability leading to sustained human to human transmission, followed by a zoonotic spillover like Human Immunodeficiency virus (HIV) or others.

Especially the aerosolization of the virus at the Wuhan sea food market, and perhaps nosocomial dissemination in medical setups made this virus exhibit the possible stabilization in human differing from other spillover agents such as SARS, Lassa and Ebola viruses. In addition, anxiety has emerged over the possibility of a future genetic recombinant virus with the SARS-CoV-2 and a human respiratory CoV such as OC43 or 229E strains or SARS-CoV or MERS, due to the close proximity between animals and humans in majority of the countries around the world and high prevalence of human CoV infections.

11. Conclusion

This review provides the detailed analysis of COVID-19 research updates in terms of public health impact, clinical manifestations and management, diagnosis, emergency response and preparedness which can be utilized in future health emergencies and pandemic responses. Overall, the experience from this pandemic will be a resource to design policies and devise strategies to combat such large-scale human health crisis with existing facilities and resources.

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O.S. and A.S. carried out the studies (data collection and data analysis). O.S., A.S, M.M.R. and N.N.R. drafted the manuscript. M.M.R. developed the hypothesis, supervised the whole work and critically review the drafted manuscript. All authors significantly contributed to, read and approved the final manuscript.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be considered as a potential conflict of interest.

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